Electronic Data Capture—Study Closeout

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Abstract

With the growing prevalence of electronic data capture (EDC) in clinical trials, the importance for clinical data management (CDM) to fully understand the impact of EDC upon all phases of the research process has grown. It is imperative that data presented to regulatory agencies come from a study that is not only planned and conducted properly, but also closed out in accordance with sound data management principles.

Introduction

Many professionals in clinical data management (CDM) have been forced to reevaluate how they approach their work as electronic tools and systems have gained wider usage in the industry. These tools and systems have had a profound effect on all phases of clinical research, changing the way the CDM team approaches data collection, data transfer, data analysis, reporting, security, archiving, and storage.

Proper closeout activities for these studies are crucial, especially for clinical research presented to regulatory agencies such as the Food and Drug Administration (FDA). The time, energy, and resources employed to collect clinical data is wasted if data cannot be properly verified, validated, transferred, and stored.

The term “lock” may refer to not only locking a study or database, but may also refer to locking specific forms or casebooks. While not all topics discussed in this chapter actually occur during study closeout, they are components of the data lock process and closeout of a study.

Scope

This chapter focuses on how to properly close out a clinical trial when electronic data capture (EDC) has been used. It examines the standards, practices, and procedures to close out an EDC study, including final source document review, database locks, audits, media generation, and hardware disposal.

Many of the tasks described in this chapter may be joint responsibilities between different groups, just as there may be many different groups involved in the implementation of various tasks. However, clinical data managers need to be conscious of whether or not these tasks have in fact been performed in a satisfactory manner.

With the huge impact electronic data capture is having on clinical research, separate chapters are devoted to EDC study startup (see chapter entitled "Electronic Data Capture—Concepts and Study Start-up") and EDC study conduct (see chapter entitled "Electronic Data Capture—Study Conduct").

Minimum Standards

- Ensure completion of all required source document verification and data review.
- Ensure all investigator signatures (principal and sub) are in place at closeout.
- Ensure the procedures established for locking fields or forms in a CRF have been followed, including those with open queries or unreviewed and/or unverified status.
- Perform a final review of data listings to identify and resolve any remaining data discrepancies that may generate queries.
- Perform a final review of query status for both open and answered queries through reports and task summaries.
- Ensure defined procedures have been followed for locking the database, and for unlocking the database if necessary.

- Ensure defined processes have been followed for restricting user access once the database is locked, and for revoking access to the production database.

- Ensure adherence to definitions of the audit plan and postaudit data transfer process, as well as identifying audit team members well before study closeout.

- Define specifications for formatting subject profiles, as well as a process for generating and reviewing subject profiles.

- Ensure investigative sites have access to their CRF data after study completion. Once they have received the appropriate media for this data, their access to corresponding data in the EDC system can be revoked.

- Ensure any hardware provided to sites is retrieved according to organization standard operating procedures (SOPs).

- Determine requirements for creating additional media to represent the study database if needed.

Best Practices

- Ensure investigators and other site staff are educated in the signature-break process long before study closeout so there is no confusion on the topic at closeout. Signature-break may occur when data has been changed post investigator signature. Should signature-break occur, this information will help avoid confusion, and will ensure the investigator is available to re-sign if necessary.

- Implement a verification procedure to ensure data received or extracted from the database matches data entered in CRFs, especially in cases where additional output programming is conducted. This practice confirms integrity of the data being released for statistical analysis.

- Review and refine the source data verification timeline with monitors and clinical operations after the last subject visit occurs and data entry is completed, (In some cases these processes can also be performed prior to the last subject visit).

- Ensure all medical coding activities have occurred as required.
- Use an incremental form or casebook lock strategy to reduce the amount of data review and locking needed upon study completion.
- Ensure all tasks documented in the data management plan are complete, and coordinate with clinical operations personnel to ensure all site monitoring activities are complete prior to database lock.
- Use an established checklist of tasks to be completed prior to database lock in order to meet database lock timelines.
- In preparation to meet database lock deliverables, adjust timelines as needed for all queries to be answered by sites.
- Use an established communication plan between the clinical team, site staff, statisticians, and data management. This communication plan should ensure all data reviews are completed and queries are answered in time to meet database lock deliverables.
- Create a calendar of vacations or out of offices for all team personnel to ensure proper resources are available for study close out activities.
- Review current regulatory standards and guidelines for how data should be presented in the subject profile (e.g., headers, footers, and margins).
- Determine the appropriate media to use for reporting of subject profile data.

Final Review

Verifying Source Document Verification of All Records

Before a form can be locked and the database closed, source documentation and data review must be completed as required for all forms and fields. It is beneficial if the EDC system can indicate source document verification (SDV) status and data review activity. Prior to locking a database, ensure all required SDV has been completed by clinical research associates (CRAs).

Frequent communication between the clinical study team, including CRAs and data management team, is critical. Changes to data in the CRFs are

possible as late as the day of database lock. A plan should be established to ensure CRAs are available to source verify any changes, if necessary.

Verifying All Queries Have Been Closed

All reasonable efforts should be made to ensure all queries are answered or closed prior to database lock, particularly for those queries that may impact the analysis or outcome of study results. Depending on the details of the DMP, it may be acceptable to lock noncritical forms with open queries. During study startup, conditions for locking an CRF should have been defined; thereby ensuring the CRF cannot be locked with open query status. Prior to locking a database, CDM should ensure all queries have been answered or closed, including automatic queries and manual queries created by CRAs and data managers. This task may be accomplished through use of varied system reports and status indicators, according to the EDC system's features.

Verifying e-Signatures

It is necessary to verify that all CRFs have been electronically signed by the investigators (principal and sub) responsible for a particular site. The investigators are responsible for reviewing each subject's CRF, and to confirm that data entered are complete and accurate. Sponsor organizations must determine the level of detail required for investigators' signatures. For example, some organizations will decide that the investigator's e-signature must be applied to every individual CRF, while others may decide one investigator signature on the final page of each subject's CRF is acceptable. While there are many studies using e-Signatures, some are also still working with paper-based signatures, even with those studies utilizing EDC.

Regardless of the final signature method being used, a process should be established for notifying sites that CRFs are ready for investigator signature. Policies and processes related to re-signing a CRF should also be defined and adhered to. If a site changes a data point on a CRF already signed by the investigator, the rules must be in place to decide whether the data change "breaks" the signature. If the signature is broken due to the change, the investigator must re-sign the CRF.

It is expected that the CRA will track the investigator's progress signing the CRFs. However, the data manager is responsible for conclusively verifying that all CRFs have been signed by the investigator prior to database lock. For any data changes that "break" the signature, the data manager must verify those CRFs are re-signed.

Final Locking of Data and Database

It is recommended that a checklist be established to ensure completion of required tasks prior to database lock. These tasks may include, but are not limited to:

- Identifying data management staff responsible for carrying out database lock
- Ensuring required medical coding of adverse events, prior and/or concomitant medications, and medical history verbatim terms has been completed and is accurate
- Ensuring issues identified in edit checks performed outside the EDC system and data listing reviews have been resolved
- Resolving and/or closing all outstanding queries
- Importing and/or reconciling all external data (and listing external data reconciled)
- Completing serious adverse event (SAE) reconciliation

Once all database lock tasks have been completed, the database can be closed and soft- or hard-locked according to the sponsor-approved definition. This step implies that all forms in the study have been locked according to defined procedures, all tasks are completed, all conditions have been met as defined in the data management plan, and the final data transfer has been received or extracted according to data extraction specifications defined at the start of the study.

After database lock, an audit may be performed on the final data. Based on findings from the audit of final data, further data corrections may be requested of the site. Once corrections have been made and verified, and additional investigator signatures have been obtained as necessary, another data transfer

or extraction should occur. It is recommended that a comparison program be run to determine if requested changes to the database were successfully executed, as well as any other changes that were made to data other than what was expected.

Soft Lock

Typically, records that are soft-locked cannot be updated by sites, but the sites may still be able to respond to open queries. Many EDC systems support soft locks at a visit, page or data point level. This capability supports a process of "rolling" or gradual soft locking of data throughout the course of a study, reducing the effort required by the data manager to lock data at the end of the study. Incremental soft locks can also be an effective approach to supporting midstudy or interim data review activities.

Hard Lock

Database hard lock typically occurs when all data have achieved soft lock status and all other study closeout activities have been completed. After a database has been hard locked, tightly controlled procedures for unlocking the database must be employed, and only a few privileged users should be able to modify data. Once the database has undergone a hard lock, the data are considered ready for final analysis and archiving.

User or System Access Revocation

At the conclusion of a study, user access rights must be modified. During study closeout activities, rights should be modified to only allow the site to read data but not to enter or change data. Once the required media have been created and sent to the site, all access to the corresponding data in the EDC system should be removed.

User access (including view access) to a subject's data should be completely revoked once a copy of the subject data is received and confirmed by the site. Prior to this revocation, the site must continue to have access to the study database in the event of a site inspection or audit.

Audits

The process of auditing data for a CRF will be different than the process used for a paper CRF. However, the end result is the same—the data entered are the data presented for analysis. While the audit process may differ from one sponsor or contract research organization (CRO) to the next, the auditing process will be determined by how the sponsor or CRO extracts data from the EDC system. Any additional programming required to transform study data into SAS® datasets could affect how data are displayed. An audit ensures that the datasets received match data entered in the CRF. Additional EDC issues to consider for auditing include, but are not limited to, reconciling medical coding, data management plan comparison, external data import, query verification, and completion of all queries that required data changes.

A plan should be established in advance to identify approaches to be taken, including a sampling plan, acceptable error rates, and escalation in the event of audit findings.

Generating Archive Media for Sites

At the conclusion of a study, media must be created that represent the data collected throughout the study.

Quality Review and Replacement of Subject Data

Subject data should present the data collected in a CRF system organized by subject identifier, visit, and form. The data are typically presented in a manner that allows for effective navigation of the subject profile in a format such as a pdf file or a similar format. The subject data should also include an audit trail, electronic signature, and query information, which allow a reviewer the ability to see all data entry and modification that have occurred since it was created. Subject data should be provided on durable media, such as a CD-ROM. A master copy of the durable media should be created to contain all the subject profile data. In addition to this master copy, individual CD-ROMs or other durable media with site-specific data should be created and forwarded accordingly.

Archive Media

After the study is complete and a copy of subject data have been generated and securely distributed to sites successfully, a complete copy of the study database should be created for archival purposes.

Ensuring Compliance with Applicable Guidance

A final review of all study documentation should be performed to ensure defined processes have been adhered to such that end of study deliverables from the EDC system meet the requirements specified in applicable regulatory guidance documents. This review should ensure that the study documentation address expectations from regulatory agencies. Some of the guidance and specifications for this review include *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*[1], and *ICH M2 EWG Electronic Common Technical Document Specification*[2].

Provisioned Hardware Disposition

For studies in which hardware was used for data collection, a determination must be made once the study has concluded regarding hardware disposal. Any hardware that was provisioned to sites should be retrieved per organizational standards and requirements. The hardware may be refreshed and used in future studies, recycled for other uses within the organization, or retired.

Recycle

If the hardware will be recycled, the responsible parties (e.g., sponsor, CRO, site, vendor, etc.) must ensure all data and applications are removed from the hardware.

Retire

If hardware used to store information is to be retired and never used again for data entry purposes, the process for retiring the hardware should be determined. This process should consider how the hardware will be secured if

data are maintained on it, or how data will be removed and the hardware destroyed if it is not to be used again.

Recommended Standard Operating Procedures

- Study Closeout
- Database Lock
- Reconciliation of Electronic Lab Data
- Serious Adverse Event Reconciliation
- Study Close Audit (typically handled by the QA/QC department)
- Audit of Data Extraction and Output
- Generation and Review of Archive Media
- Maintenance of Coding Dictionaries
- Vendor Audits/Management

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Further Reading

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Chapter Revision History

Publication Date	**Comments**
September 2003	Initial publication as Electronic Data Capture Principles.
May 2007	Revised for style, grammar, and clarity. Substance of chapter content unchanged.
September 2008	Revised to reflect the orientation of chapter towards the closeout phase of EDC. Content updated and organization of material revised. Study concept and start up, and study conduct content moved to separate chapters.

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