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WHITE PAPER

**Risk Management Planning and
Mandated Post-Authorization Studies**
Risk Management & Late Phase Studies for Real-World Research

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EXECUTIVE SUMMARY

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

In recent years, post-marketing safety and risk management have witnessed a fundamental shift from safety monitoring to the benefit-risk paradigm with proactive signal detection and periodic benefit-risk evaluation being the key focuses. FDA has moved from RiskMAP to Risk Evaluation and Mitigation Strategy (REMS) and required post-marketing studies to collect

real-world evidence to support NDAs/BLAs (FDAAA 2007). EMA has also introduced the new Good Vigilance Practice (GVP), which replaces the previous Volume 9A. Many ROW countries (e.g., Canada, Switzerland, Nordic states, Australia and New Zealand, as well as others in Asia Pacific) are closely following these changes. The call for collecting and analyzing real-world data to support periodic benefit-risk evaluation of the product warrants developing, evaluating and adapting proactive measures to minimize critical risks of the medicinal product and improve overall effectiveness.

PRA's Safety and Risk Management (SRM) and Late Phase Services (LPS) experts provide sponsors with unique strategies they have developed from years of significant first-hand experience in this area. Our global SRM and LPS groups have significant experience identifying innovative solutions to satisfy key regulatory requirements for their individual risk management planning and execution needs. Our integrated team works seamlessly with in-house and sponsor groups (e.g., medical affairs, safety, regulatory affairs, data management and biostatistics) to:

- Develop strategic and tactical plans.
- Design studies that align with the associated risk management and data collection objectives.
- Effectively implement these studies in the post-marketing world.

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

Proactive planning is a key to successful post-marketing risk management execution. By planning for post-marketing and risk management activities early in the drug development process, sponsors can facilitate a greater “return on investment” and avoid paying for unnecessary activities.

The numbers and types of patients taking a product post-approval vary greatly from those studied in earlier phase clinical trials (Figure 1). The length of exposure can be significantly greater as well. Post-marketing studies help to identify trends, outcomes and signals in large “real-life” populations.



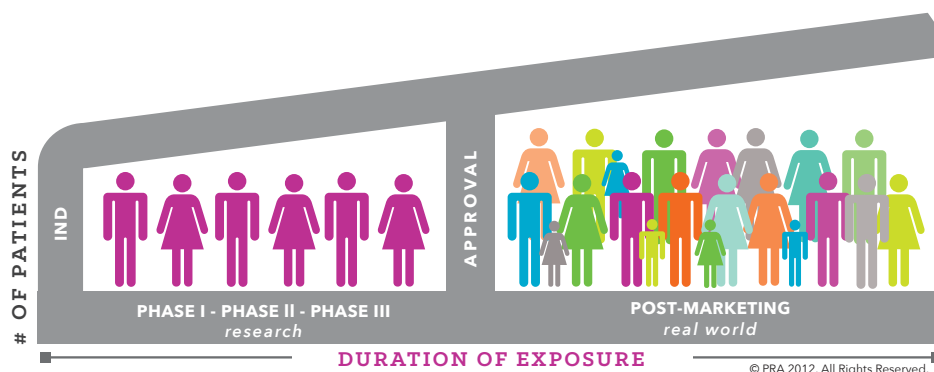


Figure 1: Phase IV - An Integral Stage of Drug Development

Regulatory agencies often mandate that sponsors conduct periodic benefit-risk evaluation and effective risk management planning and submit either a Risk Management Plan (EMA) or REMS (FDA) to achieve product approval. To effectively address these regulatory requirements, it is vital to understand how the key agencies (e.g., FDA and EMA) define risk management. In addition, more regulatory agencies in the ROW (e.g., several countries in Asia Pacific, as well as Australia and New Zealand) now require companies to submit risk management planning documents at the time of licensing application.

According to FDA, risk management is an iterative process of:

1. Assessing a product’s benefit-risk balance.
2. Developing and implementing tools to minimize its risks while preserving its benefits.
3. Evaluating tool effectiveness and reassessing the benefit-risk balance.
4. Making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance.¹

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 medicinal products, including the assessment of the interventions’ effectiveness.²

¹ FDA Guidance for Industry - Development and use of risk minimization action plans - 2008

² Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions, 12 December 2012, EMA/876333/2011 Rev. 1*; DIR 2001/83/EC Art 1(28b)



Strategy and Design Implementation

PRA's overall strategy in the design of a product-specific risk management system is to minimize the burden on the key stakeholders, while achieving the program's stated goals. Using lessons learned and strategies acquired through decades of relevant experience, our SRM and LPS teams collaborate with companies to identify the critical regulatory requirements for successful risk management planning and execution. We take a proactive, global approach to risk management that ensures our teams effectively interact between regulatory authorities and key stakeholders, providing our sponsors with a harmonized approach to pharmacovigilance and risk minimization activities. Our risk management process encompasses the following proactive steps:

- Structured benefit-risk evaluation
- Signal detection and safety profiling
- Risk assessment and characterization
- Pharmacovigilance strategy
- Risk minimization strategy
- Implementation planning
- Effectiveness evaluation planning

Signal Detection and Safety Profiling

PRA collaborates with sponsors to create a detailed Signal Management Plan that outlines the tools, processes and periodicity necessary to conduct signal detection activities. Our risk management experts:

- Select the appropriate signal detection tools.
- Oversee implementation of the qualitative aspects of the index signal analysis.
- Consult with the biostatistician to determine suitable quantitative methods.

To determine the tools required for signal detection, we consider the stage of the product in its life cycle (e.g., pre-market or post-market) and the volume of data to evaluate in the signal analysis process. For post-marketing signal detection, the tools typically include:

- Individual case report management
- Periodic literature searches



- Periodic aggregate reports
- Trending reports
- Standard MedDRA queries (SMQs)
- Data mining.

In late-phase clinical research, PRA calculates the frequency of adverse events and serious adverse events (AEs), deaths, and serious adverse reactions (SARs) using subject years as the denominator. When the drug maker provides estimated exposure data computed from sales or prescription data, we generate crude reporting rates based on the estimates as a pseudo-denominator. Then, we forward the outputs to the safety physician, who reviews them and compares the frequency of AEs and SAEs (or crude reporting rates) with the reference safety information and results of previous reviews. Afterwards, the physician initiates the Signal Validation Report.

The signal detection process concludes with a meeting for the signal management team to discuss results. The safety scientist is responsible for scheduling this meeting, compiling reports and distributing reports. Meetings are scheduled at pre-determined intervals, which can be altered as needed (e.g., if a potential signal is deemed to require urgent action).

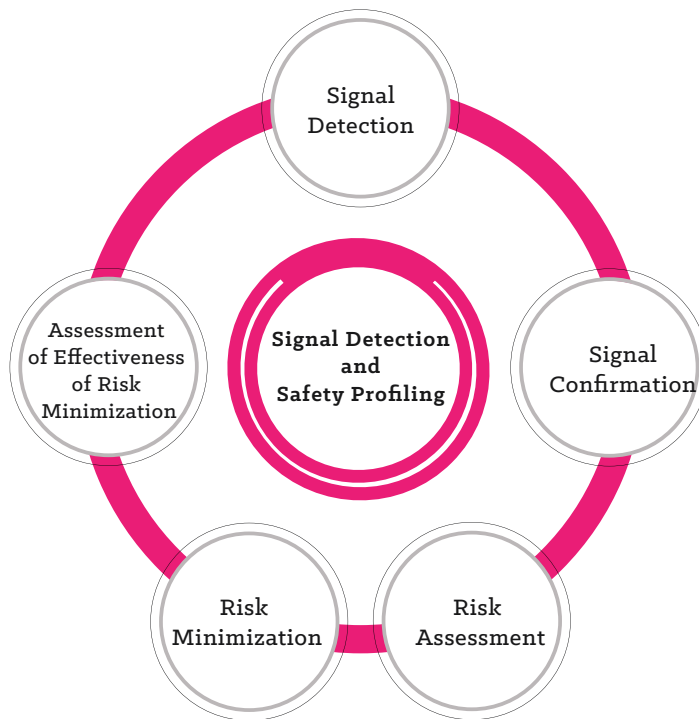


Figure 2: Signal Detection and Safety Profiling



Risk Management Planning

PRA recommends that companies begin working on risk management systems early in the product life cycle (Phase 2) by creating a developmental risk management plan (dRMP). The process of risk management planning at PRA starts with the risk assessment and characterization, followed by finalizing with the sponsor a list of “important risks” and creating Safety Specifications of the medicinal product for the Risk Management Plan (Table 1). We then perform a structured evaluation of the need for “additional measures” for pharmacovigilance and risk minimization/mitigation other than “routine activities.” After providing the evaluation report to the sponsor, PRA and the sponsor hold detailed discussions to further develop the pharmacovigilance and risk minimization/mitigation plans. PRA then evaluates and presents effective risk minimization measures (RMMs) to mitigate the important risks and drafts the agreed RMMs for submission to the regulatory agencies.

Depending on the nature of risks, therapeutic indication and level of required intervention, the RMMs may involve standard risk communications (e.g., medication guide, patient information brochure, dear HCP letters, etc.) or advanced elements to assure safe use (ETASU) for addressing the risks. PRA also helps companies answer regulatory queries related to the risk management system and draft tactical plans for implementation and Effectiveness Evaluation of RMMs with assessment variables and practical timelines, which are included in the licensing application.

RMP ACTIVITIES

Risk management planning, a global life cycle activity that preserves the benefit-risk balance of the medicinal product, involves the:

- Assessment and characterization of risks (safety specifications/safety profiling).
- Monitoring of such risks in the real world (pharmacovigilance planning).
- Designing and implementing interventions to actively minimize the occurrence of such risks (risk minimization/mitigation).
- Evaluation of these interventions to confirm if they fit the purpose and are effective, if not why (effectiveness evaluation).
- Revising and updating the risk management plan, if warranted, as an outcome of the effectiveness evaluation.

Table 1: Risk Management Planning Activities

Evaluating the Risk Management System’s Effectiveness

Regulatory authorities now mandate that drug makers evaluate their risk management plan’s effectiveness (for both EU-RMP and REMS) at predetermined time intervals in a two-tiered approach: “process evaluation” and “outcome evaluation.”



The evaluation of effectiveness must report whether both the individual RMMs and risk management system as a whole have been effective and specify if any corrective actions/improvements are mandated. The process evaluation tier involves individual RMMs (and associated implementation process), while the next tier, outcome evaluation, focuses on the risk management system's overall impact. Effectiveness indicators (EMA) or metrics (FDA) therefore can be classified as shown:

PROGRESS INDICATORS	OUTCOME INDICATORS
<ul style="list-style-type: none">• Implementations<ul style="list-style-type: none">- Reach to target audience- Use/Uptake in target audience• Impact<ul style="list-style-type: none">- Clinical knowledge (clear understanding or risks)	<ul style="list-style-type: none">• Behavioral change<ul style="list-style-type: none">- 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 encompasses the following activities:

- Stakeholder surveys: assess compliance (e.g., distribution of the Med Guide) and stakeholder awareness of product risks
- Tracking of product distribution: use of the stakeholder registry or national (proprietary) databases to monitor product
- Compliance audits: establishing stakeholder agreements to produce on-demand proof-of-compliance with program requirements
- Internet surveillance: monitor availability of product outside the program
- Targeted surveillance: use of standard pharmacovigilance activities to closely monitor adverse events of special interest linked to the product's known safety risks

Mandated Post-Authorization Safety Studies

After granting marketing authorization for a medical product, the regulatory authorities frequently request the marketing authorization holder (MAH) to conduct a post-authorization study. In accordance with EU Dir Art 1(15), this study is classified as post-authorization safety study (PASS) when the main objective is to either gather additional safety information or assess a pattern of drug utilization. Combined with recent regulations, EMA (GVP Module VIII) and FDA (FDAAA2007) increased the pressure on drug makers and moved from post-marketing commitments to post-marketing requirements for PASS, inducing the MAH to consider and implement multi-regional PASS.



In Europe, the RMP specifies the necessary steps and processes needed to conduct a PASS. According to DIR Art 107m (1), Regulation (EC) No 726/2004 (REG) Art 28b, these studies should be conducted according to the following provisions:

- DIR Art 107m-q and Commission Implementing Regulation (EU) No 520/2012 (IR) Art 36-38 for PASS initiated, managed or financed by a marketing authorization holder pursuant to an obligation imposed by a competent authority, which includes:
 - ◆ Studies imposed as an obligation in accordance with REG Art 10 and Art 10a and with DIR Art 21a and Art 22a (category 1 of studies in Module V)
 - ◆ Studies imposed as a specific obligation in the framework of a marketing authorization granted under exceptional circumstances (category 2 of studies in Module V)

Protocol Design and Development

Detailed guidance on protocol design and development is available from different sources, including EMA Guidance³, ENCePP Guide⁴, and ISPE Guidelines⁵.

Pending the main objectives, a PASS is generally observational in nature, though may involve a different study design, when necessary. PRA's specialists (including late-phase ENCePP members, as well as medical affairs, safety and biostatistics professionals) have developed the following study protocol considerations for PASS:

- Define the milestones for study progress and reporting aligned with initial agreement and development of strategy to respect milestone timing
- Develop the study rationale, including the concerns or questions leading to the study
- Determine the study's overall goal per requirements and translation of this goal(s) into specific measurable objectives
- Describe the source and study population adequately and appropriately with regard to the study research question and objectives

³ Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies EMA/623947/2012

⁴ The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 2). EMA/95098/2010.

⁵ Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology http://www.pharmacoepi.org/resources/guidelines_08027.cfm

- Provide detail about the methods used to collect, register and control the necessary information
- Detail the rationale for the study sample size and statistical analysis in view of the distinct specific objectives of the study

PRA employs the above considerations for non-interventional PASS based on official Guidelines and recent experiences in protocol evaluation by regulatory authorities.

Non-Interventional PASS Implementation and Execution

Whether epidemiological or clinical, the studies' results and findings depend on data quality. Although quality data is essential to any research project, the most frequent approach to define data quality is to consider two principles that are pillars for any type of research: data completeness and data validity.

This general consideration is also applicable to prospective non-interventional PASS with the limiting factor that medical procedures and assessments cannot be mandatory. By applying this constraint to real-world research, PRA has developed an approach based on the implementation of the appropriate oversight to validate that existing data aligned to routine practice are correctly reported according to the study protocol.

Our main objectives are to:

- Guarantee patient protection: make sure patients are appropriately informed, their confidentiality is maintained and the medical practice is based on the best benefit of the patients and not modified by their participation in the study.
- Avoid unreported data and minimize errors: all existing data of interests have to be reported and reported correctly to reflect the reality. Motivation and awareness maintenance of sites and patients are critical to reach this objective.
- Ensure that missing data are unavailable and not unreported: it is unrealistic to expect that all data as defined in the study protocol will be available even if the protocol matches the standard of care. Routine practice is subject to uncontrolled parameters such as time, instruments availability and conflict of priority impacting the existence of the data.

We further support this approach with proven and effective processes for delivering high-quality study data gathered by expert physicians and through efficient collection and review.

Physician Selection

PRA recommends establishing a Physician Selection Plan to minimize any potential biases in the selection of physicians who are prescribers of the medicinal product. When the prescriber-selection process is fully documented in the Physician Selection Plan, only a summary has to be included in the protocol and in the final study report's appendix.

During the physician-selection process, PRA:

- Identifies the product prescribers who use a data source not specifically set up for the study, but simply record prescribers for other purposes.
- Culls initial prescribers from databases in a randomized manner to minimize bias and to qualify them in the order of responses and according to the predefined distribution (e.g., location and profile).
- Ensures that selected physicians remain “blinded” to the study's primary goal at the time of contact by properly wording the Invitation Letter.
- Provides physicians with only blinded data to avoid “non-compliant prescribers” from declining to participate in the study.

EDC Tools

Selecting the appropriate EDC tools helps to ensure data completeness, reduces site burden and maintains site motivation. Although many EDC systems are available and can support the needs of non-interventional PASS, PRA considers some critical characteristics to determine or support our sponsors to define the most appropriate tool, including:

- Flexibility of the EDC system to meet the needs related to the fluctuation of data availability bound to happen in real-world research
- User-friendly, intuitive role-based workflows that avoid a long list of data per screen
- Combined system supporting medical eCRF and ePRO in one database for mitigating long-term follow-up and facilitating the review

Risk-Based Monitoring

Risk-based monitoring (RBM) can be an invaluable approach to ensuring data validity when conducting non-interventional PASS. The growing consensus among clinical researchers and regulatory authorities is that RBM is more likely to ensure patient



protection and overall study quality, and is more effective than the traditional monitoring model of routine visits to all sites with 100% source data verification (SDV).

A number of factors are leading to the paradigm shift in the way that clinical research is conducted. The increasing cost of research and the adoption of EDC technologies that provide real-time access to data have forced the industry to look at optimized methods of conducting non-interventional projects. To effectively implement RBM, it is essential to:

- Identify study-specific risks.
- Develop multidisciplinary strategies and processes to target those risks.
- Incorporate a holistic analytical and operational approach focused on centralized monitoring and action plans.

PRA's team has been applying successful RBM approaches to real-world studies, including mandated PASS, for 20+ years (Figure 3). Our professionals lead the industry, executing risk-based strategies with the support of our unique centralized site management model.

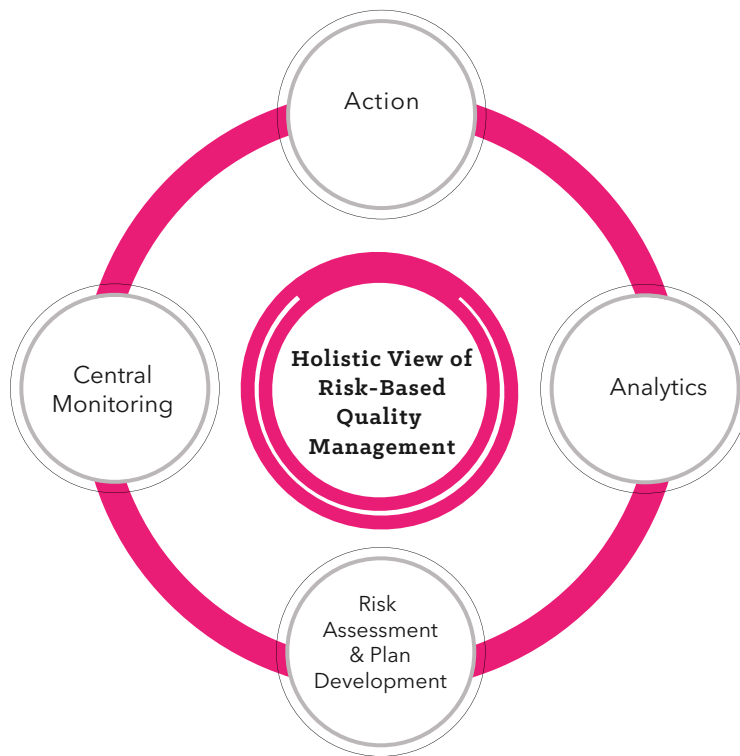


Figure 3: Holistic View of Risk-Based Quality Management

PRA’s RBM approach incorporates a holistic evaluation of each individual study, beginning with a multi-disciplinary risk assessment and associated plan development. This process is not only conducted at the onset of a study, but also reevaluated and modified, as needed.

Furthermore, PRA’s Site Management Associates (SMAs) conduct centralized monitoring and establish one-on-one relationships with sites to provide meaningful support that maximizes patient and site participation. Additionally, PRA’s global Study Coordinating Centers, which are comprised of multilingual SMAs, facilitate on-going exchanges of experience and lessons learned between SMAs and sites that promote process standardization.

MAKE THE RIGHT CHOICE WITH PRA

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

Our global Safety & Risk Management and Late Phase Services teams work seamlessly with different stakeholders (in-house and sponsor) to develop and implement a plan that aligns with the associated project objectives (Figure 4). Our experts are fully trained and highly experienced in delivering the full spectrum of services, enabling them to deliver successful post-approval, drug safety solutions.

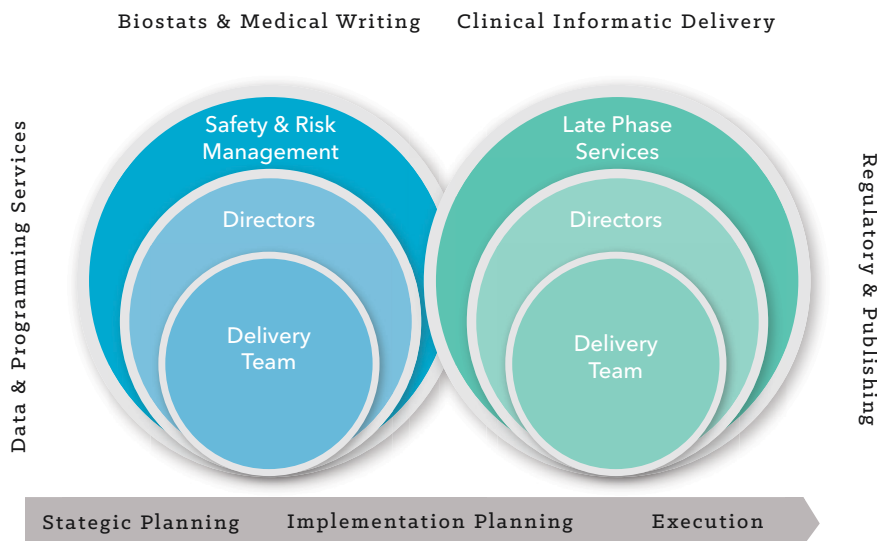


Figure 4: PRA’s Expert Pool for Full-Spectrum Services in Global Benefit-Risk Management



Insightful Approaches to Risk Management

We conduct extensive research to determine the appropriate regulatory agency's current focus on the particular drug class and the effect an RMP will have on the associated stakeholders (prescriber, pharmacy, distributor, and patient/caregiver). Once a risk has been identified, PRA discusses with the sponsor (and the regulatory authority, if requested) whether routine pharmacovigilance and risk minimization activities would be sufficient to monitor and mitigate the medical product's identified risk. In many instances, patient education through the use of a Medication Guide or a communication plan (in the US) or a risk education plan (in the EU) is sufficient, while in others certain specialized activities may be required, depending on the risk characterization and its impact on public health.

PRA has the experience to draft and implement either an FDA-mandated Medication Guide (21 CFR 280) or a European Union Patient education program. In addition, we design technological and operational models to support the program, affording the client the flexibility to efficiently expand the program to include additional indications as the product's life cycle evolves. We understand how to use the power of data-driven decision making to deliver high-quality risk management planning and execution.

Comprehensive Expertise and Services

Furthermore, PRA offers real-world and late-phase research expertise to help guide the design and implementation of 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 spectrum of services necessary to meet each program's unique objectives, such as safety mandates. Specifically, PRA Late Phase Services can address observational PASS with comprehensive solutions based on industry-leading experts, a global reach with local knowledge, a data-driven approach and intuitive and flexible technologies.

By employing state-of-the-art technologies and approaches, we support sponsors' projects, while providing insightful access to study data, metrics and industry-standard delivery models.

SRM Services Provided

PRA provides safety and risk management services during the entire product life cycle. Figure 5 outlines the SRM services that PRA offers. In addition, our SRM services also include Literature Search services for routine pharmacovigilance and for aggregate safety analysis, and Endpoint Adjudication services for both pre-and post-approval studies.



PRA Safety and Risk Management experts also provide the following services to support NDA/BLA/MAA and post marketing lifecycle activities:

- Signal detection and management
- Structured benefit-risk evaluation
- Risk Management Plans/REMS
- Pharmacovigilance planning and implementation
- Risk minimization/mitigation planning and implementation
- Effectiveness evaluation plan for Risk minimization/mitigation measures

During Product Life Cycle

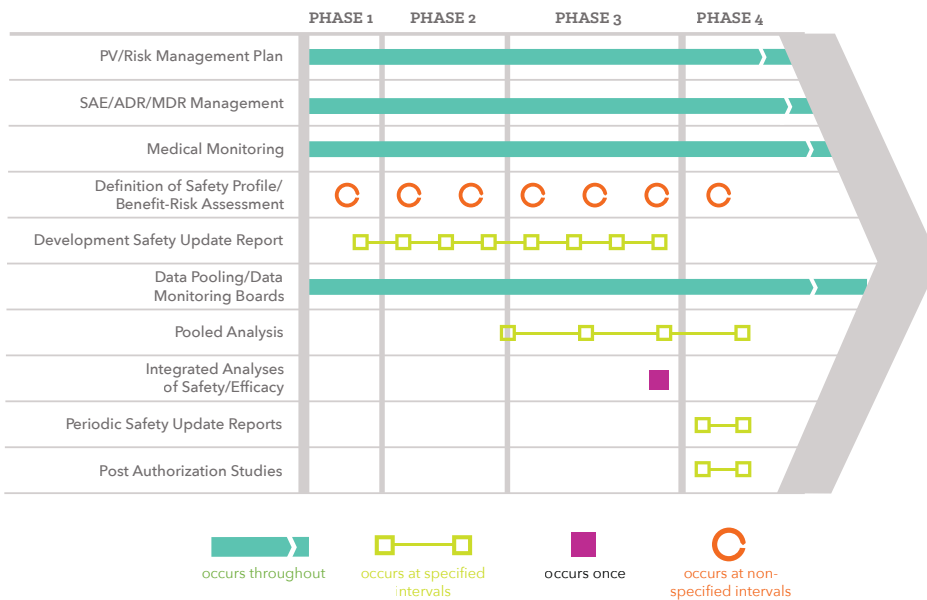


Figure 5: PRA Safety & Risk Management Services

Late Phase Services

PRA’s Late Phase Services (LPS) group is a global leader in the design, management, and execution of peri- and post-authorization programs for pharmaceutical, device, and biotech companies. Our scientific expertise and operational excellence enables our project teams to provide a full spectrum of services and flexible approach for all designs:



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- Registries: Patient, Disease, Product, Pregnancy
- Observational Studies/Non-Interventional Studies (NIS)
- Benefit-Risk Management/RiskMAPS/REMS
- Post-Marketing Safety and Surveillance
- Health Outcomes/Health Economics
- Quality of Life and Patient Reported Outcomes (PRO)
- Post-Marketing/Regulatory Commitment
- Comparative Effectiveness Research
- Retrospective Chart Reviews
- Pharmacoepidemiologic Studies

We have 100+ dedicated employees based in three LPS hubs: Horsham, Pennsylvania; Mannheim, Germany; and Singapore (Figure 6).

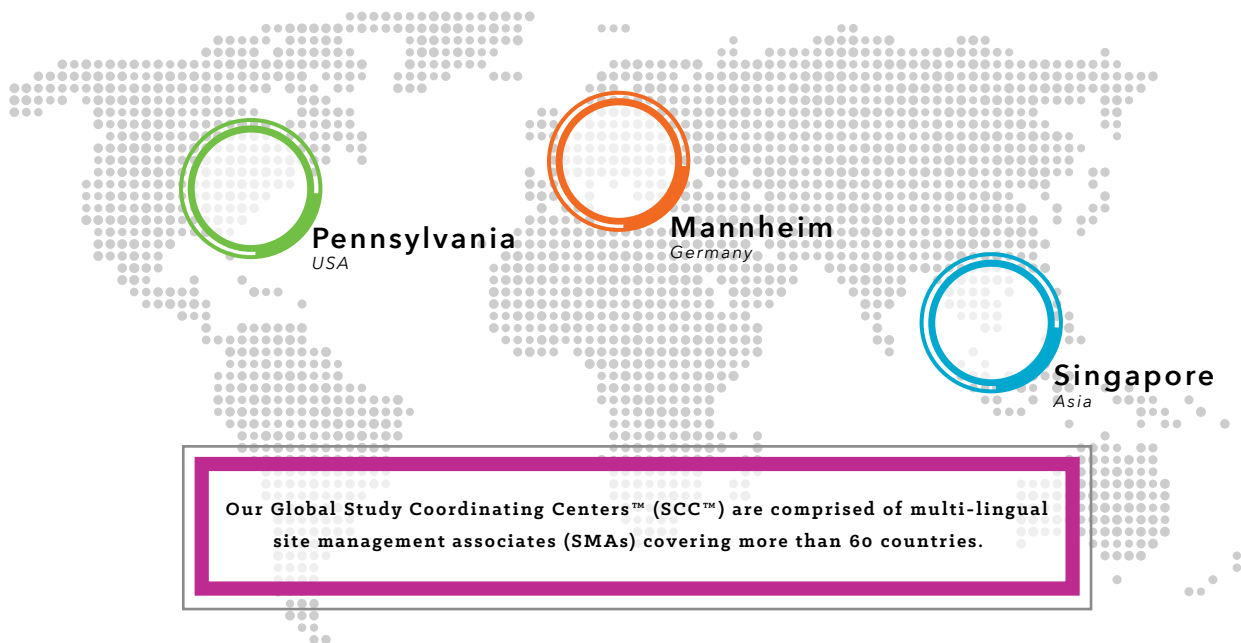


Figure 6: PRA LPS Centralized Management Locations



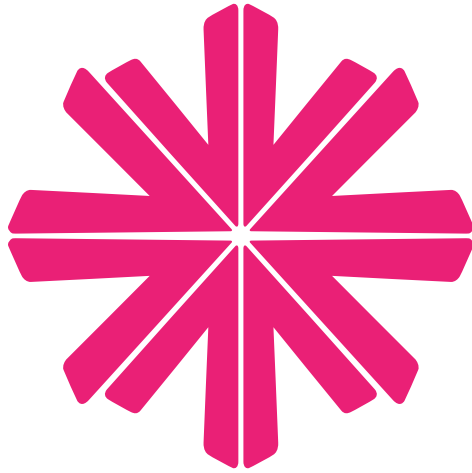
CONTACT INFORMATION

For further information on PRA's approach to risk management and late-phase research, please contact your PRA Account Director or Business Development Manager, or the PRA employee below:

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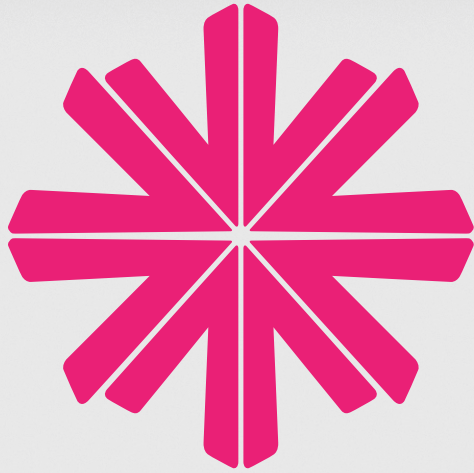
PRA Health Sciences delivers innovative drug development solutions that improve patients' lives. Our people are passionate about clinical research, working tirelessly to provide quality results for clients. We offer exceptional experience across all phases, therapeutic areas and a broad spectrum of solutions,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

With 10,000+ employees covering 80+ countries, we bolster an impressive global presence with keen local insights. Our project teams harness their understanding of local regulations, standards of care and cultural customs to effectively align our approaches with each study's unique goals.

At PRA, we love what 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 numerous drugs 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.





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