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LEADING ARTICLE

Risk Management for the 21st Century: Current Status and Future Needs

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Abstract

Global adoption of risk management principles outlined in the International Conference on Harmonisation (ICH) E2E guideline and the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI guidance introduced greater proactivity and consistency into the practice of pharmacovigilance and benefit–risk management throughout the lifecycle of a drug. However, following the release of these guidelines there have been important advances in the science and practice of risk minimisation itself, especially in terms of how risk minimisation measures (RMMs) are designed, implemented, disseminated and evaluated for effectiveness in real-world healthcare settings. In this article, we describe how the field of design, implementation, dissemination and evaluation of RMMs has advanced in recent years while highlighting current areas of challenge and possible solutions. Where possible we cite global examples to demonstrate how evidence-based approaches have informed the development of RMMs. In this context, while taking into consideration local healthcare system policies and national legislations, we conclude with a call for a global effort to harmonise certain areas that focus on, but are not limited to, standardising certain terms and definitions, consistent application of robust methodologies, and outline of best practices for risk minimisation design, implementation, and dissemination.

1 Introduction

Proactive life-cycle risk management is a hallmark of modern pharmacovigilance and is based on complementary initiatives described by the Council for International Organizations of Medical Sciences (CIOMS) in its Working Group VI entitled "Management of Safety Information from Clinical Trials" and by the International Conference on Harmonisation (ICH) in the E2E guideline entitled "Pharmacovigilance Planning" of 2004 [1, 2]. CIOMS VI recommended a developmental pharmacovigilance concept that would start early in the drug development process and continue into the post-approval period.

ICH E2E outlined a structured, iterative process for identifying and assessing risks by introducing two foundational concepts: the Safety Specification that describes the product's risk profile, and the Pharmacovigilance Plan that describes how these risks are monitored and characterised. Some regulatory agencies [i.e. the European Medicines Agency (EMA) and the Food and Drug Administration (FDA)] advanced certain general concepts of risk management that the E2E guideline did not address. One such key concept specified that there be an "overall and continuing process of minimising risks throughout a product's life cycle in order to optimise its benefit–risk balance" [3]. The latter was achieved via the use of specific measures and tools to minimise risk, and the evaluation of effectiveness of those measures [4-6]. This concept was later captured by CIOMS in its 2014 Working Group IX entitled "Practical approaches to risk minimisation for medicinal products", which provided principles for the identification

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Key Points

Despite the current availability of numerous guidelines, certain challenges (e.g. methodologies to evaluate burden on the healthcare system, barriers to patient access, and sustainability of risk minimisation programmes) and inconsistencies (e.g. terms and definitions) exist, highlighting areas that would benefit from global harmonisation.

In recent years, a number of advances have been made and best practices explored in the field of risk minimisation design, implementation, dissemination and evaluation.

There is a need for global harmonisation and an outline of best practices to address these challenges and leverage international experience with the goal of optimising patient safety.

Standardisation will help accelerate the implementation of proactive risk management planning in countries that have just begun implementing these practices.

and application of risk minimisation tools in addition to the evaluation of the effectiveness of such measures [7].

2 Adoption of CIOMS and ICH Guidelines

Since their introduction, CIOMS VI and ICH E2E concepts have been widely adopted globally, although their interpretation has varied. For example, the EMA mandates European (EU) risk management plans (RMPs) for all newly authorised products [8]. The EU RMP includes a summary of information about the safety concerns that may impact the benefit–risk profile of the drug and specifies strategies for characterising and managing those risks over time [9]. Other jurisdictions, such as Health Canada and the Ministry of Food and Drug Safety in Korea, accept the submission of RMPs in the EU format and have outlined the specific circumstances under which RMPs should be submitted [10, 11]. In contrast, the US FDA requires formal risk minimisation programmes (known as Risk Evaluation and Mitigation Strategies or REMS) to be developed and implemented for certain products such as those carrying serious risks that cannot be mitigated through product labelling alone [12]. Additionally, an increasing number of regulatory agencies have implemented the concept of monitoring the effectiveness of risk minimisation measures (RMMs) as part of the risk management continuum [8, 12, 13].

3 The Learning Pharmacovigilance System

Another trend in the field of pharmacovigilance has been the drive to become a 'learning healthcare system' [14-18]. A learning pharmacovigilance system is proactive, leverages innovation and emphasises continuous quality improvement by strengthening the tools to manage drug knowledge throughout its life cycle and adapts the authorisation status accordingly as new information becomes available. Risk management plays a central role in this emerging learning healthcare system by assessing the benefit–risk profile of the drug over time, implementing measures to minimise its risk(s), evaluating the impact of such measures and modifying them, as needed, to ensure maximal effectiveness (Fig. 1) [19, 20].

4 Bridging the Gap: Current Reality Versus Envisioned State

While the concept of risk management is now firmly embedded in pharmacovigilance, recent reviews have highlighted significant shortcomings in its actual practice to date [21-23]. The EMA's landmark 2017 Public Hearing on the risk management of valproate, a teratogenic medicine, revealed numerous problems with both the design and implementation of the valproate RMMs [24]. Findings from the hearing underscored the importance of understanding contextual factors associated with delivery of the RMMs (e.g. type of health care setting[s]; degree of understanding of the risk and support for the RMM within the implementing organisation), in addition to ensuring that patients and health care professionals (HCPs) receive the necessary education and training at the right time. Other findings included considerations relating to both barriers and facilitators to RMM adoption. In its final report, the EMA called for specific improvements in the design of the RMMs, greater attention to implementation, and shared responsibility among stakeholders to ensure programme success [25].

Other recent systematic reviews have found mixed or insufficient evidence on the effectiveness of RMMs as well [21, 26, 27]. Researchers have also documented the uneven reporting quality in published studies on risk minimisation evaluation, citing this as a barrier to robustly appraising the scientific rigor of these studies, interpreting the results and advancing the science in this area [21, 28, 29]. Mazzaglia et al. [22], in a study assessing the impact of RMMs for cardiovascular, endocrine and metabolic drugs, concluded that there was a need for more comprehensive, real-time reporting of programme implementation metrics to allow for timely programme modifications. Others have also concluded that it remains challenging to perform RMM

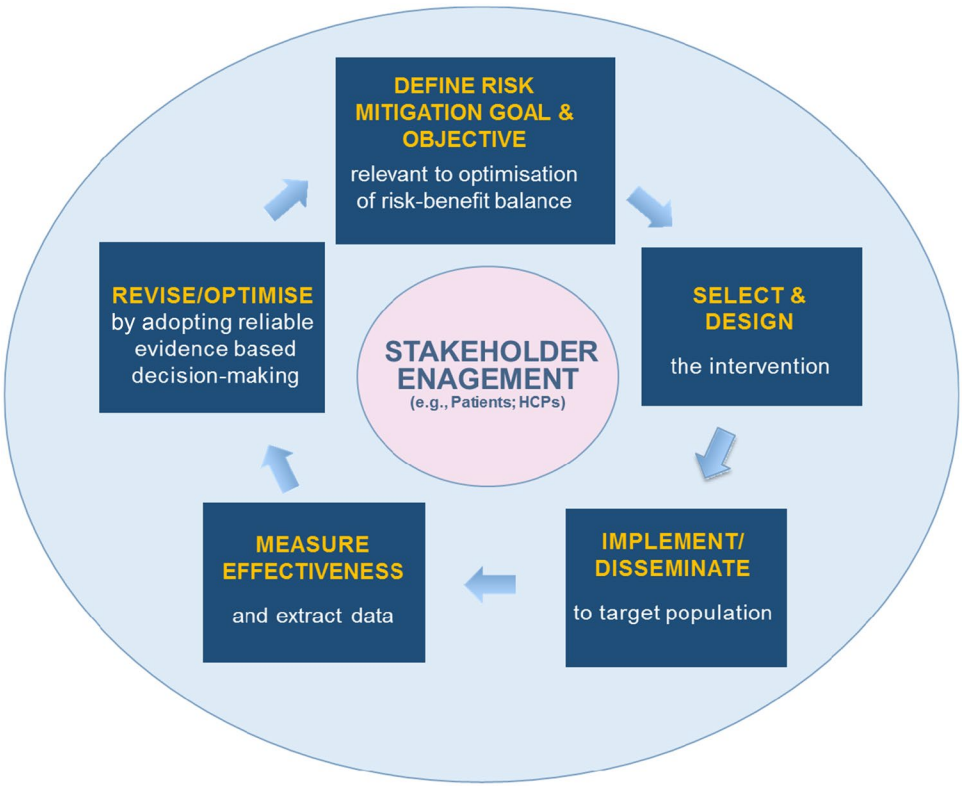

Fig. 1 Cyclical feedback loop for evidence-based design and evaluation of effectiveness of risk minimisation measures. *HCPs* health care professionals

effectiveness evaluation in a timely and scientifically rigorous manner to optimise public health protection [30].

It has been over a decade since the practice of risk management planning was adopted worldwide and now is an opportune moment for reflection and critical questioning. How can we move the field of risk minimisation, including programme evaluation, from its current state to one that is more fit-for-purpose, flexible and responsive to the needs of a 'learning healthcare system'? We contend that there are several key challenges that need to be addressed encompassing all aspects of RMMs, including design, implementation, dissemination and evaluation. Below we briefly highlight several such challenges along with possible solutions and strategies. A number of these solutions draw upon evidence-based principles and best practices from implementation science, a branch of public health intervention research that seeks to promote the adoption/delivery (implementation) and spread (dissemination) of new knowledge, innovations and desired behaviours among HCPs and patients [31]. In turn, successful design, implementation and dissemination strategies drive the attainment of positive programme outcomes [32]. Wherever possible, we cite examples of how these evidence-based approaches have informed the development of RMMs from a regulatory, industry and academic perspective.

5 Designing RMMs that Promote Desired Behavioural Changes and Are Successfully Integrated into the Target Health Care System(s)

Risk minimisation measures represent a type of public health intervention aimed at preventing or minimising the risk associated with exposure to a drug [9, 31]. These measures always include the label (also known as routine measures). The label is required at the time of drug approval and provides authorised product information. For some drugs, labelling alone may not be sufficient and additional RMMs are necessary to ensure that the benefits of the drug outweigh the risks. Additional RMMs vary in stringency, ranging from educational or risk communication (RC) materials (low stringency) to restricted distribution programmes (high stringency). For example, in Taiwan the rates of laboratory testing for tuberculosis and viral hepatitis infections prior to initiation of antitumor necrosis factor-α (anti-TNF-α) therapy increased when patient and HCP educational materials were implemented in addition to the label to reinforce the labelling message [33].

Non-adherence to the RMMs, whether on the part of the patient or the HCP, is well documented and in some cases may lead to poorer health outcomes [24, 34-36]. For example, a study by Eguale et al. noted that 11% of drugs are

not prescribed according to their listed indication [37]. A number of factors leading to non-adherence have been postulated; in some cases it may stem from programme requirements that are burdensome or instructions for use that are confusing and not clear to both patients and HCPs [38, 39]. Alternatively, in other cases, non-adherence may be due to lack of awareness of the actual risk on the part of the patient and/or HCP [24, 25].

A number of possible strategies have been explored to promote desired behavioural changes in the health care setting in order to enhance adherence. One of these strategies is the design of RMMs that are flexible and adaptable to country- and/or region-specific health care systems [40]. This can be achieved by pre-determining which core elements are believed to be essential for risk minimisation effectiveness and which ones can be subject to flexibility. RMMs that are sufficiently flexible to accommodate local differences in clinical practice patterns and are likely to have higher rates of adherence than those that lack such flexibility [41]. For example, in designing the RMMs for vernakalant (an injectable antiarrhythmic agent) in Canada, a pre-infusion checklist was developed as a key tool to aid HCPs in making appropriate patient selection prior to treatment initiation and in monitoring patients during and following infusion [42]. Taking into consideration that the drug will be administered in a carefully monitored clinical setting, it was purposely not specified which HCP was to complete the checklist for which tasks. This provided each health care institution with the flexibility to implement the RMMs in a manner that fit best within their established workflow. On another note, the EU centralised system outlines key elements with respect to additional RMMs and these are legally binding on the sponsor. Depending on the RMM, the sponsor and EU member states may then need to collaborate on the details of how the additional RMMs will be implemented in each country according to local health system practices.

Although the design of required RMMs is a shared responsibility between the regulator and the sponsor, HCPs and patients are ultimately responsible for adopting them into practice. As a result, collaboration among various stakeholders is vital to ensure that RMMs are acceptable to these end-users and that they fit into existing clinical care procedures. This approach was used in the US in developing the REMS for the transmucosal immediate-release fentanyl products where the existing claims adjudication system was utilised to provide authorisation to dispense, allowing outpatient retail pharmacists to integrate these requirements into their workflow when processing prescriptions for these products [43]. Regulators have also sought the advice of external multidisciplinary groups of experts including HCPs, academics and patient groups, by convening scientific advisory committee meetings to elucidate and achieve integrated views on challenges and solutions with respect to the RMMs for certain drugs [44, 45].

Additionally, a study conducted in Canada sought to understand factors influencing uptake of the Canadian Heart Health Kit (HHK) by HCPs. The HHK is a risk management and patient education resource for the prevention of cardiovascular disease (CVD). Based on HCP feedback, factors influencing the adoption of the kit included its relative advantage over existing resources and that the research evidence was clearly visible [46].

Pilot testing of RMMs with the intended user population(s) and in the intended health care settings can provide valuable insights regarding not only the clinical care delivery process, but also whether and to what extent programme tools and elements will prove feasible and acceptable when implemented under 'real world' conditions. For example, the RMMs developed in the US by the Veterans Administration for dofetilide, an anti-arrhythmic agent, featured a multi-disciplinary collaboration that resulted in a deep understanding of the clinical context of use. The results of this consultation yielded a programme that integrated successfully into the health care system, was accepted by the end users and led to improved patient outcomes [47].

6 Effective Implementation and Dissemination of RMMs

In order for the RMMs and information to reach the intended audience(s), appropriate outreach and distribution channels need to be determined in advance of implementation. In addition, careful consideration should be given to both the timing and frequency of disseminating any intervention, as such one-off distribution of educational tools may be insufficient to ensure that all potential prescribers and/or users, including new prescribers and users, are reached and the impact is sustained [48].

Social marketing techniques, such as market analysis and segmentation, can aid in this regard. An in-depth analysis of the needs and preferences of the target audience(s) within different settings and geographical locations is a proven technique for increasing the integration of a programme. Determining whether and to what extent needs and preferences differ within specific subgroups of the recipient population can also improve the cultural sensitivity of the risk messaging and enhance both programme outreach and uptake [49]. Qualitative research methods can be used to determine the needs and preferences of different targeted subgroups and to enhance the cultural sensitivity of the risk messaging as well.

Piening et al. (2013) study is an example of how market analysis was used to improve the impact of a risk minimisation programme. In the study, the authors first conducted a survey of prescribers to determine their preferences and practices related to drug safety communications. Based on

survey results, an intervention was developed that leveraged email messaging to enhance the likelihood that prescribers would receive and read the drug safety messages [50]. Results showed that prescribers in the intervention group were more likely to have taken action in regard to the safety issue than those in the control group.

Other techniques have been shown to be effective in increasing programme dissemination as well. These include the establishment of communities of practice to support shared learning, collegial interactions, and the exchange of best practices among those responsible for programme implementation [46, 51].

7 Designing Risk Minimisation Programmes that Sustain Their Impact Over Time

As with many public health interventions, RMMs must be sustainable to continue to meet their objectives over time, often for the entire life cycle of the drug. Risk minimisation designs that are based on well tested behavioural change models (e.g. Theory of Reasoned Action [52], the PRECEDE-PROCEED model [53] and Diffusion of Innovation [51]) are more likely to be effective in achieving the desired behavioural changes in the target population(s), and in sustaining their impact over time [54]. A behavioural change model represents a theoretically informed framework that could be utilised in understanding and predicting the impact of a specific intervention (e.g. an RC message) on the target recipients' attitudes, behaviours and extent of adoption of the intervention.

Other approaches explored to promote sustainability over time of clinical knowledge and desired behaviour have included repeated exposure of HCPs to the educational materials. As such, Korea has implemented a Narcotics Information Management System (NIMS), a national monitoring system developed by the Korea Institute of Drug Safety and Risk Management (KIDS), on medical narcotic usage. When misuse or overprescribing are suspected the government sends out safety alerts to HCPs to remind them of the desired prescribing practices [55]. Also, to ensure sustained effectiveness of the isotretinoin pregnancy prevention programme in Korea, the Ministry of Food and Drug Safety and KIDS repeatedly disseminate information on the risk of teratogenicity with isotretinoin to the public through educational materials such as posters and video clips. This is coupled with the sending of alerts in real time, managed by the Health Insurance Review and Assessment Service, when unsafe drugs are prescribed and/or dispensed to a pregnant woman [56, 57]. Similarly, in the US, the FDA determined that educating clinicians was one way to improve safe opioid prescribing [58]. Data from a study that evaluated effectiveness of this strategy concluded that without repeated exposure, deterioration of knowledge is an expected outcome [48].

In recent years, digital materials have been used to facilitate integration of an intervention into health care practices, thus potentially driving its sustainability. This has included making the information related to the RMM publicly available on the regulator's website (e.g. e-labelling) and integrating this information electronically into the health care system (e.g. electronic health records [EHRs]) [21, 59].

8 Evaluating the Effectiveness of RMM(s)

The longer that the relationship between a risk and a drug goes unrecognised, the longer the public is exposed to unnecessary harm; therefore, effective processes in risk management are essential and steps should be incorporated that allow for the modification or elimination of ineffective elements. Moreover, additional RMMs required at the time of drug launch may no longer be necessary once those measures have been available for a number of years and have been integrated into routine clinical care or based on effectiveness data [9]. For example, the REMS for erythropoiesis-stimulating agents (ESAs), which included training for HCPs on the risks in cancer patients with anaemia from myelosuppressive chemotherapy and required patient counselling on these risks, was deemed no longer necessary by the FDA to ensure that the benefits of ESAs outweigh their risks [60]. The FDA based this decision on a broad evaluation of the impact of all regulatory actions including results collected from the evaluation of the effectiveness of the REMS [60]. The FDA also acknowledged that the desired practice change had begun prior to the REMS approval.

Impact evaluation on prescribing practices or on the occurrence of health outcomes is generally carried out for different types of interventions such as black-box warnings and contraindications included in the label, as well as RCs, educational materials and for more stringent interventions such as controlled distribution programmes [23, 61-68]. While there has been an increase in the number of publicly available studies assessing effectiveness of various types of health interventions, there is marked heterogeneity noted in study conduct stemming from variations in study design, data choice, methods used for evaluation, in addition to main outcomes evaluated and study reporting [20, 26].

Risk minimisation evaluation studies assess different aspects of RMM performance using a combination of process and outcome indicators. Process indicators can include, but are not limited to, impact on knowledge and behavioural changes of patients and HCPs [6, 20, 61, 69]. Some have emphasised that the ultimate measure of success of a RMM

is in terms of positive clinical outcomes, such as a decline in the occurrence or severity of adverse reactions [6, 30-32]. Evaluation studies have relied on the utilisation of both quantitative and qualitative methods using different types of data sources, such as surveys or EHRs for the former, and focus groups or semi-structured interviews for the latter [20, 23, 70]. Although a number of guidances and conceptual frameworks/models have been published, they differ in terms of granularity. In addition, a variety of terms and definitions have been used to describe, for example, the indicator(s) that are being measured [6, 30, 61, 62, 69]. Moreover, when designing risk minimisation evaluation strategies, consideration should be given as to which aspects of implementation (i.e. choice of indicator) can be feasibly measured, and under which situations it might be acceptable not to evaluate clinical outcomes, in addition to employing a range of methods that generate information on different aspects of programme implementation and impact [22].

Attention in recent years has been directed towards examining other aspects of intervention impact, including unintended consequences, burden on the health care system and barriers to patient and HCP access [6, 69]. Examples include negative impact on patient access such as treatment interruptions or delays, unintended adverse consequences (e.g. unexpected harm to patients), or disincentives to HCPs from prescribing due to burdensome requirements. This is a nascent field, and methods for assessing these aspects of RMM impact are gradually beginning to emerge [71].

Few of the studies evaluating effectiveness of RMMs have pre-determined measurable thresholds for effectiveness making it difficult to determine whether the RMMs were actually successful in achieving their desired effect. The EU and FDA guidances both cite the importance of setting a realistic priori specification of success thresholds and the FDA further indicates that an 80% or higher 'pass rate' for knowledge and awareness surveys is generally acceptable [6, 72]. Whether this level of knowledge is acceptable to patients has not been evaluated. Thresholds for success for other types of programme evaluation outcomes can be derived from corresponding phase III clinical trial results, considering that there will need to be realistic adjustments for real-world use. Relevant research studies in the published literature [32] and experiences with risk minimisation for other drugs provide additional opportunities for threshold determination. However, a direct relationship between any thresholds and actual risk minimisation or behaviour change remains unknown and further research on this topic is warranted.

Other challenges relate to the timing and frequency of conducting the effectiveness studies, and selecting appropriate study designs and high-quality datasets (e.g. surveys, EHRs). It may take time for an intervention to integrate into the health care system; therefore, evaluation studies should be carried out at a point post-implementation of the RMM(s) that permit accurate conclusions to be drawn regarding their impact on outcomes, which more and more requires access to data in real time. The choice of appropriate data sources for evaluation depends on a number of factors such as the drug and the safety concern in question and the range of available data sources. In addition, questions remain as to whether carrying out a single evaluation study is sufficient or whether a combination of studies using complementary data sets is preferred. For example, a mixed-methods approach was used to evaluate the effectiveness of RMMs for a fentanyl buccal tablet in Canada using complementary data sources from surveys, medical chart review and web surveillance [73].

To date, little emphasis has been placed on exploring questions as to why and how the programme worked (or did not work), for whom, and under what types of circumstances. Mixed methods research designs may offer a way to address these questions. However, the use of mixed methods designs in risk minimisation evaluation has been limited to date. Exceptions to this include a study by Piening et al., which assessed the use of a targeted e-mail to HCPs for delivering safety messages on macular degeneration treatment using a sequential set of qualitative and quantitative methods [50], and later a study by Kesselheim et al. described a multimodal evaluation of FDA drug safety communications for a sleep medication [74].

9 Discussion

Pharmacovigilance processes have become well established since the inception of ICH and CIOMS guidelines. As a result, many regulatory authorities and industry are moving away from a reactive to a more proactive approach, one that begins early on before a drug reaches the market. In this context, designing, implementing and disseminating RMMs, and planning the evaluation of effectiveness of such measures, are important aspects of the benefit–risk evaluation of a drug. However, certain challenges and inconsistencies exist that would benefit from global harmonisation and convergence of best practices in order to ensure that the science of RMMs continues to evolve. Areas of focus could include, but are not limited to, (1) outlining best practices for design, implementation and dissemination; (2) standardising the methodological frameworks for effectiveness studies to ensure consistent application of robust methodologies; (3) use of common terms and definitions and (4) outlining guiding principles for reporting on effectiveness studies.

Designing, implementing and evaluating effectiveness of RMMs can be a challenging and complex process and may involve a substantial investment in resources. These resources, however, may be justifiable given the potential shift in benefit–risk balance that a risk minimisation

programme can provide. As such, it requires a wide range of disciplines and expertise, ranging from clinical, epidemiological and statistical to informatics and systems analysis. This interdisciplinary effort is challenging, especially when also coupled with the need to incorporate some of the above-mentioned best practices into the regulatory review and submission timelines for drugs. Another layer of complexity relates to stakeholder engagement. While the importance of patient and HCP engagement is increasingly recognised, its incorporation into pharmacovigilance activities remains in its infancy [75, 76].

Given the movement towards a 'learning health care system' model of pharmacovigilance and while taking into consideration local health care systems and national legislation, now is a propitious moment to seek global harmonisation in the field of risk management to address the above-mentioned challenges and incorporate best practices (Table 1). Such a step is vital if the field of risk management is to advance towards meeting its public health goals. Standardisation may further the adoption of proactive risk management planning in countries that have just begun implementing such practices, such as Korea, and efforts to harmonise RMP practices are continuously raised among Asians countries [77-79].

In addition, standardising the reporting of risk minimisation evaluations coupled with transparent dissemination of such information is crucial to improving the quality of reporting on RMM design and implementation [28, 29]. In turn, publicly available information enables researchers to conduct systematic reviews to increase knowledge on the effectiveness of various interventions and advance the evidence base to understand what types of programmes work best for minimising certain risks, in what type of settings and for which patient populations.

10 Conclusion

To our knowledge this collaborative commentary is one of the first of its kind and scale. The commentary is not intended to be a formal systematic review of the published literature. Rather, it provides a basis for stimulating future

Table 1 Guiding principles and best practices for design and evaluation

Design, Implementation and Dissemination Drive Outcomes	
Design, Implementation and Dissemination	**Effectiveness Evaluation**
Initiate risk minimisation **design and planning early** before submitting an application to the regulatory authority	Determine which aspects can be **feasibly assessed**
Engage patients and HCPs	**One single "metric" does not fit all** - use several metric indicators to assess different aspects of program performance (e.g., extent of implementation, impact on knowledge and behaviour).
Develop clear risk minimisation **goal(s) and objective(s)** and have a clear description of which safety concern is to be mitigated	**Assess potential burden and barriers** to patient & HCP access or other unintended consequences
Be aware of target **stakeholder(s)** - consider the healthcare setting and target audience	Appropriately **select complimentary data sources** and methodologies
Design RMMs that are **adaptable & compatible** with country and local health care systems - pre-determine which elements are **flexible**	**Pre-specify threshold for success** at the risk management planning stage
Consider **feasibility** of implementation - take into account local regulatory authorities and healthcare system policies	Study **timing** - should be conducted at an appropriate time that allows for an assessment of intervention impact by taking into account time to launch, estimated use of the DP etc.
Determine the dissemination plan for the RMM(s) – outline appropriate **outreach, distribution channels** and procedures to reach the target population	Study **frequency** - repeated periodic review as appropriate to determine if a) program continues to be effective, b) modifications are needed or c) the program can be terminated or otherwise as agreed upon with the respective regulatory authority
Ensure **sustainability & maintenance** of the health care intervention effects over time - address timing and frequency of disseminating the intervention	**Quality reporting** on study results.
Design, implement and disseminate RMM strategies that adopt and **integrate evidence-based health interventions** where possible	**Document best practices** - explore why and how the program worked (or did not work), for whom it worked, and under what types of circumstances
Burden and potential **barriers to access** should be balanced with benefit for the **patient** & **burden on the HCP(s)**	
Optimisation of Benefit-Risk Balance	

discussions from which to move the science of risk management forward.

As the science of risk management matures, the need for global harmonisation that reduces duplication of currently divergent approaches (e.g. reporting formats), leads to more effective programme designs that draw on empirically based best practices and encourages adoption of evidence-based risk management strategies is ever more critical. Such an approach will lead to the development of more effective and efficient risk management practices, resulting in optimised benefit–risk profiles for more drugs and improved patient safety.

Design, implementation and evaluation of risk minimisation programmes is a shared responsibility that requires the involvement of patients and HCPs, the intended end users. In parallel, there is a need for strengthened collaboration among sponsors, regulators and academia to develop more rigorous scientific methodologies to evaluate RMM effectiveness. Such collaboration, rooted in robust science and best practices, should be the foundation of successful risk management in the 21st century.

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