DOCUMENTATION in Device Studies

Proving Patient Protection

Introduction

I can still recall the voice of my thesis advisor in graduate school saying in regards to our laboratory research, ***"If it's not documented, it's not done!"***. Since those grad school days, I've had a love-hate relationship with documentation. First as a biomedical researcher in a pre-clinical lab and then as a clinical researcher, documentation, while essential to telling the story of what occurred, sometimes seemed like one big road block to actually getting anything done in a day.

In the lab, documentation served two roles. First, to communicate to the others the details of an experiment, from the exact make-up of test substances, timing of media changes, problems encountered, actions taken, test results, repeat experimental results, and even scribbled calculations. And second, documentation served to prove that we did our job in the event that the job we did got called into question.

The roles that documentation serves in clinical research are exactly the same – to communicate to other health care professionals and to demonstrate the competence with which we do our jobs, and for clinical research, that means being able to prove that subjects were protected throughout the entire clinical research process. As inferred in the terms "clinical research" there are documentation requirements pertinent to a subject's "clinical" status and there are documentation requirements pertinent to the "research" itself, thus increasing the documentation efforts required exponentially.

While many look at informed consent as the main way to document patient protection in clinical research, this is only the beginning of the story. As clinical researchers, whether we work for the sponsor, the contract research organization (CRO), or the investigative site, we are responsible for ensuring patient protection throughout the clinical research process, and we could be called on to prove that we did just that. How do we prove it? Through documentation. It's all about doing it right, and taking credit for it. This white paper will examine a small sample of the requirements in clinical research, which at times, can be confusing, and will provide recommendations for how to think through situations to ensure that your documentation adequately proves that you protected subjects throughout the study.

Regulations Governing Clinical Research

As stated on the FDA website[1], the primary regulations that govern the conduct of medical device clinical studies are included in the Code of Federal Regulations, Title 21 (CFR), as shown in Table 1.

Table 1

Federal Regulations Pertaining to Medical Device Clinical Trials	
21 CFR 812	Investigational Device Exemptions - covers the procedures for the conduct of clinical studies with medical devices including application, responsibilities of sponsors and investigators, labeling, records, and reports.
21 CFR 50	Protection of Human Subjects - provides the requirements and general elements of informed consent.
21 CFR 56	Institutional Review Boards - covers the procedures and responsibilities for institutional review boards (IRBs) that approve clinical investigations protocols.
21 CFR 54	Financial Disclosure by Clinical Investigators - covers the disclosure of financial compensation to clinical investigators which is part of FDA's assessment of the reliability of the clinical data.

The regulations describe in detail the requirements that must be followed when conducting clinical studies. Of course, there are several ways to meet the requirements, and ensuring these efforts are documented is sometimes a challenge. Thinking strictly of these regulations, we can draw the parallel to subject protection with each of them. It boils down to knowing the regulations, complying with the regulations, and documenting your efforts to prove compliance.

21 CFR 812 – Investigational Device Exemptions

The regulations for Investigational Device Exemptions cover the requirements for the conduct of medical device clinical studies. In 21 CFR 812.40, the General Responsibilities of Sponsors are described. One responsibility the sponsor has is to select qualified investigators. Although this is one relatively simple requirement, there are many documentation considerations to show compliance. How does the sponsor ensure the investigators are qualified by training and experience? They likely do so by looking at the curriculum vitaes (CVs) of the investigators and ensuring that they are qualified to practice the type of medicine under study. Many companies just collect a CV and check this requirement off their list. But is this enough? Maybe. Maybe not. Other considerations:

- If the study requires a certain level of medical professional, the corresponding licensure could be collected.
- If the device is complex, requiring special training for device delivery, training records that document the qualifications of the trainer, the topics covered in the training session, hands-on activities covered in the training session, and the demonstration of competence may be necessary to adequately fulfill the regulatory requirement of "selecting qualified investigators."
- Additional documentation to reflect training on the protocol, human subject protection regulations, or any other sponsor-specific requirement may also add depth to the documentation described herein.

Adequate documentation of how qualification and experience was assessed can look differently for two different studies. It is important that your study team examine the requirements of the study and then determine what documentation will be needed to demonstrate compliance with this regulation for the particular study on which you are working.

21 CFR 50 – Protection of Human Subjects

Compliance with 21 CFR 50 clearly demonstrates patient protection, as the title of this Part illustrates. For this example, let's consider 21 CFR 50.27, which describes the documentation of informed consent. In general, the requirements are that consent shall be documented by a written IRB-approved consent form that is signed and dated by the subject, and a copy shall be provided to the subject. It sounds simple, but if you ask clinical research professionals what is required, answers will vary. Some will say having an original signature on a consent form is sufficient, while others will passionately argue that a documented description of the process is necessary, and must be entered into the hospital record.

How can you determine what is sufficient for your study? Consider the following scenario, which demonstrates that there are different ways to comply with this regulation.

A subject has been enrolled into a peripheral stent study. The procedure took place on Tuesday, March 6th, 2012, at 8 a.m. The consent form for the study was signed and dated March 6th, 2012, on the IRB-approved version of the consent, and the Principal Investigator also signed and dated the form on that day.

Is the signed consent form enough documentation for this subject?

In this case, the document itself is probably not enough. If the procedure was at 8 a.m., that does not leave very much time for that subject to arrive at the hospital and prepare for the procedure, let alone consider participation in a clinical trial. And if the consent was signed on the way to the procedure, did the copy of the consent make it home with the subject?

You ask the Research Coordinator about this particular case, and you learn that the subject had been to the hospital at an earlier date, and the study was presented at that time. The subject was sent home with the consent form to consider participation in the study and was called between visits to discuss the study schedule and requirements. Upon presentation to the hospital on March 6th, 2012, the subject felt that all of her questions had been answered and signed the document prior to entering the cath lab. A copy of the consent was given to her husband for their records.

If all of these activities were written in the subject's research chart, or possibly even the hospital chart, this would clearly demonstrate proper informed consent. The study site should take credit for all the steps taken to protect subjects by using thorough documentation.

Conversely, there may be cases where the consent document alone is enough to demonstrate compliance with this regulation. Consider that the consent was signed days or weeks before the procedure. There is a statement on the consent form to indicate that by signing the form, the subject confirms that all questions were answered and a copy had been provided. The signature on the document would indicate that the subject was properly informed of the procedure and consented willingly.

Again, documentation can look different for different studies, or even for different subjects in the same study. In this case, the Principal Investigator and her team would need to consider the circumstances for each subject's participation in order to adequately document compliance with the regulation.

21 CFR 56 – Institutional Review Boards

IRBs play a large role in patient protection and have their requirements described in 21 CFR 56. As detailed in 21 CFR 56.108 (b) IRBs must follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA. This includes adverse event and noncompliance reporting. Oftentimes IRBs base their requirements for prompt reporting on whether or not the event caused unnecessary risks to subjects, if they were anticipated or unanticipated, serious or nonserious. The responsibility for identifying and reporting of events lies in the hands of the site staff, and the IRB reviews and acknowledges/approves the information as it comes through the door. Is this sufficient to protect subjects enrolled in clinical studies? Depending on the information the IRB receives it may not be. Consider:

- If the study is using a novel, high-risk procedure with multiple subjects enrolled and no adverse events are reported at the continuing review, the IRB may document in the response that the study team must confirm that all hospital records were reviewed and no events were noted. The IRB may also require the study team to report more frequently than annually to ensure subject records are reviewed regularly for events.

- If events are reported to the IRB and repeatedly fall outside of the reporting requirements, the IRB may document in their response to the site that they require a documented plan to ensure events are reported in a timely manner. The IRB would document review and approval of the plan.

- If monitoring visits repeatedly result in events being reported to the IRB outside of their policies, the IRB may review policies with the study staff, providing training records to the staff as documentation. The IRB may also perform an internal audit of the records to ensure no additional required information went unreported and document their findings in an internal report for the study files.

For many studies, the information the IRB receives is reviewed as it is received and considerations are made for whether or not the study remains appropriate for the site. However, there may be cases where the IRB will need to document efforts to ensure prompt reporting of events and in turn demonstrate the efforts to protect the subjects being treated at the institution.

21 CFR 54 – Financial Disclosure by Clinical Investigators

FDA reviews data to ensure appropriate steps have been taken in the design, conduct, reporting, and analysis of the studies to minimize bias. One source of potential bias is financial conflict of interest. 21 CFR 54 describes the requirements for sponsors to disclose those potential sources of bias as they occur.

In 21 CFR 54.4 (a), the applicant must submit either a certification or disclosure statement for each clinical investigator that participates in the clinical trial.

Now, this requirement not only lies on the sponsor. In 21 CFR 54.4 (b), the investigator shall provide to the sponsor sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure. Furthermore, the investigator shall promptly update this information if any relevant changes occur in the course of the investigation and for one year following completion of the study.

Many sponsors ask investigators to complete their own financial disclosure form and then use this information to submit the appropriate information to the FDA. Is this adequate documentation to show compliance with the stated regulations? Possibly. Other considerations:

- If the study has a multi-year follow-up, annual updates may be requested.
- If the study requires assistance from many study team members, including multiple coordinators and specially-trained imaging technicians, disclosure forms may be required of all staff who assist in collecting study-specific data.
- If there is potential for turnover in study personnel during the course of the study, the monitoring reports may include a question to confirm that all relevant team members have disclosed financial interests.
- If an investigator discloses a financial interest, the sponsor and/or investigative site should document a plan to minimize bias from that investigator, and have documentation to show the plan was properly carried out.

Conclusion

In summary, regulations that govern clinical research were put in place to protect clinical research subjects, and during an FDA inspection, the extent to which a clinical researcher complied with those regulations – or protected subjects – will come under scrutiny. If in doubt about appropriate documentation practices, read through the regulation in question and think to yourself, how can I document my compliance with that regulation? Oftentimes we make decisions in order to meet the regulations, but neglect to take that extra step to document our actions. If someone was to review your work, would it be clear that the regulations were followed? That subjects were protected?

Regardless of our role on the clinical research team, we are all responsible for ensuring patient protection throughout the clinical research process. It all comes down to doing it right and taking credit for it. Good documentation of how you met the subject protection requirements could come down to whether or not your actions were documented.

After all, ***"If it's not documented, it's not done!"***

Reference:

[1] *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm*

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As Chief of Clinical Operations, Brandy works with Sponsors, CROs, AROs and CRAs regularly to help ensure proper documentation for various regulatory, site and study requirements. She has used her monitoring skills in studies across the US, Europe and Japan, assisting in the management of monitors working in a wide range of therapeutic areas.

For more information on how you can help prepare your sites for a better outcome, starting from Day One, please contact John Lehmann at 440.801.1540 or via e-mail at jlehmann@imarcresearch.com.

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