From: OC GCP Questions
To: [redacted]
Subject: TMF
Date: Thursday, August 18, 2016 8:17:00 AM

Good morning –

FDA's regulations related to records for drugs/biologics sponsors are found at 21 CFR 312.57, and for clinical investigators who conduct trials related to drugs/biologics at 21 CFR 312.62. As you know, FDA's regulations are general and require that sponsors and investigators maintain adequate and accurate records of any clinical investigations that are carried out.

The term "trial master file" (TMF) is not found in FDA's regulations, and while the term is mentioned in the Section 8.1 of the ICH E6 (the Introduction to the section on "Essential Documents for the Conduct of a Clinical Trial"), it is not specifically defined. FDA has adopted ICH E6 as official guidance, such that compliance with E6 provides assurance that the rights, safety and welfare of trial subjects, and that clinical trial data are
credible.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

So, in answer to your question, because "trial master file" is not defined in FDA's regulations, sponsors and investigators have flexibility in determining the records that might be included in it. Maintaining documents listed in "Essential Documents" in ICH E6 would be a reasonable way to assure that the agency (in the event of an inspection) could reconstruct the clinical trial and how it was conducted.

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.

It would be helpful for you to review the following FDA guidances:

Part 11, Electronic Records; Electronic Signatures — Scope and Application

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072322.pdf

For general information on the use of computer systems in clinical trials in FDA regulated clinical trials, please reference the following guidance:

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf

Or draft e-Source Guidance:

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM239052.pdf

From: [redacted]
Sent: Wednesday, August 17, 2016 3:38 PM
To: OC GCP Questions
Subject: TMF

Hi,

I would like to know if it is acceptable to have sections of the TMF in multiple locations as long as they are retrievable? For example, we have a validated system that houses all our protocols, IBs, CSRs, etc. This system is not part of the eTMF maintained by the CROs we use. So when the CRO sends us the eTMF content at the end of the trial, these documents would not be included. They would be in our computer system. Is this ok?

Thank you.