ICH M11, TransCelerate, CDISC & HL7 Vulcan: Driving the Adoption of Digital Protocol

Presented by 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, 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?

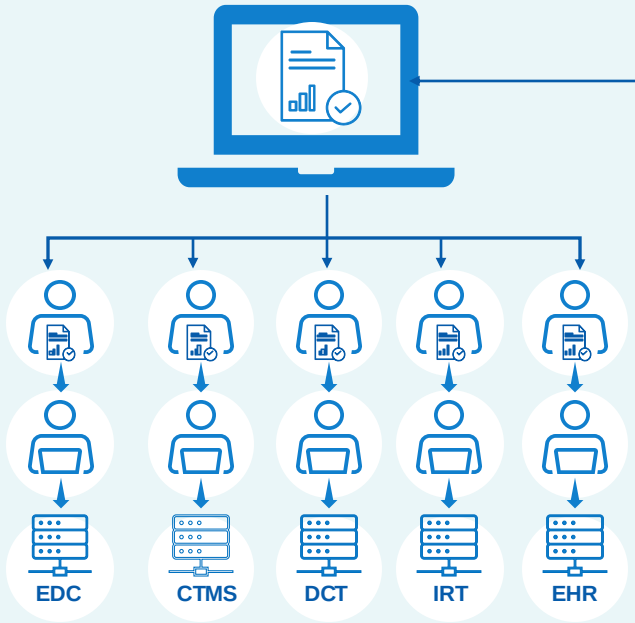
Introduction to the Digital Data Flow Project (DDF) and the Unified Study Definition Model (USDM)

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

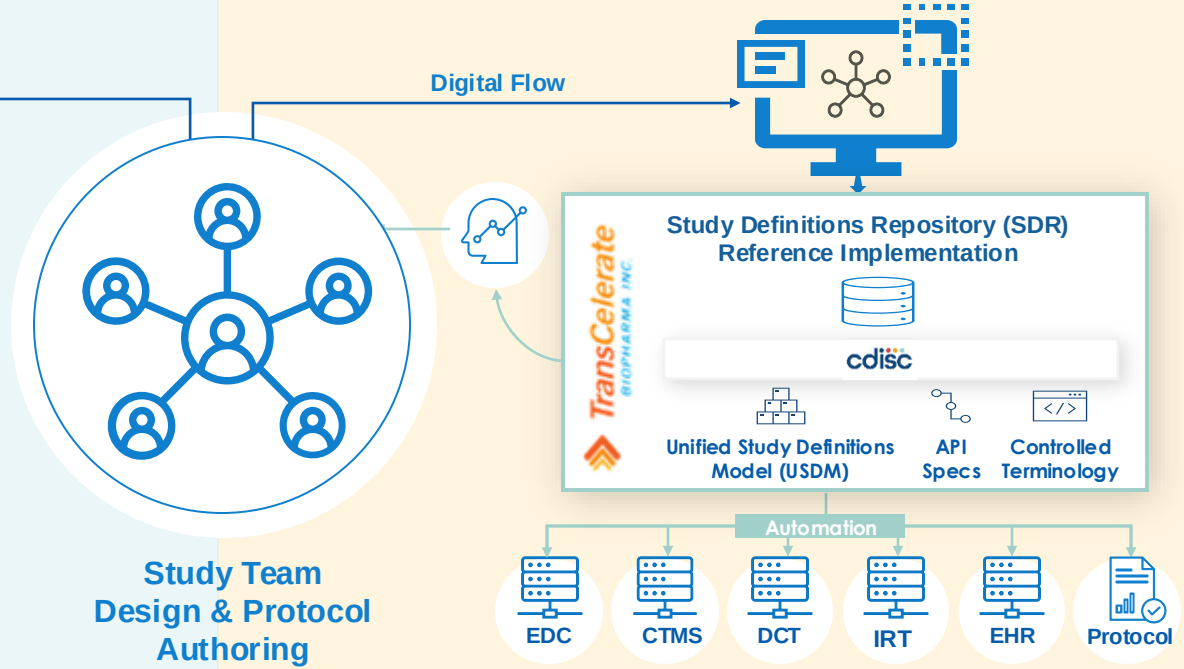
TransCelerate Digital Data Flow (DDF) Ambition

Write Once, Read Many

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



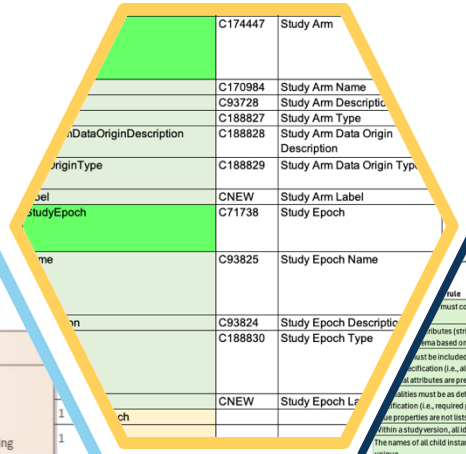
TOMORROW: Digital paradigm for protocol creation, with fully automated data flow and interoperability between systems



The USDM Standard

CDISC Controlled Terminology

Provides further semantics, complementing the UML model.
Includes the definition of classes, attributes, and value sets



	C174447	Study Arm
	C170984	Study Arm Name
	C93728	Study Arm Descriptio
	C188827	Study Arm Type
nDataOriginDescription	C188828	Study Arm Data Origin Description
riginType	C188829	Study Arm Data Origin Typ
el	CNEW	Study Arm Label
tudyEpoch	C71738	Study Epoch
me	C93825	Study Epoch Name
n	C93824	Study Epoch Descriptio
	C188830	Study Epoch Type
	CNEW	Study Epoch La
ch		

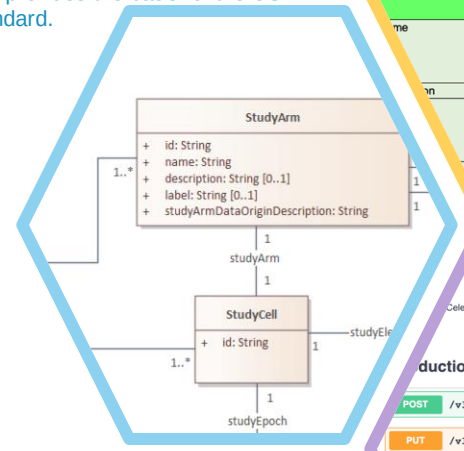
Examples

Example protocols implemented in the USDM with associated JSON files and visualisations

```
"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 collec
    "dataOriginType": {
      "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
      "codeSystemVersion": "2022-12-
```

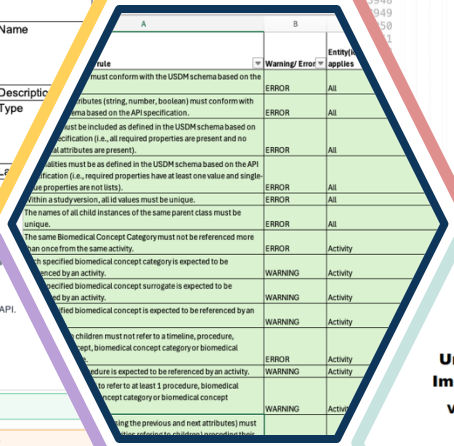
Logical Model

The UML logical model (a class diagram) that provides the basis for the USDM standard.



CORE Rules

Specification of the rules that define USDM compliance



Rule	Warning/ Error	Entity(ies) applies
must conform with the USDM schema based on the	ERROR	All
ributes (string, number, boolean) must conform with ema based on the API specification.	ERROR	All
ust be included as defined in the USDM schema based on ecification (i.e., all required properties are present and no al attributes are present).	ERROR	All
ities must be as defined in the USDM schema based on the API ification (i.e., required properties have at least one value and single- properties are not lists).	ERROR	All
Within a study version, all id 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 an once from the same activity.	ERROR	Activity
n specified biomedical concept category is expected to be enced by an activity.	WARNING	Activity
pecified biomedical concept surrogate is expected to be d by an activity.	WARNING	Activity
ified biomedical concept is expected to be referenced by an	WARNING	Activity
children must not refer to a timeline, procedure, ept, biomedical concept category or biomedical	ERROR	Activity
dure is expected to be referenced by an activity.	WARNING	Activity
to refer to at least 1 procedure, biomedical ncept category or biomedical concept	WARNING	Activity
ing the previous and next attributes) must		

API for DDF

2.4 Provisional (0.39)

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

duction 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

/v3/studyDesigns Study designs for a study

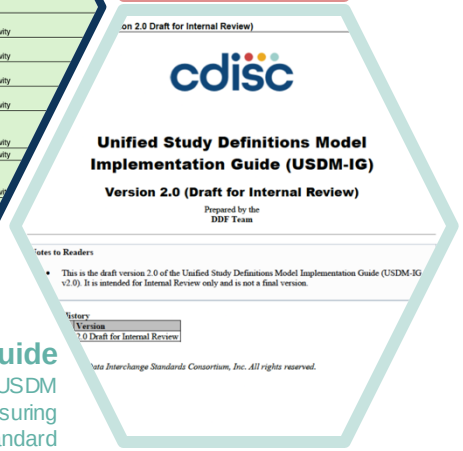
Expand all object

API Specification

Provides the means to exchange a single study between machines using a JSON API

Implementation Guide

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



on 2.0 Draft for Internal Review)

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Unified Study Definitions Model Implementation Guide (USDM-IG)

Version 2.0 (Draft for Internal Review)

Prepared by the DDF Team

otes 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.

istory

Version
2.0 Draft for Internal Review

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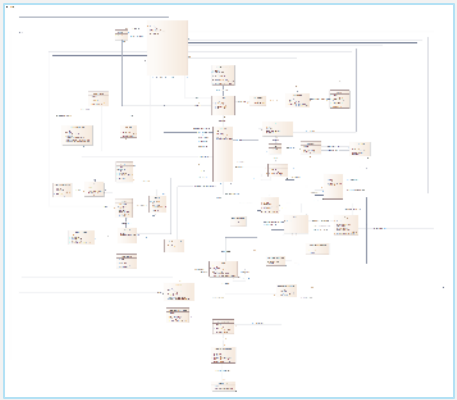
USDM Content



Controlled Terms

Study, Identifiers, Amendments

Estimands

Populations

Inclusion & Exclusion

Interventions & Indications

Objectives & Endpoints

Unstructured Content

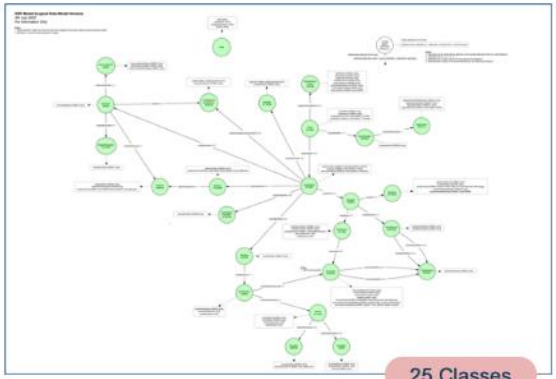
Study Designs, Arms, Epochs

Detailed Study Logic, Encounters

Procedures, Biomedical Concepts

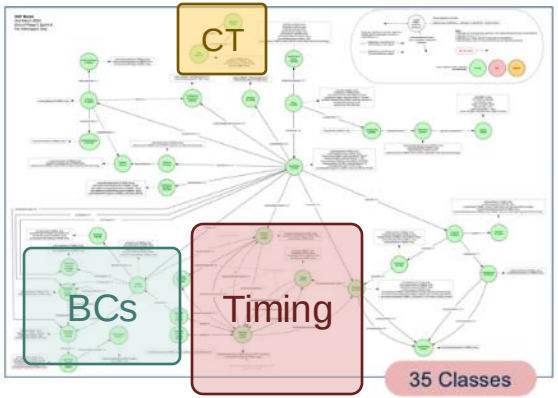
CDISC USDM: Phases One, Two and Three

Phase One



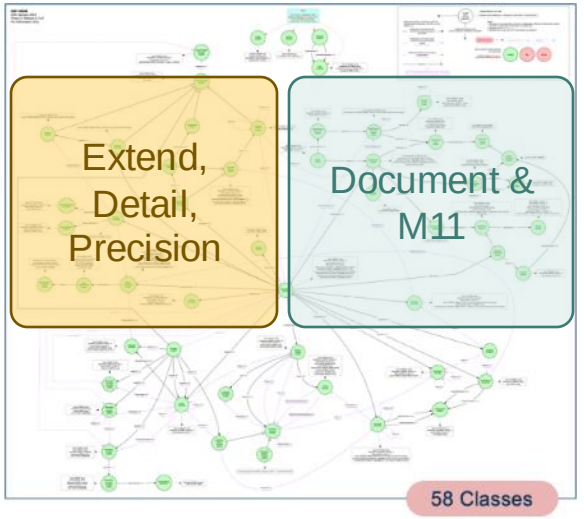
- Solid foundation
- The protocol document was an external entity into which the structured content could be exported

Phase Two



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

Phase Three



- 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

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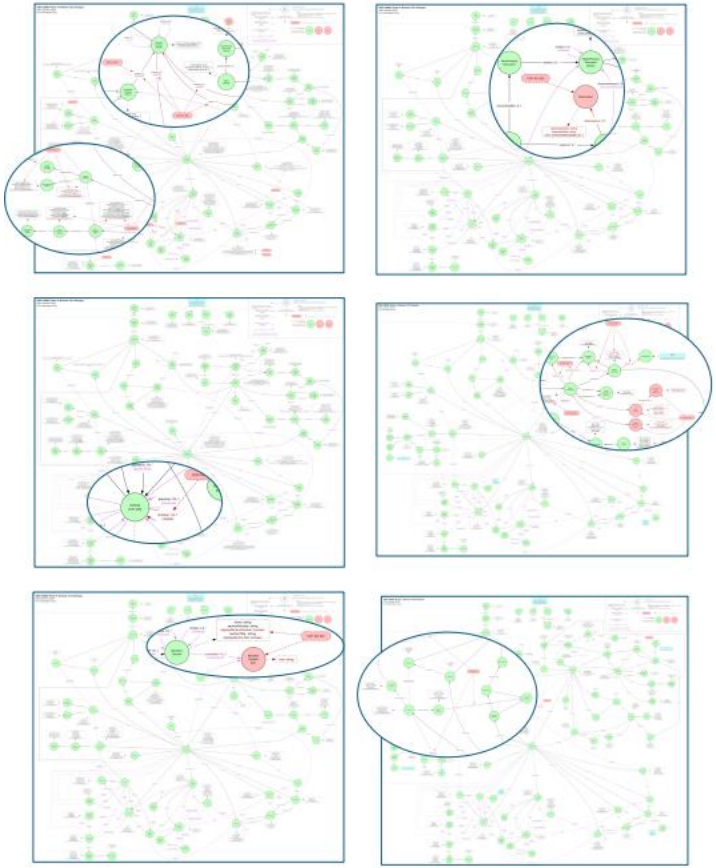
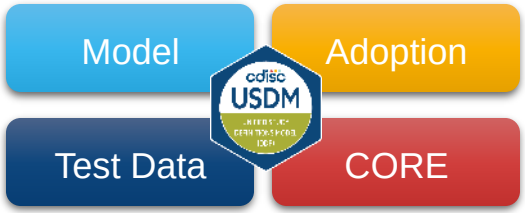
CDISC USDM: Phase Four

- 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**



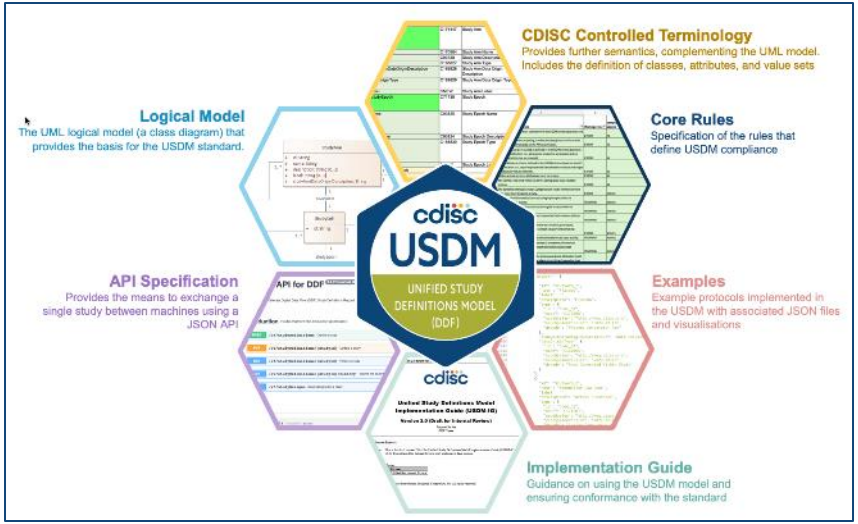
Phase 4 Overview

- 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

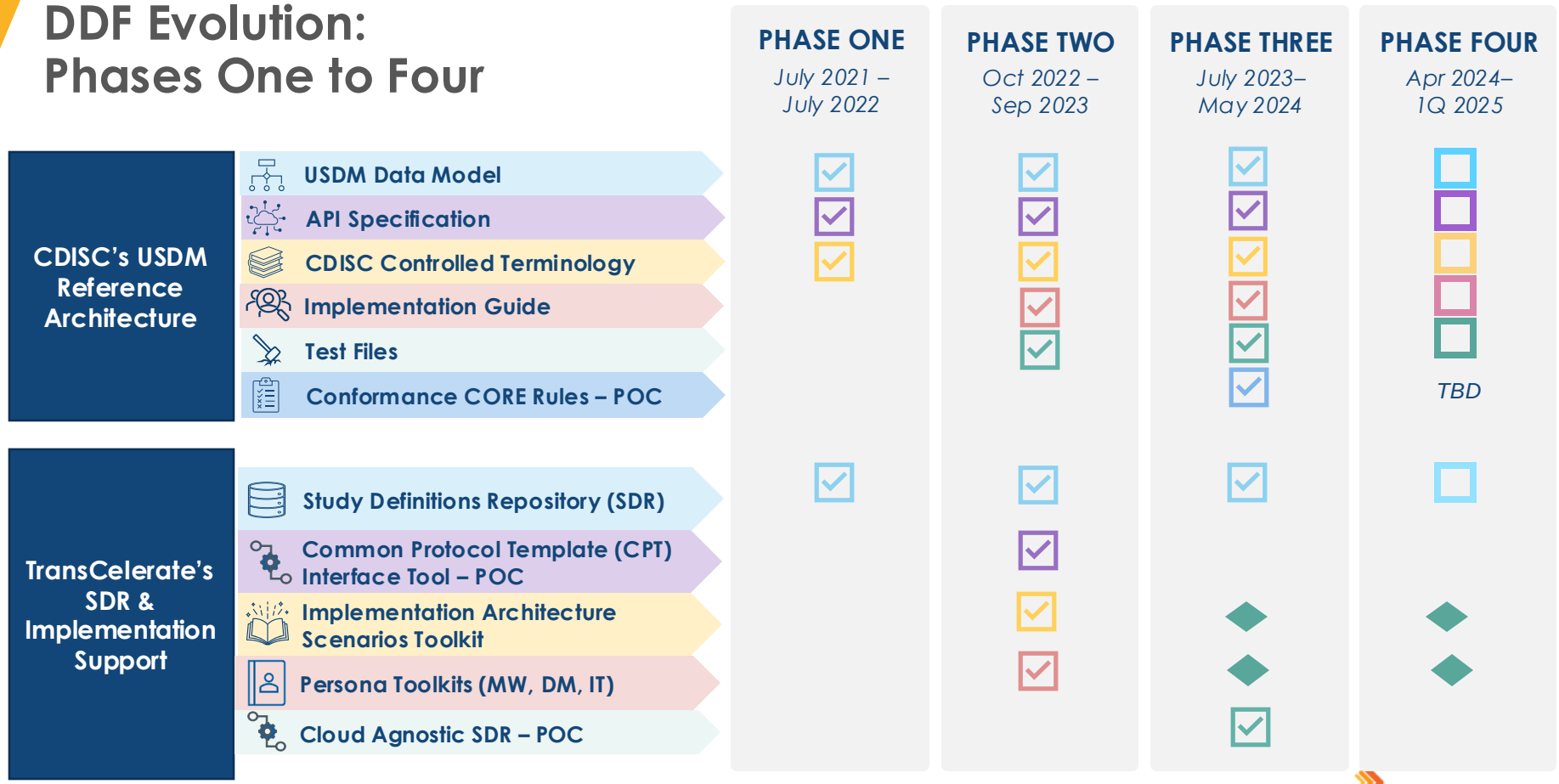


Phase Four Focus

1. USDM Enhancements Further IDMP Alignment, M11 amendments and versions, complex studies designs such as multiphase seamless designs, additional trial registration mappings, and statistical / estimands enhancements
2. Continued alignment of USDM with ICH M11
3. Participation in the Utilizing the Digital Protocol (UDP) project with TransCelerate, ICH and HL7 Vulcan
4. Continue development of USDM Conformance Rules to support USDM v3.0 and v4.0
5. Continue support and development of test data and test tools
6. Development of training and, education materials in conjunction with TransCelerate's Change and Engagement team to foster adoption of DDF



DDF Evolution: Phases One to Four

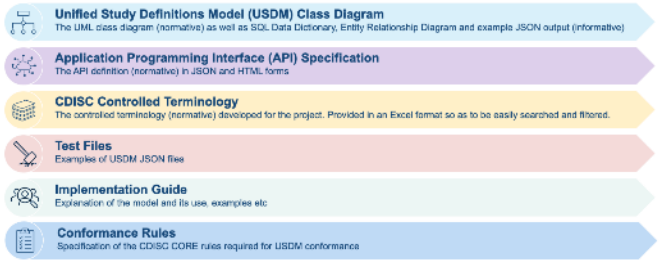


Legend: Still Applicable

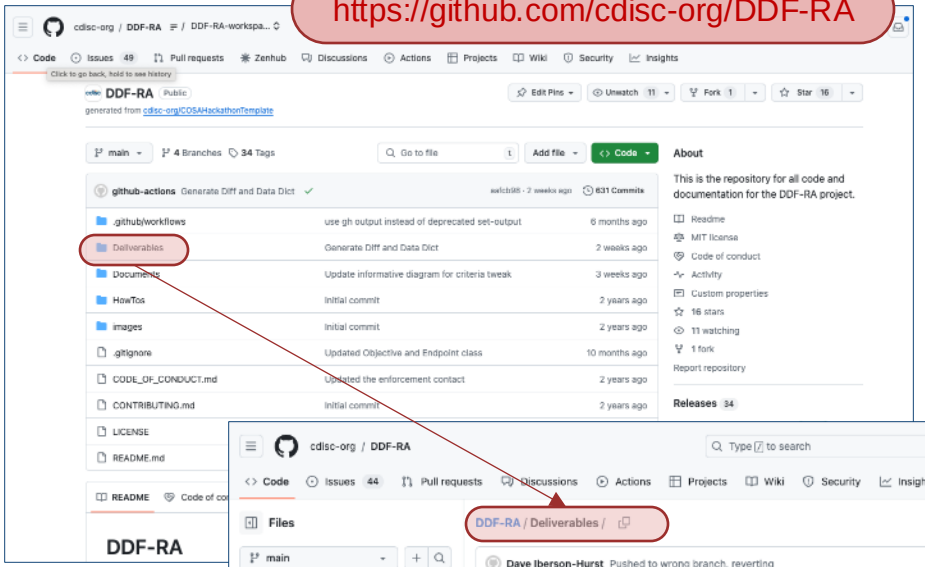
TransCelerate BIOPHARMA INC.

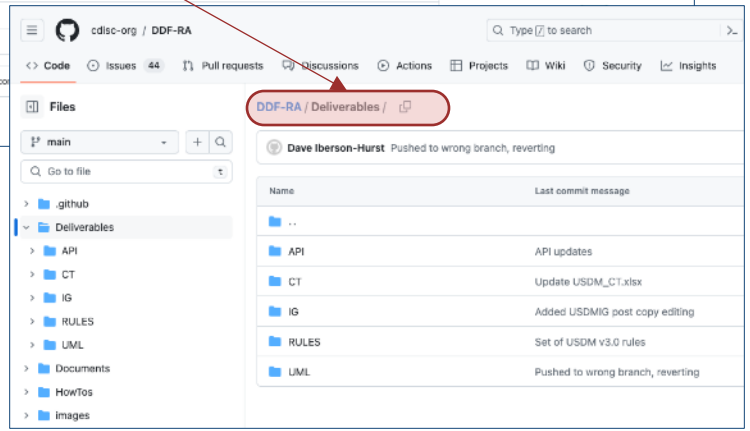
DDF Reference Architecture & Github

- The source of DDF Reference Architecture deliverables

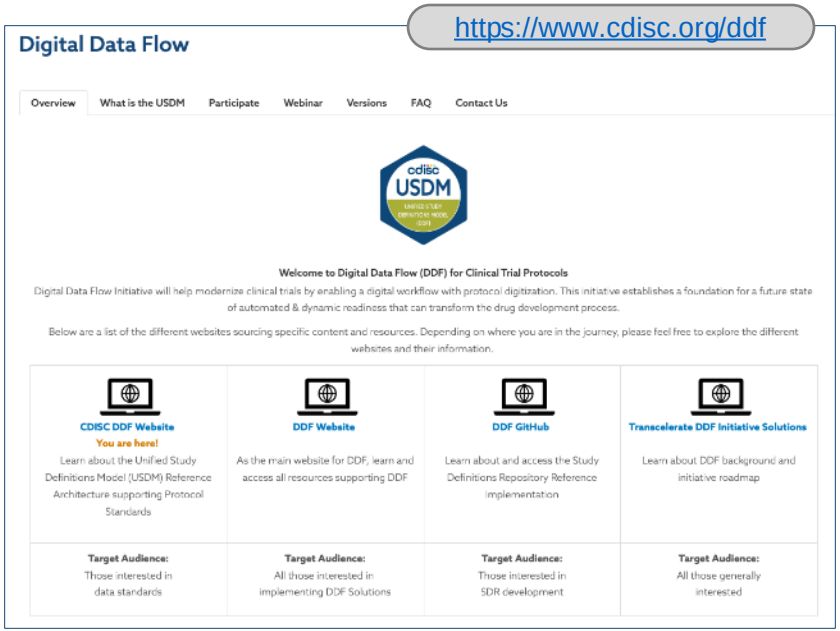


https://github.com/cdisc-org/DDF-RA





Example Resources – CDISC



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

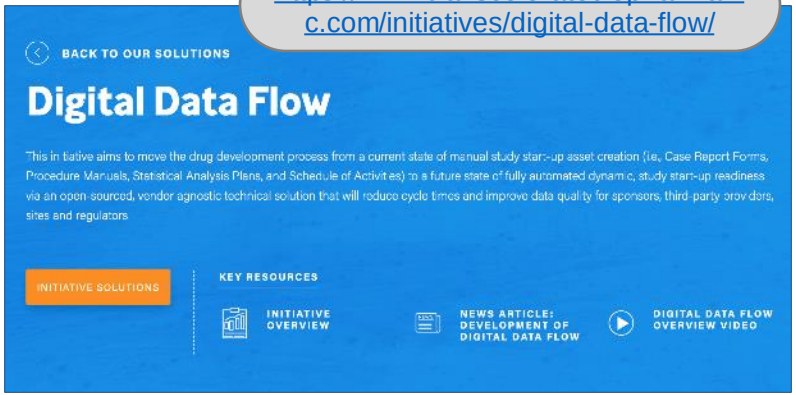
https://pypi.org/project/usdm/

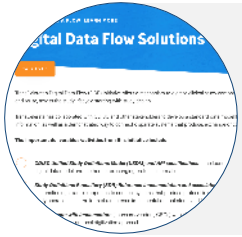
Web-based version of the USDM test tooling.

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

Example Resources – TransCelerate

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



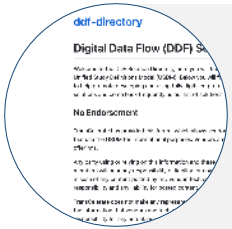


TransCelerate web page holding.a significant number of DDF and USDM resources including the persona guides

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



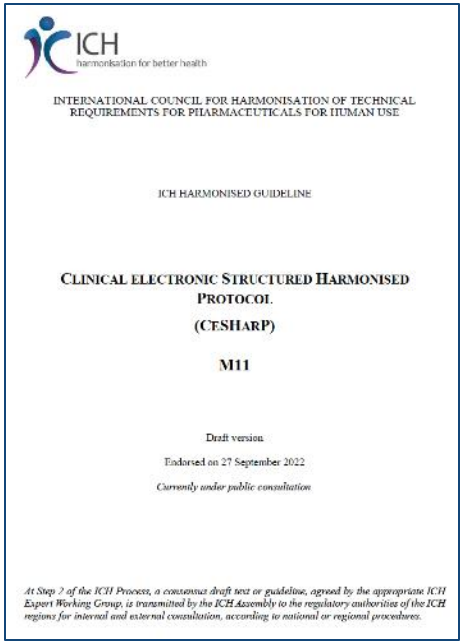
DDF solutions directory. A growing list of self-reported solutions which utilize and follow the DDF Unified Study Definitions Model (USDM)
https://transcelerate.github.io/ddf-directory/directory/directory.html

Overview of M11 and the ICH/CDISC Partnership

M11 Is …

ICH CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL (CeSHarP)

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



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

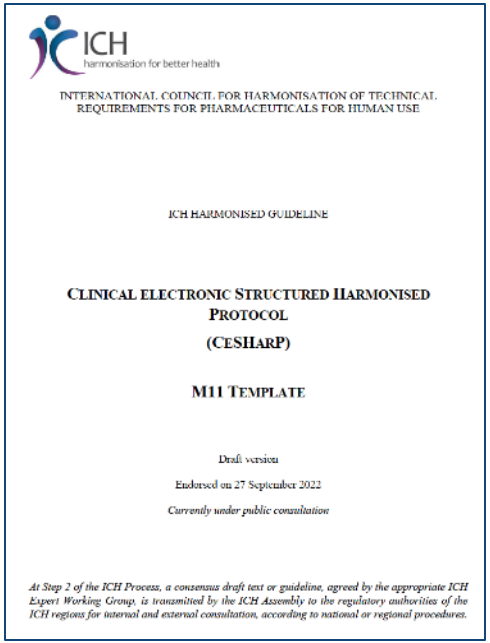
Draft version

Endorsed on 27 September 2022

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

Provides background, purpose, and scope as a guideline



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

Draft version

Endorsed on 27 September 2022

Currently under public consultation

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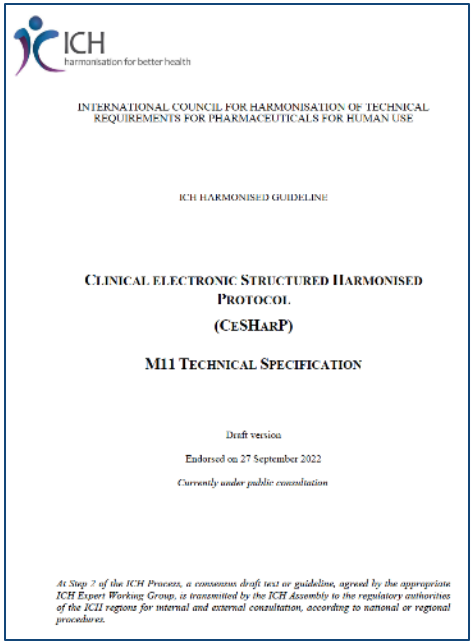
Provides the written format for the Interventional Clinical Trial Protocol Template



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

Draft version

Endorsed on 27 September 2022

Currently under public consultation

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Provides the technical representation aligned with the guideline and protocol template

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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
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",

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

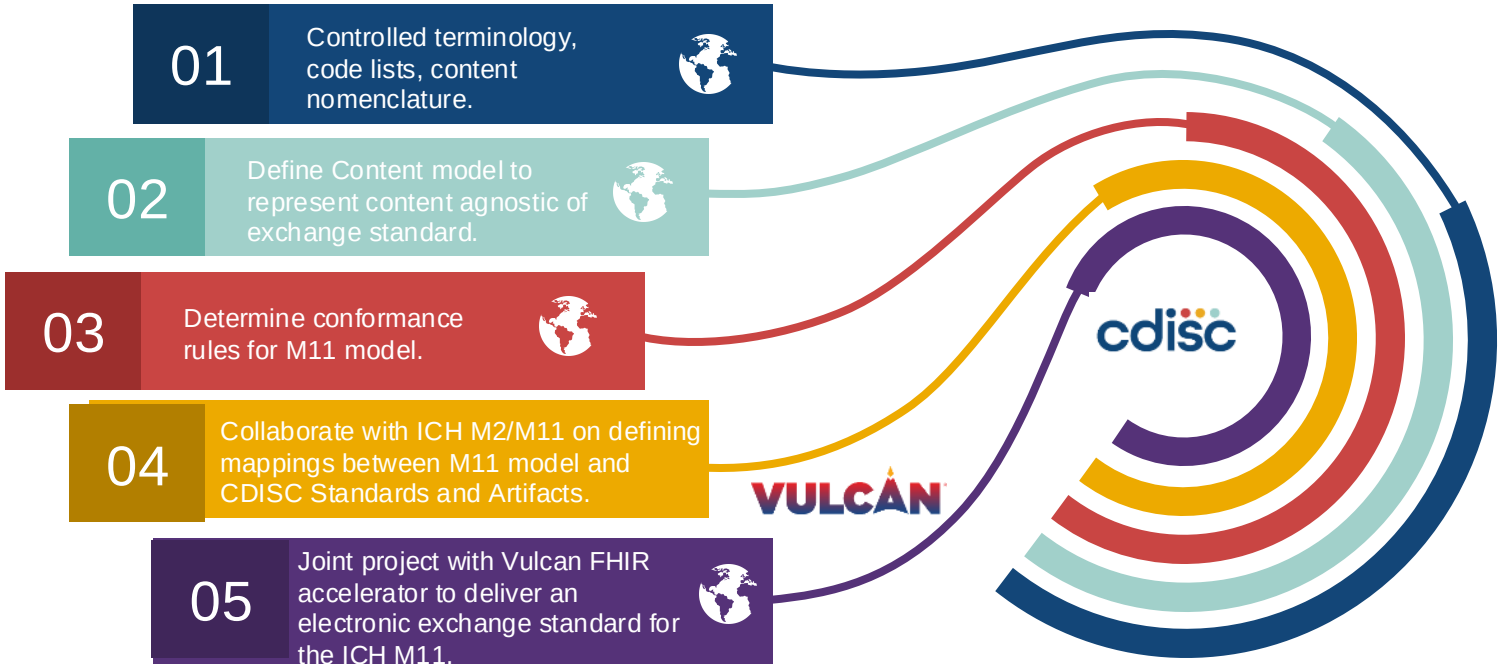
Term (Variable)	Trial Phase
Data Type	Pick list
Topic, Value or Header	D
Definition	
User Guidance	For trials combining investigational drugs or vaccines with devices, classify according to the phase of drug development.
Conformance	Required
Cardinality	
Relationship content from ToC representing the 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.

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ICH harmonisation for better health

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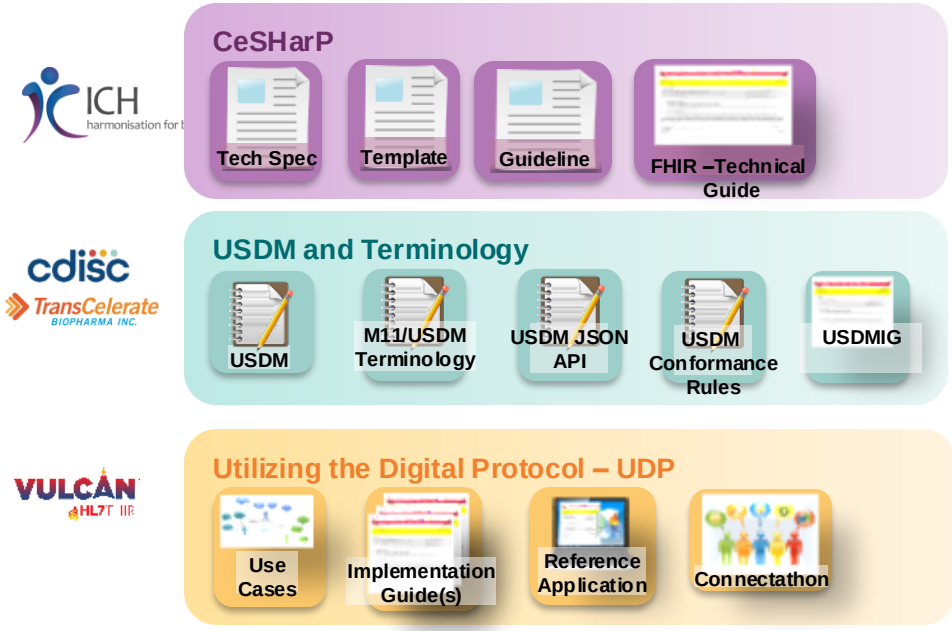
USDM, M11, and the HL7 UDP – how do they come together?

ICH M11 and Vulcan Utilizing Digital Protocol (UDP)



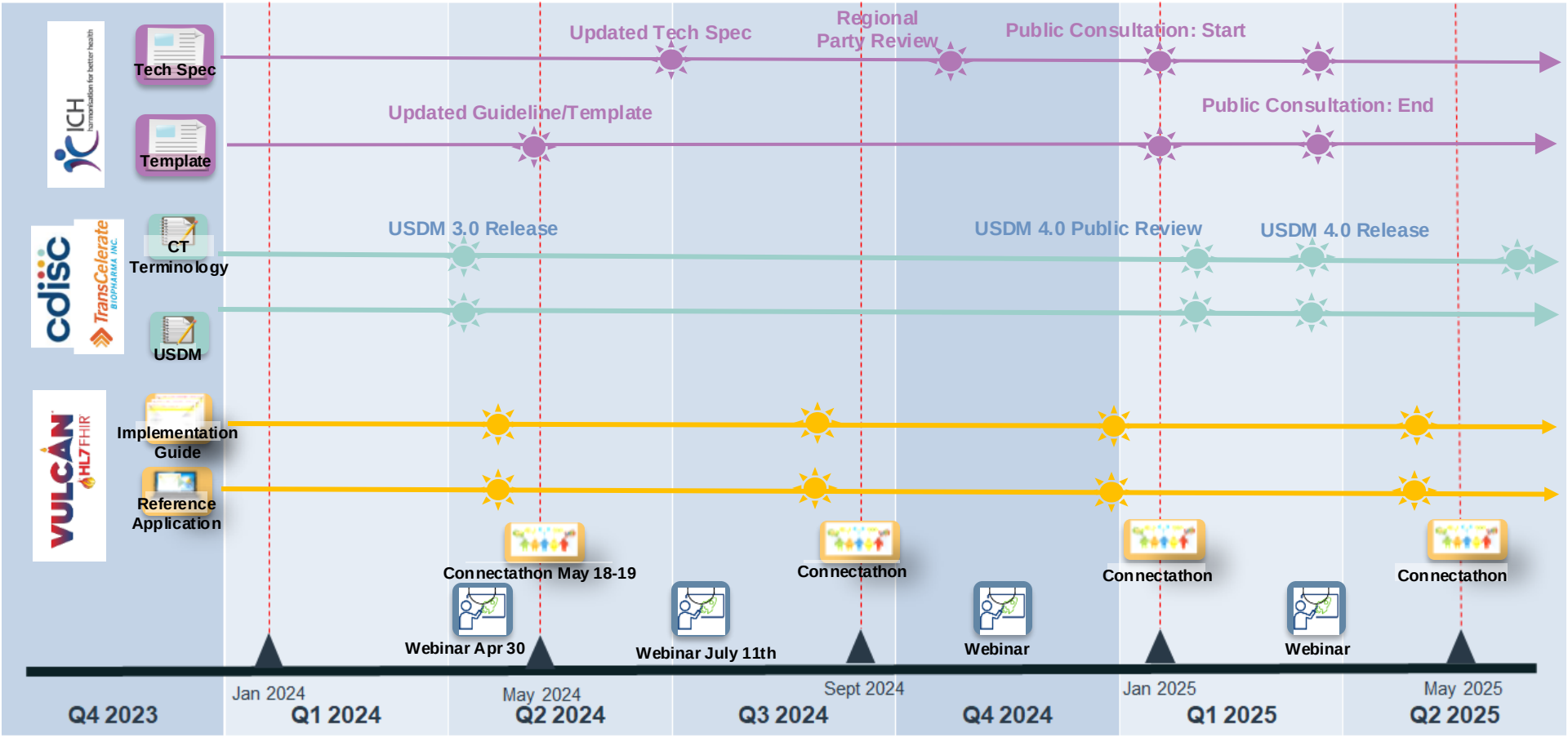
Inputs:

- 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


Tech Spec
Template
CT Terminology
USDM
Implementation Guide
Reference Application
Updated Tech Spec
Regional Party Review
Public Consultation: Start
Updated Guideline/Template
Public Consultation: End
USDM 3.0 Release
USDM 4.0 Public Review
USDM 4.0 Release
Connectathon May 18-19
Connectathon
Connectathon
Connectathon
Webinar Apr 30
Webinar July 11th
Webinar
Webinar
Jan 2024
May 2024
Sept 2024
Jan 2025
May 2025
Q4 2023
Q1 2024
Q2 2024
Q3 2024
Q4 2024
Q1 2025
Q2 2025

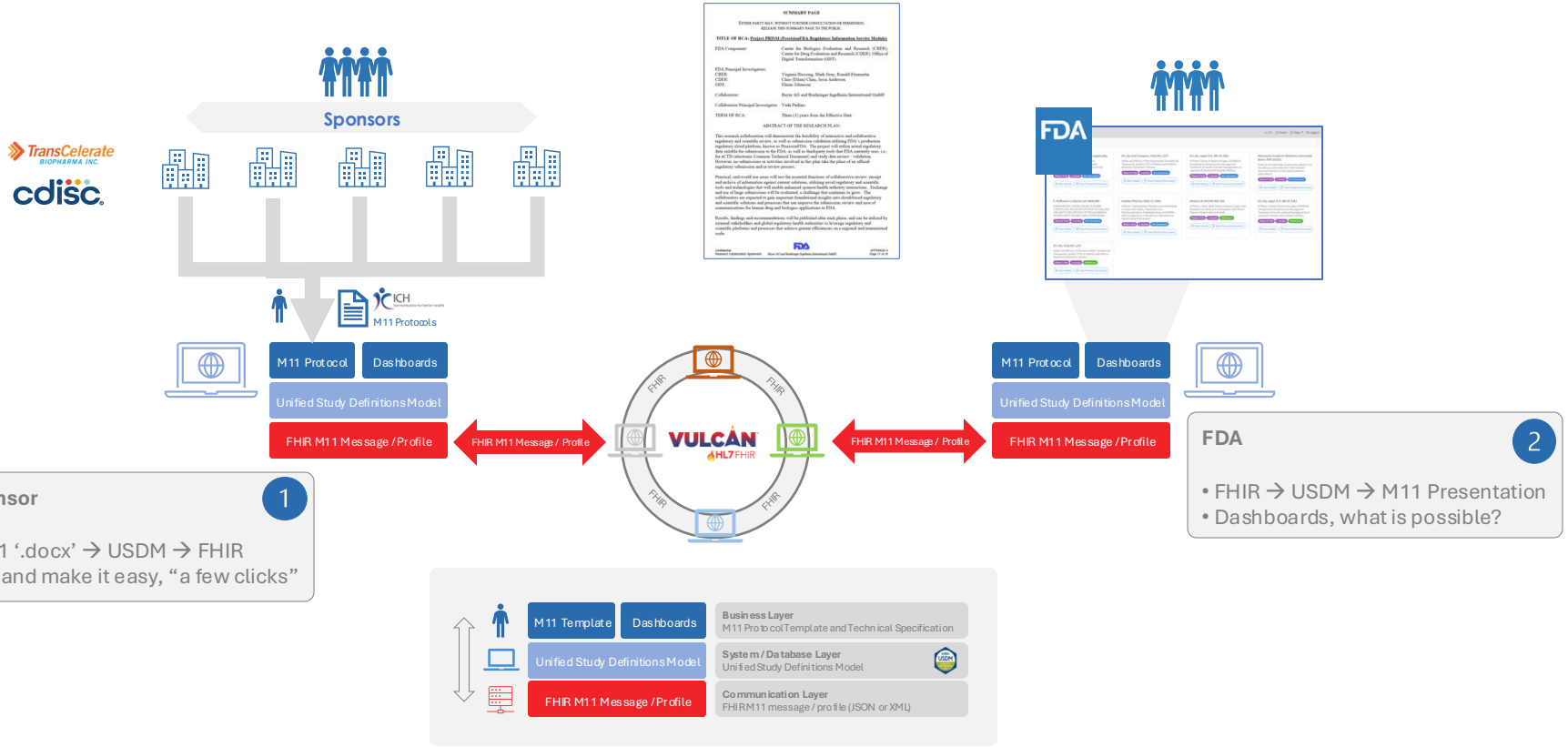
PROJECT PRISM

A Regulatory Cloud Collaborative Initiative

precisionFDA **R**egulatory **I**nformation **S**ervice **M**odule
FDA-Industry Research Collaboration Agreement
(Public-Private Partnership)

U.S. FOOD & DRUG ADMINISTRATION
DNAnexus
Boehringer Ingelheim
BAYER
EMD SERONO
Takeda
Bristol Myers Squibb™

PRISM USE CASE



CDISC 360i

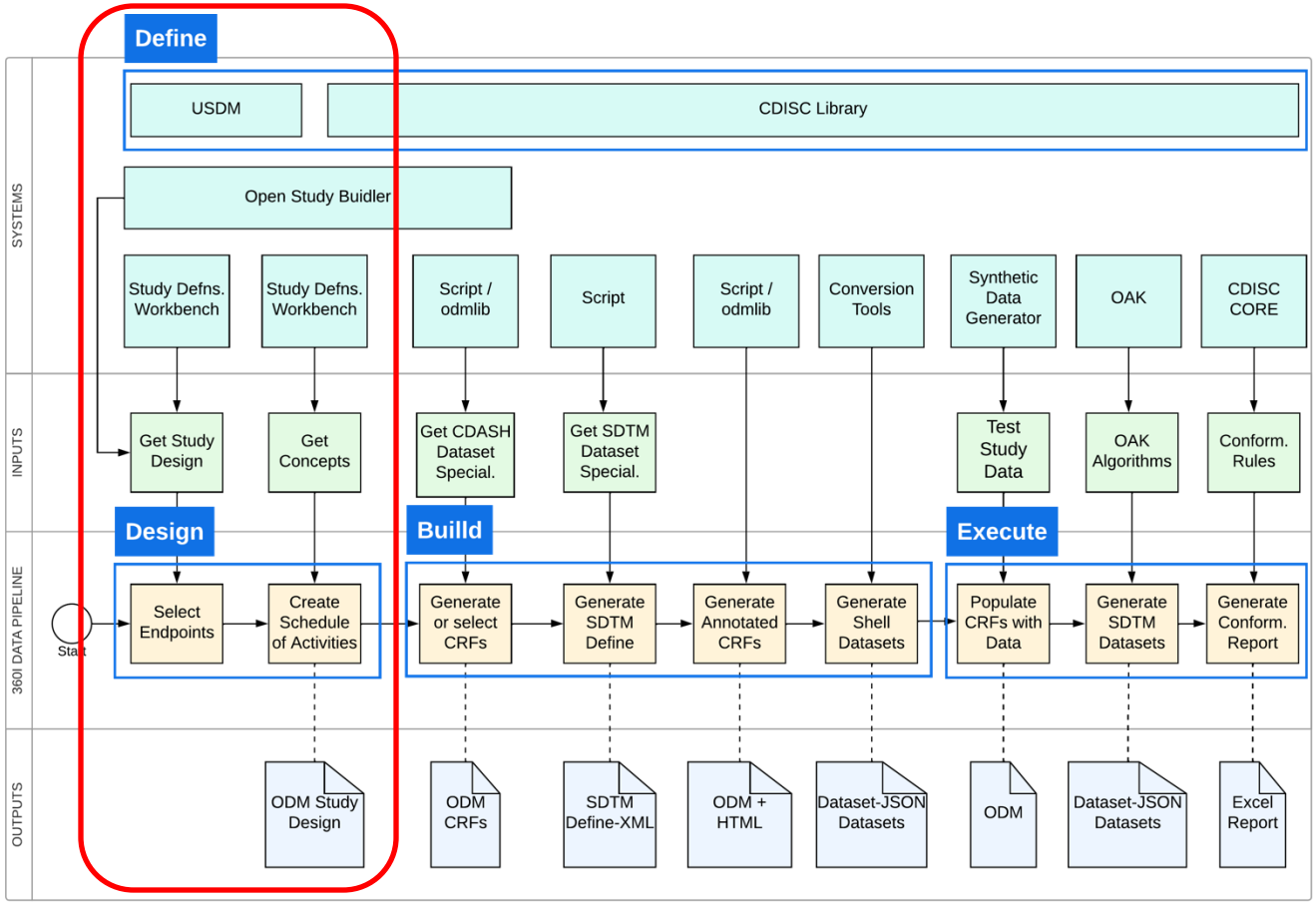
- Define end to end standards
  - Digitalize information from protocol to reporting
  - Link concepts to representation standards
    - Forms definition, eDTs, DHT, SDTM specs, ADaM specs, TFL specs, …
  - Enrich with transformation & derivation logic

- 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

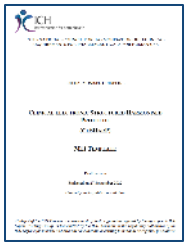
CDISC 360i Phase 1: Generating SDTM

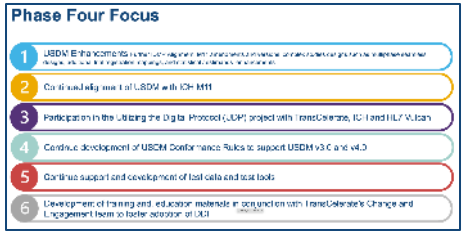
Technical Process



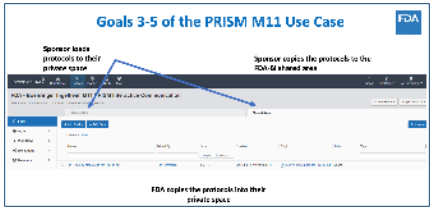
Status

ICH & M11 Specifications
USDM being kept aligned with the ICH M11 work via close communication and development of M11 CT





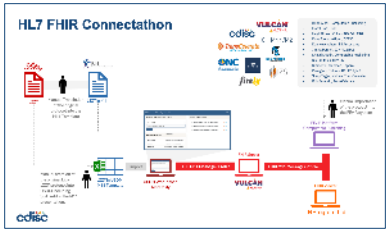
USDM Phase 4
Refine, improve, adopt



FDA & PRISM
Working with FDA to pilot first elecgronic transfer of an M11 protocol as well as tooling to support

cdisc USDM
UNIFIED STUDY DEFINITIONS MODEL (DDF)

HL7 Vulcan & UDP
Working with HL7 Vulcan to build FHIR message to support exchange of USDM / M11 content. Next connectathon is Atlanta, Sept 2024



EMA & CTIS
Working with EMA to align USDM with CTIS to faciliate work such as dashboards

TransCelerate & Adoption
Several sponsors and vendors working with USDM. Latest adoption will be visible at the TransCelerate 'DDF in Action' day

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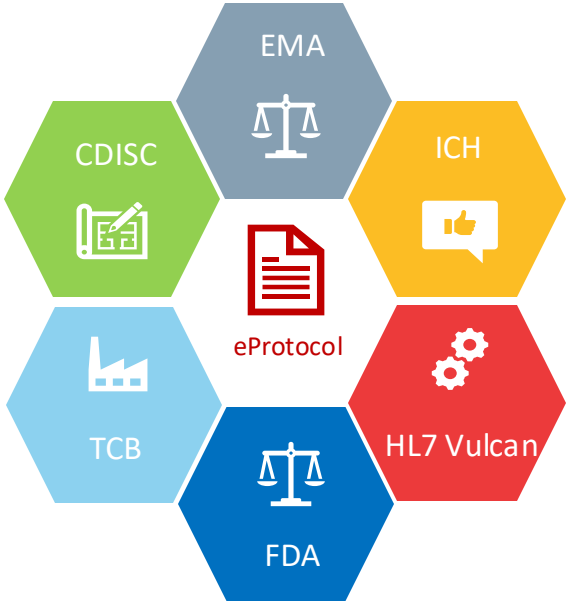
Summary

- 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!