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Quadrupling Inhaled Glucocorticoid Dose To Abort Asthma Exacerbations

Tricia McKeever*, Ph.D., Department of Epidemiology and Public Health, NIHR Biomedical Research Centre, University of Nottingham, UK

Kevin Mortimer*, Ph.D., Liverpool School of Tropical Medicine and Aintree University Hospital, UK

Andrew Wilson, M.D., Professor of Primary Care Research, University of Leicester

Samantha Walker, Ph.D., Director of Research & Policy, Asthma UK and Lecturer (Hon), Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, UK

Christopher Brightling, Ph.D., Leicester NIHR Biomedical Research Centre University of Leicester, UK

Andrew Skeggs, B.Sc. (Hons), NIHR CRN: East Midlands, UK

Ian Pavord, F.Med.Sci., Respiratory Medicine Unit and Oxford Respiratory BRC, Nuffield Department of Medicine, NDM Research Building, University of Oxford, UK
David Price, F.R.C.G.P., Observational and Pragmatic Research Institute, Singapore
and Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK

Leila Duley, M.D., Nottingham Clinical Trials Unit, University of Nottingham, UK

Mike Thomas, Ph.D., Primary Care and Population Science and NIHR Southampton Biomedical Research Centre, University of Southampton UK

Lucy Bradshaw, B.Sc., Nottingham Clinical Trials Unit, University of Nottingham

Bernard Higgins, Ph.D., Respiratory Medicine, Newcastle Upon Tyne Hospitals NHS Trust, UK

Rebecca Haydock, B.Sc., Nottingham Clinical Trials Unit, University of Nottingham, UK

Eleanor Mitchell, B.A. (Hons), Nottingham Clinical Trials Unit, University of Nottingham, UK

Graham Devereux, Ph.D., The Institute of Medical Sciences, University of Aberdeen, UK

**Timothy Harrison, M.D., Nottingham Respiratory Research Unit, NIHR Biomedical Research Centre, University of Nottingham, UK

*Shared first author

**Corresponding author

Timothy Harrison, M.D.
Nottingham Respiratory Research Unit
NIHR Biomedical Research Centre
University of Nottingham

+447557197485

e-mail: tim.harrison@nottingham.ac.uk
Abstract

Background
Asthma exacerbations are frightening for patients and are occasionally fatal. We tested the concept that a self-management plan, which included a temporary quadrupling of the dose of inhaled glucocorticoid when asthma control started to deteriorate, would reduce severe asthma exacerbations in adults with asthma.

Methods
A pragmatic, unmasked, randomized trial in adults with asthma, treated with inhaled glucocorticoids with or without additional add-on therapy and one or more exacerbation in the previous 12 months. We compared a self-management plan that included a four-fold increase in inhaled glucocorticoid dose with the same plan without an increase in glucocorticoid, over 12 months. The primary outcome was time to first severe asthma exacerbation, defined as treatment with systemic glucocorticoids or unscheduled healthcare consultation for asthma.

Results

1922 participants were randomized of whom 1871 contributed to the primary analysis. The number of participants having a severe asthma exacerbation in the year after randomization was 484 (51.6%) in the non-quadrupling group and 420 (45.0%) in the quadrupling group, with an adjusted hazard ratio for time to first severe exacerbation of 0.81 (95% confidence interval 0.71 to 0.92, p-value
Adverse effects, primarily related to local effects of inhaled glucocorticoids, were increased in the quadrupling group.

**Conclusion**

Severe exacerbations of asthma were reduced in adults with asthma with a personalized self-management plan that included a temporary four-fold increase in inhaled glucocorticoid dose when asthma control started to deteriorate.

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INTRODUCTION

Asthma is one of the commonest chronic diseases with an estimated 300 million people affected worldwide [1]. Acute exacerbations of asthma are frightening for patients, cause considerable morbidity, unnecessary mortality and account for a large proportion of the overall costs of asthma [2].

Although self-management plans have been shown to improve asthma control [3] the previously recommended step of doubling the dose of inhaled glucocorticoid when asthma control is deteriorating is ineffective at preventing acute exacerbations [4, 5]. Although some guidelines suggest a greater increase in inhaled glucocorticoid dose, a Cochrane review updated in 2016 concluded that it is unlikely that increasing the dose of inhaled glucocorticoid reduces the need for systemic glucocorticoids, hospitalizations or recovery time [6].

A large, pragmatic study, was therefore commissioned by the UK National Institute of Health Research – Health Technology Assessment Programme. We have performed an individually randomized, unmasked, pragmatic, multi-centre trial in adults to test the hypothesis that a self-management plan that included a temporary four-fold increase in inhaled glucocorticoid dose when asthma control started to deteriorate reduced the use of oral glucocorticoids and/or unscheduled healthcare consultations for asthma compared with a plan that did not include this step.
METHODS

Population

Patients aged 16 years and above with a clinical diagnosis of asthma treated with any UK-licensed dose of inhaled glucocorticoid, with or without other add-on medication, and who had experienced one or more exacerbation leading to treatment with systemic glucocorticoids in the previous 12 months were eligible to participate. See on-line supplement page 2 for further details.

Intervention

We compared two self-management plans which were based on a plan developed by Asthma UK and used in the UK at the time of study design (Figures S1 and S2). Both plans were identical other than zone 2. Zone 1 described well-controlled asthma and recommended continuing current treatment. Zone 2 described deteriorating asthma control and recommended increased bronchodilator medication and a four-fold increase in inhaled glucocorticoid dose in the quadrupling group and increased bronchodilator medication alone in the non-quadrupling group (Table 1); see on-line supplement page 2 and protocol [7] for more details. Zones 3 and 4, described the development of an exacerbation and when to start oral glucocorticoids and seek medical intervention (zone 3) and what to do with a life-threatening exacerbation (zone 4). Participants were sent an automated text message every month to remind them to follow their self-management plan. Additional inhaled glucocorticoid inhalers required to achieve a quadrupling of the dose were provided free of charge.
**Outcome measurements**

The primary outcome was time to first severe asthma exacerbation defined as treatment with systemic glucocorticoids or unscheduled healthcare consultation for asthma. Scheduled visits occurred at six and 12-months post randomization. For participants that were lost to follow-up, site staff attempted to review electronic patient records to document if they had had an asthma related general practice appointment or been prescribed systemic glucocorticoids within the study period.

Secondary outcomes included: 1) number of participants who experienced a severe exacerbation, 2) area under the morning peak expiratory flow (PEF) curve and 3) Asthma Quality of Life Questionnaire (AQLQ) two-weeks after activating stage 2 of the self-management plan (Mini AQLQ scores range from 1 to 7, For the full AQLQ, a within-patient change in score of 0.5 represents the minimal important difference [8]) and 4) cumulative dose of inhaled and systemic glucocorticoids used in the 12 months after randomization. See on-line supplement page 2 for more details.

**Safety**

Adverse events and serious adverse events relating to established adverse effects of inhaled glucocorticoids were reported during the 14 days following activation of zone 2 of the self-management plan and, following a request from the data monitoring committee, cases of pneumonia were reported for up to four weeks post activation of zone 2.
Randomisation and blinding

See on-line supplement pages 2 and 3

Sample size

A group of local general practitioners, asthma nurses and asthma experts suggested a reduction of one-third in the number of people requiring treatment with systemic glucocorticoids is a worthwhile treatment effect. With 1000 participants per group, a log-rank test (at the two sided 5% significance level) had at least 90% power to detect a difference of 30% (relative effect), assuming an exacerbation rate of 13% in the non-quadrupling group [4,9]. We initially proposed to recruit 2300 patients to allow for drop-outs but this was reduced in March 2015 to a minimum of 1774 because the combined primary outcome rate was higher than expected (see protocol [7]).

Statistical methods

All analyses were conducted using Stata v13.1. Participants were analysed according to their randomised group, regardless of their adherence with their allocated self-management plan. All participants were included in the analysis of the primary outcome apart from those with no further contact after randomization, where information was unknown about systemic glucocorticoid use or unscheduled healthcare consultations for asthma. See on line supplement page 3 for details.
Ethical considerations

The North West - Greater Manchester South, National Research Ethics Service Committee approved the protocol. Written informed consent was obtained from each participant prior to inclusion in the trial.

RESULTS

Participants

We invited approximately 30,000 potential patients via letters from general practice and volunteer databases and used posters, social media and face-to-face discussions in clinics to also recruit patients. 4811 patients were screened, from whom 1922 were randomized, 957 to the quadrupling and 965 to the non-quadrupling group. All participants received their allocated self-management plan although 51 (2.7 %) were excluded from the primary analysis (24 quadrupling group), primarily due to being lost to follow up with no outcome data, leaving 933 and 938 in the quadrupling and non-quadrupling groups respectively in the analysis (Figure 1). Participants were enrolled between May 2013 and January 2016 and follow up was completed by March 2017.

81% of recruited participants were identified in primary care and 19% in secondary care. Participants mean age was 57 years (SD 15), 1305 (68%) were female, 1495 (78%) were on 1000 mcg/day BDP or equivalent glucocorticoid or less, 1116 (58%), 125 (7%) and 681 (35%) were never, current and former
smokers respectively and 1344 (70%) of participants were using a long-acting beta-agonist/inhaled glucocorticoid combination inhaler at the point of randomization. Characteristics at baseline were well balanced between the two treatment groups (Table 2).

Attendance at the scheduled visits was similar between the two groups with 773 (81%) and 772 (80%) attending the 6-month visit and 679 (71%) and 700 (73%) attending the 12-month visit in the quadrupling and non-quadrupling groups respectively.

**Outcomes**

Of the 1922 participants, 1114 (58%) reached zone 2 or higher of their self-management plan at some point during follow up with 562 and 552 in the quadrupling and non-quadrupling groups respectively.

The number of participants reporting a severe exacerbation of asthma in the year after randomization was 420 (45.0%) in the quadrupling group and 484 (51.6%) in the non-quadrupling group, giving an adjusted hazard ratio for the time to first exacerbation of 0.81 (95% confidence interval 0.71 to 0.92, p-value 0.002, Figure 2). Additional adjustment for age, sex and peak flow at randomization had little effect on the hazard ratio (0.80, 95% CI 0.71 to 0.92, p-value 0.001). There was also no evidence of a difference in the hazard ratio according to smoking status or dose of inhaled glucocorticoid (high/low) at randomization (Table S1).
Sensitivity analysis to include all 1922 participants gives a hazard ratio for time to first exacerbation of 0.81 (95% CI 0.72 to 0.92).

Analysed separately; use of systemic glucocorticoids and unscheduled healthcare consultations for asthma were also lower in the quadrupling group compared to the non-quadrupling group. 311 (33%) v 377 (40%) started systemic glucocorticoids with a mean number of courses of 0.50 v 0.61 (incidence rate ratio 0.82, 95% CI 0.70 to 0.96). For unscheduled healthcare consultations, the total numbers were 379 (41%) v 442 (47%) with a mean total number of visits of 0.73 v 0.84 (incidence rate ratio 0.86, 95% CI 0.75 to 0.99). For full details of secondary outcomes see Tables S2 and S3.

Self-reported adherence with the instruction to quadruple or to not adjust inhaled glucocorticoid dose was also similar between groups with 50% and 42% of patients with a reported activation of zone 2 judged as good adherence by the researcher and 6% and 3% judged as poor adherence in the quadrupling and non-quadrupling groups respectively although no information was available in 28% and 39% of participants respectively.

Approximately 50% of participants had a peak flow value recorded on activation of zone 2 of their self-management plan and at least one value on or after day 10 (54% and 41% of the quadrupling and non-quadrupling groups respectively). From these values mean area under the peak flow curve was 1166 and 1130
L/min/day in the quadrupling and non-quadrupling care groups respectively, adjusted difference in means 38 (95% CI 13 to 62, n = 529, see Table S4). Similarly, mini AQLQ data after first activation of zone 2 was only available for 44% of participants with more participants in the quadrupling group than non-quadrupling group (51% v 39%). Mean mini AQLQ score 2-week post zone 2 activation was also higher in the quadrupling group, with an adjusted difference in means of 0.2 (95% CI 0.03 to 0.46, n = 499, see Table S4).

For participants attending the 12-month follow up visit the estimated mean total dose of inhaled glucocorticoids taken in the 12 months after randomization was 385 mg in the quadrupling group (n=679) and 328 mg in the non-quadrupling group (n=700) and the mean total dose of systemic glucocorticoids was 121mg and 151 mg in quadrupling and non-quadrupling groups respectively. Full details of secondary outcomes are provided in Table S3.

Eleven participants (2%) in the quadrupling group (9 on high maintenance dose corticosteroid) and 22 (4%) in the non-quadrupling group (8 on high maintenance dose corticosteroid) reported 11 and 32 serious adverse events in the 14 days after zone 2 activation. The commonest serious adverse event was hospitalization for asthma occurring 3 and 18 times in the quadrupling and non-quadrupling groups respectively. As these events also fulfil the criteria for the primary outcome they are included in the primary outcome analysis so caution is needed when considering total adverse events in the two groups. There were 5
events in the quadrupling group and 6 in the non-quadrupling group relating to pneumonia, or lower respiratory tract infection in the 4 weeks after activating zone 2 of the self-management plan. One participant in the quadrupling group died of severe pneumonia (see on-line supplement page 4 for details).

Forty-one participants in the quadrupling group (7%) and 10 in the non-quadrupling group (2%) reported 56 and 13 non-serious adverse events in the 14 days post zone 2 activation. Oral candidiasis and dysphonia accounted for the great majority with 36 (19 oral candidiasis) and 9 (7 oral candidiasis) episodes of in the quadrupling and non-quadrupling groups respectively.

Discussion
Our study demonstrated that a temporary quadrupling of inhaled glucocorticoid dose at the time of worsening asthma control, reduced severe exacerbations of asthma in adult from 51.6% in the control group to 45.0% in the quadrupling group.

The main strength of our study is its pragmatic design and 80% recruitment in primary care giving it excellent external validity. Broad inclusion criteria ensured that the study results are applicable to adult patients with a clinical diagnosis of asthma on any licensed dose of inhaled glucocorticoid, with or without add-on medication, regardless of smoking status. We minimized study visits after training.
participants to follow a personalized self-management plan to reflect follow up in clinical practice as closely as possible, although the requirement to report zone 2 activations is different to real-life clinical practice and may have influenced adherence with the allocated self-management plan. Finally, we chose a primary outcome which is directly relevant to the trial participants and, due to the time to event analysis, only 2.7% of participants could not be included in the primary analysis.

The pragmatic design of our trial may also be considered to limit the implications of its findings. The open label nature of the intervention means there may be a bias because the participants and many of the treating physicians may have been aware of the individual’s intervention and this may have influenced the decision by participants to seek medical help or for physicians to advise treatment with systemic glucocorticoids. If such an effect occurred it reflects the beneficial effects likely to be seen in clinical practice which are missed in strict explanatory studies. The pragmatic nature of the study also impacted on the quality of secondary outcome data such as the number of peak flow measurements and quality of life questionnaires completed but the data that were collected were consistent with better asthma control in the quadrupling group. A further potential bias was that more participants in the quadrupling group attended a post-activation visit and, therefore, provided more diary card data; the extent to which this impacted the outcomes observed is unknown.
The estimated severe exacerbation rate was deliberately conservative, to ensure adequate power and was based on our previous studies, in which participants did not have to have had an exacerbation requiring systemic glucocorticoids in the previous 12 months [4,9]. In reality, our severe exacerbation rate was much higher in the non-quadrupling group than we estimated, enabling a reduction in the number of participants required to detect a 30% effect size without a loss of statistical power. Our finding that approximately 50% of patients included in the study experienced an exacerbation, within a year, leading to treatment with oral glucocorticoids or an unscheduled health care consultation confirms our inclusion criteria identified a group of patients at high risk of an asthma exacerbation and is consistent with general poor asthma control reported in many asthma surveys [10, 11]. It also highlights the pragmatic nature of our trial as the exacerbation rate is much higher than that seen in more explanatory trials in which patient selection, increased follow up and adherence with medication are all likely to reduce the background exacerbation rate.

Previous studies investigating the beneficial effects of self-management plans have demonstrated that provision of a written self-management plan based on symptoms or peak flow recordings improves asthma control and reduces exacerbations and hospital attendances compared with no self-management plan [3]. We and others have, however, shown that the previous recommendation to double the dose of inhaled glucocorticoid when asthma control is deteriorating is no more effective than not changing the dose [4, 5] and a Cochrane review
update in 2016 concluded that it is unlikely that increasing the dose of inhaled glucocorticoid reduces the need for courses of systemic glucocorticoids, hospitalizations or recovery time [6]. When we designed our trial a 30% reduction in asthma exacerbations was thought to be a minimum that was clinically meaningful. Although we achieved a statistically significant 19% reduction in severe exacerbations, we failed to achieve the magnitude of reduction we had hoped.

We believe that our safety data support the clinical benefit of temporarily quadrupling the inhaled glucocorticoid dose, as participants in the quadrupling group reported fewer asthma related hospitalizations (3 versus 18), however, the bias of the open label aspect of the study, may have altered the threshold to hospitalize participants and cannot be measured.

As expected, the quadrupling group did experience a higher frequency of treatment related adverse effects such as oral candidiasis that led to treatment with topical antifungal medication. We paid particular attention to the issue of pneumonia because of reports of pneumonia associated with inhaled glucocorticoid use in asthma [12] and COPD [13], but we found no evidence of a difference in incidence of pneumonia in our trial. The median dose of inhaled glucocorticoid in our trial was 0.8 mg/day so quadrupling this would equate to the equivalent of 3.2 mg/day inhaled beclomethasone for 7-14 days. Unfortunately, the systemic effects are of high dose inhaled glucocorticoids are not well
understood. In terms of milligrams of prednisolone, adrenal suppression from 1.0 mg/day budesonide has been estimated to be as high as 8.7 mg prednisolone [14]. As we included patients on 1.6 mg of inhaled budesonide and 2 mg inhaled fluticasone propionate and, if the dose potency ratio between inhaled glucocorticoids and prednisolone is linear, then the quadrupled dose in these participants could have the same systemic effects on adrenal suppression as a course of prednisolone used to treat severe asthma exacerbations.

In our study, the number of patients needed to be provided with such a self-management plan in order to prevent one severe asthma exacerbation is 15 (95% CI 9 to 43). Given the potential benefit on preventing exacerbations, and in view of the toxicities of inhaled glucocorticoids, and the biases that may have been introduced by the absence of masking, individual practitioners, patients and guideline committees will need to consider whether the magnitude of the reduction achieved is clinically meaningful.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Independent Data Monitoring Committee who monitored patient safety and treatment efficacy data.

Steven Julious (Chair), Professor of Medical Statistics, University of Sheffield; Ian Sabroe, Profession of Inflammation Biology, University of Sheffield and Stephen Scott, Consultant Respiratory Physician, Countess of Chester Hospital.
REFERENCES


7. Skeggs A, McKeever T, Duley L, Mitchell E, Bradshaw L, Mortimer K et al. FourFold Asthma Study (FAST): a study protocol for a randomized controlled trial evaluating the clinical cost-effectiveness of temporarily quadrupling the dose of inhaled steroid to prevent asthma exacerbations. Trials 2016;17:499


10. Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the Recognise Asthma and Link to Symptoms and Experience (REALISE) survey. Npj Primary Respiratory Medicine 2014;24, Article number:14009


Figure Legends

Figure 1
Consort Diagram

Figure 2
Kaplan-Meier curves for time to first asthma exacerbation by allocated group
<table>
<thead>
<tr>
<th>Table 1 Baseline demographics</th>
<th>Non-quadrupling group (n = 965)</th>
<th>Quadrupling group (n = 957)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean [SD] 56.7 [15.2]</td>
<td>56.2 [15.5]</td>
</tr>
<tr>
<td></td>
<td>Min, max 19, 94</td>
<td>16, 91</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 316 (33%)</td>
<td>301 (31%)</td>
</tr>
<tr>
<td></td>
<td>Female 649 (67%)</td>
<td>656 (69%)</td>
</tr>
<tr>
<td>Recruited from</td>
<td>Primary care 774 (80%)</td>
<td>785 (82%)</td>
</tr>
<tr>
<td></td>
<td>Secondary care 191 (20%)</td>
<td>172 (18%)</td>
</tr>
<tr>
<td>Peak expiratory flow at screening (litres/min)</td>
<td>Mean [SD] 381.1 [112.2]</td>
<td>386.9 [110.8]</td>
</tr>
<tr>
<td>Type of inhaler</td>
<td>Glucocorticoid 303 (31%)</td>
<td>275 (29%)</td>
</tr>
<tr>
<td></td>
<td>Combination 662 (69%)</td>
<td>682 (71%)</td>
</tr>
<tr>
<td>Type of ICS</td>
<td>beclometasone 388 (40%)</td>
<td>325 (34%)</td>
</tr>
<tr>
<td></td>
<td>budesonide 220 (22%)</td>
<td>225 (24%)</td>
</tr>
<tr>
<td></td>
<td>fluticasone 350 (36%)</td>
<td>401 (42%)</td>
</tr>
<tr>
<td></td>
<td>ciclesonide 7 (1%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Maintenance dose of inhaled glucocorticoids (BDP µg/d)</td>
<td>Median [25th, 75th centile] 800 [400, 1000]</td>
<td>800 [400, 1000]</td>
</tr>
<tr>
<td></td>
<td>Min, max 100, 4000</td>
<td>80, 4000</td>
</tr>
<tr>
<td></td>
<td>Low (≤ 1000 BDP µg/d)</td>
<td>752 (78%)</td>
</tr>
<tr>
<td></td>
<td>High (&gt; 1000 BDP µg/d)</td>
<td>213 (22%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never 552 (57%)</td>
<td>564 (59%)</td>
</tr>
<tr>
<td></td>
<td>Current 66 (7%)</td>
<td>59 (6%)</td>
</tr>
<tr>
<td></td>
<td>Former 347 (36%)</td>
<td>334 (35%)</td>
</tr>
<tr>
<td>Pack years for current or former smokers</td>
<td>n 413</td>
<td>393</td>
</tr>
<tr>
<td>Mini Asthma Quality of Life (AQLQ)</td>
<td>overall score n 959</td>
<td>944</td>
</tr>
<tr>
<td></td>
<td>Mean [SD] 5 [1.2]</td>
<td>5.1 [1.2]</td>
</tr>
<tr>
<td>Mini Asthma Quality of Life (AQLQ)</td>
<td>symptom score n 954</td>
<td>938</td>
</tr>
<tr>
<td></td>
<td>Mean [SD] 4.8 [1.3]</td>
<td>4.9 [1.3]</td>
</tr>
</tbody>
</table>

All data are n (%) unless otherwise indicated.
AQLQ scores range from 1 to 7, higher scores indicating better Quality of life. For the full AQLQ, a within-patient change in score of 0.5 represents the minimal important difference.
### Table 2  Asthma self-management plans used by a) Quadrupling group b) non-quadrupling group

<table>
<thead>
<tr>
<th></th>
<th>a) ZONE 2</th>
<th>b) ZONE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Your asthma is getting worse if you have ONE or MORE of the following:</strong></td>
<td>• You need your reliever inhaler more than usual</td>
<td>• You need your reliever inhaler more than usual</td>
</tr>
<tr>
<td></td>
<td>• You have more difficulty sleeping because of your asthma</td>
<td>• You have more difficulty sleeping because of your asthma</td>
</tr>
<tr>
<td></td>
<td>• Your peak flow is below _________</td>
<td>• Your peak flow is below _________</td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>Use your reliever inhaler to relieve your symptoms and increase your preventer medication as described below:</td>
<td>Use your reliever inhaler to relieve your symptoms and continue your preventer medication at your normal dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Once your symptoms or peak flow have returned to normal or after a maximum of 14 days return to your normal treatment. If your symptoms get worse follow Zone 3 instructions.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Start to record your morning peak flow, symptoms and medication in the study diary.</td>
<td>Start to record your morning peak flow, symptoms and medication in the study diary.</td>
</tr>
<tr>
<td></td>
<td>Phone your research nurse to arrange a study visit</td>
<td>Phone your research nurse to arrange a study visit</td>
</tr>
</tbody>
</table>