Clinical Research Standards and their Link with Healthcare

HIT Standards Committee
16 January 2013

Rebecca Kush, PhD
President and CEO, CDISC

Strength *through Collaboration*

Primary Topics

- The Opportunity to Link Healthcare with Research
- Standards and Enablers Available Now
- Standards in Progress
- Successes and Challenges
- Discussion

Information from healthcare (private, aggregated) to enable research

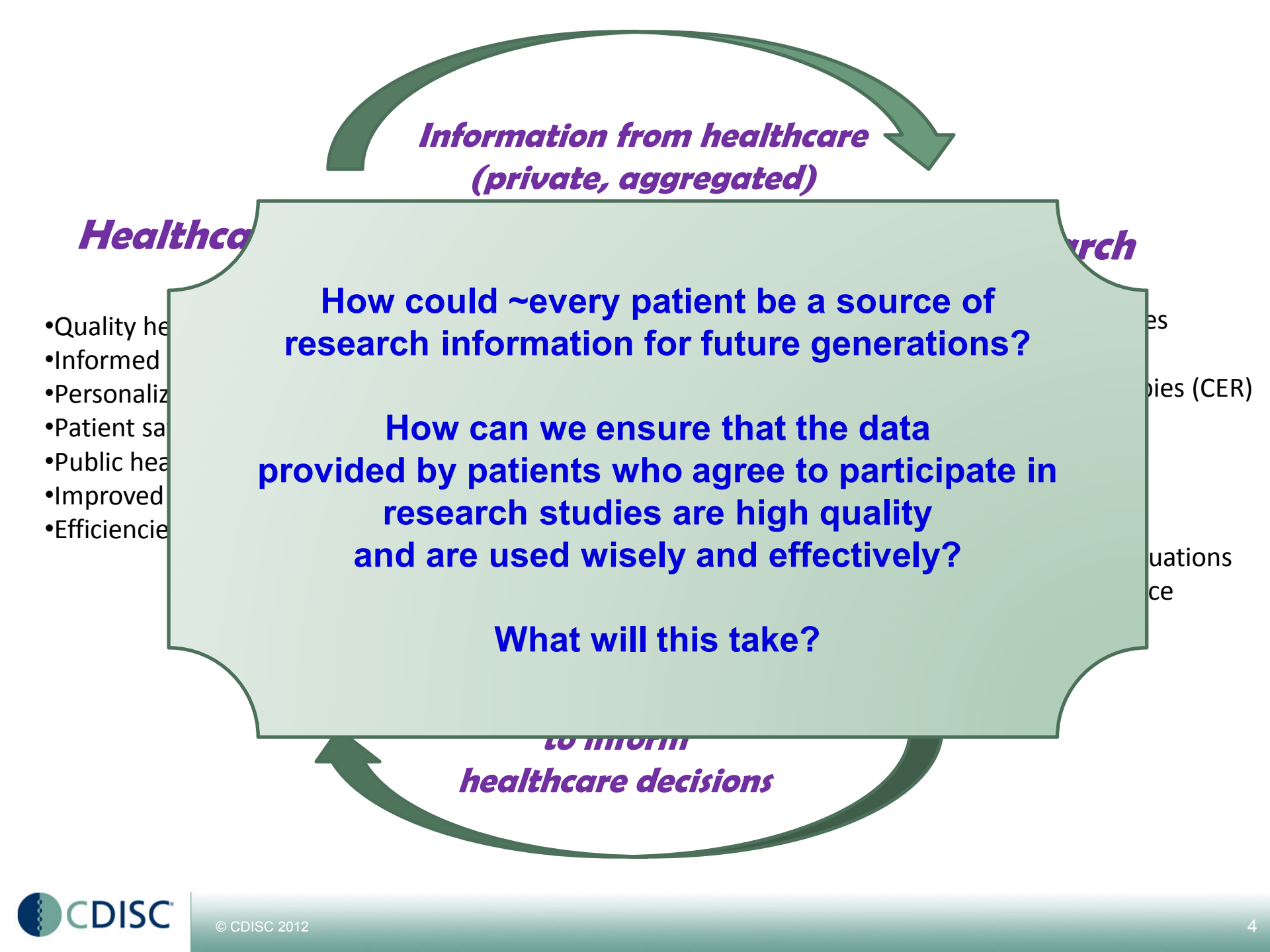
Healthcare

- Quality healthcare
- Informed decisions
- Personalized medicine
- Patient safety and privacy
- Public health
- Improved therapies
- Efficiencies/reduced costs

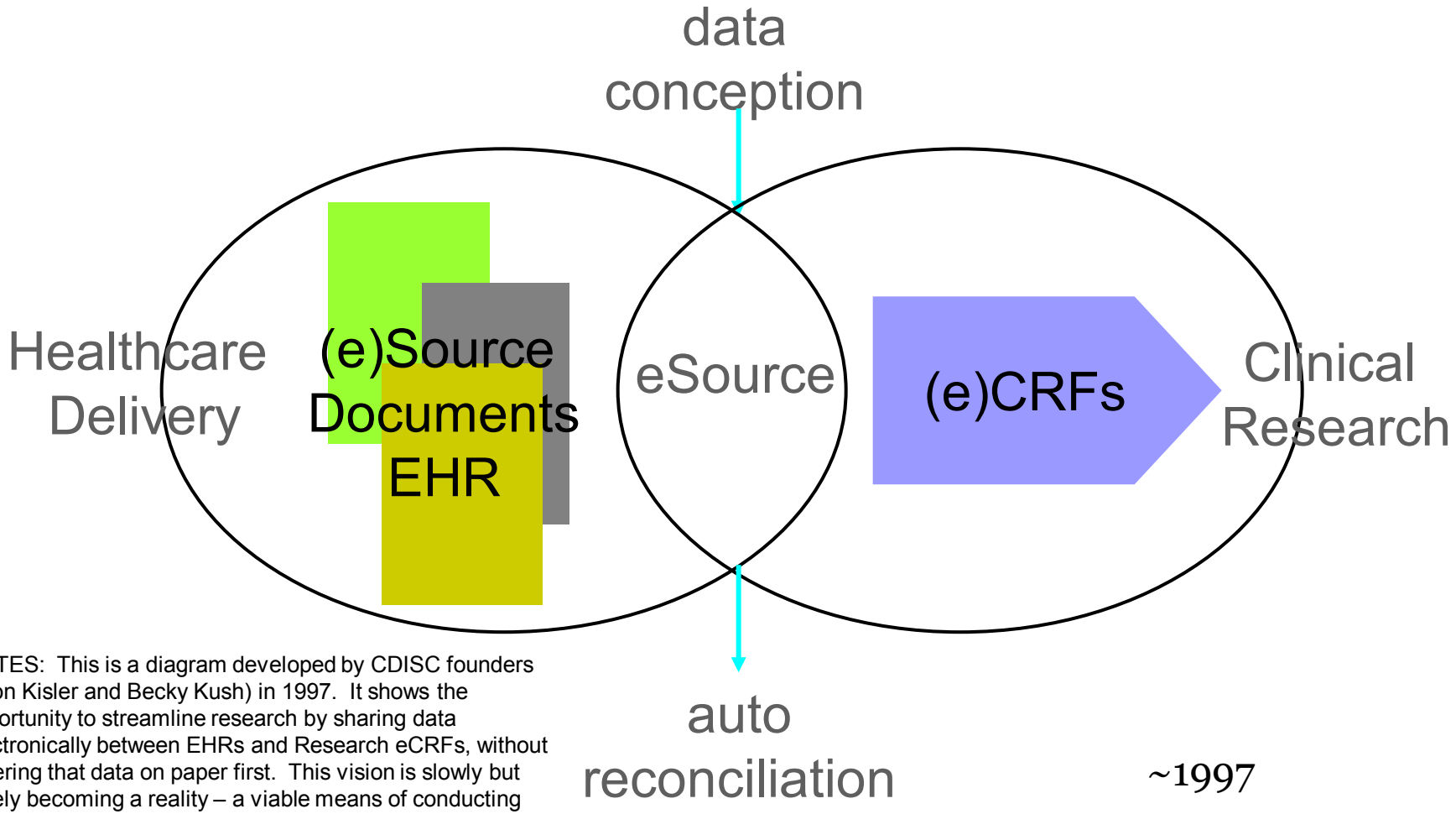
Research

- Discovery of new therapies
- Understanding diseases
- Testing/comparing therapies (CER)
- Assessing efficacy
- Monitoring safety
- Understanding responses (genomics, biomarkers)
- Public health/quality evaluations
- Post-marketing surveillance

Research findings to inform healthcare decisions


Information from healthcare
(private, aggregated)
Healthca
rch
•Quality he
•Informed
•Personaliz
•Patient sa
•Public hea
•Improved
•Efficiencie
es
ies (CER)
uations
ce
How could ~every patient be a source of research information for future generations?
How can we ensure that the data provided by patients who agree to participate in research studies are high quality and are used wisely and effectively?
What will this take?
to inform
healthcare decisions

CDISC Healthcare Link: Optimize the Research Process



NOTES: This is a diagram developed by CDISC founders (Bron Kisler and Becky Kush) in 1997. It shows the opportunity to streamline research by sharing data electronically between EHRs and Research eCRFs, without entering that data on paper first. This vision is slowly but surely becoming a reality – a viable means of conducting clinical research.

~1997

The Problem

Photos courtesy of Women's Clinic of Lincoln, NE

Research: Situation and Standards Requirements

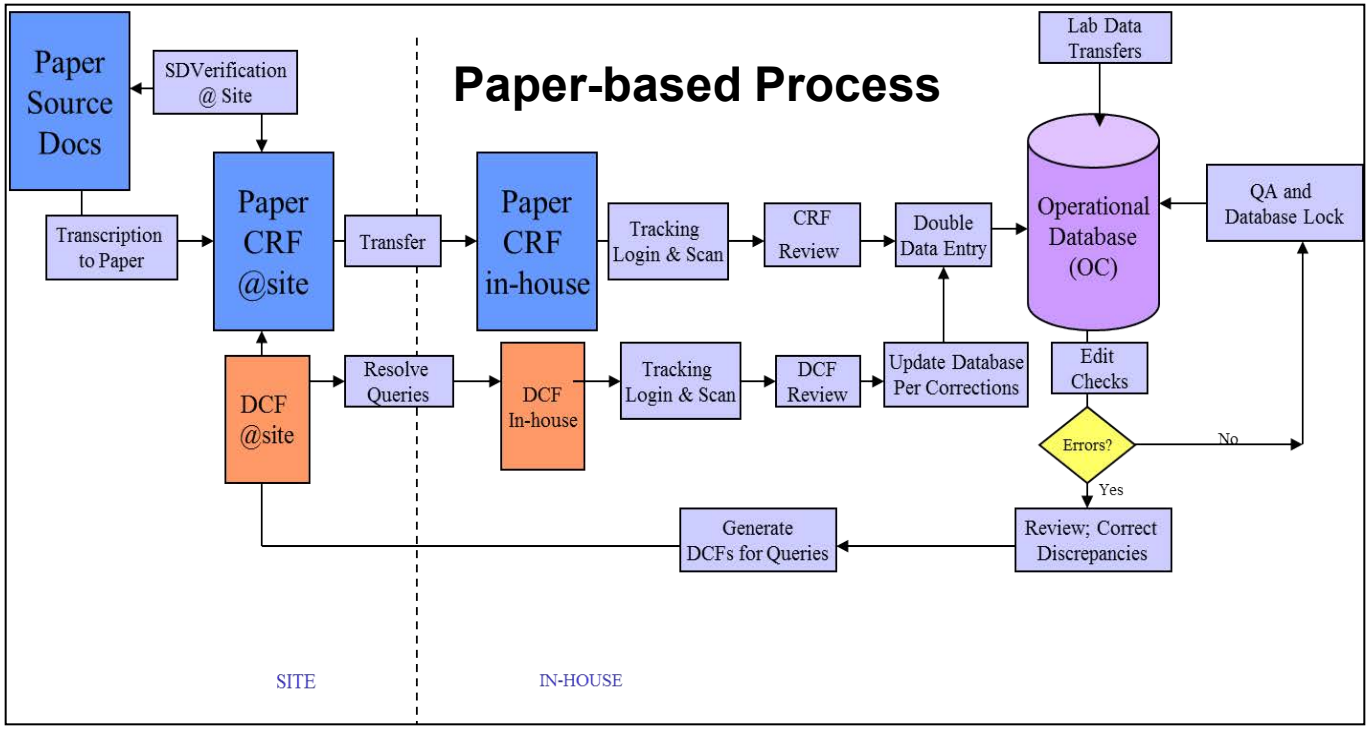
- "The Plight of the Site"
  - Paper-based studies required data to be entered 4-7 times; EDC requires transcriptions/re-entry 2-4 times
  - Most busy clinicians do one regulated clinical research study and no more
  - Thus, research studies are being "outsourced"
- Research is increasingly **global**
- Research must constantly address new questions to gain insight, learning from the prior studies
- Research standards, terminologies, metadata:
  - Maintenance must be "highly responsive"
  - Research standards should be global and freely available
  - Research standards must be 'fit for purpose' (including analysis)

Broad Definition of Clinical Research

Patient-oriented research is research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) in which a researcher/clinician directly interacts with human subjects.

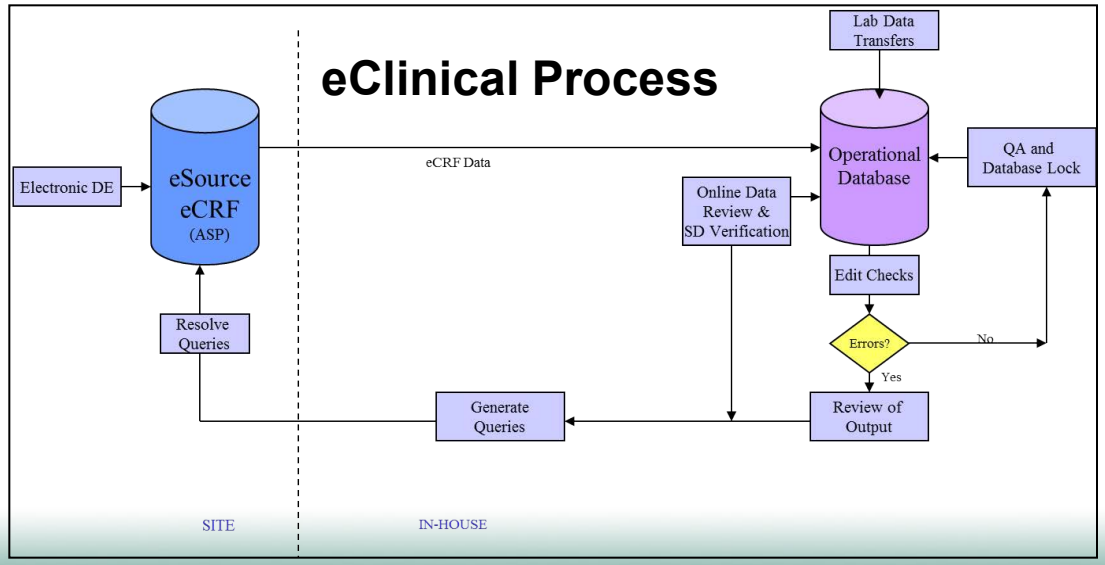
- epidemiologic and behavioral studies
- outcomes research
- health services research
- research on mechanisms of human disease, therapeutic interventions, clinical trials, and development of new technologies
- does not include *in vitro* studies using human tissues not linked to a living individual.

The Opportunity



Flow charts published in eClinical Trials book (CenterWatch, 2003)

It has taken >10 years for the technology and standards to be available such that we can now realize this vision.



Available Standards and Enablers

- *Suite of global consensus-based standards* to support common data from protocol representation through data collection, analysis and reporting (i.e. regulatory submissions or study reports for publication)
- *A model to harmonize all of the research standards and provide a link to healthcare standards*
- *Controlled terminology* for the research standards
- *Documentation for using EHRs and eDiaries for regulated research*
- *Integration profiles developed (and tested) with quality, research and public health experts to facilitate workflow for clinicians* using EHRs to provide high quality data for numerous secondary use cases

CDISC Snapshot

- Global, open, multi-disciplinary, vendor-neutral, non-profit standards developing organization (SDO)
- Founded 1997, incorporated 2000
- Member-supported (>300 member organizations: academia, biopharma, government, service and technology providers and others)
- Liaison A Status with ISO TC 215
- Charter agreement with HL7 (2001)
- Leadership of Joint Initiative Council (JIC) for Global Harmonization of Standards
- Member of ANSI-led ISO TAG
- Active Coordinating Committees (3C)
  - Europe, Japan, China
- >> 90 countries in participant database and/or downloading CDISC standards

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

CDISC Standards are freely available via the website www.cdisc.org

CDISC – Key Partnerships/Collaborations (Examples)

NATIONAL CANCER INSTITUTE

EVS ENTERPRISE VOCABULARY SERVICES

Controlled Terminology

CRITICAL PATH INSTITUTE
collaborate · innovate · accelerate

CAMD (AD, PD)
CPTR (TB)
…TA Standards

CFAST
Coalition For Accelerating Standards and Therapies

DukeMedicine
DCRI
CTRI

CV, TB, HL7 CIC Workgroup

TRI

Translational Research Informatics Institute (TRI) Kobe, Japan

Use of CDISC in research projects by academia funded by TRI.

imi
Innovative Medicines Initiative

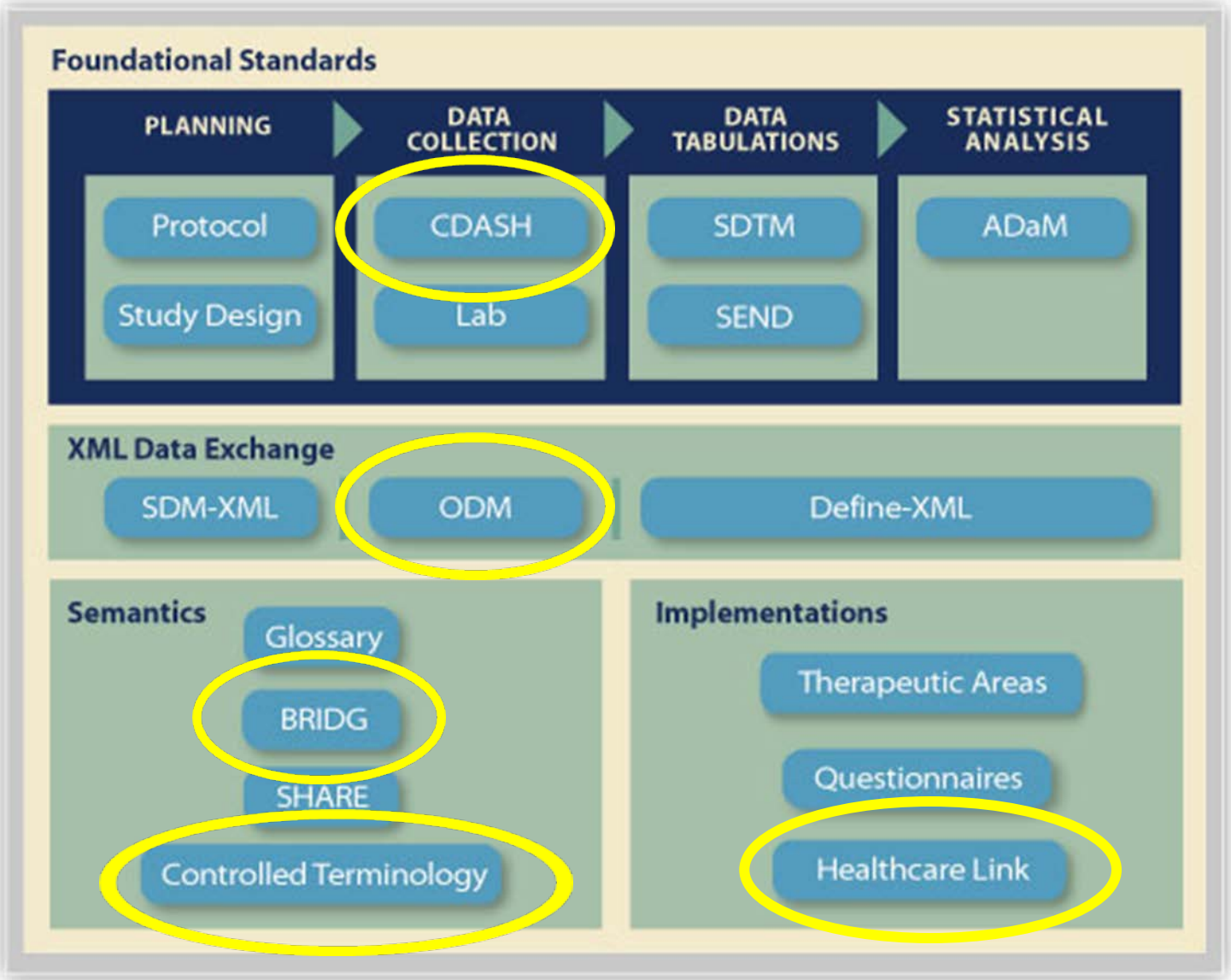
IMI = European Union and EFPIA; > 250 IMI consortia academics/SMEs are CDISC Members. Default is for IMI projects to use CDISC if available, If not, partner in developing new standard.

MAYO CLINIC

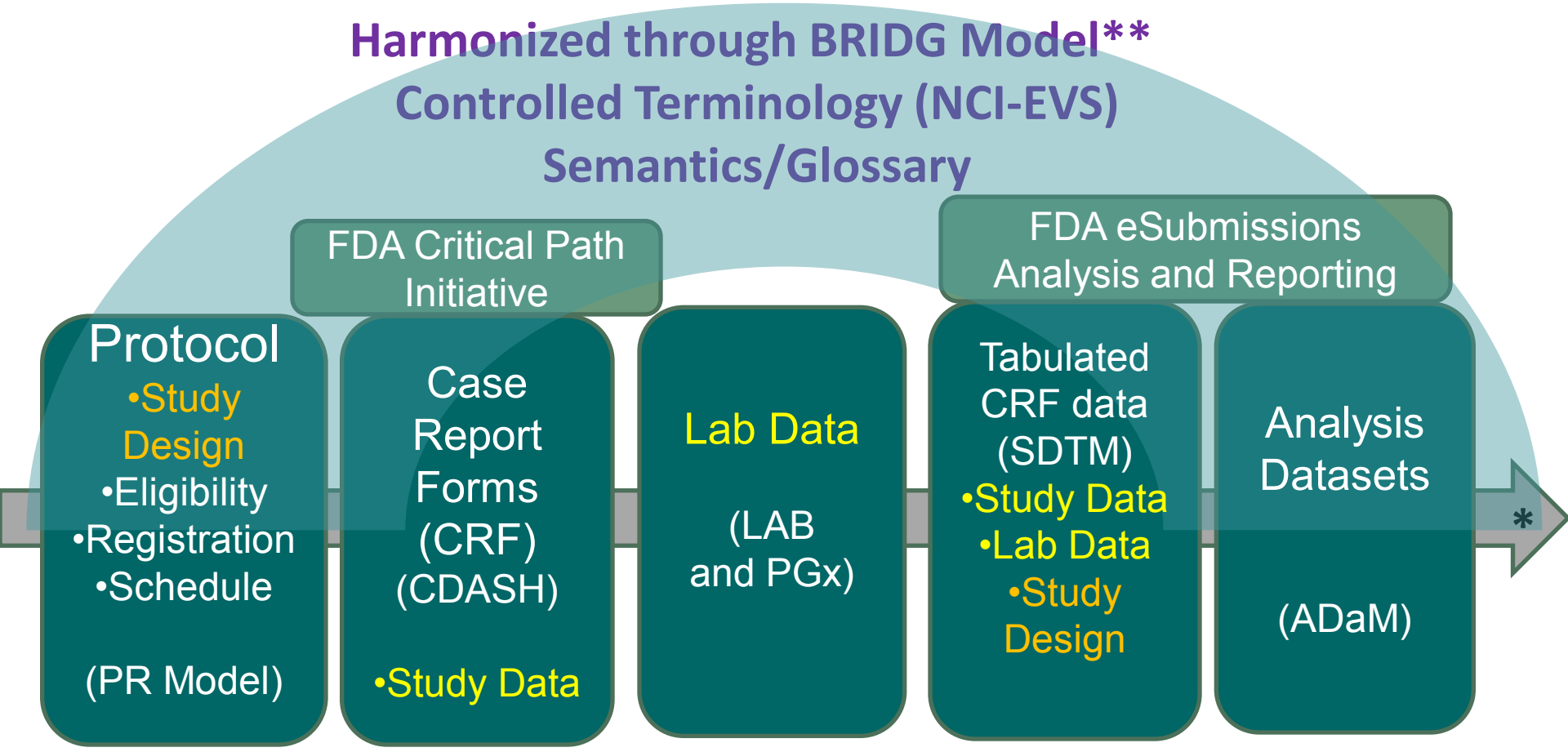
SHARPn.org

CDISC is known for bringing together the expertise of thousands of individuals from around the world toward productive collaboration to develop clinical research standards.

CDISC Global Standards – Research from Planning through Analysis/Reporting



Global Content Standards for Clinical Research (Protocol-driven Research; Protocol→Reporting)

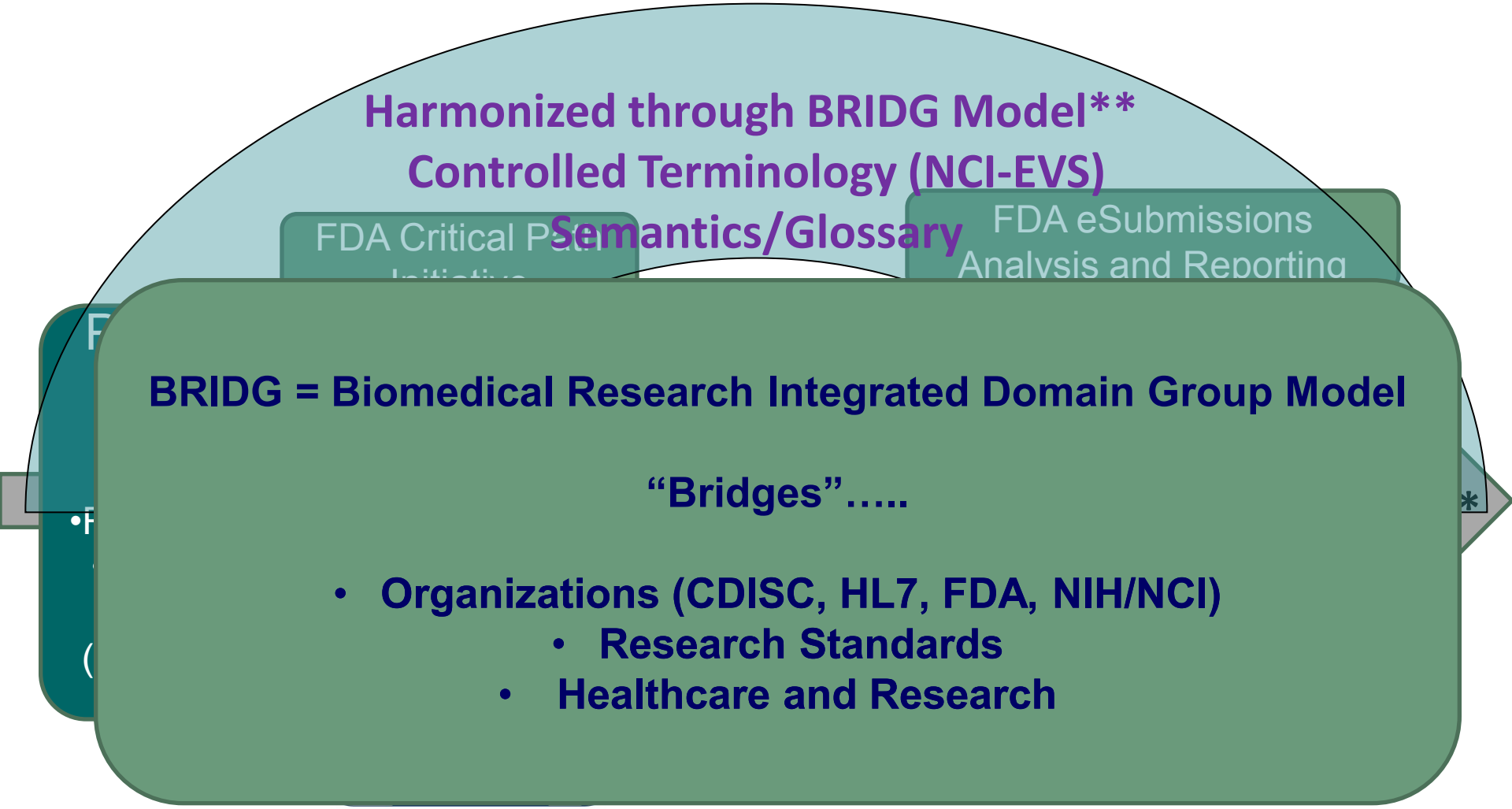


CDASH

** CDISC, HL7 Standard→ ISO/CEN

**Transport: CDISC ODM, SASXPT, etc.*

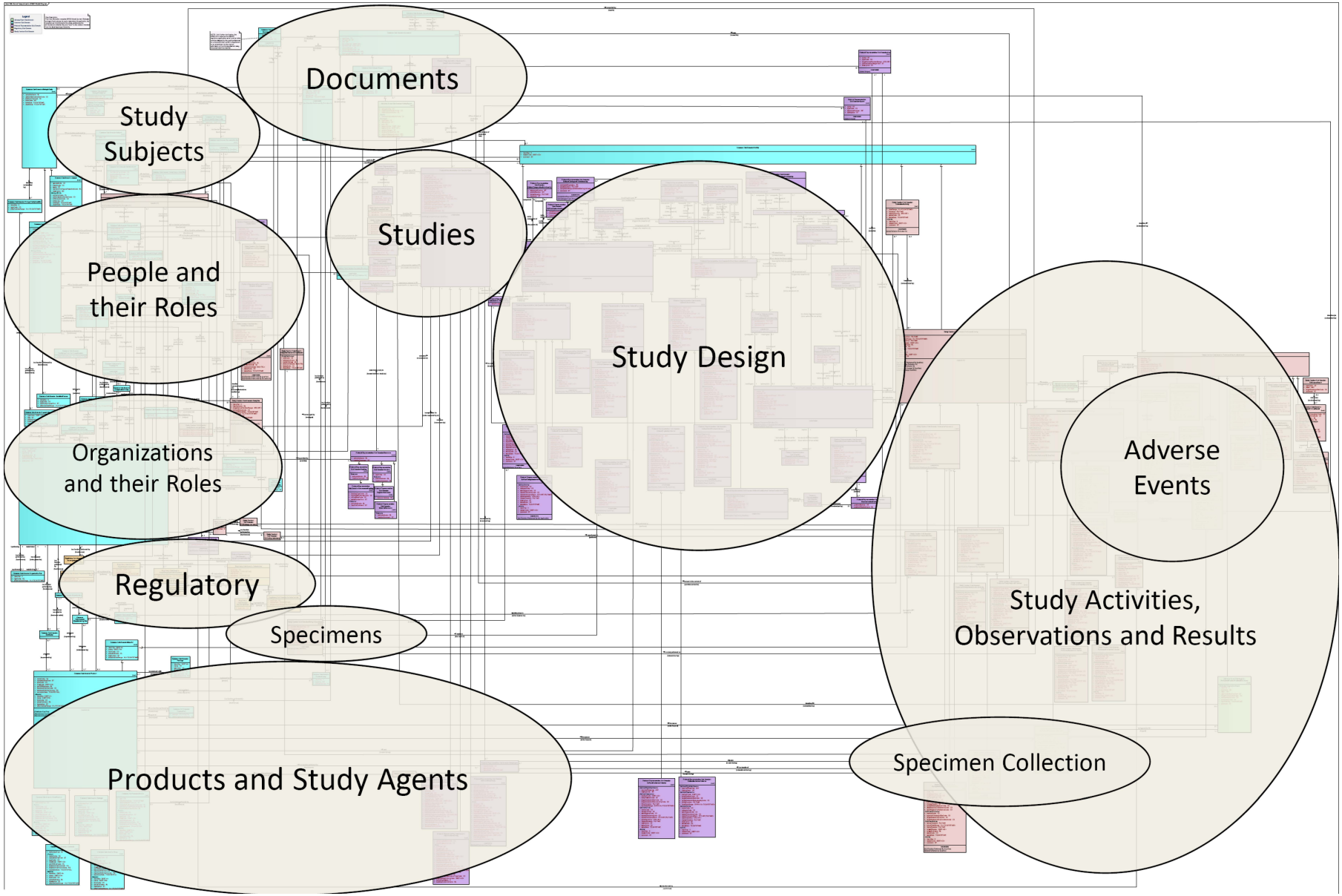
Global Content Standards for Clinical Research (Protocol-driven Research; Protocol →Reporting)



** CDISC, HL7 Standard→ ISO/CEN

Transport: CDISC ODM, SASXPT, etc.

BRIDG Model Content (Layer 2)



NCI EVS Collaboration

CDISC and NCI share many of the same requirements for freely available open source, international content standards. NCI Enterprise Vocabulary Services (EVS) has therefore committed expertise and significant resources in support of the CDISC Terminology Initiative…

NCI-EVS supports development and production of CDISC CT and provides infrastructure that supports semantic interoperability between terminologies in common use by the biomedical research community.

NCI EVS Collaboration

- CDISC, FDA and many other terminology subsets are published as open source subsets of NCI Thesaurus (NCIt).
- This builds on EVS collaborations across multiple NIH ICs, FDA and other Agencies, SDOs and many other research and clinical care consortia.
- EVS also provides integration of biomedical data standards from 76 national and international sources into one database through the NCI Metathesaurus (NCIm), a mapped overlap and inter-relation of current versions of CDISC CT, NCIt and other research and clinical required terminologies including the ICD's, MedDRA, SNOMED, LOINC, drug and gene nomenclatures.

CDASH Overview

Common minimum dataset across all clinical research protocols in accordance with global regulatory requirements

- Streamlines data collection at investigative sites - addresses FDA Critical Path Opportunity #45
- Continuation of ACRO's Initiative started October 2006
- Supported by a collaborative group of 17 organizations, including Biopharma, NIH, FDA, Academia

- Hundreds of volunteers developed the domains through work streams
- Consolidated document of 18 domains posted for public review May 2008 – received over 1800 comments from ~50 organizations
- All 3 ICH regions were represented in the public comment process (US, Europe, Japan) as was China

V1.0 published in October 2008

V 1.1 published in 2011

CDASH

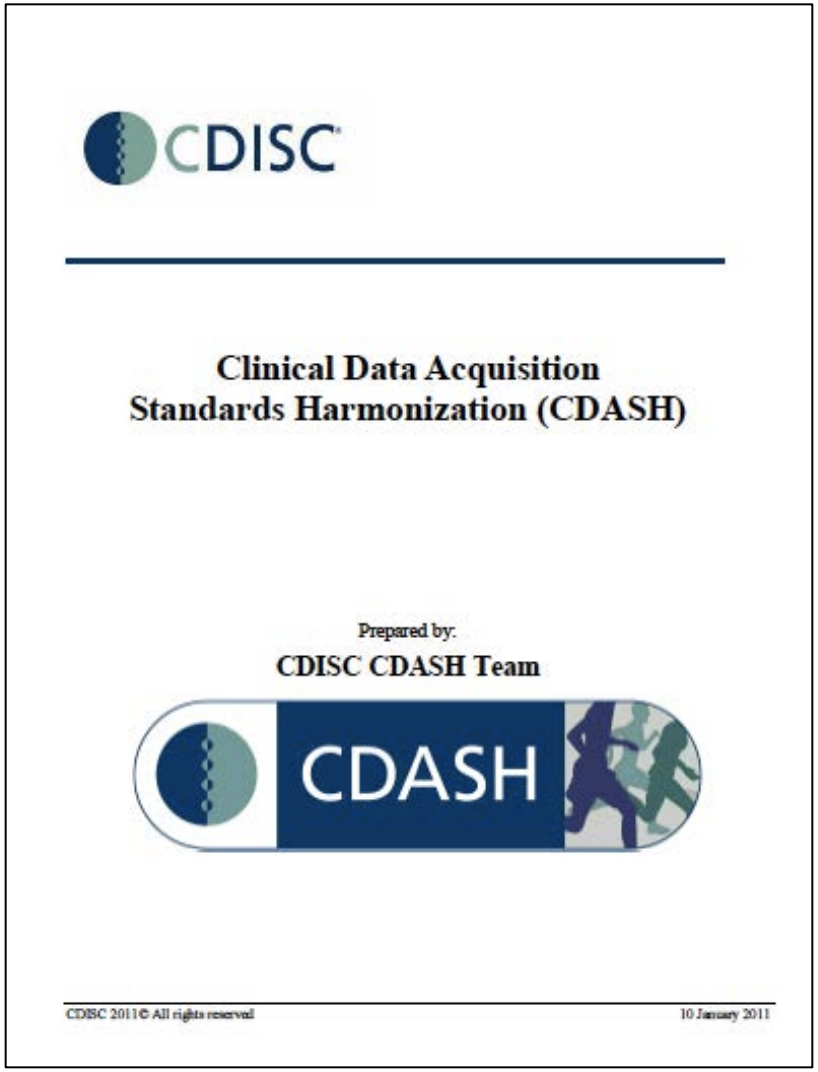
CDISC CDASH V 1.1 2011

DOMAINS:

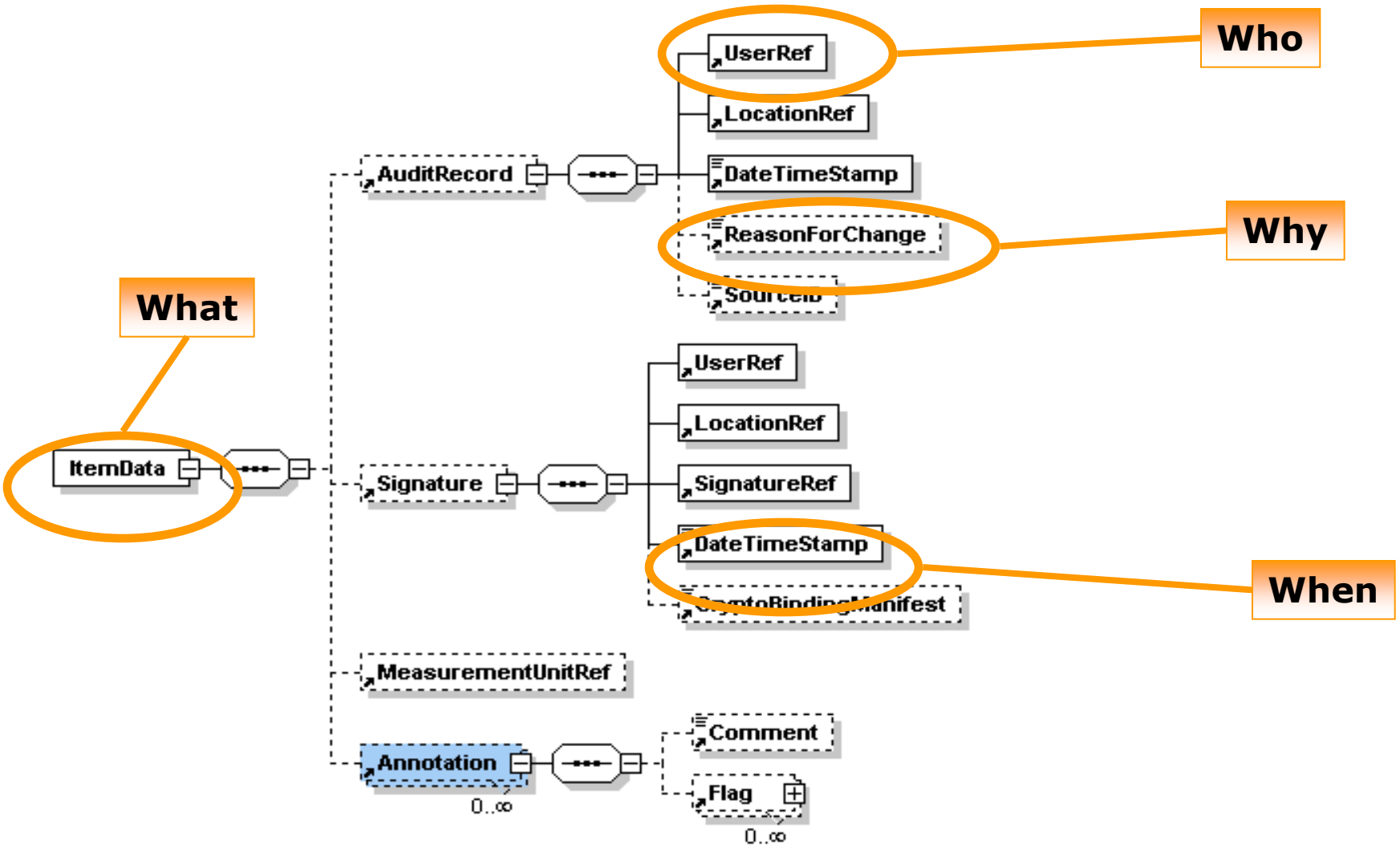
- **Adverse Events (AE)**
- **Concomitant Medication (CM)**
- **Demographics (DM)**
- **Subject Characteristics (SC)**
- **Inclusion/Exclusion Criteria (IE)**
- **Medical History (MH)**
- **Substance Use (SU)**
- **Physical Exam (PE)**
- **Vital Signs (VS), Disposition (DS)**
- **Drug Accountability (DA)**
- **Exposure (EX)**
- **Protocol Deviations (DV)**
- **Comments (CO)**
- **Lab (LB), ECG (EG)**

CRF Examples

CDASH in ODM (eCRFs)



ODM & Audit Trail



CFR - Code of Federal Regulations Title 21 - FDA

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 11 ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

eSource Data Interchange (eSDI) Initiative

- **Purpose:** FDA initiative to facilitate the use of electronic technology in the context of existing regulations for the collection of eSource data in clinical research **(e.g. eClinical Tools, EHRs, eDiaries)**
- **Overarching Goals:**
  - To make it easier for physicians to conduct clinical research,
  - Collect data only once in an industry standard format for multiple downstream uses, and thereby
  - Improve data quality and patient safety
- **Product:**
  - **eSDI Document -Available at www.cdisc.org/eSDI-document**
  - **12 requirements for eSource**
  - **Referenced by EMA in Guidance for Site Auditors**
  - ***Formed the basis for the Retrieve Form for Data Capture (RFD) Integration Profile***

NOTE: The eSource Data Interchange Initiative began in 2006 through a request from FDA representatives in the Department of Scientific Investigation (DSI) now the Office of Scientific Investigation (OSI). eSource means to enter the data electronically initially (not on paper) and it pertains to Electronic Health Records (EHR) or Electronic Medical Records (EMR), eDiaries, ePRO and other such opportunities to capture research data in a way that helps avoid transcription (which is time consuming and error prone).

Retrieve Form for Data Capture (RFD) Implementations (Examples)

- H1N1 Reporting – CDC
- EHRs for Research – Hamamatsu University (Japan)
- IMI EHR4CR Project – Europe (EU/EFPIA)
- Phase IV Research Study – Georgia, U.S. (Greenway)
- Academic Research – Florida Hospital (Cerner)
- Adverse Event Reporting – Harvard (Pfizer)

ASTER (AE Reporting from EHRs, RFD)

30 Ambulatory care physicians at Harvard and Brigham and Women's

with Pfizer, CDISC, CRIX

Nov 08 – Jun 09, > 200 Reports Sent to FDA

Physician Reporting:

*91% of participating physicians had submitted no ADE reports in the prior year

**During the study, participants reported an average of approximately 5 reports in a 3 month time period*

*All participants reported at least 1 AD

* Process: *Time to report decreased from ~35 min to* ***< 1 min***

Slide Source: Michael Ibara, Pfizer; Results published in Lancet

EHR Clinical Research Priority Value/Use Case

- With support/encouragement from HHS/ONC and others, ANSI convened an EHR Clinical Research Value Case Workgroup for prioritization of clinical research use cases.

- Initial Prioritized Value Case: *Identify a common set of core research data elements that can readily be exchanged between EHRs and clinical research systems to support global clinical research*

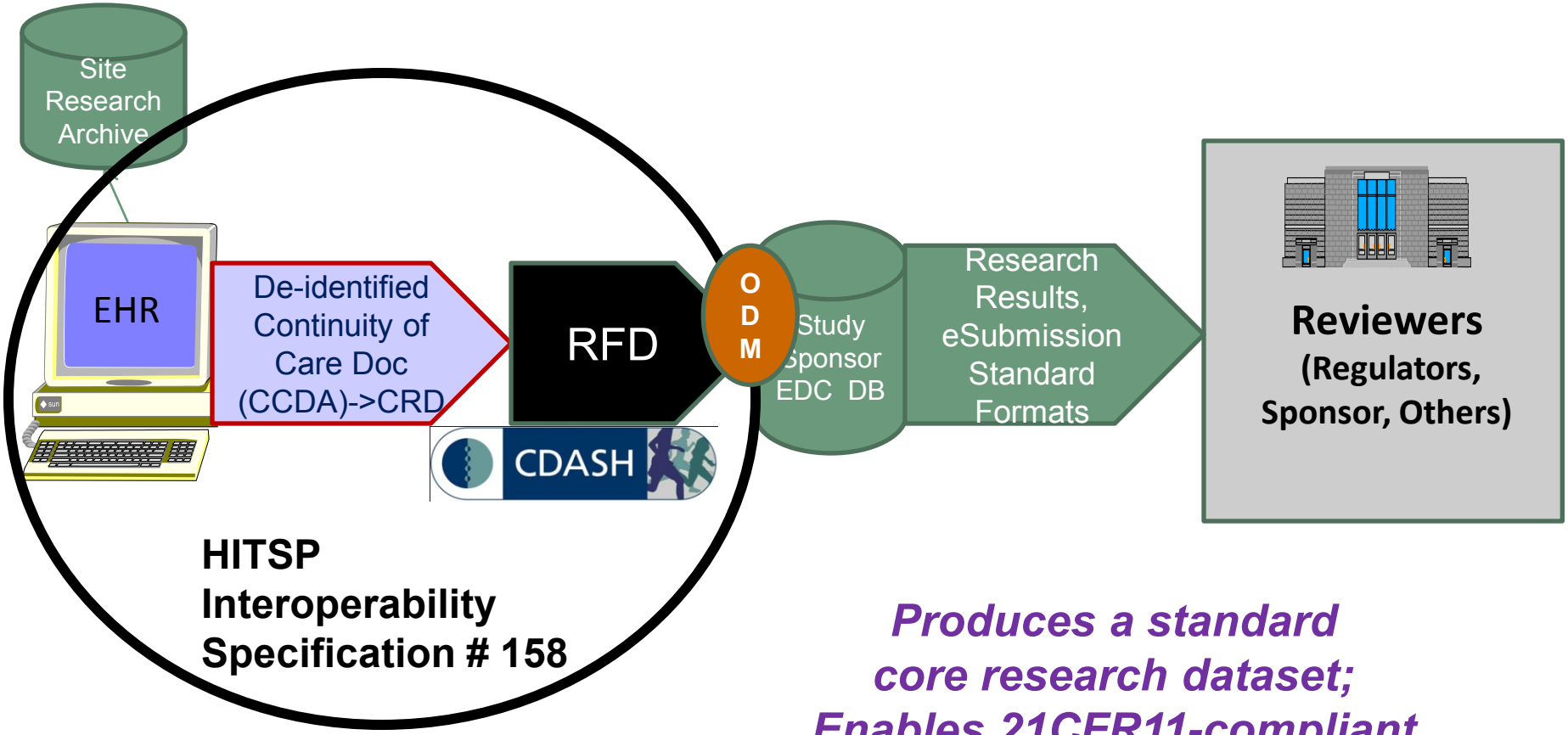
- Anticipated to provide a foundation for future use cases:
  - Patient eligibility and recruitment
  - Pharmacogenomics and biomarkers
  - Safety reporting
  - Compliance reporting

- Long-term objective: Create an infrastructure through which health care advances clinical research which, in turn, informs clinical care

2010

Funding: Contributions from 32 interested organizations + 6 government agencies.

Patient Value:
Quality of Healthcare, Safety



Produces a standard core research dataset; Enables 21CFR11-compliant interoperability and eSource

CDISC's Healthcare Link

Existing profiles

- Representing and sharing a *clinical research protocol for its execution*:
  - Retrieve Process for Execution (RPE)
  - Clinical Research Process Content (CRPC)
- Representing and *sharing clinical research documentation such as an eCRF or adverse event reporting form*, to be pre-populated by existing clinical data in EHRs:
  - Retrieve Form for Data Capture (RFD)
  - Clinical Research Document (CRD)
  - Drug Safety Content (DSC)
  - Redaction Service Profile (RSP)
- Addressing *confidentiality and security aspects*
  - Consistent Time (CT)
  - Cross-Enterprise User Assertion (XUA)
  - Audit Trail Node Authentication (ATNA)

Newly approved (Oct 2012) profiles to be developed

- Data Element Exchange
- Research Matching (identification of eligible patients)
- CRD – Patient Authored Note

CDISC Therapeutic Area Projects

- **Tuberculosis** (Duke NIH, TB Alliance, Gates**)**: v1.0 standard for Pulmonary TB published; future work - Pediatric TB
- **Alzheimer's Disease** (CAMD): v1.0 standard published
- **Parkinson's Disease** (C-Path, NIH/NINDS): v1.0 standard published
- **Cardiovascular Disease** (NIH, Duke): standard for 400+ data elements due Q2 2013; future CV Endpoints and CV Imaging
- **Pain & Analgesics** (FDA, ACTTION): v1.0 standard published
- **Virology** (FDA): v1.0 standard published
- **Polycystic Kidney Disease**: (PKD Foundation, C-Path, Tufts) v1.0 standard due Q1 2013
- **Asthma** (TransCelerate): launched Q4 2012
- **Oncology / Tumor Response** (CDISC, NCI): in development
- **Traumatic Brain Injury** and **Post Traumatic Stress Disorder** (OneMind for Research) TBI project launched January 2013
- **Others 2013 –** Schizophrenia (FDA, Duke); Diabetes (TransCelerate), MS (C-Path)

PDUFA V - Section XII

ELECTRONIC SUBMISSIONS AND STANDARDIZATION OF DRUG APPLICATION DATA

- Clinical Terminology Standards: Using a public process that allows for stakeholder input, FDA shall develop standardized clinical data terminology through open standards development organizations with the goal of completing clinical data terminology and detailed implementation guides by FY 2017.
  - FDA shall develop a project plan for distinct therapeutic indications, prioritizing clinical terminology standards development within and across review divisions. FDA shall publish a proposed project plan for stakeholder review and comment by June 30, 2013. FDA shall update and publish its project plan annually.

CDISC Projects and Synergies with IMI / European Commission

- IMI Therapeutic Area projects
  - Asthma (Severe) – U-BIOPRED
  - Autism
  - Cancer (Colon) – OncoTrack
  - Cancer (Prostate, Breast, Lung Cancer) – PREDECT
  - Chronic Pain – EUROPAIN
  - Diabetes Type II – DIRECT
  - Neurodegenerative Diseases – Pharma-Cog
  - Rheumatoid Arthritis – 2 IMI projects
  - Tuberculosis – PredictTB
- IMI Projects with CDISC as partner organization
  - EHR4CR
  - BioVacSafe – Vaccine Clinical Trials
  - eTRIKS – Translational Research

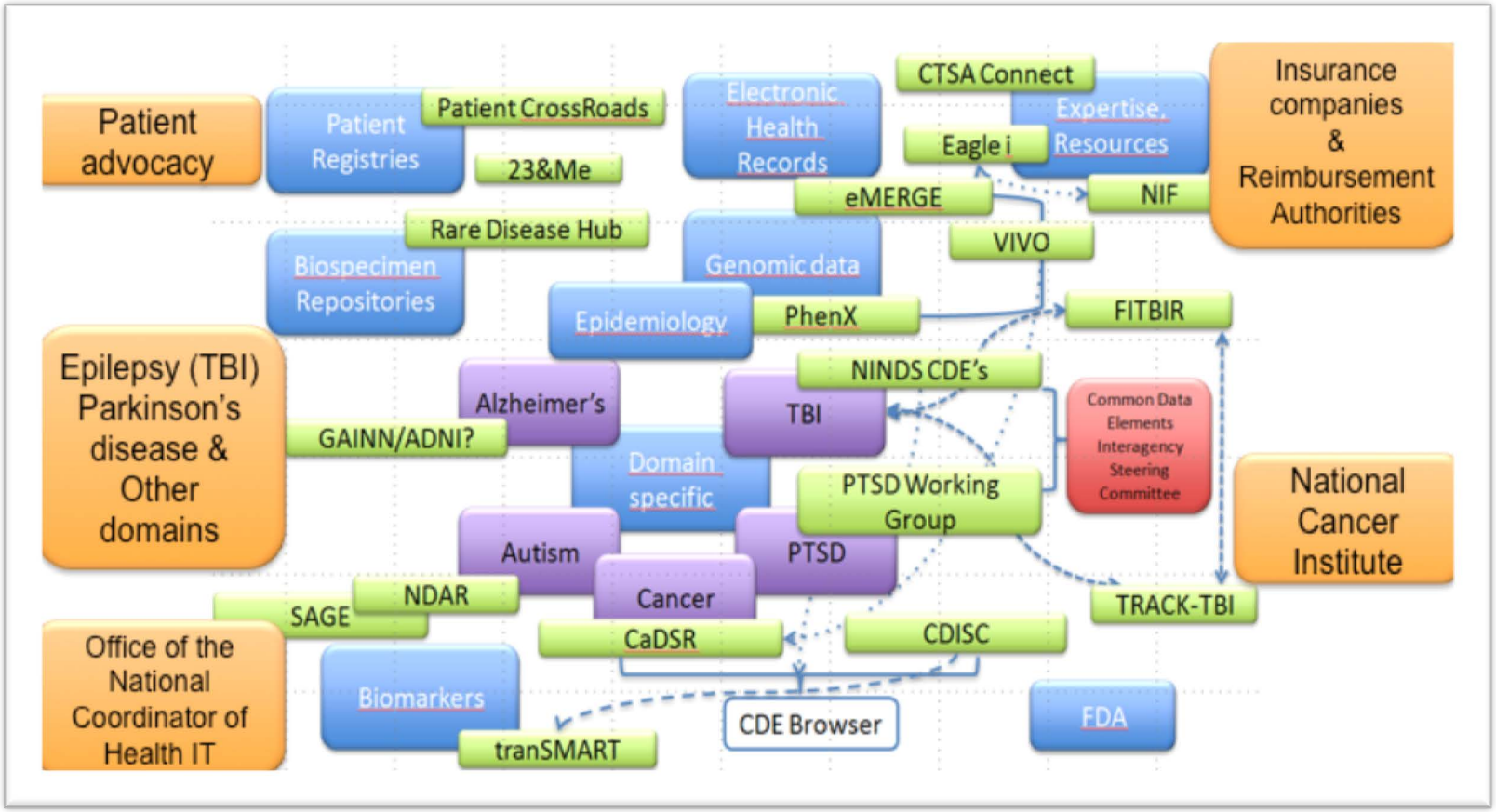
TRI (Japan govt) using Alzheimer's standard in study with China

Common Data Elements (CDEs)

- A CDE is a CRF Question and the associated responses/valid values
- Common Data Element C19984 (NCI Thesaurus)

  Data terms or concepts that have been determined to be identical between projects or contexts.
- Common data element. A structured item characterized by a stem and response options together with a history of usage that can be standardized for research purposes across studies conducted by and for NIH. NOTE: The mark up or tagging facilitates document indexing, search and retrieval, and provides standard conventions for insertion of codes (CDISC Glossary)
- Common data elements (CDEs) are annotations that are collected in a uniform manner across multiple institutions, derived from their broader set of DEs, that allow sharing of data in a standardized format and are defined in detail using a metadata dictionary. (One Mind for Research Position Paper) *DE = Locally derived, institution- or organization-specific standardized metadata structure.*

Figure 1. Organizations Actively Involved in the Development of CDEs and Data Curation



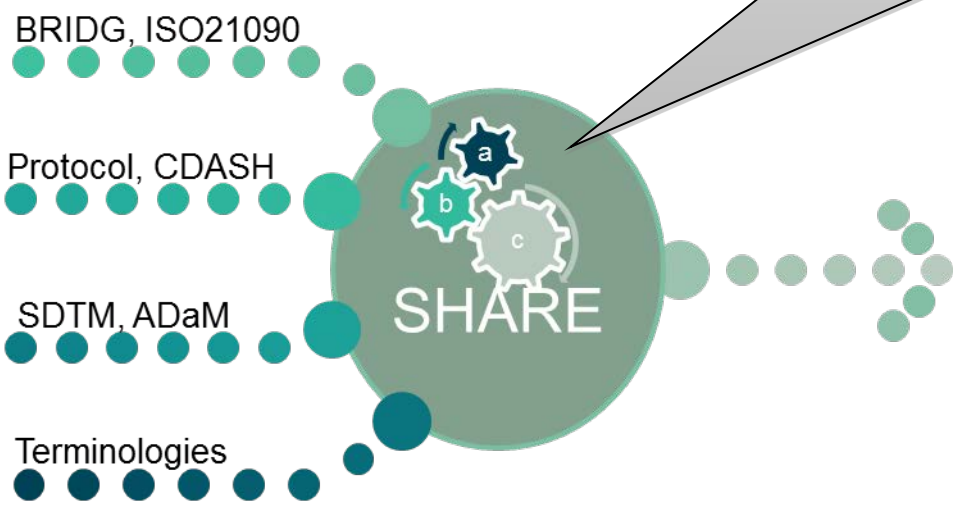
One Mind for Research: Position Paper V1.0: Surveying and Navigating the CDE Landscape, October 2012

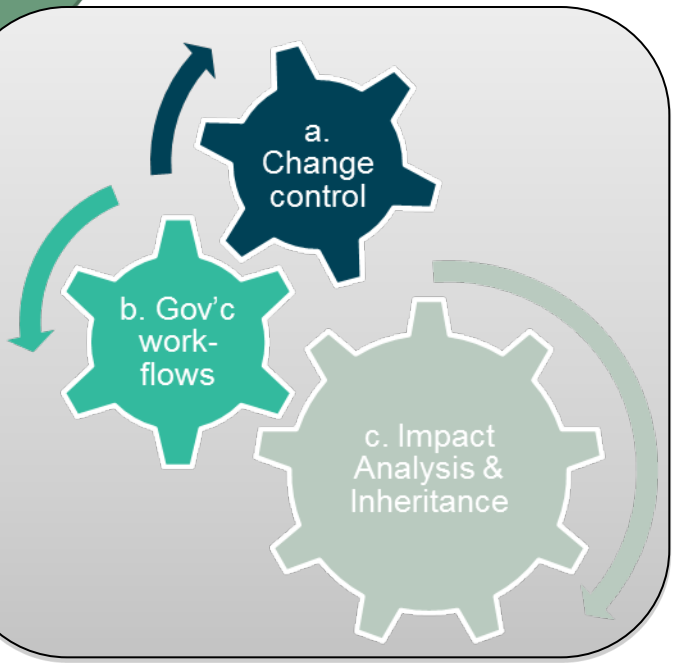
(accessible via the CDISC eJournal - www.cdisc.org/Resources)

CDISC SHARE
SHARED HEALTH AND CLINICAL RESEARCH ELECTRONIC LIBRARY

Strictly speaking, still a "dream"

- Single, trusted, authoritative source for CDISC data standards
- Concepts, metadata, collections, relationships, value sets across the full spectrum of CDISC content
- Links research to healthcare concepts to support interoperability
- Aligned with NCI Semantic Systems





Facilitates Data Exchange

- Access to data standards
- Source to target mapping & traceability
- Transformation logic

Adapted from Source by Sue Dubman, Sanofi-Aventis

bridg inside

Healthcare Space

- Patient Care Documentation (CDA, Clinical Statement Model)
- Continuity of Care Document (CCD)
- EHR functional profiles and other standards

Collaborative Space: Healthcare and Research

BRIDG
Unifying Information Model

Example (IS):
EHRs for Clinical study execution - integration profiles, CDISC content standards, and CCD/ HL7 CDAs for data export

SHARE
Research concepts and relationships

Clinical Research Space

- Data Submission (SDTM & SEND)
- Research Protocols (PR and Study Design Model)
- Data Analysis (ADaM)
- Data Capture (CDASH)
- eSource document data interchange requirements (eSDI)

Knowing is not enough;
we must apply.
Willing is not enough;
we must do.

- Goethe-

With appreciation of the gracious volunteers and supporters who 'apply' and 'do'…

CDISC®

Strength through collaboration

International Conference on Harmonisation (ICH)

- Launched in 1990, ICH is a unique undertaking that brings together the drug regulatory authorities (i.e. FDA, EMA, PMDA) and the pharmaceutical industry of Europe, Japan and the United States
- Mission is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines.
- Products in 4 categories
  - Clinical Guidelines for Quality (e.g. Good Clinical Practices)
  - Safety (e.g. adverse event reporting and risk Assessment)
  - Efficacy (e.g. use of pharmacogenetics/genomics techniques)
  - Multidisciplinary (MedDRA medical terminology and eCommon Technical Document)