SYSTEMATIC REVIEW

Drug Saf 2012; 35 (7): 535-546
0114-5916/12/0007-0535/$49.95/0

Impact of Regulatory Guidances and Drug Regulation on Risk Minimization Interventions in Drug Safety

A Systematic Review

Lenhangmbong Nkeng,[1,2] *Anne-Marie Cloutier*,[1,2] *Camille Craig*,[1,2] *Jacques Lelorier*[2] and *Yola Moride*[1,2]

1 Faculty of Pharmacy, Université de Montréal, Montreal, QC, Canada
2 Research Center, University of Montreal Hospital Center (CRCHUM), Montreal, QC, Canada

Abstract

Background: Therapeutic risk management has received growing interest in recent years, particularly since the publication of regulatory guidances in 2005 and 2006, paralleled with a change in drug regulation. The characteristics of risk minimization interventions (RMIs) that have been implemented or approved remain inadequately explored.

Objective: The aim of this study was to review RMIs published in the literature or posted on regulatory agency websites over the past 10 years, and to assess whether publication of regulatory guidances on risk management is associated with changes in the number and types of interventions.

Methods: Sources were searched for RMIs published/posted between 1 January 2000 and 31 December 2009. For the literature search, MEDLINE and EMBASE databases were used using key words related to drug safety (i.e. 'drug toxicity') and the individual RMI names. The website review involved searches of major regulatory authority websites such as the European Medicines Agency, US FDA, Health Canada, the UK's Medicines and Healthcare products Regulatory Agency, Japan's Pharmaceutical and Medical Devices Agency and Australia's Therapeutic Goods Administration. The following eligibility criteria were applied for inclusion in the review: published/posted between the years 2000 and 2009, inclusive; involving drug products; use in humans; and involving RMIs, or tools used to increase the reporting of adverse events (AEs). Natural healthcare products, devices, diagnostic chemicals, pregnancy registries without follow-up, medication errors and products not used as therapy for illness were not retained. For each source, the following characteristics were extracted: nature of the intervention, target population, therapeutic area, AE(s) of special interest, country/regulatory agency and year of publication.

Results: A total of 119 unique interventions were identified in the literature (54 published in 2000–4 and 65 published in 2005–9). Interventions included

educational material (n = 37; 31%), black-box warnings (n = 22; 19%) and therapeutic drug monitoring (n = 11; 9%). The website review produced a total of 1112 interventions: 326 posted between the years 2000 and 2004, and 786 between the years 2005 and 2009. The main interventions observed were: educational material (n = 956; 86%), black-box warnings (n = 45; 4%) and withdrawals (n = 39; 4%).

Limitations: Additional regulatory resource websites were available in the post-guidances periods that were not available in the earlier years of the pre-guidances periods, and may bias the post-guidances results. Also, not all global regulatory websites were searched. Finally, only English-language websites were searched, limiting the variation of RMIs observed. Classification and categorizing for this particular review may not be consistent with future reviews by other researchers.

Conclusion: The US is the sole region with a substantial increase in published RMIs during the post-guidances period, while the EU, Japan and the US all indicated an increase in the number of interventions on their websites.

1. Background

Risk minimization interventions (RMIs) are tools that aim at enhancing the benefit-risk of medicines beyond product labelling.[1] In the broad spectrum of RMIs, one may find educational interventions, on one end, and more stringent programmes, such as restricted distribution, on the other end. Among the most well known educational interventions are Dear Healthcare Professional (DHCP) letters issued by drug manufacturers or regulatory agencies,[2] black-box warnings, medication guides, regulatory agency safety warnings/alerts and public advisory warnings. Therapeutic drug monitoring (TDM) is another type of RMI used mainly for drugs that have a narrow therapeutic range. The patient's blood level of the drug is monitored in order to ensure that it does not reach levels more likely to cause adverse events (AEs).[3] Registries are also used where prescribers and/or patients are enrolled so that restrictions can be monitored or screening for abnormal test results maintained. RMIs may target prescribers (e.g. educational and training) or patients (patient alert cards, informed consent) and can be implemented by different stakeholders such as drug manufacturers, regulatory authorities or a healthcare institution.

Although RMIs have been in use for several decades, it was not until 2005–6 that both the US FDA and the EMA introduced their guidances on therapeutic risk management. The guidances define a risk management plan (RMP), conditions of requirement, and risk minimization activities that may be required in instances of specific safety concerns.[1,4]

Since then, the field of therapeutic risk management has received growing interest. Because of the novelty of the subject, however, the characteristics of the various RMIs that have been implemented remain poorly explored. Although reviews have been published in the literature [5-7] few have aimed at comprehensively examining trends of RMIs, or the effect of the publication of risk management guidances on their frequency and type. Leiderman[5] performed a review of selected examples of risk management programmes and RMIs implemented prior to the introduction of guidelines. However, the review was not comprehensive or systematic nor was there an attempt or the ability to examine the effect of the regulatory guidances on the characteristics of RMIs. Similarly, the review by Hirst et al.[7] summarized some of the RMIs used between 1997 and 2005, with a main focus on product withdrawals during that time period (n = 22). In

the Wise et al.[6] review, the authors' focus was the overall field of pharmacovigilance, and tools used for such. Consequently, the review was general and not specifically geared towards risk minimization.

Since the initial submission of this article, two additional reviews of RMIs conducted by Nicholson et al.[8] and Zomerdijk et al.[9] were identified from literature searches: Nicholson et al.[8] conducted a review only of US Risk Evaluation and Mitigation Strategies (REMS) approved by the FDA between 2008 and 2011, and also did not analyse trends of the REMS in terms of therapeutic class or AEs of interest. Although Zomerdijk et al.[9] covered a longer time span than our review (1995–2010), and included analyses of therapeutic class and AEs, their review focused solely on those risk minimization activities implemented in the EU and did not take on a global analysis of the trends in RMIs. Furthermore, it did not include an analysis of population-specific RMIs. Lastly, neither of these two reviews incorporated a literature search of published RMIs.

2. Objectives

Our study aimed at characterizing RMIs implemented during the 5 years before, and the 5 years after, the introduction of the regulatory guidances on risk management. This was achieved through the conduct of a systematic review with the following specific objectives: (i) to identify the RMIs published in the literature or posted on selected regulatory agencies websites; (ii) to describe the RMIs with respect to the target population, drug class, safety issue(s) and nature of the intervention; (iii) to determine whether the issuance of regulatory guidelines on risk management had an influence on the type and/or frequency of RMIs being implemented.

3. Methods

3.1 Search Strategy

The review was conducted through the literature as well as agency websites, and followed the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies.[10] The literature search was conducted using MEDLINE and EMBASE databases. Medical Subject Heading (MeSH) terms were used where possible; however, few were located through individual RMI names. In addition, terminology varied slightly for the MEDLINE and EMBASE databases. Consequently, keywords related to the following subjects were used: 'drug toxicity' (MeSH term) AND 'patient education' (MeSH term) OR 'HCP education' OR 'prescriber education' OR 'patient alert card' OR 'patient registry'; OR 'medication guide' OR 'drug legislation' (MeSH term) OR 'informed consent' (MeSH term) OR 'restricted distribution' OR 'physician authorisation' OR 'drug monitoring' (MeSH term) OR 'Dear Health Care Professional letter' OR 'Dear Doctor Letter' OR 'black box warning'. All articles, including review articles, were scanned for potential relevant references (snowballing). The EMBASE and MEDLINE initial reviews were performed by two separate researchers. The MEDLINE review was completed on 22 January 2010 by LN and the EMBASE review was completed on 29 January 2010 by AMC. The resulting articles were scanned, and snowballing was performed by one individual (LN). The excluded articles were then scanned by one of two secondary individuals (AMC and CC) to ensure that any qualifiable RMIs remained. Any disagreements were resolved with a majority (two out of three) decision (LN, AMC and CC).

The website review involved an initial search by one researcher (LN) of the following agency sites, with the initial data collection process for each website completed on the dates indicated: Health Canada safety alerts/advisory warnings (16 June 2010);[11] EMA (Europe-approved RMPs; 6 August 2010);[12] FDA (US-approved REMS; 14 July 2010[13] and medication guides; 11 July 2010[14]); FDA safety alerts/advisory warnings (9 July 2010);[15] Therapeutic Goods Administration (TGA) [Australia] advisories (13 October 2010);[16] Medicines and Healthcare Products Regulatory Agency (MHRA) [UK] safety alerts/advisory warnings (20 September 2010);[17] Pharmaceutical and Medical Devices Agency (PMDA) [Japan] pharmaceuticals safety information (30 September 2010).[18] The excluded warnings/alerts were then scanned by one of two secondary individuals

(AMC and CC) to ensure that the first had not excluded any important RMIs. Any disagreements were decided with a majority (two out of three) decision.

3.2 Eligibility Criteria

To be included in the review, RMIs needed to have been published or posted between 1 January 2000 and 31 December 2009, involved drug products, used in humans, RMIs or tools used to increase the reporting of AEs. The RMI could be sponsored by any organization (e.g. regulatory authority, commercial organization, or institution, etc.) Natural healthcare products, devices, diagnostic chemicals, pregnancy registries without follow-up, medication errors and products not used as therapy for illness were not retained.

For each RMI, the following characteristics were extracted and recorded into a harmonized information matrix: nature of the RMI, target population, therapeutic area as per the Anatomical Therapeutic Chemical (ATC) classification system, AE(s) of special interest, regulatory region and year of publication/posting. The characteristics of the RMIs were also compared across two 5-year time periods: before publication of the guidances (pre-guidances period: 2000–4) and after the implementation (post-guidances period: 2005–9).

Some RMIs involve a combination of different intervention types. For the review, if more than one RMI for a particular safety concern was published in a given year, they were counted as one RMI. Furthermore, only the most stringent component (e.g. patient alert card or restricted distribution) was retained for the synthesis of information. Regions for categorizing RMIs were based on regulatory jurisdictions (e.g. EU, US, Canada, Japan, Australia). The region recorded corresponded to the site of the RMI's execution. If a source described an RMI as present in more than one region, it was considered an 'international RMI'.

3.3 Classification of Risk Minimization Intervention (RMI) Types

Classifying the RMI types was completed in the following manner: educational materials comprised DHCP letters, regulatory agency safety warnings/alerts, public advisory warnings and medication guides. Patient alert cards included both the UK MHRA yellow card reporting process and patient alert cards themselves. Restricted distribution incorporated restricted/controlled prescription and distribution, and TDM included both laboratory results' monitoring systems (to ensure that a marker for a certain AE is being kept within normal limits), as well as TDM of the drug concentration itself. Withdrawals included voluntary withdrawals, regulatory agency-mandated withdrawals, as well as suspensions.

3.4 Comparison of RMIs in the Period Before and After the Regulatory Guidances

The proportion of RMIs published before and after the regulatory guidances were compared through Chi-squared tests or Fisher's exact tests in instances of low numbers.

4. Results

4.1 Literature search

Figure 1 displays the results of the literature search. A total of 2103 articles were initially identified from the bibliographic databases. Of these, 135 met the inclusion criteria, and another 34 sources were obtained from snowballing, yielding 169 sources. After applying the inclusion/exclusion criteria listed above, a total of 119 distinct interventions were retained for the review. Since some interventions were associated with more than one publication, only one source was retained. Information extracted into the harmonized matrix is found in the Literature Review Data Extraction table (see Appendix I, Supplemental Digital Content, http://links.adisonline.com/DSZ/A69).

In the pre-guidances period, 54 (45%) RMIs were published, while in the post-guidances period, there were 65 (55%). This increase was, however, not statistically significant ($p = 0.313$).

Table I displays the geographical distribution of publications. The majority of interventions were implemented in the US (n = 65; 55%) and the EU (n = 22; 18%). Other regions included Australia (n = 3; 3%), Canada (n = 2; 2%) and Singapore

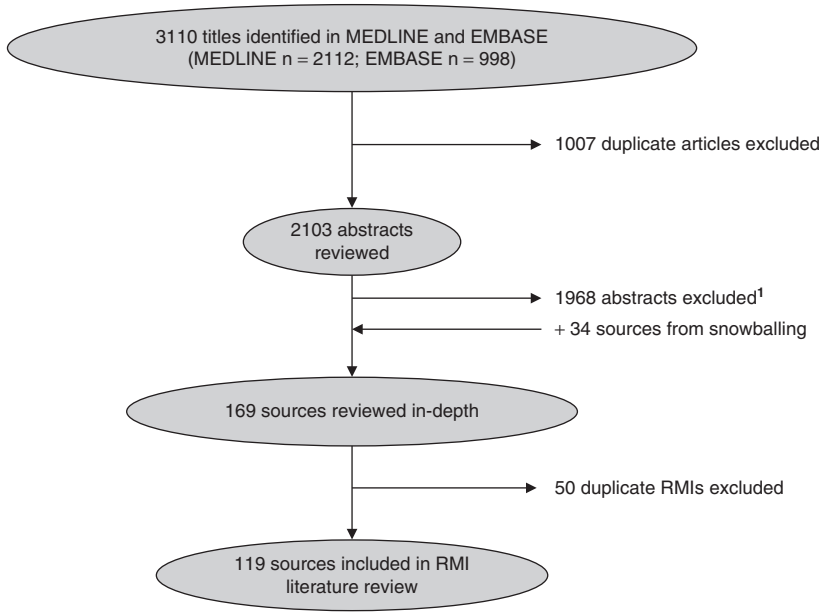

Fig. 1. Literature review: source identification flowchart. **RMI** = risk minimization intervention.

(n = 1; 1%). There were nine sources (8%) that involved an RMI that was simultaneously implemented in more than one region (i.e. international). There were 17 RMIs (14%) for which the region of implementation was unspecified and therefore unknown.

Across the various regions, there were 11 different publications (each discussing an RMI) that together described a total of five duplicated RMIs implemented in different regions, i.e. RMIs of the same type and same safety issue, however implemented in varying regions.

Table I. Literature review distribution of risk minimization interventions by geographical region across pre- and post-guidance periods

Geographical region	2000–4 [n (%)]	2005–9 [n (%)]	Total [n (%)]	Chi-squared p-value (pre- vs post-guidances)
US	25 (46.3)	40 (61.5)	65 (54.6)	0.09[a]
EU	10 (18.5)	12 (18.5)	22 (18.5)	0.99
INTL	3 (5.6)	6 (9.2)	9 (7.6)	0.51[a,b]
AUS	3 (5.6)	0 (0.0)	3 (2.5)	0.09[b,c]
CAN	2 (3.7)	0 (0.0)	2 (1.7)	0.20[b,c]
SGP	1 (1.8)	0 (0.0)	1 (0.8)	0.45[b,c]
UNK	10 (18.5)	7 (10.8)	17 (14.3)	0.23[c]
Total	**54 (100.0)**	**65 (100.0)**	**119 (100.0)**	

a Increased proportion in post-guidances period.

b Fisher's exact test.

c Decreased proportion in post-guidances period.

AUS = Australia; **CAN** = Canada; **INTL** = international (more than one region); **SGP** = Singapore; **UNK** = unknown/unspecified; **US** = United States.

Table II. Literature review: overall distribution of risk minimization intervention type

RMI	N (% of educational material)	Percentage of total RMIs
Educational material	37 (100.0)	31.0
Patient/public safety warning	17 (45.9)	14.3
Healthcare Professional safety warning	10 (27.0)	8.4
Dear Healthcare Professional letter	6 (16.2)	5.0
Medication guide	3 (8.1)	2.5
Warning with unspecified target audience	1 (2.7)	0.8
Black-box warning	22	18.5
Therapeutic drug monitoring	11	9.2
Educational programme	9	7.6
Restricted distribution	8	6.7
Informed consent	6	5.0
Withdrawals	8	6.7
Patient registry	4	3.4
Pregnancy registry	1	0.8
Pharmacogenetics	2	1.7
Black triangle symbol	3	2.5
Patient alert card	1	0.8
Other	7	6.0
Total	**119**	**100.0**

RMI(s) = risk minimization intervention(s).

According to table II, the three most frequent RMIs published in the literature were educational material (n = 37; 31%), black-box warning (n = 22; 19%) and TDM (n = 11; 9%). These rankings were relatively consistent across pre- and post-guidances periods: educational material, n = 13 (24%) versus n = 24 (37%); black-box warning, n = 6 (11%) versus n = 16 (25%); TDM, n = 6 (11%) versus n = 5 (8%); educational programmes, n = 2 (4%) versus n = 7 (11%) for the pre- and post-guidances periods, respectively.

There were 12 RMIs that were in fact a combination of different RMI types: five combinations involved restricted distribution in combination with either registries alone or along with educational materials or educational programmes. Four were in the pre-guidances period; three combinations involved informed consent (two pre- and one post-guidances) in combination with either educational material or TDM; two groupings of TDMs were observed, one with educational material and the other with an educational programme. Both were implemented in the pre-guidances period. One black-box warning was combined with educational material in the post-guidances period, and one patient alert card was combined with educational material also during the post-guidances period.

Distribution of the RMIs by ATC class, and subdivided into pre-guidances (2000–4) and post-guidances (2005–9) is displayed in figure 2. Most RMIs involved drugs of the 'nervous system' classification (n = 40; 34%), followed by the 'alimentary tract and metabolism' classification (n = 17; 14%) and finally the 'blood and blood forming organs' classification (n = 9; 8%). Distribution of the RMIs by ATC class between the two 5-year time periods remained relatively consistent. The System Organ Classes (SOC) of AEs of interest (as per the Medical Dictionary for Regulatory Activities [MedDRA®]) are reported in figure 3, where the majority were simultaneously geared towards a combination of AE SOCs (n = 45; 38%). Again, distribution of the RMIs by ATC class remained fairly consistent across the two 5-year time periods.

Overall, 70% of RMIs published over the 10-year period applied to the general population (refer to

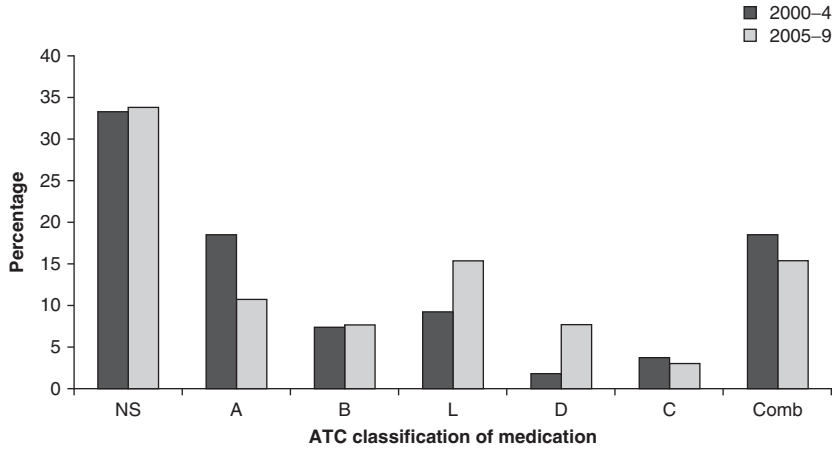

Fig. 2. Literature review: distribution of risk minimization interventions by drug Anatomical Therapeutic Chemical classification. **A** = Alimentary tract and metabolism; **ATC** = Anatomical Therapeutic Chemical; **B** = Blood and blood forming organs; **C** = Cardiovascular system; **Comb** = Combination; **D** = Dermatologicals; **L** = Antineoplastic and immunomodulating agents; **NS** = Nervous system.

table III). The remaining 25 were specific to a subpopulation, with 11 being women-specific and geared largely towards avoiding pregnancy and/or congenital malformations and teratogenic effects (n = 6). These were mainly with medications such as isotretinoin and thalidomide. Other RMIs were specific to the paediatric population (n = 10) [mostly for nervous system drugs; n = 7] and for the elderly (n = 3, all involving nervous system drugs).

4.2 Website Search

Figure 4 displays the results of the website review search. Altogether, 1112 interventions were identified through the website review. In table IV it is seen that the overall number of RMIs more than doubled, from 326 in the pre-guidances period to 786 during the post-guidances period. As shown in table V, the most frequent RMIs observed from the website review were as follows:

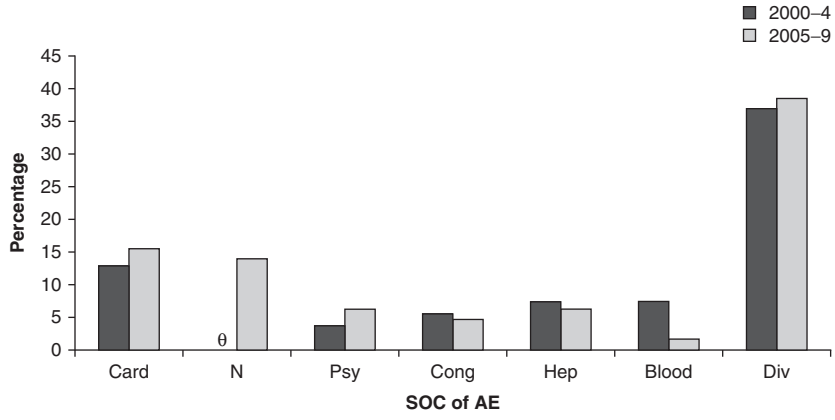

Fig. 3. Literature review: distribution of risk minimization interventions by Adverse Event System Organ Class (MedDRA® terminology). **AE** = Adverse event SOC; **Blood** = Blood and lymphatic system disorders; **Cong** = Congenital, familial and genetic disorders; **Card** = Cardiac disorders; **Div** = Diverse (combination of AE SOC); **Hep** = Hepatobiliary disorders; **MedDRA®** = Medical Dictionary for Regulatory Activities; **N** = Neoplasms benign, malignant and unspecified; **Psy** = Psychiatric disorders; **SOC** = System Organ Class.

Table III. Literature review: risk minimization intervention distribution per risk minimization intervention target population

Population	2000–4 [n (% of pre-guidances RMIs)]	2005–9 [n (% of post-guidances RMIs)]	Total [n (% of total RMIs)]	Chi-squared p-value (pre- vs post-guidances)
Paediatric	4 (7.4)	6 (9.2)	10 (8.4)	1.00[a,b]
Adults	0 (0.0)	1 (1.5)	1 (0.8)	1.00[a,b]
Women	7 (13.0)	4 (6.2)	11 (9.2)	0.22[a,c]
Men	0 (0.0)	1 (1.5)	1 (0.8)	1.00[a,b]
Geriatric	1 (1.8)	2 (3.1)	3 (2.5)	1.00[a,b]
All	38 (70.4)	49 (75.4)	87 (73.1.0)	0.54[b]
Unknown	4 (7.4)	2 (3.1)	6 (5.0)	0.41[a,c]
Total	**54 (100.0)**	**65 (100.0)**	**119 (100.0)**	

a Fisher's exact test.

b Increased proportion in post-guidances period.

c Decreased proportion in post-guidances period.

RMIs = risk minimization interventions.

educational materials (n = 956; 86%), black-box warnings (n = 45; 4%) and withdrawals (n = 39; 4%). This distribution was also generally consistent across the different regions. The overall regional distribution was as follows: US, n = 538 (48%); Canada, n = 258 (23%); EU, n = 183 (17%); Japan, n = 115 (10%) and Australia, n = 18 (2%). Changes in regional distribution across periods are shown in table IV.

Combination RMIs (n = 41) were exclusive to three regions: EU (n = 19), US (n = 12) and Canada (n = 10). Among the combination RMIs, nine involved patient alert cards combined with educational programmes and/or educational material, one of which was combined with TDM; 11 withdrawals were combined mainly with educational materials, one including a TDM; five RMIs involved restricted distribution in combination with educational programmes and/or educational materials; five involved groupings of black-box warnings with educational materials; five TDM programmes were combined primarily with educational materials, one including an informed consent; two registries were combined with restricted distribution and/or educational material; and one involved a combination of informed consent and educational material. There was one informed consent that included a patient agreement, and two educational programme/educational material combinations.

4.3 Literature Review versus Website Review

The review revealed major differences between the results of the literature search and the website review. In table I it is seen that in the literature search, the US was the sole region with a substantial increase in published RMIs during the post-guidances period: n = 25 (46%) and n = 40 (62%), respectively, for the pre- and post-guidances period. However, from table IV the website review shows that many regions increased their RMIs during the post-guidances period; namely US, n = 127 (39%) and n = 411 (52%); EU, n = 37 (11%) and n = 146 (19%); and Japan, n = 24 (7%) and n = 91 (12%), respectively, for the pre-and post-guidances periods. The two most common RMIs used in both reviews were similar: educational materials and black-box warnings. The percentage of educational materials observed in the website review (n = 956; 86%) was greater than those of the literature review (n = 37; 31%), offsetting the percentages of all other RMIs. Such differences in numbers and characteristics according to data source suggest the presence of a publication bias.

5. Discussion

From the literature review alone, there was no significant difference in the overall number of RMIs

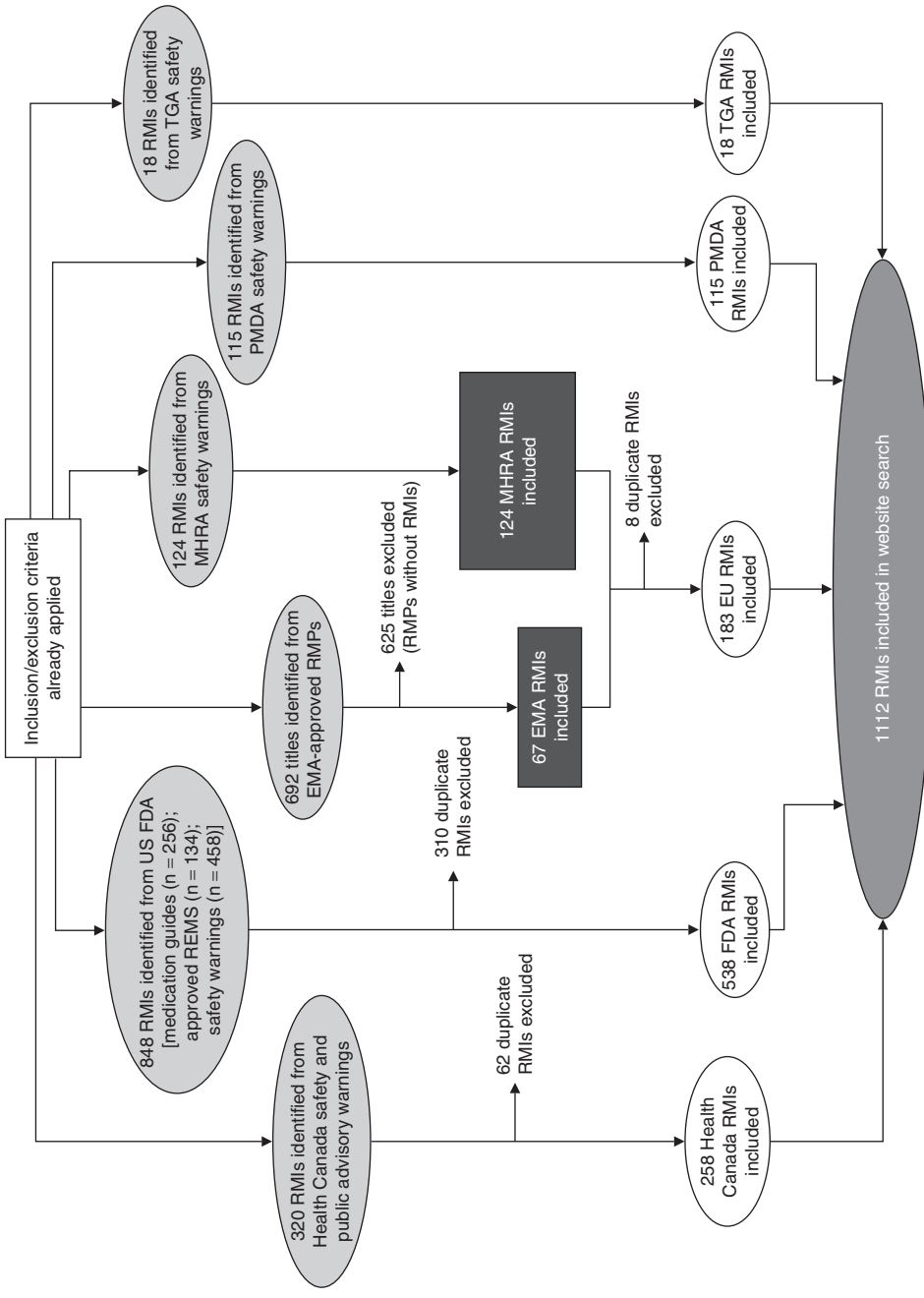

Fig. 4. Website review: risk minimization intervention identification flowchart. **EMA** = European Medicines Agency; **MHRA** = Medicines and Healthcare products Regulatory Agency; **PMDA** = Pharmaceutical and Medical Devices Agency; **REMS** = Risk Evaluation and Mitigation Strategies; **RMIs** = risk minimization interventions; **RMPs** = risk management plans; **TGA** = Therapeutic Goods Administration;

Table IV. Website review: distribution of risk minimization interventions by region

Region	2000–4 [n (%)]	2005–9 [n (%)]	Total	Chi-squared p-value (pre- vs post-guidances)
TGA (AUS)	7 (2.1)	11 (1.4)	18 (1.6)	0.38[a]
PMDA (JPN)	24 (7.4)	91 (11.6)	115 (10.3)	0.04[b]
EU (MHRA + EMA)	37 (11.3)	146 (18.6)	183 (16.5)	0.003[b]
Health Canada (CAN)	131 (40.2)	127 (16.1)	258 (23.2)	<0.001[a]
FDA (US)	127 (39.0)	411 (52.3)	538 (48.4)	<0.001[b]
Total	**326 (100.0)**	**786 (100.0)**	**1112 (100.0)**	

a Decreased proportion in post-guidances period.

b Increased proportion in post-guidances period.

AUS = Australia; **CAN** = Canada; **EMA** = European Medicines Agency; **JPN** = Japan; **MHRA** = Medicines and Healthcare products Regulatory Agency; **PMDA** = Pharmaceutical and Medical Devices Agency; **TGA** = Therapeutic Goods Administration; **US** = United States.

published in the literature during pre-and post-guidances periods. However, the US had a large increase between these time periods in their numbers. This could in part be due to the fact that the US is one of the two regions that implemented the guidances, and possibly both the FDA and US drug manufacturers became more active in this regard. In addition, the US took additional measures to launch a web page dedicated to the posting of approved REMS as well as medication guides. This could in part be a reason for their apparent increased number as other regions, such as Canada, continue to display only safety alerts, and do not have additional web pages for approved RMPs that may be implemented. Finally, the US has a unique RMI step in the black-box warning that other countries do not have. This could be adding an extra RMI to the lifecycle of a drug which would not exist in other countries. The website review results differ. There is a clear increase in RMIs during the post-guidances period, and the increase of RMIs is reflected in two additional regions: the EU and Japan. The large proportional increase of RMIs observed in the US region in the literature review but not the website review could be largely due to the fact that there are many more journals available in the US as opposed to the rest of the world. Thus, a literature review provides a larger source of US information as opposed to Canadian or European information. The literature review shows that population-specific RMIs mainly involve two subpopulations: women and paediatrics. The RMI types targeting women do appear to be population-specific, displaying a predominance of educational programmes. Within the guidances, both the FDA and the EMA encourage the development of additional risk minimization activities designed to address safety concerns in target populations versus those populations that have been included in clinical trials. Such target populations include, among others, children, the elderly and pregnant or lactating women. It is believed that for this reason we see some RMIs targeting children and pregnant women. However, this number is still very low considering the guidances. Furthermore, the extremely low number of RMIs targeting the elderly is particularly concerning, thus highlighting an important gap in the current conduct of RMIs.

Table V. Website review: overall distribution of risk minimization intervention type

RMI type	Total [n (%)]
Educational material	956 (86.0)
Black-box warning	45 (4.0)
Withdrawals	39 (3.5)
Therapeutic drug monitoring	19 (1.7)
Restricted distribution	16 (1.4)
Registry	14 (1.3)
Patient alert card	9 (0.8)
Educational programme	12 (1.1)
Informed consent	2 (0.2)
Total	**1112 (100.0)**

RMI = risk minimization intervention.

This comprehensive review is the first of its kind and, to our knowledge, there are no publications that specifically summarize RMIs over this length of time, or that attempt to analyse the effect of the publication of guidances. Secondly, this article is a systematic and aggregate analysis of various features of RMIs, and no other article has taken on such a comprehensive approach at detailing and analysing trends concerning the RMIs published within the literature. Finally, the global perspective taken with this review permits its application worldwide as the information is relevant across regions and can be used by many countries for RMI information.

Although the website review was quite detailed, the search is not completely exhaustive for a few reasons: (i) there were challenges concerning access to data. For example, the Japanese Regulatory Authority (PMDA) only provides information on its website as of 2004 onwards. This could potentially bias the results with regard to the post-guidances numbers of the website review as the site could be missing some RMIs that the PMDA may have implemented before 2004; (ii) only a selected number of the regulatory authorities' websites were reviewed. For example, some RMIs specific to the individual EU country regulators could be missing from this review. This review also excludes websites that were not posted in the English language. All of these facts could result in the exclusion of important RMIs; however, the fact that the EMA site was also searched expectantly included information for many of the non-English speaking EU countries; (iii) it is important to note that since the initial search of the Health Canada website (16 June 2010), safety alerts originating prior to 2004 are no longer available on the site itself and need to be requested from Health Canada directly. For the review, if more than one RMI in a particular region, for a particular safety concern, was published in a given year, they were counted as one RMI. Furthermore, only the most stringent type (e.g. patient alert card or restricted distribution) was retained for the synthesis of information. This assumption could also lead to discrepancies concerning the results of this review versus other reviews that may be conducted in the future.

6. Conclusions

This systematic review implies that the guidances on therapeutic risk management did lead to an important increase in the number of RMIs implemented within the US, EU and Japan. However the discrepancy with the literature review demonstrates the existence of publication bias. From the literature review, it is clear that many RMIs are simultaneously geared towards heterogeneous AEs, drug classes and patient subpopulations. More RMIs would need to be published in order to better assess trends in RMI characteristics. Although interventions found in the literature are fewer in number, more innovative interventions and variety can be obtained from these sources than on the website review.

Acknowledgements

This project was funded through a grant by the Réseau Québecois de Recherches sur l'Usage des Médicament (RQRUM). Lenhangmbong Nkeng has also received a studentship from the Canadian Patient Safety Institute for the conduct of this project, and is also the recipient of the Richard J. Schmeelk Fellowship Award and the Golden Key International Honour Society's Biomedical Science Award.

There are no conflicts of interest to declare for any of the authors.

References

1. US Food and Drug Administration. Guidance for industry: development and use of risk minimization action plans [online]. Available from URL: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf [Accessed 2010 Oct 1]
2. Health Canada. Guidance for industry: issuance of health professional communications and public communications by market authorization holders [online]. Available from URL: http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2010-guid-dir_indust_hppc-cpsp/index-eng.php [Accessed 2011 Sep 28]
3. Touw DJ, Neef C, Thomson AH, et al. Cost effectiveness of therapeutic drug monitoring: an update. EJHP Science 2007; 4 (13): 83-91
4. European Medicines Agency. Guideline on risk management systems for medical products for human use. Incorporated into: Volume 9A of the rules governing medicinal products in the European Union. Guidelines on pharmacovigilance for medicinal products for human use. Part I-3: requirements for risk management systems [online]. Available from URL: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf [Accessed 2012 May 27]
5. Leiderman DB. Risk management of drug products and the U.S. Food and Drug Administration: evolution

and context. Drug Alcohol Depend 2009; 105 Suppl. 1: S9-13

6. Wise L, Parkinson J, Raine J, et al. New approaches to drug safety: a pharmacovigilance tool kit. Nat Rev Drug Discov 2009; 8 (10): 779-82
7. Hirst C, Cook S, Wanju D. A call for international harmonization in therapeutic risk management. Pharmacoepidemiol Drug Saf 2006; 15: 839-49
8. Nicholson SC, Peterson J, Yektashenas B. Risk Evaluation and Mitigation Strategies (REMS): educating the prescriber. Drug Saf 2012; 35 (2): 91-104
9. Zomerdijk IM, Sayed-Tabatabaei FA, Gianluca T, et al. Risk minimisation activities of centrally authorized products in the EU: a descriptive study. Drug Saf 2012; 35 (4): 299-314
10. Liberati A, Altman G, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009; 6 (7): 1-29
11. Health Canada, MedEffect™ Canada. Advisories, warnings and recalls [online]. Available from URL: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index-eng.php [Accessed 2012 May 28]
12. European Medicines Agency. European public assessment reports [online]. Available from URL: http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124 [Accessed 2012 May 22]
13. US FDA. Approved risk evaluation and mitigation strategies [REMS; online]. Available from URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm [Accessed 2012 May 28]
14. US FDA. Approved medication guides [online]. Available from URL: http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm [Accessed 2012 May 28]
15. US FDA. MedWatch safety alerts for human medical products [online]. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ [Accessed 2012 May 22]
16. Australian Government, Department of Health and Ageing, Therapeutic Goods Administration. Alerts [online]. Available from URL: http://www.tga.gov.au/safety/alerts.htm [Accessed 2012 May 28]
17. Medicines and Healthcare products Regulatory Agency. Safety warnings and messages for medicines [online]. Available from URL: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/index.htm [Accessed 2012 May 22]
18. Pharmaceuticals and Medical Devices Agency, Japan. MHLW pharmaceuticals and medical devices safety information [online]. Available from URL: http://www.pmda.go.jp/english/service/precautions.html [Accessed 2012 May 22]

Correspondence: Dr *Yola Moride*, PhD FISPE, Associate Professor, Faculty of Pharmacy, Université de Montréal, C.P.6128, succursale Centre-ville, Montreal, QC H3C 3J7, Canada.
E-mail: yola.moride@umontreal.ca

