Protocol Adherence and Recordkeeping: The Twin Pillars of GCPs

by Carl Anderson

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The study coordinator was clearly nervous. She had only been on the job a couple of weeks and already the FDA was conducting an audit. The former study coordinator, the one who actually worked on the study, had gotten married and was traveling in California and I was here to perform a clinical investigator inspection for a Phase III clinical trial.

This could be a nightmare situation for anyone. After all, it is the study coordinator, not the clinical investigator, who takes care of many day-to-day responsibilities during a clinical trial. The principal clinical investigator of this trial had hired the right people for the job, though. Both the study coordinator and her predecessor were experienced registered nurses. And both were well versed in the good clinical practice regulations (GCPs) that require following the protocol and keeping the necessary records for a successful clinical trial. By the end of the inspection, when I walked into the study coordinator's office she was sitting calmly at her computer, playing solitaire. Her biggest worry was finding a black knave to cover the Queen of Diamonds.

Year after year the two most common GCP deficiency categories for clinical research listed on the form FDA 483, Inspectional Observations, are protocol adherence and recordkeeping. If a clinical site fails to follow the protocol and keeps lousy records, the data generated are basically worthless and the FDA will consign them to the dustbin of clinical trials. Let's take a look at some common problems.

First, the clinical investigator needs to understand the difference between the practice of medicine and the conduct of research. In FDA regulated research the clinical investigator, usually a physician, conducts a scientific investigation *within the parameters of the protocol*. The protocol is part of the investigational plan that is required by the GCP regulations. It determines all facets of the study including who may participate, what the dosing levels are, the length of the study, important safety considerations, and the set data endpoints for determining efficacy. It is the blueprint for how the study is conducted.

It is important to remember that the protocol may require actions that differ from the usual practice of medicine. Here's an example. Many studies require performance of blood chemistry tests. I conducted an inspection of a study that required close monitoring of creatinine levels, which indicate kidney function. The Agency was concerned about the impact of the test article on the subject's kidneys.

This was an inpatient study and a blood test was taken at baseline, when the subject was enrolled. Then, 48 hours after the subject received the test article, a second blood test was taken. If the creatinine level had increased by 50%, a third test was required to make sure there weren't safety problems with kidney function before the subject was discharged from the hospital.

Normal creatinine levels are typically very low, perhaps .4-1.2 milligrams per deciliter (mg/dc). If the subject had a baseline test of .6 mg/dc and a second test of 1.0 mg/dc, both tests would be *within normal limits* for a blood creatinine test. However, this isn't the practice of medicine, it is a clinical trial. The rise between .6 and 1.0 mg/dc is 67%. The protocol *requires* a retest if the level rises 50%. The clinical investigator should perform the test to be in compliance with the protocol and the GCPs.

However, this clinical investigator didn't pay attention to the protocol. He looked at the second blood test, saw it was within normal limits, and failed to order the retest. He did this several times and I placed this protocol violation on the form FDA 483, Inspectional Observations. He was furious with me. He kept repeating, "This is a normal value." What he repeatedly failed to realize is that *it didn't matter that the lab test was within normal limits*. The protocol required a retest when the level rose over 50% and he repeatedly

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failed to order the retest. It was a clear and significant violation of the GCPs. The investigator had numerous other 483 observations and received an "Untitled Letter" requiring corrective actions within 30 days. (An Untitled Letter is one significant step below a Warning Letter.)

The inclusion and exclusion criteria for participation in a study are another source of frequent protocol violations. For many clinical trials, subject recruitment is a challenge. Sometimes there is the temptation to "enlarge" the inclusion criteria and "shrink" the exclusion criteria to meet recruitment goals. That's why I focused on the protocol's inclusion/exclusion criteria when conducting an inspection. They are important for subject safety and often proved fertile ground for 483 items. The criteria are there for a reason and inappropriate subject recruitment has found its way onto a Warning Letter more than once.

Records are another critical issue in a clinical trial. They are the single most important factor in determining how long an FDA inspection will last. FDA investigators don't go home just because the records are a mess. They stay as long as necessary to complete their job. One inspection I was on should have taken the usual one week to complete, yet I was there over a month because the recordkeeping was a disaster.

Records were everywhere. When I could find them they showed that the clinical investigator had failed to consistently document significant data endpoints required for the study. At the end of the inspection I issued a long 483 – and the data turned out to be useless.

Important Tip

Have you ever noticed that life happens in chronological order? Well, it certainly helps when records are in chronological order as well. Many medical charts are organized in reverse chronological order with the most recent records on top. This is also effective recordkeeping. When you organize your records helter-skelter, you're inviting the FDA to spend some extra time at your clinical site!

ALCOA: Best Practices for Recordkeeping

Attributable:
A record should indicate who completed it, and who entered observations. This will confirm that the appropriate person performed the study related activity.

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Legible:
Physicians are infamous for their lousy handwriting. However, the purpose of a record in a clinical trial is to allow the Agency to recreate what happened. If I can't read someone's handwriting, I ask. If they can't read it, the record is worthless. Don't forget to line out mistakes – and hide the white out! Never obscure original data.

Contemporaneous:
Data should be entered onto the record at the time the activity is performed. For example, if the study coordinator takes a subject's blood pressure, the value should be immediately recorded in the source documents. Don't wait for the end of the day or a slow period to record data.

Original:
Original means where the data are first recorded, even if it's a paper towel or little yellow sticky. If you transcribe data to the proper form at a later time, you need to maintain the original record with study documents. Also, when the FDA arrives for an audit they want original records, not a "shadow chart" of photocopies.

Accurate:
Let's take a closer look at a word we all are familiar with: *accurate*. Is a record accurate if you don't know who created it? Then it should be *attributable*. If you can't read it, is it accurate? Then it needs to be *legible*. Can you guarantee the accuracy if you don't know if there is another document with the first recording of the data? Then it needs to be *original*.

It is the failure to *contemporaneously* record data that most often leads to simple mistakes and inaccurate records. Don't leave worksheets for the end of the day to complete. Don't put off filling out the case report forms (CRFs) until the next monitor visit either. If you have a question about a record, because memories fade, you have inaccurate data. The rushed completion of worksheets and CRFs often results in errors as well. Records need to be contemporaneous for them to be accurate. And the FDA wants accurate, verifiable records to support your NDA, BLA, or IDE.

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FDA has a recommendation for recordkeeping. They call it, "ALCOA," which stands for **Attributable, Legible, Contemporaneous, Original, and Accurate**. If you make sure the records at a clinical site are ALCOA, you should be in pretty good shape when the FDA comes for a visit. Here are a couple of examples of how ALCOA works.

A laboratory report is an important record for most studies. That's where you go to find the creatinine levels and other test results. Usually a clinical investigator shows that there was a review of the lab report by writing the date with their initials. This makes the record *attributable*. By comparing the date of the report with the date of the review, it can be determined if the review was *contemporaneous*, performed in a timely manner. In addition, the clinical investigator should annotate the lab report with an "NCS" or "not clinically significant" if there is an abnormal lab value that isn't an issue. A clinically significant abnormal lab value should appear on the adverse event case report forms so it can be reported to the study sponsor, unless the protocol has different instructions. The failure to report abnormal laboratory values is a prominent 483 citation.

What about documenting the inclusion and exclusion criteria? If pregnancy is an exclusion criterion for a study, doesn't it make sense to have a record showing how it was determined that a woman of childbearing potential wasn't pregnant? What about other inclusion/exclusion criteria? If testing is necessary to determine eligibility, shouldn't there be a record of the test? An old-timer at FDA once told me, "If it isn't documented, it's just a rumor."

Another important record is the history and physical examination a clinical investigator should conduct when enrolling a subject. In recent years I have found the record often consists of a worksheet with boxes checked for the review of systems. No comment is made unless there is an abnormal finding. In fact, if there isn't a signature line and place for a date, the clinical investigator usually doesn't sign or date the worksheet.

Is this a good idea? Will this record "stand alone" when there is an FDA audit a year or two later? Short, pertinent remarks in the medical history help establish a clinical baseline. They also document that the investigator, not an unlicensed study assistant, actually conducted the physical. Attribution by a licensed health care professional can be critical.

In the rush for "clean" data sometimes information isn't recorded. And if your study coordinator gets married and goes on a honeymoon to California without her cell phone, what type of record do you want your data – and **your NDA, BLA, or IDE** – to depend on? Remember our solitaire-playing study coordinator? She had no problems with her records. They stood the test of time. You don't want recordkeeping problems either.

Newspaper headlines are telling us that there is more concern recently from the public and Congress over safety in both clinical trials and postmarket surveillance of approved drugs. In clinical research, protocol adherence and good recordkeeping are essential to addressing those concerns. Following these two pillars of GCP is not only good science, it's also good insurance.

Editor's note: This article is based on Carl's experience conducting GCP audits for the FDA. It contains his personal views, and should not be considered FDA policy.

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