British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 419–433 419

SYSTEMATIC REVIEW AND META-ANALYSIS

Measuring the impact of medicines regulatory interventions – Systematic review and methodological considerations

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Received 8 August 2017; **Revised** 24 October 2017; **Accepted** 31 October 2017

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Keywords analytic method, before–after study design, impact evaluation, interrupted time series, pharmacovigilance, real-world effectiveness, regulatory interventions

AIMS

Evaluating the public health impact of regulatory interventions is important but there is currently no common methodological approach to guide this evaluation. This systematic review provides a descriptive overview of the analytical methods for impact research.

METHODS

We searched MEDLINE and EMBASE for articles with an empirical analysis evaluating the impact of European Union or non-European Union regulatory actions to safeguard public health published until March 2017. References from systematic reviews and articles from other known sources were added. Regulatory interventions, data sources, outcomes of interest, methodology and key findings were extracted.

RESULTS

From 1246 screened articles, 229 were eligible for full-text review and 153 articles in English language were included in the descriptive analysis. Over a third of articles studied analgesics and antidepressants. Interventions most frequently evaluated are regulatory safety communications (28.8%), black box warnings (23.5%) and direct healthcare professional communications (10.5%); 55% of studies measured changes in drug utilization patterns, 27% evaluated health outcomes, and 18% targeted knowledge, behaviour or changes in clinical practice. Unintended consequences like switching therapies or spill-over effects were rarely evaluated. Two-thirds used before–after time series and 15.7% before–after cross-sectional study designs. Various analytical approaches were applied including interrupted time series regression (31.4%), simple descriptive analysis (28.8%) and descriptive analysis with significance tests (23.5%).

CONCLUSION

Whilst impact evaluation of pharmacovigilance and product-specific regulatory interventions is increasing, the marked heterogeneity in study conduct and reporting highlights the need for scientific guidance to ensure robust methodologies are applied and systematic dissemination of results occurs.

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DOI:10.1111/bcp.13469

Introduction

Prescribing medicines is the most common health intervention globally and the safe use of medicines is paramount to public health. An estimated 3.5% of hospitalizations in Europe are caused by adverse drug reactions (ADRs), and up to 10% of hospitalized patients experience an ADR during their hospital stay [1].

To minimize the risks from medicines, pharmacovigilance systems have been established to continuously monitor their safety. These regulatory systems are designed to detect changes in the benefit–risk balance of a medicine which only become apparent during routine clinical use. Once safety signals have been evaluated and confirmed, appropriate regulatory action is taken to minimise the risks, such as labelling change, restriction, contraindication or withdrawal of a product or class of products.

Pharmacovigilance activities include monitoring of the effectiveness of risk minimization measures. The European Union (EU) pharmacovigilance legislation aimed to strengthen these activities and was found to lead to faster changes to product labelling and the conclusion of safety referrals [2]. However, despite the potential for large global public health consequences, there is limited evidence about the effectiveness and consequences of regulatory actions at the population level, particularly relating to public health outcomes. To address this knowledge gap, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) adopted in 2016 a strategy [3] aiming to assess whether pharmacovigilance activities achieve their intended objectives and to identify areas where performance could be enhanced [4].

To achieve their desired effect, regulatory interventions are expected to lead to changes in knowledge, attitudes and healthcare practices of individuals (i.e. patients, consumers and healthcare professionals) and organisations. However, the possibility of unintended consequences remains if measures are not properly implemented, which may give raise to criticism.

Measuring the impact of pharmacovigilance interventions is challenging as treatment and disease outcomes often overlap, and there may be significant time lags until clinical effects are seen with many existing studies being ecological in nature. It can also be difficult to evaluate decisions relating to single products if use is low and potential clinical outcomes are rare or when multiple interventions occur simultaneously. Nearly 50 years after the creation of the first national programmes for pharmacovigilance [5] there are no established guidelines for measuring the impact of regulatory interventions on public health [6–8].

Studies evaluating the effectiveness of risk minimization interventions often rely on surrogate measures such as changes in behaviour or prescribing rather than actual health outcomes [9]. For example, measuring drug usage in population-based electronic health records as a surrogate for changes in morbidity or mortality was one of various methods recommended at an international workshop exploring methodologies for measuring the impact of pharmacovigilance activities [10]. Heterogeneity in study design and method of analysis also mean that proper interpretation and comparisons between regulatory systems are difficult.

We performed a systematic review of studies measuring the impact of pharmacovigilance regulatory interventions worldwide to highlight their methodological challenges and inform the conduct and reporting of future studies.

Methods

Literature screening

A protocol for a systematic search strategy was constructed *a priori* to identify articles evaluating the impact of regulatory interventions on healthcare utilisation, health knowledge and behaviour, or health outcomes. The search was performed in MEDLINE and EMBASE using Medical Subject Heading (MeSH) terms and keywords related to impact research in pharmacovigilance, regulatory policy, health outcome research, risk assessment, effectiveness of risk minimisation, health behaviour and health outcomes. The database search was supplemented with hand searching of references from systematic reviews, including articles and other known in-house sources (*snowballing*). The protocol is available in the public European Union electronic Register of Post-Authorisation Studies (EU PAS Register®)[1] under study number EUPAS21337.

Study selection

Eligible articles were initially screened by title and abstract by one of three reviewers with experience in regulatory science and pharmacoepidemiology (T.G., D.M., A.P.; (Figure 1). In a second stage, the eligibility of articles was independently evaluated after full text review and, where disagreement was present, discussions between the three reviewers were held to reach consensus.

Inclusion and exclusion criteria

Articles in English language published up to 31 March 2017 evaluating regulatory interventions for medicines for human use were included. Duplicates, abstracts, letters to editors, commentaries and articles analysing the impact of health policy changes and studies investigating the impact of pharmacovigilance processes were excluded. We defined a regulatory intervention as any regulatory action taken by an EU or non-EU competent authority to safeguard public health in relation to the use of medicinal products, including label changes, risk communication to the public or healthcare providers, product-specific additional risk minimization measures defined in Good Pharmacovigilance Practices module XVI [11], withdrawal or suspension of a marketing authorization.

Data extraction and analysis

A standardized data extraction form was applied to obtain the following information: publication title, year, regulatory intervention and date/period, data source, study design, country, analytical method, outcome measure and drug therapeutic class (anatomical therapeutic chemical code). In addition, key findings, conclusions and any limitations of

[1]http://www.encepp.eu/encepp_studies/indexRegister.shtml.

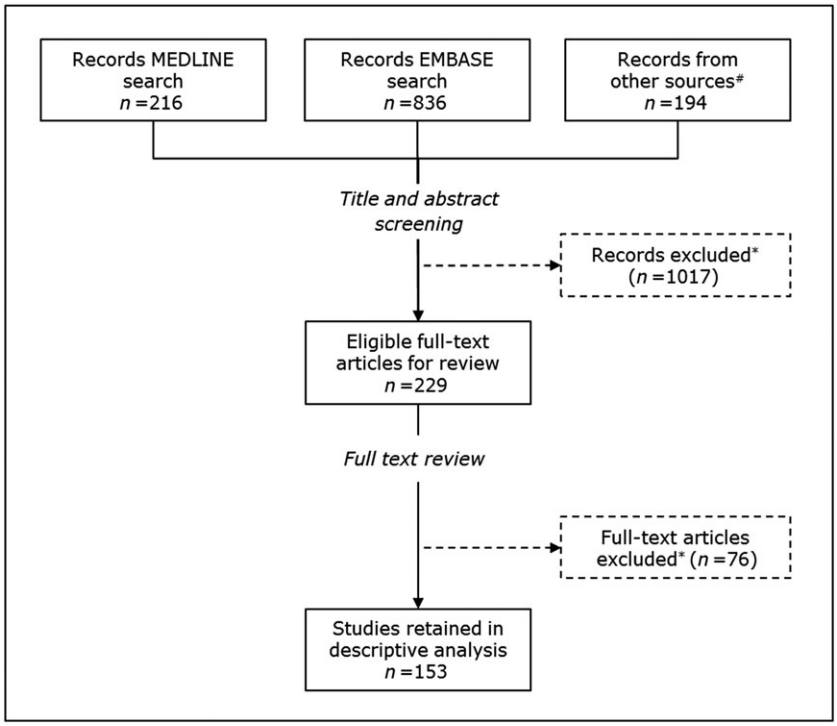

Figure 1

Literature search and systematic review strategy. #Known literature and relevant references of published systematic reviews were included. *Duplicates, abstracts, letters to editors, commentaries and articles analysing the impact of other interventions (i.e. process and health policy related) were excluded

the studies were captured to support the review process. Data extraction was performed separately by each reviewer.

To synthesize information on the methodology for impact measurement of the studies identified, we categorized studies into one of the following mutually exclusive groups based on study design and analytical approach: *before–after time series* (defined as an evaluation at three or more time points crossing the date of the regulatory intervention); *before–after cross-sectional study* (defined as an evaluation at one point in time before and after the date of the regulatory intervention); *single time point cross-sectional study* (defined by a single time point after the date of the regulatory intervention); *cohort study*; and *randomized controlled trial*.

Categorization of included variables

For descriptive purposes we defined seven categories of regulatory interventions: direct healthcare professional communication (DHPC), black box warning, product information update, regulatory safety communication (e.g. guideline update, public health advisory communication, safety communication on websites), other additional risk minimization measures (e.g. medication guide, pregnancy prevention programme, controlled distribution), product suspension/withdrawal, and others (e.g. change in legal status, pack-size restriction).

Analytical approaches for each study design were categorized as follows: descriptive analysis (with or without statistical significance tests), regression-based approaches as described in the literature including Poisson and logistic regression [12], interrupted time series (ITS) regression [13], Joinpoint regression [14], and others.

Outcome measures were categorized into three groups: i) drug utilization; ii) health outcomes; and iii) knowledge, behaviour and clinical practice. A descriptive analysis of included studies was undertaken based on the extracted study information.

Results

The systematic review identified 1246 articles of which 229 were eligible for full-text review, and 153 articles met the inclusion criteria and were retained in the descriptive analysis (Figure 1).

Overview of studies

Out of 153 studies included in our analysis, 70 (45.8%) assessed the impact of regulatory interventions in the USA, 69 (45.0%) in Europe and 14 (9.2%) in the rest of the world. Analgesics and antidepressants were the most common therapeutic classes, each being evaluated in 27 (17.6%) studies, followed by blood glucose lowering drugs with 14 (9.2%), antipsychotics with 13 (8.5%), and retinoids for systemic use with 12 (7.8%) studies (Table 1). The most frequently evaluated single regulatory interventions related to the risk associated with paracetamol poisoning and overdose, the risk of suicide in children and adolescents treated with selective

Table 1

Proportion of impact research articles (n = 153) by anatomical therapeutic chemical (ATC) classes and geographic regions (left). The right side shows the evaluated regulatory intervention(s)

		Regulatory intervention evaluated						
ATC class and region	**Articles *n* (%)**	**DHPC**	**Black box warning**	**Product information update**	**Regulatory safety communication**	**Additional risk minimisation**	**Suspension/ withdrawal**	**Other[e]**
Analgesics	**27 (17.6)**	**1**	-	**1**	**4**	**3**	**4**	**18**
Europe	24 (15.7)	-	-	1	3	2	4	18
USA	3 (2.0)	1	-	-	1	1	-	-
Rest of the World	-	-	-	-	-	-	-	-
Antidepressants	**27 (17.6)**	**1**	**17**	**7**	**22**	**2**	-	-
Europe	8 (5.2)	1		3	6	-	-	-
USA	15 (9.8)	-	14	3	13	1	-	-
Rest of the World	4 (2.6)	-	3	1	3	1	-	-
Blood glucose lowering drugs[a]	**14 (9.2)**	**4**	**5**	**8**	**7**	-	**2**	-
Europe	5 (3.3)	2	-	4	3		2	
USA	8 (5.2)	2	5	3	3	-	-	-
Rest of the World	1 (0.7)	-	-	1	1	-	-	-
Antipsychotics	**13 (8.5)**	**3**	**5**	**3**	**7**	-	-	-
Europe	5 (3.3)	-	-	1	5	-	-	-
USA	7 (4.6)	2	5	2	1	-	-	-
Rest of the World	1 (0.7)	1	-	-	1	-	-	-
Retinoids for systemic use	**12 (7.8)**	-	-	**1**	-	**11**	-	**1**
Europe	7 (4.6)	-	-	1	-	6	-	1
USA	3 (2.0)	-	-	-	-	3	-	-
Rest of the World	2 (1.3)	-	-	-	-	2	-	-
Hormonal contraceptives	**5 (3.3)**	-	**3**	-	**2**	-	-	-
Europe	2 (1.3)	-	-	-	2	-	-	-
USA	3 (2.0)	-	3	-	-	-	-	-
Rest of the World	-	-	-	-	-	-	-	-
NSAIDs	**5 (3.3)**	-	-	**2**	**4**	**1**	**3**	-
Europe	5 (3.3)	-	-	2	4	1	3	-
USA	-	-	-	-	-	-	-	-
Rest of the World	-	-	-	-	-	-	-	-
Propulsives[b]	**5 (3.3)**	**4**	**1**	**3**	-	**1**	-	-
Europe	-	-	-	-	-	-	-	-
USA	5 (3.3)	4	1	3	-	1	-	-
Rest of the World	-	-	-	-	-	-	-	-
Antihistamines	**4 (2.6)**	**2**	**4**	-	-	-	-	-
Europe	-	-	-	-	-	-	-	-
USA	4 (2.6)	2	4	-	-	-	-	-
Rest of the World	-	-	-	-	-	-	-	-

(*continues*)

Table 1
(Continued)

ATC class and region	Articles *n* (%)	Regulatory intervention evaluated						
		DHPC	Black box warning	Product information update	Regulatory safety communication	Additional risk minimisation	Suspension/ withdrawal	Other[e]
Cough and cold preparations	**4 (2.6)**	-	-	**2**	**2**	-	**2**	-
Europe	-	-	-	-	-	-	-	-
USA	4 (2.6)	-	-	2	2	-	2	-
Rest of the World	-	-	-	-	-	-	-	-
Hormone replacement therapy	**4 (2.6)**	-	-	**1**	**4**	-	-	-
Europe	4 (2.6)	-	-	1	4	-	-	-
USA	-	-	-	-	-	-	-	-
Rest of the World	-	-	-	-	-	-	-	-
Antiasthmatics	**3 (2.0)**	**1**	**1**	**3**	**2**	**1**	-	-
Europe	-	-	-	-	-	-	-	-
USA	3 (2.0)	1	1	3	2	1		-
Rest of the World	-	-	-	-	-	-	-	-
Psychostimulants[c]	**3 (2.0)**	-	**3**	**2**	**2**	**1**	-	-
Europe	-	-	-	-	-	-	-	-
USA	3 (2.0)	-	3	2	2	1	-	-
Rest of the World	-	-	-	-	-	-	-	-
Other drugs[d]	**27 (17.6)**	**6**	**5**	**7**	**12**	**6**	-	**1**
Europe	9 (5.9)	3	-	1	7	2	-	-
USA	12 (7.8)	1	5	2	4	2	-	1
Rest of the World	6 (3.9)	2	-	4	1	2	-	-
Total	**153 (100)**	**22**	**44**	**40**	**68**	**26**	**11**	**20**

[a]Thiazolidinediones
[b]Cisapride
[c]Agents used for attention deficit hyperactivity disorder (ADHD)
[d]Therapeutic classes with less than three studies identified were grouped together.
[e]Other regulatory interventions include studies evaluating the impact of paracetamol pack size restrictions, the impact of a healthcare reminder system for patient monitoring, the impact of advice on the clinical management of drug poisoning and compliance with national guidelines for isotretinoin.
DHPC, Direct healthcare professional communication; NSAID, nonsteroidal anti-inflammatory drug

serotonin reuptake inhibitors (SSRIs) and the cardiovascular risks with thiazolidinediones.

The most commonly evaluated regulatory interventions included regulatory safety communications (28.8%) and black box warnings (23.5%, USA only). A quarter of studies evaluated DHPCs (10.5%) and other additional risk minimization measures (15.7%), including pregnancy prevention programmes. About 13% of studies evaluated the impact of pack-size restrictions. Product withdrawals and individual product information updates were least frequently assessed (7.2% and 1.3% respectively). Seventy-three studies (47.7%) evaluated the impact of a single regulatory intervention, whereas 80 studies (52.3%) looked at the impact of multiple interventions occurring simultaneously or over time.

Studied outcomes

Eighty-four studies (54.9%) measured drug utilization patterns and only 42 studies (27.5%) evaluated health outcomes such as morbidity (e.g. reduction of disease or adverse reaction incidence), mortality (e.g. reduction in suicide rates), pregnancy related outcomes or changes in laboratory values as surrogate measure for health improvements as shown in Table 2. Among studies which evaluated health outcomes, a positive impact of the regulatory intervention was reported in 27 (64%) studies whereas 12 (29%) studies showed no or negligible effects and in three (7%) studies the results were inconclusive.

Twenty-seven (17.6%) studies evaluated changes in patients' or healthcare professionals' knowledge and behaviour, or changes in clinical practice targeted by the regulatory

Table 2

Distribution of outcome measures evaluated in regulatory impact research (n = 153 articles)

Outcome measure	Articles n (%)	References
Drug utilization	**84 (54.9)**	
Health outcomes	**42 (27.5)**	
Mortality	20 (13.1)	
-Drug poisoning/overdose	12 (7.8)	[15–26]
-Suicide and self-harm	7 (4.6)	[27–33]
-Other	1 (0.7)	[34]
Hospitalization[a]	9 (5.9)	[35–43]
Risk incidence[b]	6 (3.9)	[44–49]
Pregnancy related outcomes[c]	3 (2.0)	[50–52]
Adverse drug reaction(s) reporting	2 (1.3)	[53, 54]
Laboratory tests[d]	2 (1.3)	[55, 56]
Knowledge, behaviour or clinical practice	**27 (17.6)**	

[a]Hospital admission due to myocardial infarction, cancer, hip fracture, drug poisoning or overdose, pulmonary embolism, drug-induced liver injury, child unsupervised ingestion;
[b]Venous thromboembolism; breast cancer; opioid abuse, addiction or overdose; stroke; osteonecrosis of the jaw; depression;
[c]Unplanned pregnancy, spontaneous or medically induced abortion, birth defect;
[d]Serum glucose and lipid testing; change in mean HbA1c and fasting plasma glucose levels;

intervention. Only a small number of studies examined unintended consequences of regulatory interventions such as switching of therapies or spill-over effects (e.g. decrease of drug use in subpopulations not targeted by the regulatory action).

Study design, methodology and data sources

Over 80% of studies used a before–after design with 101 (66.0%) before–after time series analyses and 24 (15.7%) before–after cross-sectional studies (Table 3). There was only one randomized controlled trial identified designed to evaluate the impact of interventions, and six cohort studies. Seven different analytical approaches were identified. The most commonly used analytical approach was ITS regression in 48 (31.4%) studies, with simple descriptive analysis in 44 (28.8%) and descriptive analysis with statistical significance tests in 36 (23.5%) studies as shown in Table 3.

Administrative claims databases and electronic health records databases were the main data sources used to measure impact (Figure 2). Among the research conducted in the USA, claims databases dominated the picture, being used in 26.1% of studies whereas, in Europe, claims databases and electronic healthcare records were used in similar proportions (13.7% and 15%). Other types of data sources relevant for impact research were questionnaires, medical charts, national registers (e.g. on birth, mortality, poisoning), national surveillance systems (e.g. USA Sentinel), national patient safety incident reporting systems or electronic prescribing systems. Figure 3 shows how study designs and analytical methods evolved over time with a significant trend of increasing use of ITS regression analysis (P = 0.003).

Discussion

Our systematic review aimed to describe studies measuring the impact of regulatory interventions with a focus on study designs, analytical methods, data sources and choice of outcome measures. We found a marked heterogeneity in published studies of regulatory interventions with variation by region, study design, analytical approach and main outcomes evaluated.

The published studies evaluated regulatory interventions in Europe and the USA in similar proportions, and both regions together accounted for the majority of the global literature in English language, potentially affecting the generalizability of results to other populations. This is also the case for studies conducted in the EU where the organization of healthcare systems varies markedly between countries and may affect results of impact research. An element of this variation may be the availability of large electronic data sources in some countries only where impact studies are feasible.

Although the number of identified studies was relatively large, the range of therapeutic classes subject to impact research was limited with several studies evaluating the same regulatory intervention (e.g. suicidality with SSRIs in paediatric patients, mortality risk of dementia patients treated with antipsychotics, cardiovascular risks with thiazolidinediones, mortality associated with paracetamol poisoning and overdose; Table 3). The latter is an early example of impact research evaluating the effects of legislation which reduced the maximum pack size of paracetamol containing medicines in the UK in 1998. Despite an apparent decrease in paracetamol-associated mortality rates and hospital admissions, the public health impact of these observed changes remained unclear. The decline in mortality and hospital admissions had begun before the legislation and the variety of outcome measures and analytical approaches used made it difficult to determine whether the legislation has been a success [168].

Some articles focused on regulatory actions suggesting uncertain effects in several countries or that require adjustments in their implementation, as shown for isotretinoin pregnancy prevention programmes in Europe [169]. It is unclear why only certain regulatory interventions have been evaluated. The choice of regulatory interventions evaluated might be driven by the higher public health importance (e.g. unintended pregnancy with teratogenic medicines), by the feasibility of studies using available data sources (e.g. availability of pharmacy dispensed prescribing data versus chemotherapy or biological agents) and by funding opportunities. To help assess the need for such studies, the PRAC has developed criteria for prioritizing impact research in areas where there is a need to generate additional data to monitor the impact of regulatory interventions, which are based on

Table 3

Overview of study designs and analytical approaches of the final list of articles (n = 153)

Design and analytical method	Articles *n* (%)	References
Before/after time series	**101 (66.0)**	
Descriptive analysis only	21 (13.7)	[17, 24, 26, 49, 54, 55, 57–71]
Descriptive statistics with significance test	12 (7.8)	[19, 23, 50, 53, 72–79]
Interrupted time series regression	48 (31.4)	[22, 29–31, 38, 44, 56, 80–120]
Joinpoint regression	9 (5.9)	[28, 37, 39, 121–126]
Poisson regression	5 (3.3)	[18, 27, 32, 34, 46]
Logistic regression	3 (2.0)	[48, 127, 128]
Other	3 (2.0)	[21, 129, 130]
Before/after cross-sectional study	**24 (15.7)**	
Descriptive analysis only	4 (2.6)	[41, 42, 45, 131]
Descriptive statistics with significance test	18 (11.8)	[15, 16, 25, 33, 35, 36, 40, 43, 47, 132–140]
Poisson regression	1 (0.7)	[20]
Logistic regression	1 (0.7)	[141]
Single time point cross-sectional study	**21 (13.7)**	
Descriptive analysis only	16 (10.5)	[142–157]
Descriptive statistics with significance test	4 (2.6)	[158–161]
Other	1 (0.7)	[162]
Cohort study	**6 (3.9)**	
Descriptive analysis only	3 (2.0)	[52, 163, 164]
Descriptive statistics with significance test	2 (1.3)	[51, 165]
Other	1 (0.7)	[166]
Randomized controlled trial	**1 (0.7)**	
Logistic regression	1 (0.7)	[167]

three pillars: the public health importance of the regulatory action; the potential impact on clinical practice; and whether the study will deliver decision relevant data [170].

The vast majority of studies included in our review were drug utilization studies and relatively few evaluated clinical outcomes. Whilst drug utilization provides proxy measures of impact, it is uncertain whether the changes in drug use translate into discernible clinical or public health benefits. In this regard, the actual consequences of changes in drug usage are often unknown or unintended consequences may occur. For example, research conducted in the USA and the Netherlands showed a decrease in SSRI prescriptions for children and adolescents after US and European warnings in 2003 about a suicide risk with antidepressant use in this age group. However, this decrease in use seemed to be associated with an unintended increase in suicide rates in children and adolescents due to untreated patients [27]. In the same context, time-series analyses of antidepressant prescribing in adults showed statistically and clinically significant spill-over effects associated with the 2003 Food and Drug Administration public health advisory on antidepressant use in paediatric patients [44]. In addition, the impact of pharmacovigilance on health outcomes is often more difficult to measure due to a lack of adequate data sources and the difficulty of proving a causal association between the observed changes and the regulatory intervention, particularly at product level.

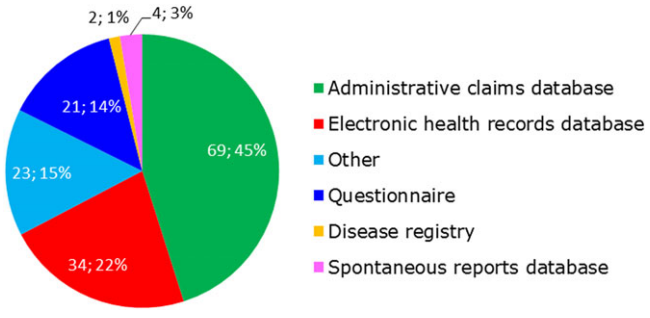

Figure 2

Types of data sources used for regulatory impact research (n = 153 articles)

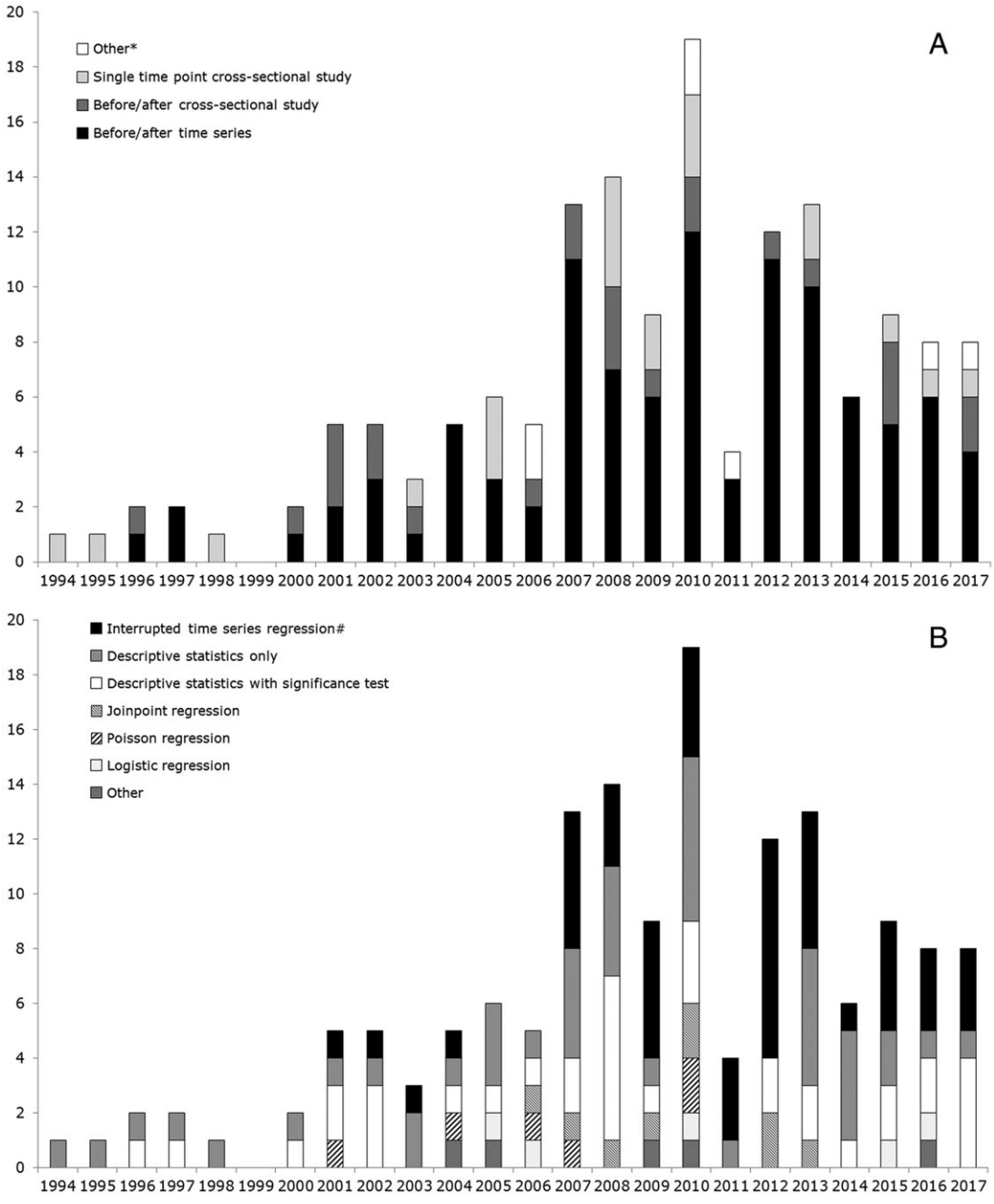

Figure 3

Distribution of study designs (A) and analytical methods (B) in impact research over time ($n = 153$). *Includes randomized clinical trials and cohort studies. #$P = 0.003$ using chi-squared test for trend

The choice of study design and analytical approach varied. Guidelines describing the optimal study design and analytical approaches for evaluating the impact of pharmacovigilance are lacking. Whilst each situation may differ, studies estimating the net attributable impact of regulatory interventions require considering the target drug, clinical outcomes and the potential for switching therapies and unintended consequences. Few studies considered possible unintended consequences, such as the effect in groups not targeted by the intervention through age or disease risk, or measuring therapeutic alternatives that may be used as substitutes [131, 133].

Uncontrolled before–after cross-sectional studies were used in 15.7% of studies and evaluated periods of time immediately before and after a regulatory intervention most commonly applying simple descriptive statistics (such as *t* test or chi-squared test) to determine if changes were significant. Although this design requires less data collection, preintervention trends are ignored potentially leading to overestimate the effect of the intervention. Such tests also

assume that data points are independent, which is often an incorrect assumption.

Before-after time series was the most widely used study design to measure the impact of regulatory interventions. However, only 65 (42.5%) studies used statistical regression-based approaches to determine significance. Although studies without regression modelling may be suitable for large immediate changes (e.g. product withdrawals) they risk producing spurious results when assessment is more subjective. ITS regression is a robust quasiexperimental design to evaluate longitudinal effects of time-delimited interventions. Segmented regression analysis of interrupted time series data can be used to quantify the immediate change in outcome following an intervention, and changes in trend [171]. However, ITS regression requires the date of the regulatory intervention to be prespecified, which can be difficult to define, particularly when implementation varies, and that autocorrelation is assessed. Furthermore, adequate power to conduct ITS regression requires sufficient data points as with all time series approaches, and changes may be influenced by other interventions occurring during the same time frame (e.g. media coverage). However, in most instances, these data were not fully reported.

In contrast, Joinpoint regression models plot trend lines at points where changes in prescribing or the incidence of an outcome have occurred. A potential advantage of such models is that the intervention date does not need to be prespecified, offering potential advantages if the implementation date varies or is unknown. All time series approaches measure associations rather than causation and due to the ecological nature of the study design are even more challenging to be applied to public health outcomes.

Approximately a third of the studies employed descriptive statistics providing only weak evidence to support a causal association, which in many cases will be considered inadequate.

Limitations

Not all impact research may have been published in scientific journals and a vast majority of studies is communicated within regulatory procedures but seldom published. Unpublished research was not captured by our search strategy and therefore not included in the review. There is also a risk of publication bias, reflected by the higher percentage of published articles that reported positive outcomes. Some articles might have been missed due to a lack of common definitions and consistent terminology to describe such studies. A previous review of the use of ITS methods in drug utilization research showed a large variation in the reporting of analytical methods [172], confirming our findings and the need for standardized reporting. Therefore, our search strategy was supplemented with references from published review articles and known in-house literature. Although different study designs and analytical methods are described, there has been no assessment of the risk of bias and of the quality, which requires further review. The challenge of evaluating multiple coinciding interventions remains to be addressed and the effectiveness of individual regulatory measures may not be discernible other than by interventional study designs.

Conclusion

Despite their potential global impact, the effects of pharmacovigilance regulatory interventions remain largely unquantified. A collaborative effort is required among regulators, health technology assessment bodies, academia and industry to help define measurable public health outcomes including intended and unintended consequences of regulatory decisions at the population level. Guidelines on the reporting of such studies and research to establish the best methods to evaluate such interventions are required. Results of impact research should be systematically disseminated to increase knowledge on the effectiveness of regulatory interventions. The EU PAS Register®, a publicly accessible platform for observational post-authorization research, could be used for this purpose.

Competing Interests

There are no competing interests to declare.

The authors thank Carla Alonso Olmo and Oscar Francos at the European Medicines Agency for the administrative support and help with reviewing the literature.

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

References

1 Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug Saf 2015; 38: 437–53.

2 Arlett P, Portier G, de Lisa R, Blake K, Wathion N, Dogne JM, *et al*. Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance risk assessment committee. Nat Rev Drug Discov 2014; 13: 395–7.

3 Pharmacovigilance Risk Assessment Committee. PRAC strategy on measuring the impact of pharmacovigilance activities (Rev 1) (EMA/165407/2017). 2017. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/01/WC500199756.pdf (last accessed 28 July 2017).

4 Coglianese C. Measuring regulatory performance. Evaluating the impact of regulation and policy. Organisation for Economic Co-operation and Development (OECD). Expert Paper No. 1; August 2012. Available from: http://www.oecd.org/gov/regulatory-policy/1_coglianese%20web.pdf (last accessed 28 July 2017).

5 Laporte JR. Fifty years of pharmacovigilance - medicines safety and public health. Pharmacoepidemiol Drug Saf 2016; 25: 725–32.

6 Briesacher BA, Soumerai SB, Zhang F, Toh S, Andrade SE, Wagner JL, *et al*. A critical review of methods to evaluate the impact of FDA regulatory actions. Pharmacoepidemiol Drug Saf 2013; 22: 986–94.

7 Kesselheim AS, Campbell EG, Schneeweiss S, Rausch P, Lappin BM, Zhou EH, *et al*. Methodological approaches to evaluate the impact of FDA drug safety communications. Drug Saf 2015; 38: 565–75.

8 Dusetzina SB, Higashi AS, Dorsey ER, Conti R, Huskamp HA, Zhu S, *et al*. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. Med Care 2012; 50: 466–78.

9 Gridchyna I, Cloutier AM, Nkeng L, Craig C, Frise S, Moride Y. Methodological gaps in the assessment of risk minimization interventions: a systematic review. Pharmacoepidemiol Drug Saf 2014; 23: 572–9.

10 European Medicines Agency. Inspections, Human Medicines Pharmacovigilance and Committees Division. Workshop report: measuring the impact of pharmacovigilance activities (EMA/59474/2017). 2017. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/03/WC500224106.pdf (last accessed 28 July 2017).

11 European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) module XVI – risk minimisation measures: selection of tools and effectiveness indicators (rev 2) (EMA/204715/2012). 2017. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf (last accessed 28 July 2017).

12 Simonoff SCJS. Handbook of Regression Analysis. Hoboken, NJ, USA: John Wiley & Sons, Inc., 2012.

13 Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol 2017; 46: 348–55.

14 Czajkowski M, Gill RS, Rempala G. Model selection in logistic Joinpoint regression with applications to analyzing cohort mortality patterns. Stat Med 2008; 27: 1508–26.

15 Flood C, Matthew L, Marsh R, Patel B, Mansaray M, Lamont T. Reducing risk of overdose with midazolam injection in adults: an evaluation of change in clinical practice to improve patient safety in England. J Eval Clin Pract 2015; 21: 57–66.

16 Sandilands EA, Bateman DN. Co-proxamol withdrawal has reduced suicide from drugs in Scotland. Br J Clin Pharmacol 2008; 66: 290–3.

17 Handley SA, Flanagan RJ. Drugs and other chemicals involved in fatal poisoning in England and Wales during 2000-2011. Clin Toxicol 2014; 52: 1–12.

18 Bateman DN, Gorman DR, Bain M, Inglis JH, House FR, Murphy D. Legislation restricting paracetamol sales and patterns of self-harm and death from paracetamol-containing preparations in Scotland. Br J Clin Pharmacol 2006; 62: 573–81.

19 Gorman DR, Bain M, Inglis JH, Murphy D, Bateman DN. How has legislation restricting paracetamol pack size affected patterns of deprivation related inequalities in self-harm in Scotland? Public Health 2007; 121: 45–50.

20 Hawton K, Townsend E, Deeks J, Appleby L, Gunnell D, Bennewith O, *et al*. Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study. BMJ 2001; 322: 1203–7.

21 Morgan O, Griffiths C, Majeed A. Impact of paracetamol pack size restrictions on poisoning from paracetamol in England and Wales: an observational study. J Public Health (Oxf) 2005; 27: 19–24.

22 Morgan OW, Griffiths C, Majeed A. Interrupted time-series analysis of regulations to reduce paracetamol (acetaminophen) poisoning. PLoS Med 2007; 4: e105.

23 Sheen CL, Dillon JF, Bateman DN, Simpson KJ, MacDonald TM. Paracetamol-related deaths in Scotland, 1994-2000. Br J Clin Pharmacol 2002; 54: 430–2.

24 Morgan O, Hawkins L, Edwards N, Dargan P. Paracetamol (acetaminophen) pack size restrictions and poisoning severity: time trends in enquiries to a UK poisons centre. J Clin Pharm Ther 2007; 32: 449–55.

25 Hawton K. United Kingdom legislation on pack sizes of analgesics: background, rationale, and effects on suicide and deliberate self-harm. Suicide Life Threat Behav 2002; 32: 223–9.

26 Inglis JH. Restricting sales of paracetamol tablets: effect on deaths and emergency admissions for poisoning in Scotland 1991-2002. Scott Med J 2004; 49: 142–3.

27 Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, *et al*. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007; 164: 1356–63.

28 Wheeler BW, Gunnell D, Metcalfe C, Stephens P, Martin RM. The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study. BMJ 2008; 336: 542–5.

29 Hawton K, Bergen H, Simkin S, Brock A, Griffiths C, Romeri E, *et al*. Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis. BMJ 2009; 338: b2270.

30 Hawton K, Bergen H, Simkin S, Dodd S, Pocock P, Bernal W, *et al*. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. BMJ 2013; 346 (feb07 1): f403.

31 Gunnell D, Hawton K, Bennewith O, Cooper J, Simkin S, Donovan J, *et al*. Programme Grants for Applied Research. A multicentre programme of clinical and public health research in support of the National Suicide Prevention Strategy for England. NIHR Journals Library: Southampton (UK), 2013.

32 Hawton K, Simkin S, Deeks J, Cooper J, Johnston A, Waters K, *et al*. UK legislation on analgesic packs: before and after study of long term effect on poisonings. BMJ 2004; 329: 1076–0.

33 Donohoe E, Walsh N, Tracey JA. Pack-size legislation reduces severity of paracetamol overdoses in Ireland. Ir J Med Sci 2006; 175: 40–2.

34 Metcalfe C, Wheeler BW, Gunnell D, Martin RM. International regulatory activity restricting COX-2 inhibitor use and deaths due to gastrointestinal haemorrhage and myocardial infarction. Pharmacoepidemiol Drug Saf 2010; 19: 778–85.

35 Hampton LM, Nguyen DB, Edwards JR, Budnitz DS. Cough and cold medication adverse events after market withdrawal and labeling revision. Pediatrics 2013; 132: 1047–54.

36 Shehab N, Schaefer MK, Kegler SR, Budnitz DS. Adverse events from cough and cold medications after a market withdrawal of products labeled for infants. Pediatrics 2010; 126: 1100–7.

37 Martin RM, Wheeler BW, Metcalfe C, Gunnell D. What was the immediate impact on population health of the recent fall in hormone replacement therapy prescribing in England? Ecological study. J Public Health (Oxf) 2010; 32: 555–64.

38 Narayan H, Thomas SH, Eddleston M, Dear JW, Sandilands E, Bateman DN. Disproportionate effect on child admissions of the change in medicines and healthcare products regulatory agency guidance for management of paracetamol poisoning: an analysis of hospital admissions for paracetamol overdose in England and Scotland. Br J Clin Pharmacol 2015; 80: 1458–63.

39 Wheeler BW, Metcalfe C, Gunnell D, Stephens P, Martin RM. Population impact of regulatory activity restricting prescribing of COX-2 inhibitors: ecological study. Br J Clin Pharmacol 2009; 68: 752–64.

40 Tricotel A, Collin C, Zureik M. Impact of the sharp changes in the use of contraception in 2013 on the risk of pulmonary embolism in France. J Thromb Haemost 2015; 13: 1576–80.

41 Hughes B, Durran A, Langford NJ, Mutimer D. Paracetamol poisoning – impact of pack size restrictions. J Clin Pharm Ther 2003; 28: 307–10.

42 Laffoy M, Scallan E, Byrne G. Paracetamol availability and overdose in Ireland. Ir Med J 2001; 94: 212–4.

43 Newsome PN, Bathgate AJ, Henderson NC, MacGilchrist AJ, Plevris JN, Masterton G, *et al*. Referral patterns and social deprivation in paracetamol-induced liver injury in Scotland. Lancet 2001; 358: 1612–3.

44 Valuck RJ, Libby AM, Orton HD, Morrato EH, Allen R, Baldessarini RJ. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry 2007; 164: 1198–205.

45 Farmer RD, Williams TJ, Simpson EL, Nightingale AL. Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of general practice research database. BMJ 2000; 321: 477–9.

46 Sharpe KH, McClements P, Clark DI, Collins J, Springbett A, Brewster DH. Reduced risk of oestrogen receptor positive breast cancer among peri- and post-menopausal women in Scotland following a striking decrease in use of hormone replacement therapy. Eur J Cancer 2010; 46: 937–43.

47 Cepeda MS, Coplan PM, Kopper NW, Maziere JY, Wedin GP, Wallace LE. ER/LA opioid analgesics REMS: overview of ongoing assessments of its progress and its impact on health outcomes. Pain Med 2017; 18: 78–85.

48 Hollingsworth K, Romney MC, Crawford A, McAna J. The impact of the risk evaluation mitigation strategy for erythropoiesis-stimulating agents on their use and the incidence of stroke in Medicare subjects with chemotherapy-induced anemia with lung and/or breast cancers. Popul Health Manag 2016; 19: 63–9.

49 Sumi E, Yamazaki T, Tanaka S, Yamamoto K, Nakayama T, Bessho K, *et al*. The increase in prescriptions of bisphosphonates and the incidence proportion of osteonecrosis of the jaw after risk communication activities in Japan: a hospital-based cohort study. Pharmacoepidemiol Drug Saf 2014; 23: 398–405.

50 Wood R, Botting B, Dunnell K. Trends in conceptions before and after the 1995 pill scare. Popul Trends 1997; 89: 5–12.

51 Henry D, Dormuth C, Winquist B, Carney G, Bugden S, Teare G, *et al*. Occurrence of pregnancy and pregnancy outcomes during isotretinoin therapy. CMAJ. 2016; 188: 723–30.

52 Schaefer C, Meister R, Weber-Schoendorfer C. Isotretinoin exposure and pregnancy outcome: an observational study of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy. Arch Gynecol Obstet 2010; 281: 221–7.

53 Garg V, Raisch DW, McKoy JM, Trifilio SM, Holbrook J, Edwards BJ, *et al*. Impact of United States Food and Drug Administration's boxed warnings on adverse drug reactions reporting rates and risk mitigation for multiple myeloma drugs. Expert Opin Drug Saf 2013; 12: 299–307.

54 Chol C, Guy C, Jacquet A, Castot-Villepelet A, Kreft-Jais C, Cambazard F, *et al*. Complications of BCG vaccine SSI(R) recent story and risk management plan: the French experience. Pharmacoepidemiol Drug Saf 2013; 22: 359–64.

55 Ehrenstein V, Hernandez RK, Ulrichsen SP, Rungby J, Lash TL, Riis AH, *et al*. Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010. BMJ Open 2013; 3: e003424.

56 Morrato EH, Druss B, Hartung DM, Valuck RJ, Allen R, Campagna E, *et al*. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. Arch Gen Psychiatry 2010; 67: 17–24.

57 Bowen ME, Ray WA, Arbogast PG, Ding H, Cooper WO. Increasing exposure to angiotensin-converting enzyme inhibitors in pregnancy. Am J Obstet Gynecol 2008; 198: 291. e1–5.

58 Burkhart GA, Sevka MJ, Temple R, Honig PK. Temporal decline in filling prescriptions for terfenadine closely in time with those for either ketoconazole or erythromycin. Clin Pharmacol Ther 1997; 61: 93–6.

59 Carlson AM, Morris LS. Coprescription of terfenadine and erythromycin or ketaconazole: an assessment of potential harm. J Am Pharm Assoc (Wash) 1996; NS36: 263–9.

60 Forrester MB. Selective serotonin re-uptake inhibitor warnings and trends in exposures reported to poison control centres in Texas. Public Health 2008; 122: 1356–62.

61 Gleason PP, Walters C, Heaton AH, Schafer JA. Telithromycin: the perils of hasty adoption and persistence of off-label prescribing. J Manag Care Pharm 2007; 13: 420–5.

62 Hanatani T, Sai K, Tohkin M, Segawa K, Antoku Y, Nakashima N, *et al*. Evaluation of two Japanese regulatory actions using medical information databases: a 'Dear Doctor' letter to restrict oseltamivir use in teenagers, and label change caution against co-administration of omeprazole with clopidogrel. J Clin Pharm Ther 2014; 39: 361–7.

63 Hassanin H, Harbi A, Saif A, Davis J, Easa D, Harrigan R. Changes in antidepressant medications prescribing trends in children and adolescents in Hawai'i following the FDA black box warning. Hawaii Med J 2010; 69: 17–9.

64 Shah ND, Montori VM, Krumholz HM, Tu K, Alexander GC, Jackevicius CA. Responding to an FDA warning – geographic variation in the use of rosiglitazone. N Engl J Med 2010; 363: 2081–4.

65 Thomson A, Meeraus WH, Wong J, Suvarna R. Monitoring and evaluating the effect of regulatory action. Ther Innov Regul Sci 2015; 49: 473–82.

66 Tuchscherer RM, Nair K, Ghushchyan V, Saseen JJ. Simvastatin prescribing patterns before and after FDA dosing restrictions: a retrospective analysis of a large healthcare claims database. Am J Cardiovasc Drugs 2015; 15: 27–34.

67 Watson J, Wise L, Green J. Prescribing of hormone therapy for menopause, tibolone, and bisphosphonates in women in the UK between 1991 and 2005. Eur J Clin Pharmacol 2007; 63: 843–9.

68 Bushnell GA, Sturmer T, Swanson SA, White A, Azrael D, Pate V, *et al*. Dosing of selective serotonin reuptake inhibitors among children and adults before and after the FDA black-box warning. Psychiatr Serv 2016; 67: 302–9.

69 Teichert M, Visser LE, Dufour M, Rodenburg E, Straus SM, De Smet PA, *et al*. Isotretinoin use and compliance with the Dutch pregnancy prevention Programme: a retrospective cohort study

in females of reproductive age using pharmacy dispensing data. Drug Saf 2010; 33: 315–26.

70 Sheen CL, Dillon JF, Bateman DN, Simpson KJ, MacDonald TM. Paracetamol pack size restriction: the impact on paracetamol poisoning and the over-the-counter supply of paracetamol, aspirin and ibuprofen. Pharmacoepidemiol Drug Saf 2002; 11: 329–31.

71 DiSantostefano RL, Yeakey AM, Raphiou I, Stempel DA. An evaluation of asthma medication utilization for risk evaluation and mitigation strategies (REMS) in the United States: 2005-2011. J Asthma 2013; 50: 776–82.

72 Cluxton RJ Jr, Li Z, Heaton PC, Weiss SR, Zuckerman IH, Moomaw CJ, *et al*. Impact of regulatory labeling for troglitazone and rosiglitazone on hepatic enzyme monitoring compliance: findings from the state of Ohio medicaid program. Pharmacoepidemiol Drug Saf 2005; 14: 1–9.

73 Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess MJ. Liver enzyme monitoring in patients treated with troglitazone. JAMA 2001; 286: 831–3.

74 Schachtele S, Tumena T, Gassmann KG, Fromm MF, Maas R. Implementation of warnings from dear doctor letters (rote-hand-Briefe): an analysis of medication data from a large cohort of elderly patients. Dtsch Arztebl Int 2014; 111: 255–63.

75 Smalley W, Shatin D, Wysowski DK, Gurwitz J, Andrade SE, Goodman M, *et al*. Contraindicated use of cisapride: impact of food and drug administration regulatory action. JAMA 2000; 284: 3036–9.

76 Wilkinson JJ, Force RW, Cady PS. Impact of safety warnings on drug utilization: marketplace life span of cisapride and troglitazone. Pharmacotherapy 2004; 24: 978–86.

77 Katz LY, Kozyrskyj AL, Prior HJ, Enns MW, Cox BJ, Sareen J. Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults. CMAJ. 2008; 178: 1005–11.

78 Eworuke E, Popat V, Moeny DG. Bone mineral density testing, and bisphosphonate and oestrogen prescribing associated with depot medroxyprogesterone acetate utilization-the impact of the boxed warning. J Clin Pharm Ther 2017; 42: 483–94.

79 Crijns HJ, van Rein N, Gispen-de Wied CC, Straus SM, de Jong-van den Berg LT. Prescriptive contraceptive use among isotretinoin users in the Netherlands in comparison with non-users: a drug utilisation study. Pharmacoepidemiol Drug Saf 2012; 21: 1060–6.

80 Dorsey ER, Rabbani A, Gallagher SA, Conti RM, Alexander GC. Impact of FDA black box advisory on antipsychotic medication use. Arch Intern Med 2010; 170: 96–103.

81 Guo JJ, Curkendall S, Jones JK, Fife D, Goehring E, She D. Impact of cisapride label changes on codispensing of contraindicated medications. Pharmacoepidemiol Drug Saf 2003; 12: 295–301.

82 Herdeiro MT, Soares S, Silva T, Roque F, Figueiras A. Impact of rosiglitazone safety alerts on oral antidiabetic sales trends: a countrywide study in Portugal. Fundam Clin Pharmacol 2016; 30: 440–9.

83 Kurian BT, Ray WA, Arbogast PG, Fuchs DC, Dudley JA, Cooper WO. Effect of regulatory warnings on antidepressant prescribing for children and adolescents. Arch Pediatr Adolesc Med 2007; 161: 690–6.

84 Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am J Psychiatry 2007; 164: 884–91.

85 Libby AM, Orton HD, Valuck RJ. Persisting decline in depression treatment after FDA warnings. Arch Gen Psychiatry 2009; 66: 633–9.

86 Morrato EH, Libby AM, Orton HD, Degruy FV 3rd, Brent DA, Allen R, *et al*. Frequency of provider contact after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry 2008; 165: 42–50.

87 Olfson M, Marcus SC, Druss BG. Effects of Food and Drug Administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry 2008; 65: 94–101.

88 Pamer CA, Hammad TA, Wu YT, Kaplan S, Rochester G, Governale L, *et al*. Changes in US antidepressant and antipsychotic prescription patterns during a period of FDA actions. Pharmacoepidemiol Drug Saf 2010; 19: 158–74.

89 Piening S, Haaijer-Ruskamp FM, de Vries JT, van der Elst ME, de Graeff PA, Straus SM, *et al*. Impact of safety-related regulatory action on clinical practice: a systematic review. Drug Saf 2012; 35: 373–85.

90 Stewart KA, Natzke BM, Williams T, Granger E, Casscells SW, Croghan TW. Temporal trends in anti-diabetes drug use in TRICARE following safety warnings in 2007 about rosiglitazone. Pharmacoepidemiol Drug Saf 2009; 18: 1048–52.

91 Valluri S, Zito JM, Safer DJ, Zuckerman IH, Mullins CD, Korelitz JJ. Impact of the 2004 Food and Drug Administration pediatric suicidality warning on antidepressant and psychotherapy treatment for new-onset depression. Med Care 2010; 48: 947–54.

92 Weatherby LB, Walker AM, Fife D, Vervaet P, Klausner MA. Contraindicated medications dispensed with cisapride: temporal trends in relation to the sending of 'Dear Doctor' letters. Pharmacoepidemiol Drug Saf 2001; 10: 211–8.

93 Weatherby LB, Nordstrom BL, Fife D, Walker AM. The impact of wording in "dear doctor" letters and in black box labels. Clin Pharmacol Ther 2002; 72: 735–42.

94 Nyeland ME, Laursen MV, Callreus T. Evaluating the effectiveness of risk minimisation measures: the application of a conceptual framework to Danish real-world dabigatran data. Pharmacoepidemiol Drug Saf 2017; 26: 607–14.

95 Bergen H, Hawton K, Murphy E, Cooper J, Kapur N, Stalker C, *et al*. Trends in prescribing and self-poisoning in relation to UK regulatory authority warnings against use of SSRI antidepressants in under-18-year-olds. Br J Clin Pharmacol 2009; 68: 618–29.

96 Breen CL, Degenhardt LJ, Bruno RB, Roxburgh AD, Jenkinson R. The effects of restricting publicly subsidised temazepam capsules on benzodiazepine use among injecting drug users in Australia. Med J Aust 2004; 181: 300–4.

97 Carracedo-Martinez E, Pia-Morandeira A, Figueiras A. Impact of a health safety warning and prior authorisation on the use of piroxicam: a time-series study. Pharmacoepidemiol Drug Saf 2012; 21: 281–4.

98 Deslandes PN, Jenkins KS, Haines KE, Hutchings S, Cannings-John R, Lewis TL, *et al*. A change in the trend in dosulepin usage following the introduction of a prescribing indicator but not after two national safety warnings. J Clin Pharm Ther 2016; 41: 224–8.

99 Du DT, Zhou EH, Goldsmith J, Nardinelli C, Hammad TA. Atomoxetine use during a period of FDA actions. Med Care 2012; 50: 987–92.

100 Guthrie B, Clark SA, Reynish EL, McCowan C, Morales DR. Differential impact of two risk communications on antipsychotic prescribing to people with dementia in Scotland: segmented regression time series analysis 2001-2011. PLoS One. 2013; 8: e68976.

101 Hawton K, Bergen H, Simkin S, Wells C, Kapur N, Gunnell D. Six-year follow-up of impact of co-proxamol withdrawal in England and Wales on prescribing and deaths: time-series study. PLoS Med 2012; 9: e1001213.

102 Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJ, Belitser SV, Warmerdam J, de Valk V, *et al*. A 10-year analysis of the effects of media coverage of regulatory warnings on antidepressant use in The Netherlands and UK. PLoS One 2012; 7: e45515.

103 Kales HC, Zivin K, Kim HM, Valenstein M, Chiang C, Ignacio RV, *et al*. Trends in antipsychotic use in dementia 1999-2007. Arch Gen Psychiatry 2011; 68: 190–7.

104 Kornfield R, Watson S, Higashi AS, Conti RM, Dusetzina SB, Garfield CF, *et al*. Effects of FDA advisories on the pharmacologic treatment of ADHD, 2004-2008. Psychiatr Serv 2013; 64: 339–46.

105 Kurdyak PA, Juurlink DN, Mamdani MM. The effect of antidepressant warnings on prescribing trends in Ontario. Canada Am J Public Health 2007; 97: 750–4.

106 McIlroy G, Thomas SK, Coleman JJ. Second-generation antipsychotic drug use in hospital inpatients with dementia: the impact of a safety warning on rates of prescribing. J Public Health (Oxf) 2015; 37: 346–52.

107 Musleh S, Kraus S, Bennett K, Zaharan NL. Irish medicines board safety warnings: do they affect prescribing rates in primary care? Pharmacoepidemiol Drug Saf 2011; 20: 979–86.

108 Ooba N, Yamaguchi T, Kubota K. The impact in Japan of regulatory action on prescribing of dopamine receptor agonists: analysis of a claims database between 2005 and 2008. Drug Saf 2011; 34: 329–38.

109 Ruiter R, Visser LE, van Herk-Sukel MP, Geelhoed-Duijvestijn PH, de Bie S, Straus SM, *et al*. Prescribing of rosiglitazone and pioglitazone following safety signals: analysis of trends in dispensing patterns in the Netherlands from 1998 to 2008. Drug Saf 2012; 35: 471–80.

110 Sanfelix-Gimeno G, Cervera-Casino P, Peiro S, Lopez-Valcarcel BG, Blazquez A, Barbera T. Effectiveness of safety warnings in atypical antipsychotic drugs: an interrupted time-series analysis in Spain. Drug Saf 2009; 32: 1075–87.

111 Thomas SK, Hodson J, McIlroy G, Dhami A, Coleman JJ. The impact of direct healthcare professional communication on prescribing practice in the UK hospital setting: an interrupted time series analysis. Drug Saf 2013; 36: 557–64.

112 Valiyeva E, Herrmann N, Rochon PA, Gill SS, Anderson GM. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis. CMAJ 2008; 179: 438–46.

113 Valkhoff VE, van Soest EM, Masclee GM, de Bie S, Mazzaglia G, Molokhia M, *et al*. Prescription of nonselective NSAIDs, coxibs and gastroprotective agents in the era of rofecoxib withdrawal – a 617,400-patient study. Aliment Pharmacol Ther 2012; 36: 790–9.

114 Barber C, Gagnon D, Fonda J, Cho K, Hermos J, Miller M. Assessing the impact of prescribing directives on opioid prescribing practices among veterans health administration providers. Pharmacoepidemiol Drug Saf 2017; 26: 40–6.

115 Hsu JC, Ross-Degnan D, Wagner AK, Zhang F, Lu CY. How did multiple FDA actions affect the utilization and reimbursed costs of thiazolidinediones in US Medicaid? Clin Ther 2015; 37: 1420–32.e1.

116 Lu CY, Zhang F, Lakoma MD, Butler MG, Fung V, Larkin EK, *et al*. Asthma treatments and mental health visits after a Food and Drug Administration label change for leukotriene inhibitors. Clin Ther 2015; 37: 1280–91.

117 Mittal M, Harrison DL, Miller MJ, Farmer KC, Thompson DM, Ng YT. Have antiepileptic drug prescription claims changed following the FDA suicidality warning? An evaluation in a state Medicaid program. Epilepsy Behav 2014; 34: 109–15.

118 Eworuke E, Lee JY, Soule L, Popat V, Moeny DG. The impact of the boxed warning on the duration of use for depot medroxprogesterone acetate. Pharmacoepidemiol Drug Saf 2017; 26: 827–36.

119 Kruik-Kollöffel WJ, van der Palen J, Kruik HJ, van Herk-Sukel MPP, Movig KLL. Prescription behavior for gastroprotective drugs in new users as a result of communications regarding clopidogrel–proton pump inhibitor interaction. Pharmacol Res Perspect 2016; 4: e00242.

120 Kimura T, Shiosakai K, Takeda Y, Takahashi S, Kobayashi M, Sakaguchi M. Quantitative evaluation of compliance with recommendation for sulfonylurea dose co-administered with DPP-4 inhibitors in Japan. Pharmaceutics 2012; 4: 479–93.

121 Bedson J, Belcher J, Martino OI, Ndlovu M, Rathod T, Walters K, *et al*. The effectiveness of national guidance in changing analgesic prescribing in primary care from 2002 to 2009: an observational database study. Eur J Pain 2013; 17: 434–43.

122 Cohen A, Rabbani A, Shah N, Alexander GC. Changes in glitazone use among office-based physicians in the U.S., 2003–2009. Diabetes Care 2010; 33: 823–5.

123 Nemeroff CB, Kalali A, Keller MB, Charney DS, Lenderts SE, Cascade EF, *et al*. Impact of publicity concerning pediatric suicidality data on physician practice patterns in the United States. Arch Gen Psychiatry 2007; 64: 466–72.

124 Acheampong P, Cooper G, Khazaeli B, Lupton DJ, White S, May MT, *et al*. Effects of MHRA drug safety advice on time trends in prescribing volume and indices of clinical toxicity for quinine. Br J Clin Pharmacol 2013; 76: 973–9.

125 Wijlaars LP, Nazareth I, Petersen I. Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in the health improvement network (THIN). PLoS One. 2012; 7: e33181.

126 Martin RM, May M, Gunnell D. Did intense adverse media publicity impact on prescribing of paroxetine and the notification of suspected adverse drug reactions? Analysis of routine databases, 2001-2004. Br J Clin Pharmacol 2006; 61: 224–8.

127 Busch SH, Frank RG, Leslie DL, Martin A, Rosenheck RA, Martin EG, *et al*. Antidepressants and suicide risk: how did specific information in FDA safety warnings affect treatment patterns? Psychiatr Serv 2010; 61: 11–6. https://doi.org/10.1176/ps.2010.61.1.11.

128 Shatin D, Gardner JS, Stergachis A, Blough D, Graham D. Impact of mailed warning to prescribers on the co-prescription of tramadol and antidepressants. Pharmacoepidemiol Drug Saf 2005; 14: 149–54. https://doi.org/10.1002/pds.961.

129 Sultana J, Fontana A, Giorgianni F, Pasqua A, Cricelli C, Spina E, *et al*. The effect of safety warnings on antipsychotic drug

prescribing in elderly persons with dementia in the United Kingdom and Italy: a population-based study. CNS Drugs 2016; 30: 1097–109.

130 Wright NM, Roberts AJ, Allgar VL, Tompkins CN, Greenwood DC, Laurence G. Impact of the CSM advice on thioridazine on general practitioner prescribing behaviour in Leeds: time series analysis. Br J Gen Pract 2004; 54: 370–3.

131 Wax D, Doshi A, Hossain S, Bodian CA, Krol M, Reich DL. Changing patterns of postoperative nausea and vomiting prophylaxis drug use in an academic anesthesia practice. J Clin Anesth 2007; 19: 356–9.

132 Leal I, Romio SA, Schuemie M, Oteri A, Sturkenboom M, Trifiro G. Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone. Br J Clin Pharmacol 2013; 75: 861–8.

133 Kessler T, Harrison D, Hagemann T. Promethazine prescribing patterns in pediatric inpatients younger than two years before and after the product black box warning. Hosp Pharm 2010; 45: 389–92.

134 Singh T, Prakash A, Rais T, Kumari N. Decreased use of antidepressants in youth after US Food and Drug Administration black box warning. Psychiatry (Edgmont) 2009; 6: 30–4.

135 Starner CI, Schafer JA, Heaton AH, Gleason PP. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. J Manag Care Pharm 2008; 14: 523–31.

136 Stockl KM, Le L, Harada AS, Zhang S. Use of controller medications in patients initiated on a long-acting beta2-adrenergic agonist before and after safety alerts. Am J Health Syst Pharm 2008; 65: 1533–8.

137 Thompson D, Oster G. Use of terfenadine and contraindicated drugs. JAMA 1996; 275: 1339–41.

138 Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A study of compliance with FDA recommendations for pemoline (Cylert). J Am Acad Child Adolesc Psychiatry 2002; 41: 785–90.

139 Guzman JZ, Merrill RK, Kim JS, Overley SC, Dowdell JE, Somani S, *et al*. Bone morphogenetic protein use in spine surgery in the United States: how have we responded to the warnings? Spine J 2017; 17: 1247–54.

140 Leclerc-Foucras S, Bagheri H, Samii K, Montastruc JL, Lapeyre-Mestre M. Modifications of low-molecular weight heparin use in a French university hospital after implementation of new guidelines. Drug Saf 2007; 30: 409–17.

141 Hagiwara H, Nakano S, Ogawa Y, Tohkin M. The effectiveness of risk communication regarding drug safety information: a nationwide survey by the Japanese public health insurance claims data. J Clin Pharm Ther 2015; 40: 273–8.

142 Bhatia SK, Rezac AJ, Vitiello B, Sitorius MA, Buehler BA, Kratochvil CJ. Antidepressant prescribing practices for the treatment of children and adolescents. J Child Adolesc Psychopharmacol 2008; 18: 70–80.

143 Brinker A, Kornegay C, Nourjah P. Trends in adherence to a revised risk management program designed to decrease or eliminate isotretinoin-exposed pregnancies: evaluation of the accutane SMART program. Arch Dermatol 2005; 141: 563–9.

144 Ceilley R, Eisenthal A. The unintended effects of a boxed warning. J Clin Aesthet Dermatol 2009; 2: 33–9.

145 Orrico KB, Lin JK, Wei A, Yue H. Clinical consequences of disseminating the rosiglitazone FDA safety warning. Am J Manag Care 2010; 16: e111–6.

146 Richards JR, Weiss SJ, Bretz SW, Schneir AB, Rinetti D, Derlet RW. The effects of the FDA warning on the use of droperidol by U.S. emergency physicians. Cal J Emerg Med 2003; 4: 3–9.

147 Castaneda CP, Zeldis JB, Freeman J, Quigley C, Brandenburg NA, Bwire R. RevAssist®: a comprehensive risk minimization programme for preventing fetal exposure to lenalidomide. Drug Saf 2008; 31: 743–52.

148 Einarson A, Schachtschneider AMK, Halil R, Bollano E, Koren G. SSRI'S and other antidepressant use during pregnancy and potential neonatal adverse effects: impact of a public health advisory and subsequent reports in the news media. BMC Pregnancy Childbirth 2005; 5: 11.

149 Crijns I, Mantel-Teeuwisse A, Bloemberg R, Pinas E, Straus S, de Jong-van den Berg L. Healthcare professional surveys to investigate the implementation of the isotretinoin pregnancy prevention programme: a descriptive study. Expert Opin Drug Saf 2013; 12: 29–38.

150 Exton LS, Cheung ST, Brain AG, Mohd Mustapa MF, de Berker DA. Compliance with national guidelines on isotretinoin: where are we 2 years since the last audit? Results of the National Isotretinoin re-Audit 2014. Clin Exp Dermatol 2017; 42: 381–9.

151 Mitchell AA, Van Bennekom CM, Louik C. A pregnancy-prevention program in women of childbearing age receiving isotretinoin. N Engl J Med 1995; 333: 101–6.

152 Pastuszak A, Koren G, Rieder MJ. Use of the retinoid pregnancy prevention program in Canada: patterns of contraception use in women treated with isotretinoin and etretinate. Reprod Toxicol 1994; 8: 63–8.

153 Robertson J, Polifka JE, Avner M, Chambers C, Delevan G, Koren G, *et al*. A survey of pregnant women using isotretinoin. Birth Defects Res A Clin Mol Teratol 2005; 73: 881–7.

154 Holmes SC, Bankowska U, Mackie RM. The prescription of isotretinoin to women: is every precaution taken? Br J Dermatol 1998; 138: 450–5.

155 Arana A, Allen S, Burkowitz J, Fantoni V, Ghatnekar O, Rico MT, *et al*. Infliximab paediatric Crohn's disease educational plan: a European, cross-sectional, multicentre evaluation. Drug Saf 2010; 33: 489–501.

156 Enger C, Younus M, Petronis KR, Mo J, Gately R, Seeger JD. The effectiveness of varenicline medication guide for conveying safety information to patients: a REMS assessment survey. Pharmacoepidemiol Drug Saf 2013; 22: 705–15.

157 Ishihara L, Beck M, Travis S, Akintayo O, Brickel N. Physician and pharmacist understanding of the risk of urinary retention with Retigabine (Ezogabine): a REMS assessment survey. Drugs Real World Outcomes 2015; 2: 335–44.

158 Garbutt JM, Sterkel R, Banister C, Walbert C, Strunk RC. Physician and parent response to the FDA advisory about use of over-the-counter cough and cold medications. Acad Pediatr 2010; 10: 64–9.

159 Habib AS, Gan TJ. The use of droperidol before and after the Food and Drug Administration black box warning: a survey of the members of the Society of Ambulatory Anesthesia. J Clin Anesth 2008; 20: 35–9.

160 Paschall S, Kaunitz AM. Depo-Provera and skeletal health: a survey of Florida obstetrics and gynecologist physicians. Contraception 2008; 78: 370–6.

161 Bester N, Di Vito-Smith M, McGarry T, Riffkin M, Kaehler S, Pilot R, *et al*. The effectiveness of an educational brochure as a risk minimization activity to communicate important rare adverse events to health-care professionals. Adv Ther 2016; 33: 167–77.

162 Lokker N, Sanders L, Perrin EM, Kumar D, Finkle J, Franco V, *et al*. Parental misinterpretations of over-the-counter pediatric cough and cold medication labels. Pediatrics 2009; 123: 1464–71.

163 EU-ADR Alliance. Monitoring the effectiveness of risk minimisation in patients treated with pioglitazone-containing products. Final report on the study results for service contract EMA/2011/38/CN PIOGLITAZONE. 2013. Available at http://www.encepp.eu/encepp/openAttachment/studyResultLatest/16136;jsessionid=1gJWG5gnW4kfaJeLV-7MwTmMSxl1UHVVNRxx_0VFxLOPo8HDGV4A!1888174422 (last accessed 28 July 2017).

164 Greene SL, Dargan PI, Leman P, Jones AL. Paracetamol availability and recent changes in paracetamol poisoning: is the 1998 legislation limiting availability of paracetamol being followed? Postgrad Med J 2006; 82: 520–3.

165 Zomerdijk IM, Ruiter R, Houweling LM, Herings RM, Sturkenboom MC, Straus SM, *et al*. Isotretinoin exposure during pregnancy: a population-based study in The Netherlands. BMJ Open 2014; 4: e005602.

166 Morrato EH, Nicol GE, Maahs D, Druss BG, Hartung DM, Valuck RJ, *et al*. Metabolic screening in children receiving antipsychotic drug treatment. Arch Pediatr Adolesc Med 2010; 164: 344–51.

167 Feldstein AC, Smith DH, Perrin N, Yang X, Rix M, Raebel MA, *et al*. Improved therapeutic monitoring with several interventions: a randomized trial. Arch Intern Med 2006; 166: 1848–54.

168 Hawkins LC, Edwards JN, Dargan PI. Impact of restricting paracetamol pack sizes on paracetamol poisoning in the United Kingdom: a review of the literature. Drug Saf 2007; 30: 465–79.

169 Crijns HJ, Straus SM, Gispen-de Wied C, de Jong-van den Berg LT. Compliance with pregnancy prevention programmes of isotretinoin in Europe: a systematic review. Br J Dermatol 2011; 164: 238–44.

170 Pharmacovigilance Risk Assessment Committee. Checklist for prioritisation of EU regulatory network collaborative impact research (EMA/318043/2017). 2017. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/06/WC500229968.pdf (last accessed 28 July 2017).

171 Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002; 27: 299–309.

172 Jandoc R, Burden AM, Mamdani M, Levesque LE, Cadarette SM. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. J Clin Epidemiol 2015; 68: 950–6.