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Conducting Clinical Research in Medical Device Studies Utilizing A Quality Systems Approach

What does this mean?

What is meant by "Taking a Quality Systems Approach to Medical Device Clinical Research"?

FDA is encouraging a quality systems approach to conducting clinical trials. The Clinical Trials Transformation Initiative (CTTI) established the Quality by Design initiative for clinical research. This provides a quality framework to those designing clinical studies. Patients and those who care for them want access to new drugs, devices, and biological products as quickly as possible, while also being assured that the benefits of these products outweigh the risks. Well-designed randomized clinical trials are the most reliable way to get unbiased information to achieve this outcome. However, poor quality and inefficiency in clinical research can seriously limit the number of questions that can be answered about the appropriate uses of new medical products, and also significantly delay access to new therapeutic innovations. This whitepaper will address what utilizing a quality systems approach to clinical research means, why a quality systems approach is important and initial steps to consider taking when conducting a clinical trial using a quality systems approach.

What is quality?

Quality is the ability to effectively and efficiently answer the intended questions about the risk/benefit ratio of a medical product or procedure while ensuring human subject protection. CTTI defines quality as "the absence of errors that matter to decision making- that is, errors which have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients)".

Quality systems were initially developed for controlling manufacturing processes and practices. The research community embraced clinical quality assurance and quality control as evidenced by Sections 4.4, 8.1 and 9.2 of ISO 14155 and FDA's BIMO guidances.

ISO 14155, Sections 4.4 and 8.1 specify the implementation and maintenance of written quality procedures governing all aspects of a study including: the design, conduct, monitoring and data recording and reporting in compliance with the protocol, applicable standards and the regulations. Records must be maintained to document compliance of all involved parties. Significant exceptions must be justified and documented. Section 9.2 of ISO 14155 requires that internal audits be conducted to assess conformance to and maintenance of quality system requirements. In Part III- Section H of FDA's Bioresearch Monitoring Compliance Program for Sponsors, Contract Research Organizations and Monitors (7348.810), U.S. regulatory inspectors will determine if and how quality assurance units function, are organized and operate.

IN CLINICAL RESEARCH THERE ARE MANY QUALITY STAKEHOLDERS.

In addition to FDA, Sponsor scientists, project managers, research associates/monitors, regulatory staff, data and biostatistical managers are quality stakeholders. The reviewing IRB/EC have a stake in assuring the quality of research conducted in their institutions. Quality stakeholders also include the clinical investigators, research coordinators, relevant hospital staff (radiology processors and reviewers and clinical laboratories) that comprise the crucial first line of study conduct. And last, but certainly not least, are the study participants themselves.

Why implement quality?

Today's clinical research environment is challenging and the stakes are high. The environment is challenging due to the evaluation of innovative, highly complex investigational products and protocols. The patients are complex meaning that they may present for treatment with a myriad of co-morbidities. In addition to efficacy, there are questions to be answered about medical product safety. The advent of multi-disciplinary teams utilizing electronic medical records and unique charting systems add to the complexity. Additionally, many multi-center studies underway today are global trials. These factors contribute to a large potential for errors.

FDA's Bioresearch Monitoring (BIMO) program covers all regulated products. The number of BIMO inspections able to be conducted is resource constrained, and inspections at a limited number of sites per trial may not be generalizable to the study as a whole. Bear in mind that the purpose of conducting these studies is to generate data to support product approval. FDA can refuse to accept study data in support of a marketing application if there are concerns about the quality of the study.

Building quality into clinical study conduct begins on Day 1 of the planning phase and continues throughout all phases of study conduct.

This is a critical point as one device study typically has:

- 10-20 sites (where 25-35 sites were assessed in order to identify 10-20 study sites)
- 100-200 subjects (where 400 subjects may have been screened to identify 100)
- 40-50 case report form pages
- 1000-2000 data points per patient
- 200,000-400,000 data points per study

WHAT ARE THE ELEMENTS
OF A QUALITY SYSTEM?

A clinical research quality system consists of five elements:

1. an ethically sound and scientifically valid investigational study design that has undergone FDA and IRB/EC reviews and approvals;

2. ensuring that adequate human subject protection is in place, compliant with the requirements specified in the 21 CFR Part 50 regulations. Adequate informed consent will help prospective subjects understand study requirements, follow-up expectations and may reinforce their commitment to a study. Informed subjects may be more compliant and less likely to drop out of a study, since they are equipped with information and know what to expect;

3. ensuring that qualified personnel, per 21 CFR 812.43, and sites that have successfully undergone the site qualification and selection processes, are conducting the study;

4. ensuring that adequate monitoring, in compliance with 21 CFR 812.46, is in place. Adequate monitoring is supported by timely and regular review of monitoring reports to take immediate corrective actions where necessary. Sponsors should consider having a predetermined compliance strategy, i.e. suspending shipments of investigational product to a non-compliant site until evidence of compliance or conditions governing termination of the site; and

5. including Investigators who collect, maintain and report current, complete, and accurate study data. This is followed by source data verification, a quality control process, performed by a study monitor. These responsibilities are essential to trial quality in concert with the Sponsors monitoring investigator compliance.

Implementation of Quality Systems Approach

The following steps are instrumental in building quality into your clinical research process.

A. Optimize the protocol and data requirements of the study, for example has there been appropriate medical expert feedback on the protocol prior to finalization? This feedback can come from steering committees composed of clinicians, global or national principal investigators, clinical scientists or FDA reviewers, clinical monitors and biostatisticians. Taking this extra step in protocol development can avoid costly misunderstandings and protocol deviations down the road. Does the study design answer the right questions? Determine if the study eligibility criteria are appropriate and not unnecessarily restrictive. Obtain clinician feedback on protocol required procedures- are they clinically reasonable and appropriately timed?

To optimize the data set, collect only essential data relevant and critical to safety and effectiveness endpoints. Consider asking FDA to review and provide feedback on the data plan to be sure it meets guidance. Design the data collection forms to collect numbers electronically versus text fields to avoid mis-interpretation/mis-classification of data. Implement remote data checks for missing or out-of-range data. Considering projected adverse event rates for the type of technology under investigation, to allow for the ongoing measure of whether safety and pre-determined performance results are trending as expected?

Steps should be taken to minimize the incidence of protocol deviations. Analyze protocol deviation patterns to determine if they are site specific or across the entire study; for example determine:

- if protocol required testing is commonly being omitted;
- that appropriate subjects are being enrolled;
- if there is a common set of inaccurate or missing data fields; and/or
- if there is high subject non-compliance.

Remediation is indicated if problems are noted. This could include discussions with investigators to determine causes. If across site problems are noted, in concert with FDA determine if the study is salvageable or if a new study is needed. Other solutions include revising study Inclusion/Exclusion criteria or modifying endpoints and measures.

B. Select qualified investigators. Review CVs and evaluate the research experience of prospective investigators. Get a sense of their commitment to research by asking a few basic questions:

- have they done human studies before and are they knowledgeable of clinical research regulations and guidances?
- do they have sufficient time, adequate staff and equipment/support systems?
- is there understanding that the Investigator Agreement is a contract?
- do they understand the difference between a clinical investigator versus clinician?
- do they possess the appropriate skill level and experience with similar products and relevant experience with the disease under study?
- are research staff members certified by one of the professional associations?
- do they know what essential documents are?

C. Be sure to provide adequate study training. Emphasize the importance of the informed consent process, clearly communicate study-specific expectations, review any procedures that are unique to the study or product focusing on compliance with non-standard of care procedures required by the protocol. Providing a rationale why a particular non-standard of care procedure is required a priori may help the investigative sites be compliant with non-standard of care requirements. Review regulatory requirements with the Investigators and site staff. Explore human factors concerns that may be relevant to the product. If the study is modified, train on significant changes to the product or study protocol and document training on study modifications.

D. Ensure adequate monitoring. Monitoring is only one aspect of Sponsor oversight of a clinical trial. Standard Operating Procedures (SOPs) should exist for all aspects of study conduct to promote consistency. Select qualified monitors and promote the "everyone's a monitor" mentality. Monitoring reveals problems and can help identify solutions; query generation and follow-up action items/guidance alone do not secure compliance. If a repeatedly non-compliant site is retained there must be compelling, documented reasons to retain them.

In some circumstances risk based remote monitoring may be more efficient and effective. Risk based remote monitoring can be combined with traditional monitoring which is essential for some aspects of study conduct, i.e. verification of site facility and resources. Frequent and early monitoring catches non-compliance before recurrence and provides an opportunity to course correct before study integrity is in jeopardy. Regular source data verification avoids large number of queries and late database problems and can provide regular training opportunities to continuously improve site performance. Adequate monitoring should routinely evaluate human subject protections, communication with the IRB/EC, protocol compliance, rationale for and documentation of protocol deviations, source data verification, current, complete and accurate Case Report Forms and evidence of 100% investigational product accountability.

E. Ensure investigator compliance. Concerns about the study can result in FDA refusal to accept site data in support of a marketing application. Work with the site to resolve compliance issues as they arise. FDA does not expect perfection when they conduct inspections, but what they do expect is that when mistakes are made or errors are detected, that corrections and preventions are put in place to avoid repetitive occurrences. In order to implement an effective correction/prevention, the root cause of the problem must be determined. Many times root cause analysis is not done correctly which leads to an ineffective corrective action. Document efforts aimed at correcting quality issues.

F. Internal Audits. Consider implementation and maintenance of quality procedures and conducting quality assurance audits of the Sponsor and clinical research sites to assess compliance. Sections 6.11 and 8.1 of ISO 14155:2011 [E] outline the steps to be taken to conduct process level checks of the design, conduct, and monitoring of a study, as well as the generation, documentation, recording and reporting of trial data compliant with applicable standards and regulations.

BUILDING QUALITY INTO A CLINICAL STUDY

STARTS ON DAY 1

It involves a multifunctional approach that includes input from FDA, Sponsors, IRB/ECs, monitors, sites and investigators and clinical vendors (i.e. Core Labs). Implementation of a quality systems approach ensures human subject protection, regulatory compliance, and data integrity. Utilizing a Quality Systems approach in clinical research can lead to consistency and process improvements in the conduct of human clinical studies.

MARY LEWIS Senior Clinical Research Specialist

Mary arrived at IMARC in April 2012, bringing with her a wealth of clinical research experience. She has been involved in research since 1974, starting her career at Union Carbide Corporation as a Senior Research Technician performing carbon fiber technology patent work. Since then, Mary has held various positions of importance in the clinical research field, including diversified experiences as a Decentralized Senior Clinical Research Associate at Parexel International, as a Manager of Clinical Studies at NeuroControl Corporation, and as Director of Clinical Research at Fujirebio Diagnostics.

Her most recent role before joining IMARC was as Senior Director of Clinical Research at Stryker Orthobiologics where her responsibilities included: managing clinical studies in support of new product regulatory clearances, establishing clinical operating procedures, executing sponsor and clinical site GCP audits, pre- and post-market study management and training and supervising staff.

Mary is involved in IMARC's auditing activities, utilizing her extensive knowledge in clinical monitoring and auditing, along with previous involvement managing multiple site and Sponsor audits by FDA. Clinical auditing involves taking a big-picture view of research related activities and comparing them to pertinent federal and international regulations and standards as a means to assess compliance. Within IMARC, Mary is a resource for monitors looking for that auditor's perspective on handling compliance questions. Additionally, her familiarity with the research process requirements for Sponsors allows her to provide a helpful perspective. Mary's clinical experience has covered various therapeutic areas including: spinal implant technology, biomarkers for epithelial ovarian cancer and malignant epitheloid and biphasic mesotheliomas, vertebroplasty in treatment of osteoporotic vertebral compression fractures, and post-stroke rehabilitation using functional electrode stimulation.

Mary received her Bachelor of Science Degree from Bowling Green State University. She is also a member of the Society of Clinical Research Associates (SoCRA).

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