Role of eClinical Systems in FDA Regulated Studies

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- The contents of this presentation are my own, and do not necessarily reflect the views and/or policies of the Food and Drug Administration or its staff as per 21 CFR 10.85.

Overview

- Introduction
- Updates on Draft eSource & Summary Level Clinical Site Data Guidances
- Role of eClinical Systems from FDA Compliance Perspective
- Emerging Trends
- Case Examples

Introduction

- Relevant FDA Regulatory Requirements
  - 21 CFR Part 11
    - Electronic Records
    - Electronic Signatures
  - Predicate Rules
- BIMO Sponsor/CRO Compliance Program Guidance Manual (CPGM)
  - Part III Inspectional, Section M, Electronic Records & Electronic Signatures

Updates

- Draft Guidance: Electronic Source Data in Clinical Investigations
  - eCRFs
  - Electronic Health Records
  - Automatically Integrate Data from Medical Devices
    - Public Comment Period Still Open
- Draft Guidance: Providing Regulatory Submissions in Electronic Format - Summary Level for Clinical Site Data
  - Focus on submitting NDA clinical data set aggregated by Clinical Investigator Site

Role of eClinical Systems

- Electronic Data Capture (EDC)
- Electronic Patient Reported Outcomes (ePRO)
- Clinical Trial Management Systems (CTMS)
  - Clinical Data Management Systems (CDMS)
- Interactive Voice/Web Response Systems (IXRS)
  - Randomization Trial Management Systems (RTMS)

Emerging Trends

- Critical Role of Vendors/CROs
- Implementation of International Consensus-Based Standards
- Portal-Based Technologies & Platforms
- “Virtual” Clinical Trials
- SAS Programming Environments

Common BIMO Deficiencies

Sponsor:

- Inadequate Monitoring
- Failure to secure investigator compliance
- Inadequate AE/UADE analysis and reporting
- Failure to obtain signed Investigator Agreement
- Failure to provide the Clinical Investigator with information necessary to conduct the investigation properly

Clinical Investigator:

- Failure to follow study protocol
- Failure to obtain Informed Consent
- Failure to document and report Adverse Events
- Failure to obtain IDE approval and IRB approval prior to initiating study
- Failure to maintain accurate, complete, and current records

Case Example #1

- PDA devices were issued to each subject and taken home to make daily reports
- The electronic information was transferred through the phone lines, to a server in Microsoft SQL format, when the PDA was docked each night
- After the last transfer of information, the ePRO data on the PDA was erased
- At the conclusion of the studies, the Sponsor sent archive CDs to all study sites in PDF format

Case Example #1 (Continued)

2 things could have been done differently:

1) The Clinical Investigator (CI) should have had access to each nightly transfer of data so that the CI can maintain source records on site as required by FDA
2) Sponsor should have had a process to demonstrate that accurate and complete data sets were able to be successfully transmitted from the PDA to the server

Case Example #1 (Continued)

- Clinical Investigator was cited on the 483 for:
  - "Failure to maintain complete records" (21 CFR 312.62(b))
- Sponsor was cited on the 483 for:
  - "Failure to provide the Clinical Investigator with information necessary to conduct the investigation properly" (21 CFR 312.50)

Case Example #2: Integrating SAS (*Training of Personnel*)

- A Sponsor was using computers for direct entry of clinical data by the Clinical Investigators, representing the study's primary endpoint
- The computer integrated a built-in Statistical Analysis Software (SAS) function to "analyze" all source data
- The SAS was "rounding up/down" certain inputted values as part of the "analysis"

Case Example #2: Integrating SAS

(*Training of Personnel*)

- These were critical clinical values that should not have been “rounded” but recorded as is
- The protocol for gathering and maintaining source data should ensure that the data is being captured accurately and not altered
- Source data needs to be separated from SAS analysis

Case Example #3: IVRS
(*Internal Security Safeguards*)

- An Interactive Voice Response System (IVRS) was used to collect clinical data, representing the study's primary endpoint, from Subjects responding to a survey of questions using a touch-tone telephone
- There are 3 requirements to access the IVRS:
  - Toll free number from International Country of Origin
  - 6 digit Patient Identifier (Uniquely Assigned for each patient)
  - 6 digit PIN (Patient's Birth-date)

Case Example #3: IVRS

(*Internal Security Safeguards*)

- What design feature of the IVRS could possibly lead to questionable data capture?
- The PIN # is not encrypted, since it is the Subject's birth-date, and the Sponsor had access to this information!
- The IVRS had minimal security features to prevent unauthorized access
- Password should have been protected!!!

Case Example #4: Scanned Informed Consents (*Source Documentation & Retention*)

- To eliminate all paper source records, a Sponsor wanted the Clinical Sites to scan all paper informed consent documents and save them as source documents in PDF format
- The scanning of signed and dated informed consent documents would be acceptable to FDA provided that there is a process in place to certify that the scanned copy is an accurate representation of the original paper document
- FDA recommends that the certification itself should include a signature and a date

Case Example #4: Scanned Informed Consents (*Source Documentation & Retention*)

- Sponsors/Clinical sites should give careful thought to the certification process (have written procedures to ensure consistency)
- In addition, the scanned informed consent documents must be made available to FDA Field Investigators or personnel for viewing and/or copying

Case Example #5: ePRO

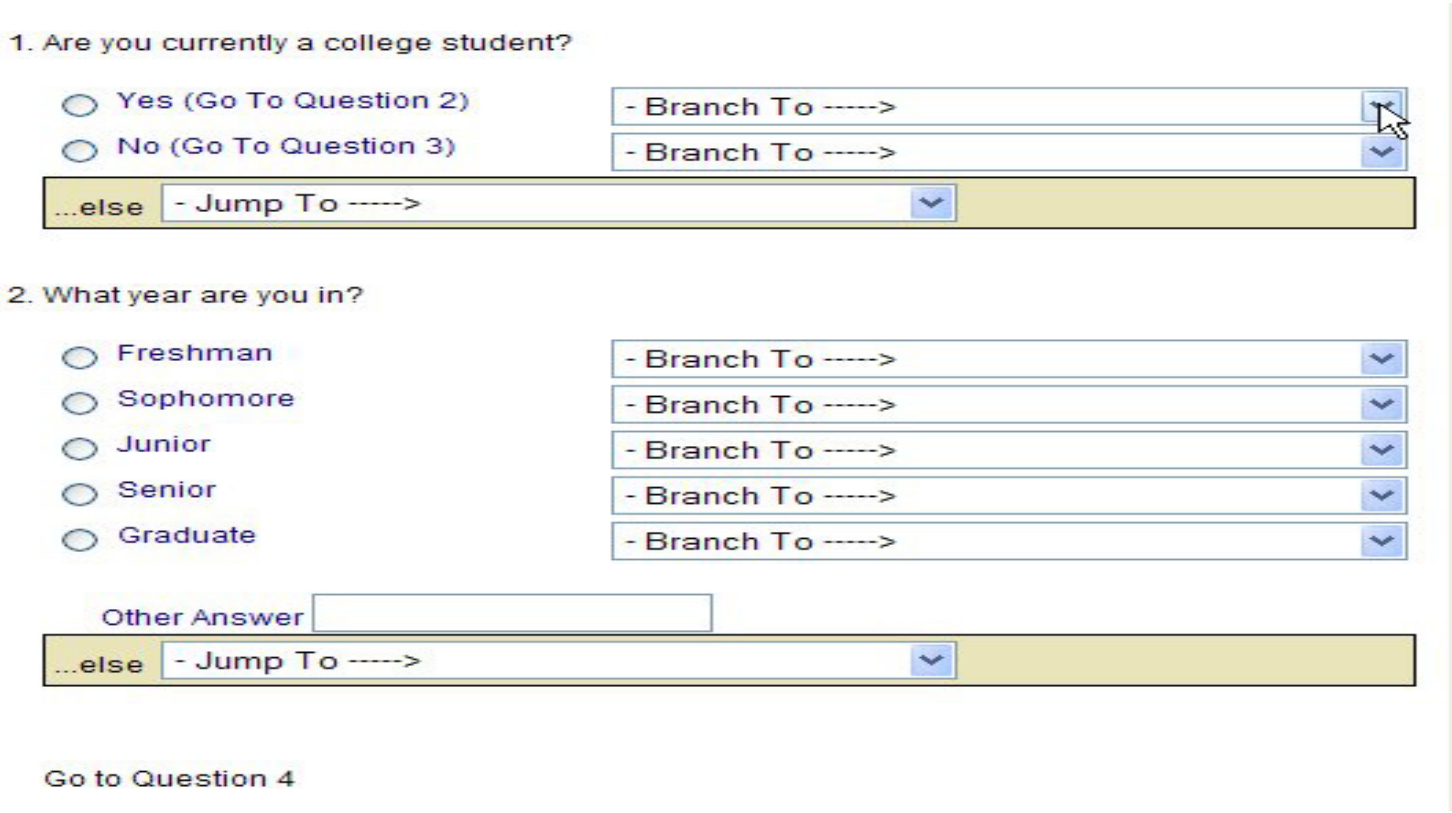
(*Direct Entry of Data*)

- A Questionnaire is used to collect clinical data, representing the study's primary endpoint, from Patients responding to a survey of questions on a Computer (ePRO)
- Certain responses to the questionnaire would "default" other downstream question responses, without notifying the Patient, allowing Patients to input values different from what was recorded by the system

Case Example #5: ePRO

(*Direct Entry of Data*)

- The Sponsor should have designed the system to *block* Patient input of responses to the "defaulted" questions
- Poor human-factor considerations



Case Example #6:
The Application Service Provider (ASP) Model/ Validating Changes When Using An EDC Vendor
(SOPs)

- Since the outside vendor was making this change, the Sponsor performed "User-Acceptance-Testing," whereby the Sponsor signed into the system as the role of a CI, to verify the appropriate privileges were granted, as well as verifying the accuracy of the new acceptable parameters, before the change was implemented at the clinical sites
- The Sponsor printed screen shots of these activities to document that they validated the change to the system

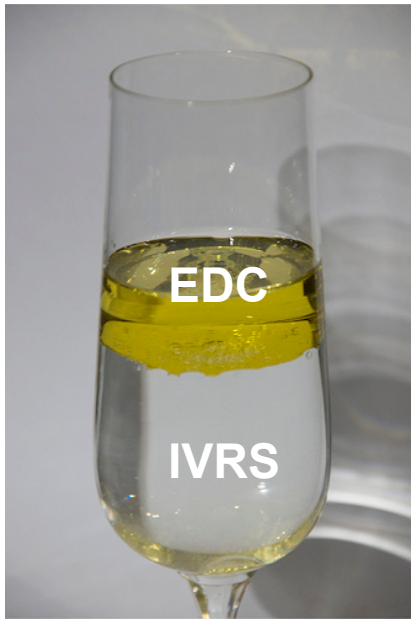
Case Example #6:
The Application Service Provider (ASP) Model/ Validating Changes When Using An EDC Vendor
(SOPs)

- A Sponsor uses a computer system to gather primary clinical data, which was purchased by an outside vendor
- The Sponsor wanted to change the range of certain “acceptable” values, as well as the blinding for the Clinical Investigators (CI)

Case Example #7

- A Sponsor selected an IVRS and EDC vendor independent of each other
- The IVRS data and the EDC repository were in separate silos
- In order to properly maintain blinding throughout the duration of the clinical trial, the Sponsor did not integrate the IVRS data with the EDC system until study completion

Case Example #7 (Continued)



- At trial completion, the Sponsor attempted to integrate the data from the IVRS to the EDC system, to allow for the initiation of statistical analysis, however, there were major bugs in the system
- The Sponsor spent almost an entire month debugging the system until the data was integrated and suitable for analysis

Case Example #8:

(*All 21 CFR Part 312 & 812 regulations apply equally to both paper records and electronic records*)

- Sponsors have used Clinical Data Liaisons (CDLs) to conduct Real-Time data review facilitating centralized control and monitoring of clinical studies
- CDLs have assisted Clinical Investigators (CI), who were collecting the wrong data, because the CDLs were able to monitor the study in Real-Time and notify the CI's of their errors, thus salvaging the data

Case Example #9:
Use of Computers from Home

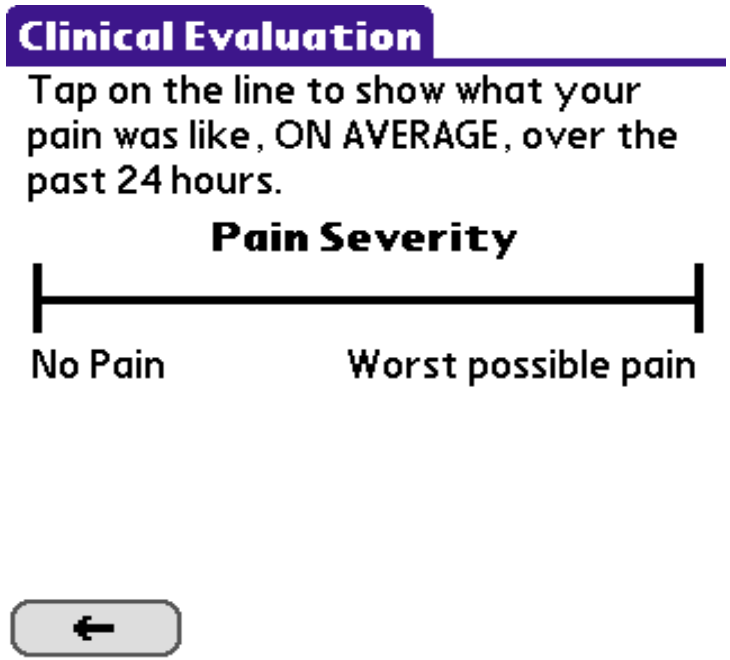
(LIMS/510(K))

- A Sponsor wanted participants in a clinical study to assess themselves from their home computers (potentially using everything from videos of tremors to a mouse that senses motor abilities)
- The clinical study recruited 150 people, half with Parkinson's disease and half without, to examine occupational risk factors behind Parkinson's

Case Example #9: Use of Computers from Home (LIMS/510(K))

- The volunteers will also submit saliva samples to be sequenced for more than 580,000 single-base variations
- Their genetic information will be matched with information they provide online to compare the genomes of those with a particular disease to the genomes of those without
- Although this may not be considered a "significant risk study," and warrant an IDE, the use of proper controls over the computer system's security is imperative

Case Example #10
(ePRO in Israel)

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