Building Quality in Clinical Trials With Use of a Quality Systems Approach

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There is an increasing focus on having quality systems in place during the planning stages of clinical trials. Such systems require the development and implementation of standards for each step. Although this is not imposing something totally new on clinical research, a systematic approach will produce a more reliable and useful end product—high-quality data obtained without compromising the protection of human subjects’ rights and welfare. A suggested quality system with standards for each step is addressed in this article.

Defining and measuring quality in the clinical trial setting can be difficult. The most important variable involved is the ever-unpredictable human, and advancements, such as electronic data capture and internationalization, are constantly altering the clinical trials landscape.

Defining quality often accounts for the satisfaction of customers in meeting their needs and expectations. However, the stakeholders (customers) in the research community are numerous and varied and include but are not limited to the public, the medical community, the clinical research community, investigators, sponsors, contract research organizations, academia, government agencies, and institutional review boards. Moreover, the standard level of quality acceptability of the customer is not a static target. This forces focus on the importance of having continual process improvements for all stages of performance in the clinical trial enterprise, to guarantee quality (Figure 1).

No clinical trial is perfect, and therefore, no dataset is perfect. Even if complete accuracy of the records could be achieved, it cannot define a quality clinical trial, because a useful study design, well-defined end points, assurance of subject safety, and the assurance of unbiased observations must also be affirmed. In other words, if one were to accurately record ingestion of an investigational product in an appropriate, healthy population that led to the demise of each participant, one would not argue that the clinical trial was inadequate. In attempting to define quality in the clinical trial, the Institute of Medicine’s Roundtable on Research and Development of Drugs, Biologics, and Medical Devices has instead defined “high-quality data”: data strong enough to support conclusions and interpretations equivalent to those derived from error-free data [2]. In other words, for regulated products, the data must allow the US Food and Drug Administration to make accurate regulatory decisions about the safety and efficacy of the product, and the data should be able to support the sponsor’s labeling claims. Although the research community is in agreement that certain data points (eg, the primary efficacy end point and adverse events) should receive the greatest attention toward guaranteeing 100% completeness and accuracy for decision-making purposes, the most cost-effective and efficient monitoring and auditing techniques to achieve this are still being debated [3–7].

THE CLINICAL TRIALS TRANSFORMATION INITIATIVE (CTTI)

In light of these issues, the CTTI, a public-private partnership involving industry, government, patient advocates, trade organizations, professional societies, academia, and nonacademic investigators, was formed in...
November 2007 to identify practices that will increase the quality and efficiency of clinical trials [8]. The CTTI has characterized quality as "the ability to effectively answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure, while assuring protection of human subjects" [9]. One of the first projects planned and approved under this initiative is "Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials." Although current regulations [10, 11] require sponsors to ensure proper monitoring of clinical investigations of products subject to Investigational New Drug Applications and Investigational Device Exemptions, monitoring methods that are ineffective or overly burdensome may inadvertently contribute to poor data quality. A white paper to be developed from this project will establish the key quality-assurance objectives in clinical trials and promote effective and efficient monitoring, both in the United States and internationally.

A CHANGING LANDSCAPE

Historically, the research community has instituted quality-assurance processes after a problem or crisis has developed rather than a priori as part of a quality-management system. The current system of inspecting clinical sites to ensure quality in clinical trials also encourages an approach similar to old-fashioned manufacturing systems: produce the product, catch the defective ones, and throw them out. Throwing out clinical trial data after the fact is ineffective and wasteful. It also does not build confidence in the system for the volunteers who participated in the research.

The current system has also not developed with changing demands. Studies have become increasingly more complex, leading to increased demand for resources [3, 4]. The responsibilities of the sponsor [10, 11] are being outsourced to third parties, such as contract research organizations [12–14]. Oversight of clinical trials is shifting toward centralized institutional review boards [15]. Sponsors are increasingly involving sites in many countries in a single clinical trial [16], shifting resources and creating consequences for which the full impact may not be felt for many years (eg, the decreasing experience of new, young clinicians and research staff in the clinical trials arena in the United States when research is shifted overseas).

DEVELOPING QUALITY SYSTEMS FOR CLINICAL RESEARCH

There is an increasing focus on having quality systems in place during the planning stages of clinical trials. Such systems require the development and implementation of standards for each step. Experience has shown that the value of standards is greatest when they are implemented from the start [17]. Although this is not imposing something totally new on clinical research, a systematic approach will produce a more reliable and useful end product—high-quality data obtained without compromising the protection of human subjects’ rights and welfare. There are a number of general requirements of a quality system.

Personnel roles and responsibilities. The investigator, sub-investigator, clinical trial manager, research assistant, and all others involved in the planning and implementation of a clinical trial should understand and accept their roles and responsibilities as outlined not only in the regulations, international guidances (eg, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E6 Good Clinical Practice: Consolidated Guideline [18]), and other external sources but also as outlined in the internal policies and procedures of their respective organizations. It is not uncommon for a Food and Drug Administration inspector to cite an investigator for lack of a required action or transference of a responsibility and hear “I did not know that I was responsible for that” [19].

A document (eg, a log) that describes the delegation of duties should be created before a clinical trial begins. It should always be checked against any responsibilities outlined in the clinical protocol (eg, the electrocardiogram must be read by a cardiologist). As the trial progresses, the delegation-of-duties document should be periodically reviewed and updated as needed. There should also be a written plan for coverage of key personnel if there is need for one (ie, sickness or resignation).

Training. The sponsor is responsible for hiring investigators qualified by experience and training [20, 21]. The American Society of Clinical Oncology recommends that all trial investigators in the United States be specialty board certified and that international investigators obtain board certification when it is available [22]. Confirmation of all relevant experience and
training is needed. This includes training in good clinical practices and human subject protection. This does not mean that the sponsor is required to provide good clinical practice training, because many programs are readily available [23]. There are also several agencies within the Department of Health and Human Services that provide online training on this subject (Table 1). Sponsors should have policies in place that approve the robustness of the good clinical practice training offered to research staff and that require periodic updating of all such training.

When a clinical trial involves an investigational product, all key personnel should be knowledgeable of all applicable regulations, including those that pertain to human subject protections [24]. Protocol training should also be documented and, especially for complex trials, periodically repeated. To ensure the adequacy of training procedures, testing of knowledge is highly recommended.

**Policies and procedures.** Before a protocol is written, the investigator should be aware of his or her institution’s policies and procedures. These include protocol review procedures, handling of biological samples, human subject protections, confidentiality, data management, and procedures for handling possible scientific misconduct. Frequently, the record retention policy specifies a longer retention period than that required in the federal regulations [25, 26]. Many such policies may need to be outlined in the protocol, as appropriate.

The importance of having written standard operating procedures (SOPs) in place for each clinical site cannot be overstated. A number of standard clinical research SOP templates are available and can be customized as needed [27, 28]. Protocol-specific SOPs, often called a Manual of Operations, can outline the protocol procedures in greater detail; it is imperative that the SOPs are critically reviewed to ensure consistency with the protocol. All staff should have documented SOP training. SOPs should be reviewed on a scheduled, periodic basis for potential updates.

**Quality assurance and auditing.** Clinical trial staff who have worked with paper case report forms are familiar with double data entry into a database and the associated extensive quality-assurance procedures (eg, data queries on missing or questionable data points). Staff are also often familiar with sponsor audits and/or regulatory audits. However, quality-assurance programs at the investigator site are less frequently seen. Establishing such a program is not arduous and should be done promptly if none exists [22, 29, 30].

**Document management, record retention, and reporting.** Archival procedures should be documented, and all staff should understand these procedures. The handling of documents, including conventional naming, tracking, filing, version control, and the systematic back-up of real-time data collection, should follow standardized procedures. Clinical research generates an immense amount of data. Simplification is the key for all data capture forms, assessment instruments, and instruction sheets. Standardization is also strongly encouraged. There are a number of organizations working toward case report form standardization, including the National Cancer Institutes Standardized Case Report Form Work Group [31].

All files should be kept in a locked area with restricted access. All computers should be password protected. Any breach of subject confidentiality is a violation that should be reported to the institutional review board. If any such violation were to occur, a swift corrective action plan should be implemented.

**Corrective and preventive action.** Potential problems should be anticipated, and steps should be taken to avoid them. Nevertheless, problems will inevitably arise, and the discovery of a problem should trigger swift corrective action and the development of a plan to prevent recurrences. A reevaluation of the system should be performed to ascertain how the problem occurred. Documentation of these actions is necessary to avoid any questions from an auditor.

**METHODS FOR QUALITY IMPROVEMENT**

There are 4 types of errors in randomized clinical trials: design, procedural, recording (both random and fraudulent) and analytical [32]. A quality system must address each of these. One solution for identified problems is adopting a Quality Management System approach that uses identified problems to make products safer and ensure data validity. After such a system is in place, it can achieve maximum customer satisfaction efficiently while improving the process. Among the most widely used tools for continuous improvement is a 4-step quality

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<th>Table 1. Department of Health and Human Services Online Training Courses.</th>
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<td><strong>Agency</strong></td>
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<tr>
<td>National Institutes of Health</td>
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<td>National Drug Abuse Treatment Clinical Trials Network</td>
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<td>National Institute of Allergy and Infectious Diseases</td>
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model—the plan-do-check-act cycle, also known as the Deming Cycle or Shewhart Cycle [33] (Table 2). Other widely used methods of continuous improvement are Six Sigma, Lean, and Total Quality Management.

IMPROVING CLINICAL RESEARCH

There are a number of steps that can be taken by the research community to improve the clinical research process.

**Human factors.** Address the human factors in the clinical trials system. Hire experienced, well-qualified staff. Avoid conflicts of interest and financial incentives. Decrease the number of times that data are handled.

**Systems and standardization.** Create systems that limit the opportunity for errors. Simplify protocols and outcomes assessed. Be realistic about the amount of data to be collected. Standardize systems and formats when possible. Use validated instruments and definitions. Write down all procedures that need to be followed by clinical staff. Use checklists. Do not reinvent the wheel: there are many templates [27, 28], forms, and case report forms that have already been developed and assessment instruments that have already been validated [34]. Keep amendments to a minimum, and check case report forms and consent forms against each change.

**Integrated plans.** Develop an integrated framework with a data and safety monitoring plan [35], a data management plan, a quality-assurance plan [36], and a data analysis plan. Have the appropriate experts review these plans before implementation.

**Training.** Insist on good clinical practice, protocol, and SOP training for all key clinical trial staff. Consistently retrain and test the training.

**Unblinding.** If the clinical trial involves blinding, think carefully about unblinding procedures, both intentional and unintentional. Make sure that all staff are aware of these procedures, including who to contact if intentional blinding is anticipated and who to alert if unintentional blinding occurs.

**Disaster planning.** Have a disaster plan. The plan should detail what needs to occur if the disaster is external, such as a hurricane, or internal, such as a disgruntled employee.

**Beta-testing.** Do beta-testing of procedures and have dry-runs of anticipated protocol events before the first subject is enrolled.

**Communication.** Communication cannot be emphasized enough. If an investigator is too busy for a weekly team meeting or call, then he or she is probably too busy to be involved in the clinical research protocol. For multisite clinical trials, lessons learned from actively enrolling sites are extremely useful to those sites that have not begun enrolling. Obvious errors in the protocol and/or interpretation of the protocol can be more easily caught and corrected with open communication.

**Data management.** The transfer of data from source documents to data collection forms and/or electronic data capture should be done systematically and as expeditiously as possible. The data management staff should run checks and close data queries so that there is real-time data cleaning. It is much more difficult to resolve discrepancies found months after subjects have withdrawn from the trial or staff have moved to other jobs.

**Audits.** Implement systems and procedures, and then, encourage internal audits. Be open and honest. It is important to know what is wrong and needs correcting before an external auditor finds it. An example for institutional review boards can be found at the Office for Human Research Protections Web site [37].

A strong, clear mandate with active participation from the highest level of an organization is required for a quality system implementation effort to succeed. Such success breeds more success. In the rapidly changing clinical research environment, continuous vigilance is needed to ensure data integrity and human subject protections. The extra work in initial planning and preparation, in addition to continuous process improvement, will increase the quality and efficiency of clinical trials.

**Table 2. The Plan-Do-Check-Act Cycle**

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<th>Step</th>
<th>Stage of cycle</th>
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<td>Identify the error in the process and develop solutions</td>
<td>Plan: Who is authorized to consent subjects? Is there a pattern? How is the staff trained? Are there other factors involved? Develop a retraining plan</td>
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<tr>
<td>Apply the planned changes</td>
<td>Do: Retrain the identified staff.</td>
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<tr>
<td>Measure the results by monitoring and checking for any errors</td>
<td>Check: Directly observe staff performing the consent procedure; conduct an internal audit of the next 20 consent forms before the subjects leave the clinic</td>
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<td>Implement the plan on a wider scale if all consent forms checked have been signed; if unsigned consent forms are still found, begin the cycle again</td>
<td>Act: If dates are still missing, have subjects date their consent forms, retrain staff or authorize another staff person to consent incoming subjects, correct any other factors that may be involved (eg, overburdened staff or distracted staff member).</td>
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**NOTE.** In the Plan-Do-Check-Act model, there is no end. In the example shown here, suppose that (hopefully found through systematic auditing) subjects are not dating consent forms in a clinical trial.
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References