

PHUSE EU Connect 2024

DS08 ICH M11, TransCelerate, CDISC & HL7 Vulcan:

Making the Electronic Protocol a Reality

13th November 2024

Peter Van Reusel



Meet the Speaker

Peter Van Reusel

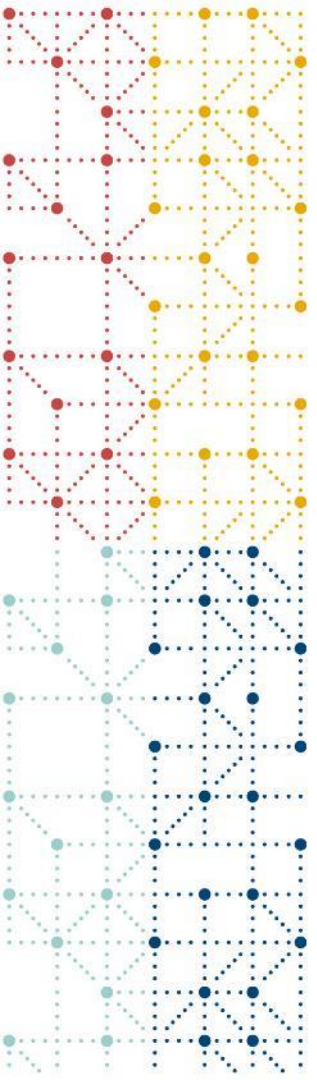
Title: Chief Standards Officer

Organization: CDISC



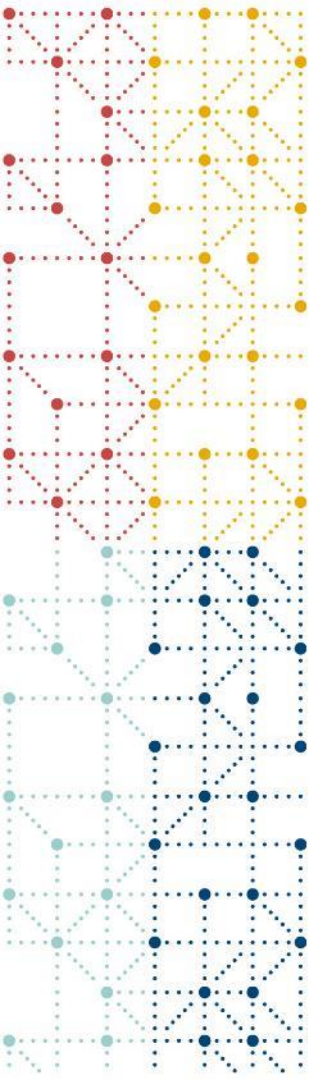
Peter Van Reusel provides executive leadership to the development and implementation of clinical standards in line with CDISC's strategy and operational plans, working closely with the President and CEO, as well as CDISC staff and stakeholders. He has over 20 years' experience in senior roles in pharma 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, fostering relationships with key European regulatory, academic, and biopharma stakeholders. Peter is also an active PHUSE collaborator.



Agenda

1. Introduction to the Digital Data Flow Project and USDM
2. Overview of M11 and the CDISC/ICH Partnership
3. USDM, M11, and the HL7 UDP – how do they come together?

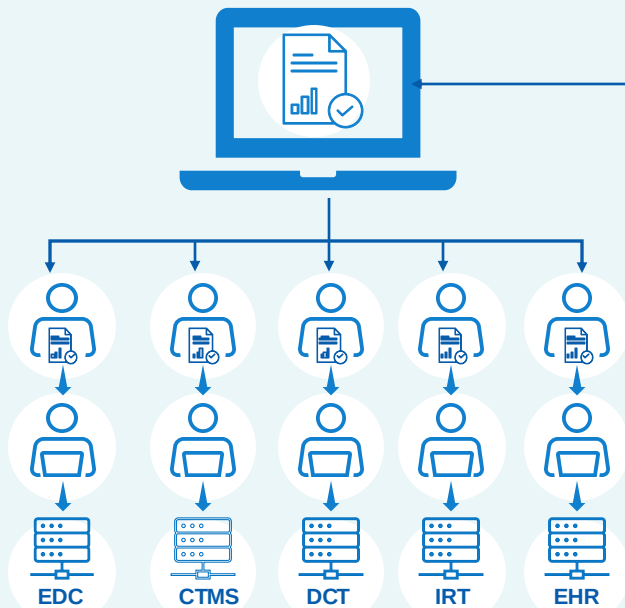


Introduction to the Digital Data Flow Project (DDF) and the Unified Study Definition Model (USDM)

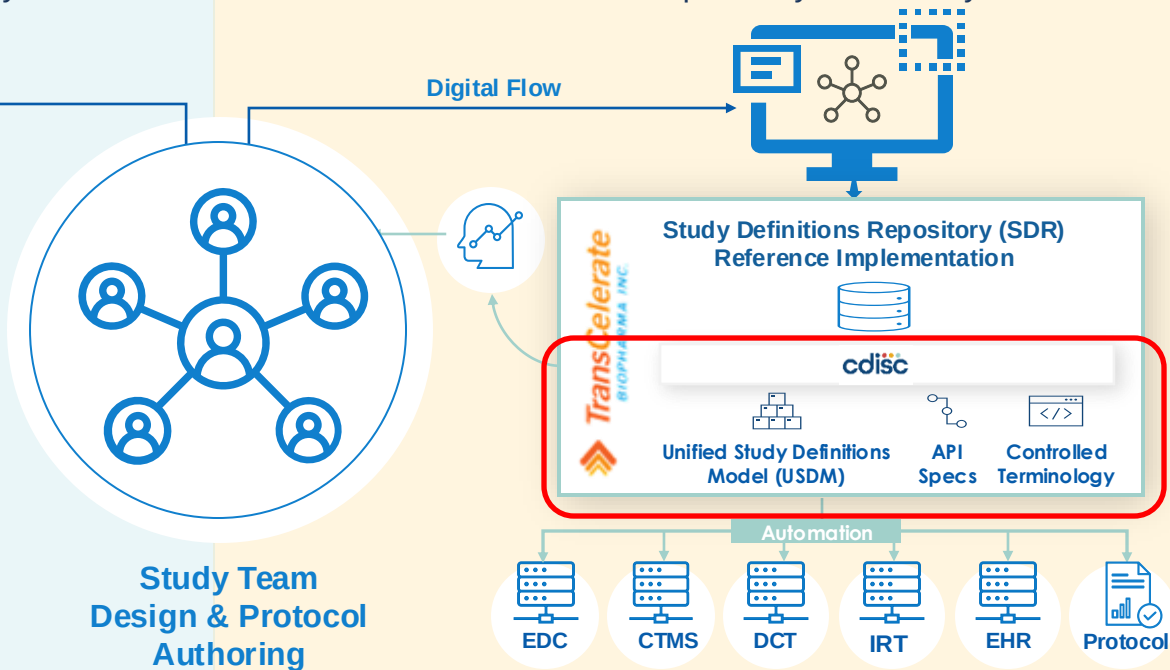
TransCelerate Digital Data Flow (DDF) Ambition

Write Once, Read Many

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



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



	C174447	Study Arm
	C170984	Study Arm Name
	C93728	Study Arm Description
	C188827	Study Arm Type
DataOriginDescription	C188828	Study Arm Data Origin Description
OriginType	C188829	Study Arm Data Origin Type
Label	CNEW	Study Arm Label
StudyEpoch	C71738	Study Epoch
EpochName	C93825	Study Epoch Name
EpochDescription	C93824	Study Epoch Description
	C188830	Study Epoch Type
	CNEW	Study Epoch Label

	A	B	
Name	Rate	Warning/ Error	Entity/ applies
Descriptive type	must conform with the USDM schema based on the USDM schema.	ERROR	All
	Attributes (string, number, boolean) must conform with the USDM schema based on the API specification.	ERROR	All
	Attributes must be included as defined in the USDM schema based on the API specification (i.e., all required properties are present and no additional attributes are present).	ERROR	All
	Properties must be as defined in the USDM schema based on the API specification (i.e., required properties have at least one value and single-valued properties are not lists).	ERROR	All
	Within a study/session, all values must be unique.	ERROR	All
	The names of all child instances of the same parent class must be unique.	ERROR	All
	The same Biomedical Concept Category must not be referenced more than once from the same activity.	ERROR	Activity
	A specified biomedical concept category is expected to be referenced by an activity.	WARNING	Activity
	A specified biomedical concept surrogate is expected to be referenced by an activity.	WARNING	Activity
	A specified biomedical concept is expected to be referenced by an activity.	WARNING	Activity
	Children must not refer to a timeline, procedure, concept, biomedical concept category or biomedical concept.	ERROR	Activity
	A procedure is expected to be referenced by an activity.	WARNING	Activity
	An activity is expected to refer to at least 1 procedure, biomedical concept category or biomedical concept.	WARNING	Activity
	An activity is expected to refer to at least 1 procedure, biomedical concept category or biomedical concept.	WARNING	Activity
	Activities must not refer to the previous and next attributes must not refer to the previous and next attributes.	WARNING	Activity

```
StudyArms: [
  {
    "id": "StudyArm_1",
    "name": "Placebo",
    "label": "",
    "description": "Placebo",
    "type": {
      "id": "Code_61",
      "code": "C174268",
      "codeSystem": "http://www.cdisc.org",
      "codeSystemVersion": "2022-12-16",
      "decode": "Placebo Comparator Arm"
    }
  },
  {
    "studyArmDataOriginDescription": "Data collected from within study",
    "id": "Code_62",
    "code": "C188866",
    "codeSystem": "http://www.cdisc.org",
    "codeSystemVersion": "2022-12-16",
    "decode": "Data Generated Within Study"
  }
],
{
  "id": "StudyArm_2",
  "name": "Xanomeline Low Dose",
  "label": "",
  "description": "Active Substance",
  "type": {
    "id": "Code_63",
    "code": "C174267",
    "codeSystem": "http://www.cdisc.org",
    "codeSystemVersion": "2022-12-16",
    "decode": "Active Substance"
  }
}
```

```

classDiagram
    class StudyArm {
        +id: String
        +name: String
        +description: String [0..1]
        +label: String [0..1]
        +studyArmDataOriginDescription: String
    }
    class StudyCell {
        +id: String
    }
    class StudyEpoch {
        +id: String
    }
    StudyArm "1" -- "1..*" StudyCell : studyArm
    StudyCell "1..*" -- "1" StudyEpoch : studyEpoch
    StudyArm "1" -- "1" StudyEpoch : studyEpoch
  
```

API for DDF (2.4 Provisional (0.39))

Accelerate Digital Data Flow (DDF) Study Definitions Repository API.

Introduction

Routes that form the production specification.

POST	/v3/studyDefinitions	Create a study
PUT	/v3/studyDefinitions/{studyId}	Update a study
GET	/v3/studyDefinitions/{studyId}	Return a study
GET	/v3/studyDefinitions/{studyId}/history	Returns the study history
GET	/v3/studyDesigns	Study designs for a study

1 > Expand all object

Guidance on using the USDM model and ensuring conformance with the standard

Version 2.0 (Draft for Internal Review)

Prepared by the
DDF Team

Notes to Readers

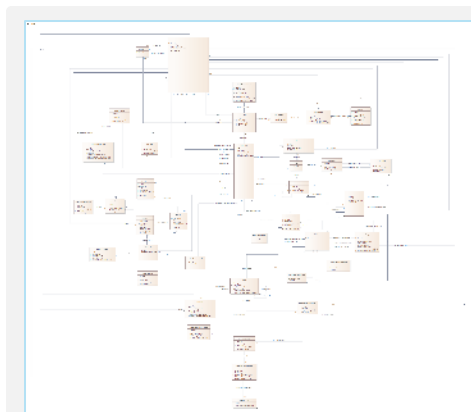
- This is the draft version 2.0 of the Unified Study Definitions Model Implementation Guide (USDM-IG v2.0). It is intended for Internal Review only and is not a final version.

History

Version
2.0 Draft for Internal Review

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USDM Content



Controlled
Terms

Study, Identifiers,
Amendments

Estimands

Unstructured Content

Populations

Inclusion &
Exclusion

Study Designs,
Arms, Epochs

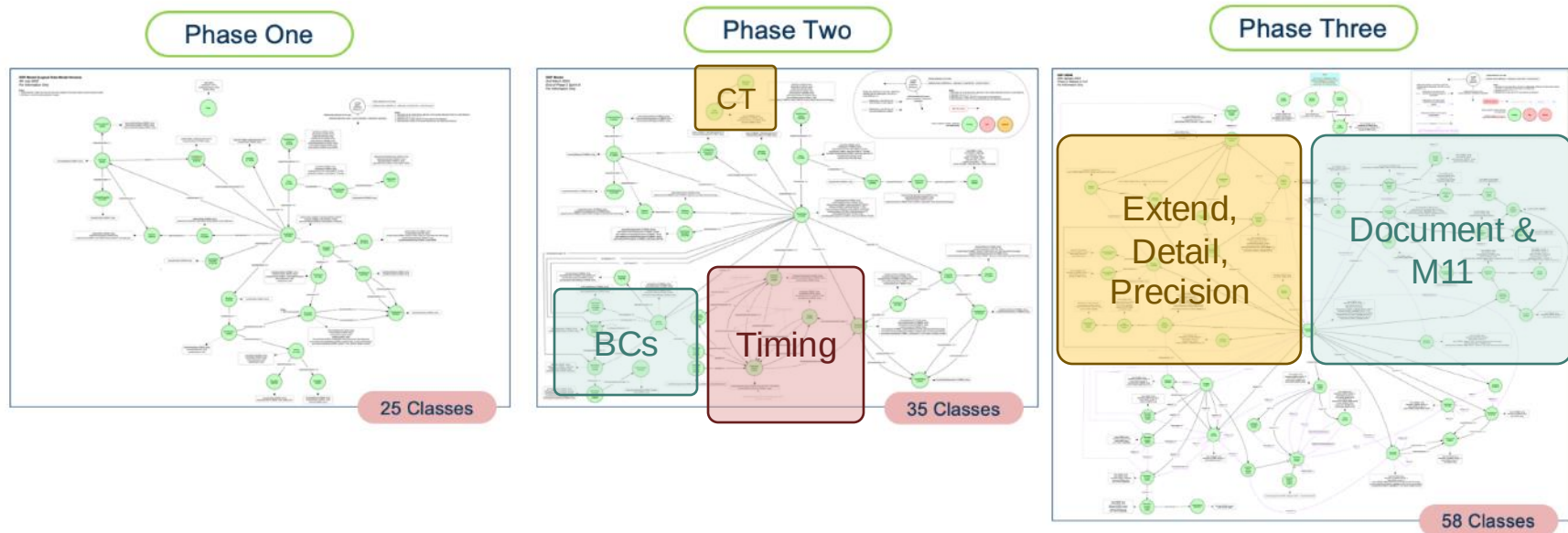
Interventions &
Indications

Objectives &
Endpoints

Detailed Study Logic,
Encounters

Procedures, Biomedical Concepts

CDISC USDM: Phases One, Two and Three



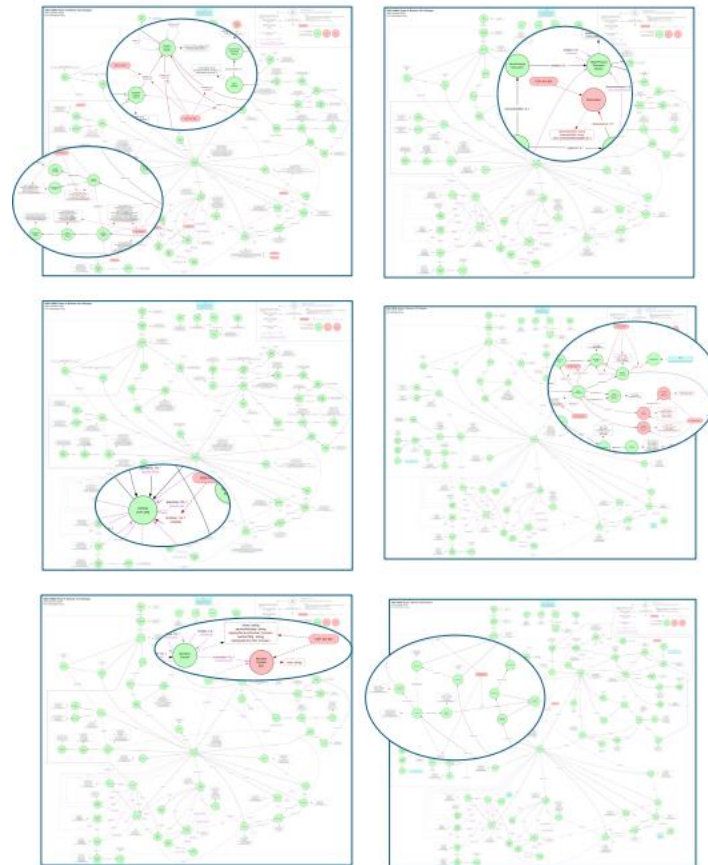
- Solid foundation
- The protocol document was an external entity into which the structured content could be exported

- Focused on the structured elements of the protocol, e.g. the Schedule of Activities (SoA) & Biomedical Concepts (BCs)
- The protocol document is still an external entity

- Now contains structured and unstructured elements
- The entire protocol document can be held within the USDM
- Allows for the protocol document to be generated from the model

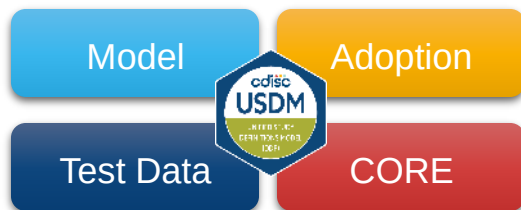
CDISC USDM: Phase Four

- Notes & Criteria
- Activity Groups
- Multiple Template Support (M11 alignment)
- Abbreviations
- Interventions, Identifiers & Roles (M11 alignment)
- Amendments (M11 alignment)
- Estimands (M11 alignment)
- Observational & Device Studies
- Final M11 alignment



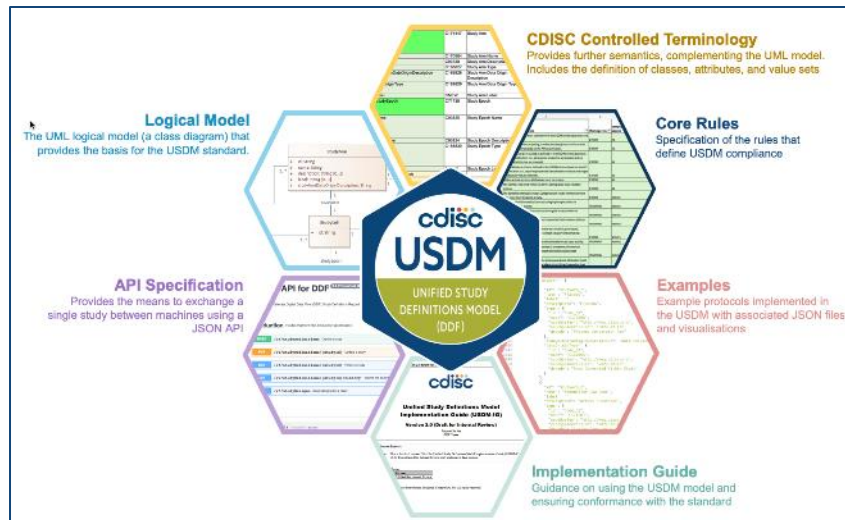
Phase 4 Overview

- More focus on refinement rather than new content
- Need to pay attention to backward compatibility
- Maximum alignment with ICH M11
- Conformance Rules now part of the standard



Phase Four Focus

- 1 USDM Enhancements
- 2 Continued alignment of USDM with ICH M11
- 3 Utilizing the Digital Protocol (UDP) collaboration
- 4 USDM Conformance Rules to support USDM v3.0 and v4.0
- 5 Test data and test tools
- 6 Development of training and education materials
- 7 Align USDM and Trial Master File (TMF)



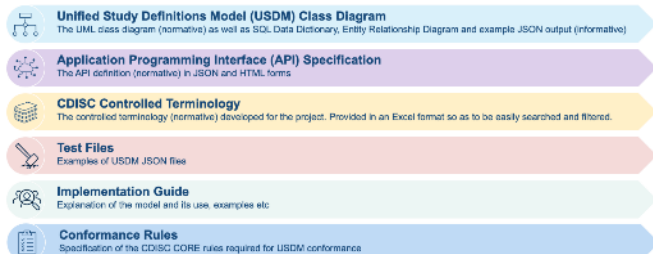
DDF Evolution: Phases One to Four

		PHASE ONE July 2021 – July 2022	PHASE TWO Oct 2022 – Sep 2023	PHASE THREE July 2023– May 2024	PHASE FOUR Apr 2024– 1Q 2025
CDISC's USDM Reference Architecture	USDM Data Model	✓	✓	✓	□
	API Specification	✓	✓	✓	□
	CDISC Controlled Terminology	✓	✓	✓	□
	Implementation Guide		✓	✓	□
	Test Files		✓	✓	□
	Conformance CORE Rules – POC			✓	TBD
TransCelerate's SDR & Implementation Support	Study Definitions Repository (SDR)	✓	✓	✓	□
	Common Protocol Template (CPT) Interface Tool – POC		✓		
	Implementation Architecture Scenarios Toolkit		✓	◆	◆
	Persona Toolkits (MW, DM, IT)		✓	◆	◆
	Cloud Agnostic SDR – POC			✓	

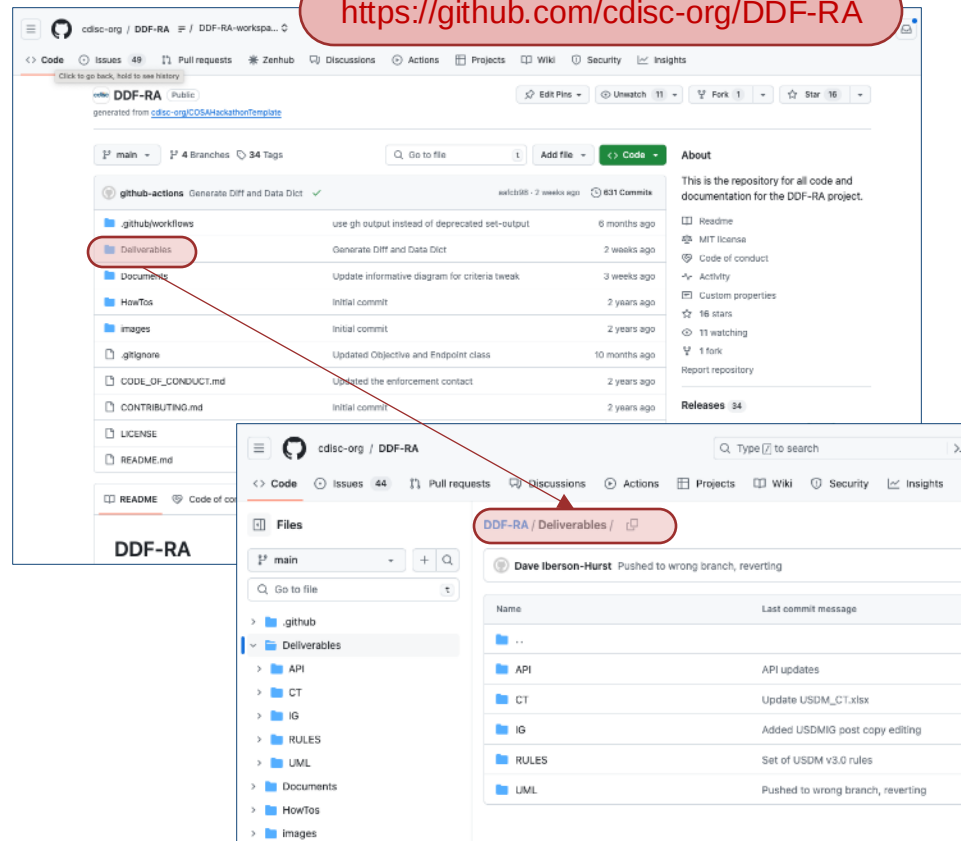


DDF Reference Architecture & Github

- The source of DDF Reference Architecture deliverables



<https://github.com/cdisc-org/DDF-RA>



Example Resources – CDISC

Digital Data Flow

<https://www.cdisc.org/ddf>

Overview | What is the USDM | Participate | Webinar | Versions | FAQ | Contact Us



Welcome to Digital Data Flow (DDF) for Clinical Trial Protocols

Digital Data Flow Initiative will help modernize clinical trials by enabling a digital workflow with protocol digitization. This initiative establishes a foundation for a future state of automated & dynamic readiness that can transform the drug development process.

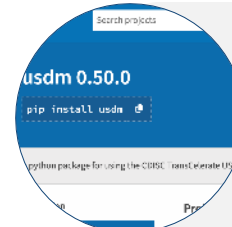
Below are a list of the different websites sourcing specific content and resources. Depending on where you are in the journey, please feel free to explore the different websites and their information.

 CDISC DDF Website <i>You are here!</i>	 DDF Website	 DDF GitHub	 Transcelerate DDF Initiative Solutions
Learn about the Unified Study Definitions Model (USDM) Reference Architecture supporting Protocol Standards	As the main website for DDF, learn and access all resources supporting DDF	Learn about and access the Study Definitions Repository Reference implementation	Learn about DDF background and initiative roadmap
Target Audience: Those interested in data standards	Target Audience: All those interested in implementing DDF Solutions	Target Audience: Those interested in SDR development	Target Audience: All those generally interested



CDISC Github housing the USDM deliverables (model, CT, API etc) along with examples of protocols placed into USDM.

<https://github.com/cdisc-org/DDF-RA>



Open-source python package that implements USDM V3. Can be used by anyone to build test data

<https://pypi.org/project/usdm/>



Web-based version of the USDM test tooling.

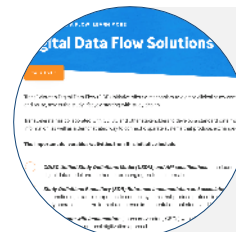
<https://usdm-service.fly.dev/>

U: PHUSE
P: learning_usdm

Example Resources – TransCelerate



<https://www.transceleratebiopharmainc.com/initiatives/digital-data-flow/>



TransCelerate web page holding a significant number of DDF and USDM resources including the persona guides

<https://www.transceleratebiopharmainc.com/assets/digital-data-flow-solutions/>



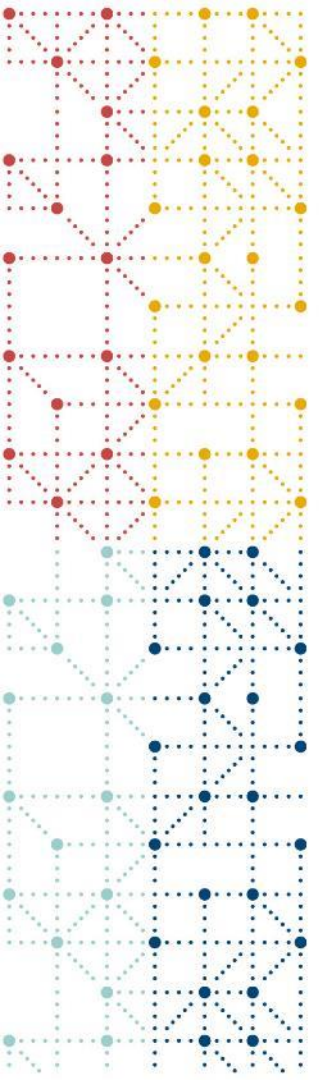
Github housing the source for the Study Definition Repository (SDR) Reference Implementation of the USDM

<https://github.com/transcelerate/ddf-sdr-platform>



DDF solutions directory. A growing list of self-reported solutions which utilize and follow the DDF Unified Study Definitions Model (USDM)

<https://transcelerate.github.io/ddf-directory/directory/directory.html>

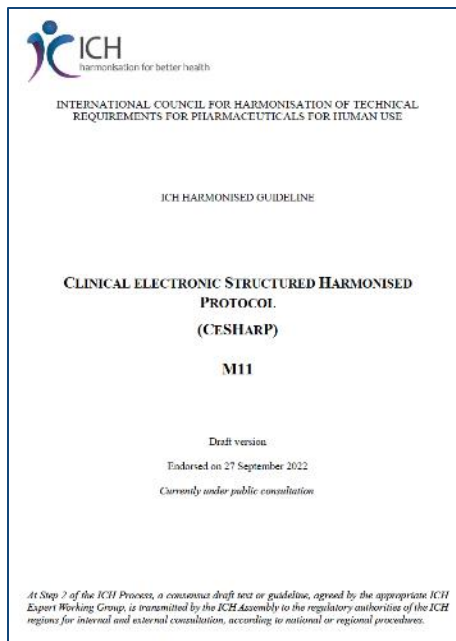


Overview of M11 and the ICH/CDISC Partnership

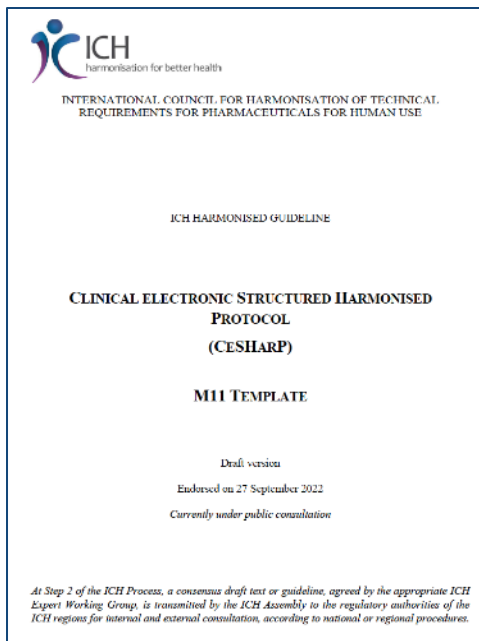
M11 Is ...

ICH CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL (CeSHaRP)

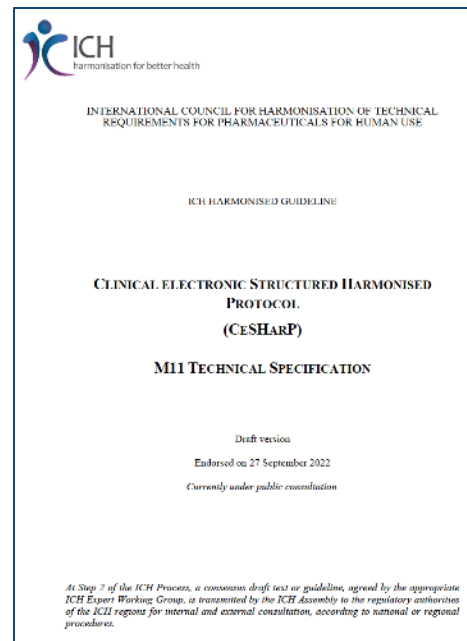
<https://www.ich.org/page/multidisciplinary-guidelines>



Provides background, purpose, and scope as a guideline



Provides the written format for the Interventional Clinical Trial Protocol Template



Provides the technical representation aligned with the guideline and protocol template

M11 Controlled Terms

Template Specification

Protocol Full Title:	[Protocol Full Title] The protocol should have a descriptive title that identifies the scientific aspects of the trial sufficiently to ensure it is immediately evident what the trial is investigating and on whom, and to allow retrieval from literature or internet searches.
Sponsor Confidentiality Statement:	[Sponsor Confidentiality Statement] Insert the Sponsor's confidentiality statement, if applicable, otherwise delete.
Protocol Number:	[Protocol Number] A unique alphanumeric identifier for the trial, designated by the Sponsor, is a standard part of trial data, and should be included for most trials.
Version:	[Version] An optional field for use by the Sponsor at their discretion.
Amendment Number:	[Amendment Number] Enter the amendment number. If this is the original instance of

Trial Phase:

[Trial Phase] [Description of Trial Phase Other]

Acceptable entries are: "Early Phase 1", "Phase 1", "Phase 1/Phase 2", "Phase 2", "Phase 2/Phase 3", "Phase 3", "Phase 4",

Compound Number(s):	[Compound Number] Enter the Sponsor's unique identifier for investigational compound(s) in the trial. Add or delete additional fields as needed.
Compound Name(s):	[Nonproprietary Name] [Proprietary Name] [Additional Proprietary Name] Delete this line from the table if a nonproprietary name has not yet been assigned. Omit proprietary name fields if not yet established.
Trial Phase:	[Trial Phase] [Description of Trial Phase Other] Acceptable entries are: "Early Phase 1", "Phase 1", "Phase 1/Phase 2", "Phase 2", "Phase 2/Phase 3", "Phase 3", "Phase 4",

Technical Specification

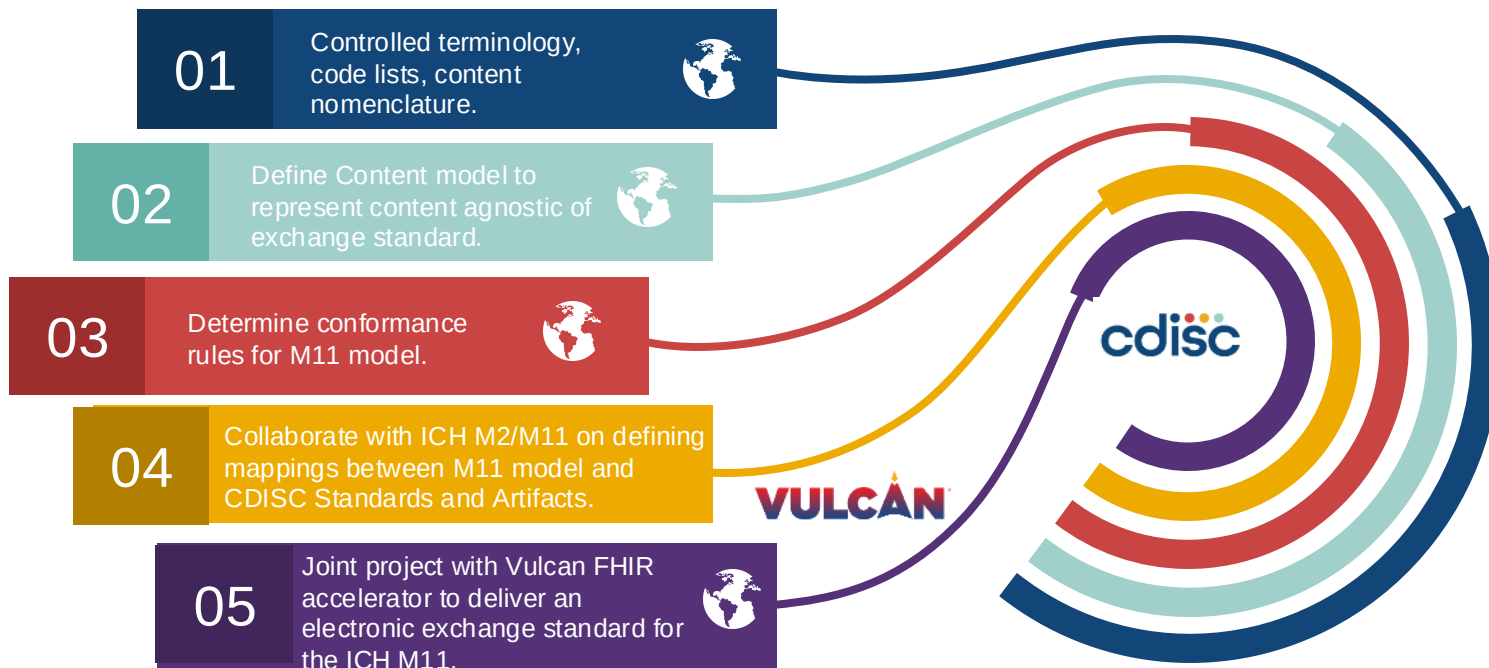
Term (Variable)	Trial Phase
Data Type	Pick list
Topic, Value or Header	D
Definition	
User Guidance	For trials combining investigational drugs or vaccines with devices, classify according to the phase of drug development.
Conformance	Required
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Title Page
Relationship (reference to high level conceptual model)	
Value	Early Phase 1 Phase 1 Phase 1/Phase 2 Phase 2 Phase 2/Phase 3 Phase 3 Phase 4 Other
Business rules	Value Allowed: yes Relationship: n/a Concept: Protocol short title
Duplicate field in other sections	

CDISC CT

Trial Phase Response (C66737)

NOT APPLICABLE
 PHASE 0 TRIAL
 PHASE I TRIAL
 PHASE I/II TRIAL
 PHASE II TRIAL
 PHASE II/III TRIAL
 PHASE IIA TRIAL
 PHASE IIB TRIAL
 PHASE III TRIAL
 PHASE IIIA TRIAL
 PHASE IIIB TRIAL
 PHASE IV TRIAL
 PHASE V TRIAL

CDISC M2/M11 Engagement



ICH and CDISC MOU (Memorandum of Understanding)

As a collaboration between ICH and CDISC, the goals of the agreement are to:

- Use a unified governance process and terminology services for the long-term support of ICH controlled terminologies
- Curate and maintain ICH controlled terminologies
- Follow a robust process for the public review and publication of ICH terminologies
- Ensure the terminologies are freely available to the public following public review

Scope

For ICH members to adopt and implement a clinical information standard it is critical that all terminology components, including but not limited to definitions described in the technical specification, are part of a greater international controlled terminology resource managed by an internationally recognized standards development organization (SDO). CDISC has been identified by ICH as a reputable SDO with the qualifications and capabilities to support the maintenance and facilitation of the governance process for ICH controlled terminology.

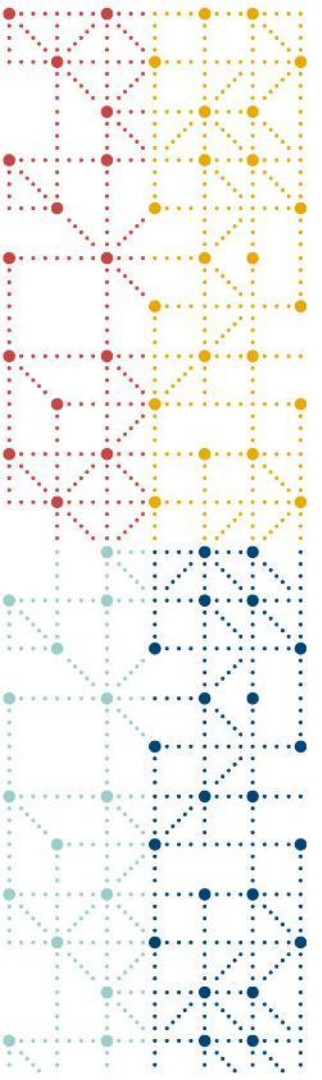
This Memorandum of Understanding (MOU) sets forth the roles and responsibilities of each party as they relate to the governance of the ICH terms and definitions developed in collaboration with CDISC. This MOU is intended to describe the goals, the high-level governance process, and how each party will collaborate. Specific projects (e.g., M11 controlled terminology) will be defined in detail as part of an annex to this MOU mutually agreed upon by CDISC and ICH.

Goals

As a collaboration between ICH and CDISC, the goals of the agreement are to:

1. Use a unified governance process and terminology services for the long-term support of ICH controlled terminologies.
2. Curate and maintain ICH controlled terminologies.
3. Follow a robust process for the public review and publication of ICH terminologies
4. Ensure the terminologies are freely available to the public following public review.



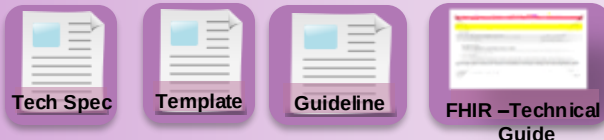


USDM, M11, and the HL7 UDP – how do they come together?

ICH M11 and Vulcan Utilizing Digital Protocol (UDP)



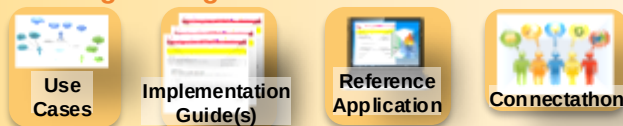
CeSHarP



USDM and Terminology



Utilizing the Digital Protocol – UDP



Inputs:

ICH M11 template

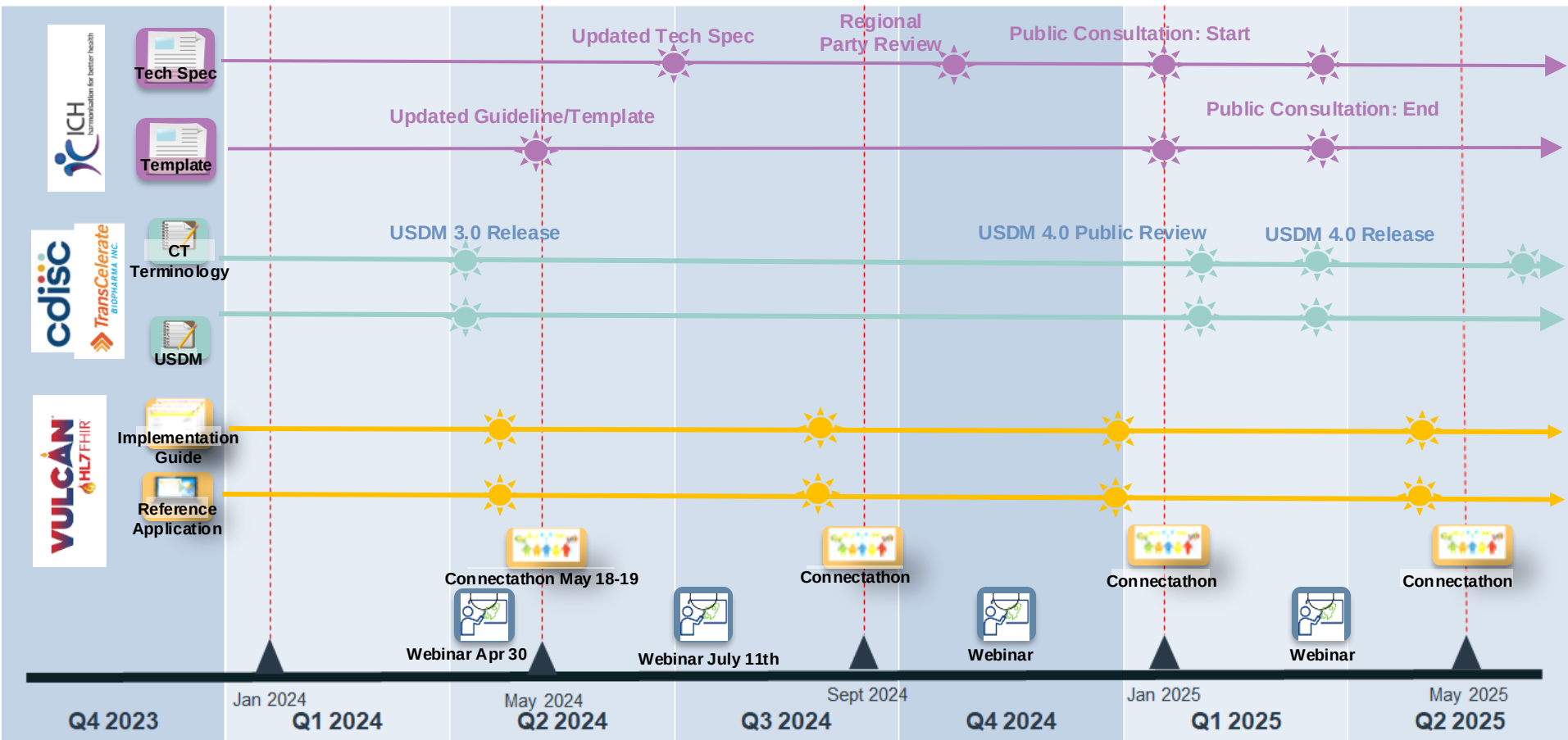
ICH M11 technical specification

Models, definitions

FHIR will carry CDISC CT and USDM content

The technical specification can be used to develop other Implementation Guides

Timelines

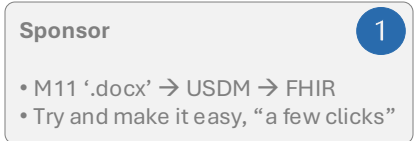


PROJECT PRISM

A Regulatory Cloud Collaborative Initiative



precisionFDA Regulatory Information Service Module
FDA-Industry Research Collaboration Agreement
(Public-Private Partnership)





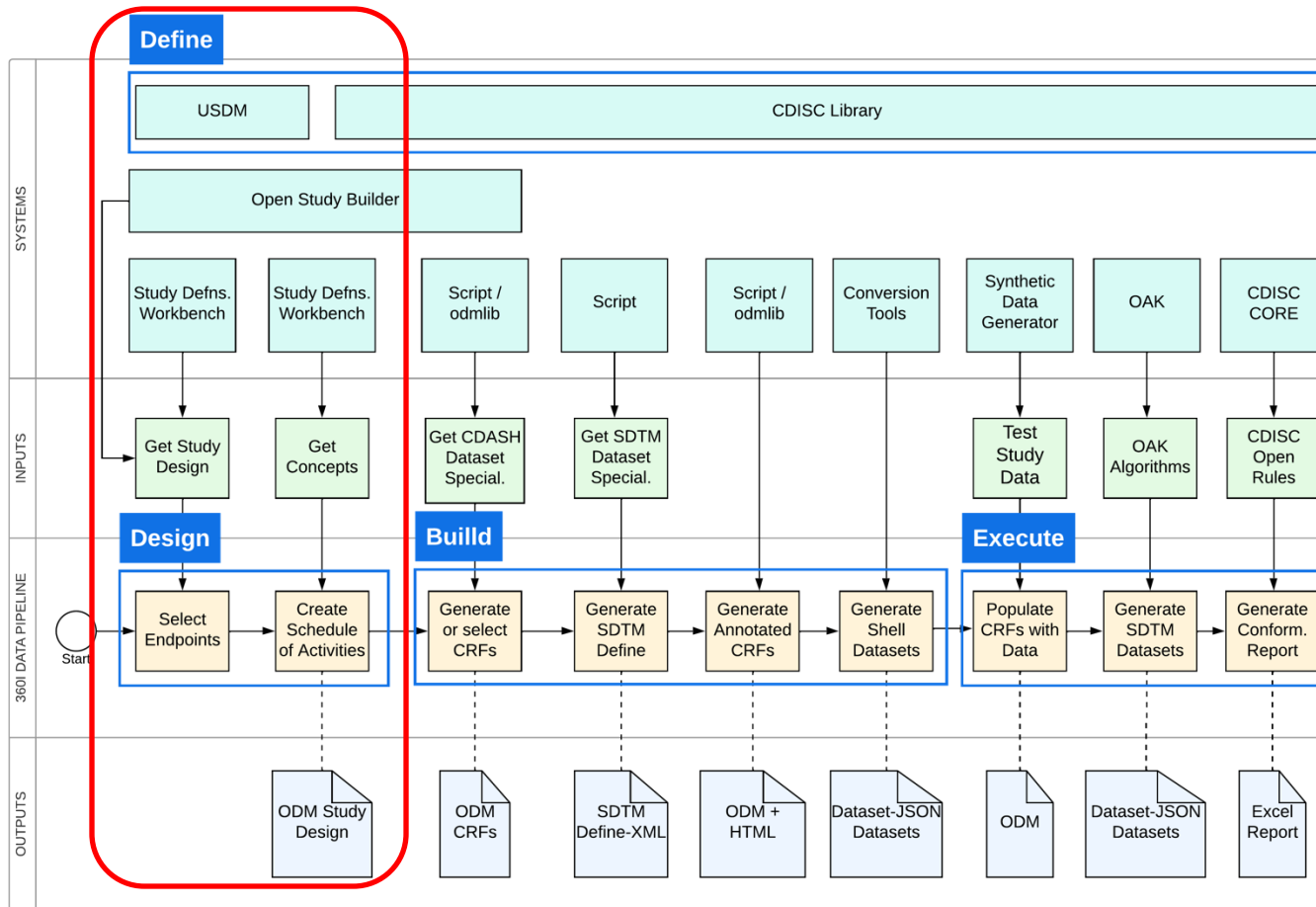
CDISC 360i

- Define end to end standards
 - Digitalize information from protocol to reporting
 - Link concepts to representation standards
 - Forms definition, eDTs, DHT, SDTM specs, ADaM specs, TFL specs, ...
 - Enrich with transformation & derivation logic
- Study design & build
 - Select concept and concept groups in digital Schedule of Activities
 - Automates study builds
 - Forms definition, SDTM specs, ADaM specs, TFL specs, ...
 - Provides derivation & transformation algorithms
- Automate data flow
 - Demonstrate end to end automation
 - Starts with linking Schedule of Activities to Concepts (and Concept Groups)
 - Automates transformations & derivation between data states
 - Collection, tabulation, analysis, results



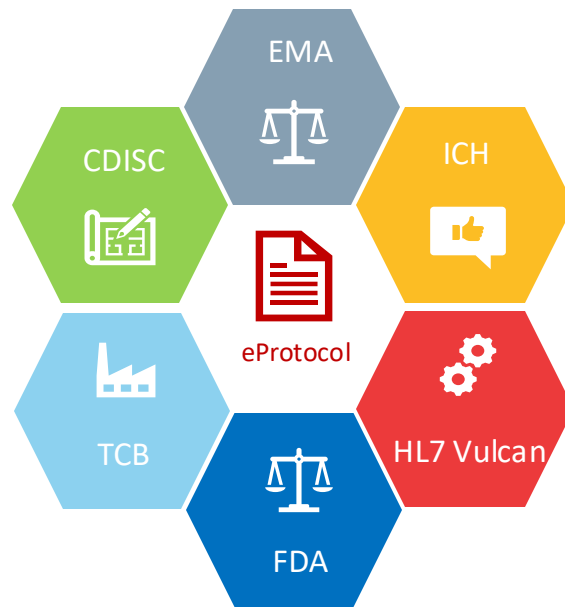
CDISC 360i Phase 1: Generating SDTM

Technical Process



Summary

- Digitalizing protocol is well underway
- This collaboration will accelerate the operationalization of the digital protocol
- Sponsors and vendors have started to pilot and implement





Thank You!

