QUALITY RISK MANAGEMENT AS A SURVIVAL KIT:

From Idea to Implementation

Guide for Risk-Based Monitoring Technologies

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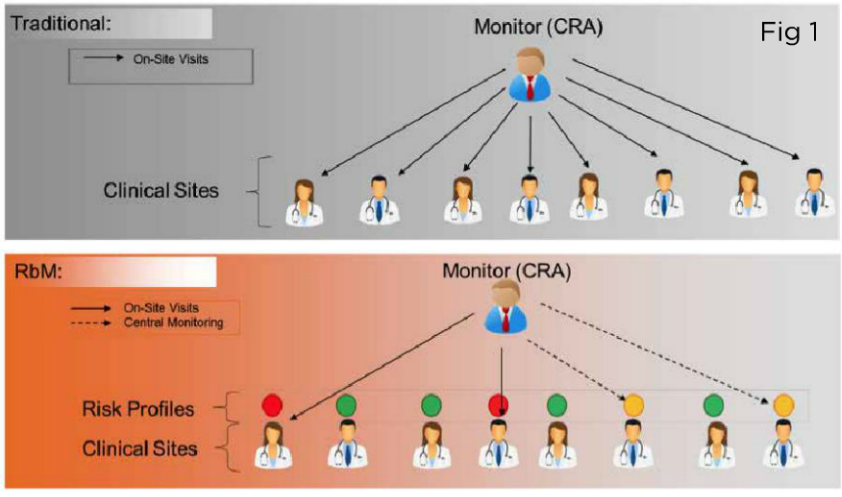
Research and development returns in the pharmaceutical industry have halved in the past ten years[1], due to increasing trial complexity, regulatory scrutiny, and competition for patients and high quality sites. Efficient risk management has become more than advice today – it is part of the survival kit for a modern pharmaceutical company.

FDA's monitoring guideline (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf) advises: "Monitoring should be tailored to your organization, the study protocol, and the product being tested"[2]. This implies that the selection of monitoring methods should involve a thorough analysis of the study protocol, its execution, and the contributing parties, as well as the associated risks. Only after analysis of information critical to the success and quality of the study is one prepared to define a Risk-based Monitoring (RbM) strategy that is commensurate with the study risk profile (See Figure 1).

Initially, GCP referred to RbM indirectly in §5.18.13, although the upcoming GCP E6R2 addendum (currently undergoing regulatory review) puts stronger emphasis on this procedure. In accordance with the addendum, a sponsor should develop an approach to monitoring clinical trials which is systematic, prioritized, and **risk-based**. The addendum advises that **a combination of on-site and centralized monitoring activities is appropriate**. Additionally, it points out that **emerging advances in**

Figure 1:
Comparison of the Traditional Monitoring approach and RbM.



technology may facilitate the remote monitoring of source data. This article will categorize available RbM technologies and how they can support clinical operations.

RbM Technology Can be Categorized by Different Factors:

BY IT INFRASTRUCTURE: CLOUD-BASED VS. ON-SITE SOLUTIONS

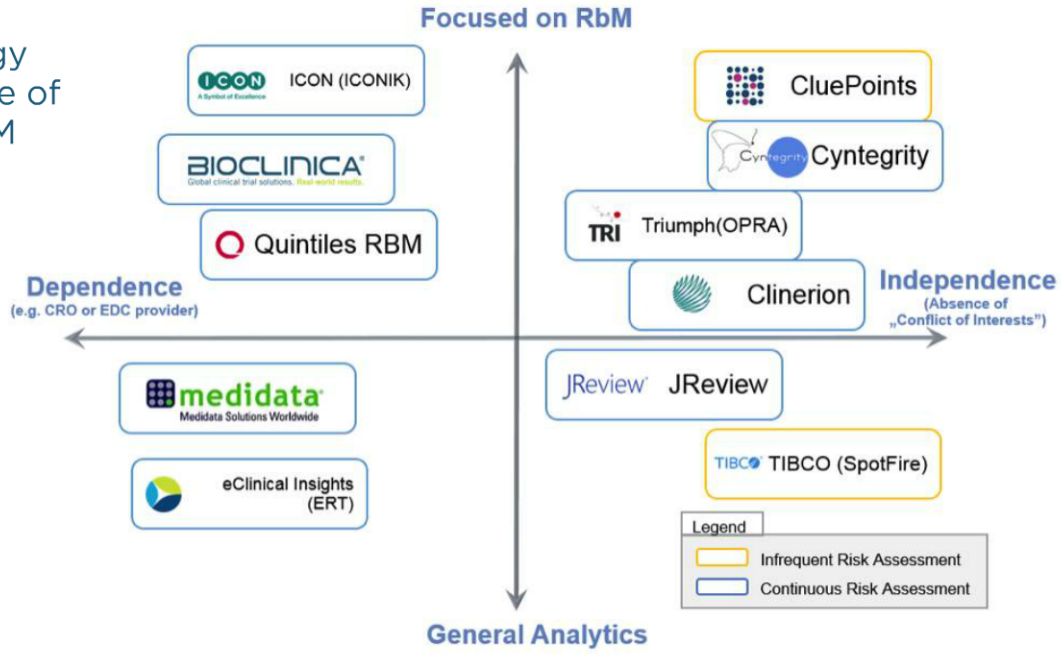
1. **Cloud-Based:** Software as a Service (SaaS) approach makes RbM available via a web-portal. Organizations using these solutions do not need to take care of IT infrastructure.
   a. **Commodity Service:** These systems use the commodity cloud solutions and share resources with other services. Sometimes concerns about data security keep some companies from using this infrastructure.
   b. **Private Cloud:** Allocates a dedicated infrastructure for each customer so that computing resources and a higher level of stability and availability are assured. Data security is generally not a concern.
2. **On-Site Solutions:** These solutions are located on servers of consumers of the RbM solution. An important advantage of this solution is nearness of data sources and, as a result, high speed of data access.

Major influencing factors regarding IT infrastructure are location of service, skill specialization, and scalability. Location strongly influences the price. As a result, cloud solutions are cost efficient. Traditionally, on-site solutions have been implemented but cloud-based solutions are now more in demand as they also provide high levels of service but at significantly lower cost and more flexibility than traditional internal IT departments can generally provide.

BY DATA SOURCING

Data sourcing capabilities of RbM technology can differ by its data sources (e.g., EDC, CTMS) and by its data acquisition method (push vs. pull). Most of today's RbM solutions focus on EDC because EDC can deliver many risk-relevant parameters

Figure 2: Technology Landscape of Some RbM Providers



(e.g., the number of enrolled patients, visit schedules, etc.). Some technology providers consolidate data sources in a data warehouse (data gets stored at one central location), while others apply an elastic network approach enabling configurable data source interfaces, where networks crawl different clinical recording systems and capture risk-relevant information.

BY ASSESSMENT FREQUENCY

The risk assessment frequency is an important criterion. Some solutions offer quarterly assessments, while others conduct periodic automatic or semi-automatic assessments. The advantage of the first approach is that the assessment may be done deeper with preliminary data cleaning and preparation. In the latter, the RbM operator can observe the development of risk dynamics (speed and direction).

BY RISK AREAS

1. Basic Risk Areas (Patient Safety, Site Performance, Data Quality, Fraud Detection)
2. Protocol-specific Risk Areas (Protocol Compliance)
3. Therapy-specific Risk Areas (ECG, Spirometry, Imaging, ePro)
4. Resource Availability
5. Vendor Oversight

Choice of technology should be driven by requirements and risk tolerance. For larger trials with extensive requirements, a solution with a broad set of features and predictive analytics is suitable. A cloud solution with an elastic network is usually well suited for smaller trials.

BY FUNCTIONS

1. Risk Detection
2. Issue Management
3. Risk Mitigation Process
4. Predictive Analytics, Heuristics

Each solution differs in the provided feature set (see Figure 2). Risk detection, risk dashboards and reporting, issue management, and risk mitigation process, are among the most universal features. More advanced solutions provide predictive analytics and heuristics to identify residual risks.

About the Authors

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