

Could 100% Source Document Verification Become a Risk in a Fixed-Unit Price Environment?

This article explores how monitors currently utilize time on site and how restriction of time on site may alter that utilization. It also explores a targeted monitoring approach that pinpoints the data most critical for analysis as the primary focus of time spent on site while maintaining the study budget.

The interpretation of appropriate monitoring of clinical trials has, for many years, been tied to the scope and frequency of site monitoring. Sponsoring companies have been reluctant, when contracting through contract research organizations (CROs), to reduce the amount of source document verification (SDV) below 100% due to fears of missing or erroneous data or trends. Today, however with more contracts restricting the amount of time on site while still requiring 100% SDV, the goals of the sponsoring company may be compromised when monitors attempt to achieve both on-site time restrictions and 100% SDV. This article explores how monitors currently utilize time on site and how restriction of time on site may alter that utilization. It also explores a targeted monitoring approach that pinpoints the data most critical for analysis as the primary focus of time spent on site while maintaining the study budget.

Background

Section 5.18.1 of the E6 Consolidated Guidance: *Guideline for Good Clinical Practice*¹ (GCP) outlines three simple goals to be accomplished when monitoring a clinical study. Monitoring is to be performed to ensure:

- “(a) the rights and well-being of human subjects are protected;
- (b) the reported trial data are accurate, complete, and verifiable from source documents;
- (c) the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirements.”

The same section states that sponsoring companies should “ensure that the trials are adequately monitored,” and explains that factors including “objective, purpose, design, complexity, blinding, size, and endpoints” should be part of the analysis of what constitutes adequate monitoring.

How can we, from both the sponsoring company and CROs, ensure that “adequate” monitoring is occurring? Our approach, historically, has been to apply standard definitions. For years, “adequate” monitoring oversight was defined by many in the pharmaceutical, device, and CRO industries as a trip to the site at least every six weeks. Even with the advent of electronic data capture

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(EDC), the industry still struggles with the re-evaluation of the frequency of site monitoring to achieve the goal of “adequate” monitoring. With some specific company exceptions, we have, as an industry, also been guilty of requiring 100% SDV, the most conservative approach, in order to achieve the goal of (b) above.

Further weight is placed on the use of 100% SDV because studies are now frequently awarded in a piecemeal fashion, making essential communications between the groups involved in trial design, site monitoring and management, data management, and statistical analysis more difficult. As a result, data quality has become more narrowly defined as being composed of only site monitoring quality and the database error rate,

rather than defining data quality along a continuum. For this reason, it has become increasingly difficult to develop a targeted monitoring plan, taking a “broad-brush” or “most conservative” approach to SDV instead.

These gaps in knowledge and communication were manageable in the time and materials contract environment in which estimates were given for trial costs to perform monitoring and data services. The question that has not been answered is whether the reputation given to CROs for often exceeding these estimates is due to mismanagement or due to the fact that there is insufficient communication up front between the trial design group, monitoring, statistical, and data resources involved in the trial.

The environment has continued to change over time. In the past three years, there has been a renewed interest in the fixed-unit-price concept in budgeting for clinical trials. With some sponsoring companies, this has included a requirement for establishing the number of hours to be spent on site rather than managing the overall number of hours to complete a monitoring visit. So how do we manage to the premise presented by Schuyl and Engel when they stated, “The amount of time devoted to SDV must be dependent on the nature and volume of information generated during the study, not on time or budgetary constraints that may be placed on study monitoring activities”²

Risk Analysis

What is the risk of *not* performing a 100% SDV? Christian and coauthors published one of the few articles describing the results of an audit of a large trial for the express purpose of assessing data quality.³ The trial was the National Cancer Institute’s National Surgical Adjuvant Breast and Bowel Project Protocol B-06, in which a total of 7,577 data variables collected from 1,507 patients and 37 sites were verified. Only 70 (0.9%) were found to be discrepant, which did not

alter the adequacy of the original results prior to the audit. The risk of SDV errors, therefore, is relatively small, making it reasonable to consider the use of a targeted monitoring plan that focuses the largest amount of on-site effort on targeted efficacy and safety variables critical to the analysis and utilizing a lower percentage review for noncritical data points.

To establish the percentage of SDV needed for a trial, other points should also be assessed as part of the overall risk analysis for a study. Califf and coauthors contend that there are several methods that should be examined to reduce the need for 100% SDV.⁴ Therefore, sponsoring companies and CROs alike should assess

- the overall trial design. Focus should be given to overall trial simplicity, collection of only essential data, control for confounding

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variables, and the clarity of the methods being used for collecting critical endpoints.

- the thoroughness of capabilities assessments and training of investigators and coordinators. An analysis should be made of the type of investigator training to be performed and whether adequate on-site time is being given to perform thorough training in the event that an investigator’s meeting is not planned. Previously collected data quality metrics should also be assessed as part of determining the overall training level of the investigator, when possible.
- the availability and consistency of information. A determination should be made as to whether planning has included the use of a centralized repository of information or coordinating center to ensure rapid and consistent responses to questions posed by site personnel.
- the robustness of the trial database. This segment should include an assessment of whether the number and overall quality of database-level data integrity checks expected to be applied to the critical variables are sufficiently stringent to match the overall goals of the study if the SDV is not at the 100% level.
- subjective clinical endpoints. An evaluation of whether a clinical events committee is needed and planned for should be made, as well as a review of any methods to be used, to ascertain early feedback from such a committee to assure site training has been successful.

When the requirement for 100% SDV is maintained, however, the impact of the combination of fixed-unit pricing and the requirement for 100% SDV become risks on a variety of levels. An environment of direct conflict between quality

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and cost control can be created when contracts fix the amount of time spent on site for monitoring, while still requiring a 100% comparison of source documents to CRF data.

First and foremost is the potential negative impact to the overall monitoring quality when time on site is fixed. This places a burden on the monitor such that he or she may be forced to prioritize one aspect of on-site monitoring over an equally important, but less time-

intensive part. A second risk that develops in this scenario is initial agreement that the work can be performed under the time constraints in a contract, only to discover that it cannot be done without compromising quality and/or quantity, producing a “no-win” situation for the sponsoring company and the CRO. The final risk that emerges is one of diminished data quality, because the requirement to review a higher number of data points in a fixed amount of time will undoubtedly yield more queries than would be generated if the number of data variables was limited to those defined as key efficacy and safety variables.

Analysis of Current Practice

An informal, nonvalidated survey was developed for the express purpose of assessing how time was spent on site by individuals currently working as field monitors.⁵ The survey was provided to 21 individuals who are currently performing or who have performed monitoring functions within the past six

Table 1. Results from Monitor Survey of Current On-Site Time Utilization Ranked by Percentage

Average Percentage of Tasks Performed at Each Monitoring Visit While On Site	Average Percentage of Time Spent on Task (N=19)
CRF to source document comparison to perform data quality checks, including write-ups of issues	46
Perform regulatory review requirements (regulatory binder review, informed consent reviews, [Institutional Review Board] IRB documentation review and maintenance), including write-ups of reviews	13
Communications with coordinator	13
CRF review for consistency (without performing source document review), including write-ups of issues	12
Drug accountability	11
Communications with principal investigator	5
	<u>100%</u>

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months. Nineteen responded to the survey, with this group representing CRO employees and independent contractors working for multiple clients. The question on SDV comparison was consistently ranked as the task requiring the most time on site; 19 respondents indicated an average of 46% of their on-site time being spent on this one activity. The results for all tasks listed in the survey are shown in Table 1.

This informal survey confirms that the single most time-consuming task during the monitoring visit is consistently SDV. Therefore, it is reasonable to expect when the time on site is limited from a contractual standpoint to a given number of hours that the tasks that do not drive CRF retrieval may not be performed as thoroughly.

The article by Schuyt and Engel also described two alternate methods in use:

- an assessment of 100% of critical data combined with an assessment of 25% of the noncritical data variables for the same study and
- use of 100% SDV at all sites until the sites can meet predetermined error rates for critical and noncritical variables described in the study-specific monitoring plan.

Goals for Managing/Mitigating Risk

Although standard approaches worked in our industry's infancy, as we mature and as the demands for more cost-sensitive development efforts increase, we

must not only look at how to control costs, but we must also assess the impact of cost control from a quality perspective. We can no longer take the same approach to monitoring, which is the single largest clinical development cost driver in a Phase II or Phase III clinical trial, representing approximately 40% of the average clinical trial costs.⁶

As an industry, we should focus on goals to aid in cost containment without compromising quality. The goals that we should strive to attain include:

- development of a "fit-for-purpose" monitoring strategy that is based on a risk analysis of items more inclusive than SDV.
- identification of an overall database error rate that is truly aligned with the intended goals of the study.
- a feasibility assessment that identifies whether the combination of the "fit-for-purpose" monitoring strategy and any time requirements for on-site monitoring is achievable.

How do we achieve these goals? Whether a study is being outsourced or performed internally, the analysis goals and the method for achieving them should be articulated before time estimates can be given. This can only truly be achieved if there is a melding of trial design, clinical data, and statistical mindsets prior to the Request for Proposal (RFP) process in order to minimize redundancy in the data-cleaning process and to target those data that are essential to the analysis phase. The result of this effort ensures that quality and cost-containment measures are evaluated simultaneously rather than independently.

The following should then be outcomes of this collaboration that can be used to achieve the goals:

- A targeted monitoring approach that focuses on the key safety and

efficacy variables being evaluated in the clinical trial. Although this percentage may be close to 100% in a Phase I study, the percentage of data falling into this category may represent only 40-60% of the total data collected in a Phase III study. By targeting the subset of data points that require 100% review and confirmation with source documents and then identifying a percentage data review for other data points, the time on site can focus on a more thorough review of the data essential for analysis.

- An analysis of requirements for the final database error rate that is truly associated with the intended goals for the study. Again, it has become the unspoken standard that 10 errors per 10,000 fields (or 0.1%) is the generally accepted database error rate, although there is no written standard provided in the Good Clinical Data Management Practices.⁷ Questions to consider should review whether the overall database error rate expectations should be the same for a study even if the study is not pivotal. The necessity for all datasets within a Phase III study to have the same database error rate should also be reviewed based on their criticality for analysis.
- A determination of whether task-specific time requirements are appropriate to be included in any RFPs. If they are, the sponsoring company must ensure that the estimates (1) are a reflection of the requirement for 100% SDV or a targeted monitoring approach; (2) are based on similar phase studies with similar study complexity and CRF size; (3) include adequate time to ensure the informed consent process meets requirements and that documentation is complete; (4) include adequate time to

ensure the IRB process and documentation is complete; and (5) include sufficient time to perform test article accountability.

- A means of assessing proposal responses in terms of quality goals as well as cost. As a means of assessing quality, one reasonable assessment is to review the number of queries anticipated to be generated in conjunction with the monitoring frequency and approach described. Altering the monitoring frequency may be an appropriate and creative approach to achieving the study goals, but it should not be done at the expense of data quality, which can be assessed by the anticipated query rate. Another means of assessing quality during the proposal process would be to identify how the use of technology will be incorporated into the overall monitoring plan. It is logical that the overall time for monitoring would remain the same whether EDC is or is not utilized, but the distribution of time between in-house data review and on-site time should differ from a traditional paper study. This assessment would provide a good indicator of whether the technology is being used as a constructive aid to improve study efficiency or whether it is simply being applied on top of traditional paper-based monitoring procedures. An evaluation of whether the proposal has included other means of auditing overall data quality in the field should also be performed. A creative strategy of combining a targeted monitoring plan with a quality assurance review for purposes of assessing data quality as well as regulatory compliance may serve the sponsoring company well as a means of corroborating the use of a targeted monitoring plan versus use of 100% SDV.

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By focusing more on the intent of the analysis during the design and early implementation stages of a trial, a monitoring plan can then be designed to maximize productivity on site while preserving the overall quality considerations for the study. In the event any component of the trial is to be outsourced, sponsoring companies should seriously consider providing this information as part of the RFP process, so that the quality of proposals can be maximized. Similarly, an exchange of this information within a company's departments will only serve to improve the knowledge base of those contributing to the trial.

In summary, monitoring will continue to be a tremendous cost driver in the development of new drugs and devices. In an effort to control this cost, an increasing number of sponsoring companies are looking to cap the number of hours actually spent on site, but without an evaluation of what activities get performed during that time. If not managed, this could create an environment in which quality takes a back seat to contractual requirements. The best means of managing this risk is to ensure

that options are evaluated simultaneously from both a quality and a cost perspective and that careful review is given to the use of "fit-for-purpose" monitoring plans and database error rates that focus quality efforts on the areas of the study most critical, ensuring the goals of the analysis are achieved.

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