CDISC Key Initiatives for 2023 and beyond

Peter Van Reusel

Chief Standards Officer

CDISC

Meet the Speaker

Peter Van Reusel

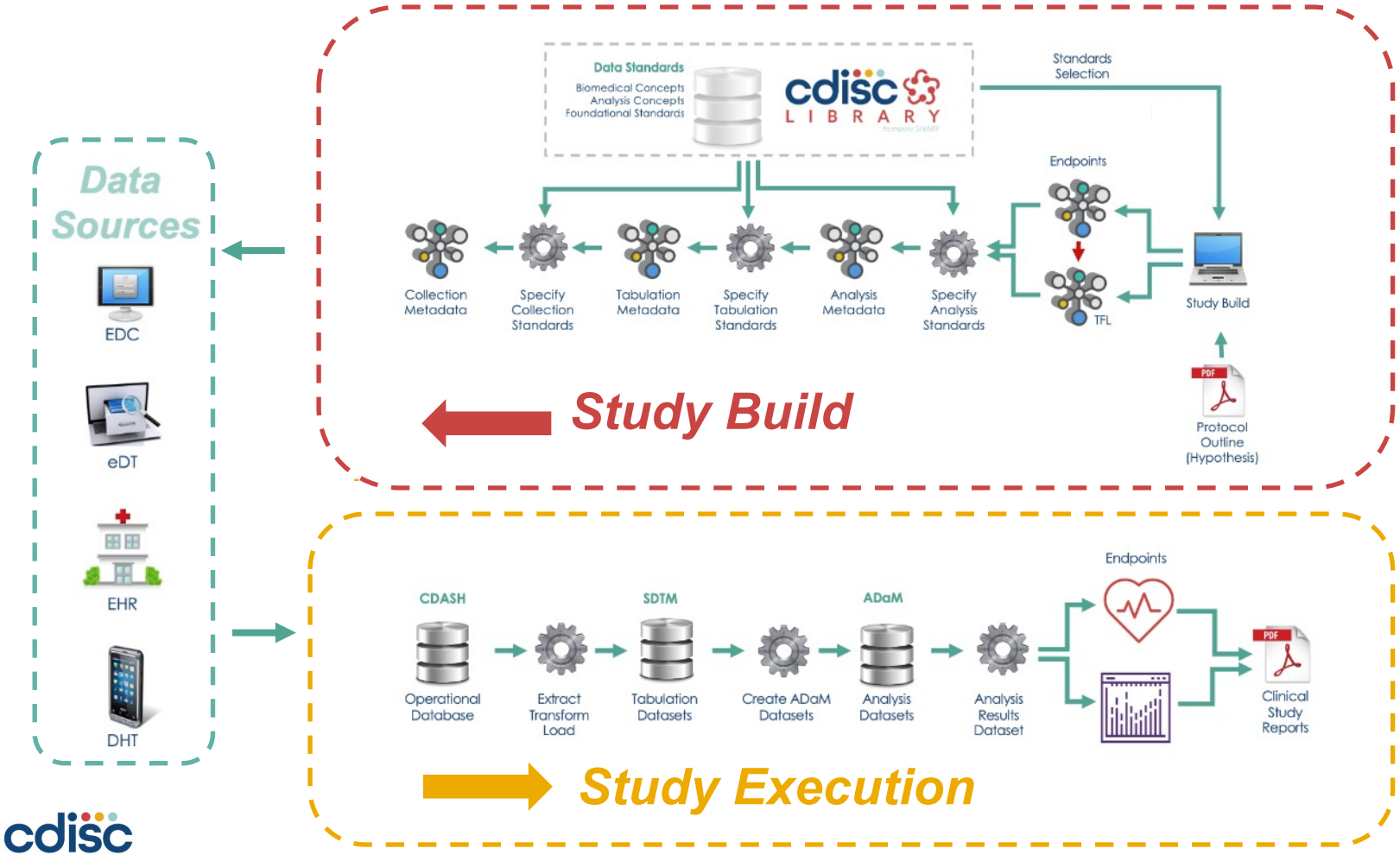
Title: Chief Standards Officer
Organization: CDISC

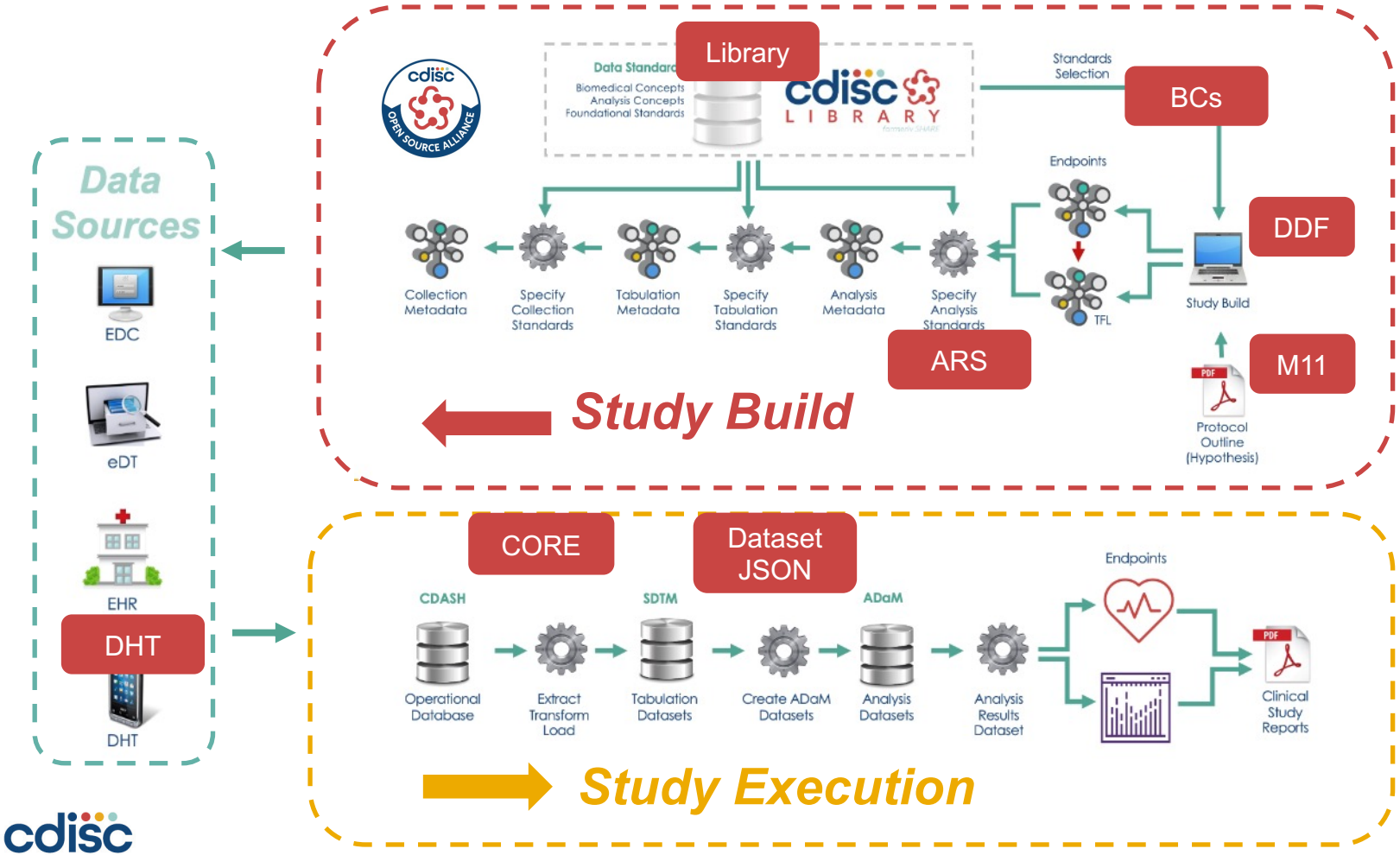
Peter Van Reusel provides executive leadership to the development and implementation of clinical standards in line with CDISC's strategy and operational plans, working closely with the President and CEO, as well as CDISC staff and stakeholders. He has over 20 years' experience in senior roles in pharma and at CROs, providing standards expertise and carrying out other standards work in various organizational settings. A long-time, CDISC-authorized instructor, Peter has helped significantly in developing CDISC training courses.

He previously served as CDISC's European Liaison, shepherding relationships with key European regulatory, academic, and biopharma stakeholders. Peter is also an active PHUSE collaborator.

Agenda

- CDISC Key Initiatives
- CORE : CDISC Conformance Rules


Data Sources
EDC
eDT
EHR
DHT
Data Standards
Biomedical Concepts
Analysis Concepts
Foundational Standards
cdisc LIBRARY
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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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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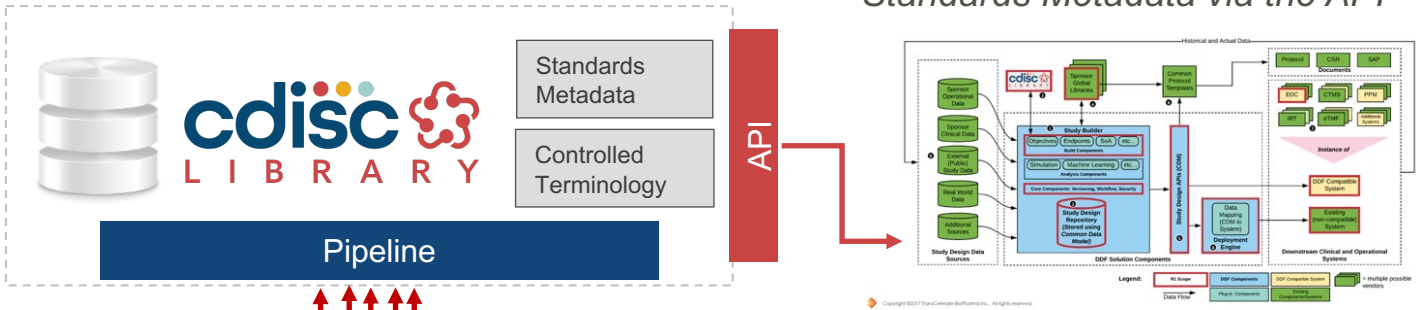
CDISC Library: Standards as a Service

Software Applications Consume Standards Metadata via the API



Executable Conformance Rules

Biomedical Concepts	Codelist Subsets	Dataset Specializations	Implementation Guide Text	Standards Mappings
Analysis Results Standard	TAUG Metadata	Derivations and Mappings	Machine-readable Examples	Draft Standards Metadata
Tables, Listings, and Figures	QRS Metadata	Trial Master File Reference Model	CRF Collection	Diff Content Between Versions

REST architecture principles at work

CDISC Open-Source Alliance (COSA)

Community Driven Development

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

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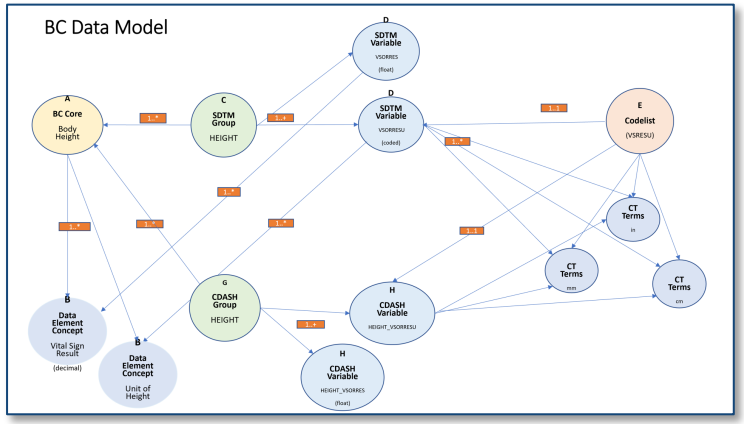
https://cosa.cdisc.org

CDISC 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

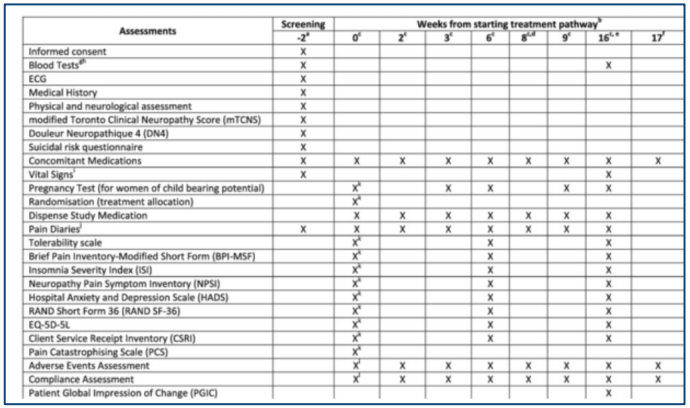
Key Components:

- Conceptual layer
- Implementation layer
- Logical data model

CDISC Biomedical Concepts: Semantics

Representation of a BC in a specific standard with implementation details such as value level metadata, formats, terminology – alignment across standards

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,d]	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[k]		X	X		X	X	
Randomisation (treatment allocation)		X[k]							
Dispense Study Medication		X	X	X	X	X	X	X	
Pain Diaries[l]	X	X	X	X	X	X	X	X	
Tolerability scale		X[d]			X			X	
Brief Pain Inventory-Modified Short Form (BPI-MSF)		X[d]			X			X	
Insomnia Severity Index (ISI)		X[d]			X			X	
Neuropathy Pain Symptom Inventory (NPSI)		X[d]			X			X	
Hospital Anxiety and Depression Scale (HADS)		X[d]			X			X	
RAND Short Form 36 (RAND SF-36)		X[d]			X			X	
EQ-5D-5L		X[d]			X			X	
Client Service Receipt Inventory (CSRI)		X[d]			X			X	
Pain Catastrophising Scale (PCS)		X[d]							
Adverse Events Assessment		X[j]	X	X	X	X	X	X	X
Compliance Assessment		X[j]	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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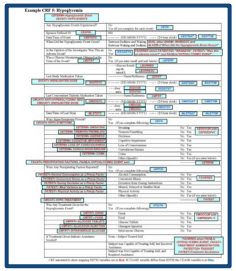
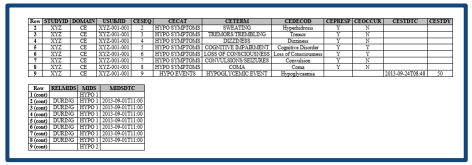
Why Analysis Results Standards



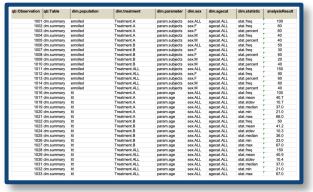
Data Collection

CDASH



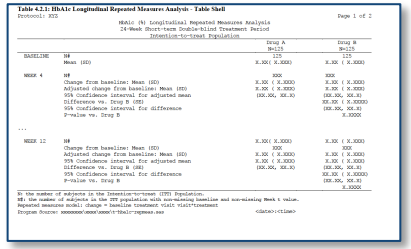
Data Aggregation

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 Standards Key Objectives

Leverage analysis results metadata to drive the automation of results

Support storage, access, processing, traceability and reproducibility of results

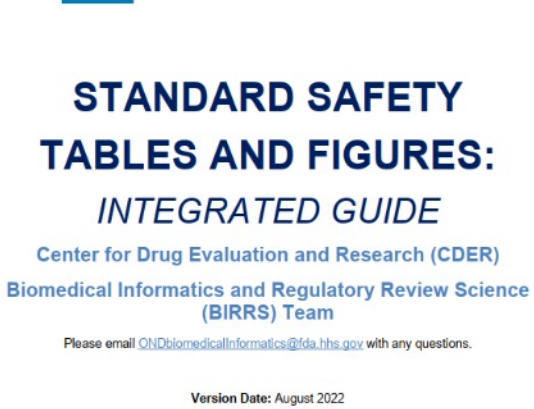
Develop a logical model that describes analysis results and associated metadata

User Guide to illustrate and exercise model with common safety displays

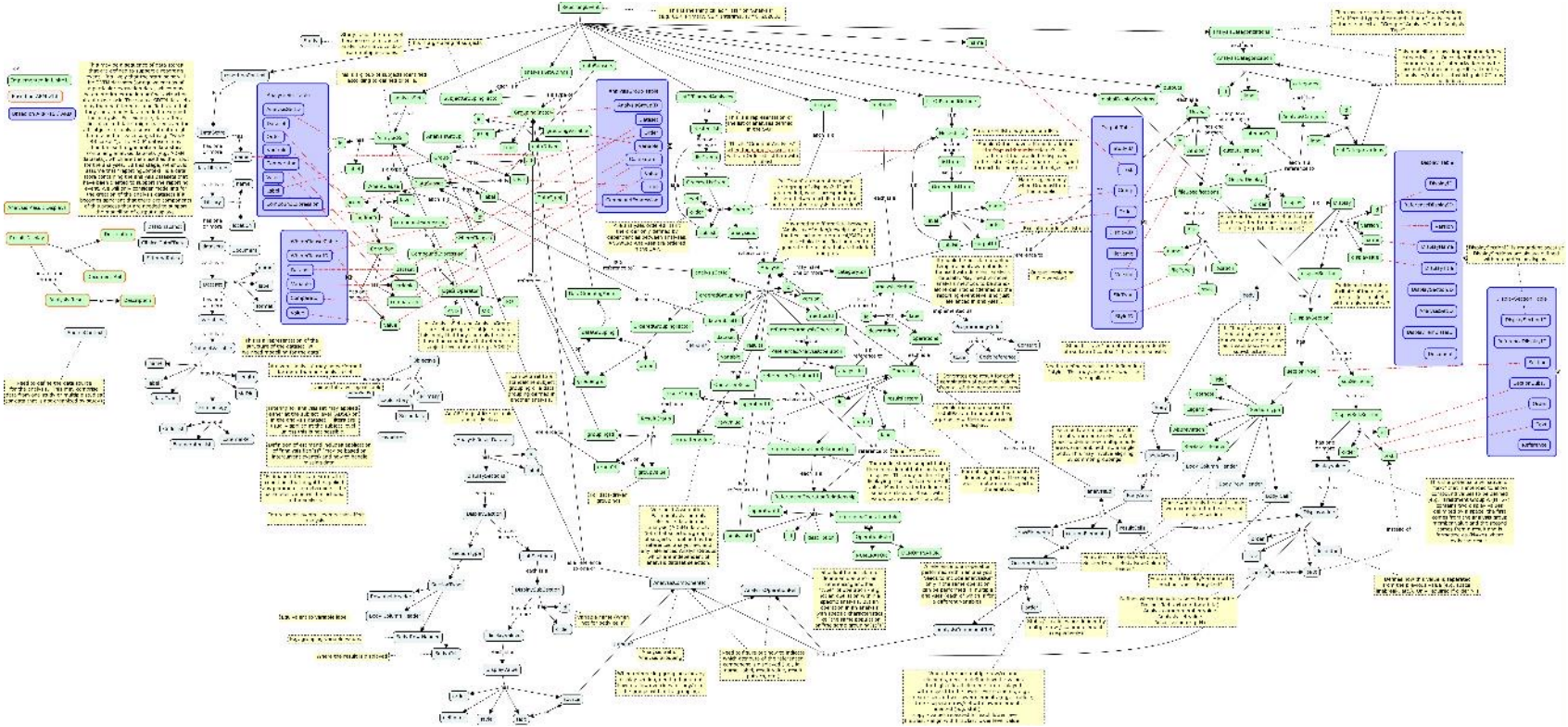
Analysis Results Standard

- ARS COSA Hackathon is completed
  - Readout at CDISC US Interchange
  - Readout at COSA spotlight December
- ARS model / schema complete
- Public Review scheduled Oct 6

- Planning to implement 4 example TFLs in ARS
- Release as example implementation package
- Ideating eTFL Portal



ARS Schema



https://github.com/cdisc-org/analysis-results-standard

Digital Health Technologies (DHT)

Increased industry 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 Digital Health Technologies (DHT) Team

Purpose:

- To explore and enhance standardization of digital health technologies data

Goals:

- Increase our collective knowledge of digital health technologies and related data;
- In collaboration with a diverse group of stakeholders;
- To determine how CDISC standards can further support use of DHTs; and to
- Develop and publish new supporting standards

CDISC Digital Health Technologies (DHT)

Standardize

- Key concepts
- Device attributes, and
- Endpoints
- With supporting best practices

Partner

- Expert organization partnership
- Announcement in October

Scope

June - October

Develop

Start in November

Deliver

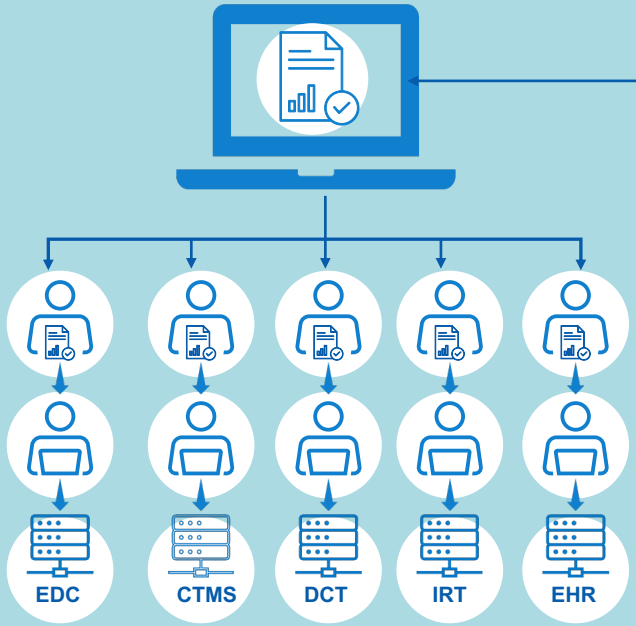
By Q4 2024

Staged releases preferred

Digital Data Flow (DDF) Initiative

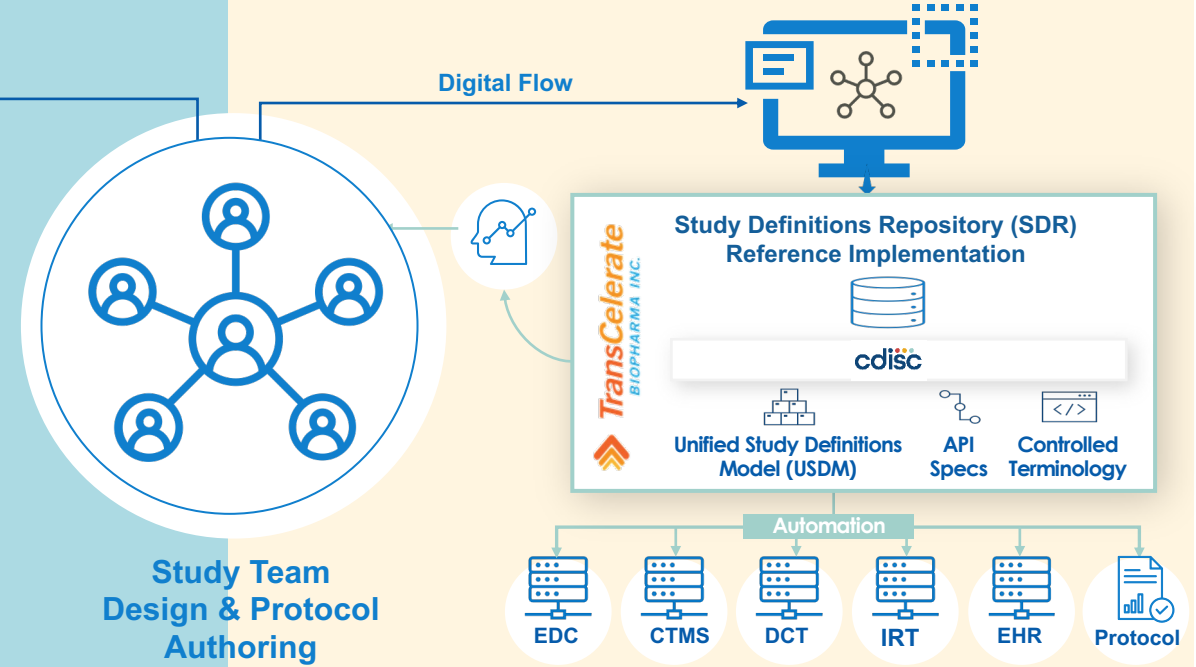
Write Once, Read Many

TODAY: Document-based paradigm for protocol creation, interpretation, and transcription into consuming systems



Study Team Design & Protocol Authoring

TOMORROW: Digital paradigm for protocol creation, with fully automated data flow and interoperability between systems



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➡ *See next presentation from Berber*

SAS v5 XPT format is the current standard for exchanging tabular datasets

- Currently Mandated by regulatory agencies
- Limitations of XPT v5
  - Numeric limitations, antiquated format
  - Stores data in its own numeric way
  - Character limitations, no UTF-8 encoding
    - No support for characters from other languages
  - String & Column limitations (variable names > 8, labels > 40, data > 200)
  - No metadata extensibility
- Considered outdated and antiquated
- Technology ‘stigma’

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**

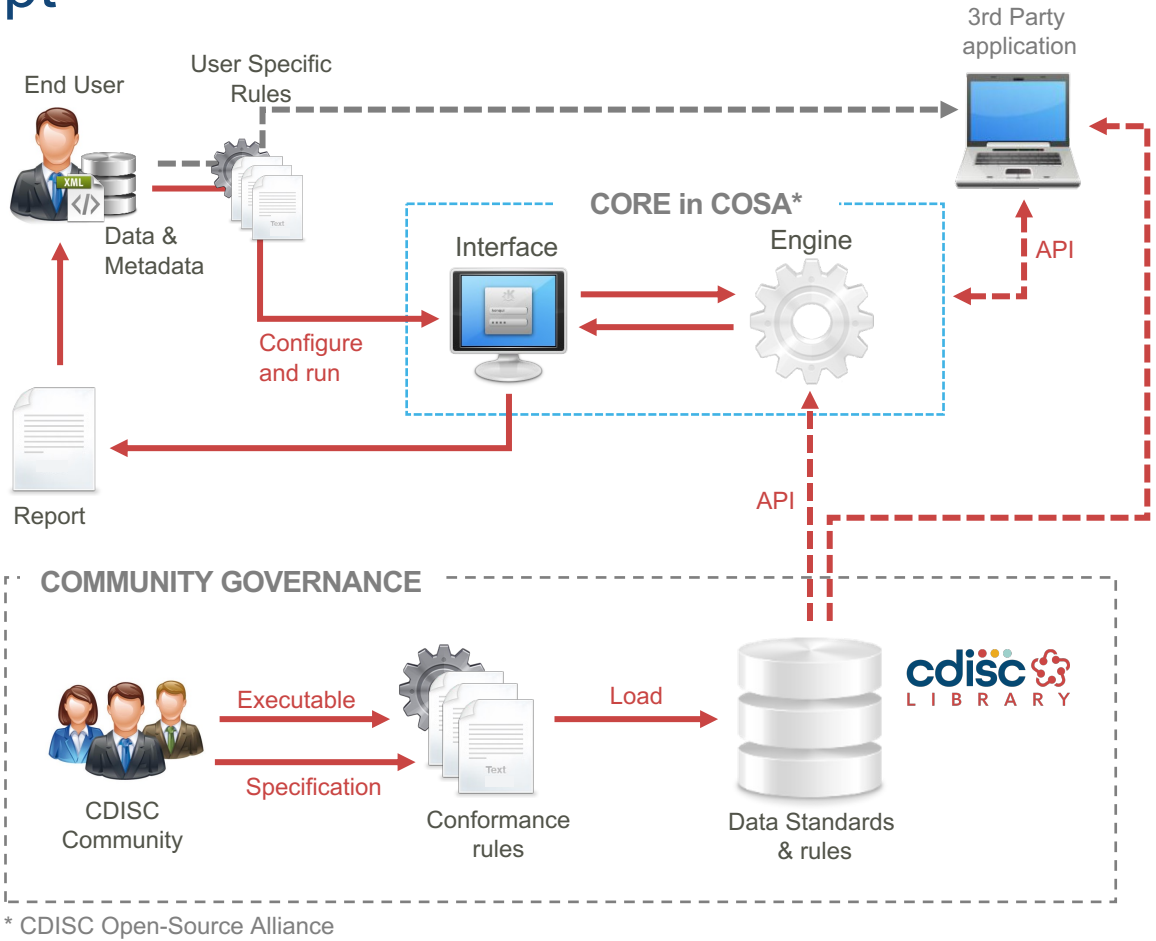
Dataset-JSON Pilot: draft Timeline

Conformance Rules - CORE

The Challenge

- A single source of truth for all conformance rules
- Consistency across conformance rule implementations

CORE Concept



CORE Rules Governance

Rules Governance Team

(CDISC; FDA; Community)

Rule Specifications

cdisc Standards — Provide rule specs

FDA — Provide validation rules

Community — Propose new / updated rule specs

Rules Gov Team Activities

- Receive specifications
- Load to central catalog

Rules Gov Team Activities

- Govern specs content
- Curate content
- Mark rules for dev.
- Prioritize rules for dev.

Central Specifications Catalog

Freely Available

CORE Rules (executable)

Rules Gov Team Activities

- Govern CORE Rules dev. process
- Assign Rules for development
- Review/approve Rules for release

Rules Development — Community

Publish

CDISC Library

API

3rd Party Applications

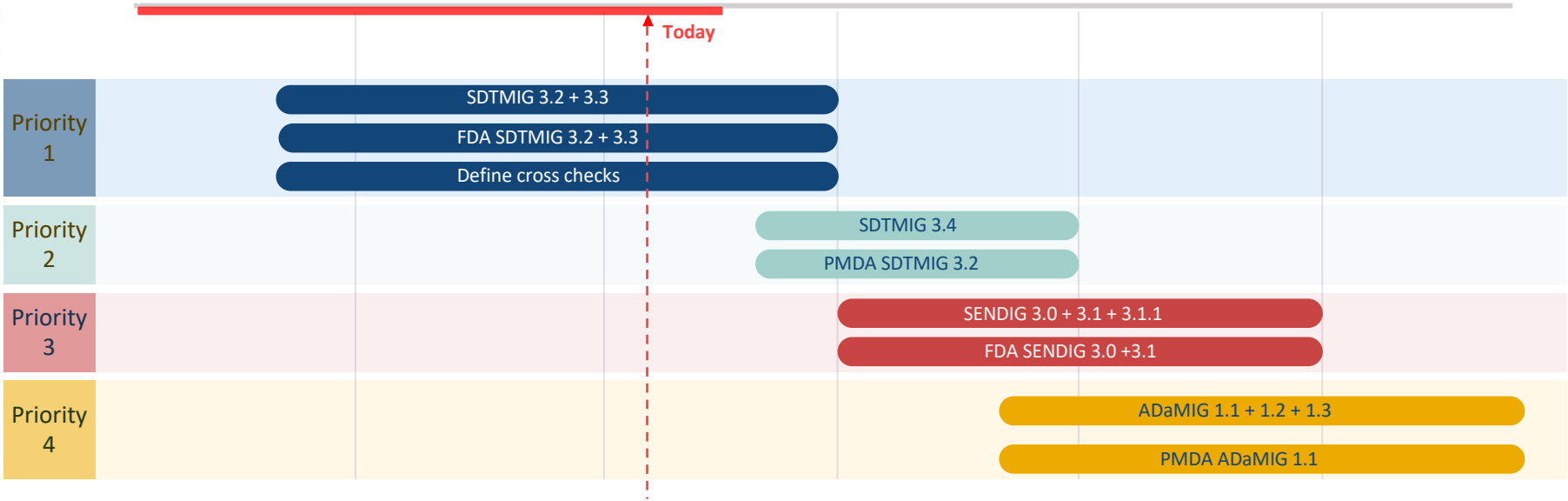
CORE Engine (cdisc CORE OPEN RULES ENGINE)

Rules Development Progress

Components	Status										
	OPEN	DONE	BLOCKED	UNIT TESTING	QC IN PROGRESS	READY TO PUBLISH	PUBLISHED	AWAITING QC	AUTHOR IN PROGRESS	BACK TO AUTHOR	T:
ADaMIG v1.0	312	0	0	0	0	0	7	2	0	0	**321**
ADaMIG v1.1	417	0	0	0	0	0	7	2	0	0	**426**
ADaMIG v1.2	589	0	0	0	0	0	7	2	0	0	**598**
ADaMIG v1.3	549	0	5	4	0	0	8	11	17	2	**596**
FDA SDTMIG v3.2	493	0	0	0	0	0	0	0	0	0	**493**
FDA SDTMIG v3.3	501	0	0	0	0	0	0	0	0	0	**501**
FDA SENDIG DART v1.1	350	0	0	0	0	0	0	0	0	0	**350**
FDA SENDIG v3.0	316	0	0	0	0	0	0	0	0	0	**316**
FDA SENDIG v3.1	330	0	0	0	0	0	0	0	0	0	**330**
FDA SENDIG v3.1.1	335	0	0	0	0	0	0	0	0	0	**335**
FDA SENDIG-AR v1.0	466	0	0	0	0	0	0	0	0	0	**466**
SDTMIG v3.2	169	35	11	0	1	0	192	0	7	2	**417**
SDTMIG v3.3	150	45	11	1	1	0	232	0	7	2	**449**
SDTMIG v3.4	6	59	45	10	3	0	277	2	40	1	**443**
SENDIG v3.0	259	0	0	0	2	0	3	0	0	0	**264**
SENDIG v3.1	174	2	2	3	2	5	7	96	11	1	**303**
SENDIG v3.1.1	307	0	0	0	2	0	3	0	0	0	**312**
SENDIG-DART v1.1	353	0	0	0	2	0	3	0	0	0	**358**
Total Unique Issues:	**6076**	**141**	**74**	**18**	**13**	**5**	**746**	**115**	**81**	**8**	**7277**

Statistieken **18** van **18**.
Bekijk in Jira

Rules Development Priority



➡ *Timelines depend on community engagement*

CORE Engine is Open-Source

- Open-source framework
  - Listed in the COSA (CDISC Open-Source Alliance) directory
  - Permissive MIT open-source license
  - Provided via GitHub
- Free to all in CDISC community
- Very flexible implementation options

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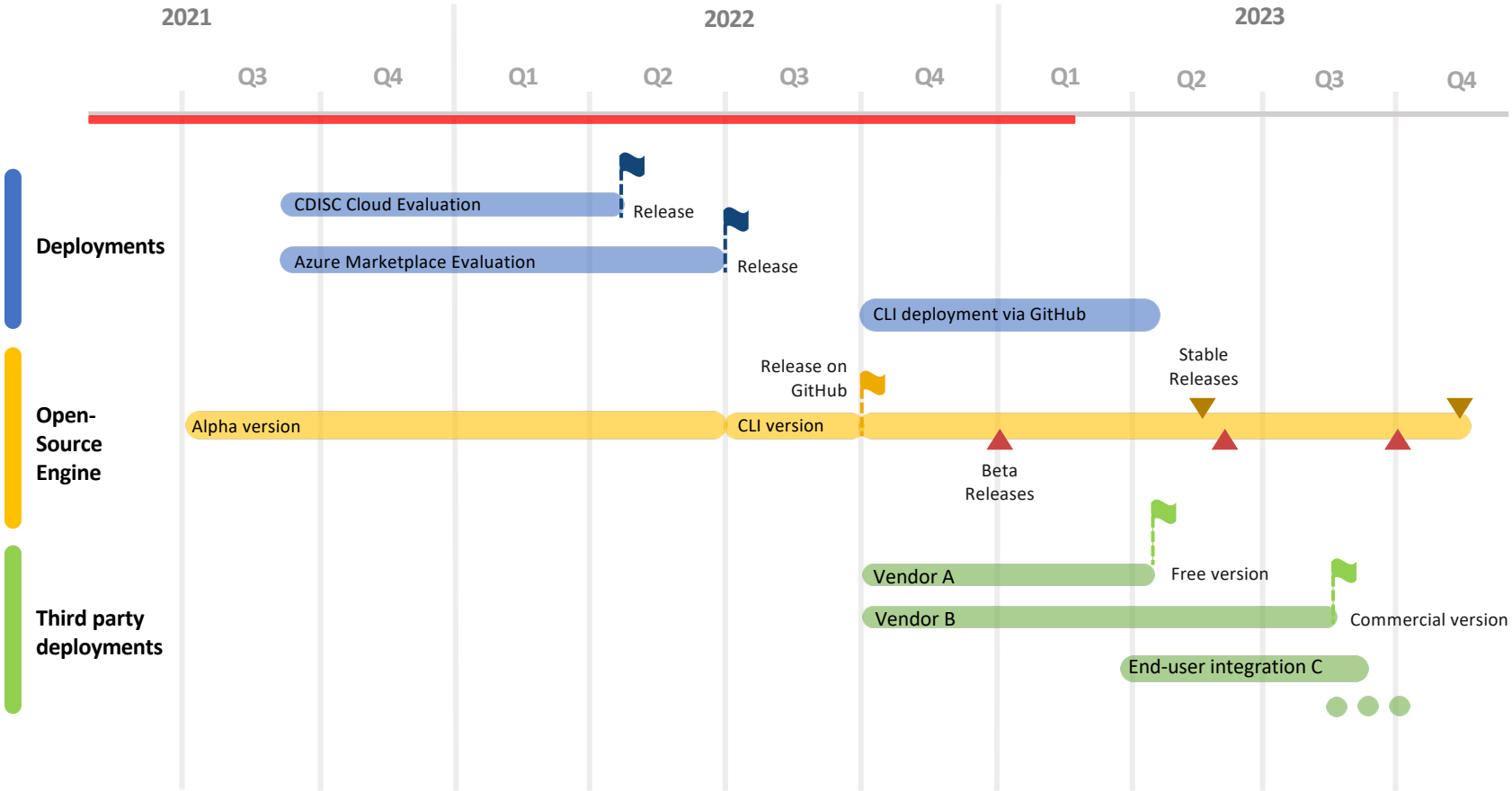
Engine and Deployments Overview

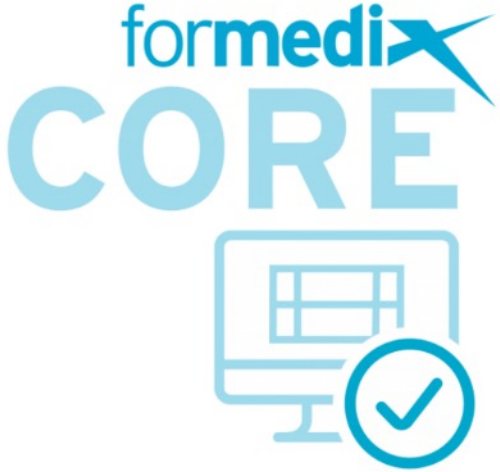


First vendor launch

Introducing Formedix CORE: a free-to-use desktop app incorporating the CDISC Open Rules Engine

Formedix CORE is a free, downloadable Windows desktop application that allows you to validate datasets using the CDISC Open Rules Engine (CORE). The application provides an easy way to run validations on local data and identify standards conformance issues.

DOWNLOAD CORE



Next Milestone

- The complete ruleset for
  - SDTM 3.2 and SDTM 3.3
  - Define.xml crosscheck rules
  - FDA validator rules v1.6 (that apply to SDTM 3.2 and SDTM 3.3)
  - FDA rejection rules

- CORE Engine Stable Release
  - Engine can run all the rulesets above
  - Thorough testing and validation documentation

- Purpose
  - Test with real study data and roll out rules governance process

Implementers can integrate this stable version
Drive adoption and test with real study data

CORE Future State

- Rules
  - Full set of executable rules for submission standards (SDTM, SEND, ADaM)
  - Including Regulatory-specific rules
  - Including Define.xml cross-check rules

  ➔ *Continuing volunteer engagement is critical!*

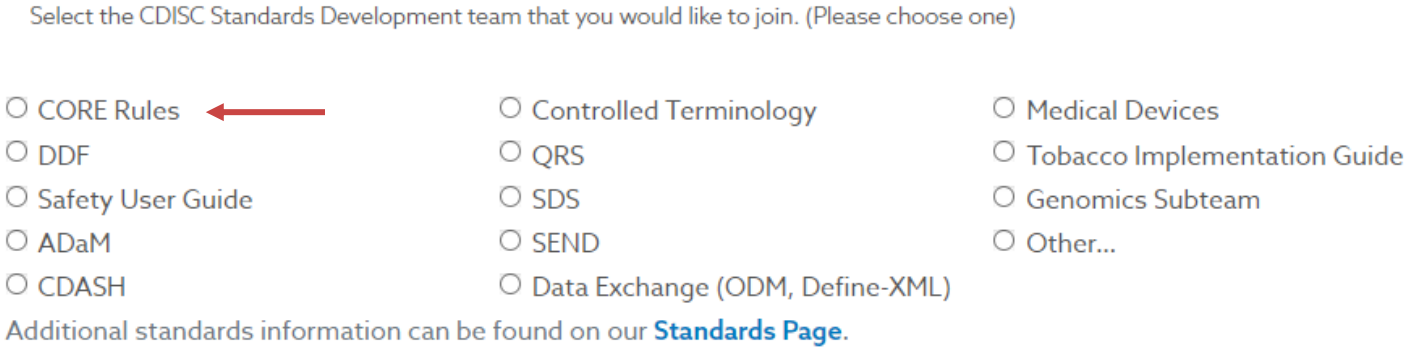
- CORE is the Reference Engine
  - Engine with all basic functionality for full set of machine-executable rules
  - Includes a validation package

- CDISC will establish a CORE certification program
  - To verify output of different applications versus the CORE Reference Engine
  - CDISC conformance rules are the single version of the truth

Rules are part of the Standards!
Expect Regulatory Agencies to mandate use of CDISC Conformance Rules

How to sign up as a volunteer

- https://www.cdisc.org/volunteer/form
  - Select CORE Rules Team



Relentless Collaboration

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Thank you!