

## **A CTTI Survey of Current Monitoring Practices**

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### **Clinical Trials Transformation Initiative**

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### **ABSTRACT**

The Clinical Trials Transformation Initiative (CTTI; [www.trialstransformation.org](http://www.trialstransformation.org)) is a public–private partnership between the U.S. Food and Drug Administration (FDA), academia, clinical research organizations (CROs), biopharmaceutical companies, patient and consumer representatives, professional societies, government researchers, and other government agencies whose mission is to identify practices that through broad adoption will increase the quality and efficiency of clinical trials. The goal of this CTTI-sponsored project was to describe current clinical monitoring methods for a range of clinical trial types, and to explore the rationale for the use of those methods. An electronic survey concerning current monitoring practices was developed, and over 300 organizations and individuals in academia, government, industry, and clinical research were invited to provide their input. The survey collected information on institutional demographics, overall study oversight methods, the use of risk-based monitoring and factors that influence monitoring risk assessments, and details on quality assurance and monitoring practices. As of November 30, 2009, approximately 74 organizations had completed the survey. Respondents were from academic institutions (27%), CROs (16%), government institutions (8%), and industry (48%). Data from the survey are still being analyzed, and results and conclusions are preliminary at this time. Nonetheless, data to date are consistent with the hypotheses that: 1) a wide variety of monitoring practices are currently being employed; 2) the choice of monitoring approach is correlated with the type of organization sponsoring the clinical trial; and 3) the rationale for using a specific monitoring approach does not appear to be based on empirical evidence.

### **INTRODUCTION**

A number of quality assurance procedures are typically implemented to ensure that clinical trials are carried out as designed, that Good Clinical Practices and regulations governing the conduct of trials are followed, and that data used to compare treatments are accurate. This is important because well-implemented clinical trials provide strong evidence on the risks and benefits of different treatment interventions.

Onsite monitoring for the purposes of training, assessing adherence to study procedures, and auditing of data is a frequently employed quality assurance procedure. Study reports, however, usually do not describe in detail onsite monitoring methods or other quality assurance procedures employed. There also is little empirical evidence to determine which, if any, onsite monitoring practices lead to improved patient safety and data quality. Thus there is a substantial lack of information to guide the planning of trials that include this commonly used and expensive quality assurance procedure.

Because of growing concern about the effectiveness and efficiency of monitoring practices, the Clinical Trials Transformation Initiative (CTTI)—a public–private partnership developed under the FDA’s Critical Path Initiative<sup>1</sup>—has made monitoring the focus of its first project. CTTI was formed in 2008 by the FDA and Duke University to identify practices that through broad adoption will increase the quality and efficiency of clinical trials. As founding partners, the FDA and Duke have sought to engage diverse stakeholders in the clinical trials industry to participate in the initiative. Currently, more than 50 organizations participate in CTTI, including government (FDA, Centers for Medicare & Medicaid Services, Office of Human Research Protections, National Institutes of Health, and other national and international government bodies), industry (pharmaceutical, biotech, device, and clinical research organizations), patient and consumer organizations, professional societies, investigator groups, academia, and other interested parties.

A key component of the CTTI monitoring project, “Effective and Efficient Monitoring as a Component of Quality in Clinical Trials,” was a survey of different organizations involved in the clinical trial enterprise to determine the types of monitoring practices that are currently performed in clinical trials. This poster summarizes the preliminary results of that survey.

## **Survey Design & Target Audience**

An electronic survey of over 55 questions, with sub-questions, multiple choice and open-ended answers, was developed to collect feedback from a broad group of stakeholders, both public and private, regarding the methods of monitoring being used across the full spectrum of clinical trial settings for drugs, devices, and biologics. The scope of the survey questions was determined by CTTI project volunteers from the pharmaceutical/biotech industry, academia, CROs, and the FDA in consultation with CTTI Steering Committee members. The survey included questions regarding organization demographics, the types of trials most frequently conducted, trial oversight and governance committees typically used, risk assessment methods for developing monitoring plans,

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<sup>1</sup> The Critical Path Initiative (CPI) is the FDA’s national strategy for driving innovation in FDA-regulated product development. The goal is to modernize the sciences through which FDA-regulated products are developed, evaluated, manufactured, and used. Collaboration is the cornerstone of the CPI. For more go to <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm>

monitoring plan development, remote monitoring methods, and the frequency and content of onsite monitoring visits. A list of potential respondent organizations was assembled by CTTI project volunteers with additional input from members of the CTTI Steering Committee. The target audience for the survey included all organizations performing clinical trials: pharmaceutical, biotech, and device companies; CROs; academia; NIH and other government-sponsored clinical organizations; and cooperative investigator groups.

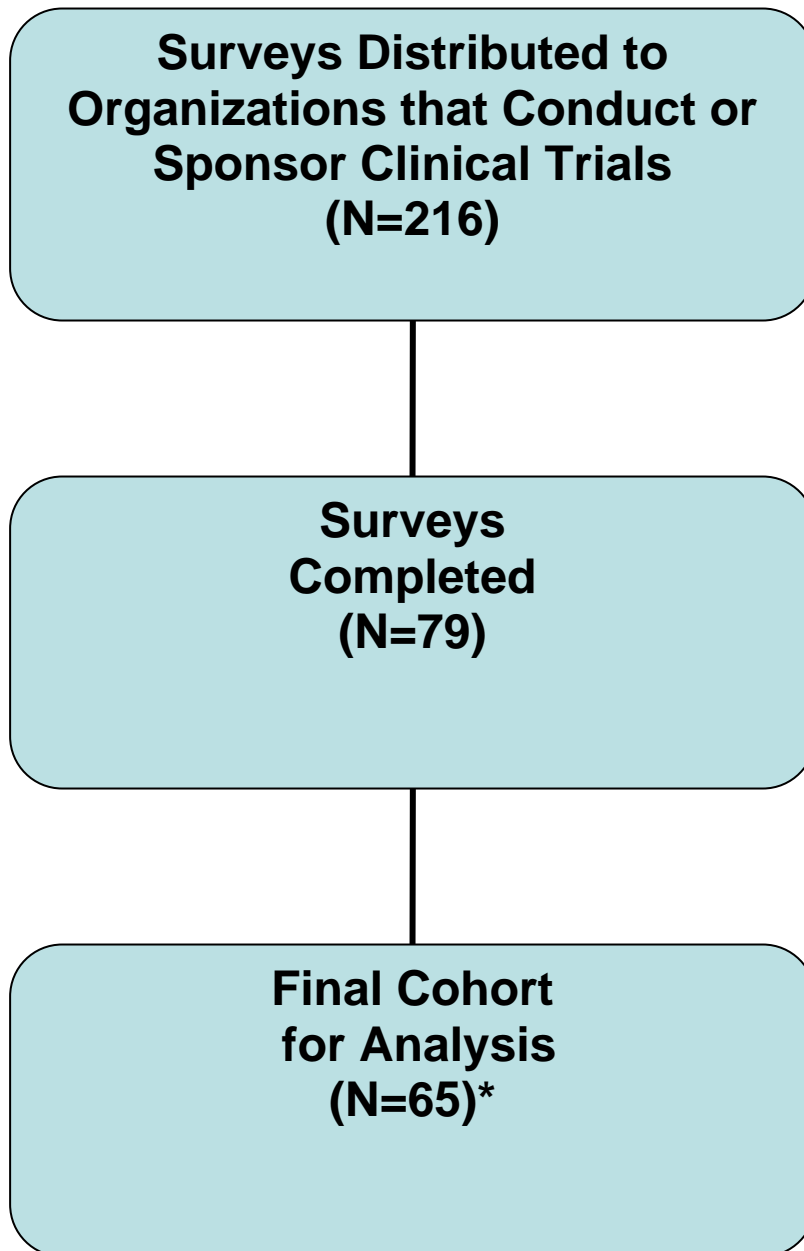
### **Data Collection**

Data collection took place via an online survey that was distributed in October 2009. Final responses to the survey were received in December 2009. At the time that the questionnaire was sent, each organization was provided with a username and password and was asked to change the password at the initial login in order to ensure security and confidentiality. Respondents were requested to be of a sufficient level in the responding organization to be adequately informed regarding the scope of monitoring practices being used in their organization and the rationale for their selection. No individual identifying information was collected on respondents themselves. Feedback on organizational practices was aggregated for the analysis.

### **Data Analysis**

For this report, the survey responses are summarized by organization type. Organizations were grouped as follows: 1) academic coordinating centers/cooperative groups/government; 2) CROs; 3) industry (pharmaceutical and biotech); and 4) industry (device). Some organizations surveyed did not conduct or sponsor clinical trials (e.g., institutional review boards); these organizations were excluded from this report.

## RESULTS



Of the 79 respondents, 12 were excluded from the analysis because they checked “No” to the survey question “Does your organization perform clinical trials?” The exclusions were academic (2); CRO (1); and government (9). Two additional respondents left the question on performing clinical trials blank and were also excluded: CRO (1) and industry (1). Thus, the final cohort for the analysis of monitoring practices included 65 respondents.

**Table 1**

**Survey Response Rate for 65 Organizations That Conduct or Sponsor Trials**

Type of Organization	Number of Surveys Distributed N	Number of Respondents	
		N	% <sup>+</sup>
Academic/Cooperative Group/Government	98	18	18
CRO	19	11	58
Industry	99	36	36
<b>Total</b>	216	65	

<sup>+</sup> Percent of organizations sent the survey that provided a response.

**Table 2**

**Survey Respondent Characteristics**

Characteristic <sup>+</sup>	Academic/Govt/ Coop. Group N (%)	CRO N (%)	Industry – Pharmaceutical N (%)	Industry – Device N (%)
Total	18 (100)	11 (100)	25 (100)	11 (100)
Type of Trial Most Commonly Conducted				
Phase I or II	2 (11)	3 (27)	5 (20)	1 (9)
Phase III	5 (28)	8 (73)	16 (64)	6 (55)
Phase IV or Post- Marketing or Non-IND/IDE Studies	9 (50)	0 (0)	0 (0)	3 (27)
Other	2 (11) <sup>++</sup>	0 (0)	4 (16) <sup>+++</sup>	1 (9) <sup>+++</sup>
No. of Sites Most Common in Trials				
<50	7 (39)	4 (36)	8 (32)	10 (91)

≥50	11 (61)	7 (64)	17 (68)	1 (9)
No. of Subjects Most Common in Trials <sup>++++</sup>				
< 1500	9 (50)	9 (82)	17 (68)	10 (91)
≥1500	9 (50)	2 (18)	8 (32)	1 (9)
Conduct International Trials	16 (89)	9 (81)	25 (100)	9 (82)
Have QA Department	14 (78)	7 (64)	23 (92)	6 (55)

<sup>+</sup> Information collected in the 'Background' section of the survey.

<sup>++</sup> These two respondents stated: "Not sure which is most common" and "Phase I, II, and III."

<sup>+++</sup> These five respondents (4 pharmaceutical and 1 device) stated: 1) "All phases"; 2) "Ex-US"; 3) "All of the above"; 4) "510 (k)"; and 5) "As a large pharma, we conduct clinical trials in all phases 1-4."

<sup>++++</sup> Five respondents indicated multiple answers for the question concerning number of subjects most commonly enrolled into their organization's trials: "What size trials does your organization usually conduct?" For these respondents, the category of the maximum number of subjects entered was used (1500-4999 for 3 respondents, 500-1499 for (1), and 100-499 for (1)).

**Table 3**

**Use of Centralized and Onsite Monitoring Across Organization Types <sup>+</sup>**

	<b>Academic/Govt/ Coop. Group N/Total (%)</b>	<b>CRO N/Total (%)</b>	<b>Industry – Pharmaceutical N/Total (%)</b>	<b>Industry – Device N/Total (%)</b>
Use centrally available data to evaluate site performance (% "Yes")	14/16 (88)	6/9 (67)	19/23 (83)	9/10 (90)
Use a centralized monitoring process to guide, target, or supplement site visits (% "Always")	4/15 (27)	2/6 (33)	5/22 (23)	3/9 (33)

Use a centralized monitoring process to replace onsite visits (% “Always” or “Frequently”) <sup>++</sup>	3/15 (20)	2/6 (33)	1/21 (5)	0/9 (0)
Perform onsite monitoring visits (% “Always”)	5/16 (31)	8/9 (89)	21/25 (84)	8/10 (80)
Conduct an assessment of risk prior to developing monitoring plan (% “Yes” or “Sometimes”)	13/15 (87)	7/10 (70)	17/24 (71)	9/10 (90)
Typically perform site visits more often than once per year (%)	6/13 (46)	8/9 (89)	18/22 (82)	5/8 (63)

+ Numbers cited are those with indicated response, total, and (percent).

<sup>++</sup> Only one respondent checked “Always.”

**Table 4**

**Factors<sup>+</sup> Likely To Trigger a Site Monitoring Visit:  
Four Factors Consistently Considered Across Organization Types**

<b>Factor</b>	<b>N (%)</b>	<b>Range across Organizations (%)</b>
Number of protocol deviations	44 (92)	86–100
Suspected fraud	43 (90)	80–100
Rate of enrollment	40 (83)	60–89
Missing CRFs	38 (79)	64–89

+ From total of 13 factors assessed.

**Table 5**

**Factors<sup>+</sup> Likely To Trigger a Site Monitoring Visit:  
Two Factors Inconsistently Considered Across Organization Types**

<b>Factor</b>	<b>Academic/Govt/ Coop. Group N/Total (%)</b>	<b>CRO N/Total (%)</b>	<b>Industry – Pharmaceutical N/Total (%)</b>	<b>Industry – Device N/Total (%)</b>
Incidence of adverse events	7/14 (50)	4/5 (80)	19/20 (95)	8/9 (89)
Lack of experience with site	4/14 (29)	2/5 (40)	19/20 (95)	8/9 (89)

+ From a total of 13 factors assessed.

**Table 6**

**Factors that Determine Frequency of Onsite Monitoring Visits Across Organization Types**

<b>Factor+</b>	<b>Academic/Govt/ Coop. Group N/Total (%)</b>	<b>CRO N/Total (%)</b>	<b>Industry – Pharmaceutical N/Total (%)</b>	<b>Industry – Device N/Total (%)</b>
Study design	8/14 (57)	6/9 (67)	18/22 (82)	8/9 (89)
Critical study requirement/procedure	7/14 (50)	5/9 (56)	17/22 (77)	7/9 (78)
Monitoring plan in protocol	6/14 (43)	5/9 (56)	15/22 (68)	6/9 (67)
SOPs	5/14 (36)	6/9 (67)	15/22 (68)	5/9 (56)
Usual practice	8/14 (57)	4/9 (44)	12/22 (55)	5/9 (56)
Pre-defined analysis of risks	7/14 (50)	3/9 (33)	10/22 (46)	6/9 (67)
Study population	4/14 (29)	1/9 (11)	8/22 (36)	2/9 (22)

Budget 4/14 (29) 4/9 (44) 3/22 (14) 3/9 (33)

+ Factors are ordered by overall frequency indicated across all organizations.

Most common factors within organization type.

Least common factors within organization type.

**Table 7**

**Verifications Performed During Onsite Monitoring Visits Across Organization Types<sup>+</sup>**

<b>Assessments Made<sup>++</sup></b>	<b>Academic/Govt/ Coop. Group N/Total (%)</b>	<b>CRO N/Total (%)</b>	<b>Industry - Pharmaceutical N/Total (%)</b>	<b>Industry - Device N/Total (%)</b>
Staff's understanding of study procedures (% "Always")	9/15 (60)	6/9 (67)	14/23 (61)	7/9 (78)
Ability of staff to explain study to participants (% "Always")	6/15 (40)	4/9 (44)	10/23 (44)	2/9 (22)
Subjects understanding of trial (% "Always")	2/15 (13)	1/9 (11)	6/23 (26)	2/8 (25)
Adequacy and timeliness of additional information provided to participants (% "Always")	3/15 (20)	3/9 (33)	9/23 (39)	3/9 (33)
Informed consent updates/modifications (% "Always")	10/13 (77)	9/9 (100)	20/22 (91)	9/9 (100)
Verification of CRF data versus source documents (% "Always")	7/14 (50)	7/9 (78)	18/22 (82)	8/9 (89)
Regulatory documents and communications	5/13 (39)	6/9 (67)	19/22 (86)	7/9 (78)

(% “Always”)

Security of study data and documentation 6/14 (43) 6/9 (67) 16/22 (73) 3/9 (33)  
(% “Always”)

+ Numbers cited are those with indicated response, total and (percent)

\*\*Other verification elements were assessed in the survey but are not reported here.

**Table 8**

**Specific Items Verified 100% of the Time during Onsite Monitoring Visits Across Organization Types**

<b>Item</b>	<b>Academic/Govt/ Coop. Group N/Total (%)</b>	<b>CRO N/Total (%)</b>	<b>Industry - Pharmaceutical N/Total (%)</b>	<b>Industry - Device N/Total (%)</b>
Consent	13/13 (100)	9/9 (100)	20/22 (91)	7/8 (88)
Eligibility Criteria	6/13 (46)	7/9 (78)	19/22 (86)	8/8 (100)
Primary endpoint reports	8/13 (62)	8/9 (89)	18/22 (82)	6/7 (86)
Secondary endpoint reports	2/13 (15)	5/9 (56)	10/22 (46)	3/7 (43)
Serious adverse event reports	9/12 (75)	8/9 (89)	19/21 (91)	7/7 (100)
Non-serious adverse event reports	3/13 (23)	5/9 (56)	14/22 (64)	2/7 (29)

**SUMMARY OF RESULTS**

- Across all responding organization types, the majority use centrally available data to evaluate site performance, yet 1/3 or fewer of the responding organizations “Always” use that process to guide, target, or supplement site visits.
- Responding Academic/Government/Cooperative Group organizations and CROs are more likely than responding Industry-Pharmaceutical or

Industry-Device organizations to use a centralized monitoring process to replace onsite monitoring visits.

- More than 80% of responding CROs and both Industry types “Always” perform onsite monitoring visits, while less than 1/3 of responding Academic/Government/ Cooperative Group organizations “Always” do so.
- A strong majority (>80%) of responding CROs and Industry-Pharmaceutical organizations typically perform site visits more often than once per year, while a lower percentage of responding Academic/Government/Cooperative Group and Industry-Device organizations do so.
- Across all organization types, most respondents at least “Sometimes” conduct an assessment of risk prior to developing a monitoring plan for each protocol.
- Consistently across organization types, the most likely factors reported to trigger a site monitoring visit are: number of protocol deviations, suspected fraud, rate of enrollment, and missing CRFs.
- “Incidence of adverse events” is less likely to trigger a site monitoring visit in responding Academic/Government/Cooperative Groups than all other organization types.
- “Lack of experience with site” is considerably more likely to trigger a site monitoring visit in both Industry types as compared to responding CROs and Academic/Government/Cooperative Groups.
- Across all organization types, “study design” is reportedly the factor that most commonly determines the frequency of onsite monitoring visits.
- For both Pharmaceutical and Device industry respondents, “critical study requirement/procedure” is the second highest rated factor for determining the frequency of onsite monitoring visits, while for responding CROs that factor is “SOPs”.
- During onsite monitoring visits--across all organization types--the majority of respondents “Always” assess site staff’s understanding of study procedures while to a far lesser degree respondents reported “Always” assessing the subjects’ understanding, ability of staff to explain study to participants, subjects’ understanding of trial, and adequacy/timelines of additional information provided to participants.

- With the exception of responding Academic Center/Government/Cooperative Group organizations, a strong majority (>77%) reportedly “Always” verify CRF data vs. source data at some level.
- Academic Center/Government/Cooperative Group organizations are reportedly less likely to conduct 100% source data verification for all items except Patient Consent.
- All organization types reported higher rates of 100% source data verification for consent, eligibility criteria, primary endpoints, and serious adverse events as compared for secondary endpoints and non-serious adverse events.

## **LIMITATIONS**

The overall response rate to the survey was only 30%; less than 20% for academic coordinating centers/government/cooperative groups. As a consequence, sample size is small for all 4 organization groups and, therefore, responses may represent a biased sample and may not be fully representative of these organization types. The majority of respondents conduct many types of trials but responses primarily pertain to Phase III/IV and post-marketing studies. Thus, these results may not generalize to Phase I/II studies. In addition, for the purpose of data analysis, we combined academic coordinating centers (10), cooperative groups (2) and government sponsors (6); there may be differences among these groups that could not be reliably demonstrated in this study.

## **CONCLUSIONS**

This is the first extensive survey to assess monitoring practices utilized across clinical trial settings and by various organization types. Onsite monitoring is routinely performed by industry and CROs but less frequently and less extensively by academic coordinating center/cooperative group/government organizations. The scope of onsite monitoring visits varies by organization type with some procedures (e.g., randomization, product blinding, and compliance with study intervention), source documents (e.g., adverse event reports and eligibility criteria) and regulatory documents reviewed more often by CROs and industry sponsors than by academic/cooperative group/government organizations. While over 50% of respondents indicated that they had quality indicators to assess the quality of monitoring, it is clear that more research is needed to assess the potential impact of the variations in monitoring practices we observed.