

Monitoring the quality of conduct of clinical trials: a survey of current practices

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Background There is a little empirical evidence to determine which, if any, monitoring practices best achieve the goals of trial monitoring set forth in ICH E6 under the variable circumstances of different clinical trial settings.

Purpose The purpose of this project was to describe current methods of monitoring clinical trials and to explore the rationale for the use of those methods.

Methods An electronic survey of known monitoring practices was developed and sent to over 200 organizations involved in conducting clinical research. The survey collected information on institutional demographics, methods of overall study oversight, use of risk-based monitoring and factors that influence assessments of risk, and details on quality assurance and monitoring practices.

Results Seventy-nine organizations completed the survey; our analysis included the 65 organizations that indicated they perform clinical trials. Data from the survey indicate that a wide variety of monitoring practices are currently being employed. Eighty-three percent of respondents use centrally available data to evaluate site performance, but only 12% of respondents always or frequently used centralized monitoring to replace on-site visits. Eighty-seven percent of respondents indicated that they always performed on-site visits. This varied by type of organization, with 31% of academic coordinating centers/cooperative groups/government organizations always performing on-site monitoring visits versus 84% of other organizations. The rationale for using a specific monitoring approach does not appear to be based on empirical evidence. Fifty-four percent of respondents stated that 'usual practice' determined the frequency with which they conducted on-site monitoring visits.

Limitations The overall response rate to our survey was only 30%; thus, we may not have captured the full variance of current monitoring practices, and our responding sample may not be representative.

Conclusion These findings underscore the necessity of research to provide an evidence base for monitoring practice. *Clinical Trials* 2011; 8: 342–349. <http://ctj.sagepub.com>

Introduction

A variety of quality assurance (QA) procedures are typically implemented to ensure that clinical trials are carried out as designed, that good clinical

practices (GCP) and regulations governing the conduct of trials are followed, and that data used to assess treatment effects are accurate and complete. This is important because well-executed clinical trials provide strong protections for

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participating patients and strong evidence regarding the risks and benefits of different treatment interventions.

On-site clinical trial monitoring is a frequently employed QA procedure. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for GCP E6 provides guidance on the monitoring of clinical trials [1]. Monitoring is defined as 'the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).' ICH E6 further states that 'the purposes of trial monitoring are to verify that: the rights and well-being of human subjects are protected; the reported trial data are accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).' ICH E6 provides latitude in the extent and nature of monitoring, and describes a series of monitoring activities that can be carried out 'when relevant and necessary to the trial and the trial site.'

Published reports of clinical trial results generally do not describe in detail the monitoring methods or other QA procedures employed. Furthermore, there is little empirical evidence to determine which, if any, monitoring practices best achieve the goals of trial monitoring stated in ICH E6 under the variable circumstances of different clinical trial settings. Thus, there is a substantial lack of information to guide the choice of monitoring methods to be used in clinical trials and a lack of information on the range of methods that have been found to be consistent with ICH E6 and that will generate data that are acceptable to various regulatory agencies. This is an important topic, given the contention by some in the clinical research field that cumbersome, monitoring practices contribute to more work and higher costs for clinical studies [2]. Some have suggested that central monitoring is a practical and sensible means of achieving QA [3,4]. Others have suggested that reducing the number of visits and reviewing only a sample of records would allow a much less expensive QA plan but may increase the number of undetected problems [5]. Some data have suggested that more robust monitoring may be needed [6].

Because of growing concern about the effectiveness of monitoring practices (i.e., the extent to which they result in improved patient safety and data quality) and their efficiency (i.e., the cost of achieving monitoring objectives), the Clinical Trials Transformation Initiative (CTTI) has made monitoring the focus of its first project. CTTI is a

public-private partnership between the US Food and Drug Administration (FDA), academia, clinical research organizations (CROs), biopharmaceutical companies, patient and consumer representatives, professional societies, government researchers, and other government agencies. CTTI's mission is to identify practices that through broad adoption will increase the quality and efficiency of clinical trials. The project titled 'Effective and Efficient Monitoring as a Component of Quality in the Conduct of Clinical Trials' comprises several phases, one of which involved surveying organizations that conduct clinical research regarding their monitoring practices. Given the lack of empirical evidence, we carried out a survey to describe the trial methods in use today by various sponsors of clinical trials.

Materials and methods

An electronic survey of over 55 questions, including multiple-choice and open-ended queries, was developed to collect feedback from a broad group of public and private sponsors of clinical research regarding the methods of monitoring being used across the full spectrum of clinical trial settings for drugs, devices, and biologics (a copy of the survey can be found at <https://www.trialstransformation.org/>). 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 organizational demographics, the types of trials most frequently conducted, trial oversight and governance committees typically used, risk assessment methods for developing monitoring plans, monitoring plan development, remote monitoring methods, and the frequency and content of on-site 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 US and international organizations performing clinical trials: pharmaceutical, biotech, and device companies; CROs; academia; the National Institutes of Health (NIH) and other government-operated research organizations; and cooperative investigator groups.

Data collection took place via an online survey, which was distributed in October 2009. Final responses to the survey were received in December 2009. At the time the questionnaire was sent, each organization was provided with a username and password and was asked to change the password at the initial login 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 selection of the monitoring approach. No individual identifying information was collected from respondents themselves. Feedback on organizational practices was aggregated for the analysis.

At the beginning of the survey, respondents were asked if their organization performed clinical trials. Those who did not were excluded from this report. Respondents were asked to identify the most common type of trial that their organization conducted – phase 1, 2, 3, and 4, noninvestigational new drug, other. The answers to all subsequent questions on the survey were to be completed with the type of trial identified in this question as the point of reference.

Survey responses are summarized by organization, which were grouped as: academic coordinating centers/cooperative groups/government; CROs; industry (pharmaceutical and biotech); and industry (device). *p*-Values corresponding to chi-square statistics (three degrees of freedom) are used to summarize differences among organizations. These should be interpreted with caution as no adjustment was made for the number of comparisons made. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina, USA).

Results

Two hundred and sixteen surveys were distributed to organizations involved in the conduct of clinical trials, and 79 responses were obtained, yielding an overall response rate of 37%. 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 ($n=2$), CRO ($n=1$), and government ($n=9$). Two additional respondents left the question on performing clinical trials blank and were also excluded: CRO ($n=1$) and industry ($n=1$). With these exclusions, survey results for 65 respondents comprise the basis of this report.

Response rates by organizational type are provided in Table 1. The response rate from academic coordinating centers/cooperative groups/government organizations was lower than for CRO or industry organizations; the largest number of surveys analyzed came from industry organizations.

Characteristics of the organizations described by survey respondents are given in Table 2. Organizations differed significantly in the type of trial typically conducted ($p=0.005$). Whereas

Table 1 Survey response rate for 65 organizations that conduct or sponsor clinical trials

Type of organization	Number of surveys distributed, <i>N</i>	Number of respondents	
		<i>N</i>	(%) ^a
Academic/cooperative group/government	98	18	18
CRO	19	11	58
Industry	99	36	36
Total	216	65	30

^aPercentage of organizations sent the survey who conduct clinical trials and provided a response.

respondents identifying their organizational type as academic coordinating centers, cooperative groups, or government more often conducted phase 4 (post-marketing) trials, CROs and industry organizational types most often conducted phase 3 registration trials. Fewer sites were involved in trials carried out by the device industry organizations compared with trials carried out by other organizations ($p=0.009$). The majority of trials involved fewer than 1500 patients. The majority of all organizational types conducted international clinical trials, and most organizations (although not all) reported having a QA department overseeing the organization’s clinical trial program.

Table 3 summarizes survey responses regarding centralized and on-site monitoring. With the exception of the question on whether the organization performed on-site visits, for which the percent indicating ‘always’ varied by organization ($p=0.001$), the responses to other questions did not vary by organization. A greater proportion of CRO and pharmaceutical and device industry organizations reported always conducting on-site monitoring visits than did academic coordinating centers/cooperative groups/government organizations (80–89% vs. 31% of respondents, respectively). This difference between organizations was evident even for phase 3 trials, which are often pivotal (79% vs. 20%). While the majority of all organizational types used centrally available data to evaluate site performance, one-third or fewer of any organizational type reported always using a centralized monitoring process to guide, target, or supplement site visits. Similarly, a minority of all organizational types reported always or frequently using centralized monitoring processes to replace on-site visits. The majority of all organizational types (but not all respondents) reported conducting an assessment of risk prior to developing the monitoring plan.

The variation in use of on-site monitoring visits by type of organization was investigated further to

Table 2 Survey respondent organizational characteristics

Characteristic ^a	Academic/government/ cooperative group, N (%)	CRO, N (%)	Industry– pharmaceutical, N (%)	Industry–device, N (%)
Total	18 (100)	11 (100)	25 (100)	11 (100)
<i>Type of trial most commonly conducted</i>				
Phase 1 or 2	2 (11)	3 (27)	5 (20)	1 (9)
Phase 3	5 (28)	8 (73)	16 (64)	6 (55)
Phase 4 post-marketing or non-IND/IDE studies	9 (50)	0 (0)	0 (0)	3 (27)
Other	2 (11) ^b	0 (0)	4 (16) ^c	1 (9) ^c
<i>Most common number of sites in trials</i>				
< 50	7 (39)	4 (36)	8 (32)	10 (91)
≥50	11 (61)	7 (64)	17 (68)	1 (9)
<i>Most common number of subjects in trials^d</i>				
< 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)

^aInformation collected in the background section of the survey.

^bTwo respondents stated: 'Not sure which is most common' and 'Phase 1, 2, and 3.'

^cFive respondents 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.'

^dFive 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 respondent, and 100–499 for 1 respondent).

Table 3 Use of centralized and on-site monitoring across organizational types^a

Academic/government/cooperative group, N/total (%)	CRO, N/total (%)	Industry–pharmaceutical, N/total (%)	Industry–device, N/total (%)
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 on-site visits (% 'Always' or 'Frequently') ^b			
3/15 (20)	2/6 (33)	1/21 (5)	0/9 (0)
Perform on-site 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)

^aNumbers cited are those with indicated response, total, and (percent).

^bOne respondent checked 'Always.'

determine if there was also variation by type of trial, number of sites, and number of patients (Table 4). For none of these factors did the percent of organizations always performing on-site monitoring vary.

Tables 5 and 6 summarize factors likely to trigger a site monitoring visit based on central data. Thirteen specific factors were assessed. For most factors, there was consistency across organizational type. The number of protocol deviations (44 of 51

respondents) and suspected fraud ($n=43$) were common reasons for all organizations. The rate of enrollment ($n=40$) and missing case report forms (CRFs) ($n=38$) were also common. For three factors, there were significant differences among organizations. Laboratory data signals triggered a site visit among two-thirds of pharmaceutical industry organizations and no device organizations. The other two organizational groups were intermediate ($p=0.008$ for difference). Lack of

experience with the site was more likely to trigger a site visit for pharmaceutical and device industry organizations than for academic coordinating centers/cooperative groups/government and CROs ($p=0.0001$). Geographic location was more likely to trigger a site visit among pharmaceutical

Table 4 Percent 'always' performing on-site monitoring visits by type of trial, number of sites, and size of trial

Subgroup	N (%)
<i>Type of trial</i>	
Phase 1 or 2	8 (88.9)
Phase 3	24 (70.6)
Phase 4 post-marketing or non-IND/IDE studies	6 (54.5)
Other	4 (66.7)
<i>Most common number of sites in trials</i>	
< 50	19 (73.0)
≥ 50	23 (67.6)
<i>Most common number of subjects in trials</i>	
< 1500	32 (78.1)
≥ 1500	10 (52.6)

Table 5 Factors likely to trigger a site monitoring visit: four factors consistently reported across organizational types

Factor ^a	N (%)	Range across organizations (%)
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

^aFrom total of 13 factors assessed. The question read: 'Which of the following factors would be likely to trigger a site monitoring visit? (1) Number of protocol deviations; (2) incidence of adverse events; (3) suspected fraud; (4) missing CRFs; (5) number of data queries; (6) number of unanswered queries; (7) rate of enrollment; (8) subject drop-out rate; (9) screen failure rate; (10) laboratory data signals; (11) lack of experience with site; (12) geographic location of site; (13) other.'

Table 6 Factors likely to trigger a site monitoring visit: three factors noted to be used differentially by organizational types

Factor ^a	Academic/government/ cooperative group, N/total (%)	CRO, N/total (%)	Industry– pharmaceutical, N/total (%)	Industry–device, N/total (%)
Laboratory data signals	6/15 (40)	2/6 (33)	14/21 (67)	0/9 (0)
Lack of experience with site	4/14 (29)	2/5 (40)	19/20 (95)	8/9 (89)
Geographic location of site	1/15 (7)	0/6 (0)	7/21 (33)	0/9 (0)

^aFrom a total of 13 factors assessed. The question read: 'Which of the following factors would be likely to trigger a site monitoring visit? (1) Number of protocol deviations; (2) incidence of adverse events; (3) suspected fraud; (4) missing CRFs; (5) number of data queries; (6) number of unanswered queries; (7) rate of enrollment; (8) subject drop-out rate; (9) screen failure rate; (10) laboratory data signals; (11) lack of experience with site; (12) geographic location of site; (13) other.'

organizations as compared with other organizations ($p=0.03$).

The frequency of on-site monitoring is one of the largest drivers of the costs in monitoring a clinical trial [7]. We therefore were interested in the factors that are used to determine how frequently sponsors conduct on-site monitoring. This information was collected via a survey question asking: 'The frequency of your organization's on-site monitoring visits is most commonly determined by: (select all that apply).' Table 7 summarizes the data from this question. For none of the factors assessed was there a significant difference among organizational types. Study design was the most common factor cited across all organizational types (40 of 54 respondents). Other factors considered by more than one half of the organizations were 'critical study requirement/procedure' ($n=36$), 'monitoring plan specified in protocol' ($n=31$), 'SOPs' ($n=31$), and 'usual practice of organization' ($n=29$). Pre-defined analysis of risks was not very frequently cited (26 of 54 organizations) as a factor in determining the frequency of on-site monitoring.

The survey also assessed the frequency of specific activities conducted during an on-site monitoring visit. Table 8 lists the verifications that organizations reported were 'always' conducted during an on-site visit. Most factors were generally reported at similar frequencies across organizational type, with verification of 'informed consent updates/modifications' being the activity most frequently cited by all organizations. In contrast, across all organizational types, there was a low (11–26%) reporting of always verifying 'subject understanding of the protocol' and a relatively low (20–39%) reporting of verification of 'adequacy and timeliness of additional information provided to participants.' CROs and both industry groups reported 'conducting source document verification' and 'verifying regulatory documents and communications' more frequently than academic coordinating centers/cooperative groups/government organizations ($p=0.03$ for differences among organizations).

Table 7 Factors that determine frequency of on-site monitoring visits by type of organization

Factor ^a	Academic/government/ cooperative group, N/total (%)	CRO, N/total (%)	Industry– pharmaceutical, N/total (%)	Industry–device, N/total (%)
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)

^aThe question read: 'The frequency of your organization's on-site monitoring visits is most commonly determined by: (select all that apply).' All options are listed in the table. Factors are ordered by overall frequency indicated across all organizations.

Table 8 Verifications performed during on-site monitoring visits by type of organization^a

Assessments made ^b	Academic/government/ cooperative group, N/total (%)	CRO, N/total (%)	Industry– pharmaceutical, N/total (%)	Industry– device, N/total (%)
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 (% 'Always')	5/13 (39)	6/9 (67)	19/22 (86)	7/9 (78)
Security of study data and documentation (% 'Always')	6/14 (43)	6/9 (67)	16/22 (73)	3/9 (33)

^aThe question read: 'Does your organization assess...?' Answer options included always, frequently, occasionally, never, NA, and not sure. Numbers cited are those with indicated response, total, and (percent).

^bOther verification elements were assessed in the survey but are not reported here.

Among organizations that 'always,' 'frequently,' or 'occasionally' verify CRF data versus source data, we assessed how many organizations carried 100% verification of six items (Table 9). Across all organizational types, a higher rate of 100% source verification was reported for consent forms, primary end points, and serious adverse events. Compared with other categories of trial sponsors, academic coordinating centers/cooperative groups/government organizations were less likely to verify eligibility criteria 100% of the time during on-site monitoring visits ($p=0.02$).

Discussion

To our knowledge, the current analysis offers the only broad characterization of monitoring practices to be reported since the approval of ICH E6 in 1996. Over the past 14 years, significant enhancements to clinical trial technology have been globally

implemented, including electronic data capture and clinical trial management systems. It is important to understand how these technologies have modified sponsors' interpretations of ICH E6 and whether these technologies have resulted in the conduct of more efficient clinical trials with higher quality data. Thus, CTI conducted this survey of sponsors to characterize current monitoring practices, the primary finding of which is that significant variation exists across the wide range of clinical trial sponsors. While we have highlighted the differences observed by organizational type, it is also likely that heterogeneity in practices exist *within* organizational types as well.

It is a widely accepted hypothesis among CTI members that on-site clinical trial monitoring is a source of significant inefficiency in the conduct of clinical trials, and that current monitoring activities do not always lead to increased quality in clinical trials. Indeed, Eisenstein et al. conducted an analysis that estimated the cost of on-site

Table 9 Specific items source-verified 100% of the time during on-site monitoring visits across organizational types^a

Item	Academic/government/ cooperative group, N/total (%)	CRO, N/total (%)	Industry- pharmaceutical, N/total (%)	Industry-device, N/total (%)
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 end point reports	8/13 (62)	8/9 (89)	18/22 (82)	6/7 (86)
Secondary end point 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)
Nonserious adverse event reports	3/13 (23)	5/9 (56)	14/22 (64)	2/7 (29)

^aThe question read: 'Does your organization verify CRF data vs source data (source data are contained in source documents; e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, X-rays).' Answer options included always, frequently, occasionally, never, NA, and not sure.

If 'Always/Frequently/Occasionally,' then: 'What proportion of each of the following does your organization verify? For each of the following record: None, 1–25%, 26–75%, and 75–99%, All.' Options are listed in the table.

monitoring to constitute between 25% and 30% of clinical trial costs [7]. Given this investment in time and resources by the clinical research enterprise, it is incumbent upon all stakeholders to ensure that current methods are achieving their desired intent of protecting patients and data integrity. According to ICH E6, monitoring is the responsibility of the sponsor, although it is important to note that the guideline also states that 'the investigator/institution should conduct the trial in compliance with the protocol' and that 'the investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.' Hence, it appears that there is dual responsibility for the conduct of the trial and for accurate reporting of study data, with the sponsor providing the overall context both to ensure that investigators and institutions *can* carry out their responsibilities and to verify that they *do indeed* carry out such responsibilities. Recognizing the possible complexity of this arrangement, the PhRMA BioResearch Monitoring Committee recently published their perspective on acceptable approaches for clinical trial monitoring, underscoring its intent 'to provide flexibility in approaches' [8].

The results of our survey revealed that the majority of all sponsor organizational types used centrally available data to evaluate site performance; however, one-third or less of any organizational type reported always using a centralized monitoring process to guide, target, or supplement site visits. A similarly small number of respondents across organizational types reported always or frequently using centralized monitoring processes to replace on-site visits. These results suggest that sponsors may be suboptimally using their clinical trial and data management systems and

consequently are missing an opportunity for significant increases in clinical trial efficiency [4].

CRO and both industry organizational types reported always conducting on-site monitoring visits at a higher rate than academic coordinating centers/cooperative groups/government organizations (80–89% vs. 31% of respondents). The reasons for this difference are not clear. Regardless, it will be important in future research to understand whether these differences in practices are associated with differences in data quality and efficiency of clinical trials.

We observed a number of similarities among all organizational types regarding the factors that trigger an unscheduled on-site monitoring visit (Tables 5 and 6). While it seems obvious why an on-site monitoring visit would be triggered by suspected fraud or significant protocol deviations, it is not obvious that a low rate of enrollment warrants an on-site visit. Given the diversity of existing technologies, it seems quite possible that at least some verifications that are conducted today (Tables 8 and 9) could be effectively – and more efficiently – conducted remotely. Therefore, we encourage the exploration, analysis, and validation of innovative and efficient monitoring techniques.

Our study has a number of limitations. First, the overall response rate to our survey was only 30% and was particularly low among academic coordinating center/cooperative group/government organizations. Thus, we may not have captured the full variance of current monitoring practices, and our responding sample may not be representative. In addition, the low response rate and relatively small sample sizes may have led to biased comparisons between organizational types. Another limitation concerns the specific answers provided by CROs. While CROs have their own SOPs and approaches

to monitoring, they may adopt the practices of the company for which they are working. We do not know for certain whether their answers represent their practices or those of their clients, but we suspect they represent current CRO approaches. Nonetheless, our data suggest significant variation both between and within organizational types; a further understanding of this variation may yield important insights regarding efficient methods of monitoring. Our results primarily describe phase 3 and phase 4 post-marketing trials and may not be applicable to phase 1 and 2 trials. Perhaps the greatest limitation of our results is that we do not have systematic data to determine the effectiveness of the various monitoring approaches. One approach to addressing this limitation is to quantitatively define quality in clinical trials, and then to measure the quality achieved in trials using various quality control methods, including various monitoring methods. A more focused attention to trial quality metrics, combined with systematic attempts to incorporate quality control processes during the design of a study, may provide improved quality and efficiency in the conduct of clinical trials.

Conclusions

This is the first extensive survey to assess monitoring practices used across US clinical trial settings and by various organizational types. On-site monitoring is routinely performed by industries and CROs, but less frequently and less extensively by academic coordinating center/cooperative group/government organizations. The scope of on-site monitoring visits varies by organizational type, with CROs and industry more frequently reviewing the following items at a site visit compared to academic/cooperative group/government organizations: randomization, product blinding, compliance with study intervention, source documents (e.g., adverse event reports and eligibility criteria), and regulatory documents. 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 the monitoring practices observed. It is time that we use the methodologies that we have so assiduously applied to clinical research to now study the effectiveness of monitoring.

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