Electronic Clinical Data Capture

Position Paper Revision 1
May 1, 2005

Clinical Trial Electronic Data Capture Task Group

PhRMA Biostatistics and Data Management Technical Group

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1. Background

The Clinical Trial Electronic Data Capture (EDC) Task Group was initially chartered in August 2000 by the PhRMA/FDA Electronic Regulatory Submission (ERS) Working Group to identify ways to advance the use of electronic clinical data capture. The initial task group was chaired by a member of PhRMA's Electronic Regulatory Submissions Working Group (Donna Park, P&GP). Membership included industry representatives from Data Management and Regulatory groups of thirteen PhRMA member companies, and liaisons from PhRMA's Bioresearch Monitoring Committee and Biostatistics and Data Management Technical Group. FDA representatives from CDER, CBER, and GCP auditors worked with the task group during the initial issue identification phase.

This position paper was initially issued in March 2003. At the same time, the PhRMA Electronic Regulatory Submissions Task Group on Clinical Trial Electronic Data Capture also issued a Benefits/Risk Document on the use of electronic clinical data capture (*Electronic Clinical Data Capture Benefits-Risk)*.

At the end of 2003, sponsorship of the Task Group was moved from the ERS Working Group to PhRMA's Biostatistics and Data Management Technical Group (BDMTG). Catherine Celingant took over as chair. The membership was adjusted to include some new members and remove some former members who no longer had time or interest.

The rejuvenated EDC task group met with FDA representatives from CDER's Division of Scientific Investigation (DSI) in April of 2004. The position paper was presented to them with a focus on the issues and their resolution. Additional issues that had surfaced since the initial paper were also discussed. This revised paper includes the results of those discussions, updates based on industry's continued experience in EDC, as well as revisions due to changes in FDA guidance on 21 CFR Part 11.

2. Purpose

The purpose of this position paper is to recommend processes and standards that advance the use of electronic capture of clinical trial data and inclusion of that data in regulatory submissions, with the intent of reducing clinical data error, increasing productivity of communication between sponsor and investigator, and reducing time to regulatory submission. This paper does not contain all the information needed to conduct a clinical trial. It only contains additional information needed to conduct a trial using electronic data capture instead of paper case report forms.

In addition, this paper will:

- Recommend processes and standards for effectively implementing EDC in clinical trials based on industry experience

- Identify EDC-related issues in federal documents:
  1. The FDA's industry guidance documents for electronic submissions,
  2. 21 CFR Part 11 and its current guidance document,
  3. Guidance for Industry on Computerized Systems Used in Clinical Trials (Note: This paper identifies issues in the April, 1999 version of CSUCT as the Sept 2004 version is still a Draft. Section 16.4 of this paper identifies whether the CSUCT issue has been resolved with the 2004 draft),
  4. 21 CFR 312.62b for regulating investigators' responsibilities regarding case histories,
  5. GCP Regulations and ICH E6 Guidance, and
  6. European and US privacy laws/regulations.
- Propose solutions to these identified issues and recommend changes in FDA's regulations and/or guidance documents to enable these technologies.

Section 15 contains an overview of the issues that were identified and addressed.

3. Notes for Reviewing This Paper

This position paper recommends the use of the Adobe Portable Document Format (PDF) file format for archival records and to communicate the "Case Report Form" data to the FDA. At this time, PDF format is a universally recognized format for most documents and CRFs being submitted electronically to the FDA. It also plays a prominent role in the electronic Common Technical Document. It is recognized that as technology evolves, this format may no longer be the preferred mechanism for these two purposes. PDF is the current standard; however the draft CSUCT recommends XML and SGML as well.

The task group also recognizes that there is an emphasis in this paper regarding the ability to present the "Case Report Form" (CRF) data in a manner that resembles the data entry form that was used to collect the data. This emphasis in no way discourages the display or use of the data in tabular format. Tabular format is the traditional way companies have managed the clinical data in the past and the FDA has emphasized this capability for many years (i.e. electronic Case Report Tabulations). Presentation of the data in data entry form is required for 1) the site inspection performed by the FDA Division of Scientific Investigation (DSI) and 2) the CRFs submitted to the FDA for patients who died or dropped out due to an adverse event (AE).

While ePRO (such as patient-recorded diaries) are considered electronic data capture, this paper is focusing on investigator-recorded data. Many of the topics and issues in this paper do apply to ePRO, however the paper does not cover all the nuances of running an ePRO trial.

This paper identifies issues in the Guidance for Industry on Computerized Systems Used in Clinical Trials (April, 1999 version), as the Sept. 2004 version of this guidance is still a Draft. Section 16.4 of this paper identifies whether the CSUCT issue has been resolved with the 2004 draft

The task group also asserts that the ability to create archival records of the data in the form that closely resembles the entry mechanism is critical to their recommended position of retiring the EDC system when the archival records have been created and maintained according to the controls required by the FDA.

4. Audience

This document is intended to be used by those implementing EDC within pharmaceutical / biotechnology companies.

5. References

- 21 CFR Part 11; Electronic Records, Electronic Signatures Final Rule (March 20, 1997)
- 21 CFR 312 ; Investigational New Drug Application
- Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999)
- Guidance for Industry: Computerized Systems Used In Clinical Trials DRAFT (September, 2004)
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Biologics Marketing Applications (November 1999)
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs (January 1999)
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format -General Considerations (January 1999)
- ICH Harmonised Tripartite Guideline for Good Clinical Practice (January, 1997)
- See Appendix 3, "List of Privacy Regulations and Guidances"

6. Roles and Responsibilities

The following roles and primary responsibilities for an EDC trial are defined for the purposes of this paper.

Sponsor – The pharmaceutical or biotechnology company that has filed with a regulatory agency to conduct the trial. Responsibilities of the Sponsor include:

- Approval of protocol
- Review of EDC system owner's documentation to establish that system is compliant with all regulations and to ensure said documentation is sufficient
- Oversight of CRO (if applicable)
- Oversight of the EDC System Owner
- Review of study setup

EDC System Owner - The organization responsible for the maintenance of the computer system and for providing additional services with regard to setting it up and supporting its use. This may be the sponsor or a third party service provider. If the sponsor (who is ultimately responsible to the FDA for the software used to process the data they submit) has decided to use a system that is maintained by someone other than themselves, then the sponsor must audit to be certain the system is adequate for their use and they can prove that it meets all appropriate regulations.

Responsibilities of the EDC System Owner may include, but are not limited to:

- Validation of the EDC system
- Installation and support of the EDC system
- Control of system documentation per 21 CFR Part 11
- System compliance with all relevant regulations and guidance(s)
- Change control
- Setting up studies
- Site installation, training, and system support
- Decommissioning of hardware and software at the completion of the study if needed
- Preparing archival copies of study data for sites and sponsor

While the Sponsor may not actually do these activities, the Sponsor is ultimately responsible for ensuring compliance with regulations and guidance(s). Because of this responsibility, the body of this paper may refer to the Sponsor performing these activities, when in fact they may have been assigned to a third party provider.

Contract Research Organization (CRO) – An organization retained by the sponsor to act as its agent for a variety of activities related to the trial. For purposes of this paper, activities referred to as performed by the sponsor may be performed by the sponsor and/or the CRO.

Clinical Research Associate (CRA) - The person retained by the sponsor or CRO to oversee the conduct of the clinical trial at the investigator site and to verify the data collected against source documents.

Investigator – 21 CFR 50.3(d) defines the investigator as "*The individual who actually conducts a clinical investigation – i.e., under whose immediate direction the test article is administered*." For the purpose of this paper, "investigator" will mean investigator and/or investigator staff unless specified otherwise.

7. Definitions and Acronyms

7.1. Electronic Data Capture (EDC)

EDC is a technique for collecting clinical trial data in such a way that they are delivered to the sponsor in electronic form instead of on paper. This includes the following scenarios:

1) Clinical laboratory data that are transmitted to the sponsor electronically and are not re-entered by the sponsor

2) Patient data that are directly captured by instrumentation

3) Information that is entered by the patient directly (ePRO) into an electronic device, such as personal digital assistant (PDA) diaries.

4) Information that is entered by the investigator's staff directly into a computer, without first writing the data on paper, i.e., electronic source (eSource) data.

5) Information that is first recorded by the investigator's staff or patient on paper, that is subsequently entered into a computer at the investigator's site, and is delivered electronically to the sponsor or sponsor's representative (such as a CRO) without a hand-written case report form.

7.2. Source Data

The following definition is from the ICH Harmonised Tripartite Guideline for Good Clinical Practice (January, 1997) (ICH E6).

- Source data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of a trial. Source data are contained in source documents (original records or certified copies).

- Source documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments involved in the clinical trial).

The CDISC standards effort provides the following definitions of data that are directly entered/captured by an automated system:

- eSource Data: Source data (per FDA/ICH definition) captured initially into a permanent electronic record. [Note: "Permanent" in the context of these definitions implies that any changes made to the electronic data are recorded via an audit trail.]

- Transient Data: A "state" of data being used internally by the system without ever being permanently stored.

DSI representatives have stated (April 2004) that there should be two independent data sets: The source data and the sponsor's data. FDA representatives should be able to review the source dataset to corroborate the datasets used by the sponsor for reporting and analysis. Given that all systems can be violated regardless of the controls in place, the sponsor cannot be the sole repository of the data in which they have a vested interest, as this would create a conflict of interest in the view of the FDA. Thus, no source data (paper or electronic) should be held by the sponsor. It is reasonable to expect that electronic source held by a "trusted third party" would be acceptable, however at this point a "trusted third party" does not have any regulatory standing.

If the EDC system contains source data, current DSI direction suggests that the server containing the EDC system should not be maintained by the sponsor. This issue is still under discussion.

7.3. Electronic Case Report Form Data

When EDC is used in a clinical trial, electronic case report form (e-CRF) data are defined to be the data that are manually entered into a computer by the patient or by the investigator's staff. This defines items 3, 4, and 5 in the list in section 6.1 as e-CRF data. Data that are captured directly by instrumentation or computerization without any manual entry are not considered "e-CRF data". This defines items 1 and 2 in the list as non-e-CRF data.

Note that in any one study, data may be collected using a combination of all five of the EDC methods listed as well as paper CRFs. In these instances, the complete "CRF data" would include the paper CRF data in addition to the data that are manually entered into a computer by the patient or by the investigator's staff (e-CRF data).

7.4. e-CRF

CDISC defines e-CRF as a CRF in which related data items and their associated comments, notes, and signatures are linked electronically.
Note: e-CRFs may include special display elements, electronic edit checks and other special properties or functions used for both capture and display of the linked data.

7.5. Blank e-CRF

A blank e-CRF would present any instruction screens (screens customized for the study which provide instructions to the patient, investigator, or investigator's staff on how to provide information or use the system) in addition to all screens on which data or comments/notes/annotations are entered. The blank e-CRF should reflect all possible decodes available when data are entered (i.e., drop-down menus or buttons listing all possible options and decodes (such as 1= good, 2= fair, etc)).

7.6. Completed e-CRF

A completed e-CRF is defined as a PDF file that is a close facsimile to a printout of the screens used to enter data

A completed e-CRF is defined as a PDF file that is a close facsimile to a printout of the screens used to enter data. It presents the final data values, in a decoded fashion where appropriate and reasonable, so that the meaning of the responses is clear to a reviewer or auditor. Instruction screens that do not contain any data need not be included in a completed e-CRF unless knowledge of those instructions is required for a clear understanding of the meaning of the responses. If comments, notes or annotations are entered into the system, these should also be presented either on the same PDF page as the corresponding data field or with a hypertext link from the data field to the comment/ note/ annotation.

7.7. Archival e-CRF

The archival e-CRF is defined as a PDF file that consists of the completed e-CRF (see Section 6.6) along with the associated e-CRF audit trail. The archival e-CRF may be an electronically signed record, depending on the approach for investigator signatures chosen by the sponsor for use in the EDC trial. Having the archival e-CRF book-marked to easily navigate sections within each patient would be a valuable feature for both the investigator and any auditors that visit the site and need to review the data.

7.8. Electronic Submission CRF (e-Sub CRF)

An electronic Submission CRF is a CRF electronically submitted to a regulatory agency as per their requirements (for subjects who die, experience SAE, or withdrew from study). e-Sub CRFs may be produced either from paper CRFs or e-CRFs.

7.9. Annotated e-CRF

An annotated e-CRF is required when submitting case report tabulations (CRTs) in an electronic submission for an EDC study. The annotated e-CRF is a blank e-CRF including treatment assignment forms that maps each blank on the e-CRF to the corresponding element in the datasets provided. The annotated e-CRF should provide the element names. Each page and each blank of the CRF should be

represented. The sponsor should write "not entered in database" in all sections where this applies. The annotated e-CRF should be provided as a PDF file.

7.10. Acronyms

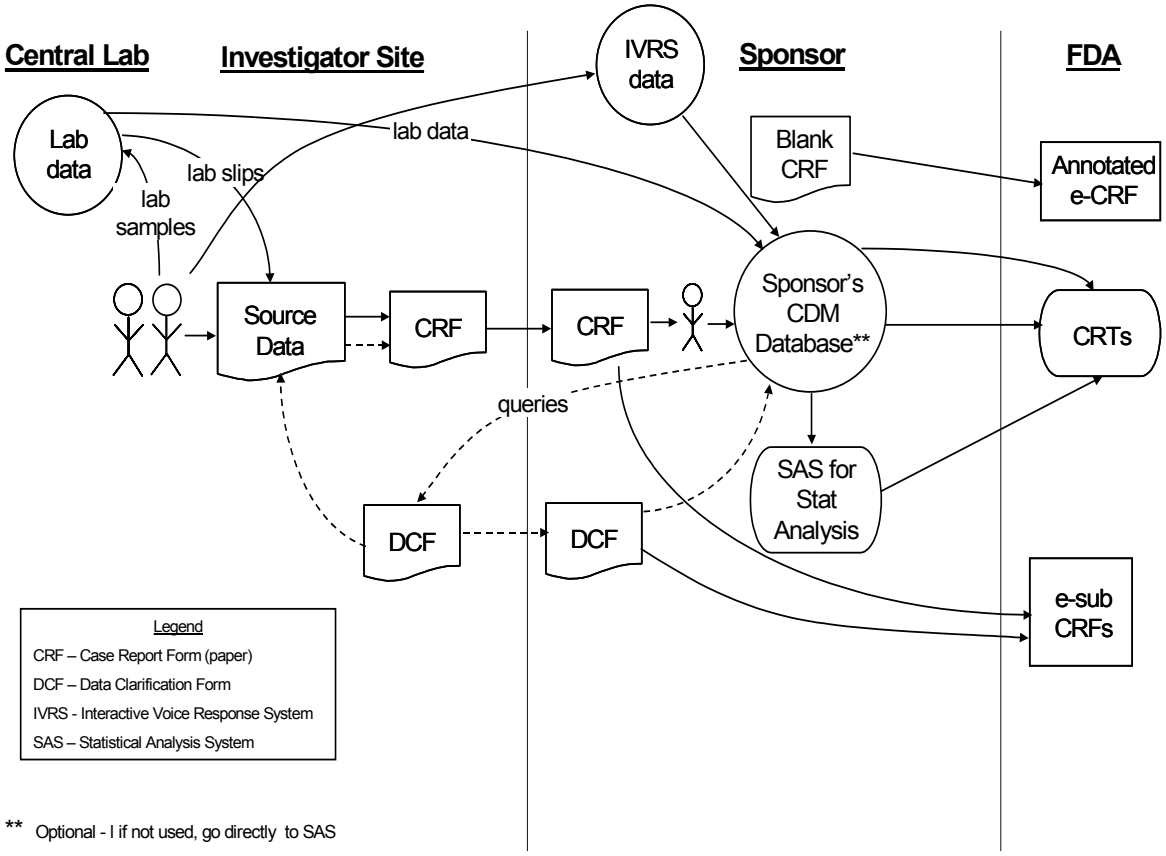
CBER	FDA Center for Biologics Evaluation and Research
CDER	FDA Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRT	Case Report Tabulation
DSI	FDA CDER Division of Scientific Investigation
EDC	Electronic Data Capture
EHR	Electronic Health Record
GCP	Good Clinical Practices
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IVRS	Integrated Voice Recognition System
PDA	Personal Digital Assistant (handheld device)
PDF	Portable Document Format (from Adobe)
PRO	Patient Reported Outcomes
SLA	Service Level Agreement

8. Data Flow for Paper and EDC Study

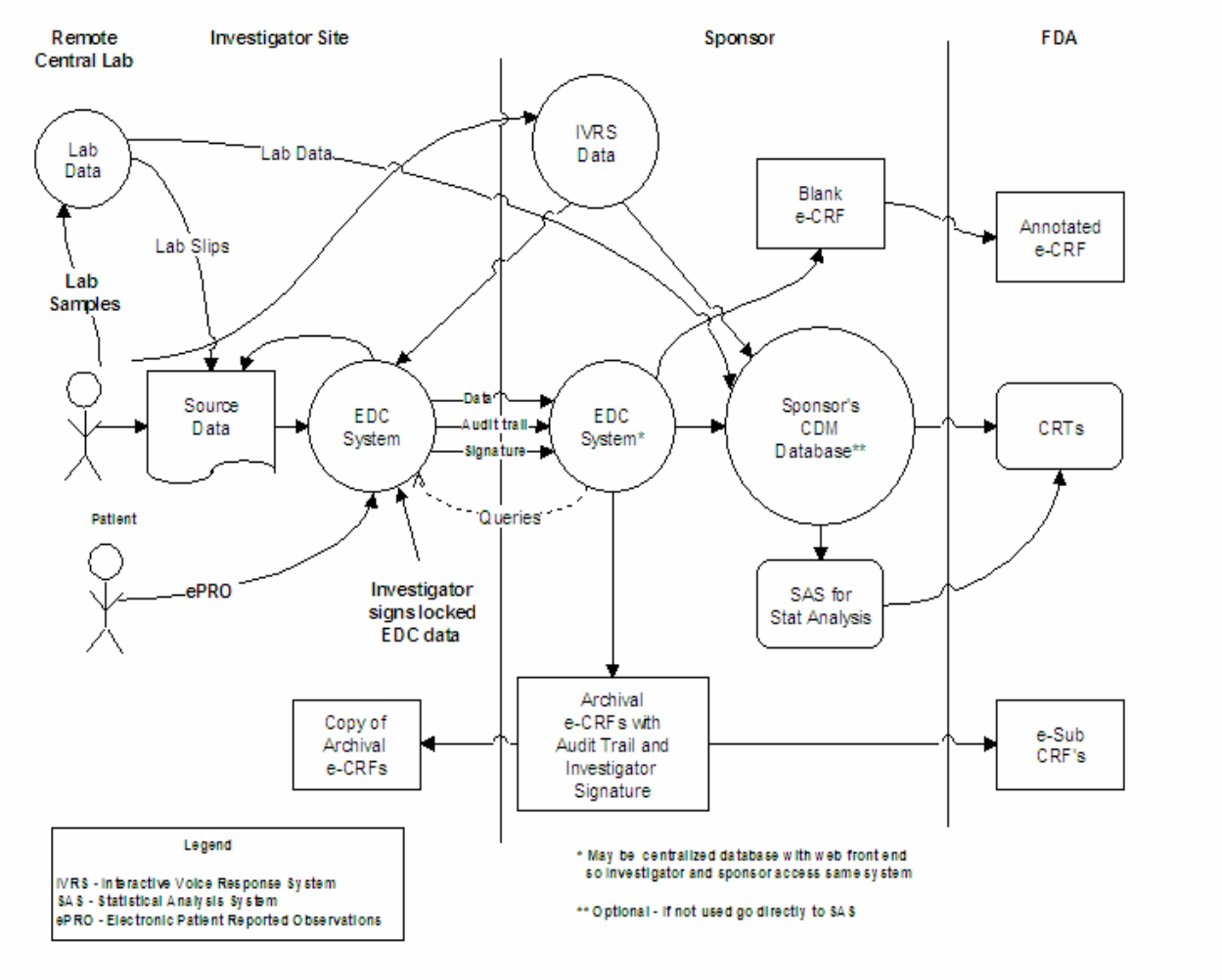
A sponsor must change their standard paper CRF based processes to successfully implement and achieve the maximum benefit when employing EDC technology. Using EDC technology without a directed effort to change existing processes may fail to deliver expected improvements/benefits.

It is very important that the Sponsor and Investigator understand the data flow for an EDC study. This data flow will be different from the standard paper CRF study and will be the driver of many of the process changes and potential benefits.

An Example of the Data Flow in a Paper CRF Study



An Example of the Data Flow in an EDC System with Investigator Signature in the EDC System Passing Through to Archival e-CRFs



9. Current Approaches For Implementing EDC

There are several different approaches to implementing electronic data capture. Each approach has different implications, and may be appropriate in different circumstances. However, it may be practical for a sponsor company to standardize on one EDC system (including custom or commercial EDC application and sponsor-specific procedures and SOPs) and use it at all sites where EDC can be implemented.

Off-line approach
In the "off-line" approach (also referred to in industry as "stand-alone"), software and data reside on a local laptop or desktop PC at the investigator site. This approach is very desirable in regions where connectivity via phone line and/or Internet is difficult to achieve or maintain, is sporadic, or takes an extraordinary amount of time for initial set-up. The hardware and software must be validated and measures must be taken to maintain this validated state during the life of the study. Methods to transfer the data to the sponsor site depend on how reliable a phone or Internet connection can be; the approach can range from courier-delivery of CDs to periodic data transfer via phone line or the internet. A distinction of the off-line approach is that the clinical data exists physically in at least two different places.

Thick client approach
The thick client approach is similar to an off-line approach in that the application is loaded locally and must follow similar validation measures; however it is designed such that it could operate in an on-line or off-line mode.

Thin client (web browser) approach
In the "thin client/web browser" approach, a web browser is used, and all EDC-related software, forms, and data are stored on the central server and accessed through a secure browser connection (i.e., internet). This approach is very desirable in regions where connectivity via Internet is reliable and easy to achieve and maintain. Data are entered on-line so that the sponsor sees them and can respond in real-time. While there is minimal necessity to validate the investigator's workstation as it is being used only as a "terminal" and not processing data or associated software, systems should have the capability to "validate" or confirm the Operating System and Browser upon logon, thus ensuring that the correct system is connecting to the server. However, some hospitals or other investigative institutions may have firewalls that will cause difficulty in passing information to/from the server, and Internet speed (due to bandwidth or mobile connection speed) can be problematic. Some sponsors using this approach still feel it necessary to provide a validated laptop for the investigator to use for their EDC studies, to reduce the chance of hardware or software failure (and downtime) due to other uses. See also issues concerning control over electronic source data (section 6.2).

Hybrid approach
The "hybrid" approach is a catchall term for any combination of the above two approaches. One example of a hybrid is to have software on the laptop and data on the server. This approach is suited for sites that have slow Internet performance, but where there is concern over the validated state of the investigator workstation and/or a more real-time communication between the sponsor and the investigator is desired. Another hybrid approach for combating slow Internet performance is to use an "off-line" EDC tool for data entry, and transfer the data and communications between the investigator and sponsor server at a time when Internet performance is expected to be acceptable. If security and reliability of phone line and/or internet transfer is an issue, a hybrid approach where a CRA could perform real-time data monitoring and communication with the investigator by viewing the data on the laptop via a read-only view provided through a phone connection can be used. Some hybrid EDC tools offer the option of either online or offline data entry in order to take advantage of web-based features, but allow work to continue if the web

connection cannot be maintained. In these systems, synchronization between the laptop database and the server database is critical. Typically data edit checks only occur after synchronization.

10. Getting Started

10.1. Data Entry/Collection Methods

Data entry/collection methods can vary depending on sponsor, protocol, site and type of data, and it is typical for a site to use two or more of the methods for a given study. The most common data entry/collection methods used are: 1) Manual transcription of data into the EDC system from paper source or other electronic source (EHR) maintained by the investigator to the EDC system, 2) direct entry into the EDC system by the investigator, 3) data from a third party (i.e. laboratory service) that is received by the sponsor and/or investigator in electronic form, 4) capture of data from automated equipment at the investigator site (e.g., Holter monitor, EKG), and 5) direct entry by the patient into a separate data collection device such as a PDA. The method of storing, managing and transferring are similar to those described in *Current Approaches for Implementing EDC* above. See Appendix 1 for a discussion of the benefits and ramifications of various methods.

The approach for data entry/collection, management and transfer should consider technical capabilities, data type, value/cost, and staff abilities and work preferences (both investigator and sponsor). The task group believes that the direct entry of data into the EDC system rather than recording it on paper first may offer a significant advantage. In this case additional controls would be needed and further discussion on electronic source with FDA need to take place (see section 6.2 Source Data for explanation of DSI position regarding eSource).

In addition, the following must be satisfied:

- Sponsor should identify in the protocol what data are to be captured directly on the e-CRF (i.e., that will be considered electronic source).
- EDC system is 21 CFR Part 11 compliant (functionality and deployment)
- EDC system is supported by adequate back-up and disaster recovery procedures
- E-source will be adequately protected and available to the site
- An acceptable method in place to ensure that the investigator maintains control of the patients' case histories as per 21 CFR 312.62b.
- Investigator should have access to any data collected electronically in as close to real-time as consistent with the requirement to preserve blinded data.
- Any data collected electronically that is critical to the medical care of the patient should be immediately accessible and should be attached to the patient's chart.

- Some sponsors have found it to be very productive for their CRAs to have the ability to monitor the data from any location and this capability needs to be designed in. In some cases, the ability for the CRA to review the data in real-time may encourage the investigator to enter data on a more timely basis. The data entry/collection methods should be discussed with the investigator early on so that investigator and sponsor can agree on which methods will be used and the appropriate training and SOPs required to support those methods.

10.2. Privacy

Although data privacy concerns relate to both paper and EDC studies, there are additional concerns with EDC as they relate to the transmission of data across country borders. Privacy laws and regulations vary from country to country and are still evolving. Identification of individuals by means of date of birth, gender and initials (as has been typically done), provides less protection with the onset of "personal" information readily available via the Internet.

The task group recommends that individual sponsor companies implement and maintain a data privacy policy defining what data may be collected electronically and transmitted within or across borders. The EDC system should be capable of supporting the company's policy (such as encrypting data or omission of certain patient information, as necessary).

A list of privacy rules to consider can be found in Appendix 3.

10.3. Identification of Computerized Systems in Protocols

The Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999) states in Section III A "Each study protocol should identify at which steps a computerized system will be used to create, modify, archive, retrieve, or transmit data." It would be very difficult at the time a protocol is written for the sponsor to know all the different systems that may be in use at each of the investigator sites that may be involved in the study.

The task group recommends that the guidance be changed to the following: "Each protocol should identify those steps at which a computerized system is provided or endorsed by the sponsor to create, modify, archive, retrieve or transmit data and which data are affected. The protocol should state whether the use of such systems is required or optional."

10.4. System preparation, testing, and installation

10.4.1. Startup Time considerations

EDC studies may have longer setup time than paper-CRF based studies due to the increased number of tasks that must be completed before the study may start. These additional tasks include: Designing, programming and testing the data entry screens and associated edit checks, and training the investigator(s) on the EDC system.

Some activities, such as site preparation (obtaining phone lines, setting up equipment) can be started during the protocol drafting period. However, programming the study and all its parameters into the

EDC tool, if started before a protocol is finalized, may require rework and must be thoroughly checked to be certain it matches the approved protocol. Training of staff is best done with a finished EDC system in place.

10.4.2. Data Entry Screen design considerations

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Data entry screen design should take into consideration the requirements of the protocol, the technical features of the selected application, the experience and preferences of the investigator(s) where possible, and the migration of data to the sponsor's database.

Technical approach considerations: Data entry screens must be designed for efficient use with the technical approach chosen, in particular with the speed of data and forms transfer if web browser technology is being used. Depending on the system, software, and experience of the end-users, the design of simple data entry screens may be desirable for access through a web browser in order to achieve quick screen establishment and refresh.

Experience and preference of investigator: Data entry screen design should take into consideration investigator's experience and openness to computer technology. For instance, would it be preferable for the screen to look more like a paper CRF, or can it take full advantage of technology bells and whistles? For example, an advantage EDC has over paper is the ability to provide such things as bitmap images (by drop-down pick-list) of different body parts or different types of "conditions" and allow the investigator to be more pictorial in describing the problem. Another screen design consideration is whether the fields should be labeled in the local vs. standard language. Should screens be designed so field names can change depending on the predominant language of the study site? Decisions as to what language to use for field labels may affect the quality of data coming in. If local language is used for data entry fields, it is likely that the data will be represented in the local language and may need to be translated to a standard language for reporting. If the language chosen is a standard language (such as English) and the staff is not fluent in this language, there is the risk of misinterpreting what data are being asked for in the study.

Navigational tools: The EDC system needs to support a flexible method to navigate between the data entry screens in order to allow for differences in the data entry flow between investigator sites and staff. Some systems may support the study specific design of additional navigational aids, such as links between related data entry screens and conditional navigation based on the value of entered data. Information on the CRF should not be obscured (hidden/shown) based on values of data fields. The cost of building, testing and implementing additional navigational aids needs to be balanced against the value they add to help the investigator to do data entry or to increase the quality of the data entry. Also, the task group recommends that navigational aids not prohibit the entry of particular data items regardless of any navigational rules based on data values.

Re-usability of standard data entry screens: Some data types (e.g. adverse experience) are consistent from study to study and standard data entry screens can be created, tested, and catalogued for use with multiple studies. Using standard data entry screens affords significant production efficiencies during study start-up by reducing the development and testing time.

Data migration to the sponsor's database and requirements of the protocol: As with paper CRFs, EDC data entry screens must be carefully planned such that the correct data are collected in the right format to answer questions posed in the protocol, and that these data can be collated into a database that facilitates querying and analysis required to answer these questions. The use of standards (such as CDISC ODM) for the import/export of data is one way of reducing costs and repeating work.

Sponsor SOPs should ensure that the data entry screens and edits are reviewed by the same functional staff who review the CRFs and edits for a paper study.

10.4.3. Edit considerations

The *Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999)* states in Section VI. A1: "Prompts, flags, or other help features within the computerized system should be used to encourage consistent use of clinical terminology and to alert the user to data that are out of acceptable range. Features that automatically enter data into a field when that field is bypassed should not be used."

While edit checks at the point of data creation are one of the key factors in allowing EDC to harvest cleaner data than paper CRFs, this task group recommends that

- Edit checks should not prohibit investigator from continuing entry if there is an error (should notify and flag for subsequent sponsor review but allow them to continue), nor should they lead the investigator to the "correct" entry.
- Error messages resulting from edit checks should be written in clear and easily understood language.
- The cost of development and testing of sophisticated edits needs to be balanced against the resulting benefit, and one should take into consideration whether the site staff entering the data can actually respond to the edit and/or the likelihood that the error condition it is looking for will ever occur.

10.4.4. Customization of the EDC tool

Setting up new studies and providing study-specific edit checks should be part of the configuration of the EDC system and requires testing (see below) but should not require changing the programming of the underlying core software in the EDC system. If additional customization to the underlying EDC system were required to support a study specific need, an assessment of the changes and validation implications should be performed followed by an amended validation or a complete revalidation (if necessary). This assessment should be based on a clear understanding and definition of the changes made to the system and how those changes affect the original validation effort, and the integrity of the data (see section 13.9). Such customizations should be carefully balanced against a perceived benefit and should be kept to a minimum.

10.4.5. Testing considerations

Initial validation of the EDC system should be performed by the sponsor / system owner in accordance with their SOPs for completeness, accuracy, reliability, and consistent intended performance (see section 13.9). This section assumes the EDC system has been validated. In addition, each EDC study must be tested on the environment on which it is intended to be run prior to release at a study site. The following minimum recommendations are offered:

- All data entry screens, navigation aids and edits that are customized or developed specifically for the study must be tested. This testing should include boundary testing, testing of derived values, and other testing meant to stress the system. Standard data entry screens and edits that have previously been tested need only to have the link within the study tested, however it is suggested that standard data entry screens be reviewed to ascertain that standard fields and edit checks are appropriate for the new study. Testing might include both data entry of one or more sets of test data that would use all new edits and data entry screens and could also be used to check the data migration method and ensure the integrity of the data upon arrival into the sponsor database. Using standard data entry screens and edit checks that have previously been validated and are under change control can greatly reduce the amount of testing required per study.

- Study setup activity that is table or menu driven rather than source code driven can often be more thoroughly tested via review of the setup tables than by devising test data for all cases.

- When using a thick client deployment, a predefined installation procedure and operational test should be performed on each workstation used (regardless if owned by the sponsor or investigator) to ensure the system has been installed correctly. If the EDC system is web-based and does not require additional software to reside on the investigators' computer system, performance testing of the system with the investigator's browser and line speed should be conducted.

- The migration of the EDC data to the sponsor's database must be tested to ensure all data are accurately transferred. The setup and testing of this interface can be delayed until after the study starts, but it is recommended that it occur soon after the study has started and is not left until the data are needed for sponsor analysis.

- Other data migrations from or to the EDC system need to be validated.

Testing of each EDC study and migration to sponsor's database can be time consuming and costly. These factors should be considered by the sponsor prior to deployment and may be a consideration in the decision as to what EDC system architecture should be used, and what type of studies are most beneficially done with EDC.

10.4.6. Hardware and Telecommunications acquisition and installation

Providing hardware, software, phone lines, internet connection, and user training to remote areas can be extremely difficult in some cases.

Depending on the technical architecture approach taken, different scenarios for who supplies and who owns the hardware can apply. If data and/or software are to reside on the local hardware, then the hardware must be kept in a controlled and valid state and is typically supplied by the sponsor. Conversely, if a thin client (no local software and/or data) is employed, an investigator's workstation could be used (such as one already in use at the investigator's site). Note that some sponsors feel that it is still necessary to provide a validated laptop with a thin client, in order to maintain a validated workstation and to reduce the chance of hardware or software failure (and downtime) due to other ancillary software used by the investigator on their workstation. However, the task group believes that performing a robust site technical assessment of the investigators' hardware, software and telecommunications capabilities is sufficient to support web-based / thin client EDC applications.

If the sponsor provides hardware, the hardware must be purchased based on the technical (electrical and telecommunication) standards of the region in which it will be employed. It should also comply with the investigator's infrastructure. Often a standard set of hardware can be used and converters purchased to allow them to be employed in different regions. If local hardware is purchased, the keyboard keycaps and configuration may have additional implications on the data collected (e.g. if the keycaps are using a local character set and data are expected to be entered using a common language, there may be confusion).

If an investigator owned workstation is to be used, both the hardware and software already installed on the workstation, including firewalls, need to be assessed to ensure that it will not adversely impact the functioning or performance of the EDC system. This assessment would be part of the site technical assessment process. Also, the sponsor and any site inspectors need to have access to the workstation and / or EDC system during the course of the study.

Acquiring appropriate electrical and telecommunications connections and phone lines may be most effectively done locally at the site rather than from a central sponsor location. If the sponsor has a local office, the assessment is best done through the local office. Some sponsors have required investigators to provide electrical and telecommunications connections and phone lines. Lead-time for implementing electrical and telecommunication capabilities needs to be considered to ensure that study start timings are not affected. In some regions, acquiring a new phone line is a complicated and extremely time-consuming process.

10.5. Preparing the Investigator

10.5.1. Review of investigator responsibilities

Adequate and appropriate training must be provided to the investigator to review and get agreement for policies and procedures regarding hardware, software, data security, electronic signature requirements, and what records need to be maintained for EDC. The review should also manage investigator expectations for what EDC can and cannot do for them.

If the investigator is expected to provide any assistance in acquiring hardware or phone lines, or providing any other pre-EDC service (such as pre-screening of patients for enrollment), these expectations should be clearly identified and agreed upon.

The investigator needs to have a good understanding of the overall design and data flow of the system, where the data resides and at what time, and who has rights to modify the data. It is very important that the investigator understands that the use of EDC does not change their responsibility stated in 21 CFR 312.62.b, i.e., they continue to be responsible to prepare and maintain accurate case histories.

Careful consideration must be given to ensure investigator sites are prepared for entering data into an EDC system. The sponsor needs to assess the site's willingness, capability and capacity to perform timely data entry based on clearly defined goals for entry of patient data. The sponsor may recommend that additional staff be retained to perform data entry tasks if site resources are limited. The equipment at the investigator's office must be kept in a secure area to prevent theft and all other security measures must be followed.

Contingency plans must be developed by the system owner to ensure that any EDC system outage does not compromise the integrity of the trial. If source data are maintained on paper documents, data entry can be delayed until the EDC system is operational without any change to procedure. However, when the EDC system is to be used to collect e-source, a backup plan must be developed by the site to handle the situation when the computer is not available at the time of the patient visit/exam. This plan should require documentation of the problem in the site's study files.

The investigator is also expected to make the EDC system and/or archival e-CRFs available to an FDA inspector. In case of an inspection when the EDC system is still being employed, the system owner personnel should be available to train and/or assist the FDA inspector. Once the archival e-CRFs are available, the investigator's staff should facilitate the inspector's review of the archival e-CRF. (See also sections 10.7 and 12.2).

10.5.2. On Site SOPs/Policies

Standard Operating Procedures should be available to the clinical site. The Operating procedures may be kept as paper documentation or read-only electronic copies. Care must be taken when providing electronic access to operating procedures that the information on how to access the SOPs is kept as hardcopy. The policies and operating procedures should include at a minimum the following:

1) Operating instructions for the system including log on procedures, data entry, electronic signatures (where applicable), backup procedures and access to help and support

2) Method for access to SOPs pertaining to systems provided to the site

3) Policy and procedure on electronic records and electronic signatures (including password sharing, time out, and log off when leaving station)

4) The verification of individual identity prior to assigning an electronic identity (such as electronic signature or user id) as required by 21 CFR Part 11

5) The password expiration criteria and frequency of resets, as appropriate

6) Procedures for archival e-CRFs that describe maintenance and storage conditions for the electronic records, retrieval and access restrictions, and responsibility for relevant tasks.

10.5.3. Documentation Requirements

The *Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999)* requires that system documentation be readily available on the site where the clinical trials are conducted. The task group recommends that the following information be available:

1) User manuals (for as long as EDC system is available to the investigator site)

2) Training materials and training records for the site (for the retention period of the data)

3) A list of users with their unique user ID and access privilege, and dates privileges were granted, changed, or revoked (kept onsite or with system owner). Passwords must be kept confidential to each user and must not be kept in any list (for the retention period of the data)

4) Any local administration procedures and manuals (for the retention period of the data)

5) Notification of changes to EDC system if any mid-study changes were made (for as long as the EDC system is in operation at the investigator site)

6) Investigator role in disaster recovery procedures as well as a description of the impact of a disaster on the investigator see section 13.10) (for as long as the EDC system is available to the investigator site)

7) Contingency plans (for as long as the EDC system is available to the investigator site)

8) Log of use of contingency plans (for the retention period of the data)

9) SOPs, policies and procedures noted in section 9.5.2 (for the retention period of the data)

10.5.4. Electronic Signatures

If the sponsor intends to use electronic signatures, it is recommended that contracts with clinical investigators include: 1) a statement to indicate that electronic signatures are to be considered the

legally binding equivalent of handwritten signatures, and 2) a reminder to file electronic signature document with the FDA as per 21 CFR Part 11. It is preferable that the investigator files this electronic signature document once rather than for each sponsor and /or each study. The sponsor should ensure that the electronic signature document has been filed with the FDA.

For future consideration, the task group recommends that if electronic signatures are used, they are compliant with Secure Access For Everyone (SAFE) standards. Once an investigator is credentialed by SAFE, his/her identity and electronic signature can be used by all SAFE compliant sponsors. Refer to http://safe-biopharma.org for more information on SAFE standards.

10.6. Preparing Sponsor Staff

Adequate and appropriate training must be provided to all sponsor staff, including managing sponsor staff expectations for what EDC can and cannot do for them. Sponsor staff in contact with investigative sites (e.g., CRAs) should also be responsible for managing, on an ongoing basis, investigator expectations as well as monitoring investigator adherence to EDC procedures set by the sponsor. This includes doing source data verification (if the data were not directly entered into the EDC system). CRAs will need to be well trained on all aspects of the EDC system in order to provide coaching for the investigator. CRAs and/or Clinical Data Management staff should monitor time elapsed between when patients were expected to have visits and when the corresponding data appear in the EDC system and be proactive to avoid data stockpiling at the investigator site. Allowing data to age before being entered will negate many of the benefits of early data collection, including cleaner data and early detection by the sponsor of problems with a particular drug program, study or study site.

10.7. Training

Adequate and timely training is essential to a successful EDC study. All investigator and sponsor study staff must be trained prior to being granted access to the system. Training must take into consideration how computer-literate the staff is (i.e. will training need to include general computer use and/or Windows use?), and whether training needs to be provided in the local language. Using an experienced trainer for pre-study training is preferable to training provided by study personnel or an on-line tutorial. Study personnel and on-line tutorials are excellent for during-study refreshers and support and should be provided. A suggestion for on-line assistance is to provide a process map that can be drilled down for specific training and hands-on examples.

It is recommended that the sponsor develop test data (test patients that simulate situations that may be encountered during the course of the study). As part of the training curriculum, study staff should be required to enter test data for each area of the EDC they will be using, and any difficulty encountered must be addressed. Training should include all areas of EDC study management (not just entering data) that the study staff are expected to handle (such as keeping a log of access privileges, change control, keeping workstations in a validated state, management of system documents, password and computer system security and control, etc.)

Documentation that site staff has been trained and successfully performed test data entry must be retained in the site's training records (see sections 9.5.3 and 9.7.1).

10.7.1. Training Records

21 CFR Part 11 requires that staff education, training, and experience be documented and show that study staff are qualified for their assigned tasks. The task group recommends that the sponsor establish a process by which all pertinent sponsor and investigator staff (and patients if appropriate) will be trained in those processes directly related to EDC initially or whenever new personnel are added during the course of the study. The process should include change control procedures for training materials. The process should provide for the retraining of individuals in the event of a change of operating procedure, systems manuals, administration procedures, or data collection methodology. Training records should be maintained both on site and at the sponsor and should include the approved materials used for training. Training materials and training records may be managed in a paper system or as electronic records (if maintained as electronic records they must adhere to requirements set forth in 21 CFR Part 11).

10.8. Support

It is recommended that a Service Level Agreement (SLA) be developed by the EDC system owner and be communicated to the Investigator and sponsor staff. This agreement should clearly state the following:

- Method used to communicate problems regarding the study and the EDC system
- Scope of responsibilities (i.e. types of questions handled by system support staff vs. CRAs or others)
- Time support staff are available
- Expected response time
- Problem escalation process
- Problem tracking and resolution communication process
- Disaster recovery plan.

Support in local language and/or during appropriate times may be an absolute necessity in some sites, but may be difficult for the sponsor to provide from a central location. The sponsor may want to develop this expertise at local offices or contract it out. Demand for support is highest during study start-up and shut-down (rather than mid-study) and sponsor should anticipate and plan for this. Mid study changes may require local language support and assistance.

10.9. Recommended SOPs for EDC Studies

Standard Operating Procedures are required to govern all aspects of a clinical trial. A list of recommended EDC SOPs for sponsors can be found in Appendix 2 . Recommended SOPs/Policies for investigator sites are discussed in section 9.5.2.

11. Study Conduct

11.1. Investigator Data Entry

Double data entry is not needed with EDC since site personnel knowledgeable of the data perform the entry process with the aid of EDC edit checks. However, the staff should be instructed to check their data entry to minimize errors, especially data transcription errors. Sponsor site visits should include source data verification that will check the quality of the data entry if paper source records exist or if the investigator maintained other electronic source records (e.g., electronic medical charts).

For those data entered directly into the EDC system without other source documents, it is recommended that copies of the data that are critical to patient care and safety be attached to the patient's chart in a timely manner.

Electronic signatures executed at pre-defined intervals during the course of the study by the investigator, directly into the EDC system, helps ensure that the investigator has ongoing oversight of the data being entered. If this approach is taken, the EDC system must support electronic signatures as defined by 21 CFR Part 11.

Investigator signature post study closure is addressed in section 11.3.

11.2. Safety monitoring

Some EDC systems can provide notification of serious adverse events (SAEs) to the sponsor via email, based on criteria specified within the edit check capabilities. If electronic notification is used, it must be tested and documented. Additionally, it is recommended that a process separate from the EDC system be established for the communication of SAEs to the sponsor by the investigator, regardless of whether electronic notification will be used, in order to ensure timely delivery in the case of electronic notification failure. SAE data must be provided to meet timings dictated by regulations and sponsor SOPs.

Regardless of the process used by the investigator to communicate SAE data, it is required that all AE data be reviewed by the sponsor to ensure that all SAEs have been identified and dealt with in a timely manner. It is important that a sponsor define the point in time within the data flow of an EDC study that AE data are instantiated, that is, the point in time that the clock starts regarding the need for sponsor review and reporting. Although this starting time may not be when the data are first entered, it should be soon after the data are readily available to the monitoring staff for review.

11.3. Query processing

There are typically two ways that queries are generated within an EDC system: 1) Automated queries (i.e., those based on computer programmed checks upon e-CRF entry and/or completion and upon submission of e-CRF data to the central server); and 2) Manually generated queries (i.e., those based

on data review by the CRA during source document verification and / or through the sponsor's review of data).

There are generally at least three query states: Open, Answered and Closed (there may also be more states with different names). Electronic data capture systems should have ways of identifying each of the query states.

"Open" queries are those that need to be addressed by the site. Site staff are electronically alerted that a query has been submitted. Desirable timing for resolution of queries needs to be established by the sponsor and communicated to the investigator site prior to study start. Functions within the EDC system identify when a query has been "Answered". Often, automated queries are automatically closed by the EDC system when the data are corrected (i.e. when the query is "Answered") and the problem no longer exists. Other "Answered" queries must be reviewed by the CRA or other sponsor staff and are "Closed" once the response has been officially reviewed and accepted by the sponsor. Electronic data capture systems will typically provide ways to view queries according to clinical site, patient, and e-CRF form.

11.4. Allowable sponsor changes

During the course of a clinical trial, data may be changed on a CRF by investigators and/or designated site staff personnel as a result of data cleaning procedures. Additionally, sponsor personnel are also permitted to make data changes provided they follow ICH E6 guidance. According to ICH E6 section 4.9.3., sponsors should have written procedures to assure that changes or corrections in the CRF made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of all study changes.

In the traditional paper environment, most data changes are accomplished using queries or data clarification forms. Where sponsor personnel are allowed to make obvious corrections, clear documented guidelines have been created. This has the benefit of limiting queries to the site to those issues that necessitate their involvement and increasing efficiency by reducing the overall volume of queries to be processed by both site and sponsor staff. In order to ensure the sites endorse the obvious data changes made by sponsor personnel, the sites are provided with a document that outlines the types of obvious changes that may be made by the sponsor. This usually occurs during or around site initiation. DSI agreed with this task group (April 2004) that the same applies to electronic case report forms.

A guiding principle, however, is that the sponsor can only change data that can be verified by source maintained at the investigator site (i.e. if data are entered directly into an e-CRF or obtained electronically with no source documentation, then that data cannot be altered by the sponsor).

The following regulations support this approach:

ICH-GCP 4.9.3 - 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.

ICH-GCP 5.1.3 Quality control should be applied to each stage of the data handling to ensure that all data are reliable and have been processed correctly.

ICH-GCP 5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should: (e) Maintain a list of the individuals who are authorized to make data changes.

21 CFR 312.62 b Investigator record keeping and record retention
(b) Case histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

11.5. Investigator signature for patient data

As with paper studies, the investigator or authorized member of the investigator staff must confirm the observations recorded on the electronic case report forms. Many EDC systems provide for electronic signatures. If the EDC system has electronic signature capability, the sponsor must ensure that it is in compliance with 21 CRF Part 11, FDA's guidance on electronic signature (see section 9.5.4).

Regulations do not specify when the investigator must sign the CRFs / e-CRFs. Signoff on e-CRFs may occur on an ongoing basis (e.g., as patients complete the study) or at the end of the study for all patients at once. Signatures should be obtained in compliance with the sponsor's and / or investigator's internal operating processes. ICH E6 recommends for paper studies that the sponsor maintains the original CRF and the investigator maintains a copy. However, with EDC, PDF files are created and used as archival e-CRFs (see section 6.7). DSI agrees with this task group (April 2004) that this satisfies the guidance provided in ICH E6. If the EDC system does not support electronic signatures, then a paper signature must be obtained on a paper document, however the corresponding archival e-CRF need not be printed. The original of this paper signature will be provided to the sponsor with a copy maintained at the investigator site.

11.6. Mid-study changes to EDC system

Mid-study changes to EDC systems do occur. These changes may be due to a protocol/study design change, an issue with the original implementation of the study design, or an upgrade to the EDC system software or hardware. Changes due to a protocol/study design change need to follow existing sponsor procedures to effect a protocol amendment, as well as the system change control called for in the following discussion.

A change control SOP should be in place that describes the process to be followed to identify, evaluate, approve and implement a change once data entry has begun for a study where EDC has been implemented. It should also describe the documentation required at both the EDC system owner site as well as at the investigator sites impacted by the change. Minimally, the investigator site should have a notification of the change stored with their study records.

A formal change request should be prepared describing the change, rationale, and impact. It is important to consider the impact and nature of any changes with regard to system validation, study setup testing, the clinical site, destination clinical database, and institutional review board (IRB). General testing/validation, installation, data conversion, and site communication and training plans should be included in the change request process. The change should be approved before it is implemented. NOTE: Mid-study changes implemented to the EDC system should be done with discretion and judgment.

EDC systems that have server based applications and databases, i.e. thin client applications, generally require less effort to implement most mid-study changes as the database and application are not widely dispersed on separate investigator computers.

The sponsor must coordinate implementation of any system change with the clinical sites. This is to ensure that the sites are aware of any system changes and the impact as well as to minimize the disruption of the clinical trial. The implementation of changes at the study sites should be tracked by the sponsor.

Documentation of the change should be filed, as called for by the Change Control SOP at both the EDC system owner site as well as at the investigator sites.

11.7. Implementation of Contingency plans

If it becomes necessary to implement a contingency plan to collect data in some other manner than the intended use of the EDC system, the investigator should document this fact in their study records and notify the support staff of this situation.

11.8. Site visits by CRA

CRAs are responsible for reviewing the conduct of the study at an investigator site and, if eSource is not utilized, for performing source document verification. The EDC system does impact the way the CRA accomplishes many review tasks. It will be important that the CRA and any backups assigned to a specific site are granted rights to review, query and source verify data at that investigator site.

It is recommended that the CRA review study data on an ongoing basis in order to familiarize themselves with the data, to identify and address data quality issues (e.g., protocol violations), before their site visit and to ensure the site is maintaining a consistent schedule of entry of the study data.

Source verification of data is impacted by EDC. It is recommended that the CRA notify the investigator of their intention to do source verification before their trip to the site. Specific information regarding the patients to be verified will help the site ensure those records are available.

During the site visit, the CRA should verify the data contained in the EDC system against the patient's records maintained by the investigator site. Data that are only collected electronically in the EDC system do not need to be source verified. The sponsor must have plans to assure the existence of the patients and should instruct the sites that patient's records will be checked to this end. Any discrepancies identified during source document verification can be addressed with site staff during the monitoring visit or queries can be manually generated so that the sites can correct the data as their time allows. The CRA should document the records verified as well as their findings as called for in the sponsor's SOPs. Many EDC systems provide tools to help the CRA with the source verification task as well as other tasks associated with monitoring visits.

11.9. Site Inspections of on-going studies by Regulatory Agency

For inspections conducted while a study is "live", the sponsor must ensure that Regulatory Agency personnel have access to all hardware, software and documentation necessary to perform site inspections of EDC studies.

If requested, an account will need to be set up to provide read-only access to the system for the inspector. The inspector may also review data in the system with site personnel based on their rights and roles. It is recommended that system owner staff be available to provide application specific training as required. All relevant documentation (i.e., Operating instructions, roles and responsibilities matrix with data entry and electronic signature privileges, standard operating procedures, etc.) should be easily accessible at the site. Refer to section 9.5.2 "On Site SOPs/Policies", section 9.5.3 "Documentation Requirements", section 9.5.4 "Electronic Signatures", and section 9.7 "Training".

Site inspections that occur after the study closure are addressed in section 12.2.

12. Study Close Out

12.1. Preventing changes in EDC system

There are many different times during the lifecycle of clinical data when it may be appropriate to prevent the Investigator from making changes to the data. These include but are not limited to: Preventing changes to data that the CRA has verified against the source at the site, preventing changes prior to interim analysis, preventing changes at the time of final database closure. The process implemented for EDC will dictate when these lockdowns should occur. It is critical that the data also are able to be 'unlocked' so that changes after that point in time can be made if necessary.

The only time that changes *must* be permanently prevented in the EDC system is when all the data for a patient have been collected, cleaned, and are ready for creation of the archival e-CRFs. It will be important that the EDC system clearly identifies that all the data for a patient have been locked and the date/time of the locking. (Post closure changes are discussed in section 11.4).

12.2. Creation of Archival e-CRFs

Archival e-CRFs are created after a patient's data are deemed final and locked in the EDC system for the last time. (See section 6.6 and 6.7 for information on format of e-CRF.)

Current practice is to have the archival e-CRF created at a central location, either sponsor or third-party, and then to have CDs burned and shipped to the investigator site. The sponsor retains archival e-CRFs as well.

The archival e-CRF must include the entire audit trail. Having the audit trail electronically linked to the original data item would be a nice feature for both the investigator and any inspectors that visit the site and need to review and reconstruct the data trail for a study. See section 12.1 for more information regarding reconstruction of the study.

The Task Group recommends that the CD containing the archival e-CRFs shipped to the investigator should also contain a copy of the reader required to access the files.

12.3. Acceptance and signature of archival e-CRFs

Archival e-CRFs are sent to the site at the end of the study to be kept as the record of the study data, and an acknowledgement that the site received the media and can read the content is sent back to the Sponsor. The task group recommends one investigator signature per shipment if the investigator has already electronically signed off on each patient. Otherwise, one signature per subject might be desirable and this signature could suffice as the only signature needed by the investigator and could be handwritten.

If the archival e-CRF does not contain all the instruction forms and possible decodes available for each data item, it is recommended that a blank e-CRF be provided to the investigator also. This will ensure that any site inspectors will be able to reproduce what was presented to the investigator during data entry, after the EDC system has been retired. See section 6.5 for a definition of a blank e-CRF.

In addition, see section 12.1 for more details regarding the controls necessary to maintain the integrity of electronic signatures in migrated records.

12.4. Post-closure changes

Sponsor SOPs need to be in place that document how changes to e-CRF data are made after the study site has been closed down and the archival e-CRF accepted by the site. An important element of this procedure needs to be the mechanism used to communicate and secure investigator agreement to the change and how the sponsor will document the change.

The data for the patient must not be unlocked in the EDC system after the archival e-CRF for the patient has been created, unless called for in the sponsor's post-closure change SOP. Unlocking the data in the EDC system would require the same documentation as with paper-based studies, in order to maintain the integrity of the archival e-CRFs stored at the investigator site.

13. Record Retention and Submission to Agencies

13.1. Reconstruction of study

The guidance for computerized systems in clinical trials states in section VI.D *"Although FDA expects sponsors or vendors to retain the ability to run older versions of software, the agency acknowledges that, in some cases, it will be difficult for sponsors and vendors to run older computerized systems."* Given the rate of evolution of technology and the length of time that potentially could elapse between the time a study is run and the necessity to reconstruct it, it is an unreasonable expectation that the equipment and software be retained in an operational state.

The task group recommends that the hardware and software only be maintained at the site until the site signs and accepts the archival e-CRF (see section 11.3). The sponsor and investigator must maintain the appropriate records and documentation through retention periods defined by regulations and guidance.

The task group recommends that the guidance be modified to state that migration of e-records to a new system / format, in compliance with 21 CFR Part 11 and other relevant guidance, can eliminate the need to retain old versions of a system's hardware, software and operating system once the archival e-CRF has been created and accepted by the site.

13.2. Site Inspections by Regulatory Agency

The guidance for computerized systems in Clinical Trials states in Section XI.B *"The sponsor should be able to provide hardware and software as necessary for FDA personnel to inspect the electronic documents and audit trail at the site where an FDA inspection is taking place."* The Task Group recommends that for an active trial, the sponsor needs to make the EDC system accessible for an inspection at the investigator's site (read-only access) (see section 10.9). From the time that the archival e-CRF (in PDF format, or as otherwise accepted by FDA) is accepted by the investigator (see section 11.3), the EDC system is no longer needed for inspection and the inspector will use the archival e-CRF to review the e-CRF data and audit trail.

Given that the archival e-CRF is in PDF format, no special training should be needed for the FDA inspector. The investigator's staff should be able to help the inspector get started with their review.

13.3. Record retention by Investigator

Use of an EDC system when conducting a clinical trial does not change the records retention requirements for the Investigator regarding study documentation. However, there are some items

unique to EDC that need to be accounted for in the record retention policy of the Investigator. The following items need to be considered:

- Archival e-CRFs (for same retention period as paper CRF)
- EDC system (only until archival e-CRFs are received and accepted by the investigator)
- Documentation noted in Section 10.5.3 (retention period noted in 10.5.3)
- Documentation of post-closure changes supplied by sponsor (for same retention period as paper CRFs)

13.4. Record Retention by Sponsor

Use of an EDC system when conducting a clinical trial does not change the records retention requirements for the sponsor regarding study documentation. However, there are some items unique to EDC that need to be accounted for in the record retention policy of the Sponsor. The following items need to be considered:

- Archival e-CRFs (for same retention period as paper CRF)
- Confirmation of receipt of archival e-CRFs by each investigator (for same retention period as paper CRFs)
- EDC system (only until archival e-CRFs are confirmed received by all sites)
- Sponsor SOPs related to EDC system and processes (for same retention period as other company SOPs)
- EDC system validation file (for same retention period as data from study)
- Data transfer/migration validation documentation (for same retention period as data from study)
- Study-specific design information including data entry screens, additional navigational aids, edits, system source code customizations, and migration to sponsor database specification (for same retention period as data from study)
- EDC setup testing (for same retention period as data from study)
- Statement that the process to produce the archival CRF is compliant with 21 CFR Part 11 (for same retention period as data from study)
- Change control documentation for mid-study changes (for same retention period as data from study)
- Documentation resulting from any recovery activities (for same retention period as data from study)
- Documentation resulting from support of investigator staff (for duration of study)
- Service Level Agreement for EDC system support (for duration of study)

- Training records for sponsor and investigator staff, including training materials (for same retention period as data from study)
- Documentation of post-closure changes (for same retention period as data from study)
- Documentation of periodic review and possible media refreshment of archival e-CRFs (for same retention period as data from study). This may include the need to migrate to new media if the hardware needed to read archival e-CRFs becomes obsolete.
- User Manuals (for as long as EDC system is available to the sponsor)
- A list of all EDC system users with their unique user ID and access privilege, and dates privileges were granted, changed, or revoked. (For the retention period of the data)
- Investigator notification of changes to EDC system if any mid-study changes were made. (For as long as the EDC system is available to the investigator site)
- Investigator role in disaster recovery procedures as well as a description of the impact of a disaster on the Investigator, see section 13.10 (for as long as the EDC system is available to the investigator site)
- Investigator contingency plans (see section 9.5.1) (for as long as the EDC system is available to the investigator site)
- Investigator procedures for archival e-CRFs that describe maintenance and storage conditions for the electronic records, retrieval and access restrictions, and responsibility for relevant tasks. (For the retention period of the data)

13.5. Electronic Submission CRFs (e-Sub CRFs)

The task group recommends that the e-Sub CRFs be created from the archival e-CRFs or directly by the EDC system as long as sufficient controls are in place to ensure that the e-Sub CRF accurately represents the archival e-CRF. The e-Sub CRFs should be created per FDA guidance and provided as PDF files with the audit trail linked to the data items they refer to.

13.6. Electronic case report tabulations (e-CRTs)

E-CRTs for EDC studies should be no different than e-CRTs for paper studies. They should be created in the format called for in the FDA submission guidance. A minor difference is that the annotated CRF may be created through different tools/process using the blank e-CRF rather than a blank CRF from a paper study.

To further clarify what should be included on the annotated CRF, the task group recommends the following:

- When providing an "annotated CRF" for studies using electronic data capture, the "annotated CRF" should only cover data that are included in the e-CRF (see sections 6.3 and 6.4 for a definition of the what data are considered e-CRF data). Data captured by other means need

not be displayed on an annotated CRF. Instead, the corresponding comment column of the define.pdf or define.xml file should document the method used to collect/derive those data.

- Data included in the e-CRT should be reflected in the "annotated CRF" as a PDF file that is a representation of the screens used to enter data. This representation should include a complete set of all codes used during the entry process.

14. System Design Considerations

14.1. User Identification

There must be unique user identification for clinical EDC. User identity is different from electronic signatures and should not be confused. The sponsor or a third party designee such as a bank can establish identity. It is the sponsor's responsibility to ensure that user identification is unique and assigned to only one person. Identity can consist of a username and password, biometric identifiers or pin numbers such as that provided by banks. The user identification should be maintained in the audit trail for all fields that are created, modified or deleted. Either name or unique identification (such as the username) should be displayed on the screen during data entry with the intent of preventing inadvertent data entry under the wrong name. The system administration must establish a process that records and retains the names of authorized personnel, their titles, and a description of their access privileges. The system may use a paper or an electronic process to record this information. Electronic systems should treat this information in a manner similar to other electronic records.

The *Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999)* Section V.A.2a states "*The printed name of the individual who enters data should be displayed by the data entry screen throughout the data entry session. This is intended to preclude the possibility of a different individual inadvertently entering data under someone else's name."* The task group recommends revision of this guidance to specify the display of either the name or the unique user identification. The intent is that any user can easily check that they are doing data entry under their unique user identification.

14.2. Audit trails

An audit trail is a method of tracking the creation, modification or deletion of an electronic record. According to 21 CFR Part 11, it must be a secure, computer-generated record containing old data/information, new data/information, person making the change, and date/time stamp (and reason for change as required by predicate rule and ICH E6). This information should be linked to the records in such a manner that a reviewer can trace the history of an entry that has been modified after its creation. If the EDC system has an "off-line" functionality, then the transmission to the server should include both data and the associated audit trail.

Date and time information should be managed in a manner that makes the sequence of events obvious to anyone reviewing the information. There is a need to ensure that system clocks are accurately set and maintained in off-line EDC systems so that the date and time in audit trails are correct. If more than one time zone is involved in the study, either 1) a time zone indicator should be stored with the time, or 2) the time may be stored according to a central clock and the offset time for each site indicated in the documentation for the study.

The sponsor is responsible for providing a readable copy of the audit trail to the site inspector upon request. Processes for storing and accessing the audit trail will be based on sponsor SOPs.

An EDC study may involve two distinct audit trails. The first audit trail is of the e-CRF data maintained by the EDC system (unless otherwise specified, this is the audit trail we are referring to in this paper). The second audit trail is of the changes to records in the sponsor's database. This second audit trail need not include the audit trail of the e-CRF data. It should be concerned with the creation, modification and deletion of data records in the sponsor's database.

14.3. Password resets

The *Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999) Section V.A.4* recommends that passwords or other access keys be changed at established intervals. For less sophisticated approaches, the task group recommends that sponsor SOPs dictate the interval for changing passwords. For more sophisticated approaches, such as secure ids in combination with user ids/passwords or smart cards, password resets are not appropriate based on inherent advanced security models accepted by the department of justice and widely utilized by the banking industry. We recommend that the guidance be changed to allow these new approaches.

14.4. Operational checks

21 CFR Part 11 requires operational checks to enforce permitted sequencing of steps and events, as appropriate**.** With EDC, the data collection flow is not the same as the data entry flow and both may vary from site to site. Therefore, it is rarely appropriate to include operational checks to control the data entry flow in EDC systems. Some examples of where operational checks may be appropriate are in the use of certain real time data collection devices and the synchronization of databases.

14.5. Minimum security measures

The *Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999)* Section III states, *"Security measures should be in place to prevent unauthorized access to the data and to the computerized system."*

Where systems are managed by the clinical institution, the sponsor must rely on the security measures established by the institution. The following minimum-security measures are recommended.

- The investigator and his/her staff must be trained on the security measures, must understand why they are important to the integrity of the data, and must be able to comply with them.
- The EDC system should provide for a configurable time-out consistent with the security requirements identified for the trial and circumstances.
- A password unique and known only by the user logged into the system is required after a time-out event.
- The sponsor must establish a unique identification for all users.
    - No user identification can be reused.
    - Each user must have a unique password, pin number or biometric authorization.
    - Each user must have defined rights and access privileges.
- The system must be in a secure area to prevent theft.

14.6. Controls for open systems

Open systems are such where the system owner does not exercise complete control over the accessibility and transmission of information, and additional security and controls are required to ensure data integrity and authenticity. Exchange of electronic information can be achieved with the use of physical media such as phone systems, public and/or shared networks, or other public services such as mail and courier delivery.

Procedures and design standards must exist to describe the minimum-security requirements to ensure record authenticity and integrity for data exchanged over open systems and to be in compliance with 21 CFR Part 11, section 11.30 Controls for Open Systems.

14.7. Controls for electronic signatures

The sponsor must ascertain that the EDC system is compliant with 21 CFR Part 11, and that if the EDC system provides for the use of electronic signatures, they are compliant with the requirements set forth in 21 CFR Part 11, sections 11.50, 11.70, 11.100, 11.200, 11.300.

If the EDC system provides for the use of electronic signatures, it is recommended that the name of the person signing and the purpose of the signature be displayed when the user 'signs' the record. The task group recommends that electronic signatures be compliant with SAFE.

14.8. Data transmission / migration to sponsor database

Methods for data transmission and/or migration to sponsor databases depend on the technical approach taken for the EDC system (EDC database on the local hard-drive or on the server) and the type of sponsor system storing/managing the data (it may be the same as the EDC system and therefore no data transformation is necessary). In any case, reformatting into an analysis database typically occurs, however migration is no different for EDC records than for other e-records. Sponsors must have procedures that establish continuity of electronic record integrity and retain compliance with 21 CFR Part 11. As noted in section 13.2, the audit trail maintained for the sponsor database is separate from the EDC systems audit trail and does not need to include the EDC system

audit trail. Instead, its audit trail should keep track of all additions, changes and deletions of data within itself.

14.9. System Validation

It is the responsibility of the sponsor to ensure that the EDC system is initially validated in accordance with SOPs for completeness, accuracy, reliability, and consistent intended performance. The *Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999)* states that this validation should include written design specifications, written test plan based on design specifications, test results and an evaluation of how results demonstrate the predetermined design specifications has been met.

If mid-study changes to hardware or software are made, some aspect of the validation needs to be repeated in order to reestablish the validated state of the software and hardware that is collecting the patient data. The *Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999)* states *"Revalidation should be performed for changes (such as software upgrades, equipment or component replacement, or new instrumentation) that exceed operational limits or design specifications"*. It can be expected that an average study will have two mid-study changes to the EDC screens, and at least one vendor-originated service patch or software upgrade.

A validation and testing strategy for the EDC system should include the following

- Complete validation of the system
- Minimum installation qualifications
- Regression testing and change control to maintain validation state.
- Testing of study specific set-up

14.10. Disaster recovery

Disaster recovery procedures are necessary to warrant against possible hardware or software failures, transmission failures, vandalism or theft. Disaster recovery procedures should be in place at the investigator sites, sponsor location and vendor location, if a vendor is used. Disaster recovery procedures should be included for all hardware devices (including PDAs, laptops, web appliances and servers.) System owner SOPs should dictate disaster recovery procedures.

The information provided to the investigator site should describe the various disaster scenarios that may occur and the impact on the investigator site if such an event should happen. The role of the investigator in identifying and reporting a problem/disaster situation as well as their role in the recovery of data should be clearly stated. It is recommended that a separate disaster recovery policy be customized for the investigator to reduce confusion and to ensure they understand their role and the impact of any such disaster.

For off-line systems which contain copies/original clinical data, the disaster recovery responsibilities and activities are greater for the site staff than in the case of web-based applications.

14.11. Back-up procedures

Back-up procedures are necessary to support disaster recovery procedures for the case of possible hardware or software failure, transmission failures, vandalism, theft or simply human error. Back-up procedures should be in place both at the investigator sites, sponsor location and owner location (if different than the sponsor). Back-up procedures should be included for all hardware devices and should include off-site storage of back-up media. Sponsor SOPs should dictate back-up procedures at investigator sites for offline systems as well as internal sponsor back-up procedures. It is recommended that sponsor periodically check that backup procedures are being followed.

For off-line systems which contain copies/original clinical data, the data backup responsibilities and activities are greater for the site staff than in the case of web-based applications.

14.12. Synchronizing multiple electronic data sources

If EDC data will reside in more than one database, then synchronization of these databases is critical to maintain the integrity of the data and to be certain that all changes to data are reflected in all representations of that data. Some technical approaches to EDC (such as a hybrid approach in which data can reside on a local laptop database or a server database) require frequent synchronization.

If data are to be collected and centrally stored in different time zones, it is critical that the data be stored and audited such that the accurate sequence of events can be understood.

14.13. Clearing cache

The EDC system should ensure that any memory or disk caches created that contain patient and study information are cleared before the EDC system shuts down. This is to prevent subsequent users of the workstation from browsing the cache areas and finding confidential study data.

14.14. Storage of case report data off-site from the Investigator

The Task Group position based on discussions with FDA (April 2004), is that as long as the EDC system is 21 CFR Part 11 compliant and has security methods that prevent unauthorized modification of the data, the data do not need to be stored at the investigator site in order to meet requirements to maintain adequate and accurate case histories per 21 CFR Part 312.62b. Currently, this applies if the EDC system does not contain source data (i.e., the investigator maintains patient source data that can be compared with data maintained on the EDC system). If the EDC system contains source data however, the DSI position (April 2004) is that it must not be maintained by the sponsor, suggesting that a TTP (trusted third party) would be acceptable.

As stated earlier, any EDC system must make the e-CRF data available to the investigator throughout the record retention period. The intervention of a third party or sponsor should not be necessary for

the investigator to access this information during the record retention period. It is important that this access include the ability to review the records electronically as well as via printed copy. It must be possible to make a machine-readable copy of the record.

When archival e-CRFs are received and accepted by the investigator, these copies of the e-CRF data provide the investigator with the ability to retain adequate and accurate case histories following the study and until the record retention period expires. Access to the original EDC system can then be eliminated.

15. Implications of Different Data Collection Methods

In general, all data collected (while needing to be reported in some way) does not have to be part of the e-CRF. Data can come from many sources and combined at the sponsors' discretion in any form they choose. Such sources and data types can include laboratory data, ECG data, IVRS data and many other device data sources. As long as systems providing these data are 21 CFR Part 11 compliant, each piece of electronic data contains its own audit trail, and appropriate date time stamps are applied, the regulatory requirements should be met.

15.1. Durable Media and Personal Data Assistants (PDAs)

The term "durable media" is understood to mean non-volatile storage devices including, but not limited to, floppy disk, hard drive, magnetic tape, CD ROM and some PDAs, all of which retain their electronic records even with no power applied. These media are contrasted with transient and volatile storage devices, including keyboard buffers and battery-backed RAM that cannot retain data without power applied (as may be the case with PDAs.)

It is recommended that all PDAs used for the collection of clinical data be password protected and provided with a configurable time-out consistent with the security requirements identified for the trial. If the PDA contains a non-volatile memory card, or other data storage device, then the audit trail starts upon the initial data entry. If the memory is volatile and the data cannot be retained without power applied, then the audit trail would begin when the PDA is synchronized with a system with durable media.

15.2. Electronic Health Record Systems

If an investigational institution used an electronic system to maintain patient records, the sponsor can obtain data from this system or ask the site to use it to collect protocol data; however it is usually more difficult for the sponsor to implement than using a sponsor-provided system.

In the future, we anticipate the high availability of Electronic Health Records (EHRs) due to a US executive order (April, 2004) creating a new Office of the National Coordinator for Health Information Technology, which would enable the building of an infrastructure to link electronic health records nationwide within 10 years. This development can make the integration of EHR systems with

EDC and/or CDM systems more feasible and attractive. However, currently, the variability and unregulated nature of the existing EHR systems makes the use of EHR data for clinical research purposes unreliable. Electronic exchange between these systems must be accompanied by proper procedures to assure the integrity and reliability of the data. In addition, the sponsor must still maintain a separate database from the investigator.

16. Recommended Changes and Clarifications in Regulations and Guidances

16.1. ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH E6)

16.1.1. Definition of CRF

ICH E6 defines a CRF as "A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject." This is inconsistent with current industry practice in that even in a paper CRF, study data such as clinical laboratory test results may be transmitted between the clinical site and the sponsor directly without being recorded on a case report form.

The task group recommends changing the definition to be "A printed, optical, or electronic document designed to record protocol required information to be reported to the sponsor on each trial subject that is not captured and communicated via external systems, such as laboratory test results."

16.2. Guidance for Industry: Providing Regulatory Submissions in Electronic Format -Biologics Marketing Applications (November 1999)

16.2.1. Presentation of CRFs

There is differing guidance as it relates to the presentation of CRFs as described in the Guidance for Industry: Providing Regulatory Submissions in Electronic Format -Biologics Marketing Applications (November 1999) *and the* Guidance for Industry: Providing Regulatory Submissions in Electronic Format - NDAs (January 1999).

The task group recommends that the CBER guidance be changed to match the CDER guidance.

16.3. Guidance for Industry: Providing Regulatory Submissions in Electronic Format - NDAs (January 1999)

16.3.1. Annotated CRFs

Section K.3 of the guidance: Documentation of the datasets/ annotated CRF states: **"**The annotated CRF is a blank CRF including treatment assignment forms that maps each blank on the CRF to the corresponding element in the database. The annotated CRF should provide the variable names and coding. Each page and each blank of the CRF should be represented. The sponsor should write "not entered in database" in all sections where this applies."

In both electronic and paper data collection systems not all information and data are transmitted via a form. It is unclear how to handle database elements without a form. The task group proposes clarification of the guidance based on the following recommendations

- When providing an "annotated CRF" for studies using EDC, the "annotated CRF" should only cover data that are included in the e-CRF (see sections 6.3 and 6.4 for a definition of what data are considered e-CRF data). Data captured by other means need not be displayed on an annotated CRF. Instead, the corresponding comment column of the define.pdf (or define.xml) file should document the method used to collect/derive those data.
- Data included in the e-CRT should be reflected in the "annotated CRF" as a PDF file that is a representation of the screens used to enter data. This representation should include a complete set of all codes used during the entry process.

16.4. Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999)

Note: A draft guidance was issued in September 2004. Issues and task group recommendations are based on the April 1999 Guidance, which is still in affect. A note in italics at the beginning of each item indicates if the issue was eliminated in the draft guidance or still remains.

16.4.1. Reconstruction of study

This issue has been eliminated in the draft guidance (Sept 2004).

In Section VI.D the guidance states "Although FDA expects sponsors or vendors to retain the ability to run older versions of software, the agency acknowledges that, in some cases, it will be difficult for sponsors and vendors to run older computerized systems. Given the rate of evolution of technology and the length of time that potentially could elapse between the time a study is run and the necessity to reconstruct it, it is an unreasonable expectation that the equipment and software be retained in an operational state.

The task group recommends changing the guidance to state that the hardware and software used by a clinical trial need only to be maintained at the site until the site signs and accepts the archival e-CRF (which we recommend be provided in PDF format). Migration of the electronic records to a new system and/or format in compliance with 21 CFR Part 11 and associated guidance and other applicable regulations can eliminate the need to maintain old versions of the hardware, software and operating systems beyond the time the systems are used to create and maintain the records during the clinical trial.

16.4.2. User Identification

This issue has been eliminated in the draft guidance (Sept 2004).

Section V.A.2a states, "The printed name of the individual who enters data should be displayed by the data entry screen throughout the data entry session. This is intended to preclude the possibility of a different individual inadvertently entering data under someone else's name."

The task group recommends changing the guidance to specify the display of either the name or the unique user identification. The intent is that any user can easily check that they are doing data entry under their unique user identification.

16.4.3. Password Resets

This issue remains in the draft guidance (Sept 2004).

Section V.A.4 recommends that Passwords or other access keys be changed at established intervals. For more sophisticated approaches such as those used in other regulated industries, password resets may not be appropriate based on inherent advanced security models. Examples of this include but are not limited to: secure ids in combination with user ids and passwords, smart cards, credit cards and other biometric models. Many of these advanced security models are accepted by the department of justice and widely utilized by other regulated environments such as the banking industry.

The task group recommends changing the guidance to allow other security schemes that do not require periodic changing of passwords.

16.4.4. Identification of Computerized Systems in Protocols

This issue remains in the draft guidance (Sept 2004).

Section III A states: "Each study protocol should identify at which steps a computerized system will be used to create, modify, archive, retrieve, or transmit data." It is difficult for

the sponsor to know all the different systems that may be in use at each of the investigator sites involved in a study at the time a protocol is written, particularly those not provided by the sponsor.

The task group recommends that the guidance be changed to the following: "Each protocol should identify those steps at which a computerized system is provided or endorsed by the sponsor to create, modify, archive, retrieve or transmit data and which data are affected. The protocol should state whether the use of such systems is required or optional."

16.4.5. System Documentation Requirements

Draft guidance does provide details of what is needed but it does not match the recommendation of this task force.

Section VIII.A requires that system documentation be available at the clinical site.

The task group proposes clarification of the guidance based on the following recommendations

1. User manuals (for as long as EDC system is available to the investigator site)

2. Training materials and training records for the site (for the retention period of the data)

3. A list of users with their unique user ID and access privilege, and dates privileges were granted, changed, or revoked. Passwords must be kept confidential to each user and must not be kept in any list (for the retention period of the data)

4. Any local administration procedures and manuals (for the retention period of the data)

5. Notification of Changes to EDC system if any mid-study changes were made (for as long as the EDC system is at the investigator site)

6. Investigator role in disaster recovery procedures as well as a description of the impact of a disaster on the investigator (for as long as the EDC system is available to the investigator site)

7. Contingency plans (for as long as the EDC system is available to the investigator site)

8. Log of use of contingency plans (for the retention period of the data)

9. Pertinent SOPs, policies and procedures (for the retention period of the data)

10. System description to include an overview of the system architecture and the data flow for as long as the EDC system is available at the investigator site.

16.4.6. Definition of Record Creation

This issue has been eliminated in the draft guidance (Sept 2004).

The guidance states that a record is created when it is saved to durable media. The industry would benefit from a standard interpretation of this requirement for 'off-line data entry systems' and for PDAs and other hand held devices.

16.4.7. Site Inspections by Regulatory Agency

This issue has been eliminated in the draft guidance (Sept 2004).

The guidance states in Section XI.B "The sponsor should be able to provide hardware and software as necessary for FDA personnel to inspect the electronic documents and audit trail at the site where an FDA inspection is taking place." The task group believes that once an e-CRF is created and accepted by the investigator, it is only necessary to review the e-CRF and not the original electronic record and associated EDC system. Migration of e-records to a new system/format, in compliance with 21 CFR Part 11 and other relevant guidance, can eliminate the need to retain old versions of a system's hardware, software, and operating system.

The guidance should be modified to state that during the study, read-only access to EDC system should be granted to the FDA inspectors. After the archival e-CRF is accepted at the site, access to the archival e-CRF as PDF will suffice. The hardware and software need only be maintained at the site until the site signs and accepts the archival e-CRF (PDF).

16.5. 21 CFR Part 11 Electronic Records; Electronic Signatures; Final Rule (March 20, 1997)

16.5.1. Open System and Additional Measures

Section 11.30 prescribes open systems must have controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. 21 CFR Part 11 provides the following definition: "Open system means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system."

This definition of what constitutes an open system seems open to interpretation across the industry. More clarifications and examples of adequate controls for an open system would assure consistency.

16.5.2. Linking Signatures to Electronic Records

It is required that electronic signatures and hand-written signatures executed to electronic records be linked to their records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means. There has been a great deal of discussion around what constitutes an adequate link and what is meant by ordinary means. It would be useful to have examples that represent adequate means.

16.6. 21 CFR Part 312

16.6.1. Investigators must prepare and maintain adequate and accurate case records

21 CFR Part 312.62 states that Clinical Investigators must *"maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation".*

Some interpretation of this regulation is that records that are not 'physically' at the investigator site or records that reside on a system hosted by the sponsor fail to comply with this regulation. The Task Group position based on discussions with FDA (April 2004), is that as long as the EDC system is 21 CFR Part 11 compliant and has security methods that prevent unauthorized modification of the data, the data do not need to be stored at the investigator site in order to meet requirements to maintain adequate and accurate case histories per 21 CFR Part 312.62b. Currently, this applies if the EDC system does not contain source data (i.e., the investigator maintains patient source data that can be compared with data maintained on the EDC system). If the EDC system contains source data however, the DSI position (April 2004) is that it must not be maintained by the sponsor, suggesting that a TTP (trusted third party) would be acceptable. The task group requests clarification on what a TTP is (i.e. can it be part of the sponsor organization (IT dept.)?) and regulations to specify TTP obligations and responsibilities.

In addition, the task group requests clarification of this regulation with regard to web based data collection systems as well as those that utilize a server not at an investigator site.

17. Contributing Members

The following task group members played a major role in providing the content for the initial version of this paper:

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All members of the task group reviewed their work.

Appendix 1: Discussion of Data Entry Methods

- *Direct entry into the EDC system*: There are many advantages to direct entry into the EDC system: edit checks on entry enable data to be corrected while the patient is still there, additional forms will automatically be called up for entry as needed (i.e. if female, a pregnancy history form will show), data are instantly available for review. There is no need to verify electronic database against source since the electronic records are the source. In all, data will be cleaner and available sooner. However, with this method, a site may require several laptops or electronic notebooks. It may be necessary to have the EDC system available in every exam room, or carried with every physician or with every patient as they make the rounds to different stations (e.g. lab, radiology, exam room). In addition, many investigators feel that this is impersonal and takes the focus away from the patient and onto the PC. The use of hand-held devices or even electronic notepads (similar to a hand-held, but larger) for checklist type forms has been successful as it is considered less intrusive to the patient visit than typing on a laptop. In this method of data collection, the electronic record is the source data and typically the investigator will print a copy of the completed forms from the EDC to keep with the patient chart, especially those portions critical to patient care and safety. With this method of entry, the location and control of the database into which entry is made is important. See section 6.2 Source Data for a discussion of this issue. This method of entry is more appropriate for databases that reside locally on the PC, or are web-based and hosted by a vendor (not the sponsor).

- *Hand-written entry onto a patient chart and later transcription to the EDC system*: Many investigators feel that direct entry into the EDC system while the patient is present is less personal and takes the focus off the patient and onto the PC and the form. They may prefer to take notes in the patient chart or print blank copies of some EDC forms and attach them to the patient chart to be certain they are collecting all the necessary information, particularly for information not typically found in the patient chart. These forms, once filled out, constitute source documentation and must be handled accordingly. All hand-written patient information is part of the patient chart and should be part of the source verification check done by the CRA during a site visit. The use of EDC workbooks (a collection of blank paper copies of the entire EDC study forms set) can also be used; however, this requires additional transcription and doubles the risk of transcription error and the work of source data verification. Individual worksheets for particularly complex data collection, rather than a complete workbook, could also be used to be certain required information is collected (similar to printing blank copies of some EDC forms, above). This would also constitute source document and should be treated as such. This method of data entry would require only one PC per site, as the data would not be entered at the time of the patient visit. Having only one PC provides a cost advantage not only in the initial purchase of the PC but also in the revalidation of the PC if mid-study changes are made to the software or hardware (as is the case with vendor software patches). There is also a cost advantage in that with this method, the site could possibly use their own PC (if it met

minimum requirements for performance and 21 CFR Part 11 compliance), and not need to find room for an additional one. This method may "feel" like a paper-based study to the investigative staff, and training, SOPs and sponsor monitoring must address the process and timeliness of data entry. Often sponsors attach payment schedules to data entry and require that data be entered within a specific timeframe of the patient visit. This method of data entry is more appropriate for web-based systems where the database resides at the sponsor.

- *Automated equipment:* Data from automated equipment (such as laboratory, EKG, blood pressure monitors etc.) in theory could be interfaced with the EDC system or with the sponsor's clinical data management system, however with the current lack of data standards in this area, such interfaces are costly to write and maintain. Efforts by the CDISC group in developing standards for data interchange could have significant impact in this area.

Appendix 2: Recommended SOPs for EDC Studies

The following standard operating procedures are recommended for sponsors using Electronic Data Capture for clinical studies.

- EDC Preparation of Investigator Site
- EDC Study Set-up Process
- EDC Study Set-Up Testing
- EDC Installation Procedures (should include requirement for Installation Qualification)
- EDC Help Desk Process
- EDC Training Process
- EDC User Access
- EDC Data Migration
- EDC Site Monitoring
- EDC Change Control
- EDC Disaster Recovery
- EDC Records Retention
- EDC Study / Server Close Down
- EDC Post Closure Changes

In addition, company SOPs governing software development life cycle activities and other appropriate security measures should be followed for the EDC system.

Appendix 3: List of Privacy Regulations and Guidances

The following list of regulations and guidances should be considered when developing company privacy policy (see Section 9.2). This list should be considered a starting point rather than an exhaustive list of all national privacy policies.

- EU
    - Directive 95/46/EC – Protection of Personal Data
    - Directive 92/242/EEC – Security of Information Systems
    - Directive 97/66/EC – Replaced by 2002/06 – Protection of Telecom Data
    - Document 500PC0385 – Incorporated into above 97/66/EC
    - Directive 2001/20/EC – Clintrials directive
- France
    - Data protection in France is governed by Commission Nationale de L'informatique et des libertes (CNIL) http://www.cnil.fr/
- Germany
- Data protection in Germany is governed by Federal Data Protection: BDSG (2); German Data Protection (AMG 40/41)
- US
    - HIPAA Privacy Rule; Standards for Privacy of Individually Identifiable Health Information 45 CRF Part 160 & 169
    - US Department of Commerce Safe Harbor; http://www.expert.gov/safeharbor
    - US Department of Commerce Encryption Export and Re-Export
- Web sites
    - http://www.eudra.org/humandocs/PDFs/ICH/013595en.pdf
    - http://www.eudra.org/humandocs/PDFs/ICH/029196en.pdf