Quality Risk Management & Risk-Based Auditing

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Our Journey
Regulatory perspectives

- ICH Q9: Quality Risk Management
- ICH Q10: Pharmaceutical Quality System
- FDA Guidance for Industry: Q9 Quality Risk Management
- ASTM E2500
Risk

- Where to begin?
- What direction to go?
- How do you know when the traffic lights are broken?!
- Do you know when/if you will arrive in good shape???
## Defining Risk

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Risk</td>
<td>“The combination of the probability of occurrence of harm and the severity of that harm” from ICH-Q9</td>
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<tr>
<td>Risk Management</td>
<td>The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk</td>
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<td>Risk Assessment</td>
<td>A systematic review to determine risks – one piece of risk management</td>
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<td>Harm</td>
<td>Damage to health, including the damage that can occur from loss of product quality or availability</td>
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<td>Hazard</td>
<td>The potential source of harm</td>
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<td>Control Mechanism</td>
<td>The approach defined to maintain the output of a specific process within a desired range</td>
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Integration of QRM

QRM is a process that supports science-based & practical decisions when integrated into quality systems

Examples:
- Product Development
- Validation
- CAPA/Deviations
- Training
- Documentation
- Auditing & Inspection
- Quality Defects – Inspections
- Change Management
Avoidable vs. Unavoidable Risk

- Availability of data and benefit-risk analysis
- Zero risk is not scientifically achievable

“Although medicinal products are required to be safe, safety does not mean zero risk. A safe product is one that has reasonable risks, given the magnitude of the benefits expected and the alternatives available. As such, quantified risk must be balanced against unmet medical needs”

- U.S. FDA Risk Management Task Force, 2009
Risk Assessment (ICH Q9)
A systematic process of organizing information to support a Risk decision to be made within a Risk Management process. The process consists of the identification of Hazards and the analysis and evaluation of Risks associated with exposure to those Hazards.

Risk Management
- Overall risk program
- Living
- Management accountability
- Processes to coordinate, facilitate and improve science-based decision making with respect to risk

Risk Assessment
- Specific event
- Point in time
- Subject Matter Expert
- Deep technical knowledge
- Produces individual documents consisting of hazards and risk evaluations

Risk Management (ICH Q9)
A systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating and controlling risk.
Risk Management: Nothing New
Risk Assessment in Traditional Audit Programs

- **Audit target selection:**
  - Protocol selection: complexity, regulatory impact, development phase
  - Site selection: number of subjects recruited, SAEs reported, protocol deviations, site qualification and non-compliance history

- **Audit sampling for review:**
  - Subject sample
  - Data points
  - Which site staff to interview
Leveraging Intel KQIs
Centralized Monitoring
Proactive management
QbD
Lessons Learned
Root Cause Analysis
STATISTICAL PROFILING
Real time data review
Risk identification
Data Mining
Signal Detection
Trend Analysis
Outliers
Proactive management
“It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used”

– ICH Q9 EWG Briefing Pack

- The ability to manage quality risks may suffer if we apply a “one size fits all” QRM tool approach
- Meaningful, effective, and efficient QRM when the selected tool fits the problem statement and intent of the risk assessment
- Tool selection will impact usefulness, ease of execution, quality, and validity of the risk assessment
Approach to QRM

- **Early trial optimization review**
  - Desired outcome: QbD during protocol writing phase

- **Project Risk Assessment:**
  - Assess protocol inherent risks
  - Assess trial set-up, responsibilities of 3rd parties, impact on primary & secondary study endpoints
  - Desired outcome: Proactive risk mitigation during development of operational project plans

- **Risk analysis during site selection:**
  - Desired outcome: effective balance between Quality & Delivery

- **Real-time data and trend analysis (e.g. RBM):**
  - Desired outcome: early detection of adverse signals to allow rapid escalation and mitigation of potential risks
Example

Traditional On-Site Monitoring

- 100% Source data review/verification
- Scout (transcription) errors
- Identify underreporting
- React, escalate, report, address, document

Centralised Risk-based Monitoring

- Understand Critical-to-Quality data points
- Proactive risk profiling
- Lean protocol
- Integrated Quality by Design project plans
- Cross-functional real-time data analysis
- Determine tolerance levels
- Proactive signal detection
- Statistical approach to risk calculation
- Data driven decision making
- Root cause analysis
- Mitigate
- Adjust quality management approach
- Less dependencies on monitor experience, however more on use of appropriate tools and methodologies
Traditional Auditing vs. 2 Monitoring Models

Traditional monitoring:
- Data includes 2323 audits
- Top-10 findings account for 85% of audit findings

RBM/Reduced SDV monitoring model:
- Data includes 213 audits
- Top-10 findings account for 86.5% of audit findings

Data source: PPD TrackWise, Client & PPD investigator site audits reported between 01Jan2008-31Oct2013
Pause

An indication we are heading the right direction?

- REDUCING non-compliance that matters (Medical Care related observations)
- MISSING on what may not matter (or at least correctable)

Based on a “traditional” audit approach

So what is Risk Based Auditing?
Risk-based Auditing

DILEMMA?

- Auditing by applying the same risk based methodology as used in e.g. RBM

or

- Auditing of risk based operational activities, e.g. RBM
Risk-based Auditing

Risk Based Auditing = Improving selection of audit targets
Understand better what risky sites are

- What is risk?
  - Perspective of Sponsor (Pharma/Biotech) vs. Perspective of CRO
  - No “One size fits all”
Example: Early Risk-based Auditing

- Risk assessment:
  - identifying audit target based on available data
- Early version based on monitored data
- Risk profile: Red/Amber/Green
- Traditional auditing: highest risk were the “lowest risk sites”
  - Not monitored: not reported, unknown
  - Audit
- Understand the data
- Parallel with RBM and Inspections
Risks to Risk-based Auditing

- Data pollution/data gaps
- Focus only on projects and sites that were identified as “high risk”
Full Circle

- What is important to monitoring is important for auditing (traditional)
- What is not important to monitor should be covered by auditing the process assuring no deviations that matter are introduced

- We should not teach Auditors to copy RBM
- We should teach Monitors/Start-up teams to apply quality and risk management
Full Circle

- **William Edwards Deming**: “Eliminate the need for massive inspection by building quality into the product in the first place”
- Shift from “Quality Assurance” to ‘monitoring’ as part of preventive measures
- “The key is prevention of non-compliance and this requires well trained and experienced CRAs.
  - Proactive: feasibility, site initiation, selection,
  - Quality by Design: Lean protocol (CTQ data point collection) - Traditional auditing

Risk-based Auditing: conclusion

Audit the Methodology

- Understanding risk based methodology
  - E.g., investigator site audits

- Central: Process/Model
  - Data (Real Time Data)
  - Calculations
  - Key Quality Indicators
  - Decisions
  - Follow up: risk mitigation plan (is model adapted?)

- On site
  - Traditional
  - Focus on Critical to Quality data
Your Journey?