



Developing Effective Quality Systems in Clinical Trials: An Enlightened Approach

Summary of an Expert Meeting held October 13–14, 2010

Clinical Trials Transformation Initiative

Developing Effective Quality Systems in Clinical Trials: An Enlightened Approach

A Clinical Trials Transformation Initiative (CTTI)-Sponsored Meeting

October 13–14, 2010

Bethesda Marriott Suites

Bethesda, MD

Meeting objectives

The Clinical Trials Transformation Initiative (CTTI) has been conducting a project to identify effective and efficient methods to monitor clinical trials. In exploring how best to ensure the protection of trial participants and the reliability of study results, the project team has recognized that quality cannot be “inspected into” a trial but rather must be built in from the outset in the trial’s protocol design and planned operational conduct. To be effective, monitoring should be one component of an overall quality framework that allows potential issues to be identified and addressed as early as possible.

To further explore these issues, CTTI invited representatives from a broad cross-section of the clinical trial enterprise, including regulators, government sponsors of clinical research, academia, industry, patient advocates, clinical investigators, and other interested parties, to an expert meeting held in Bethesda, MD, on October 13–14, 2010. The key objectives of the meeting were as follows:

- To describe, discuss, and evaluate novel approaches to clinical trial oversight
- To identify the critical aspects of clinical trials that should be the focus of risk-based approaches to creating quality systems
- To propose an integrated model of quality management that will promote more efficient approaches to design, conduct, and oversight of clinical trials

Overview of CTTI monitoring project

The meeting commenced with an overview of CTTI and the monitoring project provided by *Martin Landray, PhD, FRCP, of the University of Oxford*. Dr. Landray defined appropriate monitoring as activities that enhance quality for participants in a trial and for future patients whose care relies on the results. Ineffective or inefficient practices should be abandoned, he noted, as they fail to protect participants or study integrity, waste resources, limit recruitment and follow-up, and deter participation and enthusiasm. With this in mind, he conveyed the overarching goal of the CTTI monitoring project: To identify best practices and provide sensible criteria to help sponsors select the most appropriate monitoring methods for a clinical trial, thereby ensuring reliable and informative trial results and human subjects protection.

Two of three workstreams comprising this project have been completed: 1) describing the range of current monitoring practices and examining factors that drive their adoption; and 2) defining key quality objectives for monitoring clinical trials. Dr. Landray described the challenges that remain to be addressed, including the need for flexible interpretation and implementation of

regulations governing clinical trial oversight, understanding of varying perceptions of risk inherent to “risk-based” monitoring, and examination of which data are essential for reliable assessment of the protocol question.

Defining the underlying principles of quality in clinical trials

Quality design of clinical trials: *Rory Collins, MBBS, MSc, of the University of Oxford* presented on quality design of clinical trials. He listed the key features needed for reliable results as follows:

- Proper randomization (and intent-to-treat analysis)
- Sufficient numbers of relevant clinical outcomes
- Unbiased ascertainment of key study outcomes
- Comparisons with the randomized control group (except for assessing big effects on rare events)
- Avoidance of undue emphasis on subgroup findings and non-randomized “on-treatment” analyses

Going into more detail, Dr. Collins described proper randomization and intention-to-treat analysis as that in which there is no foreknowledge of likely study treatment allocation, followed by minimization of post-randomization withdrawals and losses to follow-up (e.g., after primary event occurs or study treatment stops). In explaining what constitutes a sufficient number of relevant clinical outcomes, he noted that the number of events, not patients, is the chief determinant of power (e.g., primary prevention trials are more inefficient than secondary prevention trials). Also, composite outcomes that combine events that may involve different directions of effect are less sensitive and generalizable (e.g., total versus cause-specific mortality, or total versus site-specific cancer).

Dr. Collins then observed that undue emphasis has been placed on data accuracy when, in fact, reliable results can be obtained even from imperfect data. Unbiased ascertainment of key study outcomes is needed, he explained, putting greater reliance on comparison with the randomly allocated control group and paying less attention to missing data and adjudication of study outcomes. He offered statistical monitoring of data as a viable alternative to on-site visits. Such activities might involve: 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); quality control assessments in random samples of investigators, patients, and data items (supplemented by systematic checks of particular sites prompted by other analyses). He further cautioned against reliance on subgroup and non-randomized “on-treatment” analyses, noting that findings in small subgroups, even when a trial has compelling overall results, may be seriously misleading and that “on-treatment” comparisons of patients who have larger versus smaller response to treatment are non-randomized (and so open to bias).

Finally, Dr. Collins underscored the need to review underlying assumptions for statistical power during the trial, including assessing overall rates of the main clinical outcomes (blinded to allocated treatment), assessing impact of compliance to allocated treatment on risk factor levels

(e.g., unblinded differences in lipids or blood pressure), and modifying study duration, number of events, and/or pre-specified outcomes (blinded to effects of allocation on clinical outcomes). Potential for false-negative findings if power assumptions are not assessed during trials, he noted, could have adverse public health implications.

Quality risk management in clinical trials: *Janet Woodcock, MD, Director of the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA)*, then presented on quality risk management for clinical trials. She noted that, given the ever-growing and ever-changing clinical trial landscape, stakeholders in the research enterprise have shared concerns regarding whether the current trial oversight model is sustainable and effective. Dr. Woodcock observed that the drug manufacturing sector confronted similar issues. In response, the FDA launched the Pharmaceutical Quality for the 21st Century Initiative, with the stated purpose of creating “a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.” Subsequently, the International Conference on Harmonization (ICH), to which FDA is a party, finalized the Q8 (pharmaceutical development) and Q9 (quality risk management) guidances in November 2005, which embodied a quality-by-design and quality systems framework. The guidances, she explained, emphasize sponsor ownership of the oversight process. She advocated similar use of a quality systems approach to clinical trial conduct, based on the assumption that such rigorous and predictable systems enable full integration of quality and quality improvement into clinical trials.

Dr. Woodcock proceeded to describe quality by design (QbD)—a quality systems approach that has proven successful in drug manufacturing—which comprises four basic principles: a systematic approach to development; predefined objectives; emphasis on product and process understanding and process control; and a foundation in sound science and quality risk management. Based on the successful application of this model within the drug manufacturing arena, she noted, there is good reason to believe that the QbD model could be adapted to the requirements of clinical trial conduct, thereby better achieving the goals of patient safety and data integrity without needlessly expending resources.

The QbD model, she explained, supplies a quality framework extending across a drug’s development lifecycle, from pre-clinical studies through post-marketing requirements. Trial sponsors espousing this approach would attempt to prospectively understand and manage potential sources of variation at critical control points in a trial’s conduct, paying closest attention to those activities that have been shown to undermine quality. For example, a QbD system would take processes such as monitoring and reconfigure them based on risk assessments to maximize efficiency and coordination of effort. In doing so, sponsors may conduct their trials in compliance with applicable statutes while producing the key data needed to facilitate regulatory decision-making.

She noted that adoption of a risk-based approach to clinical trial oversight may meet with resistance from those in the clinical trials enterprise who have long adhered to an oversight strategy based on risk aversion. Worst-case scenario thinking and intense scrutiny of every process step, data point, or activity in a clinical trial, however, will not ensure that all conceivable risks are avoided. Instead, Dr. Woodcock observed, what is required is a shift in

thinking that will prioritize thoughtful risk assessment and the building of quality into study designs to facilitate trial conduct and ensure data quality. By taking this risk-based approach, trial sponsors will be able to apply their limited compliance resources to activities that are identified as posing the greatest risks to human subjects protection and data quality. Dr. Woodcock believed this would allow sponsors to focus resources on conducting trials that provide answers to more medical questions rather than adhere to the perceived obligation to mitigate every potential risk, especially for those activities that minimally affect data quality and patient safety.

Dr. Woodcock ended her presentation by listing the four main components of a quality system:

1. **Say what you do**— Senior management must oversee the development and dissemination of strong quality and compliance standards and clearly voice full support for these standards. Protocols should define what data are important and establish quality measures to make sure those data are collected and reported in a manner that supports the protection of participants and regulatory decision-making.
2. **Do what you say**— Policies, procedures, study requirements, and responsibilities should be communicated prospectively to affected staff, CRO and service provider personnel, and clinical investigators. Adequate training should be provided to all participants.
3. **Prove it**—Risk-based monitoring, risk-based auditing, and trend analysis/metrics from monitoring and auditing should be used to make sure that planned procedures are being followed.
4. **Improve it**— Corrective and preventative actions must be designed holistically, evaluating issues broadly for impact across departments and studies as necessary.

Regarding monitoring in particular, Dr. Woodcock observed that FDA regulations speak broadly to a sponsor's obligation to monitor trial progress and do not obligate sponsors to carry out monitoring via on-site visits. Instead, she advised that monitoring should address all critical activities for which process failure might pose a risk to study participants' safety or undermine a study's data. A spectrum of monitoring activities, therefore, may be appropriate for a given trial based on numerous factors, including trial complexity, end points, intended use of data, experience of the investigators, etc. In particular, she noted, for data monitoring, a variety of approaches complement, can be used to target, and may even obviate the need for on-site monitoring visits.

Statistical monitoring applied to research trials: With this information as a backdrop, *Tomasz Burzykowski, PhD, of the International Drug Development Institute, Brussels*, provided an overview of statistical monitoring applied to research trials. Dr. Burzykowski observed that current monitoring practices may succeed only in detecting those errors that do not have a significant effect on trial results. In particular, errors that are not biased with respect to treatment (e.g., errors due to poorly calibrated equipment or sloppiness) are often a main focus of site monitoring visits, but the impact of such mistakes on trial results is unbiased and usually minimal. However, error introduced by treatment-related fraud can have a definite bias, making it impossible to draw reliable conclusions, and is best identified through cross-center comparisons made most readily by central statistical monitoring.

He then described three monitoring strategies: extensive, reduced, and targeted. The extensive strategy—which calls for 100% source document verification for primary and key secondary outcomes—can prioritize the absence of clerical errors over the validity and reliability of the results; obviously, not a desirable balance. The reduced strategy relies on random sampling of centers, patients, and/or outcomes to ensure a rate of error below an established percentage. Finally, targeted monitoring includes monitoring based on key risk indicators (such as adverse event rates, number of protocol violations, query rate, percent of patients with dose reductions, etc.) and statistical monitoring. With site management comprising an estimated 20% of trial expenses, it has been hypothesized that this targeted monitoring strategy would save millions of dollars for trial sponsors while increasing the efficiency and success of the monitoring effort (Eisenstein et al., *Clinical Trials*, 2008;5:75).

Three principles, Dr. Burzykowski explained, underlie the statistical monitoring approach: 1) randomness, as people are poor random number generators; 2) plausibility, as plausible data are hard to fabricate; and 3) comparability, as clinical trial data are highly structured. He described SMART (Statistical Monitoring Applied to Randomized Trials), a software that uses SAS macros to systematically perform a large battery of statistical tests on the values of all variables collected in a clinical trial. These tests generate p-values, ranks, and other statistics that are kept in a database for checks of randomness, plausibility, and comparability. Tests, such as χ^2 statistics, t-test, F-test, and multivariate test statistics, can be applied automatically, without regard to meaning or plausibility, yielding a very large number of center-specific statistics. Meta-statistics can then be applied to these statistics to identify outlying centers of concern. He concluded that, given evidence that a statistical approach to quality assurance could yield huge cost savings and increase the reliability of trial results, regulatory guidance should evolve accordingly to encourage and facilitate its use.

Approaches to risk-based quality management

A number of presentations showcasing existing approaches to risk-based quality management then followed, brief synopses of which appear below.

Quality by Design/Quality Systems, *Beat Widler, F. Hoffmann-La Roche*: Widler explained that a non-compliance finding discovered through monitoring, auditing, or other quality oversight activities should be regarded as a “call to action” to understand the significance of such a deviation on patients’ safety and data integrity rather than as a “disaster” that needs immediate attention. Trial sponsors must understand and figure out how best to deal with such deviations: if they represent a critical fault, mitigating and corrective actions are needed; however, if their impact on quality is negligible, then they may not represent a fault that needs much follow-up, if any. Roche has developed a quality management system that is based on the Failure Modes and Effects Analysis (FMEA) methodology and that focuses on two quality dimensions: the safety and integrity of patients, and the integrity of data. Ongoing mining and analysis of key risk indicator (KRI) data, as well as diagnostic tools such as questionnaires, reporting, and mitigating action templates (examples of which were presented), support the quality management system. The Roche quality assurance (QA) system uses comprehensive and robust calculation logic to evaluate study risks related to safety processes and data integrity, and then generates reports on

aggregate data to highlight problem areas. Widler concluded by emphasizing the need for controlled sharing among sponsors of data, such as monitoring outcome data, auditing outcomes, KRI data, and corrective and preventive action (CAPA) and mitigating action data, to further enhance the compliance oversight “universe” via continuous benchmarking and quality improvement.

Clinical Data Mining as a Basis for an Information-based Clinical QA Program, C. Grant Simmons, Novartis Pharmaceuticals Corporation: Simmons observed that the increasing volume of trials and reality of resource constraints mean that a traditional approach to clinical monitoring is no longer feasible. At Novartis, the Clinical Quality Assurance group determined that some types of clinical data and trial management metrics were good indicators of potential issues at clinical investigator sites, and thus decided that an automated process was needed to identify sites that were potentially “interesting” from an auditing perspective. The resulting system—TAPAS (Trend and Pattern Alert System)—selects potential audit sites based on predefined risk criteria, thereby replacing manual review, eliminating errors, and increasing the scope of sites that are reviewed. Simmons emphasized that TAPAS relies on data generated out of operational activities, potentially supplemented by risk questionnaires and based upon an understanding of the limitations in terms of availability and reliability.

Quality System Approaches Using Existing Data and Systems, Eileen Magruder, Amgen: Magruder described Amgen’s audit strategy, which is based on risk management involving identification and assessment of compliance risk, advising teams to mitigate compliance risk, and auditing to confirm compliance. Risk factors are identified for therapeutic area programs or specific protocols, contract research organizations that provide services across programs, and internal processes (e.g., randomization, safety case management, regional product labeling). For each risk factor, Amgen defines the level of risk; i.e., what constitutes high, medium, and low risk? Based on this assessment, numerical values are assigned for each level of risk and for overall risk assessment of the protocol, service providers, and internal processes. An annual audit strategy is developed and refined based on the results of these risk assessment tools, and a risk mitigation plan is created and evaluated. Magruder related that Amgen has seen increased communication on risk and improved mitigation of risks with the implementation of this quality system, but new challenges constantly arise as changes occur at sites and with service providers.

Quality Risk Management Tools, Raffael Jovine, International Institute for the Safety of Medicines: Jovine described the Quality Information Exchange (QIX), which is a suite of tools and services designed to enable research organizations to exchange information with their partners and with each other about audit scheduling and planning, auditor performance, auditee feedback, service level of service providers, and findings—including positive “non-findings”—to create a quality baseline. Such exchange of QA information, Jovine explained, enables better scheduling, planning, and targeting of audits, as well as risk baseline specification, benchmarking, and objective comparison of performance. The software is available as a hosted service so that users can access it worldwide, eliminating maintenance and enabling the coordination of activities and mapping of data. QIX participants can benefit from shared information that provides new perspective on internal data, access to a pool of standardized and credentialed service provider and audit data, and analysis of trends, quality heat maps, and warning flags for outliers. Jovine observed that, by actively reaping tangible benefits of

information sharing, research organizations likely will overcome their reservations about compromising confidentiality or company-specific methodologies.

The NIH/NCI Data Quality Initiative, *Edward Helton and Larry Wright, NIH/NCI:* Helton and Wright provided background on Enterprise Vocabulary Services (EVS), created in 1997 to provide the semantic foundation for sharing and re-use of data and services by analyzing and organizing diverse coding and by mapping meanings between different terminologies to facilitate interoperability. Helton and Wright observed that systems cannot exchange or use information if they use incompatible codes or tokens to signify meaning. Terminology services such as EVS provide those tokens, codes, and compatibility with the goal of ensuring consistent meaning across and among enterprises. They reviewed a number of tools designed to achieve interoperability, such as the NCI Thesaurus, NCI Metathesaurus, and terminology collaborations with FDA and CDISC. Noting that consensus and interoperability can build durable quality standards, Helton and Wright commented that it is worth exploring how such efforts could be applied to auditing/monitoring activities to enable data-sharing and the development of standard process metrics.

An Academic Approach: Combining Quality by Design with Central Monitoring, *Martin Landray, University of Oxford:* Landray began his presentation with an assertion that quality can be designed into a clinical trial. Through the use of targeted site visits, proactive site mentoring and training, remote assessment (e.g., incident alerts, tracking systems, statistical analysis), and trial oversight committees, quality can be monitored as part of the trial design, from enrollment to results. Landray went into more detail regarding central monitoring techniques such as: incident alerts, including serious adverse events and unblinding; tracking and reviewing systems to monitor follow-up, early recall, safety bloods, data queries, outcomes, etc.; regular reports by center, site, or at the global level concerning such topics as recruitment rates, compliance, and outcome measure tracking; automated detection of potential problems such as missing bloods or duplicate blood results; and statistical analysis of aggregate data as a means to flag potential monitoring targets. Such analyses, Landray explained, could address recruitment rates, physical or laboratory measurements, compliance with study treatment, serious adverse event reporting, and duration of study visits, but do pose some challenges (e.g., adjustment for confounders, finding appropriate comparisons, false positives, false negatives). The problems identified by such monitoring efforts may pertain to the design, procedures, data recording, and/or analysis in a trial, and the solutions can be tailored accordingly. He noted that lessons learned via central monitoring may be useful for ongoing or planned trials.

Quality Risk Management in Clinical Trials: FDA/DSI Perspective, *Leslie Ball, FDA, Division of Scientific Investigation:* Ball observed that all clinical research stakeholders seek the truth about the safety and effectiveness of drugs, but, she noted, risk/benefit evaluation is an ongoing, nuanced process. Current challenges—such as clinical trial complexity, globalization, and regulatory hurdles—lead to greater uncertainty regarding drug development, and this uncertainty threatens the sustainability of the clinical trial enterprise. To address this problem, clinical trial conduct and oversight must be transformed through adaptive (rather than technical) change. Technical change, Ball explained, involves applying current knowledge, skills, and/or tools to solve a problem; adaptive change, on the other hand, recognizes that existing knowledge and skills are not sufficient, and requires a shift in values, expectations, attitudes, or habits. To

implement *adaptive* change, we must clarify any conflicts in values and bridge the gap between our values and the current conditions. In terms of values, Ball noted that clinical research stakeholders adhere to varying epistemological frameworks: academia favors generation of knowledge, regulators prioritize assessment of knowledge, and industry uses knowledge to develop, test, and market products. To accommodate these values and bridge the gap between “knowledge” (in its many forms) and current conditions, quality must be built into trials. This will require, first and foremost, a fresh view of what constitutes “high-quality” data, which Ball posited should be defined as data that sufficiently support conclusions and interpretations equivalent to those derived from error-free data (i.e., data “fit for purpose”). She observed that the traditional model of assessing trial and data integrity through on-site inspections does not always focus on what matters (key efficacy or safety parameters) and does not reveal how results from one site translate across a study or an application. By moving towards a quality risk management approach to clinical trial oversight, quality can be built into a trial, focusing on key risks to trial integrity and data quality as well as subject safety. If sponsors were to adopt this approach, Ball remarked that FDA will also need to shift the focus of its inspections to evaluating sponsor quality systems, incorporating risk-based inspection planning, using data to inform inspection prioritization, planning, and scope, and enhancing external collaborations with groups such as the European Medicines Agency (EMA) and CTTI.

Risk-based Quality Management of Clinical Trials—A European Regulator’s View, *Gabriele Schwarz, German Federal Institute for Drugs and Medical Devices:* Schwarz outlined the basic principles of a risk-based quality management approach, which are applied throughout the life of a trial, from design and initiation, through conduct, and during data evaluation and reporting. She noted that systematic risk identification and assessment, as well as definition of mitigation activities, require an interdisciplinary team involving personnel from trial management, preclinical and pharmaceutical development, data management, biometry and statistical analysis, pharmacovigilance, quality control, and quality assurance. Defined as a systematic and proactive risk assessment on an organizational and trial level, risk-based quality management, as envisioned by Schwarz, incorporates: a focused allocation of resources (monitoring visits, audits, technical services, trainings, data quality checks) to the highest priority risks; close performance measurement focusing not only on timelines and budget, but also on quality in relation to pre-specified acceptance criteria or predefined ranges; timely escalation of any issues; implementation of risk mitigation actions and follow-up of agreed corrective and preventive actions; and close collaboration and efficient communication between quality areas, functional services, and business partners.

Roundtable discussion: Working together to deliver quality

Day two convened with a panel of expert speakers offering their perspectives on how clinical research stakeholders might work together to deliver quality. The panel included: Robert Temple, MD, and Rachel Behrman, MD, of FDA; Fergus Sweeney, PhD, of the EMA; Rory Collins, MBBS, MSc, of the University of Oxford; Briggs Morrison, MD, of Pfizer; Felix Gyi, PharmD, MBA, CIP, of Chesapeake IRB; and Nancy Roach, patient advocate, Colorectal Cancer Coalition. Once each of the panel members had spoken, the discussion was opened to all meeting participants. Below is a synthesis of the main points of this discussion.

Panelists and participants agreed that what is needed is an enlightened approach to trial quality through improvements in trial design, implementation methods, and oversight. This approach would involve prospective risk identification (e.g., bias, poor compliance, poor recruitment, and low event rate), protocol design, and plans for study conduct intended to mitigate those risks. Prospective identification of quality objectives and associated metrics and systematic monitoring of these metrics during study conduct should enable early identification of quality defects related to patient safety and data quality, thus facilitating rapid response to remediate these issues. Subsequent follow-up should seek to confirm that quality issues previously identified were adequately addressed.

To implement this sort of change, all stakeholders in the clinical trial process must modify their view of risk. Perception of risk will vary according to the stakeholder and/or the circumstance. Furthermore, it must be recognized that there is a risk that if the requirements for conducting trials are too onerous, patients may be harmed by the lack of reliable evidence for the effects of treatment and by a reduction in the number of new treatments that are developed. As such, we will need to evaluate the process of clinical trial development and implementation to identify potential risks. Beyond identifying risks, one also must consider how to mitigate those risks. This engenders the question: How do we define and quantify quality? “Fit for purpose”—a phrase used earlier to describe the data needed to ensure the integrity of a trial’s results—is difficult to operationalize.

It was asked what incentives are currently offered to risk-averse organizations that will encourage them to retool their quality oversight plans. It was suggested that regulators may need to take the lead in this regard. Although, to date, FDA has been relatively unsuccessful in convincing trial sponsors that frequent monitoring isn’t the only approach to ensuring human subjects protection, data quality, and compliance with regulations, the need remains to demonstrate more credible alternatives that will convince industry that the benefits outweigh the risks. Several people noted that sponsors need more predictability from FDA. The risk aversion that currently plagues the industry can be traced to varying interpretations of the regulations and to the potential repercussions of a mismatch between sponsor and FDA interpretations. If sponsors know what to expect from FDA, it was suggested that they will be inclined to take more risks. To this end, it was recommended that regulatory inspectors be more proactively involved in the review and revision of quality assurance plans in advance of trials being initiated.

It was remarked that a culture shift involving sponsors, clinical research associates, auditors, and inspectors is needed. Unfortunately, it is difficult to change an entrenched system while it is still being used. Although some have endorsed wide-sweeping change, a number of participants noted that incremental change may be more realistic. One panelist remarked that we should focus immediately on two or three things that we can alter, keeping things simple and making measurable changes in the short term. By breaking down this adaptive change into manageable steps, we can counter pessimism by showing people what *can* be done.

Conclusions and future directions

- **Guidance from FDA:** It would be helpful if FDA were to clarify that it is not necessary to follow any particular monitoring methodology. In general, guidance documents should emphasize the key principles (ensure human subjects protection, data quality, and compliance with regulations) without specifying any particular methodology, and should give examples of various approaches by which these have been achieved.
- **Integrated quality management plans:** Sponsors should develop an “integrated quality management plan” (QMP) in parallel with the protocol. This should provide evidence that the risks have been appropriately assessed and that mitigation plans have been put in place (e.g., as part of the protocol, study systems and procedures, training, monitoring). The emphasis should be on key high-level issues rather than an in-depth description of monitoring activities, the details of which may, and often should, evolve over time. This approach would encourage trial sponsors to do their thinking in advance (e.g., about critical factors, risk mitigation, and quality control measures). Sponsors should also consider engaging in more discussion with FDA reviewers and inspectors regarding the QMP. (FDA is currently piloting such interactions, although it may need to increase its staffing to accommodate demand.)
- **End-of-trial reporting of quality management issues:** It was suggested that, on completion of a trial, a report should be produced describing any issues found (either with the performance of the trial or with the QMP itself) and explaining how any issues identified might affect the analysis and interpretation of the results. This could be included in regulatory submissions and in publications of the trial results. The International Committee of Medical Journal Editors might consider including such quality information among its requirements for scientific publication.
- **Sharing quality management knowledge, methodologies, and data:** A number of different approaches to quality management are being developed by industry, academia, clinical trialists, and regulators. Greater collaboration would accelerate these developments. For example, some analysis approaches and presentation techniques could be applied more generically, while shared benchmarking data could be used to assess performance in new trials.
- **Education and awareness:** It is important that all stakeholders understand the critical elements of a high-quality clinical trial so that attention is focused on those aspects that matter to the care of the participants in the trial and the reliability of the results that are produced. This applies to those that are involved in the design, implementation, analysis, interpretation, regulation, and inspection of clinical trials, as well as to those who use the results, such as healthcare providers, doctors, and their patients. The meeting highlighted a need for increased education and awareness of these issues.
- **International adoption:** International adoption of basic principles of clinical trials and harmonization of regulations would facilitate global adoption of the proposed changes.

Potential role for CTTI

It is possible that CTTI could provide a forum for the development of a sample quality management plan for vetting and dissemination among stakeholders. CTTI might also consider creating an online forum for lessons learned and convening a roundtable to accelerate the adoption of this approach.

CTTI is well placed to increase awareness of the importance of appropriate quality management in clinical trials. A position paper will be written for a leading medical journal, explaining the need for this change of emphasis. Other educational activities could be considered as part of future projects.

**Participant List
Meeting of Invited Experts**

**Developing Effective Quality Systems in Clinical Trials:
An Enlightened Approach
A Clinical Trials Transformation Initiative (CTTI)-Sponsored Meeting**

October 13–14, 2010

Bethesda Marriott Suites
6711 Democracy Boulevard, Bethesda, MD 20817

<u>Name</u>	<u>Organization</u>
Brenda Aker	Biosense Webster
Landen Bain	CDISC
Leslie Ball	Food and Drug Administration, CDER
Rachel Behrman	Food and Drug Administration, CDER
Alex Boddy	Sanofi-Aventis
Richard Burlingame	Merck and Co., Inc.
Tomasz Burzykowski	International Drug Development Institute (IDDI)
Chrissy Cochran	Food and Drug Administration, CDRH
Rory Collins	University of Oxford
Steve Cummings	San Francisco Coordinating Center
Michael Delahunty	St. Jude Medical
Andrew Emmett	Biotechnology Industry Organization (BIO)
Fred Feldstein	Pfizer
Terry Ferguson	AstraZeneca
Cheryl Grandinetti	Food and Drug Administration, CDER
Joe Griffin	Food and Drug Administration, CDER

Felix Gyi	Chesapeake Research Review
Ruyi He	Food and Drug Administration, CDER
Jonathan Helfgott	Food and Drug Administration, CDRH
Ed Helton	National Cancer Institute , NIH
Debby Holmes	ICON
Pat Holobaugh	Food and Drug Administration, CBER
Grant Huang	US Department of Veterans Affairs
Cheri Janning	Clinical Trials Transformation Initiative
Raffael Jovine	International Institute for the Safety of Medicines
Jonathan Kagan	National Institute of Allergy and Infectious Diseases, NIH
Michael Katz	International Myeloma Foundation
Cynthia Kleppinger	Food and Drug Administration, CDER
Judith Kramer	Clinical Trials Transformation Initiative
Martin Landray	University of Oxford
Mike Lauer	National Heart, Lung, and Blood Institute, NIH
Joanne Less	FDA, Good Clinical Practice Program
Diane Maloney	Food and Drug Administration, CBER
Eileen Magruder	Amgen
Louise Mawer	Medicines and Healthcare Products Regulatory Agency
Jennifer Marsh	Eli Lilly and Co.
Clare Matti	Duke Clinical Research Institute
Louise Mawer	Medicines and Healthcare Products Regulatory Agency

Robert McCormick	PPD
Amanda McMillan	Duke Clinical Research Institute
Ann Meeker O'Connell	Food and Drug Administration, CDER
Briggs Morrison	Pfizer
Jean Mulinde	Food and Drug Administration, CDER
David Nickerson	Pfizer
Bob O'Neill	Food and Drug Administration, CDER
Doug Peddicord	ACRO
Ray Policare	Amgen
Tejashri Purohit-Sheth	Food and Drug Administration, CDER
Andrea Rathe	Population Health Research Institute
Roland Rich	Novartis
Nancy Roach	Colorectal Cancer Coalition
Melissa Robb	Food and Drug Administration, CDER
David Rodin	Merck and Co., Inc.
Peter Schiemann	Hoffman La Roche LTD
Gabriele Schwarz	BfArM
John Simes	National Health and Medical Research Council
Grant Simmons	Novartis
Mark Stacy	Duke University
Norman Stockbridge	Food and Drug Administration, CDER
Linda Sullivan	Metrics Champion Consortium
Fergus Sweeney	European Medicines Agency

Barbara Tardiff	PAREXEL
Robert J. Temple	Food and Drug Administration, CDER
Kathleen Uhl	Food and Drug Administration, CDER
Janet Vargo	Johnson and Johnson Medical Devices and Diagnostics
Susan Vogel	National Institute of Allergy and Infectious Diseases, NIH
Lorraine Waring	Pfizer
Beat Widler	Roche
Steve Wiviott	Brigham and Women's Hospital / Harvard Medical School
Janet Woodcock	Food and Drug Administration, CDER
Craig Wozniack	GlaxoSmithKline