Building Quality into Clinical Trials – A Pilot with the FDA

David Nickerson
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Overview

- Introduce the Integrated Quality Management Plan (IQMP) pilot with FDA
- Describe the key concepts and components of the IQMP
- Share Pfizer study team perspectives
- Summarize key challenges
Origins of the IQMP Pilot

• Pilot program with FDA Office of Scientific Investigations (OSI), Office of Compliance, CDER consistent with recommendations from CTTI “Monitoring Project” meeting in October 2010

• Sponsors should develop an “Integrated Quality Management Plan” concurrent with protocol development

• Emphasis on key high-level issues rather than in-depth monitoring – monitor where quality matters

• Ensure that important risks to quality are prospectively identified and that mitigation plans are put in place
Elements of the IQMP

- A process for continuous improvement
- Prospective identification of quality objectives and metrics
- Prospective identification, assessment, and mitigation of risks to quality
- Quality management plans to guide implementation
Plan – Quality objectives and metrics; risks to quality; quality management plans

Do – Study conduct

Check – Measure/monitor

Act – Respond to deviation

http://www.iso.org/iso/catalogue/management_standards/understand_the_basics.html
Quality Objectives and Metrics

**Quality Drivers:** Common objectives
- Patient safety
- Data quality/integrity
- Protocol compliance

**Critical to Quality (CTQ) requirements identified**
- Determined appropriate metrics to enable measurement/monitoring of quality performance
- For each metric, quality performance expectations were determined
<table>
<thead>
<tr>
<th>CTQ Requirements</th>
<th>Metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects randomized meet inclusion/exclusion criteria</td>
<td>Number of subjects randomized that do not meet inclusion/exclusion criteria</td>
</tr>
<tr>
<td>All subjects are properly consented prior to study enrollment and/or properly re-consented during study conduct (if required)</td>
<td>Percent of subjects with inadequate informed consent</td>
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## Examples of Study Specific Quality Objectives and Metrics

<table>
<thead>
<tr>
<th>CTQ Requirements</th>
<th>Metrics</th>
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<tbody>
<tr>
<td>Qualitative scales are administered and rated in a consistent manner</td>
<td>Percentage of raters that are certified before carrying out subject rating in trials</td>
</tr>
<tr>
<td></td>
<td>Rater error rate as detected by vendor review of qualitative scales</td>
</tr>
<tr>
<td>No breach of the study medication blind to blinded personnel</td>
<td>Number of incidences of inappropriate or unauthorized unblinding of subjects, study site staff, vendor staff, or Pfizer staff</td>
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</tbody>
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Overview of Clinical Trial Process

- **Study Design**
  - Protocol
  - Country Selection
  - Site Selection*

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

- **Vendor**
  - Data

- **Database**
  - Datasets for Analysis
  - Tables, Listings, Figures
  - Clinical Study Report

- **Monitoring & Oversight**
  - Monitoring
  - Dedicated Safety Monitoring
  - Drug Supplies
  - Vendor
  - Data Collection Tools

*Note: The diagram illustrates the process flow of a clinical trial, from protocol design to data analysis and reporting.
Risks to quality were assessed and prioritized by **Failure Modes and Effects Analysis (FMEA)**

The process to complete the FMEA involved:

1. Identification
2. Prioritization
3. Prevention / Mitigation
How Do We Identify and Assess Risks?

Clinical Trial Process

Identify
- Failure Mode - What could go wrong?
- Failure Effect - What could happen if it did go wrong?
- Potential Cause - What are the possible causes of the issue?

Assess/Prioritize
- Severity - How bad would it be if the risk happened?
- Occurrence - How frequently does the cause occur?
- Detection - How easy is it to detect the issue if it occurs?
Example of a Quality Risk in FMEA

Potential Failure Mode
• Clinically significant protocol deviations are not detected and reported

Potential Failure Effect
• Sponsor is not aware that clinically significant protocol deviations have occurred

Potential Cause
• Site monitoring is not conducted according to the Study Monitoring Plan
Example of a Quality Risk in FMEA

**Current Controls**
- Study Monitoring Plan and associated training of monitors
- Documented review of monitoring reports
- Safety data monitoring

**Recommended Actions**
- Co-monitoring to ensure monitoring is completed per the Study Monitoring Plan
- Repeat/supplemental training as necessary
- Replacement of monitors as necessary
Quality Control Process
Check-Act Phases

Start

Monitor Metric Performance

Monitor Metric Performance

No

Start

Yes

Outside Limits?

No

Yes

Assess the deviation

Root Cause Analysis

Identify Solution(s)

Implement Solution / CAPAs

Update standard Processes, Policies, and/or Procedures (as necessary)

No

Yes

New Metrics?

No

Yes

New Failure?

No

Yes

Update FMEA

New Metrics?
Pfizer Study Team Experiences

• Process enabled an integrated, cross-functional approach to proactively build quality into the clinical trials

• The team, collectively, developed a much better appreciation for what could go wrong

• Resulted in greater ability to systematically manage quality

• Enabled the team to take ownership of quality
Key Challenges

• Developing the processes, tools, and systems needed to make the IQMP process scalable and to facilitate company-wide implementation

• Ensuring that all stakeholders’ needs are met in determining what is critical to quality

• Identifying appropriate specification limits for quality metrics

• Determining what current practices are not adding value and can therefore be eliminated

• Ensuring that we can measure success criteria to confirm that the IQMP process is adding value
Thank You