From:	OC GCP Questions
To:	[redacted].
Subject:	Thank you for an answer, one clarification from Doreen Kezer, of possible? Fw: Help with question re microsoft applications and source documentation, please
Date:	Wednesday, July 20, 2016 2:25:00 PM
[redacted]	[redacted].

Good afternoon –

FDA regulations do not specifically speak to audit trails. However, both regulations regarding the conduct of clinical trials (21 CFR Part 312 for drugs and biologics and Part 812 for devices) require that adequate and accurate records be maintained by clinical investigators (21 CFR 312.62 and 812.140(a)). For records to be accurate, any changes to the original data that was entered need to be visible, attributed to the person making the change, and explained. Therefore, some type of audit trail needs to be maintained for clinical study documents. This is discussed in the guidance document on the use of computerized systems in clinical investigations (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf - see IV.D.2. in particular).

This means that hard copies of records can be printed when an alteration is found necessary, and changes made - with initials, date, and reason for the change - and maintained with the study file in lieu of an electronic audit trail for that document.

For corrections to study documents –

Additionally the steps described in ICH E6 4.9.3 represent an acceptable method to make changes or corrections in study documents. The FDA recognized ICH E6: Good Clinical Practice: Consolidated Guidance, available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf, does include the following recommendations:

Section 4.9.3: "Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see section 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections."

Generally, the change should be crossed out with a single line, initialed, dated in real time, and explained by writing “error” without obscuring the original document.

For more complicated corrections, a note to file might be appropriate.

You also may want to develop a standard operating procedure (SOP) for all study staff to follow with regard to corrections. This will minimize inconsistencies. Make sure that the corrections you describe are in line with your institution's policies and procedures.

Lastly, I think the best way to handle the scenario you describe is highlighted in your email below. Again it is probably best to develop a SOP so that all staff is consistent with how they handle the study documents.

I hope this helps!

Take care,

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

From: [redacted]
Sent: Wednesday, July 20, 2016 9:09 AM
To: OC GCP Questions
Subject: Re: Thank you for an answer, one clarification from Doreen Kezer, of possible? Fw: Help with question re microsoft applications and source documentation, please

Hello Doreen,

Oh my goodness, this is life-changing news to this whole staff. We are jumping around screaming with joy upon receipt of your email!

We were actually suffering physical injury from trying to go back and rewrite all of the logs by hand. One of us is a competition kick boxer, and had their wrist on ice and elbow in a sling from writing for days on end.

Thank you so much for the good news.

Yesterday, the sponsor and trial manager decided together to over-rule the CRAs who instructed us to rewrite it all, but they did bring up this new point. They said that every entry on the paper copies has to show an audit trial. So, for instance, when the person remembers another current medical condition at the next visit and I add that to the log, and print that copy out maybe after the 3rd visit, where they remembered or developed 2 more conditions--so now from the first date, 3 more entries have been added since the first entry and they all have cumulative information entered on different dates--we can't prove *when* the information was added and *from* which *source we obtained the info to input on our "trial Source Documents*."

A better example is the "Systemic Antibiotic Log." They said if you show the whole course of ABX on one printed page, and there are entries for different treatment visit weeks, we can't prove with an audit trail that we just didn't add all of the information on the last day for all of the weeks before it, so they're all late entries and we could be wrong about the information if we enter it all, 4 weeks later.

In other words, how do they know all of the info wasn't just made up and entered on the latest day on the log. I'll attach an example. They're talking about the 2 abx highlighted by green and orange. The earliest date is on the 1st abx, the latest date on the 2nd abx. They're saying those cannot be on the same sheet, there is not an

audit trail to show when each was added, or what the source was to enter it on this log.

(In normal record-keeping at the private practice, the progress note in the chart just says abx prescribed. Then copies of the prescriptions are inserted in the record. For the clinical trial, we record this information for the 1st time on this excel spreadsheet source document. These abx were added to the log where he brought in his current Rx bottles and I recorded them here first as the trial log source document.

So they said the best thing to do is enter week 1, print it out. For week 2 or anytime new information is obtained, enter on it's own spreadsheet and page. Do not continue it on the spreadsheet with the previous information from week one. Sign and date each page. So for a 5 week trial, you could have 5 pages that all say Con Med at the top, with one sheet of new info for each week on each page, not all 5 weeks info on one page. Does this make sense?

Would you please advise the best way to keep an "audit trail" that the FDA is looking for? Enter 5 separate spreadsheets of one new one each week? Or keep all the info with different dates of obtaining new info on one spreadsheet.

I think this should be the final definitive answer when you can let us know about the "audit trail" requirement and how we should meet it. It will determine what we must do to be compliant.

Thank you so very much, it is one of the best days of the year because of your email!
[redacted]