



**Workshop on Quality Risk Management:
Making Clinical Trials Fit for Purpose**

Summary of Meeting held August 23-24, 2011

Project: Workshops on Quality by Design

Clinical Trials Transformation Initiative (CTTI)

February 2012

Workshop on Quality Risk Management: Making Clinical Trials Fit for Purpose

**A Clinical Trials Transformation Initiative (CTTI) Meeting
August 23–24, 2011
Hyatt Regency Bethesda, Bethesda, Maryland**

MEETING BACKGROUND

During an expert meeting held in October 2010 for the CTTI monitoring project, representatives from a broad cross-section of the clinical trial enterprise discussed clinical trial monitoring as one component of an overall quality framework. Panelists and participants agreed that broad adoption of an enlightened approach is needed to ensure trial quality and efficiency. Such an approach would apply risk management principles to clinical trials by prospectively identifying critical trial deliverables and important associated risks and then tailoring protocol design and delivery to mitigate those risks. This approach borrows concepts and solutions from the pharmaceutical manufacturing sector, which has confronted challenges to product quality as the number of products, facilities, and processes have expanded nationally and globally. In the manufacturing sector, a holistic approach to quality management that incorporates risk management principles has been well described in ICH Q8 and ICH Q9— this approach is involves the concept of “quality-by-design” (QbD).^{1,2,3}

The August 2011 workshop was the first in a planned series intended to share among participants examples of how risk management and QbD principles can be applied to clinical trials and therapeutic development programs. Meeting participants included a broad array of stakeholders, with representatives from government agencies, industry (including pharmaceutical, biotech, and contract research organizations), academic institutions, patient advocacy, investigator groups, and other interested parties.

The key objectives of the workshop included the following:

- Develop consensus QbD and QRM principles for the drug development lifecycle.
- Review case studies of QbD and QRM approaches applied in commercial and academic clinical trial settings, including tools, methodologies, and potential best practices.
- Discuss methods for evaluating the success of QbD and QRM approaches in enhancing the quality and efficiency of clinical development.

¹ International Conference on Harmonisation. Harmonised Tripartite Guideline: Pharmaceutical Development Q8(R2) Current Step 4 version (ICHQ8, August 2009). 2009.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf. Accessed on 9-22-2011.

² International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Quality Risk Management (ICHQ9). 2005. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf. Accessed on 9-22-2011.

³ International Conference on Harmonisation. ICH Harmonized Tripartite Guidance: Q10 Pharmaceutical Quality Systems. 5-9-2007. <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128031.pdf>. Accessed on 9-22-2011.

- Identify mechanisms to disseminate principles and best practices identified during the workshop to a broad array of stakeholders.

WELCOMING REMARKS

Robert J. Temple, MD, Deputy Director for the Clinical Science, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA), kicked off the meeting with introductory remarks concerning the present state of clinical research. He observed that trials are becoming larger, are increasingly multinational, and often are managed by outside contractors. He further described how many industry-sponsored trials include frequent on-site monitoring visits in an attempt to avoid any problems that could potentially derail their development programs. However, he noted that this model may not be effective in detecting the most important problems that undermine trial integrity and patient safety. Temple stressed that what is needed are more large, credible and affordable trials, and then pointed to the QbD principles at the core of the meeting's agenda, emphasizing that they supply a valuable roadmap for building quality into trials. Temple highlighted the need for trial sponsors to focus on what matters in a trial at the time of protocol development. He concluded his remarks by noting that the shift to a new way of thinking about trial quality will not be an easy one, but encouraged meeting participants to engage in meaningful discussion about concrete steps that can be taken to make clinical trials more fit for purpose.

SESSION I: PRINCIPLES FOR BUILDING QUALITY INTO CLINICAL TRIAL DEVELOPMENT

Participants in this sessions discussed principles of QRM that may enhance the quality and efficiency of pharmaceutical and device development, considering, in particular, the key role of protocol design in applying QRM approaches to clinical trials. A review of collaborative development of QbD in the manufacturing sector was provided, along with considerations (similarities and key differences) for building quality into clinical development.

Monitoring Workstream 3 Key Findings: *Briggs Morrison, Pfizer Inc.*

Briggs Morrison provided an overview of the results and recommendations stemming from the CTTI monitoring project. A survey of monitoring practices used by research sponsors yielded findings in keeping with the following hypotheses:

- A wide variety of monitoring practices are employed;
- The choice of monitoring approach correlates with the type of organizational sponsor;
and
- The rationale for using any specific monitoring approach does not appear to be evidence-based.

On-site monitoring remained popular among industry sponsors and contract research organizations (CROs) (80%), whereas only 33% of all survey respondents reported use of centralized data monitoring to guide, target, or replace site visits.

The following were identified as key quality objectives for monitoring: protecting study participant rights, safety, and well-being; ensuring the reliability of study results; and maintaining protocol adherence. Monitoring was also cited as a means to provide focused training and elicit feedback that can improve study processes.

Discussion at the October 2010 expert meeting centered on the need to tailor the monitoring approach as well as overall quality oversight to a given trial, focusing on what is most important for that trial and on what errors are most likely to adversely affect trial quality. Specific recommendations resulting from this meeting may be viewed at:

<https://www.trialstransformation.org/projects/effective-and-efficient-monitoring/>.

Learning from Quality-by-Design in the Manufacturing Sector: *Fergus Sweeney, European Medicines Agency (EMA)*

Fergus Sweeney began by stating the need to strike a balance between research innovation and regulation of pharmaceutical industry activities to protect the public's health. He referenced the development of the International Conference on Harmonization (ICH) Q8 (pharmaceutical development), Q9 (quality risk management), and Q10 (pharmaceutical quality system) guidelines for the manufacturing sector as an example of a new quality paradigm in the making.

He then described a number of key quality concepts from these ICH quality guidelines that could be applied to clinical trials to help define what really matters and ensure acceptable trial quality, including:

- **Quality by design**—a systematic approach to development that begins with predefined objectives and emphasizes process, product understanding, and process control, based on sound science and quality risk management
- **Process analytical technology (PAT)**—a system for designing, analyzing, and controlling manufacturing through timely measurement of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality
- **Control strategy**—a planned set of controls, derived from current product and process understanding, that ensures process performance and product quality
- **Critical quality attribute**—a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure desired product quality; and
- **Design space**—the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality

This last concept of design space is critical, Sweeney explained, because, in the manufacturing sector, once a design space has been authorized, movements within it are not considered a change requiring additional regulatory approval. Sweeney emphasized that changes to incorporate these principles into a clinical trial setting are not limited by current regulations or legislation. He described several initiatives that have been undertaken in Europe to promote a QbD approach to pharmaceutical development that might be models for promoting similar initiatives for clinical development:

- The ICH Implementation Working Group on Q8, Q9, Q10 (which has offered training on these guidance documents internationally); and
- A pilot project for joint assessment of Chemistry, Manufacturing, and Controls (CMC) applications between EMA and FDA.

- The EMA's PAT team, which combines GMP inspection and pharmaceutical assessment (reviewer) expertise in offering assistance to companies embarking on these concepts and enables sharing of case studies and workshops with regulators and industry.

In addition, he noted that initiatives were already under way to encourage QbD and risk-based approaches in clinical development, including efforts made by CTTI, the European Science Foundation, the Organization for Economic Cooperation and Development, Germany's Federal Institute for Drugs and Medical Devices (BfArM), Britain's Medicines and Healthcare products Regulatory Agency (MHRA), the European Commission, and, most notably, the *Reflection Paper on Risk-based Quality Management in Clinical Trials* recently issued by the EMA (available at:

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500110059&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc). Sweeney explained that the purpose of this paper is to facilitate the development of a more systematic, prioritized, risk-based approach to quality management of clinical trials to support the principles of Good Clinical Practice (GCP) and to complement existing quality practices, requirements, and standards. The EMA welcomes comments on the paper through February 15, 2012.

Principles for Building Quality into Clinical Trial Development: *Beat Widler, Widler & Schiemann Ltd.*

Beat Widler began his presentation with the observation that quality must be understood in context. Audits, he noted, cover only about 2% of clinical-related activities, and so continuous risk evaluation should be employed by research sponsors to ensure ongoing, comprehensive quality assessment through all stages of therapeutic development. Such evaluation comprises three steps:

- 1) Determining the base risk profile (BRP) (periodic or annually). The following definition for base risk profile was proposed: The BRP of a single process or multi-stakeholder process of a given entity is the calculation of the risk this process yields based on assessments of the theoretical factor's "impact" (if this process fails, what theoretical outcome is to be anticipated?), "likelihood" (how likely is it that this process fails?), and "detectability" (how well can we detect errors before the process fails?).

The impact factor is almost always a self-explanatory or pre-defined value because, depending on the process concerned, this refers to a financial or other measurable value that is at stake (e.g., rejection of a trial supporting a filing). The likelihood factor reflects the robustness of the business processes: the more robust a process, the less likely it is to fail and vice versa. And, last but not least, the detectability factor reflects the robustness of our controls of the process being assessed. The better and earlier that a deviation can be detected (and vice versa), the lower the risk. All factors—impact, likelihood, and detectability—are assessed based on the theoretical set up of a process to determine the baseline of a risk.

An example could be drawn from the auto insurance industry:

- Likelihood to be involved in an accident is driven by sex (female drivers known to cause fewer and less serious accidents), age, yearly mileage, etc.
- Impact depends on type of car (expensive and new vs. old and cheap), etc.

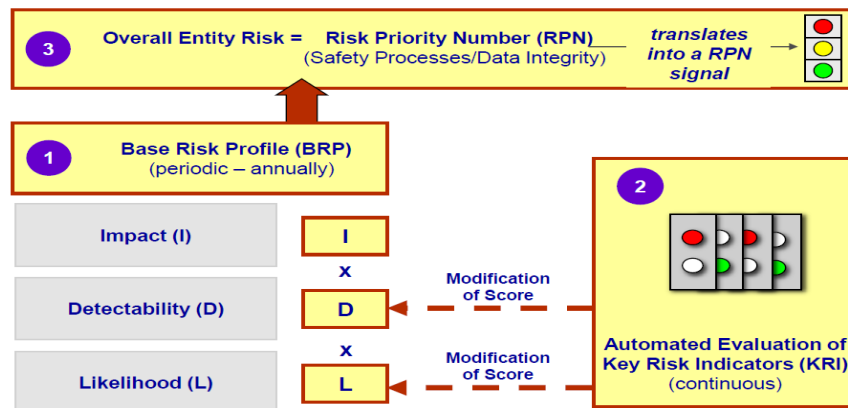
- 2) Continuously evaluating key risk indicators (KRI). Key risk indicators are designated to detect trial issues—such as delayed enrollment, missed visits, and early termination—early on before they become problems. Automatic analyses of existing data identify areas with increased quality risk.
- 3) Defining overall entity risk (represented by a risk priority number [RPN], which translates to an RPN signal) (see Figure 1 below).

Widler observed that such QRM tools should be embedded in a framework that includes traditional tools (e.g., audits). However, the scope and aim of auditing must change in a QRM approach, where auditing, he explained, becomes an input as well as a verification and “challenge” tool for QRM analysis. Widler also noted that a QRM process is successful not when we detect errors, but when we understand how they occurred and what they mean. By reframing the evaluation as “understood vs. not understood” (instead of “right vs. wrong”), we avoid the danger of sounding too many alarms (or signals) or relying too much on workarounds, both of which can result in continued lapses in quality.

Widler concluded his presentation by describing the essential elements to drive quality-by-design in clinical development:

- Creating shared standards for what matters in clinical trials;
- Devising common practices (e.g., templates, standard operating procedures [SOPs]);
- Sharing lessons learned; and
- Avoiding adhering blindly to “my way” vs. better approaches and adopting what others have developed.

Figure 1.



Session I concluded with a question-and-answer period, during which the meeting participants considered the logistics of implementing QbD and QRM. Key points included:

Developing models: In addition to sharing best practices, research sponsors should share their failures so that inefficient and ineffective practices will not persist.

Quality controls. Monitoring serves largely as a detective control in a QRM approach. It was agreed that the nature and extent of tools, such as monitoring, should be guided by the complexity of the trial. Risk indicator signals should be evaluated within a range of tolerability (i.e., a design space), and the trial sponsor should then act accordingly. Furthermore, rather than conducting routine on-site monitoring visits, sponsors can use centralized data monitoring to

draw inferences about quality within a sample of sites, which can then be extrapolated to the entire trial, with monitors dispatched on an as-needed basis.

Regulatory infrastructure to support QbD and QRM. One participant asked whether the FDA is prepared to take an active role in the transition to the QbD paradigm: Do they have the necessary staff? What documentation do they want to see? FDA representatives responded that they are already in the process of evaluating resources and process needs and cultivating the necessary expertise to facilitate proactive discussions with sponsors about their quality planning. Regarding documentation, the FDA encourages sponsors to prospectively define what matters most for their trials—i.e., identify those critical risks that may harm study participants and/or data integrity and describe necessary measures to mitigate and/or prevent these risks from occurring. Research sponsors were encouraged to discuss these risks and planned mitigation with the FDA and document those discussions.

SESSION II: REGULATORS' PANEL

In this panel discussion, regulators from around the world discussed risk-based approaches to clinical oversight in a global regulatory environment. They addressed how regulatory agencies help to ensure quality through inspections and other activities, and they identified ways in which regulatory agencies can foster QRM approaches in clinical development.

Regulatory Agencies and Quality in Clinical Trials: Risk Adaptive Approach: Kathleen Meely, Medicines and Healthcare products Regulatory Agency (MHRA)

Kathleen Meely discussed the U.K. Medical Research Council (MRC)/Department of Health (DH)/MHRA joint project on risk-adapted approaches to the management of clinical trials of investigational medicinal products (IMPs). This project focuses on trial-specific risks to participant safety (e.g., from the trial intervention and clinical procedures), participant rights (e.g., inadequacy of the consent process and failure to protect participant data), and the reliability of results. Implementing a quality system to address these key risks involves informed protocol development and targeted management and monitoring plans. The approach guiding these efforts, Meely explained, is one that emphasizes working within the bounds of current legislation, identifying what can be done differently/less frequently for certain types of trials, and developing guidance.

The first step in the risk-based quality system is to determine the intervention safety risk—that is, to assess both the risk associated with the trial intervention (IMP) and the risk in relation to normal standard of care. Trials are categorized accordingly:

- Type A (comparable to standard care),
- Type B (somewhat higher than standard care), and
- Type C (markedly higher than standard care).

Risk adaptations are then tailored by category and affect a range of trial activities, including MHRA role in approvals, content of applications, labeling of trial drugs, safety surveillance, IMP management, documentation, and GCP inspections. Non-IMP risks are also identified; these include risks related to the design and methods of the trial (e.g., participant safety and rights, reliability of results) and can be multifactorial and less amenable to simple categorization at the trial level. Accordingly, non-IMP risks must be assessed independently and

a mitigation plan developed that identifies and addresses areas of vulnerability. With this information in hand, informed protocol development can take place in conjunction with creation of a targeted management and monitoring plan.

Meely noted that 11 trials have completed the risk adaptive process since April 2011, and plans are being made for additional guidance and training.

What We Can Do to Ensure Quality: *Tomoko Osawa, PhD, Pharmaceuticals and Medical Devices Agency (PMDA)*

Tomoko Osawa provided an overview of PMDA activities designed to ensure quality in clinical trials, highlighting the importance of capturing problems as early as possible and communicating solutions to all related sites. The MHLW/MEXT has implemented a five-year clinical trial activation plan, which involves building a clinical trial infrastructure, developing human resources for clinical research, publically promoting clinical trials and encouraging participation, and improving clinical research management efficiency. The plan also emphasizes the need to review GCP regulations and clinical research guidelines for further international harmonization and patient protection. Major activities undertaken to date include: PMDA consultations before application, inspections after application, and annual workshops for sponsors, medical institutions, CROs, etc., to provide information on inspection expectations and processes.

Osawa noted that protocol design plays a key role in ensuring the quality of clinical trials, and the PMDA is involved by consultation to help trials to be fit for purpose. Deviations from the protocol can have a large impact on the quality of clinical trials and may result from ill-defined criteria or procedures and/or misinterpretation of the protocol by sites. In the course of PMDA consultation, frequently asked questions regarding implementation issues include the composition of the data monitoring committee (DMC) and/or institutional review board (IRB), procedures to manage changes in IRB membership during the course of trial, appropriateness of informed consent procedures, handling of adverse events, and use of electronic data capture (EDC) systems. Osawa also reviewed PMDA procedures for post-marketing re-examination applications.

She concluded by noting that the PMDA strives to improve public health by offering the inspectors' point of view to research sponsors during the pre-approval and post-marketing stages of IMPs.

CDER Perspective: Challenges in Clinical Trials and the Path Forward: *Ann Meeker-O'Connell, CDER, FDA*

Ann Meeker-O'Connell began her presentation by observing that current oversight models for clinical trials may be outmoded, noting that they are reactive and premised on retrospective detection of errors, often lack proportionality, can be resource-intensive, and may not optimally address significant risks to trial integrity (particularly systemic error). She drew attention to a recent compliance review of marketing applications performed by the Office of Scientific Integrity, which revealed that, despite resources devoted to monitoring clinical investigator sites, systemic errors had occurred that threatened marketing application approvals. Some of these systemic errors persisted due to deficits in sponsor monitoring, but many had their root cause in study design and planning. Specifically, in 2/5 of the applications reviewed, concerns arose from internal processes at the sponsor and CRO and were unrelated to clinical investigator activities. Meeker-O'Connell observed that inefficient practices may consume valuable resources while simultaneously, inadvertently detracting from quality.

She continued by emphasizing that FDA regulations permit a variety of monitoring approaches. Moreover, the agency's desired state for clinical development is similar to the QbD ideal in manufacturing: "Maximally efficient, agile clinical development programs that reliably produce high quality data [a.k.a. data that are fit for purpose] and protect trial participants without extensive regulatory oversight." To this end, she advocated for a systematic, proportionate approach to clinical development that emphasizes process control. At the trial level, she posited, the protocol is the blueprint for quality as it is where a sponsor should prospectively identify the important risks to subject safety and data reliability. Risks may accrue from a variety of sources, and so the protocol and its delivery should be tailored to eliminate or mitigate these important risks. Monitoring and auditing, she noted, become tools in a quality toolbox, with flexibility in approaches.

Meeker-O'Connell listed a number of key dependencies that must be addressed to facilitate development of appropriate QbD and QRM principles and practices for clinical trials:

- Recognition of differences in manufacturing and clinical development as well as the inherent variability of clinical trials;
- Broad engagement of stakeholders;
- Effective communication regarding fundamental changes in oversight;
- Early identification of barriers;
- Evaluation of different approaches and methodologies; and
- Changes in FDA oversight and inspection processes.

In conclusion, she noted that CDER is doing its part to spur change by shifting inspection resources to permit assessment of clinical trial oversight in real-time, supporting risk-based inspection planning, and enhancing external collaborations such as the EMA/FDA GCP Initiative. The agency is also adopting an enterprise compliance intelligence approach that uses data analysis to identify risk concentrations and craft targeted solutions.

Regulatory Agencies and Quality in Clinical Trials: *Pierre Henri Bertoye, Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS)*

Pierre Henri Bertoye observed that involvement of regulatory authorities in the adoption of a risk-based approach to clinical trials begins with developing consensus definitions and tools. First and foremost, regulators must establish what constitutes acceptable risk (i.e., the design space) and what quality means (in terms of trial patient safety and the reliability and accuracy of the trial results). Next, they should identify and assess risk (by origin [IMP, trial design, site capacity] and category), perhaps through the use of a common risk assessment tool. Risk-adapted approaches to trial-related activities (such as information submitted to regulatory bodies, product traceability and labeling, monitoring, and safety surveillance and reporting) should be encouraged and facilitated through the development of common standards, both for sponsors and for regulators (regarding rules/expectations for assessments and inspections).

Bertoye also noted that education is critical for promoting this risk-based approach. Information must be disseminated to sponsors (via guidance, policies, feedback, training, and working groups), and it must be exchanged between regulatory bodies.

At the conclusion of the panel members' presentations, a question-and-answer period was held. A few queries concerned practical matters inherent to a risk-based approach—namely:

- The possibility of mandatory central monitoring (Response: not advocated unless appropriate for a specific trial);
- The potential for tailoring data collection only to end point and safety data (Response: if so, then tailor monitoring approach accordingly); and
- Management of investigator error at clinical sites due to staff turn-over. On this last point, the observation was made that improving protocol design can ease investigator burden, thereby decreasing the potential for error.

Sponsors were encouraged to think creatively about their protocols to identify means to streamline and simplify these critical documents, such that they focus on critical data and processes necessary to answer scientific questions. It was also recognized that systemic change is needed across sponsors, sites, and regulatory authorities. Sponsors, in particular, must take a prospective approach to finding errors. They have the data that they need to identify problems; they must bear the responsibility for finding them. Importantly, once errors are identified, sponsors must act swiftly, to address the root cause(s) and to prevent the error from recurring.

Although it was broadly acknowledged that trials have different levels of complexity, some interest was expressed in the creation of guidelines, standards, and templates to facilitate the application of basic QbD principles across the clinical trial enterprise. Specifically, it was proposed that inclusion/exclusion criteria could be broadened to incorporate more patients into trials—a change that would need to be accounted for in the statistical analysis plan. Additionally, a protocol template might be a desirable product from this undertaking—one that could be presented, perhaps, in tabular form and made easily understood by investigators.

SESSION III: CASE STUDIES

The case studies presented during this sessions highlighted models/methods applied in the public and private sectors in creating a QRM approach to clinical development. Presenters evaluated the strengths and weaknesses of these approaches and the desirability and/or feasibility of scaling up the widespread use of such designs. They also identified best practices that could be broadly adopted by both commercial and academic researchers to reduce inefficiency and enhance quality of clinical trials. QbD in the context of sponsor–CRO relationships was also discussed.

Building Quality into Clinical Development: The Academic Perspective

Quality in Clinical Trials: What Really Matters?: *Rory Collins, Oxford University*

Rory Collins began his presentation with the premise that randomized controlled trials already possess features in keeping with QbD—specifically, use of randomization (the unbiased comparison of patient groups that differ randomly) and control groups (unbiased ascertainment of outcomes in study treatment groups). Collins described several key features that should be emphasized in trial design to ensure reliable results:

Proper randomization (and intent-to-treat analysis). Proper randomized comparison allows no foreknowledge of likely study treatment allocation, minimizes post-randomization withdrawals (i.e., intent-to-treat), and minimizes losses to follow-up (e.g., after primary event occurs or study treatment stops). This design ensures that patient groups differ only randomly, thereby allowing unbiased assessment of treatment.

Sufficient numbers of relevant clinical outcomes (with efficacy and safety considered separately). Collins noted that the number of events, not patients, is the chief determinant of power. Composite outcomes that combine events that may involve different directions of effect are less sensitive and generalizable. Collins urged sponsors to review the underlying assumptions for statistical power during the trial: he cautioned that there is potential for false negative findings if power assumptions are not assessed during trials, which could have adverse public health implications.

Unbiased ascertainment of key study outcomes (without excessive checking and adjudication). Collins remarked that undue emphasis has been placed on data quality, postulating instead that high-quality data do not always yield reliable results. In randomized controlled trials, the unbiased ascertainment of major study outcomes relies on comparison with the randomly allocated control group; missing data have little impact if this is unbiased with respect to allocation. In fact, he proposed, adjudication of study outcomes adds substantial cost but typically little gain—an argument he supported with evidence from the Heart Protection Study of simvastatin. With this information in mind, he advocated for statistical monitoring of data (rather than physical monitoring of sites). Such monitoring includes: standard checks of range, consistency, and completeness of data; checks for unusual distribution of data within and between study sites (e.g., too little variance, lack of outliers, unlikely dates); and quality control assessments in random samples of investigators, patients, and data items (supplemented by systematic checks of particular sites prompted by other analyses). In addition, he concluded, we should stop distracting investigators with undue focus on processes of unproven value (e.g., site monitoring, suspected unexpected serious adverse reaction [SUSAR] reporting, source data verification).

Comparisons with the randomized control group (except for assessing big effects on rare events) and avoidance of undue emphasis on subgroup findings and on non-randomized, “on-treatment” analyses. As for subgroup and non-randomized, “on-treatment” analyses, he observed that emphasis on findings in small subgroups (e.g., North American patients), even when a trial has compelling overall results, may well be seriously misleading. Likewise, “on-treatment” comparisons of patients who show larger versus smaller response to treatment are non-randomized and thus not appropriate when randomization is needed to reliably assess the overall effect.

Another analytical pitfall described by Collins involved adverse events analysis. He noted that, while large effects on rare outcomes may be detected by the reporting of SUSARS per regulations, this does not require randomization. On the other hand, reliable assessment of moderate effects on common outcomes does need large-scale randomized evidence, which is best monitored by a Data and Safety Monitoring Board (DSMB) rather than by the reporting of multitudes of adverse events.

Building Quality into Clinical Development: ASCEND-HF as a Case Example: *Adrian Hernandez and Craig Reist, Duke University*

Adrian Hernandez and Craig Reist provided an overview of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), the largest acute heart failure study to date, designed to answer safety questions about nesiritide. In 2005, when nesiritide was becoming a popular treatment for heart failure patients, some meta-analyses indicated that patients who took the medication had a much higher risk of kidney problems and

death. A panel of experts recommended a large outcomes study to better answer these safety questions. ASCEND-HF began enrolling patients in 2007.

Hernandez and Reist described the study design, emphasizing that quality was built into the trial from the outset. Principles for quality operations/data were established before the trial began and were integrated throughout the trial. Quality expectations were communicated to sites and trial teams, and surveillance plans were implemented to provide feedback on whether quality objectives were being met. The overarching goal was to adhere to pragmatic principles that would yield an efficient, effective, and economical trial. Operational checks (including both on-site monitoring and centralized data surveillance) were put into place to determine whether the right participants were enrolled, whether they received the correct treatment, and whether the primary efficacy and safety data were complete and correct. Additional statistical surveillance efforts focused on key data points, such as creatinine values, duration of infusion, and vitals, comparing them to the regional average to assess expected variability in the data. Sites with data at a level of variability that was much smaller than the regional average were flagged, as were those where the standard deviation of a variable was less than a fourth of that of all sites in that region. Flagged sites were forwarded to the sponsor's global clinical operations group for follow up with the clinical research associate and the principal investigator.

In conclusion, Hernandez and Reist observed that global surveillance depends on the following:

- Keeping site investigators informed of planned visits and ensuring that data entry and cleaning are kept current throughout the trial;
- Rapid processing and adjudication of suspected events by the clinical events committee;
- Provision for regular feedback reports to sites on data quality by statistics/data management groups; and
- Documentation of findings, plans, and the outcome(s) of the intervention.

Building Quality into Clinical Development: The Pharmaceutical Industry Perspective

Building Quality into Clinical Trials: a Pilot with the FDA: *David Nickerson, Pfizer Inc.*

David Nickerson described Pfizer's Integrated Quality Management Plan (IQMP) pilot project with the FDA. The pilot evolved from discussions at the CTTI monitoring project expert meeting held in October 2010, during which it was proposed that sponsors should develop IQMPs in conjunction with their protocols. Participants at the previous CTTI meeting suggested that placing emphasis on key, high-level issues rather than on in-depth non-risk-based monitoring would aid sponsors in ensuring that important risks to quality are prospectively identified and that mitigation plans are put in place. Nickerson outlined the basic features of the Pfizer IQMP, including:

- A process for continuous quality improvement (based on the Plan-Do-Check-Act model);
- Prospective identification of quality objectives and metrics;
- Prospective identification, assessment, and mitigation of risks to quality; and
- Quality management plans to guide implementation.

Pfizer defined the following common objectives of quality management efforts: patient safety, data quality/trial integrity, and protocol compliance. To meet these objectives, concurrent with the process of protocol development, Pfizer prospectively developed quality metrics for

critical-to-quality (CTQ) requirements. These metrics are used to enable ongoing measurement/monitoring of quality performance during the conduct of the study to assess whether performance is in line with predetermined expectations. Examples of CTQ requirements include adherence to inclusion/exclusion criteria, proper consent of all subjects, and no unintended breach of study blind.

Risks to quality, in the context of the CTQ requirements, were then prospectively identified (what could go wrong? what would happen? possible causes?) and assessed/prioritized (how bad would it be if the risk happened? how frequently does the cause occur? how easy is it to detect the issue if it occurs?). Controls were identified to prevent/mitigate high priority risks to quality.

Nickerson noted that the IQMP enabled an integrated, cross-functional approach to proactively build quality into clinical trials. By working together to develop the IQMP, the Pfizer team collectively developed a better appreciation for what could go wrong, which resulted in greater ability to systematically manage quality. Moreover, by submitting the IQMP to the FDA and engaging in discussions with the FDA's Office of Scientific Investigations regarding the submission, Pfizer and the FDA had the opportunity to evaluate the resources and effort needed for such prospective quality planning. Key challenges for future efforts include:

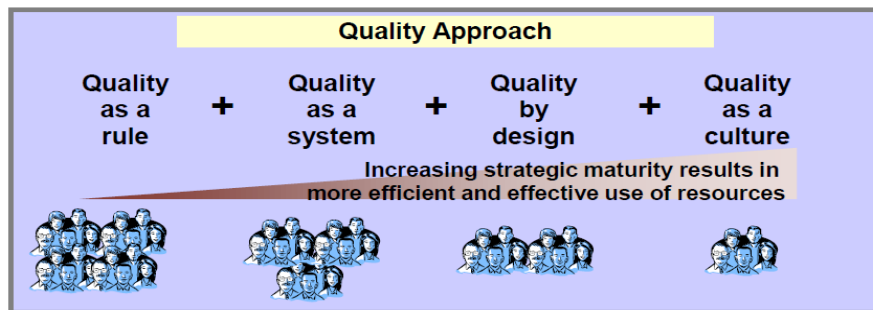
- Developing the processes, tools, and systems to make the IQMP process scalable and to facilitate company-wide implementation;
- Ensuring that all stakeholders' needs are met in determining those factors that are critical to quality;
- Identifying appropriate specification limits for quality metrics;
- Determining current practices that are not adding value and can therefore be eliminated; and
- Ensuring that we can measure success criteria to confirm that the IQMP process is adding value.

Medical Quality by Design: the Journey Continues: *Jeff Kasher, Eli Lilly*

Jeff Kasher described Eli Lilly's overhaul of its clinical development organization four years ago, which culminated in the crafting of a new vision statement that the organization will "reliably deliver the portfolio with quality, on time, and on budget." This goal can be met, he asserted, if quality becomes part of the organizational culture, thereby ensuring more efficient and effective use of resources (see Figure 2 below). Lilly's medical quality system redesign was multifaceted:

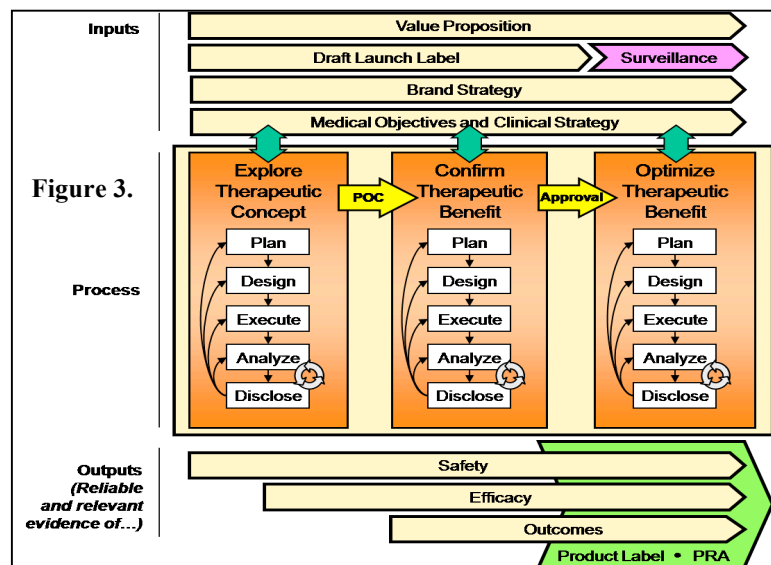
- A streamlined set of global quality system documents was created, resulting in a ~90% reduction in global controlled documents;
- A comprehensive, process-based approach to support effective implementation was designed, emphasizing process streamlining, role clarification, and strengthened governance;
- A fully integrated pharmaceutical network (FIPNET) was enabled through requirements applicable internally and externally; and
- Integration with other related quality systems (e.g., Lilly Global, Safety, Regulatory, Product Research & Development Quality Systems) was facilitated.

Figure 2.



As part of this new quality foundation a single process map was devised, many aspects of which are generic and can be applied across the spectrum of Lilly’s activities, from business processes to management controls (Figure 3).

Kasher went on to describe the elements comprising integrated quality risk management: risk-based monitoring, deviation management, sponsor trial master file, trial-level safety reviews, data validation and review, and third-party management oversight. Regarding this last element, he noted a number of mechanisms in place to oversee quality parameters in the context of strategic partnerships, including quality agreements, third-party audits, quality oversight assessments of investigator sites, and metrics reviews.



As for risk-based monitoring, he explained that Lilly’s clinical trial monitoring plans are based on statistical/scientific data elements in the protocol and incorporate on-site monitoring, statistical data monitoring, and internal monitoring of key processes.

Making Trials Fit for Purpose: *Andrew Lee, Genyzme*

Andrew Lee described the “value chain,” which begins with an experimental concept (embodied by the protocol), moves along to operationalization (and into the hands of clinical project managers, who oversee logistics, timelines, and regulatory approvals), engages with monitoring (and the monitors, who oversee site start-up, protocol fidelity, data integrity, and human subject protection), and ends with database lock. Components for a quality management system integrated with this chain include process/design, controls, assurance, evaluation, and continuous improvement. Within this framework, Lee asserted, quality becomes an enabler and not an impediment to innovation.

Planning is critical for ensuring success in quality management. Most project plans, he observed, are over-optimistic and struggle to deliver on cost, speed, and quality expectations. Initiation is often premature and occurs before processes and controls are in place. In contrast,

thorough planning is time-consuming and requires input, mostly on highly variable estimates. Furthermore, plans need to be updated regularly as information becomes available because clinical trials are very dynamic. Good protocol design can do much to facilitate planning both at the outset of a trial and throughout its course. Lee recommended external validation (or “field testing”) of protocols to see how well they interface with the practice of medicine. Likewise, sponsors should strive to simplify their designs and reduce the number of required procedures as much as possible. Ongoing training of research-naïve investigators and staff, as well as vendors and CROs, is also essential, as turn-over poses problems for adherence. Lee suggested the use of e-learning tools (in lieu of large meetings) to deliver training and track training compliance.

Enterprise-level tracking, along with a variety of data-driven reports, can support risk-based monitoring that is tailored to the characteristics of the trial and/or sites (e.g., clinical research experience of site and staff, complexity of design and disease [risk], phase of study, recruitment rate). Other technological advances—such as EDC, clinical trial management systems (CTMS), electronic trial master files, and interactive informed consent—can likewise increase quality without taxing business.

Facilitated Clinical Reviews: an Approach for Better Quality Protocols: *Craig Wozniak, GlaxoSmithKline*

Craig Wozniak described a GlaxoSmithKline undertaking to retool the protocol design process, thereby improving overall quality and minimizing risks. By incorporating peer review as part of the protocol process, he explained, the company has created an opportunity to challenge thinking about what constitutes an effective, quality protocol and to incorporate best practice considerations. The objectives of this redesign included the following:

- Deliver results for overall product development strategy;
- Reduce unnecessary protocol complexity and mitigate risks associated with more complex designs;
- Prevent avoidable (and expensive) protocol amendments;
- Reduce effort, errors, and burden at clinical sites;
- Improve oversight of subjects, sites, and trials;
- Highlight training, data collection, and quality activities;
- Increase the percentage of on-time study delivery; and
- Reduce time and expense of trial conduct

In the new protocol design process, peer review teams with broad functional representation gather for three to four hours to discuss protocols with objectives, end points, inclusion/exclusion criteria, and time and events outlined. The semi-structured discussions are led by trained facilitators who are experienced drug developers and who engage the teams in dialogue, encouraging them to find answers for themselves. A “safe” environment is established for these dialogues, whereby candor is encouraged and mutual respect mandated. Discussions generally center on study alignment with established plans, study design, and operational best practice. To date, over 100 protocols have undergone this review process.

Risk-based Approach: Case Study: *Andy Lawton, Boehringer Ingelheim*

Andy Lawton delivered an overview of a risk-based approach to study quality employed by Boehringer Ingelheim that combines reduced source data verification (SDV) with site risk assessment. He described the application of this approach to an outcomes trial with 17,000

patients at 1,200 sites in 50 countries. Lawton explained that the sponsor must understand and control risks, for example increasing SDV based on pre-identified fixed risk factors. As the level of risk increases, so too does the percentage of patients who are randomly allocated for complete SDV at a site. Early detection of risks or non-compliance leads to earlier implementation of actions and increased quality of the trial. Weekly risk reports are generated and reviewed by the study team. Such reporting, Lawton noted, is essential to form quality feedback loops for site-related issues. Data used in the reports come from a number of easily accessed sources: SDV web tools, clinical trial management systems, interactive voice response systems, databases, etc.

Lawton showed examples of the report format, which includes five sections: summary risk scores (by site, clinical research associate [CRA], and overall), identification (center, investigator, country, CRA assessment of site risk level), site data (e.g., number of serious adverse events, lost-to-follow-ups, patients meeting inclusion/exclusion criteria), CRA by site data (e.g., timing of on-site visits, follow-up on flagged serious adverse events), and individual risk scores. Using such data, the sponsor can detect fraud and misconduct by contextualizing the information within predefined acceptable limits (i.e., a design space). Lawton observed that much remains to be done; specifically, site selection could be improved by identifying the parameters that distinguish “good” from “bad” sites. By creating a site selection database, forecasting models could be developed to prevent selection of potentially problematic sites.

Clinical Trial Quality-by-Design Case Study: a Small Company Experience: *Lynn Seely, Medivation*

Lynn Seely addressed the question of how a small company can implement QbD. In many ways, she observed, small companies are well-suited to a QbD approach:

- They have limited resources, and QbD promotes efficiency and cost-savings.
- They have little tolerance for error, and QbD and QRM incorporate real-time risk management and corrective action plans, so that problems remain small and contained.
- They are flexible and agile, and QbD enables rapid decision-making and adaptation.

Seely’s company focuses on “critical success factors,” which she defined as clinical trial factors most likely to affect patient safety and data reliability. These factors vary by phase of development, patient population, and therapeutic area. Extra process and quality checks are then put in place to ensure high-quality data on critical success factors. For example, to ensure adherence to protocol inclusion/exclusion criteria in an Alzheimer’s disease phase 3 multi-national trial, a randomization authorization form was instituted requiring prior approval by a medical monitor to enroll trial participants. In a phase 3 overall survival oncology trial requiring complete long-term follow-up of a large number of patients even after they discontinued study drug, a contact form requiring contact information for 3 people who would always know the patient’s whereabouts was proactively implemented. Another example included tracking real-time patients discontinuing study drug early for reasons other than those specified in the protocol. A medical monitor contacted investigators to retrain them and to ensure compliance in the future.

QbD principles can influence numerous aspects of the small company’s trial: protocol design (fit for purpose, simple), continuous training (of monitors, investigators, study coordinators), site selection and evaluation, data tracking (enrollment, adverse event, and discontinuation rates; timeliness of data entry and SDV; overall data quality), safety (combination of on-site monitoring and data review), and audits (audit plan set up at outset but

responsive to trial realities). Seely emphasized that, with QbD, there can be no silos—each member of the overall project team is actively engaged in a process of continuous quality improvement.

She noted some challenges for QbD adoption. While a risk-based approach to auditing is well-defined by regulators, such approaches to monitoring are not well-defined, leaving companies unwilling to risk that inadequate monitoring will be uncovered at an inspection. Seely suggested, however, that a design space could be defined for clinical trial monitoring, so that risk-based targeting could be used and the sponsor could make adjustments to the monitoring and quality management plans in real-time based on accumulating data. She urged regulators to guide the way in defining this “design space” for trial monitoring.

Building Quality into Clinical Development: Outsourcing

Building Quality into Clinical Development: CRO Point of View: *Regina Freunsch, Accovion GmbH*

Regina Freunsch presented three case studies to examine the successes and pitfalls of a risk-based approach to monitoring. The first case study involved a global mega-trial in which all sites were monitored, all patients received limited SDV, and some patients received 100% SDV (at random). Risk assessments were supplied by CRAs at each site (based on data and monitoring findings, as well as on CRA “suspicion/gut feeling”), and a central monitoring system performed risk assessment for sites automatically. Unfortunately, this approach was found to be inflexible and burdensome to CRAs, and some CRAs attempted to keep risk assessment levels low by correcting mistakes without reporting them. The central monitoring system, too, had shortcomings—risk analyses were not always communicated back to the CRAs, and the information systems used (eCRF, SDV tool, CTMS, IVRS) were isolated and unconnected. Freunsch listed some opportunities for improvement in this case, including: selecting individual visits for targeted SDV, tailoring specific data management reports for CRAs, and relaying risk reports to CRAs to enable adaptive monitoring.

The second and third case studies involved trials for which the sponsors had outsourced many trial activities, including data management and monitoring, to different vendors. Problems arose due to poorly designed eCRFs that confused site staff and CRAs, lack of a data monitoring plan (thus escalating data cleaning costs), storage of data across different vendor systems, and, in one case, oversight of 100+ vendors that became overwhelming and ineffective.

In reflecting on these examples, Freunsch observed that quality begins with the protocol, and CROs are beholden to the study designs mandated by the trial sponsors. Further, many sponsors still require 100% SDV. Freunsch advocated that protocols be made patient- and investigator-friendly, taking the globalization of research into account. CROs should be encouraged to apply QbD-based approaches in their work bids and not be penalized for any associated costs that may arise. Quality management plans should be developed in conjunction with protocols, and measures and evidence from data should be used as triggers for action and adaptation during trial execution. Freunsch concluded by observing that the question of where to spend the right amount of resources, time, and money to achieve an adequate level of quality can only be answered with educated decision-making.

Building Quality into Clinical Development: Outsourcing: *Ken Getz, Tufts Center for the Study of Drug Development*

Ken Getz began with the question: Do QRM and QbD comprise an initiative to exert more quality control and oversight or to sustainably improve patient safety and data integrity while streamlining performance and increasing success rates? He posited that such efforts are not just about measuring and controlling operating processes; rather, they must target the root cause(s) of the problems in trials. The planning process, he emphasized, guides operating processes; therefore, to build in quality, sponsors must start with improving the protocol design process.

Getz explained that, in the past decade, protocols have become increasingly burdensome and complex—the total investigative site work burden has increased by 54% since 2004. At the same time, site performance has decreased, with more days taken from protocol approval to enrollment and more patient drop-outs. Concurrently, the number of protocol amendments has also increased, with 69% of all protocols having at least one amendment. Notably, Getz pointed out, each amendment adds 61 days to a trial and costs \$450,000+ to implement. To address such troubling trends, we must build quality into the protocol design process, identifying where and why protocol complexity is increasing and finding opportunities to balance scientific and operating objectives.

Getz stressed the necessity of obtaining early input from CROs, sites, and patients about whether a trial is even feasible. The current top-down approach (e.g., from agencies and sponsors) is out of touch with emerging realities of drug development, he remarked, noting that over 20% of the global drug development budget now goes to CROs. He advocated for integrated clinical research alliances, which are formalized and virtual/competency-based with planned, portfolio outsourcing, lean operation (integrated/coordinated), multi-level shared governance and SOPs, and shared operating risk/fixed pricing. Such alliances should include management committees at operating and senior levels, routine project team meetings, a relationship management liaison role, regular communication, communication policies, issue escalation and management policies, SOPs and practices, key performance indicators, and interim and post-project feedback. Getz concluded by asserting that parties on the front line and with rich, multi-sponsor breadth of experience (i.e., CROs and investigative site personnel) need a seat at the table if QbD is to take root and succeed.

At the conclusion of Session III, an interactive discussion was held. Robert Temple of the FDA kicked off the conversation by asking whether the methodologies presented during the session would go very far in making monitoring more intelligent. He worried that on-site visits seemed to remain a significant part of some monitoring programs, to which another participant responded that on-site interactions can never be abandoned completely because of the need for face-to-face training with study coordinators and investigators.

At this point, the conversation shifted to protocols and how to make them more user-friendly. It was suggested that study coordinators and patients be included in protocol development in an effort to better gauge the impact that study demands may have on sites and trial participants. The idea of field testing protocols (presented by Andrew Lee) garnered support as a means for thinking about how to make trials as easy as possible for patients, thereby improving compliance. Simple things such as reducing the number of visits or simplifying drug packaging can have a big impact on trial participant enrollment and retention. It was also

proposed that elements of the protocol could be incorporated into the EDC form as a way to remind study coordinators about required activities.

Meeting participants then considered ways in which overall trial design could be improved; specifically, it was suggested that what is needed is fewer sites with more patients (as opposed to hundreds of sites with one to two patients each). Participants proposed that one approach to increasing enrollment numbers could be to minimize inclusion and exclusion criteria to enable the acceptance of as many patients as possible into a study. Such a move could potentially be accounted for in the statistical analysis plan and could allow the label for the approved product to apply to the broadest population possible. Other ideas for increasing enrollment numbers included prescreening of patients and reviewing site records for recent patients to screen for eligibility. One meeting participant commented that monitors who conduct on-site visits also contribute useful information about site quality that may not be readily available from data.

In terms of improving site quality, it was agreed that performance-related data should be given to site investigators, so that they can see for themselves where issues pertaining to data quality or site conduct may exist. Furthermore, benchmark data showing a site's performance in relation to peer sites may also prove an effective means of building more accountability into site management, as investigators would be alerted as to whether their sites are considered outliers in terms of quality. Overall, participants agreed that transparency and communication between sponsors and sites are critical components to the QbD model.

SESSION IV: NEXT STEPS FOR QRM IMPLEMENTATION

This session comprised a panel discussion featuring *Leslie Ball* of CDER (FDA), *Fergus Sweeney* of the EMA, *Beat Widler* of Widler & Schiemann Ltd., *Rory Collins* of Oxford University, and *Ken Getz* of the Tufts Center for the Study of Drug Development. The panel was originally designed to be a conversation about evaluation of QRM implementation. However, the session was retooled by the panelists to address concrete next steps that could be taken following the meeting to jumpstart the definition of consensus principles for QbD and QRM in clinical trials and widespread adoption of a QbD approach to clinical trials. The assembled participants seemed to be of two minds on this topic: on the one hand, interest was expressed in crafting discrete examples of tools that could be used to implement QbD in trials (e.g., protocol templates for different therapeutic areas). On the other hand, some felt that it is more important for the clinical trials community to first come to agreement about high-level principles for quality before delving into real-world applications. Those of the former mindset asserted that people need illustrative examples that they can put into action; otherwise, their efforts to integrate QbD into trial operations might stall as philosophical conversations linger on. A protocol template would help sponsors to decide what matters, identify risks, and determine design space parameters and variability thresholds. As it was widely agreed that the protocol is a key document for designing quality into trials, it seemed to some to be the logical place to begin this system-wide overhaul.

Those of the latter opinion, however, felt that retooling the protocol was akin to putting the cart before the horse. In this case, the “horse” constitutes the core principles for good clinical design. Quality means different things to different people. An essential thrust of the QbD approach is the return of thinking to the design process. As one participant remarked, we can't give people a formula (e.g., a protocol template) because that will enable them to stop thinking.

Instead, QbD should encourage thoughtful protocol development, based on consensus definitions of quality and an understanding of what really matters for clinical trials.

Participants ultimately agreed that both approaches have their merits but that principle definition should precede case study and tool development. It was remarked that the protocol is the end point of a QbD process; everything that comes after comprises quality assurance. Therefore, efforts should be devoted to clearly delineating the design space encompassed by that critical document. Limits of variability and areas of regulatory flexibility should be examined and defined. To this end, representatives of the FDA stated that, while it is not the agency's place to dictate terms of protocol design and implementation, they can engage in conversation and provide guidance as to what is most critical to their considerations. Other meeting participants suggested that statisticians, investigators, CROs, and patient groups should be invited to contribute to the discussions in an effort to avoid reinforcing the silo mentality that currently separates protocol design from implementation.

The point was raised that issues related to ethics of trial conduct may need special attention, as the tools addressing clinical issues will likely not apply to ethical considerations. For example, what really matters for informed consent? What level of understanding was achieved by the patient as a result of the informed consent process? More research is needed before agreement can be reached as to what constitutes proper informed consent.

Once QbD principles are established and an initial protocol template is devised, training and certification of site teams might be considered as a means to ensure widespread adoption and comprehension of this new model for trial design and conduct. Some uncertainty was expressed as to the appropriate organization to spearhead such an effort, although the Association of Clinical Research Professionals (ACRP) was proposed as a possible option. The association's existing curriculum would need to be expanded and improved, however, to suitably represent the newly established principles.

To summarize, action items agreed upon by the meeting participants include:

- Defining quality and outlining high-level principles of good clinical trial design
- Defining what really matters—i.e., what we really need to get right to ensure data reliability and patient protection
- Engaging an array of stakeholders in a series of workshops to discuss principles and tools and to arrive at consensus agreement for their widespread adoption
- Promoting a transformation of culture across the clinical research enterprise

SESSION V: COMMUNICATION

This session began with a panel discussion among persons involved with communications efforts in the clinical research community: *Debra Madden*, FDA patient representative, *Jacques Demotes*, European Clinical Infrastructure Network (ECRIN), and *Lee Zwanziger*, Risk Communication, FDA. Debra Madden emphasized the need to engage all stakeholders—including patients—in this process of change. Patients, in particular, need to be educated about data integrity and trial design/implementation so that they understand that QbD is about enhancing protections and not cutting corners. She also stressed the need for more transparency, suggesting that the International Committee of Medical Journal Editors should consider requiring the inclusion of quality management plans in all accepted manuscripts reporting the results of clinical trials. Jacques Demotes related findings from the Organization for Economic Cooperation and

Development working group and expressed a desire that outcome of this CTTI meeting should dovetail with this pre-existing initiative to promote risk-based oversight of non-commercial trials. Given the globalization of clinical research, harmonization across national borders will be critical if QbD principles are to succeed in transforming the industry. Lee Zwanziger noted that the FDA had recently published an evidence-based guide for communication of risks and benefits (available for download at:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM268069.pdf>).

She commented that it is beneficial to consider communication early in the QbD process because risk-related information will enable decision-making. To do so effectively, she stressed the importance of identifying the audience, assessing their awareness of the issue and how it relates to them, crafting a simple message, testing it with the audience, revising it accordingly, and, finally, delivering it and evaluating its impact. When testing the message, she counseled, it is important to know what goal you want to achieve and then to decide whether the message has achieved this goal with the test audience. She cited focused interviews, focus groups, and internet-based panels as useful tools for the collection of this critical information.

The discussion was then opened to all meeting participants. Interest was expressed in including patients in the communication effort. Suggestions were made for incorporating patient representatives (like Debra Madden) in meetings such as this one. Also, inclusion on protocol design and peer reviews, as well as audience testing activities, would ensure that patient concerns are being addressed. An FDA participant asserted that patients should be empowered to demand clear communication from the clinical trials community; by seizing that power, they can drive the evolution of clinical research.

The point was made that a QbD transformation must be characterized as a shift in culture and that the public must be educated about the context driving this shift—i.e., what has worked, what has not, and what could be improved. Communications efforts must take into consideration whether the public will believe a message conveying the merits of risk-based decision-making. One participant pointed out that the public is becoming more health literate and is beginning to grasp the notion that less is more. If the clinical research community can explain why change needs to happen, the public will likely understand and see that a mind shift to QbD principles promises a better future for health care.

Finally, it was noted that one size does not fit all, and so the message will need to be tailored to the stakeholder. For example, pharmaceutical companies will want to know whether QbD will produce cost savings, patients will wonder whether it will improve care, and regulators will ask whether it will decrease their work burden. Repeated and simple messaging is key.

CONCLUSIONS

As the meeting drew to a close, Fergus Sweeney reminded participants that the EMA is inviting comment on its *Reflection Paper on Risk-based Quality Management in Clinical Trials* through February 15, 2012. All input will be published. It was suggested that the EMA paper could be used as a springboard for moving forward. To this end, Leslie Ball of the FDA wondered whether her agency could supplement the EMA paper with a companion piece. The observation was made that regulators in attendance would be striving for harmonization of efforts and the development of collective wisdom to be transmitted to regulated industry.

Sweeney cautioned that, going forward, we should aim not to add processes on top of existing processes, but rather to transform how things are done in the first place. Quality and regulations should act as enablers and not obstacles to innovation.

POSSIBLE DELIVERABLES GOING FORWARD

- A benchmark survey may be administered to patients and investigators to ascertain what quality means to them and what matters most in clinical trials. Similarly, they may be asked about what they consider to be barriers to quality.
- A core set of principles, ideas, and examples should be assembled by a working group to set the stage for future discussions among stakeholders. A series of workshops may be held as forums for those discussions.
- CTTI may host a website, wiki, or chat room to encourage continued exchange between workshops. It was also suggested that a Shareweb platform be established to share documents and drive future exchanges.
- Industry stakeholders should report back on efforts within their companies that result from this meeting. Lessons learned and mistakes made should be shared whenever possible.
- Harmonization both within and across agencies should be actively pursued so that QbD and QRM principles inform regulatory processes and decision-making related to medical product development.
- Presentations about this QbD initiative should be submitted for upcoming conferences (e.g., ACRP, Society for Clinical Trials, Drug Information Association). Feedback from this CTTI workshop will also be shared at the Berlin DIA QRM & QbD Conference to be held from November 10–11, 2011.
- Meeting participants should act as QbD ambassadors, spreading the word about the initiative in all feasible venues. To this end, it was suggested that CTTI provide a brief slide set of key talking points.

CTTI invites meeting participants to send additional ideas for potential deliverables to its mailbox (CTTI@mc.duke.edu).

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PARTICIPANT LIST

Workshop on Quality Risk Management: Making Clinical Trials Fit for Purpose

**A Clinical Trials Transformation Initiative (CTTI)-sponsored Meeting
August 23–24, 2011
Hyatt Regency Bethesda, Bethesda, Maryland**

Brenda Aker	Biosense Webster
John Alexander	Duke University
Carlos Ammann	Booz & Company GmbH
Patrick Archdeacon	Food and Drug Administration, CDER
Leslie Ball	Food and Drug Administration, CDER
Robert Ball	Food and Drug Administration, CBER
Mark Behm	AstraZeneca
Lisa Berdan	Duke Clinical Research Institute
Pierre Henri Bertoye	AFSSAPS (French Health Products Safety Agency)
Kelly Blackburn	Vertex Pharmaceuticals Inc.
Jean Bolte	Clinical Trials Transformation Initiative
Oana Brosteanu	Universitaet Leipzig
Sara Calvert	Duke Clinical Research Institute
Chrissy Cochran	Food and Drug Administration, CDRH
Rory Collins	University of Oxford
Karena Cooper	Food and Drug Administration, CDER
Steve Cummings	San Francisco Coordinating Center
Jacques Demotes	European Clinical Research Infrastructures Network (ECRIN)

Regina Freunsch	Accovion GmbH
Larry Friedman	Independent Consultant
Ken Getz	Tufts University
Cheryl Grandinetti	Food and Drug Administration, CDER
Melina Griffis	Food and Drug Administration, CDER
Manish Gupta	St. Jude Medical
Felix Gyi	Chesapeake Research Review
Jonathan Helfgott	Food and Drug Administration, CDER
Ed Helton	National Cancer Institute, NIH
Adrian Hernandez	Duke Clinical Research Institute
Greg Hockel	Pharmanet
Patricia Holobaugh	Food and Drug Administration, CBER
Grant Huang	US Department of Veterans Affairs
Cheri Janning	Clinical Trials Transformation Initiative
Elizabeth Joseph	Boehringer Ingelheim Pharmaceuticals, Inc.
Jeff Kasher	Eli Lilly and Company
Cynthia Kleppinger	Food and Drug Administration, CDER
Judith Kramer	Clinical Trials Transformation Initiative
Andy Lawton	Boehringer Ingelheim Limited
Andy Lee	Genzyme
Barbara Leishman	Roche
Joanne Less	FDA, Office of Good Clinical Practice
Lisa Horne Lucero	Eli Lilly and Company

Debra Madden	Breast Cancer Patient Representative/Research Advocate
Diane Maloney	Food and Drug Administration, CBER
Michael Marcarelli	Food and Drug Administration, CDRH
Amanda McMillan	Duke Clinical Research Institute
Ann Meeker O'Connell	Food and Drug Administration, CDER
Kathleen Meely	Medicines and Healthcare Products Regulatory Agency (MHRA)
Jerry Menikoff	Office for Human Research Protections (OHRP)
Thomas Moreno	Food and Drug Administration, CBER
Bob Moroz	Merck
Briggs Morrison	Pfizer, Inc.
Jean Mulinde	Food and Drug Administration, CDER
Mike Neidl	Genzyme
Dave Nickerson	Pfizer, Inc.
Paul Okwesili	Food and Drug Administration, CDER
Tomoko Osawa	Pharmaceuticals and Medical Devices Agency (PMDA)
Jacqueline O'Shaughnessy	Food and Drug Administration, CDER
Doug Peddicord	Association of Clinical Research Organizations (ACRO)
Ray Policare	Amgen
Ivor Pritchard	Office for Human Research Protections (OHRP)
Tejashri Purohit-Sheth	Food and Drug Administration, CDER
Craig Reist	Duke Clinical Research Institute
David Rodin	Merck

Volker Roenicke	Booz & Company GMBH
Peter Schiemann	Independent Consultant, Widler & Schiemann Ltd.
Ken Schiff	Quality Risk Management Associates, LLC
Gabriele Schwarz	BfArM (Federal Institute for Drugs and Medical Devices)
Lynn Seely	Medivation, Inc.
Jonathan Seltzer	Applied Clinical Intelligence, LLC
Stephanie Shapley	Food and Drug Administration, CDER
Mari Shirovani	Pharmaceuticals and Medical Devices Agency (PMDA)
Ken Sprenger	Pfizer, Inc.
Kirsten Steinhausen	European Science Foundation (ESF)
Norm Stockbridge	Food and Drug Administration, CDER
Linda Sullivan	Metrics Champion Consortium (MCC)
Fergus Sweeney	European Medicines Agency (EMA)
Mathew Tarosky	Food and Drug Administration, CDRH
Bob Temple	Food and Drug Administration, CDER
Mathew Thomas	Food and Drug Administration, CDER
Cook Uhl	Food and Drug Administration, CDER
Ann Wambolt	Bristol-Myers Squibb
Beat Widler	Independent Clinical QA Expert, Widler & Schiemann Ltd.
Craig Wozniak	GlaxoSmithKline
Lee Zwanziger	Food and Drug Administration, OOP