The Importance of Standard Operating Procedures in Clinical Trials

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This special contribution provides insight into the role that standard operating procedures (SOPs) play in an imaging department and their value in building a high-quality research site. If you have ever participated in a clinical trial, many of the principles described in this article should be familiar. However, this article goes a step further by presenting information from a pharmaceutical or device sponsor's point of view—what the sponsor expects from a site during the course of a research study. This article is intended not to provide a complete set of instructions on how to create a great SOP but, instead, to present guidelines to ensure that the key elements are included. After reading the article, you will be able to define SOPs as they pertain to the clinical trial environment, describe key components of an SOP, list the clinical research SOPs that exist in your institution and imaging department, identify which additional SOPs might improve site performance, and describe how the sponsor relies on SOPs to ensure that the highest quality of research is attained.

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Standard operating procedures (SOPs) are everywhere and are especially important in nuclear medicine. They are a set of detailed instructions that define and standardize procedures in clinical trials. Even without realizing it, you have used SOPs in clinical practice. However, they are particularly essential in helping sites follow protocol-specific parameters in clinical trials, which are often quite different from most clinical procedures. SOPs act as an effective catalyst to obtain usable results for the sponsor, often after years of work have been completed and millions of dollars have been spent. They have a large-scale effect, as they ensure reproducibility and consistency from site to site, thereby confirming the reliability of the data as a whole. SOPs are a lot like protocols, but in the world of clinical trials, the word *protocol* is actually the entire layout of the research plan: a document that describes the objectives, design, methodology, statistical considerations, and organization of a trial.

The key purpose of clinical research SOPs is to help you and your research department stay in compliance with good clinical practices (GCPs): an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. GCPs are published by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and cover every aspect of clinical trials. Since clinical research is global, the ICH recognizes the importance of standardizing methods of performing, analyzing, and regulating clinical trials across nations. Representatives from Europe, Japan, and the United States (the Food and Drug Administration [FDA]) make up the ICH, which meets at scheduled intervals to review established guidelines on many topics to determine current relevance and application within the ICH member countries. Some of the published topics include safety management in clinical trials. Others are about dose response, data collection, statistical principles, and, of course, GCPs. The guiding principle of the ICH is to develop scientific consensus between regulatory authorities and industry. The ICH is considered the authority on clinical research, and all of its publications are available on its Web site (www.ich.org). The ICH does not override federal U.S. regulations governing clinical research; instead, this body is considered to be complementary. When a pharmaceutical or device sponsor refers to the ICH or GCP, the sponsor is indicating these established guidelines.

The ICH publication most important for a clinical research site is the GCP guideline, publication E6. It is a tremendous reference with which all research personnel must become familiar, since all clinical research must follow GCPs (*1*). Table 1 lists the main topics found in this publication.

Although the ICH GCP guidelines mention SOPs as a way to implement quality processes that protect the safety and welfare of human subjects, SOPs are not specifically mentioned in the FDA regulations as a requirement. However, there is guidance in the regulations that infers responsibilities

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TABLE 1
Main Topics in ICH Publication E6: Guideline for GCPs

Topic	Subject
1	Glossary
2	Principles of ICH GCPs
3	Institutional review boards
4	Investigator
5	Sponsor
6	Clinical trial protocols
7	Investigator brochure
8	Essential documents for conduct of clinical trials

associated with clinical research, and SOPs formalize them in written form. Sponsors closely monitor study sites regularly to supervise the quality and integrity of the study data. This close monitoring also helps to ensure the protection of human subjects. Just as a study site has to report to the sponsor, sponsors must report to the FDA and other regulatory bodies. SOPs support a strong clinical research environment and provide the best way to help your site stay in compliance and contribute to the overall success of a study. Table 2 lists the main U.S. regulations that cover clinical research.

Establishing and following SOPs is usually routine for many clinical research departments, but often some exact parameters for imaging contained in the SOP are not communicated to the imaging technologist. Introducing imaging into a clinical trial creates novel challenges regarding study logistics, technical standardization, and regulatory compliance. One of the biggest concerns for pharmaceutical and device sponsors is image standardization, which increases quality across sites in a multicenter trial. Many a product has required extra months to reach market because the sites did not follow the protocol, with the result that data had to be discarded and new patients enrolled to replace the lost data. Even worse, the FDA may have to tell the sponsor to perform an additional study because the initial images provided insufficient data to support the new drug application. An ethical concern that arises from these errors is the need to discard data collected from subjects who have donated hours of their time for research while often in poor health and receiving no direct benefit. Setting up SOPs for an imaging department is a starting point to ensure these types of situations are avoided or, at the least, minimized.

When any SOP is developed, a key and required component is an effective date on which the research study will begin and, if applicable, an expiration date on which the study will end. For example, the date could be a timeline such as "2 y from the effective date." This component will help in developing a way to ensure that SOPs are reviewed regularly to keep them effective as useful, working documents. SOPs may range from the general and broadly based to the very specific. Many institutions have standard SOPs on patient identification and confidentiality, patient safety and the reporting of incidents, and infection control. These SOPs may also be applicable to your department and should be kept available in case a sponsor requests to see them. SOPs used as an educational tool, especially for new personnel, on day-to-day procedures in a department may be quite extensive, but others can be just a couple of pages. As long as the topic is completely covered within the SOP, length is not an issue. Table 3 list specific items recommended for inclusion in clinical research imaging SOPs.

TABLE 2
Key CFRs for Clinical Research

CFR title and part	Subject
21 CFR 312	Requirements for investigational new drug
21 CFR 50	Protection of human subjects
21 CFR 56	Institutional review boards
21 CFR 46	Health Insurance Portability and Accountability Act
21 CFR 812	Investigational devices

In all clinical trials that use an investigational drug or device, control of the product is a key focus of federal regulations on the ICH guidelines. Investigational radiopharmaceuticals require additional oversight, and nuclear medicine departments must follow strict rules (either those of the Nuclear Regulatory Commission or those of the state) about how radiopharmaceuticals are handled. The best way to meet all requirements is to develop an SOP that addresses the use of investigational radioactive materials, following the guidelines established by ICH (E6 4.6.3.) and 21 CFR 312 (*2*), title 21 of *Code of Federal Regulations* part 312. Sponsors want to know who is authorized to receive, handle, dispense, store, or dispose of any type of investigational product. They also want to know that it will be kept in a locked location not accessible to the public or nonauthorized personnel and how will it be accounted for at the end of the study. Incorporating the items listed in Table 4 will help get you started.

In addition to the SOPs that address handling the drug, sometimes special radiation safety precautions should be in place to protect the subject and family members. ICH E6 (guideline 4.6.6) offers guidance on this issue. Certain

TABLE 3
Components for Clinical Imaging SOPs

Component	Subject
1	General background information on what type of imaging SOP covers
2	Required imaging personnel to perform tasks and their minimum level of training
3	Definitions for any imaging-specific terms
4	Required equipment (e.g., minimum PET camera specifications)
5	Specific equipment settings to use for different imaging requirements
6	When, how, and what quality control is done to ensure optimal results
7	Image interpretation and reporting criteria
8	Information technology support required for data acquisition, transfer, and storage of study images

TABLE 4
SOP Topics for Managing and Handling Radioactive Materials

Topic	Subject
1	Receipt, administration, disposal, and storage of radioactive materials
2	ALARA (as low as reasonably achievable) protocols
3	Employee safety/exposure to radioactive agents
4	Managing radioactive spills
5	Safety training (cardiopulmonary resuscitation, fire extinguisher location and use)
6	Emergency safety SOPs, such as crash cart locations and emergency response team numbers

radioactive tracers also require specific preparation instructions (e.g., fasting vs. not fasting), and an SOP for these is helpful. These written instructions reduce the risk of having to repeat the scan and expose the subject to additional, unnecessary radiation. If there are standard paper logs already developed in your department on these subjects, they can be assembled into one SOP that may be titled "Patient Imaging Guidelines."

Patient identifiers and private information must be managed per HIPAA (The Health Insurance Portability and Accountability Act of 1996–21 CFR 46), especially when research is involved. Often, sponsors set up a naming system for study identifiers, such as using initials or numbers, which are used both for completing case report forms and for transferring image data over the Internet to a sponsor. If your facility uses electronic medical records, such as electronic signatures, they need to be 21 CFR 11–compliant to ensure that an audit trail can be followed. Even if a hospital system uses electronic medical records, a nuclear medicine department may still keep paper records for internal use, or a radiopharmacy may have a software program for tracking patient dosing history that is not integrated with electronic medical records. Developing and maintaining an SOP that describes where each data point is kept and how it is managed are extremely helpful for the study monitor and your own department.

We have covered SOPs for the study drug, protocol procedures, and protection of human subjects—3 critical areas of clinical research. However, documentation is also vital to the success of a study. If something is not written down, it did not happen—and that one missing element can have a major impact on the subject's care in the study. The federal regulations require that the investigator keep a case history of the subject, and source documentation must match clinical research records. Documentation in the medical record that a patient provided written informed consent (21 CFR 312.62 (b)) is one of the first things for which a sponsor checks. An SOP on this topic would include key points such as never using eraser fluid, never erasing records or making them illegible, making sure that the person who changes the record signs and dates the change, and keeping records transparent (i.e., ensuring that the original entry and the changed entry are always visible). A clinical trial audit by the institutional review board, the FDA, or other regulatory agencies can occur many years after the study is completed. Records must be stored in a protected location in an orderly fashion (by study) so they can be retrieved at any time, and this storage method itself must be documented in an SOP. In most cases, one SOP may be enough since many of these principles can conceivably cover both standard departmental policy and research. Do not duplicate efforts.

To begin, do not simply assume you need to create new SOPs. Gather existing institutional and departmental SOPs that cover the areas mentioned in this article. Most academic centers have SOPs that are accessible to view via the Internet, and some are even downloadable. Reviewing these can assist you in your task. Determine what you have and where gaps exist, and then create SOPs to cover the missing areas. Use these SOPs as training tools for new employees and as a refresher reference for staff. By offering the sponsor a chance to review your SOPs, you increase the sponsor's confidence that you have the skill and capability to complete what is required by the protocol and you show the sponsor that the data are more likely to be standardized, reproducible, and accurate. However, SOPs will not be helpful if they are not kept current or are not followed. Even when the best SOPs are in place, they have to be followed in order to produce good and credible data.

If you are being evaluated for a potential study or plan to expand your research department, creating and following SOPs as described in this article can help contribute to recognition of the excellence of your site.

DISCLOSURE

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