Drug Saf 2011; 34 (12): e1-e9
0114-5916/11/0012-0001/$49.95/0

Modified Prescription-Event Monitoring Studies

A Tool for Pharmacovigilance and Risk Management

Deborah Layton,[1,2] *Lorna Hazell*[1,2] and *Saad A.W. Shakir*[1,2]

1 Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton, UK
2 Associate Department of the School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK

Contents

Abstract

Prescription-Event Monitoring (PEM) is a well established postmarketing surveillance technique designed to monitor the overall safety of newly marketed medicines as used in real-life clinical practice, usually in cohorts of at least 10 000 patients.

At the Drug Safety Research Unit in the UK we are now moving towards a more targeted safety surveillance known as Modified PEM (M-PEM). These studies combine the advantages of conventional PEM studies (in monitoring general safety and identification of unexpected risks of a medicine) with that of a more targeted safety study that addresses specific questions (to better understand known or partially known risks with a medicine). Through the use of enhanced data collection questionnaires, M-PEM expands the range of applications of conventional PEM, which include more detailed characterization of real-life drug use, adherence to prescribing recommendations and targeted analysis of events requiring special monitoring by regulatory authorities. A particularly useful application is the evaluation of the safety of a medicine in special populations or subgroups (e.g. patients switching from another therapy or patients with a particular risk factor) or following important changes in the product's lifecycle (e.g. a licensing or formulation change). M-PEM studies therefore have an important contribution to make to pharmacovigilance and the risk management of medicines by providing valuable information on the use of new medications under real-life situations.

At the time of marketing, there may be unanswered questions regarding the safety of a medicine because it is not possible to identify all possible risks for all possible users during the drug development programme. The first suspicions of uncommon or rare safety concerns may come from routine pharmacovigilance either through spontaneous reporting or other complementary bespoke postmarketing surveillance systems, such as Prescription-Event Monitoring (PEM).[1] PEM is a prescription-based monitoring system that we have used at the Drug Safety Research Unit (DSRU) in the UK for many years. A similar scheme operates at the Intensive Medicines Monitoring Programme in New Zealand and pilot studies using similar methodology have been introduced in Japan and some African countries.[2-4] Here, we report on the evolution of PEM at the DSRU into a new 'Modified PEM' methodology and its wider application as a pharmacoepidemiological tool for risk management and within pharmacovigilance.

1. The Process of Prescription-Event Monitoring (PEM) (in England)

PEM uses a non-interventional observational cohort design to provide active surveillance of targeted medicines on a national scale in England. Data collection begins immediately postmarketing and thus provides 'real-world' clinical data for the first cohorts of patients prescribed the medicine of interest in the community. Identification of these patients relies on data from dispensed National Health Service (NHS) prescriptions provided to the DSRU, securely under long-standing arrangements, by a central NHS prescription processing centre, known as the NHS Prescription Services.

For each patient identified, a questionnaire is sent by post (according to chronological order of prescription issue date) to the prescribing primary-care general practitioner (GP) until the target sample size (usually 10 000 patients) is achieved. Historically, this questionnaire was designed to be simple in order to expedite data collection to enhance surveillance and encourage response, given there was no remuneration for completion. The questionnaire requests data on patient demographics (age, sex), prescribing information and details of all significant events that have been recorded in the patient's medical records during a specific time period after starting the PEM study drug, usually between 6 and 12 months. Within the NHS structure, all individuals are registered with a primary-care GP. Medical records held by the GP are generally lifelong, transferable when a patient relocates, and include information on healthcare consultations and interventions provided by both primary and secondary care.

In addition to providing valuable drug utilization information for new medicines, PEM provides estimates of incidence rates for events reported in the exposed cohort, and also provides the opportunity for further clinical evaluation of selected events of interest using bespoke follow-up questionnaires. The DSRU has completed 109 PEM studies to date with a median cohort size of 11 680 patients (interquartile range 8670–13 632). A wide range of drugs have been studied, including agents to treat hypertension, angina, asthma, chronic obstructive pulmonary disease, diabetes mellitus, epilepsy, depression, schizophrenia and urinary incontinence. A number of important safety issues have been studied, including serious cardiovascular events with erectile dysfunction drugs,[5,6] deep vein thrombosis with the oral contraceptive Yasmin® (Bayer plc, Newbury, Berkshire, UK)[7] and serious skin reactions with selective cyclooxygenase 2 inhibitors.[8]

2. Modified PEM (in England)

PEM is perhaps traditionally regarded as a general safety surveillance method used to generate or further evaluate safety signals of uncommon or rare outcomes. In recent years, in parallel with pharmacoepidemiological developments in general and the emergence of the requirements for risk management of medicines, a number of enhancements have been made to the study questionnaire to facilitate more targeted safety surveillance. This has led to the evolution of 'Modified PEM' (M-PEM) studies. The customized questionnaires used in M-PEM studies are designed to collect relevant supplementary information in order to

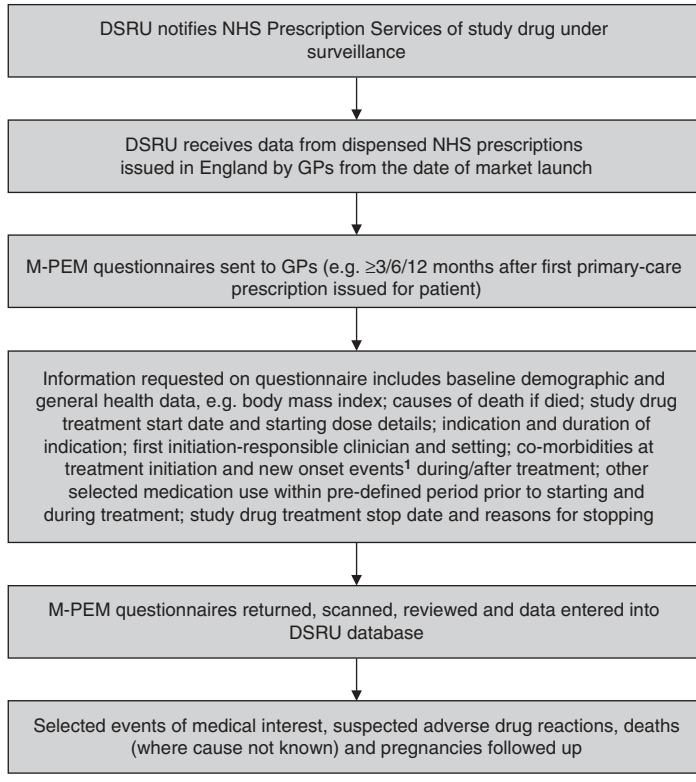

Fig. 1. Modified Prescription-Event Monitoring (M-PEM) study process. Patient confidentiality is maintained throughout (under Section 251 of the National Health Service Act 2006, the DSRU has received support from the Ethics and Confidentiality Committee of the National Information Governance Board to gain access to and process patient identifiable information without consent for the purposes of medical research [October 2009][9]). **DSRU** = Drug Safety Research Unit; **GPs** = general practitioners; **NHS** = National Health Service. **1** The term 'event', as used in this study, is defined as "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter into the patient's notes".

perform more detailed exploration of specific safety issues.

In M-PEM, the underlying process remains the same as in conventional PEM (figure 1). As described in the following subsections, this retains the strengths of the conventional method but also tries to overcome some of its limitations.

2.1 Early User and Incept Cohort Design

Prescription data collection for both PEM and M-PEM begins immediately after the new drug has been launched and covers the national population in England. Hence, patient cohorts can be accrued rapidly and provide the opportunity to detect safety issues as early as possible after market launch, a fundamental principle in pharmacovigilance. The cohort is also regarded as an inception cohort (where study drug is a new entity) or a new user cohort (e.g. where the drug under study might be a new formulation or new indication). Here, the observation period begins as soon as the patient starts the medication, which is particularly important if the risk of an event is higher in the early period after starting therapy. Some observational study designs have been criticized for the inclusion of patients who have been using the study drug for some time prior to the start of the observation period ('prevalent users') due to the risk of under-estimation of early-onset events.[10] An advantage of an inception cohort is that potential confounding

factors can be measured before treatment starts and adjusted for in subsequent statistical analysis. Unlike PEM, the M-PEM questionnaires can offer greater scope to collect this baseline data.

2.2 Generalizability

In PEM and M-PEM, all GPs who have prescribed the study drug are eligible for inclusion, thus the system samples from all GPs in England. This wide coverage aims to provide a cohort that is representative of not only the whole population of patients who are registered with an NHS GP in England but also patients who take the study drug in the early postmarketing period. The cohort, however, may be biased by phenomena such as 'channelling'[11] (preferential prescribing to subsets of patients defined by specific characteristics, such as having a condition that is resistant to previous therapy) or 'switching' (past experience with an alternative drug may modify the risk of adverse events associated with current use of the study drug).[12] These may affect the generalizability of the study results since the study cohort may not be fully representative of the target study population. In M-PEM, whilst prescribing patterns of a new drug cannot be predicted or controlled for, the issues of channelling or influence of previous therapy can be examined through careful data capture and provide a better understanding of the cohort characteristics and the population to whom the results may be applicable.

An important limitation of PEM is that only a proportion of questionnaires are returned. Non-response bias, a form of sampling bias, becomes important if the characteristics of the study cohort are different from those of the non-responders, especially if response itself is correlated in some way with one or more study variables. For example, there may be a 'depletion of susceptibles'[13] if GPs selectively respond for those patients who tolerate and continue to use the drug. The reverse is also possible whereby GPs may be more likely to respond if patients have experienced adverse events with a new medicine. The extent to which this affects the study results remains unknown since non-response bias is not easily measured. Furthermore, predicting a simple linear relationship between response rate and non-response bias is not straightforward.[14] GPs are offered a modest reimbursement to cover administrative costs in recognition of the increased time spent completing the more detailed M-PEM questionnaires. In M-PEM studies carried out to date where GPs receive this financial reimbursement, the median response rate has been 64%[1] compared with approximately 50% in 'standard' PEM studies.

2.3 Enhanced Data Quality

The M-PEM questionnaire, whilst retaining the ability to provide general safety surveillance by collecting simple data on *all* events, collects more detailed information on outcomes (including specific events that comply with pre-specified case definitions), drug exposure and other relevant disease risk factors at the start of treatment. This improved data accuracy and quality reduces the possibility of information bias through misclassification.

2.4 Increased Scope for Analysis and Hypothesis Testing

PEM is a simple, single-group cohort design where subjects have been assembled based on a common exposure (the particular medication under surveillance). Compared with the 'classic' cohort design with multiple exposure groups, it is more efficient in terms of resources, but the absence of data on an unexposed comparator can, in some cases, be a limitation. To attempt to address this, it is possible to undertake calculations of measures of effect (relative risks) for internal comparisons between subgroups defined by particular characteristics, or external comparisons to carefully selected data sources. In conventional PEM, the scope for this analysis is limited to crude estimates since information cannot be collected on all important confounding factors for all outcomes because of the nature of the simple questionnaire design balanced with no remuneration

1 Based on the first 'clinical' questionnaires sent, which, in some studies, is sent after an initial eligibility questionnaire has been used to identify eligible patients.

to respondents. In M-PEM, additional information is collected for all patients within the cohort regarding relevant co-morbidities and other potential confounding factors, which can, through statistical modelling techniques, provide adjusted measures of effect for selected outcomes.

The bespoke M-PEM questionnaire also offers greater scope for analysis within the cohort using self-controlled methodology that helps control for within-subject change in disease severity as well as reducing between-group differences. This approach includes comparisons of particular outcomes 'before and after' starting the study drug using a repeated measures matched pair analysis,[15] or using the self-controlled case-series analytical technique (SCCA)[16] to calculate effect measures for outcomes of interest. The 'before and after study' is particularly useful when monitoring the safety of a new formulation of an existing product. The SCCA is not applicable to all outcomes but it has advantages in that it requires time-varying co-variate data on cases only and not for the whole cohort and is thus efficient in terms of sample size and resources.

2.5 Sample Size

In conventional PEM studies, the sample size of 10 000 has been driven by PEM's original objective to bridge the gap between randomized controlled trials and spontaneous reporting regarding sensitivity to rare and uncommon events that can be achieved by including a larger sample size than pre-marketing studies. Based on the general 'rule of 3',[2] it follows that the larger the sample size, the rarer the event that can be detected.[17] Because of the customized nature of M-PEM studies, a specific sample size is calculated depending on the research question of interest. This is advantageous in terms of study conduct and limiting costs particularly when the projected usage of the product is low, but is at the expense of the sensitivity to detect signals for rarer outcomes.

3. Contribution of Modified PEM to Pharmacovigilance

In the EU, when a marketing authorization for a new medicine or a new indication, new formulation or use in a new population of an existing medicine is submitted for regulatory approval, a 'Risk Management Plan' with regards to the safety of the product is required.[18] This document outlines plans to enhance or further clarify the safety profile of the product by means of postmarketing pharmacovigilance methods. PEM is included within EU regulatory guidelines as a pharmacoepidemiological method that can be used in post-authorization safety studies.[18]

In contrast to alternative data sources, such as those primarily designed for medical insurance claims or prescription reimbursement, PEM is a bespoke research tool that combines both retrospective and prospective aspects in that previous history can be studied, as well as providing opportunities for following up subgroups of patients of interest in a prospective manner. Because of wide recruitment in PEM, the cohort size relates to the uptake of the new product (or new indication, formulation, etc.); thus, cohort accrual is likely to be faster and larger than in postmarketing clinical trials or existing longitudinal medical records databases that sample from a subset of the population. Furthermore, the study design is highly reactive, such that newly emerging safety issues can be investigated while a study is in progress.

M-PEM studies combine the advantages of conventional PEM studies (in monitoring general safety and identification of unexpected risks of a medicine) with that of a more targeted safety study that addresses specific questions (to better understand known or partially known risks with a medicine). A number of M-PEM studies have been completed and several are ongoing. The results of these studies have been published separately elsewhere or the studies are in process and

2 The rule for safety data is commonly referred to as the 'rule of 3'. In many situations involving rare reactions it is assumed that the frequency of the event is small, so that the occurrence of the event follows a Poisson distribution, and the 95% confidence interval is calculated based on the number of events. If no events are observed in a study of X individuals then one can be 95% certain that the event occurs no more often than $3/X$.

Table I. Examples of applications of Modified Prescription Event Monitoring methodology: completed studies

Drug (n)	Background	Data collection	Targeted population or event surveillance	Applications
Carvedilol (1666)[19]	UK licence extended to treat mild to moderate chronic heart failure subject to supervision of hospital specialist	Patient demographics, treatment initiation and supervision, dose titration, severity of heart failure, pre-treatment tests, past medical history, concomitant medication	Heart failure subgroup identified by initial eligibility questionnaire	Assessment of compliance with prescribing recommendations and clinical management guidelines post-licence extension
Flixotide™/Seretide™ Evohalers™ [Allen & Hanburys Ltd, Uxbridge, Middlesex, UK] (13 413/13 464)[20,21]	Regulatory requirement to monitor introduction of CFC-free inhalers in Europe	Patient demographics, severity of indication, use of oral corticosteroids, spacer devices and other respiratory treatments	Event rates compared for specific respiratory event rates (paradoxical bronchospasm) before and after starting CFC-free inhalers	Active surveillance post-formulation change from metered dose inhaler to CFC-free Evohalers™ Identification of off-label use in COPD
Travoprost eye drops (1441)[22]	Licence extension to first-line use in the treatment of ocular hypertension in open-angle glaucoma granted in 2003	Patient demographics, hospital initiation and specific questions on the occurrence of abnormal eyelash growth, abnormal eyelid hair growth, and iris or periocular skin discolouration	Eligibility questionnaire used to identify population of patients who started treatment post-licence extension Incidence of specific ocular events reported in pre-marketing trials assessed	Active surveillance post-licence extension Quantification and better understanding of specific events of interest
Modafinil [post-licence extension cohort] (1096)[23]	Licence extended to include the treatment of ''excessive sleepiness associated with chronic pathological conditions'', in 2004. Low projected use	Prescribing patterns, plus selected aspects of patient management in terms of contraception. Data also collected on risk factors for cardiovascular and psychiatric adverse events and serious skin reactions	Subcohort of users identified post-licence extension. Analyses further stratified by indication	Enhanced characterization of real-life drug use Active surveillance post-licence extension
Rimonabant (10 011)[24]	Anti-obesity drug launched in the UK in 2006 (product withdrawn from market during course of this study)	Patient demographic data, health status (BMI, weight, smoking), past medical and psychiatric history and specific questions on events of depression, anxiety, insomnia and seizures	Comparison of specific psychiatric event rates occurring in the 6 months prior to and after starting treatment	Assessment of risk of specific psychiatric/nervous system events of regulatory concern
Varenicline (12 159)[25]	Smoking cessation therapy. Regulatory concern over psychiatric events (suicidal ideation)	Demographic data, past and current smoking habit, past medical history, current morbidities and reason for stopping (if stopped)	Focused time-to-event analysis on pre-specified events of interest: myocardial infarction, depression, anxiety, aggression, suicidal ideation and non-fatal self-harm	Characterization of real-life drug use Hypothesis testing on pre-specified events of particular concern
Atomoxetine (5079)	Licensed for treatment of attention-deficit hyperactivity disorder. Regulatory concern over an increased risk of suicidal thinking[26]	Demographic data, prescribing patterns, targeted capture of data (both prior to and during usage) on psychiatric events, convulsions, abnormal liver function and selected cardiovascular events	Matched cohort analysis on events of interest	Hypothesis testing on pre-specified events of particular concern

BMI = body mass index; **CFC** = chlorofluorocarbon; **COPD** = chronic obstructive pulmonary disease.

Table II. Examples of applications of Modified Prescription Event Monitoring methodology: ongoing studies

Drug (target number for cohort)	Background	Data collection	Targeted population/event surveillance	Applications
Ivabradine (2500)	Licensed in the UK in 2006 for treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contraindication or intolerance for β-blockers[27]	Demographic data, information on treatment initiation, past medical history, current morbidities, contraindications for use, baseline and ongoing results of tests of heart rate and concomitant medications	Targeted data capture and analysis for selected ocular and cardiovascular events	Specific evaluation of use of ivabradine in relation to diseases/conditions that are contraindicated or where precaution is advised Quantification and characterization of specific ocular and cardiovascular events of interest observed in pre-marketing clinical trials
Fentanyl buccal tablets [Effentora;™ Cephalon (UK) Ltd, Welwyn Garden City, Hertfordshire, UK][28] (300)	Launched in the UK in January 2009, licensed for the management of breakthrough pain in patients with cancer already receiving and tolerant to opioid therapy	Data collected on demographics, initiation of therapy (setting and titration) and past opioid use. Specific questions to identify potential misuse or inappropriate/off-label use	Targeted capture of data (both prior to and during usage), including respiratory, renal and hepatic conditions and concomitant medication	Enhanced characterization of drug use and misuse Specific evaluation of use of medicine in relation to concomitant medication or diseases that are contraindicated or where precautions are advised
Quetiapine extended release [Seroquel XL®; AstraZeneca UK Ltd, Luton, Bedfordshire, UK][29] (10 000)	XL formulation licensed for the treatment of schizophrenia, manic episodes associated with bipolar disorder or as add-on therapy for major depressive disorder	Data collected on demographics, use of medication that may cause somnolence or EPS and other risk factors for these events	Nested matched case-control study to explore relationship between dose and events of somnolence and EPS Targeted data capture and analysis of pattern of events related to diabetes mellitus/metabolic syndrome over time	Hypothesis testing on pre-specified events of particular concern in risk management plan

EPS = extrapyramidal symptoms; **XL** = extended release.

hence are not repeated here; however, tables I and II provide an overview of the methods used to illustrate the potential applications of M-PEM in the context of pharmacovigilance and risk management.[19-25] These studies were designed to address specific research questions, including characterization of real-life drug use, adherence to prescribing recommendations or guidelines, and targeted surveillance or analysis of specific events, including those considered to require special monitoring by regulatory authorities. Through M-PEM it is possible to evaluate the safety of a medicine in particular subpopulations (e.g. patients prescribed the medicine by a hospital specialist or after switching from another therapy) or following important changes in the product's lifecycle (e.g. a licensing or formulation change).

4. Conclusions

PEM is a method of postmarketing surveillance of newly marketed drugs in the 'real-world' conditions of general medical practice. Through careful consideration of ongoing methodological enhancements in the field of pharmacoepidemiology, PEM studies have evolved such that some of the limitations associated with 'standard' PEM have been addressed. The revised M-PEM methodology offers opportunities for a number of additional research applications that can be used to generate signals of potential adverse drug reactions and to further evaluate safety concerns identified by other pharmacovigilance methods. In particular, M-PEM studies provide the opportunity to investigate specific regulatory concerns and should be considered a

valuable tool when developing a Risk Management Plan for the evaluation of the safety a new medicine.

Acknowledgements

The DSRU is a registered independent charity (no. 327206), which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or publication of the studies conducted by the DSRU. The DSRU has received unconditional support from the manufacturers of Flixotide™ and Seretide™ Evohalers™ (Allen & Hanbury), carvedilol (Roche), travoprost (Alcon), modafinil (Cephalon), atomoxetine (Lilly), rimonabant (Sanofi), ivabradine (Servier) and varenicline (Pfizer). In addition, Saad A.W. Shakir has received lecturing fees (and related travel expenses) from Lilly and has acted as an expert witness for an unrelated product manufactured by Sanofi. The authors would like to thank Dr Victoria Cornelius for statistical advice in the preparation of this manuscript.

References

1. Shakir SAW. Prescription-event monitoring. In: Mann RD, Andrews EB, editors. Pharmacovigilance. 2nd ed. Chichester: John Wiley & Sons Ltd, 2007: 307-16
2. Clark D, Harrison-Woolrych M. The role of the New Zealand Intensive Medicines Monitoring Programme in identification of previously unrecognised signals of adverse drug reactions. Curr Drug Saf 2006; 1 (2): 169-78
3. Kubota K. Prescription-event monitoring in Japan (J-PEM). Drug Saf 2002; 25 (6): 441-4
4. Dodoo AN, Fogg C, Asiimwe A, et al. Pattern of drug utilization for treatment of uncomplicated malaria in urban Ghana following national treatment policy change to artemisinin-combination therapy. Malaria J 2009; 8: 2
5. Boshier A, Wilton LV, Shakir SAW. Evaluation of the safety of sildenafil for male erectile dysfunction: experience gained in general practice use in England in 1999. BJU Int 2004; 93: 796-801
6. Hazell L, Cornelius V, Wilton L, et al. The safety profile of tadalafil as prescribed in general practice in England: results from a prescription-event monitoring study involving 16,129 patients. BJU International 2009; 103: 506-14
7. Pearce HM, Layton D, Wilton LV, et al. Deep vein thrombosis and pulmonary embolism reported in the prescription-event monitoring study of Yasmin®. Br J Clin Pharmacol 2005; 60 (1): 98-102
8. Layton D, Marshall V, Boshier A, et al. Serious skin reactions and selective COX-2 inhibitors: a case series from prescription-event monitoring in England. Drug Saf 2006; 29 (8): 687-96
9. The National Information Governance Board. Register of approved section 251 applications [online]. Available from URL: http://www.nigb.nhs.uk/ecc/reg. [Accessed 2010 Sep 3]
10. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003; 158 (9): 915-20
11. Leufkens HG, Urquhart J, Stricker BH, et al. Channelling of controlled release formulation of ketoprofen (Oscorel) in patients with history of gastrointestinal problems. J Epidemiol Community Health 1992 Aug; 46 (4): 428-32
12. Layton D, Souverein PC, Heerdink ER, et al. Evaluation of risk profiles for gastrointestinal and cardiovascular adverse effects in non-selective NSAID and COX-2 inhibitor users: a cohort study using pharmacy dispensing data in The Netherlands. Drug Saf 2008; 31 (2): 143-58
13. Moride Y, Abenhaim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. J Clin Epidemiol 1994; 47: 731-7
14. Groves RM, Peytcheva E. The impact of nonresponse rates on nonresponse bias: a meta-analysis. Public Opin Q 2008; 72: 167-89
15. Cummings P, McKnight B, Greenland S. Matched cohort methods for injury research. Epidemiol Rev 2003; 25: 43-50
16. Whitaker HJ, Hocine M, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res 2009; 18 (1): 7-26
17. Strom B. Sample size considerations for pharmacoepidemiology studies. In: Strom B, editor. Pharmacoepidemiology. 4th ed. Chichester: John Wiley & Sons Ltd, 2005: 29-36
18. European Commission. Volume 9A. Pharmacovigilance for medicinal products for human use. September 2008 [online]. Available from URL: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf [Accessed 2009 Apr 7]
19. Aurich-Barrera B, Wilton LV, Shakir SA. Use and risk management of carvedilol for the treatment of heart failure in the community in England: results from a modified prescription-event monitoring study. Drug Saf 2009; 32 (1): 43-54
20. Perrio M, Wilton LV, Shakir SAW. A modified prescription-event monitoring study to assess the introduction of flixotide Evohaler™ into general practice in England: an example of pharmacovigilance planning and risk monitoring. Pharmacoepidemiol Drug Saf 2007; 16: 969-78
21. Perrio M, Wilton LV, Shakir SAW. A modified prescription-event monitoring study to assess the introduction of seretide Evohaler™ in England: an example of studying risk monitoring in pharmacovigilance. Drug Saf 2007; 30 (8): 681-95
22. Davies MN, Paiba N, Wilton LV, et al. A 12-month modified prescription-event monitoring report for travoprost [abstract no. P.020]. 7th Annual Conference of ISOP. 2007 Oct 21-24; Bournemouth. Drug Saf 2007; 30 (10): 919-90
23. Davies MN, Wilton LV, Shakir SAW. Safety profile of modafinil used in general practice in England: a modified prescription-event monitoring study [abstract]. Drug Saf 2008; 31 (10): 892
24. Buggy Y, Cornelius V, Wilton L, et al. Risk of depressive episodes with rimonabant: a before and after modified prescription event monitoring study conducted in England. Drug Saf 2011; 34 (6): 501-9
25. Kasliwal R, Wilton LV, Shakir SA. Safety and drug utilization profile of varenicline as used in general practice in England: interim results from a prescription-event monitoring study. Drug Saf 2009; 32 (6): 499-507
26. Food and Drug Administration. FDA issues public health advisory on Strattera (atomoxetine) for attention deficit

disorder [online]. Available from URL: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108493.htm [Accessed 2011 Apr 17]

27. European Medicines Agency. Procoralan® (ivabradine). European public assessment report. London: European Medicines Agency, 2005
28. Cephalon Europe. Effentora® buccal tablets: summary of product characteristics. Cephalon, 2008 [online]. Available from URL: http://www.medicines.org.uk/emc/medicine/21401 [Accessed 2011 Sep 8]
29. Astra Zeneca UK. Seroquel XL® tablets: summary of product characteristics. AstraZeneca, 2008 [online]. Available from URL: http://www.medicines.org.uk/emc/medicine/21175 [Accessed 2011 Sep 8]

Correspondence: Professor *Saad Shakir*, Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton SO31 1AA, UK.
E-mail: saad.shakir@dsru.org

