



## **Quality Objectives of Monitoring**

### **Workstream 2 Final Report**

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

Clinical Trials Transformation Initiative

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## Background

Currently, there are numerous monitoring approaches in use of varying intensity, focus, and methodology; many are very complex and time-consuming to implement, contributing substantially to clinical trial inefficiencies. It is not clear that these types of clinical trial monitoring activities add value in protecting trial participants and the quality of the data in all clinical settings. Recent research has documented that 25–30% of trial expenses can be attributed to site monitoring.<sup>1</sup> Although trials and the resulting data need to be of sufficient quality to support healthcare decision-making, monitoring methods that are expensive but inefficient and/or ineffective can waste valuable resources that could be applied to more productive activities.<sup>2,3</sup> By improving monitoring efficiency in clinical trials, existing human and financial resources could be made available to monitor many more trials and address many more questions about the risks and benefits of candidate diagnostics and therapies.

The current predominant model for monitoring clinical trials relies heavily on multiple visits to clinical trial sites, with a focus on source data verification and study documentation. Multiple site visits can be time-consuming and costly because they require monitoring staff time, study investigator and study coordinator time, and extensive travel. Use of site resources for monitoring purposes can also divert attention and resources from other important trial activities.

While a single predominant model for monitoring clinical trials does exist, there is broad diversity in the characteristics of clinical trials to which this model is applied. Factors that contribute to this diversity include:

- Broad range of intervention types evaluated
- Wide spectrum of disease states
- Diverse study populations
- Differing trial durations
- Varying complexity of trials (e.g., limited data collection vs. intensive data collection)
- Broad range of study designs
- Ethical, legal, and social expectations of jurisdictions in which trials are conducted
- Wide range in numbers of subjects per site
- Varying investigator and sponsor perspectives
- Stage of product development (i.e., amount of past experience and information)
- Nature of study end point

Given this diversity, a single model is not always going to be the most effective or efficient way to assess the aspects of trial conduct that are most relevant to major quality objectives (i.e., protection of human subjects and reliability of study data) for every clinical trial. Alternative methods of quality assurance, such as central monitoring, investigators' training and meetings,

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<sup>1</sup> Eisenstein EL, Lemons PW 2nd, Tardiff BE, Schulman KA, Jolly MK, Califf RM. Reducing the costs of phase III cardiovascular clinical trials. *American Heart Journal*. 2005;;149(3): 482–488.

<sup>2</sup> Baigent C, Harrell FE, Buyse M, Emberson JR, Altman DG. Ensuring trial validity by data quality assurance and diversification of monitoring methods. *Clinical Trials*. 2008; 5:49–55.

<sup>3</sup> Eisenstein EL, Collins R, Cracknell BS, Podesta O, Reid ED, Sandercock P, Shakhov Y, Terrin ML, Sellers MA, Califf RM, Granger CB, Diaz R. Sensible approaches for reducing clinical trial costs. *Clinical Trials*. 2008;;5:75–84.

data query communications, site accreditation, and extensive written guidance, appear to be used less frequently<sup>2</sup> but may be more effective for certain types of trials. Where appropriate, alternative methods may also make better use of monitor, clinical site, and financial resources.

For these reasons, the Clinical Trials Transformation Initiative (CTTI) launched its initial project, “Effective and Efficient Monitoring as a Component of Quality in the Conduct of Clinical Trials.” This project is intended to provide medical product researchers with information that will help them select the most appropriate monitoring methods for each trial, thereby improving quality and resource utilization. A planned product of the project is a paper intended to promote effective and efficient monitoring in the conduct of clinical trials both within the U.S. and internationally.

The project encompasses three workstreams: (1) review of current practices, (2) definition of key quality objectives, and (3) qualitative assessment of monitoring techniques. This paper is the product of Workstream 2 (WS-2), and its purpose is to identify the key quality objectives of monitoring. Because different stakeholders may have diverse views about what aspects of trial quality are important, representatives of many different organizations were invited to participate in this workstream in an effort to capture varying perspectives on appropriate quality objectives. From the findings, a single set of quality objectives was developed that should generally be met in all clinical trials.

WS-2 included participants from CTTI member organizations and other interested volunteers. The team was led by Rachel Behrman and Melissa Robb (Food and Drug Administration; FDA) and consisted of the following volunteers representing academia, government, patient advocates, and the regulated industry: Kathy Beaver (Medtronic), Mark Behm (AstraZeneca), Sandra Benton (FDA), Susan Donahue (PMG), Bunny Donohue (Duke University), Christine Drabick (FDA), Joe Griffin (FDA), An Liu (A and L Consulting, LLC), Debra Madden (Breast Cancer Patient Representative, FDA Oncologic Drug Advisory Committee and National Breast Cancer Coalition), Paula McKeever (FDA), and Julian Rimmer (ICON Clinical Research).

WS-2 used the following approach to collect evidence in accomplishing this goal.

- Identify concerns and potential quality objectives of monitoring through:
  - Review of the literature to identify citation of monitoring quality objectives
  - Review of FDA warning letters to identify issues that have arisen in past trials
  - Survey of over 300 organizations representing all stakeholders to rate identified monitoring objectives on a scale of importance
- Define a set of important quality objectives by:
  - Convening an expert panel to gain consensus on key quality objectives of monitoring for clinical trials and to define a set of common monitoring goals

To evaluate the effectiveness and efficiency of monitoring methods, it is critical to have a complete understanding of the important quality objectives of monitoring. WS-2 identified a range of important monitoring objectives that can be applied to all clinical trials in all settings for all investigational products and within all study designs and procedures.

## Potential Quality Objectives of Monitoring

### A. *Review of Literature*

#### *Overview*

The literature was reviewed to identify key measurable quality objectives described in relevant publications that could be used for future guidance. Identified quality objectives could be used to inform the discussion of what monitoring should achieve within a clinical trial.

#### *Methods*

Several search methods were used to identify relevant publications:

1. Journal articles were identified by members of CTTI's monitoring project.
2. A search was performed on PubMed, using the keywords "clinical trial monitoring" and "quality."
3. A literature search on monitoring methods was obtained from Workstream1 (WS-1), that utilized various keywords, including: "clinical trial monitoring" (methodologies, best practices, cost reduction, efficiencies), "site visit clinical trial monitoring," and "clinical monitoring methods."
4. Multiple web searches were performed using engines such as Google, High Beam, and clinical research organization web sites.

This initial search identified many articles related to clinical trial monitoring and methods. The search was narrowed to literature that included both monitoring and quality as the main topics of research.

#### *Results*

The initial literature search yielded many articles in which clinical monitoring was the main topic. The majority discussed either the monitoring process or data and safety monitoring board (DSMB)<sup>4</sup>-related issues, which were not within the scope of this project. Although the articles discussed the process of monitoring, they did not include a discussion on how any of the methods related to quality nor did they identify the monitoring method as a measurable quality objective. These articles were not included in the literature references. The references included in the review specifically discussed monitoring and identifiable quality objectives for clinical trial monitoring.

Twenty-one publications (see Attachment 1) were identified in which clinical monitoring was the main research interest AND the clinical monitoring quality objective was mentioned in at least one section of the article. The following quality objectives were identified within these literature sources:

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<sup>4</sup> Also referred to as data monitoring committees or DMCs.

1. Ensuring data quality and protection of human subjects (which includes proper execution of informed consent and subject eligibility) are the most common clinical monitoring objectives listed.
2. Ensuring training and qualifying clinical investigators and sites (these objectives are often mentioned together in articles).
3. Adhering to established procedures and defined protocol.
4. Ensuring scientific integrity; however, few articles defined the term “scientific integrity.” One article described it as minimizing missing data to protect statistical power.
5. Detecting fraud. The consensus on fraud detection is that fraud is rare, but its impact is large and long-term.
6. Ensuring compliance with FDA regulations and Good Clinical Practice (GCP).
7. Ensuring compliance with adverse event reporting.
8. Ensuring investigational drug/device accountability and storage.

Other objectives identified infrequently included: ensuring comparable conditions in clinical operation of each site, early detection of any trial management problems, and improving communication between sites and sponsors.

The table below shows in decreasing order the number of instances in which the identified articles referenced various quality objectives of clinical monitoring. In many cases, more than one objective was noted in an article, and the table represents the cumulative tally.

Table 1 – Literature Review Findings

<b>Category</b>	<b>Counts</b>
Data quality	13
Subject rights and safety	10
Ensuring training	8
Procedure adherence	7
Qualification of investigators	7
Qualification of sites	6
Scientific integrity	6
Fraud	6
FDA regulation	5
Adverse event reporting	4
GCP	4
Informed consent	2
Ethical integrity	2

Category	Counts
Sites are comparable in operation	2
Identify problem in trial management	1
Communication between site and sponsor	1
Drug/device accountability and storage	1
Compliance with IRB requirements	1

## B. *Review of Warning Letters*

### *Overview*

The FDA issues Warning Letters for violations of federal regulations that require implementation of corrective action. The Warning Letters are available to the public in redacted form, and the federal regulations violated are cited in each letter.

### *Methods*

A subgroup of WS-2 conducted a review of Warning Letters issued by the FDA that are available on its website at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm> to assess which violations were most frequently cited.

The subgroup reviewed Warning Letters issued by the **Center for Biologics Evaluation and Research (CBER)**, the **Center for Drug Evaluation and Research (CDER)**, and the **Center for Devices and Radiological Health (CDRH)** from December 1997 through April 2009 for findings related to the monitoring of clinical trials. The Warning Letters reviewed were issued to clinical investigators, sponsors, sponsor/clinical investigators, sponsor/monitors, and sponsor/monitor/contract research organizations.

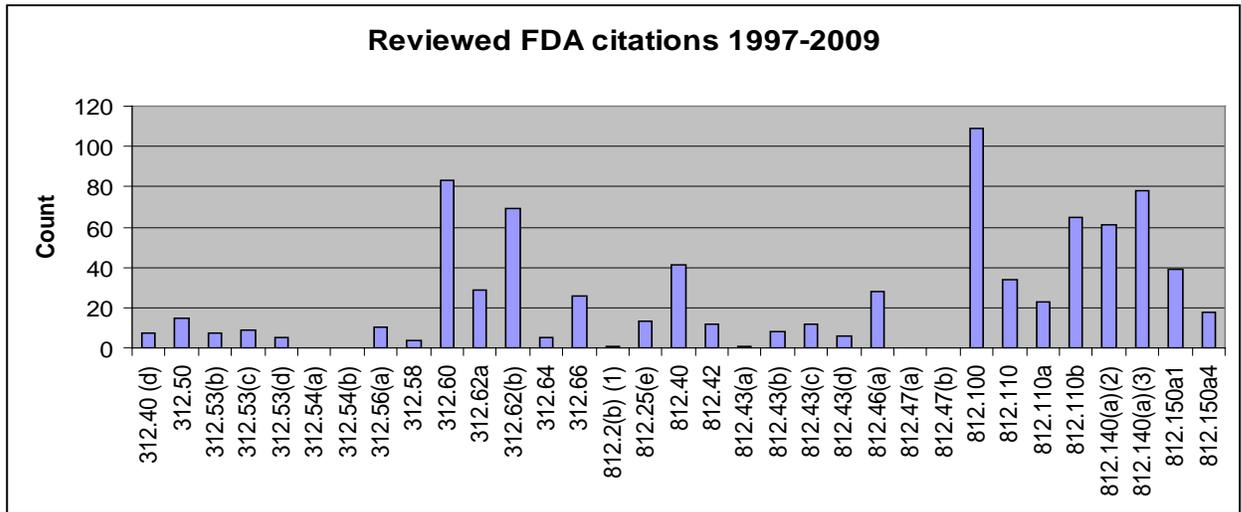
The letters were assessed for inclusion of citations from Title 21, Code of Federal Regulations (CFR), applicable to clinical trial monitoring.

Citations directly related to monitoring, and citations that could have been prevented by adequate monitoring are included in the tabulation. The Warning Letters reviewed often contained more than one monitoring-related violation.

Citations were tabulated for drug, biologic, and device studies. Applicable sections of the regulations were referenced from 21 CFR 312 for drug and biologic products and 21 CFR 812 for devices.

Figure 1 shows the citations that were tracked and the number of times each citation was noted during review of 271 Warning Letters. The WS-2 subgroup tracked the citations in a Microsoft Excel database.

Figure 1 – Reviewed FDA Citations<sup>5</sup>



*Results*

The most frequently cited violations identified during the Warning Letter review and the numbers of times they were cited are listed below:

- **812.100** General responsibilities of investigators (N= 109)
- **312.60** General responsibilities of investigators (N= 83)
- **812.140(a)(3)** Investigator records of each subject’s case history and exposure to the device (N= 78)
- **312.62(b)** Investigator recordkeeping and record retention: Case histories (N= 69)
- **812.110(b)** Specific responsibilities of investigators: Compliance (N= 65)
- **812.140(a)(2)** Investigator records of receipt, use, or disposition of a device (N= 61)

The tabulated citations from the FDA Warning Letters suggest that fulfillment of investigators’ general and specific responsibilities, including accurate, complete recordkeeping, are primary areas requiring improvement and should be a focus of monitoring.

**C. Survey to Rate Monitoring Objectives**

*Overview*

A survey was conducted to assess the relative importance of various quality objectives of monitoring in clinical trials. The underlying assumption when designing this survey

<sup>5</sup> See Attachment 2 for citation descriptions.

was that the main objectives of monitoring are to ensure the protection of human subjects and data quality.

### *Methods*

Respondents were asked to provide input based on their organizations' view of high-level quality objectives of monitoring. Specific potential objectives were identified, and respondents rated identified objectives on a Likert scale of "very important," "important," "moderately important," "of little importance," or "unimportant." The proposed objectives fell into one of three main categories:

- Human subjects protection (HSP)
  - Subjects adequately informed about the trial
  - Written consent obtained from subjects
  - Assurance of subject safety
  - Maintenance of confidentiality and privacy of human subjects
- Data quality
  - Few or no protocol violations
  - Identification and documentation of deviations from protocol or investigational plan
  - Selection of qualified clinical investigators (experience with intervention or condition)
  - Assurance that the clinical investigator and staff are appropriately trained on protocol or investigational plan
  - Few or no data errors on key efficacy data
  - Few or no data errors on safety data
  - Few or no data errors on non-key data
  - Identification of fraud or misconduct
  - Accurate, complete, and timely maintenance of study records
- Other
  - Assurance that required documentation is obtained from participating investigators (e.g., CV, financial disclosure, regulatory documentation)
  - Appropriate documentation of adverse events where there is a reasonable possibility that the event may have been caused by the medical product
  - Investigational product accountability

Additionally, those who responded were invited to list what they consider to be the most important objectives of monitoring clinical trials.

The workstream developed a comprehensive list of stakeholders within the clinical trial enterprise to participate in the survey. In addition, CTTI's Executive Board and Steering Committee both provided other relevant organizations and contacts for distribution. Upon completion, the list comprised over 300 organizations representing the regulated industry (pharmaceutical, biopharmaceutical, and medical device), contract research organizations, government agencies, academic institutions, non-profit organizations, cooperative groups and consortiums, investigative sites, investigational review boards, patient advocacy organizations, and others.

The survey was distributed beginning October 2, 2009, and the database was closed on November 22, 2009.

### *Results*

There were 107 responses, of which 81 addressed questions related to WS-2.<sup>6</sup> The distribution of responses by type of organization is represented in Table 2.

Table 2 – Survey Responder Profile

<b>Organization</b>	<b>Frequency</b>	<b>Percent</b>
Academic	14	17.28
Contract Research Organization (CRO)	8	9.88
Cooperative Group/Consortium	2	2.47
Government	12	14.81
Industry	30	37.04
Institutional Review Board	4	4.94
Investigational Site	4	4.94
Non-Profit	3	3.70
Other	3	3.70
Patient/Study Participant Advocate	1	1.23

The analysis plan for the survey involved descriptive statistics for each survey question. Histograms were created to represent the number of responses to each question grouped by questions on human subjects protection, data quality, and other topics.

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<sup>6</sup> A survey was also conducted for WS-1, which was distributed with the survey for WS-2. Therefore, some respondents only provided responses related to the questions from WS-1.

Figure 2 – Human Subjects Protection

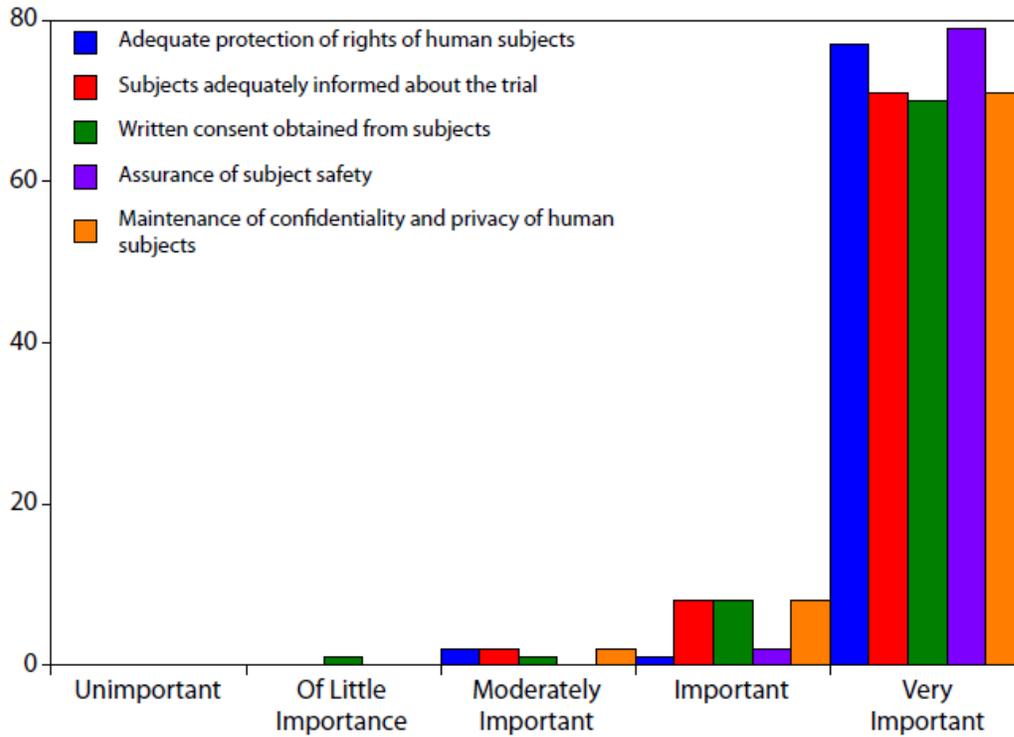


Figure 3 – Data Quality

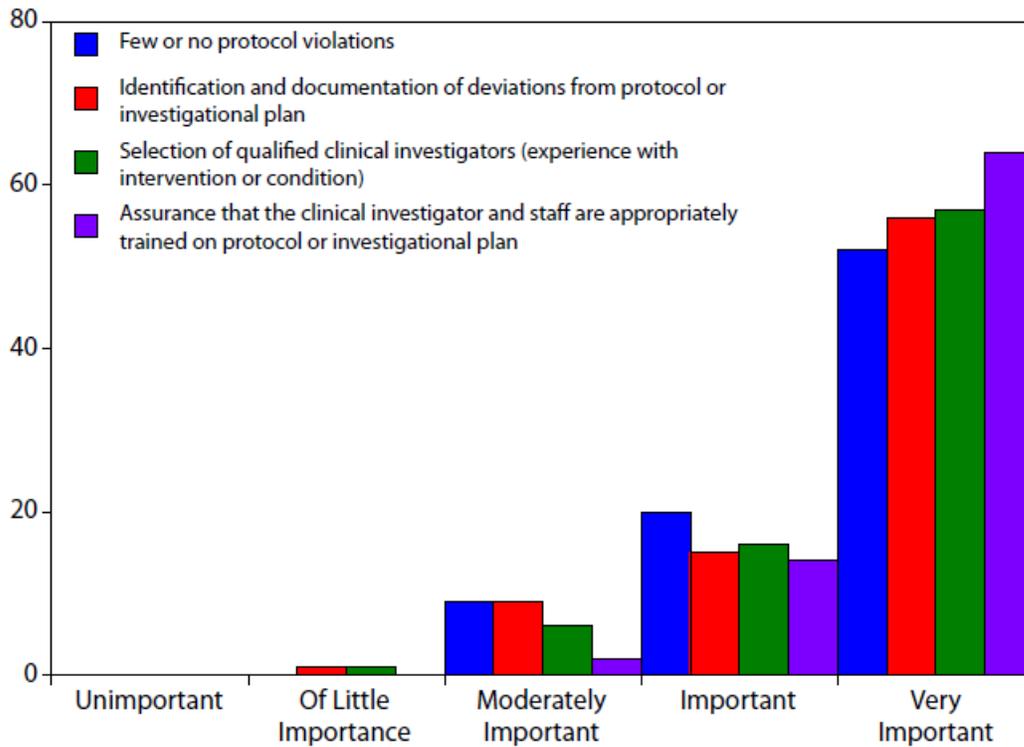


Figure 4 – Data Quality, Continued

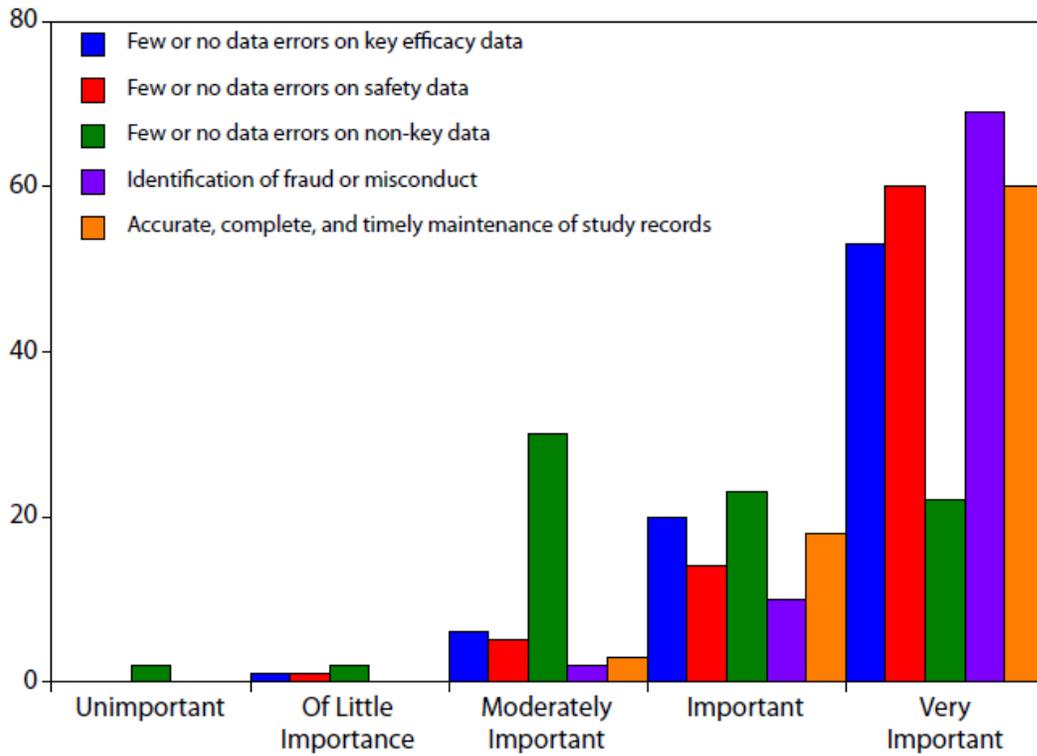
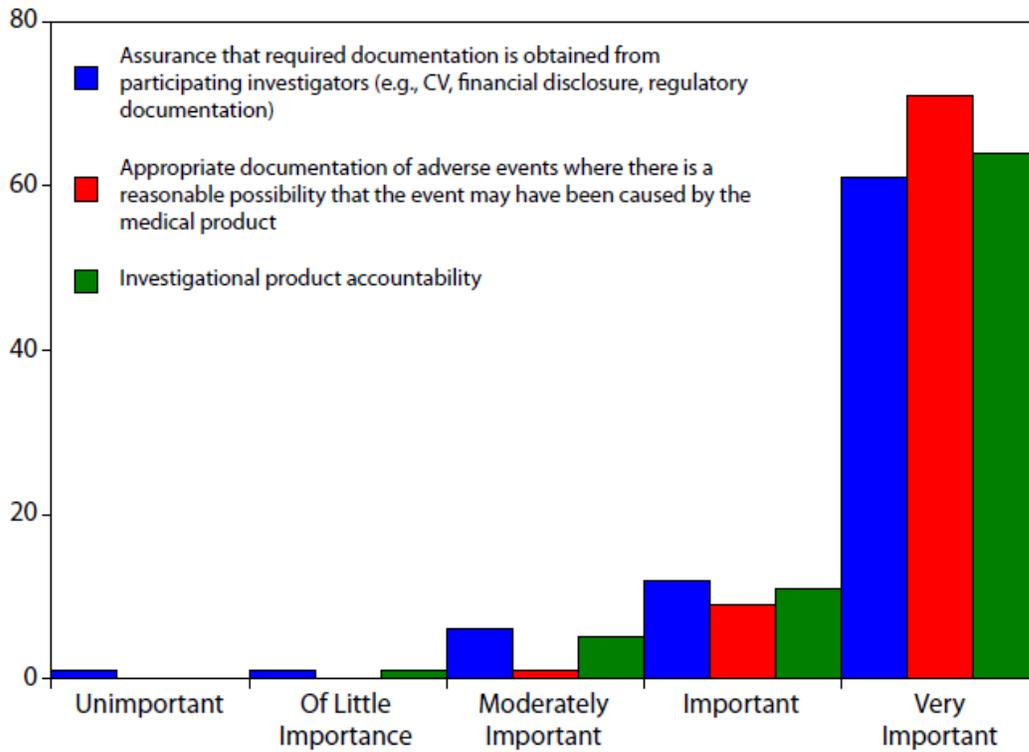


Figure 5 – Other Topics



A review of the free text responses generally reinforced findings from structured questions; one exception was an emphasis on training. The majority of comments emphasized aspects related to HSP and data quality.

## **Define a Set of Key Quality Objectives – Expert Meeting**

A meeting was convened on November 4, 2009, in Rockville, MD, to discuss the critical quality objectives of monitoring clinical trials. Meeting participants included representatives from government, industry, academia, and research organizations. An overview of the workstream research results to date (i.e., the review of literature, the review of warning letters, and the survey) was presented. With those results as a starting point, the meeting participants discussed their three main objectives for monitoring, acceptable errors in data sets, and risk-based monitoring (an approach to risk assessment for trial conduct and data collection that deploys available monitoring resources based on identified risks).

A summary of this meeting is included as Attachment 3.

## **Conclusions and Recommendations**

The findings of WS-2 largely confirm our original assumptions—that the major quality objectives for monitoring of clinical trials are related to ensuring the integrity of data generated in clinical trials, and thus the reliability of the study findings, and ensuring that risks to human subjects are minimized and that subjects are treated ethically.

The literature review identified a range of quality objectives that are, or are variations on, data integrity (data quality, scientific integrity, and fraud detection). The review also identified ensuring protection of human subjects as a key quality objective. Furthermore, a range of objectives were observed in the review that relate to both data integrity and patient safety, including adherence to the protocol and compliance with applicable regulations (which are primarily focused on data integrity and HSP). Compliance with adverse event reporting requirements was singled out as being of particular importance.

The survey of entities and individuals involved in the conduct of clinical trials enabled us to rank the quality objectives of monitoring. Objectives related to the safety and ethical treatment of human subjects ranked highest, followed by data integrity concerns, including fraud detection and ensuring accurate and complete data collection, which allows for data to be used in regulatory decision-making and to inform clinical practice. Again, compliance with adverse event reporting requirements was singled out and ranked higher than protocol and regulatory compliance. This would suggest that accurately characterizing the safety of an investigational agent is a high priority both for study subjects and future patients, and, therefore, should be a major focus of monitoring.

The review of FDA compliance activities related to clinical trials confirmed that investigator noncompliance with protocol and recordkeeping requirements—activities directly related to

data integrity and subject safety—are a major compliance problem, as these types of violations were the most frequently cited.

The expert meeting convened to process the Workstream 2 findings had representation similar to the survey participants—government, industry, academia, and commercial research organizations. The participants were in accord with the findings concerning the major quality objectives—patient safety, accuracy of key data, and compliance. The meeting also emphasized an additional quality objective: that monitoring leads to quality improvement during the conduct of the study through the implementation of study-wide corrective actions to address problems identified during monitoring.

Furthermore, the meeting identified issues and themes to consider in going forward with activities to improve the quality and resource utilization of clinical trial monitoring, including the following:

- Participants agreed that the quality of the protocol is likely an important determinant of the quality of monitoring. Participants believe that an emphasis on the quality and clarity of the study design, inclusion/exclusion criteria, data collection, and adverse event reporting requirements will facilitate better and more efficient monitoring.
- Participants agreed that there should also be emphasis on a priori, detailed, high quality monitoring plans that are appropriate to the study design and agreed upon by sponsors and regulators.
- Participants agreed that the quality of training of study staff has implications for the quality of monitoring. Participants believe that the better the training, the better the conduct of the study and the more consistent the behavior across study sites, which should make monitoring more effective and less resource intensive.
- Participants believe that adoption of risk-based alternatives to traditional periodic site-visit monitoring could be as effective as or more effective than traditional monitoring but will require a major cultural shift within the clinical research enterprise. As such, it is important that we refine our understanding of the risks and advantages of alternative monitoring methods. Participants believe that evidence to support use of alternative monitoring methods is vital to overcoming cultural barriers and facilitating wide-scale implementation.
- Participants agreed that there may be an acceptable level of error for trials of certain design or for certain data types, and the intensity of monitoring could vary depending on the design or the data type. In other words, following the principle of “fitness for use,” if an error does not affect the decision supported by the data, then it is not of consequence. For example, the outcome assessment may be dependent on a small number of findings on the primary end point so that end point data may require intensive monitoring, but covariate data describing patient subsets are typically less important to the outcome

assessment and, therefore, a lower level of certainty about accuracy may be acceptable for these types of data.

- Participants agreed that regulators should provide more specific guidance related to expectations for clinical trial monitoring.

There was also broad agreement that there should be ongoing involvement and input from all affected stakeholders in refining the clinical trials monitoring paradigm.

## Attachment 1 – References

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## Attachment 2 – Citation Descriptions

Citation	Brief Description
312.40 (d)	Investigator may not administer study drug until IND in effect
312.50	General responsibilities of sponsors
312.53(b)	Sponsor control of drug
312.53(c)	Obtaining information from the investigator
312.53(d)	Sponsor selecting monitors
312.54(a)	Emergency research exception from informed consent
312.54(b)	Emergency research IRB cannot approve
312.56(a)	Sponsor monitor ongoing investigation
312.58	Inspection of sponsor records by FDA
312.60	General responsibilities of investigators
312.62a	Investigator recordkeeping: disposition of drug
312.62(b)	Investigator recordkeeping: case histories
312.64	Investigator reports
312.66	Assurance of IRB review
812.2(b) (1) (iv)	Complies with 812.46 with respect to monitoring
812.25(e)	Sponsor's written procedures for monitoring
812.40	General responsibilities of sponsors
812.42	FDA and IRB approval
812.43(a)	Sponsor: selecting investigators
812.43(b)	Sponsor: control of device
812.43(c)	Sponsor: obtaining agreements
812.43(d)	Sponsor: selecting monitors
812.46(a)	Sponsor: securing compliance
812.47(a)	Emergency research exception from informed consent
812.47(b)	Emergency research IRB cannot approve
812.100	General responsibilities of investigators
812.110	Specific responsibilities of investigators
812.110a	Investigator: awaiting approval
812.110b	Investigator: compliance
812.140(a)(2)	Investigator records of receipt, use, or disposition of device
812.140(a)(3)	Investigator records: case history and exposure to device
812.150a1	Investigator reports of unanticipated adverse device effects
812.150a4	Investigator reports of deviations from the investigational plan

## **Attachment 3 – Meeting Summary: November 4, 2009 Expert Panel, Effective and Efficient Monitoring as a Component of Quality in the Conduct of Clinical Trials**

### **Effective and Efficient Monitoring as a Component of Quality in the Conduct of Clinical Trials**

*November 4, 2009, Rockville, MD*

*Summary Document—Workstream 2*

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.”<sup>7</sup> 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

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<sup>7</sup> 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.

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 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

**Effective and Efficient Monitoring as a Component of Quality  
in the Conduct of Clinical Trials  
Quality Objectives Panel Discussion  
November 4, 2009  
Participant List**

<b><u>Name</u></b>	<b><u>Organization</u></b>
John Alexander	Duke Clinical Research Institute
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Mark Behm	AstraZeneca
Rachel Behrman	Food and Drug Administration
Sandy Benton	Food and Drug Administration
Courtney Bryant	Quintiles
Malcolm Burgess	ICON
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Chrissy Cochran	Food and Drug Administration – CDRH
Rosemary Cook	Pharmaceutical Research and Manufacturers of America
Susan Donahue	Piedmont Medical Group
Bunny Donohue	Duke Clinical Research Institute
Susan Edwards	Novartis Clinical Operations, Inc.
James Ferguson	The Medicines Company
Lawrence Friedman	Independent Consultant
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Tara Hegarty	AstraZeneca
Heidi Hinrichs	St Jude Medical
Gregory Hockel	PharmaNet Development Group, Inc.
Pat Holobaugh	Food and Drug Administration – CBER
Grant Huang	Department of Veterans Affairs
Cheri Janning	Duke Translational Medicine Institute

Workstream 2 – Monitoring Objectives

Michael Jones	Eli Lilly
Jeffrey Kelman	Centers for Medicare & Medicaid Services
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Judith Kramer	Duke Translational Medicine Institute
Darlene H Krueger	Department of Veterans Affairs
Christine Laine	Annals of Internal Medicine
Martin Landray	University of Oxford
Joanne Less	Food and Drug Administration
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Michael Marcarelli	Food and Drug Administration – CDRH
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Janet Norden	Food and Drug Administration - CDER
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Janice Pogue	
James H. Powell	National Medical Association
Ivor Pritchard	Office for Human Research Protections
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Julian Rimmer	ICON Clinical Research
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Workstream 2 – Monitoring Objectives

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Lorraine Waring	Pfizer