

# Panel Discussion 3

## *Electronic Capture of Patient-Reported Outcome (ePRO) Data in Clinical Trials: Regulatory Consideration*

**THIRD ANNUAL  
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP**

April 4, 2012 ■ Silver Spring, MD

Co-sponsored by



# PRO Consortium and ePRO Consortium Collaboration

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- Employee of Merck Research Laboratories
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- PRO Consortium
  - PRO Consortium Working Groups
    - Develop and qualify PRO instruments
  - ePRO Subcommittee
    - Coordinate with ePRO Consortium
    - Provide ePRO guidance to Working Groups
    - Encourage ePRO best practices
    - Sponsor PRO Consortium ePRO measurement projects
- ePRO Consortium
  - Consortium of ePRO Vendors to promote advances in ePRO science and methodology

# Goals of ePRO Consortium



- Work with PRO Consortium to migrate PRO instruments to all relevant EDC platforms
- Provide a non-competitive, neutral environment to test measurement equivalence of migrated PRO measures
- Develop specification documents for migrating existing PRO instruments to relevant EDC platforms
- Provide guidance on methodological considerations for PRO instrument migration and adaptation

# Collaborative Model



- ePRO Consortium
  - Propose initiatives to PRO Consortium
    - Measurement equivalence projects
    - Standards development
- PRO Consortium Working Groups
  - Request consultations from ePRO Subcommittee
  - Request ePRO Consortium members to participate in testing and validation of ePRO versions of their PRO instruments
- ePRO Subcommittee
  - Propose best practices for consideration by Working Groups
    - ePRO touchpoints in PRO instrument development
    - CDISC survey
    - Vendor-neutral developer requirements document

- ***Implementation of ePRO in Clinical Trials: Unresolved Challenges***
  - Barbara Marino, PHT Corporation
- ***Sponsor Topics in ePRO: eSource and Study Conduct***
  - David Reasoner, Sunovion Pharmaceuticals Inc.
- ***Electronic Records, Source and PRO Devices***
  - Sean Kassim, FDA Office of Compliance
- Open floor discussion (20 minutes)

# ***Implementation of ePRO in Clinical Trials: Unresolved Challenges***

**Barbara Marino**

**Senior Scientist, Director of Outcomes and Study Design  
PHT Corporation**

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# The Promise of ePRO



Use technology to:

- Improve measurement of patient outcomes
  - More complete data
  - Prevent illogical data
  - Collection of data according to protocol schedule
- Gain efficiencies
  - Transcription and SDV eliminated with eSource
  - Reduced variance may allow reduced sample size
- Meet expectations of regulatory agencies

# Regulatory Expectation



- Migration testing when adapting paper and pencil instrument to electronic format
- ISPOR provided actionable guidelines for migration testing
- Challenges for migration:
  - Redundant testing efforts
  - Conflicting opinions on migration testing
  - Lack of industry standards for electronic formats

# Unresolved Challenge #1

## Redundant Testing Efforts



- Migration testing at the level of cognitive debriefing is common
- Variables in the testing need to align:
  - PRO instrument
  - Technology (IVR, IWR, Handheld, Tablet, etc)
  - Patient population
- Results not available publicly
- Needed: a model for sharing results to prevent repeated effort

# Unresolved Challenge #2: Conflicting Opinions on Testing



- ISPOR Guidelines for testing format change align with FDA expectations
- Authors or licensing agents for the paper version may expect more rigorous level of testing
- Those expectations are often enforced in the licensing agreement for electronic use
- Needed: negotiation and testing accomplished once and published

# To Retest or Not to Retest?

How **troubled** have you been by each of these activities during the **last week** as a result of your nose/eye symptoms?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
1. REGULAR ACTIVITIES AT HOME AND AT WORK (your occupation or tasks that you have to do regularly around your home)	0	1	2	3	4	5	6

**Activities**

The first question will ask you how **TROUBLED** you have been by **REGULAR ACTIVITIES** at home and at work during the **LAST WEEK**

(your occupation or tasks that you have to do regularly around your home)

← →

**Activities**

1. REGULAR ACTIVITIES AT HOME AND AT WORK

0 Not troubled  
1 Hardly troubled at all  
2 Somewhat troubled  
3 Moderately troubled  
4 Quite a bit troubled  
5 Very troubled  
6 Extremely troubled

← →

Concordance established

The first question will ask you how **TROUBLED** you have been by **REGULAR ACTIVITIES** at home and at work during the **LAST WEEK**

(your occupation or tasks that you have to do regularly around your home)

← →

1. REGULAR ACTIVITIES AT HOME AND AT WORK

Not troubled  
 Hardly troubled at all  
 Somewhat troubled  
 Moderately troubled  
 Quite a bit troubled  
 Very troubled  
 Extremely troubled

← →

Does concordance testing need to be repeated?

# Unresolved Challenge #3: Lack of Industry Standards



- Vendor-established best practices guide migrations so that appearance or scripts vary with vendor
- Equivalence studies have not published the screen shots or scripts used in the study limiting reproducibility
- FDA has no insight into the presentation of the instrument as subjects see or hear it
- Needed: industry standards to ensure sound migration practices

# One Question, Two Designs



- ePRO has recognized benefits for data quality in clinical trials
- Clear regulatory expectations related to migration to electronic format
- Current challenges are to:
  - reduce duplicative efforts,
  - reconcile author requirements with that of the agency,
  - develop industry standards for the design of electronic instruments



# **Sponsor Topics in ePRO: eSource and Study Conduct**

**David S. Reasner  
Sunovion Pharmaceuticals**

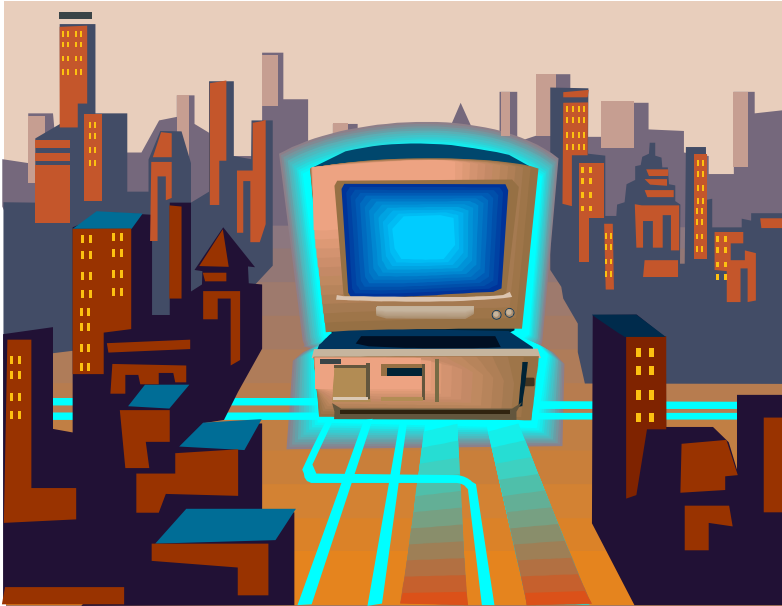
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# Presentation Outline



- eSource
- Clinical Trial Roles
- Tangled Web
- Current Practice: Examples
- Current Practice: Options

# Source Data Defined



- **Original observations** recorded for the first time about the subject's medical condition or treatment (e.g., patient diary, office charts, evaluation checklists, diagnostic results, or subject's history). ICH GCP 1.51/1.52 states that source data are contained in source documents (original records or certified copies); ICH GCP 8.3.13 assigns the responsibility for source documents to the Investigator/Institution. The purpose of source documents (per ICH) is to **document the existence of the subject and substantiate the integrity of the collected trial data**. Sponsors specify a subset of source data per protocol for transfer, either directly via a certified copy, or indirectly by first transcribing to a paper or electronic case report form (see Transcribed data below).

# eSource Data Examples



- ePRO – patient diaries are explicitly referenced.
- Medical Devices – electronic documents created by medical devices that were previously paper documents.
- Health Records - original records created in the ERMS for the management of the subject's medical treatment under the clinical protocol.

# Clinical Trial Roles



- Investigator
- Sponsor
- eSource  
System  
Provider

The FDA requires:

- The Investigator 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.” (FDA 21 CFR Part 312.62(b))

The Investigator also has responsibility to appropriately document any changes to the data:

- “Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections.” (ICH GCP, section 4.9.3)

While the Investigator must prepare the source data, the Sponsor must be able to verify the data. The FDA requires that:

- “The Sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the Investigator.” (21 CFR Part 312.56( c))

ICH GCP guidance states:

- “The Sponsor should utilize appropriately qualified individuals to [supervise the overall conduct of the trial, to handle the data, to verify the data](#), to conduct the statistical analyses, and to prepare trial reports.” (*Section 5.5.1*)
- “The purposes of trial monitoring are to verify that... (b) The reported trial data are [accurate, complete, and verifiable from source documents](#).” (*Section 5.18.1*)

# Investigator & Sponsor



The FDA directs that:

- “An Investigator shall retain **records required to be maintained** under this part [including case histories or source documents] for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.”  
*(FDA 21 CFR Part 312.62(c))*
- “A Sponsor shall **retain records** and reports required by this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.”
- *(FDA 21 CFR Part 312.57(c))*



# eSource System Provider



- This person/group/entity designs, builds, and validates the eSource system technology. The system provider supplies the tools and technical support to conduct an eSource trial. This person/group/entity may also administer access to the system and the eSource data during the trial.
- [c.f., Technology Provider and Trusted Party]

(The term 'trusted third party' has been frequently used in the industry although the appropriateness of this term has been a matter of debate.)

# Tangled Web I



“Oh what a tangled web we weave, When first we practise to deceive!” - Sir Walter Scott (Marmion, Canto vi. Stanza 17, 1808)

# Tangled Web II



The intent of the storage responsibility was that changes to the data by either party (investigator or sponsor) would be detectable to the regulator. Thus, after source verification and collection, the various copying operations by the sponsor could be verified for **inadvertent or malicious changes** by comparison of the submission copy with the site source documents. Therefore, it is important that the sites receive and store the original electronic source document, or a certified copy, as soon as practicable after its creation.

# Current Practice: Examples



- Data Sources
- Data Examples
- Thought Questions

# Data Sources



- Investigator
  - Clinical Chemistry Laboratory \*
  - Institution's Record Management System
  - Medico-Technical Departments \*
  - Pharmacy \*
- Sponsor
  - Bioassay Laboratory \*
  - Biostatistics Department
  - Clinical Research Organization
  - Data Safety and Monitoring Board \*

\* The sponsor may have qualified and retained these centralized resources to enable a larger number of clinical investigators to participate in the clinical trial.

# Data Examples



- Investigator
  - Clinical Laboratory Report †
  - Patient History †
  - Diagnostic Images †
  - Drug Reconciliation †
- Sponsor
  - Drug Concentration Values †
  - Randomization Schedule †
  - Study Master File †
  - Interim Analysis †

† Original observations that are not part of the management of the subject's medical treatment or the operation of the protocol at the investigational site remain with the Trusted Entity.

# Thought Questions I



- Are original observations created away from the investigational site source documents as originally intended under ICH 8.3.13 (e.g., genotyping)?
  - When an expert cardiologist **over-reads** the EKGs from a clinical trial either during or subsequent to execution of the trial, are the resulting QTc values necessarily source data or are they more similar to derivation of the primary efficacy endpoint? (Both values may be specified in the study protocol, but neither may be required by the investigator to safely manage the subject or conduct the site's activities under the protocol.)
  - When a central clinical laboratory runs a **repeat sample** per SOP and provides only the second confirmed electronic value to the investigator is there a regulatory requirement that all raw data in the laboratory system be transcribed and returned to the investigational site?
  - Should drug **concentration values** that are not required to operate the protocol be returned to the investigational site either during or after the clinical trial?

# Thought Questions II



- As the “length of the wire” increases, are eSource data records at vendor sites under the control of the investigator?
  - Would delegation of responsibility be necessary for the **offsite storage** of medical records defined as source documents or for e-Diary records that are also clearly source documents?
  - Similar to electronic banking, when the institution’s **ERMS** is hosted in the next office, next building, or next state are the eSource data records protected from fraudulent or inadvertent data manipulation by the sponsor?
  - Are regulated records, in a general sense under 21 CFR Part 11, out of compliance or a barrier to efficient regulatory inspection when they are no longer available at the physical location of the investigational site (e.g., **validation documentation** of a computerized system)?



# Thought Questions III



- Does migration from paper to electronic systems create new regulatory requirements?
  - If a diagnostic laboratory typed out a report for a clinical trial subject, then **the storage responsibility would seem to begin with receipt of the study record**. Therefore, in the eSource world, the storage responsibility could begin upon receipt of the eSource data.
  - If an investigational site copied medical records in order to manage the subject's medical treatment under the clinical protocol, then the GCP **record requirements would seem to begin with creation of the study copy**. Therefore, in the eSource world, the GCP record requirements should not apply to the ERMS.

# Current Practice: Options I



- Provide transparency by complying with CSUCT (2004) and describing computerized systems in the study protocol.
- Provide transparency by listing eSource vendors on the investigator's 1572.
- Ensure explicit delegation of responsibility from the investigator for the storage of eSource.
- Ensure sponsor contracts with third party vendors address regulatory responsibilities under 21 CFR Part 312.58(a) among others.
- Train investigational, sponsor, and vendor staff on eSource.

# Current Practice: Options II



- Synchronize ePRO devices with a local workstation at the investigational site during each visit to create an independent copy for the investigator (i.e., interim transfers of eSource).
- Employ procedural controls (query system) and system features (security and audit trail) to ensure that source data cannot be altered without the knowledge and approval of the investigator.
- Build storage contracts between the investigational site and the eSource system provider.

# Regulatory Contention



- If the following questions can be answered in the affirmative then the intent of the predicate regulations is met:
  - Are all data necessary for management of the subject's medical treatment and operation of the protocol returned to the investigational site and retained under the investigator's control as source documents?
  - Are other regulated data available for audit and inspection and retained to support the integrity (and potential reconstruction) of the clinical trial?

# Request for Guidance



- Similar to the recognition that CROs assume sponsor responsibilities, acknowledgement in the regulations that [eSource System] providers may assume investigator responsibilities, will ensure appropriate documentation of quality data.
- Further, guidance in these highlighted areas is essential to promulgate best practices under the current regulatory framework.

# Acknowledgements

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# ePRO and eSource: Data Types, Clinical Trial Roles, and Examples from Current Practice

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Katarina Halling (Astra Zeneca)  
Jean Paty (invivodata)  
David Reasner (Sepracor)  
Teri Stokes (GXP International)





# Electronic Records, Source and Patient Reported Outcome Devices

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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.

## What is Part 11?

- FDA regulation describing requirements for maintaining FDA-required records and signatures in electronic form
- Requirements are intended to ensure the integrity, validity and trustworthiness of e-records and e-signatures
- Regulation went into effect August, 1997

## Part 11 Guidance

- Part 11 Scope and Application Guidance (Aug 2003)
- Computerized Systems used in Clinical Investigations (May 2007)
- Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (Dec 2009)

# Regulatory Challenges

- Requirements for clinical data *do not change* for paper, computer, or hybrid approaches
- Computerized systems should meet all regulatory requirements with the same degree of confidence as that provided with paper systems.

# General Suggestions

- Utilize appropriate controls to ensure that e-records/data and electronic signatures are *trustworthy, accurate, and complete*
- Use appropriate controls to ensure that clinical data are *protected* so that study related activities *can be reconstructed*
- Use a *risk-based approach* for designing/utilizing computerized systems for clinical data
  - flexible regulations support a risk based approach (e.g., case history, monitoring)

# Inspection Expectations

- Records must to preserved to meet regulatory requirements
  - Available for FDA inspection and copying
  - Retained for appropriate length of time
  - **Independently preserved at clinical site** and/or some other designated site (e.g., technology provider)
- Audit trails are not explicitly required in GCP/HSP regulations; however to reconstruct study, we need these details

# 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 (cont)

2 things could have been done differently:

- 1) The Clinical Investigator 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 the data transmitted from the PDA was accurate, complete and worked successfully

## Case Example 2

- 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 2 (cont)

- 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?

Yes (Go To Question 2)      - Branch To ----->

No (Go To Question 3)      - Branch To ----->

2. What year are you in?

Freshman      - Branch To ----->

Sophomore      - Branch To ----->

Junior      - Branch To ----->

Senior      - Branch To ----->

Graduate      - Branch To ----->

Go to Question 4



## Draft eSource Guidance

# *Electronic Source Documentation in Clinical Investigations*

## FDA Draft Guidance Overview

<http://www.fda.gov/downloads/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/UCM239052.pdf>

## Guidance Overview

- Defining Electronic Source (eSource) Data & Documentation with common examples
  - Data Elements & Data Element Identifiers
- Electronic creation, modification, transmission, and storage of eSource (3 Tiers of Data)
- Investigator Responsibilities for review, archiving, and transmission of eSource clinical data
  - Data Integrity & Communication with Sponsor
- Information Sponsors should provide as part of protocol, investigational plan, and site inspections

## Definition of eSource

- *eSource documents* and *eSource data* are used to describe source documents and source data for which the original record and certified copies are initially captured electronically
  - ePRO
  - eCRFs
  - Electronically generated lab reports
  - Medical Images

# Investigator Responsibilities

- The eCRF should permanently carry the electronic signature of the investigator who reviewed it
- The clinical investigator should generate a write-protected copy of the eCRF for the study archives following review & sign off
  - Make available for purposes of an FDA inspection
- When an investigator has transcribed data elements from paper documents into an eCRF, the investigator must also retain the paper documents for review by FDA

# Sponsor Responsibilities

- Protocol should include information about the intended use of computerized systems during the conduct of a clinical study
  - Description of the security measures employed to protect the data
  - Detailed diagram and description of the transmission of electronic data
- Describe electronic tools intended to be used to detect events in the eCRF such as, but not limited to, data inconsistencies, missing data, and entries out of range



# References

- Preamble to 21 CFR 11
  - [http://frwebgate.access.gpo.gov/cgi-bin/getpage.cgi?position=all&page=13430&dbname=1997\\_register](http://frwebgate.access.gpo.gov/cgi-bin/getpage.cgi?position=all&page=13430&dbname=1997_register)
- Part 11 regulation
  - <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11>
- Part 11 Scope and Application Guidance
  - <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126953.pdf>
- Computer Systems Used in Clinical Investigations
  - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf>
- Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims
  - [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf)