A case study of a clinical trial demonstrating a QbD approach to quality risk management

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Case Study: Outline of Project

PROJECT X

- Randomized, double-blind, placebo-controlled, global clinical trial
- 3 treatment arm, n=500/arm
- Biologic - IV dosing
- Needed to be reconstituted and added to an IV infusion bottle at site
- Required an “un-blinded” pharmacist at site and a different CRO to monitor the un-blinded process
**Definitions**

- **QbD** – A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. (ICH Q8)

- **Risk** – an issue which might occur
  - The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51). (ICH Q9)

- **Juran Trilogy:**
  - Quality planning
  - Quality control
  - Quality improvement
Principles Used in QbD in Clinical Trials

- The QbD/QRM activities should occur in conjunction with protocol development
- Determine the factors that are critical to quality (ie, where does quality matter?)
- Use a risk-based approach to determine where quality should be improved
- Prioritize the risks and mitigate those of high priority
- Develop a “closed loop system” to manage quality, including a feedback mechanism to check that the mitigating plans are working, and to modify the risk factors and plans if necessary
The Quality Management Process

“Closed Loop System”

Plan.
- Identify the factors critical to quality (CTQ).
- Perform risk assessments and mitigate these risks

Do.
- Conduct Clinical Trial

Check.
- Use CTQs and risk metrics to monitor performance

Act.
- Perform root cause analysis, take corrective and preventative actions
Determining What is Critical to Quality:
The CTQ Control Plan
Team held cross-functional workshops to discuss quality in the clinical trial

- Involved all relevant functional roles (clinical, clin pharm, QA, clinical safety, project management, study management, data management, pharm sci)

Determined that customer needs for quality objectives were:

- Patient safety and rights
- Data quality and trial integrity
- Compliance with the investigational plan
Customer Need

Sponsor demonstrates quality assurance & quality control systems are implemented & maintained

Quality Objective

Patient Safety/Rights

Data Quality & Integrity

Protocol Compliance

Critical to Quality Requirements

Timely safety & monitoring reporting

Subjects are properly consented

Subjects are dosed according to the investigation plan

Assessments are consistently administered & recorded

Maintain study medication blind

Proper contracting & effective oversight of vendors

Trial is conducted per the investigator plan

Investigator & site staff are properly trained

Drug supplies are stored, handled, & disposed of according to the investigator plan
Workshop outputs

- List of factors critical to quality (CTQs), and for each:
  * the metric(s) associated with each CTQ,
  * the targets and thresholds for each metric,
  * the frequency of assessment of each metric

- The output of the workshop is the CTQ Control Plan
<table>
<thead>
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Risk Assessment & Prioritization
Various tools available for assessing risks

- Failure Mode and Effects Analysis (FMEA)
- Fault Tree Analysis (FTA)
- Preliminary Risk Analysis (PRA)
- Hazard Operability Analysis (HAZOP)
- Informal tools
Ask the questions
- Where are the risks?
  Identify potential failures
- What are the potential effects of failure?
- What are the potential causes?

Evaluate/assess
- Rank each potential failure mode by
  * Severity
  * Occurrence (frequency)
  * Detectability
Overview of Clinical Trial Process

Study Design

- Protocol
- Country Selection
- Site Selection

Qualified Site

Monitoring & Oversight

- Drug Supplies
- Vendor
- Data Collection Tools

Vendor

- Subject
  - Drug
  - PI / Site Staff
  - Equipment / Facility
  - Procedures

Database

Data Analysis

- Datasets for Analysis
  - Tables, Listings, Figures

Interpretation & Reporting

Clinical Study Report
Process for Assessing and Mitigating Risks

- Similar workshops to CTQ process
- Failure Modes and Effects Analysis, Considered by:
  * Process Step
  * Potential Failure
  * Potential Failure Effect
  * Potential Cause
- Output was a typical FMEA spreadsheet
Select the high priority risks

- Can’t reasonably expect to mitigate all risks
  * Select those that are critical to quality and mitigate them
  * Accept the rest

- “By establishing the priorities, mitigating the most significant risks and operating within sensible tolerance limits, the required quality standard can be described, and its achievement (or failure to achieve it) can be more readily measured, reported and recognised.”

* EMA Reflection paper on risk based quality management in clinical trials. Aug 2011
# FMEA Risk-Level Guidelines

## Definitions

<table>
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<th>Risk-Level</th>
<th>Severity</th>
<th>Occurrence</th>
<th>Detection</th>
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<tr>
<td>1</td>
<td>Minor impact to Data Quality/Study Integrity or Compliance with Investigational Plan</td>
<td>Rare or Never</td>
<td>Detected failure immediately</td>
</tr>
<tr>
<td>4</td>
<td>Minor impact to Patient Safety /Rights OR Significant impact to Data Quality/Study Integrity OR Compliance with the Investigational Plan</td>
<td>Sometimes</td>
<td>Detected failure at quality control checkpoint</td>
</tr>
<tr>
<td>7</td>
<td>Significant impact to Patient Safety/Rights OR Major impact to Data Quality/Study Integrity OR Compliance with the Investigational Plan</td>
<td>Most of the time</td>
<td>Detected failure at internal audit inspection</td>
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<td>10</td>
<td>Major impact to Patient Safety/Rights (e.g., life threatening) OR Major impact to both Data Quality/Study Integrity AND Compliance with the Investigational Plan</td>
<td>All the time</td>
<td>Detected failure at external audit or inspection</td>
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**Overall Risk Level = Risk Priority Number (RPN)**  
**= Severity * Occurrence * Detection**
Mitigating plans
Study blind is not maintained during the conduct of the trial

Pharmacy Manual: (to reduce occurrence)

- Specific site pharmacists will be appointed as “un-blinded” personnel
- An unblinded CRO selected to perform oversight of unblinded site activities.
- At each monitoring visit, the unblinded site monitor was to ensure that the un-blinded site pharmacist had minimal contact with the rest of the study team and did not conduct any study related activities, other than to receive and prepare drug and complete the appropriate documentation
- Training video to be developed by Pharm Sci with assistance from the study team to train site personnel on dosage preparation and to ensure blinding
Investigator fails to report safety event(s) in a timely manner

**New process** (to reduce occurrence and improve detection)

- The Serious Adverse Event Monitoring form will be updated to capture the date and time at which an investigator becomes aware of a serious adverse event to enable the sponsor to detect and track the time from awareness to reporting
  - Increases investigator awareness of the reporting requirements
  - Enables an immediate calculation of the time to reporting from the date/time on the form and the date/time stamp on receipt
The Quality Management Process

“Closed Loop System”

Plan. Identify the factors critical to quality (CTQ). Perform risk assessments and mitigate these risks

Do. Conduct Clinical Trial

Check. Use CTQs and risk metrics to monitor performance

Act. Perform root cause analysis, take corrective and preventative actions
The CHECK-ACT Phase

- During the conduct of the clinical trial, monitor the metrics on a regular basis to ensure that quality is meeting requirements.
- If quality is found to have crossed specification limits, then take appropriate actions to remediate the quality issue.
- Ensure that actions are built back into the standard processes (“continuous improvement”).
- Maintain vigilance to ensure that the actions have had the desired effect on quality.
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Closed loop Quality Control Process

Start

Monitor Metric Performance

No

Yes

Outside Limits?

Yes

Systemic issue?

No

Remediation

Root Cause Analysis

Solution Generation

Implement Solution / CAPAs

Update Processes, Policies, and/or Procedures (if applicable)

No

New Metrics?

Yes

Update FMEA

New Failure?

No

No

Yes

Implement New Metrics

New Metrics?
Advantages & Challenges

Challenges

- Need to assemble the team for workshops (clinical, clinical, QA, clinical safety, project management, study management, data management, pharm sci)
- Takes time to go through the FMEA process in particular
- Setting up the metrics reporting system
- Organizational change
Advantages & Challenges

Advantages

- Allows teams to discuss risks across functional boundaries – breaks down silos
- Provides a process within which a rigorous risk assessment can be done
- Allows for an objective prioritization of risks
- Provides for consistency across studies and programs
- Provides a library of risks and mitigation plans for other teams to draw on (but need to ensure that it is not just a check-box process)
- Builds in continuous improvement
Q & A