Quality Objectives of Monitoring

Summary of a Panel Discussion held November 4, 2009

Project: Effective and Efficient Monitoring as a Component of Quality in the Conduct of Clinical Trials

Clinical Trials Transformation Initiative

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This meeting was convened as one component of the plan for Workstream 2 of CTTI's monitoring project. The overall goal of this meeting was to answer the question: What are the critical quality objectives of monitoring clinical trials? Little attention has been focused on this issue to date, as was revealed by a recent literature review that found only 21 print sources in which monitoring objectives for clinical trials were mentioned. Of the objectives listed in these articles, most were related to data quality and patient safety. These findings mirrored those of a CTTI survey of approximately 100 organizations in the clinical research arena, which found that most respondents agreed that the main objectives of monitoring should be to ensure data integrity and human subjects protection. As these two high-level objectives underlie most discussions about monitoring practices, the question then arises of how they should be assessed. It is one thing to say that "human subjects protection" is a high priority, but it is entirely another to define exactly what constitutes such protection and whether its definition varies from one stakeholder to the next. Team leader Rachel Behrman of the FDA observed that the challenge is to put "meat on the bones" of these broad objectives.

To gain some understanding of the problems with clinical trial conduct that monitoring might detect, results were presented from a review of warning letters issued by CBER, CDRH, and CDER between 12/1997 and 4/2009. A total of 271 citations from 7614 warning letters were determined to have implications for monitoring—most of these letters concerned "general responsibilities of investigators" and investigator recordkeeping and record retention. The reviewers noted that, although the most frequently cited violations were attributed to investigators, proper and thorough monitoring of the clinical trials might have prevented these violations. Given this observation, meeting participants highlighted the necessity of ongoing site training (in tandem with monitoring) to ensure data quality. The case was also made that some violations are of greater significance than others, and so auditing efforts should be targeted to these more important problems. One participant observed that documentation of a procedure doesn't guarantee that the procedure was actually executed correctly. For example, in the case of informed consent, documentation that a participant was consented to participate in the trial does not translate into assurance

that the patient understood the benefits and risks of his participation. Therefore, methods must be devised to accurately measure performance in the aspects of trial conduct that are most important to the study question being examined and to patient safety.

To stimulate further conversation about these issues, representatives from a variety of organizations involved in research were asked to share their perspectives on key objectives of monitoring. These speakers included an individual with over 30 years of experience conducting clinical research within the NIH, as well as agents from a commercial IRB, an independent AIDS research and policy think tank, a biopharmaceutical company, and the FDA. Although these representatives came from very different corners of the clinical research world, a number of common themes emerged from their remarks. Each stakeholder has an interest in reducing duplication of monitoring effort in order to make the best use of resources, thereby underscoring the need to identify monitoring practices that are actually useful. Monitoring is most useful when it identifies errors early so that corrective training can be carried out. It was also observed that current monitoring processes often involve time- and labor-intensive techniques that are not actually required by regulations. Risk-based monitoring, focusing on defects that would make a critical difference to data quality and patient safety, might be considered as a means of efficiently ensuring the data quality and subject protection that everyone wants without requiring intensive effort and incurring unnecessary costs.

With these general observations in mind, each meeting participant was then invited to list his or her three main objectives for monitoring. The responses were wide-ranging (see Appendix), but many participants named the following four objectives (or versions thereof) as critical:

1. **Patient safety**, from ensuring informed consent to guaranteeing appropriate communication with patients during and after the trial.

2. **Accurate representation of key data**, as manifested by proper reporting of data, reliability of results, ability of data to address the study question, reproducibility of study results, etc.
3. **Protocol compliance**, which, it was noted, actually encompasses points 1 and 2 above if the protocol is carefully designed and thoughtfully written.
4. **Quality improvement**, using the monitoring process not only to identify errors but, if possible, to also provide a means by which the errors may be corrected via site training, protocol amendment, and so forth.

Numerous participants emphasized that regular visits to study sites to evaluate procedures, provide supplementary training, and gain a general sense of the site's dependability should remain a part of many monitoring plans—the so-called "sniff test." Additionally, site visits provide an opportunity for training and corrective action early in study execution.

The question was posed as to whether some level of error is acceptable within a clinical trial dataset and, if so, whether intensive monitoring efforts—such as repeated site visits, source document verification, and CRF review—might be reduced or avoided with the understanding that these errors would not affect study results in any meaningful way. (The discussion did not address "directed error" such as fraud or bias, as this type of error remains unacceptable.) Robert Temple of the FDA presented his thoughts on the matter, noting that, in trials attempting to demonstrate superiority of one treatment over another, random (i.e., undirected) error in the effectiveness assessments or, possibly, in meeting entry criteria will bias the results toward the null (that is, toward a finding of no difference), making a false positive finding unlikely but increasing the chance of a false negative. People conducting studies have a major interest in minimizing such errors. On the other hand, random error in a non-inferiority trial will bias the results toward the alternative hypothesis (that being there is no difference between the treatments), a major concern of regulators. The safety aspects of studies have properties similar to non-inferiority studies, so that errors in critical safety assessments are very important. Dr. Temple noted also that important safety and effectiveness

conclusions can turn on a small number of cases, again suggesting major interest in ensuring accuracy of the important effectiveness and safety end points. He proposed, however, that often data, such as covariate data describing patient subsets, are almost always less critical to main study results and wondered whether a modest error rate could be acceptable in these datasets; for example, in data concerning date of birth/age, other illnesses, concomitant drugs unrelated to the disease being studied, non-end point evaluations, and less critical secondary end points.

In light of these remarks, meeting participants came to a tentative consensus that, in fact, some degree of error in non-critical data may be acceptable in many clinical trials as long as important effectiveness and safety end points have been verified; therefore, monitoring plans could be tailored accordingly. One participant commented that what constitutes “reliable data” depends on the question being asked, and so trial planners must decide with what degree of certainty they want their questions answered. It was also noted that ensuring total accuracy of the large amount of covariate data can distract from primary end point data, and so monitoring of the information typically collected may further consume resources that could be better targeted. Participants agreed that safety data were a primary concern and, therefore effort should be made during the writing of the protocol to identify potential safety issues and adverse events so that the parameters of the monitoring of these issues and events can be more clearly defined. Along these lines, the protocol was deemed a critical means for ensuring reliability of data by dictating requirements for study design, recruitment, and data collection, as well as the monitoring practices needed to assess the quality and possible correction of these various elements. It was noted that protocols generally do not mention monitoring plans.

Much recent discussion in the monitoring domain has revolved around the merits and limitations of “risk-based” monitoring—an approach to risk assessment for trial conduct and data collection that deploys available monitoring resources based on identified risks. Critical to the use of this monitoring approach is the definition of “risk”—a concept that may vary by stakeholder. As observed by the ICH in a 2005 guideline on quality risk

management: “It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. However, achieving a shared understanding of the application of risk management among diverse stakeholders is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring, and attribute different severities to each harm.”[1] In light of this consideration, a discussion was then initiated to explore how risk is perceived differently across a range of stakeholders in the mission of determining what monitoring methods add the most value to the clinical research process without sacrificing patient safety. More specifically, we examined the types of risk that different stakeholders try to avoid. Sponsor representatives indicated that they are wary both of harm to patients and harm to their product. Harm to patients can imply not only direct patient harm, but also risk of litigation. Harm to a product includes the following possibilities: data at one or more sites being rejected by regulators, delays in product approval, failure of a marketing application, or harm to a company’s reputation such as might occur with a public warning letter. In the bigger picture, it was noted that the public trust in clinical research must be preserved so that patients will be willing to participate in future trials. Given these concerns, the meeting participants pondered whether and how risk-based monitoring may be responsibly and effectively deployed across the clinical research enterprise.

A distinction was made between “perceived risk” and “actual risk”—how these concepts are defined in a trial could vary by stakeholder perspective, and so some sort of consensus must be reached and a set of standards defined that will both protect patients from harm and protect the interests of the entities involved in the conduct of clinical trials. Members from the FDA’s reviewing and auditing divisions mentioned that it is unusual for a sponsor to submit monitoring plans to the Agency, a comment that raised the question of whether monitoring plans should be submitted as part of protocols or as a general plan for a group of protocols (e.g., phase 3 studies). If so, it

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *ICH Harmonised Tripartite Guideline: Quality Risk Management*. Available at: http://www.ich.org/LOB/media/MEDIA1957.pdf. Updated November 9, 2005. Accessed November 11, 2009.

was suggested that a multi-stakeholder group (such as CTTI) collaborate in the creation of recommendations that address such questions as: what elements are most critical in a monitoring plan? In what areas of trial conduct and data collection is some flexibility permissible and in what areas of trial conduct should there always be maximal attention? To what extent does the nature of the trial and its end points (outcome vs. symptom improvement) affect the nature of monitoring? It was noted that ICH E-6 explicitly describes monitoring as "flexible," taking into account the nature of the study and critical observations, but that ICH E-6 gives no explicit guidance on translating this flexibility into practice. The more candor and explicitness employed in the drafting of these recommendations, the better, and whatever approaches are endorsed should be supported by evidence of their validity and reliability. There are, for example, formal studies comparing local and central monitoring approaches, and the value of the two approaches in particular settings at particular stages of the study (early vs. later) needs to be considered.

Participants agreed that, with a more refined understanding of the risks and advantages of various monitoring practices, sponsors and investigators will feel empowered to design and conduct their research using innovative monitoring techniques that add value to studies by maximizing the efficient use of resources while also ensuring patient safety and study quality. This transition, however, will almost certainly require a cultural shift among all stakeholders, who must commit to effecting real change and to reviewing the entire system of clinical research in an effort to streamline its interrelated processes (e.g., through use of centralized monitoring). It was articulated, however, that, whatever approach and requirements are endorsed, they will need to be broadly adopted (across the industry and across national and international regulatory bodies) if they are to be successful in improving the overall quality and efficiency of clinical trials.

As the meeting concluded, an attempt was made to summarize some of the day's major themes. First and foremost, it was apparent that it would be helpful if the FDA could provide more clarity about its expectations around monitoring practice. Continued input is needed, however, from the many stakeholders comprising the clinical research

enterprise. It is important, in designing protocols, to consider what elements of data collection are important and avoid collection of information that demands effort but is of little value. Monitoring plans should indicate candidly which elements are most critical and will be most closely monitored. Monitoring should also be considered a prime opportunity for site assessment and remedial training, as trial data are only as good as the sites that collect them. Whatever innovative monitoring methods are attempted, they should always encompass an element of oversight that will ensure human subjects protection and data reliability. Finally, monitoring should strive to balance the public's trust in clinical research against the opportunity costs resulting from an inefficient research system burdened by unnecessary procedures and expenses. A major shift in thinking is required to allow for innovation that will expand research horizons in the twenty-first century—we must delineate and accommodate varying perceptions of risk in the formulation of a rational plan for monitoring clinical research that will add value to clinical trials without sacrificing quality or efficiency.

Appendix. Monitoring objectives proposed by meeting attendees

Improve patient care
Ensure patient safety
Preserve data quality
Protocol compliance
Appropriate recruitment and retention
Assurance of informed consent
Quality improvement feedback loop
Evaluation of investigator quality and credibility
Ensuring investigator diversity (does the investigator reflect the patient population?)
Making sure that the study population reflects the target population
Strike appropriate balance between risk tolerance and risk management
Identification of errors early on to salvage data and amend protocol, if necessary
Improve trial conduct and adherence to the protocol
Supplemental training of staff and investigators
Establishing confidence in results, ethical standards, and regulatory compliance
Avoiding bias in estimates of treatment effect; reducing “noise” to increase power
Determining differences in sites, patients, etc. for data quality
Ensuring stakeholder trust in final product
Deciding whether to change protocol or stop study
Establishing a trail of accountability and transparency of data
Ensuring that data quality is sufficient to answer study question
Guaranteeing reproducibility of results in trials and practice
Oversight function (policing) to ensure that resources are not wasted
Evaluating site competency (selection and education of investigators)
Evaluating research practice at the site level; holding investigators accountable (and retraining as necessary)
Sharing responsibility and information across stakeholder groups (IRBs, sponsors, FDA, etc.)
Source document verification

Accurate reporting of adverse events

Outlining a chain of communication that details what is monitored

Relationship-building with site staff and retraining as staff turns over; getting a sense of the site (establishing its credibility)

Consistency, transparency, communication

Ensuring respect for patients' participation in research

Ensuring communication between sponsor, site, and patient

Ensuring that expectations of stakeholders are met

Inclusion of mechanisms to solve problems identified

Flexibility

Maximizing efficiency for minimal resource use

Identifying issues that prevent protocol adherence

Evaluating site, sponsor, and IRB

Establishing a baseline for data analysis