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Case Report Form Mapping to Ensure Data Integrity

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The rapid adoption of electronic health records (EHRs) means that vast amounts of patient data are now available for use in clinical trials. However, the integrity of this data is at risk when (a) sites have not established standard, reliable procedures for moving EHR data into study databases or case report forms (CRFs), (b) data is collected on source document worksheets and also separately recorded in the EHR, and (c) site monitors (and auditors) do not have direct access to the data in the EHR. To ensure data integrity, the clinical research enterprise should develop and implement Best eSource Practices (BeSP).

EHRs are designed to support clinical practice, not clinical research. As a result, only a few commercial EHR systems allow sites to grant site monitors and auditors access that is limited to just the records for a specific consented subject. Access to these medical records is required to validate study data and verify study eligibility.

To provide the EHR data that sponsors require when direct access to the EHR is not feasible, sites commonly use three awkward and time-consuming options: They print copies of the EHR records and certify that the copies are correct, they sit with the site monitor and access the records jointly (when the site monitor visits the site in person), or they view the data together on separate computer screens (which supports remote monitoring).

In any study, the clinical research coordinator (CRC) typically starts by reviewing the case report form (CRF) and deciding which data will be obtained from the EHR, which directly from the patient, and which from other sources, if any. The CRC then creates source document worksheets (SDWs) that might mirror the CRF or be organized in a more convenient manner. (Some sponsors create SDWs on behalf of the research sites.) An SDW might include data taken from the EHR, or the study coordinator might collect the same data directly from the study subject. The study coordinator should copy data directly from the patient's EHR to the CRF, but often they first copy it to the SDW and then recopy it to the CRF. If access to the final CRF is delayed during study start up, study coordinators might find themselves designing data collection tools without knowing what data will, in fact, be needed.

Copying data from an EHR to a SDW does not make the SDW the original source of the data and might introduce human error during multiple transcriptions of the data. Often, sites do not explicitly specify which data is available from the EHR, further confusing matters for site personnel, site monitors, auditors and, possibly, FDA investigators. Some CRCs might copy certain data, while others might collect it directly from study subjects, such as current medications lists. Some might switch methods after a few months and then, perhaps, switch back. Some might copy data point A but not data point B, while others do the reverse. When the CRC or site monitor changes, practices might change. Some CRCs might collect data, compare it to the data in the EHR, and then choose which to use, based on criteria known only to the CRC. In other words, the possibilities for inconsistency (and possibly bias) are endless.

The potential for multiple sources of data arise when a patient visits a site for both clinical care and clinical research, on the same or different dates. In a long visit with multiple tests and procedures in various departments, blood pressure, pulse, medical history, and other data might be collected multiple times. When a study coordinator collects data directly from a study subject, and that data has also been recorded in the EHR, the two pieces of data might be different, perhaps significantly. For example, the patient might forget and then

remember a symptom or medication. Or, the patient's blood pressure reading might change significantly between the two measurements because of differences in technique or equipment, or because the patient received a stressful telephone call. Or, a nurse might neglect to record the administration of a medication.

If the data in the EHR differs from that in the SDW, which data is valid and "official" for study purposes? How is a study monitor to know whether the CRF is correct? The short answer is that he or she probably can't, unless one value is obviously incorrect. However, obviousness is in the eye of the beholder. For example, what if the CRF shows a weight history of 100, 100, 100, 100, 100, 100, but the EHR shows a weight history of 100, 100, 100, 110, 100 kg? Is the 110 reading a data entry error or an adverse event that caused water retention?

If the site limits direct EHR access for the site monitor but grants more complete access to the auditor, it is highly likely that the auditor will find discrepancies and possibly errors in the site monitor's source data verification (SDV). If the site limits access to the EHR for both the site monitor and the auditor but grants full access to the regulatory inspector, it is highly likely that the regulatory inspector will find SDV discrepancies and possibly errors, not a pleasant prospect.

Instead of providing direct access to the EHR, a site might provide certified copies of the patient's EHR records. The ICH E6 Good Clinical Practice Guideline, Revision 2 Addendum[6], currently in Step 2 of the drafting process, defines the term "certified copy," but not the term "validated process" that should be used to create them[6]:

> ICH E6 1.11.1 Certified Copy: A paper or electronic copy of the original record that has been verified (e.g., by a dated signature) or has been generated through a validated process to produce an exact copy having all of the same attributes and information as the original.

U.S. regulations, as well as FDA guidance documents and training materials address data integrity concerns related to use of EHRs [1, 2, 3, 4, 5]. Although FDA does not regulate healthcare practices, it has communicated that it intends to use "enforcement discretion" with regard to EHRs. Yet it also states that "Sponsors are responsible for assessing the validity, reliability and integrity of any data used to support a marketing application for a medical product."[3]

The recent release of FDA's Draft Guidance: Use of Electronic Health Record Data in Clinical Investigations[3] does not address this issue. However, FDA personnel have shared their thoughts verbally: If direct access to the EHR is not appropriate and printed "certified" copies will be provided, there should be a written process, adequate training of the staff delegated these duties, a quality control cross check at the site, and a sponsor-driven quality assurance step if the data is to be accepted as valid. If the sponsor has not reviewed the written process, verified the training and delegation of the duties, and *verified the accuracy and reliability* of the process, it should refuse the printed copies. This means that, without process verification, sponsors must rely on "over the shoulder" access to the EHR for SDV purposes.

There are three philosophies as to what data should be in a certified copy:

- Data that has been collected for the study
- Data that is relevant to the study
- All data for the patient

Few sites have validated processes for generating certified copies. Any incomplete certified copy is prone to errors of omission, e.g., an adverse event treated by another physician or a problematic psychiatric evaluation. Discrepancies can occur when updates are made to the

EHR after records have been printed for the study files, or, alternately, when hand-written corrections to the printed copy of the EHR are not transcribed back into the EHR. Nevertheless, most sponsors accept partial certified copies and rely on site monitors and auditors to find any deficiencies.

Case Report Form Mapping

Case Report Form Mapping (CRF Mapping) is an emerging methodology for documenting the source of patient data. It is similar to the data mapping that enables data from laboratories, EKG equipment, and ePRO devices to be entered directly into both the EHR and the study database. Some Phase I units are uploading data from bedside equipment (e.g., blood pressure monitors and oxygen saturation devices) directly into study databases. This type of data transfer required some technical work but can reduce the risk of human error and automate much of the data retrieval used in clinical research today.

CRF Map creation, use and revision should be governed by an SOP. A CRF Map can be as simple as a copy of the CRF form with an annotation for the source of each entry. Some entries, like those for adverse events, might specify multiple sources.

The process of CRF Mapping is simple in theory: Identify and document the source of each data point that appears in the CRF. It is more complex in practice if there is more than one potential source for a data point. In that case, the map would specify which data point will be used or define an adjudication process for deciding which data point to use. The site should obtain the sponsor's approval for the map since the sponsor might have its own preferences, e.g., to maximize consistency across sites in the study. While CRF maps are study-specific, consistency will develop over time across studies, thus minimizing complexity for the CRC.

The CRF Map then becomes the basis for the process that CRCs consistently use to complete the CRF. A CRF Map also reduces the risk that different data will be made available to regulators than was provided to site monitors or auditors. If the CRF is electronic, it is even possible to automate the process of moving data from the EHR to the CRF. Site monitors, auditors and regulatory inspectors can also use the CRF Map to verify source data.

Conclusion

Creating a CRF Map takes some time, but the alternative — just winging it — is prone to error and inconsistency. It requires study coordinators to remember where to find data. It also creates problems for site monitoring, auditing and regulatory inspections, and might not detect adverse events.

References

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