Electronic Health Records and Clinical Data Interchange Standards

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US Food and Drug Administration
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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Acknowledgements

• Becky Kush, CDISC
• Chuck Cooper, (formerly FDA/CDER)
• Ron Fitzmartin, FDA/CDER
• Shannon Labout, CDISC
• Lilliam Rosario, FDA/OTS
Science, Statistics and Experimental Design

Science is concerned with understanding variability in nature.

Statistics is concerned with making decisions about nature in the presence of variability.

Experimental design is concerned with reducing and controlling variability in ways which make statistical theory applicable to decisions about nature.

Data Transparency

- Patients and their physicians depend on clinical trials for reliable evidence on what therapies are effective and safe.
- Responsible sharing of the data gleaned from clinical trials will increase the validity and extent of this evidence.
My Assumptions – What You Have Already Learned in this IPPCR Course

- Good Clinical Research Practice
  - Design
  - Conduct
  - Statistical Analysis
  - Legal and Ethical Principles
- Data Management
- Drug Development
- FDA Product Regulation
Steve’s Black Box Warning

• FDA/CDER-Centric -- There are regulation/guidance differences between Centers at FDA
• FDA regulation /guidance codifies Good Research Practice
• Primary focus: Confirmatory (Phase III) Trials
• A CDER statistical reviewer perspective
• If you feel that your clinical research will contribute to the development of marketed medical products ... please pay special attention
• Good clinical research practice is a global concern
Outline

• Substantial Evidence and FDA/CDER Review of Confirmatory (Phase 3) Clinical Trials

• CDISC Data Standards
  – New CDER/CBER Requirements
  – CDISC Basics

• Using eHealth Records in Clinical Research for Drug Development
FDA Mission

• FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.

• FDA is responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.
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NDA/BLA Review at CDER
(Center for Drug Evaluation and Research)
Almost all clinical research associated with New Drug Applications (NDAs) and Biologics License Applications (BLAs) are reviewed by CDER.

Within CDER -- Primary offices for planning and review of clinical trials:
- Office of New Drugs (OND)
- Office of Biostatistics (OB)
Office of Biostatistics (OB)
Statistical Review Staff
We Worry About Bias That Will Affect Our Decisions – Due Decision Diligence (DDD)

Bias is a preconceived personal preference or inclination that influences the way in which a
- measurement
- analysis
- assessment
- or procedure
...is performed or reported
Always a Risk-Benefit Decision
We Worry About Bias
We Worry About Bias
Substantial Evidence / Adequate and Well-Controlled Studies

• The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of section 505 of the act.

• Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs.
ICH E9 – Confirmatory Trials

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

Recommended for Adoption
at Step 4 of the ICH Process
on 5 February 1998
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
FDA’s “Gold Standard” for Approval

• NDA/BLA
• Two adequate and well-controlled, confirmatory clinical trials (AWCCCT)
• Pre-specified endpoint(s), sample size & analysis
• Two-sided, p-value < 0.05
• Clinical benefit
21st Century Review of NDAs/BLAs

CDER 21st Century Review Process

Desk Reference Guide

New Drug Application and Biologics License Application Reviews
(NDA/BLA Review Process)

Version: September 2012
Answering Some Review Questions

- Assess compliance with protocol / blinded analysis plans
- Assess traceability and quality of submitted data
- Verify results reported in the NDA.
- Check appropriateness of statistical models and conclusions.
- Assist DSI in planning investigator audits
- Modify models and assess robustness/sensitivity of the results.
- Evaluate Patient entry errors (cancelled patients, ineligible patients)
- Determine impact of “non-evaluable” patients
- Assess extent and potential impact of missing data
- Check consistency of results within and across studies
- Examine the trial and data for bias:
  - Results by center
  - Treatment assessment
  - Baseline predictors
  - Important subgroups (sex, age, race, etc.)
- Assess impact of audits
The Call from a CDER Reviewer

SHOW ME THE DATA!
Review Tools: Patient Profiles

Korvick & Szarfman, 2000
Review Tools: OCS/CSC JumpStart Service

- Provides a recommended sequence for using the outputs
- Allows reviewer to follow a safety signal from a high-level to the specific patient details with complementary tools

MAED: System Organ Class
Identifies a difference between treatment arms for both risk difference and relative risk.

MedDRA at a Glance Report
Shows same signal across multiple levels of the hierarchy for the treatment arm.

JReview: Risk Assessment
Magnifies the safety signal when viewing patients that were not treated with the study drug.

JReview: Graphical Patient Profile
Shows which patients experienced the Adverse Event shortly after taking a specific concomitant medication.

Rosario, 2014
OCS/CSC JumpStart Service

Starts a review by performing many standard analyses and identifying key information.
Required Submission of CDISC Standardized Data Standards

Published Final
Dec 17, 2014

Published Final
May 5, 2015

http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Fitzmartin, 2015
Required Submission of CDISC Standardized Data Standards

Published Final
Dec 17, 2014

Published Final
May 5, 2015

24 months after final guidance, sponsors must use standards identified by FDA (NDAs, ANDAs, BLAs).

http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Fitzmartin, 2015
The New Call from a CDER Reviewer

SHOW ME THE HIGH QUALITY, CDISC-STANDARDIZED DATA!
CDISC
Clinical Data Interchange Standards Consortium

- What is CDISC?
- Submission Data Standards to CDER
- Developing Ebola TAs
What is CDISC?
www.cdisc.org

• Global Standards Development Organization (SDO)
• Founded in 1997 (all volunteers)
• Incorporated in 2000 as a non-profit organization
• Over 300 member organizations
• 90 countries; Coordinating Committees in Europe, Japan, China, Asia-Pacific; 20 user networks
CDISC Vision and Mission

- **Vision:** informing patient care and safety through higher quality medical research.

- **Mission:** The CDISC mission is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare.

CDISC Standards …

• Streamline research processes and enable data sharing/aggregation
• Support all types of research from protocol through analysis and reporting
• Include link to healthcare through EHRs
Do you need Data Standards?

- Do you have limited time to complete research programs?
- Do you do protocol-based clinical research?
- Do you annotate, acquire, aggregate, analyze, archive data?
- Do you want high quality data?
- Do you have limited resources?
- Do you want to save time and costs?
Do you need Data Standards?

If you said Yes! to any of these – you need standards!
Do you need CDISC?

- Do you intend to or have you acquired another company or organization?
- Do you submit data to the US FDA or to PMDA?
- Do you want to retrieve data from EHRs?
- Do you work with partners (CROs, technology providers, research partners)?
- Do you need to be transparent and compliant?
- Do you track and report safety data?
- Do you need patients and investigators?
Do you need CDISC?

Do you want to retrieve data from EHRs?

Do you submit data to the US FDA or to PMDA?

Do you need to be transparent and compliant?

Do you track and report safety data?

Do you intend to or have you acquired another company or organization?

If you said Yes! to any of these – you need global community-wide standards!
CDISC Data Standards in the Clinical Research Process

Planning → Data Collection → Data Tabulations → Analysis → Reporting

CDISC Standards support the process from end to end

Adapted from Kush and Howard, CDISC, 2014
CDISC – End to End (quality, speed, provenance)

Adapted from Kush and Howard, CDISC, 2014
CDISC Data Standards for Submission to CDER

- Study Data Tabulation Model (SDTM)
- Analysis Data Model (ADaM)
- Therapeutic Area (TA) Standards
Study Data Tabulation Model (SDTM)

Adapted from Kush and Howard, CDISC, 2014
Basic Concepts of SDTM

One model – multiple implementations

- Pre-clinical (SEND)
- Clinical (SDTMIG)
- Therapeutic areas / Devices / PGx

Model concepts

- Standard variable names
- Standard list of values (CT)
- Standard sets of data (domains) with standard names
- Standard data types, formats and other attributes
- Standard assumptions for implementation
- Standard way to submit “non-standard” variables

Designed to hold anything you collect

Backward compatible, but evolving

Adapted from Kush and Howard, CDISC, 2014
Value of SDTM

Originally designed as a standard for data submissions to regulators to support

- Initial review of the data
- Warehousing of the data
- Data mining

Potential to improve the review / approval process

Supports data warehousing / data mining for organizations

Creates the opportunity of re-usability for organizations

Facilitates collaborations, acquisitions, mergers

Adapted from Kush and Howard, CDISC, 2014
Without SDTM ...

Variability ...

Study #2 – dmg.xpt

<table>
<thead>
<tr>
<th>ID</th>
<th>GENDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
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<tr>
<td>A2</td>
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<tr>
<td>A3</td>
<td>Female</td>
</tr>
<tr>
<td>A4</td>
<td>Female</td>
</tr>
<tr>
<td>A5</td>
<td>Male</td>
</tr>
</tbody>
</table>

Subject identifiers look different in every study…not clear if the same person was in more than one study.

Study #4 – axd222.xpt

<table>
<thead>
<tr>
<th>USUBID</th>
<th>SEX</th>
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</thead>
<tbody>
<tr>
<td>00011</td>
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<tr>
<td>00012</td>
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<td>00013</td>
<td>1</td>
</tr>
<tr>
<td>00014</td>
<td>0</td>
</tr>
<tr>
<td>00015</td>
<td>1</td>
</tr>
</tbody>
</table>

Gender or Sex, which one will this study use?

Adapted from slide courtesy of Armando Oliva, M.D. and Amy Malla, FDA

Name for demographics dataset varies

Name for Subject ID is never the same

Is Sex Male or Female, M or F, 1 or 2?
With SDTM
No Variability!

Column Header (Variable) for Subject ID is always same

Name for demographics dataset always the same!

Study #1 – DM.xpt

USUBJID | SEX
---|---
ABC-001 | M
ABC-002 | F
ABC-003 | F
ABC-004 | M
ABC-005 | F

Study #2 – DM.xpt

USUBJID | SEX
---|---
DEF-001 | M
DEF-002 | M
ABC-001 | M
DEF-004 | F
DEF-005 | M

Study #3 – DM.xpt

USUBJID | SEX
---|---
JKL-011 | M
JKL-012 | F
GHI-003 | F
JKL-014 | M
JKL-015 | F

Study #4 – DM.xpt

USUBJID | SEX
---|---
GHI-001 | M
GHI-002 | M
GHI-003 | F
GHI-004 | F
GHI-005 | M

Consistent format and standard definition for USUBJID makes it clear which subjects were in more than one study

Sex is always reported using the same variable

Adapted from slide courtesy of Armando Oliva, M.D. and Amy Malla, FDA
SDTM Logically Organizes Data

**Trial Design Data**
- TE (Trial Elements)
- TA (Trial Arms)
- TV (Trial Visits)
- TD (Trial Disease Assessments)
- TI (Trial Inclusion/Exclusion Criteria)
- TS (Trial Summary Information)

**Subject Data**
- General Observation Class Domains
  - VS (Vital Signs)
  - LB (Lab Results)
  - EG (ECG Results)
  - FA-- (Findings about…)
  - AE (Adverse Events)
  - MH (Medical History)
  - DS (Disposition**)
  - EX (Exposure**)
  - CM (Con Meds)
  - SU (Substance Use)

**Special Purpose Domains**
- SE (Subject Elements)
- SV (Subject Visits)
- CO (Comments)

**General Observation Class Domains (Standard Variables)**
- VS (Vital Signs)
- LB (Lab Results)
- EG (ECG Results)
- FA-- (Findings about…)
- AE (Adverse Events)
- MH (Medical History)
- DS (Disposition**)
- EX (Exposure**)
- CM (Con Meds)
- SU (Substance Use)

**General Observation Class Domains (Non-Standard Variables)**
- RELREC (Related observations, stored in separate datasets. are identified and linked),

**Associated Persons Data**
Mimics Subject Data structure, but used for data about persons who are not subject in the trial, but whose data is useful for the study, such as parents, siblings, device operator who experiences an Adverse Event with the device.

Gary Walker, Quintiles
Analysis Data Model (ADaM)

Adapted from Kush and Howard, CDISC, 2014
Basic Concepts of ADaM

- Standard presentation of analysis data
- Supports the analyses in the CSR
- “One PROC away from TLFs”
- With the ADaM Define-XML, provides traceability back to SDTM

Adapted from Kush and Howard, CDISC, 2014
Value of ADaM

Describes consistent presentation of analysis data

- Flexible enough to support the analysis
- Standardized enough to support regulatory review needs

Provides part of traceability from analysis results back to CRFs

Describes standardized approach to common analyses, e.g., AE, Time to Event

Adapted from Kush and Howard, CDISC, 2014
OCS/CSC JumpStart Service

Starts a review by performing many standard analyses and identifying key information.
CDASH – Data Collection

Adapted from Kush and Howard, CDISC, 2014
Ebola Virus Disease Case Study - Global Harmonization to Increase Power and Accelerate Outcomes in Clinical Research Data

Facilitator: Shannon Labout
Vice President Education
CDISC
A Case Study: A Randomized, Controlled Trial To Evaluate Ebola Therapies

Dionne L. Price, Ph.D.
Director, Division of Biometrics IV
OB/OTS/CDER/FDA
Setting the Stage and Understanding the Challenges of Ebolavirus Disease Clinical Research

Laura Merson, Clinical Trialist, Oxford University

Consulting Expert to CDISC Ebolavirus Therapeutic Area standards development team
Leveraging CDISC standards to support Ebola research

- Maura Kush, Pharmastat consultant
- Co-lead of CDISC Ebolavirus Therapeutic Area standards development team
WHO CORE CRF Annotations
Efforts to standardize data collection and reporting began last October.

Started to annotate CRFs we received from the Oxford University Clinical Research Unit (OUCRU) using CDASH and SDTM variables:

- EVD CORE CRF (World Health Organization)
- RAPIDE BCV (Chimerix)
- Plasma Convalescence

Ended up with a finalized four-page CRF the WHO shortened to only collect the most important, pertinent information.
Development of an EVD-specific Standard

- Project Team includes representatives from Oxford, CDISC teams, government, and pharma
- Face-to-face meetings at CDISC Interchange Conferences in November 2014 (Washington, DC) and May 2015 (Basel, Switzerland)
- Following the CDISC Standards Development Process (COP-001) for TA standards
Expanding CDISC Standards

► Most variables and terms can be taken from the existing SDTMIG and TAUGs (TB/Virology/Hepatitis C)

► Epidemiological data presents an opportunity for growth

► TB TAUG contains some ‘contact investigation’ criteria, controlled terms in SC domain:
  – CNTCINV, CTRYDDTC, CTRYDEXP, EDLEVEL, EMPJOB, JOBCLAS, NATORIG, PRICON, RISKPOP, RISKSOC, SETCON, SRCCSINV, TYPCON

► Terms may need to be added
  – Discussion in Basel of a new ‘Contact Investigation’ domain, or a set of implementation rules to assist the collection and reporting of epidemiological data
What’s next?

- Broadening use of CDISC standards from the traditional clinical trial setting to outbreak and public health situations

- For Ebola, this includes:
  - Names, surnames, addresses using GPS coordinates
  - Death occurring pre-’exposure’ or pre-’admission’
  - Contact investigation information
    - Friends/family (names and addresses using GPS coordinates), healthcare workers, animals
  - Missing information

- Ensuring broad public review of the EVD draft standard will ensure that it will be useful for research on future outbreaks of EVD and related viruses
How can this be done?
CDER e-Source Guidance

“…promotes capturing source data in electronic form…,”

[assists] “in ensuring the reliability, quality, integrity, and traceability of electronic source data.”
“Real World Data”
Rob Califf and Rachel Sherman, FDA 12/10/2015

• Networked systems, electronic health records, electronic insurance claims databases, social media, patient registries, and smartphones and other personal devices together comprise an immense new set of sources for data about health and healthcare.

• ... these “real-world” sources can provide data about patients in the setting of their environments—whether at home or at work—and in the social context of their lives

“Electronic health records: new opportunities for clinical research”

• ... emerging research infrastructures are being developed to ensure that EHRs can be used for secondary purposes such as clinical research, including the design and execution of clinical trials for new medicines.

• ...EHR systems should be able to exchange information through the use of recently published international standards for their interoperability and clinically validated information structures (such as archetypes and international health terminologies), to ensure consistent and more complete recording and sharing of data for various patient groups.

Coorevits, et al., 2013
Electronic Health Records (EHRs)

- Digital versions of a medical chart
- Real-time, patient-centered records
EHR in Clinical Research

- EHR – EDC - eSource
- eCRF
- Use of remote data capture (RDC) is increasing
  – Oracle Clinical, Clintrial, Macro, Rave, eClinical Suite
- Electronic CRFs
What can EHRs do?

- Make patient information easier to find
- Automate providers' workflows
- Provide evidence-based tools
- Support changes in insurance requirements
What are the benefits of EHRs?

**Improved**
- quality of patient care
- accuracy of diagnosis
- care coordination

**Increased**
- patient participation
- practice efficiencies
- cost savings
EHR vs EMR

“An EHR is an EMR with interoperability.”

- **Electronic Medical Record**
  - Medical and treatment history of patients in one practice

- **Electronic Health Record**
  - Information can be shared
  - Information from all clinicians involved

Example -- Weight

Patient’s **weight**  EDC:

1. Pull up the patient in EHR and EDC (one system on each monitor)
2. Print out EHR form
3. Write the cycle and week on the document
4. Hole punch and insert the form into the patient “Chart” (manila folder)
5. Locate patient’s weight on the form and enter it into EDC
6. Redact the patient health information (PHI) on the form with adobe
7. Add a header (trial, id, week/cycle, title, date) to the form
8. Save the form (format: date, ID, cycle #, form name) to a Shared folder
9. Attach the document in EDC as source data in the comments section
Source Data Capture From Electronic Health Records: Using Standardized Clinical Research Data

A Notice by the Food and Drug Administration on 06/26/2015

ACTION
Notice.

SUMMARY
The Center for Drug Evaluation and Research (CDER) is interested in supporting demonstration projects to test the capability and evaluate performance of using an end-to-end Electronic Health Record (EHR)-to-Electronic Data Capture (EDC) single-point data capture approach, using established data and implementation standards in a regulated clinical research environment. A demonstration project should ideally test the use of a standards-based technology solution to...
Source Data Capture from Electronic Health Records (EHRs)

Using Standardized Clinical Research Data

The Center for Drug Evaluation and Research (CDER) encourages seamless exchange of structured, re-usable information between health care and clinical research systems so that data may be entered once at the point of care and used many times without manual re-entry or manual source data verification. In September 2013, FDA published the Electronic Source Data in Clinical Investigations guidance promoting the need for capturing source data in electronic form including data originated in health care systems. To achieve this goal, CDER is interested in fostering collaboration of regulated industry, EHR and Electronic Data Capture (EDC) vendors, academic medical centers, and Standards Development Organizations (SDOs) and other parties. On June 26, 2015, the Center...

Proposed Demonstration Solutions

Table 1 summarizes proposed solutions of various stakeholders as submitted to the Federal Register docket focused on Source Data Capture from Electronic Health Records: Using Standards Clinical Research Data.

**Table 1: Summary of Organizations and Proposed Demonstration Solutions**

<table>
<thead>
<tr>
<th>Number</th>
<th>Organization</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Medidata</td>
<td>Demonstrate interoperability between their EDC system, Medidata Rave, and an EHR system using the Integrating the Healthcare Enterprise (IHE) Retrieve Form for Data Capture (RFD) profile.</td>
</tr>
<tr>
<td>2</td>
<td>Crayne Consulting</td>
<td>Wombat, A scalable, open source technical solution, based on the mediator pattern.</td>
</tr>
<tr>
<td>3</td>
<td>Health Level Seven International (HL7)</td>
<td>Leveraging HL7 Fast Healthcare Interoperability Resources (FHIR) data standards and other standards such as Structured Data Capture (SDC) to encapsulate and transfer relevant data from the EHR to the EDC systems.</td>
</tr>
<tr>
<td>4</td>
<td>Society for Clinical Data Management (SCDM)</td>
<td>The Society proposes to be a consulting resource for organizations participating in the EHR to Electronic Data Capture demonstration.</td>
</tr>
<tr>
<td>5</td>
<td>OmniComm Systems, Inc.</td>
<td>Leverage OmniComm’s TrialMaster EDC product along with their suite of related clinical technologies (e.g., data management review capabilities, auto-encoding tools, Clinical Data Interchange Standards Consortium (CDISC) Operational Data Model (ODM) import listener and ODM import capability).</td>
</tr>
</tbody>
</table>
In Conclusion

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• CDISC Data Standards
  – New CDER/CBER Requirements
  – CDISC Basics
• Using eHealth Records in Clinical Research for Drug Development
Thank You for your attention!!

stephen.wilson@fda.hhs.gov

Adapted from Oliva,, 2007