Workshop on Quality Risk Management: Understanding What Matters

Executive Summary of Meeting held September 20-21, 2012

Project: Workshops on Quality by Design

Clinical Trials Transformation Initiative (CTTI)

December 2012

Workshop on Quality Risk Management: Understanding What Matters

A Clinical Trials Transformation Initiative (CTTI)-hosted Meeting
September 20–21, 2012, Bethesda, Maryland

EXECUTIVE SUMMARY

During an inaugural CTTI workshop held in August 2011, participants explored how principles of risk management and quality by design (QbD) from other disciplines could be adapted to enhance clinical trial design and execution. These approaches could improve clinical trial efficiency by relieving sponsors and investigators of perceived obligations to mitigate every potential risk, while enabling them to effectively protect research volunteers and maintain data quality. The August 2011 workshop also identified the need for a foundational document outlining general principles about what aspects of a trial underpin the reliability of results and patient protection. CTTI subsequently formed a small working group to develop a principles document (PD) with the goal of refining it for various stakeholders during July 2012 and subsequent workshops.

Meeting goals

The goal of the September 2012 session was to gain a deeper understanding of how QbD principles might be applied in practice with clinical trials of drugs (drawing from real world examples and hypothetical case studies). The workshop objectives were to demonstrate some of the advantages of this approach, build confidence in its use, identify obstacles in its adoption, and highlight opportunities for dissemination of these principles and practices. Participants included a broad cross-section of stakeholders, including regulators, government sponsors of clinical research, representatives from academia and industry, patient advocates, and clinical investigators.

Background: Quality by Design – avoiding and addressing errors that matter

The workshop introduced a working definition of quality: "the absence of errors that matter to decision making". "Errors that matter" have material impact on the protection of research participants

or the ability to draw conclusions based on a trial's data. Introductory sessions provided an overview of quality management and how it might be employed in clinical trials to prevent or minimize the opportunity for such errors. Presenters also described key drivers of quality in a "good" clinical trial, defined as a trial that asks an important question and answers it reliably. The session emphasized that QbD can provide a unifying concept for enhancing trial efficiency and quality, provided that there is recognition that the types of errors that matter may vary depending on trial design, the product under study, and other factors.

Meeting participants then discussed the U.S. regulatory perspective on enhancing trial quality which included highlights from a recent Food and Drug Administration (FDA) draft guidance,[1] a European Union Good Clinical Practices Inspectors Working Group draft "Reflection Paper" on risk-based quality management,[2] and the European Commission's final draft Regulation on clinical drug trials.[3] These documents, contrary to common perception, do not specify a particular type of protocol or methodology for trial oversight; they simply call for evidence of sufficient quality to support decision-making throughout a product's clinical development and use lifecycles. Participants agreed that communication in both directions is required during protocol development, as is education between sponsors and investigators regarding trial conduct.

The group then proceeded to discuss and refine the PD which was organized into 6 "critical to quality" (CTQ) domains: feasibility, protocol design, patient safety, study conduct, study reporting, and third-party service providers.

Several broad themes emerged during the discussion.

1. Validity/importance of the research question. Individuals involved in trial design and implementation should ask if the trial is asking a relevant question that needs to be answered. Many

[1]FDA. Guidance for Industry: Oversight of Clinical Investigations—Risk-Based Approach to Monitoring. August 24, 2011. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf.
[2] European Medicines Agency. Reflection paper on risk based quality management in clinical trials. EMA/INS/GCP/394194/2011
[3]European Commission. Proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. July 17, 2002. http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf.

attendees thought that the PD should include a way to evaluate the relevance of the research question, not only to the sponsor but also relative to other stakeholders (patients, clinicians, international parties).

2. Need for early and continuing involvement of patient advocates during protocol development.

3. Ensuring that all the views of all stakeholders are represented. Along with patient advocates, it is important to take into account the perspectives of regulators, institutional review board representatives, site coordinators, drug supply/pharmacy specialists, and third-party payers during protocol development.

4. Consider whether the PD needs to be modified to ensure its applicability to novel trial designs (e.g. adaptive and enrichment designs).

5. CTQ factors must be identified before they can be measured. It would be helpful to develop a list of factors that can influence the reliability of a trial's findings, for various trial settings and designs.

6. Plan for trial communications. This should include methods for internal and external communications from initial protocol meetings, to the use of social media for recruitment and publicity, to continued contact with participants, to publication of findings.

7. Education is critical to combat misperceptions. For sites, this includes education about noncritical reporting, Inspectional Observations (FDA Form 483), and adverse events. For sponsors, this includes education about actual regulatory requirements. For regulators, this means open discussions with research sponsors early and often during protocol development, to identify and address potential problems early and to avoid unneeded and prolonged inspections. Critically, for all parties, education must include the concept of acceptable error rates.

Two examples of actual clinical trials that have incorporated risk-based QbD approaches were presented. The efforts devoted to prospective consideration of quality provided several benefits. It allowed teams to discuss risks across functional boundaries – breaking down "silos" within the organizations. The process encouraged rigorous assessment and objective prioritization of risks for these trials and permitted the organizations to develop a methodology that could be consistently

applied across studies and programs, with a library of risks and mitigation plans for other teams to use as a reference. Finally, it built in continuous improvement.

Putting principles in to practice: A two-part exercise

Attendees then participated in a two-part exercise in which they were assigned to a cross-functional working group and tasked with applying QbD principles to a hypothetical protocol outline, taking into account the concerns of key stakeholders. Two groups addressed each of the 3 protocols, covering cardiology, oncology, and mental health (schizophrenia).

In Part I, the groups identified and then ranked factors that for their protocol would be critical to quality. Each group then presented their top five CTQ factors, including, their approach to identifying these factors and the challenges/obstacles they encountered in adopting the QbD principles.

When all attendees reconvened, the consensus was that having cross-functional groups talk about the protocol during its development was important to a robust discussion of what aspects of the trial were critical to quality and to prioritizing them in terms of impact. Additionally, discussions highlighted the importance of a first step not included in the Principles Document: critically questioning the scientific questions posed by a trial and the rationale for its design. For example, patient advocates questioned the relevance of the oncology protocol (and the secondary endpoint of tumor size, in particular) to patients with cancer, and identified this as a significant barrier to successful recruitment.

In Part II, the breakout groups took their top 5 CTQ factors from Part I, selected the 3 most important, and identified potential challenges to ensuring these aspects of the trial were successful, and developed risk-mitigation plans for each. The goal of the exercise was not necessarily to develop complete solutions, but to identify challenges in the process of developing potential solutions.

Learning points and future developments

Several valuable suggestions emerged from the exercise. The most common suggestion for improving the PD was to better differentiate between CTQ factors, risks, and mitigations. Several

attendees also suggested soliciting input from patients/advocates. Highlighting a theme from the earlier part of the exercise, another frequent suggestion was to include protocol design issues in the PD, including assessment of the value of the question and the approach to answering it (i.e. hypothesis, rationale, objectives, subgroups, research questions, and superiority and non-inferiority aspects). Meeting participants also suggested that the PD be adapted for use as a tool.

The most common challenge to identifying CTQ factors was the likely disagreement among stakeholders in identifying critical factors and acceptable error rates. Some participants felt that more standard definitions and nomenclature for CTQ factors would be helpful in assessing and communicating risks, and mitigations. Several attendees mentioned resistance to change, including organizational, cultural, regulatory, and behavioral. Finally, several attendees asked if there are ways to measure if adequate quality has been achieved and risk minimized.

Several of the participants stated an intention to move their organization toward formal, cross-functional, risk-based review of study plans. Many others also indicated that they will keep thinking about "what matters" and will devote more energy to prospective planning for quality rather than trying to monitor quality into a trial. Others will seek to incorporate QbD elements into their existing workstreams, and improving patient advocacy in study development.

In the meantime, future workshops will continue the iterative process of further refining the Principles Document by using the results of this workshop and through future discussions. The group will continue to seek opportunities for dissemination of the QbD principles and practices to a broad array of stakeholders.

Conclusion

The workshop was well received by participants and was successful in demonstrating the advantages of a QbD approach. Future workshops are being planned for 2013, including extension to other disease and therapeutic areas, and involving those working in other healthcare settings or regions of the world.