Asthma Self-Management Using Mobile Telephone Technology

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This thesis is submitted to the Department of Engineering Science, University of Oxford, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.
An early cartoon featuring a futuristic vision of telemedicine. Punch, 1931.

Declaration

I declare that this thesis is entirely my own work, and except where otherwise stated, describes my own research.

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Abstract

Asthma is now one of the most common long-term illnesses in the UK: with over 5.2 million individuals suffering from this condition, asthma represents an annual cost to the NHS of over £800 million. There is a large body of evidence, particularly from the US, indicating that patient self-management is useful in improving asthma control, and the “always on” internet connection provided by the latest GRPS mobile phones offers an opportunity to use a readily available technology to provide a real-time telemedicine system for asthma self-management. This thesis focuses on the use of a real-time telemedicine system for asthma self-management using mobile phone technology evaluated in two clinical studies.

Patient engagement with the system and compliance with the technology were found to be good. The control of mild-to-moderate asthma as assessed by variability in peak flows was worse than expected. Nevertheless, there was a 30% drop in variability from the start to the end of the main study, and during that time, the use of reliever inhalers decreased by 0.6 puffs per peak flow reading. Significant diurnal variability (i.e. large differences between morning and evening peak flow readings) was found in 24% of patients in the main study.

Correlations between respiratory disease and environmental conditions such as temperature and pollution are well documented in the literature. Patient data shows that peak flow values in one third of patients can be partly explained by environmental conditions on a day-to-day basis.

Two real-time telemedicine systems are proposed based on the analysis of the results presented in the thesis, one to collect regular data to diagnose and characterize an individual's asthma, the other to provide back-up support and advice to patients if they are experiencing episodes of poor control.
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Chapter 1

Introduction

1.1 Long-term Conditions

Throughout the second half of the twentieth century, life expectancy has increased rapidly. Enhanced use of technology in healthcare means that many more people are now beginning to live into their seventies and beyond. This greater longevity has brought with it an increased burden of heart disease, stroke, cancer, arthritis, diabetes mellitus, mental illness, asthma and other conditions [1]. As a result, the predominant disease pattern in developed countries, is now one of chronic\(^1\) or long-term condition\(^2\) rather than acute disease. In Great Britain, at any one time, as many as 17.5 million adults may be living with a long-term condition [1]. The number of individuals suffering from such conditions continues to increase, this can be seen in Figure 1.1 which shows analysis from the general household survey (2002). The World Health Organisation (WHO) predict that long-term conditions will be the leading cause of disability throughout the world by the year 2020 and that if they are not successfully prevented and managed, they will become the most expensive problem faced by healthcare systems [3].

\(^1\)Chronic diseases have a long course of illness. They rarely resolve spontaneously and they are generally not cured by medication or prevented by vaccine [2].

\(^2\)The term long-term condition used in this Thesis, is directly comparable to the more common term of chronic disease, it has been chosen in accordance with Department of Health recommendations, January 2005. Much of the research in this area therefore uses the terms long-term condition and chronic disease interchangeably.
CHAPTER 1. INTRODUCTION

The demand both on funding of treatment and on clinician time caused by the management of these patients is already significant: around 80% of GP consultations relate to long-term conditions, and patients with such conditions or their complications account for over 60% of hospital days [4]. A body of emerging evidence, primarily from the USA, has given fresh impetus to the development of long-term disease policy.

It is generally accepted that there are three stages in the care of long-term conditions. These can be represented by the “pyramid of care” in which patients are divided into levels of increasing criticality, Figure 1.2.

Figure 1.1: Percentage of respondents to general household survey 2002 (n = 13 000) reporting a long-term condition.

Figure 1.2: The long-term care pyramid [5].
This structure was originally described by Kaiser Permanente, a large managed care organization in California, USA [5], and has subsequently been adopted by the Department of Health in the UK [6]. Improvements in patient care, particularly through techniques such as self-management are aimed at delaying patients’ progression to the top of the pyramid. The three levels of the pyramid can be described as follows:

**Level 1 - Supported self-care**  The vast majority of patients will fall into this category (70-80%) which is of the lowest priority for healthcare providers. Improving education and support will help patients to manage their own disease, improving compliance and helping to slow the progression of the disease. Self-management will be reviewed in greater detail below.

**Level 2 - Specialist disease management**  This group of patients requires more attention from healthcare providers; they include patients in more advanced stages of their disease, who are at higher risk. These patients will benefit from close monitoring at home to detect poor control of conditions and to help regulate medications.

**Level 3 - Case management**  Patients in the advanced stages of their disease with highly complex conditions; they require close monitoring to help to limit inappropriate hospital admissions and to enable safe hospital discharge.

This Thesis is concerned with the development of appropriate technology and algorithms to help support self-management of Level 1 patients in the context of asthma which is a highly prevalent respiratory condition. Level 1 patients represent the largest percentage of the long-term condition population and are the least impacted by their condition; if the control of the long-term condition is sufficiently good, progression up the pyramid can be slowed down and a better quality of life maintained [7].

### 1.2 Self-management

In the broadest sense, the treatments for different long-term conditions are very similar. Current thinking tends to focus on self-management programmes which emphasize the patients’ central role
in the management of their illnesses. Such practice aims to help patients to overcome the emotional impact of the disease by enabling them to monitor and appropriately to manage their condition on a day-to-day basis. In addition, programmes provide patients with the necessary knowledge, skills, and self-efficacy\(^3\) to deal with disease-related problems [8]. Such a treatment model differs from the more conventional model where the clinician dictates a treatment regime to the patient, as it encourages patients to collaborate with their clinicians and health care provider.

The necessary shift in the way in which health care is provided is becoming widely recognized as creating new challenges to the providers of health care. There are many new Department of Health publications [9, 10, 11] and even a specially themed edition of the British Medical Journal in March 2005 [12]. The evidence base backing the use of generic supported self-care programmes to assist patients, such as the Expert Patients Programme, discussed later, and disease specific management programmes for conditions like diabetes or Chronic Obstructive Pulmonary Disease (COPD) is strong [13].

One study, carried out in Stanford by Lorig in 1993, considered the benefits of a disease-specific self-management programme for people living with chronic arthritis [14]. There was no formal control group used in this study. However, the study concluded that the main benefit to patients was the growth of confidence and feeling of self-efficacy which helped to reduce pain by a mean of 20% and physician visits by 40%. Follow up research investigated the effects over a four year period and found that people who had been enrolled in the programme were still benefiting from the experience. Additionally, improved self-management has also been proven to reduce the cost of the disease management [8].

One of the ways in which the NHS has recognized the many potential benefits of self-management has been by introducing the *Expert Patients Programme* [11], which aims to improve patients' understanding of their long-term conditions. The Expert Patients Programme is a lay-led self-management training programme providing opportunities for people living with long-term conditions to develop new skills to improve management of their condition on a day-to-day basis. The programme focuses on the social aspects of living with a long-term condition. A typical self-management course is led by two volunteer lay tutors who have good knowledge of management of long-term conditions. The weekly training sessions last for six weeks and focus on the generic aspects of long-term conditions,

\(^3\)The capacity to judge one's own ability to succeed in reaching a specific goal.
building skills, resourcefulness and improving confidence to enable patients to work in partnership with health care professionals.

Self-reported data in England from 250 Expert Patients Programme course participants [15] offers good support for expansion of the programme:

**Self-assessed well being**

- 10% more participants took their medicine as prescribed
- 30% showed a significant reduction in depression
- 30% showed a reduction in ‘lacking in energy’
- 20-30% experienced a reduction in the intensity of pain and breathlessness
- 30-50% experienced an increase in confidence levels.

**Accessing health services and information** The report also showed that there was:

- 9% reduction in visits to the GP
- 6% reduction in visits to A&E
- 9% reduction in visits to outpatient department
- 15% increase in visits to pharmacists
- 17% reduction in number of days off work
- 6% increase in the use of health information.

There are currently 12 000 trained patients, and although the initiative is showing mixed results, it is clearly having a major impact on many patients [16], the challenge facing the NHS being how to extend the programme to one that can support the many millions of patients who might benefit [17]. Initiatives such as the Expert Patients Programme take a general approach to the management of long-term conditions with more actively engaged patients complying better with medical regimes and learning to manage their condition. For truly effective self-efficacy, it is important to recognize the different objectives of the interventions and the complexity of the issues that they are attempting to tackle [13].

For diseases such as asthma and diabetes, clear objectives concerning the underlying control of the condition have been identified with strategies to achieve the desired outcome. A review of self-management interventions for asthma in 2004 concludes that self-management can be efficacious

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4Post-course questionnaires three to four months after course participation, compared with pre-course data.
and provides guidance for components required in future programmes [13]. A total of 18 random controlled trials published between 1997 and 2002 were analyzed; 57% of the studies showed an improvement in lung function. Most of these studies used a combination of education and action-plan based on either measured lung function or symptoms [18, 19, 20, 21, 22]. The majority (78%) of asthma interventions targeted some aspect of behaviour, usually adherence to preventative medications, recognition and appropriate use of rescue medications as well as inhaler technique, self-monitoring and avoidance of asthma triggers. Significant changes in behaviour were reported in eight of the studies, six of which used an education and action-plan approach, which Newman recommends as being effective at reducing use of health care in asthma [13].

Education and improved self-efficacy is augmented by a range of different interventions encompassing, education, feedback and reminders [23]. However, the underlying pattern is one of healthcare professionals providing information and support to enable patients to become more empowered and learn to take decisions in the ongoing behaviour and medication for their condition. With time, patients obtain greater understanding of their own condition, control improves and their use of healthcare services subsides.

1.3 Appropriate Technology for Self-Management

In order to assist clinical understanding of their conditions, patients with long-term conditions are encouraged to monitor the appropriate physiological parameter (blood glucose or peak flow level for diabetes or asthma respectively) and record them on a chart in a patient diary [24]. However, paper diaries are often poorly kept and highly inaccurate [25]. Under the recommendation of Newman [13], technology is justified if it will improve the ease of use, eliminate errors in data recording and ideally provide reminders and feedback to patients. This will remove much of the burden of recording symptoms and assist decision making. Ideally, this technology will be easy to use, unobtrusive and easily adopted in the lifestyle of chronic disease sufferers.

Electronic monitors are increasingly available for the home monitoring of an expanding range of physiological parameters. As the newer generations of meters supersede existing manual devices, electronic storage and transmission of measured data becomes increasingly practical [26]. This improves data reliability and reduces the demands on the patients.
CHAPTER 1. INTRODUCTION

Transmission of medical data via electronics media is a form of telemedicine, which is reviewed in Chapter 3. The technology used to transmit data has evolved significantly over the past decade, progressing from the use of a personal computer with a dial-up modem to send data directly to a remote computer to the use of a home computer with an internet connection.

This Thesis thus focuses on the most recent development in telemedicine; the use of mobile phones for self-management, the rationale for which will be given at the end of Chapter 3. Mobile phones are small, portable and convenient to use, they are increasingly becoming integrated into many individuals’ daily routines. Chapter 2 describes some of the background to the condition of asthma and focuses on some of the ways in which the disease is quantified and treated. A brief outline of the structure of the telemedicine system used in this Thesis is presented in Chapter 4. The development of this system for use in the self-management of asthma and analysis of results are outlined in the following two Chapters. Since environmental factors such as weather and pollution have been recognized to affect people with asthma [27], Chapters 7 and 8 describe the analysis of effects across a global population of asthmatics and the development of individual models to assist patient self-management. Conclusions and recommendations for future work are presented in Chapter 9.
Chapter 2

Review of Asthma

Over 25% of the population suffer from one of the spectrum of respiratory conditions shown in Figure 2.1. The majority of these suffer from non-life threatening conditions such as rhinitis. However, towards the more severe end of the spectrum an increasing number of individuals have more serious conditions.

**Rhinitis**
Rhinitis is defined as inflammation of the nasal membranes and is characterized by any combination of the following symptoms: sneezing, nasal congestion and nasal itching. Allergic rhinitis, or hay fever as it is usually referred, is the most common, affecting approximately 20% of the population.

**Asthma**
The term asthma encompasses a wide range of conditions characterized by difficulty in breathing. Asthma manifests through extra sensitive or hyper-responsive airways. The airways react by narrowing or obstructing when they become irritated, making it difficult for the air to flow to the lungs. Any one or a combination of reversible symptoms such as wheezing, coughing, shortness of breath and chest tightness can result.

**Chronic Obstructive Pulmonary Disease**
Chronic Obstructive Pulmonary Disease (COPD) is a disease state characterized by limitations in lung airflow that are not fully reversible. COPD is a general term which includes the conditions chronic bronchitis (inflammation of the bronchial mucous membrane) and emphysema (enlargement of the air vesicles of the lungs). COPD is a major cause of hospital admissions in the UK, accounting for over one million in-patient bed days each year.

Figure 2.1: The spectrum of worsening respiratory conditions from Rhinitis to COPD [28].
2.1 Asthma

This Thesis concentrates on asthma, a condition where use of effective self-management has been shown to improve quality of life and arrest progression of the disease [29, 30]. Asthma can be further sub-divided into two categories, “extrinsic” or “intrinsic” asthma. Extrinsic, or allergic asthma which typically develops in childhood, is the most common and accounts for 90% of all asthma cases. Intrinsic asthma accounts for the remaining 10% of cases, it usually develops after the age of 30, often following a respiratory tract infection [31].

An individual’s lungs are dependent on both physiological and environmental factors. A person’s size, age and level of fitness determine their lung performance. Compliance and timing of medication and the underlying diurnal variation linked to sleep patterns also complicate the overall assessment [32]. There are also second order effects which are specific to individuals; weather, pollution, fungal spores and pollen are all recognized as exacerbating asthma in some individuals. These effects lead to a commonly used classification system which describes the triggers that make asthma worse for a particular individual. The main four categories are listed below:

- **Exercise-Induced Asthma** - Exercise can make asthma symptoms worse. With medication and monitoring, people with exercise-induced asthma can participate in physical activities.
- **Nocturnal Asthma** - Worsening of asthma at night is very common. Consideration of underlying causes is important in managing nocturnal asthma.
- **Occupational Asthma** Workplace exposure to certain chemicals or dusts can induce asthma. Quick recognition and control of workplace exposures is important.
- **Steroid-Resistant Asthma (Severe Asthma)** - While the majority of patients respond to regular inhaled glucocorticoid (steroid) therapy, some are steroid resistant.

2.1.1 Asthma Symptoms

Asthma manifests itself in poor control of fluctuations in physiology resulting from underlying airway inflammation [33]. The International consensus report on the diagnosis and treatment of asthma describes asthma as, “a chronic inflammatory disorder of the airways .... in susceptible individuals, inflammatory symptoms are usually associated with widespread but variable airflow obstruction and an increase in airway response to a variety of stimuli. Obstruction is often reversible, either spontaneously or with treatment” [34].
Three things make it harder to breathe during episodes of asthma; the inflammation of the lining of the airways, the tightening of the muscles around the airways, and mucus filling the airways [35]. These factors reduce airflow and produce the characteristic wheezing sound. A representative section of airway is shown in Figure 2.2, comparison can be made to a normal airway.

![Figure 2.2: Comparison between a normal airway (left) and an airway from an asthmatic with inflammation, tightening of surrounding muscles and mucus (reproduced from [35]).](image)

The classification of asthma earlier identified a number of types of asthma, in sensitive individuals, asthma symptoms can be triggered by inhaled allergens (allergy triggers) such as pet hair, dust mites, moulds, or pollens. Asthma symptoms can also be triggered by respiratory infections, exercise, cold air, tobacco smoke and other pollutants, stress, food, or drug allergies [35]. Some of these triggers such as pet hair, are very localized. Others such as cold air have more wide ranging effects on the population [36].

### 2.1.2 Asthma Exacerbations

Severe episodes of asthma symptoms are commonly referred to as asthma attacks or exacerbations. There is no generally accepted definition of an asthma exacerbation, but one is generally regarded to be “a sustained worsening of the patient’s condition from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication” [37]. Exacerbations will commonly require additional medication to be taken by the patient most likely with an
unscheduled visit to a GP. In extreme cases, patients will require hospitalization, so that they can be closely monitored until their symptoms return to normal.

### 2.1.3 Asthma Prevalence

Asthma is now one of the most common long-term illnesses in the UK and numbers have been increasing steadily over the past few decades. 5.2 million people in the UK are currently receiving treatment for asthma: 1.1 million children (1 in 10) and 4.1 million adults (1 in 12) [38]. There were just under 1,400 deaths (1,381) from asthma in the UK in 2004 (40 were children aged 14 years or under) [39]. A 12 month study of 12,203 patients from the UK [40] found that the average annual cost per patient who had an asthma attack in the year 2000 was £381 compared with £108 for those patients with asthma who did not experience an attack in that year. The total cost of asthma treatment to the NHS was estimated as £850 million in the year 2005.

### 2.2 Effects of Environmental Conditions on Asthma

In February 2006, New Scientist reported the work being undertaken by the Meteorological office in the UK [27], their project *Forecasting the Nation’s Health* focusing particularly on COPD where exacerbations tend to peak around 12 days after a drop in temperature. These exacerbations are also associated with high humidity, low wind speeds and poor air quality, all of which increase the transmission of viruses, potentially leading to chest infections.

Many of these triggers are specific to individuals, for example only those who are allergic to a particular form of pollution or pollen spore. Compared to medication use, environmental factors such as weather, pollen and pollution, tend to exhibit a second order effect but can still have quite marked influence on some individuals. Local factors such as allergies to dust mites or cats may trigger problems in a person’s home or if they have visited a new location. Other influences are more globalised and may be experienced by a larger fraction of the population.

Previous epidemiological studies have been carried out to measure the effect of weather, pollen and air pollution on asthma, these are summarized in Table 2.1. However, they have all focused on severe exacerbations leading to visits to Accident and Emergency Departments which can be easily
quantified. Hospital admission data for people with asthma can be regressed against the historical weather, pollen and air pollution data and measurements which quantify correlations with asthma epidemics are identified. Table 2.1 also includes the delays between cause and effect which have been identified. It clearly takes some time for patients to get to Accident and Emergency Departments, but it is also evident from the literature that environmental conditions can take time to have an effect on lung responses.

Weather and pollutants forecasts are a common feature, if the effects on the lungs of some individuals can be determined to be linked to environmental conditions, it should be possible to use forecasts to counter act potential exacerbations with preventative medication.
### 2.2.1 Previous Studies of Environmental Factors

<table>
<thead>
<tr>
<th>Paper</th>
<th>Findings</th>
<th>$p$</th>
<th>Lag</th>
<th>Study Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chew [41]</td>
<td>Paediatric&lt;br&gt;$SO_2$ - increase of 2.9 A&amp;E visits for every $20\mu g/m^3$ on days above $68\mu g/m^3$&lt;br&gt;$TSP\textsuperscript{1}$ - increase of 5.8 A&amp;E visits for every $20\mu g/m^3$ on days above $73\mu g/m^3$&lt;br&gt;$NO_2$ - also found to be correlated with A&amp;E visits.</td>
<td>$p &lt; 0.001$</td>
<td>1-2 days</td>
<td>5 Years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chew [41]</td>
<td>Paediatric&lt;br&gt;$SO_2$ - increase of 2.9 A&amp;E visits for every $20\mu g/m^3$ on days above $68\mu g/m^3$&lt;br&gt;$TSP\textsuperscript{1}$ - increase of 5.8 A&amp;E visits for every $20\mu g/m^3$ on days above $73\mu g/m^3$&lt;br&gt;$NO_2$ - also found to be correlated with A&amp;E visits.</td>
<td>$p &lt; 0.001$</td>
<td>0-2 days</td>
<td>23400 Visits</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$p &lt; 0.05$</td>
<td>1-2 days</td>
<td></td>
</tr>
<tr>
<td>Rosales-Castillo [42]</td>
<td>$10\mu g/m^3$ increase in $PM_{10}$ results in 3.11% increase in A&amp;E visits&lt;br&gt;$10ppb$ increase in $O_3$ results in 3.17% increase in A&amp;E visits</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Newson [43]</td>
<td>High levels of grass pollen and thunderstorms indicate a 15% probability of an asthma epidemic, culminating in A&amp;E visits.</td>
<td>-</td>
<td>15 hrs</td>
<td>8 Years 650000 Visits</td>
</tr>
<tr>
<td>de Diego Damiá [44]</td>
<td>$SO_2$ is associated with hospital admissions - $r = 0.32$&lt;br&gt;Particulate black smoke is associated with hospital admissions - $r = 0.35$&lt;br&gt;Temperature is associated with hospital admissions - $r = -0.29$</td>
<td>$p &lt; 0.05$</td>
<td>-</td>
<td>1 Year 515 Visits</td>
</tr>
<tr>
<td>Ivey [45]</td>
<td>Paediatric&lt;br&gt;Association with Temperature&lt;br&gt;Association with Wind Speed&lt;br&gt;Adults&lt;br&gt;Association with Temperature&lt;br&gt;Association with Humidity</td>
<td>$p &lt; 0.05$</td>
<td>-</td>
<td>1 Year 27848 Visits</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$p &lt; 0.05$</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$p &lt; 0.05$</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$p &lt; 0.05$</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$p &lt; 0.05$</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
| Hajat [46, 47] | Paediatric<br>Association with $NO_2$
$PM_{10}$ is associated with A&E visits | $p < 0.009$ | 0-1 days | Pop. of 290000 |
| | | $p < 0.02$ | 0-3 days |  |
| | | $p < 0.006$ | 0-3 days |  |
| Dobson [36] | When mean temperatures are below 5°C each 1°C drop in temperature can cause a 10.5% increase in respiratory consultations in the elderly (Note COPD rather than asthma) | - | 15 days | Pop. of 40000 |
| Dales [48] | Thunderstorms increased daily asthma visits by 16%
Association with airborne spores | $p < 0.05$ | - | 4 Years 6820 Visits |
| Wilson [17] | An inter quartile range (IQR) increase in $SO_2$ results in an 6% increase in asthma admissions<br>An IQR increase in $O_3$ results in an 5% increase in asthma admissions | - | - | 3 Years Pop. of 425000 |
| Lierl [49] | Association with Pollen Count | $p < 0.001$ | 3 days | - |

Table 2.1: Triggers of exacerbations resulting in visits to Accident and Emergency Departments (A&E).

\textsuperscript{1}Total Suspended Particles is approximately equal to $PM_{10}/0.55$
Weather

The best known weather driven initiator of asthma exacerbations is thunderstorms. A significant epidemic occurred in 1994 [50], when storms caused large increases in presentations at Accident and Emergency Departments across Southern England. Similar effects were noted surrounding storms towards the end of June 2005. Therefore thunderstorms appear to be particularly significant if they follow days with high pollen counts, as they only appear to affect a subset of hay fever sufferers and allergic asthmatics who react to pollen and/or fungal spores. Thunderstorm asthma is also associated with very specific weather conditions - a combination of high pollen, pollution and hot, still air before a storm. As the clouds gather, strong up draughts suck pollutants and pollen grains up from the ground, the grains freeze and shatter when they reach the tops of the clouds, spilling their contents and becoming more allergenic. When rain carries these pollen fragments back down to the ground they set off violent allergic reactions.

An alternative hypothesis is that the drop in temperature, or the increase in humidity which commonly accompanies thunderstorms [51, 52] causes these problems. Temperature has been identified as a precursor to asthma exacerbations. High temperatures can cause hyperventilation which can aggravate asthma. In combination with humid conditions, warm temperatures make ideal conditions for growth of allergens such as dust mites or fungal spores [45]. Wind speed has also been noted as being a precursor to epidemics; this may be attributable to wider distribution of allergens. In contrast to warm temperatures initiating exacerbations, lung function can also decrease in cold weather [36, 53, 54]. This may be associated with use of indoor heating which may harbour dust particles. The response due to cold temperatures may be significantly delayed. Indeed in COPD there may be as much as a 15 day delay between cold weather and asthma-induced visits to GP surgeries [36].

Pollution

Air pollutants were first recognised as having a severe effect on lung function in the 1950s. The London fog of December 1952 saw very high levels of pollutants in the air and there was a significant increase in deaths (around 4,000) [55]. Continuous exposure to low/moderate levels of contaminants over long periods of time is now a daily phenomenon [42]. These may still initiate problems, especially
when levels rise above the norm. Sulphur dioxide (SO$_2$) has been found to increase bronchial constriction in asthmatic individuals [56], and particulate matter $PM_{10}$, such as black diesel smoke will reach deep within the bronchial structure and aggravate lung problems [57]. Both of these findings are corroborated by controlled laboratory findings and in clinical settings [41].

**Pollen**

Pollen is also associated with causing problems in people with asthma. Small particles containing allergen can penetrate deep into the airways of the lungs where they can cause irritation. Pollen is synergistic with other factors as a predictor of asthma visits. Investigations have found two effects due to pollen, an immediate response upon exposure to the spores, followed by a more delayed response of up to three days as the irritation in the lungs causes inflammation [49].

### 2.3 Management of Asthma

Optimum management of asthma requires medication to be used as a feedback mechanism to maintain steady-state control of symptoms [58]. Figure 2.3 shows example data sets for two patients. The scale on the y-axis is a measure of lung condition, for both patients episodes of good control, poor control and exacerbations are shown. They have the following characteristics [58]:

- **Good Control** High level of performance with little variability,
- **Poor Control** High level of variability,
- **Exacerbation** Rapid dip to low level, little variability.
2.3.1 Common Day-to-Day Medications

A range of inhaler medications are employed in the management of asthma, with the intention of reducing the effect of symptoms and averting exacerbations. This day-to-day treatment consists of two main functions: Reliever Inhalers which quickly act to alleviate symptoms, and Preventer Inhalers or Bronchodilators such as the inhaled steroid beclomethasone dipropionate are commonly used on a regular daily basis to counteract inflammation.
• Reliever - A short acting inhaled medication that delivers rapid relief of symptoms. It works quickly to relieve wheeziness and/or cough by relaxing the tightened muscles around the airways. Reliever inhalers are often coloured blue to differentiate them from other treatments. They are also known as beta-2 agonists, consisting of salbutamol and terbutaline amongst others.

• Inhaled Preventer - A regular inhaled medication, often taken twice daily, that reduces the inflammation in the airways of the lungs. Patients should continue to take the inhalers, which are colour coded to differentiate them from relievers, even when symptoms are under control. Inhaled Preventers fall into two main groups:
  – Inhaled Steroids - The most commonly used preventers amongst both adults and children. Taken twice a day in very small doses, delivered directly to the airways in the lungs, they work to reduce airway inflammation. Examples of Inhaled Steroids include beclomethasone dipropionate, budesonide and fluticasone propionate.
  – Combination Inhalers - Inhalers with contain both a preventer (Inhaled Steroid) and a protector (long acting reliever). These two components help to control inflammation, twitchiness and thickening of the airways. Combinations include salmeterol and fluticasone propionate, and formoterol fumarate and budesonide.

• Inhaled Protector - A long acting reliever (Beta-2 agonists) which helps to open up narrowed airways by keeping them relaxed; this makes it easier to breathe and relieves symptoms. These include salmeterol xinafoate, oxisotropium bromide and formoterol fumarate.

Although inhaled corticosteroids such as those mentioned above are highly effective in the treatment of asthma, they have a potential for causing dose related side effects [59, 60, 61]: bruising, cataract, glaucoma, reduced bone density and adrenal suppression. Many treatment regimes therefore aim to use a ‘step-up’, ‘step-down’ which adapts the amount of medication taken to the level of symptoms the patient is current experiencing. Large doses of inhaled steroids are used if control is poor and doses are then reduced once good control has been reached [59, 62, 63]. If correctly administered, this approach has been shown to enable high doses to be used to instigate and maintain good control without the complications associated with long-term use of high levels of medication [59].

2.3.2 Treatment of Exacerbations

The treatment of Exacerbations can be separated from the day-to-day management of asthma symptoms. Doses of the inhaled steroids are increased, often doubled [64]. In addition, stronger medications may be used for a shorter period to relieve symptoms and return to normal levels of control [30]. These medications are often administered in unscheduled GP visits or during hospitalization [65].
2.4 Diagnosis and Monitoring of Asthma

Unfortunately there is no gold standard to diagnose or monitor asthma [58, 66]. However, one of two approaches are generally used; either qualitatively through symptom assessment or quantitatively to obtain numerical values representing lung condition.

2.4.1 Symptom Assessment

Traditionally the assessment of asthma has been based on the severity of a variety of non-asthma specific symptoms; wheezing, shortness of breath, tightness of chest and coughing. However, a significant proportion of asthma sufferers find it difficult to perceive the subjective increase in airway resistance which signals an approaching asthma attack; this poses problems for the management of asthma, limiting the patient’s ability to implement an appropriate self-medication regime [25, 67, 68, 69]. Hence, symptom-based management may not be suitable for every patient. Rushford [67] goes as far as to categorize patients into poor, normal and exaggerated perceivers based on the correlation of their perception of severity of symptoms with the qualitative approaches described in the next section.

There has been much variation in the way symptoms have been collected. Ranging from a few basic questions; wheeze, cough, activity and sleep requiring yes/no answers [70] to a much larger range of questions where answers are graded on a scale of zero to three [71]. The Royal College of Physicians have recognized that in order to collect information in a standardized way, and to address the problems of patient perception, a small range of questions requiring only simple yes/no answers are required. A set of questions known as the Royal College of Physicians 3 Questions or RCP3 have been reached by common consensus [72].

In the last week (or month),

1. have you had difficulty sleeping because of your asthma symptoms (including cough)?
2. have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?
3. has your asthma interfered with your usual activities (e.g. housework, work/school etc)?

These three questions are answered with either ‘yes’ or ‘no’, they are occasionally used on a daily
basis to provide a weekly score (the count of yes answers) out of 21.

2.4.2 Spirometry

Spirometry is commonly used to measure lung function as it provides simple, reproducible results. The air flow through the lungs is measured to assess flow rate and/or total lung volume. Spirometry in various forms has been around for approximately 200 years. However, the introduction of computerized spirometers has led to reports containing multiple parameters, which are used extensively in many obstructive lung diseases such as chronic obstructive pulmonary disease (COPD) [33]. Full spirometry tests involve large, expensive pieces of equipment and are often only available in specialist clinics. Figure 2.4 shows an example of a modern spirometer from Welch Allyn [73], this monitor measures both flow rate and volume over a complete breath from which many different parameters can be analyzed. These parameters are identified in the example flow rate v. volume plot for one complete respiration cycle in Figure 2.5 and their definitions are given in the subsequent list.

Figure 2.4: Example of a contemporary spirometer from Welch Allyn [73].
CHAPTER 2. REVIEW OF ASTHMA

Figure 2.5: Flow-Volume loop for one respiration cycle. Positive values represent expiration, negative values represent inspiration. The trace moves clockwise for expiration followed by inspiration [74].

**FVC** Forced Vital Capacity - This is the total amount of air that one can forcibly blow out after full inspiration, measured in litres.

**FEV\textsubscript{1}** Forced Expiratory Volume in 1 Second - This is the amount of air that you can forcibly blow out in one second, measured in litres. Along with FVC it is considered one of the primary indicators of lung function.

**FEV\textsubscript{1} / FVC** This is the ratio of FEV\textsubscript{1} and FVC, which shows the proportion of the FVC that can be expelled in one second. In healthy adults this should be approximately 80%.

**PEF** Peak Expiratory Flow - This is the speed of the air moving out of the lungs at the beginning of the expiration, measured in litres per second.

**FEF 25-75% or 25-50%** Forced Expiratory Flow 25-75% or 25-50% - This is the average flow (or speed) of air coming out of the lung during the middle portion of the expiration.

**FIF 25-75% or 25-50%** Forced Inspiratory Flow 25-75% or 25-50% - This is similar to FEF 25-75% or 25-50% except the measurement is taken during inspiration.

**FET** Forced Expiratory Time - This measures the length of the expiration in seconds.

PEF is the most commonly used measure and is the one most commonly associated with self-monitoring. The portable peak flow meter was first developed as a test by Wright [75] in the 1950s, Wright designed a small mechanical meter in which a spring-loaded deflector with ratchet measures the maximum air flow rate during expiration. Because of the simplicity of the device its use has
grown rapidly in general practice throughout the Western World and it is the most common test used to monitor asthma. Until recently devices capable of integrating the area under the flow-volume or flow-time curves have not been available at low prices and this test has therefore been much less widely used and the literature demonstrates that PEF remains the dominant measure in clinical practice. In 2003, a new European Standard (EN 13826) was introduced for peak flow meters and new devices have to be calibrated to this scale.

2.4.3 Measurement Issues

Even the most recent spriometers have drawbacks, as ambient conditions such as temperature or altitude may alter the scale for the instrument used to measure lung function [76]. Poor technique using the device (known as manoeuvre technique) may introduce significant variability to a patient’s measurements and if data is being allocated to either “morning” or “evening” sessions to take account for diurnal variation, these session times may overlap between patients. A system which automatically transmits or stores all data will not be able to discriminate if different users use the system, friends may try the technology and could introduce artefacts into the data. Therefore, it is common practice when measuring lung function to take three readings (or manoeuvres) to allow for outlying measurements [77].

2.4.4 Interrelationship of PEF and Symptoms

All of the symptoms relating to asthma are non-specific, and given the subjective nature of symptom assessment, the correlation with spirometry is hard to assess [78]. Based on a symptom score derived from symptom frequency over the past three months, Reddel found a correlation with PEF of approximately -0.58 ($p < 0.0001$). This result is similar to the correlation found between the lowest PEF divided by best PEF and percentage of symptom free days ($r = 0.52$) [79].

2.4.5 Predicted Spirometry Values

The capacity of an individual’s lungs varies as a function of their stature and age. There have been numerous studies undertaken to derive equations for predicting an individual’s spirometry values. These studies have used large patient populations to construct models able to predict PEF and
FEV₁ based on, sex, age and height. The results are summarized for PEF in Table 2.2 and FEV₁ in Table 2.3. Examples are presented for PEF in Figure 2.6 which shows a large variation with height and age for individuals.

There are very significant differences between the predicted values of PEF for these example patients, in excess of 200 l/min in some cases. Hankinson’s results were based on a population of 7429 subjects compared with Nunn’s 453 so patient numbers and the type of function fitted to the data is likely to explain this.

### 2.4.6 Diurnal Variability

An increased variability of PEF is one characteristic of asthma, and the circadian rhythms in PEF and diurnal variation of asthma are both well established [32, 86]. Studies have shown that the circadian pattern can be approximated to the first order as a sinusoid, which is very closely related to sleep patterns [32, 86], shown through the response in shift workers where the circadian pattern rapidly adjusts to sleep times. Reddel [58] also notes that that the circadian rhythm changes with waking time, being a mean of 81 minutes later at weekends.

A sinusoidal function is frequently used to fit the raw PEF data:

\[
P EF(t) = Co + C. \cos \left( \frac{2\pi t}{T} + \phi \right) + \epsilon_t
\]  

(2.1)
### Table 2.2: PEF prediction models

<table>
<thead>
<tr>
<th>Model</th>
<th>Formula</th>
<th>Gender</th>
<th>Age Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF</td>
<td>$0.00150 \text{height}^2 (\text{cm}^2) - 7.41 \text{age(years)} + 0.788 \text{age}^2 \text{(years}^2) - 35.7$</td>
<td>Males</td>
<td>8 - 20</td>
<td>Hankinson [80]</td>
</tr>
<tr>
<td>PEF</td>
<td>$0.00150 \text{height}^2 (\text{cm}^2) + 4.96 \text{age(years)} - 0.0781 \text{age}^2 \text{(years}^2) + 63.1$</td>
<td>Males</td>
<td>20 - 80</td>
<td>Hankinson [80]</td>
</tr>
<tr>
<td>PEF</td>
<td>$0.0112 \text{height}^2 (\text{cm}^2) + 36.4 \text{age(years)} - 1.01 \text{age}^2 \text{(years}^2) - 217$</td>
<td>Females</td>
<td>8 - 18</td>
<td>Hankinson [80]</td>
</tr>
<tr>
<td>PEF</td>
<td>$0.0112 \text{height}^2 (\text{cm}^2) + 4.16 \text{age(years)} - 0.0619 \text{age}^2 \text{(years}^2) + 55.6$</td>
<td>Females</td>
<td>18 - 80</td>
<td>Hankinson [80]</td>
</tr>
<tr>
<td>$\ln[\text{PEF}] = 0.544 \ln[\text{age(years)}] - 0.0151 \text{age(years)} - \frac{74.7}{\text{height(cm)}} + 5.48$</td>
<td>Males</td>
<td>15 - 85</td>
<td>Nunn [81]</td>
<td></td>
</tr>
<tr>
<td>$\ln[\text{PEF}] = 0.376 \ln[\text{age(years)}] - 0.0120 \text{age(years)} - \frac{5.63}{\text{height(cm)}}$</td>
<td>Females</td>
<td>15 - 85</td>
<td>Nunn [81]</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2.3: FEV$_1$ prediction models

<table>
<thead>
<tr>
<th>Model</th>
<th>Formula</th>
<th>Gender</th>
<th>Age Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$</td>
<td>$0.00014098 \text{height}^2 (\text{cm}^2) - 0.04106 \text{age(years)} + 0.00477 \text{age}^2 \text{(years}^2) - 0.7453$</td>
<td>Males</td>
<td>8 - 20</td>
<td>Hankinson [80]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.00014098 \text{height}^2 (\text{cm}^2) - 0.01303 \text{age(years)} - 0.000172 \text{age}^2 \text{(years}^2) + 0.5536$</td>
<td>Males</td>
<td>20 - 80</td>
<td>Hankinson [80]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.00014098 \text{height}^2 (\text{cm}^2) + 0.06537 \text{age(years)} - 0.0000 \text{age}^2 \text{(years}^2) - 0.8710$</td>
<td>Females</td>
<td>8 - 18</td>
<td>Hankinson [80]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.00014098 \text{height}^2 (\text{cm}^2) - 0.00361 \text{age(years)} - 0.000194 \text{age}^2 \text{(years}^2) + 0.4333$</td>
<td>Females</td>
<td>18 - 80</td>
<td>Hankinson [80]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.00144 \text{height(cm)} - 0.0244 \text{age(years)} - 2.6830$</td>
<td>Males</td>
<td>15 - 91</td>
<td>Crapo [82]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.0342 \text{height(cm)} - 0.0255 \text{age(years)} - 1.5780$</td>
<td>Females</td>
<td>15 - 91</td>
<td>Crapo [82]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.0362 \text{height(cm)} - 0.0320 \text{age(years)} - 1.2600$</td>
<td>Males</td>
<td>20 - 84</td>
<td>Morris [83]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.0350 \text{height(cm)} - 0.0250 \text{age(years)} - 1.9310$</td>
<td>Females</td>
<td>20 - 84</td>
<td>Morris [83]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.0358 \text{height(cm)} - 0.0232 \text{age(years)} - 1.5072$</td>
<td>Males</td>
<td>15 - 79</td>
<td>Cherniack [84]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.0237 \text{height(cm)} - 0.0194 \text{age(years)} - 0.1869$</td>
<td>Females</td>
<td>15 - 79</td>
<td>Cherniack [84]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.0460 \text{height(cm)} + 0.0450 \text{age(years)} - 4.808$</td>
<td>Males</td>
<td>6 - 25</td>
<td>Knudson [85]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.0520 \text{height(cm)} - 0.0270 \text{age(years)} - 4.203$</td>
<td>Females</td>
<td>6 - 20</td>
<td>Knudson [85]</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>$0.0270 \text{height(cm)} + 0.0850 \text{age(years)} - 2.703$</td>
<td>Females</td>
<td>20 - 80</td>
<td>Knudson [85]</td>
</tr>
</tbody>
</table>
where \( t \) = time (days), \( T = 1 \) day, \( C_0 \) = constant term, \( C \) = amplitude, \( \phi \) = phase and \( \epsilon_t \) = residual error.

The three most common indices used to quantify PEF variability are [87]:

\[
PEF_{\text{var}} = \frac{\text{highest} - \text{lowest}}{\text{highest}},
\]

(2.2)

\[
PEF_{\text{var}} = \frac{\text{highest} - \text{lowest}}{\text{mean}},
\]

(2.3)

\[
PEF_{\text{var}} = \frac{\text{standard deviation}}{\text{mean}}.
\]

(2.4)

Equation 2.3 had been determined, by a small margin, to be the most repeatable and closely related measure of diurnal variability to asthma symptoms. The following results are reported for patients without respiratory diseases:

<table>
<thead>
<tr>
<th>Index</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude % mean</td>
<td>8.9</td>
<td>3.1 - 25.8</td>
</tr>
<tr>
<td>Amplitude % highest</td>
<td>8.4</td>
<td>3.1 - 23.1</td>
</tr>
<tr>
<td>Absolute amplitude L.min (^{-1})</td>
<td>42.3</td>
<td>17.1 - 104.7</td>
</tr>
<tr>
<td>Cosinor amplitude % mean</td>
<td>4.7</td>
<td>0 - 23.3</td>
</tr>
<tr>
<td>Standard deviation L.min (^{-1})</td>
<td>18.8</td>
<td>7.8 - 4.0</td>
</tr>
<tr>
<td>Standard deviation % mean</td>
<td>3.9</td>
<td>1.4 - 112.1</td>
</tr>
<tr>
<td>Morning dip L.min (^{-1})</td>
<td>-17.8</td>
<td>-61.2 - +25.6</td>
</tr>
</tbody>
</table>

Table 2.4: Distribution of peak expiratory flow variability using seven different indices [87].

Other investigators have found similar results; Hetzel [86] found that a low amplitude circadian rhythm could be found in the airway calibre of the majority (65%) of normal subjects, mean 8.3% s.d. 5.2%, Quackenboss [88] finds an upper limit of 11.3 - 14.1% as the range of diurnal variability in non-asthmatics. Diurnal variability is often more pronounced in asthmatics, especially preceding an exacerbation [89]. Exacerbations are often, although not entirely, characterized by a precursor of diurnal variation which can exceed 20% [32]. Increases in diurnal variation may well be proven to be a useful precursor to exacerbations.

The effect of this natural circadian rhythm adds potentially large problems to the measurement of PEF [58]. To give the most accurate results, the measurements should be taken at fixed times after waking rather than fixed times of day, but even then the maximum variation cannot be assured. It
is not easy to obtain data in which time after waking is known, however, such a data set would likely be complemented by the use of patient specific models to track performance.

### 2.4.7 Environmental Effects

Work described in Section 2.2 to model the number of arrivals at Accident and Emergency Departments only reflect those individuals experiencing extreme responses to conditions. In contrast, daily PEF measurements could provide a real time description of the effects of environmental factors on asthma. Much less research has been carried out on the effects of ambient conditions on day-to-day variation of lung function and asthma symptoms. Work in the Netherlands by van der Zee and Boezen identified pollution factors which influence PEF in children and middle aged adults. They asserted that the most vulnerable subjects to ambient air conditions are those with bronchial hyper-responsiveness (BHR) and relatively high serum concentrations of total IgE \(^2\) (> 60 kU/L, the median value). Increased levels of \(PM_{10}\), \(SO_2\) and nitrogen dioxide \((NO_2)\) are all significant in a decrease in PEF of 10% or more, and analysis showed the lag between cause and effect, and found that delays of zero to five days are significant with a peak occurring around one day after high pollution levels [90, 91]. Von Klot [92] carried out a similar analysis, investigating longer lags to determine the effects on asthma symptoms of corticosteroid and \(\beta_2\) agonist use. \(PM_{10}\), \(SO_2\), \(NO_2\) and carbon monoxide \((CO)\) were identified as being significant. The unconstrained lag model showed a contribution of the exposure over 10 preceding days. The largest effect estimates for wheezing and for corticosteroid use were seen with the 14-day running mean, which was explained by an accumulation of particles over several days. Other work shows the effect on asthma symptoms of air pollutants. In a study of 82 asthmatic children, \(NO_2\) and black smoke were associated with increases in the occurrence of nocturnal cough and respiratory infections and ozone \((O_3)\) was associated with irritation of the nose and throat on days when no steroids were taken [93].

### 2.5 Daily Management of Asthma

In Section 2.3 the treatments used to manage asthma symptoms were outlined. In practice to maintain steady control of asthma, a patient’s use of these medications needs to vary from day-to-day

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\(^2\)Immunoglobulin E - Main function to protect against invading parasites.
depending on their condition. It is now common practice for clinicians to use action plans, which dictate the level of medication a patient will use, based on either their symptoms or spirometry values. Paper-based diaries are often used by patients to record their symptoms, medication and function test results. It is generally recognized that such diaries are invaluable in identifying exacerbations [24] and as teaching tools to help patients learn about triggers [70]. Plaut [70] complains that there are very few published asthma diaries which meet the minimal standards of completeness, clarity, and ease of use. Only four are referenced which facilitate all of the essential diary and spirometry data to be recorded [94, 95, 96, 97]. A well designed diary has the following attributes [70]:

- graphically displays fluctuations in peak flow rates (if recorded);
- provides space to record asthma triggers, signs and symptoms;
- provides space to list all medicines;
- provides a place to log comments;
- clearly shows the relationships among triggers, medication and other features of the condition.

### 2.5.1 Symptom-based Action Plans

Jones [29] describes a symptom diary which quantifies coughing, wheezing and shortness of breath on a scale of 0-3. A binary scale is used for nocturnal waking, activity restriction and time off work/school, with actual bronchodilator dose recorded. Such studies monitor a wide range of parameters and base medication on patient condition. There have been a number of reports which have identified a significant reduction in exacerbations or hospitalization when using a symptom-based scheme when compared to no intervention [19, 24, 68, 98, 99]. It can therefore be concluded that observations of symptoms are valuable in the self-management of asthmatics. Reddel [78] found that diary cards with symptom scores written in real time correlate better with the patient’s actual condition than when the symptoms are classified retrospectively. Very few action plans have been used based on symptoms, some examples are given in Table 2.5.

<table>
<thead>
<tr>
<th>Author</th>
<th>Action points used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibson [100]</td>
<td>Nocturnal waking due to asthma</td>
</tr>
<tr>
<td>Mortimer [101]</td>
<td>Use of $\beta_2$-agonist more than four times a day</td>
</tr>
<tr>
<td>Tattersfield [102]</td>
<td>Cough, wheeze, chest tightness and PEF lability</td>
</tr>
<tr>
<td></td>
<td>Prescription of oral corticosteroids</td>
</tr>
</tbody>
</table>

Table 2.5: Action points based on symptoms obtained from the published literature.
2.5.2 Spirometry-based Action Plans

Management regimes tend to focus around changes in medication at fixed points on an individual’s PEF scale, these action points are much simpler to define than ones based on symptoms. A brief summary of different action points which have been used in the literature, is given in Table 2.6. A wide range of different metrics have been used, and in many cases the exact level of these thresholds varies depending on different authors, so that to date there is no gold standard.

<table>
<thead>
<tr>
<th>Author</th>
<th>Action points used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones [29]</td>
<td>75% &amp; 50% of personal best PEF + double dose of inhaled steroid</td>
</tr>
<tr>
<td>Plaut [70]</td>
<td>80%, 65% &amp; 50% of personal best PEF</td>
</tr>
<tr>
<td>Cowie [98]</td>
<td>70% &amp; 50% of predicted PEF and greater than 20% diurnal variability</td>
</tr>
<tr>
<td>Charlton [99]</td>
<td>70% &amp; 50% of personal best PEF</td>
</tr>
<tr>
<td>Ignacio [103]</td>
<td>70% &amp; 50% of normal PEF</td>
</tr>
<tr>
<td>Fuhlbrigge [104]</td>
<td>80% &amp; 60% of predicted FEV₁</td>
</tr>
<tr>
<td>Hankinson [80]</td>
<td>70% &amp; 50% of predicted PEF</td>
</tr>
<tr>
<td>Guendelman [105]</td>
<td>80% &amp; 50% of personal best PEF</td>
</tr>
<tr>
<td>Gibson [100]</td>
<td>Three tests based on mean and -2 S.D., -3 S.D. of baseline</td>
</tr>
<tr>
<td></td>
<td>Test 1; 1 point below the mean − 3 S.D. line</td>
</tr>
<tr>
<td></td>
<td>Test 2; 2 of 3 points between the mean − 2 S.D. and mean − 3 S.D. lines</td>
</tr>
<tr>
<td></td>
<td>Test 3; 4 of 5 points between the mean − 1 S.D. and mean − 2 S.D. lines</td>
</tr>
<tr>
<td></td>
<td>80% &amp; 60% of personal best PEF</td>
</tr>
<tr>
<td></td>
<td>80% &amp; 60% of predicted PEF</td>
</tr>
<tr>
<td>Hawkins [59]</td>
<td>80% &amp; 70% of mean baseline PEF</td>
</tr>
<tr>
<td>Leuppi [62]</td>
<td>Use of Gibson Test 1, (100)</td>
</tr>
<tr>
<td>Tattersfield [102]</td>
<td>Reduction of morning PEF &gt; 30% on two consecutive days</td>
</tr>
<tr>
<td>Douma [61]</td>
<td>80% &amp; 60% and 70% &amp; 50% of personal best PEF</td>
</tr>
<tr>
<td>Holt [63]</td>
<td>50%, 75% &amp; 85% of personal best PEF</td>
</tr>
<tr>
<td>Wensley [106]</td>
<td>70% &amp; 50% of personal best PEF</td>
</tr>
<tr>
<td>Reddel [107]</td>
<td>Mean morning pre-bronchodilator PEF for 2 days &lt; mean − 2 S.D.</td>
</tr>
</tbody>
</table>

Table 2.6: Action points based on spirometry values obtained from the published literature.

The British Thoracic Society recommends 75% and 50% of personal best as being the most appropriate levels of PEF for action points [30].

2.5.3 Review of Symptoms v. PEF for Management

Action points based on spirometric values are the simplest to define clearly, and suffer from much less subjectivity than symptom based plans alone. The number of studies reported in Tables 2.5 and 2.6 being a clear testament to the relative popularity of this approach. Despite this overwhelming
support for the use of spirometry, opinions are divided on the usefulness of PEF-based management, with a number of authors reporting no improvement over symptom-based management \[33, 68, 108\] and others concluding that there are advantages to such a scheme \[19, 24, 69, 98, 99, 103\].

Patients need to be well controlled before being able to use action plans to self-manage their condition. This can be achieved by administering treatment with the inhaled corticosteroid, such as budesonide. Personal best PEF (defined as best in the previous two weeks) reaches a plateau after only three weeks of treatment \[109\]. Other measures of control such as average morning prebronchodilator PEF and Reliever use, take an average of 8 and 13 weeks respectively until they show no statistical improvement with continued corticosteroid treatment. It is likely that patients will require at least two months of stabilization before they are in a position to self-manage their asthma. There are a number of management regimes for asthma that require some form of monitoring and recording of symptoms. All scientific trials have shown that even the most basic form of management programmes offer benefits in control over no intervention.

### 2.6 Patient Self-management

In Chapter 1 the concept of self-management was introduced. A self-management regime reduces direct clinician involvement with routine decisions to be made about control of the condition, and therefore, has huge potential for cutting costs. Rapid response to deteriorating symptoms by increasing use of preventative treatment is both beneficial to the patient and cost effective for the health services \[110, 111\]. Self-management of asthma has been used in the USA for several years \[29\] and there is an extensive literature on the subject, including the British Thoracic Society \[30\] which provides a comprehensive overview of self-care for asthma. There are many benefits to a scheme of patient self-management; which by its very nature, promotes a culture of education and improved understanding. This ultimately leads to better control of the disease and reduced morbidity \[24\].

Charlton \[99\] describes how patients should be given a complete package of care; by improving patients’ knowledge of their own conditions, they will learn to improve control and improved understanding should assist to improve compliance and effective use of medication. Patients should not be dismissed from the clinic solely to take medication and/or measure symptoms according to a clinician prescribed schedule. To compliment this and promote self-management of the disease, patients
should be educated in the disease to improve their understanding of the underlying causes and control of the symptoms. Enabling a more active role in the management of the condition promotes faster action to deal with exacerbations and can relieve suffering. Multimedia is playing an increasing role in supplementing the education of patients. The ability to present information in an interesting and stimulating format renders multimedia well suited to a role in paediatric health education [38]. McPherson describes how adults using computer assisted instructions about asthma management and practical techniques believe that it is useful for supporting self-management decisions [38].

2.7 Compliance

High compliance with medication is key to well controlled asthma [68]. However, similarly to other chronic conditions synonymous with level 1 of the management pyramid in Figure 1.2, patients with asthma tend to exhibit poor compliance during periods of stable asthma and hence suffer greater fluctuations [112, 113]. The design and usability of the diary and meter are very important considerations and can have significant impacts on the frequency of use of the product [114]. Two trials have used surreptitious electronic storage facilities on PEF monitors to compare actual measured data with that recorded in paper-based diaries [25, 68]. Malo [25] describes a study where 20 patients were asked to write down their morning and evening PEF values; they were not aware that the values were being stored. The mean duration of PEF monitoring was 89 days (range, 44 to 131 days). For the 20 patients, it was estimated that a total of 3482 values should have been written down and stored on the flow meter. It was found that 1897 values (54%) were written down, whereas only 1533 values (44%) were stored, with the difference accounted for by values invented by patients. Written-down values corresponded precisely with stored values on 90% of occasions and were close (within ±20 L/min) in 94%. The survey showed that compliance with daily PEF assessments is generally poor. However, those values which are written-down, when not invented, are generally accurate. Côté [68] uses the electronic storage to measure actual patient compliance of 26 patients, recording data in a paper diary, reporting figures of 63% at 1 month, 51% at 6 months and 33% at 12 months. Alemi [115] blames patients’ poor effort to collect PEF data on the fact that they perceive that it is not used by themselves or clinicians. One of the key features that any new system must incorporate is an improved sense of value and importance to the user.
2.8 Technology to Support Self-management

Since poor control of lung function remains a fundamental issue amongst many individuals with asthma, improved control in the global population through effective self-management or conditions has the capacity significantly to reduce exacerbations and their associated costs. The level of lung control can be relatively easily measured in the form of PEF. However, there are many confounding factors which complicate an effective management plan. Although it is possible for an individual using paper based recording techniques to monitor the baseline level of their PEF, it is not possible for individuals to personally undertake the signal processing and forecasting which is suggested by the inclusion of other influential factors. Computer based algorithms are capable of analyzing data to detect outliers and compensate for effects such as diurnal variability, or environmental influences. If data can be analyzed in real time, there is the added potential of using such analysis to pre-empt episodes of decreased lung function and advise patients accordingly. Telemedicine offers the opportunity to overcome many of these challenges, and hence to support patient understanding of their condition. Real time access to computing power can also facilitate signal processing which can augment the analysis of individual results and help to put measurements into context for patients, which forms the subject of the next few chapters.
Chapter 3

Review of Telemedicine

In Chapter 2, asthma was identified as representing a significant drain on healthcare resources. Self-management has been shown to be effective in the maintenance of good asthma control. Self-management requires patients to be knowledgeable about their condition and how external factors influence their lung function and to use this knowledge in the assessment of their symptoms to guide medication usage. Technology is becoming increasingly ubiquitous in healthcare, many people with asthma use peak flow meters to assess their condition. Remote access to clinicians through telemedicine, offers the opportunity to further improve the role of technology in patient care. Providing improved communication with clinicians and the opportunity for advanced computational methods to support the patients’ decision process.

3.1 Introduction to Telemedicine

Governments and medical providers have been instrumental in promoting the use of technology in medical care, especially Information and Communications Technology (ICT). In the UK, the NHS is currently expanding ICT spending through The National Programme for IT in the NHS [116]. This programme includes headline projects such as integrated electronic patient records [117], due to be in place in England by 2010, and information services such as NHS Direct [118] which is already operational. The cost of this expansion is put at £12 billion over the next 10 years, however, some estimates are as high as £20 billion [116].

NHS Direct is a form of telemedicine, whereby medical advice is delivered to the patient by a
remote carer. Telemedicine has been defined as the use of ICT for medical diagnosis and patient care when the provider and client are separated by distance [119].

The most common telemedicine application is video conferencing, widely recognized as a way of improving access to specialist consultants, improving facilities for those who would otherwise be unable to have access to experts in a particular field. This is especially notable in the case of third world countries. There are now several charities such as Medical Missions for Children [120], which enable “western” doctors to advise local clinicians.

Telemedicine, however, is much more than video conferencing. It also incorporates remote monitoring, telecare and patient education amongst others. It includes the following:

**Telehealth** A generic term for provision of healthcare and information to patients via electronic media: a typical example would be a web page containing healthcare advice [121].

**Telemonitoring** Telemonitoring is defined as the use of telecommunication networks to monitor patients at a distance [122].

**Telecare** Telecare is the delivery of health and social care to individuals within the home or wider community, with the support of systems enabled by ICT [123].

**Assistive Technology and Smart Homes** The use of technology to assist patients to care for themselves at home [124]. Technology such as alarms and sensors can be used to provide a safer environment for patient who require care assistance. Smart Homes use technology to monitor a person’s activity to check that he/she is carrying out usual activities. This form of accommodation is primarily considered for elderly people who can still maintain a level of independence, embedded sensors in the home can also measure physiological parameters [125].

The focus of this Thesis are the areas of Telemonitoring and Telecare. These are studied in the context of self-management of patients with mild-to-moderate asthma.
3.2 Telemedicine for Chronic Conditions - An Overview

Figure 3.1 shows the number of references listed on the Telemedicine Information Exchange (TIE) [126] which are related to chronic conditions. Diabetes accounts for 38% of the studies, asthma is the second most investigated disease with 12% of research.

![Pie chart showing chronic conditions](image)

Figure 3.1: The number of references listed on the Telemedicine Information Exchange that have assessed the use of telemedicine in various chronic conditions (n=686) CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease. [126]. It is noted that chemotherapy is not a chronic disease; it is included here in the interest of clarity to compare with the other investigations in this thesis. (Results retrieved - 16-02-2006)

Most of the research into telemonitoring for chronic diseases has focused on intermittent monitoring. In this form of telemonitoring, the patient initiates the monitoring, and is fully involved in the process of managing care and treatment. This is particularly relevant to asthma where experts recommend the measurement of symptoms twice daily.
3.3 Intermittent Telemonitoring

The generic intermittent system can be split into a number of separate components which are shown in Figure 3.2. Patient data which can be quantitative (measured using a medical device) or qualitative (graded by the patient) is recorded either automatically or by the patient, entered into the patient interface; data are then uploaded to a server using some form of telecommunications link. Data are stored on the server where they are processed and made accessible to assist clinical decisions. The patient may receive feedback, either directly from the clinician or through the electronic system from either the clinician or via automated systems directly from the server. The following sections discuss previous work in each of the main aspects of this generic system.

![Figure 3.2: A generic schematic diagram of an intermittent telemonitoring system.](image)

3.3.1 Measurement Device

There is a wide range of physiological measurement devices on the market for home use. People with diabetes frequently measure blood glucose at home; people with high blood pressure (hypertension) may have their own blood pressure monitor and those with asthma often have a peak flow meter, see Section 2.4.2. Some of the newer monitors have serial ports which enable data to be transferred to a PC or other device, however, the majority still lack such a capability.

Not only do meters with data connections offer the chance of improved accuracy of measurements; they also make the process easier for patients. Some studies such as the T-IDDM (Telematic Management of Insulin Dependent Diabetes Mellitus) [127] or Home Asthma Telemonitoring (HAT) System [128] have used custom-made serial interfaces. The most recent telemedicine studies have begun...
to use devices that already have serial connectors; Woodward [129] uses a meter with infra-red communications to a mobile telephone to collect electrocardiograph signals. Blood pressure meters [130], peak flow meters [131, 26] and blood glucose monitors [132] are now available with the capability to download occasional data to a personal computer using custom-made software rather than immediate transmission of data via telecommunications. Many technical challenges remain if the data are to be transmitted in real time.

3.3.2 Patient Interface

Intermittent telemonitoring tends to be patient initiated. As such it requires a simple system that enables patients to enter data into the system. The predominant technologies tend to use either telephones (landline or mobile) or computers connected to the internet. Increasingly, studies appear to be moving towards mobile internet connections with devices such as palmtop computers. The usual approach is to store the data and transmit them at times convenient to the patient, either when the memory is full or on a weekly basis.

Patients may send data of various forms; there may either be measurements from the medical device or diary information. The measured data, such as peak flow or blood glucose measurements, may either be typed into the system by the patient or transferred electronically from the medical device. Diary information has to be entered by the patient and is often used to record the amount of medication or exercise the patient has taken. The Telephone-Linked Care (TLC) system developed by Mooney provides an interactive patient diary to record patient symptoms on a daily basis [133]. The whole process takes between 3 and 10 minutes during which the patient enters data using the touch-tone handset and voice commands.

Earlier telecommunications systems required the patient to get in touch with a call centre and enter their data into a computer based system using the telephone keypad [134, 133]. These low-cost systems are often slow and cumbersome for the patient to use. Similarly web-based systems that enable data to be entered using a computer connected to the internet are slow if they require patients to connect with a dial-up modem. The general trend amongst more recent studies has been towards the use of mobile telecommunications, either using palmtop computers [135] or mobile telephones [136, 129, 137]. These enable patients to transmit readings from multiple locations.
3.3.3 Data Storage and Processing

Data storage in telemedicine systems usually consists of a central store, in most cases a computer server, which can then distribute patient data over a network as required. Data security issues in these networks are covered by industry standards [121].

Data are often processed automatically by the server, where algorithms can monitor patients’ condition and compliance. The server can keep track of the patient’s compliance and send automated reminders to patients if desired. Periodic compliance reports can also be generated and sent to clinicians [128]. There are also a number of studies which track patient conditions such as blood pressure using simple signal processing software [138]. Threshold limits or pre-defined limits have been used to detect precursors to events in both Hypertension and Chronic Heart Failure [122, 139], in both cases alpha-numeric pager messages were used to alert clinicians who then accessed the data on a computer before contacting the patient.

3.3.4 Clinician Interface

Some telemedicine systems send data to a stand-alone computer [137], with the limitation that the data are only accessible in one location and are more vulnerable to being lost as a result of hardware failures. Other studies have used secure websites for clinicians to log on and view their patients’ data from any workstation [140]. This adds greatly to the flexibility of the system as these interfaces can make use of sophisticated graphing and analysis techniques to highlight data for the clinician [127]. Albisser [141] describes an interface which manages all components of the telemonitoring system enabling new patients to be added easily and other patients to be managed. One common characteristic of the clinician interface is the use of reports. These can either be generated by the clinician from data collected by the telemedicine system, for example in the use of cardiac monitoring [142] or through the use of automated weekly reports on the patients’ blood pressure [143].

3.3.5 Patient Feedback/Advice

One of the key benefits of home telemedicine is the provision of feedback to the patient [144]. This may either be synchronous if data are sent in real time or asynchronous if data are sent in batches.
CHAPTER 3. REVIEW OF TELEMEDICINE

Feedback is often used to assist patients’ management of their disease, at the simplest level, it may be used to improve patient compliance, for example SMS compliance reminders [112].

The four most common long-term conditions are hypertension, asthma, diabetes type 2 and diabetes type 1; in the first three of these conditions, current self-management techniques require adherence to a medication regimen or Patient Management Plan (PMP). Hypertension and type 2 diabetes regimens are simple and medication doses do not change from day-to-day. As described in Section 2.3 asthma requires use of medication to stabilize the condition before using a step up - step down process to handle short term events. Type 1 diabetes requires daily adjustment of short-acting insulin dose to maintain steady control of blood glucose. Type 1 diabetes and asthma therefore require patients to make decisions on a daily basis. Although it might be possible to suggest medication, this is not ideal and the Oxford Telemedicine projects have taken the approach of providing “decision support” to empower the patient to make appropriate decisions. A more advanced system [128] sends patients a “Tip of the Day” to improve their understanding of their condition. The T-IDDM system for people with diabetes gives feedback from a local computer to suggest insulin doses to the patient [127]. The regimen is downloaded to the local computer remotely by a clinician following a review of submitted data and consultation with the patient.

3.4 Cost Effectiveness of Telemedicine Interventions

Although telemedicine is become an increasingly popular area of research with many proponents championing its potential economic benefits, major questions about the cost effectiveness of telemedicine systems remain. Reported studies such as the ones described in this literature review place much more emphasis on the technology and medical outcome than the economic benefits.

In a review of cost effectiveness of telemedicine, Whitten concludes that there is no good evidence that telemedicine is a cost effective means of delivering health care [145]. None of the 612 articles mentioning both telemedicine and cost analysed in the review used cost utility analysis to establish the value for money provided by telemedicine or discussed it in comparison with traditionally organised health care. Whitten reports that only seven studies have attempted to explore the level of utilisation that would be required for telemedicine to compare favourably with conventional health care, of these seven, none addressed the problem in sufficient detail to provide an adequate answer.
The cost benefits of telemedicine and the impact on healthcare workers and their utilization remains an open question which will remain unanswered until current small telemedicine trials to address technical developments are superseded by larger long-term studies capable of accurately assessing the economic benefits.

### 3.5 Telemedicine for Asthma

The literature on telemedicine for asthma is much less advanced than the equivalent body of work for diabetes. Table 3.1 summarizes the eight telemedicine studies for asthma reported in the literature where data are transmitted. Despite small patient populations (mean 35) and short duration (mean three months), the studies show that participants tend to be enthusiastic about the technology. There is also an indication that compliance and symptom scores are improved. However, large scale Randomized Controlled Trials (RCTs) which randomly allocate patients to either investigation or control groups are required to assess the efficacy of the technology in treatment.

The studies of Table 3.1 are now reviewed under three categories: modem transmission of data, web-based systems on mobile phone-based systems.

#### 3.5.1 Modem Transmission of Data

In 1997, Bruderman [146] monitored 39 patients using a PEF meter connected directly to a telephone line. As data was received, all previous transmissions of spirometric data were analysed retrospectively to detect low PEF readings acting as early signs of asthmatic deterioration which triggered clinical involvement. In 49% of the patients, analysis of spirometric data detected early signs of asthmatic deterioration. However, no information is given in the paper on the rate of false alarms.

More recently, Steel has used a similar system to monitor 33 patients (mean age of 34) who had been discharged from hospital following acute asthma exacerbations [149]. The patients were given education about asthma and were instructed in the use of the system. 96% of the patients found the system easy or very easy to use, and 92% said they would use it again in the future. The study lasted for two weeks only, with medical intervention, taking the form of increased medication, in 48% of patients. Compliance was high for twice daily readings (80%), but the transmission of the data was
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Intervention</th>
<th>Duration</th>
<th>Results</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruderman <a href="1997">146</a></td>
<td>39</td>
<td>Home monitoring - portable spirometer, data sent by a telephone modem</td>
<td>N/A</td>
<td>Analysis of spirometry detected early signs of deterioration in 19 patients</td>
<td>Home monitoring may improve management</td>
</tr>
<tr>
<td>Finkelstein <a href="1998">147</a></td>
<td>10</td>
<td>Home monitoring - portable spirometer, data sent from a palmtop by a telephone modem</td>
<td>2-21 days</td>
<td>Average data transmission 1 min for fixed line and 6 min by mobile telephone used as a modem</td>
<td>Feasibility study</td>
</tr>
<tr>
<td>Kokubu <a href="1999">148</a></td>
<td>Numbers not specified</td>
<td>Home monitoring, nurse gives feedback via telephone</td>
<td>6 mths</td>
<td>83% Reduction in A&amp;E visits $p &lt; 0.01$ and improved PEF variability in telemed group</td>
<td>Effective system for poorly controlled asthma</td>
</tr>
<tr>
<td>Albisser <a href="2000">141</a></td>
<td>100</td>
<td>Touch-tone telephone for patients to enter data. Sent to computer for review by clinician</td>
<td>N/A</td>
<td>Patients and doctors enthusiastic about system</td>
<td>Feasibility study</td>
</tr>
<tr>
<td>Steel <a href="2002">149</a></td>
<td>33</td>
<td>Remote monitoring from home - data transmission via telephone modem</td>
<td>2 wks</td>
<td>80% compliance with monitoring, 52% compliance with data transmission</td>
<td>Feasibility Study</td>
</tr>
<tr>
<td>Anhøj <a href="2004">150</a></td>
<td>12</td>
<td>SMS messages to remind patients and collect data</td>
<td>2 mths</td>
<td>Participants enthusiastic about diary and median compliance 69%</td>
<td>Feasibility study</td>
</tr>
<tr>
<td>Lee <a href="2005">140</a></td>
<td>N/A</td>
<td>Recording diary and PEF information on a website, accessed from mobile devices</td>
<td>N/A</td>
<td>Patients sent customised information and found graphs particularly useful</td>
<td>Feasibility study</td>
</tr>
<tr>
<td>Ostojic <a href="2005">137</a></td>
<td>16</td>
<td>SMS transmission of data followed by therapy adjustment by nurse via SMS</td>
<td>16 wks</td>
<td>PEF variability and symptoms improved in study group $p &lt; 0.05$</td>
<td>SMS system is cheap and may improve control when added to a written action plan</td>
</tr>
</tbody>
</table>

Table 3.1: Previous Telemedicine Studies for Asthma
less frequent (52%) of the time.

3.5.2 Web-Based Systems

Websites can be relatively easily implemented and then made accessible to distant users via a wide array of interfaces. An example of a web-based asthma telemonitoring system in the system described by Lee [140]. With this system, activity and sleep were recorded daily and PEF and symptoms [cough, wheeze and sputum (scored 0-3)] were recorded morning and evening. The patient logged on to the website and data were entered along with medication usage. Trend graphs were available on the website and automatically determined patient alerts (which are not described) prompted email and SMS messages to be sent to the patients. To improve patient accessibility to the system, it was designed such that patients could log in and submit data from either a desktop PC, a PDA or a mobile phone. It was found that the use of a mobile device helped to improve compliance, and the combined use of fixed and mobile units showed about 10-30% higher frequency of server access than that from a fixed unit only.

3.5.3 Mobile Phone Based Systems

The widespread availability of mobile phones make them an ideal device for data collection and transmission, particularly as their functionality continues to increase. As described in the previous section, Lee [140] used a mobile phone as a means of connecting to a webform for a patient to enter data. Other mobile-phone based systems have revolved around Short-Message Service (SMS) technology to communicate information.

In Anhøj's study [150], patients received a sequence of four automated SMS messages on their mobile phone each day, at a self-selected time of the day:

1. Remember to take your preventer medication.
2. Remember to measure your peak flow - what was your peak flow?
3. Were you awake during the night due to asthma symptoms?
4. How many doses of your reliever medication have you taken during the last 24 hours?

Patients were then expected to reply to messages 2-4. This technique, although rather basic, has many advantages; it has no need for client software application and can be used on any mobile
phone with ease. It relies on SMS messages to prompt a response from the user, as this can help improve compliance and adherence with medication. The median response rate was found to be 69% throughout the two month study period.

Ostojic [137] reports a short study which investigated the use of SMS messages to monitor people with asthma. Sixteen persistent moderate asthmatics, in their twenties, were divided into intervention and control groups. Both groups kept paper diaries (lung function and symptoms) three times a day and were given 1 hour's education in clinic with a specialist and a personal self-management plan. The intervention group used their own mobile telephone to send daily SMS messages containing their PEF readings to a central computer. Asthma specialists used these readings to recommend adjustments to therapy, and this advice was then conveyed to the patients in a weekly SMS message. A brief overview of the study is shown in Figure 3.3.

![Figure 3.3](image-url)

**Figure 3.3:** The study design - patients were split into two groups. The intervention group sent daily SMS messages containing readings, and treatment was adjusted weekly [137].

To enable comparison between the two patient groups, spirometry, see Section 2.4.2, was performed at the start and end of the study; paper diaries were also compared to the transmitted data. The number of patients used in this study was small, and the duration of the study was also limited. However, significant ($p < 0.05$) improvements were found between the paper diaries and mobile phone (intervention) groups. There was increased clinician involvement in the intervention group, which in conjunction with the novelty of the technology, helped artificially to elevate compliance, reported as being as high as 99%. As a result of using the patients' own mobile phones and restricting data
transmission to daily SMS messages, the costs of the study were kept to a minimum. However, patients were required to type in the data in order for it to be transmitted; the authors themselves comment that this relies extensively on accurate transcription by the patients.

3.6 Conclusions

The review of previous telemedicine studies which have been used to monitor people with asthma, shows a trend towards using mobile technology. The key components of an ideal telemonitoring system can be summarized as follows:

- Simple and quick for patients to use,
- Improved self-management compared with usual care as a result of high compliance and better understanding of condition,
- No significant increase in clinicians’ work load,
- Use of mobile phone to allow access at any time in any place.

These criteria were used during the design of the Oxford Telemedicine System which is described in the next chapter. The system was designed as a generic system which could be adapted to assist patient self-management for a wide range of chronic conditions, but its use specifically for asthma self-management is the focus for the rest of this thesis.
Chapter 4

The Oxford Telemedicine System

4.1 Introduction

The Oxford Telemedicine System has been developed as a generic telemonitoring system based around the mobile phone. The majority of patients with a long-term condition will expect to lead a normal life and indeed should be able to, provided that they self-manage properly. They will not want to change their routine or be confined to one specified location for self-monitoring. For such patients, the mobile phone, now that data services have been added to voice and text messaging, is a convenient, readily-available means of transmitting data between sensor to a remote server. Using a mobile phone, all parts of a self-management package can be implemented. Data, both from sensors and diaries can be reliably collected from patients, real-time feedback can be provided to empower the patients to make the right decisions and occasional advice from clinicians based on review of data transmitted can be sent to the phone. Ninety-percent of the adult population in the UK now owns a mobile phone [151], which ensures near-equal access to mobile-phone based telemedicine for all socio-economic classes.

The Oxford Telemedicine System architecture has been developed as a flexible set of libraries which allow the software to be customized for a range of conditions and individual care plans. It has been designed to promote regular self-monitoring, by providing immediate feedback to patients and targeted support from informed health care professionals who have full access to the data patients have transmitted. The degree of patient support will vary according to the severity of the condition (levels one or two from Figure 1.2) but the components of the model are generic. Figure 4.1 illustrates the
key components of the system, some of which are described in this thesis.

Figure 4.1: The Oxford Telemedicine System.

4.2 The Mobile Phone

As a result of using a mobile phone, the patient can engage with the telemedicine system at any time and in any location, without being constrained to a fixed location, such as Brunderman's use of a PEF meter connected to a fixed telephone line through a modem, described in Section 3.5.1. Should the user moves into an area with poor network connectivity, data can be stored on the handset and transmitted the next time there is a connection.

The current generation of mobile phones include a number of technical features which are useful in the design of a telemedicine system. These include:

- **Programmability**: many phones include either a Java or Symbian runtime environment or a version of the Windows operating system. This allows custom applications to be developed in high level languages. Updating software with new versions is simple, and can be done remotely “over the air”. The Oxford telemedicine system has also been designed so that it is possible to
update individual aspects of the system independently, for example, the patient diary questions.

- **High Resolution Screen**: the combination of flexible programming and the ability to display reasonable amounts of data on the screen allows the use of patient diaries on the phone and the display of recent self-monitoring data on the screen.

- **Variety of communication options**: the phone sends readings and diaries securely over the internet using a data network. Increasingly this will be using the high-speed data link offered by third generation (3G) UMTS handsets, although the current method is using the “second and a half” generation (2.5G) GPRS network. This allows an always-on, modest data speed of 56kbps which is sufficient for relatively low bandwidth applications. Such as the transmission of intermittent self-monitoring data (see Chapter 3). The patient’s handset also acts as a single communication channel with the patient, if the healthcare professional wishes to discuss any of the self-monitoring data or its trends.

- **Serial communication**: many mobile phone handsets now include a serial port to allow communication with a desktop PC. This can also be used to communicate with any of the medical devices used for self-monitoring that support data communication. Readings stored from the peak flow meter can be automatically transferred to the phone, and then directly to the server.

In summary, the phone and its software have four main functions: to receive and store readings from the self-monitoring device (peak flow meter for asthma), to record and store diary responses from the patient, to send data to the server and to give feedback to the patient based on the analysis of the data by algorithms running on the server. For the mobile phone solution to be fully integrated into a patient’s lifestyle, the handset used to collect data must be their regular mobile phone, so that it is convenient to use.

### 4.3 The Server

#### 4.3.1 Storage and Data Processing

The server receives data transmitted by the phone through the secure mobile internet connection, and stores them in a database. This allows future review by a health care professional or in some cases the patient. Prioritization algorithms running on the server could rank patients by level of
control, highlighting to carers those patients whose control is worst and who will therefore benefit most from targeted support.

Most of the time, the self-monitoring data from a long-term condition patient is normal. When abnormal readings do occur there are two possibilities: either, the patient is sufficiently concerned to call his or her surgery directly - indeed they may be prompted to do so by the self-care plan stored on their phone - or analytical software on the server could automatically generate alerts.

The alerting algorithms should be based on the identification of significant deviations from expected values, i.e. changes which are of greater magnitude or occurring more rapidly than is desirable. It is possible either for clinicians to define clearly conditions that constitute an alert, or for novelty detection algorithms to be employed [152, 153]. In either case, the processing of an alert should be to respond to a worsening condition or loss of control as early as possible, preventing subsequent hospitalization if at all possible. The alert could be communicated to the healthcare professional either via a combination of email, SMS or pager message - depending on the seriousness of the alert.

4.3.2 Data Security

As confidential patient data is transmitted to, and subsequently accessed via the internet, encryption is used to protect the data. Handsets are configured to use a unique patient identification number and internal password in order to setup a Secure Socket Layer (SSL) link over https, which adds additional encryption and authentication layers to conventional http (hypertext transfer protocol) this protects data as it is sent to the server. Data is assigned by the server to the correct patient using the patient identification number.

The secure websites used by clinical staff are also accessed via https and several user privilege levels have been developed to prevent technical and administrative staff from viewing personal patient data and to restrict clinicians such that they can only view their own patients.
4.3.3 Clinical Interface

Healthcare professionals can view data from their own patients, and can use the website to add new patients or update the records of existing patients. Patients can be permitted access to their own data, which may help to encourage compliance. The main benefits of the website are the data summary and visualization. Historical data can be simply logged in a tabular format, such as the example shown in Figure 4.2.

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Peak Flow</th>
<th>Nocturnal</th>
<th>Aged</th>
<th>Symptoms</th>
<th>Act. Fast.</th>
<th>Extra Reliever</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 January 2005</td>
<td>18:19</td>
<td>453 l/min</td>
<td>1-2</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>20 January 2005</td>
<td>06:29</td>
<td>398 l/min</td>
<td>0</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>21 January 2005</td>
<td>18:24</td>
<td>417 l/min</td>
<td>1-2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>22 January 2005</td>
<td>06:26</td>
<td>398 l/min</td>
<td>1-2</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>23 January 2005</td>
<td>17:16</td>
<td>424 l/min</td>
<td>0</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>24 January 2005</td>
<td>12:49</td>
<td>431 l/min</td>
<td>3-4</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>25 January 2005</td>
<td>21:14</td>
<td>433 l/min</td>
<td>1-2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>26 January 2005</td>
<td>06:26</td>
<td>417 l/min</td>
<td>1-2</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>27 January 2005</td>
<td>23:12</td>
<td>431 l/min</td>
<td>1-2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>28 January 2005</td>
<td>06:26</td>
<td>438 l/min</td>
<td>0</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>29 January 2005</td>
<td>19:19</td>
<td>438 l/min</td>
<td>1-2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>30 January 2005</td>
<td>06:29</td>
<td>424 l/min</td>
<td>1-2</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>31 January 2005</td>
<td>21:39</td>
<td>445 l/min</td>
<td>0</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2 Brown</td>
</tr>
<tr>
<td>1 February 2005</td>
<td>05:29</td>
<td>452 l/min</td>
<td>1-2</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>2 Brown</td>
</tr>
</tbody>
</table>

Figure 4.2: An example table of historical data from an asthma subject from the Isle of Man Study (Chapter 6).

The data can also be shown in the form of a time series, for example Figure 4.3 which is taken from the Isle of Man Study, it shows PEF and FEV$_1$ and the amount of reliever and preventer inhaler the patient has taken on a daily basis. By running the mouse over the data points on the chart, the exact values, symptoms and time of day are displayed at the top of the chart.
CHAPTER 4. THE OXFORD TELEMEDICINE SYSTEM

4.4 Design of the Oxford Telemedicine System

Conceived using a generic approach, the Oxford Telemedicine System was first developed in early 2002, prior to the commencement of this D.Phil. It was initially developed by Paul Hayton for the Thames Valley Study which is described in Chapter 5. As this study was sponsored by O2 the choice of the mobile phone was limited to their hand-held computer, the xda. The author did not participate in the design of this system. Findings from this first study were used to develop the telemedicine system to one based around a mobile phone which has been used in a range of applications; from asthma as described in this thesis, to diabetes and the monitoring of the side-effects of chemotherapy. The author did not participate in programming the mobile telephones instead assuming the role of constructing the interface between the medical devices and the handset.

Figure 4.3: Example chart of PEF and FEV$_1$ data from the Isle of Man Study.
4.4.1 Hardware Interface

At the start of this project, Motorola was the only manufacturer of mobile phones who offered suitable programmability and hardware interface. Initially this took the form of the Motorola 720i phone, which was later replaced by the compatible Motorola V600 handset. Motorola offer a Serial Data Kit to communicate with a PC using either RS232 or USB. This kit consists of an active data head which plugs into the base of the phone and a cable. To enable future development, this kit was replaced with a custom-made data head designed by the author and shown in Figures 4.4 and 4.5. The new data head was conceived such that it would have maximum flexibility to connect to a variety of different devices. This is achieved using a programmable PIC in the data head which can be configured in situ using a serial PIC programmer. The circuit is shown in Figure 4.6 and the signals on each of the output pins are described in Table 4.1.

![Figure 4.4: Photographs of both sides of the printed circuit board.](image)

![Figure 4.5: The data head in its plastic case plugged into the T720i phone.](image)
Figure 4.6: Circuit diagram of the custom designed data head, which offers a generic solution to connect physiological monitors to the Motorola 720i.

Table 4.1: Description of output pins in circuit diagram of data head shown in Figure 4.6.
CHAPTER 4. THE OXFORD TELEMEDICINE SYSTEM

Power Supply

The design of this circuit which regulates the power to 3V and controls the charging of the handset battery when plugged into a mains charger is taken directly from the original Motorola design. The Motorola handset has two separate ground pins on its connector, for both analogue and digital grounds. Full use is made of these, to enable the ground plane around the voltage regulator circuit to be separated from the rest of the circuit to facilitate the higher voltages required when the PIC is programmed. During normal operation, the two grounds are connected together internally in the handset, so that the power in the circuit is regulated to 3V. A voltage regulator, the \textit{NCP500SN30T1} is used.

CMOS Applications

The phone communicates with the data head using a CMOS interface. This can either be passed directly through the data head or alternatively the PIC can be used to add additional flexibility not offered by the phone. For example, work to interface the Piko meter has shown that the Motorola handset does not communicate correctly at a baud rate of 1,200 bits/s. In that case a bi-directional path through the PIC has been used to adjust the communication speeds such that the data head and piko communicate at 1,200 bits/s while the handset and data head communicate at 9,600 bits/s.

RS232 Applications

Some monitors such as the Vitalograph peakflow meter use the RS232 protocol. In order to facilitate this, a \textit{SP 3220E} RS232 driver chip has been included in the design. For maximum flexibility, once again, both the transmit and receive paths are through the PIC.

Optical Communications

Medical devices often use optical communications to interface with other equipment. Opto-isolators are a single package containing an LED and a photodiode or phototransistor to emit and detect light pulses. The two parts of the circuit are then electrically isolated, and this can be used to provide patient isolation. The Omron 705IT [130] Blood Pressure Monitor (which has also been interfaced with the Motorola phone) uses this form of communication. Hence transistors to invert the CMOS
signal and provide a current to drive the LED are included in the design and a ‘pull-up’ resistor is included on the return path to convert the current generated by the phototransistors to a voltage.

**Configuring the Data Head**

The data head is configured by using a serial PIC programmer to install software directly to the PIC in the circuit. This program sets the input and output pins and any other operations required.

### 4.4.2 Connecting the Piko meter to the Motorola

The Piko meter is designed to communicate with a PC via infra-red communications using a cradle. In order to maintain the certification of the meter, it was decided to adhere an optical circuit to the base of the meter. This simple circuit shown in Figure 4.7 uses CMOS signals to drive infra-red optical communications. It is encased in a plastic housing adhered to the base of the meter, which can be seen in Figure 6.1. The circuit connects to pins 1,4,10,14 and 15 of the data head.

![Figure 4.7: The interface circuit which uses CMOS to drive the optical IR communications on the Piko meter.](image)
4.5 Technology Used to Measure PEF and FEV$_1$

In 1959, Wright developed a small mechanical peak flow meter [75], which revolutionized measurement of asthma enabling home monitoring to supplement the use of spirometry in clinics. The Wright meter is based on the principle of blowing into a tube against a resistive plunger attached to a spring. A marker records the maximum displacement of the plunger which corresponds to the peak flow rate of expired air. The faster the flow rate of expired air, the greater the movement of the plunger in the resistive tube. Wright used a linear scale to calibrate his mechanical meter. This has subsequently been recognized as inaccurately reflecting true spirometry values as measured by clinical multi-parameter spirometers (Section 2.4.2). Since 2004, a new European Standard, EN 13823 [154] has recalibrated this scale replacing the linear Wright scale with a non-linear scale more accurately reflecting the true peak flow rate.

Newer self-monitoring devices tend to be electronic. They also measure the flow rate of the expired air, and use integration to sum the total expired volume in the first second (FEV$_1$). The two meters used in the research described in this Thesis use different techniques which are outlined below.

**Vitalograph Meter [26]** This meter is fairly large, weighing 165g, and is quoted by the manufacturer as being accurate to within $\pm$10% for PEF and $\pm$3% for FEV$_1$. These figures have not been verified as part of this project. However, an engineer from Vitalograph did visit to explain the numbers quoted by the manufacturer. This was taken on trust as the device has been awarded a CE marking. The flow rate is measured by detecting the pressure difference across a resistive mesh. An empirical look-up table is then used by the electronics to convert the pressure difference into a flow rate. The Vitalograph meter is shown on the left-hand side in Figure 4.8. This meter has an external communications port which uses RS232 protocol to upload data. Some patients, particularly those with cystic fibrosis or asthmatics with lower peak flow values have found it difficult to take readings on the Vitalograph meter, it results in very low, or zero readings.

**Piko Meter [131]** The Piko meter is considerably smaller (only weighing 35g) and cheaper than the Vitalograph. The manufacturer's stated accuracy is similar to that of the vitalograph, i.e. $\pm$5% for PEF and $\pm$3% for FEV$_1$. Once again, this has not been verified as part of this research however,
the device is CE marked. Flow rate in this device is obtained by sensing the movement of a thin metal deflection plate due to expired air; the deflection is converted internally into a flow rate using an empirical look-up table. The Piko meter is shown on the right-hand side in Figure 4.8. This meter used infra-red to transfer data from its internal memory. It is easier to obtain a reading on the Piko meter than the Vitalograph. However, coughing or partly blocking the air vents with fingers when taking a reading can lead to a rapid release of air through the device. As a consequence, unusually high PEF readings are recorded, there were many such readings in the Manx Study which is described in Chapter 6.

Figure 4.8: The Vitalograph meter (left) and Piko meter (right). The images are not to scale.

4.6 Conclusions

The Oxford Telemedicine System has been used in the last three years in ten studies which have obtained Medical Research Ethics Committee (MREC) approval across a range of conditions ranging from asthma to monitoring patients on chemotherapy. The remainder of this Thesis focuses on the results of two asthma studies carried out with this system. The first study, based in the Thames Valley Region in 2003, was followed by a second study on the Isle of Man in 2005. The lessons learnt from these studies are presented at the end of Chapter 6.
Chapter 5

The Thames Valley Observational Study

The Thames Valley Observational Study, hereafter referred to as the Thames Valley Study was the first “in field” trial of the Oxford Telemedicine System, described in Chapter 4. Ninety-one people with mild-to-moderate asthma were included in the study which was given medical ethics approval by the East Berkshire Research Ethics Committee. The primary objective of the study was to investigate the usefulness of the telemedicine system in practice and to monitor patient compliance during the nine-month study.

5.1 Design of Thames Valley Study

The Thames Valley Study was conducted over a nine-month period in 2003. Patients in primary care were selected for the study by their GP according to the following criteria: mild-to-moderate asthma, with regular use of inhaled preventer and reliever inhalers (Section 2.3.1). Patients between 12 and 55 years of age were recruited from nine General Practices in the Slough and Maidenhead area (west of London). Their asthma had to be stable, as evidenced by no occurrence of exacerbation in the previous three months. There was no scheduled review with the patients and no therapeutic intervention was offered.
CHAPTER 5. THE THAMES VALLEY OBSERVATIONAL STUDY

5.1.1 Hardware

The Vitalograph handheld electronic peak flow meter (see Section 4.5) was used, and was connected to the O₂ xda, a GPRS mobile phone integrated with a palmtop computer via a customized serial cable. This equipment is shown in Figure 5.1 below.

![Image of patient with Vitalograph and O₂ xda](image_url)

Figure 5.1: A patient with the Vitalograph peak flow meter and O₂ xda used in the Thames Valley Study, the two devices are joined by a customized serial cable.

Patients were instructed in the use of the system by their GP and advised to complete peak flow readings in the morning and evening, using the software application provided on the phone. Diary entries and PEF lung function readings were transmitted in real time to the study server where they were stored and made available for display on a secure website for the patient’s clinician to review. If no peak flow readings were received on the previous day, Short Message Service (SMS) reminder messages were sent from the server to the patient’s phone in the morning.

5.1.2 Software

Many of the patients were unaccustomed to using handheld computers, and so the software on the O₂ xda was designed to be as simple as possible to use. It was extensively tested by members of the department and prior to the main study the system was used for two months by six beta testers. Their comments were incorporated into the application used in the main study. The icon for the application was designed to be clearly visible on the desktop screen and its size was made to be proportional
to the length of time since the last set of readings. Figures 5.2 and 5.3 shows a flow chart of the application, with the relevant screenshot shown by each stage of the software. At the request of the clinicians who were involved in the design process, flow through the application is a linear with no opportunity for patients to go back and correct readings. This was decided upon to reduce confusion and simplify use. Patients start by recording how much reliever inhaler they have used the previous day, the amount of preventer they intend to take, and they then score their symptoms on a scale of one to five (1 = no symptoms, 2 = slight, 3 = moderate, 4 = bad, 5 = severe). Patients are subsequently instructed to connect the cable from the Vitalograph to the phone prior to taking their peak flow readings. Data are then transferred automatically to the phone, and displayed on the colour screen. The readings and entries in the patient diary are sent to the server via the GPRS network without the need for any patient interaction.

Compliance and PEF data from the previous seven days are sent by the server to the phone and displayed on the final screen for the patient. This screenshot is shown in the bottom of Figure 5.3, the patient's compliance is clearly indicated for the twice daily readings using ticks and crosses and the best PEF reading taken each day is also shown.
Figure 5.2: Flow chart of the O₂ xda mobile phone application for asthma - Part 1.
5.2 Technical Problems Encountered

A number of major technical problems were encountered in the Thames Valley Study. The most fundamental of these was foreseeable but unfortunately impractical to resolve. As the study was sponsored by O₂, it was a requirement that the xda should be used. This handset suffers from a volatile memory and once the battery had discharged all software and data is lost. Patients on this study were not accustomed to using this type of technology, so many inadvertently experienced this problem which required the software to be reinstalled. This accounted for many of the patients who dropped out of the study - they did not re-engage following battery failure. Consequently subsequent studies have opted for handsets which do not have volatile memory. The other problems encountered involved lack of connectivity with the O₂ network in some localities\(^1\) and the difficulty some patients experienced when taking a valid reading on the meter. These were overcome by asking patients to

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\(^1\)At the time of this study GPRS was a new technology and the network was continually improving. Coverage information was not disclosed by service providers due to commercial sensitivities.
try using the system in different locations in order to make a connection with the server and by educating them to improve their manoeuvre technique.

5.3 Results Summary

Normal management of diabetes requires regular measurement of blood glucose four times a day. In contrast, asthma is different and for many individuals, such regular measurement is unnecessary, peak flow need only be measured when a patient is experiencing symptoms. For the purposes of the studies described in this thesis, patients were asked to complete readings twice a day, as this is required to assess the patients’ level of control and response to the system. This is directly comparable with other studies such as Steel and Ostojic [149, 137]. The primary objective of the Thames Valley Study was to assess patient compliance with the telemedicine technology. Of the 91 patients recruited to the study, 38 (42%) were under 18 years at completion of the study, referred to from this point as adolescents and 53 (58%) were over 18 (adults). The mean study duration, calculated across all 91 patients as being the time between the first and last recorded data, was 204 days, with a standard deviation of 94 days.

5.3.1 Compliance

Four indices of patient compliance were calculated: at least one reading taken every day; at least two readings taken every day; at least one morning reading, and at least one evening reading taken. The compliance figures for the 38 adolescents and 53 adults can be seen in Table 5.1 and Figure 5.4. Within the group of 91 patients, it is clear that there are three distinct sub-groups:

**Sub-group 1**: the patients whose data have at least one large gap during the study, mostly due to significant technical problems. There were 13 such patients (7 adolescents, 6 adults), i.e. 14% of the total. The predominant technical problems were loss of battery power, which unfortunately resulted in the loss of the settings on the O2 xda, damage to the cable connecting the peak flow meter to the mobile phone and persistent lack of GPRS connectivity.

**Sub-group 2**: the patients who sent fewer than 100 readings in total during the study. These were occasional users or low-compliance patients. It is not known whether their low compliance was
due to technical problems, such as poor GPRS network connectivity. There were 20 patients in this sub-group (9 adolescents, 11 adults), i.e. 22% of the total.

**Sub-group 3:** these patients were highly compliant and dedicated users of the system. They represented 64% of the total (22 adolescents, 36 adults).

The compliance for the 58 patients who comprise sub-group 3 is summarized in Table 5.2 and Figure 5.5. There was no significant difference in the morning or evening compliance for any of the three categories in the table (adolescents, adults or all patients). When comparing adults and adolescents, there was a significant difference in compliance ($p<0.05$, Mann Whitney test) for the once-a-day, twice-a-day and morning readings, but not the evening readings. This would seem to indicate that adolescents are significantly less likely to take readings in the morning before school than adults are before work.

<table>
<thead>
<tr>
<th></th>
<th>Adolescents (38)</th>
<th>Adults (53)</th>
<th>All Patients (91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (%)</td>
<td>IQR (%)</td>
<td>Median (%)</td>
</tr>
<tr>
<td>Once-a-day</td>
<td>66</td>
<td>45 - 80</td>
<td>81</td>
</tr>
<tr>
<td>Twice-a-day</td>
<td>51</td>
<td>29 - 65</td>
<td>62</td>
</tr>
<tr>
<td>Morning readings</td>
<td>52</td>
<td>30 - 66</td>
<td>67</td>
</tr>
<tr>
<td>Evening readings</td>
<td>49</td>
<td>28 - 65</td>
<td>61</td>
</tr>
</tbody>
</table>

Table 5.1: Median and Inter Quartile Range (IQR) compliance figures calculated for each of the four metrics by patient group - all patients shown.

<table>
<thead>
<tr>
<th></th>
<th>Adolescents (22)</th>
<th>Adults (36)</th>
<th>All Patients (58)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (%)</td>
<td>IQR (%)</td>
<td>Median (%)</td>
</tr>
<tr>
<td>Once-a-day</td>
<td>91</td>
<td>85 - 93</td>
<td>96</td>
</tr>
<tr>
<td>Twice-a-day</td>
<td>75</td>
<td>66 - 85</td>
<td>83</td>
</tr>
<tr>
<td>Morning readings</td>
<td>73</td>
<td>66 - 86</td>
<td>86</td>
</tr>
<tr>
<td>Evening readings</td>
<td>80</td>
<td>68 - 85</td>
<td>85</td>
</tr>
</tbody>
</table>

Table 5.2: Median and IQR compliance figures calculated for each of the four metrics by patient group - Sub-group 3.
5.4 Analysis of Peak Flow Data

As pointed out in Section 2.7 patients invent approximately 50% of the entries in paper-based diaries [25]. In addition, asthma paper diaries only have a 12-hour resolution at best, in contrast to the accurate timing information available in this study. There were 16,128 PEF and FEV$_1$ readings, collected reliably from the 58 patients in sub-group 3 over approximately a nine-month period.
5.4.1 Interrelationship Between PEF and FEV\textsubscript{1}

Although FEV\textsubscript{1} is viewed by some as a more sensitive test [25, 155], common medical practice tends to focus on PEF which is simpler to measure. Several studies have accessed the relationship between the PEF and FEV\textsubscript{1}, taking individual readings across a large number of individuals it has been shown that the two measurements are correlated ($r \approx 0.8-0.85$) [155, 156]. PEF and FEV\textsubscript{1} which measure different aspects of the spirometry loop (Section 2.5) are obviously related across a population as larger individuals with larger lungs will exhibit both a larger peak expiration rate and a larger lung volume than smaller individuals. Figure 5.6 below, shows the relationship between readings recorded from all 91 patients taking part in the Thames Valley Study. The linear “best-fit” shown in red indicates the strong correlation between the two ($r = 0.73$), comparable to other studies.

A more interesting aspect is how PEF and FEV\textsubscript{1} are related for an individual patient across multiple recording occasions. In Figure 5.6 we observe clusters of readings obtained from individuals. These clusters appear to indicate that for individuals with little variation in PEF and FEV\textsubscript{1} who appear to be well controlled there is no discernable relationship between the two measurements. PEF was therefore used as the parameter to control in the protocol for this study in alignment with common medical practice.

![Figure 5.6](image_url)  
Figure 5.6: The correlation between PEF and FEV\textsubscript{1}, two clusters of readings from individual patients are shown in magenta.
5.4.2 Rescaling PEF

In common with other physiological measurements, PEF is unique to individuals. A particular level, for example 300 lmin$^{-1}$ might be an exceptional reading for a young child. However, by comparison, it will be a low reading for an average adult. It is possible to compute an individual’s improvement, or lack thereof, throughout the trial by using the raw PEF data alone. However, this is only sufficient to analyse an individual’s data on its own. If changes in lung function during the study are to be computed across the whole study population, a measure of PEF which is independent of absolute values is required. To achieve this, two new concepts are introduced here; Adjusted Personal Best (APB) and Adjusted PEF (PEF$'$).

Medical intervention for asthma is commonly driven by action points based on a certain percentage of an individual’s “best” reading, as described in Table 2.6. This “best” value can be difficult to determine from a single reading, and so the criterion of APB, defined as the mean of the top five PEF readings for any one patient, is proposed here as a more robust alternative. The Adjusted PEF scale, or PEF$'$, is then generated by dividing each PEF value by the patient’s APB.

5.4.3 Age Correction

An individual’s PEF depends on their chest volume, which varies with their age and height. There are several models (see Table 2.2) which estimate an individual’s PEF based these two parameters. Lung capacity increases rapidly with growth during the childhood and teenage years, and then gradually reduces over time. As the Thames Valley Study was conducted over a nine-month period, it is possible that age will have had an effect on the PEF values of some adolescents in the study.

The Hankinson equations [80] presented in Table 2.2 were generated by regressing measured values of PEF and FEV$_1$ against age and height across a population of 7,429 people. The Hankinson equations were selected as they are based on a larger sample population than the alternative Nunn equations which are also shown in the table and were recommended by the clinicians working in collaboration on this project. The Hankinson equations take the following form:

\[ PEF = a_1 \{height^2\} + a_2 \{age\} + a_3 \{age^2\} + a_4, \]  

(5.1)
where $a_1, a_2, a_3$ and $a_4$ are constants.

Figure 5.7 shows two examples of variation obtained with the Hankinson models. On the left, the variation of PEF with height is shown in blue for 50-year old males; our first example patient is 181cm tall, so a predicted PEF of 606 lmin$^{-1}$ can be read off from the plot. On the right, the effect of age for females 130cm tall is shown in red, the Hankinson models are split into functions up to the age of 18 and greater than 18 years of age, the two polynomials are joined together for representative purposes in this example. Our second example is 13-years old, her predicted PEF is 274 lmin$^{-1}$. Height variation has a simple relationship, with PEF increasing as a function of larger body size. The age variation is more complex, the plot illustrates a rapid increase during adolescent years, reaching a plateau through early adulthood before declining from middle age.

Time-varying models  At recruitment, date of birth, height and baseline PEF were recorded. Height and baseline PEF were not recorded by clinicians at the end of the study. If we assume a linear time-varying model over the 9-month study, we can estimate the PEF at time $t$ using the following equation:

$$P\text{EF}(t) = P\text{EF}(0) + \Delta t \times \frac{dP\text{EF}(0)}{dt},$$  \hspace{1cm} (5.2)

where $P\text{EF}(0)$ is the patient’s predicted initial PEF using Hankinson’s models and $\Delta t$ is the time since the start of the study. The value of $\frac{dP\text{EF}(0)}{dt}$ can be obtained at the start of the study by selecting
the one relevant Hankinson equation and differentiating with respect to time,

\[
\frac{dP_{\text{EF}}(0)}{dt} = \frac{d}{dt} \left( a_1 \{\text{height}^2\} \right) + a_2 + 2a_3 \{\text{age}\},
\] (5.3)

where \text{height} and \text{age} are the individual's height (cm) and age (years) at the start of the study.

**Adults** Once an individual has reached adulthood, their height changes very little. The differential of height with respect to time can be set to zero in Equation 5.2 giving:

\[
\frac{dP_{\text{EF}}(0)}{dt} = a_2 + 2a_3 \{\text{age}\},
\] (5.4)

which can be substituted into Equation 5.2,

\[
P_{\text{EF}}(t) = P_{\text{EF}}(0) + \Delta t \left[ a_2 + 2a_3 \{\text{age}\} \right].
\] (5.5)

A scaling factor at time \( t \), \( SF(t) = \frac{P_{\text{EF}}(t)}{P_{\text{EF}}(0)} \) is created using these predicted values and subsequently applied to each of the measured PEF values in turn. Figure 5.8 shows the adjustment for a 50-year old man in the study. PEF gradually decreases as adults age, so the “adjusted” points are higher than the measured values but the differences are very small indicating that the correction is unnecessary. However, adolescents also experience growth which is added to the model in the next section.
Adolescents  Adolescents experience a rapid change in their height over the course of a few years, hence changes of height as well as age variation need to be accounted for. Figure 5.9 shows the relationship between age and height for girls. (Similar charts are also available for boys [157].) Although the relationship is clearly non-linear, it can be assumed to be linear over small age ranges, of up to one year. Gradients can then be obtained for each adolescent patient in the study, according to their age at the start of the study. For the purpose of our example, it is shown that 13-year old girls grow at approximately 4.5cm per year. These gradients will obviously vary from individual-to-individual taking a population average is therefore a best approximation.
Figure 5.9: Growth Chart for Girls aged 2 to 20 [157]. The growth rate for a typical 13-year old girl is calculated as $\frac{63\text{cm}}{14\text{years}} = 4.5\text{cm/year}$.

An individual’s height at time $t$, $height(t)$, can thus be replaced by $height(0) + kt$ where $k$ is a constant, the gradient of the growth chart measured at time $t$ in Figure 5.9. Hence, Equation 5.3 can be written:

$$\frac{dPEF(0)}{dt} = \frac{d}{dt} \left( a_1 \left( height(0) \right)^2 \right) + a_2 + 2a_3 \{age\},$$  

(5.6)

$$\frac{dPEF(0)}{dt} = \frac{d}{dt} \left( a_1 \left( height(0) \right)^2 + 2kt \left( height(0) \right) + (kt)^2 \right) + a_2 + 2a_3 \{age\},$$  

(5.7)

$$\frac{dPEF(0)}{dt} = a_1 \left( 2k \left( height(0) \right) + 2k^2t \right) + a_2 + 2a_3 \{age\},$$  

(5.8)

where $t$ comprises of the initial age plus duration in the study, $t = \{age\} + \Delta t$. This in turn can be substituted into Equation 5.2:
\[
\text{PEF}(t) = \text{PEF}(0) + \Delta t \left[ a_1 \left( h_{\text{height}}(0) \right) k + 2k^2(\Delta t + \{\text{age}\}) \right] + a_2 + 2a_3 \{\text{age}\}. \tag{5.9}
\]

The scaling factor at time \( t \), \( SF(t) = \frac{\text{PEF}(t)}{\text{PEF}(0)} \), is once again calculated and applied to each of the measured PEF readings. Table 5.3 shows that by the end of the 309 days during which a 13-year old girl has submitted data, the adjustment is 10\% (scaling factor = 0.8999) which is the limit of the quoted measurement error for the Vitalograph meter (Section 4.5), for adolescents these corrections therefore make a discernable change.

Figure 5.10 illustrates how these scaling factors have been applied across the first 140 days (scaling factor = 0.9655). The blue dots show the raw values, and the red dots show the “adjusted” values after compensation for ageing and growth according to Equation 5.9.

Figure 5.10: Compensated PEF readings for a 13-year old girl in the Thames Valley Study (130cm at the start of the study).

### 5.4.4 Computation of PEF’

To enable comparison of PEF data across all the patients, the time compensation factors are applied to the adjusted PEF values, \( \text{aPEF} \), to obtain PEF’ values, \( \text{aPEF} \) with temporal correction. PEF’ are therefore calculated as follows, with accompanying numerical examples presented in Table 5.3.
CHAPTER 5. THE THAMES VALLEY OBSERVATIONAL STUDY

1. Select the five largest PEF readings from all data submitted by the individual.

2. Obtain Adjusted Personal Best (APB) by calculating the mean of these five values.

3. The Adjusted PEF (aPEF) is obtained by dividing each recorded value of PEF by the individual’s APB. A 0-1 scale is obtained.

4. To apply temporal correction to the aPEF, a time dependent scaling factor is calculated using Hankinson prediction models, for each recorded PEF value.

4. a, b, c, d The initial height, and recruitment age of the individual are used to predict a theoretical PEF for the start of the study, \( PEF(0) \), using the appropriate Hankinson model, shown in Table 2.2.

4. e Adults are assumed not to grow, so their height does not vary over time. For the adolescents in the study, growth charts such as Figure 5.9 are used to estimate rate of growth for their recruitment age. In the example of the 13-year old girl, the gradient of the growth curve \( k \) was measured as 4.5 cm/year.

4. f Time corrected Hankinson prediction models are used to estimate PEF at time \( t \), \( PEF(t) \). These models were derived previously for both Adults (Equation 5.5) and Adolescents (Equation 5.9).

4. g Predicted \( PEF(t) \) values incorporating growth and ageing effects are calculated for each time a PEF value is recorded.

4. h These \( PEF(t) \) values are used to calculate Scaling Factors for those times, \( SF(t) \), these compensates for both growth and ageing:

\[
SF(t) = \frac{PEF(t)}{PEF(0)}.
\] (5.10)

5 The \( SF(t) \) are applied to the \( aPEF(t) \) to incorporate compensation factors, the final aPEF values (\( PEF'(t) \)) are produced.

\[
PEF'(t) = SF(t)aPEF(t).
\] (5.11)

5.5 PEF Throughout the Study

The initial data analysis focuses on general trends across the study population. The data are collated to look for any general trends. In particular, a key outcome is to identify any effects, both positive or negative that use of the telemedicine system may have on the population as a whole. Patients were recruited into the Thames Valley Study over a period of approximately four months. With this phased recruitment, it was decided that the initial analysis of the PEF data should be carried out with respect to the length of time in the study, not the day on which the reading was taken. This then allows the effect of the telemedicine system to be tracked over time. In the following analysis,
### 5. Stage of computation

<table>
<thead>
<tr>
<th>Stage of computation</th>
<th>50-year old male</th>
<th>13-year old female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Five largest values (l_{\text{min}}^{-1})</td>
<td>584, 585, 588, 588, 588</td>
<td>312, 313, 315, 316, 318</td>
</tr>
<tr>
<td>2) Calculate ABP (l_{\text{min}}^{-1})</td>
<td>586.6</td>
<td>314.8</td>
</tr>
<tr>
<td>3a) Example PEF (l_{\text{min}}^{-1})</td>
<td>550</td>
<td>535</td>
</tr>
<tr>
<td>Time since start ((\Delta t))</td>
<td>60 days = 0.164 years</td>
<td>141 days = 0.386 years</td>
</tr>
<tr>
<td>3b) (a_{\text{PEF}(t)})</td>
<td>0.938</td>
<td>0.912</td>
</tr>
<tr>
<td>4a) Initial height /cm ((h))</td>
<td>181</td>
<td>130</td>
</tr>
<tr>
<td>4b) Initial age /years ((y))</td>
<td>50.44</td>
<td>13.406</td>
</tr>
<tr>
<td>4c) Appropriate Hankinson Model</td>
<td>(PEF(0) = a_1 h^2 + a_2 y + a_3 y^2 + a_4)</td>
<td>(PEF(0) = a_1 h^2 + a_2 y + a_3 y^2 + a_4)</td>
</tr>
<tr>
<td>(a_1 = 0.0150; a_2 = 4.962)</td>
<td>(a_1 = 0.0112; a_2 = 36.36)</td>
<td></td>
</tr>
<tr>
<td>(a_3 = -0.0780 a_4 = 63.14)</td>
<td>(a_3 = -1.008; a_4 = -217.2)</td>
<td></td>
</tr>
<tr>
<td>4d) Predicted (PEF(0)) (l_{\text{min}}^{-1})</td>
<td>606</td>
<td>274</td>
</tr>
<tr>
<td>4e) Growth curve gradient ((k))</td>
<td>0</td>
<td>4.5 cm/year</td>
</tr>
<tr>
<td>4f) Time corrected model</td>
<td>(PEF(t) = PEF(0) + \Delta t [a_2 + 2a_3y])</td>
<td>(PEF(t) = PEF(0) + \Delta t [2a_1 (hk + k^2 (\Delta t + y)) + a_2 + 2a_3y])</td>
</tr>
<tr>
<td>4g) (PEF(t)) (l_{\text{min}}^{-1})</td>
<td>605.54</td>
<td>604.97</td>
</tr>
<tr>
<td>4h) Scaling Factor ((SF(t)))</td>
<td>1.001</td>
<td>1.002</td>
</tr>
<tr>
<td>5) (PEF')</td>
<td>0.939</td>
<td>0.914</td>
</tr>
</tbody>
</table>

Table 5.3: Calculations of \(PEF'\) for two patients. For each individual, to enable comparison, PEF values are selected both midway through and at the end of the study.
months are defined as 28-day periods beginning at the date of the first recorded reading for each patient. Table 5.4 summarizes the results from all patients, from the day on which readings were first transmitted by that patient.

<table>
<thead>
<tr>
<th>Month</th>
<th>No. of readings</th>
<th>Mean PEF'</th>
<th>Median PEF'</th>
<th>S.D. PEF'</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2732</td>
<td>0.814</td>
<td>0.841</td>
<td>0.121</td>
</tr>
<tr>
<td>2</td>
<td>2471</td>
<td>0.811</td>
<td>0.835</td>
<td>0.119</td>
</tr>
<tr>
<td>3</td>
<td>2399</td>
<td>0.804</td>
<td>0.826</td>
<td>0.122</td>
</tr>
<tr>
<td>4</td>
<td>2123</td>
<td>0.795</td>
<td>0.824</td>
<td>0.143</td>
</tr>
<tr>
<td>5</td>
<td>1867</td>
<td>0.790</td>
<td>0.824</td>
<td>0.140</td>
</tr>
<tr>
<td>6</td>
<td>1433</td>
<td>0.797</td>
<td>0.829</td>
<td>0.132</td>
</tr>
<tr>
<td>7</td>
<td>1143</td>
<td>0.810</td>
<td>0.830</td>
<td>0.108</td>
</tr>
<tr>
<td>8</td>
<td>805</td>
<td>0.827</td>
<td>0.838</td>
<td>0.089</td>
</tr>
<tr>
<td>9</td>
<td>512</td>
<td>0.846</td>
<td>0.859</td>
<td>0.082</td>
</tr>
</tbody>
</table>

Table 5.4: Summary table for all 58 patients.

Figure 5.11: A plot showing monthly mean and standard deviation for the PEF' data presented in Table 5.4.

Figure 5.11 shows the PEF data plotted as mean PEF' and standard deviation from the first to the last month of the study. There appears to be little change in mean PEF' during this time, although the slight deterioration across the patient population in months four to six is likely to be associated with the summer months. This may well be due to environmental factors such as warmer summer temperatures. This is discussed in Chapter 7. Patient variability, as evaluated using standard
deviation, follows a similar pattern to the mean PEF', improving overall throughout the study (i.e. decreasing), but worsening (increasing) in months four to six.

The number of readings recorded each month declines as the study progresses. This is due to a decrease over time in patient compliance with some patients stopping altogether before the end of the nine months at the top left of the figure.

The apparent improvement in control throughout the study can be seen in the normalized histograms presented in Figure 5.12, which also shows the number of patients submitting data each month at the top left of the figure. These histograms are scaled such that they each have a unit area and are independent of the number of readings they display. Twenty ‘bins’ are used, and the normalized histograms represent the distribution of the readings. As the study progresses, the histograms become more skewed towards the upper limit, 1.0 (corresponding to the patient’s ABP), and there are far fewer low readings. The reduction in variability is also evident from the histograms becoming narrower.
In order to determine whether or not the improvement is caused by less well controlled individuals dropping out of the study early, the histograms in Figure 5.12 are repeated in Figure 5.13 using exclusively the data from the 24 patients who transmitted readings for the first eight months. Eight months rather than the full nine months was selected to capture a much large percentage of the study population. No discernable difference is observed across the study for this group of patients, indicating that use of the system has not altered their asthma control. We can therefore conclude that the apparent improvement in Figure 5.12 is due to non-compliant, less well controlled patients dropping out of the study rather than improvement as a result of using the telemedicine system.
Figure 5.13: Normalized monthly histograms of the PEF’ transmitted by the 24 patients who used the system for the first eight months of the study.

5.5.1 Difference Between Adults and Adolescents

Figure 5.14 shows normalized monthly histograms for all the sub-group three adults recruited to the Thames Valley Study. The figure is very similar to Figure 5.12 appearing to indicate an improvement in control of asthma throughout the study. However, analysis of the eighteen long-term patients remaining in the study for eight months or more shows that this group of individuals have not made significant improvements in their asthma control and that the closer grouping of the PEF’ readings towards the end is caused by the early drop-out of other, less well controlled adult patients.
Figure 5.14: Normalized monthly histograms of PEF' recorded by adults from the Thames Valley Study (sub-group 3).

Normalized monthly histograms are presented in Figure 5.15 for the adolescents in the Thames Valley Study. They demonstrate a much greater improvement in asthma control than was shown by the adults, however, the dropout rate, not surprisingly is higher. The data from the six adolescents who remain in the study for eight months are re-examined in Figure 5.16 and this small number of individuals does show a clear improvement in PEF' values as a result of using the telemedicine system.
Figure 5.15: Normalized monthly histograms of PEF' recorded by adolescents in the Thames Valley Study (sub-group 3).
Figure 5.16: Normalized monthly histograms of PEF’ recorded by the six adolescents who transmitted data for eight months or more (sub-group 3).

In Table 5.5, the mean monthly PEF is presented for each of the six adolescents plotted in Figure 5.16. The means are presented with and without correcting for growth, and the mean scaling factor for each month is also given. The table shows that if we had not applied the age correction factors, the apparent improvement would be even greater. As this is the first time that such a technique has been employed, it is difficult to assess if the improvements are indeed genuine, or if we have under-compensated for the effects of growth on the adolescent patients.
| Patient | Month | aPEF | PEF’ | SF | Month | aPEF | PEF’ | SF | Month | aPEF | PEF’ | SF | Month | aPEF | PEF’ | SF | Month | aPEF | PEF’ | SF | Month | aPEF | PEF’ | SF | Month | aPEF | PEF’ | SF | Month | aPEF | PEF’ | SF |
|---------|-------|------|------|----|-------|------|------|----|-------|------|------|----|-------|------|------|----|-------|------|------|----|-------|------|------|----|-------|------|------|----|-------|------|------|----|-------|------|------|----|-------|------|------|----|-------|------|------|----|
| a       | 1     | 0.818| 0.815| 0.997| 2     | 0.723| 0.715| 0.990| 3     | 0.732| 0.719| 0.983| 4     | 0.678| 0.661| 0.976| 5     | 0.685| 0.665| 0.972| 6     | 0.563| 0.544| 0.967| 7     | 0.736| 0.707| 0.961| 8     | 0.798| 0.796| 0.951| 9     | 0.798| 0.796| 0.951| 10    | 0.835| 0.818| 0.815| 0.997|
| b       | 1     | 0.815| 0.812| 0.996| 2     | 0.838| 0.830| 0.990| 3     | 0.844| 0.828| 0.981| 4     | 0.882| 0.858| 0.974| 5     | 0.852| 0.823| 0.966| 6     | 0.863| 0.827| 0.959| 7     | 0.902| 0.859| 0.951| 8     | 0.901| 0.859| 0.944| 9     | 0.901| 0.859| 0.944| 10    | 0.901| 0.859| 0.944|
| c       | 1     | 0.831| 0.828| 0.996| 2     | 0.808| 0.799| 0.989| 3     | 0.860| 0.844| 0.980| 4     | 0.743| 0.724| 0.974| 5     | 0.753| 0.727| 0.966| 6     | 0.836| 0.800| 0.957| 7     | 0.800| 0.759| 0.951| 8     | 0.809| 0.765| 0.944| 9     | 0.809| 0.765| 0.944| 10    | 0.809| 0.765| 0.944|
| d       | 1     | 0.687| 0.684| 0.996| 2     | 0.764| 0.755| 0.988| 3     | 0.741| 0.727| 0.980| 4     | 0.828| 0.806| 0.973| 5     | 0.849| 0.820| 0.966| 6     | 0.894| 0.820| 0.959| 7     | 0.883| 0.838| 0.949| 8     | 0.952| 0.900| 0.946| 9     | 0.952| 0.900| 0.946| 10    | 0.952| 0.900| 0.946|
| e       | 1     | 0.842| 0.842| 0.999| 2     | 0.812| 0.810| 0.998| 3     | 0.768| 0.766| 0.997| 4     | 0.795| 0.791| 0.995| 5     | 0.736| 0.732| 0.994| 6     | 0.794| 0.788| 0.993| 7     | 0.839| 0.832| 0.992| 8     | 0.869| 0.861| 0.991| 9     | 0.869| 0.861| 0.991| 10    | 0.869| 0.861| 0.991|
| f       | 1     | 0.861| 0.860| 0.998| 2     | 0.841| 0.836| 0.994| 3     | 0.862| 0.853| 0.990| 4     | 0.789| 0.777| 0.985| 5     | 0.755| 0.740| 0.981| 6     | 0.771| 0.753| 0.977| 7     | 0.754| 0.734| 0.973| 8     | 0.782| 0.759| 0.970| 9     | 0.782| 0.759| 0.970| 10    | 0.782| 0.759| 0.970|

Table 5.5: Table showing mean adjusted PEF with and without correction for growth of the six adolescents shown in Figure 5.16.

Although adults do not appear to have improved their asthma control as a consequence of using the telemedicine system, there is a benefit in compliant adolescents who use the mobile phone and Vitalograph peak flow meter. This may well be a direct result of improving compliance with a measurement regime and therefore medication.

### 5.6 PEF’ Variability

The variability of PEF’ is indicative of the level of control of an individual’s asthma. Figure 5.17 shows two plots; in the one on the left, the patient is very poorly controlled with a high degree of variability, the standard deviation of their PEF’ values over a five-month period being 0.2. Similar plots for all other patients are shown in Appendix A. The right-hand plot shows a stable patient with a PEF’ standard deviation of 0.04 over the nine-month trial; despite a small exacerbation in the centre.
There are numerous reasons for this level of variability, much of it can be explained by referring to the flow chart in Figures 5.2 and 5.3. It is not clear whether patients measure their PEF before or after taking their reliever inhaler. In some cases, PEF values may have been measured directly after taking reliever inhaler, leading to PEF values improved by up to 10%. In other cases, the measurement may have been made before taking any reliever inhaler; there is some anecdotal evidence that behaviour changed from day-to-day. This lack of consistency in the timing of measuring lung function with respect to using inhalers is likely to be responsible for a significant part of the PEF variability shown by patients in this study. Other contributing factors are the diurnal variability (>8%, see Section 2.4.6) and spirometer error (± 10% for the vitalograph). In Table 2.4 Higgins’ [87] findings are reported, in adults who do not suffer from respiratory conditions, the mean standard deviation of PEF, expressed as a percentage, is around 4%. This is similar to the well-controlled patient in Figure 5.17.

### 5.6.1 Index of Variability

The PEF' used to compare patients in this study is based on a scale of 0-1, allowing variability to be compared using PEF' standard deviation. The histograms in Figure 5.12 shows that the variation of the PEF' has decreased throughout the study, with a smaller global variability in month 9 than at the start of the study. However, this is once again likely to be a consequence of patients with poorer control ceasing to submit readings. It is desirable to investigate variability in each individual [58, 107]. Figure 5.18 shows a histogram of the standard deviations of PEF' values for each of the patients.
throughout the study, showing that practically all of the patients with mild-to-moderate asthma have a higher level of variability than that found in non-asthma sufferers by Higgins [87].

![Histogram showing the variability indices of each of the patients.](image)

As people with asthma can be expected to exhibit more variability than those without, a sensible cut off point to define acceptable control would appear to be 0.1 which is at the upper end of the level of control for normal individuals [88]. Approximately half of the people with mild-to-moderate asthma would therefore appear to be poorly controlled in this study, likely to be due to the relative timing of the use of their reliever inhaler with respect to their measurement of PEF.

### 5.6.2 Sliding Variability Index

In Section 5.6.1 a PEF’ standard deviation of less than 0.1 was used to define those people with mild-to-moderate asthma who had good control. However, this index was based on all data collected from an individual during the study, and does not convey any sense of how variability could change over time. Figure 5.19 shows an individual’s variability plotted as a function of time. This index is the standard deviation of a moving window of the last 50 PEF’ readings. It facilitates a more immediate view of the level of control of a patient at a particular time. This individual exhibits much poorer control around the beginning of July, but this specific pattern is not repeated for all of the patients.
Figure 5.19: Sliding index of variability for an individual patient.

Figure 5.20 is a plot of the sliding index variability averaged across all patients. The time axis represents duration in the study and the number of patients participating in the study at 50-day intervals is indicated on the chart. There is an improvement in variability throughout the study. The dashed red line shows the underlying trend: the variability decreases by approximately 30% from 0.083 to 0.058 over the first 220 days of the study. Much of this improvement is due to poorly controlled patients dropping out of the study; analysis shows that variability of the patients who submitted data for the full duration of the study drops by 9% (0.063 to 0.056). In Figure 5.21 the sliding index of variability averaged across all patients is now shown against time. The index shows a gradual decrease from 19th May to 6th October indicating a slight improvement across all patients as the study progressed. There is a peak around the middle of June, which may be a response to increased levels of pollen in early summer.
Figure 5.20: Sliding index of variability averaged across all patients. The starting dates for each of
the patient have been adjusted so that the x-axis shows duration in the study.

Figure 5.21: Sliding index of Variability averaged across all patients, plotted against time (from 19th
May to 6th October).
5.7 Diurnal Variation of PEF

We report in Section 2.4.6 that knowledge of the circadian rhythms in peak expiratory flow rate and diurnal variation of asthma has been long established [32, 86]. This section investigates the degree of diurnal variability that was exhibited by the patients enrolled in the Thames Valley Study. Figure 5.22 shows the time distribution of the 16,000 readings collected from all 91 patients in the Thames Valley Study; it shows clear troughs in the number of readings collected around 2am and 2pm. These times have therefore been used to define cut off points to decide whether a PEF readings is a morning or evening reading, rather than using midnight and noon as first considered. Two separate distributions of recording time appear in Figure 5.22. One having a smaller standard deviation with peaks at 7am and 10 pm, the other, a larger standard deviation and peaks at 8am and 8pm. Looking at individual patient data suggests that this is due to more regulated timing of readings during the week compared to the weekend, amongst the sub-group of patients who are either school children or may well be working adults. However, we do not have access to the personal patient information required to confirm this.

In some individuals the difference in PEF levels between morning and evening readings is very pronounced. Figure 5.23 shows two such examples. The left-hand plot shows an individual for whom...
the morning readings are consistently lower than the evening readings; the right-hand plot shows the opposite effect, with the morning readings being consistently higher than the evening readings. In patients with normal physiology, morning PEF is higher due to increased steroid production during the night [86]. The patient shown on the left could have night-time asthma, possibly due to poor environmental conditions in the bedroom.

Figure 5.23: Examples of two extreme cases of diurnal variability; the left-hand figure shows a patient with consistently lower morning readings and the right-hand plot has consistently lower evening readings.

T-tests have been performed on each of the 58 patients, and it was found that 26 patients (44%) exhibited a difference between the morning and evening readings that was significant at the $p < 0.05$ level. The full set of results are shown in Table 5.6. Two further examples of patients without diurnal variability are shown in Figure 5.24. In Chapters 7 and 8, morning and evening data are considered as distinct sets.
### Table 5.6: Table showing the significance values from t-tests comparing the morning and evening PEF data of each patient.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Significant Diurnal variation p-value</th>
<th>Insignificant Diurnal variation p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.000</td>
<td>0.062</td>
</tr>
<tr>
<td>6</td>
<td>0.000</td>
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</tr>
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</tr>
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</tr>
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</tr>
<tr>
<td>7</td>
<td>0.967</td>
<td></td>
</tr>
</tbody>
</table>
5.8 Use of Reliever Inhaler

A useful indicator of the amount of discomfort being experienced by individuals with asthma, is the quantity of reliever inhaler which they are taking. The use of reliever inhaler occurs during periods of poor control, as the reliever inhaler is used to combat the symptoms of an exacerbation. When answering diary questions, patients on the Thames Valley Study were asked how many puffs of reliever inhaler they had taken in the previous 12 hours. Figure 5.25 shows the mean number of puffs of reliever across all patients throughout the period of the study where at least three-quarters (45) of the patients were submitting data. The data are displayed with respect to the time of joining the study so that the x-axis indicates the time since the start. The mean amount of reliever taken in the previous 12 hours dropped by approximately 0.6 puffs throughout the period of the study.
Recruitment into the Thames Valley Study took place over several months, Figure 5.26 shows the period of the year when at least 45 of the 58 patients were submitting data. This figure also shows a downward trend. The peak around the 16th October is difficult to explain. However, if the PEF index and environmental data plots in Appendix C are considered, there is a corresponding dip in PEF across all patients which may be explained by the first cold snap of the winter.
CHAPTER 5. THE THAMES VALLEY OBSERVATIONAL STUDY

5.9 Summary of Key Findings

Patients found the system easy to use and compliance of sub-group three patients with twice daily recording was 80%, an improvement compared to the paper-based studies reported in the literature. Adults were found to be more compliant than adolescents, although only by 8% for readings twice a day. Patients were generally supportive of the system and appreciated the fact that it gave them more support and autonomy with their condition.

5.9.1 Patient Questionnaire

Study questionnaires were distributed to all participants within one month of the end of the study. Forty-six individuals filled in the questionnaire, 51% of all patients recruited. Of these, 69% were satisfied or very satisfied with the study, citing the increased autonomy and understanding of asthma that the enhanced ability to monitor peak flow provided - none of the patients were regularly using monitoring equipment before the start of the study. Patients reported that they found the phone software easy to use: 68% reported that it was easy or very easy, and only 13% deemed it not easy to use. Generally patients indicated that the system had helped to improve their ability to manage
their symptoms (74%), with no patients indicating a negative impact. The most positive features of the telemedicine system were described as: increased awareness and information about asthma, improved ability to monitor/manage their condition with availability of feedback screens on mobile phone and ease of use. However, the patients did find the Vitalograph difficult to use, with a number reporting difficulties in blowing into the meter. Most of them did not find the compliance reminders which were sent on a daily basis if no data had been received during the previous day, to be useful, and they may have ultimately had the effect of reducing, rather than improving compliance.

5.9.2 Feedback to Patient

In this study, feedback consisting of a set of ticks and crosses demonstrating compliance over the previous seven days, complete with a summary of PEF values over this period were downloaded to the phone each time data were transmitted by the patient (Figures 5.2 and 5.3). On a small number of occasions, if network connectivity was not available, patients did not receive this feedback. Many patients reported finding this disconcerting, despite knowing that unsent data was stored on the phone and transmitted at the next available opportunity. Consequently, it is desirable to generate as much of the feedback as possible directly on the phone and check and update settings when a connection is made.

5.9.3 Analysis of PEF

Inter-patient comparison of PEF is difficult because of the different baseline levels for different patients and in the case of lengthy studies, the effects of growth and ageing. An adjusted scale from 0-1 has been introduced in this Chapter in order to facilitate direct comparisons between patients. This has demonstrated that there was little change in adjusted PEF with time during the study. This is not surprising since there was no clinical intervention based on the peak flow data. Although the normalized histograms show in the later months of the study a tighter banding and fewer very low readings, this is directly attributable to the lower number of patients in the later months of the study. The improvement in the averaged sliding index of variability throughout the study and the use of reliever inhaler does suggest an improvement in control. The mean use of reliever inhaler decreased by approximately 0.6 puffs per 12 hours from the start to the end of the study. However, these improvements may well occur as less well controlled patients drop out from the study.
Perhaps the most significant finding of the study is that people with mild-to-moderate asthma are less well controlled than their GPs believe. Many were found to have a standard deviation greater than the 10% suggested by the literature as being an acceptable level. A sliding index of variability based on the previous 50 PEF readings was introduced to give a measure of how peak flow varies with time. Some of this variability has been attributed to patients recording their PEF randomly before or after using their reliever inhaler - a major improvement to the system would be to guide users through this process in a systematic fashion to ensure consistency (see below).

5.10 Lessons Learnt from the Thames Valley Study

The key findings from the Thames Valley Study can be summarized by the four key points below.

Wrong order of questions  The main flaw was the fact that patients were asked about the management of their condition (use of inhalers) before the measurement of PEF was made. The causal relationship between measurement and action, which requires the latter to follow the former, was broken. As patients were asked to measure their peak flows last, the PEF information had little or no effect on their behaviour (adjusting their use of inhalers). Self-management requires a “measure-evaluate-act” sequence to provide the best possible information to the patient for the evaluation process and to remove the random variability introduced to the recording of PEF values.

Feedback from server to phone  All feedback provided to patients in the Thames Valley Study was generated on the server and transmitted to the phone every time a data transmission was made. Unfortunately transmission of data is not 100% reliable and in a small number of cases, data was unsent and no feedback provided. Unsented data is stored on the handset for future transmission, however, patients do not receive immediate feedback. Wherever possible, feedback should be generated on the handset, so that patients are always presented with useful information.

Introduction of a personalised model  The Thames Valley Study used a system of ticks and crosses to show recent compliance with a corresponding numerical display of associated PEF values. This does not contextualise a numerical value into a status of their current condition. A personalised
model stored on the handset is proposed, whereby a barometer scale is used to show users how their latest reading compares to their personal best PEF. Such a barometer scale can incorporate a “traffic light” scale to support an action plan determined by the patient’s GP from data collected during an initial training period.

**Use of training period** In order to construct a personalised model, a training period will be required to collect PEF data and assess the baseline value, or Adjusted Personal Best PEF, on which to base an action plan. During this assessment period, the variability of PEF can be assessed. If the patient’s asthma is not “stable” it would not be possible to construct the model. In this case, the patient should be given medication to control their asthma (see Section 6.2) before commencing with the system.
Chapter 6

The Isle of Man Asthma Study

The Isle of Man Asthma Study was conceived as a successor to the Thames Valley Observational Study, an opportunity to put into practice many of the lessons learnt from the previous study. It was designed as a small cohort group study to investigate improving self-medication of young people with asthma. Many of the technical issues identified in the Thames Valley Study were addressed for this second-generation asthma study.

There were also significant improvements to the self-management software; a more logical flow through the patient diary and the Royal College of Physicians Three questions (Section 2.4.1) were used to replace the self-grading of symptoms on a 1-5 scale. A personalised model of peak flow was also introduced. In the first instance, the software ‘work flow’ which had contributed to the high PEF variability exhibited by the Thames Valley Study patients was altered, modelling the patient as a feedback system (see Section 6.1.2). Secondly a training period was built into the study protocol (see Section 6.2) to set baseline levels for the personalised PEF model, checking that the variability of the PEF was sufficiently low to allow this. Clinical intervention was also much more proactive in this study: daily e-mail alerts were sent to the study nurses reporting any patients who had submitted readings below 75% of their baseline, and these were followed up as appropriate. Compliance SMS reminders, disliked by patients in the Thames Valley Study, were not sent to patients.
6.1 Background to the Isle of Man Study

Twelve patients were selected from the Palatine Group Practice, Douglas, Isle of Man, according to the following criteria: patients with mild-to-moderate asthma aged from 18 to 50 years, who required treatment with regular inhaled steroid preparations and bronchodilators. Ethics committee permission was granted from the relevant authorities on the Isle of Man.

6.1.1 Hardware

Two major concerns surrounded the choice of the telemedicine hardware in the Thames Valley Study. Although the O2 xda is easy to use and has a large screen, it is both expensive and the impact on compliance caused by loss of the software when the batteries are allowed to run flat was significant. For the Isle of Man Study, the xda was replaced with the Motorola V600 handset. Being a conventional clam-shell phone, this has a much smaller screen, but it has the advantage that the memory is stable and immune to exhausted batteries. It is therefore much more appropriate for such a study. In the review of telemedicine for asthma in Chapter 3 and discussion of the Oxford Telemedicine Architecture in Chapter 4 the importance of the telemedicine handset being used as the patients main mobile phone is discussed. In the majority of cases, the patients switched to using the handset provided for the study as their one and only mobile phone.

Section 5.9.1 discussed how many patients found it difficult to take readings using the Vitalograph peak flow meter. This was replaced with the Piko meter (Section 4.5), a smaller meter than the Vitalograph. The Piko meter was again connected to the handset via a cable which attached to the base of the Piko meter. The meter is designed to communicate using an infra-red (IR) communications interface with a cradle to a PC, a custom-made cable was designed by the author in order to interface with to the existing IR port with the electronics housed in a plastic moulding glued to the base of the Piko, this can be seen in Figure 6.1 which shows all of the hardware use in the study. The interface circuit is described in Section 4.4.2.
6.1.2 Self-management Software

Peak flow variability in the Thames Valley Study was high, partly, as previously discussed, as a result of the random order between the use of reliever inhaler and recording peak flow readings. Some patients would consistently either take readings pre or post use of their reliever inhaler, whereas others randomly switched between the two. The second generation software, as used in the Isle of Man Study was programmed to remove this inconsistency. Feedback was designed to empower the patient and provide information to enable them to take the correct actions to maintain control of their symptoms.

With hindsight, it is self-evident from the flow chart in Figures 5.2 and 5.3 that if a patient is answering the question about the amount of preventer inhaler they are going to take prior to record-
ing their PEF, they cannot be using this information to determine their medication. It is possible to envisage the patient as a closed-loop feedback system, steady control of asthma symptoms are desired, these can be measured, and any deviances from good control can be treated to restore the steady-state condition. From the perspective of the patient, we have used a Measure - Evaluate - Act sequence which is shown in Figure 6.2. The full set of symptom screens are shown in Figure 6.3.

**Measure:** the patient is asked questions about symptoms and the amount of reliever inhaler they have used in the past 12 hours. This requires them to think about their condition in the immediate past. They are then directed to take their PEF reading using the Piko peak flow meter.

**Evaluate:** feedback is given to the patient, using a *Traffic Light* (Red - Amber - Green) scale to display the current PEF reading with respect to their personal baseline (see Section 6.2). A simple weather forecast is presented on the phone screen, this was taken from the BBC website for the Isle of Man and informed patients of weather, sun index, wind speed and direction, temperature and pollen and pollution indices. Patients are then expected to use both sets of information to help them decide on the level of preventer inhaler they will now take (if any at all).

**Act:** the patient takes their preventer inhaler, the amount of which should vary according to the goal of maintaining a steady PEF. Patients were provided with a Personal Management Plan (approved by their GP) based on PEF as a percentage of their personal best. This plan was stored on the phone, and patient were given the option to “See Plan” which reminded them of the advice relevant to their latest PEF value. Amber conditions occur rarely and Red is even less frequent, therefore these screens assist their memory.

Another change from the Thames Valley Study (as discussed in Section 5.9.2) was the generation of the feedback screens directly on the phone. The patient’s personal baseline PEF value (used to set the Red-Green-Amber display) was stored in the phone’s memory (as well as the server) on the hand set and use this to generate the barometer scale shown in Figure 6.2. Two advice screens were available to patients to remind them of their action plan, in the case of an amber reading they were told to “Start using (or increase dose of) preventer inhaler according to their Personal Management Plan.” For a red reading, patients were advised to “Call the practice, or take 10 puffs of reliever inhaler and repeat the PEF reading in 10 minutes.”
Start application on phone.

Enter the number of puffs of reliever inhaler that have been taken.

Answer questions about symptoms.

Plug in peak flow meter and take readings as directed.

Receive feedback, asthma level and local weather information.

Enter the number of puffs of preventer inhaler.

Data is transmitted.

Charts shown on phone.

Close application on phone.

Data is transmitted.

Charts shown on phone.

Close application on phone.

Figure 6.2: Flow chart of the software used in the Isle of Man Study.
6.2 Isle of Man Study Protocol

Where possible, the patients were given a Wright peak flow meter prior to the study and asked to record their peak flow measurements in a paper diary. Paper-diaries were obtained from seven of the 12 patients. The patients were then given the phone and Piko peak flow meter and asked to record symptoms and PEF twice a day. The initial baseline level was set remotely based on the first few readings (up to five), or where available the peak flows recorded in paper-diaries. The patients then entered a “training period” during their first month in the study. The first 50 readings were analysed to calculate an index of variability reflecting asthma control. The standard deviation of the adjusted PEF, PEF$^\prime$ was once again used (see Section 5.6.1):

$$PEF_{var} = s.d.(PEF^\prime).$$

(6.1)

If patients were found to be unstable during the training period (standard deviation of PEF$^\prime > 0.1$), the Practice Nurse and GP were asked to review their data and prescribe a short course (2-3 weeks) of inhaled corticosteroid to stabilize the asthma. Reddel [109] describes the response of people with asthma to treatment with the inhaled corticosteroid, budesonide. It was found that personal best PEF (defined as best in the previous two weeks) reached a plateau after only three weeks of treatment and variability then decreased. Those individuals who were prescribed steroids then entered a second “training period” of 50 readings to obtain the baseline level following stabilisation of asthma. The baseline level is the Adjusted Personal Best (five best PEF values in the 50 readings, after outliers more than three standard deviations from the mean of the 50 readings have been removed). The green section of the red-amber-green traffic light scale is then set to represent the range 0.75 to
1.0 PEF', the amber section from 0.5 to 0.75, and the red for any readings below 0.5 PEF'. These values are based on the British Thoracic Society guidelines described in Section 2.5.2. This protocol is summarised in Figure 6.4.

All data transmitted by the patients were analysed by the server on a daily basis and e-mails were sent to the Practice Nurses informing them of any patients who had submitted PEF readings falling between 75% and 50% of their personalized baseline level (Amber) or below 50% of baseline (Red). The secure website was also used by clinicians to review data at regular checkups. The patients were
trained in the use of the telemedicine system by the author who met them at the General Practice on the Isle of Man. Technical issues were raised by nurses, patients were then contacted by telephone to direct them through any difficulties.

### 6.2.1 Symptom Questions

The asthma application on the phone was initially programmed to use the three-questions described by the Royal College of Physicians (RCP3) [72], rather than the more arbitrary self-management of asthma severity on a 0-5 scale used in the Thames Valley Study. The RCP3 questions scale, which were discussed in full in Section 2.4.1, cover topics such as sleeping difficulty, severity of symptoms and record any interference with daily routine. The questions were asked once each day, with question one being asked in the morning as it related to sleep, and questions two and three which relate to daytime activities asked in the evening. The software was designed such that if the previous session’s readings had not been taken, the relevant diary questions would also be asked in the current session. It soon became apparent from the patient answers, that the questions did not elicit appropriate answers. In particular the second question, “have you had your usual asthma symptoms during the day?” is ambiguous - a no answer can be given to both a better or a worse day. Medical advice was taken, and it was decided that patients should be offered a set of new questions for the last three months of the study. All patients agreed, and the software was subsequently updated for the last three months. The RCP3 questions are believed to work on a longer basis, in the context of a clinical visit, patients would think about their condition and their answers would prompt discussion. They would appear to be less appropriate for daily self-monitoring.

The new questions were designed with assistance from Dr Dermot Ryan and Dr David Price who are both asthma specialists, to provide clear, simple questions for the patients to answer. Five questions were used, and designed to be answered once a day, each on a scale from 0 (trouble free) to 3 (most troublesome). The phone software was used to ask questions at the most appropriate times of day; question one asked in the morning and questions two to five asked in the evening.

1. Did your asthma wake you last night?
2. Did you have any problems with Wheezing today?
3. Did you have any problems with Coughing today?
4. Did you have any problems with Breathlessness today?
5. Did you have any problems with Chest Tightness today?
6.3 Compliance

Compliance was found to be similar to that in the Thames Valley Study, with 3,599 individual readings being collected in total from the 12 patients. The patients did divide up into two subgroups; those who exhibited very high compliance, missing very few readings, and those who tended to use the system diligently for a short period of time before becoming less compliant until a gentle reminder was given by one of the Practice Nurses. Figure 6.5 shows the number of readings taken by the four most compliant and three least compliant patients using a moving seven-day average for display purposes. The patient shown in green on the left hand side started later than the other the patients and stopped submitting data in July. Full compliance is equivalent to 14 readings per week, (i.e. two per day). The gaps present in the traces are associated with no data being received during the previous week they are attributed to holidays and technical problems.

Having recruited the patient into the study, they were expected to submit readings twice a day. Average compliance across the patients is shown in Figure 6.6. This shows how well the individuals adhered to his schedule. As with Figure 6.5, a seven-day average computation is used and any weeks for which an individual submitted no readings is excluded from the calculation of the average. The figure exhibits a high level of fluctuation but the underlying trend shows a gradual reduction from the initially excellent levels of compliance. On day 200, the software with the new symptoms questions was issued to the patients. This has the effect of re-engaging the patients and hence increasing their compliance. Mean compliance also benefited, as some of the least compliant patients ceased to use
the telemedicine solution at this stage.

![Graph showing Mean compliance across 12 patients - index calculated as a sliding seven day window.](image)

**Figure 6.6:** Mean compliance across the 12 patients - index calculated as a sliding seven day window.

### 6.4 Questionnaire Analysis

As with the Thames Valley Study, patients were given an end-of-study questionnaire. The questionnaire comprised thirteen multiple choice questions on a scale of Strongly Disagree (5) to Strongly Agree (1). Eight responses from the patients were received, and in general they report on the system in a positive light. The results are summarised in Figure 6.7 below. Patients tended to find the system easy to use and feel it helped to control their asthma.
Respondents were also given the chance to offer more open-ended comments in writing. Three patients commented that they particularly liked the ‘red-amber-green’ scale, which gave them a good visual representation of their PEF. Another patient wrote that he appreciated the support of healthcare professionals and the security of having readings logged twice a day and made available to the Practice via the web. The main problem reported with the system was the transmission delay and the processing time on the phone. A couple of comments were also received concerning the accuracy of the Piko peak flow meter. Patients suggested some improvements: fewer questions than the five symptoms questions used at the end of the study, with less overlap; diary to be filled only twice a week; graphical feedback to be extended beyond two weeks. One of the least compliant patients suggested the use of reminders to use the peak flow meter, but this is very much a individual view.
6.5 PEF Analysis

The following two pages provide example summaries for two patients, Figures 6.8 and 6.9 with data for all patients shown in Appendix B. The top graphs display the raw PEF data against time. The second graphs are the same as the top graphs, except that outliers have been filtered out using two simple criteria (firstly, any values above Adjusted Best + 100 l/min, for that patient are discarded; secondly, any values below 100 l/min are also removed). On this graph, the Adjusted Personal Best PEF is shown with a green line. The 75% green-to-amber and 50% amber-to-red thresholds are shown in magenta and red respectively. Although patients taking part in the Isle of Man Study found using the Piko peak flow meter to be significantly easier than reported by patients who used the Vitalograph peak flow meter for the Thames Valley Study, the number of outliers (unusually high or low readings) was significant, in some cases as high as 20% of all recorded data. These erroneous points have been removed for the analysis in this Chapter. This does represent a significant issue which will have to be addressed in future work.

Two further graphs are produced on each page, both derived from graph 2. Graph 3 shows a running seven-day average of PEF, together with the standard deviation for the corresponding seven-day period. Finally, graph 4 is a display of the weekly mean PEF, together with the standard deviation for that week. Graphs 3 and 4 allow trends for a patient to be visualised and variability of the data to be qualitatively assessed. The patient in Figure 6.8 exhibits a larger variability than the patient in Figure 6.9 this has been explained by the GP as being due to cold weather affected asthma. In Figure 6.9, a single point which significantly affects the standard deviation remains after the abnormal outliers have been removed using the simple conditions described above. This individual point is close to triggering an amber alert (75% of baseline PEF). A Kalman filter with an innovation window could potentially be used to remove this effect.
Figure 6.8: Example data from patient 100473. Raw data, filtered data and weekly mean and standard deviation are shown.
Figure 6.9: Example data from patient 100476. Raw data, filtered data and weekly mean and standard deviation are shown.
The recorded PEF data were analysed as with the Thames Valley PEF data (see Section 5.5). However, as all patients were young adults, the ‘age correction’ described in Section 5.4.3 was not applied. The first 50 readings submitted by each patient were used to calculate individual Adjusted Personal Best levels for the red-amber-green feedback screens.

As before PEF', the normalised peak flow on a scale of 0.0 to 1.0 for each patient, was calculated to enable results for different patients to be compared. If a patient improves significantly during the study with respect to the first 50, the PEF' values can rise above 1.0. This happens in a small number of instances, which could be due to an ageing effect, but is unlikely as all patients were in their twenties.

A monthly summary of the results is presented in Table 6.1, with a corresponding plot of means and standard deviations in Figure 6.10. In contrast to the presentation of results in the previous Chapter, calendar months are used as all patients were recruited at the same time.

<table>
<thead>
<tr>
<th>Month</th>
<th>Mean PEF'</th>
<th>Median PEF'</th>
<th>SD PEF'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan</td>
<td>0.903</td>
<td>0.916</td>
<td>0.092</td>
</tr>
<tr>
<td>Feb</td>
<td>0.907</td>
<td>0.916</td>
<td>0.089</td>
</tr>
<tr>
<td>Mar</td>
<td>0.899</td>
<td>0.912</td>
<td>0.110</td>
</tr>
<tr>
<td>Apr</td>
<td>0.907</td>
<td>0.923</td>
<td>0.095</td>
</tr>
<tr>
<td>May</td>
<td>0.922</td>
<td>0.944</td>
<td>0.100</td>
</tr>
<tr>
<td>Jun</td>
<td>0.900</td>
<td>0.908</td>
<td>0.109</td>
</tr>
<tr>
<td>Jul</td>
<td>0.922</td>
<td>0.916</td>
<td>0.091</td>
</tr>
<tr>
<td>Aug</td>
<td>0.918</td>
<td>0.926</td>
<td>0.108</td>
</tr>
<tr>
<td>Sep</td>
<td>0.895</td>
<td>0.910</td>
<td>0.100</td>
</tr>
<tr>
<td>Oct</td>
<td>0.904</td>
<td>0.913</td>
<td>0.097</td>
</tr>
</tbody>
</table>

Table 6.1: A monthly summary table of PEF' collected from the 12 patients in the Manx Study.
The mean levels are consistently higher, and variance smaller than the results in the Thames Valley Study, and change very little throughout the duration of the study. With few exceptions, the patients were well controlled from the beginning, with little room for improvement, and this is further confirmed by Figure 6.11 which shows monthly histograms of the PEF data.
Figure 6.11: Normalised monthly histograms of all data recorded in the Isle of Man Study.

### 6.6 Use of Reliever Inhaler

Analysis of the use of reliever inhaler by patients on the Isle of Man study again indicates that these patients had much better control of their asthma, consistently using much less reliever inhaler, than the patients on the Thames Valley Study. In Figure 6.12, the mean use of reliever across the two
studies is shown, the plot for the Thames Valley patients being reproduced from Figure 5.25 for comparison.

![Graph](image)

Figure 6.12: Mean level of reliever inhaler used in a 12 hour period, averaged across all patients.

### 6.7 Asthma Symptoms

The use of the RCP3 questions throughout the first eight months of the study showed that patients very rarely changed their answers to any question, and no pattern could be identified. For the last three months of the study, the questions were changed, as previously discussed in Section 6.2.1. Some patients never answered the questions at all whereas some did begin to use the new questions. Figure 6.13 shows two patients; the patient shown on the left-hand side, reported no symptoms on any of the 130 days that he or she took readings. The right-hand plot shows a patient who reported symptoms on 27 of the 96 days (28.1%) on which they filled in the electronic patient diary. Ideally, the correlation between symptom score (calculated as the daily sum of the scores for each of the five questions, each of which were graded between 0 and 3) and PEF' would be strongly negative represented on the right-hand side of Figure 6.13. Even in the case of the individual, the correlation is only weakly negative, \( r = -0.05 \). This figure is improved if the days for which no symptoms are reported are excluded from the analysis, in which case, a value of \( r = -0.25 \) is obtained.
Global results are inconclusive; Figure 6.14 shows a scatter plot for 568 patient days recorded using the new symptom questions. Of these, only 98 days (17.3%) have symptoms recorded, as many of the patients never reported symptoms throughout the study.

Analysis of this data gives us a value of $r = 0.095$, which is in the wrong direction for what would be expected. If we exclude those days on which no symptoms were recorded, we obtain a value of $r = -0.061$, this time with the correct sign but of very limited significance. As these patients were generally well controlled, there are very few occurrences for which asthma worsens and hence insignificant data from which to draw conclusions.
6.8 Lessons Learnt from the Isle of Man Study

The telemedicine technology progressed significantly as a result of the Isle of Man Study, many of the technical issues highlighted in the Thames Valley Observational Study having been addressed. A more stable version of the software was produced on a conventional handset rather than a PDA with communications facility (the xda). Significant problems were highlighted due to the large number or erroneous readings produced by the Piko peak flow meter, alternative meters should be investigated for future use, or alternatively if this is not possible, the software could be adapted to capture such readings and request that the patient performs a repeat manoeuvre.

As part of the study protocol, daily e-mails were sent to the practice nurses identifying any patients who had generated amber or red alerts, defined as PEF values less than 75% or 50% of the personalised baseline. This was not found to be of great use to the clinicians; as individual outliers generated false alerts. The automated handling of outliers requires further work, which could be based on the approach described by Gibson [100]. Gibson calculates a mean value of PEF during a stable baseline period. Alerts are then generated based on the outcomes of three tests:

1. One point more than 3 s.d. from the baseline;
2. Two out of 3 points between 2 and 3 s.d. from the baseline;
3. Four out of 5 points between 1 and 2 s.d. from the baseline.

The patients’ asthma remained under control throughout the study, with very little use of reliever inhaler. The use of a training period to set the patients’ baseline levels was considered successful, but the two patients who were identified as being unstable during their training period did not start a course of steroid treatment to stabilize them as documented in the protocol. The clinicians did not feel this was necessary given their knowledge of the patients. In particular, the patient shown in Figure 6.8 was known to have asthma that was badly affected by cold weather and it was believed that steroid treatment would not assist in this case. Such environmental effects are very interesting, in Chapter 2 many confounding factors were presented which are all known to influence control of asthma. In Chapter 7 data from the Thames Valley Study are analysed using weather, pollution and pollen data collected throughout the duration of the study to investigate these effects on patients with mild-to-moderate asthma.
Modelling the Effects of the Environment on Asthma

Whoever wishes to investigate medicine properly, should proceed thus... consider the seasons of the year, and what effects each of them produces. Secondly... study the warm and the cold winds, both those which are common to every country and those peculiar to a particular locality...

— Hippocrates, 400BC

7.1 Introduction

In Chapter 6 it was mentioned that the symptoms of one patient’s asthma became worse in cold weather, a phenomenon which was noticed at the beginning of the Isle of Man study in the month of February. Recently researchers at the Meteorological Office have also found significant correlations between cold weather and hospital admissions for Chronic Obstructive Pulmonary Disease, COPD [27]. It was therefore decided retrospectively to investigate the effect of the weather on patients with mild-to-moderate asthma. If useful correlations with the weather were found, the appropriate weather information could potentially be included in the feedback provided by the telemedicine system to help patients control their condition. Although not designed for the purpose, the completed Thames Valley Study presented the best data set that was available for such retrospective analysis. All of the data are accurately measured and time stamped, thereby offering a unique opportunity to investigate how environmental conditions can affect lung function. To make the analysis possible, historic records for a range of environmental variables were obtained for the duration of the
study period; weather from the Meteorological Office [158], pollution from the National Air Quality website [159] and grass pollen from the National Pollen Database [160].

Data from the 58 most compliant patients (sub group 3 - see Section 5.3.1) were used for this retrospective analysis. Section 5.7 showed evidence of variability between morning and evening PEF readings, and the data were therefore split into two data sets, one for the morning readings, and one for the evening readings. Morning readings were considered to have been recorded between 02.00 and 14.00, with evening readings assumed to have been taken between 14.00 and 02.00 (see the histogram in Figure 5.22). As there is only a relatively small numbers of patients available for this analysis, data from adults and minors are not treated independently.

### 7.2 Global Data Sets for Analysis of Environmental Conditions

The effects of environmental conditions on PEF are a second order effect; they are much less relevant for an individual's lung function than the use of medication. In Chapters 5 and 6 we introduced the Adjusted PEF, designated PEF' using a zero to one scale, to allow inter-patient comparisons.

Global data sets for analysis of the impact of environmental conditions on morning and evening PEF readings are constructed in the following manner, with the approach summarised for the morning PEF' data of four patients in Figure 7.1.

1. Define study period as the period of time for which there were at least five patients transmitting data; i.e. 23-02-2003 to 01-01-2004.
2. Split each patient's data into two sets, morning and evening readings; 02.00 to 14.00 and 14.00 to 02.00 based on the findings of Section 5.7.
3. Figure 5.22 clearly indicates that the most likely times for measurements of PEF during the morning and evening were 8am and 10pm respectively. The morning and evening PEF' data are treated separately for each patient, and each time series is re-sampled using linear interpolation\textsuperscript{1} to produce interpolated values for 8am and 10pm on a patient-by-patient basis. Although this adds little, if any, value on days when data have been recorded, the interpolation is necessary to fill in gaps and products a regularly sampled series for comparative purposes.

---

\textsuperscript{1}Function interp1.m in Matlab [161].
CHAPTER 7. MODELLING THE EFFECTS OF THE ENVIRONMENT ON ASTHMA

This process is shown in Figure 7.1 for the morning time series. Recorded PEF' data for four patients are shown by the red, green, blue and magenta circles. These data are re-sampled and the corresponding crosses represent the interpolated data. The line going through the red circles is shown dotted as an example. If any data are missing - for example the 15/04 reading from the patient shown in red, the missing data are imputed using linear interpolation. In the figure below, the point A represents the location where the data point for 15/04 for the “red” data would be inserted.

4. Calculate the median PEF’ for the morning data for all patients on each day. In Figure 7.1 this is represented by the black line, which is the median of the morning data from the four patients. This process is repeated for the evening PEF’ data.

![Figure 7.1: An example of how the global data set is created. Here recorded morning PEF’ values are shown by red, green, blue and magenta circles. This data is re-sampled at 8am using linear interpolation to produce the correspondingly coloured crosses. The median of these re-sampled data is computed and the resulting data set shown in black.](image1)

Figure 7.2 shows the daily re-sampled PEF’ values plotted throughout the study. In this figure, the morning time series is shown in the upper plot and the evening data are shown in the lower plot. Figure 7.3 shows the morning and evening data sets combined. A period of 30 days at the beginning of the study is shown in the lower plot.
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Figure 7.2: The global PEF' data sets produced from all 58 patients. The morning time series is shown in the upper plot and the evening time series in the lower plot.

Figure 7.3: The combined morning and evening PEF' data sets. The upper plot shows the complete year, the lower plot shows a 30 day period of the combined series.
7.3 Environmental Explanatory Data

7.3.1 Introduction

A range of environmental parameters for the period from February 2003 to January 2004 for the Thames Valley region were obtained from a number of sources (see below): weather, pollution and pollen data. In all cases missing values in the data sets were imputed using a combination of linear interpolation and multiple linear regression [162]. Unfortunately, the only available sources for environmental variables were fixed sites in the general locality of the patients’ homes. This is far from ideal, however, the study did not track the location of patients throughout the study. A future study could be designed to use the mobile phone to track where the reading was taken such that environmental data could be more accurately attributed to each reading. The effect of a single location for meteorological measurement will be small as spatial variation of weather variables is limited due to widespread weather patterns across large areas. Geographic variability will be much higher for pollutants and pollen as local effects such as busy roads or hay fields will have a marked impact on levels. However, these effects have been mitigated as much as possible by selecting rural environments for measurement locations which will tend to show the underlying day-to-day trend without capturing the significant local differences.

7.3.2 Weather

The weather data were obtained from the Meteorological Office [158]. The data consists of wind speed ($ms^{-1}$), wind direction ($^\circ$), temperature ($^\circ C$), relative humidity ($\%$), pressure (mbar), cloud cover (octals - the number of eighths of the sky obscured) and rain (mm hr$^{-1}$), all collected hourly at Heathrow. Figure 7.4 summarises the global distributions of the weather parameters for the ten months of the study period. The number of 'bins' for each histogram have been optimized to give the smoothest figures. Time plots can be found in Appendix C. Temperature is the only parameter which exhibits a clear seasonal pattern.
Only two of the variables, temperature and relative humidity, show a clear 24-hour variation which is not apparent in the figures above. Figure 7.5 shows temperature and relative humidity plotted over a 20 day period. Diurnal periodicity is clearly visible, a phenomenon also present in PEF (Section 5.7).
7.3.3 Pollution

Pollution information throughout 2003 was obtained from the National Air Quality website [159]. A number of locations throughout the Thames Valley were available. Harwell was selected as the most appropriate location, because it is close to the study area and is a more rural site, which is therefore less influenced by traffic congestion and the resulting effects of traffic at the rush hour. The pollution data are consequently more representative of the geographic area than those collected adjacent to a busy road.

Thirteen types of pollutants were available for the Harwell site, each of which were also recorded hourly. However, the data set was less complete, with around 16% of data missing, particularly in the less prevalent pollutants such as o xylene (an aromatic derivative of benzene). The same interpolation techniques outlined in Section 7.3.1 were employed to compensate for this. Figure 7.6 summarizes the distributions of the pollutants throughout the study period, all measured in micrograms per cubic metre of air. Once again the most appropriate ‘bin’ size has been selected for each figure.

The pollutants can be subdivided into three categories based on their chemical composition. These
CHAPTER 7. MODELLING THE EFFECTS OF THE ENVIRONMENT ON ASTHMA

tend to relate to the clustering of the explanatory variables in the dendrogram shown in Figure 7.8. The categories are discussed below:

**Aromatic Hydrocarbons [163]** The pollution data set contains a range of aromatic hydrocarbons; benzene, toluene, ethylbenzene, o xylene, m p xylene and butadiene. These all have a very similar chemical structure, with the first five being variants of the benzene structure. All of these pollutants are released in vehicle exhaust gases either as unburned fuels or as combustion products, and are also emitted by the evaporation of solvents and motor fuels. Benzene and 1,3-butadiene are of particular concern as they are known carcinogens. The main sources of benzene in the atmosphere in Europe are from the combustion of petrol (about 2% by volume). Benzene is emitted in vehicle exhaust not only as unburnt fuel but also as a product of the decomposition of other aromatic compounds.

**Particulates [163]** Airborne particulate matter varies widely in its physical and chemical composition, source and particle size. PM$_{10}$ particles (the fraction of particulates in air of very small size ($< 10\mu m$)) are of major concern, as they are small enough to penetrate deep into the lungs and so potentially pose significant health risks. Particles are often classed as either primary (those emitted directly into the atmosphere) or secondary (those formed or modified in the atmosphere from condensation and growth). Combustion processes are a major source of fine primary particles, in particular diesel combustion, where transport of hot exhaust vapour into a cooler exhaust or stack can lead to spontaneous nucleation of carbon particles before emission. Secondary particles are typically formed when low volatility products are generated in the atmosphere, for example the hydration of sulphur dioxide to sulphuric acid.

**Oxides [163]** These are formed during combustion processes. Nitrogen oxides form during the high-temperature combustion of fuel in air. The principal source of nitrogen oxides - nitric oxide (NO) and nitrogen dioxide (NO$_2$), collectively known as NO$_x$ - is road traffic, which is responsible for approximately half the emissions in Europe. NO and NO$_2$ concentrations are therefore greatest in urban areas where traffic is heaviest. Other important sources are power stations, heating plants and industrial processes. Nitrogen oxides are released into the atmosphere mainly in the form of NO, which is then readily oxidised to NO$_2$ by reaction with ozone. Elevated levels of NO$_x$ occur in urban environments under stable meteorological conditions, when the air mass is unable to disperse. In the
presence of sunlight, it reacts with hydrocarbons to produce photochemical pollutants such as ozone (see below). NO\textsubscript{2} has a variety of environmental and health impacts. It is a respiratory irritant, may exacerbate asthma and possibly increase susceptibility to infections. Sulphur dioxide (SO\textsubscript{2}) is a corrosive acid gas which combines with water vapour in the atmosphere to produce acid rain. Both wet and dry deposition have been implicated in the damage and destruction of vegetation and in the degradation of soils, building materials and water courses. SO\textsubscript{2} in ambient air is also associated with chronic bronchitis. Power stations burning fossil fuels which contain sulphur are the principal source of this gas.

**Ozone [163]**  Ground-level ozone (O\textsubscript{3}), unlike other primary pollutants mentioned above, is not emitted directly into the atmosphere, but is a secondary pollutant produced by reaction between nitrogen dioxide (NO\textsubscript{2}) and hydrocarbons in sunlight. Ozone can irritate the eyes and air passages causing breathing difficulties and may increase susceptibility to infection. It is a highly reactive chemical, capable of attacking surfaces, fabrics and rubber materials. Ozone is also toxic to some crops, vegetation and trees.
Figure 7.6: Histograms showing the annual distribution of pollutant variables for 2003. For butadiene and nitric oxide, values $\leq 0.001 \mu \text{gm}^{-1} (53\%)$ and $\leq 0.0001 \mu \text{gm}^{-1} (67\%)$ respectively have been excluded.
7.3.4 Pollen

Pollen is a fine powder consisting of microgametophytes (pollen grains), which carry the male ga-
metes of seed plants. Pollen grains come in a wide variety of shapes, sizes, and surface markings
characteristic of the species. Allergy to pollen, known as allergic rhinitis or more commonly, hay
fever. Generally pollens that cause allergies are those which are lightweight and produced in great
quantities for wind dispersal.

Grass pollen data were obtained from the National Pollen Database [160]. Two sites were available
for the Thames Valley, Oxford and Runnymede, each providing a daily pollen count. We used the
data for Oxford. Grass pollen is only present during a short, early summer season. In 2003, this
occurred between 27th May and 2nd August. Figure 7.7 shows the distribution of pollen counts
throughout this summer season. On the majority of days, pollen counts are low, although there are a
few occurrences when they are much higher.

![Figure 7.7: A histogram showing the distribution of pollen throughout the summer of 2003.](image)

7.3.5 Test for Normality of Variables

Figures 7.4, 7.6 and 7.7 indicate that none of the distributions have a normal distribution, this can
be verified by the Lillefors’ Test for normality. This test can be used to test the null hypothesis that
states that a particular distribution is one of the family of normal distributions without specifying
the mean or variance of the normal distribution [164]. The initial distribution function, denoted by
$F(x)$ is assumed to be random. The first step in applying the test is to normalise the sample such
that it has a zero mean and unit standard deviation, $F^*(x)$. An empirical distribution $S(x)$ is then
defined as being a true normalised distribution of zero mean and unit standard deviation. The test
statistic $T$ is taken to be the greatest vertical distance (denoted by “sup” for supremum) between the
cumulative frequency plots for $S(x)$ and $F^*(x)$, where $S(x)$ is defined at the same values of $x$ as $F^*(x)$:
\[ T = \sup_x [F^*(x) - S(x)]. \] (7.1)

The null hypothesis is that the random sample comes from a population with a normal distribution. The null hypothesis is rejected at the approximate level of significance if \( T \) exceeds the value given in statistical tables [164]. This test was applied to all of the explanatory environmental data at the 5% significance level and none of the variables were found to exhibit a normal distribution. The null hypothesis was rejected in each case.

### 7.3.6 Similarity Between Variables

Correlation is used to find the relationship between two variables, and gives an indication of the amount of variance in one that can be explained by the other [165]:

\[
R_f(t) = \lim_{T \to \infty} \frac{1}{2T} \int_{-T}^{T} f(\tau)g(t + \tau)d\tau.
\] (7.2)

\( R_f(t) \) is a time-indexed set of correlation coefficients for a range of time offsets between the two variables. This provides a technique to determine the time lag between two variables \( f \) and \( g \) that gives the strongest correlation.

**Correlation coefficient** Correlation coefficients, \( \rho \), can be calculated for a pair of variables, indicating strength and direction of a possible linear relationship between two random variables [165]. The correlation \( \rho_{X,Y} \) between two random variables \( X \) and \( Y \) with expected values \( \mu_X \) and \( \mu_Y \) and standard deviations \( \sigma_X \) and \( \sigma_Y \) is defined as:

\[
\rho_{X,Y} = \frac{\text{cov}(X,Y)}{\sigma_X \sigma_Y} = \frac{E((X - \mu_X)(Y - \mu_Y))}{\sigma_X \sigma_Y},
\] (7.3)

where \( E \) is the expected value of the variable and \( \text{cov} \) denotes covariance. Since \( \mu_i = E(X) \), \( \sigma_X^2 = E(X^2) - E^2(X) \) and likewise for \( Y \), we may also write:

\[
\rho_{X,Y} = \frac{E(XY) - E(X)E(Y)}{\sqrt{E(X^2) - E^2(X)} \sqrt{E(Y^2) - E^2(Y)}}.
\] (7.4)
\( \rho \) can take any value between \( \pm 1 \). If \( \rho \) is close to 0, it means that there is no linear relationship between the variables. A positive value of \( \rho \) indicates that as one variable gets larger the other also gets larger. A negative value of \( \rho \) implies that as one variable gets larger, the other gets smaller (often called an “inverse” correlation). The square of the coefficient is equal to the percent of the variation in one variable that is related to the variation in the other. A \( \rho \) of .5 means that 25% of the variation is related to the other variation. The correlation distance, \( d \), between the two variables is calculated as \( d = 1 - |\rho| \).

Figure 7.8 shows a dendrogram which represents the similarity between all of the explanatory variables. The correlation distance shown on the x-axis indicates the similarity between the variables. A correlation distance of \( d = 0 \) indicates that the variables are either perfectly correlated (\( \rho = 1 \)) or have perfect inverse correlation (\( \rho = -1 \)). A correlation distance of \( d = 1 \) represents variables which are completely independent. In this hierarchical cluster tree, those variables which have the lowest correlation distance are grouped most closely. It shows that many of the pollutants are closely related. In the figure, the single linkage or nearest neighbour technique has been selected as the measure of proximity. This takes the smallest distance between pairs of objects and ranks the variables based on these distances.

![Dendrogram showing the correlation distances of the explanatory variables.](image)

From this dendrogram, we can observe that many of the pollutants are strongly correlated, not

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\(^2^{Matlab function dend.m.} \)
surprisingly as they originate from the same sources. The clustering identifies three strongly related pollutant groups: benzene derivative aromatic hydrocarbons (benzene, ethylbenzene, toluene, m p xylene, o xylene and butadiene), nitrogen oxides and particulates. None of the other explanatory variables fit into such highly-linked clusters.

### 7.4 Correlations with PEF'

The previous three sections have described the explanatory variables which have been used in the retrospective analysis of environmental conditions. Univariate analysis can be used to identify those individual variables which are associated with day-to-day PEF'. Variables which are not correlated with PEF' can be eliminated from further analysis.

#### 7.4.1 Variable Reduction

Some of the epidemiological studies reported in Table 2.1 analysed the time lag between extremes of weather or pollution levels and presentation at A&E departments. These results indicate that different factors take different periods of time to have their maximum physiological effect on humans. Univariate analysis in the form of auto-regression against PEF' is used with each explanatory variable in turn. This process identifies variables that are not correlated with PEF'. For the variables which are correlated with PEF', it reveals the time lag that gives the strongest correlation.

Each variable was regressed against both morning and evening PEF' values over a range of time shifts from zero to 240 hours. To represent PEF measured twice daily as required in the study a combination of the morning and evening time series (see Figure 7.3) has also been included. Correlations were considered to be significant at the 95% level using the \( \pm \frac{2}{\sqrt{N}} \) criterion where \( N \) is the number of data points in the PEF' time series. As there are 300 points in each time series, a critical value of \( \rho = \pm 0.115 \) is obtained. Figure 7.9 shows four examples of the plots that were produced, encompassing a range of the typical correlations that were found. In each of the plots, the morning PEF' index is shown in blue, and red indicates the evening index. The combination of both morning and evening values is depicted in green. Results are significant at the 95% level if they lie outside of the grey box, which is centred on \( \rho = 0 \).
PM$_{10}$ is identified as being more significant in the morning, acting with a time lag of approximately three days; this would suggest that a high level of particulates takes between two and three days to have its greatest impact on lung function. This corroborates the data in Table 2.1 which indicates a lag of up to 3 days. This effect was explained in personal communication by Dr Dermot Ryan who explains that the micro particles settle deep within the alveoli of the lungs where they irritate the tissue causing inflammation. This inflammation takes approximately two days to develop and restricts the air capacity in the lungs.

There appears to be a fairly immediate response to pollen and temperature where the maximum effect is in evening PEF with a delay of zero hours, the evening is more significant for these variables.
as people are more likely to be outside and affected by the environment in the evening. The temper-  

ture cross correlation shows a 24 hour periodicity indicating the diurnal temperature cycle - cooler  
night-time temperatures are less strongly correlated with a drop in PEF than are day-time temper-  

tures. A plot showing the correlation between PEF' and cloud cover is included as an example of a  
plot for which a variable is not significant.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\tau$ /days</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rain</td>
<td>2</td>
<td>+ 0.04</td>
</tr>
<tr>
<td>Cloud Cover</td>
<td>0</td>
<td>+ 0.06</td>
</tr>
<tr>
<td>Pressure</td>
<td>4</td>
<td>- 0.13</td>
</tr>
<tr>
<td>Pollen</td>
<td>0</td>
<td>- 0.15</td>
</tr>
<tr>
<td>Wind Speed</td>
<td>5</td>
<td>+ 0.05</td>
</tr>
<tr>
<td>Sulphur Dioxide</td>
<td>2</td>
<td>- 0.08</td>
</tr>
<tr>
<td>Humidity</td>
<td>0</td>
<td>+ 0.16</td>
</tr>
<tr>
<td>Temperature</td>
<td>0</td>
<td>- 0.35</td>
</tr>
<tr>
<td>Wind Direction</td>
<td>4</td>
<td>+ 0.07</td>
</tr>
<tr>
<td>Ozone</td>
<td>2</td>
<td>- 0.21</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>3</td>
<td>- 0.11</td>
</tr>
<tr>
<td>PM$_{10}$</td>
<td>3</td>
<td>- 0.17</td>
</tr>
<tr>
<td>Butadiene</td>
<td>0</td>
<td>+ 0.08</td>
</tr>
<tr>
<td>Nitrogen Oxides</td>
<td>3</td>
<td>- 0.07</td>
</tr>
<tr>
<td>Nitrogen Dioxide</td>
<td>0</td>
<td>+ 0.09</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>3</td>
<td>- 0.12</td>
</tr>
<tr>
<td>Benzene</td>
<td>3</td>
<td>- 0.18</td>
</tr>
<tr>
<td>Toluene</td>
<td>3</td>
<td>- 0.14</td>
</tr>
<tr>
<td>o xylene</td>
<td>3</td>
<td>- 0.17</td>
</tr>
<tr>
<td>m p xylene</td>
<td>3</td>
<td>- 0.16</td>
</tr>
<tr>
<td>Ethylbenzene</td>
<td>3</td>
<td>- 0.13</td>
</tr>
</tbody>
</table>

Table 7.1: A table showing the maximum or minimum value of the $\rho$ for each of the 21 variables and  
the time shift (lag), $\tau$, at which this value occurs.

Based on the 95% significant value of ±0.115; rain, cloud cover, wind speed, sulphur dioxide, wind  
direction, butadiene, nitrogen oxides and nitrogen dioxide are determined not to be significant and  
can be excluded from further analysis. The dendrogram in Figure 7.8 is then used to identify clusters  
in the remaining 13 variables. PM$_{2.5}$ and PM$_{10}$ are very strongly correlated in the dendrogram and  
auto-correlation identifies both as being significant with a time lag of three days. PM$_{10}$ is therefore  
chosen as the representative parameter as it had a larger $\rho$, indicating a higher significance. Similar  
analysis identifies benzene to represent the group of aromatic hydrocarbons including toluene, o  
xylene, m p xylene and ethylbenzene.

The final selection of eight explanatory variables, each with their corresponding value of $\tau$, which
were identified as significant at the 95% level using univariate regression analysis is shown in Table 7.2. The maximum or minimum (for an inverse correlation) value of \( \rho \) for each variable is also given.

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \tau )/days</th>
<th>( \rho )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>0</td>
<td>- 0.35</td>
</tr>
<tr>
<td>Ozone</td>
<td>2</td>
<td>- 0.21</td>
</tr>
<tr>
<td>Benzene</td>
<td>3</td>
<td>- 0.18</td>
</tr>
<tr>
<td>PM(_{10})</td>
<td>3</td>
<td>- 0.17</td>
</tr>
<tr>
<td>Humidity</td>
<td>0</td>
<td>+ 0.16</td>
</tr>
<tr>
<td>Pollen</td>
<td>0</td>
<td>- 0.15</td>
</tr>
<tr>
<td>Pressure</td>
<td>4</td>
<td>- 0.13</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>3</td>
<td>- 0.12</td>
</tr>
</tbody>
</table>

Table 7.2: Explanatory variables which were identified as potential factors influencing lung function and their corresponding lag times (\( \tau \)).

### 7.5 Modelling of PEF'

In the previous section potential explanatory variables with associated delays were identified. As these were determined by univariate analysis, no account was taken of the interrelationship between the variables as shown for example in the dendrogram in Figure 7.8. To address this, multivariate regression was used to analyse the data and fit linear models which identify only the most relevant terms, according to criteria to be discussed below. Multivariate models were fitted\(^3\), using multiple linear regression analysis of \( X \) (independent) on \( Y \) (dependent) and minimising the sum of the squared error [166]. A model was constructed that explains PEF' in terms of each of the variables:

\[
PEF' = \alpha^T x + b + \epsilon, \tag{7.5}
\]

where \( \alpha \) represents a set of weights, the superscript \( T \) denotes the transpose, \( b \) is a constant and \( \epsilon \) is the error term. In this model \( x \) is a vector of the selected variables with a delay equal to \( \tau \) for each of the variables in Table 7.2, so that \( x_1 = x_1(t - \tau_1) \), \( x_2 = x_2(t - \tau_2) \), etc...

---

\(^3\)Matlab, function mregress.m
7.5.1 Global Data Set (Median PEF’)

In each case the environmental data which are linked to each median PEF’ reading are those recorded at the time closest to the timestamp of the PEF’ reading either on the day of the reading, or on the appropriate preceding day as indicated by the lag time ($\tau$) in Table 7.2. As each linear model includes the constant $b$, there are 255 different combinations of variables which can be used to model PEF’, eight one-parameter models, 28 two-parameter models and so on:

$$\text{Total combinations} = \sum_{i=1}^{8} {8 \choose i} = 255.$$  

(7.6)

The performance of each combination of variables to model the averaged set of PEF’ is measured using the Root Mean Square Error (RMSE), defined as:

$$\text{RMSE} = \sqrt{\frac{\sum (y - \hat{y})^2}{n-1}},$$  

(7.7)

where $y$ represents the PEF’ to be modelled, $\hat{y}$ is the model derived from the environmental variables and $n$ is the number of data points in the PEF’ time series. The absolute value of the RMSE depends on the variability of the data to be modelled. As an indication of the quality of the model, Normalised Root Mean Square Error (NRMSE) is used:

$$\text{NRMSE} = \frac{\text{RMSE of the model for PEF’}}{\text{Standard deviation of data set to be modelled}}.$$  

(7.8)

A NRMSE value of 1.0 corresponds to estimating PEF’ simply by using the mean across the data set. The lower the value of NRMSE, the better the model.

Multivariate regression was used on the Global Data Set (median PEF’ constructed as described in Section 7.2) for each of the 255 possible combinations of parameters. The re-sampling times of 8am and 10pm were used to select the corresponding environmental conditions attached to each data point. Figure 7.10 shows the error for each possible model for both the morning and evening cases, each model represented by a blue dot. The x-axis gives the number of parameters in the model, from one to nine, with NRMSE shown on the y-axis. The red line on each plot indicates the model with the
lowest NRMSE for each number of parameters.

![Figure 7.10: NRMSE for all possible parameter combinations for all the Global Data Set. Morning results are shown on the left, and evening results on the right.](image)

The morning and evening models with two or more parameters have NRMSE values of around 0.9. The full nine-parameter morning model has an $R^2$ value$^4$ of 0.203, an NRMSE of 0.893, an F-statistic$^5$ of 9.76 and a p-value of $<0.001$ compared to the full nine-parameter evening model which has an $R^2$ value of 0.183, an NRMSE of 0.904, an F-statistic of 8.57 and a p-value of $<0.001$. The morning model thus performs marginally better than the evening model. This may be explained by the fact that there is greater exposure to environmental factors during the day. During that time, there is significantly more variation in individuals’ activities. Some people may stay indoors, others may be working outside.

Table 7.3 shows the order in which the different explanatory variables are included in each model. Once a term has been included in the model, it remains when the order of the model is increased - the best fourth-order model contains all of the terms of the third-order model plus one extra term. It is theoretically possible that this may not be the case. In both morning and evening models, very little improvement is seen after the number of parameters reaches five, indicating that the last four terms are of little significance.

$^4$The square of the correlation coefficient.

$^5$The F-statistic is effectively the ratio of explained variance over unexplained variance [165, 166, 167].
### 7.6 Improving the Model by Making it More Parsimonious

Ockham’s razor is a logical principle attributed to the mediaeval philosopher William of Ockham. The principle states that one should not make more assumptions than the minimum needed, and it can be used to argue for parsimonious models which do not over-fit the data. A parsimonious model is therefore more likely to capture the underlying trend in peak flow values (and hence lung function physiology). Parsimonious models can be obtained using regularisation techniques.

#### 7.6.1 Regularisation

Consider the generic plots for training and testing error in Figure 7.11. These show that if we attempt to fit too many terms, $K$, to the training set, we begin to model the noise in the data rather than the underlying data structure. The optimum number of terms corresponds to the minimum error in the testing set, $K^*$.
Figure 7.11: A schematic illustration of the behaviour of training and testing set errors during a
typical training session, as a function of the model complexity $K$. The goal of achieving the best
generalisation performance suggests that training should be stopped at the point $K^*$ corresponding
to the minimum of the testing set error.

In conventional statistics, various criteria have been developed, often in the context of linear mod-
els, for assessing the generalisation performance of trained models without the use of independent
testing data [168]. These include the $C_p$-statistic (Mallows, 1973 [169]) and the Akaike Information
Criterion (Akaike, 1973 [170]). These criteria take the general form of a prediction error (PE) which
consists of the sum of two terms

\[ \text{PE} = \text{training error} + \text{complexity term}, \]  

(7.9)

where the complexity term represents a penalty which grows as the number of free parameters in
the model grows. Thus if the model is overly simple, the criterion will take a large value because the
residual training error is large, while a model which is too complex will have a large value for the
criterion because the complexity term is large. Figure 7.12 shows how the minimum value for the
criterion reflects a trade-off between the two competing effects.
Figure 7.12: A schematic illustration of the use of a regularisation technique. The modified cost function is the sum of the training error and a penalty term. The model with the lowest cost function - the point $K^*$ is selected.

**Akaike**

The Akaike Information Criterion (AIC) assumes normally distributed errors and the criterion is calculated as follows:

$$AIC = 2K + n\ln(RMSE^2),$$  \hspace{1cm} (7.10)

where $K$ is the number of independent parameters estimated, $n$ is the number of observations and $RMSE$ is the root mean squared error. The model with the lowest value of AIC is selected as the optimum model for the data set.

**Mallows $C_P$**

The general procedure to find an adequate model by means of the $C_P$ statistic is to calculate $C_P$ for all possible combinations of variables and plot the $C_P$ values against $p$, the number of variables used in the model plus one, $(p = K + 1)$. The model with the lowest $C_P$ is selected as the most “adequate” model. The criterion takes the following form:

$$C_P = \frac{RMSE_{res}^2}{RMSE_{full}^2} - N + 2p,$$  \hspace{1cm} (7.11)
where, $RMSE_{res}^2$ is the residual sum of squares for the model with $p - 1$ variables, $RMSE_{full}^2$ is the residual mean square when using all available variables, $N$ is the number of observations. Once again, the model with the lowest value of $C_P$ is selected as the best model of the data.

### 7.6.2 Regularisation Models

When these regularisation techniques are applied to the models of the Global Data Set (median PEF’), they apply a penalty term to each of the models. Again as in Figure 7.10, the model with the minimum NRMSE is selected as the optimum model. Figures 7.13 and 7.14 show the AIR and Mallows $C_P$ versus model order for the optimal morning and evening models (blue line). The red spot represents the model order which is selected by each of the information criteria.

![Graph 7.13](image_url)  
**Figure 7.13:** Model orders selected by Akaike and Mallow’s $C_P$ for the morning model.
These models are presented in Tables 7.4 and 7.5. The first table shows models for the PEF' scale; the full model, with all eight explanatory variables is shown, and the coefficients and significance of each of these variables are included. AIC and Mallow’s $C_P$ models are also included in a similar fashion.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete model</th>
<th>AIC</th>
<th>Mallow’s $C_P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>1.238</td>
<td>1.24</td>
<td>1.244</td>
</tr>
<tr>
<td>Temperature</td>
<td>0</td>
<td>-0.0015</td>
<td>-0.0015</td>
</tr>
<tr>
<td>Humidity</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pressure</td>
<td>4</td>
<td>-0.004</td>
<td>-0.004</td>
</tr>
<tr>
<td>PM10</td>
<td>3</td>
<td>-0.0001</td>
<td>-0.0001</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>3</td>
<td>-0.0007</td>
<td>-0.0006</td>
</tr>
<tr>
<td>Ozone</td>
<td>2</td>
<td>-0.0001</td>
<td>-0.0001</td>
</tr>
<tr>
<td>Benzene</td>
<td>3</td>
<td>0.0016</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pollen</td>
<td>0</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>R-square</td>
<td>0.203</td>
<td>0.196</td>
<td>0.196</td>
</tr>
<tr>
<td>F</td>
<td>9.76</td>
<td>18.93</td>
<td>18.93</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 7.4: Complete, AIC and Mallow’s $C_P$ models for the morning PEF'; $\tau$ corresponds to the time lag for the variable, $\alpha$ is the coefficient for each variable, $\sigma_n$, the standard error and the significance of the term is given by $p$. 
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Table 7.5: Complete, AIC and Mallow’s $C_P$ models for the evening PEF'; $τ$ corresponds to the time lag for the variable, $α$ is the coefficient for each variable, $σ_n$, the standard error and the significance of the term is given by $p$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete model</th>
<th>AIC</th>
<th>Mallow’s $C_P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$τ$</td>
<td>$α$</td>
<td>$σ_n$</td>
</tr>
<tr>
<td>Constant</td>
<td>1.139</td>
<td>0.162</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature</td>
<td>0</td>
<td>-0.0016</td>
<td>0.0003</td>
</tr>
<tr>
<td>Humidity</td>
<td>0</td>
<td>0.0002</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pressure</td>
<td>4</td>
<td>-0.0003</td>
<td>0.0002</td>
</tr>
<tr>
<td>PM10</td>
<td>3</td>
<td>-0.0002</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>3</td>
<td>-0.0000</td>
<td>0.0003</td>
</tr>
<tr>
<td>Ozone</td>
<td>2</td>
<td>-0.0001</td>
<td>0.0000</td>
</tr>
<tr>
<td>Benzene</td>
<td>3</td>
<td>-0.0015</td>
<td>0.0014</td>
</tr>
<tr>
<td>Pollen</td>
<td>0</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

R-square 0.183 1.183 0.163
F 8.57 11.5 30.3
p <0.001 <0.001 <0.001

The above results indicate that Mallow’s $C_P$ criterion appears to be more conservative than Akaike’s and hence selects more parsimonious models. The Mallow’s $C_P$ models also contains the more significant terms as expressed by the individual $p$ values, and the overall F-Statistics of the models are superior. In both morning and evening models, temperature is identified as the most significant explanatory variable.

Two models have been identified. These represent the best parsimonious models which explain the variance in the Global Data Sets (median filtered). These models are shown below:

**Morning Model**

$$PEF' = 1.244 - 0.0015 \text{Temp} - 0.0004 \text{Pres} - 0.0006 \text{NO} - 0.0001 \text{O}_3,$$

(7.12)

**Evening Model**

$$PEF' = 1.139 - 0.0018 \text{Temp} - 0.0003 \text{Pres}.$$

(7.13)
7.7 Assessing Global Model Performance

Figure 7.2 showed the two median averaged Global Data Sets that were created from the patients’ PEF’ data. These resulting morning and evening time series have been modelled earlier in this chapter using environmental explanatory variables. Figures 7.15 and 7.16 show the result of the models described in Equations 7.12 and 7.13. The NRMSE for the morning model is 0.897 and in the evening model, the NRMSE is 0.904.

![Environmental model for the morning median averaged Global Data Set.](image)

Figure 7.15: Environmental model for the morning median averaged Global Data Set.
The following two Figures show how the different terms in Equations 7.12 and 7.13 contribute to the overall model. Figures 7.17 and 7.18 show each individual term of the two models recalibrated to zero mean for comparison. The modelled data set is also shown in the figure.

Figure 7.17: The contribution of each of the terms to the Morning model - Equation 7.12.
Although these models provide relatively good fit for the Global Data Sets, they fail to capture individual variability. Figure 7.19 shows the global model for the morning PEF’ and the recorded PEF’ for two patients (Note the extended y-axis with respect to Figure 7.15). The global model is a very poor fit to these individuals’ PEF’ data as environmental dependencies vary from patient to patient.

Figure 7.18: The contribution of each of the terms to the Evening model - Equation 7.13.

Figure 7.19: The global model and data recorded from two individual patients.
7.8 Dependencies Vary from Patient-to-Patient

In Tables 7.4 and 7.5, temperature was identified as the most significant variable in both morning and evening models. In each case a negative coefficient was identified: as temperature increases, PEF' decreases. However, part of our motivation for this modelling work was the observation that one of the Isle of Man patients had low PEF' values in cold weather and higher values in warmer weather. For this patient, the PEF' dependence on temperature was positive.

In order to investigate individual dependencies on temperature, univariate temperature models were fitted to the morning time series for each of the patients. Sixteen patients were identified as having models significant at the $P < 0.001$ level. The distribution of the temperature coefficients is shown in Figure 7.20. Seven patients have a positive dependency and nine patients have a negative dependency. The negative dependencies which have a larger magnitude dominate in the global model.

These findings are confirmed by Figure 7.21 which shows the PEF' data for two individuals. The left-hand figure shows the data for Patient A in Figure 7.19 and the right-hand figure corresponds to Patient B. In the left-hand plot PEF' is positively correlated with temperature and in the right-hand plot PEF' is negatively correlated with temperature.

![Figure 7.20: Temperature coefficients for the 16 patients exhibiting a statistically significant temperature dependency.](image-url)
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These results explain how environmental factors can affect individuals in different ways. Although a global model does explain some of the variation in the Global Data Set, a model based on the median filtered data to arrive at an “average model” for people with mild-to-moderate asthma, is inappropriate to model accurately an individual with mild-to-moderate asthma.

7.9 Individual Models

The collected patient data from all 58 patients exhibits considerable variability. When it is resampled to obtain the median smoothed data set, the baseline PEF' level is around 0.83. Some patients such as the one whose data are shown in Figure 7.19 have a higher mean PEF' so a global “average” model is a poor approximation. Section 7.8 discussed how reactions to environmental conditions may vary from patient to patient, and this suggests the use of individualised models which should improve on the poor baseline fit exhibited by the global average model for some patients.

7.9.1 Selecting Training and Test Sets

In order to investigate environmental affects on the individual time series, the data from each patient are split into training and test sets. This process is complicated by the desire to include as much of the full range of environmental parameters as possible into both each set. The optimal method of splitting the data would be to collect training data throughout an entire year, and use data from a
A system of allocating alternate points in the PEF’ time series to either training or test set was initially investigated. However, this results in the most recent data point being excluded from the calculation of the trend, inappropriate when environmental effects appear to work over short time periods (Table 7.2). A compromise method was therefore used instead which allocates blocks of 50 consecutive observed PEF’ values to training and test sets alternately. These blocks are approximately 50 days long if the patient regularly records their PEF’ (morning and evening time series separated). This ensures a full range of environmental conditions, and provides consecutive daily data with the exception of edge effects at the start and end of each block of data. At this stage three of the 58 patients were excluded from the analysis as they had insufficient data (fewer than 60 points).

### 7.9.2 Results of Individual Models

Individual models using the environmental factors identified in Section 7.6.2 were trained for each of the 55 patients in turn. The time lags determined in the univariate analysis of Section 7.4 were retained, however, multivariate regression was used to fit the coefficients to that individual’s data. The data were not resampled and environmental variables were attached to each PEF’ reading as before.

Figure 7.22 illustrates how the individual model produces a much better fit to the recorded data, in this figure model predictions for the test set are shown in red, and, for clarity, the model fitted to the training data is in green.
The NRMSE of the test set data for the patient shown in Figure 7.22 is 1.085 and the model for the morning PEF' is:

\[
PEF' = 0.1200 + 0.0012 \text{Temp} + 0.0007 \text{Pres} - 0.0003 \text{NO} + 0.0004 O_3.
\]  

(7.14)

Note that the temperature coefficient is positive in contrast to the global model of Equation 7.12.

A NRMSE value greater than 1.0 still indicates a poor model, which performs worse than using the mean of the data set. Histograms of the NRMSEs for each of the individual patient models are shown in Figure 7.23. The NRMSE terms from the morning models, shown on the left-hand side are overall better (mean = 1.143) than for the evening models (mean = 1.165), shown on the right. Eleven individuals have an NRMSE of less than 1.0 in the morning and eight have an NRMSE of less than 1.0 in the evening.
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Figure 7.23: NRMSE of models fitted to individuals containing only the terms from the models given in Section 7.6.2. Morning results are shown on the left, and evening results on the right.

The models are clearly still performing poorly as illustrated by Figure 7.24. This figure shows, for another individual, the recorded PEF' values in black and the predicted values using an individual model in red.

\[
PEF' = 1.519 - 0.0011 Temp - 0.0007 Pres - 0.0003 NO + 0.0000 O_3.
\] (7.15)

This individual has a non-stationary baseline PEF' and it is clear from the figure that the resulting model does not track the underlying trend in the patient. The predicted PEF' fails to follow the underlying trend in the recorded data and the figure suggests that some form of memory should be included to provide the model with an indication of the patient’s recent lung function history.
CHAPTER 7. MODELLING THE EFFECTS OF THE ENVIRONMENT ON ASTHMA

7.10 Conclusions

In this chapter, a Global Data Set (median PEF') has been created and used to identify, using multivariate regression analysis, eight environmental factors which potentially influence asthma symptoms. For each environmental factor, an associated delay term has been found in the range of zero to four days indicating the time duration required for these factors to have their maximum effect. The chapter has also investigated the feasibility of having one global model which could be applied to all people with mild-to-moderate asthma. It was concluded however, that it is not possible to produce a global model because environmental factors affect individuals in different ways.

Individual models were trained using blocks of 50 consecutive data points and assessed using an out-of-sample test set composed of the remaining blocks of 50 data points. These models gave a lower NRMSE test error than the global models. However, individual models are not able to track the underlying trend in patients who do not have a stationary baseline level. As this is the case for many of the patients in the Thames Valley Study, we next investigate models with memory which might allow identification of the short-term environmental effects within longer-term trends.

Figure 7.24: Modelled PEF' for an individual without a stationary baseline. This model is a poor predictor of the recorded data.
Chapter 8

Prediction of an Individual’s Lung Function

In the previous chapter, a number of environmental factors were identified as having an effect on the lung function of a global population of people with mild-to-moderate asthma. It was shown that environmental factors have contrasting effects on individuals, for example the positive and negative correlations with temperature, shown in Figure 7.21. However, it was also found (Figure 7.24) that prediction errors from individualised environmental models remain high because underlying trends in the peak flow are not accounted for solely by environmental factors.

Important factors, other than environmental, which govern an individual’s lung function on a particular day are their use of medication and their normal baseline level. In Chapter 5, an age correction technique was introduced and used on all patients to ‘adjust’ for the effects of ageing on the PEF’ values of both adults, and more significantly, children. There is no satisfactory method to confirm the effectiveness of this adjustment technique, although the median PEF’ data maintains an approximately constant level throughout the study (Figure 5.11). Many patients did not exhibit stationarity in their PEF’ time series, for example the patient whose data are shown in Figure 7.24 and for whom the baseline PEF’ values are highly variable throughout the study.

In this chapter, an approach is taken whereby the observed PEF’ is assumed to consist of two components; the underlying trend and the remaining ‘noise’. Using the terminology of Tukey [171] we can postulate:
data = fit + residual. \hfill (8.1)

Here the ‘fit’ will be the filtered PEF’, which has been smoothed to find the underlying trend, and the ‘residual’ will consist of the remainder once the ‘fit’ has been subtracted. The residual may contain short-term fluctuations which could be partly explained by short-term environmental factors and/or noise in the data.

In Section 5.6.1, 35 patients were identified as being stable, with a standard deviation of PEF’ <0.1. It is those patients whose data are analysed in this chapter, as a lack of stability indicates poorly-controlled asthma and the absence of a clear trend in the PEF values. Once again, morning and evening data are separated, and the two time series treated independently.

### 8.1 Exponentially Weighted Moving Average Filter

The standard moving-average filter operates by treating each data point in a moving window as being equally important when calculating the filtered value. In dynamic systems, such as human physiology, the most recent values tend to reflect better the state of the process. Filters which place more emphasis on the latest data are often more appropriate for such systems.

The Exponentially Weighted Moving Average (EWMA) Filter is the best known filter of this type [172], and can be expressed as:

\[
y_k = \lambda y_{k-1} + (1 - \lambda)x_k, \tag{8.2}
\]

where \(y_k\) is the filtered value of \(x_k\), \(y_{k-1}\) is the previous value of \(y_k\) and \(\lambda\) is the filter coefficient which determines the degree of filtering. When \(\lambda \to 1\), \(y_k \to y_{k-1}\), in which case all the data are heavily filtered, the most recent measurement not playing a part in the calculation of the average. As \(\lambda \to 0\), \(y_k \to x_k\) and virtually no filtering is performed.
8.1.1 Training the Filter

A smoothing filter suitable for the data of all patients with mild-to-moderate asthma is desired. There is only one parameter, $\lambda$, which needs to be optimised in an EWMA filter. In this chapter, this is done as a pre-processing step using the whole data set.

It is not possible to optimise a smoothing filter using all the data itself, as the minimum error with respect to the original data will occur when no filtering takes place. This problem can be overcome by borrowing from Kalman Filtering the result that the best predictor is also the best filter [172, 173]. All the data $[x_1, x_2, \ldots, x_{k-1}]$ are used to predict a value $\hat{y}_k$, according to the equation:

$$\hat{y}_k = \lambda y_{k-1} + (1 - \lambda)x_{k-1}, \quad (8.3)$$

such that the error in $|y - \hat{y}_k|$ is minimised with respect to $\lambda$. This process is repeated using the data from all 35 patients with $\lambda$ values from 0 to 1. The NRMSE values calculated in each instance are averaged across all patients and the value of $\lambda$ corresponding to the minimum error is selected.

Figure 8.1 shows the mean prediction error calculated across all 35 patients using both the morning and evening PEF’ data. Not surprisingly, the results are very similar and minimum NRMSE values of 0.960 and 0.965 corresponding to $\lambda$ values of 0.66 and 0.68 are obtained for morning and evening PEF’ respectively.

![Figure 8.1: Prediction error averaged across all patients identifies optimal values of $\lambda$, 0.66 in the morning and 0.68 in the evening.](image)
8.1.2 Filter Time Constant

The time constant of an EWMA filter can be expressed in terms of the sampling interval \( T \) as:

\[
\text{Time Constant} = -\frac{T}{\ln(\lambda)}.
\]  

(8.4)

As the sampling period is one day (morning and evening data have been separated), this time constant is calculated as:

\[
\text{Time Constant} = -\frac{1}{\ln(0.66)} \approx 2.5\text{days},
\]  

(8.5)

which indicates that data over the past two to three days are significant in the underlying trend. This is demonstrated in Figure 8.2 which shows the filter’s response to a unit step input.

Figure 8.2: The response (red) of an EWMA filter with \( \lambda = 0.66 \) to a unit step change at day 10 (blue).
8.2 Using an Individual EWMA Filter to Calculate the Residual

Figure 8.3 shows the PEF' data for a typical adolescent patient. The red line shows the underlying trend which is fitted to the original time series. This patient’s asthma appears to improve throughout the study, as demonstrated by an increase in baseline level (Figure 8.3) and a decrease in variability (Figure 8.4).

![Graph showing smoothed trend fitted to observed PEF'](image)

Figure 8.3: Smoothed trend fitted to observed PEF' (NRMSE 0.556).

The residual which contains the short term variability is obtained by subtracting the trend from the observed data. The residuals for this patient are shown in Figure 8.4, and Figure 8.5 shows how these residuals are normally distributed with zero mean. This variability comes from a combination of effects; measurement error, error due to timing of medication use with respect to measurement, diurnal variability and environmental effects. With the exception of environmental effects, these effects can be assumed to be random for an individual.
8.3 Variability Index of Residuals

In Section 5.6.2, a sliding index of variability was introduced and in Figure 5.21 it was demonstrated that the standard deviation of PEF' averaged across all patients decreased throughout the study. The
same analysis is applied to the residuals of the 35 stable patients analysed in this chapter. Figure 8.6 shows how the standard deviation of the residuals also decreases throughout the study, an indication that control has improved as a result of using the telemedicine system. Figure 8.7 is similar, but is scaled to show the reduction in residual variability with respect to the start of the study for each patient. The dashed red line shows the trend which reduces by approximately 23%, this value is lower than the 30% reduction in PEF' variability found in Chapter 5, but indicates the same general trend. The number of patients contributing to the figure is also shown at a number of points.

Figure 8.6: The standard deviation of the residuals averaged across all 32 stable patients reduces in the course of the study.
Figure 8.7: The standard deviation of the residuals averaged across all 32 stable patients reduces in the course of the study, the data are shifted to measure time since each patient enrolled in the study.

8.4 Environmental Modelling of the Residual

The residual values of PEF for each patient, such as shown in the example in Figure 8.4, contain the short-term information in the time series. The majority of this will be measurement noise, which is recognised as being significant in the home measurement of PEF as a result of poor manoeuvre technique (Section 2.4.3), and the variability of the timing of measurement with respect to use of medication (Section 5.6.1). Day-to-day effects caused by influential environmental variables may, however, also be present in these residual PEF time series.

8.4.1 Training the model

Here we set out to investigate if any of the variability in the residual component of the PEF time series can be attributed to environmental factors. In Section 7.4 global PEF indices were used and univariate correlations were employed to find time lags for each of eight explanatory variables which had been identified from univariate analysis as being significant. In keeping with Section 7.9, the time lags (τ) identified by the global analysis have been retained in these individual models.

Once again, multivariate linear regression is used to identify linear models capable of explaining
residual variability. Models consisting of all eight environmental factors from Chapter 7 (temperature, humidity, pressure, nitric oxide, ozone, PM$_{10}$, benzene and pollen) are presented in Table 8.1.

Figure 8.8 shows a flow chart detailing the steps through which these models are obtained.

1. The recorded data are smoothed to extract the underlying trend.
2. The residual time series is created by subtracting the trend from the observed data.
3. The training and test sets are created by allocating alternative of blocks of 50 data points to the training and test sets.
4. Multivariate regression is used to fit models which include a constant and the eight environmental variables delayed by their associated time lags (Table 7.2).
5. The model is assessed using the out-of-sample data in the test set. A value of NRMSE is calculated to quantify model performance.

Figure 8.8: The steps used to decompose the PEF$^+$ data and identify environmental factors.
Similarly to Section 7.9, three patients are excluded due to insufficient data. The mean NRMSE averaged across the 32 patients for the testing set for both morning and evening series is in each case greater than 1.0, indicating that across all patients, environmental factors do not explain the residual \( \text{PEF}' \) components. However, in six of the 32 patients, the test NRMSE is less than 1.0, suggesting that in these particular cases, some of the variability can be explained by external environmental factors, although the improvement brought about by environmental modelling is only marginal.

<table>
<thead>
<tr>
<th></th>
<th>Training Set (NRMSE)</th>
<th>Testing Set (NRMSE)</th>
<th>No. less than 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>Min</td>
<td>Max</td>
<td>Mean</td>
</tr>
<tr>
<td>Morning</td>
<td>0.858</td>
<td>0.981</td>
<td>0.945</td>
</tr>
<tr>
<td>Evening</td>
<td>0.848</td>
<td>0.992</td>
<td>0.950</td>
</tr>
</tbody>
</table>

Table 8.1: Errors for modelling of residuals using all eight environmental factors.

Figure 8.9 shows the model and residuals calculated from the recorded data for the individual whose data is shown in Figure 8.4. The model is,

\[
\text{PEF}' = 0.3904 - 0.0006 \, \text{Hum} - 0.0003 \, \text{Pres} - 0.0004 \, PM_{10} + 0.0012 \, NO + 0.0002 \, O_3 - 0.0061 \, \text{Benz}, \quad (8.6)
\]

Temperature and pollen do not feature in the model, their coefficients are zero. For this particular patient, the full (eight terms) environmental model explains some of the variability. In this case, the NRMSE for the training set \( \text{PEF}' \) residuals is 0.918 and, for the test set, 0.994. The gap in the data corresponds to data which was allocated to the training set.
8.5 Using Information Criteria to Reduce Model Complexity

In the previous chapter, Mallow’s $C_P$ was used to obtain parsimonious models. The residual models of Section 8.4.1 contain all of the environmental terms. As before variables which are not significant are retained in the model which consequently over fits the training data to the detriment of performance on the test set. Mallow’s $C_P$ can again be used to reduce the number of terms in the residual models and select only the most significant environmental factors for each individual. When these more parsimonious models are applied to the test set, many more individuals are found to exhibit environmental dependency. Figure 8.10 shows how Mallow’s $C_P$ applies a penalty term to larger models resulting in small models being selected. In these cases the models consist of a constant and one environmental variable.
Table 8.2 shows the results when these lower-order residual models are used. The mean NRMSE for the test set is now reduced for both morning and evening series. As with earlier results, evening PEF' values are less well modelled. The number of patients who now show improvements with residual modelling has increased to 13 in the morning and nine in the evening.

<table>
<thead>
<tr>
<th>Model</th>
<th>Training Set (NRMSE)</th>
<th>Testing Set (NRMSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>Morning</td>
<td>0.945</td>
<td>0.996</td>
</tr>
<tr>
<td>Evening</td>
<td>0.945</td>
<td>0.997</td>
</tr>
</tbody>
</table>

Table 8.2: Errors for PEF' residual modelling where parsimonious models are used to reduce model complexity.

The parsimonious form of Equation 8.6 for the same individual is now,

\[ PEF' = -0.0026 + 0.0009 \text{ NO}. \]  

(8.7)

Table 8.3 summarises the results found by the parsimonious models fitted to the residual PEF' values. This table identifies the environmental variables which were identified for each of the patients individually for each of the 13 patients for whom the test NRMSE is less than 1.0. In each case, the models were very much simpler than those in Section 8.4.1 as they contain only a constant and one
explanatory variable, although the latter varies from patient-to-patient as shown in Table 8.3.

<table>
<thead>
<tr>
<th>Model</th>
<th>Temp</th>
<th>Hum</th>
<th>Pres</th>
<th>PM_{10}</th>
<th>NO</th>
<th>O_3</th>
<th>Benz</th>
<th>Poll</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Evening</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 8.3: Total number of individuals found to be dependant on environmental factors and the corresponding number of patients for each explanatory variable.

For approximately one third of the patients, the residual time series has a detectable correlation with one or more of the eight explanatory environmental variables identified in Section 7.4. In contrast with Chapter 7, temperature is no longer identified as the most important environmental factor. Nitric oxide, which was found in Figure 7.9 to be the second most significant explanatory variable in the morning (6 out of 13), is now the most significant variable and humidity is the most significant one in the evening (3 out of 9).

Temperature is a seasonal variable consisting of short-term fluctuations (approximately five days as shown in Figure 7.9) superimposed on a slowly changing annual cycle. The EWMA filter used in this analysis to remove the underlying trend from the data has a time constant of less than three days, which will significantly attenuate the influence of the temperature cycles. This is a likely explanation for the lack of temperature effect identified in this analysis.

The evening models tend to be more dominated by climatic variables, especially temperature and humidity, which were identified in Chapter 7 as not having a time lag. Patients are more likely to be outdoors during the day and hence influenced by environmental conditions in the evening.

Although 80% of people with asthma are known to display symptoms of allergic rhinitis (hay fever) [174, 175], pollen has not been identified as being significant for any patient. This is caused by the short length of the pollen season and hence the lack of sufficient pollen dependent data in the overall training and test sets to affect the models.

An NRMSE slightly below 1.0 does not indicate as good a model as one would wish. However, as this study used retrospective analysis without controlled environmental conditions, it still proves that there is some information contained within the environmental data. Ideally a follow-up study designed to measure environmental effects would significantly improve these results.
8.6 Combining the Trend and Residual Model

The model of the residual PEF’ time series can be added to the smoothed trend to show how this new model represents the observed data. Figure 8.11 shows the residual PEF’ model added to the PEF’ trend, for the patient whose PEF’ data was originally shown in Figure 8.3. The test set NRMSE for the residual PEF’ values has been reduced to 0.986 through the use of the parsimonious model of Equation 8.7. The NRMSE for the combined trend and residual models is 0.620.

![Figure 8.11: Figure showing the combined residual model and trend.](image)

8.7 Conclusion

In this chapter, we have introduced the concept of dynamics in the model and the EWMA filter has been used to remove the temporal component of the PEF’ time series. Although seasonality is likely to mean that temperature has an effect on the smoothed trend, it has been assumed that the trend is not influenced by environmental conditions, being primarily dependent on the use of medication and the general health of the patient. The residual containing the short term variations has been used to look for fluctuations caused by environmental factors.

Approximately one third of the patient group has been shown to have a residual which is influenced by environmental factors. This gives a clear indication that the use of explanatory environmental
factors such as temperature, humidity and PM$_{10}$ could help to support patients in the control of their asthma.

However, it should be noted that the Thames Valley Study was not designed for this type of analysis, being set up as an observational study with no intervention based on peak flow readings recorded by the patients. Many of the patients were badly controlled (Section 5.6.1) during the study and no attempt was made to stabilise them. The data were also collected for only a short period of time, varying between three and nine months. This is not sufficient to identify all of the seasonal effects. Ideally one year’s worth of data would be used as a training set with data from subsequent years being used to test the prediction algorithms.

In Chapter 5 we discussed how the PEF’ variability was much higher than would be expected. Much of this has already been attributed to the random nature of the measurement time with respect to the use of medication. There is therefore a high level of variance in the data and so many of the second-order environmental trends may well be masked by this noise. However, it is clear that patterns do exist and an appropriately designed study should identify them more reliably.
Chapter 9

Conclusions

In Chapter 2 it was stated that asthma is the most common long term childhood illness. The literature also indicates that self-management has been shown to be beneficial: improved patient empowerment through better education and clinical guidance leads to a slowing down of the disease progression. However, as discussed in Chapter 2, there are many factors which are known to affect asthma and for many patients it is impossible to regulate their treatment regime according to measured lung function and symptoms, diurnal variability and local environmental conditions.

Previous work in the field of telemedicine has not produced any substantial evidence to support the use of remote monitoring and support. Patients and clinicians have generally been open to such technologies and although greater use of technology in the delivery of clinical care seems inevitable, as yet, current telemedicine systems require too great a time commitment for continued daily use by all but the most dedicated patients. The requirement for a more patient friendly system which is easily incorporated into daily life is clearly evident.

The Oxford Telemedicine System has been designed to fulfil this role. Using Java software running on third generation mobile phones, the system relies on a technology with which many patients are already familiar. Connection to a remote server provides real-time communication and once data have been received at the server, many tailor made algorithms can be employed to monitor and highlight trends on the patients’ condition. The benefit of using a web-based interface means that clinicians are able to log-in to a secure web page from any location to access and review their patients’ data.
CHAPTER 9. CONCLUSIONS

Although originally designed as a generic architecture to be adapted to a wide range of long term conditions, the Oxford Telemedicine System has been described in this thesis in the context of asthma. The use of the telemedicine system in the two clinical studies described in Chapters 5 and 6 has not only confirmed some of the findings from other asthma studies, but also added new knowledge to the field of asthma self-management, beyond the analysis of efficacy and patient perception of the new technology.

9.1 Summary of Asthma Management

As described in Chapter 2, the normal PEF of all individuals varies considerably. This is primarily as a function of their body size and general levels of fitness. A typical fifty year old male, 1.8m tall would have a maximum PEF of approximately 600 lmin$^{-1}$ (Table 5.3) and exhibit a diurnal variability of around 8% [86]. Individuals with asthma will typically have a similar peak level of PEF, however, their condition is characterised by much higher variability. Diurnal variability can be as much as 20% amongst people with asthma [32]. Amongst patients enrolled on the Thames Valley Study, 44% exhibited a significant diurnal variability (Table 5.6). Figure 5.18 shows that approximately 50% of the Thames Valley patients had a PEF standard deviation of greater than 10%, which shows that the variability of many people with asthma is greater than would be expected if caused by diurnal variability alone.

The primary focus of management is the prevention of exacerbations, episodes where PEF drops below 50% of an individual's personal best. This is a considerable decrease in PEF which can easily be measured with spirometers, devices which typically have an accuracy of around 10% (3.s.d). Low readings can be generated as a result of either poor technique or an exacerbation. No alerting algorithm was used in the Thames Valley study, and so there was no record of clinical intervention to enable analysis of exacerbations. In the Isle of Man study, email alerts were sent to the clinicians, but none of the patients (who were generally well-controlled) experienced an exacerbation during the study.

There is a great deal of anecdotal evidence that environmental factors can cause breathing difficulties amongst certain people with asthma. This is supported by analysis of presentations to Accident and Emergency Departments (Table 2.1). Chapter 7 has shown that individuals react differently
to various stimuli and that global regression analysis of environmental factors is of limited use in predicting PEF. Models tuned to an individual's data offer better prospects of predicting PEF on a day-by-day basis. However, measurement error of up to 10% in the spirometer and the difficulty of acquiring environmental data recorded at the location of each individual limit the power of these models in their ability to track variations caused by weather and pollutants.

9.2 Asthma Management - Lessons Learnt

The two studies described in this thesis only included patients with mild-to-moderate asthma. The most surprising observation from analysis of the data is the high level of variability in PEF shown by the patients. In the Thames Valley Observational Study (no clinical intervention), variability was higher than clinicians had expected, indicating a poor level of control within the study population. In contrast, most patients in the Isle of Man Study had very stable asthma, which has been attributed to unrepresentative patient selection by the local clinicians.

Another important lesson learnt from the Thames Valley Study was the requirement to ensure that patients record their PEF at a time consistent with taking medication, preferably before. Once inhaled steroids have been taken, the time delay until the PEF is recorded will alter the value of PEF as the drugs take effect. Ideally the PEF value is used to guide the amount of inhaler, if any, to be used. This led us to propose the feedback loop based on a measure-evaluate-act strategy which was implemented in the Isle of Man Study. The phone software guided users to measure their PEF, assess their symptoms and evaluate them in the context of their recent peak flows, before deciding how much medication to take.

T-tests in Section 5.7 showed a strong diurnal variability in some patients, with examples of both morning and evening PEF being higher. This indicates an independence between morning and evening PEF. 2am and 2pm were chosen as the most appropriate cut-off times to distinguish between morning and evening time series.

If patients, particularly children, are monitored over a long time period, their lung capacity will change as they mature. With time, the original baseline PEF level will no longer accurately reflect an individual’s best PEF. Using models of PEF based on height and age, and models of child growth with age, it was possible to model the increase in baseline values with time.
In order to define action points for the management plan, a baseline value of PEF is required, which must be obtained when the patient has good control of their asthma. Reddel determined that it takes approximately two to three weeks for a patient to stabilize following treatment with steroids [58]. Consequently a training period of approximately four weeks is suggested to determine a baseline level for an individual patient. If analysis of the patient’s PEF demonstrates them to be poorly controlled, (for example the $\frac{s.d.}{mean} \geq 0.1$, criteria of Chapter 5) high-dose steroids will be prescribed to instigate control. The patient will then be required to go through another “training period” to establish the baseline PEF level.

Although the consensus in the literature appears to favour management of asthma based on PEF (or other spirometry value), there is also evidence that management can be guided equally well using symptoms [33, 68, 108]. Analysis of the Isle of Man Study data concluded that the Royal College of Physicians’ RCP3 questions which require three yes/no answers, did not give provide sufficient variation to provide a useful daily assessment of asthma symptoms. The RCP3 questions were replaced with a simple scoring system based on the main symptoms and designed to provide more precise information about the symptoms. However, the few well-controlled patients in the Isle of Man Study did not provide sufficient data associated with poor symptoms to evaluate the potential use of symptom based management for asthma on a phone.

9.3 Technological - Lessons Learnt

Sixty-nine percent of patients in the Thames Valley Study were satisfied or very satisfied with the use of mobile phone technology to assist the management of their asthma. Despite a few teething problems, clinicians and patients agreed that this technology did have a place in the management of asthma.

The use of technology to assist the management of patients over long time periods did introduce some new challenges to the processing of the data. Firstly each individual patient has a different baseline level of PEF, and so comparisons between patients to quantify improvements or assess control are not straightforward. To overcome this, all data for each patient were scaled to be a percentage of that patient’s personal best. This enabled all patients to be directly compared, making it easier to implement clinical action plans.
Compliance with the mobile phone system (80% of patients providing two readings a day in the Thames Valley Study) was shown to be very good when compared to that achieved with paper-based diaries. This is a very important fact as good control of asthma requires good concordance with medication, which is strongly associated with high compliance in self-monitoring. Novelty factor was an important factor in the high compliance initially achieved.

In the Thames Valley Study, the technology was not designed to give any significant improvements in control. The study was meant to be an observational study with no clinical intervention as a result of the patient self-monitoring. If the poor control displayed by most patients had been acted upon and treated by clinicians, clearly the patients would have improved. However, even without such an intervention the mean use of reliever inhaler across all patients decreased by 0.6 puffs per 12 hours from the start to the end of the study. In contrast, the Isle of Man Study was designed to include a medical intervention if required, but as the patients selected by the clinical team were well controlled from the start, there was little room for improvement.

9.4 Environmental Aspects

There have been several studies which have modelled asthma epidemics and admissions to Accident and Emergency visits caused by environmental factors [41, 42, 43, 44, 45, 46, 47]. Thunderstorms, cold weather and pollution have all been identified as hazards to people with respiratory conditions. The ability to predict hospital admissions is very useful, but it is much better to help prevent an exacerbation in the first place. Global analysis of the Thames Valley Study data identified eight environmental variables which may be linked to the PEF variability exhibited by patients on a day-to-day basis. When regression models were applied to the data, it was found that individuals react in different ways to the various environmental variables. In addition, the underlying temporal structure in the PEF data throughout the year could not be explained by environmental factors. As a consequence, Exponentially Weighted Moving Average filters were used to remove the underlying trend from each patient’s PEF time series, thereby producing a residual PEF time series with short-term fluctuations. Mallow’s $C_p$ criteria was used to fit parsimonious models based on the eight selected environmental variables. For one third of the patients, the use of a residual model decreased the prediction error in the test set, indicating the influence of the environmental variables.
Given the lack of control amongst patients in the Thames Valley Study this is a promising result. A model adapted to an individual patient could easily be implemented on the telemedicine server to provide real-time advice based on weather, pollution and pollen forecasts.

9.5 Future Work

In Chapter 6, a protocol was used in which the first 50 readings (≈4 weeks) from patients were analysed to assess the initial level of asthma control and define baseline PEF levels from which action points for the management regime could be determined. Patients who were not well controlled were asked to return to the clinic so that they could be prescribed steroids to improve control. In accordance with Reddel [58], another training period of 50 readings would then be required to assess the new level of control and determine baseline PEF levels. A patient population could have their asthma stabilized as a results of their initial use of the mobile phone technology, before being asked to self-manage after that.

This strategy is proposed in a research proposal submitted to Asthma UK in November 2006, to start in November 2007. The proposal is for a six-month single blinded randomised controlled trial which will compare twice-daily monitoring of PEF and symptoms using a mobile phone with the use of a paper based diary to record the same information. Three hundred patients with poorly-controlled asthma from Primary Care practices will be enrolled and given an electronic peak flow meter. Half of the patients will be asked to record data in a paper diary, the remaining patients being given a mobile phone and access to their data through a personal secure website. Data will be reviewed by a researcher blinded to allocation at baseline, three months and six months. The primary outcome will be the change in asthma control between baseline and six months.

As no gold standard exists to define an asthma exacerbation, detection of exacerbations is very difficult. It is not possible to define an exacerbation based on PEF or symptoms, the telemedicine system used to detect the start of the exacerbation is also used to drive the intervention which will prevent the exacerbation from developing. The best approach would be to study PEF data from a large population and to look for precursor events such as increase in diurnal variability [32, 89], in the days leading to hospitalization and/or unscheduled GP visits. However, such a trial is probably too expensive because of the required sample size.
Further work to model environmental effects would also require a large study with several hundred patients, again focusing on people with more severe asthma. Ideally the study would last for 24 months for each patient with the full range of environmental conditions assessed for the first year and the second year’s data used as a test set. A sufficiently large data set would facilitate investigation of non-linear effects and enable an extension of the simple proof-of-concept models presented in this thesis.

9.6 A Future Telemedicine System?

The purpose behind this work was to investigate a mobile phone based telemedicine system and its potential benefits for people with asthma. To improve health, such individuals need to maintain steady control of their symptoms through effective management using a range of preventative inhaled steroid drugs. The most important question when considering a future, sustainable telemedicine system for asthma self-management is: “Is asthma a serious enough condition to justify full-time monitoring?” For patients with mild-to-moderate asthma, the answer is probably no. There are cases where full-time monitoring is invaluable, for example in trials of new inhalers or corticosteroids. However, as concluded by Yoos [71], twice-daily monitoring is simply too burdensome for the majority of asthma patients and would not provide sufficient benefits to maintain compliance. Two key conclusions of the analysis presented in this thesis are that many people with asthma exhibit worse control than expected, and that well-controlled patients remain stable and controlled. This suggests two potential telemedicine systems: the first a complete system used to monitor patients on a daily basis for diagnosis, stabilisation and characterisation of asthma; the second system will be much less intrusive and used on an occasional basis, to support self-management when subject to severe symptoms.

9.6.1 Full Version of a Telemedicine System

When an individual is first suspected of suffering from asthma, diagnosis will be greatly improved by collecting both symptoms and spirometry data on a twice-daily basis. A telemedicine system such as the one used in the Isle of Man Study offers unique opportunities to collect data that can be used not only to diagnose and to characterise asthma, but also, using the web site, to provide patients with a
greater ability to better understand their condition and assist in their education.

Once asthma has been diagnosed, and treatment to stabilize the condition prescribed, the system will enable clinicians to keep track of their patient’s control. The regular collection of data will also enable an individual's data to be characterised to identify any environmental predispositions. Ideally the peak flow meter will be provided with a bluetooth communications capability so that the PEF readings can be transferred wirelessly to the mobile phone. Figure 9.1 shows an outline of this system.

9.6.2 Supportive Telemedicine System

Yoos et al used an RCT to compare asthma management across 168 children using three different criteria; subjective symptom assessment, PEF monitoring during symptomatic periods and regular twice daily PEF monitoring [71]. Data were recorded in paper diaries and subsequently analysed, the results showing that patients who only measured their PEF during symptomatic periods had lower asthma severity scores, fewer symptom days and less health care utilization than patients in the other two arms. In an end-of-study questionnaire, completed after the three month observational period, 73% of the patients recording their PEF only when symptomatic indicated their willingness to continue recording their PEF in this manner compared to 61% of patients recording their PEF twice daily.

In Chapter 6 the Isle of Man Study showed that the vast majority of people with well-controlled mild-to-moderate asthma only suffer the occasional exacerbation. For these individuals, a much simpler application on the phone is suggested which borrows from the findings of Yoos. As with the Isle of Man study protocol, the patient’s clinician would set up baseline values on the web site. The patient would only use the telemedicine system when they felt their condition worsening. The phone would effectively act as a safety net, able to collect symptoms and PEF. These could simply be typed into the phone by the patient after which immediate feedback would be given to the patient encouraging them to use their inhalers according to their personal management stored on the phone. If an individual had previously used the system to characterise their asthma, according to environmental conditions, the server could be programmed to send SMS messages warning them to adjust their medication based on weather forecasts. A flow chart outlining this implementation is shown in Figure 9.2.
Figure 9.1: Proposed telemedicine system for diagnosis and characterisation of asthma.
9.7 Respiratory Disease Management

The current focus of respiratory disease management is to improve patients’ control with the intention of reducing the demand on secondary healthcare services in particular hospitalisation and overnight stays. Primary Care Trusts are actively encouraged via their funding model to take on a larger share of the management of long-term conditions such as asthma, COPD and diabetes. Money is available to provide assistance to GPs to improve day-to-day management of a wide range of long-term conditions.

t+ Medical is commercialising this work into a product called t+ Asthma [176] modelled along the lines of t+ Diabetes, the mobile phone based support system for diabetics. Although available to individuals, t+ Asthma is aimed at Primary Care Trusts offering the ability to improve the control of their patients and the efficiency of the treatment they offer.

The individual patient empowerment and support provided directly by the mobile phone is designed to improve compliance with medication and provide real-time support and advice in the event of worsening symptoms. The web-based store of PEF and diary information combined with the graphical interface improves reliability of diagnosis and aids nurses during asthma clinics.
Major benefits in efficiency will be provided by the new patient prioritisation capabilities which have recently been launched by t+ Asthma. This is designed to help healthcare professionals with large numbers of patients to better manage them. The system identifies patients who are struggling to control their asthma both through peak flow and use of reliever inhaler. These patients can then be targeted by nurses for closer examination and brought in to surgery for consultation. Early intervention which can prevent exacerbations offers huge potential cost savings within healthcare services.
Appendix A

Thames Valley Study Data

The following eight pages show the PEF' for each of the patients on the Thames Valley Study. Figure 5.17 included in Chapter 5 contains two examples from this appendix.
Appendix B

Isle of Man Study Data

The following six pages show the PEF recorded by each of the patients on the Isle of Man Study.
APPENDIX B. ISLE OF MAN STUDY DATA

Palatine Patient:100471 Raw Data.

Filtered Data (6.1538% outliers removed.)

Palatine Patient:100473 Raw Data.

Filtered Data (0.78989% outliers removed.)
APPENDIX B. ISLE OF MAN STUDY DATA

Palatine Patient: 100474 Raw Data.

Filtered Data (3.4783% outliers removed.)

Palatine Patient: 100475 Raw Data.

Filtered Data (1.6949% outliers removed.)
APPENDIX B. ISLE OF MAN STUDY DATA

Palatine Patient: 100476 Raw Data.

Filtered Data (2.1008% outliers removed.)

Palatine Patient: 100477 Raw Data.

Filtered Data (8.3636% outliers removed.)
APPENDIX B. ISLE OF MAN STUDY DATA

Palatine Patient: 100479 Raw Data.

Filtered Data (2.3904% outliers removed.)

Palatine Patient: 100480 Raw Data.

Filtered Data (8.4746% outliers removed.)
Appendix C

Environmental Data 2003

The following four pages show the PEF index created in Section 5.4.2 in the context of the complete set of explanatory environmental data collected throughout the study period. The data are described in more detail in Section 7.3.
APPENDIX C. ENVIRONMENTAL DATA 2003

PEF Index
FEV Index
Rain (mmh⁻¹)
Butadiene (µgm⁻³)
Benzene (µgm⁻³)
Ethylbenzene (µgm⁻³)
PM₁₀ (µgm⁻³)
NO (µgm⁻³)
Bibliography


