

# Computerized Systems Used in FDA Regulated Clinical Investigations



Presentation to SQA Mid-Atlantic Region

Delivered by:

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FDA, CDER, OSI

# Disclaimer

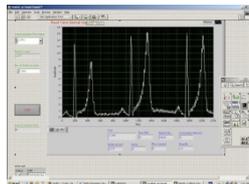
- The contents of this presentation are my own, and do not necessarily reflect the views and/or policies of the Food and Drug Administration or its staff as per 21 CFR 10.85.

# Overview

- I. Examples and Users of Computerized Systems used in Clinical Investigations
- II. FDA Regulatory Requirements & Expectations
- III. Recommendations from FDA Guidance
- IV. Developing Trends in the Use of Computerized Systems in Clinical Investigations

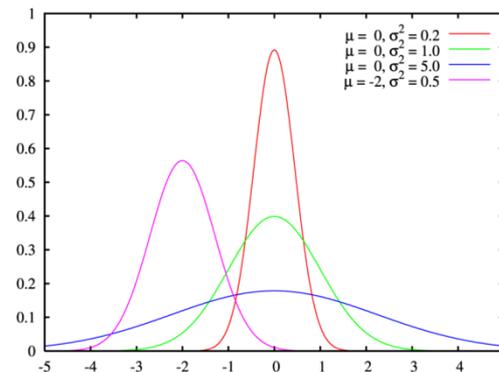
# I. Examples of Computerized Systems Used in Clinical Investigations:

- Electronic Case Report Forms (eCRFs) 
- 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...

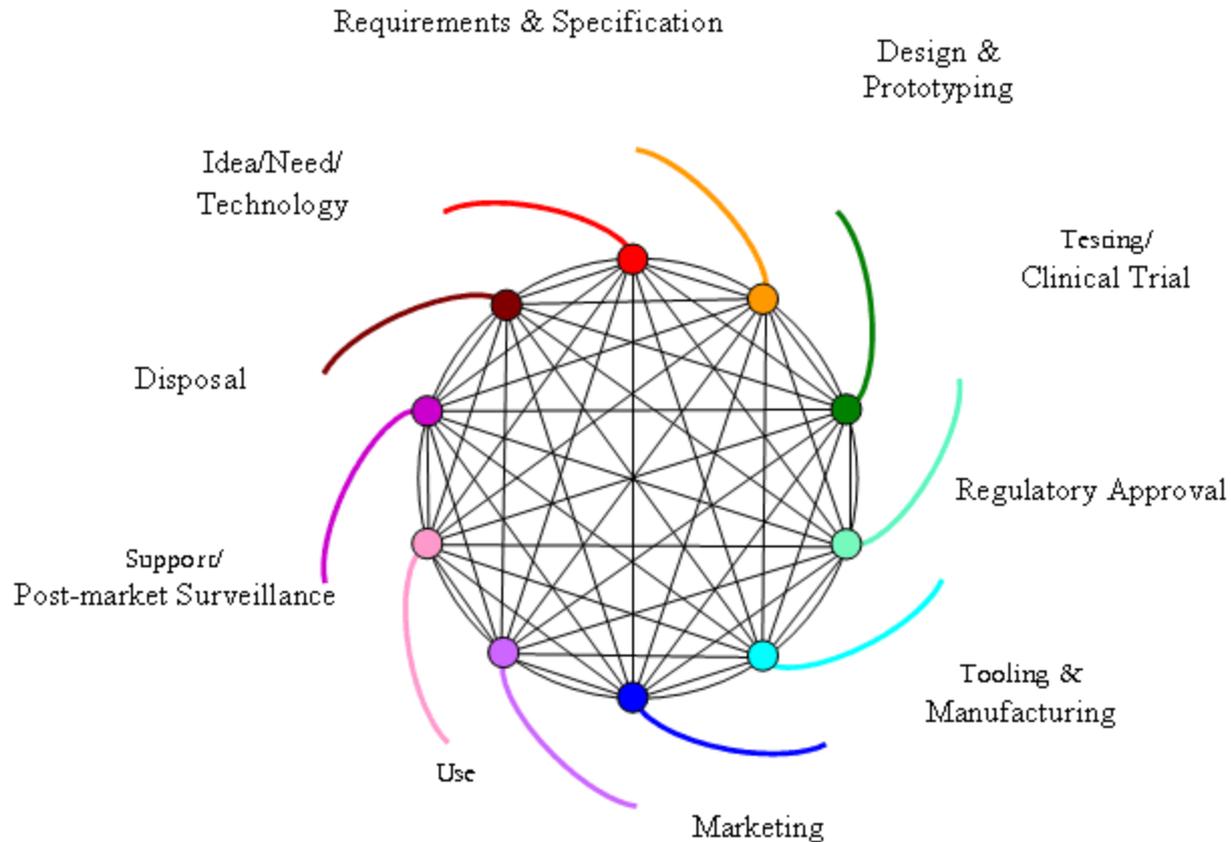


# I. Users of Computerized Systems in Clinical Investigations:

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

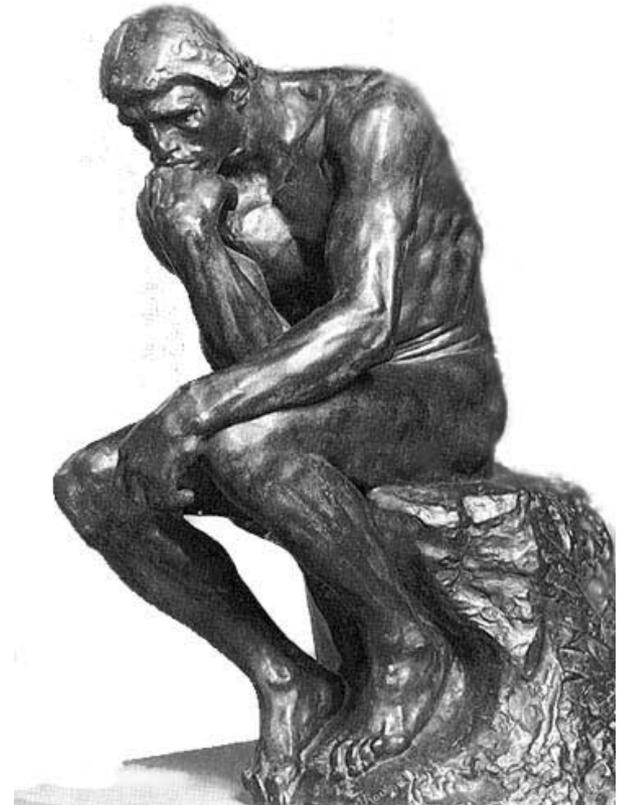


# How Do Computerized Systems Used in Clinical Investigations Fit Into the Total Product Lifecycle?



# Which Computerized System Should the Sponsor Choose?

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

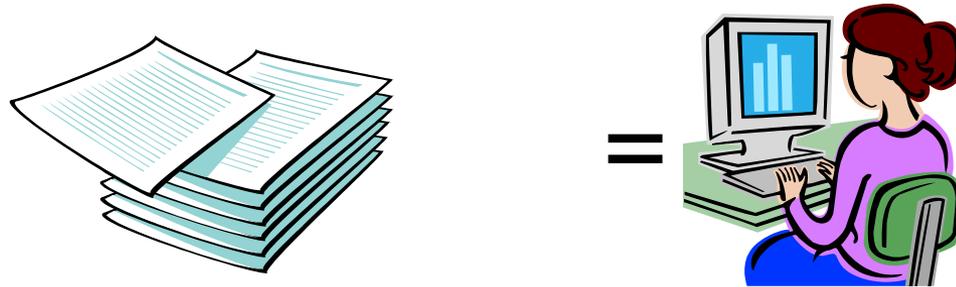


## **II. Overview of FDA's Regulatory Requirements for Clinical Investigations**

- 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/GLPs

- All 21 CFR Part 50/56/58/312/812 regulations apply equally to both paper records and electronic records
  - 21 CFR Part 11



- The use of computerized systems does not exempt INDs/IDEs/GLPs from following applicable FDA regulatory requirements

## 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. 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. Regulatory Requirements for GLPs

- 21 CFR 58.130(e) requires “...In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified.”

## 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

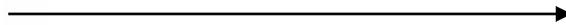


- PDA devices were issued to each subject and taken home to make daily reports
- The electronic information was transferred through the phone lines, to a server in Microsoft SQL format, when the PDA was docked each night
- After the last transfer of information, the ePRO data on the PDA was erased
- 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:

- 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)

### **III. FDA Guidance in May 2007: “Computerized Systems Used in Clinical Investigations”**

Applies to computerized systems used for records in electronic form that are used to create, modify, maintain, archive, retrieve, or transmit clinical data required to be maintained, or submitted to the FDA

# III. Software as a Medical Device

- Software can be a component to a medical device, such as a pacemaker or infusion pump
- Software can be an accessory to a medical device and assumes the same classification as the device it works in conjunction with
- Standalone software products can meet the legal definition of “Medical Device”
  - For example: Computer-Aided-Diagnostics (CADs)

**Which is the “Medical Device?”  
Which is a “Computerized System used in a  
Clinical Investigation?”**



# CDRH Regulates Software as a Medical Device

- For more information about FDA's requirements and expectations for software that meets the legal definition of a medical device, please look at "An Introduction to CDRH Regulated Software:"

<http://www.fda.gov/Training/CDRHLearn/ucm162015.htm#software>

- Point of Contact: John.Murray@fda.hhs.gov, Software Compliance Expert

### **III. FDA Guidance in May 2007: “Computerized Systems Used in Clinical Investigations”**

Recommendation Categories in May 2007 Guidance:

- Training of Personnel
- Internal/ External Security Safeguards
- Source Documentation and Retention
- Audit Trails
- Other System Features
- Standard Operating Procedures

# III. Training of Personnel

- All personnel who develop, maintain, or use the computerized systems should be trained
- Personnel must learn how to perform their assigned tasks
- Document the computer education, training, and experience

## **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

# III. Internal Security Safeguards



- Access must be limited to authorized individuals
- Each user should have an individual account
- Passwords should be changed at established intervals
- The system should limit and record the number of unauthorized log-in attempts
- Automatic log off for long idle periods

# **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!!!

# III. External Security Safeguards

Controls should be established to:

- Prevent unauthorized external software applications from altering, browsing, querying, or reporting data
- Prevent, detect, and mitigate effects of computer viruses, worms, or other potentially harmful software code on study data and software  
(e.g.-firewalls, antivirus, anti-spy, etc...)



## **III. Source Documentation & Retention**

- When original observations are entered directly into a computerized system, the electronic record is the source document
- Under 21 CFR 312.62, 511.1(b)(7)(ii) and 812.140, the clinical investigator must retain records required to be maintained under part 312, § 511.1(b), and part 812, for a period of time specified in these regulations
- Applies to the retention of the original source document or a copy of the source document

# **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

# III. Identify Electronic Source Documentation

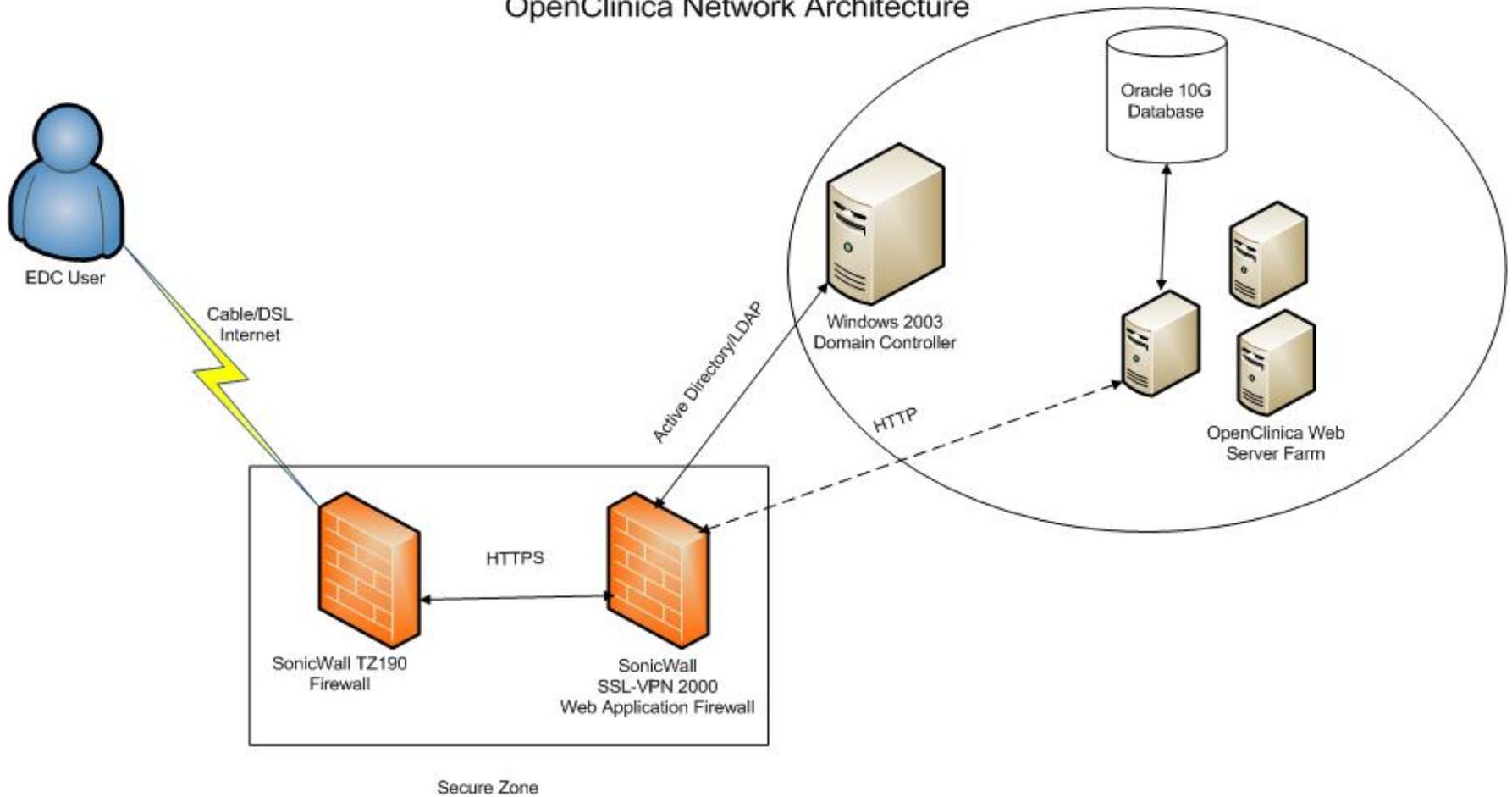
During pre-IDE meetings, identify all source documents that will be kept electronically throughout the duration of the Clinical Investigation

- It might be helpful to provide a detailed schematic of the data flow

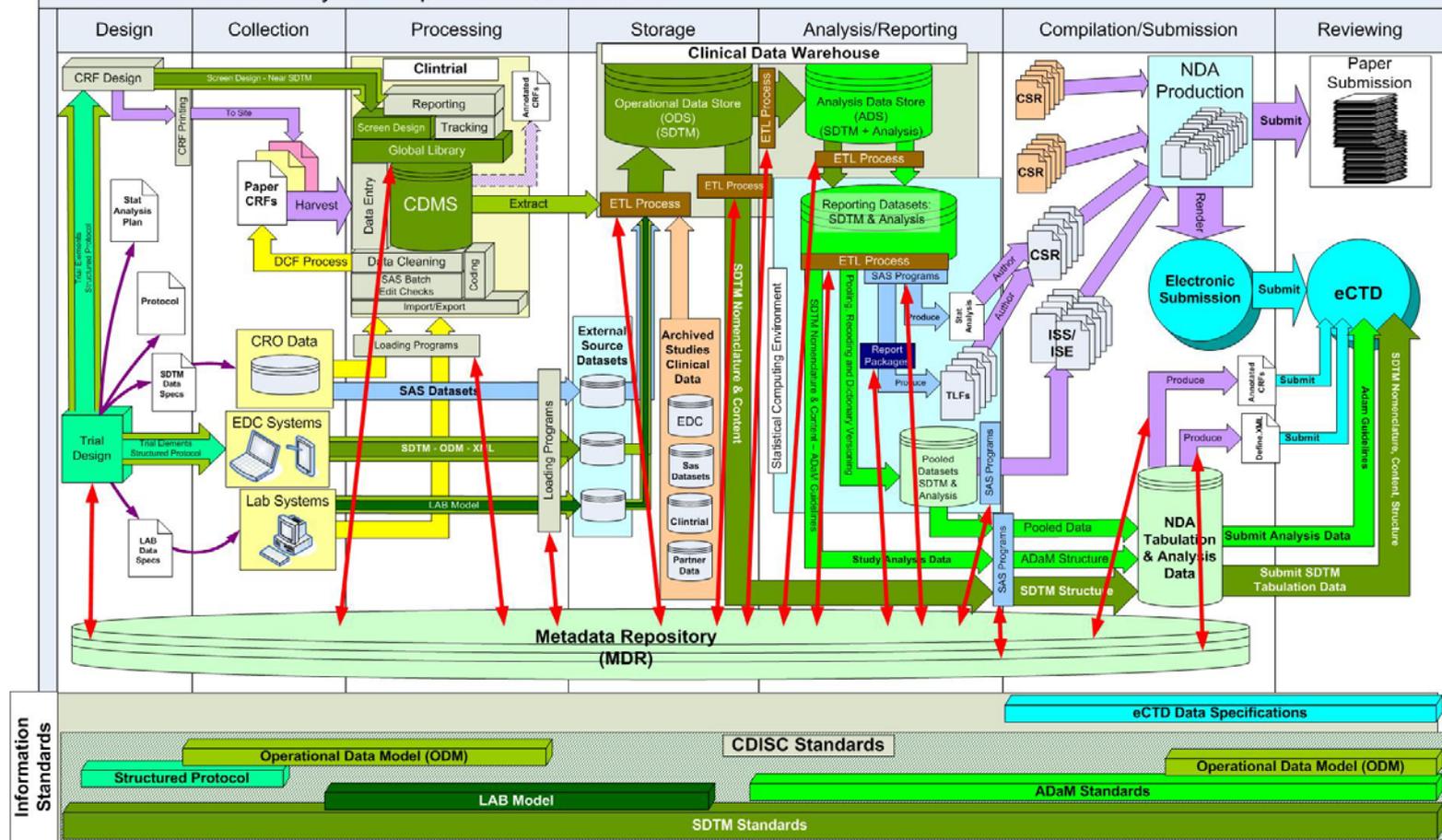
(e.g.-eCRF in XML format from clinical site→ Sponsor/CRO/IRB/Monitor/DSMB→ Data Lock→ Statistical Review→ Clinical Report→ Submission to FDA)

# System Overview

## OpenClinica Network Architecture



# Clinical Information Lifecycle – Impact of Data Standards



# III. Source Documentation & Retention

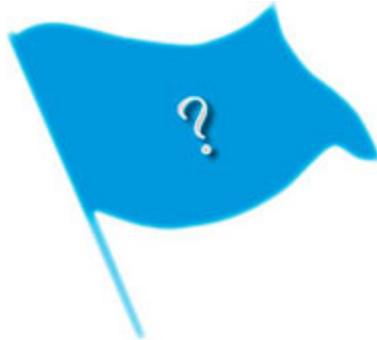
- The information provided to FDA should fully describe and explain how source data were obtained and managed, and how electronic records were used to capture data
- Maintain a cumulative record that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges
- That record should be kept in the study documentation, accessible for use by appropriate study personnel and for inspection by FDA investigators

# III. Audit Trails

- Computer-generated, time-stamped electronic audits trails are the preferred method for tracking changes to electronic source documentation
- Audit trails or other security methods used to capture electronic record activities should describe when, by whom, and the reason changes were made to the electronic record to ensure that only authorized additions, deletions, or alterations have occurred
- Ensure that audits cannot be overridden

### **III. Other System Features:** ***Direct Entry of Data***

- For direct entry of data, the system should incorporate prompts, flags, or other help features to encourage consistent use of clinical terminology and to alert the user to data that are out of acceptable range



# 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

1. Are you currently a college student?

|                                              |                    |
|----------------------------------------------|--------------------|
| <input type="radio"/> Yes (Go To Question 2) | - Branch To -----> |
| <input type="radio"/> No (Go To Question 3)  | - Branch To -----> |
| ...else                                      | - Jump To ----->   |

2. What year are you in?

|                                 |                    |
|---------------------------------|--------------------|
| <input type="radio"/> Freshman  | - Branch To -----> |
| <input type="radio"/> Sophomore | - Branch To -----> |
| <input type="radio"/> Junior    | - Branch To -----> |
| <input type="radio"/> Senior    | - Branch To -----> |
| <input type="radio"/> Graduate  | - Branch To -----> |

Other Answer

|         |                  |
|---------|------------------|
| ...else | - Jump To -----> |
|---------|------------------|

Go to Question 4

# Standard Operating Procedures

Specific procedures and controls should be in place for:

- System setup/installation
- System operating manual (User's Manual)
- Validation and functionality testing
- Data collection and handling
- System maintenance (Service/Upgrade Logs)

**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 #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

### **III. Additional Recommendations:**

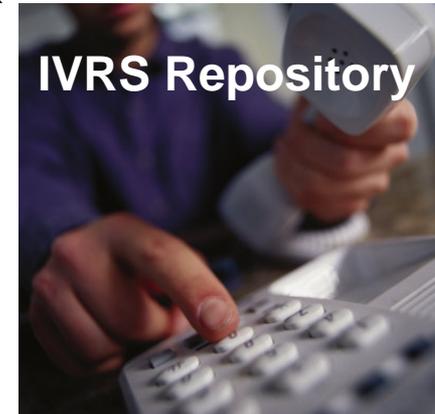
- Identify and document all the specified requirements for the system
- Ensure that the computerized system is capable of consistently meeting all specified requirements
  - If a Vendor/CRO designed/maintained a Sponsor's computerized system, did they provide a validation summary or report? Is there any documented User Acceptance Testing?

# III. Additional Recommendations

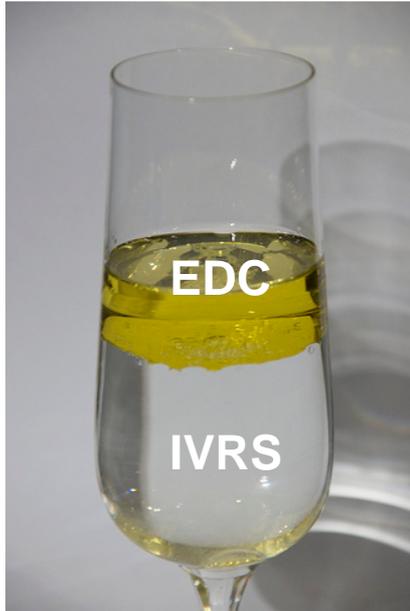
- Identify all the computer and software components used in the system
  - The identification should be a detailed list that includes product names and specific version numbers to keep track of any modifications
- Sufficient backup and recovery procedures help protect against data loss at clinical sites (e.g. Redundant Servers or Hard-Drives)

# Case Example #4

- 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 #4 (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



## **IV. Developing Trends in the Use of Computerized Systems in Clinical Investigations**

- Electronic Clinical Data Management
- Role of Standards
- Electronic Health Records (EHRs)
- Home Health Care in Clinical Research
- Use of Data Generated from Medical Devices in Clinical Research

## **IV. Developing Trends in the Use of Computerized Systems in Clinical Investigations**

- Combination Products
- Considerations for Internationally Deployed Systems
- Remote Monitoring
- Merging eClinical Systems

# IV. Electronic Clinical Data Management

- Use of a “Clinical Data Management (CDM) Plan:”
  - Can be used to document all CDM activities
  - One repository for all documents
  - Consistent CDM activities across different working groups through use of SOPs
  - Promote the use of standards
  - Useful tool for FDA Inspections



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# Data Management Plan Template



## Section 4 | Plan for the Data Validation Process

The key document of the data validation process is the [Data Validation Plan \(DVP\)](#), which contains the specifications for the automatic database validation, based on edit checks, and the manual review, which is based on listings.

As a consequence of complying with the planned specifications test cases and other documentation associated with the development and testing of edit checks and listings will be produced. With the exception of possible specification modifications, this documentation is not part of the plan.

If data validation specifications are modified during testing, or a subset of edit checks are modified, disabled or added, anytime thereafter, this section of the DMP and the DVP have to be re-reviewed and approved.

### Types of Validation

Automatic database validation

|                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Validations Run via                                                                    | <input type="checkbox"/>  CDMS<br><input type="checkbox"/> Other (specify):                                                                                                                                                                                                                                                                      |
| Frequency of Validation Runs<br>Data Tables:<br>Update Tables:                         | <input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Bi-Weekly <input type="checkbox"/> Monthly <input type="checkbox"/> Other (specify):<br><input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Bi-Weekly <input type="checkbox"/> Monthly <input type="checkbox"/> Other (specify):                                                                                                                                                        |
| Database queries processed (optional)                                                  | <input type="checkbox"/> 1-3 days <input type="checkbox"/> 4-7 days <input type="checkbox"/> 8-10 days<br><input type="checkbox"/> Other (specify): <br><small>These are targeted processing times. The frequency of when the <u>DCF<sub>s</sub></u>/<u>SDCF<sub>s</sub></u> are processed will be adjusted based on the volume of discrepancies created and the status of the study (start-up, maintenance or closure)</small> |
| <small>Specifications for automatic validations in <a href="#">Appendix 1A</a></small> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |



## **IV. The Changing Role of the Data Monitor**

- Under 21 CFR 812.43(d), a Sponsor is required to “select monitors qualified by training and experience to monitor the investigational study in accordance with applicable FDA.”
- A designated monitor may have responsibilities above and beyond that which is required under 21 CFR 812.43(d)
- Monitors wear many different hats

## IV. Monitoring a Study Remotely Using Computers

- Systems can be designed to automatically prompt a query for the data monitor
- Some systems designate the separate “Monitoring Roles”
  - For example, a “Junior Monitor,” may only have the ability to review data and initiate queries, however, a “Senior Monitor” may have the ability to both initiate and resolve queries

## **Case Example #8:**

*(All 21 CFR Part 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

## IV. Role of Standards

- Collaboration with standards organizations can be helpful in integrating computers with clinical research
- Various FDA supported initiatives such as:
  - Clinical Data Informatics Standards Consortium (CDISC)
  - Clinical Data Acquisition Standards Harmonization (CDASH)
  - Health Level 7 (HL7)
  - Healthcare Information Technology Standards Panel (HITSP)

# IV. Use of Electronic Health Records (EHRs) in Clinical Research

Possible uses of EHRs in Clinical Trials:

- Retrospective analyses
- Subject recruitment tool
- “Auto-population” of a Subject’s data from EHR to eCRF and/or MedWatch/Adverse Event Report form
  - CDISC’s RFD Pilot Program

# Patient Charts

**Facesheet** Summary Documents

**Facesheet**  
Fred Smith Age 14 months

### Clinical Forms

Genzyme Pompe Disease Registry

- [Enrollment Form](#)
- [Echocardiogram Form](#)

### Family Medical History

Family history of colon cancer

### Past Surgical History

Cleft lip repair

### Allergy List

- Egg
- Latex Pediatric

### Reason For Visit

(No Reason For Visit)

### Vital Signs

### Past Medical History

- Asthma
- Cesarean Delivery
- Pompe Disease

### Social History

Uses Child Safety Seat

### Medication List

Prescribed within Practice

- Amoxicillin 400 mg/5 mL
- Myozyme 50 mg

### Genetic Screening

Cleft Palate

### Problem List

| Problem Name  | Status        |
|---------------|---------------|
| Pompe Disease | (PMHx) Active |

### Orders Tracking History

00:02:29



## Facesheet

Forms  
 Pompe Disease Registry  
 Form  
 Program Form

Medical History  
 History of colon cancer

Surgical History  
 Repair

List

Matrix

For Visit

Person For Visit)

Signs

| BP     | HR | RR | T(°F) | Wt    |
|--------|----|----|-------|-------|
| 100/81 | 30 |    | 97.1  | 32lbs |
|        |    |    |       | 0oz   |

Tests

### POMPE REGISTRY

**Patient Enrollment**

Date of Visit  3/23/2009

Date patient authorization signed  3/21/2009

**Birth**

Date of birth  1/1/2006

Gestational age (weeks)  Known  Unknown

Weight at birth (kg)  Known  Unknown

Length at birth (cm)  Known  Unknown

**Gender**

Male  Female

**Ethnicity**

Caucasian  Black  Hispanic  Asian  Other, specify

**Pompe**

Does the patient have Pompe symptoms?  Yes  No

Age of onset  < 12 months  > 12 months  Unknown

Have any of the patient's siblings been diagnosed?  Yes  No  NA (no siblings)  Unknown

**GAA Activity**

GAA activity in dry blood spot assessed?  Yes  No  Unknown

**Informed Consent**

Open Form?  Yes  No  Unknown

00:03:22



# Patient Cl

Facesheet

## Clinical Form

Genzyme Pompe Dis  
Enrollment Form  
Echocardiogram F

## Family Medi

Family history o

## Past Surgical

Cleft lip repair

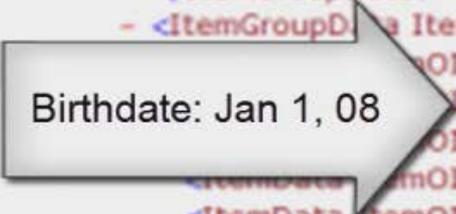
## Allergy List

Egg

```

Granularity="AllClinicalData" CreationDateTime="2009-03-31T13:48:15Z" AsOfDateTim
xmlns="http://www.cdisc.org/ns/odm/v1.2" xmlns:odm="http://www.cdisc.org/n
xmlns:xlink="http://www.w3c.org/1999/xlink">
- <ClinicalData StudyOID="S.XFORMSDEMO" MetaDataVersionOID="MDV.XFORMSDEMO"
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- <StudyEventData StudyEventOID="SE.SCR">
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  <ItemData ItemOID="I.DMMENDT" />
  <ItemData ItemOID="I.DMPGQ" />
  <ItemData ItemOID="I.DMPGCQ" />
  <ItemData ItemOID="I.ETHNICQ" Value="3" />

```



Birthdate: Jan 1, 08

00:04:51 +



# IPL

## eSource Safe Deposit



Username

Password

00:06:38





# eSource Safe Deposit

eSD Home

eSD Admin

Studies

Company

eSD Viewing

**Studies**

Change E-mail

Change Password

> eSD Home > eSD Viewing > Studies

## Studies

| Study OID    | Study Name | Description | Comments   | Protocol   | Active | My Roles | Data Uploaded | Errors |
|--------------|------------|-------------|------------|------------|--------|----------|---------------|--------|
| S.XFORMSDEN0 | XFORMSDEN0 | XFORMSDEN0  | Demo Study | XFORMSDEN0 |        |          |               |        |

First Previous Next Last

Search by - Status: [none]

Name:

OID:

Search

Admin Data Metadata Reference Data Clinical Data ODM Errors ODM Receipt

Key:

|             |                 |               |                |
|-------------|-----------------|---------------|----------------|
| Study Admin | Study Regulator | Site Viewer   | Site Regulator |
| Admin Data  | Metadata        | Clinical Data | Reference Data |
|             |                 |               | Error in data  |

Done



C:\Users\landenbain... JHE - Remote Contro... Studies - Mozill... Camtasia Studio - Un...

09:01

00:07:30



| Field                             |  | Value      | Original Value (if different)                                        | Char |
|-----------------------------------|--|------------|----------------------------------------------------------------------|------|
| Date Completed                    |  | 2009-03-23 |                                                                      | -    |
| <b>Demography (IG.DM) ↑</b>       |  |            |                                                                      |      |
| MDRYDY                            |  |            |                                                                      | -    |
| Date patient authorization signed |  | 2009-03-30 |                                                                      | -    |
| Date of birth                     |  | 2008-01-01 |                                                                      | -    |
| Insert at 2009-03-31T12:49:00     |  | 2008-01-01 | Recorded by Landen Bain on 2009-03-31T12:49:00 at CDISC Headquarters |      |
|                                   |  |            | Initial entry                                                        |      |
| Gestational age                   |  | Unknown    |                                                                      | -    |
| Known, specify                    |  |            |                                                                      | -    |
| Weight at birth                   |  | Unknown    |                                                                      | -    |
| Known, specify                    |  |            |                                                                      | -    |
| Length at birth                   |  | Unknown    |                                                                      | -    |

00:09:08



# IV. Home Health Care in Clinical Research

- Increases in the use of medical devices and other technologies within the home setting provide more opportunities to collect clinical research data from subjects
- Examples include:
  - Use of home computers and internet
  - Physiological measuring devices
  - Cellular Phones



# **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

## **IV. Use of Data Generated from Medical Devices in Clinical Research**

- A Medical Device that generates data for any clinical study should have appropriate clearance/approval (i.e. 510(K)/PMA/IDE)
- Sponsors should include a detailed description of the entire process and equipment being used to integrate data outputted from a Medical Device into the eCRF
- Establish device is working properly
  - Follow User-Manual instructions
  - Ensure proper maintenance and calibration  
(preserve all such records)

# IV. Use of Computers In Combination Product Clinical Studies

- Office of Combination Products designates a Lead Center for review based on the “primary mode of action”  
(Sec. 503g(1) FD&C)
- Request For Designation (21 CFR Part 3)
- Lead Center establishes the requirements and expectations for computerized systems used in clinical trials

# IV. Considerations for International Clinical Investigations

- Ensure compliance with all relevant requirements from the International regulatory bodies and US FDA
- International & US requirements may be different for:
  - Human Subject Protections
  - Adverse Event Reporting
  - Registration and Approval of Clinical Investigations
  - Continued Ethical Oversight

## **IV. Considerations for International Clinical Investigations (Continued)**

- Adhere to all local rules and regulations
- Records should be made available for inspection by FDA
- Demonstrate that the cumulative subject population is clinically comparable to that of the United States

## IV. Considerations for Internationally Deployed Systems

- As functions become computerized, ensure that the system being used meets the same requirements that are expected when using paper records
  - For example, a computer system used in an international clinical study may have “universal” procedures for Adverse Event Reporting, however, computers at each site, depending on its’ location, should be set up to adhere to all local requirements (i.e.-Immediate AER by CI to Sponsor/Ethical Body Oversight Vs. 10 day AER requirements)

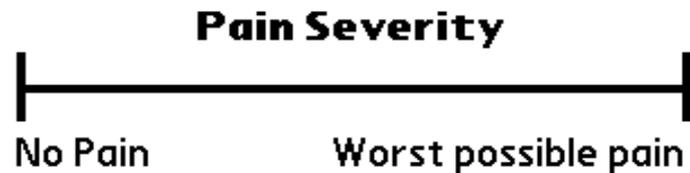
## IV. Considerations for Internationally Deployed Systems

- Clinical sites must also meet IT specification requirements
- Metrics for collecting and evaluating clinical data should be consistent across language and cultural barriers
- Pay attention to possible cultural differences to ensure that electronic source data is standardized:
  - Language (English Vs. עברית)
  - Dates (e.g.- 8/12/08 Vs. 12/8/08)
  - Times (e.g.- 21:00 Vs. 9:00 PM)
  - Lab Values

# Case Example #10 (ePRO in Israel)

## Clinical Evaluation

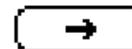
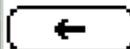
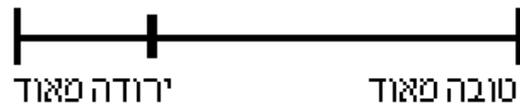
Tap on the line to show what your pain was like, ON AVERAGE, over the past 24 hours.



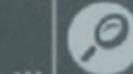


## יומן בוקר

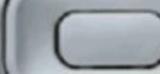
דרג את איכות השינה שלך אתמול  
בלילה ע"י סימון ברור ואנכי על גבי  
הקו פטה:



ABC

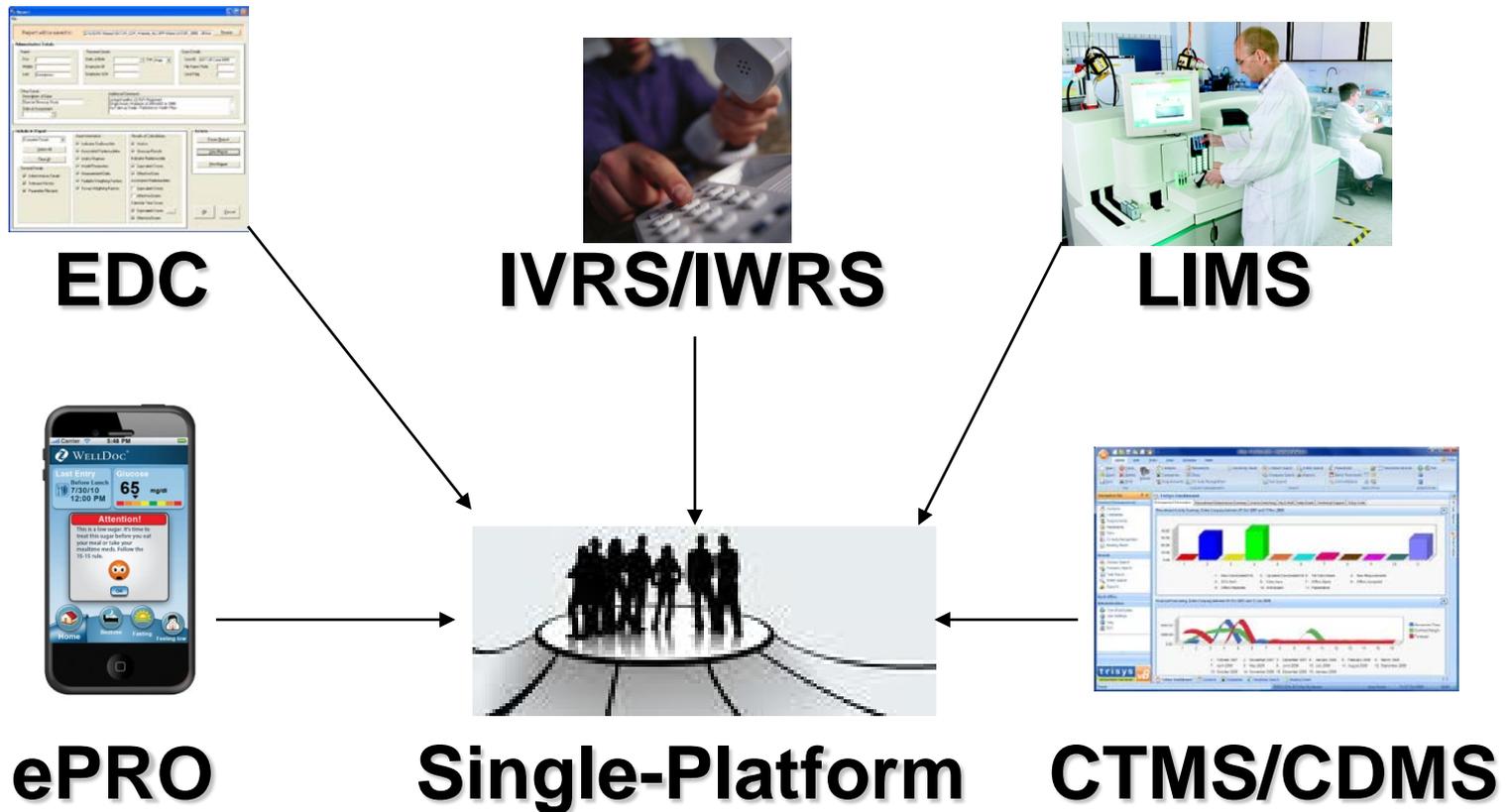


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# IV. Merging eClinical Systems



# Conclusion

The intent of FDA's regulatory requirements and guidance is:

- Ensuring confidence in the reliability, quality, and integrity of electronic source data, source documentation, and the computerized systems used to collect and store that data
- Ensure that electronic records used in clinical investigations are accurate, complete, and current

# Important FDA Regulations on Software/Computers/Electronic Records

- 21 CFR Part 11
- Predicate Rules in 21 CFR Parts 312 & 812
- 21 CFR Part 820.30(g): *Design Controls*
- 21 CFR Part 820.70(i): *Automated Processes*
- 21 CFR Part 58: Good Laboratory Practices

# FDA Guidance Documents on Software/Computers/Electronic Records

- Part 11 Guidance on Electronic Records & Signatures
  - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072322.pdf>
- General Principles of Software Validation
  - <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/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/DeviceRegulationandGuidance/GuidanceDocuments/ucm077823.pdf>

# FDA Guidance Documents on Software/Computers/Electronic Records (Cont...)

- *Computerized Systems Used in Clinical Investigations*
  - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf>
- *Specific Concerns When Using Electronic Patient Reported Outcomes (ePRO)*
  - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071975.pdf>
- DRAFT Guidance on Mobile Health Technologies
  - <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf>