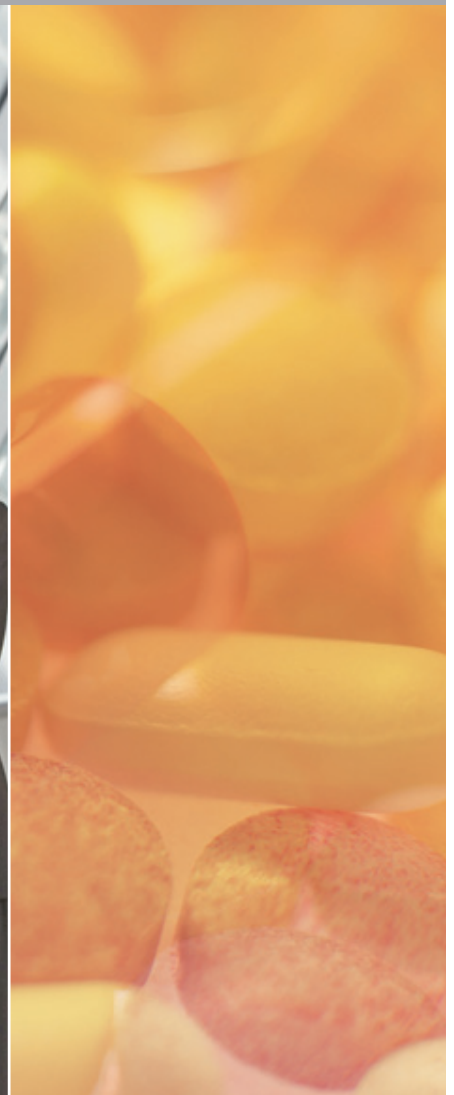


Sponsor & CRO Pharmacovigilance Alliances

Best Practices to Ensure Success



Phase I-IIa
Phase II-III
Phase IIIb-IV & Registries
Bioanalytical Laboratory
Safety & Risk Management


PRA International

On a global basis, contract research revenues reached an estimated \$21.6bn in 2009, having expanded by more than 10% per year since the mid 1990s. Over the next five years, contract research spending is expected to continue its strong growth, with total revenues rising by 9.9% per year to reach \$34.6bn by 2014. While estimates of outsourcing satisfaction vary, it is not uncommon for as many as 35% - 55% of sponsors to report moderate to significant dissatisfaction with a project; according to the report "The Future of R&D Outsourcing" published in 2010 by Business Insights. The best relationships between sponsors and contractors are those that are well defined from the outset. This whitepaper outlines the best practices to ensure success when outsourcing pharmacovigilance services.

BACKGROUND

Outsourced safety services in the past were rather limited. Traditionally, pharmaceutical companies outsourced SAE/ADR management, pharmacoepidemiology studies, and individual consultancy. Concerns about confidentiality, data security, and liability in cases of regulatory non-compliance were – and still are – important factors against outsourcing. However, the increasing demand for pharmacovigilance capacity and expertise cannot always be satisfied in-house, whether constrained by limited resources, or a lack of appropriate infrastructure or regional presence. Consequently, the changing industrial and regulatory environment leads to re-evaluation of the advantages and disadvantages of outsourcing pharmacovigilance services.

Outsourcing Advantages

The benefits of outsourcing in general also hold true for pharmacovigilance services. Fixed resource costs are converted into flexible workload-oriented costs. In the outsourcing model, pharmaceutical and biotech companies reduce costs because significantly less effort is needed for recruitment, management and training of staff. Since safety concerns about marketed medicinal products resulted in stricter regulatory requirements, the job market for hiring experienced safety personnel has become highly competitive.

The special benefits of outsourcing pharmacovigilance services include, access to unique expertise, intellectual property, and multidisciplinary knowledge at the time they are actually needed. The service provider will focus its undivided attention on the outsourced task, a benefit that is enhanced by high staff motivation. Because the contracted experts are external, they can provide an unbiased view.

This impartiality can be of special value in a decision-making process, for example, related to improving the in-house pharmacovigilance system or regarding signal detection and risk management activities required for a drug.

The External Perspective

The following example demonstrates how the involvement of an external consultant can result in a successful product approval:

As prerequisite for the marketing authorization of a known product with a new formulation, European regulators requested an active surveillance study to detect rare and serious adverse events for risk minimization. The negotiations between the pharmaceutical company and the regulatory authorities on the risk management program had been unsuccessful over years. This is when the company asked for external advice from a risk management expert. The independent expert coming from the outside with a fresh and unbiased approach to the issue, understood the problem quickly and recommended slight changes to the suggested safety surveillance approach. It was also proposed to include a methodology debate on appropriate pharmacovigilance study designs and considerations about signal investigation and proposed actions. Upon submission of the revised risk management plan the company received the marketing authorization. Consequently, this involvement of an external consultant helped the Company to resolve an issue which had been stuck for years. The time and cost savings to the company were tremendous.

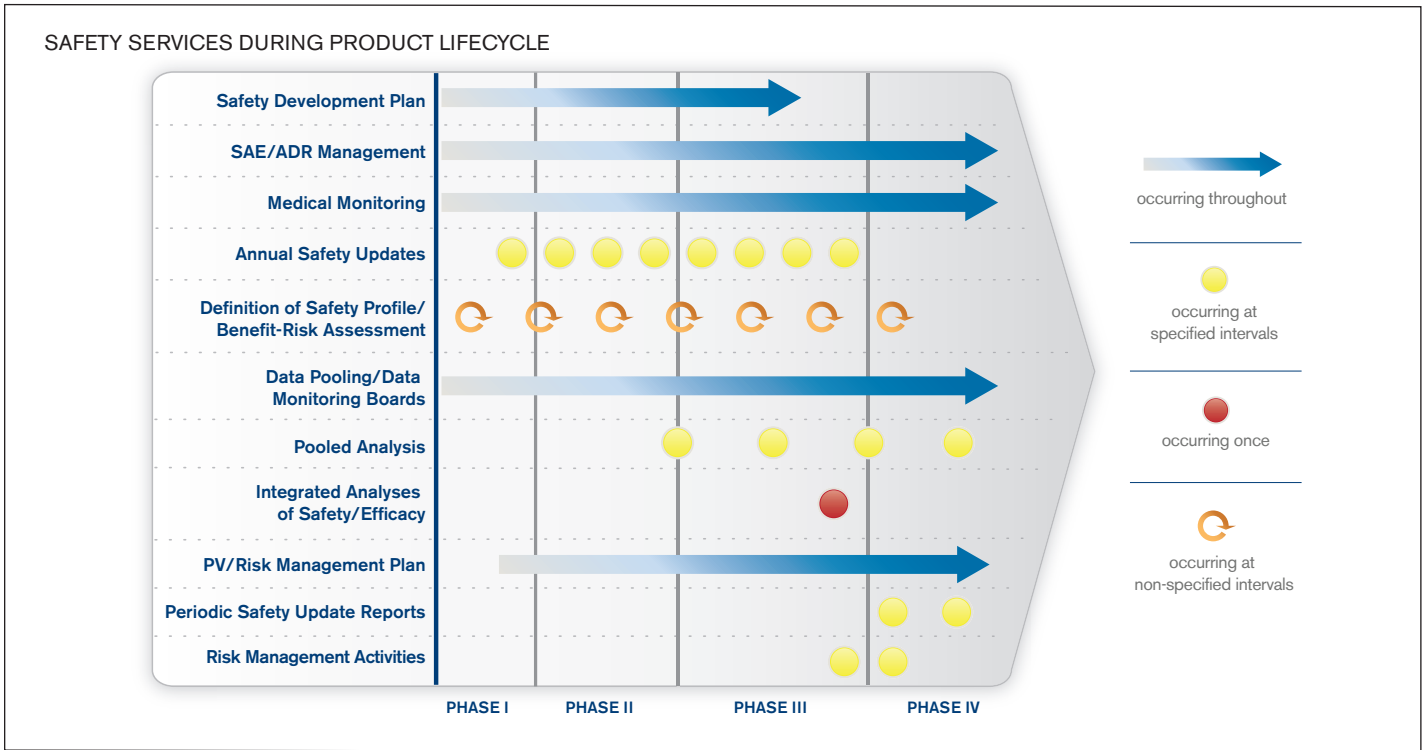
What Services Are Outsourced?

Nowadays, all of these tasks are outsourced. In addition, sponsor companies ask for specialized pharmacovigilance services, such as: pharmacovigilance audits to prepare for inspections; delegation of the role of a Qualified Person for Pharmacovigilance; development of product information; process design and SOP generation. With the growing demand of regulators for risk management programs, sponsors also seek support in the development of such programs.

Although in general all tasks related to pharmacovigilance and risk management are outsourced, the needs of individual companies vary significantly. Company size, the size of the pharmacovigilance department and existing license or development partnerships influence the outsourcing decisions.

Small Biotech Companies

Small biotech companies typically have no drug safety department and therefore have to outsource all routine safety services including the safety database. Only high level activities including analysis and decision making are kept in-house. Not only the internal safety and risk management expertise may be limited, also the resources to manage and control the vendor are limited. It is often this conflict between the sponsor's limited safety and risk management expertise; and being overzealous in the decision making process which causes the most dissatisfaction with both parties.



Mid-sized Pharma Companies

Mid-sized pharma companies generally have the knowledge and resources to cater to the demands of the global pharmacovigilance environment. Typically they require additional support to meet fluctuating resource needs associated with a changing product development pipeline. For example, support will be needed to cope with medium-term resource challenges, such as increased SAE volume due to a new clinical program. They also have limited geographic coverage and often require additional support in unrepresented countries.

Large Pharma Companies

Large pharma companies have large pharmacovigilance departments with a global safety database as well as, global infrastructure, the knowledge and expertise. Outsourcing occurs mainly for low-cost solutions and sometimes to support peak workloads. However, the areas of concern for low-cost off-shoring and outsourcing are quality issues and regulatory non-compliance. It is pertinent to maintain the necessary oversight and engagement with the outsourcing partners or the vendors. Stepping in early to mitigate or control an issue before it gets out of hand is something large companies need to be aware of and plan for.

SOLUTIONS

Making the Service Provider Selection

Pharmacovigilance activities which are outsourced vary significantly. The range of contracted services is reflected by the spectrum of safety service

Mid-size Pharma Services Example:

The sponsor delegated the submission of expedited Individual Case Safety Reports and of Cumulative Line Listings and Annual Safety Reports to health authorities, ethics committees/institutional review boards, and investigational sites for all clinical trials. The vendor's services included assessing the country-specific reporting obligations for each SAE occurring in more than 35 trials conducted in over 50 countries. Later, the vendor implemented a system for electronic distribution of safety letters to investigators, which considerably reduced costs associated with the submission of about 4,800 safety alerts monthly.

The vendor's centralized team had effectively taken the responsibility for reporting away from the pharma company's understaffed local affiliates. This centralization mitigates a problem which numerous pharma companies are facing. Regulators rightly review a company's pharmacovigilance practices globally. Often local affiliates operate to different standards and working practices causing problems for products on a global scale when reviewed by regulators. Global pharmacovigilance departments are often not able to place any pressure on local affiliates to conform with global practices. Outsourcing to a vendor, places the responsibility with one party who must ensure global compliance.

providers: individual consultants, specialty clinical research organizations (CROs), large “full-service” CROs, and global service providers under the umbrella of “business process outsourcing” (BPO). To achieve a successful cooperative relationship, it is crucial to select the best provider for the actual need. The first step should always be to establish a clear definition of the tasks to be contracted and assess what expertise and level of resources are required. When evaluating the consultant’s or vendor’s expertise, the sponsor has to consider which knowledge and experience is available in-house to support the provider selection and to assist in quality control during the collaboration. When considering outsourcing of medium- to large-scale routine work, pharmaceutical companies should also take into account that shifting work to an external provider can free up internal resources for the increasing demands of quality control and/or for more intellectual tasks, such as signal detection and/or development of risk management plans early on.

Other considerations will also affect provider selection:

- What are the future outsourcing plans?
- Is this the first in a series of contracts for similar or different services?
- Is this a one-time request for consultancy?
- How are various outsourced services linked to each other?

It is highly recommended to check provider references relevant to pharmacovigilance as an initial step in due diligence, differentiating between past and actual performance. Critical success factors are the technical expertise and tenure of senior vendor staff. In addition, important information may be derived from audits of the providers’ pharmacovigilance processes and quality management systems. A track record of regulatory compliance and a low rate of non-conformities both usually indicate a robust quality management system. In combination with flexibility in procedures, the prerequisites for high quality, tailored services are fulfilled. The due diligence should be supplemented by data on the tenure of the staff and management team. Altogether, these data are a solid basis for an informed decision.

However, such a thorough selection process requires much effort. Sponsors tend to underestimate the time required on both sides from the request for proposal to project start. Time not spent during the selection process most likely will be needed later when the project is supposed to start and, at that point, any ambiguity will already have an impact on performance. Often, a too short a timeline leads to insufficient definition of scope of work, the inappropriate outsourcing business model being selected, which then impacts contractual agreements with poor definition of tasks and responsibilities.

There may be situations where a sponsor has to react on an immediate need like an unplanned resource shortage or underestimated high

Success Checklist

- ✓ Define scope of work
- ✓ Assess expertise required for each outsourced task
- ✓ Check internal expertise present for vendor selection
- ✓ Determine internal expertise present for vendor quality control
- ✓ Define duration of collaboration
- ✓ Evaluate vendor’s expertise
- ✓ Check references
- ✓ Verify technical expertise of vendor staff
- ✓ Check tenure of vendor’s senior managers and technical staff
- ✓ Audit vendor’s processes
- ✓ Audit the vendor’s quality system
- ✓ Assess quality of proposal
- ✓ Engage with the vendor team at the Bid Defense

workload, e.g. during a pandemic, so that outsourcing is the only possible solution. Under these circumstances the vendor selection and contract negotiations have to be completed in the shortest possible time and completing the steps described above will not be an option. The scope of work may become a “moving target”, while budgetary constraints place increasing pressure on all parties, leaving them at risk for regulatory non-compliance. Outsourcing may still be a satisfactory experience, if the sponsor and vendor communicate openly and are addressing issues honestly and immediately. Such situations require extreme flexibility not only at the vendor but also the sponsor side.

Outsourcing Business Models to Consider

The selection process should also include an evaluation of the business models offered for the requested service. The model selection will be governed by such key factors as complexity and variability versus standardization, the volume of work involved, and the duration of the project.

A time and materials budget - with or without a cap - is often the best solution for consultancy or other ad hoc services when timing, volume and complexity are unknown at the start of the outsourcing or likely to evolve over the duration of the contract. A well-defined set of tasks over a limited period can be covered well in a fixed price contract. Should a fixed budget over several years be agreed upon, both parties may wish to review the budget and actual costs on an annual or another regular basis. If the tasks are well specified, but the volume of work is more difficult to estimate, the answer may be to negotiate unit prices. For a large volume project, a workforce-based contract, such as a Full Time Equivalent (FTE) model, is often advantageous compared to a unit based set-up. If significant fluctuation in

workload is likely, the business model needs to account for it to ensure that sufficient trained resources are available on demand.

Clear Path to a Successful Cooperation

Successful sponsor/provider cooperation is built on a contractual agreement with well-defined tasks and responsibilities using a matching business model. At the beginning of the collaboration it is important to define responsibilities on an individual level, communication paths and escalation procedures for both parties as well as contingency plans. The escalation plan should foresee actions to be implemented in case one party does not comply with its agreed upon roles and responsibilities.

The contingency approach should always consider that regulators will ultimately hold the sponsor or marketing authorization holder responsible.

If third parties, e.g. co-license partners, are involved, they need to be included in the communication flow. If a long-term cooperation is the goal, investing in face-to-face meetings at the start of the relationship followed by frequent formal and informal communication will pay off.

Good relationship governance should employ an oversight committee consisting of executives from parties as well as representation from the project team (both sponsor and vendor). In regular meetings the committee will assess the ongoing relationship and the operational situation. The committee is responsible for the high level senior management overview, for providing strategic direction and oversight of business relationship to ensure both parties' needs are addressed and that a high quality compliant service is delivered. Investment of face-to-face time can reap huge rewards when it comes to: harmonization of processes and business values; issue resolution; and contractual understanding and contract change control. Such relationship models should not have an impact on project budget and are seen as the "cost of doing business".

A strategic approach provides optimal results, as sponsors are able to optimize the relationship and product lifecycle through:

- Joint commitment
- Shared values
- High trust
- Governance of the relationship
- Align core competencies
- Optimize resource and cost efficiencies
- Full corporate vision alignment

Perhaps the two most important factors in such relationships is the governance of the relationship, and the ability to build and maintain a high level of trust.

Case Study

A "virtual" biopharmaceutical company decided to outsource all "back-end" functions i.e. data management, biostatistics, medical writing, and safety & risk management to a single service provider. This left them free to select the best clinical CRO for a particular study, and enabled them to leverage efficiencies in back end study set-up and execution for their clinical programs. The discussion between the sponsor and the CRO to define delegated pharmacovigilance responsibilities revealed that the sponsor's confidence in the reliability of the vendor for safety services was limited. The sponsor was extremely concerned that the CRO would not comply with agreed processes, e.g. conduct expedited reporting of individual case safety reports to regulatory authorities without approval of the sponsor. To reduce this risk the sponsor considered to implement a cumbersome process involving the clinical CRO in the expedited regulatory reporting. The proposed process would have implied a high risk for late reports and would have required additional expensive reconciliation steps between the involved parties to ensure compliance both for expedited and periodic safety reporting. Several meetings to discuss the details of the collaborations helped to build confidence and trust: The finally agreed work flows achieved both: a robust process with low risk for late reports, in which the sponsor controlled critical decisions.

Decisions made about Standard Operating Procedures (SOPs) are important and can affect cost. If the plan is to outsource not an entire process, e.g. individual steps in the case management process, and to use the pharmaceutical company's safety database, adherence to sponsor SOPs is in most instances advantageous. Additional documentation might be required to translate job titles used in the sponsor SOPs into the vendor's/contractor's organizational structure. If the responsibility for a process or task lies mostly or completely with the service provider, its SOPs might best cover the required specifications. Agreement on deviation for individual process steps might be sufficient to adjust the standard process to the project-specific needs. In rare instances the development of project-specific SOPs might be the only solution to document the desired process clearly. In most instances, project-specific plans referring to SOPs are sufficient.

A close, thorough quality control process will ensure that the service provider is meeting the sponsor's expectations. Audits during the cooperation—either by in-house staff or an external auditor—are the best tools to reconfirm that the provider meets quality standards and implements adjustments in a changed regulatory environment.

Successful Long-term Cooperation Example

A CRO serves as the safety data entry unit for a mid-size pharmaceutical company. Individual safety reports are received via e-mail. The drug safety team at the CRO uses web-based access to the sponsor's safety database and processes the safety data according to the sponsor's SOPs, user manual and entry/coding conventions. The working relationship started with support for a few individual studies. After a few years, cases from three products in five indications resulting from clinical trials and spontaneous reports were handled by the CRO. Since the sponsor drug safety team provided initial training to the CRO staff at the beginning of the relationship, the CRO is responsible for training new staff (train-the-trainer principal). Regular audits without critical findings have proven the effectiveness of this concept.

Up to 40 individual tasks orders were executed simultaneously under the umbrella of a master service agreement. This contractual set-up provides the flexibility to include additional services in some task orders, such as expedited reporting to Health Authorities in a few countries. Budget estimates are based on agreed units; compensation is done on a time and material basis. Due to the long-term relationship, the drug safety team at the CRO has become highly efficient, so that for several clinical studies the time spent per standard unit is lower than estimated. Due to the budget model the efficiency is immediately passed on to the sponsor.

ABOUT PRA INTERNATIONAL

PRA's Safety & Risk Management team has over 100 experts in Europe, North America and Latin America who can assist pharma, biotech, vaccine, and device companies in implementing and conducting safety & risk management duties throughout their products' lifecycle. Offering services such as: ICSR management (processing and reporting), safety database, literature search, product call center, aggregate report generation, signal detection, and risk management activities.

CONTACT INFORMATION

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CONCLUSION

Outsourcing pharmacovigilance activities is a standard business practice in a rapidly expanding market segment. Irrespective of the required type of support, the outcome will be a positive experience if the rules outlined in this whitepaper are followed: The service provider has the qualification for the pharmacovigilance service; the contractual agreement includes well defined responsibilities; and communication as well as escalation paths are clearly defined at project start. Regardless of the level of sponsor involvement, consensus has to be established and maintained that cooperation in pharmacovigilance remains a collaborative effort. This is the key to success.