ICH M11 Clinical electronic Structure Harmonized Protocol (CeSHarP) and CDISC: Making the Electronic Protocol a reality

Presented by Peter Van Reusel, Chief Standards Officer, CDISC

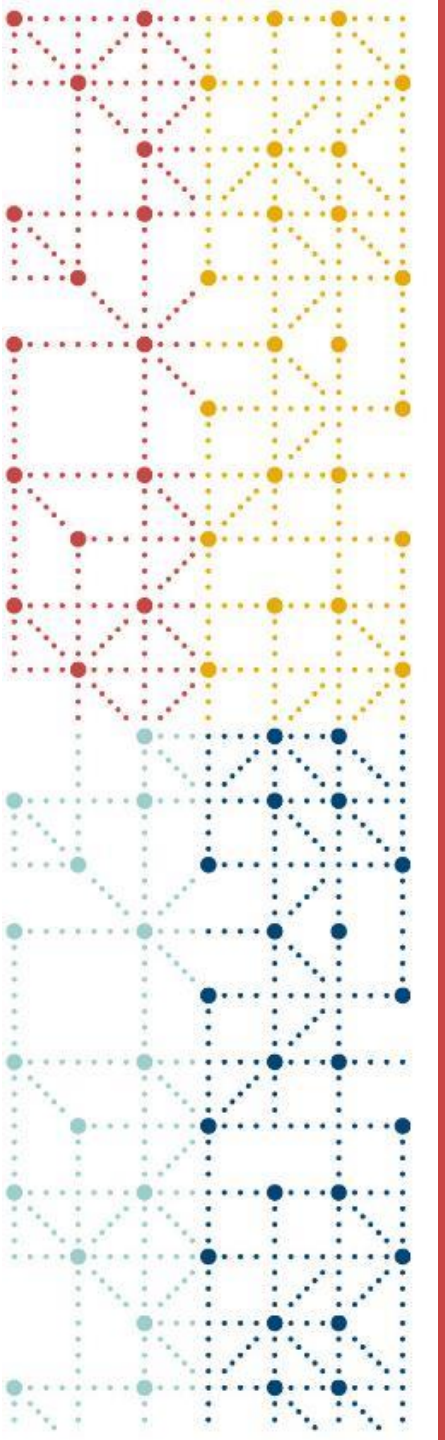
Meet the Speaker

Peter Van Reusel

Title: Chief Standards Officer
Organization: CDISC

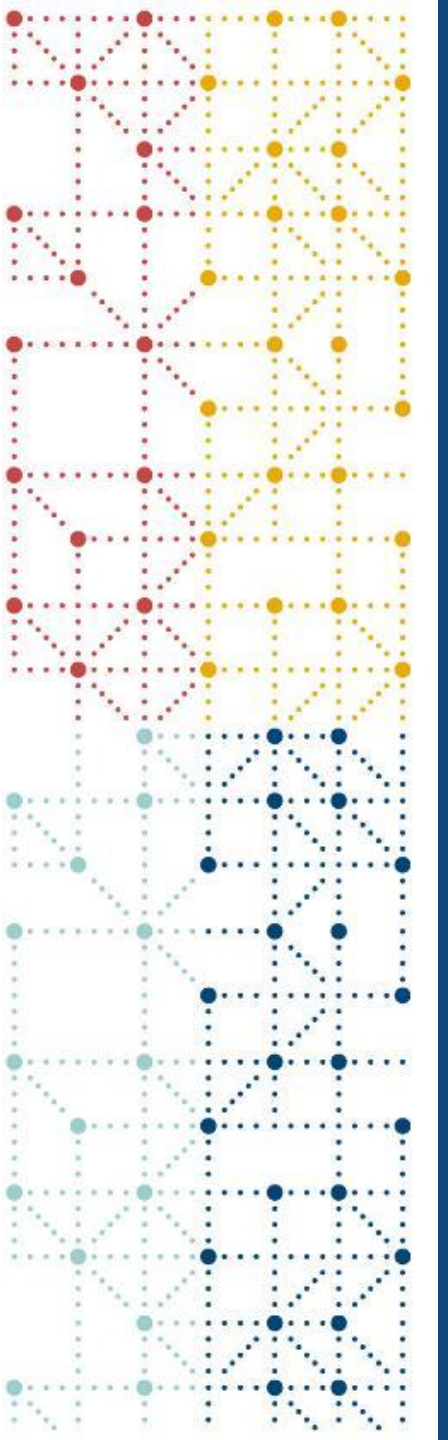
Peter Van Reusel provides executive leadership to the development and implementation of clinical standards in line with CDISC's strategy and operational plans, working closely with the President and CEO, as well as CDISC staff and stakeholders. He has over 20 years' experience in senior roles in pharma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



Agenda

- What is ICH M11
- USDM meets M11
- Collaborations and driving adoption
- Next steps



What is ICH M11?

Clinical Electronic Structured Harmonized Protocol

ICH M11 Expert Working Group

- **Regulatory Members**
  - ANVISA, Brazil
  - CDSCO, India
  - EC, Europe
  - FDA, United States
  - Health Canada, Canada
  - HSA, Singapore
  - MHLW / PMDA, Japan
  - National Center, Kazakhstan
  - NMPA, China
  - SFDA, Saudi Arabia
  - TFDA, Chinese Taipei

- **Industry Members**
  - BIO
  - EFPIA
  - IFPMA
  - IGBA
  - JPMA
  - PhRMA

ICH
harmonisation for better health

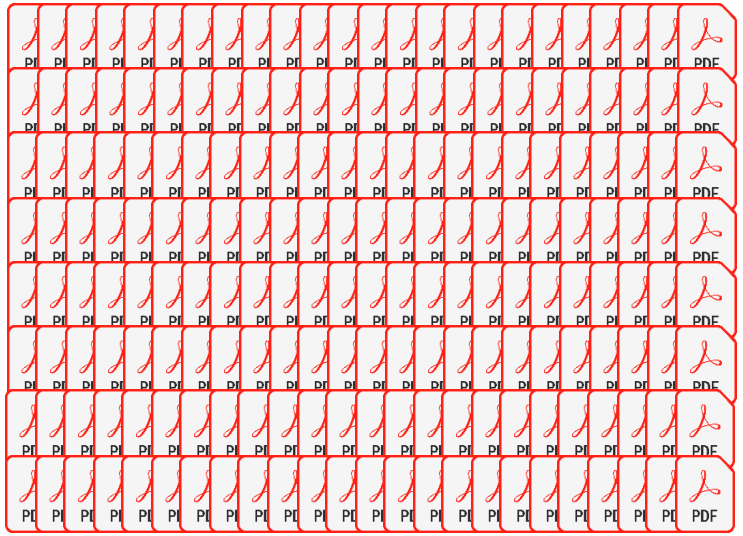
cdisc

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

Why Clinical electronic Structured Harmonized Protocol (CeSHarP)?

- Paper Submissions…
  Not like this anymore…

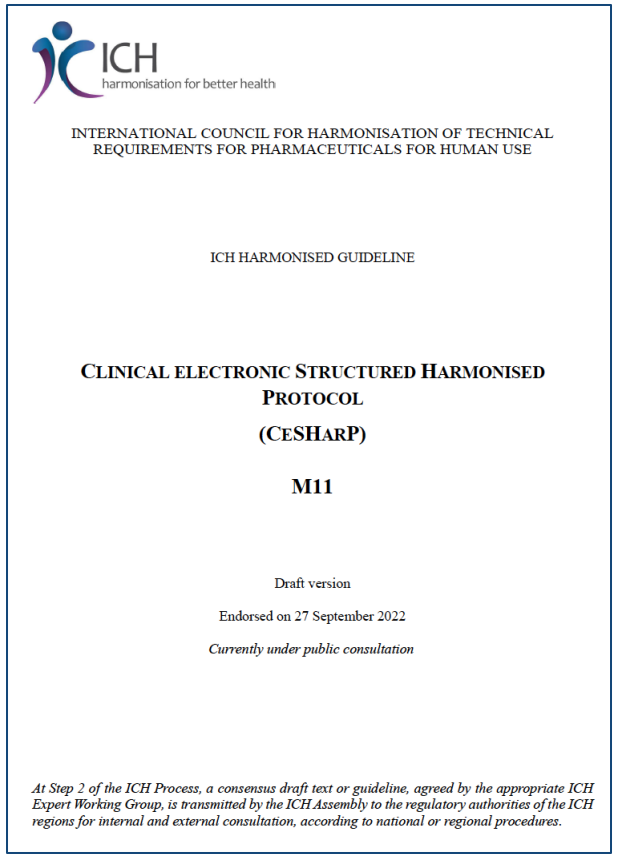
- …but this isn't much better!



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

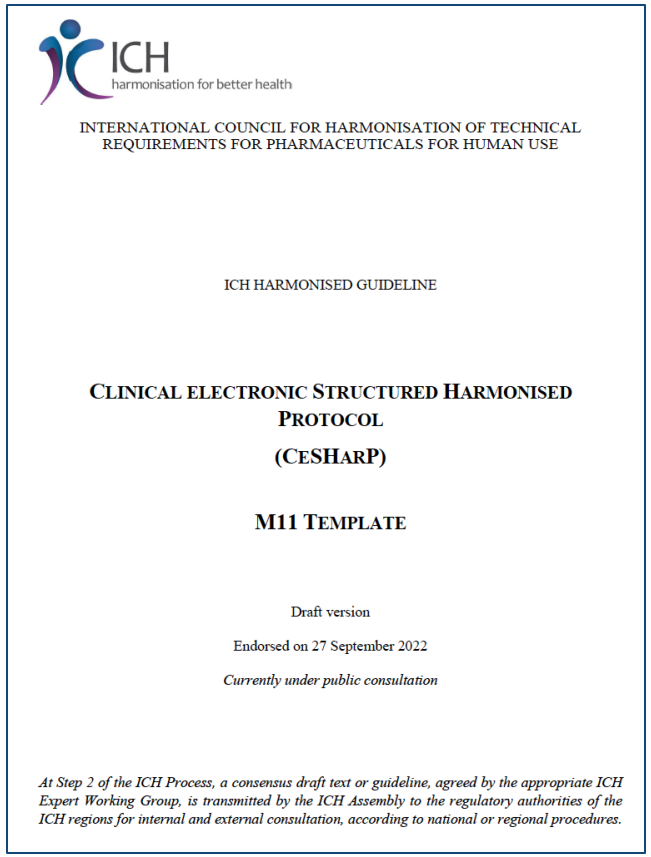
Draft version

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



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ICH HARMONISED GUIDELINE

CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

(CESHARP)

M11 TEMPLATE

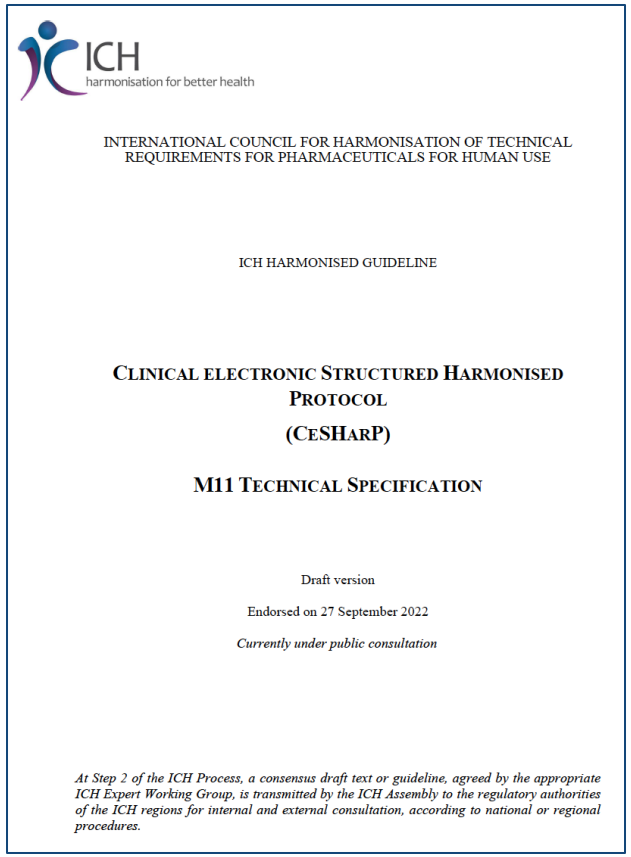
Draft version

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 the written format for the Interventional Clinical Trial Protocol Template



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ICH HARMONISED GUIDELINE

CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

(CESHARP)

M11 TECHNICAL SPECIFICATION

Draft version

Endorsed on 27 September 2022

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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 the technical representation aligned with the guideline and protocol template

cdisc

M11 Simple Example

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	

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.
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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.
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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

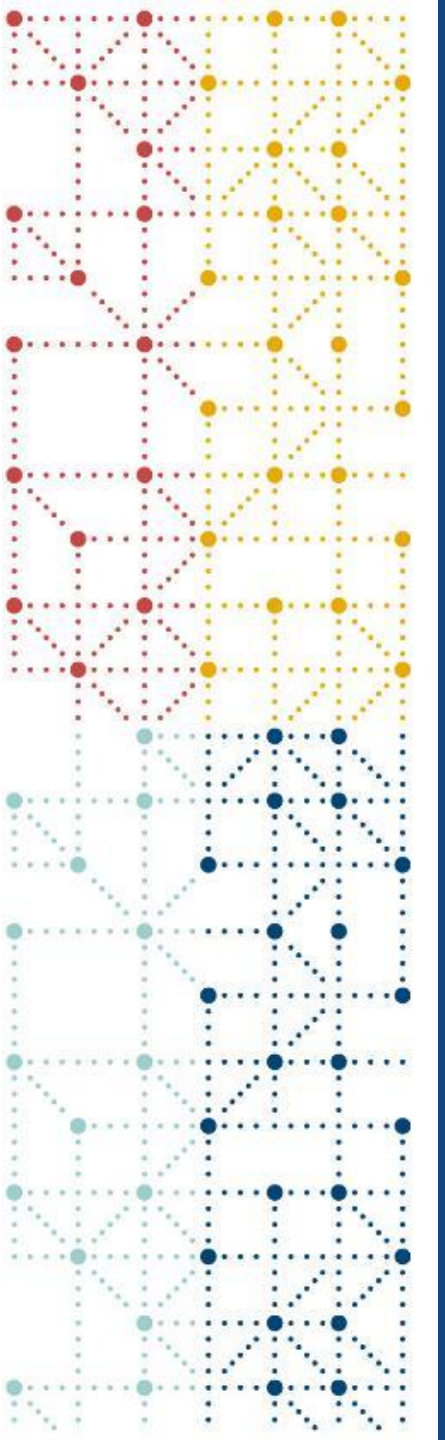
01 Controlled terminology, code lists, content nomenclature.

02 Define Content model to represent content agnostic of exchange standard.

03 Determine conformance rules for M11 model.

04 Collaborate with ICH M2/M11 on defining mappings between M11 model and CDISC Standards and Artifacts.

05 Joint project with Vulcan FHIR accelerator to deliver an electronic exchange standard for the ICH M11.



USDM meets M11

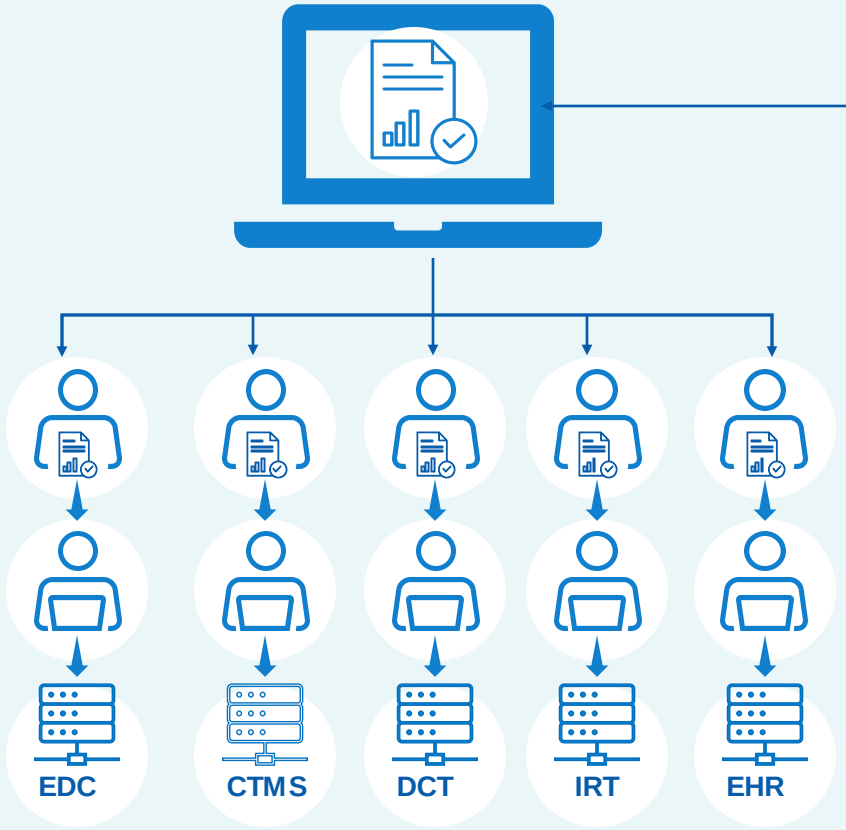
How will USDM help drive the adoption of digital protocols

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

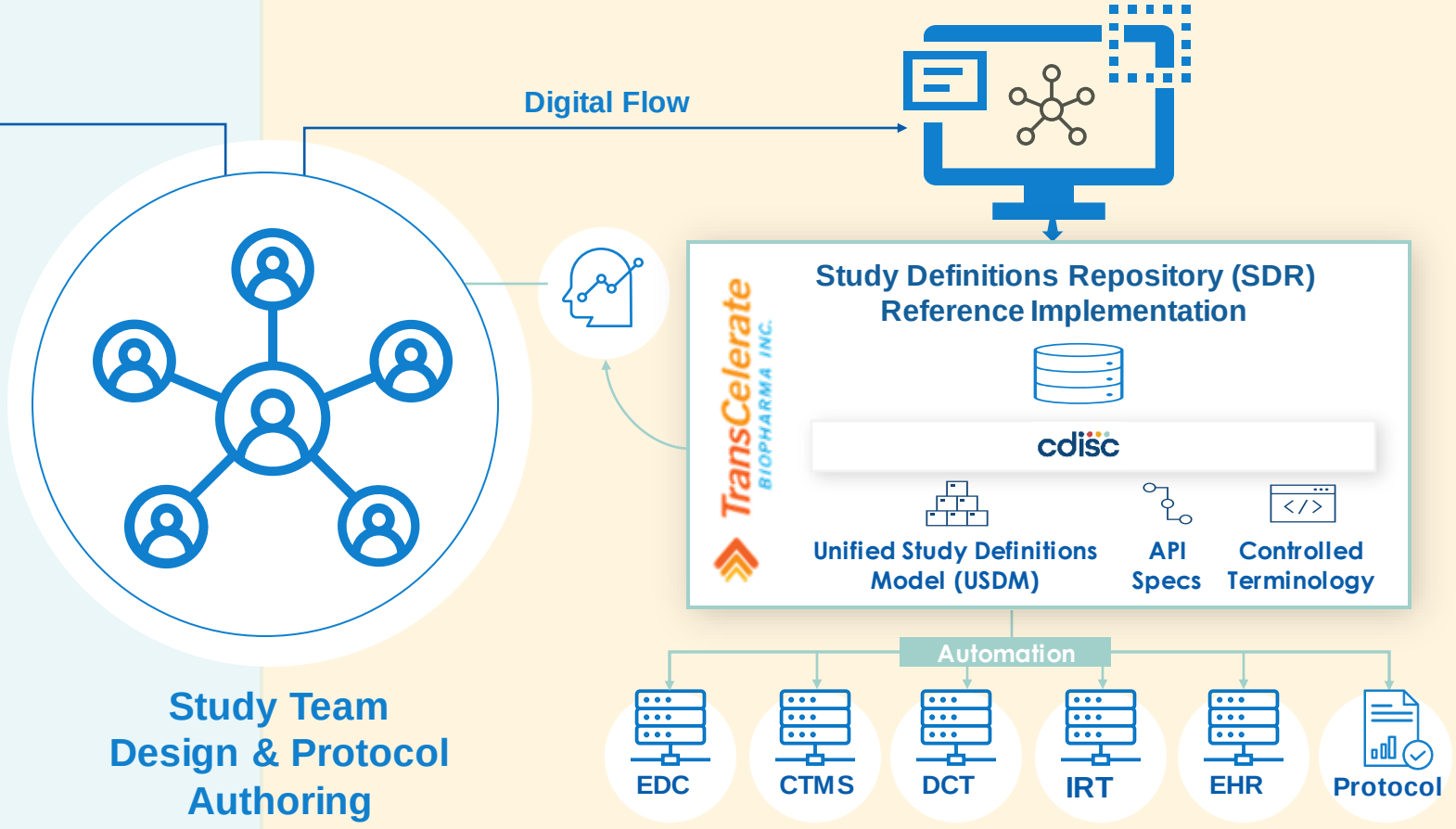
TransCelerate Digital Data Flow (DDF) Ambition

Write Once, Read Many

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



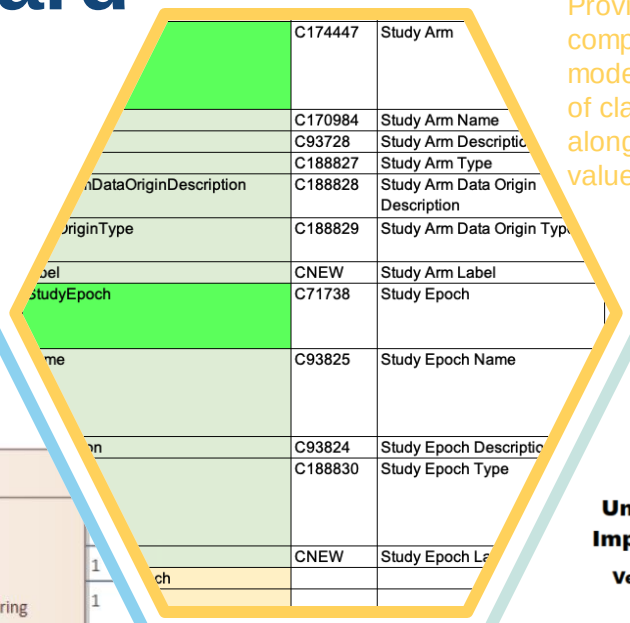
TOMORROW: Digital paradigm for protocol creation, with fully automated data flow and interoperability between systems



The USDM Standard

CDISC Controlled Terminology

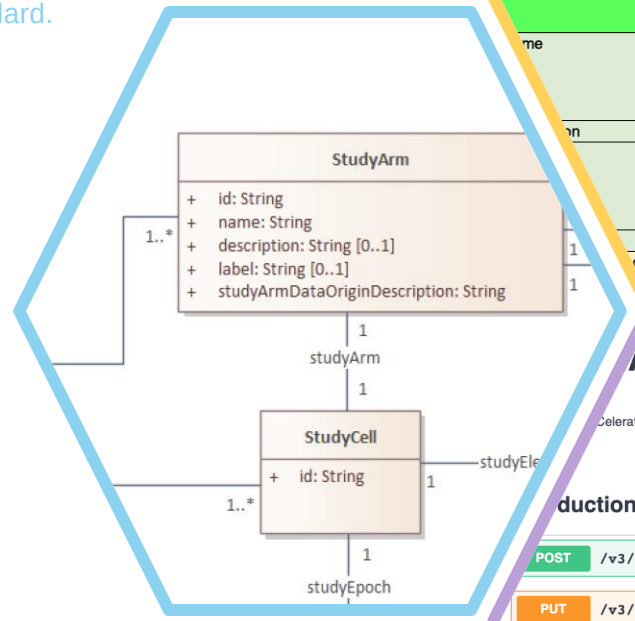
Provides further semantics, complementing the UML model. Includes the definition of classes and attributes along with the definition of value sets



	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
bel	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		

Logical Model

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



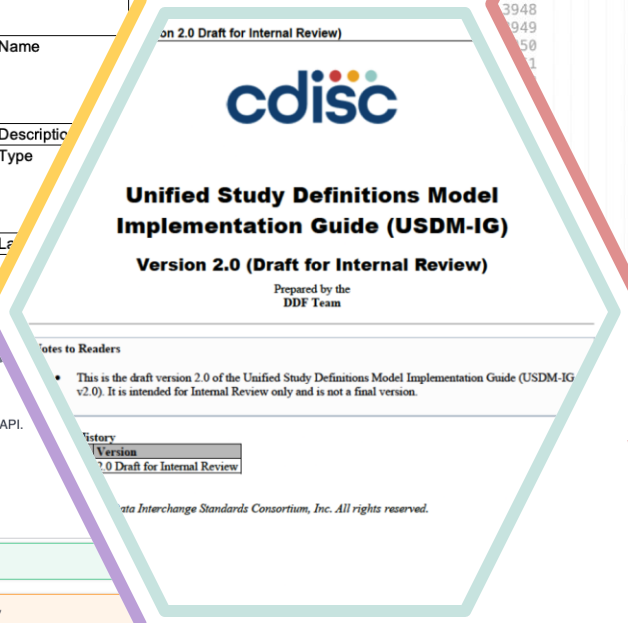
Examples

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

```
tudyArms": [
{
  "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-
```

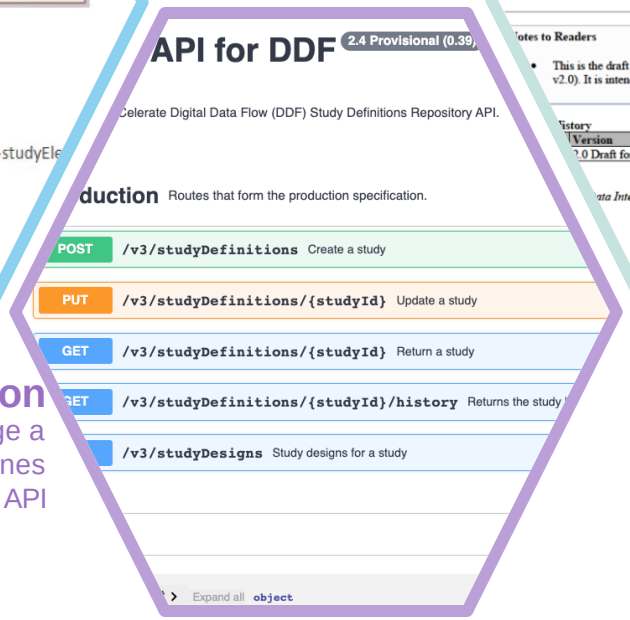
Implementation Guide

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



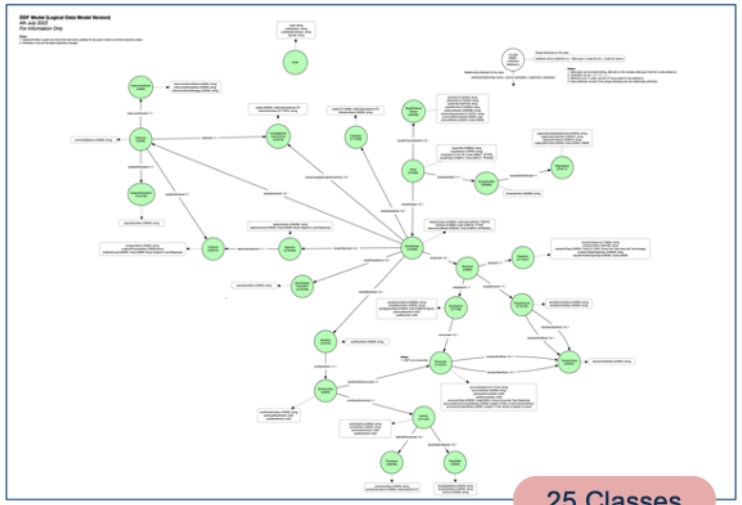
API Specification

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



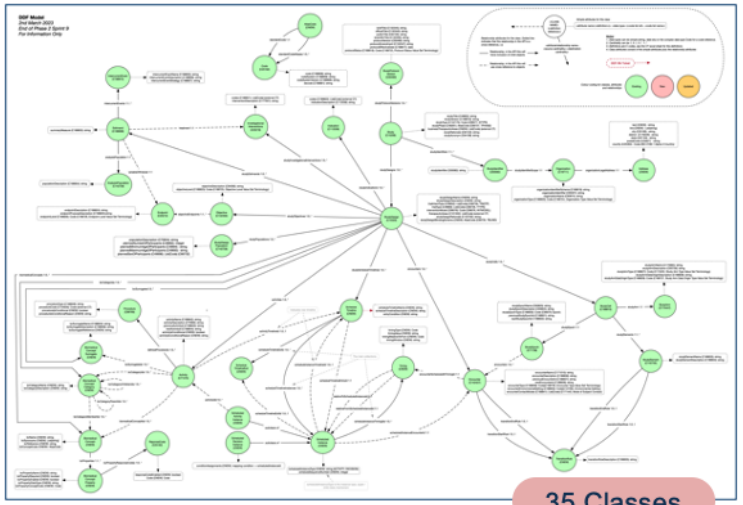
CDISC DDF / USDM: Phases One, Two and Three

Phase One



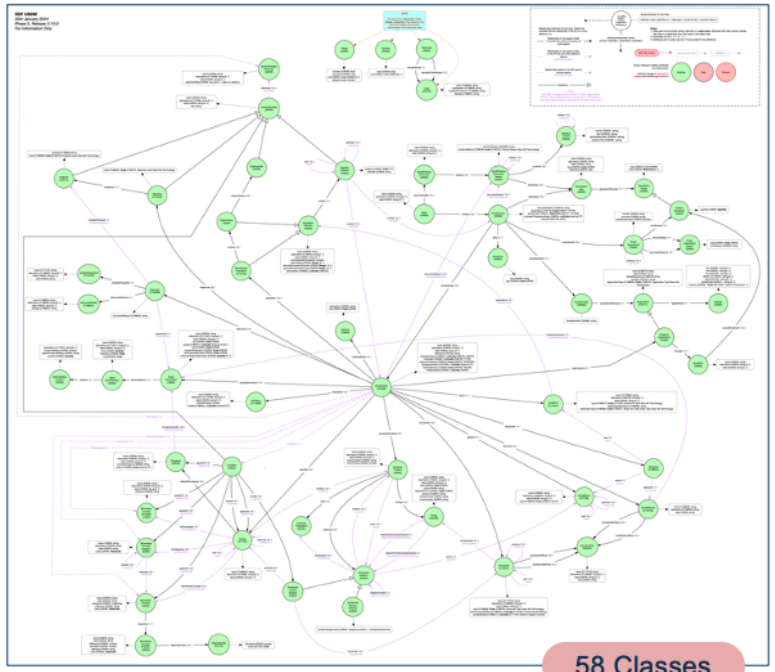
- Solid foundation
- The protocol document was an external entity into which the structured content could be exported

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

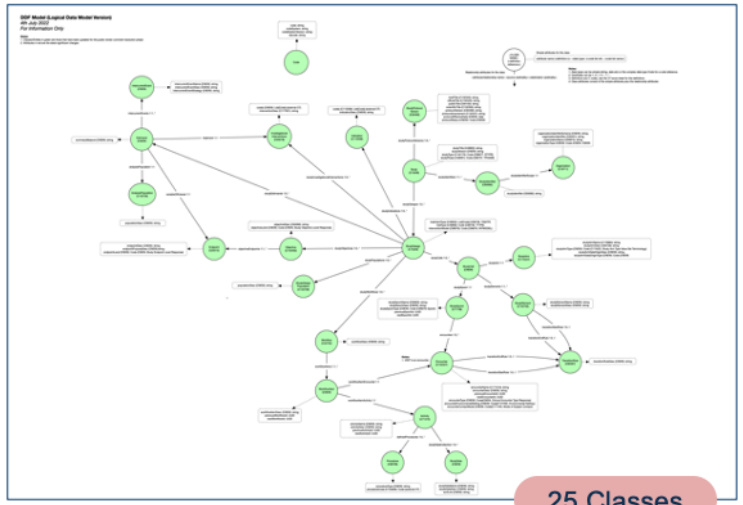
Phase Three



- 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

CDISC DDF / USDM: Phases One, Two and Three

Phase One



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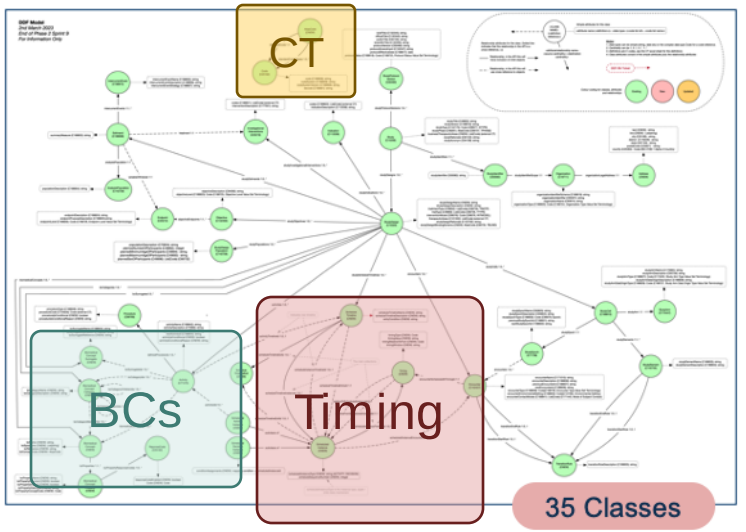
Phase Two



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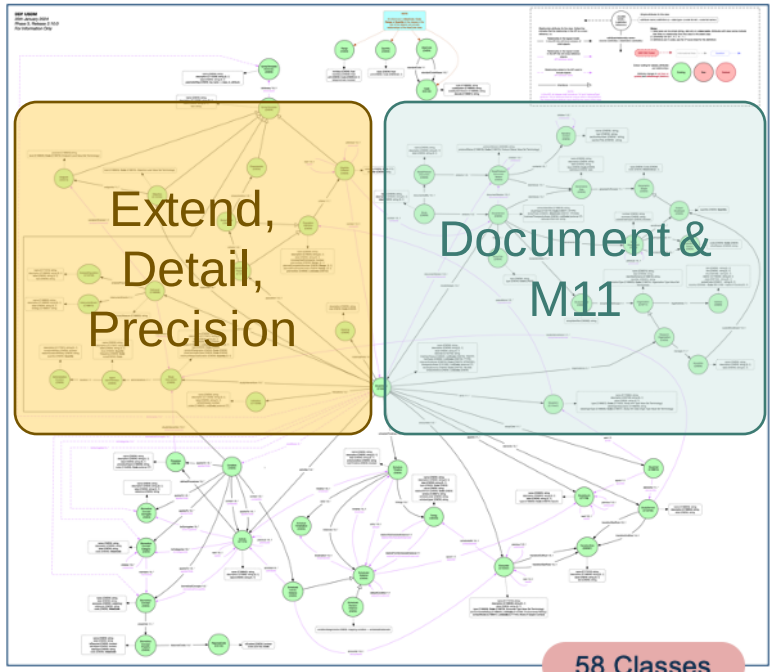

- Now contains structured and unstructured elements
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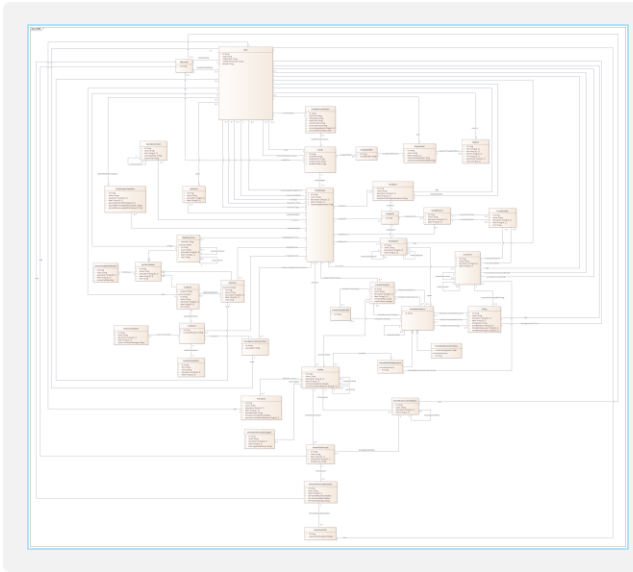
- Allows for the protocol document to be generated from the model

USDM Content



Controlled Terms

Study, Identifiers, Amendments

Estimands

Populations

Inclusion & Exclusion

Interventions & Indications

Objectives & Endpoints

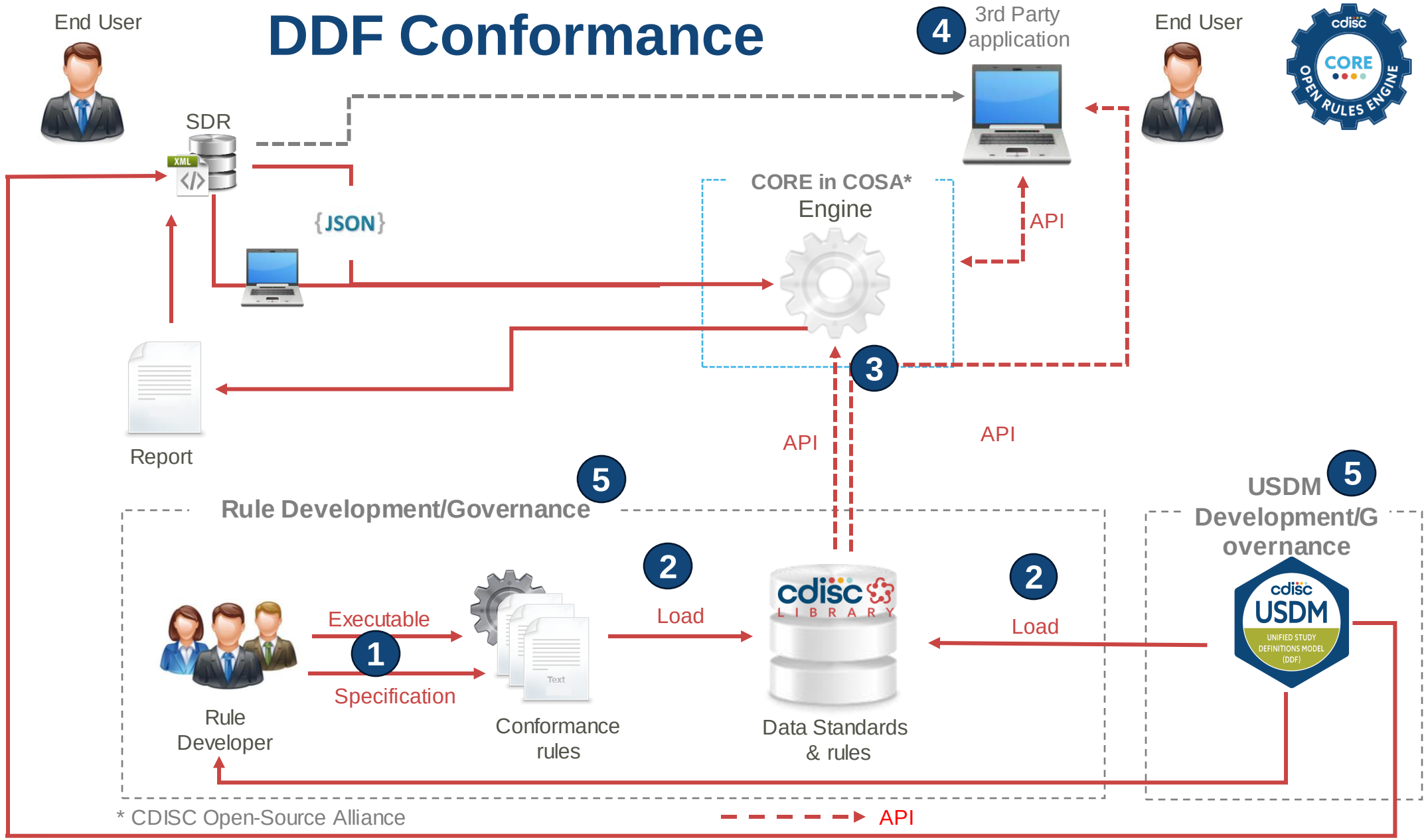
Unstructured Content

Study Designs, Arms, Epochs

Detailed Study Logic, Encounters

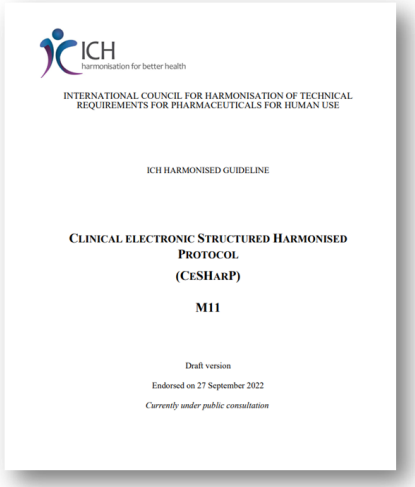
Procedures, Biomedical Concepts

DDF Conformance



USDM generates various formats

Guideline & Template → Tech Spec



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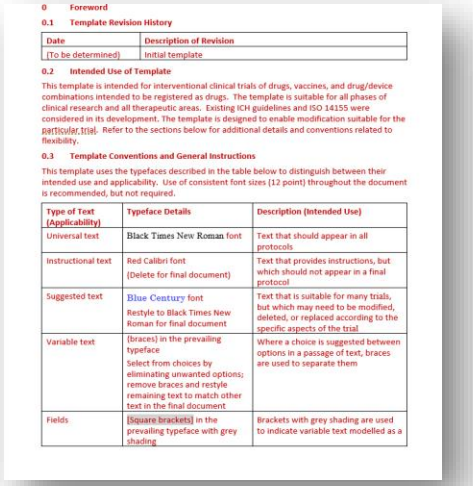


0 Foreword

0.1 Template Revision History

Date	Description of Revision
(To be determined)	Initial template

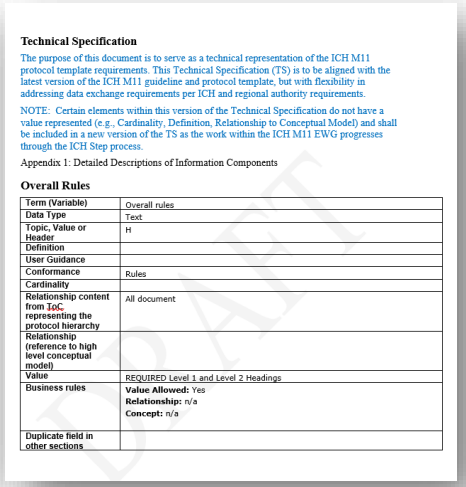
0.2 Intended Use of Template

This template is intended for interventional clinical trials of drugs, vaccines, and drug/device combinations intended to be registered as drugs. The template is suitable for all phases of clinical research and all therapeutic areas. Existing ICH guidelines and ISO 14155 were considered in its development. The template is designed to enable modification suitable for the particular trial. Refer to the sections below for additional details and conventions related to flexibility.

0.3 Template Conventions and General Instructions

This template uses the typefaces described in the table below to distinguish between their intended use and applicability. Use of consistent font sizes (12 point) throughout the document is recommended, but not required.

Type of Text (Applicability)	Typeface Details	Description (Intended Use)
Universal text	Black Times New Roman font	Text that should appear in all protocols
Instructional text	Red Calibri font (Delete for final document)	Text that provides instructions, but which should not appear in a final protocol
Suggested text	Blue Century font Restyle to Black Times New Roman for final document	Text that is suitable for many trials, but which may need to be modified, deleted, or replaced according to the specific aspects of the trial
Variable text	(braces) in the prevailing typeface Select from choices by eliminating unwanted options; remove braces and restyle remaining text to match other text in the final document	Where a choice is suggested between options in a passage of text, braces are used to separate them
Fields	[square brackets] in the prevailing typeface with grey shading	Brackets with grey shading are used to indicate variable text modelled as a



Technical Specification

The purpose of this document is to serve as a technical representation of the ICH M11 protocol template requirements. This Technical Specification (TS) is to be aligned with the latest version of the ICH M11 guideline and protocol template, but with flexibility in addressing data exchange requirements per ICH and regional authority requirements.

NOTE: Certain elements within this version of the Technical Specification do not have a value represented (e.g., Cardinality, Definition, Relationship to Conceptual Model) and shall be included in a new version of the TS as the work within the ICH M11 EWG progresses through the ICH Step process.

Appendix 1: Detailed Descriptions of Information Components

Overall Rules

Term (Variable)	Overall rules
Data Type	Text
Topic, Value or Header	H
Definition	
User Guidance	
Conformance	Rules
Cardinality	
Relationship content from ToC representing the protocol hierarchy	All document
Relationship (reference to high level conceptual model)	
Value	REQUIRED Level 1 and Level 2 Headings
Business rules	**Value Allowed:** Yes **Relationship:** n/a **Concept:** n/a
Duplicate field in other sections	

Electronic Document

Human Readable Form

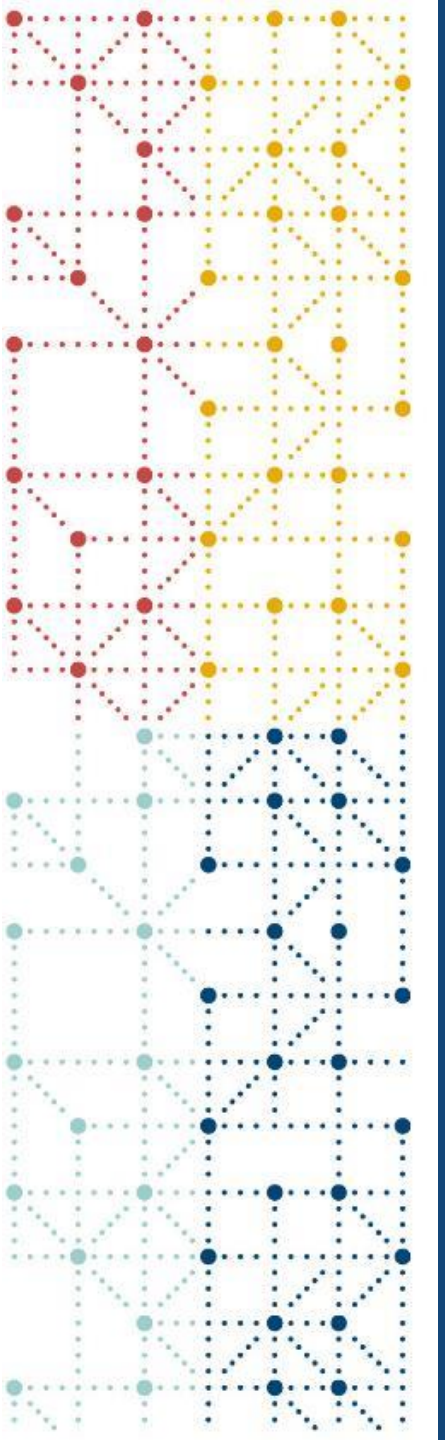
cdisc USDM UNIFIED STUDY DEFINITIONS MODEL (DDF)

Machine-Readable Form

VULCAN HL7 FHIR

cdisc

Standard Message Exchange Formats



HL7 UDP and PRISM

Vulcan UDP collaboration: Utilizing Digital Protocol

CeSHarP

- Tech Spec
- Template
- Guideline
- FHIR –Technical Guide

USDM and Terminology

- USDM
- M11/USDM Terminology
- USDM JSON API
- USDM Conformance Rules
- USDMIG

Utilizing the Digital Protocol – UDP

- Use Cases
- Implementation Guide(s)
- Reference Application
- Connectathon

Shared

Maintenance Plan

Communications Strategy

PROJECT PRISM

A Regulatory Cloud Collaborative Initiative

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

U.S. FOOD & DRUG ADMINISTRATION
DNAnexus
Boehringer Ingelheim
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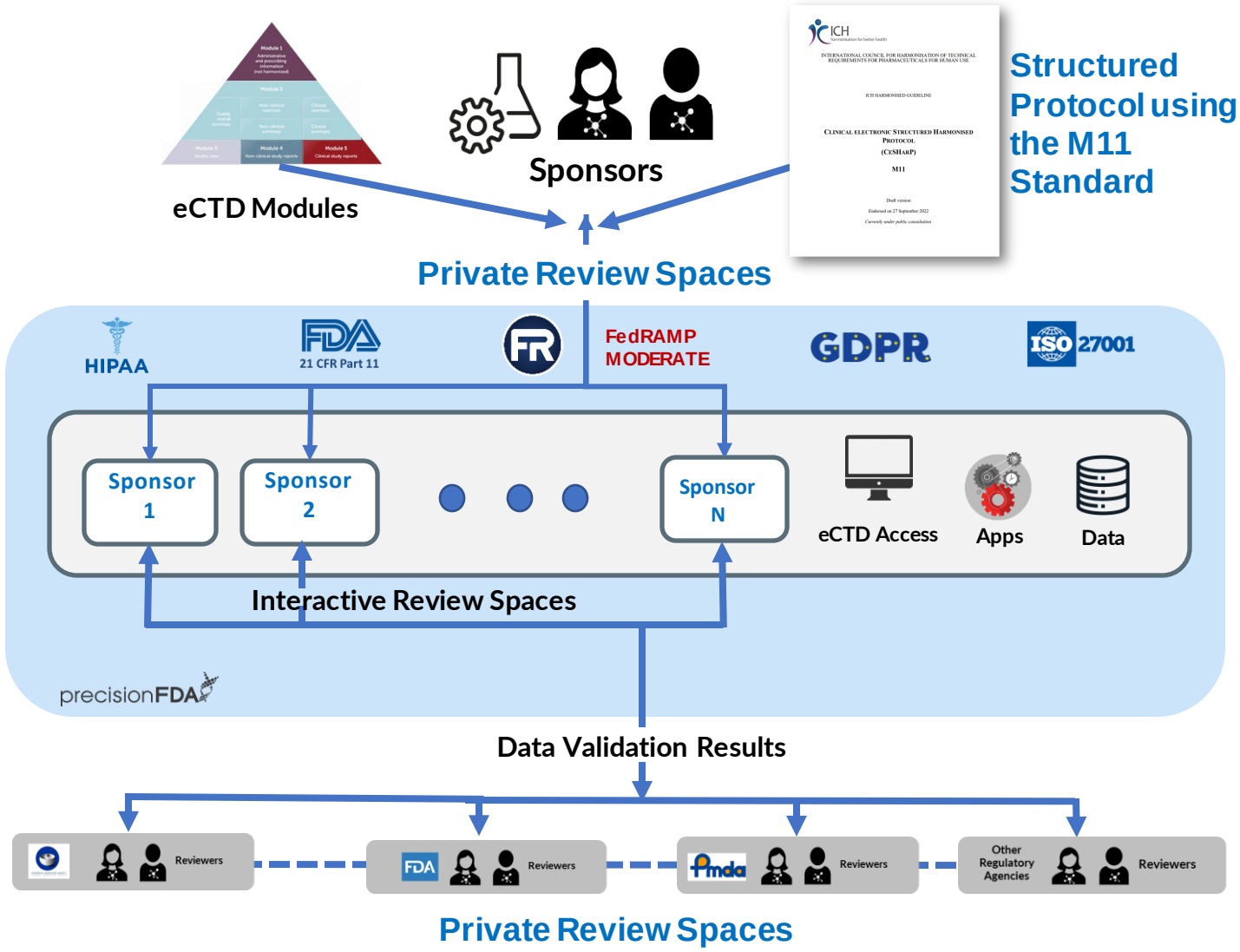
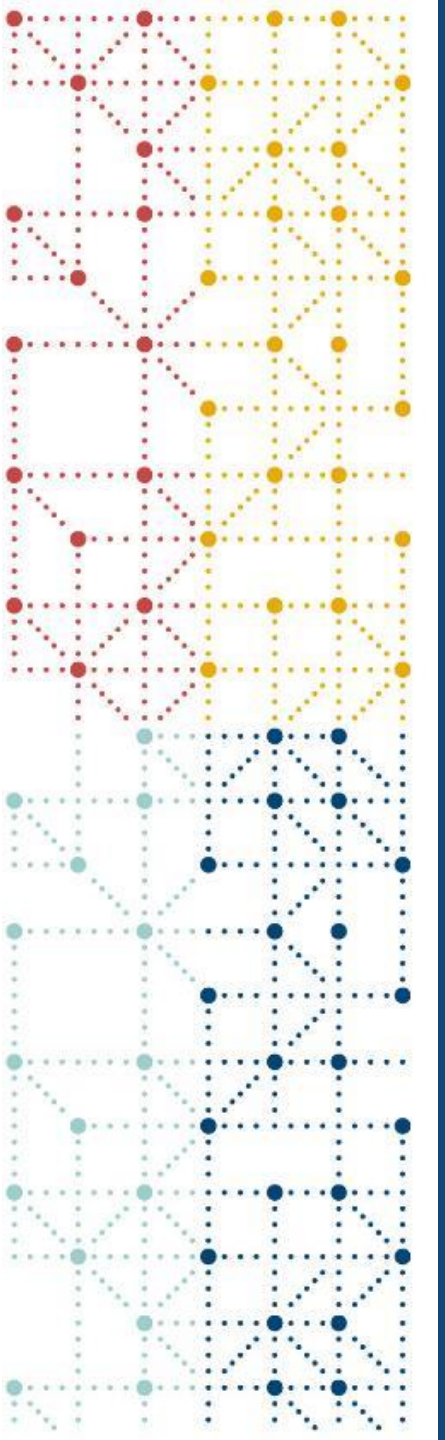
Implementation of the M11 Protocol Standard for Interactive Activities in the Cloud



M11-conformed eProtocols…

- Use a common data model & standards (e.g., CDISC)
- Can be exchanged using multiple standards: FHIR, XML, MS Word, PDF
- Can use common tools to access data repositories
- Can be real-time quality-checked
- Ensure consistency across protocol sections
- Ensure line of sight of trial objectives, endpoints, procedures and design.
- Facilitate downstream processes, e.g., SAP, CSR, Registries

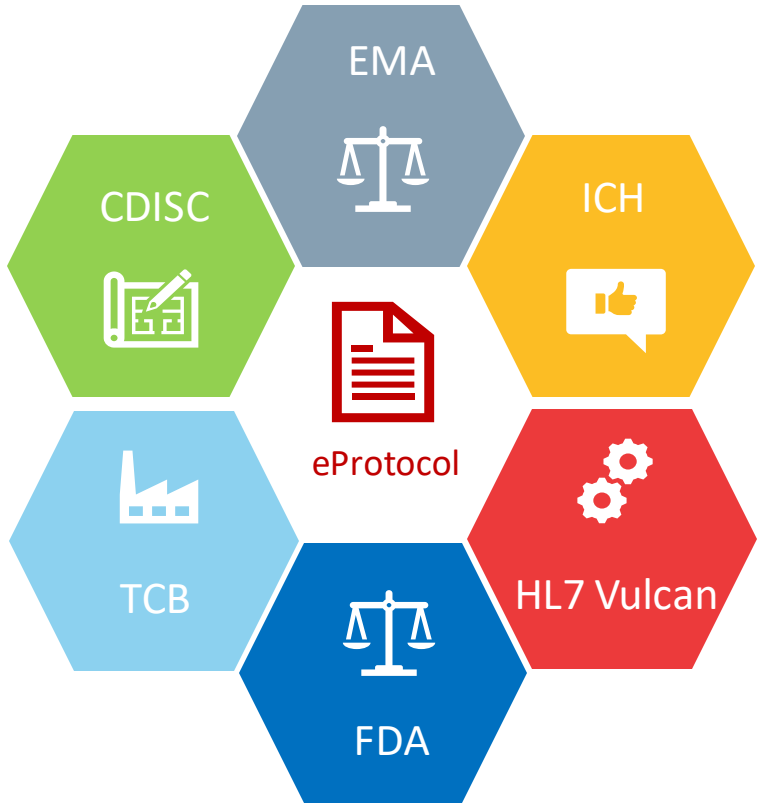
Note: This is only an example, the regulatory agencies noted above does not imply their participation



Next Steps

What to expect

- It's time to start paying attention
- Transcelerate and CDISC will accelerate the operationalization of the digital protocol
- We expect to engage in industry and regulatory pilots soon



Thank You!