

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.

5.1.1 Hardware

The Vitalograph handheld electronic peak flow meter (see Section 4.4) 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.



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. 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. Figure 5.2 shows a flow chart of the application, with the relevant screenshot shown by each stage of the software. 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 lower right-hand corner of Figure 5.2, 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.

5.2 Results Summary

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.

5.2.1 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 5.3. 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.

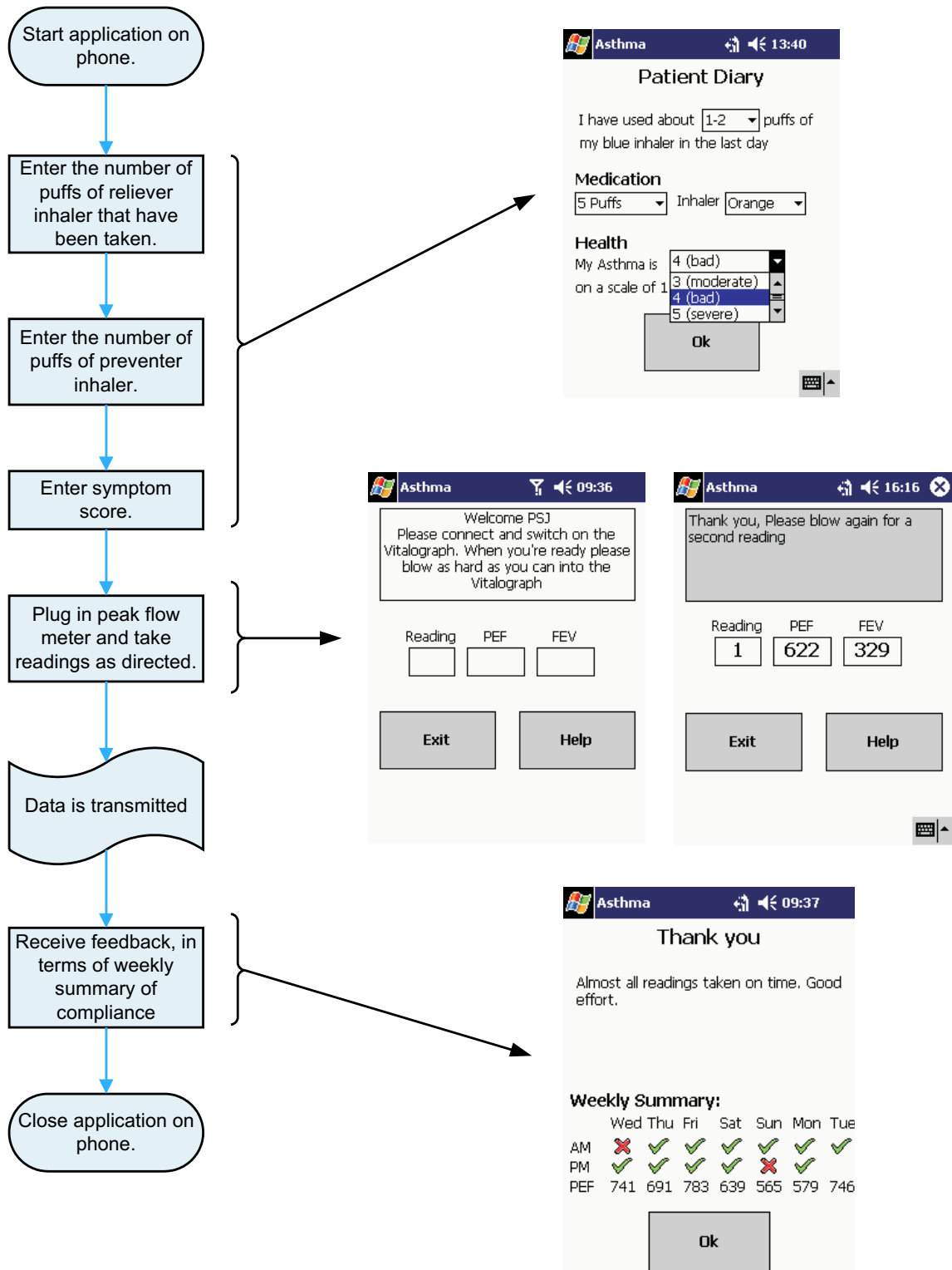


Figure 5.2: Flow chart of the O₂ xda mobile phone application for asthma.

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 5.4. 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.

	Adolescents (38)		Adults (53)		All Patients (91)	
	Median (%)	IQR (%)	Median (%)	IQR (%)	Median (%)	IQR (%)
Once-a-day	66	45 - 80	81	58 - 90	72	53 - 87
Twice-a-day	51	29 - 65	62	42 - 79	58	36 - 73
Morning readings	52	30 - 66	67	36 - 80	56	33 - 78
Evening readings	49	28 - 65	61	42 - 79	57	37 - 76

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

	Adolescents (22)		Adults (36)		All Patients (58)	
	Median (%)	IQR (%)	Median (%)	IQR (%)	Median (%)	IQR (%)
Once-a-day	91	85 - 93	96	91 - 98	93	89 - 98
Twice-a-day	75	66 - 85	83	75 - 91	80	71 - 89
Morning readings	73	66 - 86	86	76 - 91	84	69 - 89
Evening readings	80	68 - 85	85	69 - 92	82	69 - 90

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

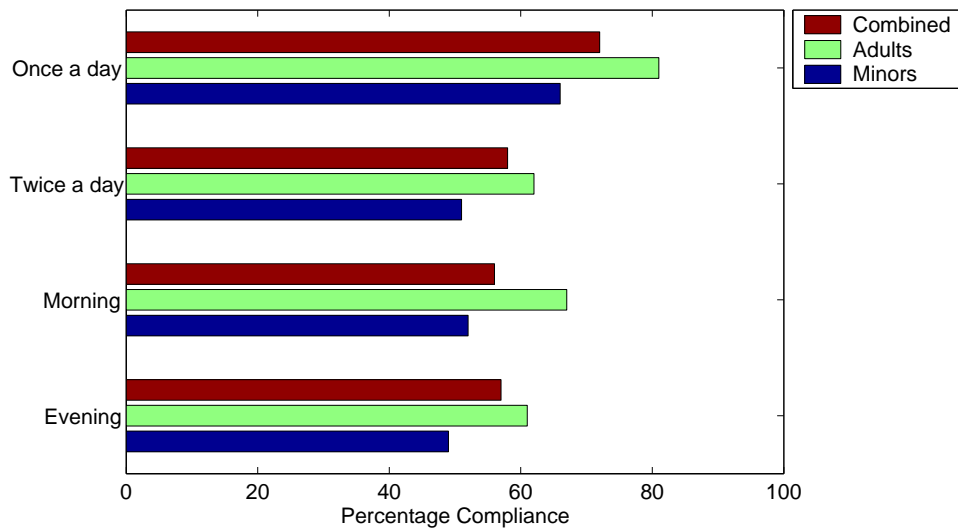


Figure 5.3: Compliance figures for each of the four metrics by patient group - all patients shown.

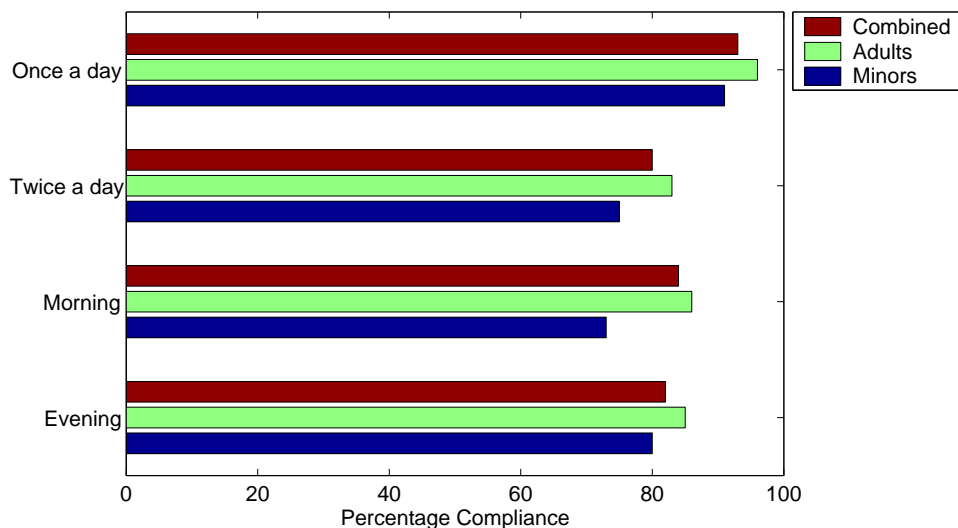


Figure 5.4: Compliance figures for each of the four metrics by patient group - Sub-group 3.

5.3 Analysis of peak flow data

As pointed out in Section 2.7 patients invent approximately 50% of the entries in paper-based diaries [24]. 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 FEV₁ readings, collected reliably from the 58 patients in sub-group 3 over approximately a nine-month period.

5.3.1 Interrelationship Between PEF and FEV₁

Although FEV₁ is viewed by some as a more sensitive test [24, 153], common medical practice tends to focus on PEF, as the latter is simpler to measure. PEF was therefore used as the parameter to control in the protocol for this study. Figure 5.5 below, shows the relationship between the PEF and FEV₁ 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 ($r = 0.73$). This is slightly lower than values previously found in other studies ($r \approx 0.8-0.85$) [153, 154]. However, these studies were conducted on outpatients rather than using data from a long-term study. Furthermore, only adults were included in these studies and only one set of spirometry readings was taken from each patient. Hence, the total number of readings in the study described here is larger by several orders of magnitude.

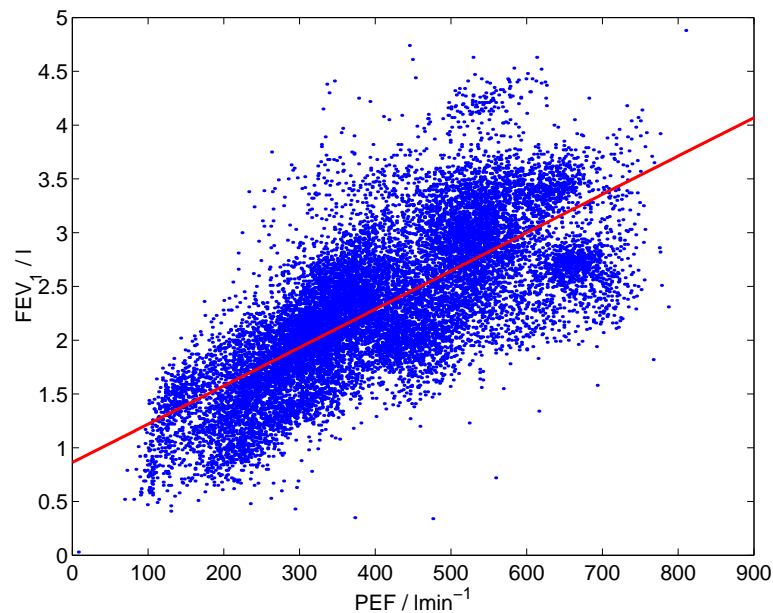


Figure 5.5: The correlation between PEF and FEV₁.

5.3.2 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.

5.3.3 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 [79] presented in Table 2.2 were generated by regressing measured values of PEF and FEV₁ against age and height across a population of 7,429 people and take the following form:

$$PEF = a_1 \{height^2\} + a_2 \{age\} + a_3 \{age^2\} + a_4, \quad (5.1)$$

where a_1 , a_2 , a_3 and a_4 are constants.

Figure 5.6 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, 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.

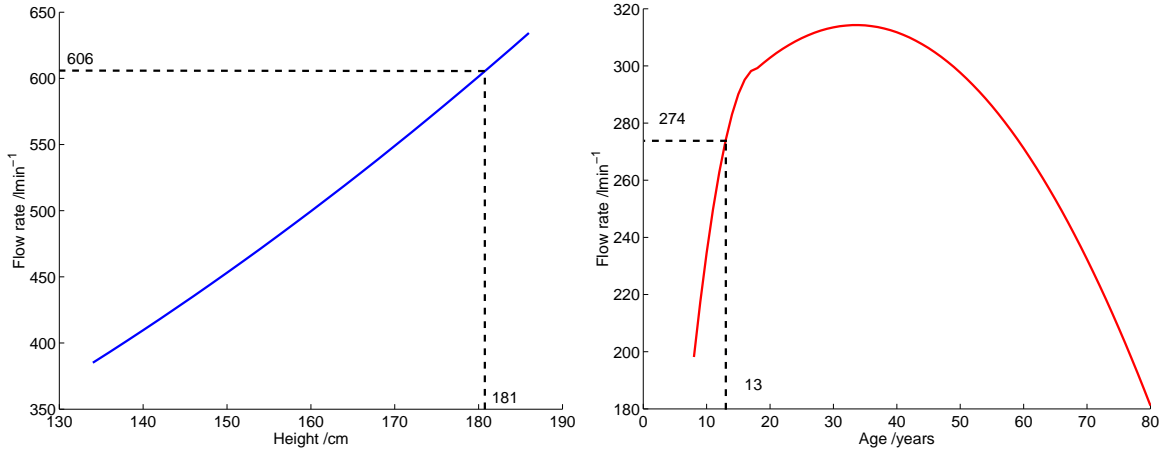


Figure 5.6: Two examples of Hankinson prediction models for PEF varying due to age and height (see Table 2.2). The left-hand plot shows the variation with height for 50-year old males; the right-hand plot shows variation with age for females 130cm tall.

Time-varying models At recruitment, date of birth, height and baseline PEF were recorded; thus 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:

$$PEF(t) = PEF(0) + \Delta t \times \frac{dPEF(0)}{dt}, \quad (5.2)$$

where $PEF(0)$ is the patient's predicted initial PEF and Δt is the time since the start of the study. The value of $\frac{dPEF(0)}{dt}$ can be obtained at the start of the study by differentiating the model in Equation 5.1 with respect to time,

$$\frac{dPEF(0)}{dt} = \frac{d}{dt} (a_1 \{height^2\}) + a_2 + 2a_3 \{age\}, \quad (5.3)$$

where $height$ and 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:

$$\frac{dPEF(0)}{dt} = a_2 + 2a_3 \{age\}, \quad (5.4)$$

which can be substituted into Equation 5.2,

$$PEF(t) = PEF(0) + \Delta t [a_2 + 2a_3 \{age\}]. \quad (5.5)$$

A scaling factor at time t , $SF(t) = \frac{PEF(t)}{PEF(0)}$ is created using these predicted values and subsequently applied to each of the measured PEF values in turn. Figure 5.7 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.

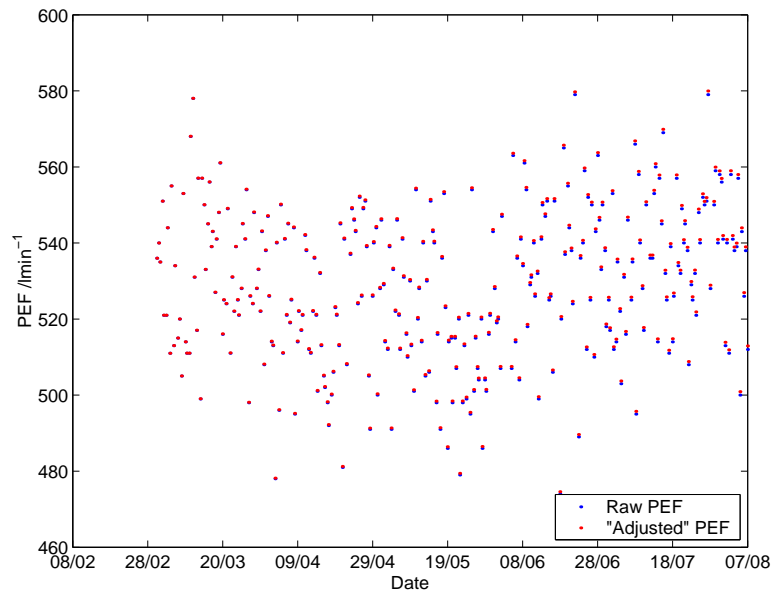


Figure 5.7: Compensated PEF readings for a 50-year old male in the Thames Valley Study (181cm).

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 5.8 shows the relationship between age and height for girls. (Similar charts are also available for boys [155].) 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.

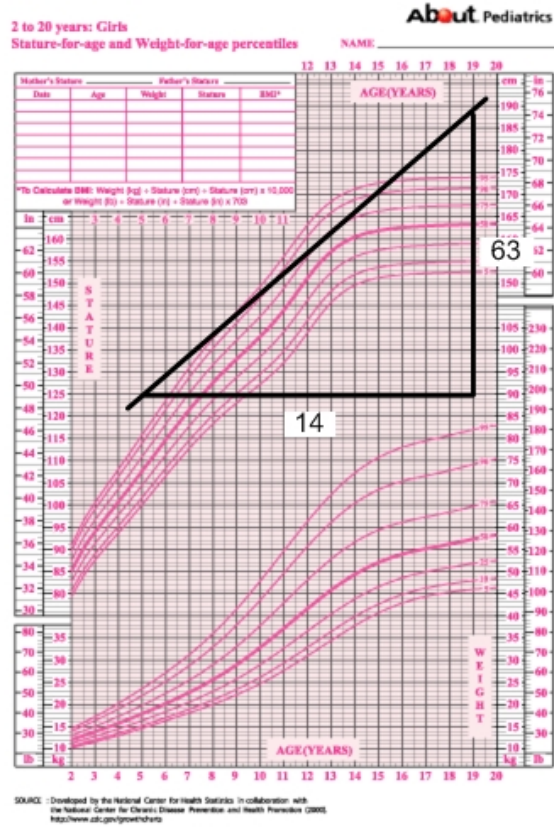


Figure 5.8: Growth Chart for Girls aged 2 to 20 [155]. The growth rate for a typical 13-year old girl is calculated as $\frac{63cm}{14years} = 4.5cm/year$.

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 5.8. Hence, Equation 5.3 can be written:

$$\frac{dPEF(0)}{dt} = \frac{d}{dt} \left(a_1 [\{height(0)\} + kt]^2 \right) + a_2 + 2a_3 \{age\}, \quad (5.6)$$

$$\frac{dPEF(0)}{dt} = \frac{d}{dt} \left(a_1 \left[\{height(0)\}^2 + 2kt \{height(0)\} + (kt)^2 \right] \right) + a_2 + 2a_3 \{age\}, \quad (5.7)$$

$$\frac{dPEF(0)}{dt} = a_1 [2k \{height(0)\} + 2k^2t] + a_2 + 2a_3 \{age\}, \quad (5.8)$$

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:

$$PEF(t) = PEF(0) + \Delta t [a_1(2\{height(0)\}k + 2k^2(\Delta t + \{age\})) + a_2 + 2a_3\{age\}]. \quad (5.9)$$

The scaling factor at time t , $SF(t) = \frac{PEF(t)}{PEF(0)}$, is once again calculated and applied to each of the measured PEF readings. Figure 5.9 illustrates how these scaling factors have been applied to an adolescent in the study. This 13-year old girl has grown considerably during the study and consequently her PEF has increased over time. 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.

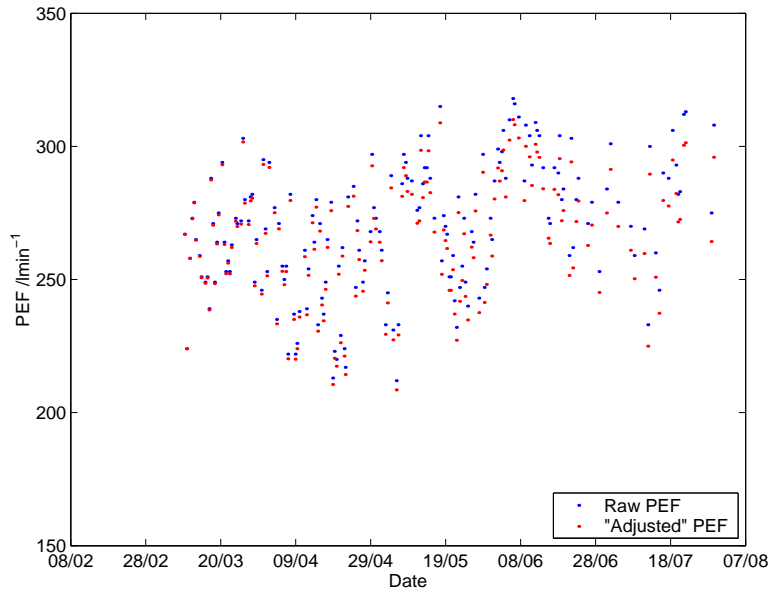


Figure 5.9: Compensated PEF readings for a 13-year old girl in the Thames Valley Study (130cm at the start of the study).

5.3.4 Computation of PEF'

To enable comparison of PEF data across all the patients, the time compensation factors are applied to the adjusted PEF values, aPEF, to obtain PEF' values, aPEF with temporal correction. PEF' are therefore calculated as follows, with accompanying numerical examples presented in Table 5.3.

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 5.8 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:

$$SF(t) = \frac{PEF(t)}{PEF(0)}. \quad (5.10)$$

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

$$PEF'(t) = SF(t)aPEF(t). \quad (5.11)$$

5.4 PEF Throughout the Study

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, 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.

Stage of computation	50-year old male	13-year old female
1) Five largest values (l_{min}^{-1})	584, 585, 588, 588, 588, 588	312, 313, 315, 316, 318
2) Calculate ABP (l_{min}^{-1})	586.6	314.8
3a) Example PEF (l_{min}^{-1}) Time since start (Δt)	550 60 days = 0.164 years	298 140 days = 0.384 years
3b) $aPEF(t)$	0.938	0.949
4a) Initial height /cm (h)	181	130
4b) Initial age /years (y)	50.44	13.406
4c) Appropriate Hankinson Model	$PEF(0) = a_1 h^2 + a_2 y + a_3 y^2 + a_4$ $a_1 = 0.0150; a_2 = 4.962$ $a_3 = -0.0780; a_4 = 63.14$	$PEF(0) = a_1 h^2 + a_2 y + a_3 y^2 + a_4$ $a_1 = 0.0112; a_2 = 36.36$ $a_3 = -1.008; a_4 = -217.2$
4d) Predicted $PEF(0)$ (l_{min}^{-1})	606	274
4e) Growth curve gradient (k)	0	4.5 cm/year
4f) Time corrected model	$PEF(t) = PEF(0) + \Delta t [a_2 + 2a_3 y]$	$PEF(t) = PEF(0) + \Delta t [2a_1 (hk + k^2(\Delta t + y)) + a_2 + 2a_3 y]$
4g) $PEF(t)$ (l_{min}^{-1})	605.54	326.1
4h) Scaling Factor ($SF(t)$)	1.001	0.9655
5) PEF'	0.939	0.916
	0.914	0.883

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.

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

Table 5.4: Summary table for all 58 patients.

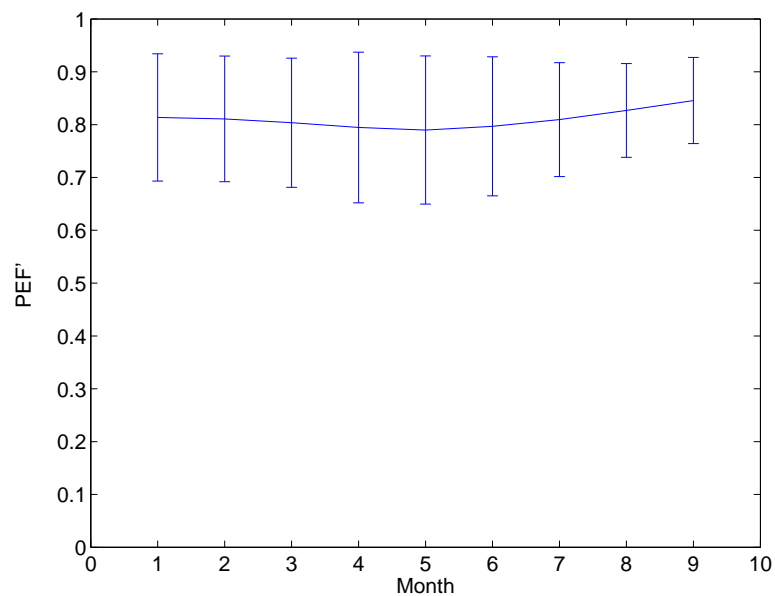


Figure 5.10: A plot showing monthly mean and standard deviation for the PEF' data presented in Table 5.4.

Figure 5.10 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 in months four to six is likely to be associated with the the summer months (see 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 5.11, 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.

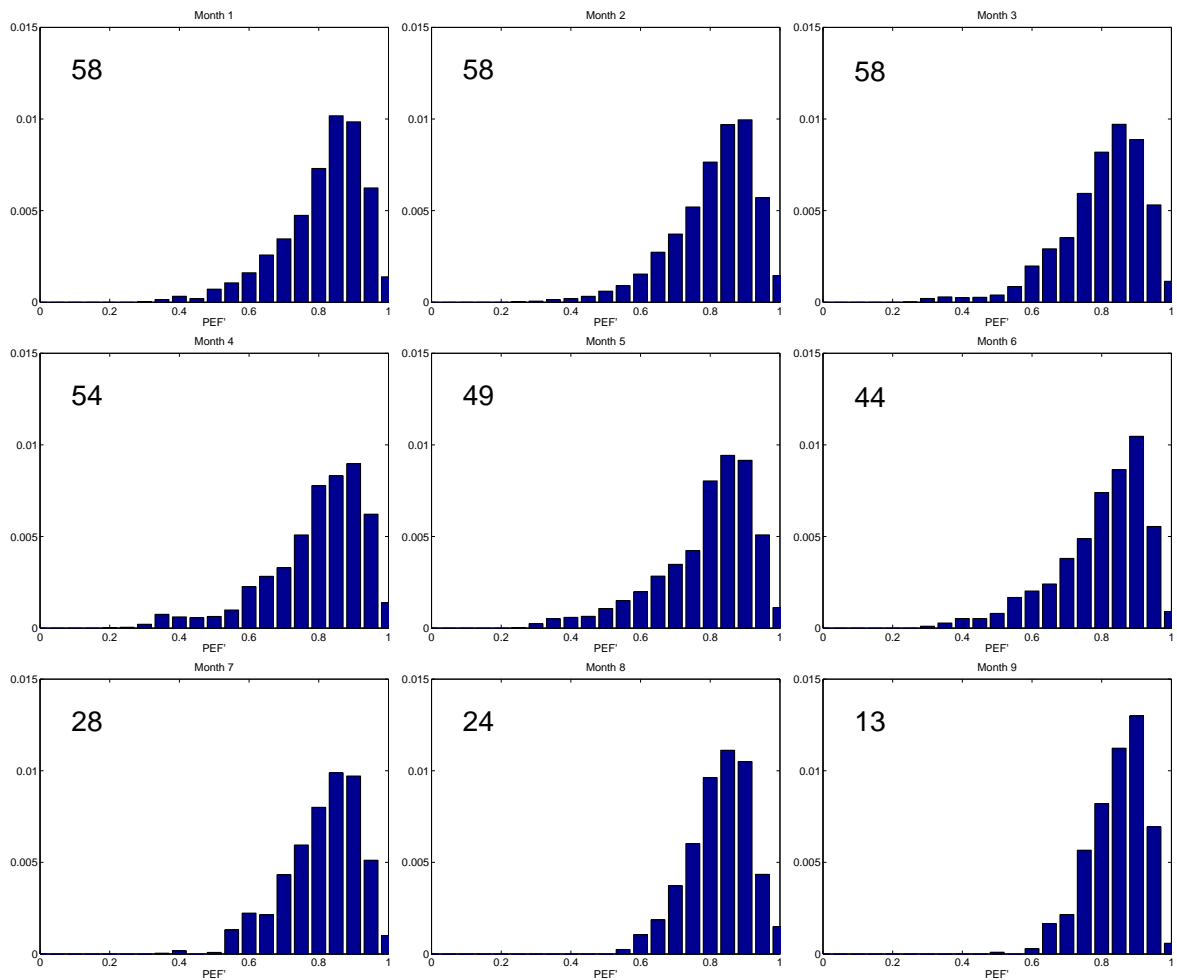


Figure 5.11: Normalized monthly histograms of PEF' data recorded in the Thames Valley Study from sub-group 3 patients. The numbers of patient contributing data each month are given in the top left-hand of each histogram.

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 5.11 are repeated in Figure 5.12 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.

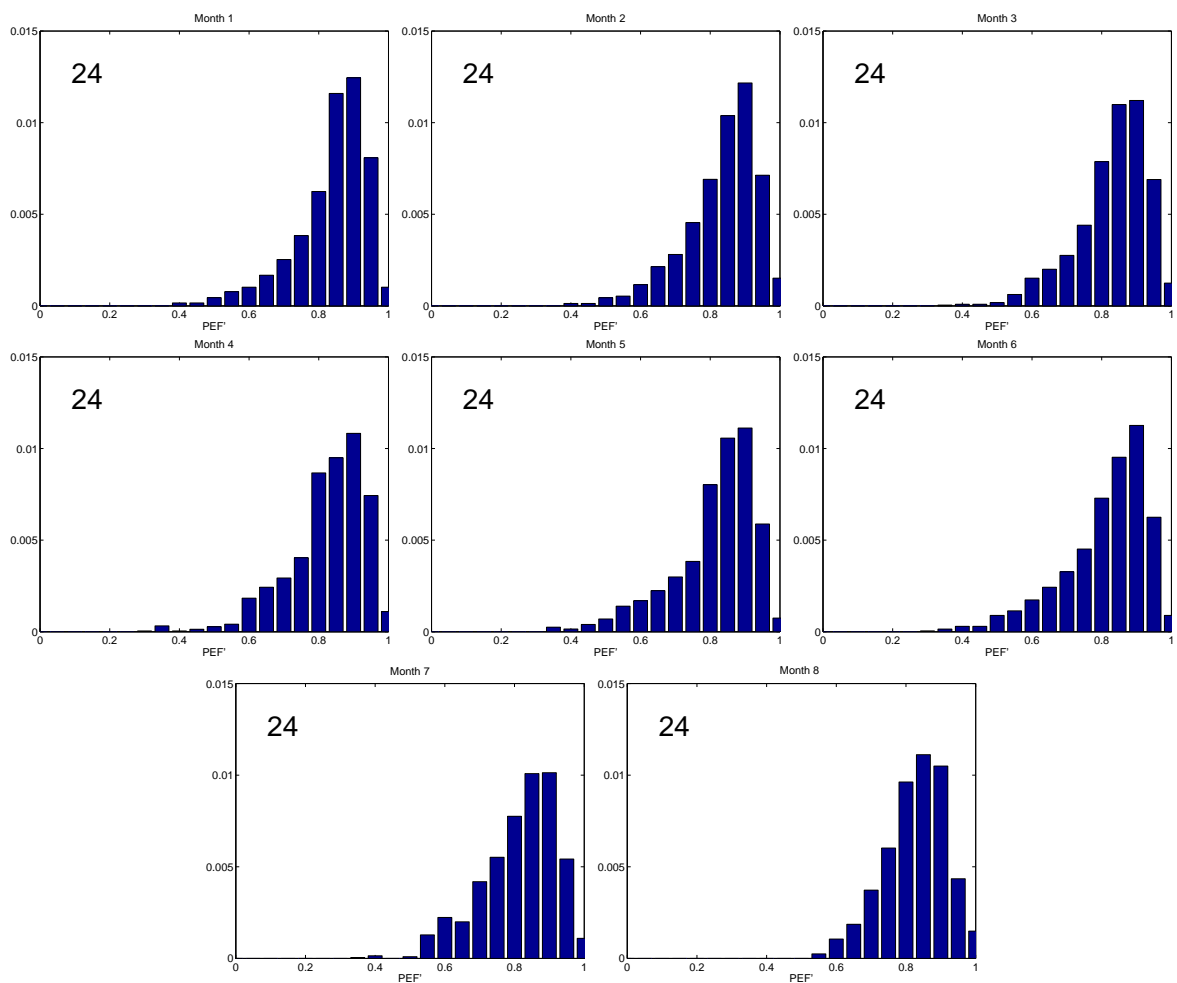


Figure 5.12: Normalized monthly histograms of the PEF' transmitted by the 24 patients who used the system for the first eight months of the study.

5.4.1 Difference Between Adults and Adolescents

Figure 5.13 shows normalized monthly histograms for all the sub-group three adults recruited to the Thames Valley Study. The figure is very similar to Figure 5.11 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.

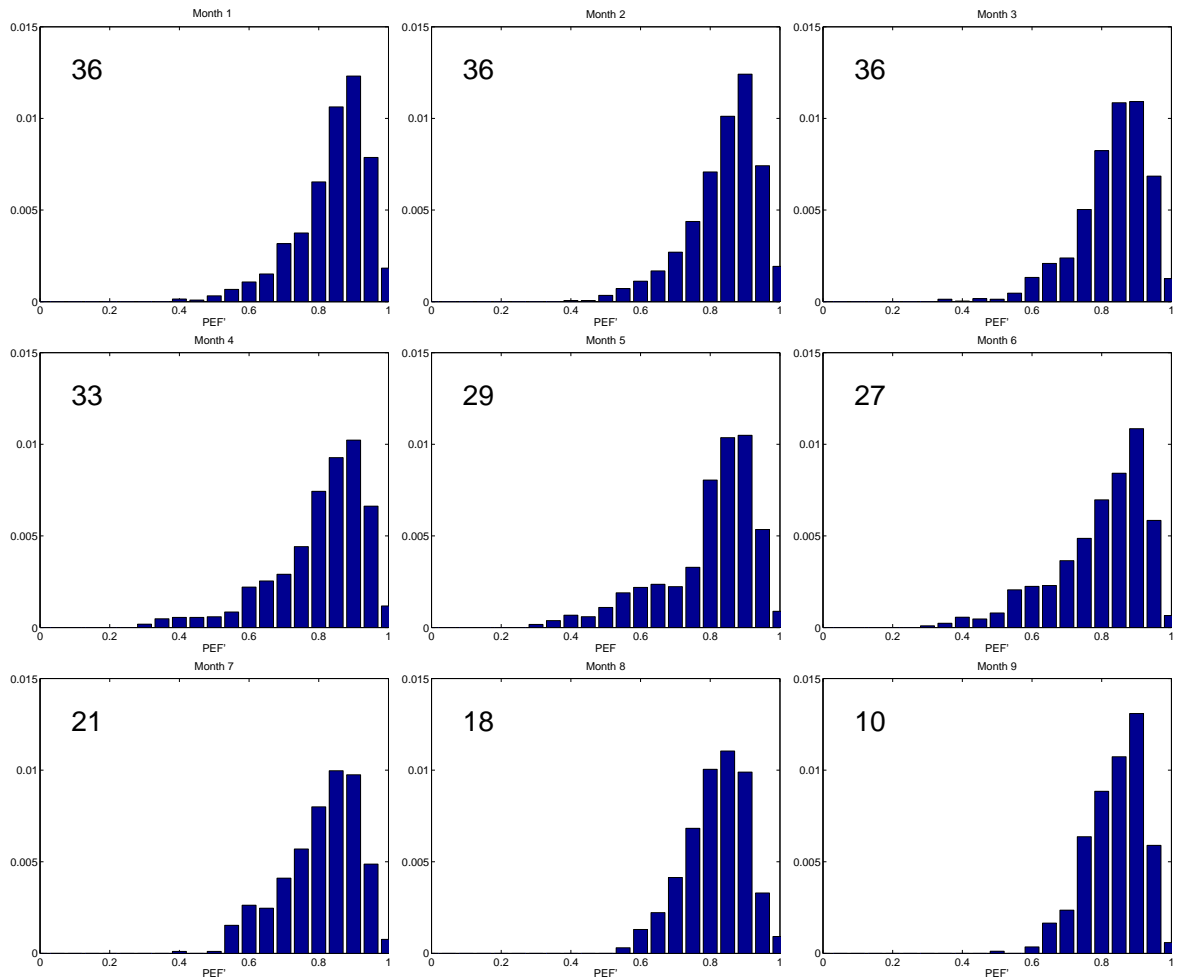


Figure 5.13: Normalized monthly histograms of PEF' recorded by adults from the Thames Valley Study (sub-group 3).

Normalized monthly histograms are presented in Figure 5.14 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 5.15 and this small number of individuals does show a clear improvement in PEF' values as a result of using the telemedicine system.

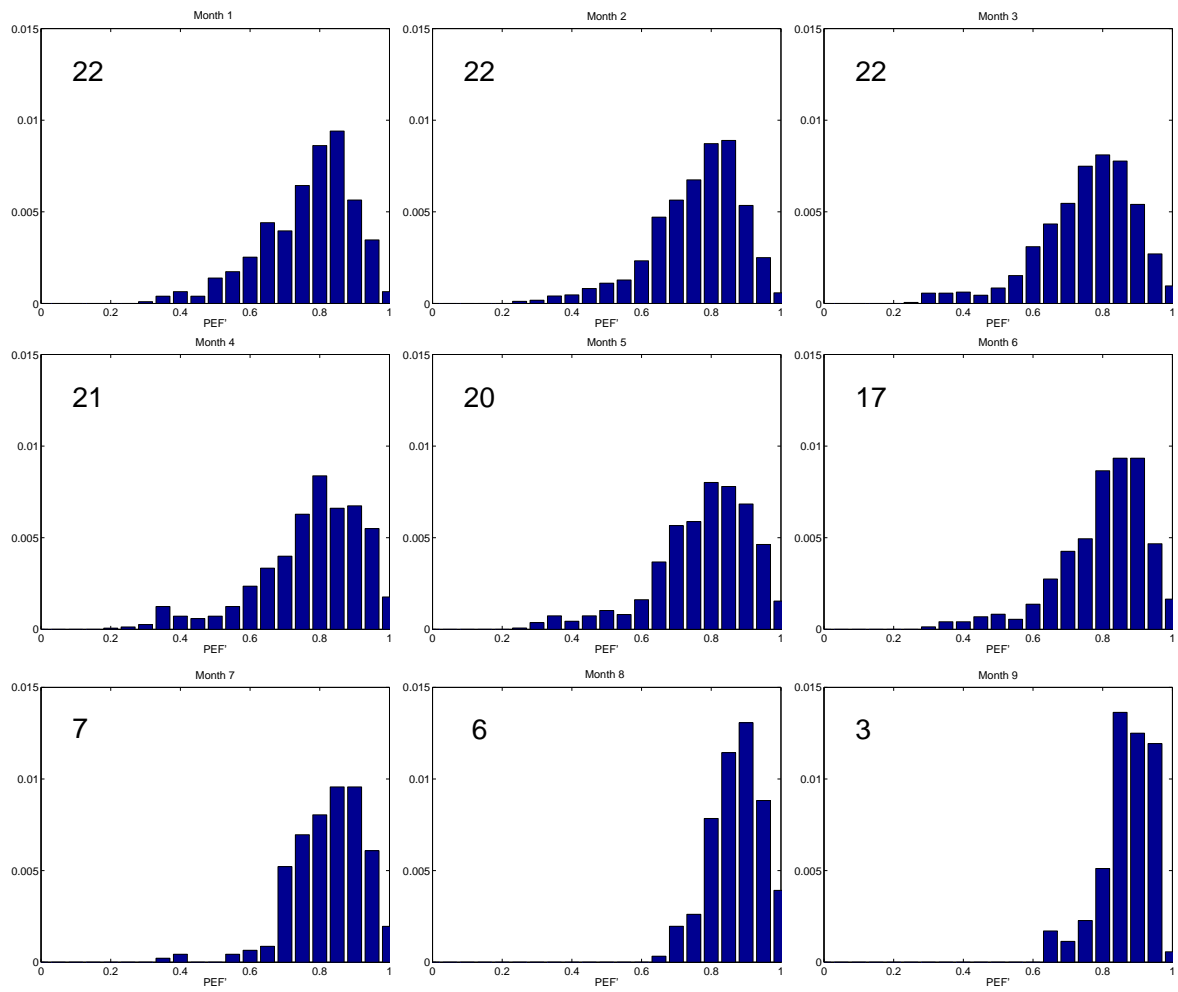


Figure 5.14: Normalized monthly histograms of PEF' recorded by adolescents in the Thames Valley Study (sub-group 3).

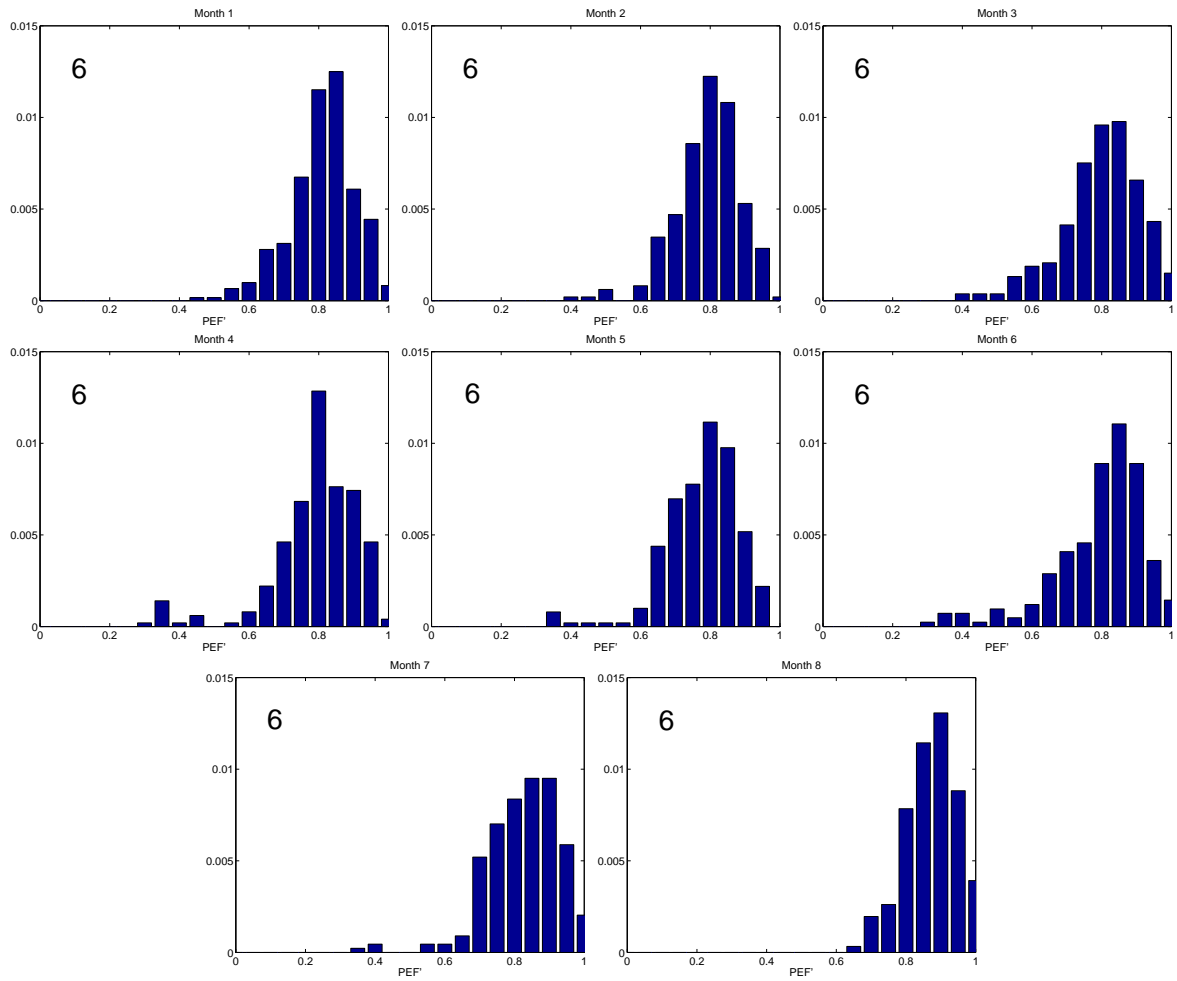


Figure 5.15: Normalized monthly histograms of PEF' recorded by the six adolescents who transmitted data for eight months or more (sub-group 3).

In Table 5.5, the mean monthly PEF is presented for each of the six adolescents plotted in Figure 5.15. 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.

	Month	1	2	3	4	5	6	7	8
Patient a	aPEF	0.818	0.723	0.732	0.678	0.685	0.563	0.736	0.835
	PEF'	0.815	0.715	0.719	0.661	0.665	0.544	0.707	0.798
	SF	0.997	0.990	0.983	0.976	0.972	0.967	0.961	0.955
Patient b	aPEF	0.815	0.838	0.844	0.882	0.852	0.863	0.902	0.901
	PEF'	0.812	0.830	0.828	0.858	0.823	0.827	0.859	0.851
	SF	0.996	0.990	0.981	0.974	0.966	0.959	0.951	0.944
Patient c	aPEF	0.831	0.808	0.860	0.743	0.753	0.836	0.800	0.809
	PEF'	0.828	0.799	0.844	0.724	0.727	0.800	0.759	0.765
	SF	0.996	0.989	0.980	0.974	0.966	0.957	0.950	0.946
Patient d	aPEF	0.687	0.764	0.741	0.828	0.849	0.894	0.883	0.952
	PEF'	0.684	0.755	0.727	0.806	0.820	0.857	0.838	0.900
	SF	0.996	0.988	0.980	0.973	0.966	0.959	0.949	0.946
Patient e	aPEF	0.842	0.812	0.768	0.795	0.736	0.794	0.839	0.869
	PEF'	0.842	0.810	0.766	0.791	0.732	0.788	0.832	0.861
	SF	0.999	0.998	0.997	0.995	0.994	0.993	0.992	0.991
Patient f	aPEF	0.861	0.841	0.862	0.789	0.755	0.771	0.754	0.782
	PEF'	0.860	0.836	0.853	0.777	0.740	0.753	0.734	0.759
	SF	0.998	0.994	0.990	0.985	0.981	0.977	0.973	0.970

Table 5.5: Table showing mean adjusted PEF' with and without correction for growth of the six adolescents shown in Figure 5.15.

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.

5.5 PEF' Variability

The variability of PEF' is indicative of the level of control of an individual's asthma. Figure 5.16 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. 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 center.

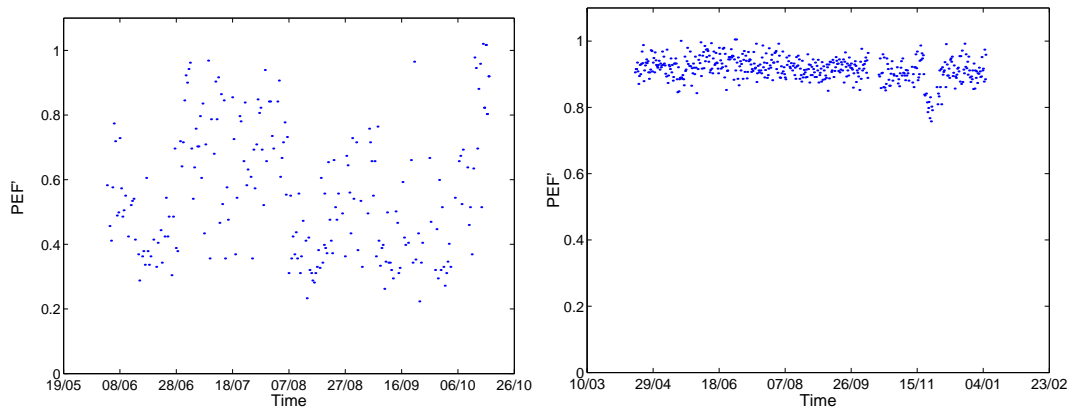


Figure 5.16: Patients with high and low variability in their recorded PEF'.

There are numerous reasons for this level of variability, the main factors being the diurnal variability identifiable in most individuals, and the poor control exhibited by some people with mild-to-moderate asthma. In Table 2.4 we report Higgins' [86] findings that in adults that 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 5.16.

5.5.1 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 5.11 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 [57, 106]. Figure 5.17 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 [86].

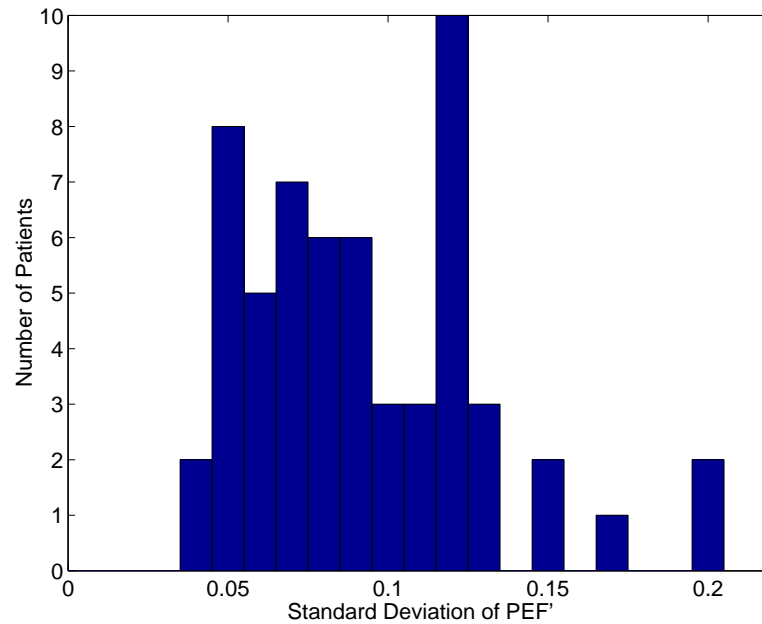


Figure 5.17: Histogram showing the variability indices of each of the patients.

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 [87]. Approximately half of the people with mild-to-moderate asthma would therefore appear to be poorly controlled in this study. This could, however be explained by referring to the flow chart in Figure 5.2. 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 values improved by 5 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.

5.5.2 Sliding Variability Index

In Section 5.5.1 a PEFⁿ 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 5.18 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 there are no such general trends across all of the patients.

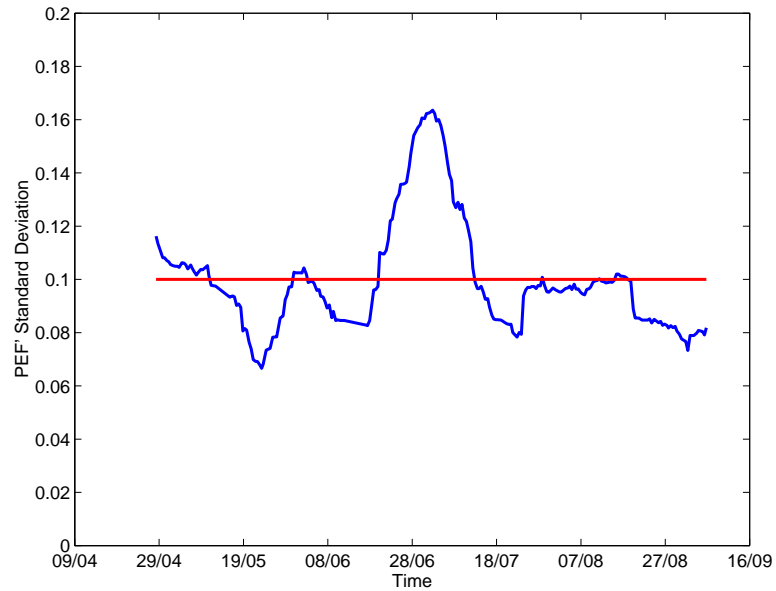


Figure 5.18: Sliding index of Variability for an individual patient.

In Figure 5.19 the sliding variability averaged across all patients is shown. The figure shows a gradual decrease throughout the study indicating a slight improvement across all patients as the study progressed.

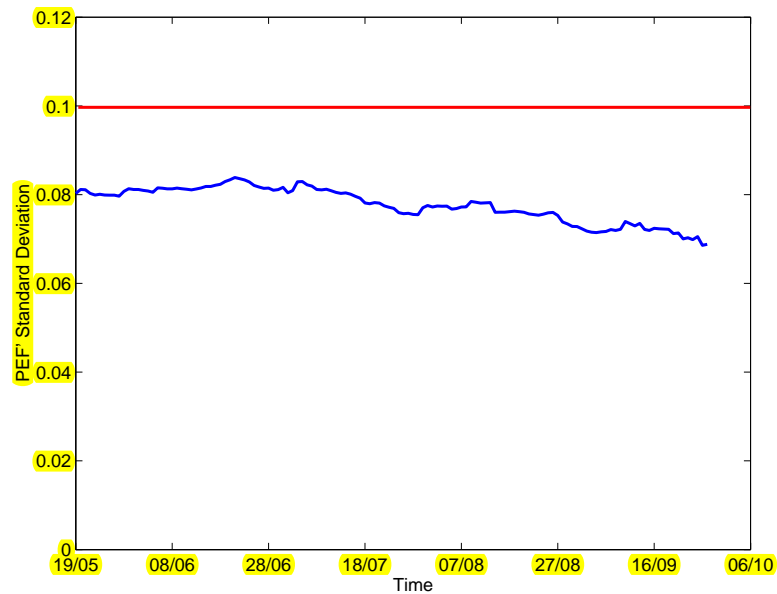


Figure 5.19: Sliding index of Variability for an individual patient.

5.6 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 [31, 85]. This section investigates the degree of diurnal variability that was exhibited by the patients enrolled in the Thames Valley Study. Figure 5.20 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.

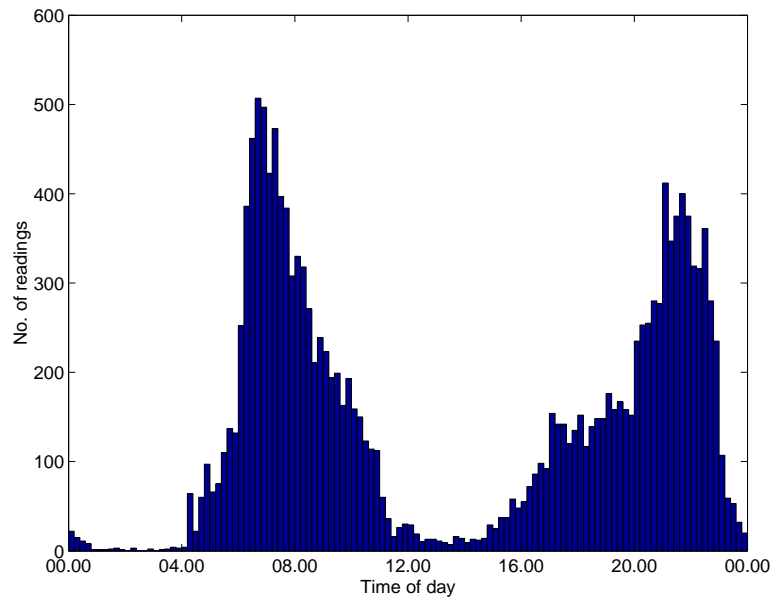


Figure 5.20: Distribution of all readings on the Thames valley study.

In some individuals the difference in PEF' levels between morning and evening readings is very pronounced. Figure 5.21 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 [85]. The patient shown on the left could have night-time asthma, possibly due to poor environmental conditions in the bedroom.

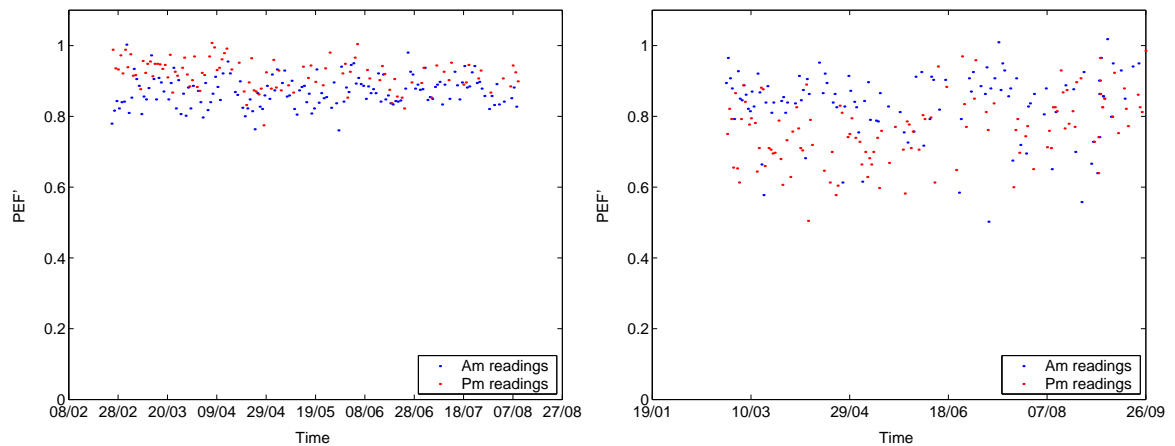


Figure 5.21: Examples of two extreme cases of diurnal variability; the left-hand figure shows a patient with consistently lower morning readings and the right-hand plot has consistently lower evening readings.

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. For later analysis in Chapters 7 and 8, morning and evening data are considered as distinct sets.

5.7 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 5.22 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.

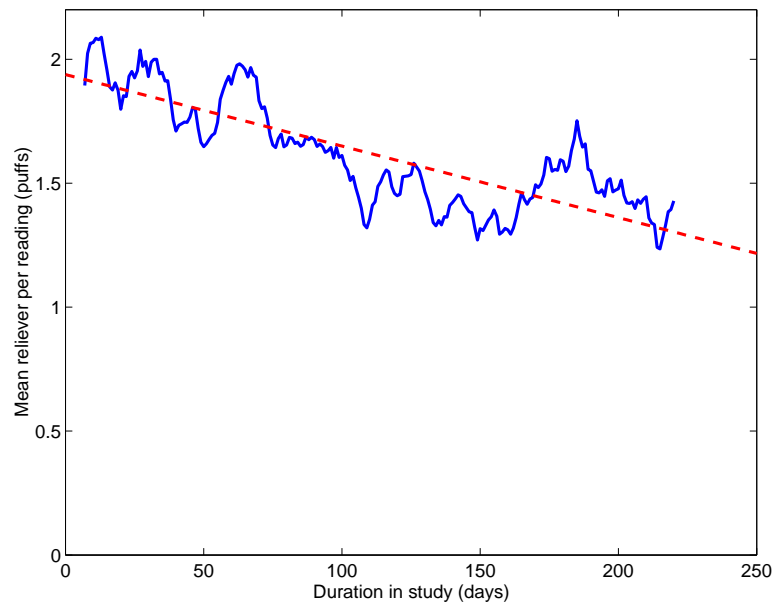


Figure 5.22: Mean number of puffs of reliever inhaler taken in 12 hours - averaged across all patients, based on duration using system.

Recruitment into the Thames Valley Study took place over several months, Figure 5.23 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 A are considered, there is a corresponding dip in PEF' across all patients which may be explained by the first cold snap of the winter.

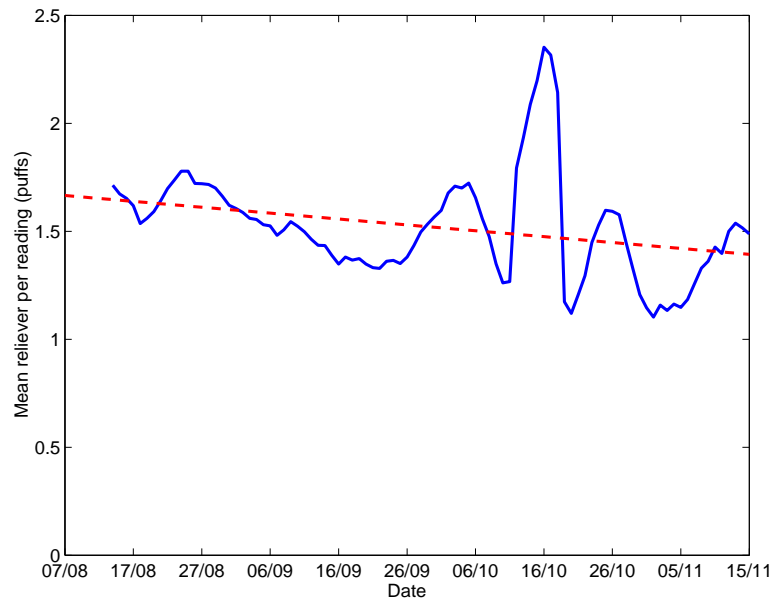


Figure 5.23: Mean number of puffs of reliever inhaler taken in 12 hours - averaged across all patients.

5.8 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.

5.8.1 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.

5.8.2 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 (Figure 5.2). 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.

5.8.3 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).

5.9 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. Unsent data is stored on the handset for future transmission, however, patients do not receive immediate . Where ever 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.