Principles of Quality Risk Management

SESSION I: Principles for Building Quality into Clinical Trial Development

CTTI Workshop on Quality Risk Management: Making Clinical Trials Fit for Purpose

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Setting the Scene
Ultimate Goals of Quality Management Principles and Goals in the World of Health Care

Patient Safety, Rights and Integrity
in all clinical trials and post-marketing activities

The Focus

Data Integrity
of data created in these clinical trials and post-marketing activities
What is Quality?
What is Quality?
The numbers are against us, for example, Audits cover only about 2% of clinical-related activities.

Main Risks
- Safety Processes
- Data Integrity

GCP & Pharmacovigilance Entities

| 10^1 | HQ functions |
| 10^2 | Affiliates   |
| 10^3 | Partners     |
| 10^4 | Trial Centers ** |

Audit Coverage
- 250 Audits
- ~ 20,000 Entities = < 2% Audit Coverage
Continuous Risk Evaluation: 

Three core steps

1. Base Risk Profile (BRP) (periodic – annually)
   - Impact (I)
   - Detectability (D)
   - Likelihood (L)

2. Automated Evaluation of Key Risk Indicators (KRI) (continuous)
   - Modification of Score

3. Overall Entity Risk = Risk Priority Number (RPN) (Safety Processes/Data Integrity)
   - Impact (I) x Detectability (D) x Likelihood (L)
   - Translates into a RPN signal
QRM “risk indicators” are designed to detect these issues early before they become problems

Risk Indicators Along the Trial Management Process

Risk indicators covering key quality issues
Continuous Risk Evaluation based on automatic Analyses of existing Data

Use existing data… … to identify areas with increased quality risks

Wealth of Existing Data at Roche Pharma

Safety data
Trial info
Clinical data...

# S/AEs

QRM Dashboard

Allowing for different views:
- Product/Project View
- Process View
- Geographical View
Example: Monitoring visits delayed

Study: XYZ

<table>
<thead>
<tr>
<th>Clinical Trial Center</th>
<th>Month</th>
<th>Monitoring within 10 Weeks After first patient enrolled or previous monitoring visit</th>
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<tbody>
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Is monitoring sufficient and on time?
Example: *Premature terminations above protocol average*

Is there an unusually high rate of unexpected drop-outs at any site?

Risk Indicator: Premature terminations of patients

Measures average drop-out per patient for a site against the protocol average

Threshold: 1.3 x Ø

Protocol Ø

Clinical Trial Centers
QRM to detect systemic issues

Are there any systematic quality issues within this study?
Protocol Violations - QRM tracks the data over time, which allows for addressing the issues as in this case: KRI Value drops

<table>
<thead>
<tr>
<th>Months: Sep-2007 - Aug-2008</th>
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<tr>
<td></td>
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<tr>
<td>Sep-07</td>
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<tr>
<td>KRI Signal</td>
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<td>KRI Value</td>
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<td>Threshold</td>
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<td>Number of patients enrolled per site</td>
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<td>Number of protocol violations per patient visit per site</td>
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<td>Number of protocol violations per patient visit per protocol</td>
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The number of violations increases: an alert for the study management team

<table>
<thead>
<tr>
<th>KRI Signal</th>
<th>Sep-07</th>
<th>Oct-07</th>
<th>Nov-07</th>
<th>Dec-07</th>
<th>Jan-08</th>
<th>Feb-08</th>
<th>Mar-08</th>
<th>Apr-08</th>
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<td>KRI Value</td>
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<td>Number of protocol violations per patient visit per site</td>
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<td>Number of protocol violations per patient visit per protocol</td>
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- Red signal
- Green signal
- KRI turned off
- No Data
Integrated Quality Management Approach

**QRM Elements**

- **Comprehensive**
  - Classical Audits

- **Intermediate**
  - Diagnostic Tools

- **Selective**
  - KRIs

**Depth & “Richness”**

- **Low**
  - < every 18 mths in few entities

- **Medium**
  - every 6–12 mths in many entities

- **High**
  - ≤ mths in all entities

**Frequency & “Reach”**

- Traditional QA
- New QRM Elements

KRI = Key Risk Indicators
Automated QRM Tools Enhanced
Impact of QRM on “traditional” Compliance & Quality Activities
Impact of QRM on “traditional” Compliance & Quality Activities
The Reward for Quality by Design and Quality Risk Management

Errors “that are understood”, do not matter!
Taking Quality beyond Compliance

The QRM & QbD Twins
A lesson from the US Navy
A Wind of Change
The Cost of Accepting Workarounds or When Murphy is the Engineer
Taking Quality beyond Compliance
What needs to be done
Essential Elements to drive Quality by Design in Drug Development
Essential Elements to drive Quality by Design in Drug Development
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