Approaches to Risk-Based Quality

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CROSS-INDUSTRY DRUG DEVELOPMENT
CLINICAL TRIALS TRANSFORMATION INITIATIVE - SPONSORED MEETING

Quality by design / Quality Systems
Management

October 13, 2010
The objective of quality management is to ensure safety of patients and integrity of data

**Focus**

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

**Data Integrity**
of data created in these clinical trials and post-marketing activities
Diagnostic tools comprise three components: questionnaires, reporting and mitigating action templates

- Diagnostic tools are self surveys which are used for **questionnaire-based risk evaluation of structural elements**, such as processes and organization
- They consist of three components: questionnaires, risk reports and mitigating action templates

**Questionnaire**
- Tailored by Risk Areas and study types
- Structured along different risk assessment categories
- Set-up to ensure quick & convenient report generation

**Risk Reports**
- Data from questionnaires transferred into the respective risk reports
- Allows standardized calculation of risk scores
- Provides signals which allow identification of further optimization potential, e.g. in operations, processes and systems

**Mitigating Actions**
- Standardized form providing structured guidance throughout the definition process
- Mitigating actions to be defined in case of high risk scores
SQA is intended to allow standardized risk assessments across different study types and guides study teams during risk mitigation

**Objectives**

- Support Senior Management and study teams with information on study set-up based risk levels
  - Prior to final protocol approval
  - Before FPI and during study conduct
- Provide **standard approach to assess study quality risk** level – allowing comparison across studies
- Offer **guidance to study teams** to mitigate high and medium risk levels

**Scope**

- SQA conducts risk assessments in first step of study value chain: ‘**Study Set-up**’
- SQA encompasses all studies with **Roche involvement**
  - PD, GPS, PA, pRED and gRED
  - Phase I-IV (global and local)
  - Sponsored and supported
  - Interventional and non-interventional
The SQA tool covers all key activities of the study design and study conduct phase

Set-up of SQA Questionnaires

Study Design → Study Conduct → Study Close out

Risk Assessment Categories

- Pharmacovigilance/Safety
- Sampling
- Randomization/Data
- Outsourcing/Contracts
- Registry
- Relationship to External Sponsor

Tailored Questionnaires for
- Sponsored Interventional Studies
- Sponsored Non-Interventional Studies
- Supported Interventional Studies
- Supported Non-Interventional Studies

1) Not all of the listed risk assessment categories apply to all different study types
SQA uses a comprehensive and robust calculation logic to evaluate study risks related to Safety Processes and Data Integrity

SQA Score Calculation Logic

- **SQA Score**
  
  \[
  \text{SQA Score} = \frac{\text{Safety Processes} \times \text{Data Integrity}}{\text{max. 1728}}
  \]

  
- **Safety Processes**
  
  \[
  \text{Safety Processes} = \begin{cases} 
  \text{low} & 1 \\
  \text{medium} & 50 \\
  \text{high} & 200 \\
  \end{cases}
  \]

  
- **Data Integrity**
  
  \[
  \text{Data Integrity} = \begin{cases} 
  \text{low} & 1 \\
  \text{medium} & 50 \\
  \text{high} & 200 \\
  \end{cases}
  \]

- **Impact**
  
  \[
  \begin{align*}
  \text{Impact} & = \text{Study purpose and value-to-the-company} \\
  & \text{Number of collaborators and centers}
  \end{align*}
  \]

- **Detectability**
  
  \[
  \begin{align*}
  \text{Detectability} & = \text{Chance to detect a problem, e.g.} \\
  & \text{degree of Roche ownership / involvement} \\
  & \text{availability of standard Roche processes and guidance (especially QC processes)} \\
  & \text{availability of Roche tools / guidelines}
  \end{align*}
  \]

- **Likelihood**
  
  \[
  \begin{align*}
  \text{Likelihood} & = \text{Chance that the risk becomes reality, e.g.} \\
  & \text{complexity of the study} \\
  & \text{# of interfaces, i.e. # of parties involved} \\
  & \text{degree of experience} \\
  & \text{deviation from standards / standard practice, # of changes}
  \end{align*}
  \]

1) Safety Processes aim to ensure the timely and complete forwarding of Adverse Event notifications stemming from individuals enrolled in clinical trials or exposed to Roche drugs in the market.

2) Data Integrity is considered as one of the main risks that is covered by QRM. It is a description for the consistency and utility of efficacy and safety data. Low quality conduct of clinical trials in development or post market surveillance potentially generates a low level of Data Integrity representing a significant source of quality risk.
The SQA Tool comprises three components and facilitates reporting and mitigation of study design-based risks

SQA Tool - Overview

- **MA Template**
  - Structured guidance throughout definition of mitigation actions
  - Mitigation actions get assigned to risk categories and underlying questions
  - Timelines and responsibilities to be defined

- **Reporting Model**
  - Allows automated evaluation of study set-up based risk levels
  - Allows identification of potential to further optimize the study set-up

- **SQA Questionnaire**
  - Structured guidance throughout completion of the questionnaire
  - Questions are structured along different risk assessment categories
  - Ensures quick & convenient report generation
SQA is now in global Phase IV mandatory for protocol approval - ensuring improvement of quality prior to study start

SQA Integration with Protocol Approval Process

Validate Gap Analysis → Create Protocol Synopsis → Produce Protocol → Plan & Select Sites → Initiate Sites → Recruit Patients

SMT¹:
- Form Study Management Team
- Refine design from outline in Medical Plan
- Define study population & methodology
- Initiate study planning
- Draft protocol synopsis
- Determine key elements of feasibility
- Agree countries/sites for feasibility
- On-site clinic records check for validation
- Incorporate assessment findings
- Conduct team review of protocol synopsis
- SQA questionnaire must be completed at this process step

PAC²:
- PAC review
- Approval of synopsis?

CTR³:
- 3 months
- 1 month
- 3 months

¹ SMT: Study Management Team
² PAC: Protocol Approval Committee
³ GK: Guidelines
⁴ CTR: Clinical Trial Registration

Roche

QRM
Quality Risk Management
Category breakdowns show similar risk distribution in both Interventional and Non-Interventional, with exceptions

### SQA Category Risk Level Distribution for Locally Sponsored PA Studies

#### Analysis as of 31st July 2010

<table>
<thead>
<tr>
<th>Category</th>
<th>Interventional Studies (n=98)</th>
<th>Non-Interventional Studies (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Environment</td>
<td>31% (Low) 64% (Medium) 5% (High)</td>
<td>44% (Low) 56% (Medium) N/A²</td>
</tr>
<tr>
<td>Medication</td>
<td>2% (Low) 92% (Medium) 6% (High)</td>
<td>N/A²</td>
</tr>
<tr>
<td>Regulatory</td>
<td>100% (Low)</td>
<td>100% (Low)</td>
</tr>
<tr>
<td>Budget</td>
<td>100% (Low)</td>
<td>100% (Low)</td>
</tr>
<tr>
<td>Processes &amp; Documents</td>
<td>11% (Low) 35% (Medium) 54% (High)</td>
<td>13% (Low) 82% (Medium)</td>
</tr>
<tr>
<td>Feasibility &amp; Recruitment</td>
<td>48% (Low) 28% (Medium) 24% (High)</td>
<td>44% (Low) 29% (Medium) 26% (High)</td>
</tr>
<tr>
<td>Pharmacovigilance &amp; Safety</td>
<td>71% (Low) 27% (Medium) 2% (High)</td>
<td>73% (Low) 14% (Medium) 13% (High)</td>
</tr>
<tr>
<td>Sampling</td>
<td>71% (Low) 29% (Medium) 2% (High)</td>
<td>N/A²</td>
</tr>
<tr>
<td>Randomization &amp; Data¹</td>
<td>35% (Low) 63% (Medium) 2% (High)</td>
<td>39% (Low) 61% (Medium) 8% (High)</td>
</tr>
<tr>
<td>Outsourcing &amp; Contracts</td>
<td>40% (Low) 60% (Medium)</td>
<td>55% (Low) 37% (Medium) 8% (High)</td>
</tr>
<tr>
<td>Registry</td>
<td>59% (Low) 27% (Medium) 14% (High)</td>
<td>72% (Low) 23% (Medium)</td>
</tr>
</tbody>
</table>

1) For Non-Interventional studies, this category does not include questions on “Randomization”
2) Not applicable for this study type

Source: Initial SQA Roll-out, 2010; Booz & Company analysis
GCP DT assesses infrastructure and clinical trial related capabilities of affiliates across all regions

GCP DT Objectives & Scope

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Support local and global Senior Mgmt. to facilitate decisions (e.g. countries’ participation in clinical trials) triggered by affiliate:</td>
<td>▶ GCP DT encompasses all affiliates across all regions with clinical trial activities conducted by Roche</td>
</tr>
<tr>
<td>- Infrastructure set-up</td>
<td>- North America</td>
</tr>
<tr>
<td>- Clinical trial capabilities</td>
<td>- Latin America</td>
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<tr>
<td>▶ Provide standard approach to assess affiliates’ GCP compliance level – allowing comparison across affiliates and regions</td>
<td>- Western Europe</td>
</tr>
<tr>
<td>▶ Offer guidance to local clinical operations functions to mitigate high and medium risk levels related to GCP compliance</td>
<td>- CEMAI</td>
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<tr>
<td></td>
<td>- Asia Pacific</td>
</tr>
<tr>
<td></td>
<td>▶ GCP DT covers clinical trial activities within an Affiliate</td>
</tr>
<tr>
<td></td>
<td>- Pharma Development (PD)</td>
</tr>
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<td></td>
<td>- Global Product Strategy (GPS)</td>
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<tr>
<td></td>
<td>- Pharma Affiliate (PA)</td>
</tr>
</tbody>
</table>
The GCP DT is set up as a self assessment questionnaire with various risk assessment categories

<table>
<thead>
<tr>
<th>Affiliate Demographics</th>
<th>Affiliate Infrastructure</th>
<th>Study Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Questionnaire Section 1)</strong></td>
<td><strong>(Questionnaire Section 2)</strong></td>
<td><strong>(Questionnaire Section 3)</strong></td>
</tr>
<tr>
<td>Information on number and type of:</td>
<td>Information on:</td>
<td>Information on:</td>
</tr>
<tr>
<td>Clinical Trials</td>
<td>Communication &amp; Support</td>
<td>Study Planning &amp; Conduct</td>
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<tr>
<td>Study Sites</td>
<td>IT Systems</td>
<td>Outsourcing</td>
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<tr>
<td>Patients</td>
<td>Archiving</td>
<td>IMP Management</td>
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<tr>
<td>Clinical Trial Staff</td>
<td>Resource Management</td>
<td>Monitoring</td>
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<tr>
<td>Vendors</td>
<td>Training</td>
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<tr>
<td>Vendors</td>
<td>Issue Management</td>
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<tr>
<td>Vendors</td>
<td>Medical &amp; Safety</td>
<td></td>
</tr>
</tbody>
</table>

Number of questions: 9  
Number of questions: 30  
Number of questions: 22

- The GCP DT Questionnaire needs to be completed on an annual basis by the local ‘GCP DT Coordinator’
- In case both local PD and GPS/PA activities are ongoing, the questionnaire needs to be completed individually
- After having completed the questionnaire, reports are generated by PDQ and discussed with the business partners
This data is used to calculate risk scores based on *Impact*, *Detectability* and *Likelihood*; red scores require mitigation.

**GCP DT Scoring and Mitigation Logic**

1) Separate GCP DT scores are calculated for Safety Processes and Data Integrity.
As a result >70 affiliate-specific GCP DT reports can be generated, which can then be aggregated to create regional and global reports.

Overview of GCP DT Reports

- **Affiliate specific GCP DT reports**
  - Key addressee: Local GCP DT Responsible

- **Regional GCP DT reports**
  - Key addressee: Regional Business Heads

- **Global GCP DT report**
  - Key addressee: P. Soriot
Example: Selected results from regional GCP DT report

GCP DT Regional Report - Previous GCP DT Version

Results for GPS/PA Trials

<table>
<thead>
<tr>
<th>HQ Comms</th>
<th>Issue Mgmt</th>
<th>Electronic Data capture</th>
<th>IMP</th>
<th>Archiving</th>
<th>Local IT Systems</th>
<th>Quality Mgmt</th>
<th>Strategic Clinical Trial Mgmt</th>
<th>Project Planning</th>
<th>AIMS/CTMS</th>
<th>Outsourcing</th>
<th>Safety</th>
<th>Infrastruct. &amp; HQ Support</th>
<th>Project Execution</th>
<th>Training</th>
<th>Monitoring</th>
<th>Approval/ Adequacy of local protocols</th>
<th>Regulatory</th>
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<td>Affiliate E1</td>
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</tbody>
</table>

Affiliates/ risk areas highlighted in red to indicate highest risk
Continuous Risk Evaluation by Analyses of Existing Data

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

Wealth of Existing Data at Roche Pharma

Safety data

Trial info

Clinical data

# AEs

QRM Report
Clinical Trial Centers (CTC) – Key Risk Indicator Landscape

- **Safety**
  - Underreporting of AEs
  - Increased Number of AEs
- **Adherence to Protocol**
  - Protocol violations
  - Unusable samples due to label issues
- **Data/Document Mgmt.**
  - Data corrections at site
  - Time period between patient visit and data entry
  - Data management discrepancies
  - Absence essential PD forms in CDC
  - Response time for data mgmt. discrepancies
- **Compliance Monitoring**
  - Delayed first monitoring visit
  - No monitoring visit
  - Monitoring frequency
- **Patient Recruitment**
  - Fast enrollment
  - Over enrollment
  - Delayed enrollment

- CTC001: Premature terminations (non-medical)
- CTC002: Premature terminations (medical)
- CTC026: Subjective safety
- CTC023: Unusable samples due to label issues
- CTC029: Time period between patient visit and data entry
First set of CTC KRI\textsc{s}

Different influence and predictive value

<table>
<thead>
<tr>
<th>KRI #</th>
<th>KRI Name</th>
<th>Influence on Detectability (D) or Likelihood (L)</th>
<th>Link to Risks and Predictive Value (H: High, M: Medium, L: Low)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Data Integrity</td>
</tr>
<tr>
<td>1</td>
<td>Underreporting of AEs</td>
<td>L</td>
<td>M</td>
</tr>
<tr>
<td>2</td>
<td>Data management discrepancies</td>
<td>L</td>
<td>M</td>
</tr>
<tr>
<td>3</td>
<td>Premature terminations (non-medical)</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>6</td>
<td>Protocol violations</td>
<td>L</td>
<td>H</td>
</tr>
<tr>
<td>8</td>
<td>Delayed first monitoring visit</td>
<td>D</td>
<td>M</td>
</tr>
<tr>
<td>9</td>
<td>Fast enrollment</td>
<td>L</td>
<td>L</td>
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<tr>
<td>10</td>
<td>Over enrollment</td>
<td>L</td>
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<td>12</td>
<td>No monitoring visit</td>
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<td>H</td>
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<tr>
<td>13</td>
<td>Delayed enrollment</td>
<td>L</td>
<td>L</td>
</tr>
</tbody>
</table>
Underreporting of AEs

<table>
<thead>
<tr>
<th>Description</th>
<th>Lower than average number of AEs reported per patient visit per site compared to the average number of AEs reported per patient visit per country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rationale</td>
<td>Possible indicator for inadequate monitoring, lack of source data verification, site-staff training and/or insufficient resources</td>
</tr>
</tbody>
</table>

### Input Parameter | Source
--- | ---
Number of patients per site, per country | Oracle Clinical, AIMS/CTMS
Number of patient visits per site, per country | Oracle Clinical
Number of AEs per site, per country | Oracle Clinical

### Results

**Selected Sites**

<table>
<thead>
<tr>
<th>Site</th>
<th>KRI Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 1</td>
<td>1.45</td>
</tr>
<tr>
<td>Site 2</td>
<td>0.56</td>
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<tr>
<td>Site 3</td>
<td>0.33</td>
</tr>
<tr>
<td>Site 4</td>
<td>0.61</td>
</tr>
<tr>
<td>Site 5</td>
<td>0.84</td>
</tr>
</tbody>
</table>

**5 Sites in Spain**

Formulas:

**A) KRI Value Above Threshold:**

\[
\text{KRI Value} = \frac{\text{Acc. } \Sigma \text{ of AEs per patient visit per site}}{\text{Acc. } \Sigma \text{ of AEs per patient visit per country}} < 0.5
\]

(1) If there are less than 4 sites in a country, the average number of AEs per patient visit per site is divided by the average number of AEs per patient visit per study.

**B) Significant Data Missing:**

At least 3 patients enrolled at site (AIMS/CTMS) and significant data missing (no AEs reported in entire country)

### Allocation

<table>
<thead>
<tr>
<th>Risks</th>
<th>D/L</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP, DI</td>
<td>Likelihood</td>
<td>Medium</td>
</tr>
</tbody>
</table>
Increased number of AEs

Description: Increased average number of AEs per patient visit at site compared to the average number of AEs per patient visit in country (or per study)

Rationale: KRI serves as an indicator for potential issues with medical care and/or disease severity and/or patient selection at site.

<table>
<thead>
<tr>
<th>Input Parameter</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients per site, per country</td>
<td>Oracle Clinical, AIMS/CTMS</td>
</tr>
<tr>
<td>Number of patient visits per site, per country</td>
<td>Oracle Clinical</td>
</tr>
<tr>
<td>Number of AEs per site, per country</td>
<td>Oracle Clinical</td>
</tr>
</tbody>
</table>

Results:

- **A) KRI Value Above Threshold:**
  - At least 3 patients enrolled at site (OC) and
  - 
  
  \[
  \text{KRI Value} = \frac{\text{Average number of AEs per patient visit per site}}{\text{Average number of AEs per patient visit in country (or per study)}} > 2
  \]

  (1) If there are less than 4 sites in a country, the average number of AEs per patient visit per site is divided by the average number of AEs per patient visit per study

- **B) Significant Data Missing:**
  - At least 3 patients enrolled at site (AIMS/CTMS) and
  - No AEs reported in entire country

Allocation:

<table>
<thead>
<tr>
<th>Risks</th>
<th>D/L</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP</td>
<td>Likelihood</td>
<td>Low</td>
</tr>
</tbody>
</table>
Premature terminations (non-medical reasons)

| Description | | |
|-------------|-------------|
| Rationale   | Possible indicator for inadequate site management, including lack of protocol adherence |

### Input Parameter | Source
---|---
Number of patients per site, per study | Oracle Clinical
Number of premature terminations per site, per study | Oracle Clinical

### Formula: Signal is Red if
A) KRI Value Above Threshold:

At least 3 patients enrolled at site (AIMS/CTMS\(^{(1)}\)) and

\[
\text{KRI Value} = \frac{\text{Acc. } \Sigma \text{ of premature terminations per patient enrolled per site}}{\text{Acc. } \Sigma \text{ of premature terminations per patient enrolled per study}} > 2.0
\]

### Results

<table>
<thead>
<tr>
<th>Site</th>
<th>KRI Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 1</td>
<td>0</td>
</tr>
<tr>
<td>Site 2</td>
<td>5.37</td>
</tr>
<tr>
<td>Site 3</td>
<td>1.79</td>
</tr>
<tr>
<td>Site 4</td>
<td>0</td>
</tr>
<tr>
<td>Site 5</td>
<td>0</td>
</tr>
</tbody>
</table>

**Selected Sites**

<table>
<thead>
<tr>
<th>Site</th>
<th>KRI Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 1</td>
<td>0</td>
</tr>
<tr>
<td>Site 2</td>
<td>5.37</td>
</tr>
<tr>
<td>Site 3</td>
<td>1.79</td>
</tr>
</tbody>
</table>

### Allocation

<table>
<thead>
<tr>
<th>Risks</th>
<th>D/L</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DI</td>
<td>Likelihood</td>
<td>Low</td>
</tr>
</tbody>
</table>

\(^{(1)}\) data source will be changed to OC in 2010.
## Premature terminations (medical reasons)
from AE, intercurrent illness, insufficient therapeutic response, death

### Description
KRI measures the number of premature terminations (due to AE, intercurrent illness, insufficient therapeutic response and death) per patient enrolled per site compared to the average number of premature terminations (same reasons) per patient enrolled per study.

### Rationale
KRI serves as an indicator for potential issues with safety management at site and investigator oversight.

### Input Parameter | Source
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Site, protocol</td>
<td>Oracle Clinical</td>
</tr>
<tr>
<td>Number of premature terminations per site</td>
<td>Oracle Clinical</td>
</tr>
<tr>
<td>Number of premature terminations per protocol</td>
<td>Oracle Clinical</td>
</tr>
<tr>
<td>Number of patients enrolled at site</td>
<td>Oracle Clinical</td>
</tr>
<tr>
<td>Number of patients enrolled at protocol</td>
<td>Oracle Clinical</td>
</tr>
</tbody>
</table>

### Formula: Signal is Red if

A) KRI Value Above Threshold:

At least 3 patients enrolled at site (OC) and

\[
\text{KRI Value} = \frac{\text{# of premature terminations (due to AEs, death, insuff. therap. response, intercrr. Illness)} \text{ per patient enrolled per site}}{\text{# of premature terminations (due to AEs, death, insuff. therap. response, intercrr. Illness)} \text{ per patient enrolled per protocol}} > 2
\]

### Results

<table>
<thead>
<tr>
<th>Site</th>
<th>KRI Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 1</td>
<td>1.95</td>
</tr>
<tr>
<td>Site 2</td>
<td>0.86</td>
</tr>
<tr>
<td>Site 3</td>
<td>0.43</td>
</tr>
<tr>
<td>Site 4</td>
<td>2.41</td>
</tr>
<tr>
<td>Site 5</td>
<td>1.24</td>
</tr>
</tbody>
</table>

### Allocation

<table>
<thead>
<tr>
<th>Risks</th>
<th>D/L</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP, DI</td>
<td>Likelihood</td>
<td>Low</td>
</tr>
</tbody>
</table>

### Selected Sites

21 Sites in Spain

5 Sites in Spain

### Allocation Value

- **KRI Value**
  - **Threshold (2.0)**

1.95 0.86 0.43 2.41 1.24
Managing Mega-Trials: a New Frontier

Further enhance compliance oversight “universe” by a controlled sharing amongst sponsors of, e.g.

- Monitoring outcome data
- Auditing outcomes
- KRI data
- CAPA & mitigating action data

Enhances credibility of own QRM data and leads to continuous benchmarking and quality improvement
We Innovate Healthcare