Medication Risk Management

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Abstract

Historically, the FDA has interpreted the requirement that a drug must be "safe" to mean that the benefits of a drug outweigh its risks. The determination was made on a "categorical" basis, where the totality of risks was weighted against the totality of benefits when considered for the purposes outlined in the drug product's labeling. If a drug did not meet this criterion, it was not approved or its label was rewritten to narrow the conditions for use. This logic was endemic in the FDA for most of the 20th century. On average, two to four drugs over each 5-year period were withdrawn from the marketplace after post-marketing surveillance data uncovered new risks. Similarly, on occasion, the FDA would require some special "tool" or intervention to improve a product's safety profile. Harm associated with medication remains the second most common type of incident in hospitals, as reported by the Clinical Excellence Commission. Health services actively review medication safety. The vast majority of medication errors result in no injury. A minor injury may result, for example, in a patient needing an increased level of monitoring. Even if incidents result in minor injury, managers and staff still take any errors very seriously, reviewing the actions around the incident and making improvements as a result. FDA's new concepts for risk management amount to a "cultural shift" in the logic of drug approval and the FDA's role. The key events that led to this change can be traced to a series of reports that highlighted the need for improved medical safety. In 1999, the IOM released a report entitled, "To Err is Human." This report reviewed the nature and cause of medication errors, estimating that up to 98,000 people died each year due to these errors. In their assessment, the IOM included both adverse drug reactions and medication errors in drug administration. The report captured the attention of news reporters and the government. Headlines proclaimed alarm at the larger number of fatalities caused by medical errors. Consequently, there was a government-wide initiative started to develop methods and institute procedures to reduce medical errors. Statements made by FDA officials regarding some of these withdrawals suggested that the FDA no longer believed that passive oversight and re-labeling drugs with new warnings was sufficient. Furthermore, the FDA no longer believed that it was sufficient to identify safe conditions of use in the label and that healthcare professionals and patients had to comply with advocated directions of use for the drug to remain on the market.

Keywords: FDA; RMP; Risk Managers; Risk Management Tools; Drug Therapy

1. Introduction

There is also a misconception among some that the risk of, say, an adverse drug reaction in an individual is the same as its frequency in the population. However, it is possible for an individual, because of some susceptibility, to have a high risk of an adverse reaction that has a low frequency in the population. It is therefore best to separate the notion of individual risk and population risk or frequency. As a summary of this new philosophy of risk management, the FDA staff issued a report to the Commissioner that highlighted processes for developing risk management systems and signaled new ideas for measuring and intervening to manage risks. US FDA (1999) Entitled, "Managing the Risks of Medical Products," the FDA report borrowed heavily from risk management philosophies in other fields, such as environmental risk management and airline safety. It emphasized the process of developing risk management plans to control and manage drug safety. The risk management "revolution" at the FDA continues today. Under FDA regulations and the Food and Drug Administration's Modernization Act, the FDA may approve new drugs with new restrictions that are intended to assure safe use (Subpart H). These restrictions include limiting distribution to certain facilities or physicians with special training or experience or limiting distribution based on the condition of the performance of specified medical procedures. The regulations specify that the limitations must be commensurate with the specific safety concerns presented by the product. In addition, drugs continue to be approved with restrictions imposed by manufacturers seeking FDA approval. The risk management guidance contained several revisions that addressed concerns from industry. The draft guidance stated that for certain drugs that pose risk management concerns, there must be a Risk MAP that describes what risks are faces and how they will be handled. The plan must identify a series of "tools" or interventions used to control risk. These tools include a series of informational interventions (to health care providers, patients, or the public) and distribution controls that specific conditions or populations of patient or providers that limit the prescribing or dispensing of the medication. The tools must be pretested, and the plan must be evaluated periodically.

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1.1. Risk perception in drug therapy

Understanding risk and how it is perceived is a crucial step toward creating programs and campaigns to raise awareness and make communities safe. In short, risk perception, or the ability to discern risk, is tied to risk tolerance, or an individual's capacity to accept a certain amount of risk. Risk perceptions (including deliberative, affective, and experiential) are often targeted in health behavior change interventions, and recent meta-analytic evidence suggests that interventions that successfully engage and change risk perceptions produce subsequent increases in health behaviors. Health-related risk perceptions play an important role in motivating health behavior change. The late Bill Inman once wrote that 'perception of risk is based less on statistics than on fear', and there is little evidence that knowing what the actual risks are affects how the general public perceives and responds to them. The factors that lead to mistaken perceptions about the risks of using particular medicines have not been thoroughly explored, although some are known. For example, in a random sample of 500 consumers aged 18 years and over in Wisconsin, 14–54% thought that generic prescription drugs were riskier than brand-name products, depending on the medical condition being treated, although financial incentives would have mitigated this view. There is also evidence that the more information consumers receive about the safety (or otherwise) of a medicine through direct-to-consumer prescription drug advertising in the USA the riskier they are likely to think it is. Media reporting is also thought to be important [1-4].

Exhibit 1. Several key terms and concepts are used in risk assessment [5]

- **Hazard**: A source of risk, such as a substance or action that can cause harm.
- Exposure: Contact with a hazard in such a manner that effective transmission of the agent or harmful effects of the agent may occur.
- **Dose-response relationship**: A relationship in which a change in amount, intensity, or duration of exposure is associated with a change in the risk of the outcome.
- **Risk**: The combination of the likelihood (probability) and magnitude (severity) of an adverse event.
- **Uncertainty**: An instance of limited knowledge, false assumption, or statistical variability that contributes to a statement of confidence in conclusions drawn from a risk assessment.
- **Risk management**: The process of formulating and implementing a course of action to mitigate hazards determined by risk assessment to be important.

1.2. The objective of therapeutic risk management

Deployment of healthcare risk management has traditionally focused on the important role of patient safety and the reduction of medical errors that jeopardize an organization's ability to achieve its mission and protect against financial liability. The hazards of not preparing for potential issues can have significant, long-term effects. Neglecting to have comprehensive risk management plans in place can compromise patient care, increase liability risks, and result in financial losses. Thus, potential risks have to be evaluated and measured in terms of their potential negative effects. Based on the risk assessment, an organization-specific management plan should be developed, implemented, and monitored. Given that each organization faces unique challenges, there is not a one-model-fits-all risk management solution. For example, the CDC recently published research that found that prolonged urinary catheter use is the leading risk factor for catheter-associated urinary tract infections. Based on this information, a risk management plan was implemented requiring physicians to regularly evaluate the catheter. The end result was a decrease in patient risk. Challenges faced by administrators that should be addressed in a risk assessment plan include but are not limited to:

- Patient safety
- Mandatory federal regulations
- Potential medical error
- Existing and future policy
- Legislation impacting the field of healthcare

Risk Management can be Beneficial in the Following Contexts:

- ERM: Comprehensive risk management of the organization from top down including financial and business viability.
- Patient care (Clinical)
- Medical staff (Such as; credentialing, privileging, job description, employee insurance, trainings, medical coverage)
- Non-medical staff (Such as; job description, training, medical coverage)
- Financial (Budgeting, cost-benefit and cost-effectiveness analysis, insurance coverage)
- Managerial (Such as; organogram, Job descriptions, delegation of work)
- Project risk management (Such as scope, time, cost, human resources, operational, procedural, technical, natural and political)
- Facility Management and safety (Such as building safety, security of the facility, HAZMAT, emergencies internal and external, fire safety, medical equipment maintenance plan and maintenance plan for each of the utility system [6-10].

1.3. The Role of Healthcare Risk Managers: Risks to patients, staff, and organizations are prevalent in healthcare. Thus, it is necessary for an organization to have qualified healthcare risk managers to assess, develop, implement, and monitor risk management plans with the goal of

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minimizing exposure. There are many priorities to a healthcare organization, such as finance, safety and most importantly, patient care. Healthcare managers identify and evaluate risks as a means to reduce injury to patients, staff members, and visitors within an organization. Risk managers work proactively and reactively to either prevent incident or to minimize the damages following an event. Risk managers are trained to handle various issues in multiple settings. The duties a risk manager undertakes are ultimately determined by the specific organization. These professionals typically work in the following areas of medical administration:

- Financing, insurance, and claims management
- Event and incident management
- Clinical research
- Psychological and human healthcare
- Emergency preparedness

A risk manager is often someone who has experience in handling risk-related issues in multiple settings. This individual should be able to identify and evaluate risks, which should then reduce the potential for injury to patients, staff members and visitors. For example, a registered nurse should notice if a bed rail should be modified. But detecting risks and making adjustments to reduce those risks goes much further. They include not filling expired prescriptions (prevents abuse), following up on missing test results (to increase consultations), tracking missed appointments (to manage risks), increased communication with patients (reduce improper taking of medication), and preventing falls and immobility. With the expanding role of healthcare technologies, increased cybersecurity concerns, the fast pace of medical science, and the industry's ever-changing regulatory, legal, political, and reimbursement climate, healthcare risk management has become more complex over time. For these reasons, hospitals and other healthcare systems are expanding their risk management programs from ones that are primarily reactive and promote patient safety and prevent legal exposure, to ones that are increasingly proactive and view risk through the much broader lens of the entire healthcare ecosystem [7], [12,13].

2. Key Components of Performing Risk Management

Risk management in health care is defined by clinical and administrative activities undertaken to identify, evaluate, and reduce the risk of injury to patients, staff, and visitors and the risk of loss to the organization itself. With the release of the risk management draft guidance the FDA has come to the conclusion that it is necessary to fully consider the risk management process for certain products considered for approval and for continuous marketing.

2.1. Identify Risk: Since risk management involves managing uncertainty and new risk is constantly emerging, it is challenging to recognize all the threats a healthcare entity faces. However, through the use of data, institutional and industry knowledge, and by engaging everyone — patients, employees, administrators, and payers—healthcare risk managers can uncover threats and potentially compensatory events that otherwise would be hard to anticipate. Sources of risk identification:

Discussions with department Chiefs, managers and staff Patient Tracer Activity (Tracing the journey of a patient from admission until discharge):

- Retrospective screening of patient records
- Reports of accreditation bodies
- Incident reporting system & Sentinel events
- Healthcare Associated Infections (HAI) reports
- Executive committee reports
- Facility management & safety committee report
- Patient complaints and satisfaction survey results
- Specialized committee reports (such as Morbidity and mortality committee, medication management and use, infection control, blood utilization, facility management and safety committee) [6], [10]

2. Risk Assessment: For most medicines the benefits are limited to a few indications and for an individual patient there is usually only a single benefit sought but the potential risks are multiple. Although at the time of approval knowledge about efficacy from small, short-term clinical-trial populations is limited, far less is known about the drug's risks. The evaluation of the benefit: risk ratio of a drug is essential throughout the whole life cycle of a drug. During the discovery phase, the analysis of the biological targets as well as medical chemistry will allow selection of lead molecules with the best BRA potential over hundreds of candidate molecules. The review of the benefits and the risks associated with a drug is called benefit: risk assessment (BRA), or benefit-risk balance, or benefit-risk ratio evaluation. BRA is basically an evaluation of two dimensions. The dimension of benefits is measured primarily in terms of therapeutic efficacy, i.e., the successful treatment of the condition for which the drug is indicated. There are other types of benefits, such as improvement of quality of life or pharmacoeconomic aspects, that are of interest in a period where the costs of medicine are closely scrutinized. The dimension of risks includes the safety profile observed in the form of the sum of all ADRs, but also includes the potential risk of unobserved ADRs anticipated on the basis of the mechanism of action [13-15].

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2.3. Risk Quantification: In Europe, part of the mandate of the CHMP is to assess risks and benefits of authorized medicines on behalf of the EMEA. In 2007, the CHMP revised its guidance and included quantitative BRA in the regulatory agenda with the publication of a report examining the potential value of existing benefit–risk models and methods. Although no specific method was recommended, several BRA features were noted as being of value, including 1) all important benefits and medically serious risks are identified; and 2) the risks and benefits are weighted according to their relative importance and the strength of the evidence available. It was also decided that a comprehensive review of available quantitative methods for BRA relevant to the CHMP was required to explore further development of tailored methodologies. The EMEA created the ENCePP, which is in the process of developing an algorithm to articulate safety and benefit profiles for pharmaceutical products [16-18].

2.4. Development and Implementation of Risk Management Tools (eg, Risk Communication and Distribution and Behavioral Control Systems): Unsafe health care provision is a main cause of increased mortality rate amongst hospitalized patients all over the world. A system approach to medical error and its reduction is crucial that is defined by clinical and administrative activities undertaken to identify, evaluate, and reduce the risk of injury. WHO dra guideline and patient safety reports from different countries were reviewed for defining ac table framework of risk management system. 7 step in the Risk Management process are establishment e co identifying, analyzing, evaluating, and t ating e risks, continuous monitoring and review, nt communi ation and consultation. The literature reports on many different methods, strategies, and easures to introduce innovations, guidelines, best ractice , or new procedures into clinical practice. Ef ti implementation of innovations seems to e ore uccessful with strategies for implementation hat ar tailore to the specific goals, target group and se ing [

2.5. Evaluation of the effectiveness of tools and implementation of design modifications: The design and conduct of a range of experimental and non-experimental quantitative designs are considered. Such study designs should usually be used in a context where they build on appropriate theoretical, qualitative and modelling work, particularly in the development of appropriate interventions. Evaluation informs the choice between alternative interventions or policies by identifying, estimating and, if possible, valuing the advantages and disadvantages of each. Campbell and colleagues have suggested that the evaluation of complex interventions should follow a sequential approach involving:

- Development of the theoretical basis for an intervention;
- Definition of components of the intervention (using modelling, simulation techniques or qualitative methods);
- Exploratory studies to develop further the intervention and plan a definitive evaluative study (using a variety of methods);
- Definitive evaluative study (using quantitative evaluative methods, predominantly randomized designs) [21].

3. Overview of risk management around the world

- **ENCePP**: In 10 years, the ENCePP has made a major contribution to the benefit-risk evaluation of medicinal products in Europe and beyond by providing methodological recommendations complementing regulatory guidance o PASS. erhaps most importantly, ENCePP has create strong Eu pean community supporting meth dolo al stan ards, transparency, and scientific ind pendence i harmaco-epidemiological research [2
- **ASHRM**: ASHR Annual onference and Exhibition 2019 is g to take p c in Oct 13 - 16, 2019 (Baltimore, Maryla with the mission statement "To provide health re risk ma agers with the resources, knowledge and support to strategically and broadly manage risk, reduce uncer inty, add value, and advance health and safety". The id ntified risks were confirmed through a survey of isk managers from a range of global healthcare organizations during the ASHRM conference in 2017. In 2014, the ASHRM proposed risk domains for healthcare organizations, but again, risk events and scenarios are not described in detail. Other institutions, such as HIROC (Canada) and the NHS (England) have developed risk taxonomies that include clinical risks and enterprise risks. Finally, the risks are categorized by group using the ASHRM domains and COSO factors as guidelines [23-25].
- **HIROC**: HIROC, together with IRM Steering Committee comprised of risk management experts from various healthcare organizations, developed a web-based IRM Risk Register program in 2014. The 2016 top active risk themes were: patient care (30%); human resources (16%); financial (12%); leadership (11%); and information management/technology (10%). The top five active risks (by frequency) were: revenue/funding, regulatory/legislation; care communication; medication; and recruitment/retention of staff. The top five active risks (by rating) were: access to care, accreditation, adverse events, aging/maintenance of infrastructure, benefits/overtime [26].

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Exhibit 2. 7 steps to IRM detailed by Borovoy, 2019 [27]
▪ Exploration & Decision ▪ Risk Register Sign-On ▪ Ownership & Coordination ▪ Risk Identification ▪ Risk Register Validation ▪ Sustainability & Review Process ▪ Risk Register IRM Ongoing Development & Knowledge Sharing

4. Healthcare Risk Management Plan

Medicinal products are given authorization on the basis that, the risk-benefit balance is judged to be positive for the target population at the time of authorization. They appear to be safe and well tolerated but safety in actual world is unclear as there are many limitations during clinical trials as medicinal products are studied in homogeneous population in limited number in ideal conditions and with limitations in terms of age, sex, race and ethnicity; co-morbidity, restricted co- medication, relatively short duration of study and follow up and the marketed drug addresses huge population and relatively longtime exposure. Thus, risk management plan plays a vital role in both pre and post approval of drug The Risk Management Plan becomes the guiding document for how an organization strategically identifies, manages and mitigates risk. Hospital leadership and all department heads should be aware of and involved in the development and on-going evaluation of the plan. Healthcare risk management plans communicate the purpose, scope, and objectives of the organization's risk management protocol. They also define the roles and responsibilities of the risk manager and other staff involved in risk mitigation. Reviewing other studies is one way to develop risk management programs. Following the directives of governing organizations such as the Department of Health and Human Services, FDA, and ASHRM ensures risk management compliance. Using analysis results, risk managers can compare the likelihood of different adverse events along with the impacts and rank potential risks in terms of severity. Plans for mitigating risks and handling them appropriately can then be developed. Risk management plans also undergo quality assessments so the interventions and actions proposed are addressed as real potential issues. Once a strategy is in place, it is monitored and modified as needed [6,7].

Exhibit 3. USAID detailed Risk Management Plan steps [28]
▪ Step 1: Establish your context ▪ Step 2: Identification of possible risks ▪ Step 3: Assessment ▪ Step 4: Potential risk treatments ▪ Step 5: Create a risk management plan ▪ Step 6: Implementation ▪ Step 7: Evaluate and review

4.1. Effective Patient Care Practices

The development and implementation of healthcare risk management programs are based on extensive ongoing research. Risk managers must stay up-to-date on relevant information in their organization because research results could prove contradictory to presumptions that would otherwise shape risk management practices. For example, one study published by JAMA Internal Medicine revealed that increasing the hours of sleep residents in teaching hospitals received actually compromised patient safety. The risk-management outcome was to ensure that strategies were in place to improve resident's sleep schedules and reduce potential risks to patients. There are several challenges ahead for cultivating an effective and positive safety culture in healthcare organizations. To keep pace with international standards, healthcare managers must employ modern methods of management in order to overcome the challenges faced by the institutionalization of safety culture and to make a difference in the healthcare system. Safety experts have suggested the essential components for safety culture such as teamwork, leadership support, communication, and a just culture as well as a reporting and a learning culture [6], [29].

4.2. RMP safety specifications

It summarizes on important identified risks, important potential risks, and missing information due to limitations of clinical trials. It helps to identify needs for data collection and helps in the construction of pharmacovigilance plan. The purpose of the safety specification in the RMP is to provide a synopsis of the safety profile of the medicinal product(s) in the intended population as described in the approved Summary of Products Characteristics (e.g. therapeutic indications, or contraindications), and should include what is known and areas of uncertainty about the medicinal product(s). In the safety specification of RMP, important identified or potential risks or missing information related to the use of the medicinal

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products in the target population and potential off-label use, should be discussed with reference to pharmacogenomics. The aspects indicated below should be considered [30].

4.3. Implementing Strategies for Patient Care

In clinical studies, for example, IRBs monitor proposed research plans before they are implemented to ensure minimal risk to human subjects. Plans for risk management must cover patient-specific risks and be well documented; they must also be accessible to those working with patients. Research indicates that clinical guidelines are often not applied. The success of their implementation depends on the consideration of a variety of barriers and the use of adequate strategies to overcome them. It is estimated that about 30%–40% of patients receive treatment that is not based on scientific evidence, and 20%–25% receive treatments that are either not needed or potentially harmful. In addition, it is estimated that more than 50% of Americans do not take medications as they are prescribed, and approximately one third do not finish the course of therapy or skip doses. A successful introduction of guidelines involves the three steps of development, dissemination and implementation. Many patient risks can be reduced by adequately training physicians and staff, encouraging strong communication among staff-members, providing counseling services for those working with patients, and conducting competency assessments. Other risks posed to patient safety can be mitigated using patient-specific risk management strategies such as:

- **Not filling expired prescriptions**: Interpersonal communication is inherent in a majority of strategies seeking to engage health care professionals in the reduction and prevention of prescription drug abuse. Sending patients adequate notification of prescription expiration will support communication between patients and physicians thus reducing potential prescription medication abuse.
- **Following up on missing test results**: Failure to follow-up can lead to missed or delayed diagnoses which impact on patient care and can also have medico-legal implications for health services and health professionals. Patients who need to take additional medical tests following appointments may fail to do so, or the test results might get lost. Developing a plan to monitor receipt of test results guarantees the results are reviewed, so patients can then be consulted.
- **Tracking missed appointments**: The problem with missed appointments is that continuity and effectiveness of healthcare delivery is compromised, appropriate monitoring of health status lapses, and he cost of health services might increase. Furthermore, some studies have shown a relationship between missed appointments and sub-optimal clinical outcomes among patients with chronic diseases Implementing a system to follow-up with patients who miss appointments but fail to reschedule is another proactive step in managing patient risks.
- **Communicating with patients**: Evidence supports the importance of communication skills as a dimension of physician competence. Effort to enhance teaching of communication skills to medical trainees likely will require significant changes in instruction at undergraduate and graduate levels, as well as changes in assessing the developing communication skills of physicians. Patients may have limited understanding of information received from physicians. Having a strategy that checks the patient's comprehension of information reduces the likelihood that the patient will misinterpret a physician's orders or will improperly take medication. Successful communication should be uncomplicated, to the specific, use some repetition, minimize jargon, check patient understanding.
- **Prevent falls and immobility**: Although estimates of fall rates vary widely based on the location, age, and living arrangements of the elderly population, it is estimated that each year approximately 30% of community-dwelling individuals aged 65 and older, and 50% of those aged 85 and older will fall. Of those individuals who fall, 12% to 42% will have a fall-related injury. Making minor modifications to things like bed rails, bathtubs and toilets lacking grab bars, institutional lighting, and the conditions of the ground can significantly reduce the risks of such hazards.
- **Sufficient record retention** - Keeping patient records on file for an extended period of time or indefinitely is useful for monitoring patient health, even when patients are not actively seeking care. Risk management protocol should also have plans in place for disposing of records in accordance with federal mandates. However, the widespread use of EHRs was delayed by high costs, data entry errors, poor initial physicians' acceptance, and lack of any real incentive. The goal of replacing the entire paper chart with an electronic record was considered problematic due to the large initial costs resulting in the view that only key data should be computerized. As a result, the EHR would complement and not replace the paper record [31-37].

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Exhibit 4. EU pharmacovigilance terminology [38]	
Term	**EMA definition**
Abuse	Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)]
Medication error	An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient
Misuse	Situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorization
Occupational exposure	For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product
Off-label use	Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization. Examples include the intentional use of a product in situations other than the ones described in the authorized product information, such as a different indication in terms of medical condition, a different group of patients (e.g. a different age group), a different route or method of administration or a different posology. The reference terms for off-label use are the terms of marketing authorization in the country where the product is used
Overdose	Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. When applying this definition, clinical judgement should always be applied

5. Pharmacovigilance planning

An RMP serves as the central document in pharmacovigilance activities for an individual product, and contains three elements: (1) a safety specification describing the potential and identified risks as well as important missing information on adverse effects, (2) the pharmacovigilance plan which describes proposals to acquire more data on possible risks, identified risks, and missing information, and (3) the risk minimization plan. RMPs are prepared and maintained by the pharmaceutical companies, but require approval by regulatory authorities, who may require companies to add new risks to the RMP or to initiate new risk minimization activities, including new studies for safety or efficacy. The newest EU legislation requires a summary of the RMP to be made public. In November 2013, a team of European regulators initiated the SCOPE Joint Action; The SCOPE Joint Action was a public initiative co-ordinated by the MHRA in the UK. The SCOPE project evaluated then-current practices and developed tools to further improve the skills and capability in the pharmacovigilance network. The project was divided into eight separate work streams, five of which concentrated on pharmacovigilance topics—collecting information on suspected adverse drug reactions, identifying and managing safety issues (signals), communicating risk and assessing risk minimization measures, supported by effective quality management systems. The other three work streams focused on the functional aspects—coordination, communication and evaluation of the project. Through the project, SCOPE delivered guidance, training in key aspects of pharmacovigilance, and tools and templates to support best practice. 2015 marks an important milestone in the maturity of medical biotechnology, with five or more biosimilar applications pending review by the US FDA. For the first time, a number of manufacturers will produce a series of highly similar but not identical medicines for the US market. It is important that the specific biologic or manufacturer is readily identified to ensure accurate tracing of AEs to the administered product. Increased use of barcodes on biologic drugs should improve tracing capabilities, as should implementation of the US DQSA/DSCSA, which outlines use of an interoperable electronic system to identify and trace prescription drugs in the USA. In the USA, post-approval safety signal detection is performed primarily using SRS and AS systems. SRSs (e.g., MedWatch and institution-based reporting) are considered passive surveillance methods, which rely on voluntary reports from physicians, pharmacists, other healthcare providers, and patients. AS methods include retrospective analysis of medical records at Sentinel-affiliated sites and drug or disease registries, as well as use of drug event monitoring (e.g., surveys of patients identified through electronic prescription data. Brand name reporting for biologics in SRSs can vary by the product class and jurisdiction. For example, 84 % use of accurate brand names has been reported for insulins in the USA, whereas product-specific attribution of epoetins approached 99 % in the European Union (EU).In recent years, the scope and objectives of pharmacovigilance have expanded manifold due to changes in the global pharma environment, improved access to medicines, varied utilization of medicines and availability of newer, more powerful tools and databases for tracking and analyzing data; however, the discipline needs to evolve further to meet both public health

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system needs and consumer expectations. The recent efforts directed to enable the shift toward proactive PV and establishing global PV practices show that harmonized PV practices are required to meet the needs of the various stakeholders in PV (including health authorities, the pharmaceutical industry, health-care professionals, and consumers). In addition, harmonization would also promote the safer use of medicines and public health protection. The existing working practices of a particular region are directly correlated to the PV legislation that exists in that region. By defining the minimal requirements and practices, PV legislation thereby helping define how safety information about medicinal products is reported to enable adequate benefit-risk assessment. While much progress has been made in PV practices, many deficiencies and issues still exist in the efforts to ensure safe medicine usage. It requires formal training for PV professionals and better communication tools. Safety information is communicated between different regulatory agencies, regulatory agencies and manufacturers, healthcare professionals and manufacturers, agencies and healthcare professionals, healthcare professionals and consumers. All parties in communication utilize different tools– from product labeling to adverse event reports [38-43].

Drug	Adverse event
Sodium glucose co-transporter 2 inhibitors	Diabetic ketoacidosis (atypical presentation)
Risperidone	Cerebrovascular events in patients with dementia
Infliximab	Non-melanoma skin cancer (particular in psoriasis)
Methotrexate	Hepatitis B reactivation
Non-steroidal anti-inflammatory drugs (over-the-counter doses used for prolonged periods)	Cardiovascular events Diclofenac – hepatotoxicity
Combined oral contraceptives and hormonal replacement therapy	Potential link with inflammatory bowel disease
Metoclopramide	Extrapyramidal events and cardiac conduction – new recommendations for prevention
Pregabalin	Suicidal ideation
Zolpidem	Next day impairment
Duloxetine	Serotonin syndrome
Rotavirus vaccine	Intussusception
Denosumab	Severe hypocalcemia
Proton pump inhibitors	Acute interstitial nephritis
Clozapine	Constipation
Exenatide	Pancreatitis

6. Developing risk minimization plans/risk mitigation strategies

An RMP documents the risk management system required to identify, characterize and minimize a product's important risks. The TGA requires RMPs to be submitted for evaluation with certain higher-risk applications to enter a medicine or biological in the ARTG or to vary an ARTG entry. An RMP (or RMP update) will normally be expected with applications involving a significant change to an existing registration, such as a: significantly different population; pediatric indication; new dosage form or route of administration with inherently higher risk (e.g. oral tablets vs IV injection); new manufacturing process of a biotechnologically-derived product or other significant change in indication. RMPs must be maintained throughout the lifecycle of the product and important updates submitted to the TGA for evaluation. A new RMP has to be submitted whenever TGA requests; whenever there is a significant (material) change to the RMP, including but not limited to: when the RMP is modified as a result of new information that may lead to a change to the benefit-risk profile; when an important (product vigilance or risk minimization) milestone is reached; or an activity is terminated, added, or substantially altered; when changes to the summary of ongoing safety concerns are made. This guidance:

- Explains when you must submit an RMP with an application for registration, inclusion or variation in the ARTG
- Describes what to include in an RMP and the required format for RMPs
- Details special requirements for RMPs for biologicals
- Outlines how the TGA evaluates RMPs
- Explains when to submit RMP updates after regulatory approval
- Describes how the TGA monitors sponsor compliance with RMP commitments

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Similarly, Companies are required submit an RMP to the EMA when applying for a marketing authorization. To help applicants, EMA developed guidance on how to submit RMPs. RMPs include information on:

- A medicine's safety profile;
- How its risks will be prevented or minimized in patients;
- Plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine;
- Measuring the effectiveness of risk-minimization measures.

In the EU, companies must submit an RMP to the Agency at the time of application for a marketing authorization. For medicines that do not have an RMP, one may be required with any application involving a significant change to the marketing authorization. In addition, for nationally authorized medicinal products, any NCA in the EU can request an RMP whenever there is a concern about a risk affecting the benefit-risk balance of a medicine. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available. Companies need to submit an updated RMP:

- At the request of EMA or an NCA;
- Whenever the risk-management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit-risk profile or as a result of an important pharmacovigilance or risk-minimization milestone being reached.

When justified by risk, the competent authority can also specify a date for submission of the next RMP as a condition of the marketing authorization in exceptional cases. RMPs can only be submitted at the same time as the PSUR if the change in the RMP comes as a consequence of the PSUR [44,45].

7. Planning and implementation of Risk Minimization Measures (RMMs)

An important element of risk management is the planning and implementation of RMMs and the evaluation of their effectiveness by process or outcome indicators. The effectiveness of RMMs can be evaluated by process and/or outcome indicators. Process indicators measure the extent to which a program was implemented, whether the execution was as planned, and the impact on knowledge and behavior of the target population. Outcome indicators provide an overall measure of the level of risk control achieved by RMM, for example, measuring rates of an adverse drug reaction or other safety-related outcome. Evaluation of effectiveness of RMMs is important to maximize the benefit-risk balance of a medicinal product. Effectiveness of RMMs can be evaluated by using cross-sectional survey studies and studies using secondary data sources. The EU PAS Register proves to be a valuable resource for identifying studies evaluating the effectiveness of RMMs in Europe. Half of the effectiveness indicators (process and/or outcome) were reported as successful [45].

Exhibit 6. A suggested set of strategic activities by the risk minimization function [46]

- Leading strategic planning for risk minimization activities for the research portfolio as a whole as well as for individual products;
- Executing or overseeing the execution of "best-in-class" risk minimization program design, implementation, and evaluation using knowledge from implementation science in health;
- Conducting targeted research to develop improved risk minimization tools, methodologies, and evaluation approaches that support the company's pipeline and marketed products' portfolio;
- Establishing a knowledge management system that: a) documents both internal and external "lessons learned" and the evolving risk minimization requirements and practices of regulatory authorities worldwide; and b) promulgates best practices in risk minimization science to internal teams;
- Optimizing operational and cost efficiencies of risk minimization processes by standardizing processes where appropriate and leveraging preferred supplier and service provider arrangements;
- Publishing risk minimization evaluations and research findings in order to advance the science in a "pre-competitive" context; and
- Achieving a sustained level of compliance globally with regard to risk minimization commitments through standard setting, monitoring, and ongoing technical support to company affiliate offices.

8. Incorporating Risk Management and Quality Improvement into Organizational Planning

Quality improvement involves a combined effort among health care staff and stakeholders to diagnose and treat problems in the health care system. However, health care professionals often lack training in quality improvement methods, which makes it challenging to participate in improvement efforts. Quality improvement and the management of risks in health care should be part of both strategic and operational planning in every area and service of healthcare delivery, clinical and nonclinical. Risk management and quality improvement should be considered as an integrated approach when determining clinical practice, equipment design and procurement, capital development, information technology, contractor management, workplace health and safety, workforce management, and financial planning, and all other areas of operation.

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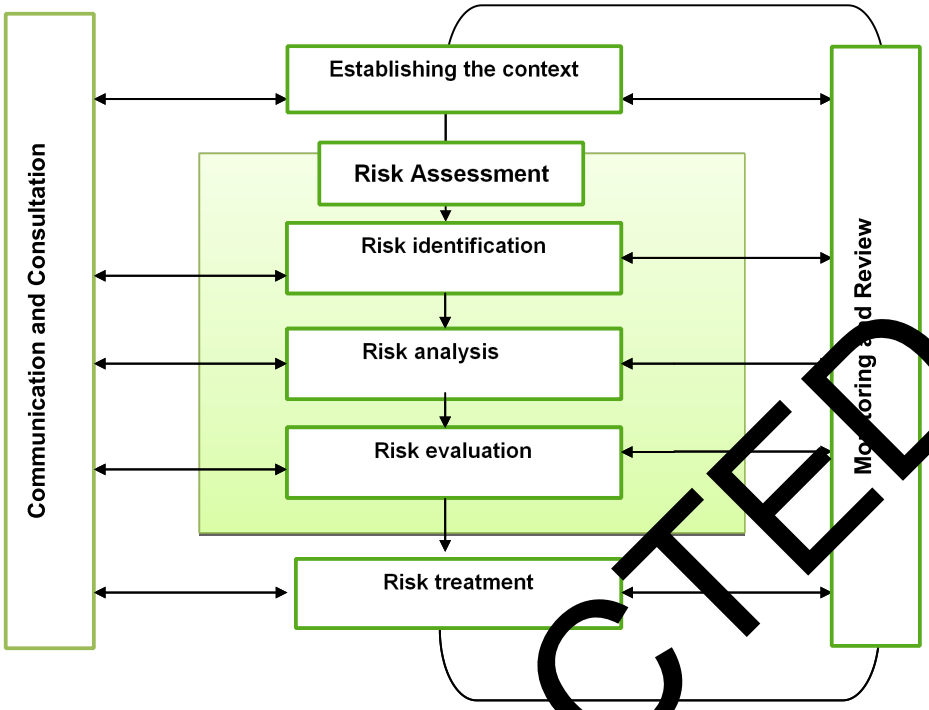

Figure 1: Risk management process overview (Source: AS/NZS ISO 31000 — 2009 Risk management — principles and guidelines)

Healthcare organizations' systems for risk management and quality improvement are reviewed within the NSQHS Standards under Standard 1: Governance for Safety and Quality in Health Service Organizations. In addition, NSQHS Standards 3-10 require organizations to undertake a risk assessment of their systems. For example, NSQHS Standard 4 requires a risk assessment of medication management systems. These risk assessments are managed by the associated governance committees with key risks also being represented on the organization-wide Risk Register. The same applies for quality plans. Organizations are required to submit a Quality Improvement Plan at each phase of their accreditation cycle and have a register of the organizational risks (Risk Register) available for ACHS surveyors at each onsite survey. For risk management and quality improvement programs to be most effective, the governing body and leadership team must demonstrate commitment to the processes and define their expectations for all stakeholders. In addition, the leadership team should ensure that there are sufficient resources to meet the requirements of the organization and systems to effectively mitigate, control and manage all risks, and that attention is focused on the core business of the organization – to care for and treat consumers / patients in a safe and high-quality clinical environment. Risk management and quality improvement systems are both directed to providing a structured framework for identification, analysis, treatment / corrective action, monitoring and review of risks, problems and/or opportunities. Communication and consultation with stakeholders are critical for these processes to work effectively. Continuous improvement and risk management are data driven. They depend on relevant information being provided to the executive, clinicians, managers and the governing body. The data and information provided should reflect the issues that are most significant to the organization, rather than just for the process of data and information collection itself. A range of tools that can be used for quality improvement also applies to analyzing risk issues [47-51].

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Exhibit 7. The integrated risk management and quality improvement framework, documented in a plan that is provided to all staff members [47]

Risk Management	Overlapping Functions	Quality Improvement
• Accreditation compliance • Claims management • Consumer / patient relations and disclosure • Contract / policy review • Corporate and regulatory compliance • Mandatory event reporting • Risk identification, e.g. near miss and adverse event reporting • Risk control, e.g. loss prevention and loss reduction • Risk financing • Safety and security • Workers compensation	• Accreditation issues • Analysis of adverse and sentinel events and trends • Board reports • Consumer / patient complaint handling • Consumer / patient education • Feedback to staff and healthcare providers • Proactive risk assessments • Public reporting of quality data • Provider credentialing • Root-cause analysis • Staff education and training • Strategic planning	• Accreditation coordination • Audits / benchmarking / clinical indicators etc. • Best practice / clinical guidelines • Consumer / patient satisfaction • Improvement projects • Peer review • Provider performance and competency • Quality methodology Quality of care reviews Utilization / resource /case management

Users of the health care system also possess unique knowledge and experiences that can inform quality improvement efforts and help design systems around the needs of the patient rather than the staff or organization. However, there is much debate over how to meaningfully involve patients and caregivers in quality improvement. Experience suggests that projects have a clear rationale and defined roles and responsibilities for patients and caregivers [48].

Exhibit 8. Roles that patients and caregivers have played in quality improvement [48]

- Identifying improvement opportunities
- Creating a sense of urgency for change with storytelling
- Acting as an outlet to solicit other patient experiences
- Offering change ideas to redesign systems of care
- Persuading healthcare providers that quality of care problems exists and need to be addressed

A staff lead is assigned as the primary liaison for the group, with one or more assistants who have the dual responsibility of supporting the lead and learning the process so they may serve as a future lead. Qualifications for staff lead include service as an assistant staff lead on a prior guideline panel, experience conducting literature searches and using a citation database, and a basic understanding of study design, medical terminology, and levels of evidence. Guidelines meeting certain quality standards are included in the NGC database, an initiative of the Agency for Healthcare Research and Quality NGC inclusion criteria are:

1. The clinical practice guideline contains systematically developed statements that include recommendations, strategies, or information that assists physicians and/or other health care practitioners and patients make decisions about appropriate health care for specific clinical circumstances.
2. The clinical practice guideline was produced under the auspices of medical specialty associations; relevant professional societies, public or private organizations, government agencies at the federal, state, or local level; or health care organizations or plans. A clinical practice guideline developed and issued by an individual not officially sponsored or supported by one of the above types of organizations does not meet the inclusion criteria for NGC.
3. Corroborating documentation can be produced and verified that a systematic literature search and review of existing scientific evidence published in peer reviewed journals was performed during the guideline development. A guideline is not excluded from NGC if corroborating documentation can be produced and verified detailing specific gaps in scientific evidence for some of the guideline's recommendations.
4. The full text guideline is available upon request in print or electronic format (for free or for a fee), in the English language. The guideline is current and the most recent version produced. Documented evidence can be produced or verified that the guideline was developed, reviewed, or revised within the last five years [51.52].

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9. Risk Management Processes and Strategies

Risks should be considered using existing processes such as audits, data, trends, literature and risk assessment tools, as well as via planned reviews of issues with stakeholders through mechanisms such as brainstorming sessions. Tools used to screen and/or assess risks will vary depending on the risk being assessed. For example, consumer / patient risk screening and/or assessments such as falls risk or mobility assessment tools will be different from tools used to assess risks to achievement of strategic goals, or workplace safety risks. It is important that any tool used is validated by an expert internal source and/or agreed for use by the governing body. Examples of processes and strategies that assist with risk identification and management include:

Exhibit 8. Five Basic Initiatives to Manage Risks [53]

- **Prevention**: Proactive risk awareness and safety programs ensure that staff members are aware of potential risks and provide an understanding of how they can help protect patients, visitors and themselves.
- **Correction**: Post-incident remedial actions minimize the impact of adverse events and help prevent future events.
- **Documentation**: Thorough and complete patient records, as well as comprehensive policies and procedures, facilitate better communication and stronger legal defense efforts when necessary.
- **Education**: Creative and meaningful programs engage personnel in organizational risk-reduction initiatives, leading to a more empowered and effective staff.
- **Interdepartmental coordination**: Creating a framework that encourages departments to work together fosters a safer organizational environment. Together, these five elements allow

Clinical examples

- Collection and effective use of clinical indicators
- Morbidity and mortality reviews
- Clinical audits
- Adverse outcome screening and clinical incident reporting
- Health record audits and clinical content reviews
- Medical emergency reviews
- Medication management strategies
- Consumer / patient risk assessments (e.g. Falls, pressure areas, VTE)
- Peer review and peer supervision
- Effective use of complaints and feedback from consumers / patients and staff
- Evidence, literature, research.

Non-clinical examples

- Collection and effective use of indicators relevant to the organization
- Audit processes
- Budget variance monitoring
- Project activity reports
- Purchasing and product evaluation
- Fraud minimization schemes
- WHS risk assessments and hazard identification
- Lost time injury reports
- Political change management strategies
- Workplace safety strategies
- Financial management strategies
- Contingency and disaster planning
- Redundancy in systems
- Information technology and data entry system infrastructure and capabilities
- Workforce planning
- Credentialing and defining the scope of clinical practice for all clinicians
- Recruitment and retention strategies
- Education and mandatory training programs for staff
- Staff performance review and development
- Equipment maintenance and replacement schedules
- External contract reviews [47].

Conclusion

Several activities proposed by the RMPs do not appear to be adequate in dealing with the potential risks of drugs. Poor communication of risk to practitioners and to the public, and above all limited transparency for the total assessment of risk, seem to transform RMPs into a tool to reassure the public when inadequately evaluated drugs are granted premature marketing authorization. As discussed previously, once the FDA guidance is finalized, certain new drug applications will require a Risk MAP. The purpose of this program will be to propose, design, implement and evaluate a number of interventions intended to minimize the risks of using the drug. In similar fashion to a clinical development program, the Risk MAP will have a defined set of goals and objectives, developed specifically for the drug in question. Each Risk MAP must specify the overall goals of the program, (eg, specifying that no pregnant woman be prescribed a specific drug). For each goal, one or more objectives should be specified. These are intermediate steps necessary for achieving the overall goal, for example, specifying that all physicians must fully inform women patients about the risks of taking a drug if pregnant. Finally, a number of tools or interventions must be specified that will aid in obtaining the specified goals and objectives, for example, specifying that there will be a brochure and a video drafted for physicians to distribute to patients. Each of these tools should be justified and pretested to help assure that they will achieve

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their intended purpose(s). Risk management is a new and evolving discipline. It is difficult to argue that drugs should be provided to patients in a manner that minimizes potential hazards. The evaluation of safety of a pharmaceutical or biological product is carried out throughout the lifecycle of the compound. In order for a biopharmaceutical company to be prepared for post-approval safety monitoring, evaluation and mitigation, it must know what is required in terms of an RMP and a REMS and development of these tools must be started during drug development. Post-approval safety is not just a post-approval consideration. The FDA has advanced the public health by fostering greater attention over the discovery, quantification, and management of risks. However, any policy that results in new activities to control one set of hazards may result in creating new, unexpected, hazards. Thus, continuing to evaluate the hazards of drugs and the interventions intended to control these hazards, is essential to assure that the benefits of a Risk Minimization Program will, itself, outweigh its risks.

Abbreviations: Institute of Medicine (IOM); Risk Minimization Action Plan (Risk MAP); Committee for Medicinal Products for Human Use (CHMP); Benefit: Risk Assessment (BRA); European Medicines Agency (EMA); European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP); Centers for Disease Control (CDC); Enterprise Risk Management (ERM); Hazardous Materials And Waste Disposals (HAZMAT); Post-Authorization Safety Studies (PASS); American Society f Health Care Risk Management (ASHRM); American Hospita Association (AHA); Healthcare Insurance Reciprocal of Canada (HIROC); National Health Service in England (NHS); Committee of sponsoring organizations of the treadway Commi (COSO); Integrated Risk Management (IRM); The United States Agency for International Development (USAID); Institutional Review Boards (IRBs); Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE); Medicines and Healthcare products Regulatory Agency (MHRA); Drug Quality and Security Act/Drug Supply Chain Security Act (DQSA/DSCSA); Spontaneous Reporting Systems (SRSs); Active Surveillance (AS); Australian Register of Therapeutic Goods (ARTG); Periodic Safety Update Report (PSUR); National Competent Authority (NCA); Risk Minimization Measures (RMMs); Healthcare Associated Infections (HAI); European Union electronic Register of Post-Authorization Studies (EU PAS Register); National Safety and Quality Health Service (NSQHS); Work Health And Safety (WHS); Venous Thromboembolism (VTE); The Australian Council on Healthcare Standards (ACHS); National Guideline Clearinghouse (NGC)

Article Highlights:

- It is estimated that about 30%–40% of patients receive treatment that is not based on scientific evidence, and 20%–25% receive treatments that are either not needed or potentially harmful.
- More than 50% of Americans do not take medications as they are prescribed, and approximately one third do not finish the course of therapy or skip doses.
- Risk perceptions (including deliberative, affective, and experiential) are often targeted in health behavior change interventions.
- During the discovery phase, the analysis of the biological targets as well as medical chemistry will allow selection of lead molecules with the best BRA potential over hundreds of candidate molecules.
- Unsafe health care provision is a main cause of increased mortality rate amongst hospitalized patients all over the world.
- Risks should be considered using existing processes such as audits, data trends, literature and risk assessment tools as well as planned reviews of issues with stakeholders through mechanisms such as brainstorming sessions.
- Risk management and quality improvement systems are both directed to providing a structured framework for identification, analysis, treatment / corrective action, monitoring and review of risks, problems and/or opportunities.
- Risk management plans also undergo quality assessments so the interventions and actions proposed are addressed as real potential issues.
- Effort to enhance teaching of communication skills to medical trainees likely will require significant changes in instruction at undergraduate and graduate levels, as well as changes in assessing the developing communication skills of physicians.
- 84 % use of accurate brand names has been reported for insulins in the USA, whereas product-specific attribution of epoetins approached 99 % in the EU.
- IRM Risk Register program in 2014. The 2016 top active risk themes were: patient care (30%); human resources (16%); financial (12%); leadership (11%); and information management/technology (10%).

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