Principles of Quality by Design and Quality Risk Management

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Topics

- Overview of Quality by Design (QbD) and Quality Risk Management
- A look at the Big Picture
- A Case Study in QbD
- Conclusions and Guiding Principles
Overview of Quality by Design (QbD) and Quality Risk Management
Some Jargon

- Harm
- Critical
- Severity
- Probability
- Empirical tools
- Informal QRM
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis
- Critical Control Points
- Hazard
- Preliminary Hazard Analysis (PHA)
The Basics

Quality by Design:

An approach to ensure that the planning, conduct, analysis and reporting of clinical trials is done in a way that eliminates errors that matter.

Quality Risk Management:

Identifies risks and takes steps to control the risks and review these results to improve quality.
QbD & QRM

Assess and manage risk, and then improve

Plan

Do

Check

Improve

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1Landray et al; *Clinical Trials: Rethinking How We Ensure Quality*; Drug Information Journal 46(6); pp 657-660
A look at the Big Picture
Big Picture Thoughts

**The Goal**: to protect rights of human subjects and achieve data integrity/reliability to answer the hypothesis

**CTTI Initiative**: Redirect efforts to focus on the things that matter

**What is our Focus**: If we are to improve, we must address root causes.

*Key opportunities exist for sponsors, investigators and regulators.*
“Say ... what’s a mountain goat doing way up here in a cloud bank?”
Investigator Opportunities
What monitors may encounter...

- Infrequently get to discuss issues with clinical investigator during monitoring visit
- No progress note generated by a physician (PI or sub-I) at a patient visit.
- Lagging review of adverse events or causality assessment not timely
- Suggestions for improvement infrequently acted upon
What Investigators may encounter…

• High monitor turnover
• Technology complexities
• Unique processes and documentation
• Multiple and sometimes conflicting guidance
• Managing multiple protocol amendments
• Review of IND Safety reports
Important for QbD

These experiences indicate that both monitoring and investigator responsibilities are in need of QbD-based reengineering.

It is critical to drive emphasis on a “right-time-first” orientation. Therefore, improving monitoring – “yes”, but helping investigators fulfill their responsibilities- “even more so”.
Sponsor Opportunities
Retrospective case studies for submissions where critical findings needed to be addressed shed light on QbD.

Review of these experiences provide clarity on how thinking should occur for meaningful critical-to-quality discussion.
What can these cases show?

- Determining critical data elements (CtQs) for issue resolution represent the study success factors that should be addressed prospectively by QbD.
- Results from inspections that point to serious quality issues should trigger questions of how to eliminate such issues in the future.
- Importance of having dialogue with regulators to agree on “Critical to Quality” factors.
Conclusions

- Challenge to be vigilant in keeping research subject rights foremost
- Challenge for stakeholders involved in clinical research to design ways-of-working/systems that emphasize “right-first-time” standards
- Challenge to pick the critical factors impacting quality across the vast number of risks and confidently commit to delivering them
- Challenge for regulators to assess quality based on limited sample
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