PHARMACOVIGILANCE SMART SOURCING STRATEGY

Vendor Selection for Safety & Risk Management Support

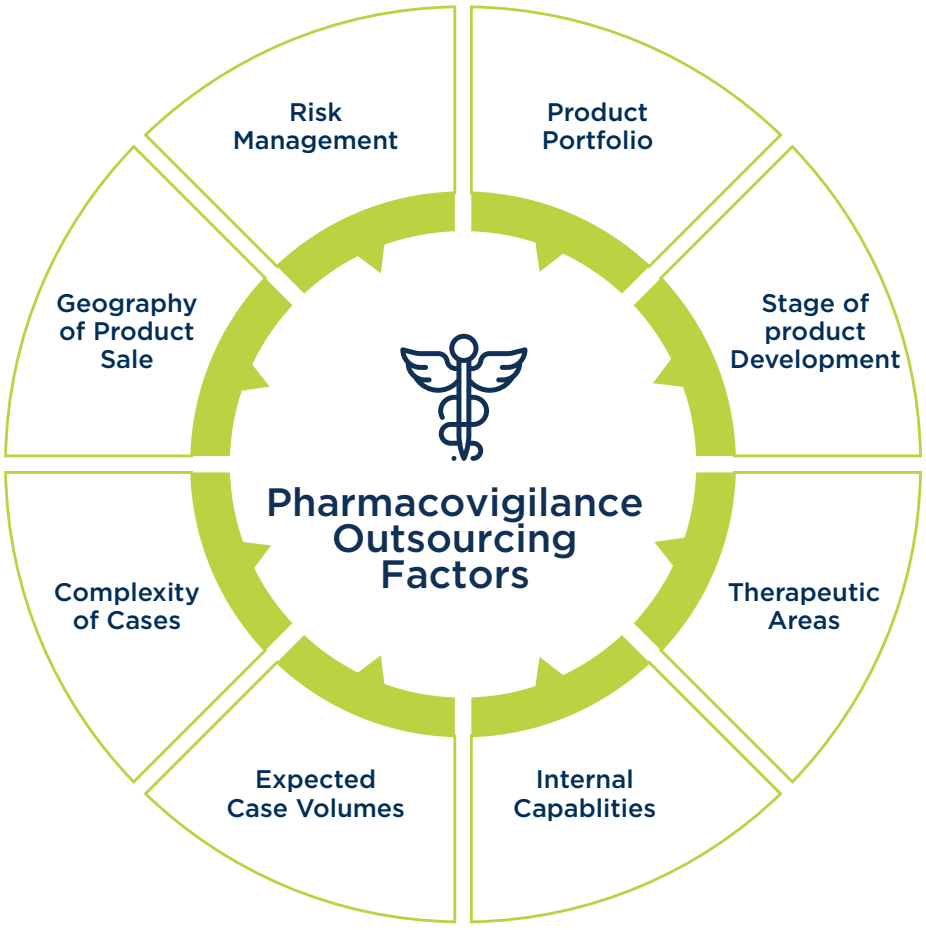
Strategic planning, sourcing and implementation of safety and risk management operations are complex activities that involve a multitude of factors. Due to the maturity of the outsourcing industry, compliant, quality and efficient safety operations are basic expectations now for the outsourcing of pharmacovigilance (PV) activities. This trend has enabled sponsors to focus their in-house resources on the strategic elements of safety and risk management while leveraging the service provider's capabilities.

Companies large and small are seeking more strategic partnerships with vendors who have specialized capabilities that go beyond call center and case processing, such as safety consulting, safety technology, medical review, aggregate reporting and signal detection. Furthermore, as companies expand into new geographies, markets and regions, or consolidate operations due to mergers and acquisitions, specialized capabilities and regulatory knowledge are a critical consideration of a company's outsourcing strategy and decisions.

An organization's sourcing strategy can vary based on its product portfolio, stage in the product lifecycle, therapeutic areas, internal capabilities, expected case volume and complexity, geography of product sales and risk management requirements (Figure 1). For instance, a large company may decide to outsource a few steps of the PV process that the organization classifies as largely process-driven and resource-intensive, or they may outsource the entire process from case receipt to submission. A smaller organization with a few drug candidates in the pipeline that works with several clinical research organizations (CROs) may need help with a database solution to centralize its data, along with case processing support. A mid-size organization may need to determine what aspects of safety operations should be kept in-house versus be outsourced. The sponsor will have to make a series of decisions on the details of the engagement like whether to begin with a pilot, how to migrate work to the vendor, how to manage the vendor and what key performance indicators (KPIs) and success metrics are critical to track quality, cost and time, for example. As a result, they may first seek consulting support to enable the decision making.

Thus the approach taken to ensure the availability of the right skills for all aspects of safety operations in a manner that optimally maximizes compliance will be different for each company. This white paper discusses facets of a SMART SOURCING STRATEGY in this context.

Figure 1: Factors Impacting an Organizations PV Outsourcing Strategy



FRAMEWORK FOR OUTSOURCING SAFETY OPERATIONS

Based on our experience of working with many clients across different partnership models, we have evolved a Partner Assessment Framework that enables clients to choose the optimal safety and risk management outsourcing strategy that aligns with their business needs. We have used this framework to help clients identify the right fit and determine the extent and volume of scale-up leading to a successful outcome of their outsourcing initiative.

By providing a roadmap to outsourcing safety operations based on the maturity of an organization's as-is state, we are able to recommend a partner selection model that is customized to the specific needs of the client's product vigilance strategy. As a second step, the framework specifies quantitative measures to facilitate a seamless transition of operations to an outsourcing vendor and key milestones to ensure a successful outcome.

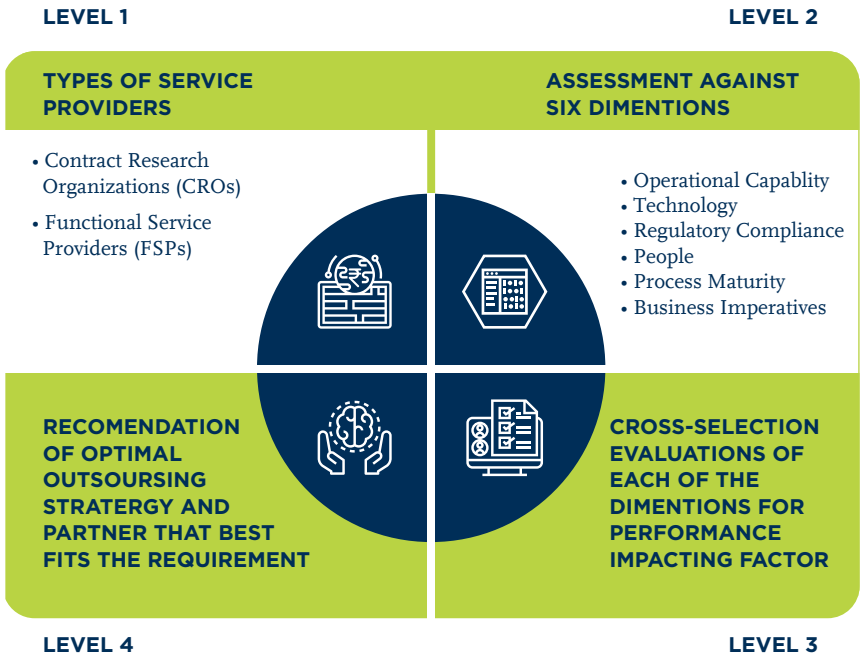
The Partner Assessment Framework (Figure 2) includes an analysis of a client's overall safety needs across three broad categories of service providers: contract research organizations (CROs), functional service providers (FSPs) and business process outsourcing (BPOs).

Assessment is performed against various aspects of the following six dimensions:

- Operational capability
- Regulatory compliance
- Technology
- People
- Process maturity
- Business imperatives

Each dimension in the framework includes 3 to 10 factors. For instance operational capability addresses a number of factors including the number of global sites/hubs for the PV team, competence to perform varied tasks associated within safety and risk management such as literature search and review, periodic reporting, Company Core Data Sheet (CCDS)/label update and signal detection. On the other hand process maturity evaluates standardized and streamlined processes, employee productivity, employee training, etc. This assessment allows a client to evaluate their processes against the industry baseline for safety operations and identify the next steps in maturing their overall operations. The key outcome of this kind of assessment is to provide a recommendation for the optimal choice of sourcing strategy and partner organization that best fits the requirements.

Figure 2: Covance Partner Assessment Framework



RISK-BASED OUTSOURCING APPROACH AND ITS EVOLUTION

By applying our Partner Assessment Framework in the context of each client's unique outsourcing needs, we help our clients make the right decisions and implement the right solutions. The approach to outsourcing depends on the sponsor organization's business model, current status and future plans. When it comes to patient safety, companies are especially risk-averse in their outsourcing decisions and the outcome of a risk-based approach to outsourcing safety services could lead to very different outcomes for different companies. A risk-averse approach for a company that has in-house PV operations and safety team could mean that they gradually transition activities to a PV service provider and it may not be critical for the provider to have the scale and end-to-end expertise from the start. On the other hand, small companies that lack in-house capabilities will look to partner with a provider who has the wherewithal to set up the entire safety system and operations for them, inclusive of people, process and technology. This is the most risk-averse scenario and decision for them.

As PV outsourcing has matured over the past decade, companies have evolved in terms of how they approach outsourcing and what they expect. Some of the large pharmaceutical companies that were early adopters of PV outsourcing and offshoring now want to work with more than one provider. And while scalability was an important factor for vendor selection the first time, the ability to provide domain-intensive (versus process-driven) safety services plays a prominent role in the selection of the second niche provider. Expectations around realizing the benefits from process and automation improvements feature prominently, and apply to both large and niche providers. In addition, a sponsor's past outsourcing experience may help identify areas of improvement. For example, over emphasis on scale and process might have compromised quality, which then required additional oversight.

The second time around, companies want to select a vendor who can fill the gaps they have experienced with the first one (for example, provide better quality narratives). Alternatively, the company might want to now also outsource medical review and aggregate reporting, for which it may not be optimal to use the current vendor. There may also be instances wherein companies have opted for an entirely offshore model the first time, but encountered certain challenges (i.e., slow ramp-up of experience level of resources and inefficient remote management of the vendor), so they now want an optimal mix of onshore/offshore resourcing.

Mid-sized companies have experienced substantial increases in their PV needs as a result of their growth, expansion and the evolution of regulations across the globe. The sourcing decisions they made a few years ago may not be valid today. If they had previously decided to have an in-house safety team, they may now want to assess what should stay in-house and what should be outsourced. If some companies had chosen to partner with a niche, near-shore safety provider, increased volumes and need for more safety expertise may lead them to explore other options, including offshoring, both for scale and skill, while simultaneously controlling the costs.

The prominence of small biotech companies has grown significantly over the past few years. Their considerations are often quite different from that of the other segments in the context of a risk-based approach to fulfilling their safety and risk management needs. They may have a few clinical trials that are being managed by CROs (often different ones), inclusive of adverse-event processing. As their first product approaches the submission stage, they have to start thinking about post-marketing safety and the need for all safety data to be consolidated in a single safety database. Thus many of these companies may evaluate speciality safety FSPs. They have to also decide whether to invest in their own database or to host the data with the service provider, as well as how much of the domain-intensive safety and risk management activities to outsource (e.g., signal detection, risk management plans).

Our Partner Assessment Framework can be effectively applied to drive vendor selection irrespective of the situation. It can provide targeted assessment across the service provider categories (CROs, FSPs and BPOs) for specific current needs across the safety operations value chain.

IMPLEMENTATION OF THE RISK-BASED APPROACH AND SUCCESSFUL TRANSITION PLANNING

Phase I: The approach and plan

Measurable and quantifiable metrics, with appropriate benchmarks, are critical to successful sourcing decisions and their implementation. We have developed a robust methodology that includes checklists and indexes to facilitate such measurements and comparisons. By working collaboratively with the client team to assign various ratings for their specific situation, we are able to assess the landscape and make a recommendation about how to plan the outsourcing and transition in a manner that mitigates any associated risk.

In Table 1, the index value helps identify the best approach to outsourcing – when, what and how. For example, if the index value is between 1 and 3, the first step would be to engage in a consulting assignment to evaluate the organization's current state, identify gaps in their overall operations and develop the safety system requirements in the context of their business plans. Only after this activity is completed can a decision about what to build internally, what to outsource, how to select the vendor, etc. be made. At the other extreme are organizations (typically large or a few mid-sized pharmaceutical companies) who have been performing all safety and risk management activities for some time. They have alignment across safety, regulatory, clinical and quality departments to ensure compliance of PV operations, so that an external vendor can quickly adapt to the company's internal processes and start delivering PV services. The index value in such scenarios is between 8 and 10.

Table 1: Transition Methodology to Determine Client Status and Optimized Approach to Outsourcing

TRANSITION METHODOLOGY TO DETERMINE CLIENT STATUS AND OPTIMIZED APPROACH TO OUTSOURCING

1-3	4-7	8-10
Client does not have adequate internal resources and know-how and is seeking recommendations and advice on how to establish an effective PV strategy and platform. A time-bound consulting project is needed to evaluate the best approach to outsourcing. Or, client is working with multiple CROs or vendors and requires centralized database and operations; decisions about hosting the database internally vs with the vendor, etc. have be made. Or, the client is looking at new TAs or geographies and hence needs to revisit its safety sourcing strategy.	Client's internal resources do not adequately support the company's growth and overall safety operations or are being stretched in too many directions that they are unable to focus on more strategic company initiatives. These organizations see the value in hybrid and/or offshore outsourcing model. Parts of the client's safety operations can be supported by an outsourced provider. In this scenario, hand-offs and dependencies between what is retained in-house and what can be supported from an external provider are understood, including what level of oversight is required to ensure continuity in operations and how to mitigate commonly encountered risk factors (e.g., delay in receipt of partner cases) when operations are transitioned to a partner. For organizations that have processes which are not as mature (e.g., safety data exchange agreements, updating CCDS, centralizing product registry information across geographies), they may want the outsourcing vendor to help define and implement best practices and baseline of activities.	Client's processes are well-defined and can be readily supported by an external provider without requirement of pre-work. In this scenario, both parties need to create expected Service Level Agreements based on the current baseline, formalize the transition plan (how much work to be supported by the outsourcing provider and how soon), evaluate the portfolio segmentation, perform product risk categorization and develop a 3-5 year projection for an outsourcing operation. Next level could be – client missing specialized skill-set and resources to perform sophisticated activities such as medical review and signal detection.

Phase II: The transition

The approach to transitioning the activities to a vendor may vary based on factors like client portfolio size, product maturity, urgency and volumes. Below are the two broad types of transition approaches:

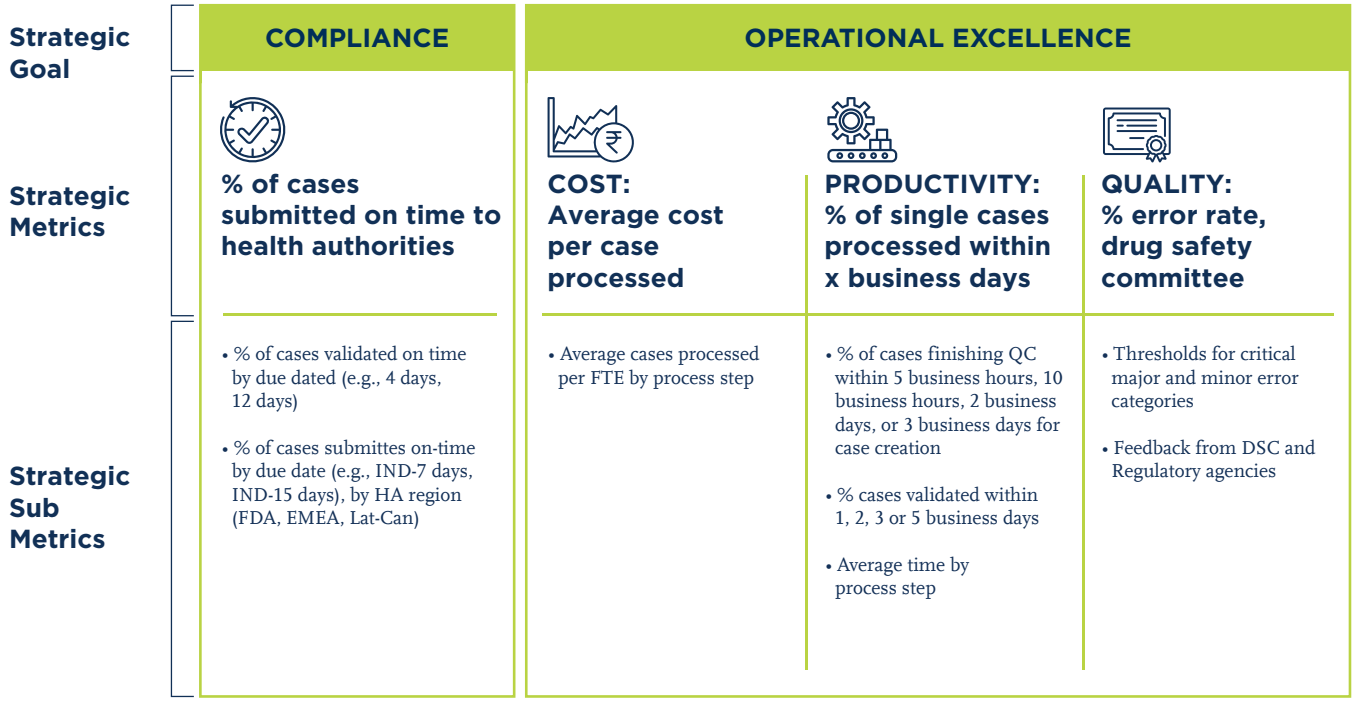
- Big Bang Approach: The transition of operations is completed in one shot.
- Wave Approach: Processes are transitioned in multiple waves over a longer period of time and the specifics of the waves may be product, function and geography specific.

Phase III and IV: Engagement lifecycle management and steady state operations

Once the planned activities have successfully transitioned to the vendor and optimized processes are in place, achieving steady state requires careful quality oversight and management. The goal is to get to a "predictable" state where processes are well documented, understood and efficiently executed across functions and locations and where hand-offs between the client and Covance are well understood and seamless.

Identifying and documenting key goals, metrics, sub-metrics and KPIs are essential for successful steady state operations. Figure 3 below provides examples around compliance and operational excellence goals, including specific metrics on quality, compliance, productivity and costs. Table 2 provides examples of Service Level Agreements (SLAs) goals and metrics that need to be established and set at the beginning of any engagement.

Figure 3: Monitoring Process as Steady State



The table below is a representative set of steady state KPIs. We work collaboratively with our clients to tailor these KPIs to their specific needs during the planning discussions at the beginning of the engagement.

Table 2: Metrics and SLAs

METRICS AND SLAs			
SLA CATEGORY	**METRICS**	**DETAILS**	**OBJECTIVE THRESHOLDS**
Regulatory Compliance	Adherence to case submissions timelines as per regulations	The KPI is measured in terms of percentage adherence	Target is 100%, but minimum 99% of ICSRs submitted within the regulatory timelines
Turnaround Times (TATs)	The days within which a case is processed by the PV operations	This KPI is measured on basis of aging of open and closed cases	4 days TAT for serious 8 days TAT for non-serious
Quality	Void cases Cases that were termed as void for not meeting the valid case criterion	The KPI is measured as a count and percentage of actual case volume. Cases are voided if information to process them in adequate and cannot be sourced further	< 1% due to incorrect initial assessments
	Case quality This metric provides insight on quality of cases including case narrative	This KPI is measured in percentage adherence against a set SLA. Case quality is usually measured at two stages: A) In line/Peer review: After case entry/pre submission B) End of line: Sample based review post case submission Case quality is further measured as: • Complete case/Case Level • Field Level where in the fields of a case are marked into category of error (Critical, Major, Minor)	Case Level – 92% quality Field level: Cat 1 – 98% Cat 2 – 96% Cat 3 – 93%

It's important to recognize that in addition to optimizing around the right metrics, there are other key components of steady state operations as mentioned below:

- Flexibility and scale are essential to achieving an optimized steady state operation. Being able to easily scale up and down means that volume fluctuations can be absorbed without compromising compliance to meet critical SLAs around quality and TAT (Table 2).
- Comprehensive quality oversight is paramount to a successful outsourcing relationship. By employing an adaptive, yet robust QA and feedback mechanism, an organization can guarantee compliance with regulatory requirements while maintaining optimal oversight levels in line with the performance metrics.
- Continuous improvement incorporates ongoing measurement and monitoring of the operations as well as application of LEAN methodology that will lead to meaningful process and productivity improvements. A practice such as weekly global team reviews, where sample cases are selected and dissected, suggests improvements in processing and assessment of adverse event cases. Removing redundancies in hand-offs can lead to improvements in TATs and hence improve reporting compliance.

Training the call center team on certain aspects of case processing and training the case processing team on certain aspects of aggregate reporting can lead to overall improvement of quality and efficiency of safety processes. Furthermore, quarterly client satisfaction surveys can be used to improve and strengthen the overall partner relationship. At Covance, our PV business has adopted the Net Promoter Score (NPS) methodology to assess customer satisfaction. Table 3 illustrates how continual oversight and looking for improvement opportunities can benefit the process.

Table 3: Preventative Measures and Benefits

PREVENTATIVE MEASURES AND BENEFITS			
PROCESS	**POTENTIAL FAILURE**	**PREVENTIVE MEASURES**	**BENEFITS**
Triage	• Incorrect case assessment • Incomplete data	• Periodic review of cases tagged as non-serious by PV Physicians • Flagging of potential serious cases using automation • Strengthening intake process to ensure complete data thereby helping TAT	100% Regulatory Compliance, Reduced TAT & Rework
Data Entry	• Prioritization of workflow • Incorrect data capture	• Automation of workflow using case/project management system • In line review of cases using automated system for effective feedback	Meeting 100% Quality SLAs
Submissions	• Incorrect submission package • Submission gateway failure	• Pre-submission regulatory requirement and E2B check • Reduced TAT thereby assuring additional timelines for submission	100% Regulatory Compliance

CONCLUSION

Drug safety processes are fundamentally very different and more complex than other clinical research processes that are outsourced and delivered from offshore providers. Even the simplest of activities such as individual case processing requires years of training to understand the mechanism of action of the drugs and to perform the label and causality assessment accurately. For more complex activities like aggregate reporting and signal detection, the subjectivity of decisions and need for additional specialization is even more exacerbated.

Through our experience in providing end-to-end safety and risk management support to many of the leading global life science organizations, Covance has a sound understanding of all aspects of safety from individual case processing to signal detection and signal management as well as the interdependency between these.

FOR EXAMPLE:

- We understand how individual case assessments shape the aggregate analysis reported in a PSUR or a PADER
- How EU RMPs and U.S. REMS evaluate the overall risk of the product in the market
- How case processing and aggregate report authoring activities enable effective management of overall risk-benefit balance for the products we support
- How qualitative and quantitative signal detection fits into the overall signal management process

Our global delivery model provides us the ability to scale up or down depending upon the evolving needs of our client's product portfolio while providing cost-effective services by leveraging a globally distributed team.

By employing a combination of proprietary automation and technology tools, methodologies such as those described in this paper, as well as industry benchmarks and best practices in drug safety operations, we are able to deliver compliant, high-quality and consistent results. Our approach balances process rigor, flexibility and adaptability to provide clients with an optimal and proactive solution for patient safety.

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