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Current Status and Future Scope of Clinical Data Standards

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What is CDISC?

- The **Clinical Data Interchange Standards Consortium (CDISC)** is a global, open, multidisciplinary, vendor-neutral, non-profit standards developing organization (SDO)
- The CDISC has been developing global standards to streamline medical research and ensure a link with healthcare.
- 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."
- The CDISC vision is “to inform patient care and safety through higher quality medical research".
- The CDISC standards supports medical research of any type from protocol through analysis and reporting of results.

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

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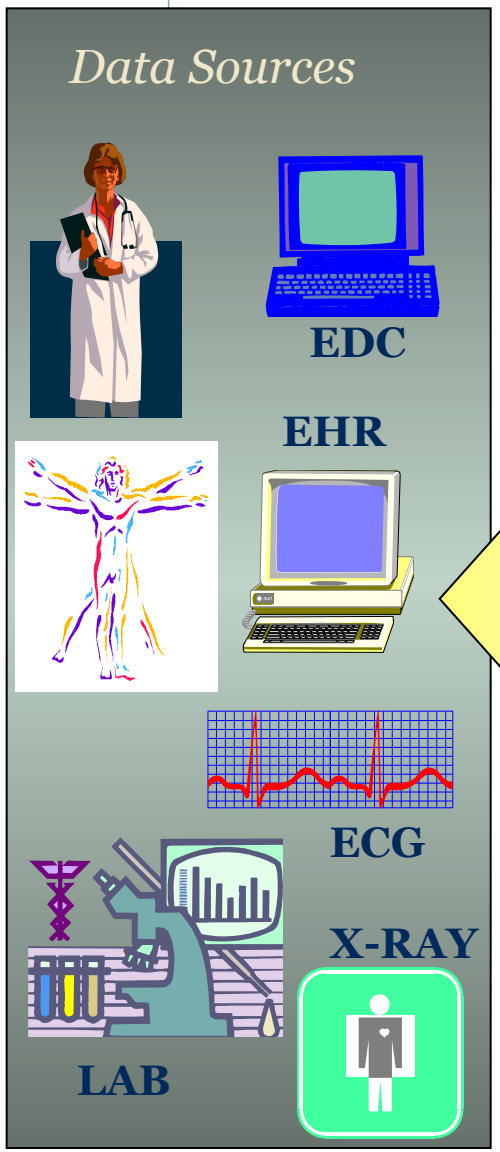
Vision – Medical Innovation

Subject Data – Enter Once for Multiple Purposes

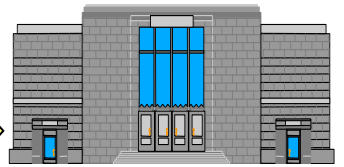
"Rolling" Warehousing, Reporting and Submissions



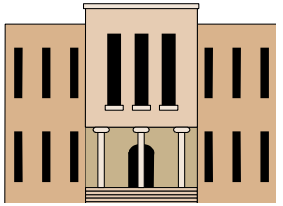
Regulatory Authority

Public Registries and IRBs

CDISC Standards Real-time Integration



Sponsor



CRO or Partner

Payer

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Interoperability

- The interoperability is the ability of exchanging and processing data successfully among systems.
- HL7 has categorized interoperability as technical interoperability, semantic interoperability, and process interoperability.

Type	Requirement	Standard
Technical Interoperability	Integrity of Data Transportation	SAS XPORT Transport Format, ODM
Semantic Interoperability	Technical Interoperability + Integrity of Understanding	Controlled Terminology, BRIDG
Process Interoperability	Semantic Interoperability + Integrity of Processes	Not Available (dynamic diagrams need to be defined in BRIDG)

- Semantic Interoperability: ‘the ability of two or more computer systems to exchange information and have the meaning of that information automatically interpreted by the receiving system accurately enough to produce useful results, as defined by the end users of both systems.

CDISC Value by Profession

Profession	Why CDISC?
CEO, Study Sponsor, Program/Project Manager Ask yourself, do you want:	a) To initiate your study quickly and economically? b) Have your CRFs easily understood and completed by investigative site personnel? c) Receive high quality data that will readily fit into the format requested by FDA? d) To have a protocol with sections that can be re-used (without re-entry) for trial registration, IRBs, generating study reports, publication, eSubmissions e) Your data to readily integrate with that of other studies? f) To be able to find your data later? g) Have your data ready in case of a merger or acquisition? h) Be able to use data from past research to improve current/future research?

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CDISC Value by Profession

Profession	Why CDISC?
Medical Writer Ask yourself, do you want:	a) To write your protocols and study reports a bit faster? b) Re-use information from your protocols without re-entering information, e.g. trial registration, study reports, publications? c) To enable others on the team to auto-generate visit schedules and CRFs?
Data Manager Ask yourself, do you want:	a) To get your CRFs ready faster and economically? b) To create your data validation specifications more quickly and effectively? c) To build your databases more efficiently? d) To reduce training and improve communication with your CRAs and sites? e) To get cleaner data, faster? f) To reduce data problems and be able to focus more on the scientific content? g) To build more effective partnerships with the whole study team?

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CDISC Value by Profession

Profession	Why CDISC?
Vendor or Information Technologist Ask yourself, do you want:	a) To ensure that your system will be able to readily exchange information with another system the sponsor may wish to use? b) To be able to provide a system based on industry standards? c) To be able to quickly respond to sponsor requests by using standard libraries?
Statistician/ Programmer Ask yourself, do you want:	a) To be able to create tables, listings and figures more efficiently? b) To be able to integrate data from multiple studies more easily? c) To be able to standardize your safety analysis programming?
Others?	What do you want from standards?

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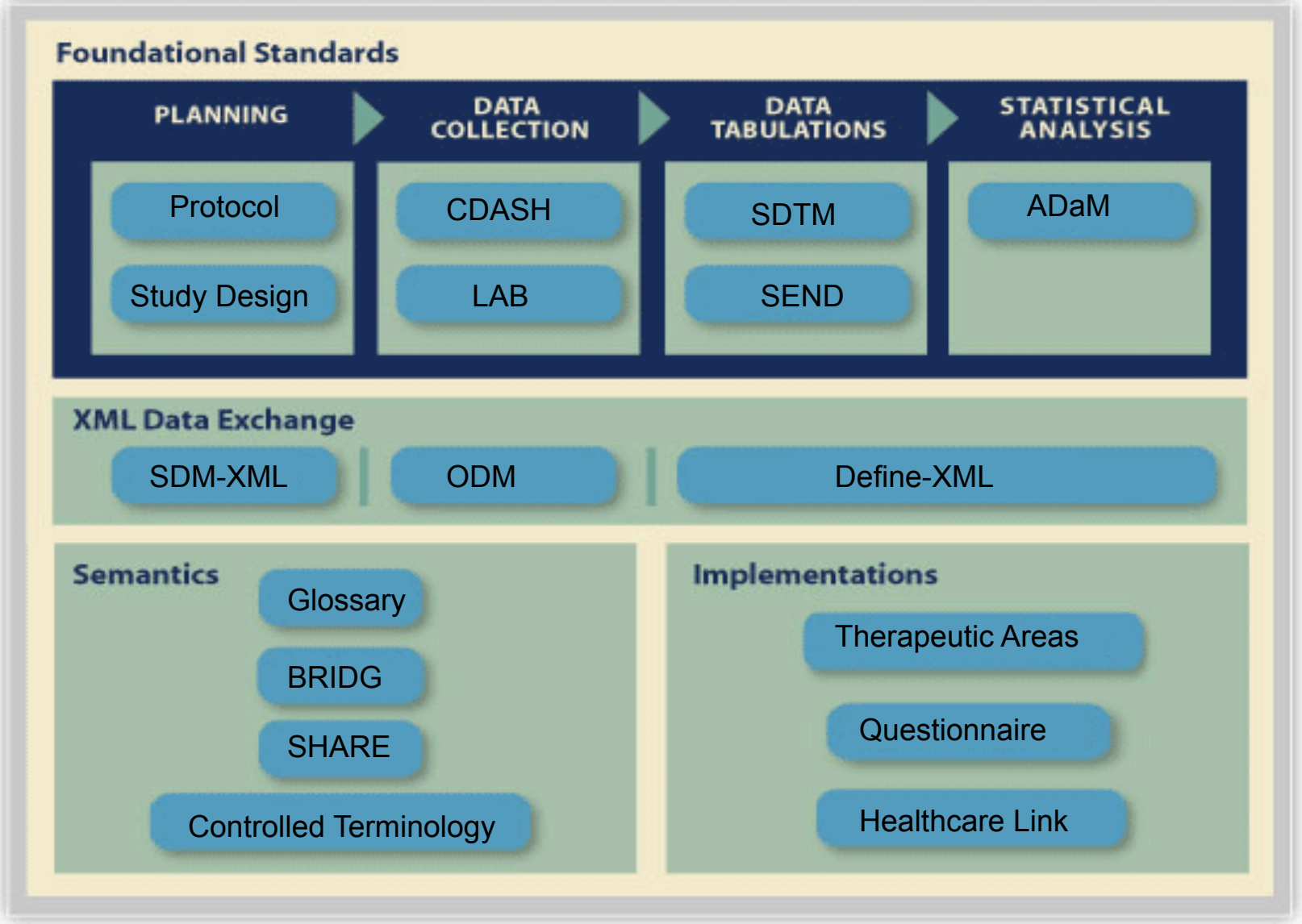
Study Data Standards for Regulatory Submission

FDA's position statement:

"FDA envisions a **semantically interoperable** and sustainable submission environment that serves both regulated clinical research and health care. To this end, FDA will continue to research and evaluate, with its stakeholders, potential new approaches to current and emerging data standards. FDA does not foresee the replacement of CDISC standards for study data and will not implement new approaches without public input on the cost and utility of those approaches."

CDISC – Functional Standards

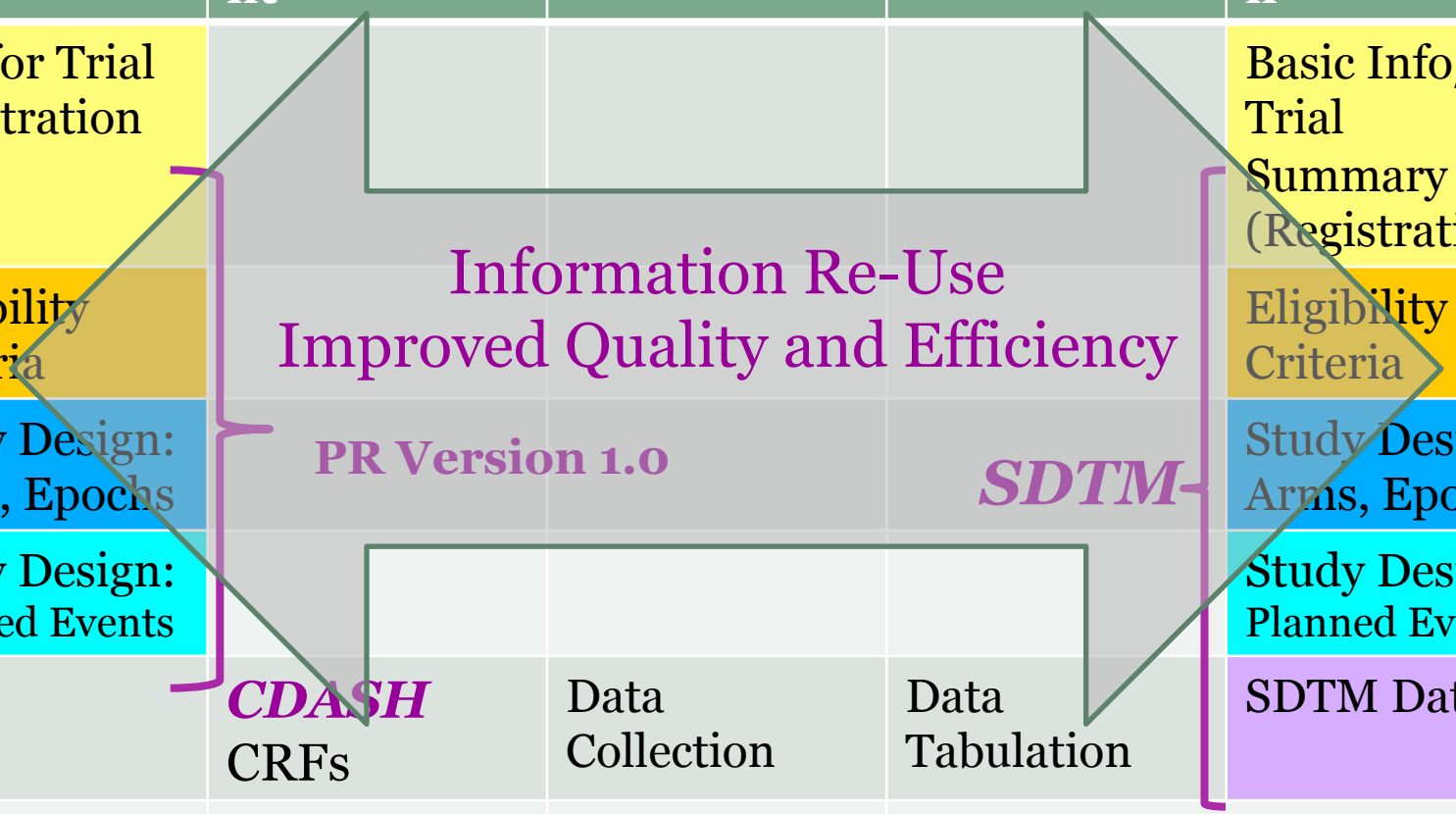


Protocol Representation Model (PRM)

- The content and format standard supporting the interchange of clinical trial protocol information. This is a collaborative effort with Health Level Seven (HL7).

- **Trial Design Model (TDM) :**The content standard that defines the structure for representing the planned sequence of events and the treatment plan of a trial. This is a subset of the SDTM and Protocol Representation.

Protocol Section	CRF Development	Data Collection	Data Analysis	Report or eSubmission
Info for Trial Registration				Basic Info/ Trial Summary (Registration)
Eligibility Criteria				Eligibility Criteria
Study Design: Arms, Epochs				Study Design: Arms, Epochs
Study Design: Planned Events				Study Design: Planned Events
	CDASH CRFs	Data Collection	Data Tabulation	SDTM Data
Statistical Analysis Plan			Data Analysis	***ADaM*** Datasets
Appendices, etc.				Appendices, etc.



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- **FDA CRITICAL PATH INITIATIVE: STREAMLINING CLINICAL TRIALS**
  - *Creating Innovative and Efficient Clinical Trials and Improved Clinical Endpoints*
  - 45. Consensus on Standards for Case Report Forms. Clinical trial data collection, analysis, and submission can be inefficient and unnecessarily expensive. A wide array of different forms and formats are used to collect clinical trial information, and most data are submitted to the FDA on paper. **Differences in case report forms across sponsors and trials creates opportunities for confusion and error**. Standardization of the look and feel of case report forms could reduce these inefficiencies and also help accelerate progress toward electronic data capture and submission.

"Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products", Critical Path Opportunities List, March 2006, page L-10.

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CDISC LAB Model

- Primary AIMS
  - Interchange of test results & reference ranges
  - Incremental and cumulative data interchange
  - Full range of transaction types
  - Interchange data from 1+ studies in single file
  - Support the bulk transfer of laboratory data

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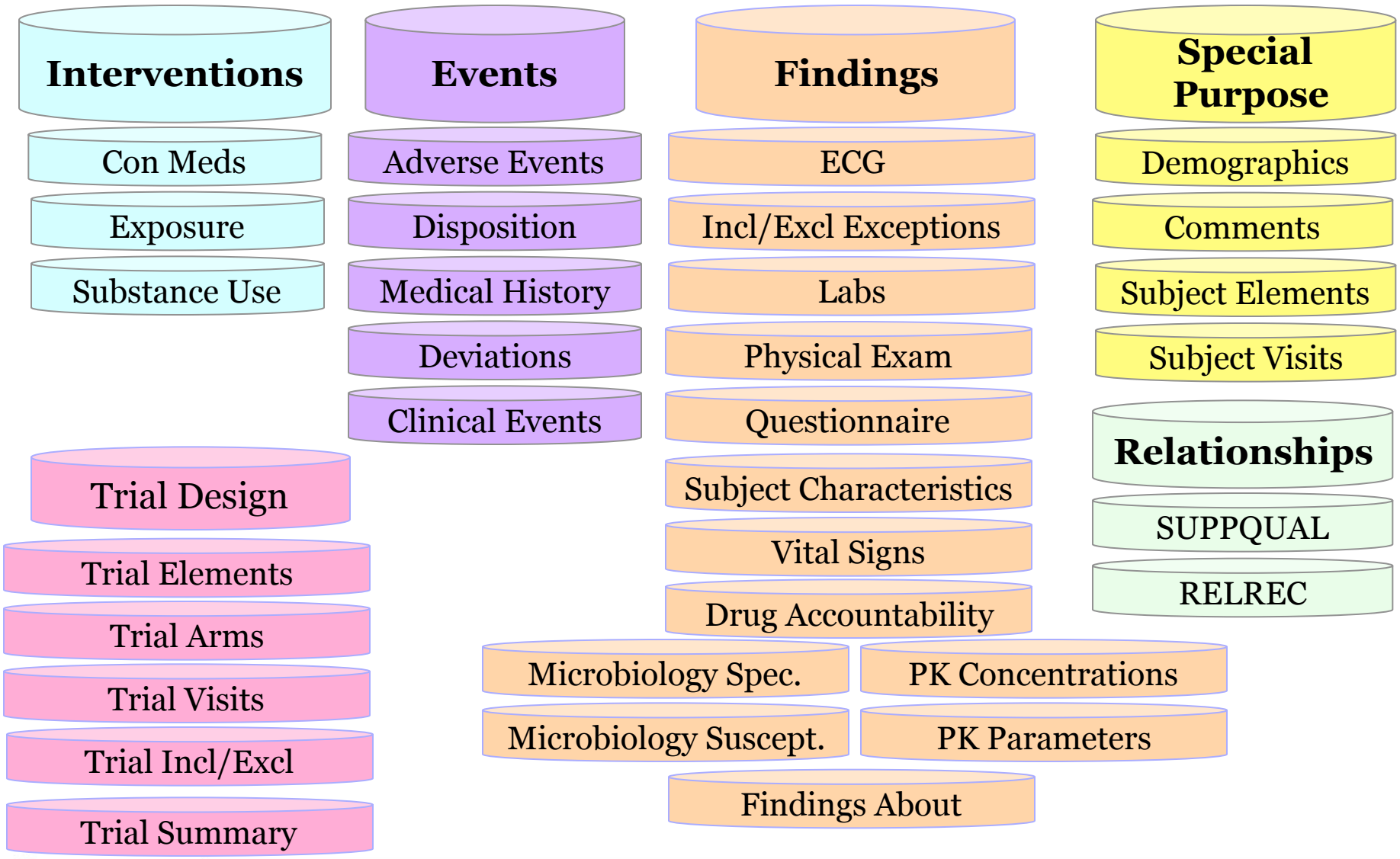
SDTM Standard Domains



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SEND

- SEND is an implementation of SDTM for animal data
- SEND defines domains and variables for submitting all data generated from animal toxicity studies
  - Includes: single- and repeat-dose toxicity, carcinogenicity, reproductive toxicity, and rodent micronucleus
  - Does not include data generated from in vitro studies or as part of basic pharmacology or efficacy studies conducted in animals

- CRADA (April 2002) between PharmQuest and CDER to develop and evaluate software tools for receiving, storing, viewing and analyzing nonclinical (i.e., animal toxicity) data based on SEND model

SEND v2.3 Findings Domains

- Animal Characteristics
- Water Consumption
- Clinical Signs
- Clinical Pathology
- Organ Weights
- Fetal Data
- Group Observations
- Drug/Metabolite Levels
- Tumor Analysis
- Vital Signs
- Food Consumption
- Body Weights
- Animal Disposition
- Macroscopic Findings
- Microscopic Findings
- Fertility
- Group Characteristics
- Study Summary
- Rodent Micronucleus

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Key Principles for Analysis Dataset Creation

Analysis datasets should:

- facilitate clear and unambiguous communication
- be useable by currently available tools
- be linked to machine-readable metadata
- be analysis-ready
- include subject-level analysis dataset named ADSL
- use the convention: ADxxxxxx for naming
- have optimum number of datasets so minor programming needed
- maintain SDTM variable attributes for same variables
- use SDTM naming fragments where feasible

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CDISC Operational Data Model

- Transport Standard (XML)
  - Developed to carry case report form data
  - Carries complete audit trail information (21CFR11)
  - Supports electronic signatures
  - Archives electronic data without need to archive original system at sites
  - Can automate generation of eCRFs
  - Enables remote monitoring or auditing
  - Facilitates exchange of data between different technologies that are ODM (supports features common to all CDM and EDC systems)

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eXtensible Markup Language

- XML - method for putting structured data in a text file
- Looks similar to HTML
  - Tags “<“ “>”
  - Attributes name=“Value”
- Very flexible standard for data/metadata exchange
- Text based & readable by humans and machines
  - Vendor neutral
  - Computer system neutral

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CDISC Terminology

- Formalized CDISC Terminology Initiative in 2005
- Primary Objective: to define and support the terminology needs of the CDISC models across the clinical trial continuum (CDASH → SDTM), Focus on “standard” terminology codelist development and publication
- Terminology Initiative comprised of 45 team members (FDA, NCI, Global Sponsors & CROs, Academia) distributed across 4 project teams
- Key partnership with NCI Enterprise Vocabulary Services (NCI EVS) with dedicated CDISC / FDA resources

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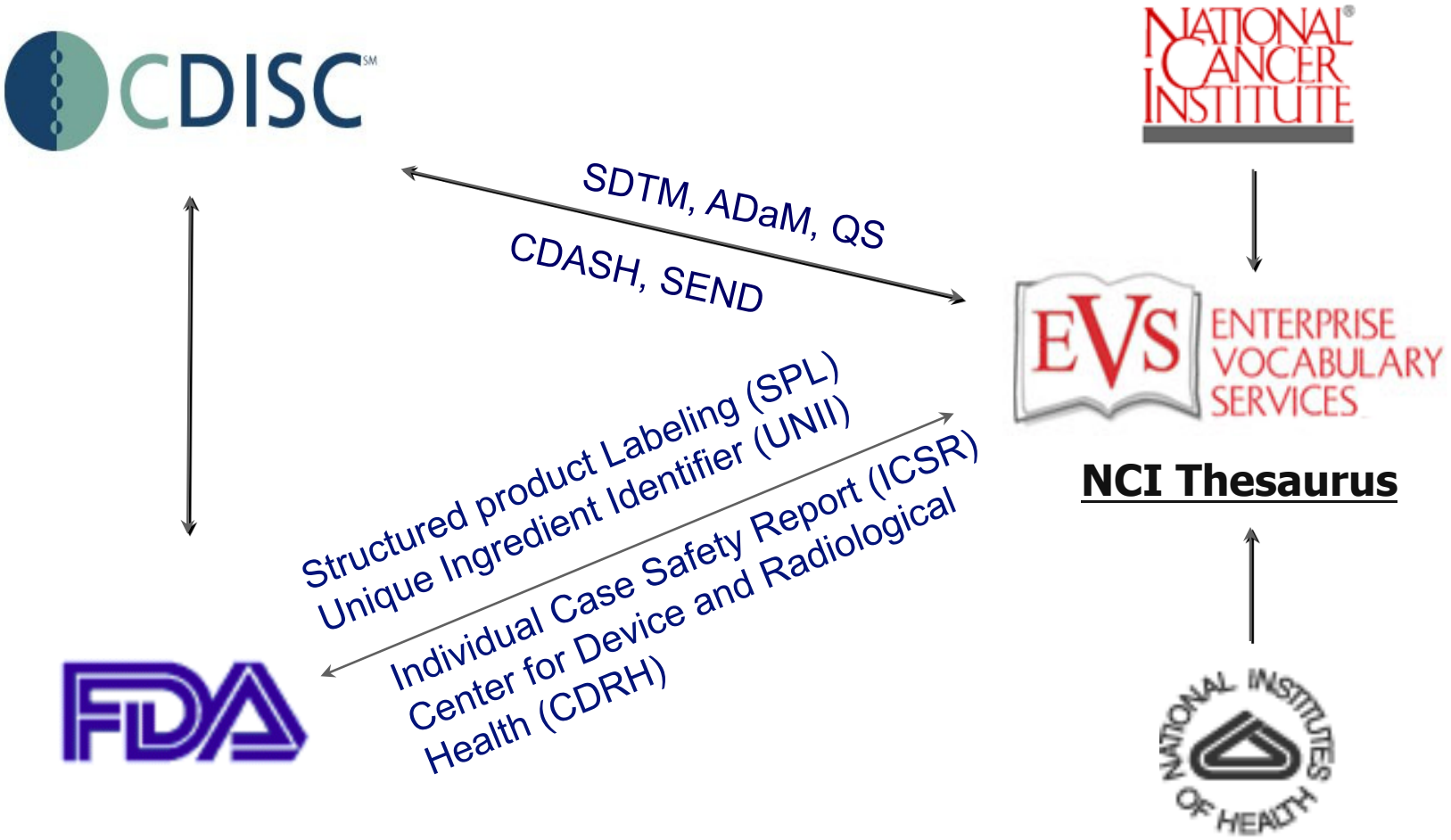
CDISC-FDA-NCI EVS Terminology Harmonization

http://www.cancer.gov/cancertopics/terminologyresources/



BRIDG Scope

Protocol-driven research and its associated regulatory artifacts:

i.e. the data, organization, resources, rules, and processes involved in the formal assessment of the utility, impact, or other pharmacological, physiological, or psychological effects of a drug, procedure, process, subject characteristic, or device on a human, animal, or other subject or substance plus all associated regulatory artifacts required for or derived from this effort, including data specifically associated with post-marketing adverse event reporting.

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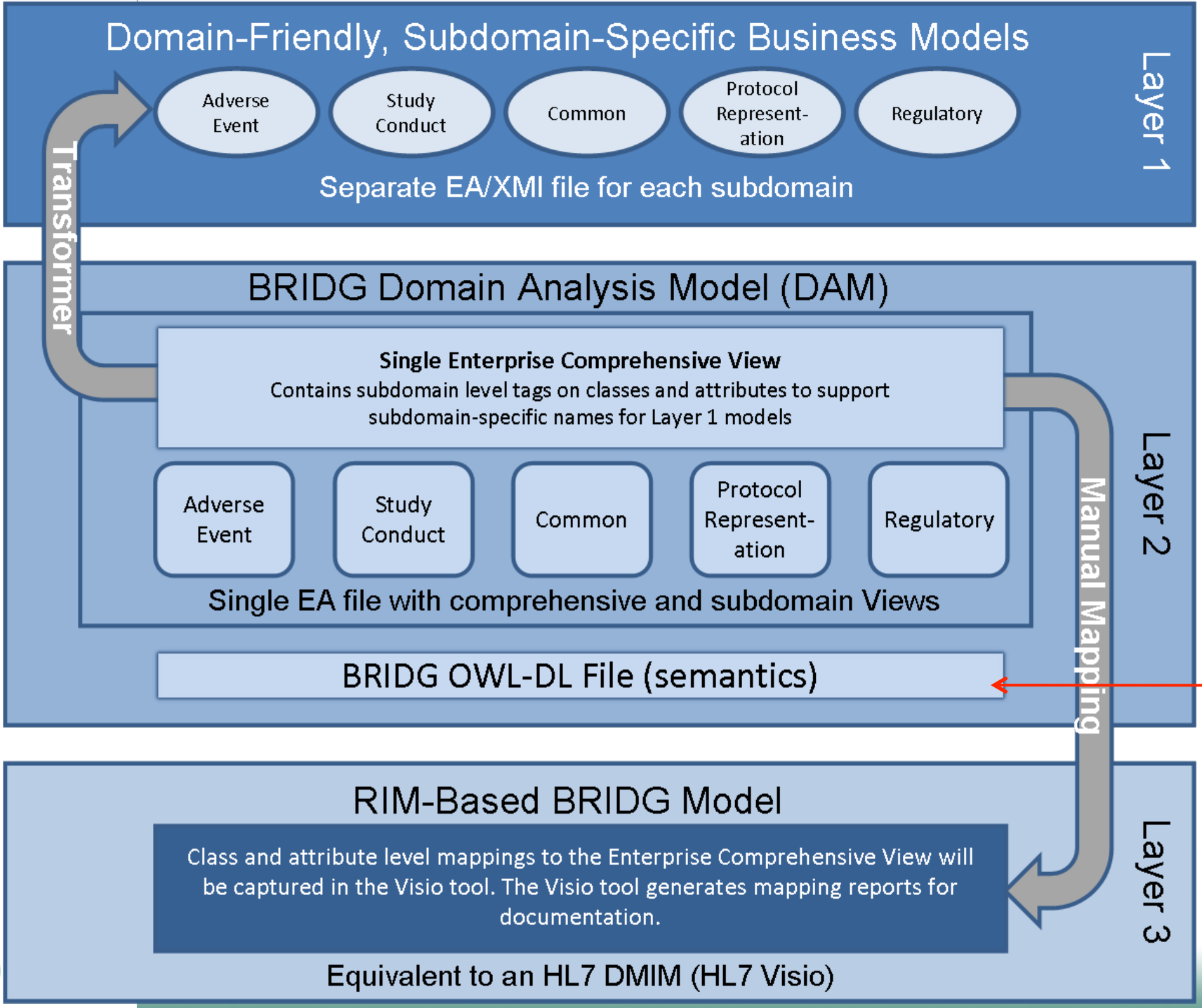
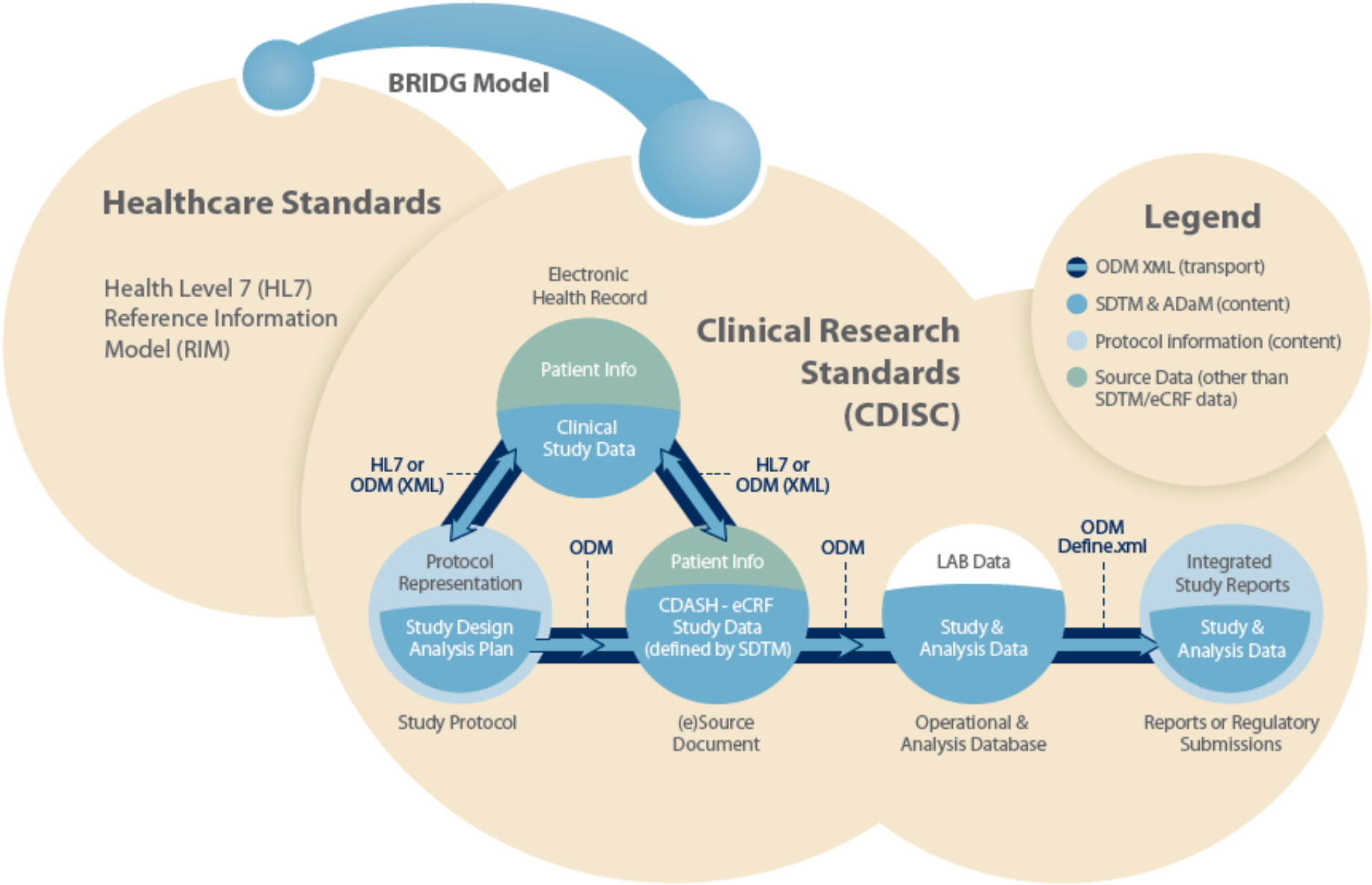
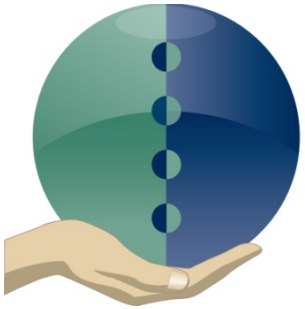

Domain-Friendly, Subdomain-Specific Business Models
Adverse Event
Study Conduct
Common
Protocol Represent-ation
Regulatory
Separate EA/XMI file for each subdomain
Layer 1
SME View
Transformer
BRIDG Domain Analysis Model (DAM)
Single Enterprise Comprehensive View
Contains subdomain level tags on classes and attributes to support subdomain-specific names for Layer 1 models
Adverse Event
Study Conduct
Common
Protocol Represent-ation
Regulatory
Single EA file with comprehensive and subdomain Views
Layer 2
Canonical View
Manual Mapping
BRIDG OWL-DL File (semantics)
OWL View
RIM-Based BRIDG Model
Class and attribute level mappings to the Enterprise Comprehensive View will be captured in the Visio tool. The Visio tool generates mapping reports for documentation.
Equivalent to an HL7 DMIM (HL7 Visio)
Layer 3
HL7 RIM View

CDISC Standards and Data Flow





CDISC SHARE

SHARED HEALTH AND CLINICAL RESEARCH ELECTRONIC LIBRARY

A global, accessible electronic library, which through advanced technology, enables precise and standardised data element definitions (including value sets) that can be used in applications and studies to improve biomedical research and its link with healthcare

Key purposes: Develop efficacy standards faster and make the CDISC standards more accessible.

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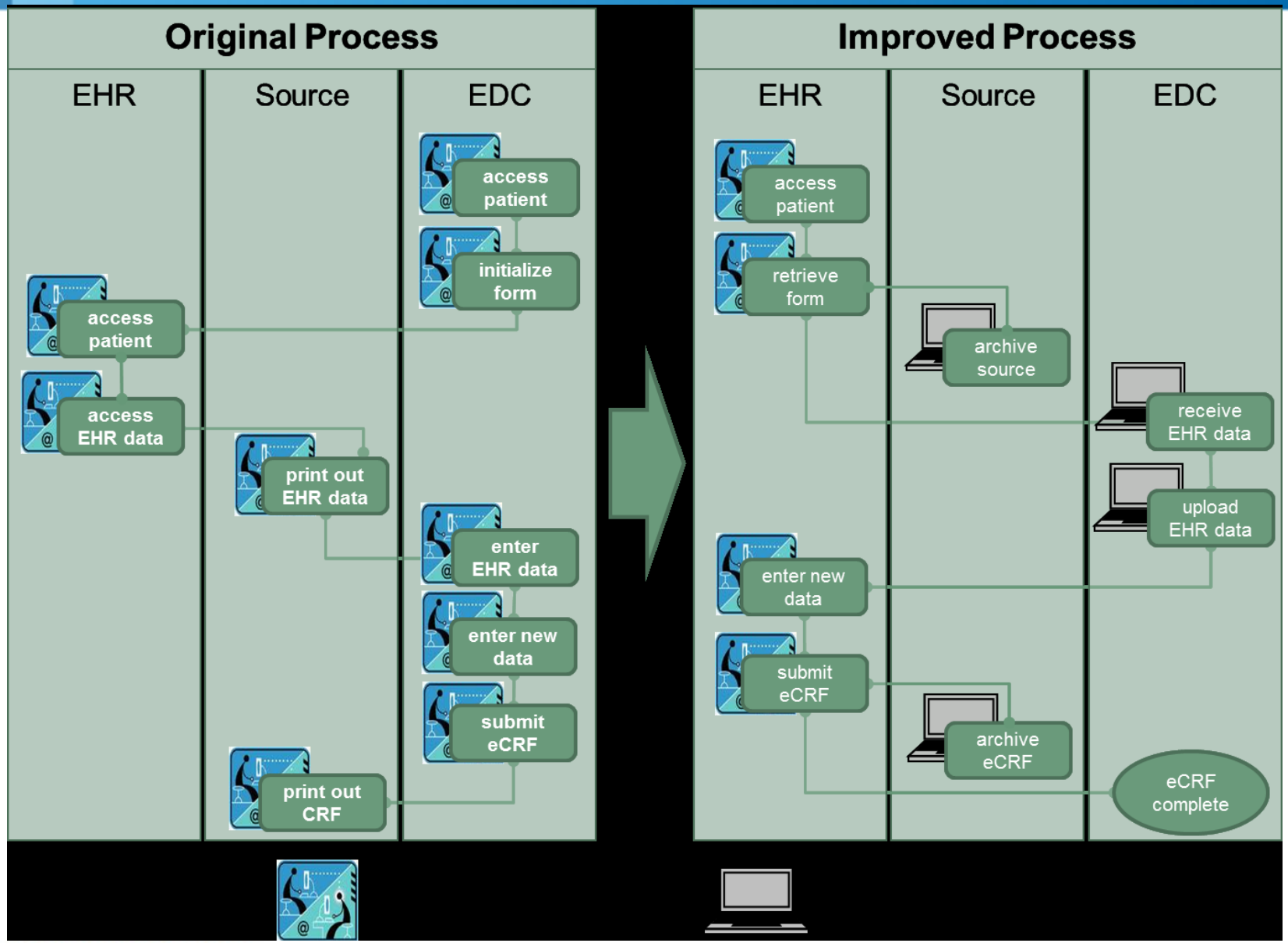
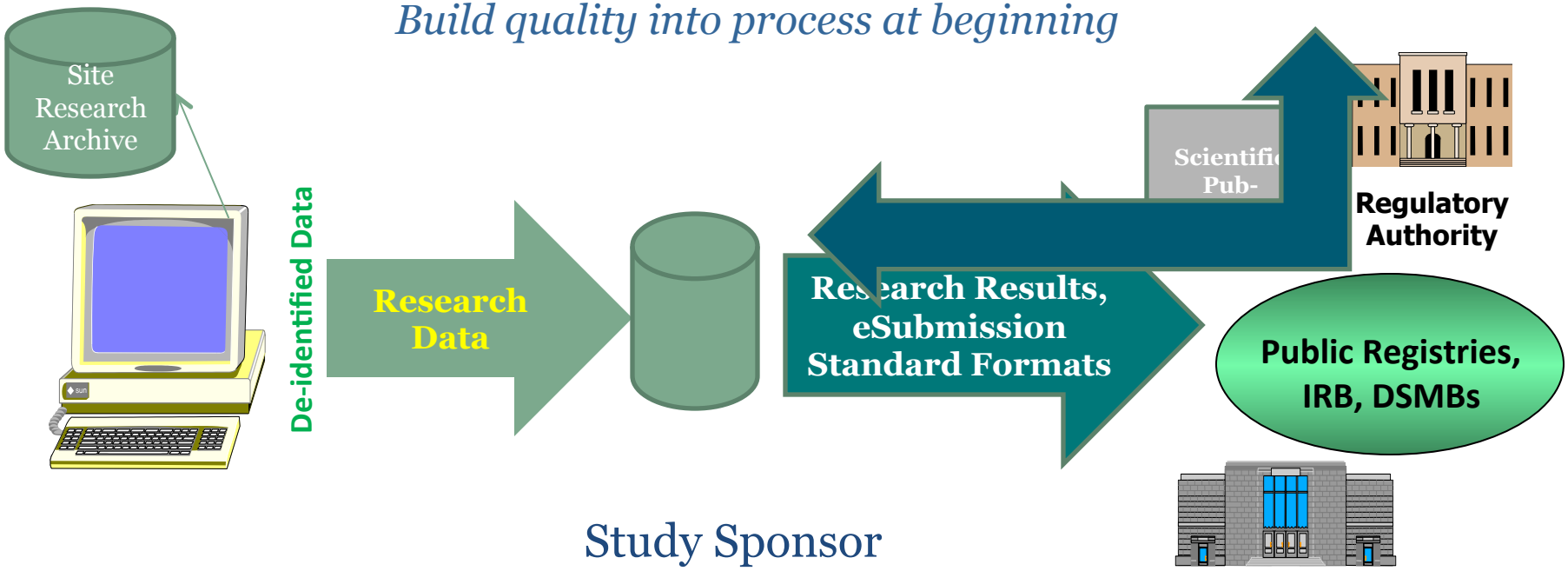
CDISC Healthcare Link



Patient Value:
Quality of Healthcare, Safety

Research informs healthcare more effectively
Build quality into process at beginning



Research Site
(Healthcare Location, Investigator, Site Personnel)

Study Sponsor
(e.g. ARO, CRO, Vendor, Principal Investigator, potentially AHRQ…)

Reviewers
(e.g. Research Partner, Sponsor, Registry, Regulator, IRB, DSMB)

CDISC Standards are NOT just for FDA eSumissions!

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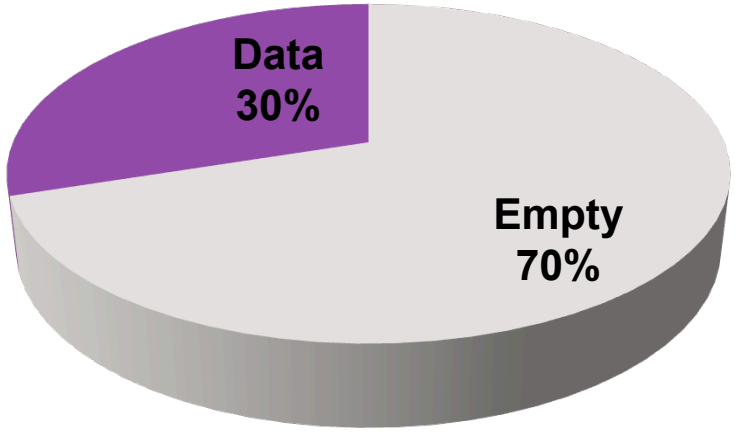
Challenges Faced Within Current Environment

- Limitations of the dataset standard for submission (SAS Transport V5)
  - Variable name length limited (8)
  - Variable label length limited (40)
  - Variable size limited
  - Variable size pre-allocated based on length
- Dataset files size – increasing dramatically



Challenges Faced Within Current Environment

- Flat, two-dimensional data structure for hierarchical, multi-relational data
- Clinical data is hierarchical and multi-relational – “round”
- Important **meaning** is lost when exchanging 2 dimensional flat files, making some interpretations and analyses difficult or impossible, i.e. decreased **semantic interoperability**
- Just like flat maps are useful for relatively short distances, they are not useful in navigating the globe