The Future of Clinical Data in Clinical Research

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SBMF International Course on Clinical Research, Brazil
1 November 2008
What if….  

• … mobile devices were used regularly to collect patient data directly from the patient to EHRs?  
• ….research data could be acquired automatically from EHRs?  
• ….research data could be readily aggregated across studies, systems, therapies?  
• …informed healthcare decisions could readily be made from sufficient aggregated data?  
• …systems (EHRs, EDC tools…) were standards-based and interoperable globally?
Outline

- Current Clinical Research Technology Applications
- State of Clinical Healthcare Information Technology
- Linking Healthcare and Clinical Research
  - Standards - Value and Status
  - Process Opportunities
Use of Data Collection Technologies in Clinical Trials

Use of data collection technologies (eCRF & ePRO) as a percentage of total number of trials initiated.

(Global Survey, n=383)
Number of Applications in Use at Sites

Number of different data collection systems in use at sites in 2004.

Source: CDISC 2004 Research Project, Analysis Q200_1 & Q200_2
“The Plight of the Site”

• For clinicians doing research today…
  ~ 50-60 % of trials - data collected on paper (3- or 4-part NCR paper) and data are entered 4-7 times total, 2-3 times by the clinicians
  ~40-50% of data are collected by eClinical point solutions
  An average active study site has 3 disparate solutions

• To report an unexpected or serious adverse event does not fit into normal clinical care workflow and takes excessive time.
Clinical Back Office…

EDC Without Standards, courtesy Charles Jaffe, MD, PhD
The Clinical Development Cycle

- **Research Hypothesis**
  - PI or Trial Sponsor

- **Protocol Development**
  - PI or Trial Sponsor

- **Site/Trial Preparation**
  - Sites; Trial Sponsor; IRB

- **Subject Enrollment**
  - Sites

- **Trial Management**
  - Trial Sponsor; Sites

- **Data Collection, Monitoring, Processing**
  - Trial Sponsor; Sites

- **Data Analysis Reporting of Results**
  - Trial Sponsor

- **Regulatory Submission**
  - Trial Sponsor to Agency

- **Drug Approval Data Archiving**
  - Trial Sponsor; Sites
Current State of Clinical Data Transfer
Current State:
Costly and Time-consuming
Healthcare Delivery

- Patient Information
- Medical Records

Basic Clinical Research
- Investigator-Sponsored Data Acquisition, Analysis

Protocol-driven Clinical Trials
- Biopharmaceutical Industry-Sponsored Data Acquisition, Analysis

Insurance Claims

Publications

Regulatory Drug Approval
Electronic Health Records

• NEJM 359:1, 3 July 2008 (DesRoches et al.)
• Fully functional EHR
  – Recording demographic and clinical data
  – Viewing and managing lab results and images
  – Managing order entry (including ePrescribing)
  – Clinical decision support

• Summary Results
  – Physicians who use EHRs believe they improve quality of care; positive effects experienced on several dimensions; general satisfaction
  – 4% of 2,758 physicians in US use fully functional EHRs
  – 13% have a basic system
    • (mainly large medical centers; Western US)
Personal Health Records?

- Markle Foundation:
  “an electronic application through which individuals can access, manage and share their health information, and that of others for whom they are authorized, in a private, secure and confidential environment”

- Patients – ‘complete control over your data’

- Three major providers:
  - Dossia (founded by AT&T, Intel, Walmart and five other large US employers) - 2006
  - Microsoft HealthVault - 2007
  - Goggle Health – 2008

Many Others, e.g. France, Beth Israel’s MyChart, Private Companies
EHRs and PHRs – Usage and Opinions

  – Patients should have access to their own electronic medical record maintained by their physician – 91%
  – The benefits of electronic medical records outweigh the privacy risks – 60%
  – Current Usage (2,153 adults surveyed)
    • 23% - Doctor maintains EHR in office
    • 2% - Person maintains personal medical record on computer
    • 1% - Person uses health record with information on Internet
    • 56% - Do not use EHR
    • 17% - Not sure
Issues/Challenges – EHRs (and PHRs) -Barriers to Adoption

• Usage/Population of Records
• Privacy
• Security
• Data Integrity (including audit trails)
• Standardized Collection and Sharing of Information
• Functional Interoperability
• Others
“Research on the quality of care reveals a health care system that falls short in its ability to translate knowledge into practice, and to apply new technology safely and appropriately.”

“Much of the potential of IT to improve quality is predicated on the automation of at least some types of clinical data.”

- Application of promising IT applications/tools
- Glean knowledge from patient care
- Enable research on outcomes
- Identification of best practices

One of the key barriers to automation of clinical data is the need for standards.

Crossing the Quality Chasm, IOM, 2001
Clinical Data Interchange Standards Consortium

- Global, non-profit standards development organization (SDO)
- Open, consensus-based approach
- Charter Agreement with HL7 since 2001
- Liaison A status to ISO TC 215 (Healthcare)
- One of four SDOs in Joint Initiative Council for Interoperability (Global Healthcare Standards)
- CDISC Coordinating Committees in Europe, Japan and China
- Established worldwide industry standards to support the electronic acquisition, exchange, submission and archiving of clinical research data and metadata
- Standards are freely available at www.cdisc.org
Top Benefits of Adopting CDISC Standards

*By Company Type*

- **Improve Partner Data Exchange**: 76%
- **Improve Data Quality Early On**: 43%
- **Reduce Data Transfer Time**: 29%
- **Reduce Submission Effort**: 24%
- **Improve Overall Trial**: 19%
- **Provide Basis for Rapid Agreement**: 12%
Quantifying the Value of CDISC Standards

- Cycle Time (and Cost) Savings -

Note: Figures are benchmarks based on aggregate data; study-specific cycle times and cost metrics will vary.
Business Case – Summary Of Findings

*Process improvement through CDISC generates financial incentives*

1. Saving time and cost with CDISC standards
   - *Clinical study time (non-subject participation) reduced approximately 60%*
   - *Critical savings especially in study start-up stage*

2. Additional clinical research benefits from standards
   - *Increased data quality and integrity*
   - *Improved data integration enhancing re-usability of data*
   - *Streamlined data interchange among partners*
   - *Simplified review of regulatory submissions*
   - *Improved data integration from disparate tools/technologies*
   - *Improved communication among project team members*

*Note: Actual savings will vary per company and study*
One Experience

“We avoided the requirement to run 3 studies at a saving of around £15 million by conducting analyses of aggregated data; we got a paediatric indication for a drug approved by analysing aggregated data rather than by running a study/studies. In both cases, we saved considerable time to boot (undoubtedly >1 year, but maybe quite a bit more than that).”

Source: Simon Bishop, GSK
<table>
<thead>
<tr>
<th>CDISC Standards</th>
<th>Description</th>
<th>Implementation Version Release Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDTM, SEND</td>
<td>Ready for regulatory submission of CRT Over 14,000 downloads as of mid-2008</td>
<td>2004*</td>
</tr>
<tr>
<td>ODM</td>
<td>CDISC Transport Standard for data interchange (acquisition, exchange, documentation and archive)</td>
<td>2001*</td>
</tr>
<tr>
<td>Define.xml</td>
<td>Case Report Tabulation Data Definition Specification (submission documentation)</td>
<td>2005*</td>
</tr>
<tr>
<td>LAB</td>
<td>Content standard – available for transfer of clinical lab data to sponsors</td>
<td>2002</td>
</tr>
<tr>
<td>ADaM</td>
<td>Analysis data for submissions - general considerations document and examples</td>
<td>2004</td>
</tr>
<tr>
<td>Protocol Representation</td>
<td>Collaborative effort to develop machine-readable standard protocol with data layer</td>
<td>2008</td>
</tr>
<tr>
<td>Terminology Codelists</td>
<td>Developing standard terminology to support all CDISC standards</td>
<td>2008 (SDTM 3.1.1 and CDASH)</td>
</tr>
<tr>
<td>CDASH</td>
<td>Data acquisition (CRF) standards</td>
<td>2008</td>
</tr>
</tbody>
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* Specification referenced via FDA Final Guidance
FDA endorses CDISC standards by including them as specifications in FDA Final Guidance

FOR IMMEDIATE RELEASE
P04-73
July 21, 2004

FDA Announces Standard Format That Drug Sponsors Can Use to Submit Human Drug Clinical Trial Data

The Food and Drug Administration (FDA) today announced a standard format, called the Study Data Tabulation Model (SDTM) developed by the Clinical Data Interchange Standards Consortium (CDISC), that sponsors of human drug clinical trials can use to submit data to the agency. It is expected that this step will lead to greater efficiencies in clinical research and FDA reviews of New Drug Applications (NDAs).

Study Data Tabulation Model, define.xml (CRTDDS), Operational Data Model (ODM): Specifications for FDA implementation of the ICH eCommon Technical Document – Final Guidance

October 2005 – Federal Register Notice of Proposed Rule and listed as DHHS Priority
“Standard” Controlled Terminology - Collaboration

Global Pharma & CROs
FDA & Academia
International SDOs
Vocabulary Developers

CDISC Terminology Director also co-leading ISO Terminology groups & working with ICH and HITSP
## The Importance of Global Controlled Terminology

### AE Relatedness to Study Drug

**Company 1**
- No
- Unlikely
- Possible
- Definite
- Probably

**Company 2**
- Not Related
- Doubtful
- Possible
- Very Likely
- Probable

**Company 3**
- NO
- YES / Unknown

**CDISC AEREL codelist**
Tufts Survey 2007: Standardization & CDASH

- 97% of participants would find it valuable if the content and format of data collection instruments were standardized

- 100% of pharma/biotech participants would find it valuable if the content and format of data collection instruments were standardized, in comparison to 90% of CROs
CDASH Snapshot

- Addresses Critical Path Opportunity #45 – Streamline data collection at investigative sites.
- Continuation of ACRO’s Initiative
- Started October 2006
- Supported by a Collaborative Group of 17 organizations
- Core team of 16 members manages...
  - 11 working groups
  - Comprised of between 8-40 volunteers
- ~190 working group volunteers
- 16 Safety data domains developed.
- Received over 1800 comments from 46 Companies, Institutions and Agencies.
- All 3 ICH Regions were represented in the public comment process.
  - US
  - Europe
  - Japan
  And others, including China
- Product = CDASH V. 1.0
Clinical Data Acquisition Standards Harmonization

- March 2004 FDA White Paper
  “Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products”

- CPI Opportunities List
  TOPIC 2: STREAMLINING CLINICAL TRIALS
  - Creating Innovative and Efficient Clinical Trials and Improved Clinical Endpoints
  - Streamlining the Clinical Trial Process

  »Opportunity # 45. Consensus on Standards for Case Report Forms.

CDASH Version 1.0 Published
3 October 2008 – 16 domains
Data Flow Using CDISC

Protocol Representation
- Trial Design (SDTM)
- Analysis Plan

Clinical Trial Protocol

ODM XML

Clinical (CRF or eCRF)
- Trial Data (defined by SDTM)

(e)Source Document

Administrative, Tracking, Lab Acquisition Info

ODM XML

CRF, Analysis Data

ODM XML

Operational & Analysis Databases

ODM XML Define.xml

Integrated Reports
- SDTM Data, Analysis Data, Metadata

Reporting and/or Regulatory Submissions Warehouse

- ODM (transport)
- SDTM and Analysis Data (content)
- Protocol information (content)
- Source data (other than SDTM/CRF data)
The mission of CDISC is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare.
Data Flow Using CDISC Standard  Linking Clinical Research and Healthcare

Electronic Health Record

Patient Info
Clinical Trial Data

HL7 and/or ODM XML

Protocol Representation
Trial Design (SDTM) Analysis Plan
Clinical Trial Protocol

ODM XML

Patient Info
Clinical (CRF or eCRF) Trial Data (defined by SDTM)

(e)Source Document

ODM XML

Administrative, Tracking, Lab Acquisition Info
CRF, Analysis Data

ODM XML

Operational & Analysis Databases

Integrated Reports
SDTM Data, Analysis Data, Metadata

Regulatory Submissions

= ODM (transport)
= SDTM and Analysis Data (content)
= Protocol information (content)
= Source data (other than SDTM/CRF data)
“The same EHR systems critical for improving patient care can also help accelerate clinical research and its impact on practice and improve pharmaceutical safety (pharmacovigilance) and biosurveillance for public health...dual use of EHR systems that could reduce total system costs.”

Clinical Research Pathway with HITSP to begin November 2008.
Optimizing the Process

Healthcare Delivery  
(e)Source Documents  
EHR  

\textit{data conception}

\textbf{eSource}

\textbf{(e)CRFs}

Clinical Research

\textit{auto reconciliation}
Initiatives to Link Healthcare and Clinical Research

• BRIDG Model
• eSource Data Interchange Recommendations
• Functional Profiles
• Single Source Proof of Concept → IHE Integration Profile (RFD)
• HITSP Clinical Research Pathway
• JIC
• eHealth Call to Action
A clinical research domain analysis model (UML) initiated by CDISC, BRIDGing

- Organizations (CDISC, HL7, FDA, NCI)
- Standards
- Research and Healthcare

Towards semantic interoperability; a Portal to Healthcare

Open source; Collaborative Project

- See BRIDG Model on CDISC website
  or www.bridgmodel.org

*Biomedical Research Integrated Domain Group (BRIDG) Model*
Achieving Interoperability

BRIDG – Domain Analysis Model for Clinical Research
eSource Data Interchange (eSDI) Initiative

- CDISC requested by FDA to lead initiative as neutral, non-profit global organization

- **Purpose of eSDI Initiative**
  - *to facilitate the use of electronic technology in the context of existing regulations for the collection of eSource data in clinical trials for regulatory submission by leveraging the power of the CDISC standards, in particular the Operational Data Model (ODM).*

  - **Note**: eSource pertains to eDiaries, ePRO, eDCI, Electronic Health Records…
eSource Data Interchange (eSDI) Initiative

• Overarching goals:
  – to make it easier for physicians to conduct clinical research,
  – to collect data only once in an industry standard format for multiple downstream uses, and thereby
  – to improve data quality and patient safety

• Product is eSDI Document – www.cdisc.org
  – Requirements for eSource studies
  – 5 Scenarios (3 using EHRs)
  – Checklists for sponsors and investigators

• EMEA Document for GCP Inspectors: Expectations on eSource Documents Used in Trials - heavily references CDISC eSDI Document
Functional Profiles (HL7)

- EHR Functional Profile
- PHR Functional Profile
- EHR/Clinical Research Functional Profile Initiative
  - HL7 EHR Functional Profile standard modified to meet core requirements for regulated clinical research – HL7 May 2008 ballot (initiative led by PhRMA and eClinical Forum with HL7 and CDISC)
  - Cross-industry committee pursuing 2010 CCHIT certification as “Expansion” of EHR certification for the research population
CDISC Initiative: Healthcare Link

2004: Proof of Concept at DCRI and DUMC (Scenario #3 in eSDI document)

2006- present: Development, Demonstration and Implementation of an Integration Profile called Retrieve Form for Data Capture (RFD) using EHRs to do Clinical Research and Safety Reporting.

Led by Landen Bain, CDISC Liaison to Healthcare
Clinical Site Before and After RFD

- The site staff engage with just one system: the EHR
- The EHR takes over as the pivotal data broker
- Primary and secondary uses of data align

- Site staff must engage with multiple systems.
- Primary and secondary uses do not align.

Source: L. Bain, CDISC Liaison to Healthcare
THE FOUR STEPS OF THE IHE PROCESS

I. Identify Interoperability Problems.
II. Specify Integration Profiles.
III. Test Systems at the Connectathon and Demonstrate at the Interoperability Showcase at HIMSS.
IV. Publish Integration Statements for use in RFPs.

Interoperability Demo at HIMSS (Health Information Management Systems Society) – 2007 and 2008

IHE Connectathon
RFD in 2008

• In use for safety reporting by Pfizer - ASTER
• Plans for use in Japan for post-marketing surveillance
• Plans for use with CDASH as basis for CRFs
• In process to become ISO standard – passed first ballot – October at Istanbul
• Endorsed by EHR Association

“Many healthcare sites would like to participate in clinical research for the betterment of health science. If this participation is to be feasible to the sites, the burden of participation must be eased. RFD, collaboration between healthcare IT and clinical research sponsors, will open the door to widespread, cost-effective clinical research participation.”

• Charles Parisot, Chair, EHRA Standards & Interoperability Work Group
“We have not thought enough about health IT as a cost-effective form of therapy. Yet, the best evidence is that when used as intended, health IT saves lives and saves money.”

- A recent study showed that
  - clinical information is frequently unavailable in primary care;
  - this missing information can be harmful to patients;
  - clinical information was less likely to be missing in practices that had electronic health records.

Dr. David Brailer, HIMSS, 17 February 2005
Standardizing How We Share Information in Healthcare

John D. Halamka MD

Clinical Research Pathway now being initiated...

Sponsored by the HITSP Education, Communications and Outreach Committee
Joint Initiative Council (JIC)

- CDISC has Liaison A status with ISO TC 215 (Healthcare Informatics)
- Applied to JIC in January – accepted provisionally (6 months probation)
- Accepted for full membership July 2008

Joint Initiative on SDO Global Health Informatics Standardization
CHARTER

» Final (v8) – August 29, 2007
» Amended 6 August 2008
July 2007, Bellagio (Rockefeller Foundation)- Call to Action

- The vision: Better Health for All through Integrated eHealth Systems
  Integrated eHealth systems for everyone, everywhere which improve access to health services (promotion, prevention and care), enable better health system management, promote equity, and allow for better health and well-being of all people.

- Detailed themes include interoperable, standards-based systems

- Mottos:
  - Health for All by All
  - From silos to systems
  - Information is care
Insurance Claims

Basic Clinical Research
  Investigator-Sponsored Data Acquisition, Analysis

Protocol-driven Clinical Trials
  Biopharmaceutical Industry-Sponsored Data Acquisition, Analysis

Healthcare Delivery
  Patient Information

Shared Information

Publications

Regulatory Drug Approval
Patient Care
Clinical Decisions

Medical
Records

Research
Clinical Decisions

Patient Care

Medical

Research
Summary

• eClinical Technologies and EHRs/PHRs are being adopted, are becoming easier to use, and have achieved certain benefits....

• Standards
  – facilitate clinical research processes
  – streamline data interchange among various tools and partners
  – improve data quality thus patient safety
  – facilitate data integration downstream to populate knowledge warehouses that reduce costs and enhance pharmacovigilence

• Global standards development and adoption will enable interoperable systems and will streamline research for the benefit of patients.
CDISC operates to advance the continued improvement of public health by enabling efficiencies in medical research and related areas of healthcare.

As a catalyst for productive collaboration, CDISC brings together individuals spanning the healthcare continuum to develop global, open, consensus-based medical research data standards.

Strength through collaboration.
Knowing is not enough; we must apply.
Willing is not enough; we must do.

- Goethe-

To the gracious supporters who ‘apply’ and ‘do’…. THANK YOU!
The “Road” to Quality Clinical Data

- Build quality into the system
- Train and educate
  - site personnel, project team and reviewers/auditors
- Decrease the amount of data collected
- Define the data set needed and specify requirements
- Standardize formats and procedures
- Also plan for data quality during post-marketing
- Decrease the number of times data are ‘handled’

(Note: Anticipated ‘by-products’ of these steps to improve quality are increased efficiency and lower costs.)

Vision – Medical Innovation

Collect Data Once, (Various Sources)

“Rolling Warehouse” Multiple Downstream Uses

Standards: Real-time Integration

EDC

EHR

ECG

X-RAY

LAB

Regulatory Authority

Sponsor

Public Registries and IRBs

CRO or Partner
<table>
<thead>
<tr>
<th>Use Case</th>
<th>Sponsorship</th>
<th>Security Provided by</th>
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</thead>
<tbody>
<tr>
<td>Drug Safety</td>
<td>Pfizer</td>
<td>CDISC</td>
</tr>
<tr>
<td>Clinical Trial: Lab &amp; Image Data</td>
<td>Novartis</td>
<td></td>
</tr>
<tr>
<td>Clinical Trial: Visit Workflow</td>
<td>Lilly</td>
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<tr>
<td>Disease Registry</td>
<td>Genzyme</td>
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<tr>
<td>Bio-Surveillance</td>
<td>SAIC</td>
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</table>

SEC provided regulatory oversight.
Study on the Adoption and Attitudes of Electronic Clinical Research Technology Solutions and Standards 2007 – Summary Conclusions

- High levels of adoption – particularly for most mature/established technology solutions and standards categories
- Growing levels of usage across broad categories of solutions
- Higher levels of positive experience reported, especially for more mature and established technology solutions and standards; certain benefits achieved
- Shift in areas of concern to implementation-oriented issues vs. nascent/emerging adoption issues
Data Collection & Mgmt
Analyses & Reporting
Submission

Clinical Trial Tracking, Summary, Registry
Structured Eligibility Criteria
CDISC Trial Design Part I (arms, elements, visits)
CDISC Trial Design Part II Planned assessments & interventions (NCI Study Calendar)
CDISC Statistical Analysis Plan

CDISC SDTM Study Summary (subset of CTR)
Structured Eligibility Criteria
CDISC Trial Design Part I SDTM (arms, elements, visits)
CDISC Trial Design Part II SDTM Planned assessments & interventions (NCI Study Calendar)
CDISC Statistical Analysis Plan

Analysis Dataset Metadata
CRF Data (AE data) LAB Data Genomics Data ECG SAE Reports
CDISC Study Data Tabulation Model (SDTM) (CRF data and other, inc. SEND)
CDISC ADaM (analysis datasets)

Report and/or Submission Preparation

Report Template Content, etc
Clinical Research Trends

• Clinical research is becoming increasingly “global”
  – India, China, Latin America, Singapore…
  – Percentage of subjects from ex-US/EU is increasing; those from US/EU is decreasing
• FDA BIMO initiative to address a ‘quality system’
• CTSA initiatives to encourage partnering among research institutions
• Initiatives to improve safety monitoring
• Healthcare IT initiatives; use of EHRs and need for interoperability
• Need for transparency of clinical research information through publicly accessible registries and databases

• Incentive for electronic clinical trials; eSource data
• Important role of data interchange standards in all of the above