Electronic Data Capture—Study Conduct

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Abstract

As electronic data capture (EDC) has become a more common and proven tool for clinical trials, understanding the principles and guidelines for EDC use has become more important for clinical data management (CDM) professionals. This chapter reviews processes and regulations that currently apply to EDC during the conduct of a study, and emphasizes the role CDM professionals have in properly maintaining an EDC system within an ongoing study.

Introduction

Electronic resources for clinical data management have developed over the last 30 years as a suite of processes and tools to enhance the management, quality control, quality assurance, and archiving of clinical trial research data. This development has led to a major paradigm shift in data management, with data capture now capable of being facilitated at investigator sites, and data transfer being expedited by Internet technologies.[1]

While pre-production activities and planning are crucial for a study employing EDC principles (see chapter entitled “Electronic Data Capture—Concepts and Study Start-up”), it is also vitally important to apply proper data management principles to the ongoing conduct of a study. Clinical research is a dynamic process, and clinical data managers must be prepared to adapt as needed to best serve the needs of a study.

Scope

This chapter provides information describing data management activities and processes that occur during the conduct of a study using EDC. It concentrates

on data reviews, trend analyses, communication, security, midstudy data requests, and various change control processes.

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.

Detailed information comparing paper-based studies with studies employing EDC principles can be found in the chapter entitled "Electronic Data Capture—Concepts and Study Start-up," along with detailed information describing pre-production activities and planning for an EDC-based study. Recommendations for proper study closeout principles for an EDC study are addressed in the chapter entitled "Electronic Data Capture—Study Closeout."

Minimum Standards

- Work with the entire project team to decide which additional edit checks and listings are necessary during the study.
- Document all changes to edit checks and data review specifications.
- Maintain accurate and up-to-date system access, including documentation for changes to access (rights, revocation, addition, etc.).
- Keep training materials updated and readily available to study team members.
- Ensure proper training has occurred for all personnel involved in the conduct of the clinical study, and that all training is documented.
- Monitor changes in study team members to ensure new or reassigned members have been trained according to the study training plan.
- Provide sites with timelines for data entry and query responses.
- Make metrics reports available and review them on a regular basis.
- Where possible, utilize predefined metrics reports and develop new reports as needed to identify performance issues.

- Notify appropriate study team members of site performance issues.
- Monitor metrics reports and data query trends to identify when additional training is needed.
- Observe the frequency of automated and manual queries.
- Conduct additional training as needed to address any system and/or study specific changes.
- Monitor query status for both open and answered queries through reports and task summaries.
- Ensure continued review of data listings to identify any remaining data discrepancies that may generate queries.
- Track progress of investigators' signoffs on CRFs throughout the course of the study.
- Notify the project team of data trends.

Best Practices

- Document ongoing training activity throughout the life of a study.
- Use all available information to identify training gaps or needs (e.g., query trends, protocol deviations, monitor reports, help desk reports).
- Take advantage of opportunities to provide additional information and training at investigator meetings, study coordinator teleconferences, and monitoring visits, as well as through communications such as newsletters or a study Web site.
- Set metric goals and communicate expectations to study team and site staff.
- Enforce timely data entry and query resolution in order to take advantage of all EDC benefits.
- Program protocol deviation reports early in the study.

- CDM should either be responsible for closing all queries, or at a minimum, reviewing queries closed by other parties.
- Run compliance and safety reports early and frequently.
- Seek input into remedial actions from the project team.

Data Reviews, Trend Analyses, and Remediation

In EDC trials, the concepts of data review and trend analysis can be applied similarly to the way they are in paper-based studies. However, EDC systems offer a tremendous advantage over paper-based studies by changing the focus of CDM's data validation activities and enabling data trends to be detected more quickly. In EDC, traditional data management roles have changed, as site staff can enter data and have edit checks programmed to trigger queries at the time of entry or immediately after submitting the data. CDM no longer make data changes in the system based on site query responses, but rather site staff enters the data changes. CDM can now focus attention on performing data reviews using listings and reports, to fully ensure data are complete, consistent, and logical. Additionally, many EDC systems allow for sponsor staff other than CDM to perform tasks that have historically been performed by CDM, such as creating manual queries and/or closing queries. The business process, roles, responsibilities, and access rights established for a study will need to dictate how issues found during data reviews are identified and resolved, as well as who is responsible for their resolution.

When data are entered into an EDC system, it typically has not been source verified. Data validation and review activities can be performed before or after data are source verified. A decision must be made whether the project team will require specific data items to undergo source document verification (SDV) prior to data review and/or edit check and manual review activities. If the project team decides to perform data review and/or edit check activities after SDV, a method of communication between clinical research associates (CRAs) and data managers should be established. Some EDC systems have the functionality to indicate when SDV is completed.

One of the most efficient ways to see data trends is to produce a report showing the frequency of queries generated. Such a report will allow the

project team to react quickly and apply various solutions to address these issues. These solutions may include:

- Retrain the site concerning the protocol.
- Retrain the site in electronic case report form (CRF) completion guidelines.
- Retrain the site in system functionality.
- Explain issues in a newsletter to sites.
- Contact sites directly either during the next monitoring visit or more promptly via phone after an issue is identified.

The frequency of particular queries may also prompt the project team to examine edit check specifications. This review of the specifications may indicate such solutions as broadening ranges, rewriting specifications, or eliminating certain checks altogether.

The rapid availability of study data in an EDC system allows project teams to make decisions much earlier in the development lifecycle than in paper-based studies. This study data availability is especially beneficial in enforcing compliance, tracking protocol deviations, detecting safety concerns, and amending protocols if needed. Additionally, as part of the development of reports and listings, it is important for CDM to consider where the most efficient location/system is for generating this information. For example, if you are utilizing a back-end Clinical Data Management System (CDMS) to bring data collected from your EDC tool together with central laboratory data, it may be necessary to establish reports within the CDMS or a statistical analysis software package such as SAS® rather than directly from the EDC system.

Early notice of protocol noncompliance is crucial to study conduct, especially with more complex protocols. Site staff may have problems complying with medication requirements, procedure steps, correct device usage, or other protocol requirements. Reports programmed at the beginning of a study to capture protocol deviations should be run frequently to monitor compliance. An EDC system enables the project team to give immediate feedback to site staff so they can provide retraining as necessary. Sometimes, analysis of

protocol deviations and errors in clinical data may indicate the need to amend the protocol. Identifying problems early is vital for study conduct, as it allows the timely entry of correct data by sites. Amending the protocol immediately after an issue is discovered contributes significantly to patient safety and overall success of the study.

In some trial designs, such as adaptive design trials, the protocol may require changes in dosing, sample size, etc. during the course of the study. In this situation, early access to the data and the ability to observe trends in the clinical data as they occur is crucial. Reports with relevant treatment parameters should be produced and reviewed by the appropriate project team members.

A comprehensive safety data review will help identify trends and alert investigators immediately of patient safety issues during the study. Although serious adverse event (SAE) notifications can occur rapidly in paper-based studies by phone or fax, an EDC study offers a more thorough, all-inclusive approach. In addition to SAEs, non-serious adverse events and other pertinent patient information can be reviewed earlier in the study, ensuring that the Data and Safety Monitoring Board (DSMB) has a current, complete picture of the patient safety profile.

Interim efficacy and safety data reviews can also be performed earlier in an EDC-based study using the most current, near real-time patient information. Decisions by the DSMB to stop a study because of safety concerns or lack of efficacy can be made much more quickly than in a paper-based study. This ensures better subject protection and lowers costs if a study must be stopped.

Communication Plan

There are a variety of methods used for communication, including verbal, written, and electronic communication. In day-to-day business, the most common means of communication are e-mail, telephone, fax, or face-to-face meetings. To lay a solid foundation for an EDC study, effective communication is an absolute necessity.

Clear and comprehensible communication is an extremely important subject for all members of a clinical research team, including vendors involved in the

study conduct. Regardless the stage or component of a study in which an individual is involved, all parties should adhere to the following principles:

- Schedule regular and frequent meetings to keep everyone informed about key study issues and status and to nurture discussions.
- Provide good documentation in a timely manner as a follow-up to all meetings.
- Send a confirmatory message if decisions about the protocol, conduct of the study, or other study-specific matters were made via e-mail.
- Seek clarification if unsure or unclear of any study-related topics, and don't hesitate to discuss.
- Adopt a proactive approach in order to save time and energy.
- Correspond clearly and succinctly. Consider the native language of each participant; communicate clearly, concisely and unambiguously, and avoid phrases or terms that are dialect-specific.
- Use good judgment. E-mail may not be the best means of communication when phone calls or face-to-face meetings can clarify problems better or more easily.
- Maintain documentation of decisions and known issues related to the data in a location accessible by all study team members.

Metrics Reports

Very early after a study begins enrollment, an EDC system can provide unique opportunities for actively improving site performance as well as training materials. Metrics reports such as query response times, frequencies of queries by form or data items, and number of queries per site should be run early in a trial to identify potential problems. Remediation can then be taken to reduce or even eliminate these issues as the study progresses. Remediation may include revisions to CRF completion guidelines, retraining site staff, retraining CDM staff regarding query wording, special topic newsletters, and teleconferences.

Metrics reports from other data sources should also be considered. For example, if used in the study, a help desk can provide information regarding site performance trends and issues. Also, if a study is integrating data from automated equipment such as an electrocardiogram (ECG), personal digital assistant (PDA), or other electronic devices for electronic patient-reported outcomes (ePRO), additional metrics report opportunities and data interfaces with the EDC system may be considered.

Security

Due to laws and regulations, such as the HIPAA privacy standards, ICH Guidelines E6 Sections 2.11, and 4.8.10, and Article 8 of EU Directive 95/46/EC[2, 3, 4], access to an EDC system must be limited to authorized staff only. Maintaining appropriate access and system security is essential throughout the duration of a clinical trial. However, security cannot be ensured without user compliance. Therefore, all users must be informed and continually reminded about system access regulations. During monitoring visits, the sponsor and/or contract research organization (CRO) should reiterate to site staff the importance of confidentiality for each user's ID and password. Suspected noncompliance with access regulations should be reported to the assigned system administrator as appropriate.

Maintaining System Rights Determined by Roles and Privacy

Throughout the course of a trial, roles and responsibilities may change, as may data management processes. CDM should manage any changes to documentation describing access rights. Because of the potential impact on specific access rights of individual users, any such changes should be communicated to all study team members. Additionally, role and responsibility definitions should be kept with user access documentation to assist auditors with understanding each user's role.

Managing Periodic System Access Review

Managing user accounts and permissions is a time-consuming task, requiring diligence to ensure security and confidentiality are maintained throughout the duration of a trial. Open communication with clinical operations is necessary to keep track of site and CRO staff changes so as to activate or deactivate corresponding user accounts as needed. The data manager should also use

reports on EDC system activity to periodically review user access to the EDC system. Additionally, as part of this period review they should ensure the access rights are appropriate for each user. However, the length of time between review periods depends on the duration of the study. Standard operating procedures should state what the minimum review period is for the EDC system.

Managing Conventions for User Login IDs and Passwords

Each user of an EDC system must have an individual account, consisting of a unique login ID and password. The sponsor should decide how the IDs and passwords are disseminated to users. Typically, the initial login ID and password can be sent to the individual user using his or her e-mail address, or through traditional methods such as mail or courier. The system administrator should only grant a user access to the system once the user's role-specific training has been completed and documented.

When a user first logs on, the EDC system should prompt the user to change their initial login ID and/or password. If the system is not capable of forcing the user to change their password on first entry, trainers will need to ensure this activity is discussed with all trainees. Users should be trained to keep their IDs and passwords confidential. Each login ID should uniquely identify the user within the EDC system's audit trail, and enable tracking of any information that the user enters, modifies, or deletes. Additionally, users should be instructed to log on to their account, complete data entry and review, and log out at the completion of review. Users should be instructed to log out of the EDC system when the personal computer (PC) used to access the EDC system is left unattended. Login ID and password requirements should include restrictions on re-use of accounts and passwords, minimum length of login IDs and passwords, required frequency of password changes, and automatic log-off when a PC accessing the EDC system exceeds a predetermined amount of inactive time.

Managing User Access

Turnover of site and study team members is likely, with the volume of turnover related to the size and duration of the trial. Therefore, management of user access will be an ongoing task throughout the course of an EDC study.

This will involve establishing processes for disabling accounts as well as for granting accounts to new users. The system should also be updated when study team members are reassigned to different roles during the course of a study. Monitoring user access will likely require both CDM and clinical operations resources to manage site and sponsor user access.

Disabling Access During a Study

Procedures must be established to define processes for disabling or revoking access to the system as needed. These processes should clearly define who is responsible for communicating staff changes (both internal and external), documenting these changes, and executing these changes. Requirements for automatic deactivation of accounts should also be established in the event of security breaches or users who do not log in for extended periods, such as not accessing the study within 90 days or some other specified time frame.

The sponsor should define appropriate lock-out rules in the event of unauthorized access, whether attempted or successful. If a user enters an incorrect ID or password, an alternative method, as specified through established standard operating procedures (SOPs) or work instructions, should be employed to provide the user with system access.

Adding New Access During a Study

Throughout the course of a trial, it will become necessary to add new users or modify access privileges for existing users. Procedures should be established to ensure these tasks occur without disruption of ongoing study activities. These procedures should detail training prerequisites, steps for requesting access, and the staff members who are responsible for ensuring all site staff and study team members have appropriate access. Documentation of completed training should be provided to system administrators so they know which users may be granted new or modified access rights.

Ensuring Effective Software Support

When available, reports (which may include surveys) detailing the responsiveness and effectiveness of software support (e.g., the average length of time the help desk takes to assist a user) should be reviewed regularly to ensure support is effective. Several factors are important to ensure assistance

is provided efficiently and expeditiously, including easy access to support staff, ability to address users' questions, and the availability of support when needed.

Providing Multiple Language Support

Although language needs for the help desk should be determined during the pre-production phase of a study, CDM staff should be sensitive to complaints regarding communication problems during the study conduct phase. The problems may be, in part or in whole, related to an inability of the help desk to provide the language support needed, and may require a revision to the original translation needs of the study.

Providing 24 x 7 x 365 Support

As with multiple language support, help desk availability must be determined prior to the start of a study. However, during the conduct of the study, CDM should evaluate feedback from users to ensure that the availability of support is adequate for the study. Reports detailing the responsiveness and effectiveness of software support should be reviewed regularly to ensure tier 1 software support is effective. Tier 1 software support is the lowest level of support needed and includes activities such as unlocking user accounts and resetting user passwords. Information gained from reports and feedback may involve reevaluating the original decisions regarding the level of support needed. For example, if 24x7x365 support was not originally set up, it may be necessary to reconsider it. If a vendor was contracted to provide help desk services, any changes to the contract will need to be considered and negotiated.

Training

EDC-related training should be provided to internal and external staff during the conduct of a study. Training is most effective when provided as close as possible to the time when the newly learned skills will be used. If a significant time lapse occurs between training and use of the learned skills, retraining should be considered.

Reviewing and Maintaining Training Materials

EDC system training is an important part of proper study management. Training is dependent on the study and target audience, therefore training materials should be developed with these considerations in mind to make the training as effective and appropriate as possible. Moreover, training should be an ongoing process, not just a one-time event. An EDC system can provide the sponsor with the ability to identify a need for retraining users. Some EDC systems can also be used by the study team to deliver updated training materials and communications to users in a timely manner. For example, updated CRF instructions can be immediately provided to all sites and study team members, and newsletters can be provided through a dedicated Web site to communicate updates or changes.

Identifying users' needs for retraining is an important activity of both CDM and clinical operations team members who interact with the site regularly. CDM should be aware of situations at a site that may present challenges and a need for retraining, such as coordinator inexperience, isolation, turnover, or competing priorities. Available information, such as help desk reports, query frequency reports, and protocol deviation reports, can be used to identify materials that need to be updated or users requiring new or additional training.

Ensuring Site and Sponsor Staff Training During Turnover

A common occurrence in clinical research is turnover of both site and sponsor staff. New staff must receive required training, and user accounts and permissions in the system should be updated to reflect staff changes. A plan should be established for new users to be trained in a timely manner so they will have the benefit of access to data on the EDC system. If new site staff are not trained and do not have access to the system, they cannot enter data, and study timelines can be negatively affected.

Change Control

Any EDC system may undergo changes during the conduct of a study because of changes in EDC software and/or changes in the study itself.

Software Change Control

Because many clinical trials occur over the course of several years, software changes and upgrades will inevitably have an impact on EDC studies. These changes or upgrades are not just limited to core EDC software, but could also include upgrades to the operating system, back-end database software, or any auxiliary software integrated with the EDC system, such as reporting or extracting software. The differences in change control strategies and processes depend on whether the software is developed internally by the sponsor or purchased from a vendor.

If software is purchased, the sponsor may decide to rely on the vendor's system validation package for the software, including all releases or upgrades, and maintain the system as a "qualified" platform rather than performing system validation upon each release. However, "qualified" software platforms should not be customized by the sponsor unless validation of the customized platform will also be performed.

Controlling Changes to the System by Incorporating Software Development Life Cycle Principles

Before making a decision to implement upgrades to the software system (whether it is a new release or a minor version update), CDM should make a complete assessment of the software changes and obtain input from other areas that may be impacted, including a thorough risk assessment. The first step in performing an assessment is to gain a clear understanding of all changes or additions that will be made to the software. For software purchased from a vendor, this task can be accomplished by ensuring that the software release notes are reviewed and well understood by appropriate staff. Release notes should include documentation of all changes, any known issues in the new release, and instructions for upgrading the software from previous versions.

For software produced internally by the sponsor, a well-developed change control process should be established. This process should include steps for reviewing change requests, grouping multiple change requests together as appropriate, updating requirements and design documentation, build, testing, and implementation.

To determine whether a software system should be upgraded, the sponsor should consider the following issues:

- Impact on data—Assess if any changes in software functionality could potentially impact data integrity. For example, if certain characters or functions will no longer be supported, the sponsor must make sure data integrity will be preserved after the software upgrade.

- Impact on existing code—The software upgrade may require you to make changes to existing programming code.

- Auxiliary systems—The sponsor should assess how related systems or programs will be affected by the software upgrade. Will other systems require corresponding upgrades or modifications?

- Impact on sites—Will the study be inaccessible during the software upgrade? Is the site required to perform certain tasks, such as installing software on their local PCs or changing browser settings? Will the site require additional training? How will the sites be notified of the impact?

- Comparison of cost and value—The costs of implementing and validating a software upgrade should be compared with the business value to be gained.

- The impact on ongoing studies—Considering the impact on the study database and remaining duration, is it worth upgrading software to a new version? Does the software for ongoing studies need to be upgraded simultaneously?

- SOPs and training materials—Will the software upgrade require revision of the sponsor's SOPs or training materials?

For internally produced or customized EDC software, new requirements documentation should be created. This effort is often led by data management. The requirements documentation should include new features and functionality, as well as changes to current features and functionality. The requirements documentation serves as the basis for design specifications. Creating design specifications is typically performed by the group who will be programming the changes.

In addition to the requirements documentation, data management will need to develop a test strategy that documents the testing and validation required for the new software. Depending on the type of upgrade, intensive testing is not always necessary. The following guidelines can be used to determine required testing efforts:

- For a minor version (bug fix or upgrade), limited testing is required.
- For a new release or major version upgrade, moderate to intensive testing is required.

For purchased EDC systems, the vendor should be able to provide and maintain testing plans and results. For internally produced EDC software, test scripts or test cases based on new user requirements should be produced. Before implementing changes in a production environment, all testing should be performed in a test environment. New features and functionality provided by the upgrade (as well as enhancements of existing features or functionality) should be tested. A problem log or Web-based error tracking system should be employed to track errors found during testing, so the status of these issues can be monitored through to their resolution.

If validation of the new release has been successfully completed, the new version or changes can be implemented in production. Please refer to the "Database Validation, Programming and Standards" chapter of *Good Clinical Data Management Practices* for more information about validation, including recommendations, minimum standards and best practices.

Training on Changed Software

While a minor upgrade to software is likely to go unnoticed by users, a new release or major upgrade to software could require additional training. The sponsor should determine the required level of training, which users should receive training, and the method of providing the training.

Typically, sponsor staff (CRAs/CDM) and site staff will require training, which can be delivered in person, from a CD, using the Web, etc. Presentations using screen images can be particularly beneficial for training purposes, as they can be reused for later training sessions. Sponsor staff should be trained first on the software's new or modified functionality and then the site staff.

Developing the Rollout Plan

Before making new software available to staff, the impact of the revised software should be assessed. For example, if software revisions will require modification of approved CRFs, the sponsor should identify Institutional Review Board (IRB) issues to be addressed (IRB issues are not likely to apply to a software upgrade but may apply to CRF revisions). The sponsor should determine whether new software should be upgraded in stages or all at one time.

Sites should be informed of the rollout of new software with sufficient time given for necessary preparations. In case the upgrade does not occur as expected, a clearly defined rollback or fallback plan should be established prior to software implementation. For international studies, the time available to perform software upgrades can be limited and may require the upgrade to be completed during normal business hours.

Managing the Legacy Release

Software vendors typically maintain all software versions for a defined period of time. The sponsor should be aware of the level of support provided by these vendors. When a vendor rolls out a new system, they may not continue to offer the same level of support for earlier versions of the software system and may eventually retire earlier versions. Typically, once a version is retired, the software vendor no longer provides support for that version.

Because of ongoing development of software systems, the sponsor should plan for future changes, and determine when it is appropriate to upgrade or retire an existing system. Some factors to consider include:

- Software upgraded during study conduct
- Vendor’s support commitment to previous versions of software
- Software or hardware that becomes obsolete
- Decreased system performance
- Trial timelines

Study-Specific Change Control

In contrast to software changes, a trial could also be affected by study-specific changes, such as protocol amendments or development issues. As a result, CRFs, edit checks, and/or reports may need to be modified. CDM should assess required changes to determine how they should be implemented in the system and deployed to sites.

Changes to CRFs

Version-control software should be used for CRFs, and electronic files should be organized by study in a hierarchical directory structure. For each study, initial release of and subsequent changes to CRFs should be indicated by directory naming conventions or labels. Identifying the date and time that files were released must be possible so the release timeline is clear for regulatory purposes or to troubleshoot issues with CRFs. All installation qualification documents should be maintained for each version release. A log documenting the version release(s) should also be maintained and signed by all appropriate parties as required and defined by sponsor procedures.

Before rolling out the new version of a CRF, CDM needs to assess who the changes will impact. If the changes resulted in revisions to already approved CRFs, the reviewer should determine if these changes will impact the sites and IRBs, and inform all appropriate study team members and sites well in advance. For international studies, the time to deploy an updated version is more limited and may require deployment during normal business hours.

CDM should consult with clinical operations to determine whether to roll out the new version in stages or all at once. If changes are rolled out midstudy, the study team should first be notified when the changes will be available, and whether the study team will have an opportunity to review changes prior to deployment to sites. Site staff should be notified of training and rollout before changes are released to the production system. Once changes have been made, all parties should be notified. To ensure appropriate sites are moved to the new version of the CRF, CDM should create a log that will keep track of when each site was moved to the new CRF version. Proper logging will ensure no sites are missed in the process. Not all sites may require the new version, such as in cases where the changes are related to a protocol

addendum. Target dates should be set and tracked for upgrading sites to the new system, which should be closely monitored and tracked.

Data entered in the previous version of the EDC study should be made available to the sites and study team. Any new data that have not been entered into the previous version of the EDC study should follow the newly released CRF format. If edit checks were modified, CDM should review old discrepancies to determine if they are still valid, and if any of the discrepancies need to be closed due to the changes.

Midstudy Requests for Patient Data

A midstudy request for subject data can occur for many reasons, including, but not limited to:

- A scheduled interim statistical analysis based on study design and protocol, which typically focuses on efficacy data
- An interim review of data focusing on safety data, such as adverse events and other data that indicated safety issues in earlier studies (e.g., ECG data, lab panels)
- DSMB or Clinical Endpoint Committee (CEC) regularly scheduled meetings
- A submission package or other type of update (e.g., 120-day safety update) for regulatory purposes
- Any other planned or unplanned data lock

A major factor affecting delivery of midstudy patient data is whether the data are stored by the sponsor or a vendor. If data are stored by the sponsor, the data should be readily available, thereby reducing costs and resources needed. If a vendor's hosted system (Application Service Provider (ASP) model) is used, the timing and frequency of deliveries are more important, and planning will be required for the additional time and costs.

Whether a sponsor or vendor system is used, the required patient data should be clearly identified. Examples of prerequisite identification for exporting patient data include, but are not limited to:

- An interim analysis planned to occur at a particular milestone (e.g., the 100th randomized patient)
- A safety review planned to occur at a particular milestone (e.g., 25% patients enrolled, 50% enrolled)
- A midstudy efficacy analysis, based on statistical design of the protocol
- Regularly schedule DSMB/CEC meeting

In addition to determining which patients are to be included in an export, the sponsor should identify which records are to be included in the delivery. The simplest solution is to include all study data, regardless of its status. However, delivery could be restricted to data verified by the CRA or monitor, or to locked (clean) data, which requires close coordination with the CRA for scheduling monitoring visits. As is the case for paper trials, if data are to be used for an interim safety analysis, reconciliation of SAEs may require additional attention.

Any external data that must be integrated into the database prior to providing any subject data midstudy (e.g., laboratory data or ECGs) should be planned in advance of the study team's timeline for reporting. As necessary, the completeness and accuracy of such data should be ensured by reconciliation before the data delivery occurs.

The recipients of requested study data and the impact to study blinding must also be considered. For interim analyses, SAS® datasets are typically provided to a biostatistician or statistical programmer, who subsequently creates tables or listings from the raw data. Other delivery formats could include Microsoft® Access or Excel, but these formats are used less frequently and are generally less preferred. Timing of the delivery (e.g., planned or on demand) is also an important component to consider. If required data deliveries are scheduled, necessary procedures can be planned in detail. However, if ad hoc requests for data are anticipated, the process for exporting and delivering data should be robust and flexible to ensure timely delivery. When ad hoc requests are received, programs should be tested and validated to ensure timely delivery. Testing should include the complete extraction and delivery process, including checking that all required variables are available in the datasets and populated

with expected values. Errors or omissions noted during testing can be corrected until the data export operates as required.

Midstudy Requests for Notable Subject CRFs

The Food and Drug Administration (FDA) requires CRFs from subjects to meet certain criteria. As required by CFR 314.50 (f), for any new drug application (NDA), individual CRFs must be provided for any subject who withdrew from the study due to an adverse event, or who died during the study.[5] Depending on the study and FDA center, the FDA may request additional CRFs for review of the NDA.

The sponsor should be prepared to transfer CRFs at any time during the study, for example, for an NDA periodic safety update or integrated safety summary. One possible solution is to provide electronic copies of CRF images. If the CRFs are to be used in a submission, the publishing software used to create the CRFs should be considered so electronic copies can be easily incorporated. When working with a vendor, the sponsor should factor the process for obtaining CRFs into the contract's study timelines and expectations (e.g., maximum number of requests).

Recommended Standard Operating Procedures:

- Data Review and Edit Checks for EDC Studies
- Data Management Plan
- System Maintenance
- EDC Training
- Study/CRF and Edit Check Change Control
- Software System Change Control
- User Management and Security

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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 conduct phase of EDC. Content updated and organization of material revised. Study concept and start up, and study closeout content moved to separate chapters.

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