## FDA Perspective: Compliant use of ePRO Instruments







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#### **Disclaimer**

 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

- I. Examples and Users of Computerized Systems used in Clinical Investigations
- II. FDA Regulatory Requirements & Expectations
- III. Case Examples using ePRO

## I. Examples of Computerized Systems Used in Clinical Investigations:



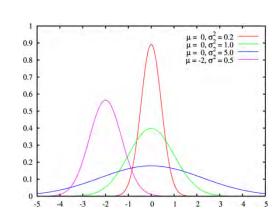


- Electronic Patient Reported Outcomes (ePRO)
- Interactive Voice/Web Response System (IVRS/IWRS)
- Adverse Event Reporting Systems (AERS)
- Laboratory Information Management Systems (LIMS)
- Systems that automatically record data by integrating data from a medical device such as an ECG, Holter-Monitor, MRI, etc...



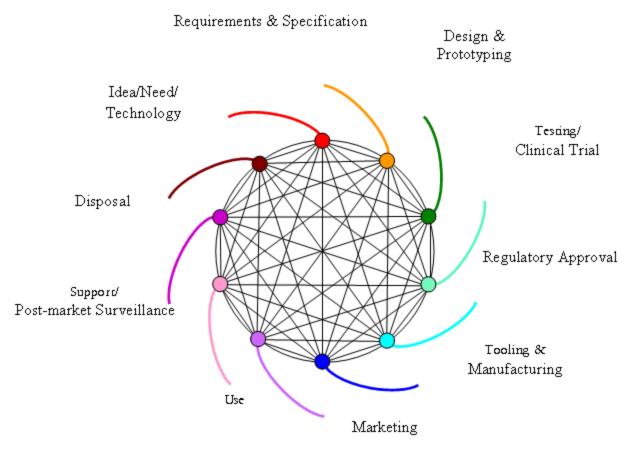
## I. Users of Computerized Systems in Clinical Investigations:

- Clinical Investigators (CIs)
- Sponsors
- Institutional Review Boards (IRBs)
- Study Coordinators (Monitors)
- Statisticians
- Data Managers
- CROs



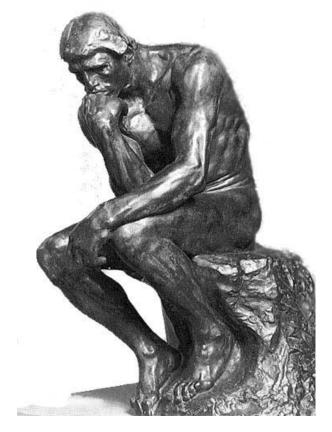


# How Do Computerized Systems Used in Clinical Investigations Fit Into the Total Product Lifecycle?



## Which Computerized System Should the Sponsor Choose?

- Design their own systems?
- Vendor-Purchased Systems?
- Hybrid-Electronic/Paper Systems?

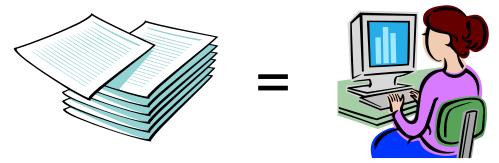


## II. FDA's Regulatory Requirements for Clinical Investigations

- FDA assesses compliance of Clinical Investigations through:
  - Regulatory requirements in 21 CFR Parts 11, 50, 56, 312, and 812; establishes the minimum threshold for compliance
  - Additional requirements established by the study specific protocol must also be followed as well as institutional policies

## II. FDA Regulatory Requirements for INDs/IDEs

- All 21 CFR Part 312/812 regulations apply equally to both paper records and electronic records
  - 21 CFR Part 11



 The use of computerized systems in clinical investigations does not exempt INDs/IDEs from any 21 CFR Part 312/812 regulatory requirement

## II. FDA Regulatory Requirements for IDEs

- 21 CFR 812.140(a) requires that participating Clinical Investigators maintain "accurate, complete, and current records relating to the Investigator's participation in an investigation"
- 21 CFR 812.140(b) requires Sponsors to maintain "accurate, complete, and current records relating to an investigation"

### II. FDA Regulatory Requirements for INDs

 21 CFR 312.57 "A Sponsor shall maintain complete and accurate records..."

 21 CFR 312.62(b) "An Investigator is required to prepare and maintain adequate and accurate case histories..."

#### **II. 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:
- 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

- 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

- 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

- 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

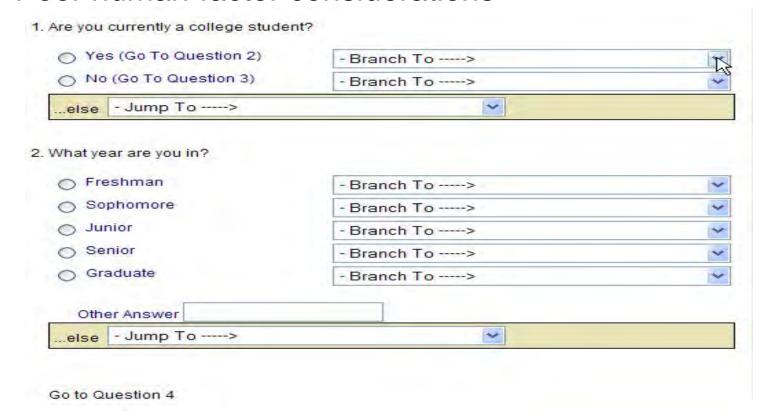
- What design feature of the IVRS could possibly lead to questionable data capture?
- The PIN # is not encrypted, since it is the Subject's birth-date, and the Sponsor had access to this information!
- The IVRS had minimal security features to prevent unauthorized access
- Password should have been protected!!!

### Case Example #4: ePRO

- 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 #4: ePRO

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



# Case Example #5: The Application Service Provider (ASP) Model/Validating Changes When Using a Vendor

- 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)

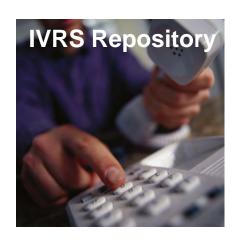
# Case Example #5: The Application Service Provider (ASP) Model/ Validating Changes When Using a Vendor

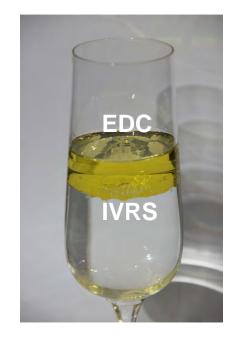
- Since the outside vendor was making this change, the Sponsor performed "User-Acceptance-Testing," whereby the Sponsor signed into the system as the role of a CI, to verify the appropriate privileges were granted, as well as verifying the accuracy of the new acceptable parameters, before the change 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

- 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 #6

- 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 #7 (ePRO in Israel)

#### **Clinical Evaluation**

Tap on the line to show what your pain was like, ON AVERAGE, over the past 24 hours.











#### Helpful Links

- Part 11 Guidance on Electronic Records & Signatures
  - http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM072322.pdf
- General Principles of Software Validation
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegul ationandGuidance/GuidanceDocuments/ucm085371.pdf
- Off-The-Shelf Software Use in Medical Devices
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073779.pdf
- Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegul ationandGuidance/GuidanceDocuments/ucm077823.pdf

#### Helpful Links

- BIMO CPGM Part III Inspectional, Section I. Electronic Records and Electronic Signatures:
  - http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133569.htm
- DRAFT Guidance on Electronic Source Documentation in Clinical Investigations:
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM239052.pdf
- Computerized Systems Used in Clinical Investigations
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegula toryInformation/Guidances/UCM070266.pdf
- Specific Concerns When Using Electronic Patient Reported Outcomes (ePRO)
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegula toryInformation/Guidances/UCM071975.pdf
- DRAFT Guidance on Mobile Health Technologies
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuida nce/GuidanceDocuments/UCM263366.pdf