From: OC GCP Questions
To: [redacted]
Cc: CDER DRUG INFO
Subject: eTMF Questions
Date: Thursday, August 14, 2014 11:11:59 AM

Good morning –

Your email was forwarded to my office for a response. Many institutions and sites are going to a fully electronic record system. Your eTMF is your source record whether or not you use paper copies in the study files. If you do make certified copies of the medical records of study subjects, monitors and auditors will want to at least spot check the completeness of these records at the source - the electronic database. How they view them is at your discretion however. Either looking over the shoulder of a study staff member or having limited access to the medical records is common.

The reason at least a spot check is necessary is that the records can be selectively copied. So even though they are certified copies they may not be complete records. The monitor/auditor is checking to ensure that study inclusion/exclusion are met and that there are no concomitant issues that would preclude the individual's participation in the study or confound the results.

In general, during an inspection FDA usually reviews original (source) records or certified copies of clinical trial records. For example, during an inspection of a clinical investigator (CI), the FDA investigator will evaluate the CI's practices and procedures to determine compliance with applicable regulations. Quite often CIs maintain copies of certain records in their study files, e.g., records from a hospital or other institution that must maintain the originals. FDA refers to these as shadow files. While it is acceptable to keep shadow files in the study records, should FDA conduct a bioresearch monitoring (BIMO) inspection of the study in question, the FDA investigator will expect to review at least a portion of the original source documents for such shadow files to verify their authenticity, even if the copies in the shadow files are certified as authentic copies. During the FDA inspection, the eTMF may be inspected for part 11 compliance

You may also want to look at FDA's Compliance Program Guidance Manual (CPGM) for the FDA inspection of clinical investigators during a bioresearch monitoring (BIMO) inspection of a clinical study site, available at: http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm. In particular, you may want to review Part III, Inspectional, which identifies some of the things an FDA investigator will look for during a clinical investigator site inspection.

We are frequently asked if sites may archive records by converting paper documents into an electronic format--in essence, creating certified copies of source documents. Neither FDA's regulations nor the ICH E-6 Good Clinical Practice: Consolidated Guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf defines certified copy", however, the term is mentioned in the E6 definitions for "source data" and "source document":

"1.51 Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

"1.52 Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

Although the term "certified copy" is not defined in the ICH E6 guidance, we attempted to define this term in the CCT Guidance referenced below:

"Certified Copy means a copy of original information that has been verified, as indicated by dated signature, as an exact copy having all of the same attributes and information as the original."

The use of certified copies as described above generally applies to situations where original records are copied to a different media for archiving purposes and the originals are destroyed.
However, if it is decided to have a certified copy substitute for the original, it would be desirable to have a "standard operating procedure" (SOP) describing how such copies would be made,
verified, and documented. The person who certifies the copy as an accurate and complete representation of the original, having all of the same attributes and information should be the same
person who actually made the copy from the original. Certification should be accomplished by having the person who makes the copy, sign or initial and date the copy to indicate it meets the
requirements of a certified copy as described above. This should be described in the SOP and can be accomplished by initialing and dating each copy or by initialing and dating a document
certifying copies in bulk. Whichever method is used the SOP should describe the procedure. (There are many ways to accomplish this, and the procedures described above are only suggested examples.)

Burning a CD at the end of the study, converting e-mails into a PDF format or adopting a procedure to make certified copies are all acceptable methods to achieve study related documents.
(FDA does not have any regulatory requirements as to the type of CD or DVD that might be used to preserve information (presumably to meet the regulatory requirements concerning clinical
data/records). A company just needs to make certain that whatever media it uses does so in a manner that preserves the integrity of the original data/information.

The guidances listed below might be helpful to you.

Part 11 –Electronic Records --
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126953.pdf

Computerized Systems Used in Clinical Investigations –
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf

Electronic Source Data in Clinical Investigations –
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf

I hope this information is helpful. Please contact us again at gcp.questions@fda.hhs.gov should you have additional information.

Kind regards

Doreen M. Kezer, MSN
Senior Health Policy Analyst
Office of Good Clinical Practice
Office of the Commissioner, FDA

From: [readcted]
Sent: Wednesday, August 13, 2014 3:06 PM
To: CDER
Subject: eTMF Questions

Dear CBER,

I am hoping to learn about FDA's plans for inspection of electronic Trial Master Files. I have the following questions:

1. Other agencies, most commonly MHRA, have written and spoken much more extensively about eTMF than FDA. MHRA has published a chapter in their GCP guide, EMA has published a reflection paper, and MHRA has presented at conferences and published some findings related to eTMF inspections on their web site. Does FDA plan to publish any guidance documents or speak about eTMF (or even TMF inspections)?
2. MHRA and EMA often conduct hands-on inspections of eTMFs where they use the electronic systems directly, often without the sponsors even being in the room. By all accounts, direct inspection of a TMF using an eTMF system is rare during FDA inspections. Do you see this changing? Do you provide any guidance to your inspectors about direct use of the eTMF? If so, do you have any specific expectations around access to the system and features that should be available to facilitate the inspection?
3. Would you anticipate inspecting an eTMF for 21 CFR Part 11 compliance and/or evidence of validation?
4. Do the guidelines that have been published by FDA concerning certified copies apply to the replacement of TMF paper originals with electronic copies, and if so can the paper copies be destroyed? Would you consider that an eTMF QC process involving the inspection of content and metadata fulfills the requirements for a certified copy?

Many thanks,
[redacted]