CDISC Standards Development & Strategy Update

October 2008

CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

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CDISC®

Setting the Global Standard for Medical Research

Clinical Data Interchange Standards Consortium (CDISC)

- Global, open, multidisciplinary, non-profit organization initiated in 1997 as a volunteer group
- Incorporated in 2000; now > 250 member organizations
  - Academic research centers
  - Global biopharmaceutical and device companies
  - Technology and service providers, etc.
- Active Coordinating Committees in Europe, Japan and China
- ISO Liaison Status A to TC 215 (Healthcare Standards); Member of Joint Initiative Council (JIC)

Update on Standards Development

What's new in 2008 ?

CDISC Standards	Description	Implementation Version Release Date
SDTM, SEND (Reg. Submission)	Ready for regulatory submission of CRT Over 10,000 downloads as of late-2007	2004*
ODM	CDISC Transport Standard for data interchange (acquisition, exchange, documentation and archive)	2001*
Define.xml	Case Report Tabulation Data Definition Specification (submission documentation)	2005*
LAB	Content standard – available for transfer of clinical lab data to sponsors	2002
ADaM (Analysis Data)	Analysis data for submissions - general considerations document and examples	2004
Protocol Representation	Collaborative effort to develop machine-readable standard protocol with data layer	2008
Terminology Codelists	Developing standard terminology to support all CDISC standards	2008 (SDTM 3.1.1 and CDASH)
CDASH (Data Collection)	Data acquisition (CRF) standards	2008

* Specification referenced via FDA Final Guidance

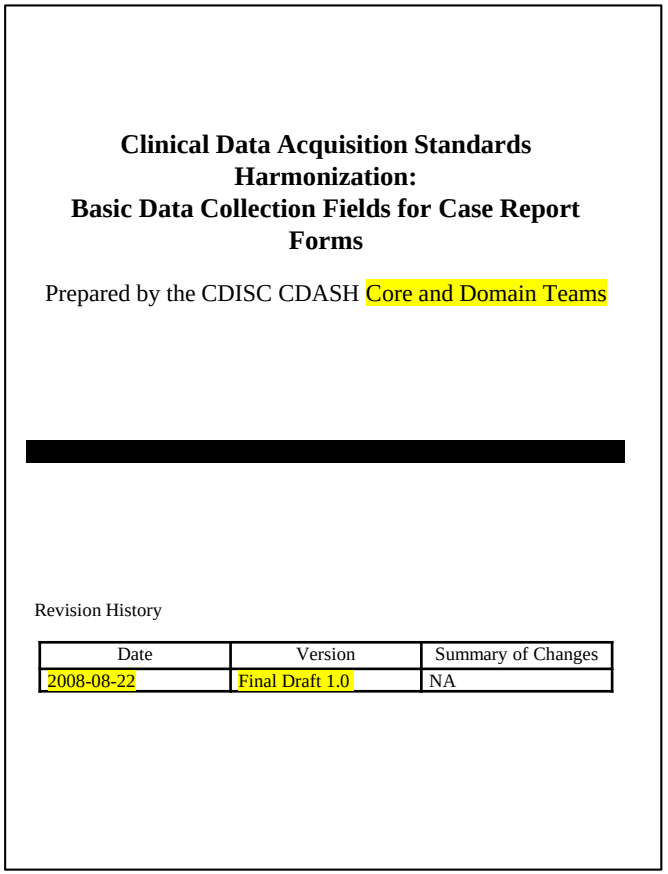
Project Snapshot

- 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.
- Consolidated document posted for Public review in May 2008.
- 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

CDASH v 1.0

Published
3 October 2008



Clinical Data Acquisition Standards Harmonization:
Basic Data Collection Fields for Case Report Forms

Prepared by the CDISC CDASH Core and Domain Teams

Revision History

Date	Version	Summary of Changes
2008-08-22	Final Draft 1.0	NA

CDASH-SDTM Terminology

“ANSWERS” to the CDASH “QUESTIONS”

- Gap analysis done – goal was to determine what terminology is needed by CDASH.
- New terminology WG was created to identify needed terminology (SDTMIG 3.1.2 & CDASH).

Goal – Aligning SDTM terminology projects with CDASH requirements to support full harmonization

Terminology Snapshot

- Primary Objective: to define and support the terminology needs of CDISC standards across the clinical trial continuum (CDASH → SDTM)
- Focus on “standard” terminology codelist development and publication, beginning with SDTM IG version 3.1.1 (safety data domains)
- Key partnership with US National Cancer Institute Enterprise Vocabulary Services (NCI EVS) with terms coded in *NCI Thesaurus*
- Key harmonization activities with FDA, ISO, NCI, HL7 RCRIM, etc.

Guiding Principles

- Adopt...Adapt...Develop Philosophy
- Evaluate and/or utilize existing terminology 1st
- Expand existing vocabularies where incomplete, working with vocabulary developer / owner
- Harmonize across CDISC standards and with other pre-existing vocabulary initiatives
- Address international needs for global projects and organizations
- Ensure a sustainable “open source” environment and infrastructure for production terminology supporting terminology evolution

SDTM Terminology

(~2300 production terms)

- http://www.cdisc.org/standards/terminology/index.html
  http://www.cancer.gov/cancertopics/terminologyresources/CDISC
- SDTM Package 1: 30 codelists & 825 controlled terms distributed broadly across SDTM
- Labtest Package 1: single codelist with 180 controlled terms for Laboratory Test Results (commonly used for Analytes)
- SDTM Package-2A: 12 codelists & 590 controlled terms for ECG, Con Meds, Drug Exposure and Substance Use, including Units & Frequency
- SDTM Package-2B: 7 codelists & 330 controlled terms for Location (LOC), Disposition Event, Race, Subject Chars, Marital Status, Skin Classification and Skin Type
- Labtest Package 2: Additional 260 controlled terms for Laboratory Test Results

SDTM & CDASH Terminology

(~220 terms available for public review)

- See What's New on CDISC homepage http://www.cdisc.org/
- SDTM Package-3:
  - 6 code lists & 70 controlled terms developed
  - Available for public review through Oct. 17 and will be moved into production by year's end
  - Drug Accountability Test (DATEST), Evaluator, Reference Range Indicator, Relationship Type, Specimen Type, Specimen Condition
- Labtest Package-3:
  - SDTM – 180 additional terms developed and available for public review through Oct. 17
  - Terms aligned between SDTM and SEND
  - Ongoing consideration to align with LOINC
- CDASH-Specific Codelists:
  - Ongoing/Resolved (MHONG) and Prompt for Substance Use (SUNCF)

Future Plans

- Complete terminology for SDTM IG version 3.1.1 (December 2008)
- Formalize terminology maintenance process via NCI EVS mechanism to address additions and change requests
- Complete terminology alignment for CDASH version 1.0 (early Spring 2009)
- Consider new SDTM domains (Pharmacokinetics, Microbiology)

Future Plans (Cont.)

- Support and harmonize terminology with other maturing CDISC standards (ADaM, SEND)
- Continue extending harmonization with other standards initiatives (ISO, HL7, CEN, HITSP)
- Align terminology with BRIDG model and to support CDISC-HL7 message project(s)
- Continue to support disease-specific standards activities (TB, CV)

Protocol Representation: Project Scope Project Description

Protocol Representation will identify standard elements of a clinical trial protocol that can be further elucidated and codified to facilitate study design, regulatory compliance, project management, trial conduct and data interchange among consumers and systems.

This work will be based upon the needs of protocol consumers, which may include regulatory authorities, IRBs, statisticians, project managers, site personnel and users of any downstream systems for the management of clinical trial information.

Project Objective(s): Publication of a standard, machine-readable model for protocol representation that will enable interchange of this data among systems and stakeholders.

Protocol Representation

3.1. Summary of Study Design

FORM: Bolded, Arial, 14pt, Heading Level 1

This is a prospective, randomized, double-blind, double-dummy, placebo controlled, forced-titration, multicenter, parallel group trial. Stage I or II hypertensive patients, age 18 years of age or older, who meet all other inclusion and exclusion criteria and successfully complete the placebo run-in period will be randomized at the site level.

FORM: Arial, 14 pt, Body text

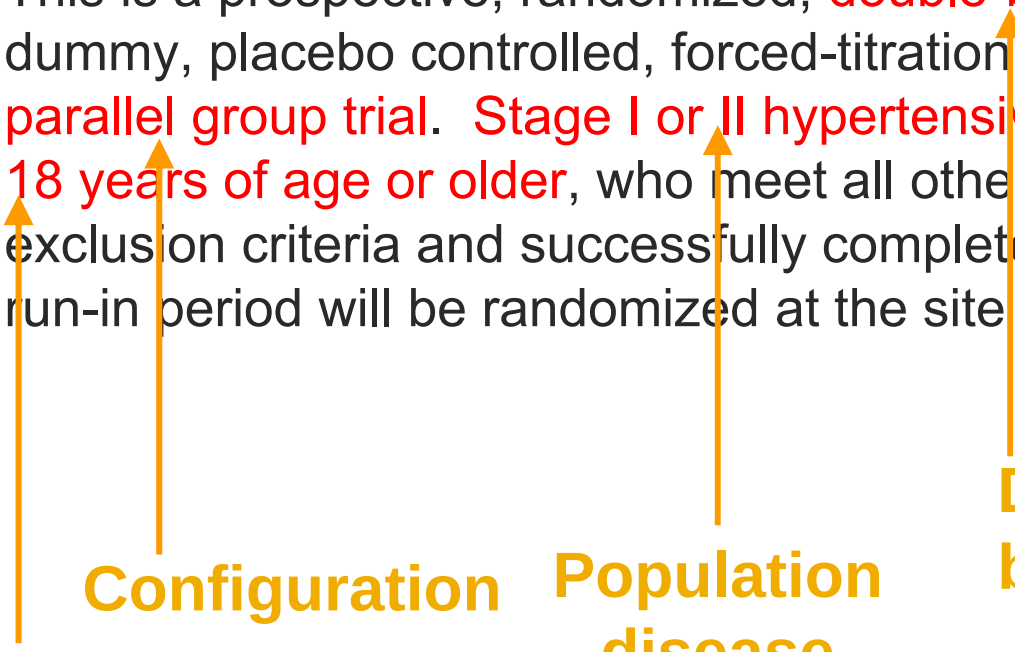
Not very Useful!

Source: Cara Willoughby

A Document Example: Structuring Information by "Meta" Information

3.1. Summary of Study Design

This is a prospective, randomized, double-blind, double-dummy, placebo controlled, forced-titration, multicenter, parallel group trial. Stage I or II hypertensive patients, age 18 years of age or older, who meet all other inclusion and exclusion criteria and successfully complete the placebo run-in period will be randomized at the site level.



Source: Kristin O'Connor

A Document Example: Structuring Information by “Meta” Information

“Meta” Information about Content	Content
Subject age description	Age 18 years of age or older
Configuration	Parallel group trial
Population disease description	Stage I or II hypertensive patients
Degree of blind	Double-blind

Much More Useful!

PRG Approach

- Development should concentrate on content first and implementation second
- Elements must be defined in a glossary, since the industry uses multiple definitions for the majority of protocol elements
  - CDISC Glossary, Applied Clinical Trials, published yearly
- Identify core set of elements initially, expand with further details as needed
- Initially based on
  - ICH E6 - Basis for the development and organization
  - ICH E3 - Terms & definitions
  - EudraCT (EMEA) - Key words and Protocol description
  - Specific topics (e.g. IRB, SAP-E9)

Protocol Representation

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

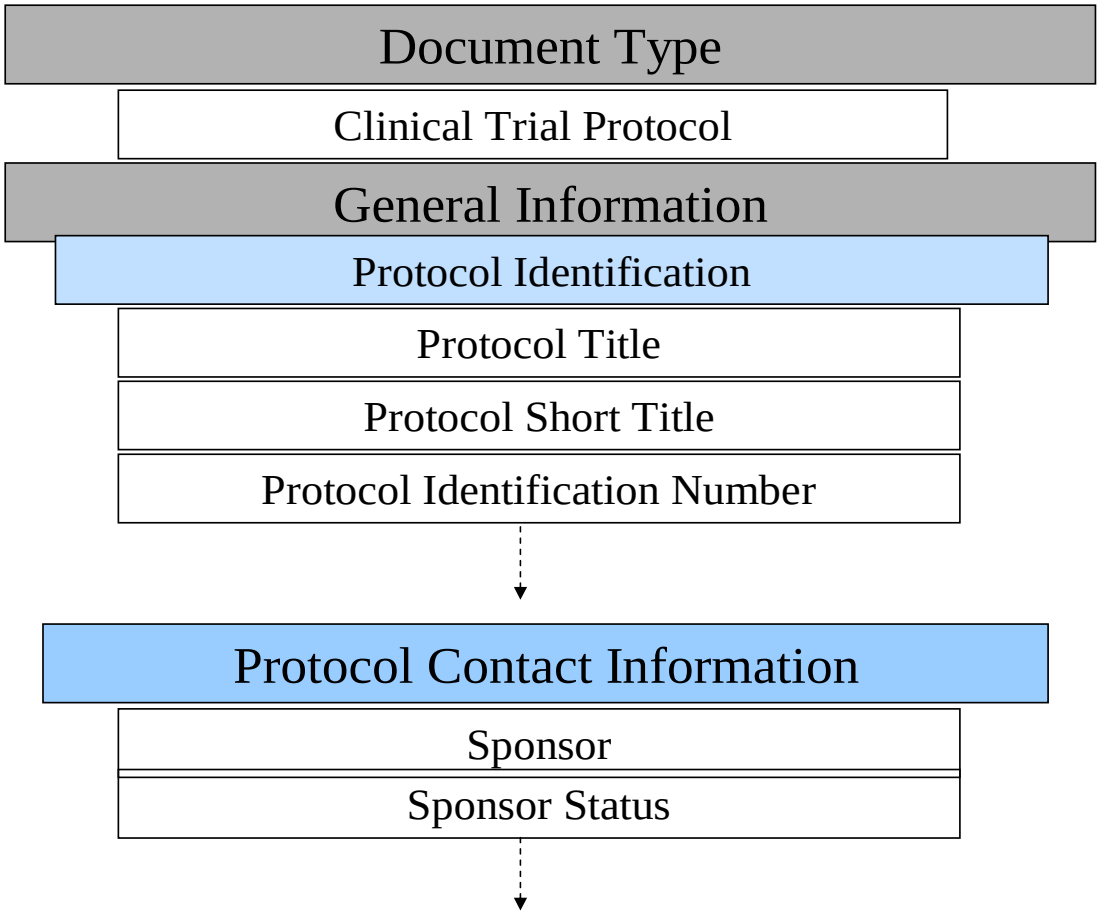
6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

ELEMENT NUM	ELEMENT NAME	ELEMENT DEFINITION (FROM GLOSSARY)	DEFINITION SOURCE	ELEMENT EXPLANATION (recommendations/ examples for usage)	ELEMENT SOURCE	ELEMENT SOURCE CONTENTS	NOTES
Document Type							
GENERAL INFORMATION							
1	Protocol Title			Full text of the protocol/study title	*ICH E6 6.1.1, EUDRACT*	*Appendix I A. Full title of the protocol*	
2	Protocol Short Title			Name or abbreviated title of the trial wherever available	*EUDRACT*	*Appendix I A.Abbreviated title of the trial*	
3	Protocol identifying			Sponsor protocol number;and/or Unique	ICH E6 6.1.1, EUDRACT	*National trial # reference, EUDRACT clinical trial number, Sponsor code = sponsor*	EUDRACT stated that this was a national identificaton
264	Provision of Data to Authors			All authors whether from within a sponsoring company or external, will be given the relevant statistical tables, figures, and reports needed to support the planned publication.	PhRMA Principles on Conduct of Clinical Trials and Communicatio n of Clinical Trial Results (http://www.ph rma.org/public ations/policy//2002-06-24.430.pdf0)		

Protocol Representation - Hierarchy

- Document Type
- General Information
- Background Information
- Trial Objectives and Purpose
- Trial Design
- Subject Selection and Withdrawal
- Subject Participation/Study Design
- Treatment of Subjects
- Efficacy Assessments
- Assessment of Safety
- Statistics
- Direct Access to Source Documents
- Quality Control and Quality Assurance
- Ethics
- Data Handling and Record Keeping
- Financing and Insurance
- Publication Policy
- Supplements

Protocol Representation – Hierarchy
Sample: *Sections, Sub-sections, Elements*

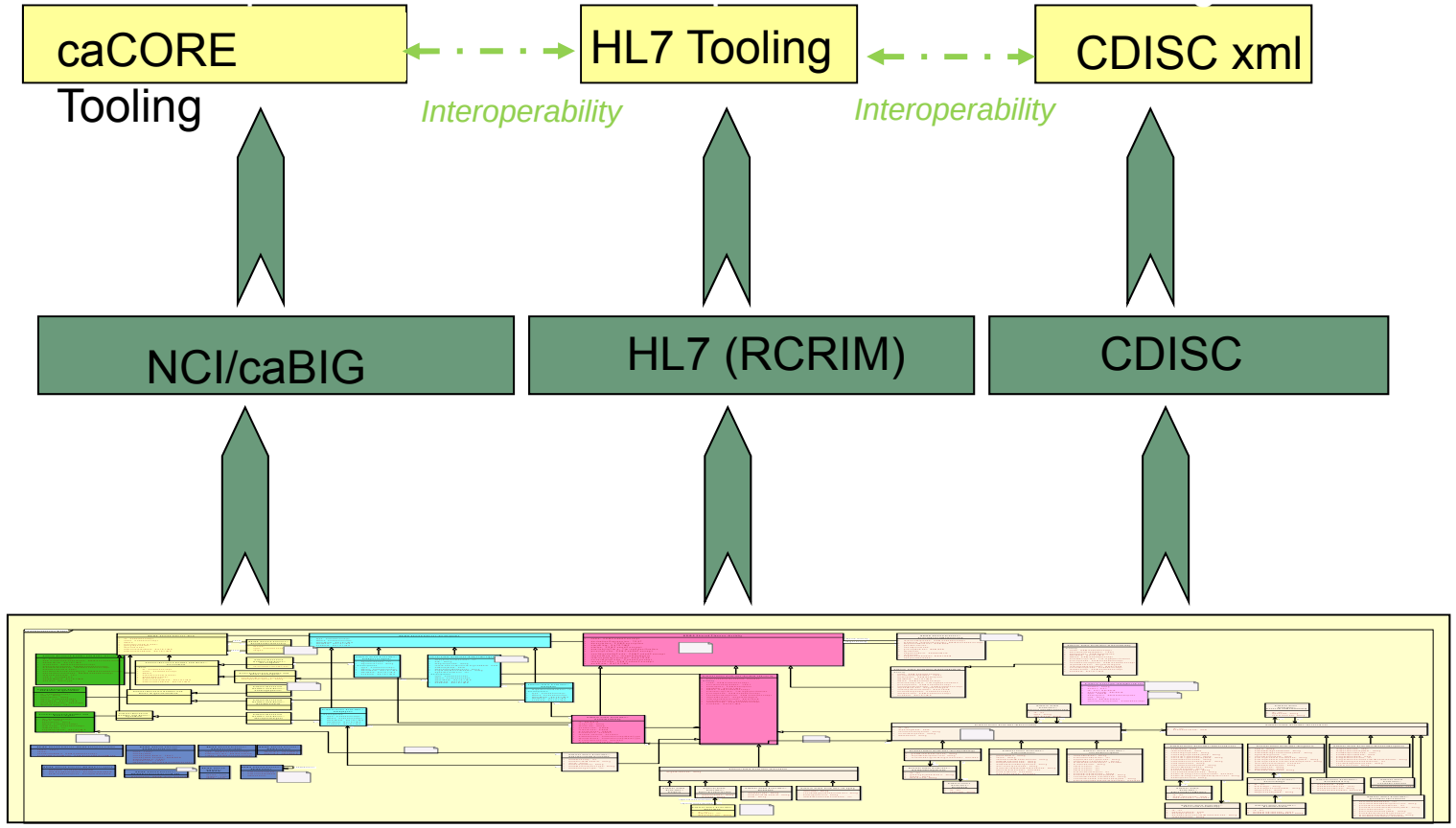


Achieving Interoperability

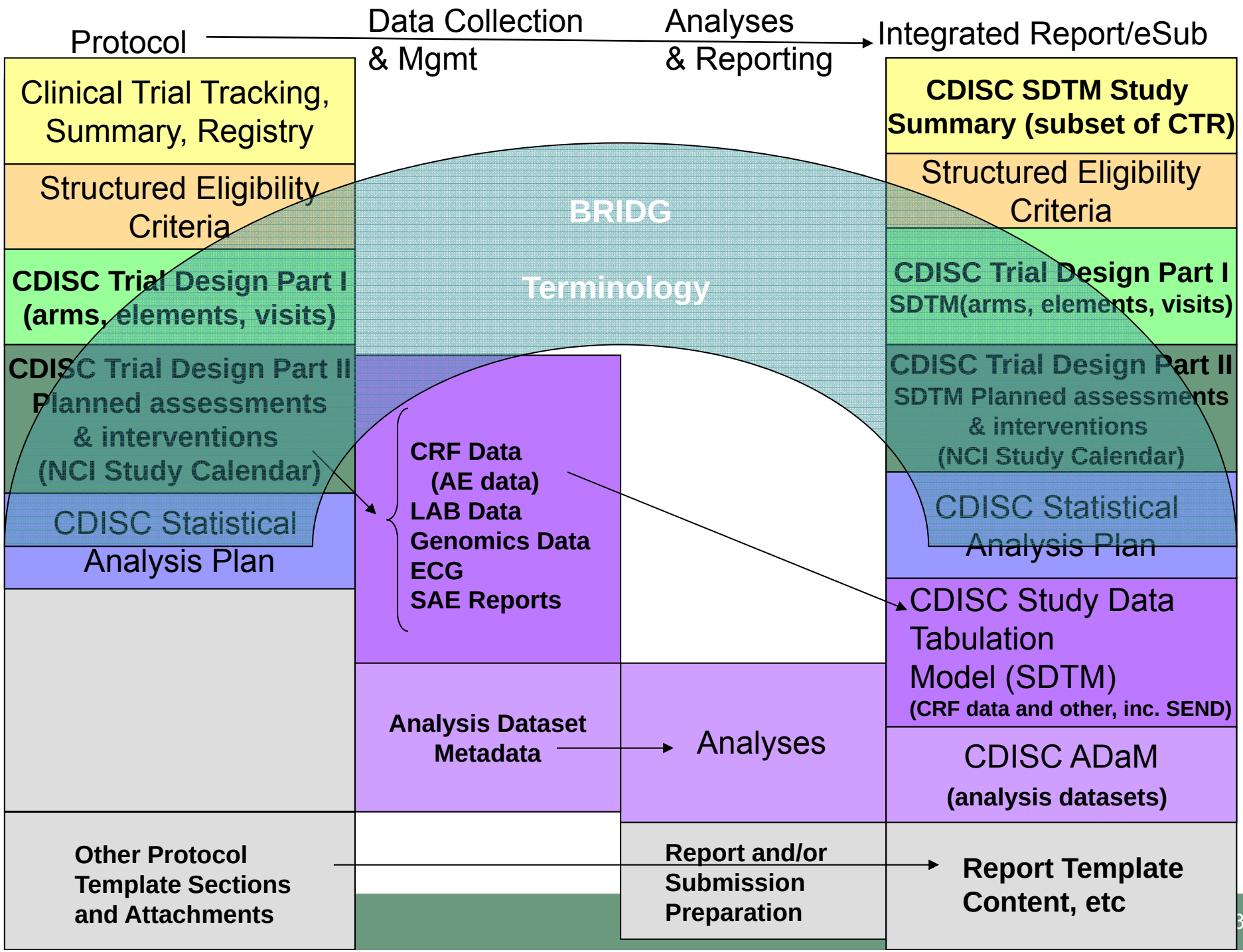
IMPLEMENTATION SOLUTIONS

STAKEHOLDERS

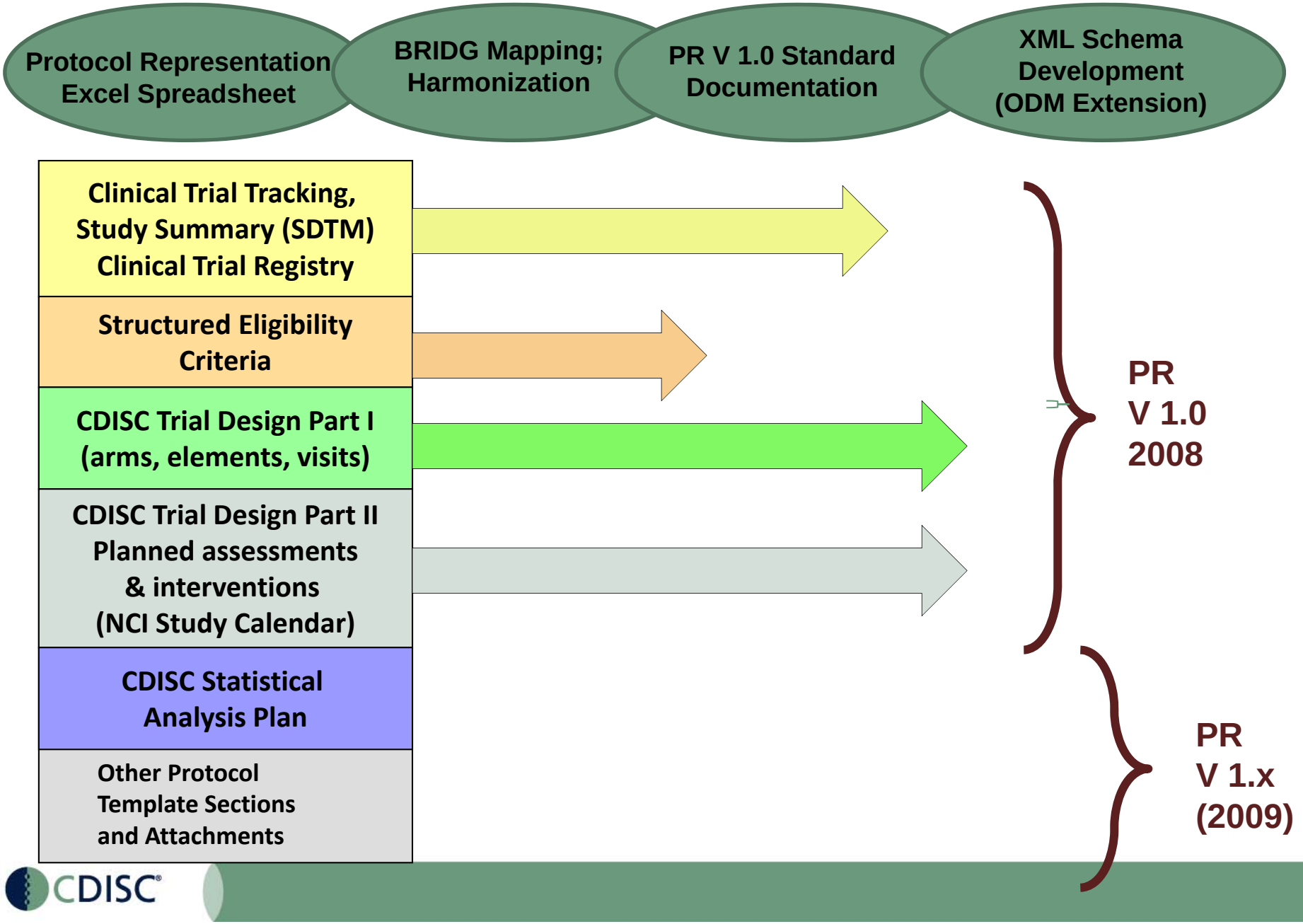
FOUNDATION MODEL



BRIDG – Domain Analysis Model for Clinical Research


Protocol
Data Collection & Mgmt
Analyses & Reporting
Integrated Report/eSub
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
Other Protocol Template Sections and Attachments
BRIDG
Terminology
CRF Data
(AE data)
LAB Data
Genomics Data
ECG
SAE Reports
Analysis Dataset Metadata
Analyses
Report and/or Submission Preparation
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
CDISC Study Data Tabulation Model (SDTM)
(CRF data and other, inc. SEND)
CDISC ADaM
(analysis datasets)
Report Template Content, etc

Protocol Representation Standard - Development



Update on CDISC strategy

Consistency across the CDISC standards

Stability of the CDISC standards

Evolution of the CDISC standards

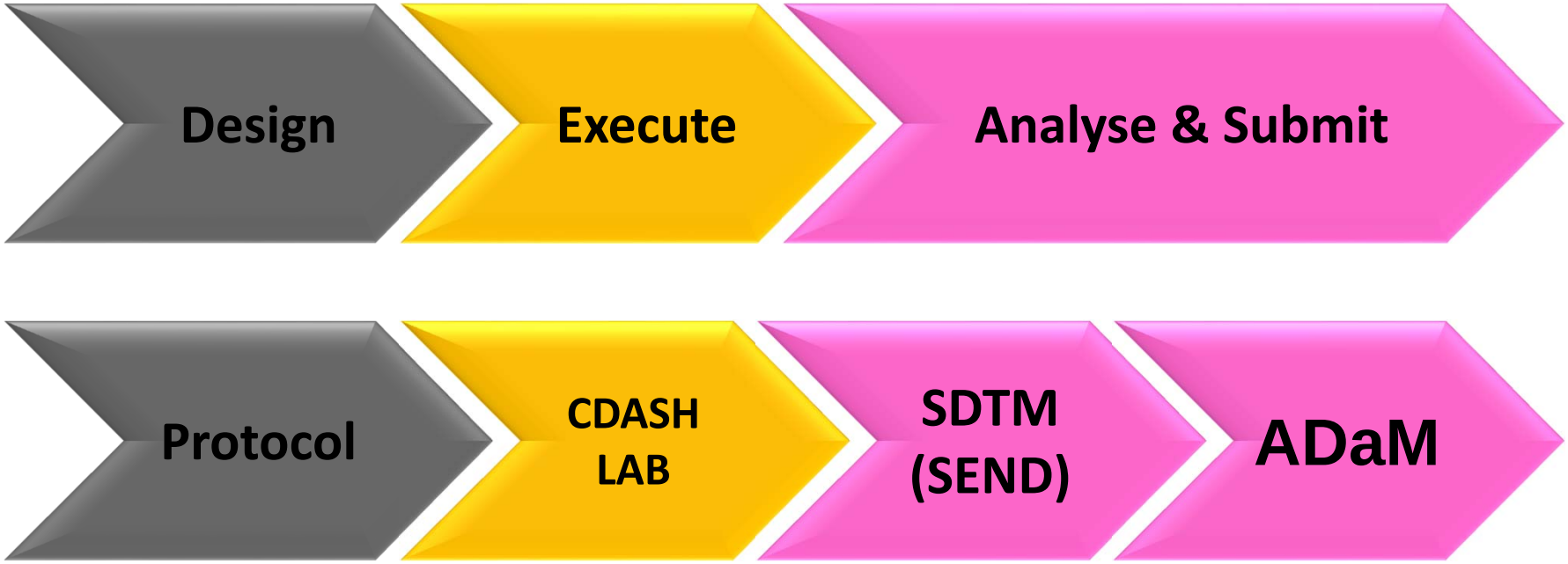
Today

- Industry and FDA have learned a lot about standards over the last ten years
- SDTM has shown the potential
- SDTM has opened people's minds
- To some extent the flood gates have opened
  - People see the benefit
  - They want more
- This is the challenge!

Technical Vision

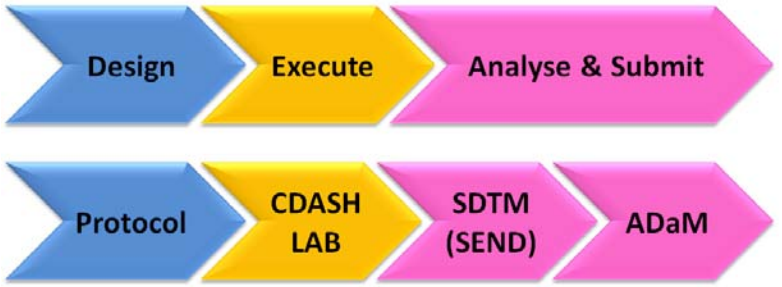
- Documented in Technical Road Map
  - http://www.cdisc.org/about/downloads/CDISC_Road_Map_Spring2008.pdf
- First step in developing a comprehensive strategy
- Next step to be taken Q4 2008
- Will encompass
  - more integrated approach
  - improved process

Build The Foundation Stone



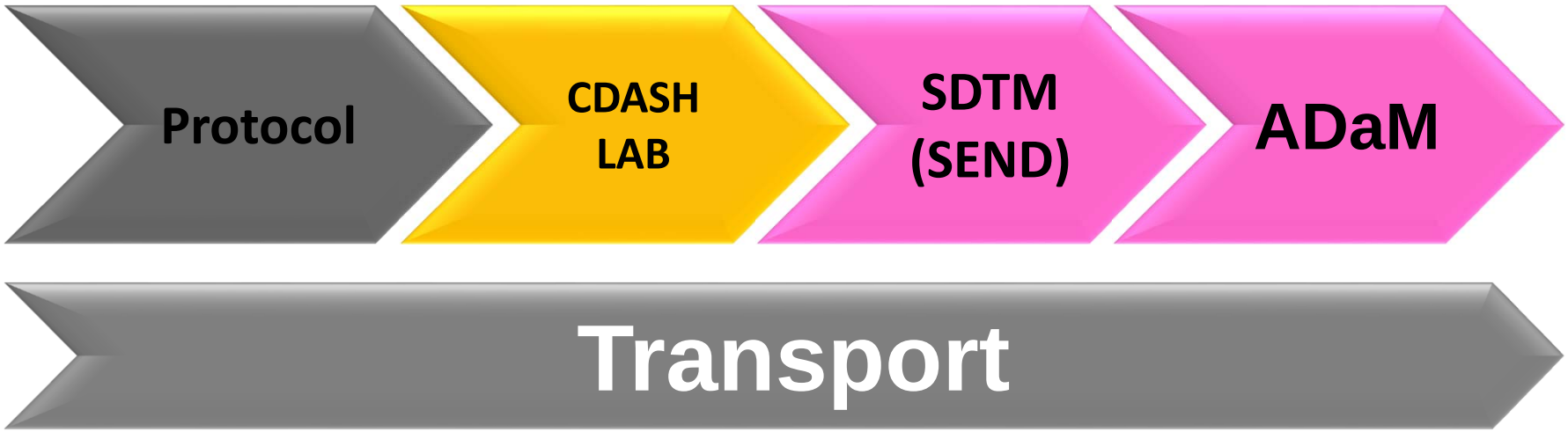
Build The Foundation Stone

- Integrated standards
- Protocol to Submission
- The foundation stone



- Then …
  - We can grow standards into other areas
  - The basis for the evolution of the CDISC products

Separation of Content and Transport

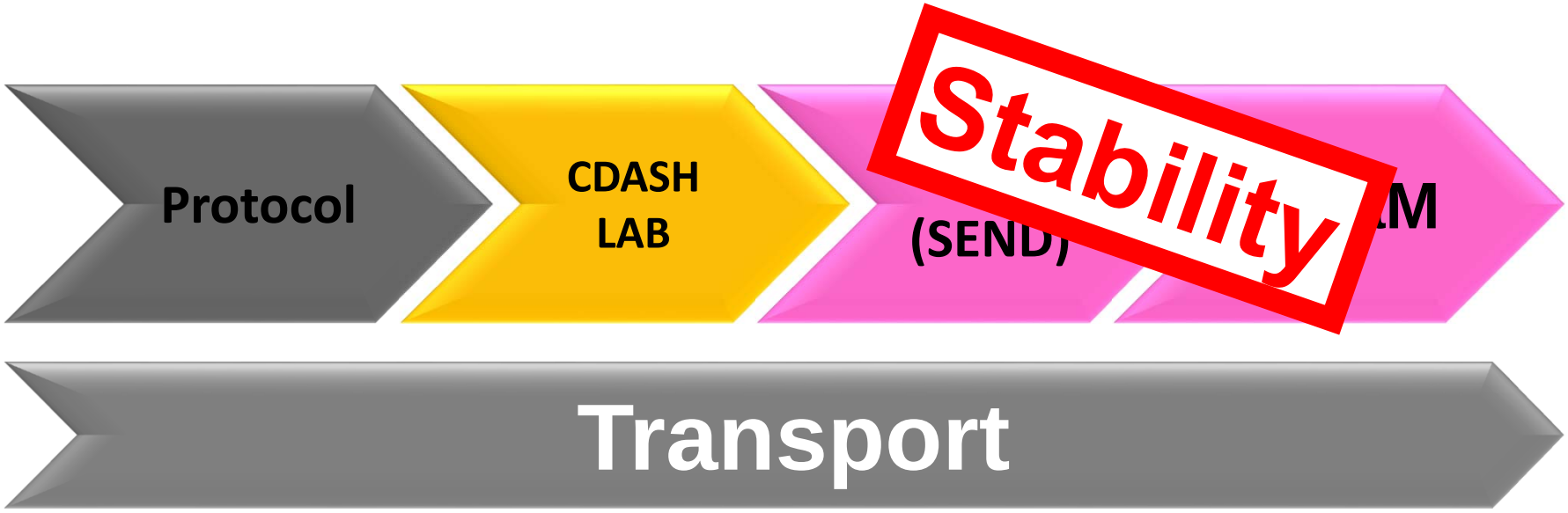


- Key Items
  - BRIDG (broader audience via ISO)
  - Terminology
  - Consistently applied across all standards

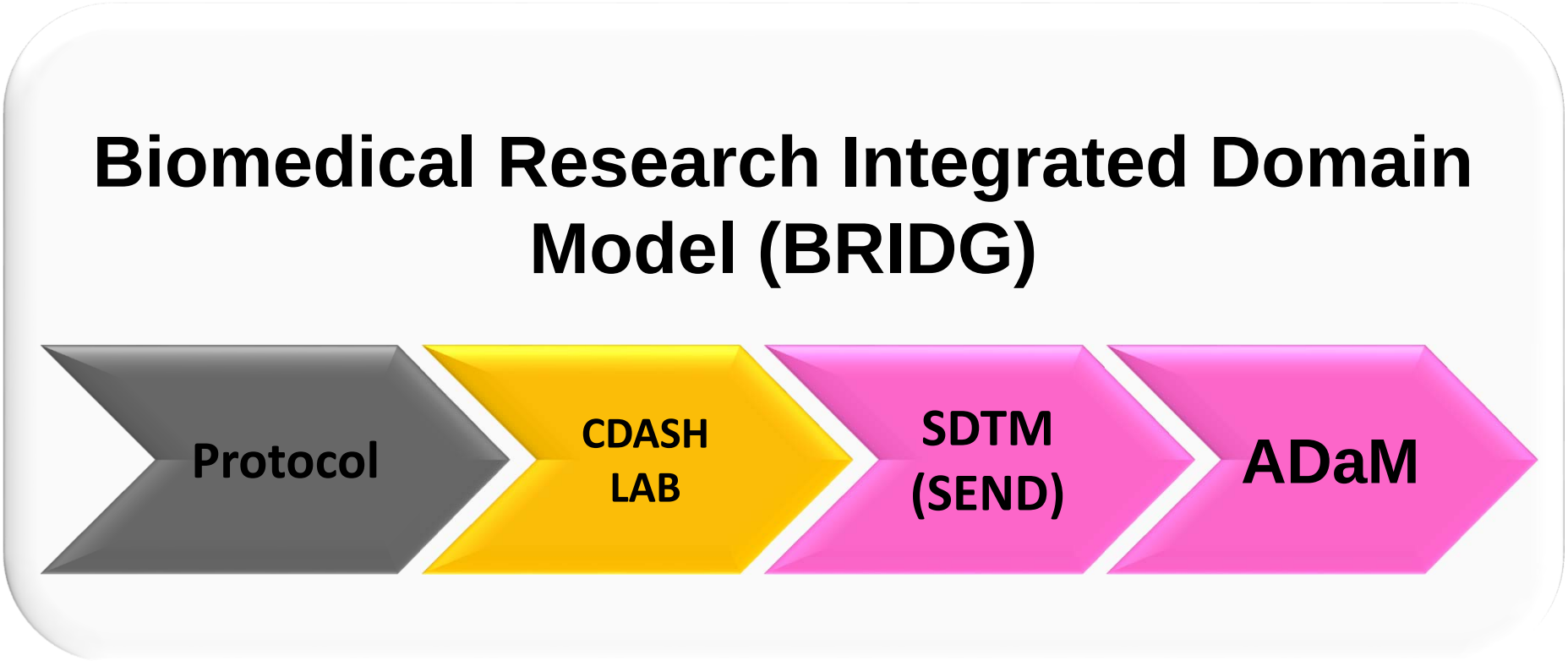
Content and Transport

Contact Details

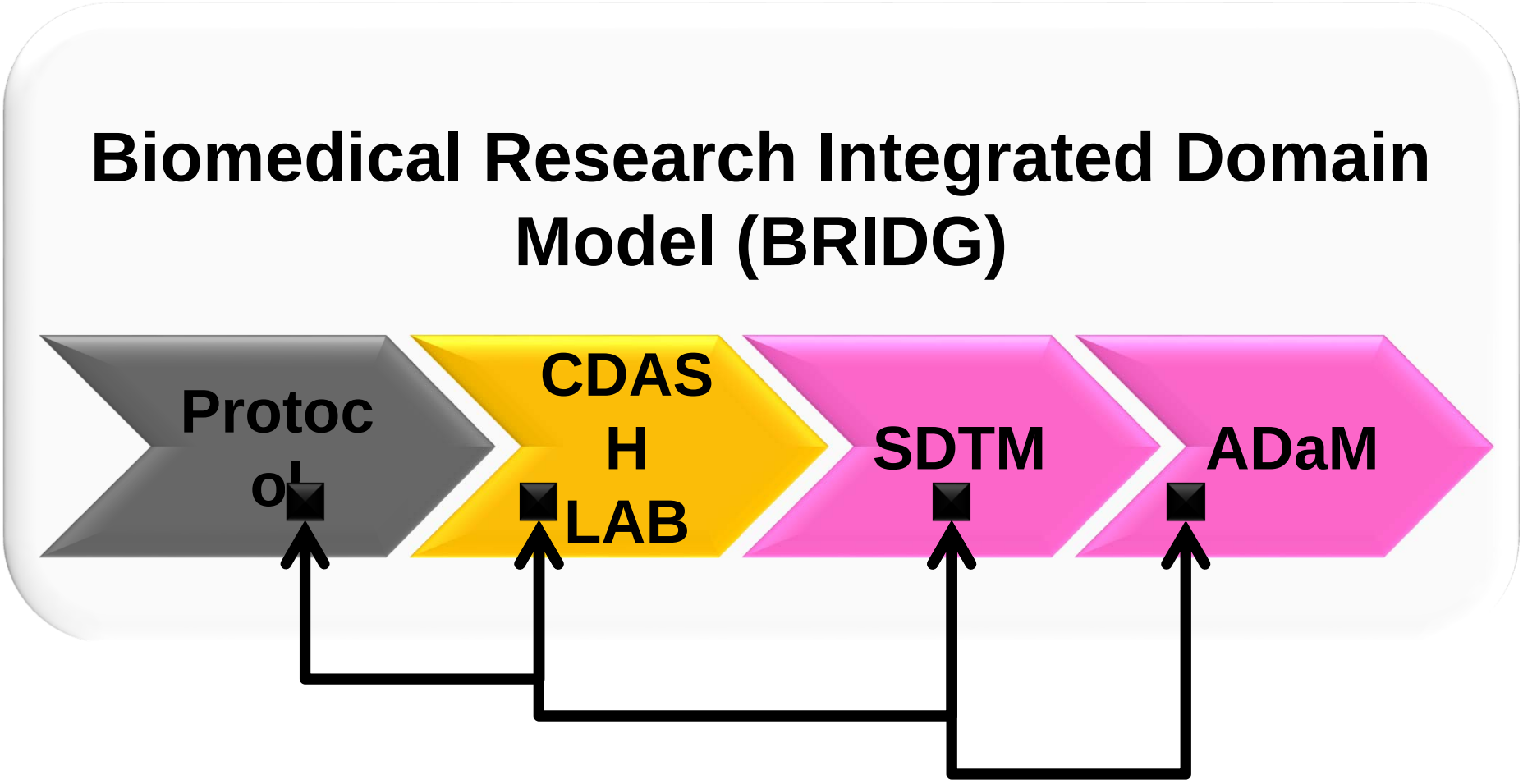
Separation of Content and Transport



Aligned With and By BRIDG



Same Concept, Same Meaning



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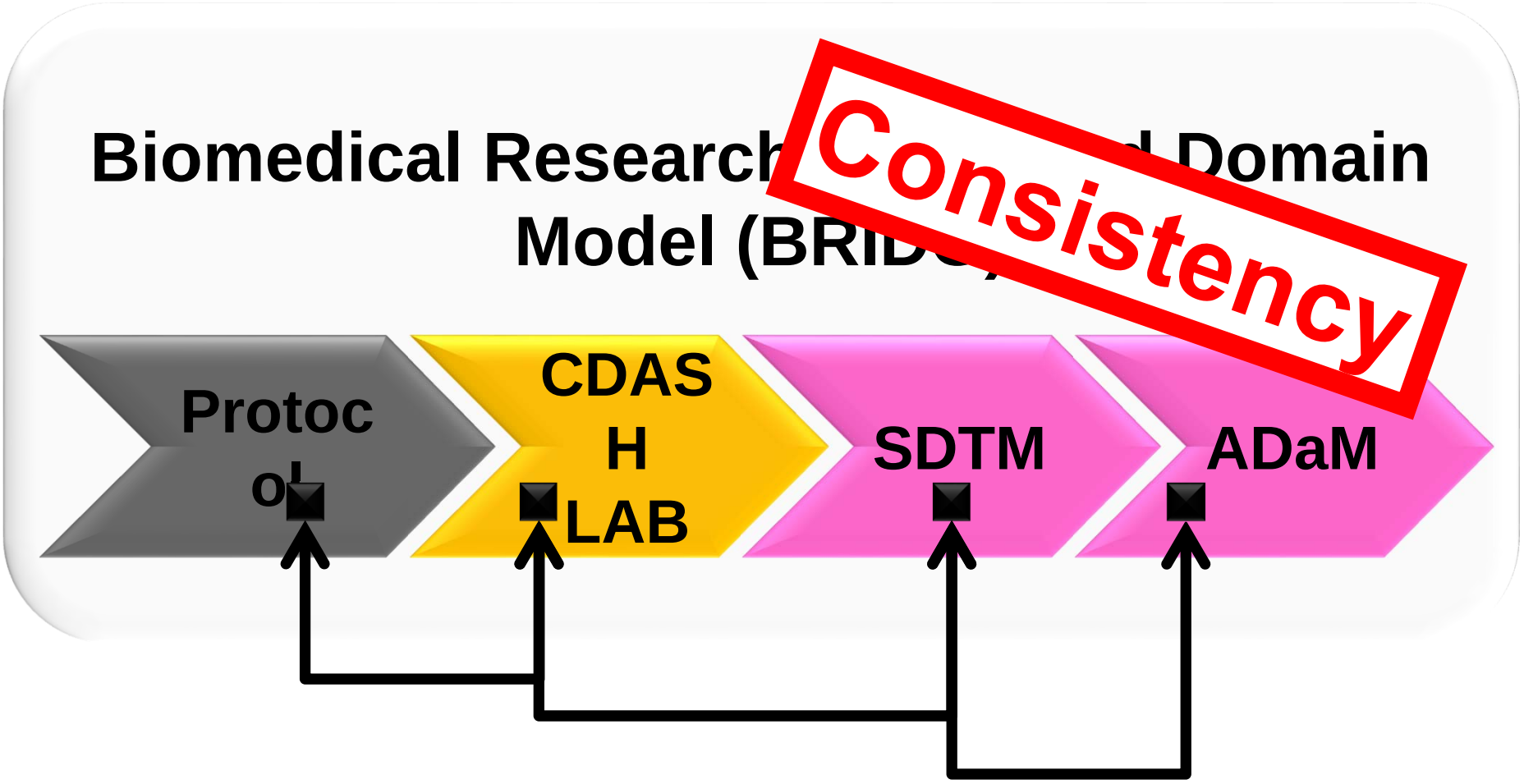


By 2009

- SDTM IG V3.1.2
- Protocol V1.0
- CDASH V1.0
- ADaM IG v1.0 (early 2009)
- define.xml to encompass SDTM & ADaM metadata

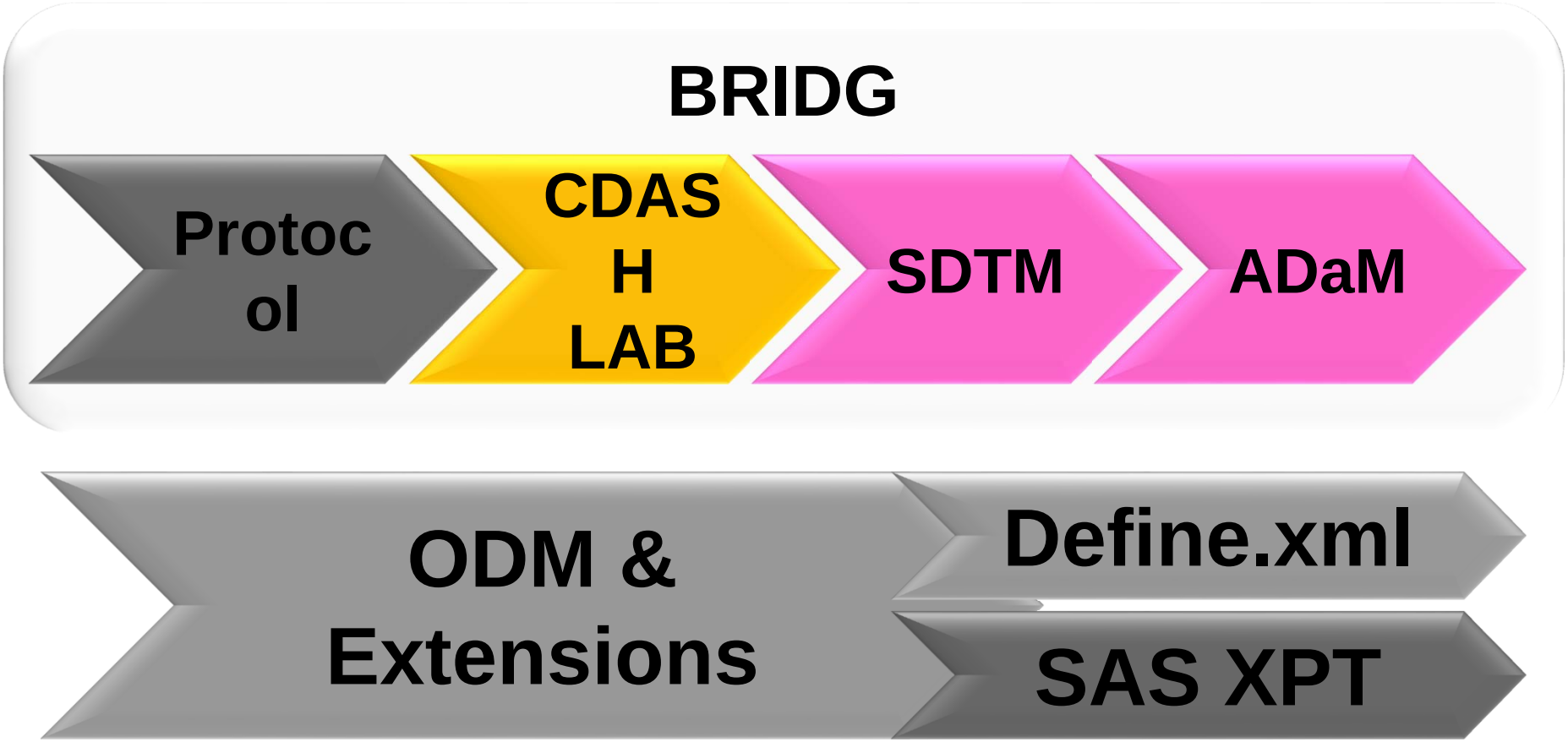
Quarter 2, 2009

Biomedical Research Integrated Domain Model (BRIDG)

By The End of 2009

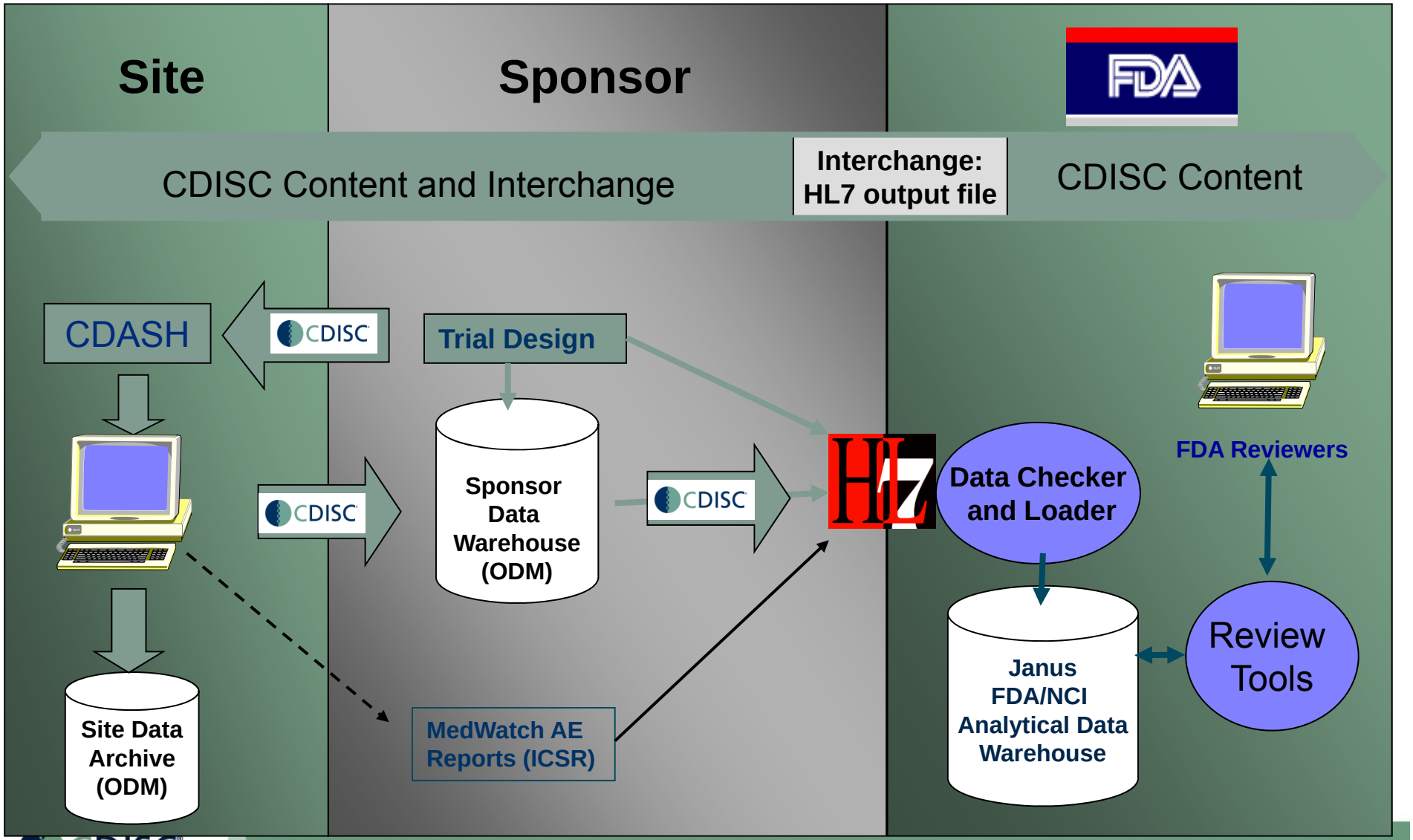
Biomedical Research Integrated Domain Model (BRIDG)

Transport


BRIDG
Protocol
CDASH LAB
SDTM
ADaM
ODM & Extensions
Define.xml
SAS XPT

FDA PDUFA IV IT Plan

Target Clinical Data Flow



PDUFA IV IT Plan

- Pages 28 to 31 lists key CDISC projects
  - SDTM
  - CDISC HL7
  - BRIDG
  - SEND
  - CDASH
  - ADaM
- Links
  - http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-N-0352-bkg.pdf
  - http://www.accessdata.fda.gov/scripts/oc/ohrms/dailylist.cfm?yr=2008&mn=6&dy=30

FDA – CDISC

- Pilots
  - Integrated Safety Data
  - ODM
  - SEND
- Communications Group
- Intrachange

CDISC HL7 Project

PDUFA IV IT Plan - HL7 CDISC Project

- CDISC - HL7 Project - The FDA plans to transition to HL7 exchange messages for submission of all study data. This initiative is based on the outcomes of the CDISC Content to HL7 Message Exploratory Project. The objective of the Exploratory Project was to;
- Harmonize the SDTM into the BRIDG model
- To identify HL7 exchange message content for submission to a regulatory authority that addresses; a) study summary (clinical trial registry), b) eligibility criteria, c) trial design (including parts I and II: arms, elements visits, planned assessments, and planned intervention(s)), d) statistical analysis plan, e) collected data/study data tabulations and f) derived data/analysis datasets, all of which are currently defined by the CDISC standard.

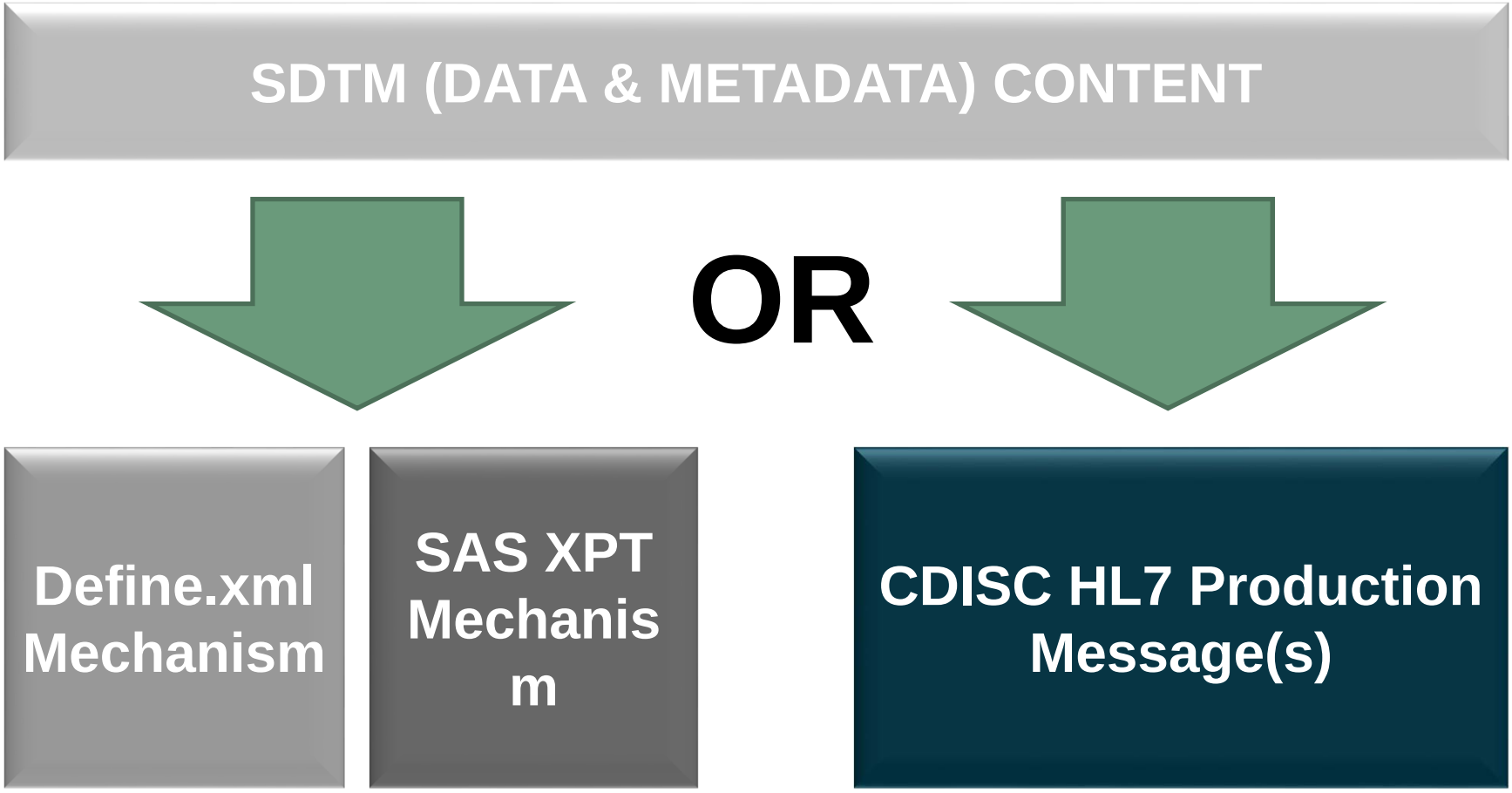
Source: PDUFA IV Plan, May 2008, Page 29

PDUFA IV IT Plan - SDTM

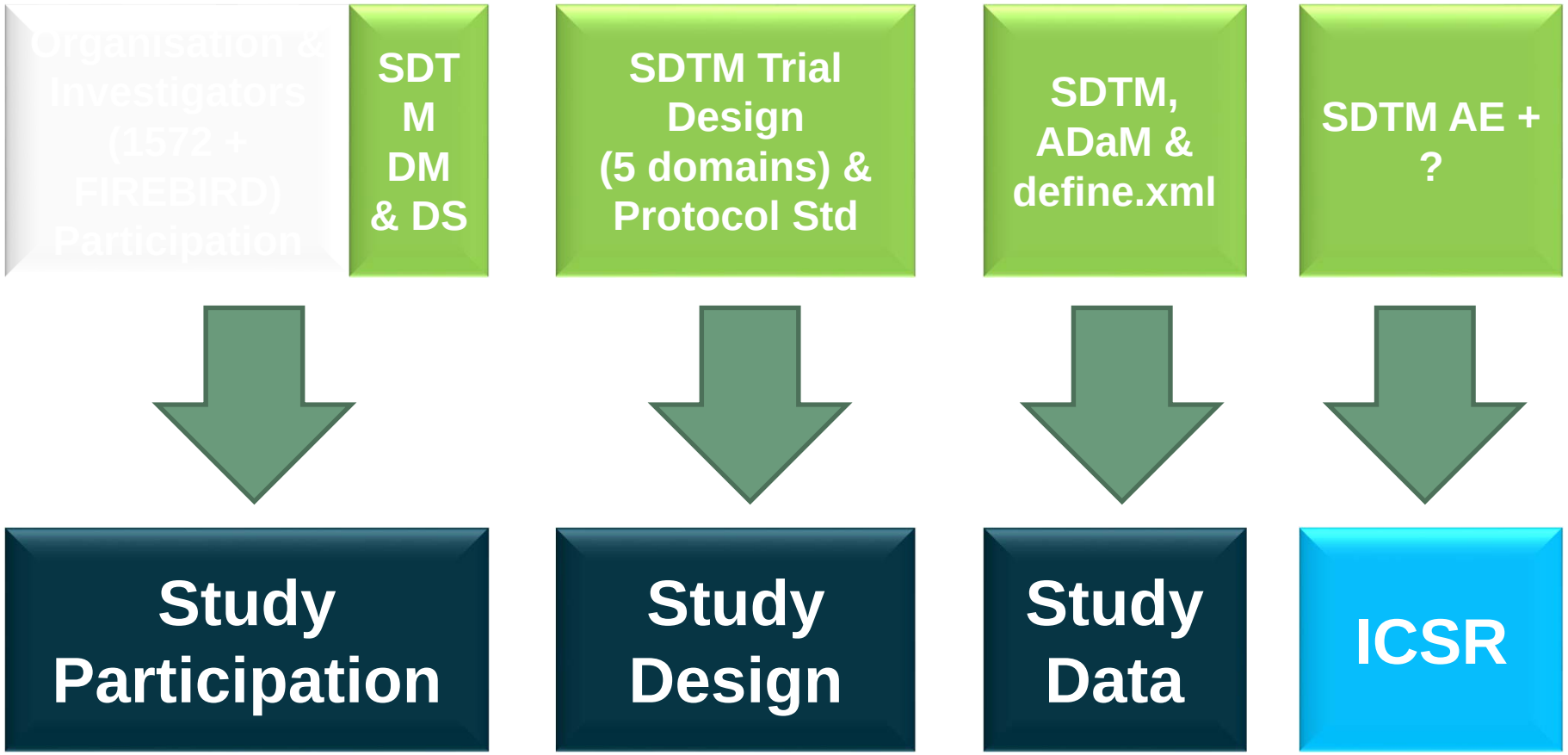
- "The foundation for the standardized clinical content is the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM). The SDTM will also include nonclinical requirements based on the Standard for Exchange of Nonclinical Data (SEND) models that is being harmonized with the SDTM. The CDISC content will be sent to FDA as an XML message using the Health Level Seven (HL7) Reference Information Model (RIM) and harmonized with the Biomedical Research Integrated Domain Group (BRIDG) Model."
- SDTM version 3.1.1 submissions are accepted by FDA. A draft implementation guide for SDTM 3.1.2 is currently under review by CDISC and FDA. FDA and CDISC are in the process of forming a communications team that will ensure SDTM meets FDA's scientific requirements.

Source: PDUFA IV Plan, May 2008, Page 28

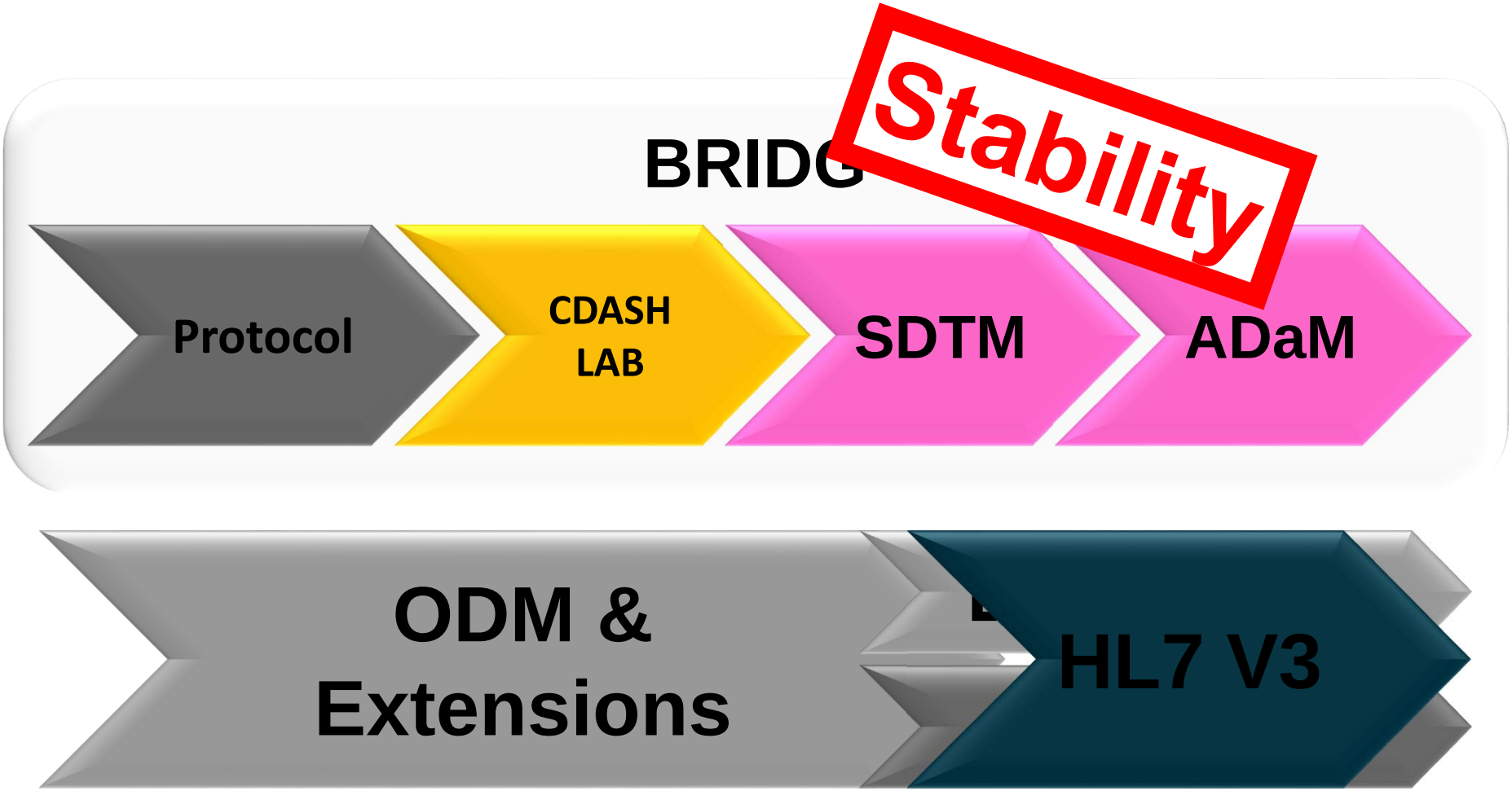
Evolution


SDTM (DATA & METADATA) CONTENT
OR
Define.xml Mechanism
SAS XPT Mechanism
CDISC HL7 Production Message(s)

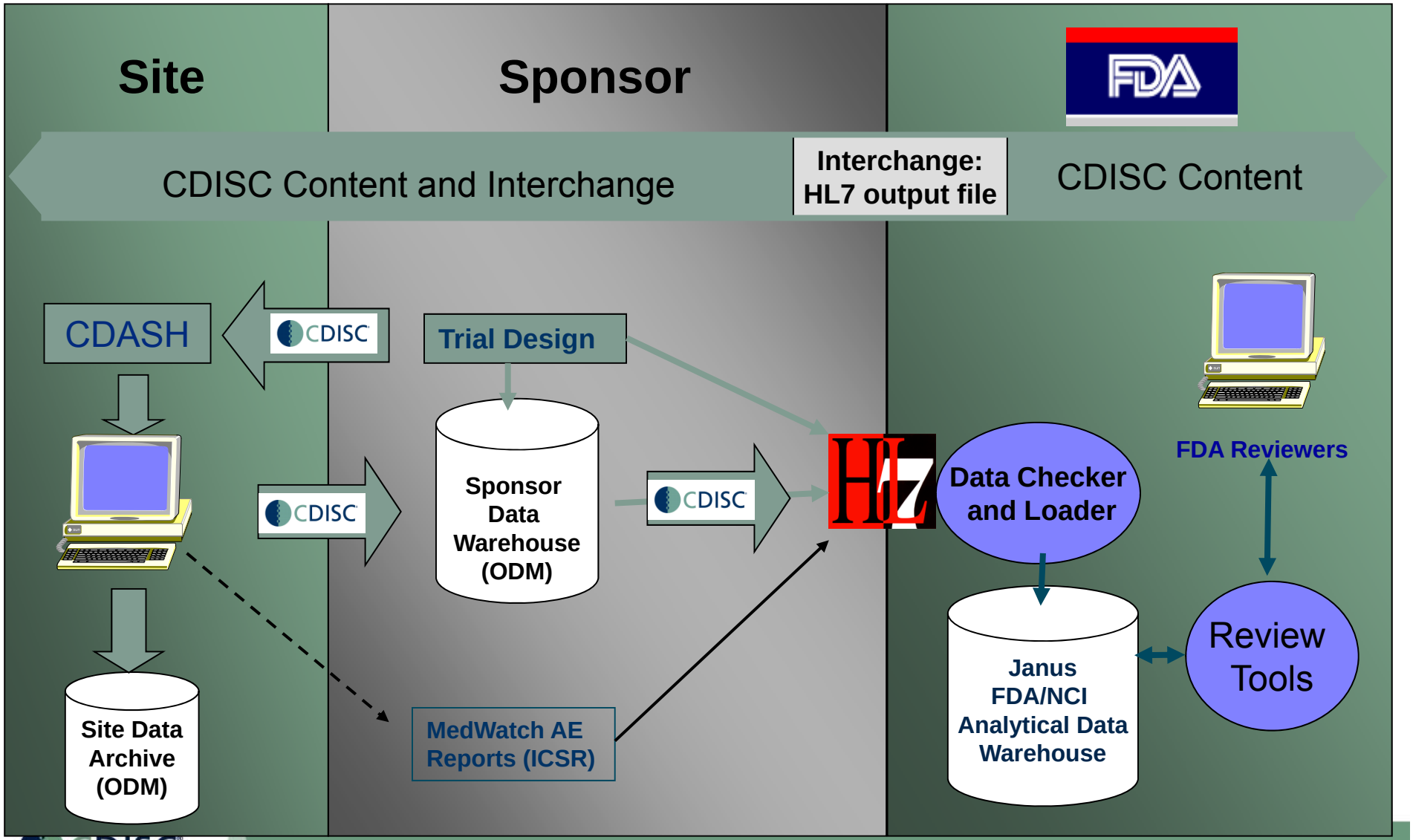
A Slightly More Detailed Picture



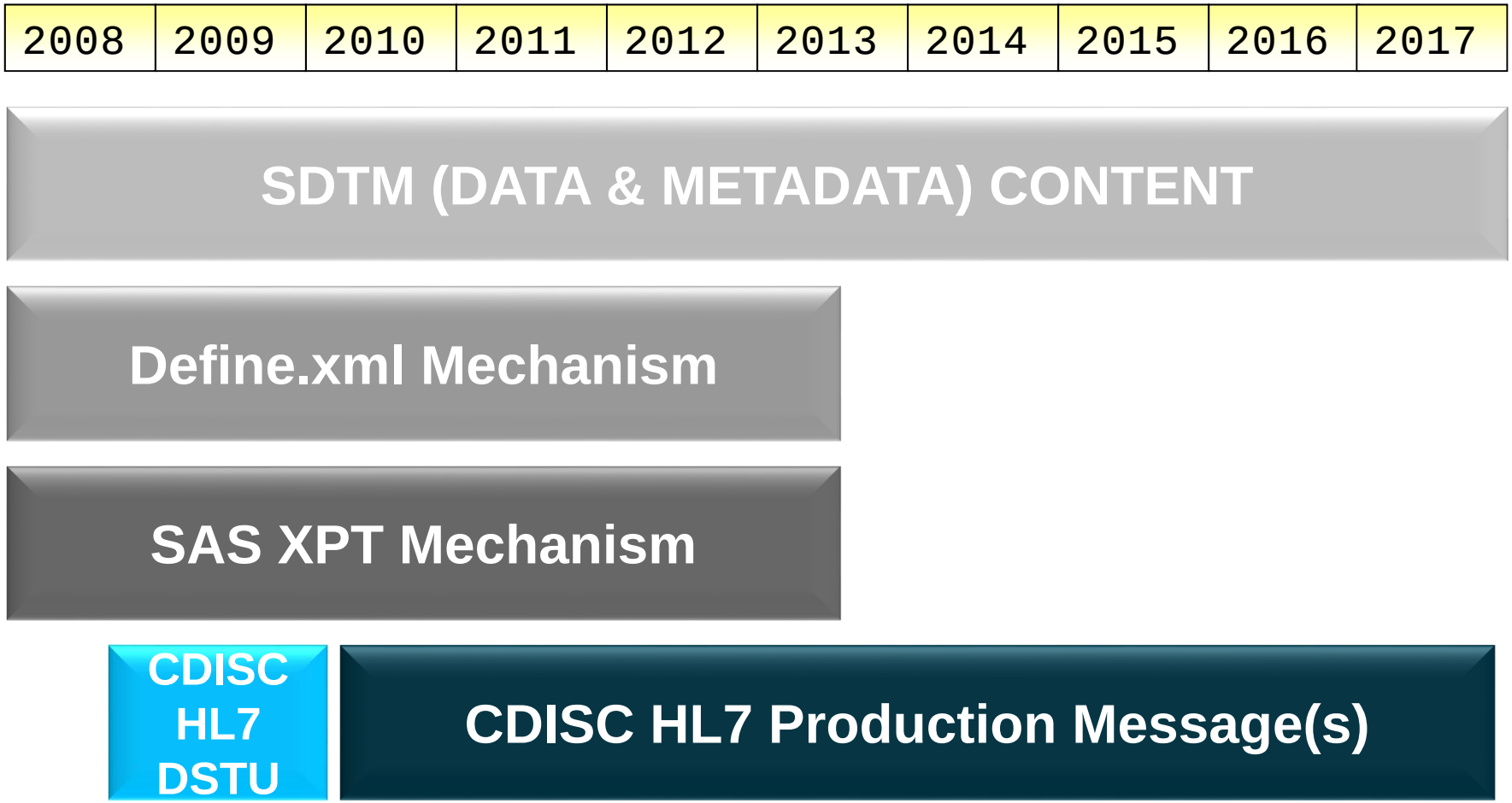
Transport


Stability
BRIDG
Protocol
CDASH
LAB
SDTM
ADaM
ODM &
Extensions
HL7 V3

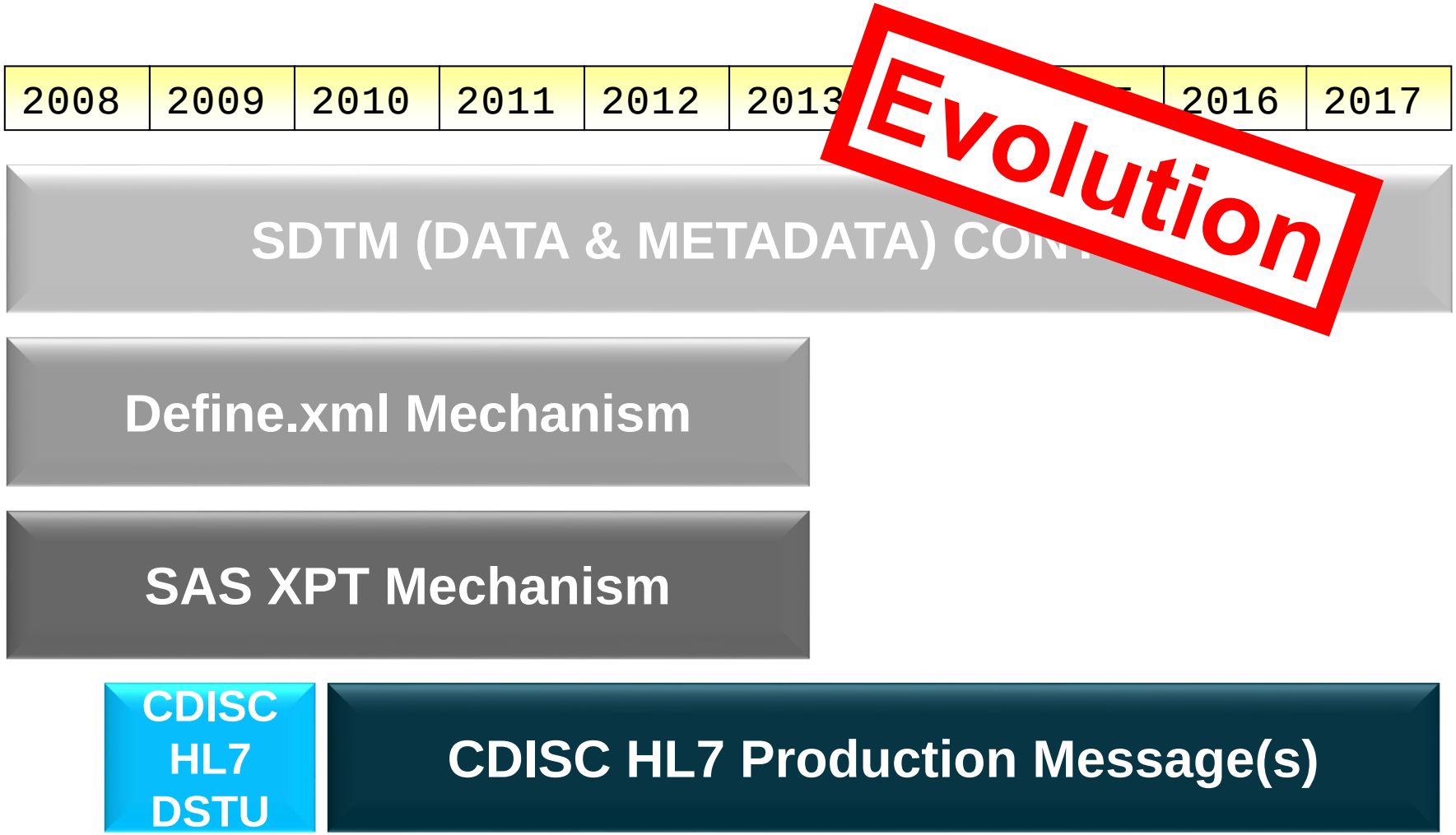
Target Clinical Data Flow



FDA Timeline



FDA Timeline

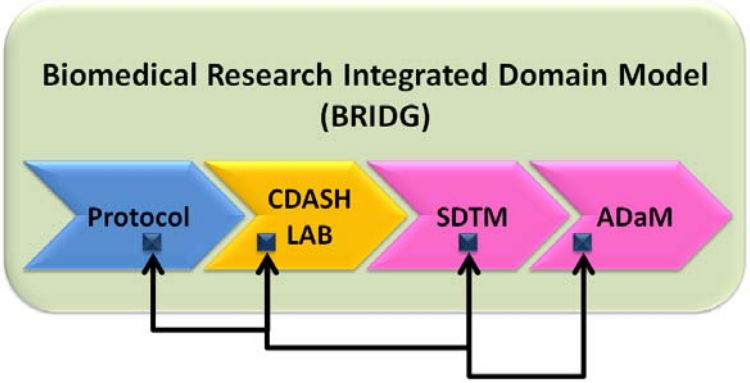


Summary

Summary

- Consistency across the CDISC standards
- Stability of the CDISC standards
- Evolution of the CDISC standards

- CDISC will, through 2009, work to complete the connection of the standards though the process



CDISC operates to advance the continued improvement of public health by enabling efficiencies in medical research and related areas of healthcare.

Strength *through collaboration…*

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