

THE PAPER TRAIL: CRFs, SOURCE DOCUMENTS and DATA COLLECTION TOOLS

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Abstract: *Food and Drug Administration (FDA) auditors cite deficiencies in record keeping as the most common shortfall when auditing. The FDA Code of Federal Regulations and the International Conference on Harmonization/Good Clinical Practice Guidelines require evidence of safety and effectiveness to support marketing approval for drugs, devices, and biologics. This article explores strategies for developing and using case report forms, source documents, and data collection tools, and provides examples. The advantages and disadvantages of each are discussed. The choice of tools is influenced by personal bias, resources, and cost. The ultimate goal is to have the most reliable and retrievable data possible. Whatever method or source is selected, if it is not documented, it did not happen.*

Introduction

One of the basic goals of clinical trials is to obtain data for the safety and/or effectiveness of a drug or a device in order to get that drug or device to market. When creating a clinical development plan, it is necessary to consider the end product: the information needed for the package insert/marketing application. The clinical development plan must be built backwards from that to meet study goals. In order to create the clinical development plan, it is necessary to consider what the protocol and case report forms (CRFs) must look like in order to obtain appropriate data to support the marketing application.

Developing Case Report Forms

CRFs should be developed simultaneously with the protocol. Investigators have many responsibilities, one of which is to “prepare and maintain adequate

and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation” (21 CFR 312.62). The International Conference on Harmonization (ICH) *Good Clinical Practice Guidelines* define CRFs as “a printed, optical, or electronic document to record all of the protocol required information to be reported to the sponsor of each trial” (ICH/GCP 1.11).

Developing CRFs should be a team approach. This enables everyone to provide input and to meet all individual needs. Members of the CRF development team include representatives of clinical staff, medical monitors, data entry/management, quality assurance, and regulatory affairs.

Standardized and Protocol- or Study-Specific CRFs

There are two classifications of CRFs: standardized and protocol- or study-specific. Standardized forms are the same across multiple studies. Examples include inclusion/exclusion criteria, demographic information, history and physical examination, medication log, and adverse events. People become familiar with standardized CRFs, which leads to efficient data collection and fewer data entry errors. However, specific protocol needs might not be met.

Protocol-specific CRFs are designed to meet specific data needs for specific protocols, disease entities, or time points. Examples include laboratory data, patient symptom assessment sheets, specific tumor disease/typing, and molecular endpoints. For example, in one study where neurologic toxicity was a concern, an extensive neurological exam was required. This was listed on the CRF, which also served as a

guide for the physician to ensure that the exam was conducted and for the data management personnel to transfer data on the neurological exam to the CRF. For breast cancer, specific tumor disease/typing could include the ERP positive status.

Protocol-specific CRFs are great for picking up specific time points and cuing study staff about specific data needs. However, staff may not be familiar with protocol-specific CRFs, leading to inefficient data collection and data entry errors.

CRF Organization

There are different schools of thought on CRF organization. CRFs can be organized by visit, type of data (log style), or a combination of visit and type of data. Organizing CRFs by visit makes it easy for the study coordinator to just pull a patient's packet when he/she comes into the clinic. CRFs can also be organized by the type of data. Some things, such as adverse events, continue throughout the trial.

We prefer to organize CRFs using a combination of visit and type of data. Thus, the CRFs are in chronological order, with some forms (e.g., concomitant medication, diagnostic radiology, and adverse events) filed individually in the back of the packet.

CRFs should be user-friendly and be designed so that researchers can obtain all necessary information. Make it easy for data collection and data entry staff. It is essential to obtain all necessary data. There is a careful balance between collecting too much data or too little data.

An Approach to CRF Design

Table 1 outlines an approach to CRF design. Certain information flows from form to form (e.g., study site number, protocol number, and patient initials). Standardize this in format headers on each form.

Keep the CRF simple and clear. Use concise and clear instructions, which can be a difficult task. Try to avoid leading questions or questions with multiple responses. Avoid blank items. Instead, use a checkbox to indicate answers such as "unknown" or "not assessed."

Allow adequate space for response. Include the number of characters allowed for each response so that people know how concise they need to be in completing the CRF.

Place date and time fields in a consistent order. There are many different formats used. Be very clear about the format used (e.g., mm/dd/yyyy). This is an important area to quality-check.

Include extra forms to accommodate additional or unscheduled visits. Test and improve the CRF before the trial starts.

TABLE 1
An Approach to CRF Design

- Standardize format headers
- Focus on simplicity and clarify
- Provide concise and clear instructions
- Avoid leading questions or questions with multiple responses
- Avoid blank items
- Allow adequate space for response
- Pose questions only once
- Use checkboxes where possible
- Place response fields consistently
- Use pre-determined responses in a consistent, meaningful order
- Place date and time fields in a consistent order
- Include extra forms to accommodate additional or unscheduled visits
- Pre-print code numbers
- Test and improve the CRF before the trial starts
- Avoid modifying the CRF during the trial

Pose questions only once. It may seem like a good Q/A check to repeat a question in multiple places but you may get different answers.

The more check boxes the CRF has, the quicker the form can be completed and the less handwriting is necessary (handwriting can be difficult to read). Place response fields consistently. Use pre-determined responses in a consistent, meaningful order (e.g., "yes", "no" "unknown"). Use pre-printed code numbers, which help data management personnel enter data.

After working so closely in developing a CRF, mistakes are difficult to detect. For example, we noted that one CRF asks for the "last date of death."

Avoid modifying the CRF once the trial begins. Once the CRF is developed, the data collection tools and source documents are set up. Changing the CRF affects these as well. Factors to consider when choosing or designing CRFs include: their advantages/disadvantages, personal bias, availability of resources, and cost.

Electronic Records, Electronic Signatures

Electronic records and signatures are covered in 21 CFR 11 (called Part 11). Subpart A, General Provisions, covers scope, implementation, and definitions of electronic records and electronic signatures. Subpart B contains the electronic records regulations, and Subpart C contains the electronic signatures regulations. The regulations define electronic records as, “Any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system” (21 CFR 11.3(6)). Basically, anything that happens to a record in a database is considered an electronic record.

Part 11 makes electronic records equivalent to paper records and electronic signatures equivalent to handwritten signatures. It is a record regulation, not a computer regulation; it is about the record in the computer. The FDA *Guidance for Industry: Computerized Systems Used in Clinical Trials* defines an electronic CRF (e-CRF) as “an auditable electronic record designed to record information required by the clinical trial protocol to be reported to the sponsor on each trial subject.” This is the same definition as a paper CRF with the addition of “electronic record.”

Table 2 outlines requirements for electronic records. Computer systems come and go, and software changes continuously. Sponsors and sites must maintain the ability to retrieve and review data from older computer systems and programs.

An electronic signature is unique to one individual. One electronic signature cannot be used for someone else or reassigned to someone else.

Part 11 defines an audit trail as “a secure computer generated, time-stamped electronic record that allows reconstruction of the course of events related to the creation, modification, and deletion of an electronic record” (21 CFR 11.10(e)). An audit trail “requires persons who use electronic record systems to maintain an audit trail as one of the procedures to protect the authenticity, integrity and, when appropriate, the confidentiality of electronic records” (21 CFR 11.10(e)). If a record is deleted, it must still be kept in the audit trail.

Source Documents

Source documents, original documents, data, and/or records, are very important. Examples of source documents include hospital records, subject diaries, X-rays, e-mail, and electronic records. When the original observations are entered directly into a computer system, the electronic record becomes the source document. If an electronic record will be used as a source document, this should be defined in the protocol.

One of the most common deficiencies cited by the FDA is a lack of documentation. When in doubt, document it. If it is not documented, it did not happen, according to the FDA.

TABLE 2
Requirements for Electronic Records

Electronic records must be:

- Reliable
- Trustworthy
- Secure
- Accurate
- Confidential
- Authentic
- Have an audit trail
- Generate accurate, readable copies
- Have a validation process
- Be compatible with the FDA’s work

Data Collection Tools

Data collection tools assist in the collection and documentation of data that are needed to complete CRFs. Formats include visual analog scales, open-ended questions, and checklists. Visual analog scales are frequently used in cancer studies, (e.g., a pain scale of 1 to 10). Using checklists is quick and easy.

Table 3 outlines examples of data collection tools. Diaries and calendars should include a lot of information, such as who to call for what, and when and where to call. Also, leave space for patients to write symptoms down. Unfortunately, patient compliance with diaries and calendars is poor.

Table 3
Examples of
Data Collection Tools

- Diaries and calendars
- Telephone interviews and logs
- Mail surveys
- Checklists
- Worksheets

Using PDAs has improved compliance somewhat. When patients sign on with a code, their signature is dated and stamped. In some studies, patients can complete diaries or calendars by phone.

The National Cancer Institute’s Medical Oncology Clinical Research Unit uses a telephone log to track patient symptoms and problems, and a progress note assessment sheet for physicians. A symptom sheet with a scale of 1 to 10 helps jog patients’ memories of any symptoms they may have experienced.

Patient Compliance

Patient compliance is a key component to clinical trials. Non-compliance impacts the required sample size. For example, with a sample size of 56 and a 90% compliance rate, accrual must be increased by 22%. This results in more patients being exposed to the study agent, and increases the amount of time and paperwork necessary to complete the study, as well as the study's cost.

Reasons for patient non-compliance include:

- Psychosocial problems
- Medical problems
- Personality conflicts with the investigator
- Inconveniences
- Feeling of being used by the medical system
- Boredom with routine visits
- A trial schedule that is too difficult.

Table 4 outlines strategies to improve patient compliance.

The ultimate goal is to have the most complete, accurate, and reliable data possible.

Table 4 Strategies to Improve Patient Compliance

- Reminders
- Pleasant/comfortable visits
- Celebrations
- Newsletters
- Education
- Contract with subject
- Graduated regimen for complex trials
- A feeling of being vested in the trial's results
- Reward compliance
- Enlist family/peer group support

Protection of Human Subjects

Since 1945, various codes and principles for the proper and responsible conduct of human experimentation in medical research have been established. The best known of these are:

The Nuremberg Code of 1947

<http://ohsr.od.nih.gov/nuremberg.php3>

Which enunciates the essential requirement of *voluntary informed consent* of the human subject.

The Helsinki Declaration of 1964

<http://www.fda.gov/oc/health/helsinki89html>

Which established principles for carrying out biomedical research, including; for any research on humans, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study, and the discomfort it may entail.

The 1978 Belmont Report

http://osophs.dhhs.gov/irb/irb_introduction.htm

Which summarized, among other issues, the basic ethical principles identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which were:

Respect for Persons, Beneficence, and Justice.

Under the principle of Respect for Persons, subjects, to the degree that they are capable, are to be given the opportunity to choose what shall or shall not happen to them.

Additional Resources

■ **Information Sheets: Guidance for IRBs and Clinical Investigators**

<http://www.fda.gov/oc/ohrt/irbs/default.htm>

■ **A Guide to Informed Consent**

<http://www.fda.gov/oc/ohrt/irbs/faqs.html>

■ **Office for Human Research Protections U.S. Department of Health and Human Services**

<http://ohrp.osophs.dhhs.gov/polasur.htm>

■ **Part 50 Protection of human subjects**

<http://www.fda.gov/oc/gcp/regulations.html>

WEB-BASED EDUCATION AND TRAINING

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Abstract: *Kaiser Permanente, Southern California uses Web-based education and training to improve investigator knowledge and compliance. This article highlights the organization's participation in the Collaborative IRB Training Initiative, a Web-based tutorial and testing site that is continually updated to reflect changes in human subject law and regulation. The Collaborative IRB Training Initiative consists of 13 core units and an option for an additional institution-specific module and quiz. More than 92 institutions currently participate. The program's advantages, which include user friendly program management; 24/7 access; cost effectiveness; CME credits; a printable certification of completion; and institutional reports, are described.*

Founded in 1945, Kaiser Permanente is the nation's largest non-profit health plan serving 8.5 million members in California, Colorado, Georgia, Hawaii, Maryland, Ohio, Oregon, Virginia, and Washington, DC. Kaiser Permanente has 29 medical centers, 423 medical offices, 90,000 employees, 12,000 physicians, and 8 independent institutional review boards (IRBs). Each IRB reviews research conducted within its region. Many people have been members of Kaiser Permanente for more than 20 years. HMOs such as Kaiser Permanente are a good resource for conducting research because they provide medical services to many members inside a closed healthcare system with combined institutional records (e.g., laboratory, pharmacy, cost, and primary care information). The particulars of this article are limited to Kaiser Permanente in Southern California.

Education and Training Programs at Kaiser Permanente, Southern California

The Department of Research and Evaluation has used seminars and discussion groups, a local education requirement, and Web-based training to improve compliance at Kaiser Permanente, Southern California. In October 2000, the requirement that all federally-funded studies have an educational component documented in the grant proposal went into effect. In November 2000, Kaiser Permanente, Southern California decided that all investigators and IRB members should complete the University of Rochester manual and obtain a certificate of completion. This was required for all research studies, regardless of the funding source. In January 2001, an e-mail announcement was sent to all investigators explaining that documentation of human subject education would be required by

April 15, 2001. In March 2001, an e-mail reminder about the deadline was also circulated.

Kaiser Permanente, Southern California uses different types of educational programs to capture different research groups. People are trained according to regions/committees, location, and specialty. Regions/committees, for example, include the accreditation and licensing committee, the data acquisition team, the regional bioethics committee, the regional cancer committee, residency program directors, and the technology assessment guidelines unit. Examples of training by location and specialty include Los Angeles Medical Center (cardiology and infectious diseases) and San Diego Medical Center (allergy and gastroenterology). Categorization by specialty also includes, for example, laboratory managers, the orthopedic study