LISTENING AND LEARNING FROM PATIENTS... P24

Risk-Based Monitoring: Hype, Paradigm Change or New Frontier? ... p14

New Medical R&D Agency in Japan... p38

EU QPPVs: The Responsibilities and Risks are Real... p46

Review: IOM Report on Sharing Clinical Trial Data... p48

Beat Widler, Quality Special Section Editor, p7

Eric Racine, Patient Centricity & Empowerment, p24
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Contents
4 Deputy Editor’s Message
5 President’s Message
6 Global Forum Editorial Board
SPECIAL SECTION
7 Why a Special Section about Quality?
8 What is Quality? DIA Quality Working Group
10 The Quality of Medical Information
14 Risk-Based Monitoring: Hype, Paradigm Change or New Frontier?
17 Quality Risk Management as a Survival Kit: From Idea to Implementation
21 A p-Value is only as Good as the Data: Challenges when Endpoints are Based on Subjective Assessments
YOU NEED TO KNOW
24 Listening and Learning from Patients
32 Australia Update: 32 Recommendations
33 Canada Update: Vanessa’s Law, Labeling Regulations, and New ICH Role
35 China Update: Innovation and Convergence Will Propel Pharmaceutical R&D
36 EU Update: Off-Label Use of Medicines; Legislative Framework for Devices
37 India Update: Improving Regulatory Practices and Clinical Trials
38 Japan Update: Roles & Responsibilities of New Medical R&D Agency (AMED)
39 Middle East and Africa Update: Ebola Lessons Inform New Collaboration Paradigms
40 United States Update: Elevating the Patient Voice: Leveraging Patients’ Expertise to Advance Drug Development
CONNECT
42 Have you Heard? DIA’s Insightful Podcasts
44 Patient Access to Medicines: European HTA Cooperation Must Evolve - An Industry View
46 EU GPPVs: The Responsibilities and Risks are Real
48 Review: IOM Report on Sharing Clinical Trial Data
IN MY VIEW
51 Viewpoint: Clinical Data Sharing Requires Culture Change
52 Viewpoint: Clinical Data Sharing Matters to Patients
53 Pediatric Medical Product Development: TIRSA September 2015
CLOSING REFLECTIONS
54 The Importance of Nomenclature — Pharmacoverging/Pharmacovergence

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Special Section

Research and development returns in the pharmaceutical industry have halved in the past ten years1, 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.

Additionally, it points out that a combination of on-site and centralized monitoring activities is appropriate.

QUALITY RISK MANAGEMENT AS A SURVIVAL KIT: From Idea to Implementation

Guide for Risk-Based Monitoring Technologies

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

CLOUD-BASED VS. ON-SITE INFRASTRUCTURE: Factors:

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

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.

BY FUNCTIONS

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

About the Authors

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RBM IMPLEMENTATION

Experience shows that a staged approach is most effective with RbM.* 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 recurrent 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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### References


### Notes

*RbM: Risk-Based Monitoring

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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 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...