RISK MANAGEMENT PLANNING AND MANDATED POST-AUTHORIZATION STUDIES
Early Planning for Customized Solutions

AUTHORS:

CARLA BARRETT, PHARM.D
Senior Director, Patient Safety & Risk Management

CATHERINE GODEFROY, PHARM.D, MSc
Executive Director, Patient Safety & Risk Management

MEG RICHARDS, PHD, MPH
Executive Director, Scientific Affairs, Real World Solutions

BETTINA RILLMANN, RPh, MSc
Director, Scientific Affairs, Real World Solutions
EXECUTIVE SUMMARY

Complex pharmacovigilance legislation in an evolving regulatory landscape has left drug makers searching for efficient and meaningful solutions for their drug safety challenges, especially in the post-marketing arena. Companies are seeking expert advice and customized approaches to collecting, managing, and analyzing real world evidence to gain a competitive advantage.

In the past decade, post-marketing safety and risk management has witnessed a fundamental shift from monitoring to applying a benefit-risk paradigm; proactive signal detection and periodic benefit-risk evaluation are the key focuses. The US Food and Drug Administration (FDA) has moved from RiskMAP to risk evaluation and mitigation strategy (REMS) and required post-marketing studies to collect real world evidence to support new drug applications (NDAs) and biologic license applications (BLAs). The European Medicines Agency (EMA) introduced the guideline on good pharmacovigilance practices (GVP), which replaced the previous Volume 9A of the Rules Governing Medicinal Products in the EU. Revisions to EMA GVP Module V Risk Management Systems and GVP Module VXI Risk Minimization Measures include a selection of tools and effectiveness indicators to provide further guidance on the expected changes to the risk management plan (RMP) during the product’s life cycle, and to clarify what should be included in an RMP. The need to collect and analyze real world data to support the periodic evaluations warrants new or revised proactive measures to minimize critical risks and improve overall effectiveness of medicinal products.

PRA Health Sciences (PRA) Pharmacovigilance & Patient Safety (PVS) and Real World Solutions (RWS) experts provide unique strategies developed from years of significant first-hand experience in this area. Our integrated global teams have significant experience identifying innovative solutions to satisfy key regulatory requirements. They work with other PRA teams (eg. Medical Affairs, Medical Informatics, Data Sciences, Regulatory Affairs, Data Operations, and Biostatistics) to provide end-to-end risk management services including post-marketing requirements such as post-authorization safety studies.

---

**POST-APPROVAL: PLAN EARLY FOR THIS KEY STAGE OF DRUG DEVELOPMENT**

Proactive planning is key in successful post-marketing risk management. By planning for post-marketing and risk management activities early in the drug development process, sponsors can facilitate a greater return on investment by anticipating future data requirements and collecting these data early in clinical development, which can then be leveraged in peri- and post-approval research.

The number and type of patients in a post-approval study vary greatly from those studied in earlier phase clinical trials (Figure 1). Post-approval studies generally involve much larger numbers of patients who are more heterogeneous (different) than their homogeneous (alike) early phase counterparts. Post-approval studies are conducted under real-world conditions, not the highly controlled conditions of a randomized controlled trial. Post-marketing studies help to identify trends, outcomes, and safety signals in large, “real-life” populations.

![Figure 1: Post-Authorization - An Integral Stage of Drug Development](image)

Regulations mandate that clients conduct periodic benefit-risk evaluations and effective risk management planning and submit either an RMP or REMS to obtain product approval. For instance, the EMA requires RMPs as part of the initial Marketing Authorisation Application (MAA), whereas the FDA may request a REMS to minimize specific risks. Several regulatory agencies in the rest of the world (ROW) also request or require companies to submit risk management planning documents as part of the licensing application. To address these requirements effectively, it is vital to understand how key agencies define risk management.
Strategy and Design Implementation

PRA’s strategy when designing a product-specific risk management system is to characterize and minimize risks to patient safety. Using lessons learned and strategies acquired through decades of experience, our PVS and RWS teams collaborate with clients to identify the critical regulatory requirements for successful risk management planning and execution. Our proactive approach ensures our teams effectively interact with regulatory authorities and key stakeholders to create a harmonized approach to pharmacovigilance and risk minimization efforts.

Risk Management Life Cycle

PRA recognizes that risk management in support of a medicinal product (drug, biologic, vaccine) is applicable at any stage of development and is often a significant component of the product’s life cycle. A risk management document is also an important element of the MAA or NDA dossier. Our teams identify innovative solutions to satisfy regulatory requirements for planning and execution needs. Our integrated team works with in-house and client groups to:

- Develop strategic and tactical plans to characterize and quantify safety concerns and minimize risks to patients
- Create risk management documents such as developmental RMP, core RMP, EU-RMP, local RMP or REMS
- Provide support throughout the submission process
- Customize risk management strategies to local requirements
- Design and implement interventions or studies that align with risk management and data collection objectives and effectively implement these actions or studies in the post-marketing world

The EMA defines a risk management system as a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent, or minimize risks relating to a medicinal product including the assessment of the effectiveness of those activities and interventions.

According to the FDA, risk management is an iterative process of:
- Assessing a product’s benefit-risk balance
- Developing and implementing tools to minimize risks and preserve benefits
- Evaluating the tools’ effectiveness and reasessing the benefit-risk balance
- Adjusting the tools to improve the benefit-risk balance
• Develop and implement additional risk minimization measures (aRMMs), including communication and educational materials, that align with the overall strategy while considering real world parameters

• Monitor/track risk management commitments to ensure oversight using a validated IT solution (eg, dashboard and report functions)

• Assess effectiveness of risk minimization measures

• Revise and update the risk management document, if warranted, as an outcome of the effectiveness evaluation, when a milestone is reached, actions are completed, or new safety concerns are identified

---

Figure 2: Risk Management Process

---

a RMD: Risk Management Document (eg, dRMP, core RMP, EU-RMP, local RMP, REMS)

b Submission step is not applicable for dRMP
PRA recommends that companies begin working on risk management systems early in the product life cycle (Phase II) by creating a developmental risk management plan (dRMP). PRA begins the risk management planning process with the signal-to-risk translation and risk assessment and characterization; these yield a list of safety concerns or “important risks.” Safety specifications are then created to describe the important identified and potential risks. We then perform a structured evaluation of the need for “additional measures” for pharmacovigilance and risk minimization/mitigation (other than “routine activities”). This is an iterative process of refining the list of additional pharmacovigilance (aPV) and additional risk minimization measures (aRMMs) that will be included in the regulatory submission.

Depending on the nature of risks, therapeutic indication, and level of required intervention, the RMM may involve standard risk communications (e.g., medication guide, patient information brochure, dear healthcare provider [HCP] letters, etc), educational materials (e.g., injector’s guide, patient alert card), or more restrictive activities (e.g., certification, controlled distribution) to assure safe use for addressing the risks. PRA also helps companies answer regulatory queries related to the risk management system and drafts tactical plans for implementation and effectiveness evaluation of aRMMs including outcome and process indicators, and practical timelines that are included in the licensing application.

**Evaluating Effectiveness of the Risk Management System**

Some regulatory authorities mandate that companies regularly evaluate their risk management plan’s effectiveness. The evaluation must report whether the individual RMMs (and risk management system as a whole) have been effective and specify whether any corrective actions/improvements are mandated. The measurement of effectiveness is achieved by looking at process indicators and outcome indicators as described hereafter.

**Process Indicators**
- Evidence of the RMM implementation
- Reach and uptake of RMMs in target audience
- Use/uptake in target audience
- Impact on clinical knowledge and prescribing behavior

**Outcome Indicators**
- Behavioral changes of health care professionals, patients, and care givers
- Clinical actions to avoid or minimize important risks
- Reduction in frequency/severity of important risks
During our comprehensive effectiveness evaluation, we perform an in-depth assessment that includes the following:

- Stakeholder surveys to assess compliance (eg, distribution of the medication guide or educational material) and stakeholder awareness of product risks
- Product distribution tracking to support stakeholder registries or national (proprietary) databases for continued product monitoring
- Stakeholder agreements for audits to produce on-demand proof of compliance with program requirements
- Internet surveillance to monitor availability of product outside the program
- Monitoring adverse events of special interest (AEOSIs) linked to the product’s known safety risks through standard pharmacovigilance activities
- Use of safety studies to measure effectiveness of additional risk minimization measures on pre-identified safety concerns

**Post-Marketing Studies (PMS)**

After granting marketing authorization for a medical product, the regulatory authorities frequently request the marketing authorization holder (MAH) to conduct a post-marketing study. In some countries PMS are mandated for all medicinal products that are marketed in that country.

These PMS have a common element to learn more about the safety and effectiveness of a medicinal product once available on the market, but PMS are also used to assess the effectiveness of risk minimization measures. Although PMS required by the different regulators globally have many similarities, there are specific requirements unique to each country and/or region. Our RWS experts have the experience to design and operationalize PMS in accordance with local requirements. This also includes communication with regulators such as the FDA and the Pharmacovigilance Risk Assessment Committee at the EMA.
**Protocol Design & Development of PMS**

Detailed guidance on protocol design and development is available from different sources, including EMA Guidance\(^4\), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide\(^5\), FDA Guidance for Industry\(^6\) and International Society for Pharmacoepidemiology (ISPE ) Guidelines\(^7\).

Depending on the primary objectives, a PMS is generally observational in nature, though may involve an interventional study design. PRA’s specialists (including ENCePP members and epidemiologists, as well as medical affairs, patient safety, and biostatistics professionals) have developed the following study protocol considerations for PMS, which are based on the requirements for EU Post-Authorization Safety Studies\(^8\):

- Define the milestones for study progress and reporting per the initial statement of work and agreed execution strategy
- Develop a strong study rationale with clear scientific objectives based on the concerns or questions that led to the study
- Develop measurable key performance indicators (KPIs) that align with the study’s scope and objectives
- Adequately and appropriately describe the data sources and study population in relation to the study’s objectives
- Detail the information collection and the control methodology that will be used
- Detail the rationale for the required sample size and statistical analysis in relation to the study’s objectives

PRA applies these considerations for PMS based on official guidelines and our experience in protocol evaluations by regulatory authorities.

---

\(^4\) Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies EMA/623947/2012


\(^7\) Guideline for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology

Implementation & Execution of PMS

The acceptability of study results and findings depends on data quality. Although quality is essential in any research project, the most frequent approach to defining data quality considers these principles that are the pillars for any type of research: data completeness and data validity.

These considerations also apply to PMS that are typically prospective and observational in design, with the limiting factor that medical procedures and assessments may not be mandatory. By applying principles that ensure data completeness and validity in real world research, PRA developed an approach that is based on stringent oversight to validate that existing data are aligned to routine practice and are correctly reported in accordance with the study protocol.

Our main objectives include:

- **Ensuring patient protection**: Make certain that patients are appropriately informed, their confidentiality is maintained, and the medical practice is based on the best benefit to the patients and not modified by their participation in the study.

- **Minimizing unreported data and errors**: All existing data of interest must reflect the reality—motivating and maintaining awareness of sites and patients are critical to meeting this objective.

- **Confirming that missing data are unavailable and not unreported**: It is unrealistic to expect that all data defined in the study protocol will be available; this is true even if the protocol matches the standard of care (SOC). Routine practice is subject to uncontrolled parameters such as time, instruments’ availability, and conflict of priority, all of which affect the existence of data.

We support this approach with proven, effective processes for delivering high-quality study data. We emphasize strong initial and ongoing site training and thorough, timely review.
Implementation & Execution of PMS

PRA’s approach to conducting risk management activities in the post-approval phase involves experienced professionals from RWS, regulatory, safety, and other key groups working together under a centralized, global operational model.

Our global PVS and RWS teams work with many PRA and client stakeholders to develop and implement a plan that aligns with the study’s objectives (Figure 3). Our experts are fully trained and experienced in delivering the full suite of services.

Insightful Approaches to Risk Management

We conduct extensive research to determine the appropriate regulatory agency’s current focus on the drug class and the effect an RMP will have on associated stakeholders (prescriber, pharmacy, distributor, and patient/caregiver). When a risk has been identified, PRA discusses it with the client and, if requested, the regulatory authority, whether routine pharmacovigilance and risk minimization activities would be sufficient to monitor and mitigate the identified risk. In many instances, patient education (medication guide, communication plan [US], or educational tools) is sufficient, while for others, specialized activities may be required based on the risk characterization and the impact on public health.

PRA is experienced in drafting and implementing FDA-mandated medication guides, communication plans, and EU patient education programs. In addition, we design technological and operational models to support the program and afford the client the flexibility to expand the program to include more indications as the product’s life cycle evolves.
Comprehensive Expertise & Services

PRA offers RWS research expertise to guide and implement high quality research programs. Our goal is to deliver end-to-end life cycle solutions across all therapeutic areas. Our scientific expertise and operational excellence enable our project teams to provide the full suite of services necessary to meet each program’s unique objectives. Specifically, RWS can apply comprehensive solutions for global and local PMS based on industry-leading experts, a global reach with local knowledge, a data-driven approach, and intuitive and flexible technologies.

PRA provides an end-to-end PVS solution by offering pre- and post-marketing services, PV systems/technology, and global footprint. Our teams work in a cross-functional fashion with other solution areas to effectively assist clients in their PV and patient safety obligations. The PVS team provides flexible services with the goal of minimizing the risks that medicinal products pose to patient safety. Our services are delivered by a team of more than 300 skilled employees around the globe.

Figure 4: End-to-End PVS Solution from Clinical Development to Post-Marketing
PVS & RWS

PRA’s PVS and RWS groups are global leaders in the design, management, and execution of peri- and post-approval programs for pharmaceutical, and biotech companies.

• Registries: patient, disease, product, pregnancy
• Observational studies/non-interventional studies (NIS)
• Post-authorization safety/efficacy studies
• Benefit-risk assessment
• Risk Management Plans/REMS
• Risk minimization measures
• Post-marketing safety and surveillance
• Health outcomes/health economics
• Quality of life and patient reported outcomes (PROs)
• Post-marketing/regulatory commitment
• Comparative effectiveness research
• Retrospective chart reviews
• Pharmacoepidemiologic studies
CONTACT INFORMATION

For further information on PRA’s approach to risk management and real world research, please contact your PRA Business Development Manager, or the PRA employees listed below:

Carla Barrett, PharmD
Senior Director, Patient Safety & Risk Management, PVS
Phone: +1 (484) 985 0043
BarrettCarla@prahs.com

Catherine Godefroy, PharmD, MSc
Executive Director, Patient Safety & Risk Management, PVS
Phone: +1 (250) 483 4566
GodefroyCatherine@prahs.com

Meg Richards, PhD, MPH
Executive Director, Scientific Affairs, RWS
Phone: +1 (434) 951 4105
RichardsMeg@prahs.com

Bettina Rillmann, RPh, MSc
Director, Scientific Affairs, RWS
Phone: +49 (621) 878 2430
RillmannBettina@prahs.com

World Headquarters
4130 ParkLake Avenue, Suite 400
Raleigh, North Carolina 27612 USA
Phone: +1 (919) 786 8200
Fax: +1 (919) 786 8201
www.prahs.com
ABOUT PRA HEALTH SCIENCES

PRA Health Sciences delivers innovative solutions that improve patients’ lives. Our people are passionate about the entire product life cycle, working tirelessly to provide quality results for clients. We offer exceptional experience across all phases, therapeutic areas, and a broad spectrum of solutions, ranging from full-service clinical development to our pioneering embedded model.

With 16,000+ employees covering 90+ countries, we reinforce an impressive global presence with keen local insights. Our project teams apply their understanding of local regulations, standards of care, and cultural customs to effectively align our approaches with each project’s unique goals.

At PRA, we love what we do because we are making a difference in the lives of patients and their family members worldwide. Over the years, we have contributed to the development of 85 products now available to countless patients. From our scientific and medical experts to therapeutically aligned project managers and monitors, we provide the commitment and expertise needed for today’s complex studies.

To learn more about PRA, please visit www.prahs.com or email us at prahealthsciences@prahs.com.