

**Assessing asthma in adult clinical trials of
inhaled β_2 -agonists: a search for a standard
primary outcome measure**

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Abstract

Since the late 1960s the safety of inhaled β_2 -agonists has been questioned and the long-term regular use of these drugs has been linked to increasing morbidity and mortality. National and international guidelines recommend that short acting inhaled β_2 -agonists should only be used on an “as needed” basis and yet the evidence for these recommendations is still unclear, one reason being the lack of common definition for an outcome. The Regular Use of Salbutamol Trial (TRUST) was designed to assess the risks and benefits of regular versus as needed salbutamol in mild to moderate asthma.

In order to establish whether a common primary outcome measure could improve the comparability and interpretation of different trials, a systematic review of randomised controlled trials of long and short acting inhaled β_2 -agonists in asthmatic subjects was undertaken to identify well designed trials in this field and primary outcome measures used. The systematic review identified five different primary outcome measures from 26 trials of long and short acting inhaled β_2 -agonists. The TRUST definition of exacerbation was compared with the five primary outcome measures identified using the TRUST diary card data. In addition, the diary card variables (changes in PEF, symptom scores and medication use) were examined to determine the extent to which they predicted exacerbations according to the different definitions.

The use of additional corticosteroids and an increase in daytime symptoms of two or more above baseline were the strongest predictors of all four definitions of exacerbation. A fall in morning PEF of 100 l/min was strongly associated with all definitions of exacerbation but was not a sensitive measure.

In conclusion, exacerbations of asthma could be identified by use of additional corticosteroids and an increase in two or more of daytime symptoms. The specificity could be improved by including morning PEF but this may reduce patient compliance with study protocol in asthma trials.

Publications arising from this work

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Abstract	2
Publications arising from this work	3
Acknowledgements	4
Contents	5
List of figures	9
List of tables	10
List of appendices	12
Chapter 1 – Introduction.....	13
1.1 Aim of thesis	13
1.2 The inhaled β_2 -agonist debate.....	13
1.2.1 Evidence from retrospective studies	14
1.2.2 Evidence from randomised controlled trials.....	21
1.3 Assessment of asthma in clinical trials	25
1.3.1 Definition of Asthma	26
1.3.2 Diagnosis of asthma.....	31
1.3.3 Measuring change in asthma.....	32
1.4 Thesis outline.....	34
Chapter 2 - Methods	36
2.1 Introduction.....	36
2.2 Aims.....	36
2.3 Method	36
2.3.1 Reference population	37
2.3.2 Study population	38
2.3.3 Selection of suitable subjects.....	40
2.3.4 Informed consent	40
2.3.5 Baseline measurements.....	40

2.3.6	Random allocation	40
2.3.7	Follow-up.....	41
2.3.8	Assessment of defined outcome	42
2.3.8	Analysis and interpretation	44
2.4	Summary.....	44
Chapter 3 – TRUST Results.....		46
3.1	Recruitment.....	46
3.2	Withdrawal rate.....	46
3.3	Baseline.....	50
3.3	Baseline.....	51
3.4	Exacerbations.....	51
3.5	Secondary outcomes	52
3.5.1	Use of rescue inhaled β_2 -agonist.....	53
3.5.2	Diurnal variation in PEF	53
3.5.3	Symptom score.....	53
3.5.4	Days lost from work / normal activities.....	53
3.5.5	Use of NHS services - including GP and hospital consultations	53
3.5.6	Changes in overall score on the quality of life questionnaire	54
3.6	Discussion.....	55
Chapter 4 – Systematic Review		46
4.1	Introduction.....	56
4.2	Methods	56
4.3	Results.....	59
4.4	Discussion.....	61
4.5	Summary.....	62
Chapter 5 – Analysis of TRUST Dataset.....		63
5.1	Introduction.....	63
5.2	Mean PEF (including diurnal variation)	64
5.2.1	Method for mean PEF (including diurnal variation).....	65
5.2.2	Results for mean PEF (including diurnal variation)	66
5.2.3	Discussion for mean PEF (including diurnal variation)	68

5.3	Symptoms	69
5.3.1	Method for symptoms	69
5.3.2	Results for symptoms.....	70
5.3.3	Discussion for symptoms.....	71
5.4	Asthma control.....	71
5.4.1	Method for asthma control.....	72
5.4.2	Results for asthma control	74
5.4.3	Discussion for asthma control.....	76
5.5	Exacerbations.....	77
5.5.1.	TRUST exacerbation	77
5.5.2	FACET severe exacerbation	78
5.5.3	Exacerbation from the paper by Wilding et al (104)	79
5.5.4	Definition of exacerbation defined by Taylor et al (105)	79
5.5.5	Results for exacerbation.....	81
5.5.6	Discussion for exacerbation.....	83
5.6	Discussion.....	84
5.7	Summary.....	84

Chapter 6 – Comparison of primary outcome measures86

6.1	Introduction.....	86
6.2	Mean PEF (including diurnal variation)	86
6.2.1	Introduction for mean PEF (including diurnal variation)	86
6.2.2	Method for mean PEF (including diurnal variation).....	86
6.2.3	Results for mean PEF (including diurnal variation)	88
6.2.4	Discussion for mean PEF (including diurnal variation)	91
6.3	Symptoms	93
6.3.1	Introduction for symptoms.....	93
6.3.2	Method for symptoms	93
6.3.3	Results for symptoms.....	93
6.3.4	Discussion for symptoms.....	94
6.4	Asthma Control.....	94
6.4.1	Introduction for asthma control	94
6.4.2	Method for asthma control.....	95

6.4.3	Results for asthma control	95
6.4.3	Discussion for asthma control.....	96
6.5	Asthma exacerbations	97
6.5.1	Introduction for exacerbations	97
6.5.2	Method for exacerbations	97
6.5.3	Results for exacerbation.....	99
6.5.4	Discussion.....	121
Chapter 7 – Discussion		123
7.1	TRUST.....	123
7.2	Comparisons of the primary outcome measures	124
7.2.1	Oral and inhaled corticosteroids	125
7.2.2	Morning PEF.....	127
7.2.3	Symptoms	129
7.3	Summary	130
7.4	Strengths	131
7.5	Weaknesses.....	131
7.6	Conclusion and future work.....	132
References.....		133
Appendices.....		152

List of figures

1.1	Sales and prescriptions of asthma preparations compared with deaths from asthma among people aged 5 - 34 in England and Wales, 1959 - 68 (40).	15
1.2	International patterns of asthma mortality (deaths per 100 000 persons) aged 5 - 34 years, 1960 - 1994, showing the different trends (59).	17
1.3	Structural diagram of salbutamol and salmeterol.	24
3.1	A map to show the location of TRUST practices.	47
3.2	Actual and expected recruitment to TRUST.	48
3.3	Number of patients randomised to TRUST by practice list size.	49
3.4	Flow of patients in TRUST.	50
4.1	A flow chart detailing the search for papers to be included.	60
6.1	TRUST exacerbation rate against categories for mean difference in morning PEF between run-in and follow-up.	90
6.2	TRUST exacerbation rate against mean difference in evening PEF between run-in and follow-up.	90
6.3	PEF diary card for a patient who experienced several exacerbations.	111
6.4	PEF diary card for a patient who experienced several exacerbations.	111
6.5	PEF diary card for a patient who experienced an exacerbation according to all definitions.	112
6.6	PEF diary card for a patient who experienced a fall in am PEF missed by all definitions of exacerbation.	112
6.7	Time to first exacerbation according to the different definitions of exacerbation as a survival function.	114

List of tables

1.1	Classification of asthma from Woolcock and Peat (125).	28
1.2	Classification of asthma using the 1995 BTS Guidelines on Asthma Management(1).	30
3.1	Characteristics at baseline in the two randomised groups.	51
3.2	Exacerbations in the two randomised groups.	52
3.3	Secondary outcome measures.	54
5.1	Mean morning and evening PEF (SD) for run-in and follow-up divided into run-in and four three-month periods.	66
5.2	Mean daily PEF (SD) during run-in and follow-up by treatment group.	67
5.3	Mean morning, evening and daily PEF and diurnal variation by treatment group adjusted for baseline levels using ANCOVA.	68
5.4	Mean symptom scores (min 0 to max 5) by treatment group.	71
5.5	Number of patients according to each category of change for asthma control and the components of asthma control, by treatment group.	75
5.6	Number of patients according to each category of change of the Chapman criteria E and F, by treatment group.	76
5.7	The results of TRUST according to the definitions of exacerbation identified by the systematic review.	82
6.1	The change in rate ratio of TRUST exacerbation according to the category of change in mean morning PEF.	88
6.2	TRUST exacerbation rate ratio and change in evening PEF.	89
6.3	Monthly TRUST exacerbation rate ratio and change in morning PEF.	91
6.4	TRUST exacerbation rate ratio and change in diurnal variation from baseline.	91
6.5	The number (%) of patients according to Sears asthma control who experienced TRUST exacerbation.	95
6.6	The change in rate ratio of TRUST exacerbation according to the	96

Chapman criteria of asthma control.

- 6.7 Number (%) of TRUST exacerbations (periods and days) 99
according to the criteria fulfilled.
- 6.8 The effect of diary card variables on the odds ratios of 100
experiencing a TRUST exacerbation or TRUST exacerbation day.
- 6.9 Number (%) FACET exacerbations according to the components 102
of the definition of exacerbation.
- 6.10 Days of exacerbation according to the TRUST and FACET 103
definitions.
- 6.11 The effect of diary card variables on the odds ratios of 104
experiencing a FACET exacerbation or FACET exacerbation day.
- 6.12 Days of exacerbation according to the TRUST and Wilding 106
definitions.
- 6.13 The effect of diary card variables on the odds ratios of 107
experiencing a Wilding exacerbation or Wilding exacerbation day.
- 6.14 The effect of diary card variables on the odds ratios of 109
experiencing a Taylor exacerbation, Taylor exacerbation day or
Taylor score.
- 6.15 Mean (SD) and median number of days to first exacerbation 113
according to the four definitions of exacerbation.
- 6.16 Number (%) of days of TRUST exacerbation with or without 116
corticosteroid use and or daytime symptoms.
- 6.17 Number (%) of days of FACET exacerbation with or without 117
corticosteroid use and or daytime symptoms.
- 6.18 Number (%) of days of TRUST exacerbation with or without 117
corticosteroid use with morning PEF $\leq 80\%$.
- 6.19 Number (%) of days of FACET exacerbation with or without 118
corticosteroid use and morning PEF $\leq 80\%$.
- 6.20 The effect of diary card variables on the odds ratios of starting a 120
course of corticosteroids.

List of appendices

1.1	Randomised controlled trials of inhaled β_2 -agonists in asthma.	152
2.1	Membership of TRUST Steering Committee.	153
2.2	Regular versus on demand salbutamol.	154
2.3	TRUST protocol.	162
2.4	Invitation letter.	176
2.5	Screening questionnaire.	178
2.6	Patient information.	180
2.7	Consent form.	182
2.8	Diary card.	184
2.9	Follow-up assessment.	187
2.10	Withdrawal from randomised treatment form.	188
2.11	Additional consent form.	189
4.1	Synthesising and evaluating outcome measures for asthma in adults and children.	190
4.2	Medline Search Strategy.	193
4.3	Data collection sheet.	194
4.4	Reasons for exclusion for papers identified by Medline search.	195
6.1	Regression analysis for the relationship between TRUST exacerbation and mean PEF.	197
6.2	Regression analysis for the relationship between TRUST exacerbation and mean symptoms.	200
6.3	Regression analysis of exacerbations on diary card variables.	202
6.4	Analysis of use of additional corticosteroids on diary card variables.	203

Chapter 1 – Introduction

1.1 *Aim of thesis*

Many composite primary outcome measures have been used to assess the response of asthmatic subjects to interventions in clinical trials and one of the common outcomes is “exacerbation”. However, definitions for an exacerbation in clinical trials have differed between studies and it is unclear which components of the composite measures are the most sensitive or specific in identifying an exacerbation. The overall aim of this project is to compare the outcome measures identified from a systematic review of randomised controlled trials of inhaled β_2 -agonists with the TRUST (The Regular Use of Salbutamol Trial) definition of exacerbation, using the TRUST dataset. This will clarify how the TRUST definition of exacerbation compares with primary outcome measures from other trials and to what extent the conclusions of trials may be affected by the precise definition of exacerbation used in the study.

The thesis will present the background to the inhaled β_2 -agonist debate to which TRUST contributed. The TRUST results will be reported and discussed. The different primary outcome measures identified by the systematic review will then be used to re-analyse TRUST to determine whether the result would have been affected by the choice of primary outcome measure. The measurement characteristics of the different primary outcome measures will be compared with the TRUST definition of exacerbation. The results of the analysis will inform a standard primary outcome measure for use in trials of long and short acting inhaled β_2 -agonists that may be relevant to clinical practice.

1.2 *The inhaled β_2 -agonist debate*

Inhaled β_2 -agonists play a vital role in the management of asthma providing rapid relief of bronchoconstriction. Since the late 1960s their safety has been brought into question and the regular long-term use of these drugs has been linked to increasing morbidity and mortality. National and international guidelines (1-3) now recommend that inhaled β_2 -agonists only be used on an “as needed” basis though the evidence for these recommendations is still unclear.

An extensive search of the published literature suggested the regular use of inhaled β_2 -agonists has been over reviewed and under researched. A thorough search of Medline and the Cochrane Clinical Trials Register yielded over eighty publications on the subject of inhaled β_2 -agonists and asthma since the paper by Speizer et al (4) was published in 1968 and first linked the use of adrenergic stimulants with asthma death.

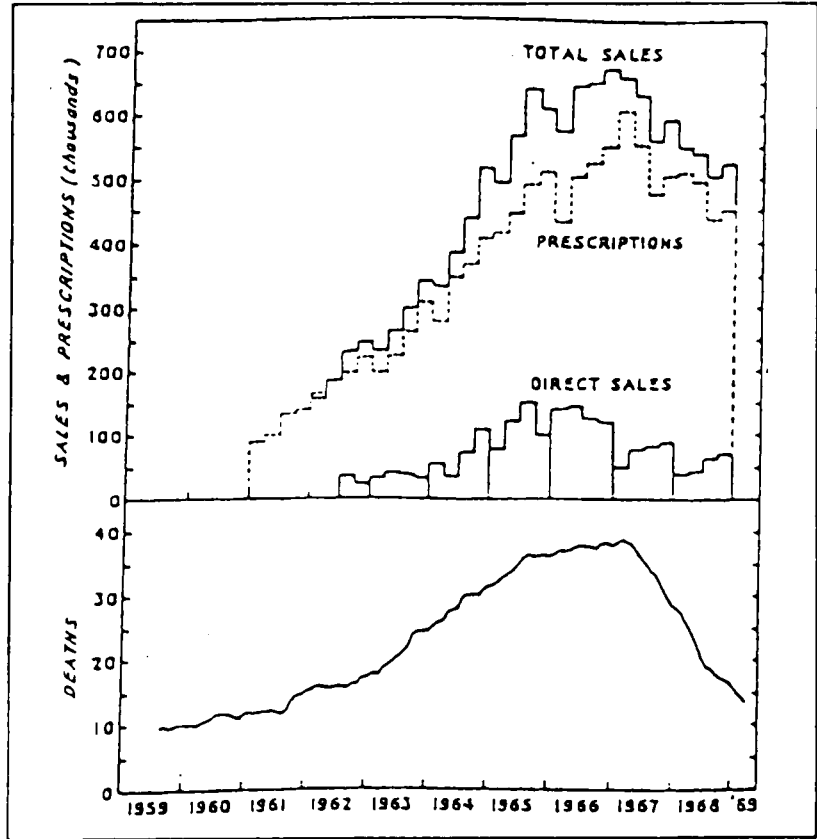
Many reviews of inhaled β_2 -agonist use in asthma have been published, the majority of which concluded that inhaled β_2 -agonists should be used with caution or that further research be undertaken (5-31). Only seven reviewers indicated that the use of inhaled β_2 -agonists is not a cause for concern (32-38). A recently published systematic review (39) suggested that there was no benefit in taking regular β_2 -agonists and that they may have a slight deleterious effect.

A review of the evidence from retrospective studies yielded 11 / 16 (69%) supporting a link between inhaled β_2 -agonist therapy and an increase in morbidity or mortality from asthma (4;40-49). However only six of the forty-one (15%) randomised controlled trials published since 1968, reported a deleterious effect of inhaled β_2 -agonists on asthma control (50-55). There is still a case for a well-designed randomised controlled trial to determine whether the regular or prolonged use of inhaled β_2 -agonists has a deleterious effect on asthma control.

1.2.1 Evidence from retrospective studies

Speizer et al reported an increase in asthma deaths in England and Wales between 1959 and 1966 (56) and also reported on the use of anti-asthma medication prior to death from asthma (4). Inhaled isoprenaline, a non-specific adrenoreceptor agonist, was introduced in 1960 and oral corticosteroids in 1952; inhaled corticosteroids were not introduced until 1971. Speizer et al reported that 84% of the cases had used isoprenaline before they died. Corticosteroids had been prescribed at some time for 71% (123 / 173) patients. However 25% (31 / 173) of patients were not prescribed them immediately before the fatal episode. The authors concluded that the disease severity was underestimated in these patients and that there was an over reliance on isoprenaline

and a failure to recognise the need for corticosteroids. Whilst the evidence suggested that there was a close correlation between adrenoreceptor agonist use and death from asthma it could not be said to be causal. Inman and Adelstein (40) also examined the details of the epidemic of asthma deaths in England and Wales in the late sixties. They reported that the number of patients admitted to hospital because of asthma was continuing to rise but that by 1967 there had been no continued increase in the number of asthma deaths. They concluded that the increase in asthma deaths may also have been associated with an over reliance on the use of isoprenaline especially as it was available to buy over the counter until 1968. It is interesting to note that deaths from asthma had already begun to decline in 1967 before the publication of the papers by Speizer et al (4;56) in 1968. However, the timing of the increase in asthma mortality did coincide with the introduction of the high dose isoprenaline inhalers (18) which in turn lead to their being linked with an increase in risk of asthma death, see figure 1.1.



Sales and prescription are expressed as actual quarterly figures.

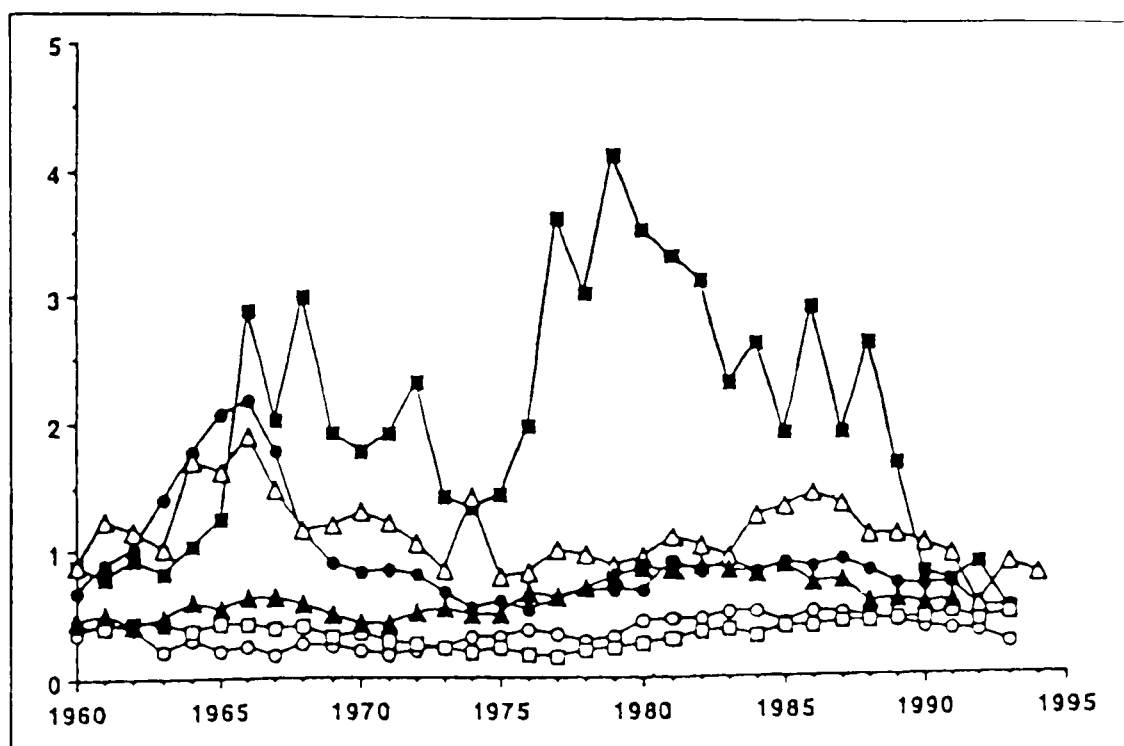
Deaths from asthma are expressed as the exponentially weighted moving averages.

Figure 1.1 Sales and prescriptions of asthma preparations compared with deaths from asthma among people aged 5 - 34 in England and Wales, 1959 - 68 (40).

There was also an increase in deaths from asthma in Australia at about the same time. However the Australian evidence did not seem to support the association between the

use of isoprenaline inhalers and asthma death (57). The number of asthma deaths increased by 13 per 1 000 000 people between 1958-1963 and 1964-1966 before subsequently decreasing in spite of the continuing increase in the sales of adrenergic agonists including isoprenaline forte which was implicated in the UK epidemic. It is likely that something else was involved in the “epidemic” in Australia. Identifying trends from a combination of mortality and sales data is difficult and the results are not always reliable because they do not provide information on individual patient usage prior to death.

A further increase in asthma mortality was reported in England and Wales between 1974 and 1984, most apparent in the 5 to 34 year age group, increasing by 4.7% per annum ($p < 0.05$) (58). The increase in the rate of death from asthma was greater in males at 6.1% per annum ($p < 0.05$) than females at 2.1% per annum ($p < 0.05$) in spite of the improvements in the treatments available for asthma. At this time the prevalence of asthma in the population had not been accurately determined which complicated the interpretation of the results although it was again postulated that failure to recognise the severity and under treatment were contributory factors in spite of rises in sales of all anti-asthma medications.



■-■ New Zealand; ●-● England and Wales; Δ-Δ Australia; ▲-▲ West Germany; ◇-◇ Canada; + USA.

Figure 1.2 International patterns of asthma mortality (deaths per 100 000 persons) aged 5 - 34 years, 1960 - 1994, showing the different trends (59).

Figure 1.2 shows the international trends in asthma mortality from asthma from 1960 until 1995. Whilst the increases in asthma mortality in England and Wales in the mid 1960s are clearly visible the increase in asthma mortality in New Zealand in the 1970s and 1980s is most striking (59). The New Zealand asthma epidemic of the mid 1980s renewed interest in the concerns over the use of inhaled β_2 -agonists. Until 1989 the reviews and the original articles tended to discuss dosing regimens and clinical trials to compare new anti-asthma treatments. The publication of the case-control study by Crane et al (42) followed by the publication of the results of the case control analysis (41) and the cohort analysis (44) from Saskatchewan in Canada reopened the whole inhaled β_2 -agonist debate.

A case control study approach to asthma deaths is valuable in order to generate a hypothesis because the actual number of asthma deaths in any one year is relatively small. For example, in England and Wales in 1994 there were 1516 asthma deaths across all ages (1994 OPCS). This approach should provide information on an association between the exposure: the use of β_2 -agonists, and the outcome of interest:

death from asthma, though the results cannot be used to infer that a relationship is causal. Crane et al calculated an odds ratio (OR) for asthma death associated with use of fenoterol metered dose inhaler (MDI) of 1.6 (95% CI 1.04 to 2.3) and 0.7 (95% CI 0.5 to 1.07) for albuterol. Spitzer et al reported a crude odds ratio of 5.3 for death from asthma associated with use of fenoterol MDI, however when this was adjusted for the weight of the drug, the odds ratio for death associated with fenoterol was 2.3 (95% CI 1.6 to 3.4) and 2.4 (95% CI 1.5 to 3.8) for albuterol. The two studies selected controls from quite different populations at risk of asthma death, which may have accounted for some of the differences in the odds ratios calculated. The controls in the New Zealand study were asthmatics admitted to hospital with severe asthma who survived (117 case and 468 controls) whereas the controls in the Saskatchewan study were selected from the cohort of asthmatics in the Saskatchewan population (129 cases and 655 controls).

The risk of fatal and non-fatal severe asthma increased in both studies when other risk factors were included, such as other hospital admissions, loss of consciousness and other anti-asthma medication. In the Saskatchewan study, loss of consciousness OR 10.6 (95% CI 5.2 to 21.5), blood gas data OR 3.0 (95% CI 1.5 to 6.1) and food allergy OR 3.8 (95% CI 2.3 to 6.4) all carried greater unadjusted odds ratios as independent risk factors than those associated with fenoterol or albuterol use (45). Hospital admission in the last year and prescription for oral prednisolone increased the odds ratio for asthma death associated with fenoterol to 13.3 (95% CI 3.5 to 51.2 $p < 0.01$) (42). Confounding factors such as these are difficult to correct for in a retrospective case-control study, but information could be collected in a prospective cohort.

Suissa et al (44) reported the results from their Saskatchewan asthma cohort from which the previous nested case-control had been taken. They reported a rate of death from asthma for any exposure to fenoterol MDI of 61.5 per 10 000 asthmatics per year, and for albuterol 9.8 per 10 000 per year. They found that fenoterol was a confounding factor for albuterol use but not *vice versa*, and the rate was further confounded by the use of oral corticosteroids and hospital admissions for asthma in the previous 24 months. They then calculated the rates associated with the number of canisters of albuterol and fenoterol and corrected for the dose of fenoterol (twice that of albuterol). The rate of death from asthma increased with increasing number of canisters per year.

However the confidence intervals were large and included zero until 25 or more canisters were used. The rate for more than 25 canisters of albuterol was 30.9 (adjusted rate difference 20.3 95% CI 1.3 - 39.4) and for the dose equivalence of fenoterol 151 (adjusted rate difference 129.8 95% CI 61.9 - 197.8). This strengthened the argument for the association of increased rate of asthma death and severity of disease. The reason for the greater risk associated with the use of fenoterol MDI was unclear though it has been speculated that fenoterol was prescribed preferentially to more severe asthmatics.

Since the publication of these three papers there have been several subsequent publications describing further analyses undertaken and examining the question of confounding by severity and investigations into the mechanism of action of fenoterol. Garret et al (60) repeated the analysis using the data from Crane et al (42). After controlling for asthma severity, hospital admission in the previous year and prescribed oral corticosteroids, the relative risk of asthma death related to the use of fenoterol compared to salbutamol dropped from 2.1 (95% CI 1.4 to 3.1) to 1.5 (95% CI 1.0 to 2.3). The effect was lost altogether after controlling for other severity markers. They concluded that fenoterol was more likely to have been prescribed to more severe asthmatics and that if baseline severity was controlled for then fenoterol use could not be linked to asthma deaths. Blais et al (61) re-examined the Saskatchewan data and assessed the extent to which the results could have been confounded by indication, i.e. more severe asthmatics would have their medication changed from salbutamol to fenoterol in the belief that fenoterol was more effective in more severe cases of asthma. They were able to confirm that patients were switched from salbutamol to fenoterol in response to severity markers. Pearce et al (62) disagreed because they felt that the New Zealand data suggested too few patients had been switched from salbutamol to fenoterol and that more patients had been switched in the opposite direction. Part of the misunderstanding arises because of the sources of the data. The Saskatchewan study was a cohort study whereas the New Zealand study was a case control study and it is more difficult to assess changes over time, such as treatment changes in response to severity changes, with a retrospective case control design.

In 1996, Bremner et al (63) reported the results of a study to investigate the extra pulmonary effects of fenoterol and albuterol in vivo in non-asthmatic subjects. They found that, at the high doses required to treat acute severe asthma, fenoterol resulted in more adverse cardiac and metabolic effects compared to albuterol at the same doses. They concluded that because fenoterol was a full agonist it would result in greater extra pulmonary effects per puff than albuterol. The effect of fenoterol's actions as a full agonist may explain the increase in asthma deaths associated with its use and why the same effect was not seen with salbutamol or terbutaline. The increased potency associated with fenoterol may also have been a reason for the preferential prescription to more severe asthmatics.

In 1993, a meta-analysis of case-control studies into the effect of inhaled β_2 -agonist use and death from asthma was published (47). The case control studies meeting the inclusion criteria were selected and the data were extracted and χ^2 for the association between β_2 -agonist use and death from asthma was used. The combination of the six studies provided 364 cases and 1388 controls (41;42;48;49;64;65) and in order to perform the analysis the study outcomes were weighted in order to take into account the different sample sizes. The association was stronger for nebulised β_2 -agonists (OR 2.5) and reduced for β_2 -agonist metered dose inhalers (OR 1.3), including fenoterol. This again pointed to a link with severity, i.e. those with more severe asthma required more treatment and also had a higher risk of asthma death.

Further attempts have been made to try to understand the reasons for the peaks in asthma deaths. Sales data and mortality data for the same country have been plotted on the same axes. The sales of inhaled β_2 -agonists continued to rise yet there was no continued increase in asthma deaths (66). The most recent paper reanalysed the New Zealand mortality and drug sale data (42) using a Poisson weighted linear regression (67). Again the results of this analysis suggested that initial visual method of analysis might have oversimplified the explanation for the epidemic overlooking the role that inhaled corticosteroids might have played in the epidemic. However these studies are of limited value because they are not able to provide insight into patterns of use in asthmatics at risk.

The most recent paper by Campbell et al (68) examined trends in asthma mortality from 1983 to 1995 in England and Wales. During this period an annual decline in asthma deaths of 6% per annum in people under 65 years of age was reported with an accelerated decline in asthma deaths occurring in the 14 to 74 year age group between 1983 and 1989. They concluded that a greater awareness of asthma and increasing use of anti-inflammatory medication might have had some impact on the decline in mortality.

Whilst the results of these retrospective studies provide valuable information on the changes over time of asthma mortality and medication use, the results can only be used to suggest an association between the use of β_2 -agonists and asthma mortality or morbidity. These types of studies are subject to potential biases in patient selection and problems with retrieving information retrospectively so they cannot be used to confirm causality. The only way to attempt to quantify whether the relationship between regular inhaled β_2 -agonists is causal is to undertake a randomised controlled trial.

1.2.2 Evidence from randomised controlled trials

A search of the Cochrane Randomised Controlled Trials Register and of Medline yielded 50 randomised controlled trials of inhaled β_2 -agonists (50-55;69-112). Many of the trials identified were too small to provide conclusive results.

There have been seventeen randomised controlled trials of short acting inhaled β_2 -agonists (salbutamol, albuterol, terbutaline or fenoterol) since 1968 (50;51;53-55;69-71;78;83;87;88;92;94;95;113;114), of which ten have reported results in favour of the use of regular β_2 -agonists with or without the concomitant use of inhaled corticosteroids (69-71;78;83;85;87;88;92;94). The trials varied in quality and the sample sizes ranged from 17 to 341 with follow-up from 15 days to 2.5 years. Five trials reported results against the use of regular inhaled β_2 -agonists with sample sizes ranging from 8 to 223 (50;51;53-55). Two of these papers were two different analyses of the same trial (51;54) and the van Schayck trial combined chronic obstructive pulmonary disease (COPD) with asthma and only eight asthmatics were randomised to regular inhaled β_2 -

agonist treatment (53;92). Three recently published trials reported no difference between inhaled β_2 -agonists and placebo in mild to moderate asthmatics over three to sixteen weeks (95;100;102). The remaining published trials compared long and short acting inhaled β_2 -agonists with or without placebo. All reported a positive result in favour of the use of the long acting inhaled β_2 -agonists and in five trials where placebo was used the use of short acting inhaled β_2 -agonists conferred additional benefit over placebo (80;84;91;105;106). For summary information on the randomised controlled trials of inhaled β_2 -agonists in asthma see Appendices 1.1 and 1.2.

The earliest randomised controlled trials of salbutamol versus placebo were small and reported that patients taking regular salbutamol experienced fewer wheezing episodes or lower symptom scores and less seasonal variation than those randomised to an as needed treatment (70;71). One of the first trials to suggest that the regular use of inhaled β_2 -agonists may have resulted in a deleterious effect was by Vathenen et al in 1988 (50). This trial was particularly interesting because it measured the effect of taking regular terbutaline, 500 μ g or 2000 μ g or placebo three times daily, on airway hyperresponsiveness with a methacholine challenge and the dose needed to produce a 20% fall (PC_{20}) in forced expiratory volume in one second (FEV_1). The investigators found that after 15 days' regular treatment with terbutaline, the ability of a single dose of terbutaline to protect against a methacholine challenge was lost. This trial has had an impact on the future trials of regular inhaled β_2 -agonist use in terms of the length of trial required, because the effect of terbutaline on bronchial hyperresponsiveness has been used as justification for other trials to be limited to only two weeks follow-up.

In 1990 three trials investigating the use of inhaled β_2 -agonists were published. Two involving the use of two new long acting inhaled β_2 -agonists. These two trials of formoterol and salmeterol versus salbutamol (73;74) both demonstrated that the long acting β_2 -agonists provided an improvement over the use of short acting inhaled β_2 -agonists alone. In neither trial was there a placebo group, so inferences could not be made about the additional benefits of long acting over short acting inhaled β_2 -agonists over placebo. The third trial to be published in 1990 by Sears et al (51) received much publicity and an additional paper was published from a further analysis in 1993 (54).

Mild to moderate asthmatics were randomised to receive regular versus as needed fenoterol for 24 weeks in a crossover design. Sixty-four patients completed the trial and they concluded that “asthma control” was improved with as needed fenoterol compared to regular use. “Asthma control” was assessed by combining different outcome measures to produce an overall score. There were several inconsistencies with the method of analysis of this trial. It was not clear what weight was given to the markers of asthma severity used in the overall score of asthma control. Evening peak expiratory flow (PEF) was much improved on regular treatment and daytime rescue use seemed to have been omitted from the presentation of their results. The second paper from the same trial reported the differences in exacerbations, PC₂₀, FEV₁, PEF and symptoms (54). Again the results were significant in favour of the use of fenoterol only as needed for symptom control, but only for the changes in PEF diurnal variation and pre-bronchodilator FEV₁.

The next major publication on this theme was by van Schayck et al (53) in 1991. A total of 223 patients with asthma or COPD were randomised to receive terbutaline or ipratropium bromide. The results suggested that regular treatment with terbutaline caused a greater decline in lung function over time. However, only 58 of the 223 patients were asthmatic and of these only eight were randomised to regular treatment. A further follow-up of 83 patients after 4 years demonstrated no deterioration associated with the regular use of terbutaline.

Since 1992 many of the published trials compared the efficacy of inhaled long acting β_2 -agonists with short acting inhaled β_2 -agonists and / or placebo. There was a general concern that if the deleterious effects of short term inhaled β_2 -agonists were real then they could also occur with the use of long-term inhaled β_2 -agonists. It was suggested that the regular use of inhaled β_2 -agonists caused the β_2 adrenoreceptors to down regulate; the receptors internalise to avoid further stimulation, but this has not been demonstrated *in vivo* in asthma. It is known that β_2 receptors can be down regulated if exposed to continuous stimulation with β_2 -agonists *in vitro*. Since 1992 there have been twenty-nine trials investigating the effects of long acting β_2 -agonists (salmeterol or formoterol) compared to short acting β_2 -agonists or inhaled steroids (52;72-77;79-

82;84;86;89-91;96;97;99;101;103-106;108-112). Those trials that have used a placebo group as well as a short acting inhaled β_2 -agonist demonstrated that a long acting β_2 -agonist was more effective than a short acting β_2 -agonist which in turn was more effective than placebo (80;84;91;105;106). The benefits associated with the use of long acting β_2 -agonists appear to have increased the uncertainty concerning the safety of short acting inhaled β_2 -agonists.

Short and long acting β_2 -agonists exert their effects on the β_2 -receptor in slightly different ways. The long acting β_2 -agonists possess a longer substitution in the amine head, which is highly lipophilic (9). The long tail is thought to bind to an exosite and this seems to enable the salmeterol molecule to continue to reassert its effect on the β_2 receptor (115). Computer modelling suggested an interaction with the α helices of the receptor itself and formoterol might also protect against acetylcholine induced bronchoconstriction. There is some evidence that tachyphylaxis is associated with the use of long acting β_2 -agonists (116-118). The downregulation and desensitisation seems to affect the bronchoprotective rather than the bronchodilator effects. Long acting β_2 -agonists may antagonise the bronchodilator effect of short acting β_2 -agonists (119) and may have clinical implications in the treatment of acute severe asthma. For the molecular structures of salbutamol and salmeterol see figure 1.3.

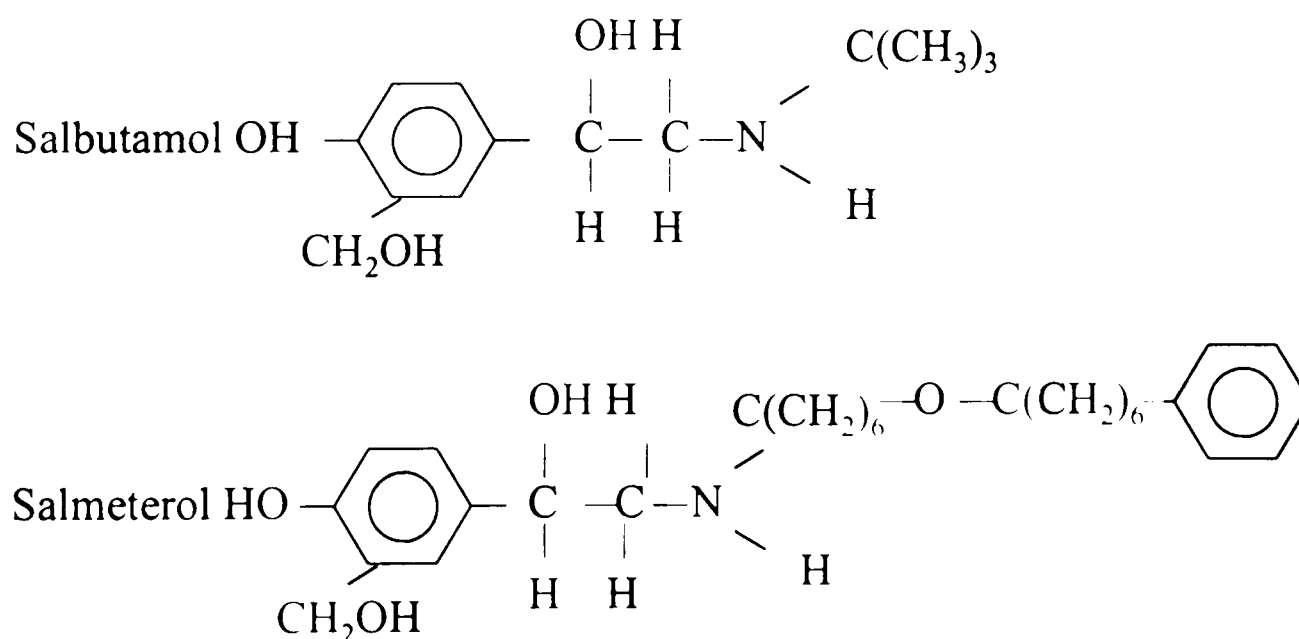


Figure 1.3 Structural diagram of salbutamol and salmeterol.

Perhaps the strongest of the most recent evidence for the use of inhaled β_2 -agonists comes from two trials, Chapman (83) and Drazen (95). Chapman (83) carried out a short trial of only two weeks and reported an improvement with the regular use of salbutamol. Because the intervention period was so short it would be difficult to extrapolate the results to determine whether their long-term regular use was appropriate. Drazen et al (95) carried out a randomised controlled trial in USA to compare regular versus as needed albuterol in mild asthmatics. The trial lasted for sixteen weeks and involved 255 patients. They reported no difference between regular and as needed treatment.

The publication of these robustly designed trials, which have failed to repeat the results reported by Sears and Taylor et al (51;54) has sown the seeds of doubt and reopened the debate. Short acting inhaled β_2 -agonists are recommended to relieve symptoms and an increase in their use indicates that the disease has become more severe and therefore additional treatment should be introduced (1). Their use should act as an alarm to trigger a change of management. The most recent British Thoracic Society (BTS) Guidelines recommend the introduction of long acting inhaled β_2 -agonists at step three (see table 1.2), bringing them forward from previous versions (1;120). The trend in the UK is to introduce inhaled steroids early in the course of the disease and to use short acting inhaled β_2 -agonists sparingly. Because the research to date has been favourable concerning the use of long acting inhaled β_2 -agonists it again raises questions as to the most appropriate use of inhaled β_2 -agonists in asthma.

1.3 *Assessment of asthma in clinical trials*

In addition to the methodological problems of study design and statistical power there are controversies over what is the most appropriate outcome measure for use in clinical trials and this is the purpose of this thesis. The choice of a clinical trial endpoint is complicated because there is considerable debate on how to define and diagnose asthma effectively and how to measure change in clinical practice.

Several of the clinical trials of inhaled β_2 -agonists have been criticised because of their choice of primary outcome measure or patient selection. The trial by Sears et al (51) was criticised because it used a measure of asthma control, a combination of morning and evening PEF, symptoms and rescue β_2 -agonist, but did not clarify the weight that was given to each of the components. The trials by van Schayck (53;92) were criticised because they included patients with COPD and the number of patients with asthma was very small in comparison. Several trials have used definitions of exacerbation (54;101;104;105;107;109;111;121-123), that have varied slightly from one another, and there is no information as to how their measurement characteristics compare.

The remainder of this introduction will discuss the problems of definition, diagnosis and measurement of asthma with particular reference to the inhaled β_2 -agonist debate.

1.3.1 Definition of Asthma

There is no clear consensus as to the exact definition of asthma. With the advent of techniques such as bronchoscopy, asthma has been described increasingly in terms of the symptoms and the underlying cellular events. The most recent working definition of asthma from the "Global Strategy for Asthma Management" (124) was:

"Asthma is a chronic inflammatory disorder of the airways, in which many cells play a role, in particular eosinophils, mast cells and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough, particularly at night and in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible, either spontaneously or with treatment. The airway inflammation also causes an associated increase in airway responsiveness to a variety of stimuli."

This very detailed description of asthma including the underlying cellular mechanisms may not be the most suitable definition for every situation. For example, the above definition could not be used to define asthma for the purposes of an epidemiological survey. For surveys the following definition may be more appropriate:

Asthma is a disease of the airways that makes them prone to narrow excessively in response to a variety of provoking stimuli (125).

Measurement of the patient's bronchial response to histamine was used to validate epidemiological questionnaires such as the International Union Against Tuberculosis and Lung Disease (IUATLD) Bronchial Symptoms Questionnaire (1984) (126). Answers to key questions were likely to predict a positive response to a histamine or methacholine challenge. Patients would be classified as asthmatic on the basis of a positive questionnaire and bronchial challenge test but may not have been given a clinical diagnosis by their doctor nor be in receipt of anti-asthma treatment. Jarvis et al (127) found that 25% of young adults in three East Anglian towns had experienced wheeze in the last twelve months yet only 6.6% were receiving anti-asthma medication. Crane et al conducted a similar survey in New Zealand and found that 26% of adults surveyed experienced wheeze in the last twelve months and only 9% were receiving anti-asthma treatment (128). Strachan et al conducted a similar study in children and found that 23% had "ever" wheezed, 15% of the children surveyed had experienced wheeze in the last twelve months and 13.6% were currently receiving medication for their asthma (129).

The discrepancy between the prevalence of asthma and the proportion of people receiving treatment may reflect the different definitions of asthma used. Epidemiological surveys were designed to estimate the number of people susceptible to provoking stimuli using a combination of specially designed questionnaires and bronchial hyperreactivity testing. People with a tendency towards mild bronchial hyperreactivity as well as those with established disease receiving medication were included.

Patients studied in the randomised controlled trials or many of the observational studies cited earlier had been diagnosed or labelled asthmatic by their doctor and were in receipt of some combination of anti-asthma therapy before they were included in the trial. The inclusion criteria for these trials tended to be based on some form of classification of asthma so that a specific group of asthmatics were selected and studied. The term

"asthma" covers a wide spectrum of disease from a mild episodic condition to a severe and persistent condition and can be classified in several ways.

In the past, asthmatics have been described as having intrinsic or extrinsic asthma. Woolcock and Peat in the Manual of Asthma Management (130) classify asthma under six headings according to the severity of symptoms, degree of airway hyperresponsiveness (AHR) and medication use; for details see table 1.1.

Description of airway disease	Baseline FEV ₁	AHR (direct stimuli)*	AHR (indirect stimuli)*	Symptoms of asthma at any time	Symptoms of asthma previous year	Medication used in previous year
Obstructed asthma	Decreased	Yes	Yes	Yes	Yes	Yes
Persistent asthma	Near normal	Yes	Yes	Yes	Yes	Yes
Episodic asthma	Normal	No	Yes / No	Yes	Yes	Yes
Asthma in remission	Normal	Yes	Yes	Yes	No	No
Potential asthma	Normal	Yes	?Yes	No	No	No
Trivial wheeze	Normal	No	No	Yes	?No	No

* AHR, airway hyperresponsiveness; direct stimuli, provocation with histamine or methacholine; indirect stimuli, provocation with exercise, hyperventilation or hypertonic saline.

Table 1.1 Classification of asthma from Woolcock and Peat (130).

The 1997 American National Asthma Education and Prevention Guidelines for the Diagnosis and Management of Asthma (2) modified the severity classification to include terms for both severity and frequency of symptoms; mild episodic, mild persistent, moderate persistent and severe persistent.

For the purposes of clinical trials asthma may be classified still further in order to define a clear study population. Several trials have used the American Thoracic Society classification to determine eligibility (53;80;83;84;89;92;131-133). The criteria used to identify the study population were:

1. An increase in $FEV_1 \geq 15\%$ of the initial value 60 minutes after inhaling 400 μg salbutamol and 80 μg ipratropium bromide.
2. Bronchial hyperresponsiveness (PC_{20} histamine $\leq 8 \text{ g/l}$).
3. Dyspnoea.
4. Allergy (positive test result to specific allergens).
5. 3 and 4 and / or wheeze.

This definition may be qualified still further by specifying the level of anti-asthma treatment permitted with or without specifying a period of stability. The BTS Asthma Management Guidelines (1;120;134) provide a useful method of classification where asthmatics could be classified according to the minimum level of treatment required to achieve control over their symptoms, for details see table 1.2. A minimum criterion for inhaled β_2 -agonist use could be set to ensure that patients were not included who were receiving more treatment than was necessary to control their symptoms. The inclusion criteria for TRUST (The Regular Use of Salbutamol Trial) specified steps one to three of the 1991 BTS Guidelines (120) excluding patients using long acting β_2 -agonists.

Step	Treatment Description	Aims of treatment
1	Occasional use of relief bronchodilators.	Minimal symptoms. Minimal exacerbations.
2	Regular inhaled steroids (or cromoglycate) plus occasional use of relief bronchodilators.	Minimal need for relief bronchodilators. No limitations to exercise. Circadian variation in PEF < 20%.
3	High dose inhaled steroids or low dose inhaled steroids plus long acting inhaled β_2 agonists plus occasional use of relief bronchodilators.	PEF \geq 80% predicted or best. Minimal adverse events from medication.
4	High dose inhaled steroids and regular bronchodilators.	Least possible symptoms. Least possible need for relief bronchodilators. Least possible limitation of activity. Least variation in circadian PEF.
5	As for 4 plus oral corticosteroids.	Best PEF. Least adverse effects.

Table 1.2 Classification of asthma using the 1995 BTS Guidelines on Asthma Management (1).

In order to assess whether an intervention has been effective or not a suitable outcome measure must be chosen. The choice of a suitable measure may depend on the type of intervention to be tested and may be different to the measurements carried out to establish an initial diagnosis of asthma.

1.3.2 Diagnosis of asthma

The diagnosis of asthma should be confirmed in every individual patient although the current American Thoracic Society (ATS) Guidelines, BTS Guidelines and the International Consensus Report on Diagnosis and Treatment of Asthma do not discuss the minimum requirements for a diagnosis (1;124;135). Evidence from an audit of the management of newly identified asthmatics in general practice found that only 19% of adults had had the results of any diagnostic test recorded in their notes (136).

Using the detailed definition from the “Global Strategy for Asthma Management”(124) the following aspects should be assessed in order to confirm the diagnosis:

1. Airway inflammation.
2. Symptoms:
 - Wheeze.
 - Breathlessness.
 - Chest tightness.
 - Cough.
 - Nocturnal waking.
3. Airflow limitation.
4. Increase in airway hyperresponsiveness.

It is not possible to measure all of these items directly and because of the episodic nature of the disease not all the signs and symptoms may be present at any one time. Some of the methods for assessing the signs are not suitable for use in general practice where most asthma is diagnosed so indirect measures tend to be used instead. Inflammation and the degree of airway hyperresponsiveness are particularly difficult to measure safely in general practice. An accurate history should include recording the symptoms and the degree of airflow limitation can be measured indirectly using spirometry. Taylor suggested that a careful history with spirometry would enable the diagnosis of asthma to be made (137). If some doubt remained then PEF and methacholine challenge could be used; one positive result confirming the diagnosis. Britton et al suggested that this would be insufficient and that a simple objective measure should be used but that this simple measure does not yet exist (138). The 2002

BTS / SIGN (Scottish Intercollegiate Guidelines Network) British Guideline on the Management of Asthma (Thorax, in press) recommend that the minimum requirements for a diagnosis of asthma in adults are a record of asthma symptoms and the results of an objective test such as 20% PEF diurnal variation or a 15% change in FEV₁ in response to treatment or a trigger.

1.3.3 Measuring change in asthma

If the diagnosis of asthma was made by confirming the signs and symptoms listed above, then it would seem logical to repeat these measurements over time to monitor change in the condition. In most cases it would not be feasible to assess the extent of the inflammation at diagnosis or after treatment unless the patient was taking part in a hospital based research project.

There is no recommended method for assessing symptoms in a clinical trial setting although several groups have developed and validated symptoms questionnaires such as the St George's Respiratory Questionnaire (139), Asthma Control Questionnaire and Asthma Control Diary (140) or the MRC Respiratory Symptoms Questionnaire (141). These questionnaires do not simply measure asthma symptoms but also measure the impact of these symptoms on the overall health status of the individual. They are often complicated to administer and the results difficult to interpret. In a clinical trial setting frequent assessments of symptoms may be advantageous because of the fluctuating nature of the disease and this could be achieved by using a detailed symptom score at each assessment or monitoring daily by diary card.

Use of inhaled β_2 -agonist is frequently used as an indicator of loss of control of asthma. The current BTS guidelines use the use of rescue inhaled β_2 -agonist as an indicator for introducing or stepping up preventive treatment (1).

Airflow limitation is the favoured method of measuring change in asthma. The best single measure for following the changes of airflow limitation is forced expiratory volume in one second (FEV₁), which provides a snapshot of the degree of airflow limitation (142). FEV₁ is linearly related to the severity of the airways obstruction

(142). The forced vital capacity (FVC) is less accurate because the patient may be experiencing air trapping behind the bronchoconstriction and the reading would be an underestimate of the true value. Both FEV₁ and FVC can easily be performed in general practice and reflect the condition of the asthmatic on that day. Measuring the FEV₁ / FVC ratio is a very sensitive test for borderline airways obstruction (142). A more useful measure might be to monitor peak expiratory flow (PEF) for two to three weeks and assess the degree of circadian variation particularly in those patients with normal spirometry at the first assessment.

Peak expiratory flow is a measure of the flow of air during forced expiration. It is very effort dependent and has twice the measurement variability of FEV₁ (142-144). The advantages of PEF are that it is extremely cheap to measure and a meter can be given to the patient to take home to record more frequent readings, which is particularly useful for very mild asthmatics. Ambulatory PEF monitoring allows a more accurate assessment of the variable nature of the disease, both within day and between day variability. The success of this does depend to an extent on the willingness of the patient to co-operate. The disadvantages of ambulatory PEF are poor compliance with the measurements and how to handle the large amount of data generated for each patient.

Giannini et al (145) compared PEF and FEV₁ for their ability to detect changes after bronchial provocation tests. They reported that PEF underestimated the change in airway calibre by about 10-15% but nevertheless is still correlated with FEV₁. A significant change in PEF corresponded to a greater change in FEV₁ (143). PEF seemed to have a low sensitivity for detecting small changes in the airways that may be important when trying to monitor mild to moderate asthmatics. Troyanov et al (146) concluded that PEF was as satisfactory as FEV₁ for describing circadian variation; in this trial the measurements were made every two hours for a two week period. Several other groups have concluded that whilst PEF was not reliable as a single measure of lung function it was very useful when performed frequently over shorter intervals. This technique is not without its problems; compliance becomes a factor when asking patients to perform measurements regularly and it has been estimated that only about 69% of measurements are performed correctly (147).

Airway hyperresponsiveness is frequently used in clinical trials to measure the effect of an intervention and is widely recommended as a diagnostic test although its use is limited to specialist centres. The degree of hyperresponsiveness correlates strongly with severity but it is not clear if this technique has any advantages over clinical monitoring (148). Airway hyperresponsiveness would not be a suitable measure for use in trials in primary care.

The overall outcome of a trial may depend on the primary outcome measure therefore it is important to standardise. For example, the Sears trial assessed the change in asthma control from baseline and reported a highly significant result (51). When the trial was reanalysed using exacerbation as a measure of effect there was no significant difference between regular fenoterol and placebo (54). In a trial of 47 asthmatics comparing low dose budesonide with placebo two different methods of assessing PEF were used; lowest PEF of the morning or evening readings (LPF) and diurnal variation (DVPF). Using LPF there was a significant result in favour of low dose budesonide and using DPVF there was no statistically significant difference between the two groups (149).

1.4 Thesis outline

The continued uncertainty of the safety of short acting inhaled β_2 -agonists prompted the development of TRUST. The trialists addressed the concerns regarding patient selection in an attempt to ensure that the safety of inhaled β_2 -agonists was assessed in a population representative of the majority of the UK asthma population. The definition of exacerbation for TRUST was developed during the pilot study to be sure that it identified clinically meaningful exacerbations.

TRUST was a collaborative trial with a trial steering committee (Appendix 2.1). Dr Graham Crompton drafted the outline proposal on behalf of the Therapy Working Group of the National Asthma Task Force and Professor Tak Lee was the principal investigator. The committee developed the draft into an application for funding with Professors Tak Lee and Peter Barnes and Dr Graham Crompton providing the clinical expertise, Mr Chris Frost provided the statistical advice and Dr Madge Vickers and

myself provided the trials advice. My role was to develop the protocol and the trial, under the close supervision of Dr Madge Vickers. My role included designing the trial questionnaires, choosing the quality of life tools, writing the standing operating manual, training the practices, setting up the quality control procedures and making applications to local research ethics committees and the Medicines Control Agency. I worked closely with the statisticians to ensure the integrity of the data. Mr Stephen Sharp and Mr Chris Frost analysed the TRUST data. The first draft of the paper was written by myself, Professor Tak Lee and Mr Stephen Sharp and revised by the members of the steering committee.

In addition to TRUST, a project to determine the measurement characteristics of different primary outcome measures compared to TRUST exacerbation was proposed. A systematic review was undertaken to identify randomised controlled trials of short and long acting β_2 -agonists. A list of the different combinations of primary outcome measures used was generated from those trials meeting the inclusion criteria. The TRUST data were analysed using the primary outcome measures identified and the results compared. I carried out the systematic review and all the statistical analysis, including the writing of all the statistical programs, with guidance from Mr Dan Altman and Mr Chris Frost. It was hoped that the results of this study would enable trialists to make an informed decision as the most effective means of assessing change in asthma in future clinical trials of long or short acting inhaled β_2 -agonists.

This thesis details the methods for TRUST with reference to the standard procedures for randomised controlled trials in Chapter 2. The main results of TRUST are presented in Chapter 3. The systematic review to identify randomised controlled trials of short and long acting β_2 -agonists is described in Chapter 4. Chapters 5 and 6 detail the analyses of the comparisons of the primary outcome measures identified in the systematic review. Chapter 5 describes the results of TRUST according to the primary outcome measure and Chapter 6 describes the comparisons with TRUST exacerbation to identify a suitable outcome for further trials. Chapter 7 concludes this thesis by summarising the current state of the inhaled β_2 -agonist debate and the proposed outcome measure resulting from the comparisons with TRUST exacerbation.

Chapter 2 - Methods

Chapter 2 describes the methods used in TRUST in the context of the general principles of clinical trials.

2.1 Introduction

TRUST was an initiative of the Therapy Working Group of the National Asthma Task Force and its membership included representatives from the BTS, the Royal Colleges, the regulatory agencies and the Department of Health. The National Asthma Task Force was set up in July 1991, under the auspices of the National Asthma Campaign, in response to the concerns over the safety of inhaled β_2 -agonists and asthma morbidity and mortality. The Therapy Working Group approached the MRC General Practice Research Framework (GPRF) to collaborate with them on the trial. The membership of the TRUST Steering Committee is listed at Appendix 2.1. The Medical Research Council (MRC) funded TRUST.

2.2 Aims

TRUST was designed specifically to answer the following questions:

Does regular inhaled β_2 -agonist therapy result in worse control of asthma than when used on demand?

Does concurrent use of regular inhaled corticosteroid therapy influence the effects of regular or on demand inhaled β_2 -agonists?

2.3 Method

TRUST was a randomised, double blind, placebo controlled trial of salbutamol 400 μ g four times daily for twelve months.

Dr G Crompton drafted an outline protocol for a pilot study on behalf of the Therapy Working Group of the National Asthma Task Force. The outline of the study was turned into an application for a pilot study and my role was to develop the protocol and the trial, under the close supervision of Dr M R Vickers. Copies of the initial outline and final protocol are at Appendices 2.2 and 2.3. Once the final version of the protocol had been approved the trial paperwork, procedures and the Standing Operating Manual could be written.

The trial followed the format below for a randomised controlled trial (150;151):

1. Define reference population.
2. Selection of study population.
 Exclude unsuitable individuals.
3. Selection of suitable subjects:
 Identify those refusing.
4. Informed consent.
5. Baseline measurements.
6. Random allocation:
 Standard or placebo treatments.
7. Follow up all subjects in both groups:
 Defaulters, losses to follow-up.
8. Assessment of defined outcome:
 Attention to compliance and losses to follow-up.
9. Analysis.
10. Interpretation.

2.3.1 Reference population

The reference population is the population to which the results of the trial will be extrapolated (150). In the case of TRUST the reference population was all adults eighteen years and over, with mild to moderate asthma treated according to steps one to three of the BTS asthma management guidelines (1) and managed in general practice.

2.3.2 Study population

The study population should be a representative sample of the reference population (150). In TRUST it was important to exclude patients with suspected COPD and those whose asthma was very stable, as they might not be expected to experience an exacerbation during the course of the trial. The inclusion criteria for TRUST were:

1. Males and females aged eighteen years and over.
2. Asthma of at least one year's duration.
3. Current use of an inhaled β_2 -agonist at least twice per week.
4. No oral steroids or increased dose of inhaled steroids within six weeks of trial entry.
5. Bronchial asthma defined as a PEF greater than 50% of the predicted normal with 15% diurnal variability and an absolute minimum PEF variability of 60 litres per minute. This was confirmed by previous documentation in the medical notes or by measurement during the run-in period.

Patients were excluded if any of the following applied:

1. Treatment with oral or increased inhaled corticosteroids within six weeks of trial entry.
2. Inhaled steroids at a dose greater than 2 mg per day
3. Admission to hospital because of asthma within six weeks of trial entry.
4. A requirement for inhaled β_2 -agonist therapy less than twice per week.
5. Treatment with sodium cromoglycate, nedocromil sodium, ipratropium bromide, oxitropium bromide, theophyllines, long-acting inhaled and any oral β_2 -agonist preparation.
6. Other significant lung disease or concomitant major illness.
7. Pregnancy or suspected pregnancy.
8. Inability to use usual inhaler or trial inhaler correctly.
9. Inability to use a peak flow meter or complete a diary card.

Patients who had experienced an exacerbation requiring additional treatment or hospital admission within six weeks of trial entry and who were keen to participate in TRUST were asked to wait six weeks and were reassessed. They were randomised and

completed the run-in if they were eligible on reassessment. This may have resulted in the exclusion of some patients who could have contributed to the exacerbation rate in TRUST but was required on safety and ethical grounds.

The results of the pilot study suggested that between 70 and 80 practices with an average list size close to 10 000 would be required to recruit 1000 patients to TRUST, with an expected recruitment of 12 to 15 patients per practice. Initially 73 practices from throughout the United Kingdom with an average list size of 7683 were recruited to TRUST. There were no selection criteria set for recruiting the practices other than an interest and willingness to take part although large practices were chosen when possible. Practices were selected from the GPRF database if they had previously expressed an interest in taking part in an asthma trial or if they had contacted other members of staff at MRC EMCU to ask if they could take part in a trial.

It quickly became apparent that more practices would be needed if the target of 1000 patients was to be reached. A further 20 practices with a mean list size of 7683 were approached and agreed to take part. A final wave of practices was recruited after the Trial Steering Committee meeting in November 1996. An additional 38 practices were recruited with an average list size of 1132. In total 115 general practices with a mean list size of 8218 recruited patients to the trial. To enable these practices to proceed required making applications to the Clinical Research Ethics Committee of the Royal College of General Practitioners and to 79 Local Research Ethics Committees (LREC) of which 78 approved the trial (152).

An initial note search was carried out once LREC approval had been granted and the practice nurse had been trained. The purpose of the note search was to identify the study population. The practices used the practice computer to generate a list of all those patients eighteen years and over who had been prescribed inhaled β_2 -agonists with or without inhaled corticosteroids. In many practices the computer could then be used to exclude those patients receiving any of the other anti-asthma medications listed in the exclusion criteria. The nurse manually searched the notes of the patients remaining on the list. The list of names, including those who were excluded, was sent to MRC EMCU where they were entered onto the computer. A list of patients, study numbers,

labels, invitation letters and a very brief questionnaire were then sent to the practices for them to send to all those people potentially eligible for TRUST.

2.3.3 Selection of suitable subjects

Invitation letters and a brief questionnaire were sent from the practice to all the patients identified from the note search (Appendix 2.4). A reminder letter and questionnaire were sent to those patients not replying within a month to the first letter. The nurse collected the returned questionnaires and identified those patients who still appeared to be eligible and invited them to a screening appointment.

At the screening interview the research nurse gave an explanation of the trial and completed the screening questionnaire (Appendix 2.5) to determine whether the patient was still eligible. Patients who were eligible and interested in participating were given an information sheet (Appendix 2.6) and an appointment was made for at least one week's time for the run-in visit. Patients were free to discuss the trial with friends and family before making a decision to take part in the trial.

2.3.4 Informed consent

Written informed consent was obtained at the run-in assessment, at least one week after the screening appointment (Appendix 2.7).

2.3.5 Baseline measurements

There was a three-week run-in period when the patients were asked to record their PEF, symptoms and medication use in a diary card (Appendix 2.8). This was used to calculate the patients' baseline values for the trial.

2.3.6 Random allocation

The research nurse informed EMCU of those patients who were eligible, had given their consent and had started the run-in period. These patients were stratified into three groups according to their baseline inhaled corticosteroid usage:

1. Inhaled β_2 -agonists alone.
2. Inhaled β_2 -agonists and inhaled corticosteroids up to and including 800 μg per day.
3. Inhaled β_2 -agonists and inhaled corticosteroids from 801 μg up to and including 2000 μg per day.

The details of the total daily dose of inhaled corticosteroids entered onto the randomisation form was checked against the total daily dose entered on the screening form. Any discrepancies were checked with the practices before the patient was randomised. Patients were randomised to receive either salbutamol 400 μg or matched placebo four times daily via a Diskhaler.

The randomisation was carried out centrally and was completely at random until the numbers in each group became imbalanced overall or within a practice. No account was taken of exclusions after randomisation in the randomisation procedure. The underlying assumption was that any exclusions would occur equally between the two groups.

2.3.7 Follow-up

Once started on trial medication all patients were followed up at monthly intervals for twelve months or until they withdrew or were lost to follow-up. At each visit the patients returned their completed diary card and the used and unused trial medication, a brief assessment form was completed (Appendix 2.9), used and unused Diskhaler blisters counted to assess compliance and new trial medication and diary card issued. At entry, six and twelve months the St George's Respiratory Questionnaire (SGRQ) and the SF-36 were completed.

A form was completed for all patients who withdrew from the trial detailing the reason(s) for withdrawal (Appendix 2.10). Patients who experienced four serious exacerbations requiring treatment were withdrawn from the trial as were women who became or suspected that they were pregnant. Patients withdrawing from the trial were asked to sign a further consent form, (Appendix 2.11), giving permission to search their

notes at the end of the period that they would have been in the trial had they completed the full twelve months' follow-up.

2.3.8 Assessment of defined outcome

The primary outcome measure for TRUST was exacerbation. The initial definition proposed in September 1992, before the start of the pilot study, was any one of the following:

1. Increased use of rescue β_2 - agonist (more than four puffs per 24 hours).
2. Decreased PEF (more than 30% of baseline or actual decrease of greater than 50L per minute).
3. Increased symptoms (greater than one point on a four point scale symptom score over one week).
4. Increase in disease severity which results in the general practitioner prescribing extra treatment.
5. Treatment with oral prednisolone.

This definition of exacerbation did not identify all clinically meaningful exacerbations in the pilot study data. The definition was modified to enable the practices and the patients to decide whether they were experiencing an exacerbation and whether the patients should be prescribed a short course of oral corticosteroids. The definition used for the pilot study and the application for funding to MRC in July 1994 was any of the following:

1. Fall in morning PEF to <70% of baseline reading on two or more consecutive days.
2. Increase in the need for rescue β_2 - agonist to six or more inhalations per 24 hours on two or more consecutive days.
3. Wakening due to nocturnal asthma and need for β_2 - agonists use on two or more consecutive nights.
4. Worsening asthma symptoms during the day on two or more consecutive days.
5. Clinical need for oral corticosteroids.

Recovery from an exacerbation was defined as:

1. Return to baseline symptom score for seven days.
2. Morning PEF returned to baseline for seven days.

Exacerbations were initially detected in two ways: the diary card and a question on oral steroid use in the past month in the follow - up assessment form. The symptom score on the diary cards used a six point scale rather than four point scale because it gave greater flexibility and the diary cards were based on those used by the National Heart and Lung Institute. Patients were asked to record their PEF as the best of three in the morning and the evening before taking any medication. They were also requested to fill in the number of puffs of their rescue β_2 -agonist taken each day.

The data from the pilot study diary cards were used to validate the definition of exacerbation. The data were entered on to the computer and a programme written, using the definition of exacerbation, to identify those patients experiencing a TRUST exacerbation. The exacerbations were then presented to the clinicians on the Steering Committee who discussed each exacerbation in turn in terms of its clinical significance. The data were presented without reference to the treatment allocation of the patients concerned. The result was a definition for the start and end of an exacerbation that represented a “true and clinically significant” exacerbation.

The final working definition of an exacerbation for TRUST was:

1. Use of oral or increased inhaled corticosteroids.

Or at least two or more of the following:

2. Fall in PEF to less than 80% of median baseline level.
3. Bronchodilator per 24 hours increased by three or more over median baseline level.
4. Symptom score increased during the day or at night, by two or more over median baseline level.

The end of an exacerbation was defined as the cessation of oral corticosteroids or return to original dose of increased inhaled corticosteroids together with all the following criteria on two consecutive days:

1. PEF > 80% median baseline level.

2. Bronchodilator inhalations per 24 hours increased by no more than two over median baseline level.
3. Symptom scores increased day and night by no more than one over median baseline level.

The baseline values were calculated using median values rather than mean values to reduce the effect of exceptionally high or low values on the average value. Because asthma is characterised by fluctuations in PEF and symptoms, using the mean to calculate the baseline value could result in a misleading high or low baseline value for an individual patient.

The secondary outcomes were:

1. Use of rescue inhaled β_2 -agonist.
2. Diurnal variation in PEF.
3. Symptom score.
4. Days lost from work / normal activities.
5. Use of NHS services - including GP and hospital consultations.
6. Changes in overall score on the quality of life questionnaire.

2.3.8 Analysis and interpretation

The results of TRUST will be presented in chapter 3.

2.4 Summary

The detailed methods for TRUST have been described with reference to general principles of clinical trials. Throughout the course of the trial there were regular Data Monitoring and Ethics Committee (DMEC) meetings and Trial Steering Committee meetings. The purpose of these meetings was to monitor the progress of the trial, to determine trial stopping rules and to ensure that the project milestones were achieved on time. Unblinded trial data were presented to the DMEC but only they and the statisticians had access to this information. The remaining trialists were blind to the

treatment allocation until the final analysis had been completed. The trial results will be presented in chapter 3.

Chapter 3 – TRUST Results

This chapter describes the main results and baseline characteristics of the patients randomised to TRUST.

3.1 *Recruitment*

One hundred and fifteen UK general practices, with a mean list size of 8218 patients, recruited 983 patients to TRUST, which was an average of 8.6 per practice. For a map of the location of the practices see Figure 3.1. Recruitment to TRUST was lower than for the pilot study when recruitment was 13 per 10 000 list size. In the main trial there were 10.5 patients per 10 000 list size. Figure 3.2 illustrates the number of patients randomised to TRUST over time and Figure 3.3 plots the number of patients randomised per practice list size. One possible explanation for the lower recruitment was the impact of the asthma management guidelines on asthma care in general practice. The pilot study was carried out between September 1993 and September 1994 and the first patient was not recruited to the main trial until July 1995. In the main trial 44% of patients not eligible at screening were excluded because their inhaled β_2 -agonist requirement was less than twice per week compared to 19% in the pilot study. This reflected a greater use of inhaled steroids and less reliance on inhaled β_2 -agonists (153). The identification and flow of patients in TRUST is illustrated by the flow chart in Figure 3.4.

3.2 *Withdrawal rate*

The withdrawal rate was similar between the two groups. Patients were considered to have completed the trial if they attended the 1-year visit or if they were withdrawn for protocol reasons: i.e. four treated exacerbations or one untreated exacerbation lasting longer than 30 days. Overall, 66% (320 / 486) of the placebo and 68% (340 / 497) of the active group completed the trial. In total 33% (323 / 983) patients did not complete the trial and of those 24% (240 / 983) withdrew for non-protocol reasons and 8% (83 / 983) were lost to follow-up (Figure 3.4).

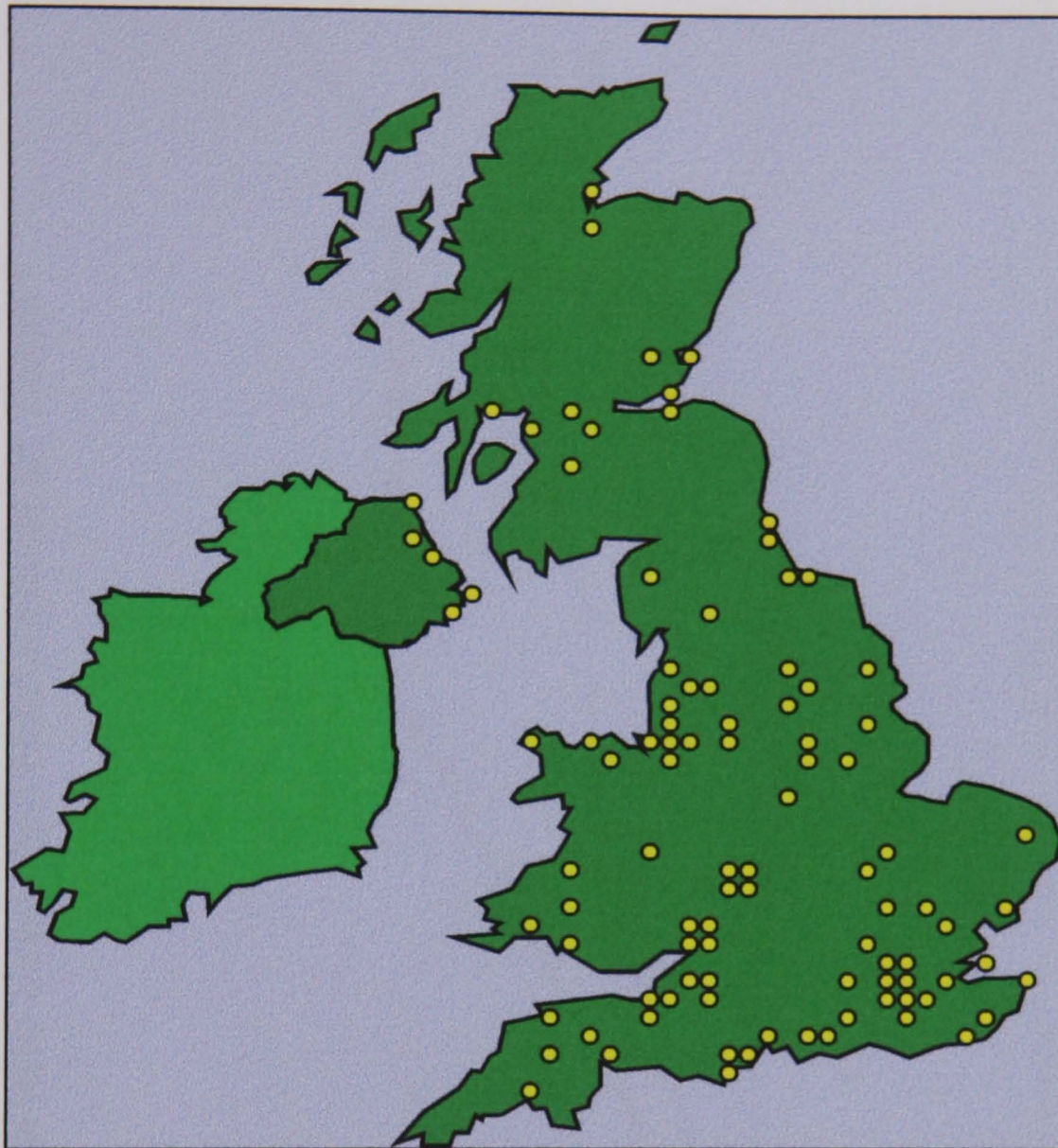
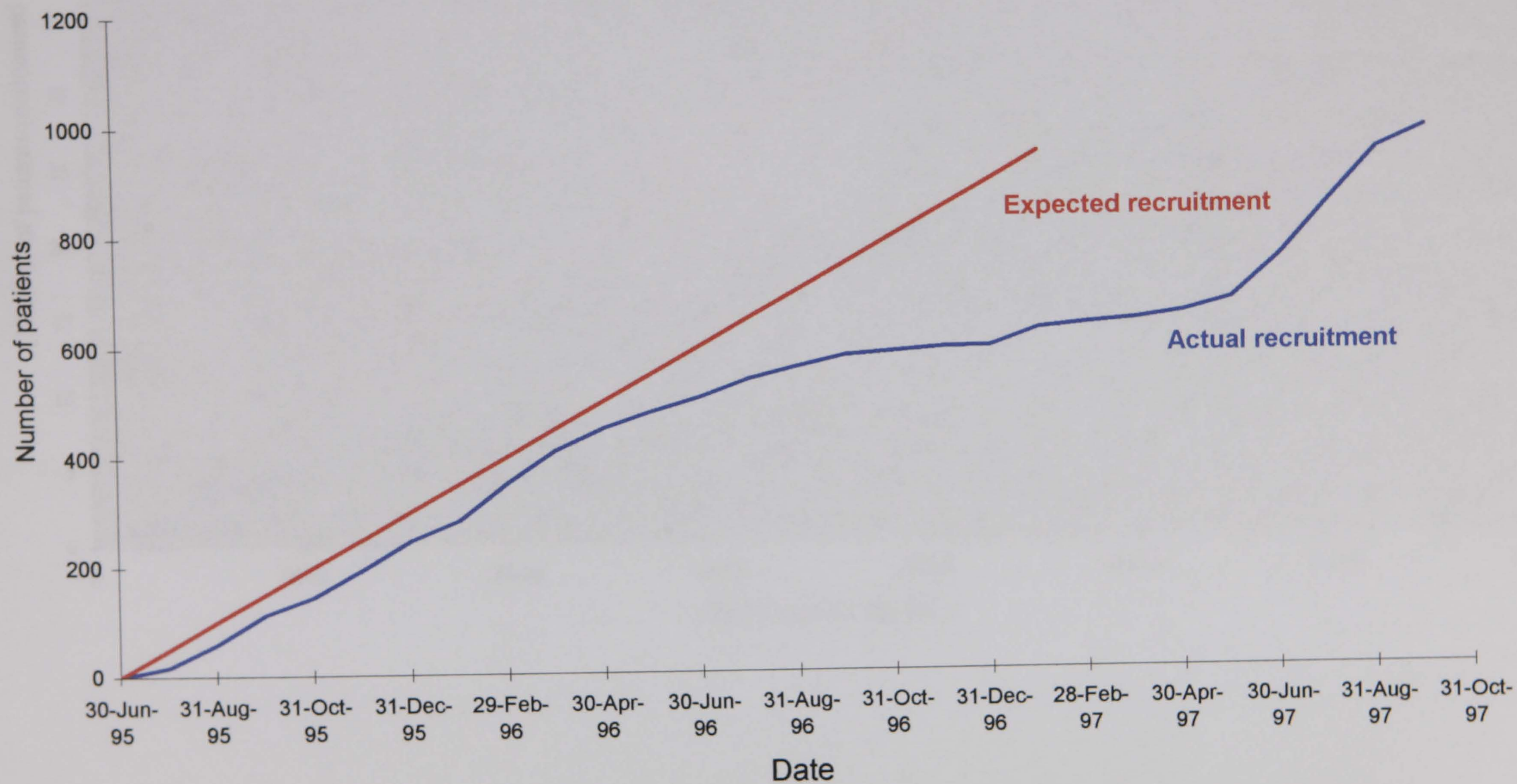
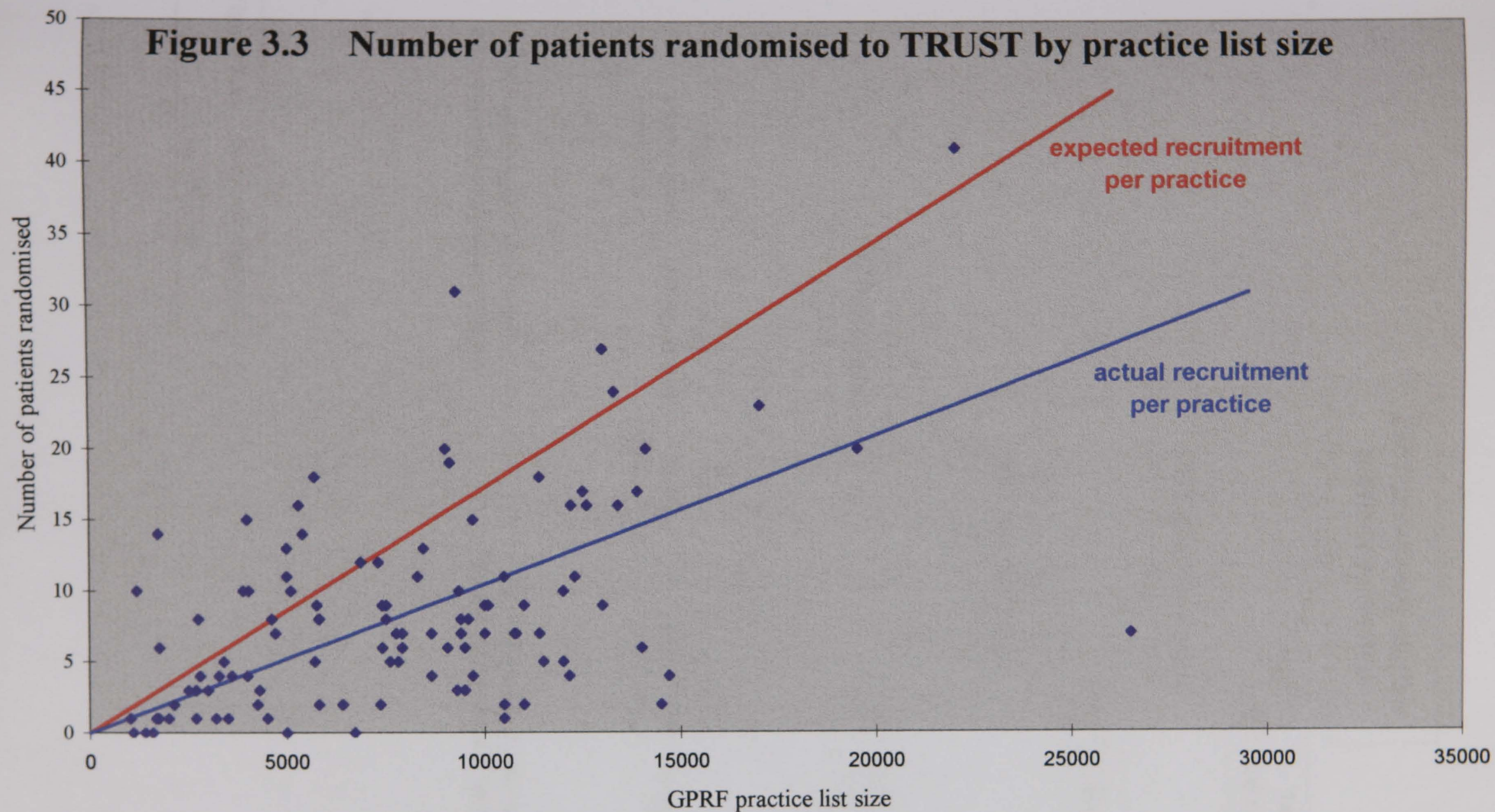


Figure 3.1. A map to show the location of TRUST practices

Figure 3.2 Actual and expected recruitment to TRUST





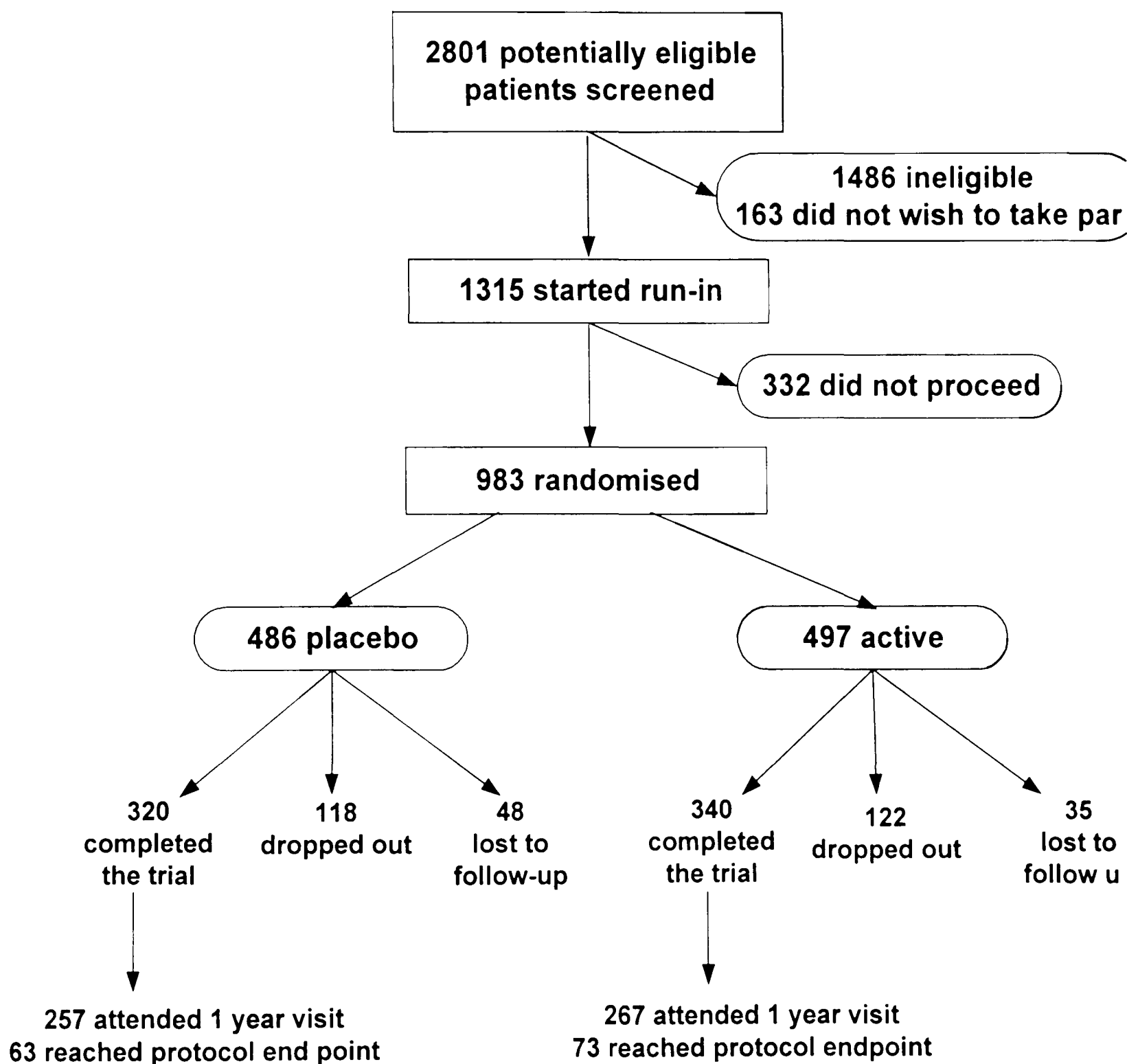


Figure 3.4 Flow of patients
in TRUST

3.3 Baseline

486 patients were randomised to receive placebo and 497 to receive active salbutamol. The two groups were similar with respect to gender, age, smoking, inhaled corticosteroids use and asthma severity (Table 3.1).

Characteristics	Placebo (n = 486)	Active (n = 497)
Number (%) male	211 (43%)	208 (42%)
Number (%) in age groups		
<25 years	39 (8%)	39 (8%)
25 – 34 years	86 (18%)	106 (21%)
35 – 44 years	100 (21%)	101 (20%)
45 – 54 years	98 (20%)	101 (20%)
55 – 64 years	89 (18%)	76 (15%)
65 – 74 years	66 (14%)	64 (13%)
≥ 75 years	8 (2%)	10 (2%)
Number (%) current smokers	78 (16%)	88 (18%)
Number (%) using steroids		
No steroids	49 (10%)	53 (11%)
800 mg or less	353 (73%)	359 (72%)
More than 800 mg	84 (17%)	85 (17%)
Number (%) on salbutamol	442 (91%)	435 (88%)
Number (%) on terbutaline	41 (8%)	56 (11%)
Mean (SD) PEF as % of predicted normal	85% (16)	86% (15)

Table 3.1 Characteristics at baseline in the two randomised groups.

3.4 Exacerbations

There was no difference in annual exacerbation rate between the two randomised groups according to the definition of exacerbation developed during the pilot study. There was no difference between the two randomised groups when the data were analysed

according to baseline inhaled corticosteroids use (see section 2.3.6). There was no difference in the number of exacerbations experienced or duration of exacerbations, table 3.2.

	Placebo (n = 486)	Active (n = 497)
Exacerbation rates		
Annual exacerbation rate (95% confidence interval) (No exacerbations / patient years of follow-up)	1.30 (1.18 to 1.43) (438 / 337)	1.25 (1.14 to 1.38) (425 / 339)
Exacerbation details		
No (%) patients with at least one exacerbation	223 (46%)	214 (43%)
No (%) patients with at least two exacerbations	114 (23%)	99 (20%)
No (%) of exacerbations according to duration of first exacerbation:		
≤ 1 week	56 (25%)	57 (27%)
1 –2 weeks	64 (29%)	67 (31%)
> 2 weeks	103 (46%)	90 (42%)
No (%) of exacerbations according to duration of all exacerbation:		
≤ 1 week	146 (33%)	134 (32%)
1 –2 weeks	121 (28%)	127 (30%)
> 2 weeks	171 (39%)	164 (39%)
No (%) of exacerbations according to criteria at start of exacerbation:		
Corticosteroid use and at least 1 diary card criterion	54 (12%)	58 (14%)
Corticosteroid use but no diary card criteria	166 (38%)	181 (43%)
Diary card criteria but no corticosteroid use	218 (50%)	185 (44%)

Table 3.2 Exacerbations in the two randomised groups.

3.5 *Secondary outcomes*

The secondary outcome measures for TRUST were:

1. Use of rescue inhaled β₂-agonist.
2. Diurnal variation in PEF.

3. Symptom score.
4. Days lost from work / normal activities.
5. Use of NHS services - including GP and hospital consultations.
6. Changes in overall score on the quality of life questionnaire.

3.5.1 Use of rescue inhaled β_2 -agonist

Daytime rescue β_2 -agonist use was significantly less in the active group compared to the placebo group ($p < 0.01$) and those on active treatment required less night time reliever use than those on placebo treatment, see table 3.3.

3.5.2 Diurnal variation in PEF

Mean diurnal variation in PEF was significantly higher with active treatment compared to placebo ($p < 0.001$). There was no difference in mean morning PEF between placebo and active but evening PEF was significantly higher with active treatment ($p < 0.01$), see table 3.3.

3.5.3 Symptom score.

There was no difference in the proportions of symptom free nights between the two treatment groups but those on active treatment had a small increase in the proportion of symptom free days, see table 3.3.

3.5.4 Days lost from work / normal activities

There was no difference in the number of days off work between the two treatment groups.

3.5.5 Use of NHS services - including GP and hospital consultations

Very few patients required hospital treatment for their asthma during the course of the trial, six in placebo group and seven in the active group.

3.5.6 Changes in overall score on the quality of life questionnaire

There was no difference in any of the dimensions of the mean Short Form 36 (SF-36) scores between the two treatment groups.

	Placebo (n = 486)	Active (n = 497)	Active – placebo* (95% CI)
Morning PEF (l/min)			
Run-in	404 (4.7)	402 (4.7)	
Follow-up	408 (4.8)	406 (4.9)	0.2 (-3.8 to 4.2)
Evening PEF (l/min)			
Run-in	417 (4.7)	419 (4.6)	
Follow-up	419 (4.7)	432 (4.7)	10.3 (6.7 to 14.0)†
Diurnal variation (%)			
Run-in	4.2 (0.4)	5.4 (0.4)	
Follow-up	3.4 (0.3)	7.7 (0.5)	3.3 (2.5 to 4.1)†
Symptom free nights (%)			
Run-in	59.0 (1.7)	56.8	
Follow-up	62.1 (1.7)	61.0 (1.7)	1.2 (-1.9 to 4.4)
Symptom free days (%)			
Run-in	37.7 (1.6)	37.9 (1.6)	
Follow-up	46.0 (1.7)	52.4 (1.7)	5.7 (2.0 to 9.3)‡
Night time rescue use (puffs)			
Run-in	0.83 (0.05)	0.78 (0.04)	
Follow-up	0.56 (0.03)	0.48 (0.03)	-0.10(-0.18 to -0.03)‡
Daytime rescue use (puffs)			
Run-in	2.40 (0.10)	2.20 (0.09)	
Follow-up	1.60 (0.08)	1.26 (0.08)	-0.30(-0.47 to -0.13)†
Days of work			
Run-in	0.6 (0.3)	0.9 (0.3)	
Follow-up	0.8 (0.2)	0.6 (0.2)	-0.2 (-0.7 to 0.3)

Baseline measurements were made during 3-week run-in period and follow-up measurements after randomisation. Values based on calculating mean value over time for each patient and then calculating the mean (SE) of these patient-specific averages for each group.

*Adjusted for baseline using analysis of covariance, †p<0.01, ‡p<0.001.

Table 3.3 Secondary outcome measures.

3.6 Discussion

The results of TRUST suggest that regular use of salbutamol for 52 weeks was not associated with more exacerbations in patients with mild to moderate asthma. These results complement those of Drazen et al (95) who reported similar results for those patients taking inhaled β_2 -agonists alone to control their asthma. These results contradict those of Sears et al (51;121) who reported worse asthma control with the regular use of fenoterol, probably because of the choice of primary outcome measure used in the Sears trial. The results of TRUST support those from trials of long acting β_2 -agonists (52;72-77;79-82;84;86;89-91;96;97;99;101;103-106;108-112).

The results of TRUST are particularly relevant to asthmatics in the United Kingdom, over 70% of whom are treated with inhaled corticosteroids up to and including 2mg per day. The sample size was large enough to detect a clinically significant difference in exacerbation rate between the two groups and the exacerbation rate in the placebo group was close to the 1.5 exacerbations per patient per year expected. A retrospective power calculation determined that with 983 patients TRUST had 86% power to detect a change of 20% in the exacerbation rate, and 55% power to detect a change of 15% in the exacerbation rate if the average annual rate of exacerbation in patients in the placebo group was 1.3. The power was lower when calculated retrospectively because the calculation was adjusted to take into account the over dispersion of exacerbations in some patients. The significant increase in evening PEF with regular salbutamol was as a result of the pharmacological effect of regular bronchodilator use but was too small to be clinically relevant.

The results of TRUST, along with the results of similar trials of long and short acting β_2 -agonists, provide strong evidence that inhaled β_2 -agonists do not cause a worsening of asthma. However, short acting β_2 -agonists should be used with caution to prevent patients relying too heavily on them and failing to seek additional treatment when control worsens.

Chapter 4 - Systematic Review

This chapter describes a systematic review that was undertaken to identify all randomised controlled trials of β_2 -agonists in mild to moderate asthma.

4.1 Introduction

The aim of this systematic review was to identify all randomised controlled trials of inhaled β_2 -agonist therapy in mild to moderate asthmatics. The primary outcome measures from those trials fulfilling the systematic review inclusion criteria were extracted. A systematic review was carried out rather than a simpler search of the literature to ensure that as many trials and their different primary outcome measures were identified as possible.

The systematic review was undertaken in response to a NHS Executive Asthma Management National Research and Development Programme call for proposals in November 1996 (see Appendix 4.1) although not funded. Thorough checks of the Cochrane Database of Systematic Reviews (CDSR), the NHS Centre for Reviews and Dissemination (CRD) Database of Abstracts of Reviews and Effectiveness (DARE) were carried out using the Cochrane Library (Issue 3, 2001) and the Internet. There were no relevant systematic reviews listed on either of the two databases searched. The NHS Executive Asthma Management National Research and Development Programme commissioned one relevant systematic review from the call for proposals in November 1996. The aim of the commissioned review was to formally evaluate the properties of the outcome measures used routinely in clinical trials in asthma for each type of anti-asthma medication.

4.2 Methods

The method for undertaking this systematic review was taken from the NHS Centre for Reviews and Dissemination (CRD) Guidelines for Those Carrying Out or Commissioning Reviews, CRD Report Number 4 January 1996 (154).

Knipschild argued that a systematic review should be an exhaustive process and should include papers from many sources including non-English language sources (155). Dickerson, in a study to examine the sensitivity and precision for Medline searches for randomised controlled trials found that the 18% of the articles identified were not in English and 20% of Medline listed articles overall were not in English (156). This was taken into account when conducting the search for this project, however because there was no funding available for translation, this search was restricted to papers in the English language with an abstract on Medline. Trials were excluded if they did not meet the inclusion criteria without incurring unnecessary expense. According to the information on Ovid Medline, over 60% of Medline records after 1975 contain abstracts.

The initial literature search was undertaken using Ovid Medline and the Cochrane Controlled Trials Register (CCTR) (Issue 3, 2001) with a further search of the reference lists of all papers fulfilling the inclusion criteria. The search was conducted through Ovid Medline and CCTR with a second search of the reference lists of all papers identified and included from the two searches. The modified Medline search method of Dickerson, from the *CRD Guidelines for Those Carrying Out or Commissioning Reviews* (154) was used to identify the initial trials. The search strategy for Medline is included at Appendix 4.2.

The inclusion criteria for trials were set as:

1. Randomised controlled trials.
2. Double blind allocation.
3. Four or more week's treatment period.
4. "Clinical" primary outcome measures.
5. Inhaled β_2 -agonist therapy.
6. Mild to moderate asthma.
7. Adults 16 years and over.
8. English language.
9. Abstract on Medline.
10. Medline database from 1966 to 2001.

It was important to limit the search to trials with a "clinical" primary endpoint as opposed to an endpoint such as bronchial hyper-reactivity. The aim of this review was to identify a standard outcome measure or combination of outcome measures for use in clinical trials of inhaled bronchodilator therapy, which would be relevant in a primary care setting. This environment was chosen because most mild to moderate asthmatics are managed by their general practitioner and because the results of this project may be of use to health care professionals to assess asthma control in their patients.

"Clinical" outcomes included PEF, symptoms, rescue inhaled β_2 -agonist use, exacerbations, hospital or primary care visits. Trials were excluded if the primary outcomes were methacholine or histamine challenges, dose-response studies, dose-reduction studies, serial FEV₁ measurements, biochemical or histological measurements or cardiovascular outcomes because these measurements are difficult to make in general practice where the majority of asthmatics are managed. Trials were also excluded where the primary endpoint was FEV₁ because measurements of FEV₁ were not made during TRUST and the data from TRUST were used for the analysis to compare the primary outcome measures.

The information was collected from all the papers using the data collection sheet at Appendix 4.3 and the information stored using Lotus 123 and Reference Manager[®] for Windows. The purpose of this data collection sheet was to ensure that all the papers were read objectively and the relevant information retrieved. It allowed a further, non-biased, decision to be made about whether a paper was included in the final selection. The checklist included the recommended inclusions for randomised controlled trials.

The results of the trial did not influence the decision as to whether to include the article in the review. The aim of the data retrieval process was to confirm that the trial met the inclusion criteria for the review and to document the primary and secondary outcome measures used.

4.3 Results

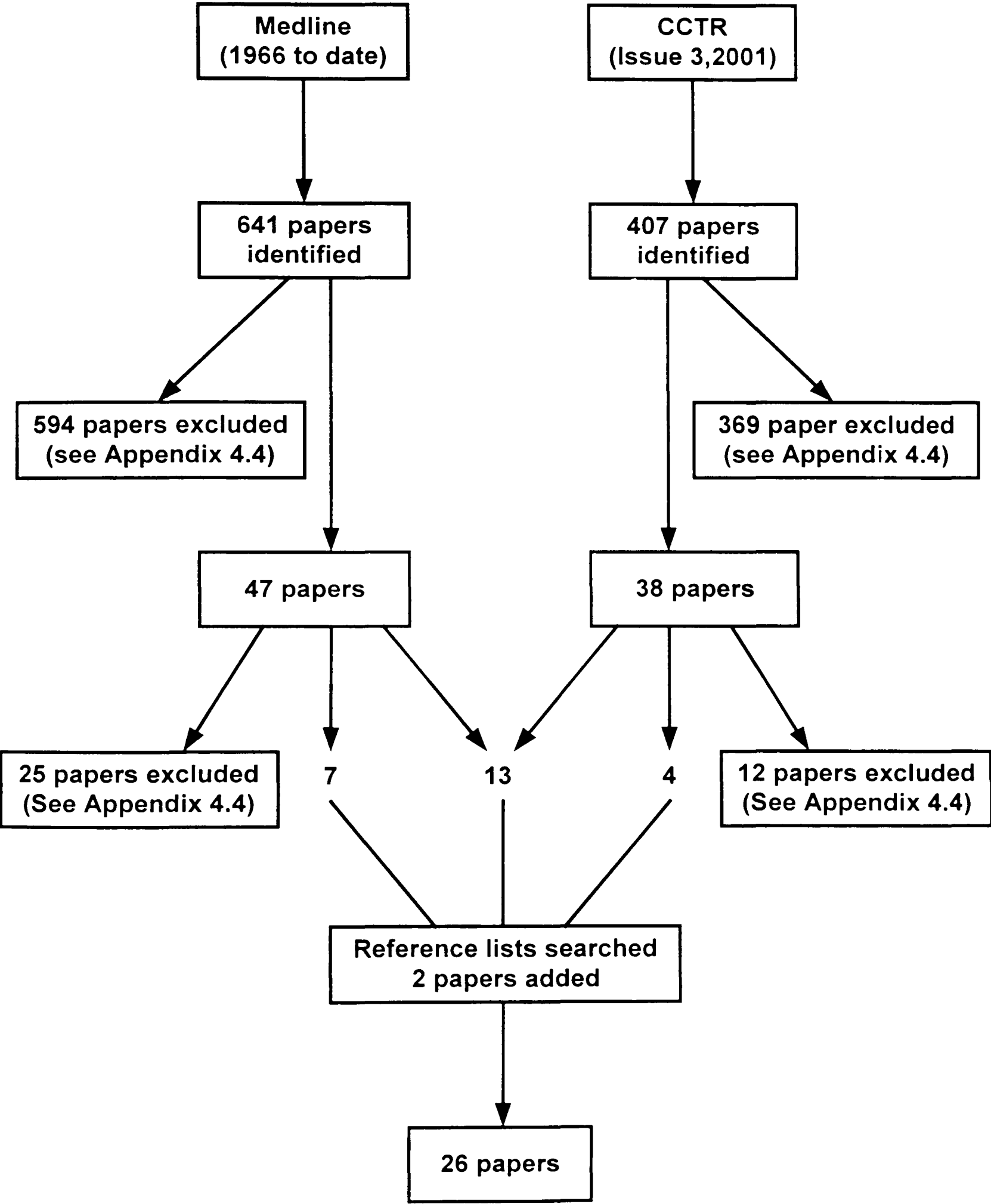
Using the Medline search strategy at Appendix 4.2, 641 papers were identified and a search of CCTR yielded 407 papers. A total of 591 papers were excluded from the Medline search and 369 from the CCTR search after reading the abstract. Eighty-five papers from the two searches appeared to fulfil the inclusion criteria of which 24 were selected after reading the papers. The reference lists of the 24 papers were searched and a further two papers identified and included. Figure 4.1 details the search for papers by flow chart and the reasons for exclusion from the review are listed in the tables at Appendix 4.4.

In total the searching procedure identified 26 papers fulfilling the inclusion criteria. The papers are listed at Appendix 4.5 and the primary outcome measures used in these trials are listed below.

1. Mean PEF (morning, evening or both) (69;71;86;91;95-98;106;108-110;112;157;158).
2. Diurnal variation (77).
3. Symptoms (94;103).
4. Asthma control (51;83).
5. Exacerbation (101;104;105;107;111;123).

The specific details of the individual primary outcome measures will be detailed in Chapter 5 when the analysis using these measures will be described.

Figure 4.1. A flow chart detailing the search for papers to be included.



4.4 Discussion

The systematic review identified 26 trials and five different choices of primary outcome measure to assess the effect of the interventions tested. Fifteen of the trials identified used PEF as the primary outcome measure, one used diurnal variation, two used symptom score and the remaining trials developed composite measures of asthma control or exacerbation that varied in the emphasis on different diary card variables. Three papers reported the use of more complex modelling techniques to analyse mean PEF using a mixed effects linear model (95;96;112). This more complex modelling was not used for further analysis in this project because it was difficult to make comparisons with TRUST exacerbation. The variety of primary outcome measures used in these 26 papers highlighted the dilemma researchers faced when trying to decide which measures to use for their particular trial.

Whilst FEV_1 provides the most reliable measure of airflow limitation because it is highly reproducible and depends less on patient co-operation than PEF it only provides a snapshot of the asthma because the measurements can usually only be made during clinic visits. When planning TRUST we decided not to carry out FEV_1 measurements because of the huge expense involved in equipping each of the 116 practices with hand held spirometers. Whilst single PEF readings are associated with more noise than FEV_1 readings when many PEF readings are averaged over a period of time they may provide a more accurate picture of the fluctuating nature of the condition. However, daily PEF recordings are associated with reduced compliance. In the primary care setting many patients do not have their FEV_1 assessed because practices may not have access to spirometers and it is unlikely that many patients would have their own hand held spirometer for daily use.

Several groups developed a primary outcome measure using a combination of factors (51;83;101;104;105;107;111;123). Whilst there were some similarities between the combination of measures chosen the emphasis or priority given to certain components may have been different.

In order to determine the measurement properties and characteristics of the different primary outcome measures identified by this systematic review they were compared using the TRUST data.

4.5 Summary

The systematic review identified 26 trials for inclusion in the next stage of the analysis to compare the primary outcome measures with the TRUST definition of exacerbation.

Chapter 5 – Analysis of TRUST Dataset

Chapter 5 describes the results when TRUST was analysed using the primary outcome measures identified in the systematic review.

5.1 *Introduction*

When taking part in randomised controlled trials to assess anti-asthma therapies, patients were frequently asked to complete daily asthma diary cards. They were typically asked to record PEF and symptoms in the morning and evening before medication, additional doses of inhaled β_2 -agonists, changes in inhaled corticosteroid medication or courses of oral corticosteroids and days off work with asthma or visits to the hospital or GP for their asthma. Each patient generated a huge amount of diary card data for the period they were in the trial. Analysing these data was very difficult because of the enormous volume of data involved and because asthma is characterised by frequent fluctuations in PEF or symptoms.

It was clear from the systematic review that several different methods for analysing diary card data from randomised controlled trials had been tried. Some of the earlier trials were analysed using a single variable such as mean morning PEF (69;71;86;91;95-98;106;108-110;112;157;158) or diurnal variation (77). More recently the emphasis seems to have been on the development of composite measures of asthma control such as the Sears measure of asthma control (51;83), various definitions of exacerbation (101;104;105;107;111;123) or complex modelling of PEF data (95;96;112). Because asthma is a fluctuating disease simply averaging variables, such as morning PEF, over the follow-up period may result in the loss of information about daily fluctuations in PEF or symptoms. For example, a patient may have experienced several severe fluctuations in PEF during the course of the follow-up but overall their mean follow-up PEF had changed little from baseline PEF. The possible advantage of the definitions of asthma exacerbations was that they attempt to overcome this loss of information and identify days of change whilst enabling the researchers to deal with the vast amount of data collected. The definitions of exacerbation were developed independently of one another with subtle variations in the emphasis on the diary card variables. There is no

information as to how they compare in their ability to detect change or whether they confer any advantage over the use of single variables alone.

The primary outcome measures identified by the systematic review were used to analyse the TRUST data. A total of 26 randomised controlled trials were identified by the systematic review (51;69;71;77;83;86;91;94-98;101;103-112;123;157;158) with a total of five different primary outcome measures.

1. Mean PEF (morning, evening or both) (69;71;86;91;95-98;106;108-110;112;157;158).
2. Diurnal variation (77).
3. Symptoms (94;103).
4. Asthma control (51;83).
5. Exacerbation (101;104;105;107;111;123).

The aim of the first part of the analysis was to determine what the overall result of TRUST would have been if an outcome measure other than the TRUST definition of exacerbation had been used to analyse the trial. Not all the statistical methods were appropriate for use on the TRUST data. In these cases the important consideration was the behaviour of the outcome measure chosen, for example morning PEF, which was compared with the TRUST definition of exacerbation in the next stage of the analysis.

The complete TRUST trial data were used for all the analyses. For all primary outcome measures the data were analysed on an intention to treat basis and when necessary the data were censored at the point of withdrawal from the trial. All data were analysed using the STATA 6 statistical package.

5.2 Mean PEF (including diurnal variation)

The primary outcome measure used in 15 papers identified was mean PEF, usually mean morning pre-bronchodilator PEF (69;71;86;91;95-98;106;108-110;112;157;158). Three trials compared the difference between the baseline and treatment period using Student's t-test (69;71;157). More recently, mean morning PEF was compared between treatment groups using ANCOVA (analysis of covariance) that enabled corrections to be made for

baseline values (69;71;86;91;97;98;106;108-110;158). The latter method was an extension of the t-test that was made possible with improved statistical programs. The remaining trials reported a more complex modelling of mean PEF to analyse the data (95;96;112).

5.2.1 Method for mean PEF (including diurnal variation)

The systematic review identified two papers that reported the analysis of mean PEF using t-test. Beswick et al (71) compared mean morning and evening PEF between baseline and the treatment period and the significant differences of mean PEF were determined both within and between treatments using Student's t-test. The mean morning and evening PEF were calculated for the run-in and four three-month periods (months 1 to 3, 4 to 6, 7 to 9 and 10 to 12). Greening et al (157) performed a similar analysis with a mean PEF value for each week of the follow - up. The mean morning and evening PEF from the run-in and follow-up periods were compared using a Student's t-test. Trembath et al (69) compared the mean daily PEF between baseline and the treatment period and the significant differences of mean PEF were determined both within and between treatments using Student's t-test. Patients were regarded as treatment failures if they required additional corticosteroids during follow-up and were withdrawn from the trial.

The systematic review identified seven papers (69;71;86;91;97;98;106;108-110;158) in which the authors have analysed the trial data using mean PEF (either morning, evening or both) or diurnal variation with ANCOVA (analysis of covariance) (77). The mean difference between the treatment groups was calculated and an ANCOVA carried out using the mean PEF values from the second period of the run-in.

Diurnal variation was calculated using the formula below where evening PEF was used for PEF_{\max} and morning PEF was used for PEF_{\min} .

$$\frac{PEF_{\max} - PEF_{\min}}{PEF_{\max} + PEF_{\min}} \times 100 = \text{diurnal variation}$$

The more complex models for analysing PEF will not be repeated in this analysis because of the difficulty in making the later comparisons with the TRUST exacerbation.

5.2.2 Results for mean PEF (including diurnal variation)

Comparing the mean morning and evening PEF with t-test there was a significant improvement in evening PEF with regular salbutamol when all periods of follow-up were compared in turn with the run-in period ($p<0.001$), table 5.1. There was no difference in morning PEF between the two groups for any of the periods of follow-up.

Months after trial entry	Mean PEF (l/min)				
	Run-in	1 to 3 Months	4 to 6 Months	7 to 9 Months	10 to 12 Months
<i>Placebo</i>	(n = 451)	(n = 459)	(n = 372)	(n = 304)	(n = 270)
Morning PEF	403 (100)	403 (100)	410 (101)	415 (100)	419 (102)
Evening PEF	416 (100)	416 (100)	420 (101)	425 (100)	428 (102)
<i>Active</i>	(n = 472)	(n = 468)	(n = 379)	(n = 320)	(n = 279)
Morning PEF	403 (103)	402 (102)	407 (105)	416 (108)	421 (109)
Evening PEF	420 (101)	428 (99)	432 (101)	439 (105)	445 (105)

Table 5.1 Mean morning and evening PEF (SD) for run-in and follow-up divided into run-in and four three-month periods.

Trembath (69) regarded patients who required a course of additional corticosteroids as treatment failures. Including or excluding patients regarded as treatment failures did not alter the result, table 5.2. The mean difference in mean PEF between baseline and follow-up was 4.23 l/min (95% CI 1.08 to 7.39) with placebo and 9.04 l/min (95% CI 5.77 to 12.32) with active treatment, $p = 0.04$ when those patients requiring an additional course of corticosteroids were excluded. When those patients requiring additional corticosteroids were included the mean differences in mean PEF were 2.17 l/min (95% CI -0.31 to 4.65) and 7.64 l/min (95% CI 5.09 to 10.18) respectively, $p = 0.003$

	Placebo	Active
Excluding patients requiring 1 or more courses of additional corticosteroids		
	(n = 280)	(n = 296)
Run-in	418 (101)	421 (100)
Follow-up	424 (101)	431 (100)
Including patients requiring 1 or more courses of additional corticosteroids		
	(n=458)	(n=472)
Run-in	410 (99)	411 (101)
Follow-up	413 (100)	418 (101)

Table 5.2 Mean daily PEF (SD) during run-in and follow-up by treatment group.

As expected there was no significant difference in morning PEF between the run-in and follow-up, see table 5.3, when the data were adjusted for baseline levels using ANCOVA. There was a significant improvement in evening PEF with active treatment compared with placebo. When daily PEF was compared (i.e. the average of the daily readings for morning and evening PEF) there was a significant improvement with regular salbutamol and this was likely to be as a result of the significant improvement in evening PEF demonstrated on active treatment. The significant improvement in the group on active treatment seen with diurnal variation was because of the significant improvement in evening PEF in those patients.

	Placebo	Active	Active-placebo (95% CI)	p
Mean (SE) morning PEF				
	(n = 472)	(n = 460)		
Run-in	403 (4.71)	403 (4.71)		
Follow-up	406 (4.69)	406 (4.75)	0.89 (-2.98 to 4.76)	0.653
Mean (SE) evening PEF				
	(n = 458)	(n = 471)		
Run-in	416 (4.67)	419 (4.64)		
Follow-up	418 (4.67)	430 (4.63)	10.35 (6.75 to 13.96)	< 0.001
Mean (SE) daily PEF				
	(n = 458)	(n = 471)		
Run-in	410 (4.66)	411 (4.64)		
Follow-up	413 (4.65)	418 (4.66)	5.55 (2.01 to 9.08)	0.002
Mean (SE) diurnal variation				
	(n = 458)	(n = 467)		
Run-in	2.15 (0.20)	2.85 (0.21)		
Follow-up	1.84 (0.16)	4.21 (0.23)	1.83 (1.41 to 2.25)	< 0.001

Table 5.3 Mean morning, evening and daily PEF and diurnal variation by treatment group adjusted for baseline levels using ANCOVA.

5.2.3 Discussion for mean PEF (including diurnal variation)

The results for the analysis of the TRUST dataset using mean morning, evening and daily PEF supported the results reported in the TRUST paper (123). There was no difference between the two treatment groups when mean morning PEF was used and there was a statistically significant improvement when evening PEF was used though in clinical terms the increase was quite small. Trialists frequently set the sample size in order to detect a change of 15 to 20 l/min in PEF. Using the mean baseline morning PEF of 403, to have 98% power at the 5% level to detect a difference of 15 l/min between treatment groups over twelve months follow-up only 66 patients would be required so TRUST had more than enough power to detect a difference of 15 l min between treatment groups.

Mean morning PEF is often used as an indicator of asthma control and is used to provide an estimate of baseline lung function in the absence of FEV₁ measurement (142). Assuming that morning PEF and exacerbation, according to the TRUST definition, were measuring the same underlying process then we would have expected the result of TRUST to be the same whether morning PEF or exacerbation were used as the primary endpoint. The improvement in evening PEF with regular treatment was as a result of the cumulative effect of regularly scheduled salbutamol during the course of a day and may not represent an actual improvement in the underlying asthma. If regular salbutamol were making asthma worse it would be expected that the increase in evening PEF would have been less and there may have been a decrease in morning PEF.

5.3 Symptoms

Change in day or night time symptoms or a composite daily symptom score were the primary outcome measures used in two of the papers identified in the systematic review (94;103).

5.3.1 Method for symptoms

Apter et al (94) simply generated mean daytime and night time symptom scores for run-in and follow-up. Van der Molen et al (103) generated a combined daily symptom score comprising daytime and night time symptoms and calculated the mean score for run-in and follow-up. Both groups used a t-test to make the comparison between treatment groups.

The symptoms recorded on the TRUST diary card were as follows:

Daytime symptoms

These were assessed each evening, just before going to bed. Symptoms were chest tightness, wheezing, breathlessness and cough.

- 0 No symptoms during the day.
- 1 Symptoms for one short period during the day.
- 2 Symptoms for two or more short periods during the day.

- 3 Symptoms for most of the day, which did not interfere with usual daytime activities.
- 4 Symptoms for most of the day, which did interfere with usual daytime activities.
- 5 Symptoms so severe that you could not perform your usual daytime activities.

Night time symptoms

These were assessed each morning immediately after awakening. Night time symptoms were chest tightness, wheezing, breathlessness and cough.

- 0 No symptoms during the night.
- 1 Symptoms on waking but not causing you to wake early.
- 2 Symptoms causing you to wake once or wake early.
- 3 Symptoms causing you to wake twice or more (including waking early).
- 4 Symptoms causing you to be awake most of the night.
- 5 Symptoms so severe that you did not sleep at all.

5.3.2 Results for symptoms

There was a significant improvement in mean daytime symptoms with regular salbutamol compared to placebo ($p = 0.007$) but no difference in mean night time symptoms ($p = 0.21$). When daytime and night time symptom scores were combined to give a total daily symptom score there was a significant improvement with regular salbutamol ($p = 0.003$). Table 5.4 details the results for mean daytime, night time and total daily symptoms.

	Placebo (n = 458)	Active (n = 471)	Active-placebo (95% CI)	p (ANCOVA)*	p T test
Mean (SE) daytime symptom score					
Run-in	1.04 (0.04)	1.05 (0.04)			
Follow-up	0.92 (0.04)	0.82 (0.04)	-0.10 (-0.17 to -0.02)	0.009	0.007
Mean (SE) night time symptom score					
Run-in	0.60 (0.03)	0.62 (0.03)			
Follow-up	0.55 (0.03)	0.55 (0.03)	-0.03 (-0.17 to -0.03)	0.3	0.21
Mean (SE) total daily symptom score					
Run-in	1.64 (0.06)	1.67 (0.06)			
Follow-up	1.46 (0.06)	1.37 (0.06)	-0.12 (-0.22 to -0.01)	0.003	0.02

*Adjusted for run-in levels using ANCOVA.

Table 5.4 Mean symptom scores (min 0 to max 5) by treatment group.

5.3.3 Discussion for symptoms

The results from the comparison of daytime and night time symptoms are consistent with the results reported in the TRUST paper, which used symptom free days and nights (123). There was a significant improvement in the number of symptom free days ($p < 0.001$) but not symptom free nights. The improvement in daytime symptoms could have been because of the cumulative effect of regular salbutamol, which also resulted in significantly higher evening PEF readings.

5.4 Asthma control

Composite measures for use in clinical trials were developed in an attempt to include more of the asthma diary card variables to determine whether a patient was better or worse with a particular treatment. A definition of asthma control was developed by Sears et al for use in their crossover trial to assess the effect of regular use of fenoterol

on asthma control (51). A subsequent trial by Chapman et al (83) used the same outcome measure in a trial of regular salbutamol. Chapman repeated the analysis six times changing the order of the components and also the emphasis of the components.

5.4.1 Method for asthma control

The trial by Sears et al (51) was a crossover trial and the comparisons were made between the placebo period and active treatment period. The period of better or worse asthma control was determined by the direction of change of the components of asthma control detailed below. If the changes in the components of asthma control were not all in the same direction the following order was used:

1. Short course of oral prednisolone.
2. Morning PEF.
3. Nocturnal β_2 -agonist use.
4. Nocturnal symptoms.
5. Daytime symptoms.
6. Evening PEF.
7. Rescue daytime inhaled β_2 -agonist use.

Applying this to a re-analysis of TRUST, baseline and follow-up data were compared using an unpaired t-test to determine whether there was better or worse asthma control during follow-up compared to run-in. Each of the components of asthma control above were classified as better, worse or no change. Overall asthma control was assigned according to the order of the components. For example, if a patient had a course of corticosteroids they were classed as experiencing worse asthma control regardless of the direction of change lower down the order. If a patient did not use corticosteroids the next component in the order, morning PEF, would be used to classify asthma control, and so on. An unpaired t-test was used rather than the paired t-test reported because TRUST was not a crossover trial and a paired t-test would not have been possible. Once the periods of asthma control had been determined the comparison between treatment groups was made using Chi square.

Chapman extended the definitions of asthma control by changing the order of the components to develop six criteria for asthma control (83). Criteria A were the same as asthma control in the Sears' analysis (51) and criteria B were:

1. Short course of oral prednisolone.
2. Morning PEF.
3. Night time rescue β_2 -agonist use.
4. Night time symptom score.
5. Daytime symptom score.
6. Evening PEF.
7. Daytime rescue β_2 -agonist use.

Rescue bronchodilator use alone was ignored and such patients were regarded as showing indeterminate differences between treatment periods.

Criteria C:

1. Short course of oral prednisolone.
2. Night time rescue β_2 -agonist use.
3. Morning PEF.
4. Night time symptom score.
5. Daytime rescue β_2 -agonist use.
6. Evening PEF.
7. Daytime symptom score.

Criteria D:

1. Short course of oral prednisolone.
2. Night time rescue β_2 -agonist use.

3. Morning PEF.
4. Night time symptom score.
5. Daytime rescue β_2 -agonist use.
6. Evening PEF.
7. Daytime symptom score.

Rescue bronchodilator use alone was ignored and such patients were regarded as showing indeterminate differences between treatment periods.

Criteria E:

Assigned control only if one or more significant differences were non-discrepant between the treatment periods.

Criterion F:

As for E but excluded differences in daytime bronchodilator use only.

Each patient's individual mean values were compared and t-tests performed. If the difference between the run-in and follow-up values was significant the variable was classified as better or worse and overall control was assigned according to the order of the components in the criteria. Any variable with a non-significant change was classified as no change. The overall comparison between the two treatment groups was with Chi Square.

5.4.2 Results for asthma control

There was no significant difference in asthma control between the two treatment groups. Significant improvements with regular salbutamol were seen with three of the individual components of asthma control: daytime symptoms ($p = 0.004$), daytime inhaled β_2 – agonist use ($p = 0.03$) and evening PEF ($p = 0.03$).

	Placebo	Active	Total	p*
Asthma control	(n = 461)	(n = 469)		0.1
Better	123	150	273	
No change	183	162	345	
Worse	155	157	312	
Corticosteroid use	(n = 461)	(n = 469)		0.4
No oral steroids	397	412	809	
Oral steroids	64	57	121	
Morning PEF	(n = 427)	(n = 445)		0.2
Better	140	166	306	
No change	180	161	341	
Worse	107	118	225	
Nocturnal β_2-agonist use	(n = 419)	(n = 430)		0.3
Better	133	155	288	
No change	240	225	430	
Worse	46	50	96	
Nocturnal symptoms	(n = 425)	(n = 440)		0.4
Better	108	130	238	
No change	258	252	510	
Worse	59	58	117	
Daytime symptoms	(n = 425)	(n = 440)		0.004
Better	140	194	334	
No change	215	188	403	
Worse	69	58	127	
Evening PEF	(n = 427)	(n = 443)		< 0.001
Better	127	203	330	
No change	177	162	339	
Worse	123	78	201	
Inhaled β_2-agonist use	(n = 421)	(n = 435)		0.03
Better	214	258	472	
No change	151	135	286	
Worse	56	42	98	

*Comparisons made using Chi square.

Table 5.5 **Number of patients according to each category of change for asthma control and the components of asthma control, by treatment group.**

The result for the TRUST analysis using the Chapman criteria A and B was the same as for the Sears asthma control. Ignoring the bronchodilator use did not result in a change in outcome for any patient. Changing the order of the components as in criteria C and D tended to result in patients changing category from “worse” control to “no change” but there was no significant difference between placebo and active treatment groups. When patients were required to have one or more non-discrepant significant differences in any

of the criteria (criteria E and F) there was a significant difference between placebo and active treatment groups in favour of regular salbutamol ($p = 0.002$ criteria E and $p = 0.001$ for criteria F), see table 5.6.

	Placebo (n = 486)	Active (n = 497)	Total	P*
Chapman criteria E				0.002
Better	228	286	514	
No change	97	73	170	
Worse	136	110	246	
Chapman criteria F				0.001
Better	222	282	504	
No change	108	79	187	
Worse	131	108	239	

*Comparisons made using Chi square.

Table 5.6 **Number of patients according to each category of change of the Chapman criteria E and F, by treatment group.**

5.4.3 Discussion for asthma control

Determining periods of asthma control using the methods of Sears (51) and Chapman (83) may not be an appropriate method of analysis for use in a trial of the design of TRUST. Firstly, TRUST was not a crossover trial. Secondly, asthma control was determined by the direction of change of those variables higher up the order irrespective of the direction of change in variables lower down the order. When asthma control was classified using Chapman criteria E and F many more patients were classified as experiencing better asthma control because classification was based on the direction of change of the majority of the components.

Significant improvements with active treatment were seen with evening PEF, daytime symptoms and daytime reliever use. However, when combined to determine overall asthma control (Chapman criteria A and B) there was no difference between the two treatment groups. On examination of the STATA log file asthma control was

determined by the use of additional corticosteroids and morning PEF, and those items lower down the hierarchy had little or no effect on whether the patient had better or worse asthma control.

The Sears trial used direct comparisons between the treatment and control periods of the crossover trial. Using a paired t-test to compare the two treatment periods, day 1 of period 1 was compared directly with day 1 of period 2 which assumed that there were no time trends and that the daily data were not connected. In the case of daily asthma diary cards this is probably not true and values for one day are dependent to an extent on the value from the previous day.

5.5 Exacerbations

Four definitions of exacerbation were identified by the systematic review (101;104;105;107;111;123). All the definitions made use of the diary card data to determine periods of exacerbation but the different definitions put the emphasis on different components of the diary card data. Not only do the definitions use different combinations of diary card variables to determine the start of an exacerbation but they also define the end of an exacerbation differently. The four definitions of exacerbation are listed below.

5.5.1. TRUST exacerbation

1. Use of oral or increased inhaled corticosteroids.

Or at least two or more of the following:

2. Fall in PEF to less than 80% of median baseline level.
3. Bronchodilator per 24 hours increased by three or more over baseline.
4. Symptom score increased during the day or at night, by two or more over median baseline level.

The end of an exacerbation was defined as the cessation of oral corticosteroids or return to original dose of increased inhaled corticosteroids and all the following criteria on two consecutive days:

1. PEF \geq 80% median baseline level.

2. Bronchodilator inhalations per 24 hours increased by no more than 2 over median baseline level.
3. Symptom scores increased day and night by no more than one over median baseline level.

5.5.2 FACET severe exacerbation

There were two types of FACET (Formoterol and Corticosteroids Establishing Therapy) exacerbation, mild and severe, but only the severe exacerbation will be considered in this analysis. The severe exacerbation was the primary outcome measure in the FACET trial (101) and also in a more recent trial comparing formoterol and terbutaline by Tattersfield et al (111).

A severe FACET exacerbation started on a particular day if the following occurred:

1. Use of oral corticosteroids.
2. Or a fall in PEF to less than 70% of mean baseline level on two consecutive days. (Only day two and subsequent exacerbating days were categorised as an exacerbation).

A patient could be classified as experiencing a subsequent exacerbation on day eleven, ten days after the first day of the previous exacerbation, on the condition that they were not still taking oral corticosteroids. For those still taking oral corticosteroids, the first day for checking for subsequent exacerbations was the first day without oral corticosteroids.

Patients taking part in the FACET trial were not permitted to increase the dose of inhaled corticosteroids to treat an exacerbation and this was not included as part of their definition of exacerbation. Writing the programs to identify the FACET severe exacerbations was complicated because of the way in which corticosteroid use was coded in the TRUST diary card. The TRUST diary card simply stated whether additional corticosteroids were used on a particular day and did not specify whether they were oral or inhaled. Those exacerbations known to have been defined by use of inhaled corticosteroids were not classified as FACET exacerbations. The analysis was

performed twice, once including only those patients treated with known oral corticosteroids and again including those patients treated with unknown corticosteroids.

5.5.3 Exacerbation from the paper by Wilding et al (104)

As with the FACET definition of exacerbation, this definition does not use an increase in inhaled corticosteroids and the data were prepared in the same way as for the FACET exacerbation. An exacerbation was defined as any two of the following:

1. 30% fall in morning PEF.
2. A fall in FEV₁ of either 0.7 litres or 30% from baseline.
3. Increased use of β_2 -agonist (by more than four puffs per day).
4. The need for oral prednisolone.
5. More bronchodilator treatment on two or more consecutive nights.
6. Increased symptom scores of one or more over baseline on two successive days.

5.5.4 Definition of exacerbation defined by Taylor et al (105)

Taylor et al described a complicated definition of exacerbation that involves generating asthma scores and then exacerbations from these scores. Hancox et al (107) used similar asthma scores but did not generate exacerbations from the asthma score. Asthma scores were determined as follows:

Score 0: Stable asthma

Either:

- Morning PEF > 90% of baseline best value and bronchodilator puffs < 7 per 24 hours.

Or:

- Morning PEF 76 - 90% of baseline best value with no deterioration in any of the symptom scores listed below in mildly unstable.

Score 1: Mildly unstable asthma

Either two or more of the following:

- Morning PEF 76 - 90% of baseline best value.
- Bronchodilator puffs = 7 on baseline rounded mean per 24 hours.
- Deterioration in day or night symptom score of one or more compared to rounded baseline mean.

- Appearance or worsening of nocturnal waking.

Or:

- Morning PEF 61 - 75% of run-in best value but without deterioration in and symptom score listed above.

Score 2: Minor deterioration

Either:

- Morning PEF 61 - 75% of run-in best value and two or more of the criteria listed for asthma score 1.

Or:

- Morning PEF 40 - 60% of run-in best value but without a deterioration in any symptom scores listed for asthma score 1.

Score 3: Major deterioration

- Morning PEF 40 - 60% of run-in best and two or more of the criteria listed for asthma score 1.

Score 4: Major exacerbation / medical emergency

Either:

- Morning PEF <40% of run-in best value irrespective of symptoms.

Or:

- Attendance at GP or hospital emergency department with severe asthma.

The criteria for determining minor and major exacerbations were as follows.

- Minor exacerbation - asthma score 2 for two or more days.
- Major exacerbation - asthma score 3 for two or more days or one day within a minor exacerbation.
- Medical emergency - asthma score 4 for one or more days.

An exacerbation ended when the asthma score returned to 0 or 1 for three or more days otherwise the exacerbation was considered to be continuing.

For all four definitions of exacerbation the total number of exacerbations were divided by the total person years follow-up to determine the overall exacerbation rate. The

distributions of these annual rates in the two randomised groups were compared using non-parametric Wilcoxon rank sum test.

5.5.5 Results for exacerbation

The results for TRUST analysed using the TRUST definition of exacerbation have been reported in chapter 4. There was no significant difference in exacerbation rate between the placebo and active group when the TRUST data were analysed using the FACET definition of severe exacerbation. The proportion of patients having at least one exacerbation, and the total number of exacerbations, were similar in the two groups.

Table 5.7 details the results for all definitions of exacerbation. There was no significant difference between the placebo and active treatment groups when using the FACET definition of exacerbation. The number of severe FACET exacerbations, including those with unknown corticosteroids, was much lower than the number of TRUST exacerbations reported but the result still reflected the TRUST results reported. Including those patients with unknown corticosteroids did not affect the comparison between placebo and active treatments. The FACET exacerbations could not be examined in terms of the length of exacerbations because of the way in which the end of an exacerbation was defined. There was no significant difference in the rate of exacerbation between the two groups when the patients were analysed according to their baseline inhaled corticosteroid use.

Using the Wilding definition of exacerbation (104) there was a slight but non-significant difference in the exacerbation rate between the treatment groups in favour of those patients taking regular salbutamol when the data included those exacerbations treated by oral corticosteroids alone and also including unknown corticosteroids.

There was no significant difference in the exacerbation rate between the two treatment groups using the definition of exacerbation described by Taylor et al (105;107). Once again the total number of exacerbations was fewer than with the TRUST definition of exacerbation.

	TRUST		FACET ¹ (oral steroids)		FACET ² (inc. unknown steroids)		Wilding ¹ (oral steroids)		Wilding ² (inc. unknown steroids)		Taylor	
	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active
Exacerbation rates												
Annual exacerbation rate (95% CI)	1.3 (1.18 to 1.43)	1.25 (1.14 to 1.38)	0.25 (0.20 to 0.31)	0.41 (0.34 to 0.48)	0.66 (0.58 to 0.76)	0.78 (0.69 to 0.78)	3.8 (3.61 to 4.04)	3.3† (3.10 to 3.50)	4.12 (3.90 to 4.35)	3.6‡ (3.37 to 3.78)	0.73 (0.64 to 0.83)	0.91 (0.81 to 1.03)
(number of exacerbations / patient years of follow up)	(438 / 337)	(425 / 339)	(79 / 319)	(135 / 331)	(212 / 320)	(258 / 331)	(1221 / 320)	(1091 / 331)	(1318 / 320)	(1181 / 331)	(233 / 320)	(302 / 331)
Exacerbation details												
Number of patients with at least 1 exacerbation	223 (46%)	214 (43%)	61 (13%)	62 (13%)	138 (28%)	135 (27%)	302 (62%)	284 (57%)	319 (66%)	307 (62%)	135 (28%)	133 (27%)
Number of patients with at least 2 exacerbations	114 (23%)	99 (20%)	17 (3%)	24 (5%)	51 (11%)	24 (10%)	207 (43%)	200 (40%)	230 (47%)	216 (43%)	56 (12%)	53 (11%)

¹ Includes exacerbations with a change in PEF and those treated with known oral steroids

² Includes exacerbations with a change in PEF and those treated with oral and unknown steroids

† p = 0.06

‡ p = 0.07

Table 5.7 The results of TRUST according to the definitions of exacerbation identified by the systematic review.

5.5.6 Discussion for exacerbation

Analysing the TRUST data using the FACET definition of exacerbation reinforced the reported TRUST result (123) that there was no difference in exacerbation rate when salbutamol was taken on demand compared to regular use. The number of FACET severe exacerbations reported was fewer than the number of TRUST exacerbations and the exacerbation rate of 0.96 per patient per year was much less than the predicted exacerbation rate with placebo of 1.5 per patient per year used for the TRUST sample size calculations. Using the FACET definition of exacerbation TRUST trial had 40% power to detect a change of 20% in exacerbation rate between treatment groups if only courses of oral corticosteroids are included. To increase the power to 98% to detect a 20% difference in exacerbation rate nearly 4000 patients would need to be followed up for one year. The reason for the reduced number of exacerbations was the emphasis on a fall of 30% in morning PEF on two or more consecutive days. For patients in TRUST, morning PEF fell to 70% or less of baseline morning PEF on less than 1% of the total days, 1425 days out of 206073.

In contrast to the FACET definition of exacerbation, the definition used by Wilding et al (104) resulted in many more exacerbations than with the TRUST definition because the criteria for change in symptom scores and additional bronchodilator use were set quite low. The TRUST definition of exacerbation stipulated a change in two or more over baseline symptom score for two consecutive days whereas the Wilding definition required only an increase in one over baseline. The Wilding definition placed less emphasis on the use of oral corticosteroids because they had to have two or more of the components for an exacerbation.

The definition of exacerbation described by Taylor (105) was very complex to code and again the emphasis on changes in PEF meant that there were fewer exacerbations than with the TRUST definition. Using the Taylor definition of exacerbation nearly twice as many patients would need to be followed for a year to have 98% power to detect a 20% difference in exacerbation rate between the two treatment groups.

5.6 Discussion

The results of this analysis reinforced the main TRUST results (123). There was no difference in the exacerbation rates between the two groups using the different definitions of exacerbation but the total number of exacerbations in the 983 subjects varied from a total of 214 FACET exacerbations to 2312 Wilding exacerbations with the TRUST definition of exacerbation in between. There were fewer exacerbations with those definitions that tended to rely on a fall in morning PEF compared to those definitions that also included changes in symptom scores. All definitions included a course of corticosteroid treatment as part of the definition. Additional corticosteroids alone could result in an exacerbation in all the definitions except the Wilding definition where it had to occur with at least one other change.

There was no significant difference in mean morning PEF between the two treatment groups and TRUST had a more than adequate sample size to detect a change in mean morning PEF of 20 l/min. PEF seemed to vary little in this group of patients as demonstrated by the very few days (0.7% 1425 / 206073) when the morning PEF fell to 70% or less of baseline. Both evening PEF and diurnal variation increased with regular salbutamol. It may be that these two measures were really measuring short-term change associated with cumulative doses of a bronchodilator rather than any long-term change in the underlying asthma.

From the results of this analysis a composite outcome measure, which included symptoms as well as PEF, was the most useful measure of change in this group of mild to moderate asthmatics because so few patients demonstrated large changes ($\geq 30\%$) in morning PEF.

5.7 Summary

This chapter detailed the results of the analysis of TRUST using the different primary outcome measures identified by the systematic review. The next stage of the analysis will compare the measurement characteristics of the primary outcome measures

discussed here to determine their sensitivity and specificity and to try to identify which components were the most important in defining an exacerbation.

By the end of the next stage of this analysis it will be clear how the TRUST definition of exacerbation performed in comparison to the other primary outcome measures identified and which measure was the most suitable measure for use in clinical trials of this nature. It will also be clear how the components of the TRUST definition correlated and whether any were more important in terms of the frequency with which they caused an exacerbation to be classified.

Chapter 6 – Comparison of primary outcome measures

Chapter 6 describes the comparison of the primary outcome measures identified by the systematic review and the TRUST definition of exacerbation.

6.1 *Introduction*

The systematic review identified five different primary outcome measures used in clinical trials of long and short acting inhaled β_2 -agonists. The aim of this analysis was to compare the measurement characteristics of the primary outcomes identified with the TRUST definition of exacerbation. The four different definitions of exacerbation were also assessed to see whether one or more component played a greater role in determining an exacerbation and whether there was any correlation between the diary card components.

6.2 *Mean PEF (including diurnal variation)*

6.2.1 Introduction for mean PEF (including diurnal variation)

It might be expected that those patients who experienced one or more exacerbation according to the TRUST definition would also experience a decrease in mean morning PEF over the course of the trial.

6.2.2 Method for mean PEF (including diurnal variation)

In order to investigate the relationship between mean morning and evening PEF and the TRUST definition of exacerbation a series of regression models were used. The aim of this regression analysis was to identify whether change in a particular variable over the period of follow-up could predict whether a patient experienced an exacerbation or not. Two basic models were used; the first model was a logistic regression model that assessed the degree to which change in a variable such as mean morning PEF between baseline and follow-up, adjusted for baseline morning PEF and length of follow-up, could predict whether a patient experienced a TRUST exacerbation or not. The second model was a Poisson regression model that assessed the degree to which change in a

variable such as mean morning PEF between baseline and follow-up, adjusted for baseline morning PEF, length of follow-up and clustering on patient number, could predict the number of TRUST exacerbations experienced during their follow-up period. It was expected that the results from the Poisson model might be more useful than the logistic regression model because the binary outcome might be too simplistic.

A further Poisson analysis of morning PEF was undertaken using TRUST exacerbations and monthly means for morning PEF. The dataset contained information on mean morning PEF and the presence or absence of an exacerbation for each month of follow-up. Details of the regression analysis are at Appendix 6.1.

6.2.3 Results for mean PEF (including diurnal variation)

The regression model explored the relationship between the change in morning PEF between run-in and follow-up and the presence or absence of one or more TRUST exacerbations during the follow-up period. The logistic regression model suggested a significant but weak relationship between the mean difference in morning PEF between run-in and follow-up and the presence or absence of a TRUST exacerbation. A 1 l/min increase in mean morning PEF resulted in a 0.8% decrease (95% CI 0.35 to 1.3, $p = 0.001$) in the odds of experiencing an exacerbation during the course of the follow-up. Therefore a 15 l/min increase in mean morning PEF resulted in an 11.6%% decrease (95% CI 5.1 to 17.7, $p = 0.001$) in the odds of an exacerbation. Expressing the change in mean morning PEF as a categorical variable with 50 l/min divisions did not improve the logistic regression model for mean morning PEF. This suggested that the relationship between the change in mean morning PEF between run-in and follow-up and the presence of one or more TRUST exacerbation was linear.

The Poisson regression model for the change in mean morning PEF and the total number of TRUST exacerbations was more complicated and the relationship was not linear. Table 6.1 details the results of the Poisson regression model with mean morning PEF expressed as a categorical variable. As the change in mean morning PEF between run-in and follow-up increased the TRUST exacerbation rate decreased but none of the results was significant and there was no trend. There was an initial increase of 25% in

TRUST exacerbation rate (OR 1.25 95% CI 0.67 to 2.36) when morning PEF increased from the reference category. This initial increase in exacerbation rate may have been because there were very few patients in the baseline group (n = 24) compared to the -50 to 0 group (n = 374). From figure 6.1 it is clear that one patient experienced a TRUST exacerbation rate of 73 per year because he or she experienced one exacerbation in six days before withdrawing from the trial, see figure 6.1. Another patient experienced 11 exacerbations. Excluding these patients from the analysis did not change the result.

Change in am PEF from baseline (l/min)	N	TRUST exacerbation rate ratio	95% Confidence Interval
Less than -50	24	1	
-50 to 0	374	1.25	0.67 to 2.37
0	429	0.83	0.44 to 1.56
50 to 100	37	0.76	0.34 to 1.69
100 or more	10	0.68	0.21 to 2.17

Table 6.1 The change in rate ratio of TRUST exacerbation according to the category of change in mean morning PEF.

The relationship between a change in mean evening PEF between run-in and follow-up and the presence of one or more TRUST exacerbation was weaker than with morning PEF. A 10 l/min increase in evening PEF resulted in a 6.5% reduction in the TRUST exacerbation rate and this relationship was found to be linear. Figure 6.2 illustrates the relationship between evening PEF and TRUST exacerbation rate.

Change in am PEF from baseline	TRUST exacerbation rate ratio (n = 798)	95% Confidence Interval
1 l/min	0.99†	0.99 to 1.0
10 l/min	0.94†	0.90 to 0.97

† p < 0.001

Table 6.2 TRUST exacerbation rate ratio and change in evening PEF.

When monthly values for the mean change in morning PEF between run-in and follow-up were used the relationship between TRUST exacerbation and mean morning PEF was stronger. The general trend was for significant reductions in the exacerbation rate as the change in mean morning PEF increased, see table 6.3.

Change in monthly mean am PEF from baseline (l/min)	N	TRUST exacerbation rate ratio	95% Confidence Interval
Less than -50	358	1	
-50 to 0	2838	0.65 [†]	0.49 to 0.87
0	3250	0.32 [‡]	0.23 to 0.43
50 to 100	438	0.32 [‡]	0.20 to 0.51
100 or more	252	0.18 [‡]	0.09 to 0.36

[†]p = 0.003, [‡]p < 0.001

Table 6.3 Monthly TRUST exacerbation rate ratio and change in morning PEF.

The relationship between change diurnal variation between run-in and follow-up and TRUST exacerbation was linear. A 10 l/min increase in diurnal variation between run-in and follow-up resulted in a 33% (95% CI 1.01 to 1.75) increase in TRUST exacerbation rate, see table 6.4.

Change in diurnal variation from baseline	TRUST exacerbation ratio (n = 798)	rate 95% Confidence Interval
1 l/min	1.03 [†]	1.0 to 1.06
10 l/min	1.33 [†]	1.01 to 1.75

[†] p = 0.04

Table 6.4 TRUST exacerbation rate ratio and change in diurnal variation from baseline

6.2.4 Discussion for mean PEF (including diurnal variation)

The relationship between TRUST exacerbation and morning and evening PEF averaged over the whole period of follow-up was weak but the relationship with diurnal variation was stronger. Simply averaging the PEF over the entire follow-up period seemed to oversimplify the relationship with TRUST exacerbations because the rapid fluctuations were not reflected in the overall mean value. Intuitively one might expect a linear relationship between PEF and TRUST exacerbation rate. The relationship with evening

PEF was linear but the relationship with mean morning PEF was more complicated, perhaps because of the distribution of the patients between the categories of PEF change. A large proportion, 92% (803/874), of patients experienced a change in mean morning PEF of between -50 and 50 l/min and this may have accounted for the non-linear and weak relationship with TRUST exacerbation.

There was a stronger relationship between change in diurnal variation and TRUST exacerbation. As diurnal variation between run-in and follow-up increased there was a linear increase in the rate of TRUST exacerbations. The stronger relationship could be because a 10 l/min change in diurnal variation represented a larger relative change between run-in and follow-up than a 10 l/min change in morning or evening PEF. An increase in diurnal variation is usually associated with worse asthma control. In TRUST, an increase in diurnal variation occurred because of an increase in evening PEF rather than a fall in morning PEF. Reddel et al (159) suggested that an increase in diurnal variation was associated with poor asthma control and not exacerbation. The difference between their patients and TRUST patients was that TRUST did not use the run-in period to modify treatment to achieve stable asthma. An increase in diurnal variation in a TRUST patient was unlikely to reflect worsening asthma control because of the significant improvement in evening PEF.

There are several reasons why the relationship between mean morning PEF and TRUST exacerbations may not have been as strong as expected. The mean follow-up PEF (morning and evening) was the mean PEF for the whole of the follow-up period for a particular patient. Simply averaging the PEF over such a period meant that there was no information about the daily fluctuations used to identify exacerbations. A patient may have experienced several sharp fluctuations in morning PEF resulting in exacerbations but their overall mean PEF remained unchanged. Most patients experienced a change in mean morning PEF of between -50 and 50 l/min, concentrating most exacerbations in this group. 51% of the TRUST exacerbations were because of courses of oral or increased inhaled corticosteroids alone (123) and there may not have been an associated decrease in PEF, either morning or evening.

Repeating the analysis to include monthly values for mean morning PEF improved the relationship with TRUST exacerbation. Generating monthly mean values increased the likelihood of sharp fluctuations in PEF having an effect on the overall monthly mean value that was more closely related to TRUST exacerbation.

In conclusion, if using mean morning PEF as a primary outcome measure, it may be more useful to look at monthly mean changes because fluctuations in asthma would be more likely to have an effect on the monthly mean value. The overall length of the trial would depend on the exact question it was designed to answer.

6.3 Symptoms

6.3.1 Introduction for symptoms

It might be expected that those patients who experienced one or more exacerbation according to the TRUST definition would also experience an increase in daytime or night time symptoms over the course of the trial.

6.3.2 Method for symptoms

The method of analysis to determine the extent to which the mean values for daytime and night time symptoms predicted whether a patient experienced one or more TRUST exacerbations was the same as that to assess the effect of mean morning PEF, details at Appendix 6.2.

6.3.3 Results for symptoms

The odds of experiencing one or more TRUST exacerbations increased by 73% (OR 1.73 95% CI 1.34 to 2.24) when the mean difference in daytime symptoms score between run-in and follow-up increased by one and this relationship appeared to be linear. When Poisson regression was used the TRUST exacerbation rate increased by 66% (OR 1.66 95% CI 1.40 to 1.97) as the mean difference in daytime symptoms between run-in and follow-up score increased by one and again this relationship was linear. Combining the daytime and night time scores to form a total daily symptoms

score did not improve the model for either the logistic or Poisson regression models, odds ratios being 1.51 (95% CI 1.27 to 1.80) and 1.49 (95% CI 1.33 to 1.67) respectively.

6.3.4 Discussion for symptoms

An increase in the mean daytime symptom score of one over baseline was associated with a 73% increase in the odds of one or more TRUST exacerbations and a 66% increase in the annual TRUST exacerbation rate. Even though the symptom scores were mean scores for the entire follow-up period, they still reflected the underlying fluctuations in symptoms that lead to TRUST exacerbation. An increase in the mean daytime symptom score did predict whether patients were more likely to have experienced one or more TRUST exacerbations. Generating a total symptom score by combining day and night time symptom scores was no stronger a predictor of TRUST exacerbation than daytime symptoms alone. This was surprising because if asthma was worse it might be expected that there would be an increase in both day and night time symptoms. A possible explanation may be that an increase in daytime symptoms did not occur with a corresponding increase in night time symptoms of the same magnitude.

In conclusion, an increase in the mean daytime symptom score over baseline did seem to be a useful measure in terms of its ability to predict TRUST exacerbations.

6.4 Asthma Control

6.4.1 Introduction for asthma control

There was no significant difference in asthma control between the two treatment groups although significant improvements were seen with active treatment with daytime symptoms, daytime inhaled β_2 -agonist use and evening PEF. When patients were required to have one or more non-discrepant significant differences in any of the criteria there was a significant improvement in favour of active treatment.

6.4.2 Method for asthma control

Because of the limited applicability of the Sears measure of asthma control to future trials the comparisons with TRUST exacerbation were simple comparisons. A regression model was used to determine whether poor asthma control predicted an increase in the TRUST exacerbation rate.

6.4.3 Results for asthma control

Patients who were classified as having worse asthma control were more likely to experience TRUST exacerbations and those patients with better asthma control were more likely to experience no exacerbations, see table 6.5.

TRUST exacerbation	Asthma control			Total
	Better	No change	Worse	
No	173 (63%)	199 (58%)	121 (39%)	493
Yes	100 (37%)	146 (42%)	191 (61%)	437
Total	273	345	312	930

Table 6.5 The number (%) of patients according to Sears asthma control who experienced TRUST exacerbation.

Using the modified asthma control proposed by Chapman (see section 5.4.1 for details) there was little change when the order of events was changed except for criteria E and F when the proportion of patients with better asthma control who also suffered a TRUST exacerbation increased, 43% (219/514) for criterion E and 42% (224/504) for criterion F.

Using a simple Poisson regression model, worse asthma control was associated with an increase in the TRUST exacerbation rate ratio of between 53.6% (OR 1.54 95% CI 1.3 to 1.9) to more than 2 fold increase (OR 2.15 95% CI 1.8 to 2.6), see table 6.6.

Asthma Control	Rate Ratio (95% CI)
Criteria A	1.54† (1.27 to 1.86)
Criteria B	1.54† (1.27 to 1.86)
Criteria C	1.83† (1.50 to 2.23)
Criteria D	1.83† (1.50 to 2.23)
Criteria E	2.15† (1.77 to 2.62)
Criteria F	2.12† (1.74 to 2.59)

† p < 0.001

Table 6.6 The change in rate ratio of TRUST exacerbation according to the Chapman criteria of asthma control.

6.4.3 Discussion for asthma control

The relationship between TRUST exacerbation and asthma control suggested that those patients with worse asthma control tended to experience more TRUST exacerbations. The relationship between TRUST exacerbation and asthma control was not investigated in more detail because of the limited applicability of asthma control in future randomised controlled trials. This method was used in a crossover trial where the period of active treatment was compared directly with the period of placebo treatment within the same patient. It was not an appropriate method for use in a parallel group design trial because the whole of the follow-up was compared with a relatively short run-in period within the same patient.

6.5 Asthma exacerbations

6.5.1 Introduction for exacerbations

There was no difference between placebo and active treatment when TRUST was analysed using the definitions of exacerbation identified by the systematic review (101;104;105;107;111) but the total number of exacerbations according to the different definitions varied enormously. The aim of this analysis was to determine how the TRUST definition of exacerbation performed in comparison to the other three definitions of exacerbation (101;104;105;107;111). Their measurement characteristics were compared, as were the relationships between the diary card variables and the definitions.

6.5.2 Method for exacerbations

The three definitions of exacerbation (101;104;105;107;111) were compared with the TRUST definition of exacerbation in two ways. Firstly, periods of exacerbation (linked days of exacerbation), using end rules to determine the end of an exacerbation, were compared with TRUST (see section 5.5 for specific details of exacerbation end rule). Secondly, exacerbation days according to the three definitions were compared with TRUST. The exacerbations were compared in two ways because of the difficulty in matching the start dates exactly for periods of exacerbation. Using the daily exacerbations solved this problem and allowed for more comparisons to be made.

The periods of exacerbation were consecutive days of exacerbation all considered to be part of the same episode. Day one of the exacerbation was identified using the specific exacerbation criteria and the exacerbation was considered to have continued until the criteria for the end of an exacerbation were met. For example, the end of a TRUST exacerbation was defined as the cessation of the use of oral corticosteroids together with all the following criteria on two or more consecutive days:

1. PEF greater than 80% of median baseline level.
2. Rescue β_2 -agonist inhalations per 24 hours increased by no more than two over baseline median levels.

3. Daytime and night time symptom scores increased by no more than one over median baseline level.

Periods of exacerbation were identified for all three definitions of exacerbation and the resulting dataset contained a start date and end date for every exacerbation and the qualifying criteria the patient fulfilled. The datasets for the periods of exacerbation for each definition were combined with the TRUST exacerbation dataset, matching exacerbation start dates. This process was complicated because the different definitions of exacerbations identified periods of exacerbation on slightly different days. The exacerbation start dates were matched with TRUST exacerbation start dates up to ten days either side to try to ensure that as many of the different exacerbations were matched as possible. Ten days either side of the start date was chosen because FACET exacerbations used a ten-day rule to determine the end of an exacerbation. It was felt that exacerbation start dates more than ten days apart might not be part of the same episode. Not all the periods of exacerbation from one of the definitions of exacerbation could be matched with periods of TRUST exacerbation because of the difference in numbers of exacerbations between definitions. The comparison of daily exacerbations was much simpler. Days when the patient fulfilled the various definitions of exacerbation were identified and no attempt was made to try and link these days into periods of exacerbation.

For both periods and days of exacerbation, logistic regression models were used to identify the extent to which the variables predicted an exacerbation, details at Appendix 6.3. Two by two tables were constructed for the exacerbation days to compare days of TRUST exacerbations with other days of the three other exacerbations. Similar tables were constructed for the variables and combination of variables to test sensitivity and specificity.

The use of additional corticosteroids was a criterion in all four definitions of exacerbation with or without accompanying criteria. In order to identify which variables predicted whether patients increased inhaled corticosteroids or embarked on a course of oral treatment two regression models were used. The first model was a logistic regression model using days of exacerbation and the diary card variables as the

explanatory variables. The second model used day one of the TRUST exacerbation and included those exacerbations with and without corticosteroids. The regression analysis was repeated for the diary card variables on day one and the preceding days. details of the models used are at Appendix 6.4.

6.5.3 Results for exacerbation

6.5.3.1 TRUST

There were 860 TRUST exacerbations and 7184 days of TRUST exacerbation. 53% (455/860) of the TRUST exacerbations were classified according to corticosteroid use alone or with at least one of the other diary card criteria. Table 6.7 details the proportion of TRUST exacerbations according to the components of the definition.

	TRUST exacerbations (n = 860)	TRUST exacerbations days (n = 7184)
Corticosteroid use	455 (52%)	5678 (79%)
20% fall in morning PEF	114 (13%)	632 (9%)
Increase in rescue β_2 – agonist	374 (44%)	1912 (27%)
Daytime symptoms	343 (40%)	2055 (29%)
Night time symptoms	235 (27%)	1217 (17%)

Table 6.7 Number (%) of TRUST exacerbations (periods and days) according to the criteria fulfilled.

A logistic regression analysis was carried out to determine which of the diary card variables were the strongest predictors of a TRUST exacerbation. Table 6.8 lists the crude and adjusted odds ratios for TRUST exacerbations and exacerbation days as well as exacerbations with and without corticosteroid use. Use of additional corticosteroids could not be included in the model because by definition it predicted TRUST exacerbation on its own and was dropped from the computer model.

Diary card variable	TRUST Exacerbations		TRUST Exacerbation Days		TRUST Exacerbations without steroids		TRUST Exacerbations with steroids	
	Crude Odds Ratio	Adjusted Odds Ratio ^a	Crude Odds Ratio	Adjusted Odds Ratio ^a	Crude Odds Ratio	Adjusted Odds Ratio ^a	Crude Odds Ratio	Adjusted Odds Ratio ^a
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
5 to 10% decrease in am PEF	2.97† (13.5 to 22.8)	1.55† (1.24 to 1.94)	2.01† (1.89 to 2.14)	1.32† (1.14 to 1.53)	3.58† (2.73 to 4.71)	1.42‡ (1.01 to 1.99)	1.17† [‡] (1.11 to 1.24)	0.95 [‡] (0.84 to 1.08)
10 to 20% decrease in am PEF	8.28† (6.65 to 10.3)	2.34† (1.72 to 3.18)	4.36† (4.0 to 4.74)	2.08† (1.68 to 2.57)	14† (10.4 to 18.8)	3.28† (2.21 to 4.87)		
>20% decrease in am PEF	17.6† (13.5 to 22.8)	2.61† (1.71 to 3.97)	11.4† (10.25 to 12.69)	4.13† (3.0 to 5.7)	35.2† (25.0 to 49.6)	4.23† (2.31 to 7.75)		
1 unit increase daytime symptoms	5.04† (4.05 to 6.27)	2.19† (1.68 to 2.87)	2.64† (2.47 to 2.84)	1.67† (1.35 to 2.06)	10.8† (7.3 to 16.1)	2.63† (1.66 to 4.19)	1.3† [‡] (1.2 to 1.4)	1.12 [‡] (1.0 to 1.26)
2 unit increase daytime symptoms	37.1† (30.2 to 45.7)	8.31† (6.14 to 11.24)	14.4† (13.37 to 15.53)	5.95† (4.67 to 5.57)	125† (86 to 182)	12.36† (7.11 to 21.47)		
3 unit increase daytime symptoms	58.8† (45.0 to 77.0)	6.60† (4.16 to 10.47)	48.0† (43.2 to 53.3)	12.28† (8.95 to 16.86)	218† (142 to 227)	9.51† (4.80 to 18.85)		
4 unit increase daytime symptoms	146† (99 to 213)	9.71† (5.54 to 17.01)	79.0† (62.8 to 99.4)	14.31† (9.29 to 22.1)	550† (314 to 965)	11.57† (4.92 to 27.23)		
5 unit increase daytime symptoms	191† (91 to 396)	21.01† (9.47 to 46.61)	245† (132 to 452)	17.76† (6.23 to 50.63)	865† (282 to 2656)	41.8† (9.44 to 184)		
1 unit increase in night time symptoms	4.84† (4.02 to 5.84)	1.65† (1.29 to 2.10)	2.91† (2.73 to 3.1)	1.25‡ (1.04 to 1.51)	10.6† (7.7 to 14.6)	1.85 § (1.2 to 2.87)	1.35† [‡] (1.23 to 1.48)	1.19† [‡] (1.04 to 1.41)
2 unit increase in night time symptoms	24.0† (19.9 to 28.9)	3.51† (2.54 to 4.86)	11.75† (10.9 to 12.64)	2.43† (1.95 to 3.03)	75.3† (55.6 to 101)	5.35† (3.17 to 9.05)		
3 unit increase in night time symptoms	59.0† (45.3 to 76.7)	4.30† (2.98 to 6.22)	27.5† (24.0 to 31.5)	2.67† (1.92 to 3.72)	197† (136 to 287)	6.76† (3.76 to 12.17)		
4 unit increase in night time symptoms	88.0† (52.1 to 148)	3.02‡ (1.43 to 6.36)	50.9† (36.8 to 70.3)	2.3† (1.39 to 3.8)	278† (138 to 562)	3.75‡ (1.21 to 11.64)		
5 unit increase in night time symptoms	41.5† (5.50 to 314)	0.43 (0.04 to 4.2)	256† (74.0 to 884)	4.4† (0.3 to 67.02)	551† (63 to 4795)	1.65 (0.22 to 12.25)		
2 to 6 puffs increase in rescue β ₂ -agonist use	19.61† (16.69 to 23.03)	4.64† (3.70 to 5.81)	10.45† (9.77 to 11.27)	3.73† (2.93 to 4.76)	82† (62 to 109)	15.3† (10.37 to 22.56)	1.3† [‡] (1.14 to 1.48)	0.996 [‡] (0.85 to 1.16)
6 to 10 puffs increase in rescue β ₂ -agonist use	34.26† (25.75 to 45.59)	3.62† (3.70 to 5.81)	45.8† (39.5 to 53.1)	9.16† (5.99 to 14.02)	151† (102 to 223)	10.8† (6.28 to 18.37)		
> 10 puffs increase in rescue β ₂ -agonist use	37.99† (23.84 to 60.53)	2.82† (1.61 to 4.96)	59.5† (45.2 to 78.2)	8.1† (3.04 to 21.34)	202† (116 to 351)	9.26† (4.91 to 17.44)		
5 to 10% decrease in am PEF	2.99† (2.51 to 3.56)	1.21 (0.99 to 1.49)	2.35† (2.21 to 2.50)	1.32 (0.93 to 1.85)	3.74† (2.89 to 4.75)	1.15 (0.84 to 1.59)	1.21† [‡] (1.14 to 1.27)	0.91 [‡] (0.79 to 1.05)
10 to 20% decrease in am PEF	6.57† (5.25 to 8.23)	1.29 (0.96 to 1.75)	4.51† (4.12 to 4.93)	1.36‡ (1.09 to 1.70)	9.83† (7.23 to 13.36)	1.20 (0.77 to 1.86)		
>20% decrease in am PEF	18.13† (13.66 to 24.06)	1.34 (0.90 to 2.0)	10.84† (9.49 to 12.40)	1.32† (1.14 to 1.52)	27.7† (18.8 to 40.7)	0.83 (0.48 to 1.43)		

† p < 0.001, ‡ p < 0.05, § p < 0.01

^a The relationship between variable and exacerbation linear, odds ratio for 1 unit change shown.

^a Adjusted for baseline values, age, sex and clustering on patient study number.

Table 6.8 The effect of diary card variables on the odds ratios of experiencing a TRUST exacerbation or TRUST exacerbation day.

An increase in daytime symptoms was the strongest predictor of exacerbation with close to an eight fold increase in the odds ratio for an exacerbation with an increase in symptom score of 2 (OR 8.31 95% CI 6.14 to 11.24) for exacerbation and a six-fold increase for exacerbation days (OR 5.96 95% CI 4.67 to 5.57). A fall in morning PEF of 20% or more resulted in a more than two-fold increase in the odds ratio for an exacerbation (OR 2.61 95% CI 1.71 to 3.97) and a four-fold increase in the odds ratio for an exacerbation day (OR 4.13 95% CI 3.0 to 5.7). When the TRUST exacerbations were split according to those treated with corticosteroids and those without corticosteroids the effect of the variables on the odds ratio for an exacerbation changed, the relationship between the variables and those exacerbations treated with corticosteroids were linear. An increase in daytime symptoms had an even greater effect on TRUST exacerbations without corticosteroids, with an odds ratio of 12.36 (95% CI 7.11 to 21.47) increase of two over baseline. Use of rescue β_2 -agonists and an increase night time symptom score of two or more over baseline had a greater effect on the likelihood of a TRUST exacerbation without corticosteroids than all TRUST exacerbations. The effect of all diary card variables on TRUST exacerbations treated with corticosteroids was much less than on all exacerbations or those without corticosteroids and the relationships were linear. This suggested that those exacerbations treated with corticosteroids were associated with fewer symptoms and changes in PEF than those exacerbations not treated with corticosteroids.

6.5.3.2 FACET

Using TRUST data there were 214 FACET (known oral corticosteroids only) and 470 FACET (including oral and uncertain corticosteroids) exacerbations. Table 6.9 details the numbers of FACET exacerbations according to the definition of exacerbation. When days of FACET exacerbation were considered 80% (2466/3095) of FACET exacerbations were as a result of additional corticosteroid use and this fell to 60% (937/1566) when only those known to have used oral corticosteroids were included.

	FACET Exacerbation	
	Including oral corticosteroids only	Including unknown and oral corticosteroids
	(n = 214)	(n = 470)
Corticosteroid use	90 (42%)	346 (77%)
Morning PEF <70% run-in	121 (57%)	121 (26%)
Both	3 (1%)	3 (1%)

Table 6.9 Number (%) FACET exacerbations according to the components of the definition of exacerbation.

All the comparisons of the measurement characteristics of the TRUST and FACET definitions of exacerbation were carried out on the daily exacerbations because it did not rely on date matching. The analysis was repeated for FACET exacerbations including those treated with known and unknown corticosteroids and those treated with known oral corticosteroids separately. Using the TRUST definition of exacerbation as a gold standard, the FACET definition had 37% sensitivity (95% CI 35.6 to 37.8) and 99.8% specificity (95% CI 99.7 to 99.8) when those exacerbations with unknown corticosteroids were included. The sensitivity fell to 16% (95% CI 14.6 to 16.3) when known oral corticosteroids only were included, table 6.10. Using the FACET exacerbation as the gold standard, TRUST exacerbation had a sensitivity of 85% (95% CI 84 to 87%) and specificity of 98% (95% CI 97.9 to 98%).

		FACET (including oral and unknown corticosteroids) TRUST exacerbation No Yes		FACET (including oral corticosteroids only) TRUST exacerbation No Yes	
TRUST exacerbation	No	219036 (99.8%)	4545 (63%)	219036 (99.8%)	6074 (84.5%)
	Yes	456 (0.2%)	2639 (37%)	456 (0.2%)	1110 (15.6%)
Total		219492	7184	219492	7184

Table 6.10 Days of exacerbation according to the TRUST and FACET definitions.

Using a logistic regression model, the odds ratio for those patients experiencing a FACET exacerbation also experiencing a TRUST exacerbation was 279 (95% CI 251 to 309) if patients with unknown corticosteroid use were included. This decreased to 89 (95% CI 79 to 98) for those patients with known oral corticosteroids only.

The extent to which the diary card variables predicted whether a patient experienced a FACET exacerbation (definition in section 5.5.2) or not was examined using a logistic regression model, table 6.11. The strongest predictors of exacerbation using the FACET definition were a fall in morning PEF of 20% or more and increase in daytime symptoms. The effect of an increase in night time symptoms was less than expected and the likelihood of exacerbation did not increase with increasing night time symptoms. The use of corticosteroids was excluded from the model because their use was logically linked to a FACET exacerbation and dramatically reduced the predictive effect of all the other diary card variables. The odds ratio for a fall in mean morning PEF was greater when only those exacerbation requiring treatment with oral corticosteroids were included compared to those including unknown corticosteroids, but was still a very strong predictor in both cases. This suggested that the exacerbations resulting in treatment with oral corticosteroids were more severe.

Diary card variable	(Including patients with exacerbations treated with oral and unknown steroids)				(Including patients with exacerbations treated with oral steroids only)			
	FACET Exacerbations		FACET Exacerbation Days		FACET Exacerbations		FACET Exacerbation Days	
	Crude Odds Ratio (95%CI)	Adjusted Odds Ratio* (95%CI)	Crude Odds Ratio (95%CI)	Adjusted Odds Ratio* (95%CI)	Crude Odds Ratio (95%CI)	Adjusted Odds Ratio* (95%CI)	Crude Odds Ratio (95%CI)	Adjusted Odds Ratio* (95%CI)
5 to 10% decrease in am PEF	2.17† (1.61 to 2.92)	1.8§ (1.29 to 2.52)	1.87† (1.69 to 2.08)	1.41† (1.31 to 1.76)	4.72† (2.48 to 8.97)	4.49† (2.16 to 9.33)	2.38† (2.0 to 2.84)	1.82† (1.36 to 2.45)
10 to 20% decrease in am PEF	5.76† (4.06 to 8.16)	3.57† (2.27 to 5.60)	3.9† (3.40 to 4.46)	2.37† (1.70 to 3.30)	13.2† (6.54 to 26.67)	10.5† (4.27 to 25.7)	6.77† (5.56 to 8.23)	4.34† (2.67 to 7.06)
>20% decrease in am PEF	61.0† (46.5 to 80.1)	31.2† (19.7 to 49.6)	44.5† (39.7 to 49.9)	22.0‡ (13.4 to 35.8)	347† (198 to 608)	221† (96.5 to 510)	122† (104.3 to 143)	60.96† (35.2 to 106)
1 unit increase daytime symptoms	2.50† (1.92 to 3.26)	1.75† (1.30 to 2.37)	2.17† (1.97 to 2.4)	1.75† (1.33 to 2.29)	3.32† (2.29 to 4.80)	1.84§ (1.23 to 2.74)	2.17† (1.89 to 2.49)	1.67§ (1.16 to 2.39)
2 unit increase daytime symptoms	8.43† (6.28 to 11.3)	3.65† (2.34 to 5.70)	5.54† (4.90 to 6.27)	3.39† (2.31 to 4.99)	8.08† (5.15 to 12.7)	2.25‡ (1.18 to 4.31)	5.43† (4.58 to 6.45)	2.76† (1.62 to 4.72)
3 unit increase daytime symptoms	18.5† (12.7 to 27.0)	4.94† (2.77 to 8.79)	12.8† (10.9 to 15.1)	5.43† (3.06 to 9.63)	19.9† (11.5 to 34.5)	2.89§ (1.31 to 6.39)	17.5† (14.4 to 21.3)	6.16† (2.87 to 13.2)
4 unit increase daytime symptoms	40.1† (22.3 to 71.9)	5.16† (2.34 to 11.4)	25.0† (18.7 to 33.5)	6.36† (3.00 to 13.5)	70.1† (35.2 to 139)	4.53§ (1.69 to 12.2)	43.4† (31.9 to 59.1)	9.24† (3.26 to 26.2)
5 unit increase daytime symptoms	86.2† (33.8 to 219)	5.56‡ (1.39 to 22.3)	97.0† (58.8 to 160)	8.29‡ (2.07 to 33.2)	197† (75.5 to 516)	6.27‡ (1.23 to 31.9)	191† (115 to 317)	14.4‡ (2.63 to 79.0)
1 unit increase in night time symptoms	2.47†* (2.26 to 2.70)	1.13* (0.98 to 1.30)	2.29†* (2.08 to 2.51)	1.2* (0.93 to 1.53)	2.81†* (2.50 to 3.17)	1.03* (0.85 to 1.24)	2.40† (2.11 to 2.73)	1.11 (0.80 to 1.53)
2 unit increase in night time symptoms			4.33† (3.79 to 4.95)	1.10 (0.74 to 1.60)			5.51† (4.66 to 6.52)	1.19 (0.71 to 2.0)
3 unit increase in night time symptoms			13.2† (10.9 to 16.2)	1.54 (0.86 to 2.75)			22.3† (17.9 to 27.7)	2.14 (0.98 to 4.67)
4 unit increase in night time symptoms			41.2† (28.9 to 58.9)	2.32 (1.11 to 4.84)			69.9† (48.2 to 102)	2.66‡ (1.05 to 6.73)
5 unit increase in night time symptoms			157† (61.0 to 406)	1.55 (0.1 to 25.5)			316† (122 to 818)	1.08 (0.4 to 32.2)
2 to 6 puffs increase in rescue β_2 -agonist use	4.34† (3.25 to 5.81)	1.1 (0.74 to 1.63)	3.86† (3.41 to 4.36)	1.30 (0.87 to 1.95)	5.27† (3.47 to 7.99)	1.13 (0.68 to 1.89)	4.63† (3.91 to 5.49)	1.15 (0.68 to 1.95)
6 to 10 puffs increase in rescue β_2 -agonist use	10.1† (5.93 to 17.1)	1.05 (0.51 to 2.17)	6.94† (5.35 to 9.01)	1.07 (0.60 to 1.93)	16.0† (8.25 to 30.8)	1.11 (0.47 to 2.63)	11.1† (8.12 to 15.1)	0.92 (0.39 to 2.19)
> 10 puffs increase in rescue β_2 -agonist use	14.9† (6.92 to 32.0)	0.94 (0.35 to 2.57)	11.6† (7.98 to 16.9)	1.53 (0.33 to 7.16)	24.9† (10.0 to 62.1)	1.12 (0.32 to 3.94)	23.8† (16.1 to 35.3)	2.41 (0.21 to 27.6)
5 to 10% decrease in pm PEF	2.21† (1.69 to 2.87)	1.14 (0.83 to 1.57)	2.01† (1.82 to 2.22)	1.17 (0.93 to 1.48)	2.93† (1.91 to 4.50)	1.01 (0.63 to 1.63)	2.33† (2.02 to 2.70)	1.08 (0.77 to 1.54)
10 to 20% decrease in pm PEF	7.44† (5.54 to 9.98)	1.38 (0.94 to 2.03)	5.67† (5.02 to 6.40)	1.37 (0.91 to 2.08)	12.8† (8.24 to 19.8)	1.16 (0.72 to 1.87)	8.52† (7.27 to 9.99)	1.31 (0.80 to 2.16)
>20% decrease in pm PEF	29.5† (21.5 to 40.5)	1.38 (0.82 to 2.33)	19.9† (17.1 to 23.2)	1.36 (0.77 to 2.41)	75.7† (47.7 to 115)	1.48 (0.84 to 2.60)	39.7† (33.3 to 47.2)	1.44 (0.80 to 2.59)

† p < 0.001, ‡ p < 0.05, § p < 0.01

* The relationship between variable and exacerbation linear, odds ratio for 1 unit change shown

*Adjusted for baseline values, age, sex and clustering on patient study number

Table 6.11 The effect of diary card variables on the odds ratios of experiencing a FACET exacerbation or FACET exacerbation day.

6.5.3.3 Wilding definition of exacerbation

Using TRUST data there were 2499 exacerbations, including oral and unknown corticosteroids, according to the definition by Wilding (definition in section 5.5.3) and 2312 exacerbations including known oral corticosteroids only. Corticosteroid use plus one other criterion accounted for only 4% (90 / 2312) of Wilding exacerbations. The most common reason for exacerbation was increase in daytime symptoms and night time reliever use, 75% (1737 / 2312) of all Wilding exacerbations when known oral corticosteroids only were included. Including those exacerbations with oral and unknown corticosteroids resulted in 11% (277 / 2499) exacerbation including corticosteroids and 70% (1737 / 2499) of exacerbations were as a result of daytime and night time symptoms.

As with FACET, comparing days of exacerbation according to the TRUST and Wilding definitions was more useful because it did not rely on matching dates. Using TRUST as the gold standard, the Wilding exacerbation definition had 34.8% sensitivity (95% CI 33.74 to 35.96) and 95.23% specificity (95% CI 95.14 to 95.32) when only patients with known oral corticosteroid use were included, increasing to 51% sensitivity (95% CI 50.02 to 52.35) when patients with unknown corticosteroids were included, table 6.5.6. When the Wilding definition of exacerbation (known oral corticosteroids only) was the gold standard TRUST exacerbation had 19.3% sensitivity (95% CI 18.37 to 19.72%) and specificity of 97.81% (95% CI 97.75 to 97.87). For those patients experiencing an exacerbation by the Wilding definition there was a 21 fold increase in the odds of experiencing a TRUST exacerbation (OR 21 95% CI 17 to 26) including patients with unknown corticosteroid use. This was reduced to an 11 fold increase (OR 11 95% CI 9 to 13) when those patients with unknown corticosteroids were excluded.

		Wilding exacerbation (including oral and unknown corticosteroids)		Wilding exacerbation (including oral corticosteroids only)	
		TRUST exacerbation		TRUST exacerbation	
		No	Yes	No	Yes
TRUST exacerbation	No	209028 (95%)	3507 (49%)	209028 (95%)	4681 (65%)
	Yes	10464 (5%)	3677 (51%)	10464 (5%)	2503 (35%)
Total		219492	7184	219492	7184

Table 6.12 Days of exacerbation according to the TRUST and Wilding definitions.

A logistic regression model was used to determine the extent to which the diary card variables predicted whether a patient experienced a Wilding exacerbation or not, table 6.13.

The strongest predictors of Wilding exacerbation days were corticosteroid use (OR 14.43 95% CI 10.41 to 19.99) followed by daytime and night time symptoms (OR 2.54 95% CI 2.25 to 2.87 and OR 2.12 95% CI 1.79 to 2.52 respectively) when patients were included with exacerbations treated with oral and unknown corticosteroids. The effect of corticosteroid use was reduced when only those courses of known oral corticosteroid were included (OR 1.66 95% CI 1.14 to 2.42). Corticosteroid use could be included in the multivariate model because it was not logically linked to exacerbation in this definition since it had to occur in combination with one other criterion. When periods of exacerbation were analysed the effect of day and night time symptoms was reduced but they were still the most important predictors of exacerbation.

Diary card variable	(Including patients with exacerbations treated with oral and unknown steroids)				(Including patients with exacerbations treated with oral steroids only)			
	Wilding Exacerbations		Wilding Exacerbation Days		Wilding Exacerbations		Wilding Exacerbation Days	
	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
Oral corticosteroids	5.05 (4.44 to 5.74)	-	13.54† (12.81 to 14.32)	14.43† (10.41 to 19.99)	1.59 (1.28 to 1.96)	-	5.17† (4.84 to 5.51)	1.66§ (1.14 to 2.42)
1 l/min increase in am PEF	0.99† (0.99 to 0.99)	1.0† (0.99 to 1.0)	0.99† (0.99 to 0.99)	1.00 (0.99 to 1.00)	0.99† (0.99 to 0.99)	0.995† (0.99 to 1.0)	0.99† (0.99 to 0.99)	1.00 (0.99 to 1.0)
10 l/min increase in am PEF	0.88† (0.87 to 0.88)	0.96† (0.93 to 0.98)	0.87† (0.86 to 0.87)	0.96 (0.92 to 1.002)	0.88† (0.87 to 0.88)	0.96† (0.93 to 0.98)	0.87† (0.87 to 0.88)	0.96 (0.92 to 1.01)
100 l/min increase in am PEF	0.26† (0.24 to 0.29)	0.63† (0.49 to 0.81)	0.24† (0.23 to 0.25)	0.66 (0.42 to 1.02)	0.27† (0.24 to 0.29)	0.63† (0.48 to 0.83)	0.25† (0.24 to 0.26)	0.66 (0.42 to 1.06)
1 unit increase daytime symptoms	3.05† (2.94 to 3.17)	1.83† (1.68 to 1.99)	4.85† (4.74 to 4.97)	2.54† (2.25 to 2.87)	3.09† (2.97 to 3.21)	1.80† (1.64 to 1.97)	4.83† (4.72 to 4.95)	2.51† (2.21 to 2.84)
1 unit increase in night time symptoms	3.21† (3.08 to 3.35)	1.63† (1.47 to 1.81)	4.43† (4.32 to 4.54)	2.12† (1.79 to 2.52)	3.31† (3.17 to 3.45)	1.68† (1.50 to 1.88)	4.56† (4.45 to 4.68)	2.15† (1.80 to 2.58)
1 puff increase in rescue β_2 -agonist use	1.40† (1.38 to 1.42)	1.17† (1.11 to 1.24)	2.02† (2.0 to 2.05)	1.62† (1.50 to 1.75)	1.41† (1.39 to 1.43)	1.18† (1.12 to 1.25)	2.09† (2.06 to 2.11)	1.65† (1.52 to 1.79)
1 l/min increase in pm PEF	0.99† (0.98 to 0.99)	1.00 (1.0 to 1.0)	-	-	0.99† (0.99 to 0.99)	1.00 (1.0 to 1.0)	-	-

† p < 0.001, § p = 0.008

*Adjusted for baseline values, age, sex and clustering on patient study number.

Table 6.13 The effect of diary card variables on the odds ratios of experiencing a Wilding exacerbation or Wilding exacerbation day.

6.5.3.4 Taylor definition of exacerbation

There were 535 exacerbations according to the Taylor definition of exacerbation. for definition see section 5.5.4. Using the days of exacerbation there was poor agreement between the Taylor and TRUST exacerbation with sensitivity of 7% (95% CI 6.5 to 7.8%) and specificity of 99.8% when TRUST exacerbation was the gold standard. Using logistic regression the odds ratio of experiencing a TRUST exacerbation if a Taylor exacerbation occurred was 40 (95% CI 25.6 to 62.3).

A logistic regression model was used to determine the extent to which the diary card variables predicted whether a patient experienced a Taylor exacerbation or not. The analysis was repeated for asthma scores from mildly unstable upwards, see table 6.14. An increase in night time symptoms was the strongest predictor of a Taylor exacerbation with an adjusted odds ratio of 1.64 (CI 1.38 to 1.95) followed by an increase in daytime symptoms with an adjusted odds ratio of 1.43 (CI 1.25 to 1.63).

Diary card variable	Taylor Exacerbations		Taylor Exacerbation Days		Taylor Scores	
	Crude Odds Ratio	Adjusted Odds Ratio*	Crude Odds Ratio	Adjusted Odds Ratio*	Crude Odds Ratio	Adjusted Odds Ratio*
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Oral corticosteroids	21.58† (18.80 to 24.76)	6.59† (4.77 to 9.12)	21.58† (18.80 to 24.77)	6.59† (4.77 to 9.12)	4.21† (3.98 to 4.45)	1.10 (0.9- to 1.35)
1 l/min increase in am PEF	0.96† (0.96 to 0.96)	0.97† (0.96 to 0.97)	0.96† (0.96 to 0.97)	0.97† (0.96 to 0.97)	0.96† (0.96 to 0.96)	0.95† (0.94 to 0.95)
10 l/min increase in am PEF	0.66† (0.66 to 0.67)	0.72† (0.68 to 0.76)	0.69† (0.68 to 0.70)	0.72† (0.68 to 0.76)	0.66† (0.66 to 0.66)	0.58† (0.54 to 0.61)
100 l/min increase in am PEF	0.02† (0.01 to 0.02)	0.04† (0.02 to 0.07)	0.03† (0.02 to 0.03)	0.04† (0.02 to 0.07)	0.02† (0.02 to 0.02)	0.004† (0.002 to 0.007)
1 unit increase daytime symptoms	3.13† (2.96 to 3.29)	1.43† (1.25 to 1.63)	3.23† (3.06 to 3.40)	1.43† (1.25 to 1.63)	4.69† (4.60 to 4.78)	5.85† (4.60 to 7.44)
1 unit increase in night time symptoms	3.86† (3.65 to 4.09)	1.64† (1.38 to 1.95)	3.86† (3.65 to 4.09)	1.64† (1.38 to 1.95)	4.98† (4.89 to 5.09)	4.61† (3.74 to 5.69)
1 puff increase in rescue β_2 -agonist use	1.34† (1.32 to 1.36)	1.06‡ (1.01 to 1.11)	1.32† (1.30 to 1.35)	1.06‡ (1.01 to 1.11)	1.42† (1.41 to 1.42)	1.11§ (1.04 to 1.06)
1 l/min increase in pm PEF	0.97† (0.97 to 0.97)	1.00 (0.99 to 1.0)	0.99† (0.99 to 0.99)	1.00 (0.99 to 1.0)	0.98† (0.98 to 0.98)	1.00 (0.99 to 1.0)

† p < 0.001, ‡ p = 0.01, § p = 0.003

*Adjusted for baseline values, age, sex and clustering on patient study number.

Table 6.14 The effect of diary card variables on the odds ratios of experiencing a Taylor exacerbation,Taylor exacerbation day or Taylor score.

6.5.3.5 PEF diary cards

Graphs were produced for each patient in turn, morning PEF was plotted against time and the start dates for the four definitions of exacerbation were marked on the graph. It provided a visual means of checking how the exacerbations related to changes in the patient's morning PEF. Figures 6.3 to 6.6 are a sample of patients' diary card data marking the exacerbations according to the different definitions.

Figure 6.3 illustrates a patient who experienced several exacerbations according to the Wilding definition before exacerbations according to the TRUST and Taylor definitions. The exacerbations according to the Wilding definition occurred with a much lower fall in morning PEF than exacerbations according to other definitions. The patient in figure 6.4 experienced exacerbations according to all of the definitions. The FACET exacerbation may have been triggered first because the fall in PEF occurred in isolation and the other definitions required it to occur in combination with another variable. The patient in figure 6.5 experienced exacerbations according to all of the definitions. Again those exacerbations according to the Wilding definition tended to occur with higher morning PEF. Finally the patient in figure 6.6 experienced a severe fall in PEF that was not identified by any of the definitions of exacerbation.

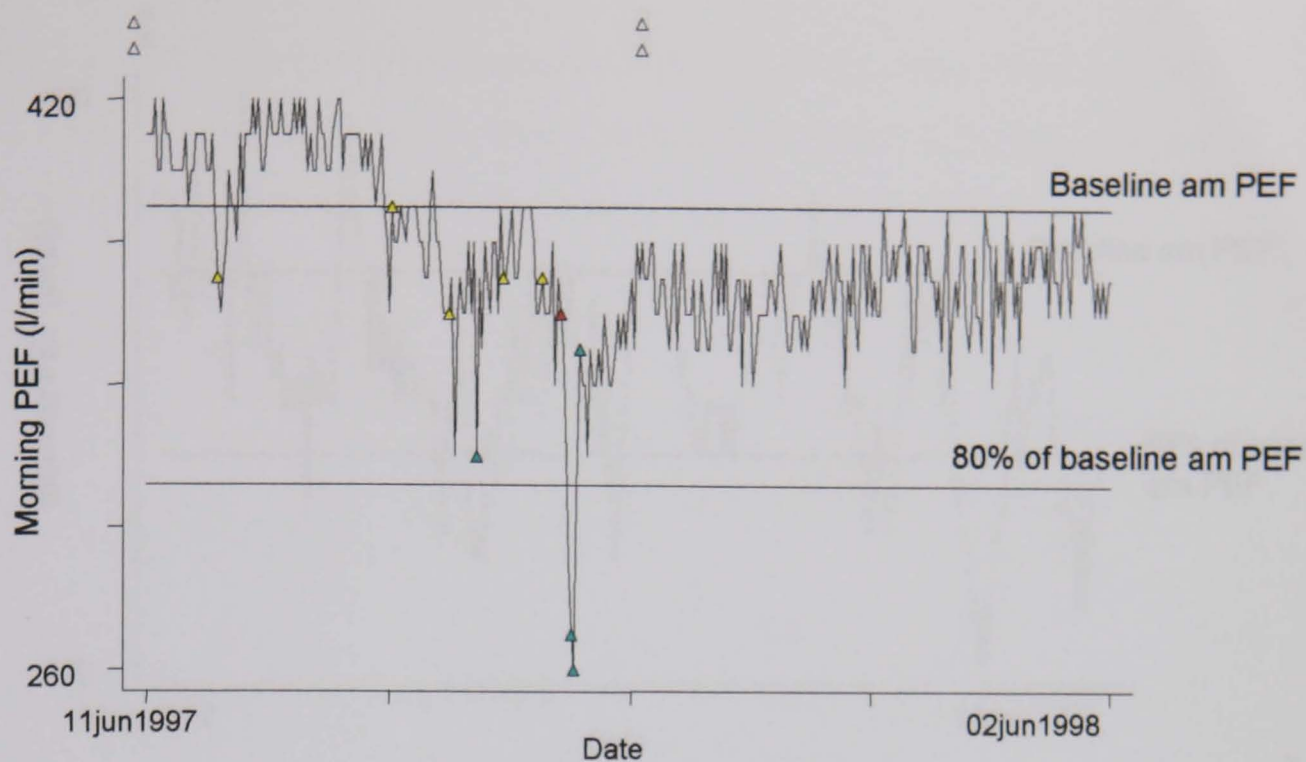


Figure 6.3 PEF diary card for a patient who experienced several exacerbations

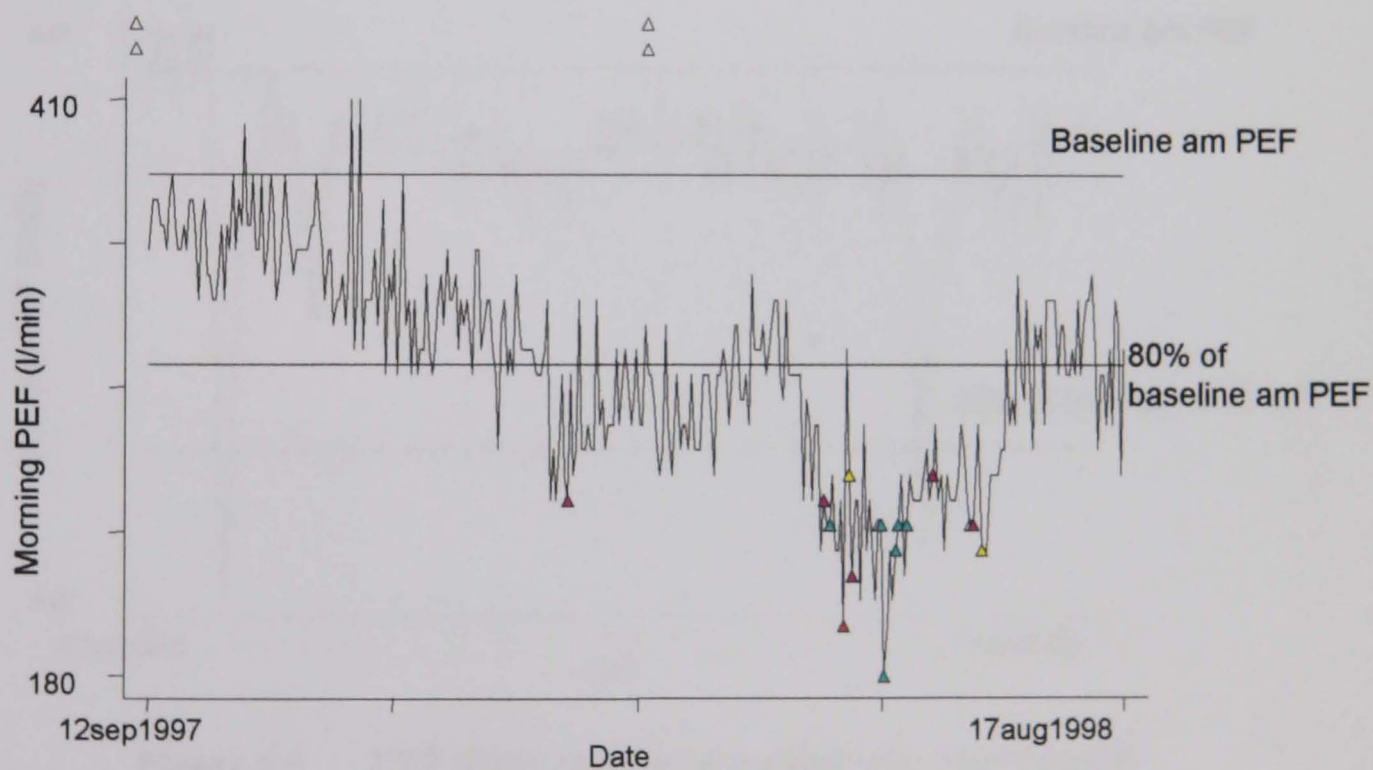


Figure 6.4 PEF diary card for a patient who experienced several exacerbations

Key

- ▲ Trust exacerbation
- ▲ Wilding exacerbation
- ▲ FACET exacerbation
- ▲ Taylor exacerbation

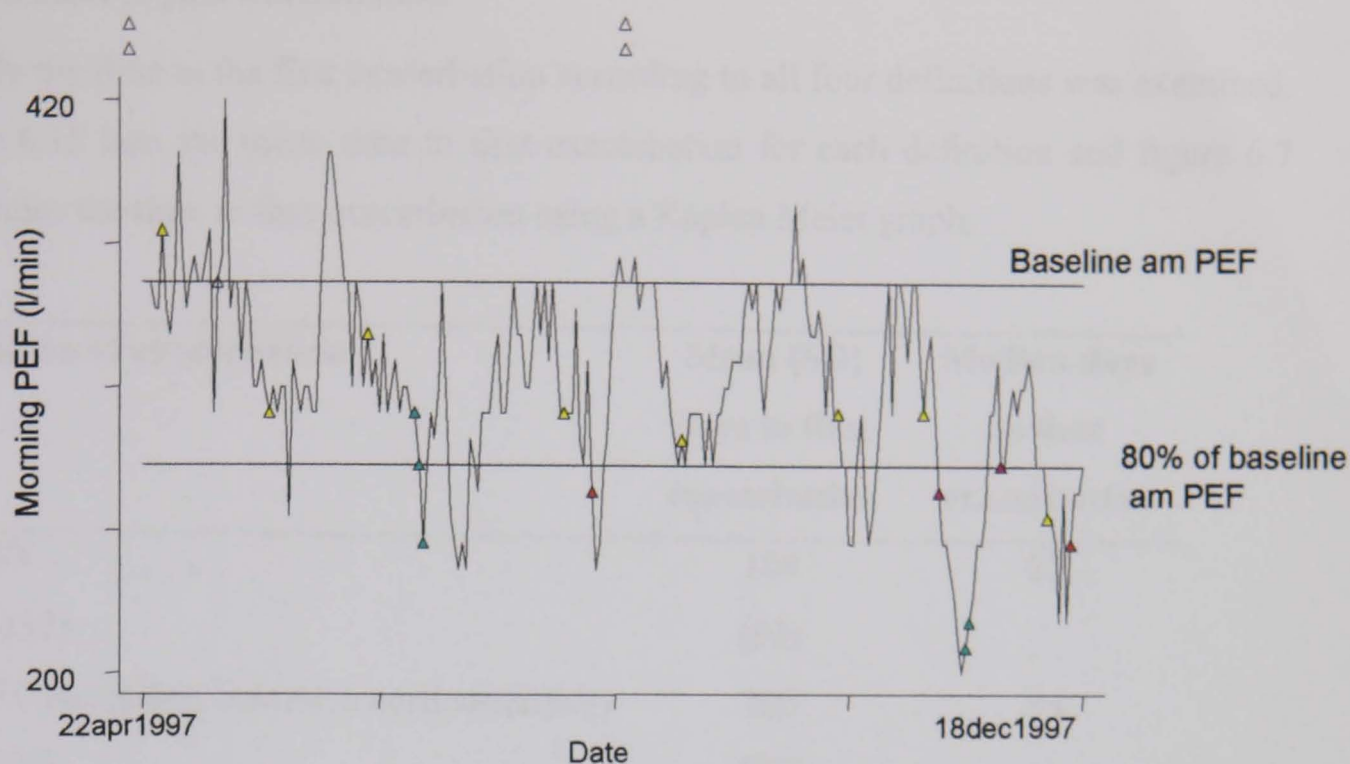


Figure 6.5 PEF diary card for a patient who experienced an exacerbation according to all definitions

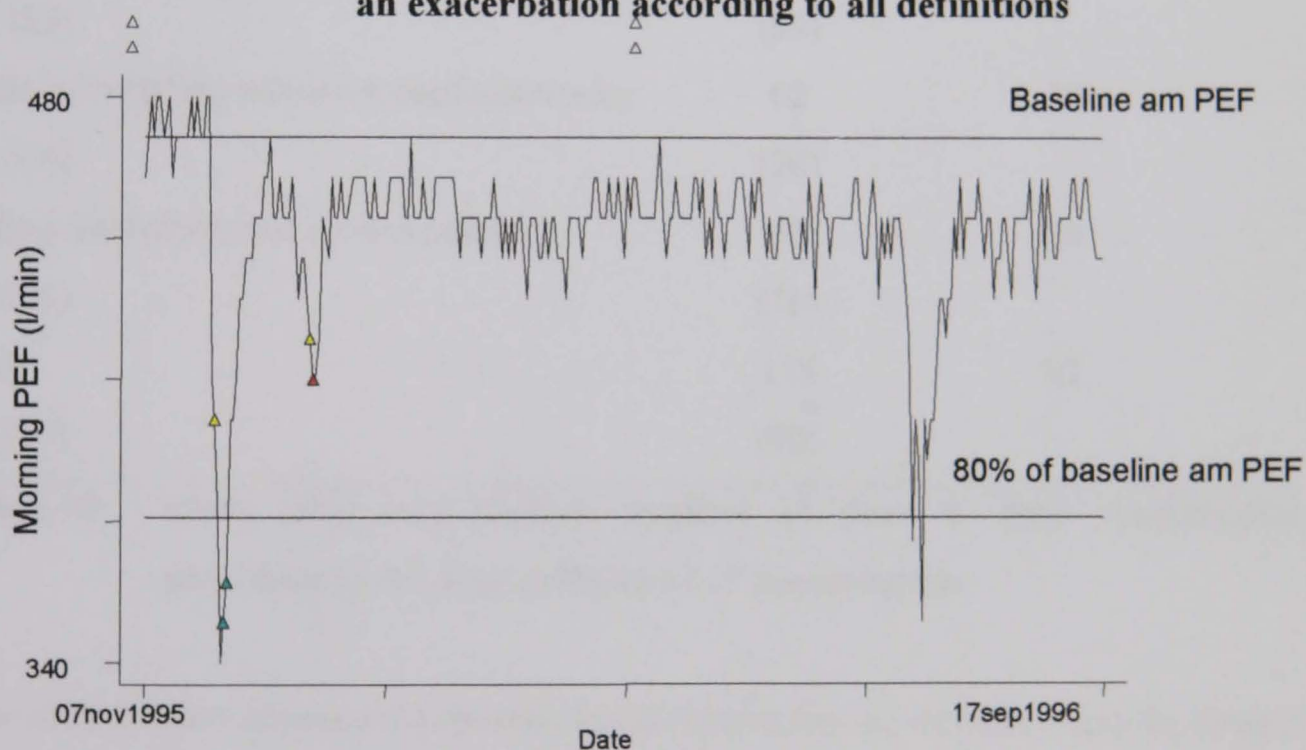


Figure 6.6 PEF diary card for a patient who experienced a fall in am PEF missed by all definitions of exacerbation

Key

- | | |
|----------------------|------------------------|
| ▲ Trust exacerbation | ▲ Wilding exacerbation |
| ▲ FACET exacerbation | ▲ Taylor exacerbation |

6.5.3.6 Time to first exacerbation

Finally the time to the first exacerbation according to all four definitions was examined. Table 6.15 lists the mean time to first exacerbation for each definition and figure 6.7 illustrates the time to first exacerbation using a Kaplan Meier graph.

Definition of exacerbation	Mean (SD) days to first exacerbation	Median days to first exacerbation
TRUST (n = 432)	108 (93)	82
FACET (including unknown corticosteroids) (n = 273)	103 (92)	84
FACET (including oral corticosteroids only) (n = 123)	121 (99)	92
Wilding (including unknown corticosteroids) (n = 626)	62 (76)	30
Wilding (including oral corticosteroids) (n = 586)	61 (76)	30
Taylor (n = 107)	115 (92)	93

Table 6.15 Mean (SD) and median number of days to first exacerbation according to the four definitions of exacerbation.

There were 60 days between the shortest mean time to first exacerbation and the longest mean time. Time to first exacerbation for three of the definitions was grouped around 112 days and the time to first Wilding exacerbation was 61 days. This was because the Wilding definition of exacerbation included small increases in day and night time symptoms and as a result many days were classified as being an exacerbation.

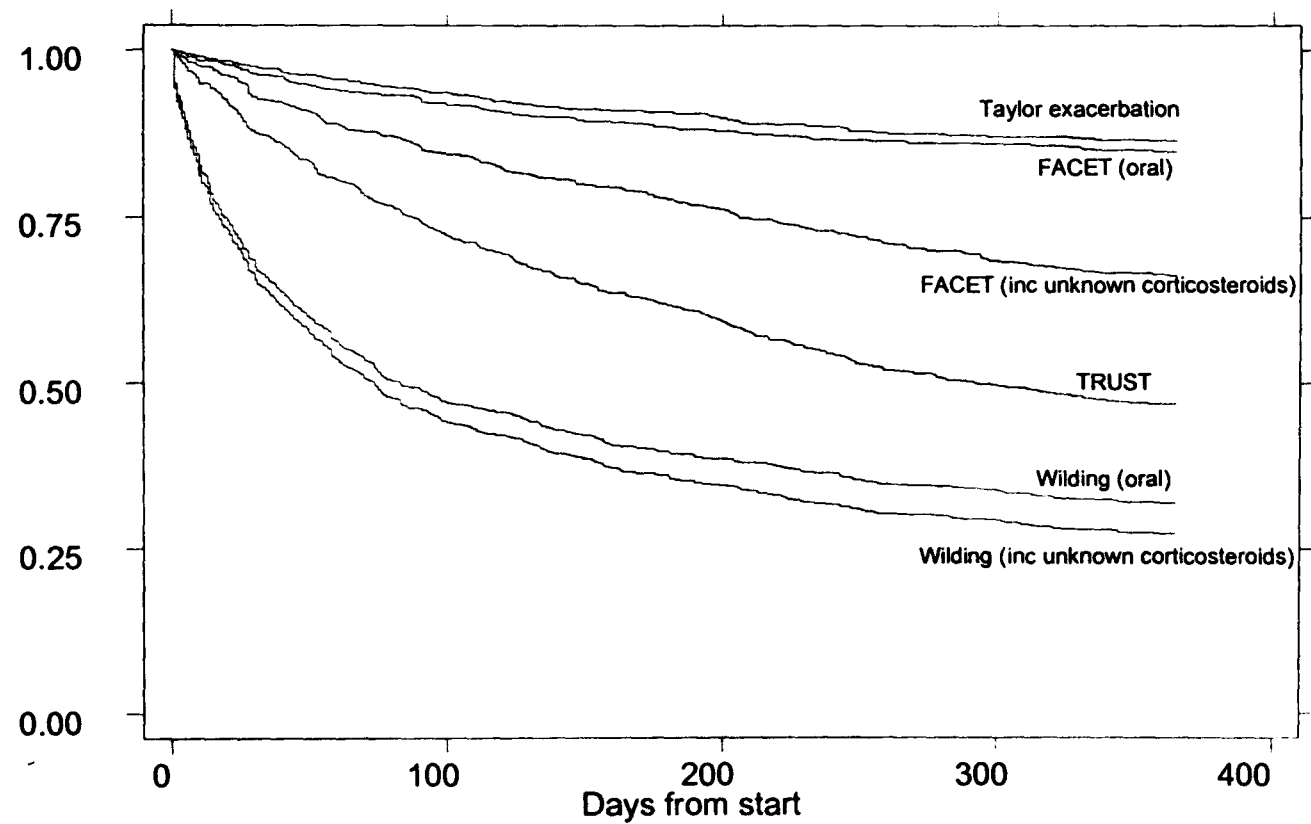


Figure 6.7 Time to first exacerbation according to the different definitions of exacerbation as a survival function.

6.5.3.5 Diary card variables

From the tables of odds ratios for the four definitions of exacerbation the strongest predictors, other than corticosteroid use, for any definition of exacerbation were:

1. Increase in daytime symptoms.
2. Decrease in morning PEF by 100 l/min.
3. Increase in night time symptoms.

Use of additional corticosteroids was strongly associated with both TRUST and FACET definitions of exacerbation but could not be included in the regression models because it was logically linked to exacerbation and was automatically dropped by the STATA program. The criterion for a fall in morning PEF of 100 l/min was chosen because it represented a fall in the mean PEF (402 l/min) of approximately 25%. Whilst these factors seemed to be strong predictors of exacerbation it was important to test each alone and in combination to determine the sensitivity and specificity of their ability to detect exacerbations.

For TRUST and FACET definitions of exacerbation the most sensitive single variable was additional corticosteroid use, with 79% (95% CI 78.1 to 80) sensitivity and 100% specificity with the TRUST definition. With the FACET definition the sensitivity was 82.8% (95% CI 81.4 to 84.1) and specificity was 98.6% (95% CI 98.6 to 98.7). The sensitivity decreased to 66% when only those exacerbations with oral corticosteroids were included in the analysis. The use of additional corticosteroids was much less sensitive with the exacerbations defined by Taylor and Wilding because they had to occur in combination with another change.

Morning PEF (80% of baseline for two or more consecutive days) was very specific (>99%) for TRUST, FACET and Taylor definitions of exacerbations but the sensitivity was only 8.8% (95% CI 8.2 to 9.5), 24.2% (95% CI 22.7 to 25.7) and 42.2% (95% CI 39.0 to 45.5) respectively. When the FACET definition was used, excluding those patients with unknown corticosteroids, the sensitivity of morning PEF increased to 45.1% (95% CI 42.6 to 47.6).

Daytime symptoms were also very specific for the definitions of exacerbation with over 98% specificity for all four definitions of asthma. The sensitivity ranged from 32.9% (95% CI 29.9 to 36.0) with the Taylor definition to 15% (95% CI 13.7 to 16.3) with the FACET definition including unknown corticosteroid use.

Daytime symptoms (increased by two or more on two consecutive days) and corticosteroid use had high sensitivity and specificity for TRUST and FACET definitions of exacerbation, see tables 6.16 and 6.17. There was high specificity (>96%) for the definitions of Taylor and Wilding but sensitivity was much lower, 50.5% (95% CI 47.2 to 53.7) and 28.2% (95% CI 27.5 to 29.0) respectively.

Corticosteroids and daytime symptoms	TRUST exacerbations	
	No	Yes
No	216539 (98.7%)	315 (4.4%)
Yes	2953 (1.3%)	6869 (95.6%)
Total	219492	7184

Sensitivity 95.6% (95% CI 95.12 to 96.1), specificity 98.7% (95% CI 98.6 to 98.7).

Table 6.16 Number (%) of days of TRUST exacerbation with or without corticosteroid use and or daytime symptoms.

Corticosteroids and daytime symptoms	FACET exacerbations (including unknown corticosteroids)		FACET exacerbations (including oral corticosteroids)	
	No	Yes	No	Yes
No	216364 (96.8%)	490 (15.8%)	216364 (96.1%)	490 (31.3%)
Yes	7217 (3.2%)	2605 (84.2%)	8746 (3.9%)	1076 (68.7%)
Total	223581	3095	225110	1566

Sensitivity 84.2% (95% CI 83.8 to 85.4), specificity 96.8% (95% CI 96.7 to 96.9) including unknown corticosteroids.

Sensitivity 68.7% (95% CI 66.4 to 71.0), specificity 96.1% (95% CI 96.0 to 96.2) including oral corticosteroids.

Table 6.17 Number (%) of days of FACET exacerbation with or without corticosteroid use and or daytime symptoms.

Corticosteroids and morning PEF \leq80%	TRUST exacerbations	
	No	Yes
No	217990 (99.3%)	1172 (16.3%)
Yes	1502 (0.7%)	6012 (83.7%)
Total	219492	7184

Sensitivity 83.7% (95% CI 82.8 to 84.5), specificity 99.3% (95% CI 99.3 to 99.4).

Table 6.18 Number (%) of days of TRUST exacerbation with or without corticosteroid use with morning PEF \leq 80%.

Corticosteroids and morning PEF $\leq 80\%$	FACET exacerbations (including unknown corticosteroids)		FACET exacerbations (including oral corticosteroids)	
	No	Yes	No	Yes
No	219162 (98%)	0	219162 (97.4%)	0
Yes	4419 (2%)	3095 (100%)	5948 (2.6%)	1566 (100%)
Total	223581	3095	225110	1566

Sensitivity 100%, specificity 98.0% (95% CI 98.0 to 98.1) including unknown corticosteroids.

Sensitivity 100%, specificity 97.4% (95% CI 97.3 to 97.4) including oral corticosteroids.

Table 6.19 Number (%) of days of FACET exacerbation with or without corticosteroid use and morning PEF $\leq 80\%$.

Adding morning PEF to daytime symptoms and corticosteroid use did not improve the sensitivity and specificity for TRUST exacerbation. Adding daytime symptoms to morning PEF and corticosteroid use reduced the specificity for FACET exacerbation by only 1%.

6.5.3.6 Corticosteroid use

The use of corticosteroids was strongly predictive of all four definitions of exacerbation but especially TRUST and FACET definitions. Because of its predictive properties and because some exacerbations were classified by use of additional corticosteroids alone it was important to determine what predicted a course of corticosteroids. The strongest predictor for all courses of corticosteroids was an increase in daytime symptoms of two or more over baseline, table 6.20. Night time symptoms of two or more over baseline resulted in a 2 fold increase in the odds of additional corticosteroids (OR 2.31 95% CI 1.50 to 3.57) but increasing night time symptoms did not increase the odds of corticosteroids in the same way as daytime symptoms. An increase in daytime or night time symptoms had a greater effect on predicting a course of inhaled corticosteroids compared to oral corticosteroids. This suggests that patients may have increased treatment in response to symptoms. A reduction in both morning and evening PEF had a greater effect on the odds of a course of oral corticosteroids suggesting patients requiring oral corticosteroids experienced a more severe exacerbation. The increase in evening peak flow was not accompanied by a large increase in night time symptoms.

Diary card variable	All Corticosteroids		Oral Corticosteroids		Inhaled Corticosteroids	
	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio ^a (95% CI)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio ^a (95% CI)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio ^a (95% CI)
5 to 10% decrease in am PEF	2.53† (1.98 to 3.24)	1.62§ (1.20 to 2.18)	3.98† (2.0 to 7.90)	2.46† (1.03 to 5.88)	2.30† (1.72 to 3.07)	1.41 (0.99 to 1.99)
10 to 20% decrease in am PEF	4.60† (3.32 to 6.37)	1.78† (1.11 to 2.85)	8.59† (3.81 to 19.3)	2.40 (0.70 to 8.21)	4.13† (2.78 to 6.12)	1.58 (0.92 to 2.74)
>20% decrease in am PEF	8.52† (5.64 to 12.9)	1.79 (0.89 to 3.60)	23.3† (9.79 to 55.4)	2.74 (0.63 to 11.9)	5.22† (2.90 to 9.39)	1.03 (0.43 to 2.45)
1 unit increase daytime symptoms	3.30† (2.52 to 4.32)	2.12† (1.52 to 2.96)	3.16† ^a (2.67 to 3.75)	2.16† ^a (1.56 to 2.87)	3.97† (2.87 to 5.48)	2.52† (1.70 to 3.72)
2 unit increase daytime symptoms	13.2† (9.89 to 17.8)	6.06† (4.10 to 8.96)			15.6† (11.0 to 22.0)	7.18† (4.57 to 11.3)
3 unit increase daytime symptoms	21.8† (14.5 to 32.6)	7.83† (4.39 to 14.0)			17.7† (10.2 to 30.8)	6.29† (3.10 to 12.8)
4 unit increase daytime symptoms	66.3† (38.5 to 114)	16.3† (7.71 to 34.5)			80.9† (43.0 to 152)	22.71† (10.3 to 50.1)
5 unit increase daytime symptoms	118† (46.2 to 302)	40.1† (13.5 to 120)			74.8† (17.8 to 314)	26.1† (5.68 to 120)
1 unit increase in night time symptoms	2.99† (2.34 to 3.81)	1.61§ (1.18 to 2.21)	2.99† ^a (2.45 to 3.65)	1.15 ^a (0.79 to 1.67)	2.83† (2.09 to 3.83)	1.57† (1.08 to 2.28)
2 unit increase in night time symptoms	8.23† (6.13 to 11.1)	2.31† (1.50 to 3.57)			9.77† (6.98 to 13.7)	3.04† (1.88 to 4.93)
3 unit increase in night time symptoms	20.4† (13.1 to 31.7)	2.81† (1.62 to 4.90)			18.2† (10.4 to 31.9)	2.93§ (1.53 to 5.62)
4 unit increase in night time symptoms	43.8† (20.2 to 95.2)	3.15† (1.13 to 8.83)			27.0† (8.47 to 86.0)	2.27 (0.63 to 8.24)
2 to 6 puffs increase in rescue β_2 -agonist use	4.43† (3.36 to 5.84)	1.15 (0.82 to 1.62)	3.28† ^a (2.52 to 4.27)	1.23 ^a (0.91 to 1.67)	4.22† (3.02 to 5.91)	1.11 (0.73 to 1.67)
6 to 10 puffs increase in rescue β_2 -agonist use	7.92† (4.51 to 13.9)	0.99 (0.51 to 1.92)			6.94† (3.40 to 14.2)	0.93 (0.42 to 2.04)
> 10 puffs increase in rescue β_2 -agonist use	5.65§ (1.79 to 17.8)	0.34 (0.08 to 1.58)			5.35‡ (1.32 to 21.7)	0.54 (0.12 to 2.47)
5 to 10% decrease in am PEF	2.45† (1.92 to 3.11)	1.31 (0.99 to 1.73)	3.86† (1.95 to 7.66)	2.03 (0.91 to 4.56)	2.32† (1.75 to 3.09)	1.35 (0.97 to 1.87)
10 to 20% decrease in am PEF	4.27† (3.06 to 5.98)	1.37 (0.88 to 2.15)	8.89† (3.92 to 20.2)	3.1‡ (1.08 to 8.88)	3.72† (2.46 to 5.64)	1.28 (0.73 to 2.16)
>20% decrease in am PEF	11.8† (7.77 to 18.0)	1.93 (0.98 to 3.80)	40.9† (17.9 to 93.1)	4.85‡ (1.56 to 20.3)	9.08† (5.25 to 15.7)	1.93 (0.83 to 4.49)

† p < 0.001, § p < 0.05, § p < 0.01

^a The relationship between variable and exacerbation linear, odds ratio for 1 unit change shown.

*Adjusted for baseline values, age, sex and clustering on patient study number

Table 6.28 The effect of diary card variables on the odds ratios of starting a course of corticosteroids.

6.5.4 Discussion

The comparisons of the four different definitions of exacerbations highlighted both the similarities and differences between the definitions.

The definition of exacerbation used by Wilding et al (104) identified many episodes which may not have been serious changes in the underlying asthma because an increase in symptoms scores of only one or more over baseline resulted in an exacerbation. In contrast, the definition of exacerbation used by Taylor et al (105;107) was complicated and relied very heavily on changes in PEF, which meant that in this population of asthmatics very few exacerbations were identified. One of the main drawbacks of this definition was the number of days with changes in symptoms that could not be classified because they were not accompanied by changes in PEF. The definition assumed that the diary card variables were closely correlated with one another.

The “ideal” definition of exacerbation would seem to lie somewhere between the TRUST and FACET definitions of exacerbation. The FACET definition of exacerbation seemed to underestimate the number of periods of worse asthma because the criteria included oral corticosteroid use and PEF only. The sensitivity and specificity analyses demonstrated there was a great deal of overlap between the definitions. If the FACET definition was used as the gold standard then the TRUST definition had a very high sensitivity and specificity, that is those patients who experienced a FACET exacerbation were also very likely to experience a TRUST exacerbation.

The regression analysis of the diary card components of all four definitions of exacerbation yielded similar results in spite of the differences in the definitions. Use of corticosteroids, daytime symptoms and change in morning PEF of 100 l/min or more were the most important variables in terms of their ability to predict an exacerbation according to the four definitions in turn. A measure of exacerbation using just corticosteroid use and daytime symptoms was highly sensitive and specific if the TRUST or FACET definitions were used as the gold standard. Use of corticosteroids and a reduction in morning PEF of 80% were highly sensitive and specific for both TRUST and FACET.

An increase in daytime symptoms strongly predicted a course of corticosteroids and was not included in the FACET definition of exacerbation. To include an increase in daytime symptoms would make the FACET definition more complete by providing an objective reason for commencing corticosteroids. The most useful diary card components to measure would be corticosteroid use and daytime symptoms, adding morning PEF (<80%) increased the sensitivity by 1.5% and reduced the specificity by <1% but the number of days when morning PEF fell to 80% or less than baseline were relatively few (<2% of days). The advantage of a measure relying on daytime symptoms and corticosteroid use may be improved compliance with diary card completion in long term trials of asthma therapy.

In conclusion, in future trials of long or short acting inhaled β_2 -agonists it would be possible to measure exacerbations using additional use of corticosteroids and daytime symptoms of two or more over baseline without morning PEF. Clear guidelines should be given to the patients and clinicians about when to commence additional corticosteroids.

Chapter 7 – Discussion

The aim of this project was to compare the outcome measures identified from a systematic review of randomised controlled trials of inhaled β_2 -agonists with the TRUST definition of exacerbation, using the TRUST dataset. This analysis identified a standard primary outcome measure for use in trials of long and short acting inhaled β_2 -agonists that may be relevant to clinical practice.

7.1 TRUST

The regular use of salbutamol in mild to moderate asthmatics did not result in worse asthma control in TRUST. The exacerbation rate was similar between the two treatment groups and the confidence intervals overlapped. There were significant improvements in symptom free days and evening PEF but there was no difference in morning PEF. The TRUST result was particularly important because the patients were representative of the majority of asthmatics in the UK (160), treated in the primary care setting with over 90% taking concurrent inhaled corticosteroids. The results extended those of Drazen et al (95) who reported no difference between regular and as needed albuterol in patients without concomitant inhaled corticosteroids. The results also complemented the results of the trials of long acting β_2 -agonists (52;72-77;79-82;84;86;89-91;96;97;99;101;103-106;108-112) which demonstrated the benefits of their use in moderate to severe asthma. The results contrasted with those earlier trials which suggested that inhaled β_2 -agonists resulted in worse asthma control (50;51;53-55).

The advantage of TRUST was that the sample size was sufficient to detect a difference of at least 15% in the exacerbation rate between the two treatment groups whereas some of the earlier trials of β_2 -agonists were often small and lacked power. The trial was carried out in primary care where the majority of asthmatics are managed in the UK. The study was pragmatic in that there was no attempt to standardise other anti-asthma treatment and stabilise asthma control during the run-in period. Instead, patients were stratified according to their inhaled corticosteroid use. The trial was managed and monitored to a very high standard. There was regular communication between the co-

ordinating centre and the practices, quality control procedures were in place and additional training was given when necessary. There was an MRC Trial Steering Committee and Data Monitoring and Ethics Committee that met regularly to monitor progress.

The disadvantage of TRUST was that because the trial was large it was not feasible to use electronic PEF meters or Diskhalers, which would have allowed for a closer assessment of compliance.

The results of TRUST will inform the most appropriate use of short acting β_2 -agonist in the latest asthma management guidelines due to be published in 2002.

7.2 Comparisons of the primary outcome measures

The results of the analysis of the primary outcome measures identified by the systematic review suggested that the use of additional corticosteroids or an increase in daytime symptoms of two or more over baseline score was a suitable primary outcome measure for use in trials of long and short acting β_2 -agonists. A fall in morning PEF of 20% or more from baseline was strongly predictive of all definitions of exacerbation but lacked sensitivity. Surprisingly an increase in night time symptoms was not a strong predictor of all definitions of exacerbations.

As expected, simply averaging the diary card variables over the period of follow-up did not allow for the fluctuations in asthma and did not reflect the degree of change seen with the TRUST definition of exacerbation. This was most marked with mean PEF, which may be more suitable for monitoring long-term decline in lung function.

Of the four definitions of exacerbation identified, there was most agreement between the TRUST (123) and FACET (101) definitions of exacerbation and less agreement between TRUST and the definitions proposed by Wilding (104) and Taylor (105;107). The FACET definition was very specific for change but lacked sensitivity for TRUST exacerbations because courses of increased inhaled corticosteroids were not included in the definition of exacerbation and there were very few days when morning PEF fell to 70% or less of baseline. Much of the agreement could be explained by the role of

additional corticosteroids in the definitions of TRUST and FACET exacerbations. There was poor agreement with the Wilding definition because the one-unit increase in day or night time symptoms over baseline resulted in many days classified as exacerbation. Additional corticosteroids were less important in the Wilding definition because they had to occur in combination with a change in symptoms or PEF. The definition proposed by Taylor assumed that changes in PEF were the most important factor therefore many days with increased symptoms were not classified as an exacerbation because there was no accompanying fall in PEF. Because the diary card variables were poorly correlated, increased asthma symptoms did not occur on the same day as fall in PEF and many days when asthma appeared worse were not classified as an exacerbation.

Most of the definitions of exacerbation identified had been developed with the assumption that changes in morning PEF and symptoms would reflect changes in the underlying asthma simultaneously. Because the diary card variables were poorly correlated in TRUST and other trials, forcing them together in a definition of exacerbation meant some days with apparently worse asthma were not classified as exacerbation. A requirement for additional corticosteroid treatment was clearly a sign that asthma control was worse and the most important factor motivating patients to seek treatment was an increase in day or night time symptoms and not a fall in PEF. This could have been because symptoms preceded the fall in PEF (161-163) or because symptoms and PEF measure different aspects of the disease.

The most important components of exacerbation, from all four definitions identified, will now be discussed in turn.

7.2.1 Oral and inhaled corticosteroids

Many definitions of asthma exacerbation incorporated the use of additional corticosteroids (54;101;104;105;107;109;111;121-123). The inclusion of “a clinical need for oral or increased inhaled corticosteroids” was included in the TRUST definition of exacerbation to allay the fears of the general practitioners, patients and LRECs. It enabled those patients in danger of experiencing a rapid and potentially fatal

worsening of their asthma to receive additional corticosteroid treatment without waiting for a change in symptoms or PEF to occur on two or more consecutive days. Whilst there were obvious safety and ethical advantages to the inclusion of this criterion inevitably it led to courses of corticosteroids with neither a fall in PEF nor an increase in symptoms. A total of 347 (40%) TRUST exacerbations were classified according to use of additional corticosteroids (oral and inhaled) alone. For FACET the proportion of exacerbations classified by corticosteroid use alone was between 42 – 77% depending on whether those patients with use of unknown corticosteroids were included. Those patients with a FACET exacerbation classified by oral corticosteroid use tended to have smaller changes in PEF and symptoms than did those patients with exacerbations and no corticosteroid use (101;164). This pattern was also observed with TRUST exacerbations because patients may have started treatment in anticipation on further worsening of their asthma.

Use of corticosteroids was logically linked to exacerbation because their use automatically resulted in the classification of an exacerbation. Because of this logical link, including them in the regression models for exacerbation distorted the role of the remaining diary card variables. It was important to understand what predicted corticosteroid use because of their link with exacerbation. The regression analysis identified an increase in daytime symptoms followed by a 100 l/min fall in PEF as the most important predictors of corticosteroid use. This reflected the results of other studies that suggested patients modified their treatment in response to symptom changes rather than PEF (161;165-167). The regression analysis used in this project was a simple between-patient multivariate logistic regression comparing corticosteroid exacerbations with days without corticosteroids, and may have oversimplified the relationship between PEF, symptoms and corticosteroid use. More complicated models have been used on the TRUST data (Chris Frost, unpublished work). A nested case control analysis of the TRUST and FACET data was undertaken; periods of corticosteroid use were matched with periods without corticosteroid use within the same patient and compared using regression analysis. Using this method, the strongest predictors for corticosteroid use in TRUST data were night time and daytime symptoms, with adjusted odds ratios of 2.22 (95% CI 1.47 to 3.34) and 1.95 (95% CI 1.39 to 2.73) respectively. A similar analysis using FACET data produced similar results. The odds

ratios from the matched case control analysis were higher than those obtained using the simpler analysis, presented in section 6.5.3.6, because they were within-patient comparisons and identified what had resulted in a course of treatment on one occasion but not another. Once again this added to evidence, which suggested that corticosteroids were used in response to changes in symptom scores rather than PEF (161;164-167).

Corticosteroid use was by definition a TRUST exacerbation because it represented a change in the underlying asthma control that resulted in increased treatment. However, the disadvantage of using courses of corticosteroids to identify exacerbations was that some patients might have started treatment in anticipation of an exacerbation, which without treatment may never have progressed. Clinicians and patients were given clear guidelines for the use of additional corticosteroids but 40% of TRUST exacerbations were not accompanied by a change in symptoms or PEF in spite of the quality control procedures designed to reduce this. Restricting corticosteroid use to oral treatments only may have reduced the proportion of exacerbations with no symptom or PEF changes because patients would have had to visit their doctor before starting treatment. It was unlikely that doctors would have recruited mild to moderate asthmatics to trial with such a design. Patients were successfully recruited to the TRUST pilot study where exacerbations were treated with oral corticosteroids alone but the protocol was modified for the main trial because of the impact of the British Thoracic Society guidelines (134) suggesting that exacerbations could be treated with increased inhaled corticosteroids.

In future trials, the protocol for the use of oral or increased inhaled corticosteroids would need to be very clear. The evidence suggested that the guidelines for the use of corticosteroids should be based on an increase in symptoms (daytime and night time) of two or more units over baseline for two or more consecutive days.

7.2.2 Morning PEF

Ambulatory PEF is frequently used in clinical asthma trials because it provides an objective measurement of airflow limitation; the meters are cheap and the readings correlate well with those from spirometers. PEF correlates well with FEV₁ (143-

145;168) and ambulatory PEF is believed to be a useful measure of asthma control because it measures the daily fluctuations that would be missed if measurements were restricted to clinic visits. The main disadvantages of PEF are the potential for reduced patient compliance with the measurements over time (142;169-171) and its poor correlation with asthma symptoms (137;144;161;163;167;172-175) both when making a diagnosis of asthma and monitoring change over time. PEF is effort dependent and of limited use in unmotivated individuals (161;174). Many patients are poor perceivers of reduced PEF during experimental conditions such as bronchial provocation tests. Using a visual analogue scale for symptom severity, patients were found to be relatively poor at detecting a fall in PEF (167).

Averaging PEF over the entire follow-up period reduced the benefits of ambulatory monitoring from a trial viewpoint. Information on sharp daily fluctuations was lost. A fall in morning PEF of 100 l / min was a strong predictor of exacerbation but it lacked sensitivity and few TRUST exacerbations were associated with a fall in PEF of 20% or more. Several detailed analyses of PEF reported the events leading up to and after an exacerbation (159;176). Both papers described a gradual decline in PEF in the days leading up to an exacerbation followed by a sharp fall and then recovery. The average fall in PEF from baseline was 27% (159) and (to separate 45% as belonging to FACET) 45% of FACET exacerbations had a fall in PEF of 30% or more (176). Studies of asthma self-management plans reported conflicting results regarding the use of PEF. Some suggested that a change in asthma symptoms was as effective as a change in PEF to guide treatment (166;177), others that change in PEF alone was an effective guide (178), other studies were too small to show a benefit (165) and another demonstrated an effect but a fall in PEF to 15% of baseline was the trigger for increasing treatment (166).

Ambulatory PEF may provide a useful physiological method of airflow limitation but this project highlighted the poor relationship between a change in PEF and the definitions of exacerbation. A fall in PEF of 20% or more was specific for all definitions of exacerbation but it was not sensitive. Because a fall in PEF was specific and strongly predicted an exacerbation it was a useful measure but the poor compliance and relatively few episodes when PEF fell to 80% of baseline or less meant it may have more limited uses.

7.2.3 Symptoms

An increase in daytime symptoms of two or more over baseline was the strongest predictor of all definitions of exacerbation after corticosteroid use. As the daytime symptoms increased above baseline the odds of exacerbation was even greater. It was surprising that night time symptoms were less important in defining an exacerbation because they were strongly predictive of a course of corticosteroids. An increase in daytime symptoms was a strong predictor of exacerbation both independently and because it strongly predicted a course of corticosteroids. The FACET definition of exacerbation did not include daytime symptoms, but an increase in daytime symptoms identified 15 – 20% of all FACET exacerbations because of the strong association between an increase in daytime symptoms and corticosteroid use.

The symptoms score used in TRUST was a simple six-point scale that concentrated on the frequency of all symptoms during the day. The different components of asthma symptoms such as cough, wheeze and breathlessness were not assessed separately. It was felt that because patients were completing diary cards for 12 months the components of the diary card should be kept simple.

Several symptoms scores or symptom questionnaires have been developed for use in clinical trials (139;140;179;180). Burdon et al (168) first tested scales such as the modified Borg scale in the assessment of dyspnoea. The scale ranges from 0 to 10 and classifies the perception of breathlessness according to a series of descriptions and was found to be a useful subjective tool. Most of these questionnaires were not suitable for use on a daily basis for measuring change because of their complexity

A simple six point symptom score was used in TRUST and an increase of two or more above baseline was found to be very strongly associated with all definitions of exacerbation. Future work might involve the development of the symptom score used in the TRUST dairy card to improve the identification of exacerbations.

7.3 Summary

There have been three recent papers reporting the analysis of exacerbations in an attempt to identify the most suitable measures for use in clinical trials (161-163). The earliest study was published in 1996; Chan-Yeung et al studied 120 patients (adults and children) taking part in a nested case control study of viral exacerbation and 41% of patients experienced an exacerbation. They compared days of follow-up to baseline levels and identified exacerbations. They found that symptoms started to increase two days before the first day of exacerbation and that this occurred before the PEF fell. PEF rarely fell to 30% or less than baseline. The authors concluded that a symptom diary identified exacerbations earlier than PEF changes.

The most recent papers report the results of much larger studies. In 2001 Shingo et al (162) investigated the correlation between asthma diary card variables of 1500 patients participating in two 1-year clinical trials. Within patient pairwise correlations of the diary card variables were made. The diary card variables were poorly correlated with one another although all comparisons were significant. The authors concluded that PEF or FEV₁ and symptoms or rescue β_2 -agonist use measured different aspects of the disease and that all aspects should be included in any outcome measure. The final study published in 2001 by Leone et al (163) utilised data from 313 patients recruited to two large randomised controlled trials. Receiver operating characteristic (ROC) analysis of diary card variables was carried out to determine their ability to predict periods when FEV₁ fell to 80% or less of baseline. None of the variables predicted this reliably.

The results of this project extend the results presented in these three papers. The relationship between the diary card variables in TRUST was weak. Symptoms, and in particular daytime symptoms were the strongest predictors of exacerbation along with corticosteroid use, which was logically linked to exacerbation. Asthma is a multidimensional disease measurable in different ways and the measures are poorly correlated with one another. Defining exacerbations by requiring two or more diary card variables to occur together may underestimate the number of exacerbations because the diary card variables are poorly correlated and therefore less likely to occur together.

A composite measure for measuring exacerbations of disease is possible when the components are well correlated.

7.4 Strengths

TRUST was a well-designed trial with an adequate sample size and the results provide important information regarding the use of inhaled β_2 -agonists in mild to moderate asthma. The trial was well managed and monitored ensuring good quality data. The analysis of the components of exacerbation made use of all the TRUST data; over 200 000 observations, a total of 983 patients compared with previous work on exacerbations which have been in small studies with short periods of follow-up. The results of the analysis may have implications beyond a use in clinical trials. Patients are frequently asked to monitor their asthma as part of self management plans and if symptoms are strong predictors of corticosteroid use and exacerbations, self management plans could be simplified and patients may not need to make twice daily PEF measurements which may improve compliance with treatment.

7.5 Weaknesses

The main weakness of this project was that the variables that predicted exacerbations were often part of the inclusion criteria for the definition of exacerbation. Therefore, by definition, the exacerbations were going to be dependent on them. This was unavoidable in this type of study but the important result was that we know which of those explanatory variables were the most important. The examination of predictors for corticosteroid use may have been too simplistic and underestimated the true result. The nested case control method (Chris Frost, unpublished work) was better because the comparisons were within-patient and enabled the events leading up to a corticosteroid course to be compared with those not leading to corticosteroids in the same patient. This approach could not have been used with the exacerbations analysis because it would not have been so different from comparing exacerbations with baseline.

7.6 Conclusion and future work

The most recent large, well designed randomised controlled trials (95;123) have confirmed that the use of short acting inhaled β_2 -agonists is safe in mild to moderate asthmatics. Analysing TRUST using the different primary outcome measures identified by the systematic review did change the results. Mean daytime symptoms and mean evening PEF demonstrated a small but significant improvement in favour of regular treatment whereas the Wilding definition of exacerbation suggested a small but significant worsening with regular treatment.

The results of this project suggest that exacerbation of asthma in clinical trials could best be measured by recording use of additional corticosteroids, according to strict guidelines, and an increase in daytime symptoms of two or more over baseline. A fall in morning PEF of 20% or more both for two or more consecutive days was specific for all definitions of exacerbation but lacked sensitivity because of the relatively few days when this occurred. The inclusion of morning PEF would not justify the additional work expected from the patients and its inclusion may result in reduced compliance. Peto argued that in large randomised controlled trials such as TRUST the focus should be on a small number of very simple outcome measures (181) and in this case it would be sufficient to use corticosteroid use and an increase in daytime symptoms or two or more over baseline alone. This was reinforced by the fact that the diary card variables were poorly correlated.

This modified definition of exacerbation is likely to be most suitable for use in randomised controlled trials or observational studies where the outcome of interest is asthma control such as trials of long and short acting β_2 -agonists or leukotriene antagonists. It would not be a suitable measure for trials designed to assess airway remodelling where lung function would be more appropriate. It is important to test this modified definition of exacerbation in another clinical trial or prospective observational study.

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First author	Year	Drugs	Treatment time	Sample	Result
P.W. Trembath	1979	fenoterol / terbutaline	2 x 4 weeks	22	for terb
G.L. Shepherd	1981	salbutamol / placebo	not clear	18	for salb
K.B. Beswick	1986	salbutamol	12 months	17	for salb
A. Ullman	1988	salmeterol / salbutamol	1 days	8	salm > salb
A.S. Vathenen	1988	terbutaline (500µg / 2mg) / placebo	1 day and 15 days	8	against terbutaline
P.R. Hekking	1990	formoterol / salbutamol	2 week crossover	301	form>salb
M.R. Sears	1990	fenoterol / placebo	24 weeks	64	against fenot
A. Ullman	1990	salmeterol / salbutamol	2 x 2 weeks	12	for salm
A. Wallin	1990	formoterol / salbutamol	2 x 4 weeks	16	form > salb
P. Arvidsson	1991	formoterol / salbutamol	1 year	18	against form
S. Kesten	1991	formoterol / albuterol	3 months	145	form>salb
C.P. Van Schayck	1991	salbutamol / atrovent (reg or exac only)	2 year	223	against salb
M.G. Britton	1992	salmeterol / salbutamol	3 months	667	salm > salb
H.A. Kerstjens	1992	terbutaline / ICS / atrovent / placebo	2.5 years	274	for terb + ics
J.B. Palmer	1992	salmeterol (50 or 100µg)	3 months	283	for 100 mg
D.S. Pearlman	1992	salmeterol / salbutamol / placebo	12 weeks	234	salm>salb
W. Castle	1993	salmeterol / salbutamol	16 weeks	180	salm>salb
B. Lundback	1993	salmeterol / salbutamol	12 months	388	salm>salb
D.R. Taylor	1993	fenoterol / placebo	24 weeks	64	against fenot
I. Wahedna	1993	albuterol / broxaterol / placebo	3 weeks	11	against fenot
K.R. Chapman	1994	salbutamol / placebo	2 week crossover	341	for salb
G.E. D'Alonzo	1994	salmeterol / albuterol / placebo	12 weeks	322	salm>salb>p
M. Heino	1994	β ₂ -agonists	2 x 1 week	54	for β ₂ -agonists
K.P. Jones	1994	salmeterol / placebo	6 weeks	427	for salm
C.S. Wong	1994	terbutaline / budesonide / placebo	2 to 4 weeks	37	terb and budes
O.E. Aldrey	1995	salbutamol / BDP	3 x weeks	22	both>either
R.A. Nathan	1995	salmeterol / albuterol / placebo	12 weeks	556	salm > alb > p
D.S. Pearlman	1995	salmeterol / albuterol	12 weeks	556	for salm
I. Steffensen	1995	formoterol / salbutamol / placebo	12 weeks	304	form>salb>p
C.P. Van Schayck	1995	salbutamol / atrovent (reg or exac only)	4 years	83	for salb
D.H. Yates	1995	salbutamol			
A.J. Apter	1996	albuterol	15 week crossover	17	for albuterol
J.M. Drazen	1996	albuterol / placebo	16 weeks	255	no diff
P. Leblanc	1996	salbutamol / salmeterol	12 weeks	367	salm>salb
P. Faurschou	1996	salmeterol / salbutamol	6 weeks	190	salm>salb
A. Woolcock	1996	salmeterol / BDP	24 weeks	738	salm + BDP
L. Boulet	1997	salmeterol / salbutamol	12 weeks	228	salm>salb
A. Ganassini	1997	broxaterol / placebo	3 weeks	24	no diff
R.A. Pauwels	1997	formoterol / budesonide	1 year	852	form + budes
V.J. Tormey	1997	salbutamol / oxitropium bromide / placebo	3 x 4 weeks	12	no diff
T. van der Molen	1997	formoterol / placebo	24 weeks	239	for form
P. Wilding	1997	salmeterol / placebo	6 month crossover	101	for salm
R.D. Taylor	1998	salbutamol / salmeterol / placebo	24 week crossover	157	salm > salb > p
T. Ekstrom	1998	formoterol / terbutaline / placebo	12 weeks	343	form > terb > p
R.J. Hancox	1999	budesonide / terbutaline / both	6 weeks crossover	47	both>either
J.A. van Noord	1999	salmeterol / fluticasone	12 weeks	362	salm > flutic
J.J. Condemii	1999	salmeterol / fluticasone	24 weeks	437	salm > flutic
F.A.A.M. Vermetten	1999	salmeterol / budesonide	12 weeks	233	salm > budes
A.E. Tattersfield	2001	formoterol / terbutaline	12 weeks	362	form > terb
S.C. Lazarus	2001	salmeterol / inhaled corticosteroids (ICS)	28 weeks	108	ICS > salm

Table 1.1 Randomised controlled trials of inhaled β₂-agonists in asthma.

Membership of TRUST Steering Committee

Professor T H Lee - Department of Respiratory Medicine and Allergy, Guy's Hospital

Professor P J Barnes - Department of Thoracic Medicine, National Heart and Lung
Institute

Dr G K Crompton - Respiratory Medicine Unit, Western General Hospital, Edinburgh.

Dr M R Vickers - MRC Epidemiology and Medical Care Unit, London.

Mr C D Frost - Medical Statistics Unit, London School of Hygiene and Tropical
Medicine.

Ms S M Dennis - MRC Epidemiology and Medical Care Unit, London.

REGULAR v ON-DEMAND SALBUTAMOL

INTRODUCTION

Inhaled beta₂-adrenoreceptor agonists are the most effective treatment for the relief of asthma symptoms and the most widely prescribed anti-asthma therapy. Recently, however, the safety of this form of treatment, particularly when given regularly and in high dose has been questioned and causal links between beta-agonists and increased asthma morbidity and mortality have to be considered.

An increase in asthma mortality and treatment with beta-agonists was first suggested in the 1960's when the introduction of isoprenaline-containing inhalers coincided with a marked rise in asthma mortality^{1,2} which fell to 'pre-epidemic' levels after a possible association between excessive use of these inhalers, particularly those containing high doses of isoprenaline, and the increase in asthma mortality was made³. Recently, several studies have demonstrated that regular treatment with inhaled beta₂ agonists is associated with an unexpected increase in airway hyper-responsiveness⁴⁻⁸. The most commonly used beta-agonists, salbutamol, terbutaline and fenoterol have all been incriminated as potential causes of increase in bronchial hyper-responsiveness when used regularly; fenoterol being linked with the increase in asthma mortality in New Zealand in the 1980's⁹. The association of fenoterol and increased asthma mortality in New Zealand could be related to the fact that fenoterol was supplied in canisters which delivered approximately twice the effective bronchodilator dose of salbutamol¹⁰. This is supported by the demonstration in a recent epidemiological study of a dose related increase in the risk of death or near-death from asthma with both fenoterol and salbutamol which was almost identical when assessed at equivalent doses¹¹.

The demonstration that regular use of inhaled fenoterol compared with on demand only use is associated with worse control of asthma has created much concern with regard to the use of inhaled beta-agonists and their possible association with increased morbidity and mortality. The finding that regular use of salbutamol, and ipratropium bromide for two years is associated with a greater annual decline in lung

function than with on demand treatment⁸ adds more concern about the problems which might be associated with the regular use of beta₂-adrenoreceptor agonists.

Recent controversies now surround the safety of long-term regular use of beta₂-agonists¹² and withdrawal or reduction of such treatment in some patients is now being advocated¹³. The evidence which most incriminates regular beta₂-adrenoreceptor agonist therapy as being harmful is the publication from New Zealand⁷ which indicates that regular treatment with fenoterol results in worse control of asthma than when fenoterol is used on demand. This paper has caused much debate, both professional and public, about beta-agonist therapy in general, and regular use in particular. The use of an inhaled beta-agonist on a regular basis is now not recommended for the treatment of most patients with chronic asthma¹⁴. However, when on-demand treatment is necessary more often than twice daily it may well be associated with similar adverse effects as regular six-hourly therapy. It is known that regular twice daily treatment with terbutaline in low dose for two years is not associated with increased bronchial hyper-reactivity or any adverse effects in patients with mild asthma¹⁵. No data generated from well designed studies are available, however, to refute the evidence that regular beta₂-agonist therapy makes asthma worse⁷. There is also no evidence to support the hope and assumption that inhaled steroid therapy protects against any adverse effects of inhaled beta₂-agonists. Indeed, in the New Zealand study of regular versus on-demand fenoterol adverse effects occurred even in patients taking inhaled steroids⁷ but the total number of patients in this subgroup was too small for definite conclusions to be drawn.

The general concern about beta-agonist therapy and its possible association with increased asthma morbidity and mortality observed recently in several countries¹⁶, including the UK¹⁷, stimulated the formation of a national Task Force on Asthma in July 1991, under the auspices of the National Asthma Campaign. A Therapy Working Group was set up to identify important problem areas and to plan and initiate research projects. The Working Group was of the opinion that the use of inhaled beta₂-agonists was the most important topic to address initially, and that with regard to regular versus on-demand inhaled beta₂-agonists a large multicentre study had to be performed which would address the following important issues:-

1. Does regular inhaled beta₂-agonist therapy result in worse control of asthma than when used on-demand?
2. Does current use of regular inhaled corticosteroid therapy influence the effects of regular or on-demand inhaled beta₂-agonist?
3. If inhaled corticosteroid therapy influences any adverse effect(s) of treatment with an inhaled beta₂-agonist therapy result in an increase in bronchial hyper-reactivity? This could only be assessed in a study restricted to a small number of centres in order to standardise technique.
4. Does regular inhaled beta₂-agonist therapy result in an increase in bronchial hyperreactivity? This could only be assessed in a study restricted to a small number of centres in order to standardise technique.

CHOICE OF INHALED BETA₂-AGONIST FOR STUDY

Salbutamol has been chosen as the study drug since it is the most commonly used inhaled bronchodilator in the UK and in most other developed countries. A positive decision not to use fenoterol, as in the Sears study⁷ has been made in order to assess whether the effects attributed to fenoterol were idiosyncratic to that drug or manifestations of a beta₂-agonist drug class effect.

Dry powder salbutamol will be used in the study to avoid any possible adverse effects of regular inhalation of Freons/surfactants/lubricants contained in pressurised metered dose aerosols¹⁸.

STUDY PLAN

Objective

To determine whether regular treatment with inhaled salbutamol has any adverse effect(s) on the control and progression of chronic asthma compared with salbutamol taken on-demand (as required for symptom relief).

Design

Randomised double-blind parallel group study of one year's duration.

Treatments

1. Salbutamol 400 µg four times daily from Diskhaler
2. Salbutamol placebo four times daily from Diskhaler

All patients entering the study will already be using a bronchodilator metered dose inhaler (MDI) which will be used on an as necessary basis for symptom control throughout the study period.

Run-in period of ? weeks

PATIENTS

Two groups of patients with chronic asthma will be studied:

Group 1 Asthmatic patients whose only treatment is an inhaled beta₂-agonist

Group 2 Patients requiring inhaled steroids for control of their symptoms in a dose range of 0.4-2.0 mg per 24 hours.

Bronchial asthma will be defined as a diurnal variation in peak expiratory flow (PEF) of greater than 15% on at least 3 days per week during the run-in period and an improvement in PEF or forced expiratory volume in one second (FEV₁) of 15% or more after an inhaled bronchodilators.

GROUP 1 PATIENTS

Adults (over 18 years). Patients with asthma of at least one year's duration who have been using a bronchodilator MDI efficiently, and who have not been treated with inhaled steroids at any time, or oral steroids within 6 weeks of study entry. All patient should be using a bronchodilator MDI at least twice in every 24 hour period.

Patients taking sodium cromoglycate, nedocromil sodium, ipratropium bromide, theophyllines, long-acting inhaled and any oral beta₂-agonist preparation will not be eligible for study.

Number of patients to be studied: 150-200?

GROUP 2 PATIENTS

Adults (over 18 years). Patients with asthma of at least one year's duration who have been using a bronchodilator MDI efficiently and who have been on treatment with an inhaled steroid in a constant daily dose for 6 months within the dose range of 0.4-2 mg per 24 hours. Patients who have been treated with oral steroids within six weeks of study entry will not be eligible.

Patients taking sodium cromoglycate, nedocromil sodium, ipratropium bromide, theophyllines, long-acting inhaled and any oral beta₂-agonist preparation will not be eligible for study.

The dose of inhaled steroid will be kept constant throughout the study period.

Number of patients to complete the study. 150-200?

EXCLUSION CRITERIA

- * Treatment with oral steroids within six weeks of study entry.
- * Admission to hospital because of asthma within six weeks of study entry
- * Inhaled steroid treatment for less than 6 months (Group 2 patients)
- * Other significant lung disease or concomitant major illness
- * Asthma requiring bronchodilator therapy less often than once/twice daily?
- * Inability to use an MDI and a Diskhaler efficiently
- * Treatment with sodium cromoglycate, nedocromil sodium, ipratropium bromide, theophyllines, long-acting inhaled and any oral beta₂-agonist preparation
- * Patients unable to use a peak flow meter and complete a diary card
- * Patients who might move to another area of the country within the next year.
- * Pregnancy

EXCLUSION CRITERIA AFTER ENTRY

- * Pregnancy
- * Need for drugs (for illnesses other than asthma) which might affect study end points
- * Need for oral prednisolone on most days for 2 months

ASSESSMENT

Exacerbations

The primary end-point will be the number of exacerbations of asthma. Exacerbations could be defined as any one of the following:-

1. Increased use of rescue beta₂-agonist (more than 4 puffs per 24 hours)
2. Decreased PEF (more than 30% of baseline or actual decrease of greater than 50 L per minute)
3. Increased symptoms (greater than one point on a four point scale symptom score over one week)
4. Increase in disease severity which results in the general practitioner prescribing extra treatment
5. Treatment with oral prednisolone.

Secondary end-point measurements will be peak expiratory flow variability, symptom-free days, days lost from work because of asthma, changes in symptom score, changes in use of rescue bronchodilator MDI.

Patient Diary Card

Twice daily measurement of PEF. Best of 3 to be recorded prior to the first dose of trial medication in the morning and immediately before the last dose in the evening.

Number of puffs of rescue bronchodilator - to be recorded once or twice daily?

Record of sleep disturbance by asthma

Symptom assessment - ? 4 point scale to be decided

Record of all additional treatment and any new treatment for conditions other than asthma

Number of days off work because of asthma

Clinical Assessment

All patients will be seen and assessed clinically every four weeks. At these times diary cards will be checked and new ones issued. Unused trial drugs for the previous month will be collected (5 week supply will be provided for each 4 week period) and new trial drugs will be issued. clinical assessment of asthma - ? 4 point scale to be decided.

FEV₁ and vital capacity and ? reversibility test

Bronchial reactivity will only be measured if the study can be performed in a small number of centres. If bronchial reactivity is measured it will be after randomisation to the two treatment limbs, and the technique will be standardised.

Treatment of Exacerbations

The dose of prednisolone for the treatment of exacerbations will be standardised. The actual dose has yet to be decided. If a treatment which involves return of peak flow to previous baseline etc. is used the total amount of prednisolone used in milligrams will have to be calculated. An alternative would be to use a standard treatment of 30 mg daily for 10 days

For Group 2 patients an increase in dose of inhaled steroid for the control of a minor exacerbation of asthma will not be used.

Ethical approval will be obtained from the Ethics Committee of all the participating hospitals. Written informed consent will be obtained from all patients.

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UK Asthma Task Force Therapy Group
in association with the
MRC General Practice Research Framework

**A randomised controlled trial to assess
the risks and benefits of long-term
regular use of salbutamol.**

September 1995

CONTENTS

	<i>Page</i>
1. <i>Title</i>	<i>1</i>
2. <i>Background</i>	<i>1</i>
3. <i>Feasibility study</i>	<i>3</i>
4. <i>Personnel and responsibilities</i>	<i>4</i>
5. <i>Ethical approval</i>	<i>4</i>
6. <i>Study design</i>	<i>4</i>
7. <i>Patient selection</i>	<i>5</i>
8. <i>Patient exclusion at entry</i>	<i>5</i>
9. <i>Treatment regimens</i>	<i>5</i>
10. <i>Trial procedures</i>	<i>6</i>
11. <i>Outcome measures</i>	<i>7</i>
12. <i>Exacerbation</i>	<i>8</i>
13. <i>Withdrawal from randomised treatment</i>	<i>9</i>
14. <i>Data handling and analysis</i>	<i>9</i>
15. <i>Compensation for injury</i>	<i>10</i>
16. <i>Dissemination of results</i>	<i>10</i>
17. <i>References</i>	<i>11</i>

PROTOCOL

1 Title

1.1 Short title

A randomised controlled trial to assess the risks and benefits of long-term regular use of salbutamol.

1.2 Purpose

1.3 The main objective of the proposed randomised controlled trial is to determine the effects of regular treatment with inhaled salbutamol on the control and progression of chronic asthma compared with the effects of salbutamol taken only when required for symptom relief.

1.4 A second objective is to determine whether the effect of salbutamol is modified by concomitant steroid use.

2 Background

Asthma is one of the commonest chronic diseases in industrialised countries. The population prevalence in the UK is around 10% in children and 5% in adults and mortality and morbidity continue to rise in the UK and in many other parts of the developed world. Since asthma is incurable and often persists throughout the life of the patient it has become a major public health concern. The health burden imposed is enormous. Care of asthmatics consumes around 2% of the UK health budget and accounted in 1987/88 for 7 million days lost from work. Identification of the most appropriate and effective treatment for asthma is of critical importance (1).

2.1 The recognition of asthma as a chronic inflammatory disease has led to earlier and more widespread use of inhaled steroids, with short-acting bronchodilators being recommended for symptom relief. Inhaled β_2 -agonists are the most effective bronchodilators for the relief of asthma symptoms and the most widely prescribed anti-asthma therapy. Recently, the long-term safety of β_2 -agonists, particularly when given regularly and in high dose, has been questioned and causal links between β_2 -agonists and increased asthma morbidity have been suggested.

2.2 An association between increased asthma mortality and treatment with bronchodilators was first suggested in the 1960s. The introduction of isoprenaline-containing inhalers coincided with a marked rise in asthma mortality (2,3) which fell to 'pre-epidemic' levels after a possible association between excessive use of these inhalers, particularly those containing high doses of isoprenaline, and the increase in asthma mortality was made (4). There was, however, no evidence for a causal relationship between isoprenaline and the increase in asthma mortality, one possibility being that the symptomatic relief experienced by patients taking isoprenaline had resulted in delays in seeking necessary anti-inflammatory treatment when the underlying asthma had worsened, so that when such treatment was given it was ineffective. In the 1980s the β_2 -agonist fenoterol was linked to an increase in asthma mortality in New Zealand but again no causal relationship was established (5). As for isoprenaline, one explanation for increased mortality is that patients and doctors had become overdependent on fenoterol, the

effective symptom relief masking an underlying disease progression and resulting in delay in seeking or prescribing anti-inflammatory therapy. Fenoterol had been used in canisters which delivered approximately twice the effective bronchodilator dose and it was suggested that the findings could not necessarily be extrapolated to other β_2 -agonists recommended for use in lower doses. However, a recent case-control study showed a dose-related increase in the risk of death or near-death from asthma with fenoterol and salbutamol, the effects being almost identical when assessed at equivalent doses (6).

- 2.3 The effect of β_2 -agonists on bronchial hyper-responsiveness is not clear, some studies reporting an increase and others no effect. Two studies cite salbutamol, terbutaline or fenoterol as potential causes of increased bronchial hyper-responsiveness when used regularly (7,8,9) but although statistically significant increases were found, the effects were extremely small and of doubtful clinical relevance. Haahtela et al (10) reported that regular twice daily treatment with terbutaline for two years did not increase bronchial hyper-responsiveness in mild asthmatics although the drug was used in an unconventionally low dose. Van Schayck, using information from his own and from other studies, concluded that β_2 -agonists alone do not increase bronchial hyper-responsiveness (11).
- 2.4 Of more clinical relevance are the studies which have included measurements of decline in lung function. In a randomised single-blind study Van Schyak compared treatment with regular versus on-demand bronchodilator therapy using salbutamol and the anti-cholinergic, ipratropium bromide, in a crossover design. 144 patients completed a two year study and a statistically significant but small decline in lung function was found in those taking regular therapy. However, only 50 of the trial patients were asthmatics, and only 8 of these were randomised to regular therapy (12).

The study most frequently quoted as evidence that regular treatment with β_2 -agonists results in worse control of asthma than when used on demand is the Sears study using fenoterol (13). In a double-blind placebo controlled crossover study 64 patients were randomised to fenoterol, 0.2 mg four times a day, or placebo with both groups being allowed fenoterol, salbutamol or terbutaline on-demand for relief of symptoms. Treatment was in two 24 week blocks and results were expressed in terms of overall control of asthma. In 7 patients there was no difference in overall control during the two treatment periods; better overall control was achieved in 17 patients with regular fenoterol and in 40 with placebo. The main criticism of this study is the lack of definition of asthma control. Various markers were used to assess worsening of asthma and in the overall assessment it is not clear what weight each individual marker was given or how apparently inconsistent effects on different markers were dealt with.

- 2.5 The Sears study (13,14) also attempted to look at whether the effect of fenoterol was influenced by concomitant steroid therapy but the total number of patients in this subgroup was too small for definite conclusions to be drawn. Van Schyak has reported that in 28 asthmatics previously treated only with bronchodilators who had shown a decline in lung function, additional treatment with beclomethasone dipropionate slowed further decline (15).

- 2.6 Despite the paucity of evidence from experimental studies the safety of long-term regular use of β_2 -agonists is now being questioned (16) and withdrawal or reduction of such treatment in some patients is being advocated (17). The use of an inhaled β_2 -agonist on a regular basis is no longer recommended for the treatment of most patients with chronic asthma (18), but patients are still advised to use inhaled β_2 -agonists as required for relief of symptoms. When on-demand treatment is necessary more often than twice daily it may well be associated with similar adverse effects as regular six-hourly therapy.
- 2.7 The general concern about β_2 -agonist therapy and its possible association with increased asthma morbidity and mortality (19,20) stimulated the formation in the UK of the National Asthma Task Force in July 1991, under the auspices of the National Asthma Campaign. The Royal Colleges, the regulatory agencies, the Department of Health, the British Thoracic Society (BTS), and interested GP groups are all represented on the Task Force. A Task Force Therapy Working Group set up to identify important problem areas and to plan and initiate research projects agreed that priority should be given to well designed studies to confirm or refute the evidence that regular β_2 -agonist therapy makes asthma worse (13). The Group proposed that a large, multicentre, randomised trial should be performed to address the following important issues:-

Main objective

"Does regular inhaled β_2 -agonist therapy result in worse control of asthma than when used on-demand?"

Secondary objective

"Does concurrent use of regular inhaled corticosteroid therapy influence the effects of regular or on-demand inhaled β_2 -agonists?"

- 2.8 Salbutamol was chosen as the trial drug since it is the most commonly used inhaled bronchodilator in the UK and in most other developed countries.
- 2.9 The trial design involves randomisation of patients to treatment which does not fully accord with the guidelines issued by the BTS. It should therefore be emphasised that the BTS guidelines are only recommendations and that one aim of the proposed trial is to provide accurate experimental evidence to inform the revision of those guidelines. The BTS is represented on the National Asthma Task Force and fully endorses this trial.

3 Feasibility study

- 3.1 Feasibility studies have been completed in the General Practice Research Framework (GPRF) providing information on acceptability, recruitment, withdrawal and exacerbation rates.

4 Personnel and responsibilities

4.1 Steering Committee

- 4.1.1 The protocol has been developed by a trial Steering Committee from the Therapy Working Group of the National Asthma Task Force in collaboration with the GPRF Co-ordinating Centre and with advice from general practitioners. The steering committee would continue throughout the trial and would seek advice from other members of the Therapy Working Group as required.
- 4.1.2 Professor Tak Lee would have overall responsibility for the trial and Dr Madge Vickers would co-ordinate the trial in the GPRF. Ms Sarah Dennis would be responsible for the conduct of the trial on a day-to-day basis, liaising with the participating general practices and with the Therapy Working Group. Statistical input would be provided by Mr Christopher Frost working with Professor Stuart Pocock. Clinical advice would be provided on a day to day basis from the Unit by Professor Tom Meade and if necessary by other members of the Therapy Group, Dr Graham Crompton in particular.
- 4.1.3 In each general practice one clinician would be responsible for the conduct of the trial and a research nurse for day-to-day trial management and data collection. All the research nurses would receive thorough training in the management of asthma. The MRC training nurses would be the first point of contact for nursing queries and would be responsible for quality control during the study.

5 Ethical approval

- 5.1 Each participating practice would seek ethical approval from its Local Research Ethics Committee. Approval for the feasibility study was obtained from the 4 LREC's covering the 5 practices taking part.
- 5.2 Approval for the study is also being sought from the Royal College of General Practitioners Clinical Research Ethics Committee.

6 Study design

- 6.1 The design is a randomised, double-blind, placebo controlled trial of salbutamol 400 µg four times daily. This choice of design minimises the potential for bias in the study. A (non-randomised) observational study comparing regular users of salbutamol with controls could be biased because controls would tend to have less extreme asthma. A crossover study (where each patient receives both salbutamol and placebo for a period of six months each with the order of treatments being randomised) could possibly be hard to interpret if the effect of one treatment persists into the period of time where the participant was on the other treatment.
- 6.2 The trial would recruit mild to moderate asthmatics: those whose asthma was controlled only by β_2 -agonists and those currently taking inhaled steroids. Unstable asthmatics and those who rarely require anti-asthma treatment would be excluded.
- 6.3 Patients would be recruited from 70-80 general practices in the GPRF. Practices from rural, urban, inner-city and industrial areas would be included in an attempt to cover variations in pollution and distribution of pollen and other allergens. The continuing recruitment to the GPRF means that there are a large number of practices available particularly for recruiting the patients on β_2 -agonists only.

- 6.4 All patients will then be randomised to receive salbutamol or placebo. Those taking inhaled steroids will continue to do so throughout the trial. All patients will continue to have their usual bronchodilator, for emergency use when it is important to have an inhaler containing a known bronchodilator.
- 6.5 Patients would be treated for one year thus covering any seasonal variation in the severity and control of their asthma.

7 Patient selection

- 7.1 Males and females aged 18 years and over.
- 7.2 Asthma of at least one year's duration.
- 7.3 Current use of a bronchodilator MDI at least twice in a week.
- 7.4 No oral steroids within 6 weeks of study entry.
- 7.5 Ability to use a MDI and a Diskhaler efficiently.
- 7.6 Bronchial asthma will be defined as a peak expiratory flow (PEF) greater than 50% of the predicted normal with 15% diurnal variability and an absolute minimum peak flow variability of 60 litres per minute. This may be confirmed by previous documentation in the medical notes or during the three week run-in period.

8 Patient exclusion at entry

- 8.1 Treatment with oral steroids within six weeks of study entry.
- 8.2 Patients taking inhaled steroids at a dose of greater than 2 mg per 24 hrs.
- 8.3 Admission to hospital because of asthma within six weeks of study entry.
- 8.4 Asthma not requiring at least twice weekly bronchodilator therapy.
- 8.5 Treatment with sodium cromoglycate, nedocromil sodium, ipratropium bromide, oxitropium bromide, theophyllines, long-acting inhaled and any oral beta₂-agonist preparation.
- 8.6 Other significant lung disease or concomitant major illness.
- 8.7 Pregnancy and risk of pregnancy.
- 8.8 Inability to use an MDI and a Diskhaler effectively as determined by the nurse.
- 8.9 Inability to use a peak flow meter and complete a diary card.
- 8.10 PEF less than 50% of the predicted normal value.

9 Treatment regimens

9.1 Allocation of treatment.

Patients would be stratified according to inhaled steroid use; with three bands comprising none, low (100 µg-800 µg daily) and moderate (between 800 µg and 2 mg daily) dose inhaled steroids. Allocation to active or placebo treatment would be at random with numbers equally balanced in each stratum between randomised groups which would be achieved by undertaking the randomisation at the co-ordinating centre. Randomised treatment will be double blind, neither the patient nor the nurse and GP knowing the treatment being received. Patients would be asked whether they thought they had been taking active or placebo and their reasons for their decision at the final assessment. Arrangements for breaking the codes have been made for 24 hours cover.

9.2 Regular inhaled salbutamol.

The adult dose of salbutamol is 400µg four times daily from a Diskhaler. Dry powder salbutamol would be used to avoid any possible adverse effects of regular inhalation of freons/surfactants/lubricants contained in pressurised metered dose inhalers.

9.3 Patients currently on regular inhaled steroids.

Patients would continue to take their current inhaled steroid preparation, the dose range would be from 0.4 to 2.0 mg daily but for individual patients would be kept constant throughout the study period.

9.4 Placebo

Salbutamol placebo preparation would be prepared specially by Glaxo and would be identical to the formulation used but would lack the active ingredient.

10 Trial procedures

10.1 Potential participants would be identified by a search of GP held patient records, contacted by post and invited to attend the surgery to discuss the study with the trial nurse.

10.2 Those patients who attend would be given a full explanation of bronchial asthma, the treatments used, the rationale for the proposed trial, the trial itself including details of all procedures involved and possible long and short term risks and benefits of participation in the trial. At the interview, current health, medical history and eligibility for the trial would be assessed by the nurse-administered assessment forms. This would provide baseline information on all patients including those who would not be entering the study. Those patients who were eligible on the basis of the assessment would be invited to consider participating in the trial and would be given clear written explanation of the points covered in the interview. Informed consent would not be sought at this stage but patients who are interested would be invited to attend for a medical examination 2 to 3 weeks later.

10.3 Prior to a medical examination, patients would be invited to participate in the trial; the nurse would ensure that they understood the procedure for the trial and that they were able to use a MDI and a Diskhaler efficiently. Those who were eligible and willing to participate would be asked to sign the consent form.

10.4 At entry a general medical examination would be carried out including a specific symptoms questionnaire and spirometry, to include peak expiratory flow (PEF). The nurse would explain how the diary cards were to be completed and how to measure and record diurnal PEF. All patients would be supplied with a mini- Wright peak flow meter.

The patient would also be issued with clear instructions on the action to take in case of any worsening of their asthma and would be given the telephone number of the surgery so that they may obtain advice at any time.

10.5 Patients would be asked to complete the diary card for an initial run-in period of 3 weeks during which time they would continue with their usual medication. At 3 weeks they would return to the surgery and the nurse would assess the stability of their asthma by reference to the diary cards.

If eligible the patient would be admitted to the trial, stratified (no current inhaled steroids, low (100 µg-800 µg daily) and moderate (between 800 µg and 2 mg daily) dose inhaled steroids) and randomised to a treatment group. Trial medication and diary cards would be issued.

Follow up checks would be undertaken at 4 weekly intervals. The trial nurse would assess the patient's asthma by reference to their completed diary cards noting in particular diurnal variation in PEF, changes in symptom score, use of rescue bronchodilator and use of oral prednisolone. The asthma assessment form and the withdrawal from randomised treatment questionnaire would be completed as appropriate. Patients withdrawing from randomised treatment would be asked to give their consent to follow up through their medical notes. New diary cards and trial medication (5 week supply) would be issued.

Quality of life would be measured at entry and at 6 and 12 months using the St. George's Respiratory Questionnaire. In addition, one or more generic health status questionnaires would be used, either the Sickness Impact Profile and/or the SF-36.

Health economic data would be collected either on a daily basis on diary cards or at the regular four-weekly follow-up visits and would include:

- i) days lost from work or college whether self-certified or GP-certified
- ii) days unable to continue with usual activities
- iii) use of medication, prescribed and over the-counter
- iv) use of all NHS services.

Costs of medication, service use, and estimates of the costs of time lost would be calculated for each treatment group.

Compliance would be measured by counting used salbutamol and placebo disks. Consideration has been given to measurement of drug concentrations in urine and to the use of inhalers with micro-chips capable of recording number and time of inhalations but in a large trial such methods are prohibitively costly. At the initial assessment it would be established how many reliever inhalers the patient has and the prescription data would be used in an attempt to validate compliance with rescue inhalers. In previous GPRF trials the good relationship developed between the research nurse and participants has been an important factor in maintaining high levels of compliance.

Patient safety would be ensured by all patients carrying a card with information about the study and indicating when they should seek medical help, with the name of the GP and practice nurse responsible for the study in that practice. A similar card with details of the study and the medication used would be inserted into the patient's medical notes for the duration of the study.

11 Outcome measures

The main outcome of the trial would be any change in the underlying disease.

- 11.1 In the main trial the primary marker of this would be the number of exacerbations, fulfilling the criteria in 12.1 over a one year period. If any patient required three separate courses of treatment for exacerbation they would be withdrawn from the study.

11.2 Secondary markers of the severity of the asthma would be:

- i) Use of rescue β_2 -agonist.
- ii) Diurnal variation in PEF.
- iii) Symptom score.
- iv) Days lost from work/normal activities.
- v) Use of NHS services - including GP and hospital consultations.
- vi) Changes in overall score on the quality of life questionnaire

12 Exacerbation

12.1 Definition of exacerbation

For the purpose of the trial the onset of a exacerbation is defined as the patient demonstrating a clinical need for oral corticosteroids or experiencing two or more of the following:

- i) Fall in morning peak expiratory flow, PEF, to <80% of baseline reading on 2 or more consecutive mornings.
- ii) Increase in the need for rescue β_2 -agonist to 3 or more occasions per 24 hours on 2 or more consecutive mornings.
- iii) Increase in night time score of 1 or more above baseline on 2 or more consecutive nights.
- iv) Increase in daytime symptom score of 1 or more above baseline on 2 or more consecutive mornings.

Recovery from an exacerbation would be defined as.

- i) Return to baseline symptom score or symptom score stable at new baseline for 7 days.
- ii) Morning PEF returned to baseline or morning PEF stable at new baseline for 7 days.

Management of exacerbation

12.2 If a patient suddenly and rapidly deteriorates, i.e. brittle asthma; they should be treated immediately.

12.3 Once a patient has experienced an exacerbation, treatment would be at the discretion of the GP. Suggested treatment regimens would be to increase the dose of inhaled steroid or to prescribe a short course of oral prednisolone.

12.4 Increase inhaled steroid.

Double the dose of the inhaled steroid until the morning PEF and symptoms return to baseline, and continue for the same number of days again before returning to the previous dose. The patient should be seen by the GP at this stage to ensure they are safe to return to the previous dose, and do not require further treatment. If after 2 weeks of increased inhaled treatment there is no improvement then they should start oral prednisolone.

Under no circumstances should the dose of inhaled steroid be increased before an exacerbation in order to prevent its occurrence.

12.5 Oral prednisolone

Oral prednisolone at a dose of 30 mg daily for 7 days. If longer than 7 days treatment was required, extra treatment days would be assessed as sevenths of a course, eg: 1 day $\frac{1}{7}$ and 5 days or $\frac{5}{7}$ etc.

13 Withdrawal from randomised treatment

Patients may withdraw from randomised treatment whenever they wish for whatever reason they wish. In addition the following events would precipitate termination of participation in the trial.

- i) Three exacerbations requiring additional treatment or 30 days continuous oral prednisolone treatment.
- ii) Any other serious illness at the discretion of the general practitioner.

14 Data handling and analysis

14.1 It is proposed that the main trial would involve 1000 patients. The main analysis will compare the 500 participants randomised to regular salbutamol with the 500 participants randomised to placebo salbutamol. This would give the trial high statistical power to detect reductions of the order of 15-20% (the order of minimum reduction that would be clinically important) in the average number of exacerbations per year between those receiving regular salbutamol and those receiving salbutamol placebo. For example the study would have 98% power to detect a decrease of 20% in the number of exacerbations and 86% power to detect a decrease of 15% in the number of exacerbations if the average number of exacerbations per year in those patients not on salbutamol is 1.5. If the number of exacerbations is lower, say 1 exacerbation on average per year, the power of the study would still be substantial: 92% power to detect a decrease of 20% in the number of exacerbations and 69% power to detect a decrease of 15% in the number of exacerbations.

A comparison of the effects of salbutamol on patients taking inhaled steroids and those not on inhaled steroids would be possible only if the difference between the two groups was large.

Analysis

The effect of regular versus on-demand salbutamol would be assessed by comparing the average number of exacerbations in the participants randomised to regular salbutamol with those randomised to salbutamol placebo.

In the analysis, the exacerbations would be categorized according the severity, with three grades of severity:-

- Severe - requiring hospitalization
- Moderate - requiring oral corticosteroids
- Mild - fulfilling 2 or more of criteria (i) to (iv)

Due to the large number of participants in the trial normal approximations would be used for the analysis of the number of exacerbations. Methods for the

analysis of ordered categorical data would also be used as would survival analysis techniques for the analysis of time to first occurrence.

15 **Compensation for injury**

The MRC does not hold insurance against claims for compensation for injury caused by participation in clinical trials. However, as with other government funded bodies, including the NHS, claims resulting from the MRC sponsored trials will be given sympathetic consideration and will be dealt with through the appropriate government channels. These arrangements are fully in accord with recommendations 6.15 and 6.16 of the Medicines Commission in its advice to Ministers on healthy volunteer studies.

16 **Dissemination of results**

- 16.1 A report would be submitted to the Medical Research Council, the full UK Asthma Task Force and the National Asthma Campaign.
- 16.2 Papers would be submitted to the appropriate scientific journals.
- 16.3 The results would be reported to all practitioners taking part in the study and a presentation would be made at the annual MRC GPRF Conference.
- 16.4 Consideration would be given to other channels of communication e.g. presentation at meetings, reports to RHAs, interested lay bodies and the general media.

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In confidence

Date

Dear

In collaboration with the Medical Research Council, the doctors in this practice are undertaking a trial into the use of regular inhaled bronchodilators (salbutamol and terbutaline) in the treatment of asthma. It is known that these drugs make breathing easier in the short - term, but it is not clear how they affect the severity of your asthma. The study we are doing will indicate how best to treat asthma patients in the long - term.

We need to recruit adults who have had asthma for more than one year and who use their bronchodilator at least twice a week. We need two groups of patients; those who take inhaled steroids (beclomethasone and budesonide) and those who do not.

We should like to invite you to the surgery to find out more about asthma and what the trial would involve. If you decide that you do not want to take part in the trial you will be under no obligation to do so. This will not affect your future medical care or your relationship with any medical staff.

Please complete the attached questionnaire and return it to the surgery whether you wish to take part in the trial or not. If you do not wish to take part we will not bother you again. All information will be treated in the strictest confidence and used for statistical purposes only.

Thank you for your time.

Yours sincerely

Dr
General Practitioner

MRC Epidemiology and Medical Care Unit

ASTHMA STUDY**In Confidence**

- 1 [Name and address label]
- 2 If you are considering the trial, please write your telephone number below so that the nurse can contact you
- 3 How long have you had asthma?
 - Less than 1 year
 - Between 1 and 5 years
 - Between 5 and 10 years
 - More than 10 years
- 4 How many times do you usually use your bronchodilator or reliever inhaler (e.g. Ventolin or Bricanyl) ?
 - Less than twice a week
 - 2 or 6 times a week
 - Every day
 - More than once a day
- 5 When was the last time you needed to have a course of steroid tablets or a nebuliser?
 - Less than 6 weeks ago
 - Between 6 weeks and 6 months
 - More than 6 months ago
 - Never
- 6
 - a) Are you taking an inhaled steroid or preventer inhaler (e.g. Becotide or Pulmicort)?

	Yes	No
--	-----	----
 - b) If yes, how long have you been taking them?
 - Less than 6 months
 - Between 6 months and 1 year
 - More than a year
- 7 Would you like to come to the practice to find out more about the asthma trial?

	Yes	No
--	-----	----

Thank you for answering the questions.

ASTHMA - SCREENING

TRUST 3

PERSONAL DETAILS

Trial number 1

Name 0 2 10

Date of birth 12

Age 18

Sex M or F 20

Date of screening 21

CURRENT MARITAL STATUS

Married or living with partner = 1

Single, never married = 2

Divorced = 3

Separated = 4

Widowed = 5 27

EDUCATION

What age were you when you left school or college?

16 years or younger = 1

7-19 years old = 2

20 years old or older = 3 28

Since leaving school or college have you had any more full-time or part-time further or higher education?

Yes No 29

OCCUPATION

paid employment = 1 self-employment = 2

unemployed = 3 housewife = 4

student = 5 retired = 6

non-disabled = 7 other = 10 30

Details of last or current employment

EMCU CODES 32

If SC3 manual = 1, non-manual = 2 34

ETHNIC GROUP

Black (African) = 1 Black (Caribbean) = 2

Black (other) = 3 Bangladeshi = 4

Chinese = 5 Indian = 6

Pakistani = 7 White (British, Irish) = 10

White (other) = 11 Other Ethnic Group = 12 35

SMOKING

Do you smoke? Yes No 37

If yes, how many per day? 38

If no, have you ever smoked? Yes No 40

When did you stop? 41

month year

Are you regularly exposed to other peoples smoke? Yes No 45

If Yes Tick ☒ Home Work 46

EXERCISE

Do you take part in vigorous exercise at least once per week?

Yes No 47

If yes, list exercise 48

..... 50

..... 52

CURRENT MEDICAL PROBLEMS

(other than asthma) EMCU CODES

..... 54

..... 58

..... 62

..... 66

Time of asthma diagnosis 70

month year

03

11

CURRENT MEDICATION

EMCU CODES

.....

12

.....

14

.....

16

.....

18

.....

20

How often do you usually use your reliever inhaler?

times

22

Tick

day

week

24

Total daily dose of inhaled steroid

µg

25

ASTHMA ASSESSMENT

What tends to trigger your asthma?

(enter Y or N in the boxes)

Exercise

29

Housedust mites

30

Cold air

31

Respiratory infection

32

Emotion

33

Cough/sneeze

34

Laugh

35

Work

36

Animals

37

Smoke

38

Seasonal

39

specify season

40

Other

41

specify

42

.....

43

Height

cm

44

Weight

kg

47

Peak expiratory flow

l/min

50

% predicted normal

%

53

How often during the last month have you experienced the following symptoms?

(Not at all = 1, less than four times a week = 2, 4-6 times a week = 3, every day/night = 4, more than twice a day/night = 5)

Wheeze

57

Cough

58

Breathlessness

59

Chest tightness

60

Waking at night because of asthma

61

Inability to take part in usual activities

62

EXCLUSION CHECK LIST

(enter Y or N into the boxes)

Asthma less than 1 year

63

Inhaled steroid use < 6 months

64

Dose of inhaled steroid

> 2 mg per day

65

Other anti-asthma medication

66

PEF < 50% predicted normal value

67

Oral steroids in last 6 weeks

68

Hospital admission for asthma

in last 6 weeks

69

β₂-agonist use < 2 per week

70

Other lung pathology

71

Other major illness

72

Suspected or known pregnancy

73

04

10

Is patient eligible?

Yes

No

12

If NO, state reason

.....

13

.....

15

Date of next appointment

17

MRC Epidemiology and Medical Care Unit

ASTHMA STUDY**BACKGROUND INFORMATION**

It has recently been suggested in the national press that drugs such as Bricanyl (terbutaline) and Ventolin (salbutamol) may cause asthma to deteriorate if used regularly. These drugs are still very important in bringing rapid relief to the asthmatic in the event of an attack. What is not clear is what effect these drugs have on the underlying disease; i.e. what effect they have on the lungs over a long period of time.

Some studies suggest that reliever inhalers either help or do not change the course of the asthma. Other studies have linked the use of reliever inhalers with a worsening of asthma in individual patients, a general increase in the number of attacks and the number of deaths from asthma.

It is important that we find out what effect the regular use of reliever inhalers has on asthma control so that doctors can decide the best combination of relievers and preventers for their patients.

The only way to do this is to carry out a trial.

The study will compare the effects of taking salbutamol regularly with taking salbutamol only when necessary to relieve the symptoms of asthma.

The Aim of the Study

The main aim of the study is to establish what effect salbutamol (ventolin) taken regularly has on the control of asthma. We will also be able to see whether taking inhaled steroids (preventers) alters the effect of salbutamol on asthma control.

This information can only be obtained from doing this sort of clinical trial. The results will enable doctors to be sure that they are prescribing the most effective combination of treatments for your asthma.

TRUST 5

What it Would Involve

We want people who have had asthma for more than one year and currently take either inhaled steroids (preventers) and inhaled bronchodilators (relievers) or inhaled bronchodilators (relievers) only to control their symptoms. We want to monitor you for one year while you continue to take your inhaled steroid and either salbutamol four times a day or placebo (a dummy inhaler, i.e. containing no effective medication) four times a day. We do not know whether salbutamol will be better than inactive inhalers in its effects on the control of asthma in the long term, so you would not be missing out on treatment known to be effective if you were given the inactive inhaler. You will still have your usual bronchodilator to relieve your symptoms should you need to. Everyone has an equal chance of being allocated to either of the treatments. The doctor and the practice nurse will not know whether you are taking the active drugs or the placebo and nor will you.

All patients will continue to have their usual bronchodilator (reliever) inhaler for use when needed (rescue inhaler).

All people taking part in the study would:

Have a thorough asthma assessment.

Be given either salbutamol or salbutamol placebo.

Be given a Mini-Wright peak flow meter.

Complete a diary card with details of peak flow, symptoms, drugs taken and days off work or when you have needed to see a doctor.

Return to the practice nurse for reassessment every four weeks for 1 year when a new diary card will be issued and also the next month's supply of trial medication.

Be given advice about what to do in the event of an asthma attack.

Be given concise information about asthma and its treatments.

Be given advice on smoking, exercise and diet if necessary.

MRC Epidemiology and Medical Care Unit

ASTHMA STUDY**CONSENT FORM****Patient's Name****Study number**

The doctors in this practice are working with the Medical Research Council and the National Asthma Task Force on a study to investigate the long - term effects of regular inhaled salbutamol on the severity of asthma. The study will investigate the long-term effects on the control of the asthma, in particular the effects on the number of asthma attacks, peak flow, symptom severity and quality of life, and whether this effect is changed with the use of inhaled steroids. Salbutamol and inhaled steroids are the most commonly used drugs to treat asthma, but the study should identify which is the most effective combination.

On entering the trial you will be given salbutamol or no salbutamol (placebo) inhalers. If you currently take inhaled steroids (preventers) you will continue to do so as directed by your doctor, and you will also have your usual bronchodilator for symptom relief when necessary. Neither you nor the research nurse will know whether you are on the active treatment. Whatever your treatment allocation, during your participation in the study you will be kept under regular medical supervision and will see the research nurse at four weekly intervals. Should you develop an illness while you are in the study you will be given appropriate medical care and withdrawn from the trial if necessary.

You are free to decide whether you do or do not take part in the study. If you do take part, you will, of course, be free to withdraw from the trial at any time and for any reason, if you wish, and if you do so this will affect neither the future medical attention that you receive nor your relationship with any medical staff.

Please would you sign below to indicate that you are willing to participate in the asthma trial.

PATIENT'S CONSENT

I have read the above explanation and the information leaflet. The trial has been explained to me orally and I have had the opportunity to ask questions. It is on the basis of the information from these sources that I agree to participate in the asthma trial.

Signed _____

Date _____

GENERAL PRACTITIONER'S AGREEMENT

I am the general practitioner of the above patient and in my opinion there is nothing in his or her medical history to contraindicate entry into the trial. The patient would enter the trial with my consent.

Signed _____ Date _____

HOW TO TELL WHEN YOUR ASTHMA IS WORSE

SYMPTOMS OF ASTHMA ARE:

COUGH

WHEEZE

BREATHLESSNESS

WAKING AT NIGHT WITH BREATHING PROBLEMS

If any of these symptoms are worse than usual, it is a sign that your asthma is getting worse.

OTHER THINGS TO CHECK:

**USING YOUR RELIEVER INHALER 3 OR MORE TIMES A DAY
AND GETTING LESS BENEFIT FROM IT
PEAK FLOW READING BELOW**

**IF YOU NOTICE ANY OF THESE CHANGES IN
YOUR ASTHMA
CONTACT YOUR GP OR PRACTICE NURSE**

CONTACT _____

TELEPHONE NUMBER _____

MEDICAL RESEARCH COUNCIL

ASTHMA STUDY

PEAK FLOW DIARY CARD

PATIENT NAME _____

TRIAL NUMBER

DATE STARTED

CHART NUMBER

PEAK FLOW

INSTRUCTIONS FOR COMPLETING THE PEAK FLOW DIARY CARD

Please read the instructions carefully before starting to complete the diary. The information you supply in this asthma diary is important in enabling us to determine how well your asthma is being controlled by the trial medication. The diaries from all the asthmatics taking part in the study will be used to determine which is the most effective treatment. We would therefore appreciate your accuracy in completing this form.

PEAK FLOW MEASUREMENTS

Always record your peak flow reading every morning and every evening before using your trial inhalers. Stand up to take your peak flow, and carefully record the best of 3 readings in the correct box. If you forget to record your peak flow, leave the box blank. If you enter a made-up value it will spoil the results for the trial.

SYMPTOM SCORE

Enter the number that best describes your symptoms for that day or night in the correct box.

NIGHT-TIME SYMPTOMS

This should be assessed each morning immediately after awakening. (Symptoms are chest tightness, wheezing, breathlessness and cough.)

- 0 = No symptoms during the night
- 1 = Symptoms on waking but not causing you to wake early
- 2 = Symptoms causing you to wake once or to wake early
- 3 = Symptoms causing you to wake twice or more (including waking early)
- 4 = Symptoms causing you to be awake most of the night
- 5 = Symptoms so severe that you did not sleep at all

DAYTIME SYMPTOMS

This should be assessed each evening, just before going to bed. (Symptoms are chest tightness, wheezing, breathlessness and cough.)

- 0 = No symptoms during the day
- 1 = Symptoms for one short period during the day
- 2 = Symptoms for two or more short periods during the day
- 3 = Symptoms for most of the day which did not interfere with usual daytime activities
- 4 = Symptoms for most of the day which did interfere with usual daytime activities
- 5 = Symptoms so severe that you could not perform your usual daytime activities

DAYS OFF WORK/COLLEGE

MRC Epidemiology and Medical Care Unit

ASTHMA STUDY

WITHDRAWAL FROM RANDOMISED TREATMENT

Trial number	1
Name _____	_0_9_10
	_0_2_12
Date of withdrawal from randomised treatment ..	14

REASONS FOR WITHDRAWAL FROM RANDOMISED TREATMENT

1. Four serious exacerbations	Y or N	20
2. Requiring additional treatment for asthma	Y or N	21
3. Development of a major illness	Y or N	22
4. Persistent poor compliance	Y or N	23
5. Moved away	Y or N	24
6. No longer wishes to participate	Y or N	25
7. Pregnancy	Y or N	26
8. Other, please specify reasons	Y or N	27

MRC Epidemiology and Medical Care Unit

ASTHMA STUDY**CONSENT FORM****Patient's Name****Study number**

Although you have been withdrawn from the Medical Research Council asthma study and will be no longer taking the trial medication, we would like your permission to follow your progress for the duration of the trial through your medical records. Any information obtained would only be connected with your asthma and no other health problems, and all information would be treated with the strictest confidence.

The information to be obtained would be the number of asthma attacks in the remaining part of the study year, and any visits to the doctor or practice nurse.

If you do not wish to be followed up for the remaining part of the study year your future medical attention and your relationship with the medical staff will not be affected.

Please would you sign below to indicate that you are willing to take part in the follow - up.

PATIENT'S CONSENT

I have read the above explanation and the method of follow - up has been fully explained to me. It is on the basis of the information from these sources that I agree to participate in the follow - up.

Signed _____

Date _____

Synthesising and evaluating outcome measures for asthma in adults and children.

Background

The health status of patients with asthma, and thus the effectiveness of treatment for asthma, have traditionally been measured by lung function, typically peak expiratory flow rates. Although this approach is entirely feasible in the context of busy clinical practice, it suffers from two main shortcomings. First it takes no account of the very different ways in which the same loss of pulmonary function affects the different patients. Secondly it provides no basis for choosing between asthma and other patients in the allocation of scarce health care resources, a responsibility that falls to all purchasers in the new NHS.

Justification

Increasing acceptance of the limited value of pulmonary function as the only outcome measure for asthma has led to proposals for alternatives. These have ranged from asthma specific scales that examine the effect of the condition on daily living ^{1,2} through patients centred scales for respiratory illness in general ³ to general scales that cover all conditions but may not be responsive to subtle variations in pulmonary function ^{4,5}. This diversity has led to those seeking to evaluate alternative models of care for asthma to use ad hoc combinations of existing measures ⁶. Thus the key issues to be addressed within the R&D priority are how valid, reliable, responsive and generalisable ⁷ are these measures? What optimal combinations of measures can be recommended for use in three different contexts – normal clinical practice, routine audit and monitoring and rigorous evaluation of alternative policies?

Description of research

When synthesising and evaluating outcome measures for asthma, recognition should be made of different clinical settings and the purposes to which the outcome will be put.

Reliable outcome measures are needed to evaluate disease status, treatment modification and prognosis in routine clinical settings, in single modality therapeutic research and health services research, such as long term disease modification and the assessment of the effectiveness of health care systems.

Outcome measures that should be considered are:

- Indices of lung function impairment: the relative sensitivities of measures of airflow obstruction and their likely variable sensitivity in relation to the severity of asthma and the type of intervention, could be evaluated by a systematic review of published randomised control trials.
- Diary cards have neither been standardised nor formally evaluated. The concept of a “symptom-free day” is increasingly used but has not been validated. Primary research in this area would be of interest. Many definitions have been used for acute episodes and a systematic review could examine their relative utility.
- Health status measurements specific for asthma have been designed, those in adults being better validated than those for children, for whom a better questionnaire may well be needed. The research needs to be focused on whether the existing measures of health status can be used to measure improvements in care and outcome in a reliable and specific way.

Resource use: outcome measures of days off (work or school), GP/hospital attendance, admissions and prescribing need to be standardised, unbiased and simple, and the validity of data collection and recording requires validation.

References

1. Sibbald B, Collier J, D'Souza M (1986). Questionnaire assessment of patients' attitudes and beliefs about asthma. *Family Practice*, 3, 37-41.
2. Hyland ME, Finnis S, Irvine SH (1991). Scale for assessing quality of life in adult asthma sufferers. *Journal of Psychosomatic Research*, 35, 99-110.
3. Guyatt GH, Berman LB, Townsend M, Pugsley JO, Chambers LW (1987). A measure of quality of life for clinical trials in chronic lung disease. *Thorax*, 42, 773-8.
4. EuroQol Group (1990). EuroQol: a new facility for the measurement of health related quality of life. *Health Policy*, 16, 199-208.

5. Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT (1993). The SF-36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *BMJ*, 308, 144-4.
6. GRASSIC (1994). Integrated care for asthma: a clinical social and economic evaluation. *BMJ*, 308, 559-64.
7. Streiner DL, Norman GR (1989). Health measurement scales: a practical guide to their development and use. Oxford, *Oxford University Press*.

Medline Search Strategy

Database: All Medline Segments <1966 to latest>

Set	Search	Results
001	randomized controlled trial.pt.	150254
002	randomized controlled trials.sh.	19914
003	random allocation.sh.	44033
004	double blind method.sh.	66288
005	single blind method.sh.	6010
006	1 or 2 or 3 or 4 or 5	210944
007	animal.sh.	3230123
008	human.sh.	7422486
009	7 not (7 and 8)	2537172
010	6 not 9	199423
011	clinical trial.pt.	317257
012	exp clinical trials/	125628
013	(clin\$ adj3 trial\$).ti,ab.	61959
014	((singl\$ or doubl\$ or treb\$ or trip\$) adj3 (blind\$ or mask\$).mp.	63903
015	placebos.sh.	21070
016	placebo\$.ti,ab.	68643
017	random.ti,ab.	60047
018	research design.sh.	28546
019	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	478870
020	19 not 9	456257
021	20 not 10	267317
022	comparative study.sh.	964881
023	exp evaluation studies/	401894
024	follow-up studies.sh.	245648
025	prospective studies.sh.	137796
026	(control\$ or prospectiv\$ or volunteer\$).ti,ab.	1181069
027	22 or 23 or 24 or 25 or 26	2422714
028	27 not 9	1830995
029	28 not (10 or 21)	1503300
030	asthma.sh.	55475
031	asthma.ti,ab.	46378
032	30 or 31	64314
033	bronchodilator agents.sh.	8705
034	adrenergic beta agonists.sh.	10164
035	inhaled.ti,ab.	15534
036	33 or 34	17676
037	36 and 35	2024
038	32 and 37	1481
039	38 and (10 or 21 or 29)	1088
040	limit 39 to english language	995
041	limit 40 to all adult <19 plus years	639
042	limit 41 to abstracts	641

Data collection sheet

Author	
Article title	
Source	
Institutional affiliation	
Refman ID	
Aim	
Primary outcome	
Secondary outcomes	
Intervention	
Number of interventions	
Condition	
Other treatment allowed	
Subjects	
Duration of intervention	
Method of collection	
Consent	
RCT	
Was it truly random?	
Was randomisation blinded?	
How complete follow-up?	
Data from losses to follow-up?	
Assessors blind to treatment?	
Comparable baseline data?	
Groups otherwise treated indentically?	
Target population	
Inclusion criteria	
Exclusion criteria	
Characteristics - age	
sex	
Time interval	
First and second	
First and last	
Analysis	
Statistics test	
To be included	
If no: reasons	

Reason for exclusion	First stage	Second stage
Challenge	94	3
Pathology	86	
ICS	71	
Mechanisms	56	
Device	47	1
Epidemiology / HSR	37	
Severity	26	
Theophyllines	22	
Dose Response	20	1
Safety / efficacy	17	1
Other	16	4
Sport / exercise	14	
Reviews	12	
Leukotrienes	11	
COPD	10	
QOL	9	
Health Economics	8	
Nocturnal	8	2
Nedocromil	7	
Age	6	
Guidelines	6	
CVS side effects	5	
Pregnancy	5	
FEV1	0	4
Table 3.4.2	0	2
Serial lung function	0	7
Total	593	25

Table 4.1
Reasons for exclusion for papers identified by Medline search.

Reasons for exclusion	First stage	Second stage
Pathology/mech	73	
Challenge	66	
Device	49	
Severity	22	
Steroids	22	
Other	21	1
Theophyllines	19	
Language	18	
Dose Response	10	
Side effects	9	
Sport / exercise	9	
Serial lung function	9	9
Leukotrienes	7	
Nedocromil	6	
Nocturnal	6	
QOL	6	
Oral b2-agonist	6	1
Open	4	
Epidemiology / HSR	2	
Health Economics	2	
Safety / efficacy	2	1
Pregnancy	1	
Total	369	12

Table 4.2
Reasons for exclusion for papers identified by CCTR search.

6.1 Regression analysis for the relationship between TRUST exacerbation and mean PEF.

The last three weeks of the run-in period were used to calculate the baseline mean values for morning, evening and daily PEF. Mean values for each of the PEF variables in turn were generated for the whole follow up period and also for each month of follow-up in turn. In addition for each patient, the dataset also contained the dates on which they entered and left the study, follow up time, number of days taking additional corticosteroids, treatment allocation and the total number of exacerbations according to the TRUST definition.

Two basic regression models were used; the first model was a logistic regression model that assessed the degree to which change in a variable such as mean morning PEF, adjusted for baseline morning PEF and length of follow up, could predict whether a patient experienced an exacerbation or not. The second model was a Poisson regression model that assessed the degree to which change in a variable such as mean morning PEF, adjusted for baseline morning PEF and length of follow up, could predict the rate of exacerbations experienced.

6.1.1 Logistic Regression Model

$$\log \text{odds}(\text{ex}) = \beta_0 + \beta_1 \text{amdiffl} + \beta_2 \text{ampefl}$$

Where “ex” was the binary variable for the presence or absence of an exacerbation, “amdiffl” was the change in mean morning PEF between baseline and follow up and

“ampefl” was mean baseline morning PEF. $\text{Exp}(\beta_1)$ represented the odds ratio for having an exacerbation per unit increase in “amdifff”, adjusting for baseline. The model was implemented in STATA as:

logistic ex amdifff ampefl.

In order to examine whether the relationship between TRUST exacerbation and the difference in mean PEF between baseline and follow up was linear; “amdifff” was divided into five 50 l/min groups. The reference group included all patients with a change in mean morning PEF from baseline of < -50 l/min. The likelihood ratio test was used to compare the earlier model with one where the categorical indicators were added. If the latter showed no statistically significant improvement at the 5% level, the simpler linear trend model was used.

6.1.2 Poisson Regression Model

$$\log \lambda = \beta_0 + \beta_1 \text{amdifff} + \beta_2 \text{ampef}$$

Where λ was the rate of exacerbations per unit follow-up time. STATA calculated this from the total number of exacerbations experienced by each patient and the total amount of follow up for each patient. $\text{Exp}(\beta_1)$ represented the rate ratio of exacerbation per unit increase in “amdifff” adjusted for baseline. Because patients could experience more than one exacerbation during the follow up period and because exacerbations do not necessarily occur independently of one another the model was adjusted for clustering of exacerbations

on patient study number in addition to follow up; this inflated the standard errors according to the degree of clustering. The model was tested for linearity as with the logistic regression model. The model was implemented in STATA using:

```
glm totex amdif ampef1, fam(pois) link(log) lnoffset(followup) scale(x2) eform
```

The generalised linear model is the same as the Poisson model but the standard error is inflated by a factor of the square root of the Pearson chi-square statistic divided by the residual degrees of freedom, in order to compensate for the over-dispersion due to the within person clustering (1). Using “glm” the distribution of the dependant variable must be specified, in this case it is Poisson, “lnoffset” specifies the person years follow up, scale(x2) sets the scale parameter to Pearson chi-squared and “eform” means that the coefficients are displayed as rate ratios.

References

- (1) McCullagh P, Nelder JA. Generalised Linear Models. London: Chapman and Hall, 1989.

6.2 Regression analysis for the relationship between TRUST exacerbation and mean symptoms.

The last three weeks of the run-in period were used to calculate the baseline mean values for day and night time symptoms. Mean values for each of the variables in turn were generated for the whole follow up period and also for each month of follow-up in turn. In addition for each patient, the dataset also contained the dates on which they entered and left the study, follow up time, number of days taking additional corticosteroids, treatment allocation and the total number of exacerbations according to the TRUST definition.

Two basic regression models were used; the first model was a logistic regression model that assessed the degree to which change in a variable such as mean daytime symptoms, adjusted for baseline daytime symptoms and length of follow up, could predict whether a patient experienced an exacerbation or not. The second model was a Poisson regression model that assessed the degree to which change in a variable such as mean daytime symptoms, adjusted for baseline daytime symptoms and length of follow up, could predict the rate of exacerbations experienced.

6.2.1 *Logistic Regression Model*

$$\log \text{ odds(ex)} = \beta_0 + \beta_1 \text{dysdiff} + \beta_2 \text{dys1}$$

Where “ex” was the binary variable for the presence or absence of an exacerbation, “dysdiff” was the change in mean daytime symptoms between baseline and follow up and “dys1” was mean baseline daytime symptoms. $\text{Exp}(\beta_1)$ is the odds ratio of exacerbations per unit increase in symptom change from baseline, adjusted for baseline. Linearity was examined as described in Appendix 6.1. “Dysdiff” was categorised into five groups differing by one unit. The reference group included all patients with a change in mean daytime symptoms from baseline of < 2.5 l/.

6.2.2 Poisson Regression Model

$$\log \lambda = \beta_0 + \beta_1 \text{dysdiff} + \beta_2 \text{dys1}$$

As described earlier, λ is the rate of exacerbations. The explanatory variables included the difference in mean daytime symptoms between baseline and follow up, “dysdiff”, and the baseline value for mean daytime symptoms, “dys1”. As described earlier the model was adjusted for clustering of exacerbations on patient study number in addition to follow up. The model was tested for linearity described in Appendix 6.1. The model was implemented in STATA using:

glm totex dysdiff dys1, fam(pois) link(log) lnoffset(followup) scale(x2) eform

6.3 Regression analysis of exacerbations on diary card variables.

Logistic regression was used to assess the effect of the diary card variables on the odds of experiencing a TRUST exacerbation. The crude regression model was a univariate model adjusting only for baseline values. The adjusted odds ratio was obtained using a multivariate model that adjusted for age, sex, inhaled steroid level, baseline values and clustering on patient study number.

For each of the four definitions of exacerbation in turn the logistic regression analysis was repeated for days of exacerbation and linked periods of exacerbation when standard errors were adjusted for clustering on patient study number. The model was:

$$\text{Log odds (exacerbation)} = \beta_0 + \beta_1(\text{ampef}) + \beta_2(\text{ampefl})$$

Where “ampef” was morning PEF and “ampefl” was baseline morning PEF. The same model was repeated for evening PEF, diurnal variation, daytime symptoms, night time symptoms and rescue β_2 -agonist use singly and together in a multivariate model.

6.4 Analysis of use of additional corticosteroids on diary card variables.

Logistic regression was used to assess the effect of the diary card variables on the odds of starting a course of additional corticosteroids. The crude regression model was a univariate model adjusting only for baseline values. The adjusted odds ratio was obtained using a multivariate model that adjusted for age, sex, smoking, baseline values and clustering on patient study number.

$$\text{log odds (corticosteroid exacerbation)} = \beta_0 + \beta_1(\text{ampef}) + \beta_2(\text{ampef1})$$

Where “ampef” was morning PEF and “ampef1” was baseline morning PEF. The same model was repeated for evening PEF, diurnal variation, daytime symptoms, night time symptoms and rescue β_2 -agonist use singly and together in a multivariate model. The regression analysis was repeated to investigate the relationship between the diary card variables and courses of oral or increased corticosteroids and inhaled corticosteroids separately.