GLOBAL FORUM

Driving Ideas to Action

LISTENING AND LEARNING FROM PATIENTS... P24

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AUGUST 2015

VOLUME 7 • ISSUE 4

DIA DEVELOP INNOVATE ADVANCE

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DIA *Global Forum* provides a multidisciplinary, neutral forum for communicating information related to drug development and life cycle management on a global basis. The *Global Forum* disseminates content that is relevant to members' professional experiences, including international industry and regulatory updates and news of the association and its programs. The magazine is circulated electronically six times a year as a benefit of DIA membership.

Publishing and Subscription:

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21 Dupont Circle NW, Suite 300
Washington DC 20036 USA
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267.419.8735
The *Global Forum* (ISSN: 1944-1991) is a publication of the Drug Information Association.

Editorial Office:

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800 Enterprise Road, Suite 200,
Horsham, PA 19044-3595,
USA; phone - 215.442.6100;
fax: 215.442.6199.

The *Global Forum* (ISSN: 1944-1991) is produced six times a year, in February, April, June, August, October, and December. Back issues of most previously published issues are available online for members at www.diaglobal.org.

Design: Influence Media - 267.419.8734

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QUALITY RISK MANAGEMENT AS A SURVIVAL KIT:
From Idea to Implementation
Guide for Risk-Based Monitoring Technologies

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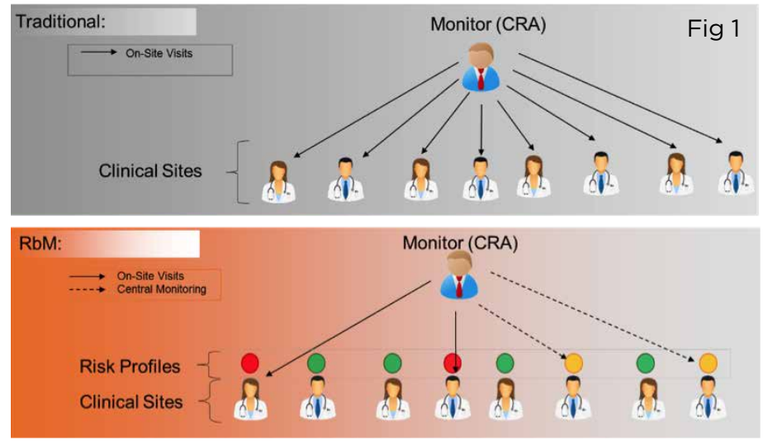
Research and development returns in the pharmaceutical industry have halved in the past ten years[1], due to increasing trial complexity, regulatory scrutiny, and competition for patients and high quality sites. Efficient risk management has become more than advice today – it is part of the survival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

(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

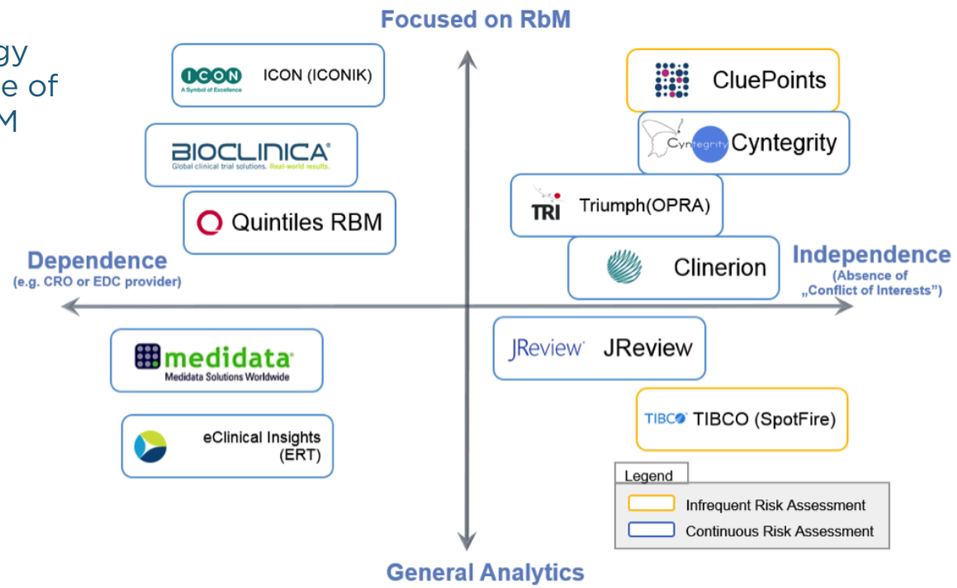
Choice of technology should be driven by requirements and risk tolerance. For larger trials with extensive requirements, a solution with a broad set of features and predictive analytics is suitable. A cloud solution with an elastic network is usually well suited for smaller trials.

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.

Figure 2: Technology Landscape of Some RbM Providers



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RBM IMPLEMENTATION

Experience shows that a staged approach is most effective with RbM.[4] It provides opportunities to reflect and adjust the process. Successful RbM includes both appropriate governance and enabling e-tools. In other words: People, Process, and Technology are key to success. The stages in this approach:

1. **Proof of Concept:** Execute workshops to determine the appropriate RbM organization, process, and technology. Choose a suitable trial. Apply simple e-tools, and establish and train an RbM Core Team on the RbM process and tools.
2. **Pilot:** In this stage, e-tools play a stronger role. The pilot team gains experience, so that an informed decision can be made on how to proceed.
3. **Lessons Learned:** During the pilot, the RbM Governance Team and the Study Management Team provide feedback regarding the process and technology. Upon pilot completion, the results are analyzed, consolidated, and presented to major stakeholders.
4. **Adjust RbM:** Adapt the RbM approach and technology to be consistent with change requests.
5. **RbM Rollout:** RbM process and technology are fully integrated for the whole trial portfolio, progressively involving more studies.

Summing up, RbM is a journey of continuous improvement requiring mechanisms for process change and a new way of working and thinking within the organization.

Key take-away Messages:

- Tools are essential for implementing RbM successfully as they enable recurring evaluation of risks and sites profiles.
- Today's technology solutions vary significantly and their suitability depends strongly on your situation and risk tolerance.
- When implementing RbM, apply a staged approach.
- Plan on bringing external expertise, if needed; it will reduce risks introduced by RbM.

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A p-Value is only as Good as the Data: Challenges when Endpoints are Based on Subjective Assessments

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When endpoints are based on subjective assessments rather than objective data, a process of centralized endpoint adjudication can improve the quality of a clinical trial.

INTRODUCTION

WHAT IS ENDPOINT ADJUDICATION?

In many therapeutic areas, the baseline and end of trial assessments are based on the assessment of an image (e.g., tumor size), a tracing (e.g., ECG), or on the patients' or doctors' subjective assessment on a scale (e.g., visual analogue scales to rate pain, Hamilton scale to rate severity of depression). To reduce the observers' bias in a multi-center trial it is critical that assessments of such endpoints be "validated" (i.e., transparent and binding rules on how to perform the assessment are defined and agreed upon). Bias can also be introduced when treatment is unblinded or becomes unblended; the rater's expectations may result in inaccurate readings. Training of raters is an essential component of the quality strategy when subjective assessments are involved. However, an adequate quality control strategy needs to be implemented as well. An effective quality management approach is represented by a central baseline assessment and at the follow-up assessments of efficacy or safety parameters by a panel of independent experts following a blinded standardized procedure. A centralized assessment by a limited number of trained raters increases the accuracy of the readings, results in more independence of the raters, and thus prevents "observers' bias" and yields more homogeneous assessments or ratings.

WHEN ENDPOINT ADJUDICATION IS USED, IN WHICH THERAPEUTIC AREAS AND HOW FREQUENTLY

Analysis[1] of new marketing authorization applications / NDAs in 2013 and first quarter 2014 to FDA and EMA, respectively, showed that in 69% of the NMEs approved in the US and 41% of EMA approvals, some sort of adjudication method was used in phase 3 development programs. Medicinal products developed for oncology and endocrinology indications typically used an independent review committee (IRC) in line with recommendations made in relevant regulatory guidance, whereas in trials in nervous system or with

Figure 1 - 2013 & 1st Quarter 2014 FDA NME approvals