From: OC GCP Questions
To: [redacted]
Subject: E-source question
Date: Monday, July 11, 2016 6:14:00 AM
[redacted]

Good morning –

Below are responses to your questions from the Office of Medical Policy.

Kind regards,

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

This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is an informal communication under 21 CFR 10.85(k) which represents the best judgment of the employee providing it. This information does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

Here are our cleared responses to the questions:

1. Can logging into the network to gain access to the restricted location housing the blank forms count as one of the signature components? I have heard different opinions on this… some say yes, and others say no, that both signature components (when required) must be entered at the time of signature execution.

   Response: If an individual logs into an electronic system using a username and password, it is not necessary to re-enter the username when an individual executes a series of signings during a single, continuous period of controlled system access. Once a user has logged into a system using a unique username and password, all signatures during the period of controlled system access can be performed using the password alone (see 21 CFR 11.50 and 11.200(a)). The signed document must contain information clearly indicating the printed name of the signer, the date and time when the signature was executed, and the meaning associated with the signature (see 21 CFR 11.50 and 11.200(a)).

   In addition, in such cases, the signing should be done under controlled conditions that prevent another person from impersonating the legitimate signer. Such controlled conditions may include: (1) requiring an individual to remain in close proximity to the workstation throughout the signing session; (2) use of automatic inactivity disconnect measures that would "de-log" the first individual if no entries or actions were taken within a fixed short timeframe; and (3) requiring that the single component needed for subsequent signings be known to, and usable only by, the authorized individual.

   In order to make it impractical to falsify records, the electronic signature component executed for initial signing must only be used by its genuine owner (see 21 CFR 11.200(a)(2)). The electronic signatures must be administered and executed to ensure that their attempted use by anyone other than their genuine owners requires collaboration of two or more individuals (see 21 CFR 11.200(a)(3)).

2. Since the software (such as Adobe) doesn't track additions/deletions/changes to individual values on a form, is it acceptable to consider the entire form to be one "electronic record" and let the signature serve as the audit trail for all of the form entries (who entered the data, when and the signing reason)? It is noteworthy that this is essentially how we do it on paper… one signature/date per completed form. Is a higher standard required if we switch to an electronic PDF form?

   Response: FDA intends to exercise enforcement discretion regarding specific part 11 requirements related to computer-generated, time-stamped audit trails (§ 11.10 (e), (k)(2) and any corresponding requirement in §11.30. However, you must still comply with all applicable predicate rule requirements related to documentation of, for example, date (e.g., §312.58(a) or 312.68), time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries. We recommend that you base your decision on whether to apply audit trails, or other appropriate measures, on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on the quality and integrity of the record.

   That said, access to source data is critical to the review and inspections of clinical investigations. The review of source data by both the FDA and sponsor is important to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the clinical investigation data. If you determine that audit trails are necessary, then the situation you describe would not be sufficient to ensure the integrity of the source data and electronic record. In the paper world, when an incorrect entry is made, the customary method of correcting FDA-related records is to cross out the original entry in a manner that does not obscure the prior data. Although paper records may be falsified, it is relatively difficult (in comparison to falsification of electronic records) to do so in a non-detectable manner. In the case of paper records that have been falsified, a body of evidence exists that can help prove that the records had been changed. Without an audit trail, there are no comparable methods to detect modification of electronic source records. Therefore, audit trails would be necessary if the electronic data elements can easily be modified or altered at any time to misrepresent information, without evidence that a change was made, and in a manner that destroys the original information.

   For more information, see Guidance for Industry, Electronic Source Data in Clinical Investigations. Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf . Also see Guidance for Industry, Part 11, Electronic Records; Electronic Signatures — Scope and Application. Available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf

3. If changes are made to a previously-signed form, the specific changes could only be detectable by visually comparing the original and new copies of the completed form. Is this an acceptable means for maintaining the audit trail associated with the form entries, and would this provide adequate means of inspection of the audit trail in human readable form? (Again, the "who, when and why" is only provided by the application of a signature to a completed form.)

   Response: No, this would not be acceptable. See response to question 2. For an electronic audit trail, we recommend that each data element should have an authorized data originator. A data originator can be a person, system, device, or instrument. There also should be data element identifiers, such as the date and time, and that along with the data originator should be attached to each data element. For more information, see Guidance for Industry, Electronic Source Data in Clinical Investigations. Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf .

4. If we had policies requiring that each form be completed in one session so that the signature timestamp is contemporaneous with the actual entries, but had no means for detecting non-compliance with the policy, would this be a concern for the audit trail?

Response: Yes, this would be a problem. See above responses. Modified and/or corrected data elements must have data element identifiers that reflect the date, time, originator and reason for the change, and must not obscure previous entries. A field should be provided allowing originators to describe the reason for the change (e.g., transcription error). For more information, see Guidance for Industry, Electronic Source Data in Clinical Investigations. Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf .

Signing only requires entering single password. Part 11 requires at least 2 for the first signing in a continuous session. Does logging into the network count? - See response to question 1 above.

- Audit trail – specifically, original and changed values - can only be discerned by comparing two copies of a form side by side - See responses above.
- Audit trail not captured for individual data elements, only for entire form, and only through the signature – however, this is how our paper system works - See responses above.
- Reliability of audit trail requires user compliance with a policy, and non-compliance is virtually undetectable - See responses above.

In spite of these concerns, could this solution be implemented in a compliant manner? See responses above.

From: [redacted]
Sent: Wednesday, June 29, 2016 7:14 PM
To: OC GCP Questions
Subject: E-source question

Dear FDA GCP office: Apologies in advance for the long question.

Would you be able to comment on whether the following process would be a Part 11-compliant method for capturing source data? Our center desires to transition from paper to digital source capture for some processes. There is a strong push from management to implement the solution below. I am concerned about the audit trail in this solution, and would like some guidance if possible. The system and process being considered would look like this:

1. We create a pre-designed electronic PDF form using drop-downs, radio buttons, free-text fields, and the like, to capture the study data.
2. Blank forms are only accessible to authorized individuals having valid login to our network and having permission to access the specific folder containing the blank forms.
3. Blank forms are accessed by authorized users through Windows Explorer.
4. User opens the blank form and saves a copy to a writeable network location.
5. User inputs patient information onto the form. Software does not have the ability to record the audit trail on individual entries.
6. When a form is completed, the user accesses the signing feature within the software (example: Adobe Acrobat) to digitally sign the document using a PKI signing certificate from a trusted certificate authority. Executing a signature requires entering only one password.
7. The signature appearance contains the user, timestamp, and signature meaning.
8. The user saves the completed, signed PDF to a network location that prevents changes to files once saved. The signature can be validated at any time using the software.
9. Because the software cannot track changes to individual entries, a workaround is necessary if a saved, signed form requires subsequent changes. In this situation, the original document cannot be modified. Instead, the user must save a copy of the original signed PDF, make any changes to the copy, digitally sign the copy, and save the newly-signed version to the network location that prevents changes to files once saved.
10. The software does not log/track changes to forms. Changes between the originally-saved form and the changed form would be detectable only by visually comparing the original and new copies of the completed form. Unchanged answers would be associated with the original signer. Changed answers would be associated with the new signer.
11. The signed form would eventually be printed to be used for transcription into the sponsor's CRF. The PDF forms

themselves would not be the CRF, but would be source documents.

Questions:

Part 11 states-

(i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.

1. Can logging into the network to gain access to the restricted location housing the blank forms count as one of the signature components? I have heard different opinions on this… some say yes, and others say no, that both signature components (when required) must be entered at the time of signature execution.

2. Since the software (such as Adobe) doesn't track additions/deletions/changes to individual values on a form, is it acceptable to consider the entire form to be one "electronic record" and let the signature serve as the audit trail for all of the form entries (who entered the data, when and the signing reason)? It is noteworthy that this is essentially how we do it on paper… one signature/date per completed form. Is a higher standard required if we switch to an electronic PDF form?

3. If changes are made to a previously-signed form, the specific changes could only be detectable by visually comparing the original and new copies of the completed form. Is this an acceptable means for maintaining the audit trail associated with the form entries, and would this provide adequate means of inspection of the audit trail in human readable form? (Again, the "who, when and why" is only provided by the application of a signature to a completed form.)

4. If we had policies requiring that each form be completed in one session so that the signature timestamp is contemporaneous with the actual entries, but had no means for detecting non-compliance with the policy, would this be a concern for the audit trail?

It bears mentioning that our center understands that there are more elegant solutions out there, particularly of the type that are attached to relational databases that track audit trails on all activities. The reason that we are exploring the above option is because the technology already exists and it could be validated/implemented with some expediency for use on studies. As the compliance officer, I'm trying to be very cautious, and I have the following concerns:

- Signing only requires entering single password. Part 11 requires at least 2 for the first signing in a continuous session. Does logging into the network count?
- Audit trail – specifically, original and changed values - can only be discerned by comparing two copies of a form side by side
- Audit trail not captured for individual data elements, only for entire form, and only through the signature – however, this is how our paper system works
- Reliability of audit trail requires user compliance with a policy, and non-compliance is virtually undetectable

In spite of these concerns, could this solution be implemented in a compliant manner? It bears mentioning that whatever solution we use will be validated and verified to perform as intended prior to its use.

I'm also available by phone at your convenience if it would be easier to have a chat.

Thank you very much.