From: OC GCP Questions
To: [redacted]
Subject: signatures/dates on paper source required in addition to electronic source?
Date: Monday, June 09, 2014 8:06:53 AM
[redacted]

Good morning –

While I am not familiar with the WL that you referenced, it appears the site did not follow the sponsor's written procedures for the signatures on the worksheet and this is why they were cited in the WL among other violations.

This is what we have said in the past regarding electronic signatures –

Electronic signatures may not conflict with FDA regulatory requirements Such transcription may be considered "Certified Copies. The term "Certified Copy" is defined in FDA's Final Guidance Computerized Systems Used in Clinical Investigations as: "A certified copy is a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original." See: http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.pdf

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 above:

"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.

Please also see guidance on Part 11 –Electronic Records --
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126953.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 for additional questions.

Kind regards,

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Office of Good Clinical Practice
Office of the Commissioner, FDA

From: [Redacted]
Sent: Sunday, June 08, 2014 10:40 AM
To: OC GCP Questions
Subject: signatures/dates on paper source required in addition to electronic source?

During a recent review of FDA warning letters I read the following:

> *…Your site utilized the sponsor's worksheet as a source document. At the bottom of this document, there was a place for the individual who filled out the form to sign and date the form. In our review of this document, we found many instances where the individual who filled out the form either did not sign and date the form or the form was signed and dated at a later time….*
>
> *Your site's lack of signature and date on the forms and/or delayed signature and date of the forms lead to concerns about the accuracy of these source documents during the course of the study.*

I then reviewed how several Sponsors ensure the accuracy of source documents and would appreciate your comments on this common process:

1) Sponsor supplies CRFs with IDE submission. Last page of each visit CRFs includes "Investigator

statement of accuracy (My signature indicates that the information supplied on this CRF is a complete and accurate record of this subject's exam, and that the study was conducted according to the protocol, the Declaration of Helsinki and Good Clinical Practice.)

2) Sponsor supplies Source Document Templates to sites based on CRFs submitted however signature lines are not included/required for each visit CRF. The protocol does not require each CRF to be signed and dated. Instead, to better assess protocol compliance, initials are required for every person conducting each portion of the exam.
3) The Investigator is only required to electronically sign the eCRF ***after*** source document verification and Data Monitoring is complete. This means the eCRFs are always dated later than the date of the subject visit/exam. At the end of the study, a copy of the "signed" eCRF is provided to the site for filing with the hand-completed paper source documents.
4) Prior to the use of eSignatures the Sponsor confirms that an original Electronic Signature Authorization Form has been sent to Office of Regional Operations (HFC-100) 5600 Fishers Lane Rockville, MD 20857.

I believe the warning letter referenced above (no date on the letter but appx 2007) was issued prior to extensive use of electronic signatures and that the processes now being utilized by Sponsors and sites to ensure the accuracy of source documents meet or exceed the agency's expectations. I would very much appreciate your assessment however especially the elimination of the "presumed requirement" (based on statement in warning letter) to have the individual who filled out the paper source document sign and date that form.

Thank you in advance for your advice.