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2023
EUROPE
INTERCHANGE
COPENHAGEN | 26-27 APRIL

State of the CDISC Standards Beyond CDISC 360

Presented by Bess LeRoy, Head of Standards Innovation, CDISC

Meet the Speaker

Bess LeRoy

Title: Head of Standards Innovation

Organization: CDISC

Bess LeRoy is the Head of Standards Development at CDISC. Bess has been a CDISC team member since 2011. She has over 20 years of experience working in public health research and has held positions at the Framingham Heart Study, the Rotterdam Study, the Arizona Cancer Center, and the Critical Path Institute.

Bess has a BS from the University of Michigan, an MPH from Boston University School of Public Health, and is a doctoral candidate at Johns Hopkins Bloomberg School of Public Health.

Agenda

- The Journey Thus Far
- How Are CDISC Standards Evolving?
  - Study Build
  - Data Sources
  - Study Execution

Over 20 Years of CDISC Standards!

Hundreds of Active Volunteers

500+ Members

Regulatory Mandates

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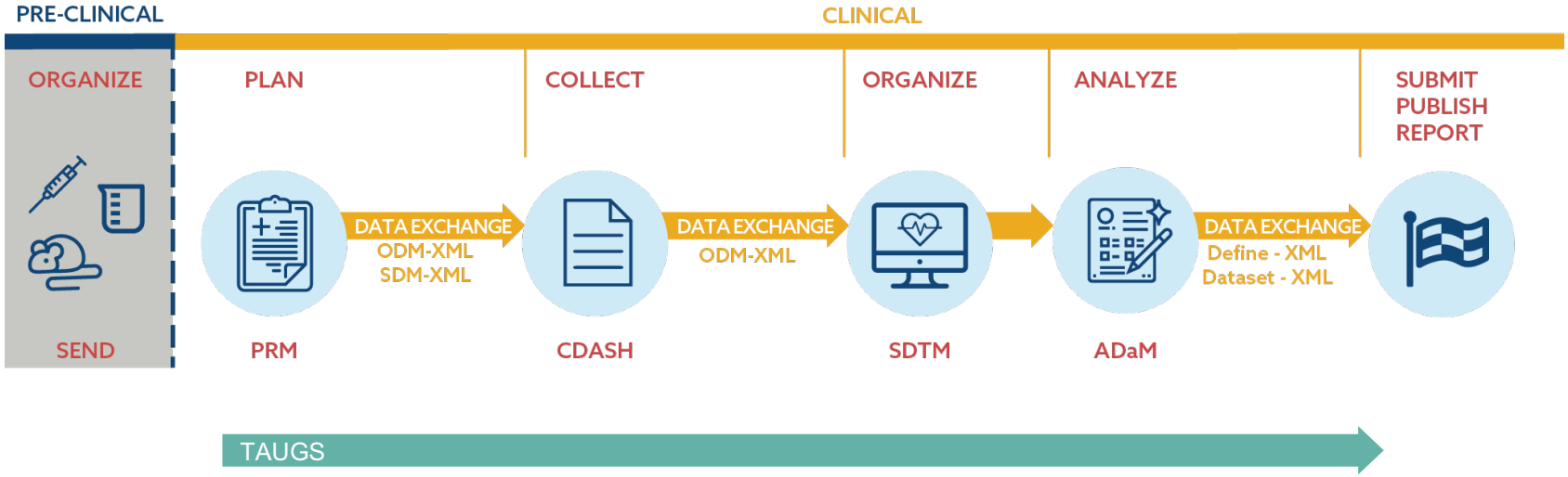
We Have Come a Long Way ….



BRIDG, CONTROLLED TERMINOLOGY AND GLOSSARY

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How Do CDISC Standards Continue to Evolve?

- Standardize the meaning of the information
- Define the data processing (data flow)
- Provide machine-executable data flow definitions
- Standardize missing parts:
  - Protocol content
  - Collection instruments
  - Analysis / endpoint definitions and outputs
- Publish standards from one trusted source
- Make standards less complex for the end users

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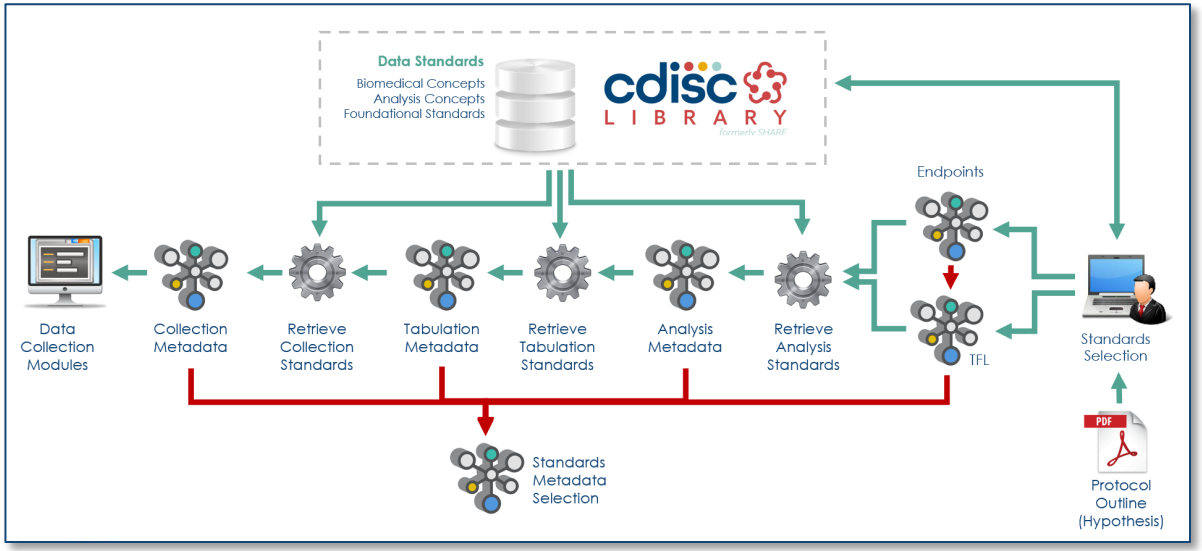
CDISC 360

Piloted development of linked biomedical concept metadata to enable end to end automation



CDISC 360: Lessons Learned

- **Complete** the end-to-end foundational standards where they are incomplete
- **Enrich** the foundational standards with the additional metadata needed for full data meaning and relationships by creating a biomedical concept layer
- **Extend** the CDISC Library model with implementation level metadata
- **Collaborate** with industry to standup and curate biomedical concepts

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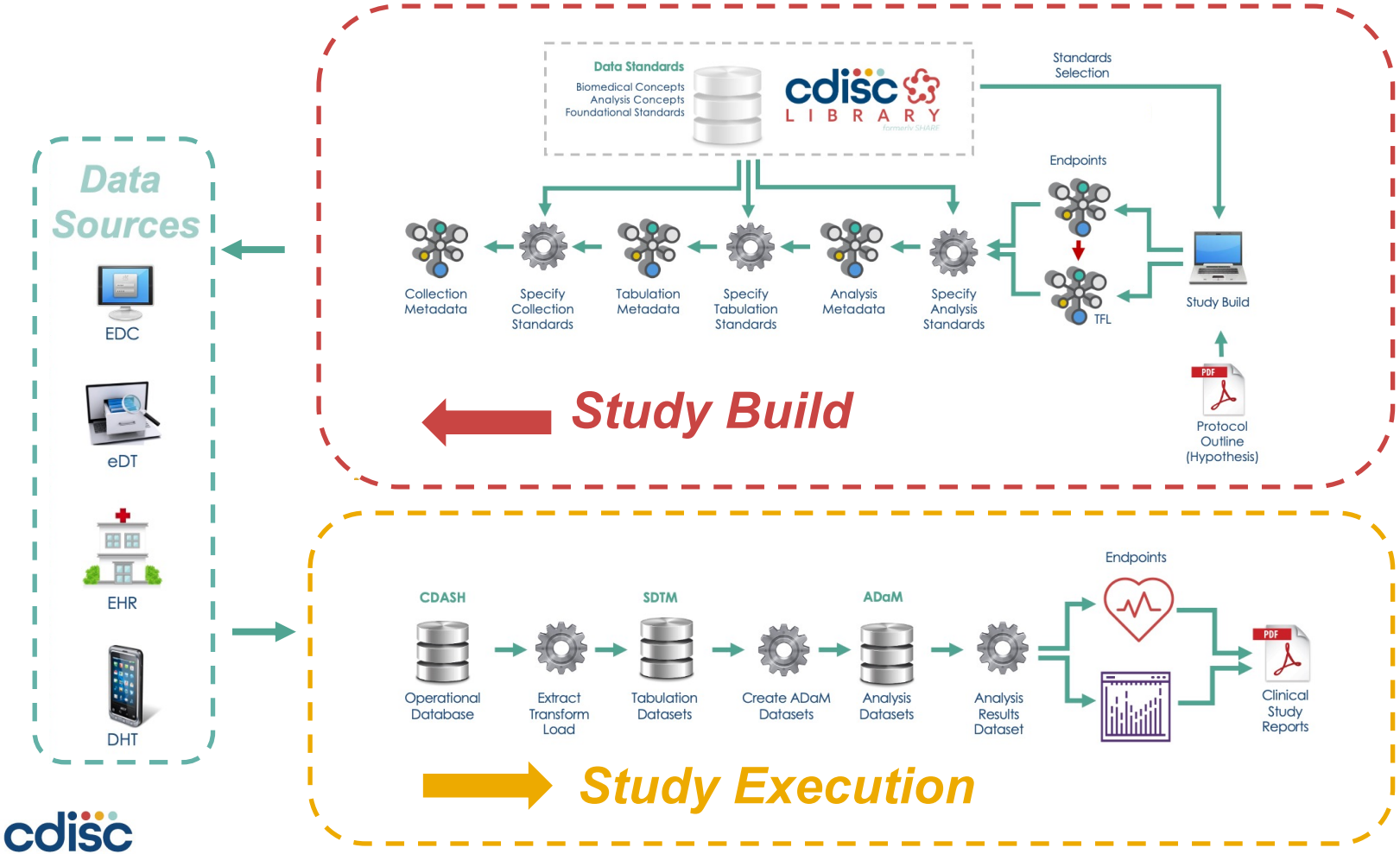

Data Sources
EDC
eDT
EHR
DHT
Data Standards
Biomedical Concepts
Analysis Concepts
Foundational Standards
cdisc LIBRARY
formerly SHARE
Standards Selection
Endpoints
Collection Metadata
Specify Collection Standards
Tabulation Metadata
Specify Tabulation Standards
Analysis Metadata
Specify Analysis Standards
TFL
Study Build
PDF
Protocol Outline (Hypothesis)
Study Build
CDASH
SDTM
ADaM
Endpoints
Operational Database
Extract Transform Load
Tabulation Datasets
Create ADaM Datasets
Analysis Datasets
Analysis Results Dataset
PDF
Clinical Study Reports
Study Execution

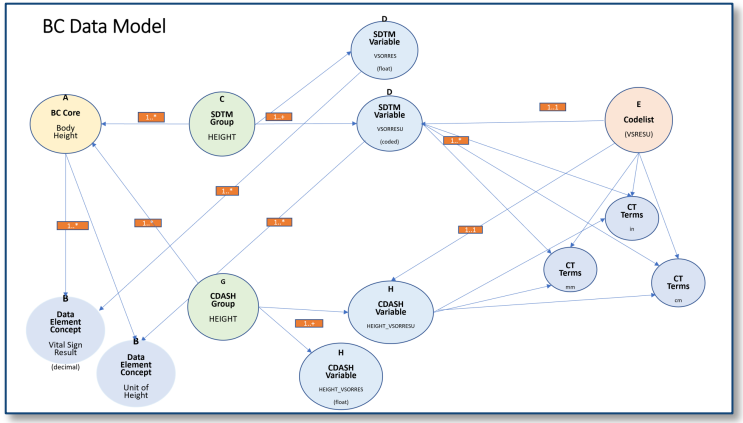
Study Build

What are CDISC Biomedical Concepts?

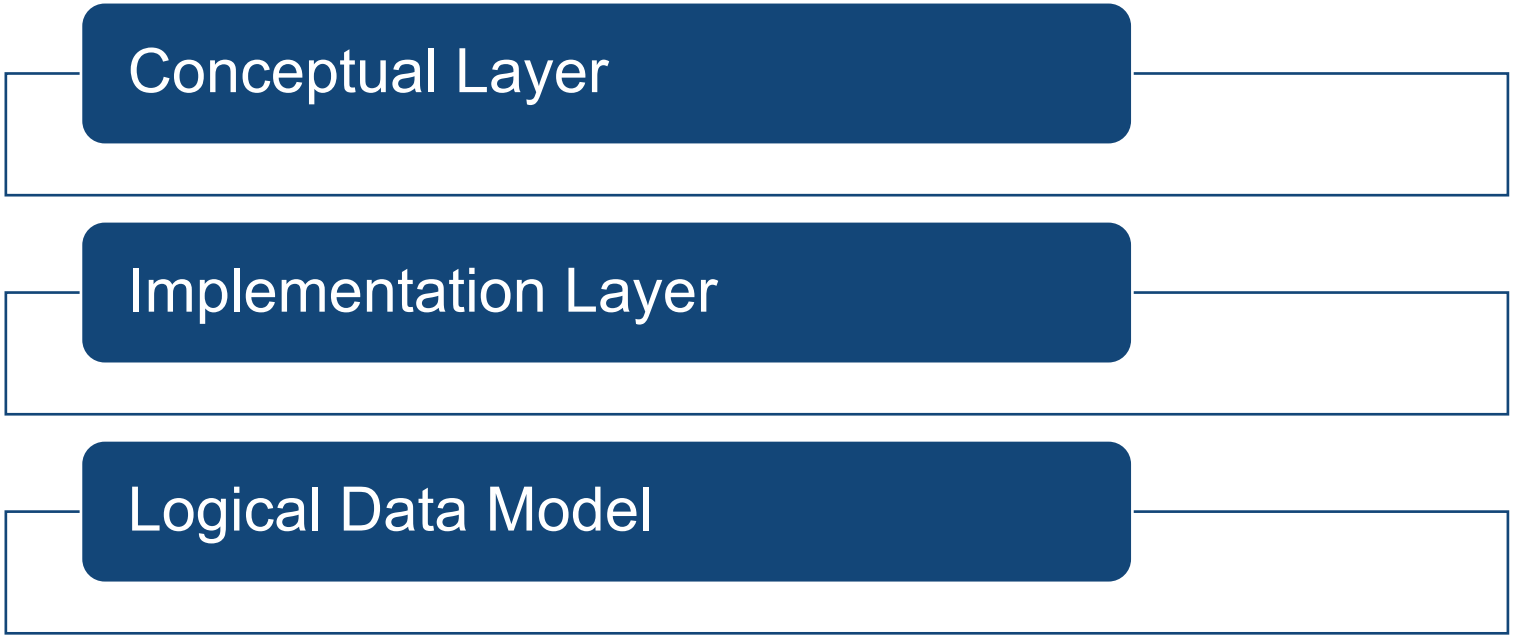
A pragmatic, iterative approach to creating biomedical concepts with a focus on providing tangible value for the CDISC community

Key Objectives:

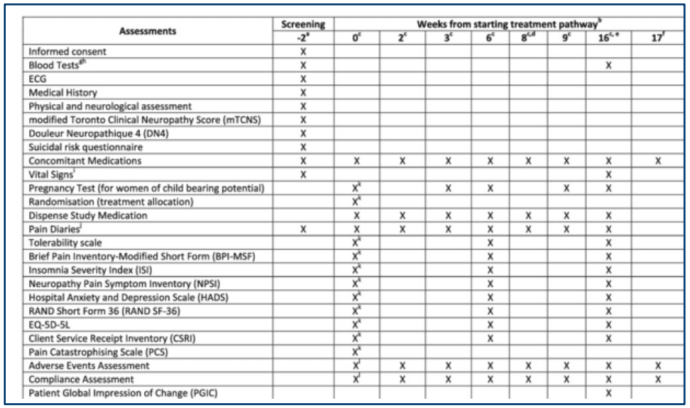
- Reduce variability in standards implementations
- Increase metadata-driven automation
- Reduce barriers to operational implementation



Key Components of CDISC Biomedical Concepts



Initial Use Cases



Assessments	Screening	Weeks from starting treatment pathway[3]							
	-2[a]	0[c]	2[d]	3[c]	6[c]	8[c,e]	9[c]	16[c,e]	17[f]
Informed consent	X								
Blood Tests[gh]	X							X	
ECG	X								
Medical History	X								
Physical and neurological assessment	X								
modified Toronto Clinical Neuropathy Score (mTCNS)	X								
Douleur Neuropathique 4 (DN4)	X								
Suicidal risk questionnaire	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Vital Signs[i]	X							X	
Pregnancy Test (for women of child bearing potential)		X[a]		X	X		X	X	
Randomisation (treatment allocation)		X[b]							
Dispense Study Medication		X	X	X	X	X	X	X	
Pain Diaries[j]	X	X	X	X	X	X	X	X	
Tolerability scale		X[a]			X			X	
Brief Pain Inventory-Modified Short Form (BPI-MSF)		X[a]			X			X	
Insomnia Severity Index (ISI)		X[a]			X			X	
Neuropathy Pain Symptom Inventory (NPSI)		X[a]			X			X	
Hospital Anxiety and Depression Scale (HADS)		X[a]			X			X	
RAND Short Form 36 (RAND SF-36)		X[a]			X			X	
EQ-5D-5L		X[a]			X			X	
Client Service Receipt Inventory (CSRI)		X[a]			X			X	
Pain Catastrophising Scale (PCS)		X[a]							
Adverse Events Assessment		X[f]	X	X	X	X	X	X	X
Compliance Assessment		X[f]	X	X	X	X	X	X	X
Patient Global Impression of Change (PGIC)								X	

Retrieve a list of assessments for a study

VS (Vital Signs) - [SDTMIG 3.1.2]

Related Supplemental Qualifiers Dataset: SUPPVS (Supplemental Qualifiers for VS)

Variable	Where Condition	Label / Description	Type	Length or Display Format	Controlled Terms or ISO Format
VSORRES VLM		Result or Finding in Original Units	text	30	
	VSTESTCD = "DIABP" (Diastolic Blood Pressure)	Diastolic Blood Pressure in Orig U	integer	2	
	VSTESTCD = "FRMSIZE" (Body Frame Size)	Body Frame Size - Orig	text	6	Size • "SMALL" • "MEDIUM" • "LARGE"
	VSTESTCD = "HEIGHT" (Height)	Height in Orig U	float	5.1	

Publish BC content as Define-XML document including value level metadata

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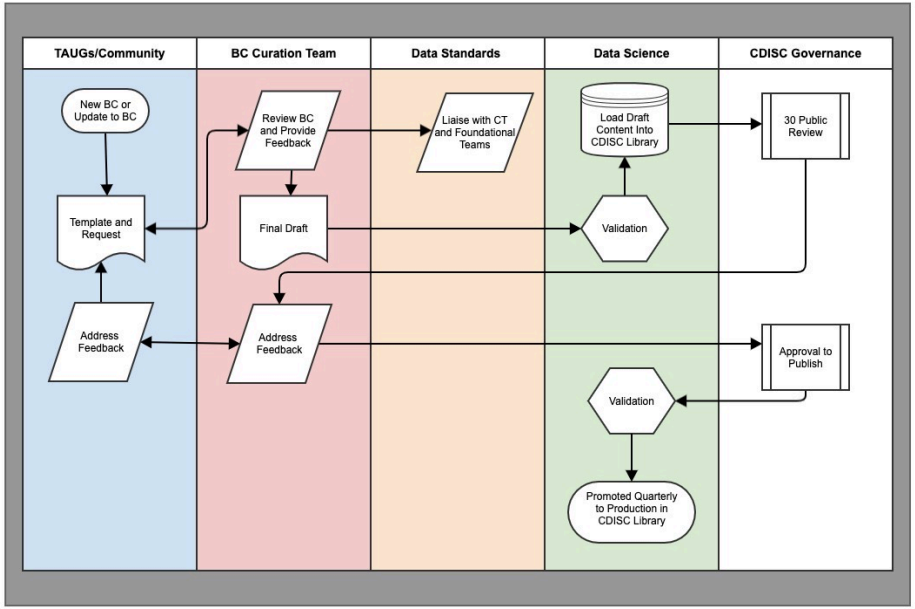
BC Governance

- Light-weight CDISC curation and governance process
- 30-day Public Review
- Published quarterly
- Mechanism for community change requests



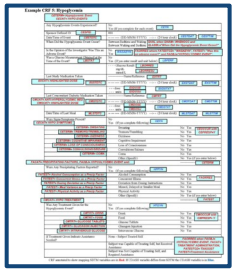
Draft governance process

Learn more about BCs!

Session 3: Track B- Biomedical Concepts

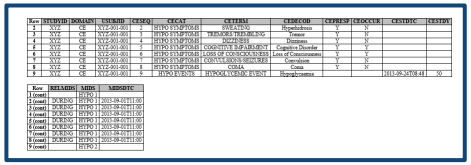
14:00 - 15:30

Standards for Analysis Results



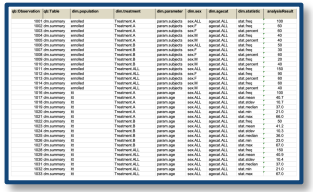
Data Collection

CDASH



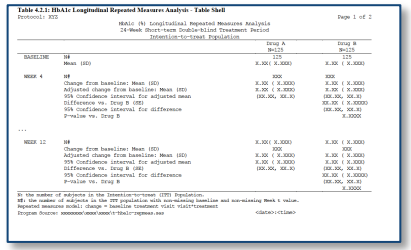
Data Aggregation

SDTM



Analysis

ADaM



Results

???

Table 4.2.2: HbA1c Longitudinal Repeated Measures Analysis Results Metadata

Metadata Field	Metadata
DISPLAY IDENTIFIER	Table 4.2.1/Figure 4.2.1
DISPLAY NAME	Mean Change from Baseline in HbA1c (Percent) Longitudinal Repeated Measures Analysis, 24-Week Short-term Double-blind Treatment Period, Intention-to-treat Population
RESULT IDENTIFIER	Treatment difference results (LSMean, confidence interval, p-value)
PARAM	HbA1c (%)
PARAMCD	HBA1C
ANALYSIS VARIABLE	CHG (Change from baseline)
ANALYSIS REASON	SPECIFIED IN SAP
ANALYSIS PURPOSE	PRIMARY OUTCOME MEASURE
ANALYSIS DATASET	ADHBA1C

ARM for Define.XML

Analysis Results Standard Objectives

- Use analysis results metadata to drive the automation of results
- Support storage, access, processing and reproducibility of results
- Improved navigation and reusability of analyses and results
- Traceability to Protocol/SAP and to input ADaM data

Learn more about ARS!

Session 5: Track A- Analysis Results Standard

9:00 - 10:30

CDISC eCRF PORTAL

- The eCRF Portal provides machine readable eCRFs
  - Visual representation of CRF layout with CDASH annotations
  - Machine-readable ODM format

- Includes CRFs from:
  - CDASH Implementation Guide v2.1
  - Crohn's Disease Therapeutic Area User Guide
  - Upcoming – COVID-19 Therapeutic Area User Guide
  - Over 54 eCRFs to date

- Formedix offers the Ryze platform at no cost

- Used as a base to create OpenClinica and REDCap CRFs

Tobacco Implementation Guide (TIG) v1.0

- Proactively designed to reflect use cases unique to tobacco product data
- A single, comprehensive implementation guide for tobacco product data submissions

An overview of standards and general implementation

With guidance by topics and use cases; e.g.

- Product Description
- Nonclinical
- Individual Health
- Population Health

Key scientific concepts and maps

Data Collection (*CDASH eCRFs*, *ODM-XML*)

Data Tabulation (*SEND*, *SDTM Human Clinical*, *Define-XML*)

Analysis (*ADaM*, *Define-XML*)

Common Language (*Controlled Terminology*)

Measures of Adherence (*Conformance Rules*)

Accessible in platforms which optimize use (including *CDISC website*, *CDISC Library*)

Education and Outreach (including *webinars*, *formal training*)

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Learn more about TIG!

Session 6: Track A- Updates Towards Regulatory

11:00 - 13:00

Foundational Standards Development 2023 Highlights

ADaM – Planning for a consolidated ADaMIG

SDS – Multiple Subject Participations – DM and DC domains

CDASH – Aligning with SDTMIG v3.4 including GF and CP domains

SEND – Implementing new domains including IS, CP, PI, OE, and SX

Medical Devices – Addressing how to represent multiple device components

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Learn more about Foundational Standards!

Session 3: Track A- CDISC Foundational

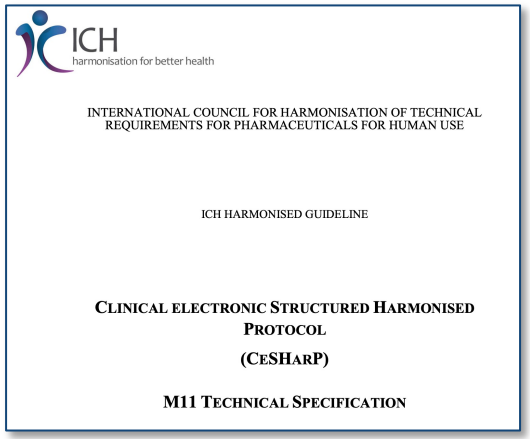
14:00 - 15:30

Session 7: Track C- CDISC Foundational, Part II

14:00 - 15:30

ICH M11:Clinical Electronic Structured Harmonised Protocol Components

The **Technical Specification** presents the conformance, cardinality, and other technical attributes that enable the interoperable electronic exchange of protocol content


ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

(CESHARP)

M11 TECHNICAL SPECIFICATION

The **Template** presents the format and structure of the protocol, including the table of contents, common headers, and contents


ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

(CESHARP)

M11 TEMPLATE

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Template for Description of Trial Design

4.1 Description of Trial Design

Describe the trial intervention model (for example, single group, parallel group, cross-over, factorial, sequential), the expected number of participants, and the control method (for example, placebo, active comparator, low dose, historical, standard of care, sham procedure, or none [uncontrolled]).

If applicable, indicate the type of trial (for example, superiority, non-inferiority, dose escalation, or equivalence).

Technical Specification for Description of Trial Design

Term (Variable)	Type of Trial
Data Type	List
Topic, Value or Header	D
Definition	
User Guidance	
Conformance	Required
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Trial Design
Relationship (reference to high level conceptual model)	
Value	Superiority, non-inferiority, dose escalation, or equivalence
Business rules	**Value Allowed:** Yes **Relationship:** n/a **Concept:** n/a
Duplicate field in other sections	

- Variables
- Concept/Terminology
- Code lists
- Conformance

Role of CDISC

- Govern controlled terminology, code lists, content nomenclature
- Define content model to represent content agnostic of exchange standard
- Determine conformance rules for M11 model
- Work directly with ICH M11 on defining mappings between M11 model and CDISC Standards and Artifacts

➔ Longer term view for CDISC to publish the model
  - ICH will remain the authority, CDISC will govern the terminology

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Learn more about ICH M11!

Session 6: Track A- Updates Towards Regulatory

11:00 - 13:00

Digital Data Flow Project

- Collaborative development project with TransCelerate Biopharma, Stakeholders, Vendors and CDISC
- Creation of the Unified Study Definitions Model (**USDM**) Reference Architecture and an open source Reference Implementation of this Architecture called the Study Definitions Repository (**SDR**)
- Goals:
  - To enable the format of information from a digitized protocol and other sources to be standardized and stored centrally
  - Allow information to be passed to systems used for study execution and data collection and reused throughout the clinical development lifecycle

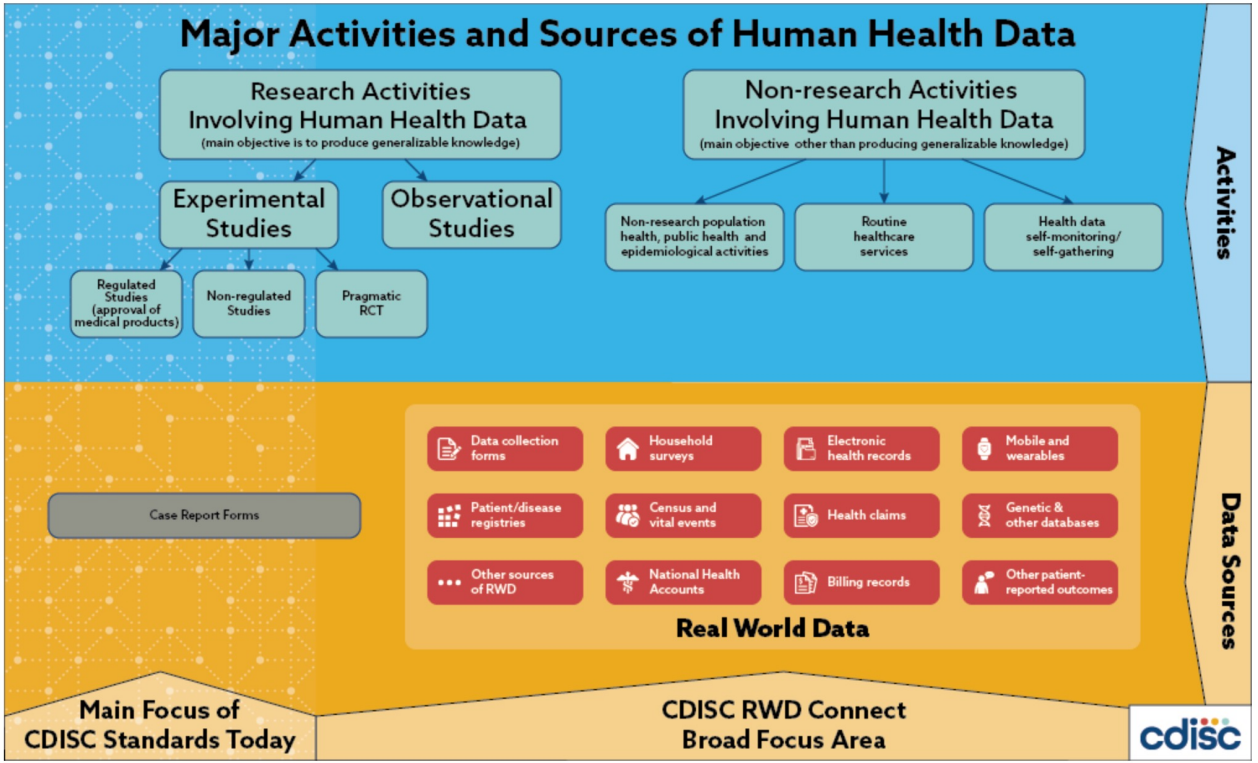
Learn more about DDF!

Session 7: Track B- Digital Data Flow

14:00 - 16:00

Data Sources

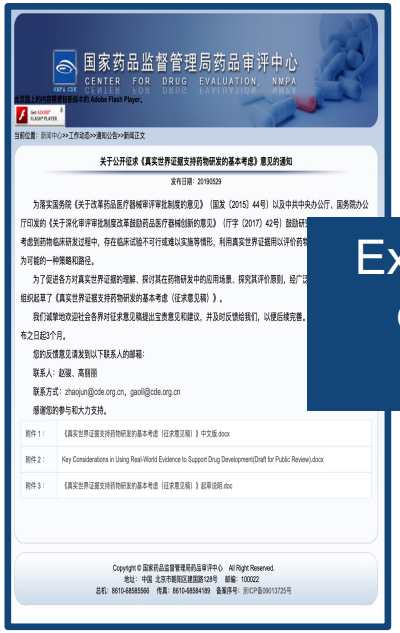
Real World Data



https://www.cdisc.org/standards/real-world-data

RWD and the Regulatory Environment

China's NMPA



http://www.cde.org.cn/news.do?method=largeInfo&id=23a2b4cbe0807fe2

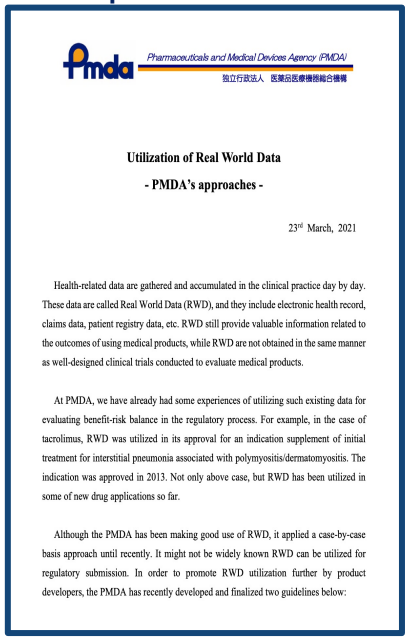
US FDA

https://www.fda.gov/media/120060/download

EU EMA

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

Japan's PMDA



https://www.pmda.go.jp/english/about-pmda/0004.pdf

Exploring and promoting the use of high-quality RWD in decision-making as a strategic goal

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HL7 FHIR to CDISC Mapping

- Fast Healthcare Interoperability Resources (FHIR) is a standard published by HL7 for exchanging healthcare information electronically
- Goal of mapping is to achieve greater interoperability and exchange of data from Electronic Health Records (EHRs) **to** clinical research submission-ready datasets
- Scope: Adverse Events, Medications, Concomitant Medications, Demographics, Medical History, Procedures, Vital Signs, Laboratory Test Results
- Mappings jointly balloted by CDISC and HL7 using their respective governance processes

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DRAGON: An IMI-Funded Project

Develop AI-enhanced tools for evaluating COVID patients' *CT scans* and *clinical data* to provide accurate diagnoses and predict patient outcome.

cdisc's Role

- EHR data harmonization design and mapping support to feed data to AI
- COVID-19 User Guide v2.0 Imaging Guide
- CDISC Basic: abridged CDASH & SDTM for non-submission research
- Considerations for using CDISC standards for observational research

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Considerations for Using CDISC Standards for Observational Studies

Goal

- To publish a CDISC-endorsed approach to working with observational research data
- Provide a “stake in the ground” for future expansion

Scope of Use Cases

- **Observational Research Studies**
  - Cross-sectional studies
  - Cohort studies
- **Clinical trials:** external control arm using RWD

Development Scope

- SDTM for now
- CDASH, ADaM could come in subsequent version

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Funding is provided by the IMI DRAGON project

imi innovative medicines initiative DRAGON

Increased Regulatory Focus on Digital Health Technologies

FDA | CDER | Small Business and Industry Assistance

INDUSTRY NEWS

FDA to Host Digital Health Technologies for Drugs Public Workshop

The U.S. Food and Drug Administration is hosting the virtual public workshop "Understanding Priorities for the Development of Digital Health Technologies to Support Clinical Trials for Drug Development and Review" on March 28th and 29th, 2023. The workshop will focus on understanding the priorities and challenges of developing Digital Health Technologies (DHTs) to support clinical drug trials.

The workshop will be convened by the Robert J. Margolis, MD, Center for Health Policy at Duke University under a cooperative agreement with FDA.

For more information on the Digital Health Technologies virtual public workshop and to register, please visit FDA's Meeting's, Conferences & Workshops (Drugs).

CDISC DHT Team: Proposed Scope

- Identify domains for the commonly generated measurements from passive monitoring and active tests
- Define Controlled Terminologies and Codetable Mapping Files for the commonly used digital endpoints
- Adoption of SDTMIG for Medical Device to accommodate DHT needs
- Release the first draft for Public Review

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CDISC Standards Are Robust Enough to Represent DHT Data

ECG Test Results Domain

Identifier Variable Connects Device Information with Results

Device Domains

Example

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Device SDTM Domains

Intended to support most or all types of devices

Device Identifiers (DI)	• Consistent unique sponsor-defined identifier that links data across domains.
Device Properties (DO)	• Important unvarying device characteristics that are not identifiers
Device-In-Use (DU)	• Measurements and settings intentionally set that may vary between uses of a device
Device Exposure (DX)	• Subject's exposure to a medical device under study
Device Events (DE)	• Reportable device-related occurrences such as malfunctions and calibrations
Tracking and Disposition (DT)	• Physical locations of device, either at each movement or just final status
Device-Subject Relationship (DR)	• Look-up table providing single consistent link between each device and subject

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Learn more about CDISC and RWD Data!

Session 4: Track A- Real World Data

16:00 - 18:00

Session 7: Track C- CDISC Foundational, Part II

14:00 - 15:30

Study Execution

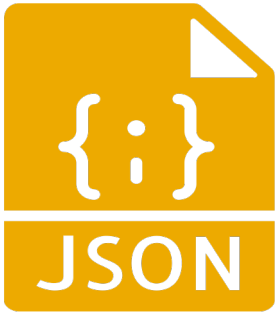
What is Dataset-JSON and Advantages

What is JSON?
An open standard file format and data interchange format that uses human-readable text to store and transmit data objects consisting of attribute–value pairs and arrays

What is Dataset-JSON?
A dataset exchange standard for exchanging tabular data leveraging JSON designed to meet the regulatory submission needs and eliminating limitations of legacy formats

Dataset-JSON advantages…

- Based on the JSON standard used worldwide
- Open-source and truly human readable
- Same or smaller file sizes relative to current required format
- Remove variable naming, width, or format limitations
- Simple transformation to/from SAS data



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Proposed Dataset-JSON Pilot

Milestone 1: Short Term

- Pilot submissions using JSON format with existing XPT ingress/egress to carry the same data
- Same content, different suitcase, no disruption to business process on either side
- In parallel, evaluate how FDA toolset can support JSON format and identify tool upgrade roadmap

➔ **Success Criteria: Accept Dataset-JSON as a transport format option (in addition to existing XPT format)**

Milestone 2: Long Term

- Enhance the CDISC SDTM and ADaM standards beyond XPT limitations (e.g. Variable names > 8, labels > 40, data > 200
- New Define-XML / Define-JSON based on ODM v2.0
- Enhanced conformance rules
- Collaborate with FDA to develop plan to retool their environment to natively consume JSON

➔ **Success Criteria: accept advanced Dataset-JSON as the only transport format option and deprecate XPT**

ODM v2.0

- ODM-XML is a vendor-neutral, platform-independent format for exchanging and archiving clinical and translational research data, along with their associated metadata

- The ODM v2.0 vision is to build on ODM's proven strength and improved support for automation
  - Improved alignment with CDISC Foundational Standards as well as healthcare standards such as HL7 FHIR.
  - Support for multiple media types (XML and JSON), enhanced semantics, the Study Design Model, data queries, more flexible data structure representations, and operational data set

- Completed Public Review – final publication scheduled for July 2023

CDISC Open Source Alliance

Supports, promotes, and sometimes sponsors open-source software projects that create tools for implementing or developing CDISC standards to drive innovation in the CDISC community

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https://cosa.cdisc.org

CDISC CORE

- Ensure each standard has a set of unambiguous, executable Conformance Rules
- Ensure consistency across Conformance Rule implementations
- Expedite the availability of executable Conformance Rules for new Foundational Standards
- Create executable Conformance Rules vetted by the CDISC standards development teams
- Develop an open-source engine that serves as a Reference Implementation
- Publish the Rules in the CDISC Library and the engine under the CDISC Open Source Alliance (COSA)

https://www.cdisc.org/core

CORE Initiative = Rules + Engine

Learn more about COSA and CORE!

Session 6: Track B- CORE Implementation
11:00 - 13:00

Session 5: Track B- Core Rules Development
9:00 - 10:30

COSA Booth and Poster Session

Trial Master File (TMF)

What is the Trial Master File?

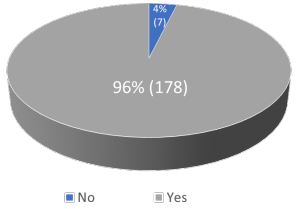
The sponsor and the investigator shall keep a clinical **trial master file**. The clinical trial master file shall at all times contain the **essential documents** relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated […]. It shall be readily available, and directly accessible upon request, to the Member States.

[EU Regulation 536/2014]

What *is* the Trial Master File Reference Model?

A Standardised structure, contents and naming of these Essential documents

2022 Survey:
Organizations using TMF Reference Model



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TMF Initiatives

- The Education Team
- The Standards Team
- The CDISC TMF Interchange!

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NEW ANNUAL CONFERENCE

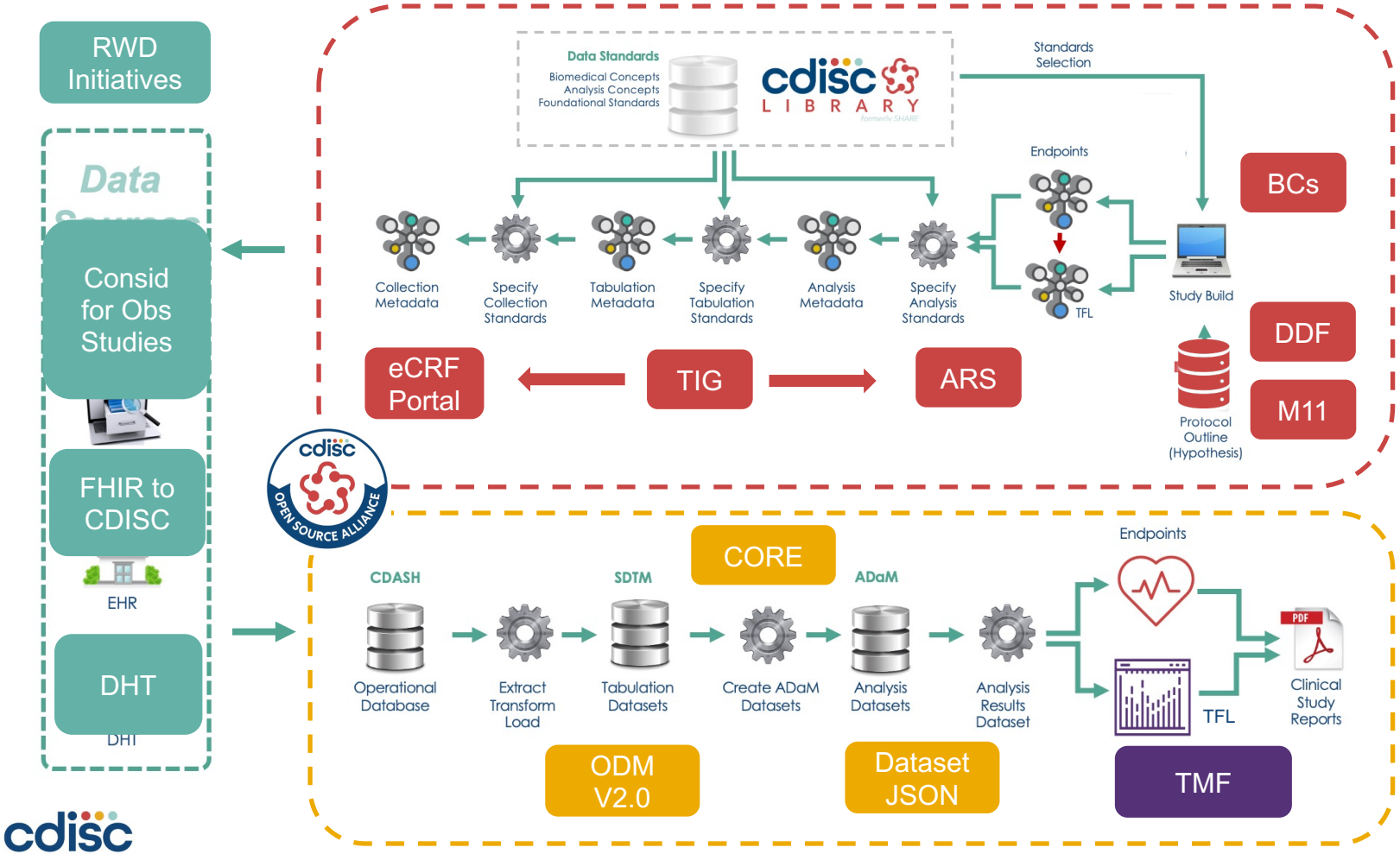
2023 CDISC TMF INTERCHANGE

28-29 SEPTEMBER
BALTIMORE

Learn more about TMF!

Session 8: Closing Plenary

16:15 - 16:45


RWD Initiatives
Data
Consid for Obs Studies
FHIR to CDISC
EHR
DHT
DHT
Data Standards
Biomedical Concepts
Analysis Concepts
Foundational Standards
cdisc LIBRARY
Standards Selection
Endpoints
BCs
Collection Metadata
Specify Collection Standards
Tabulation Metadata
Specify Tabulation Standards
Analysis Metadata
Specify Analysis Standards
TFL
Study Build
DDF
M11
Protocol Outline (Hypothesis)
eCRF Portal
TIG
ARS
cdisc OPEN SOURCE ALLIANCE
CORE
CDASH
SDTM
ADaM
Endpoints
Operational Database
Extract Transform Load
Tabulation Datasets
Create ADaM Datasets
Analysis Datasets
Analysis Results Dataset
TFL
PDF
Clinical Study Reports
ODM V2.0
Dataset JSON
TMF
cdisc

Relentless Collaboration

cdisc

Thank you!