Medical Quality by Design

“the journey continues”

Jeff Kasher
VP Clinical Development, Eli Lilly & Company
08 – 23 – 2011
Quality as a Culture

Quality Approach

Quality as a rule + Quality as a system + Quality by design + Quality as a culture

Increasing strategic maturity results in more efficient and effective use of resources

The Road to Quality as a Culture.
Vision Statement

The Clinical Development Organization (CDO) will reliably deliver the portfolio with quality, on time, and on budget

Critical **processes** are clearly defined and efficient, with single-point accountability for key decisions / process steps

**Sourcing** and capacity decisions are strategic rather than tactical, and leverage opportunities to increase organizational effectiveness

Run clinical development with a **business mindset**; measure and track performance with effective metrics

Clinical **strategy, planning, & execution** activities are tightly linked (clear ‘line of sight’). Commitments are made with a full understanding of feasibility
Medical Quality System Redesign
A Single, Integrated Quality System

What we’ve built:

- A streamlined set of global quality system documents (~90% reduction in global documents)
- A comprehensive, process-based approach to support effective implementation - process streamlining, role clarification, and strengthened governance
- Structured to enable FIPNET through requirements applicable internally and externally
- Designed to integrate with other related quality systems (e.g., Lilly Global, Safety, Regulatory, Product Research & Development Quality Systems)

Diagram:
- Integrated Standards
- Business Processes
- Organization
- Management Controls

- Clear requirements to meet both compliance and patient expectations
- Simple
- Effective
- Efficient
- Agile
- Right People
- Right Role
- Clear Accountability
- Right Span of Control
- Management Involvement
- Escalation
- Decision Making

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Establishing a Quality Foundation

Medical Single Process Map

- Value Proposition
- Draft Launch Label
- Surveillance
- Medical Objectives and Clinical Strategy
- Explore Therapeutic Concept
  - Plan
  - Design
  - Execute
  - Analyze
  - Disclose
- Confirm Therapeutic Benefit
  - Plan
  - Design
  - Execute
  - Analyze
  - Disclose
- Optimize Therapeutic Benefit
  - Plan
  - Design
  - Execute
  - Analyze
  - Disclose
- Inputs (Reliable and relevant evidence of...)
- Process
- Outputs (Safety, Efficacy, Outcomes)
- Product Label, PRA

Business Process Management

- Integrating Standards
- Business Processes
- Organization
- Management Controls

- Quality System
  - Clear requirements to meet both compliance and patient expectations
  - Management Involvement
  - Escalation
  - Decision Making

- Business Process Management
  - Simple
  - Effective
  - Efficient
  - Agile

- Right People
- Right Role
- Clear Accountability
- Right Span of Control
Building Quality into Clinical Trials

Clinical Planning
- Approved Clinical Plans
- Medical/Scientific Validity Reviews
- Operational Reviews
- Annual Clinical Plan Reviews
- Chief Medical Officer Oversight

Study Design
- Approved Study Protocols
- Protocol Review Committees
- Change Management

Study Execution
- Investigator Site Selection
- Risk-based Monitoring Program

Data Analysis
- Approved Plans of Analysis
- Analysis Program Validation
- Approval of Analysis Output

Scientific Disclosure & Dissemination
- Disclosure Approvals

Quality Governance
- Deviation Management
- Quality Plans
- Third Party Management Program
- Trial Master File Periodic Reviews
- Quality Audits & Assessments
- Quality Lead Teams
- Metrics Review
Integrated Quality Risk Management

Deviation Management

Risk-based Monitoring

Sponsor Trial Master File

Data Validation & Review

Trial Level Safety Reviews

Third Party Management Oversight
# Sourcing Model Distinctions

<table>
<thead>
<tr>
<th>Sourcing Model Distinctions</th>
<th>Functional Sourcing</th>
<th>Project Sourcing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td>Role</td>
<td>Process</td>
</tr>
<tr>
<td>Standards</td>
<td>Lilly</td>
<td>Lilly</td>
</tr>
<tr>
<td>Procedures</td>
<td>Lilly</td>
<td>TPO*</td>
</tr>
<tr>
<td>Work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Payment method</td>
<td>FTE rate</td>
<td>Activity or Deliverable unit pricing</td>
</tr>
<tr>
<td>Forecast Volume</td>
<td>Lilly Function</td>
<td>Lilly Function</td>
</tr>
<tr>
<td>Resource Planning</td>
<td>Lilly</td>
<td>TPO</td>
</tr>
<tr>
<td>Integration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM Accountability</td>
<td>Lilly</td>
<td>TPO – Process, Lilly - Project</td>
</tr>
<tr>
<td>Data Integration</td>
<td>Lilly</td>
<td>Lilly</td>
</tr>
</tbody>
</table>

* In transition to Future State with redesign efforts
Oversight of Strategic Third Parties

- Executive / Joint Operations Committees
- Quality Councils
- Metrics Reviews
- TPO Review of Standards
- Quality Oversight Plans/Work Plans
- Due Diligence
- Quality Assessments
- Third Party Audits
- Quality Oversight Assessments of:
  - Investigator Sites
  - Third Parties
  - Processes
- Quality Agreements
- Master Service Agreements
- Operations Guides
- Quality Oversight Plans/Work Plans

Governance
Documenation
Global Medical Quality
GQAAC

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Clinical trial monitoring must be driven by: scientific analysis, protocol objectives, and trial data

- Planning: Clinical trial monitoring plan which is based on statistical/scientific data elements in the protocol
  - Prioritization of data and processes critical to data integrity and subject protection
  - Development of adaptive study specific monitoring requirements
- Execution: Ongoing trial monitoring activities include:
  - Traditional on-site monitoring
  - Statistical data monitoring to assess data trends across sites and trials
  - Internal monitoring of key internal processes
- Risk-based monitoring benefits:
  - Enables the proactive identification of areas/sites of risk
  - Establishes the foundation to respond to real-time study data
  - Ultimately ensures that:
    - Clinical data answers the scientific questions/objectives outlined in the protocol
    - Meets regulatory and quality requirements for the safety of study subjects

“Sponsors must be able to answer why they are monitoring what is being monitoring”
- Leslie Ball, MD, Director, Office of Scientific Investigations, FDA
Quality Oversight Assessment Metrics
Summary – June 2011

Accomplishments

- 107 assessments have been performed year to date.
  - June 2011: 17 assessment performed globally (no critical observations).
- Trends identified in the following areas (further evaluation and response plan needed):
  - Study Documentation (especially site delegation log not available / inaccurate / incomplete)
  - Monitoring / Issue Resolution (especially issues not identified / escalated and / or resolved appropriately)
  - Training / Personnel Qualification
  - Source Document / Data Accuracy

Improvement Opportunities

- January through May 2011:
  - Of the 8 red sites identified from January through May 2011, 2 sites have moved to orange status and 2 have moved to green status. The remaining 4 red sites remain red.

![Initial Status](image1)

![Current Status](image2)
Strategic Third Party Assessment Metrics
Summary – Q2 2011

**Critical Issues**
- ICD current version not signed and/or signage incomplete
- Lack of adequate management control to ensure clinical study services are performed by appropriately qualified personnel and conducted in accordance to defined SOP/guidelines/Clinical Management Plan (CMP)
- Issues not identified, escalated and/or resolved appropriately
- Noncompliance to protocol

Only assessment findings owned by the TPO are included in the status. Findings owned by Lilly are not included in the TPO assessment summary.

<table>
<thead>
<tr>
<th></th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
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<tbody>
<tr>
<td>Number of assessments</td>
<td>19</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Total number Critical Issues</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total number Major Issues</td>
<td>53</td>
<td>22</td>
<td>0</td>
<td>1</td>
<td>21</td>
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<tr>
<td>Total number Other issues</td>
<td>134</td>
<td>39</td>
<td>0</td>
<td>0</td>
<td>34</td>
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<tr>
<td>Total Number of issues</td>
<td>189</td>
<td>62</td>
<td>0</td>
<td>1</td>
<td>56</td>
</tr>
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</table>

**Quality Oversight Assessment Top 10 Issues Cited**

1. Source documentation missing/inadequate/incomplete to support study data
2. Issues not identified, escalated and/or resolved appropriately
3. Site delegation log not available/inaccurate/incomplete
4. Data entry system/CRF data inaccurate
5. Inadequate or insufficient monitoring
6. Noncompliance to protocol
7. Drug receipt, dispense, return records are missing, inadequate, incorrect
8. Monitoring Plan not followed
9. Safety Mailings missing/incomplete
10. 1572 not available/inaccurate/incomplete
Deviations Created by Level of Criticality -- 12-Month Trend

- **Level 1**
- **Level 2**
- **Level 3**

**Trackwise Implementation**
Quality Plan Conformance
Summary – July 2011

Quality Plan Conformance (Metric #9)

Medical 2011 Quality Plan Conformance

Projects Open and Overdue (12 July 2011)
No Global Medical Q Plan projects are currently overdue.

Projects Past Due When Completed (12 July 2011)

<table>
<thead>
<tr>
<th>Action</th>
<th>Due Date</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release Sponsor Trial Master File procedure and related tools.</td>
<td>01 June 2011</td>
<td>10 June 2011</td>
</tr>
</tbody>
</table>

Projects Completed On Time (12 July 2011)

<table>
<thead>
<tr>
<th>Action</th>
<th>Due Date</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Update IMPACT to include missing network investigator site information.</td>
<td>30 April 2011</td>
<td>21 April 2011</td>
</tr>
<tr>
<td>Utilize the LQS Inspection Readiness and MQS Inspection Management processes to ensure readiness for an MHRA or FDA Inspection.</td>
<td>01 July 2011</td>
<td>08 June 2011</td>
</tr>
</tbody>
</table>
Ongoing Focus

• Execution Excellence – Right the first time!
  o Internal adherence to MQS
  o Investigator site performance
  o Third party organization performance

• Medical Quality System
  o Streamlining (e.g., Data Management, Statistics)
  o Continued harmonization of Quality System topics across Medical, Regulatory, and Safety

• Asia Pacific support

• Ongoing inspection readiness

We are continuing to progress on our Quality Journey!
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