ICH M11, TransCelerate, CDISC & HL7 Vulcan: Making the Electronic Protocol a Reality

Dave Iberson-Hurst, USDM Product Owner & Technical Expert

Version 2

Meet the Speaker

Dave Iberson-Hurst

Title: CDISC USDM Product Owner

Organization: CDISC & data4knowledge

40 years' experience across several industries with the last 25+ years spent in the pharmaceutical industry combining his technology and software development experience with clinical trial process and data standards knowledge.

During this time, he has served as the CDISC CTO, worked on, and led, several CDISC teams, presented in many forums in Europe, the US, and elsewhere across the globe. He has worked closely with the FDA, EMA, HL7, ISO, and other standards organizations and was was a member of CDISC's Blue Ribbon commission.

He is currently the CDISC Product Owner and Technical Expert for the Digital Data Flow project.

He is a partner at data4knoweldge in Copenhagen and is focused on getting greater value and utility from clinical trial data.

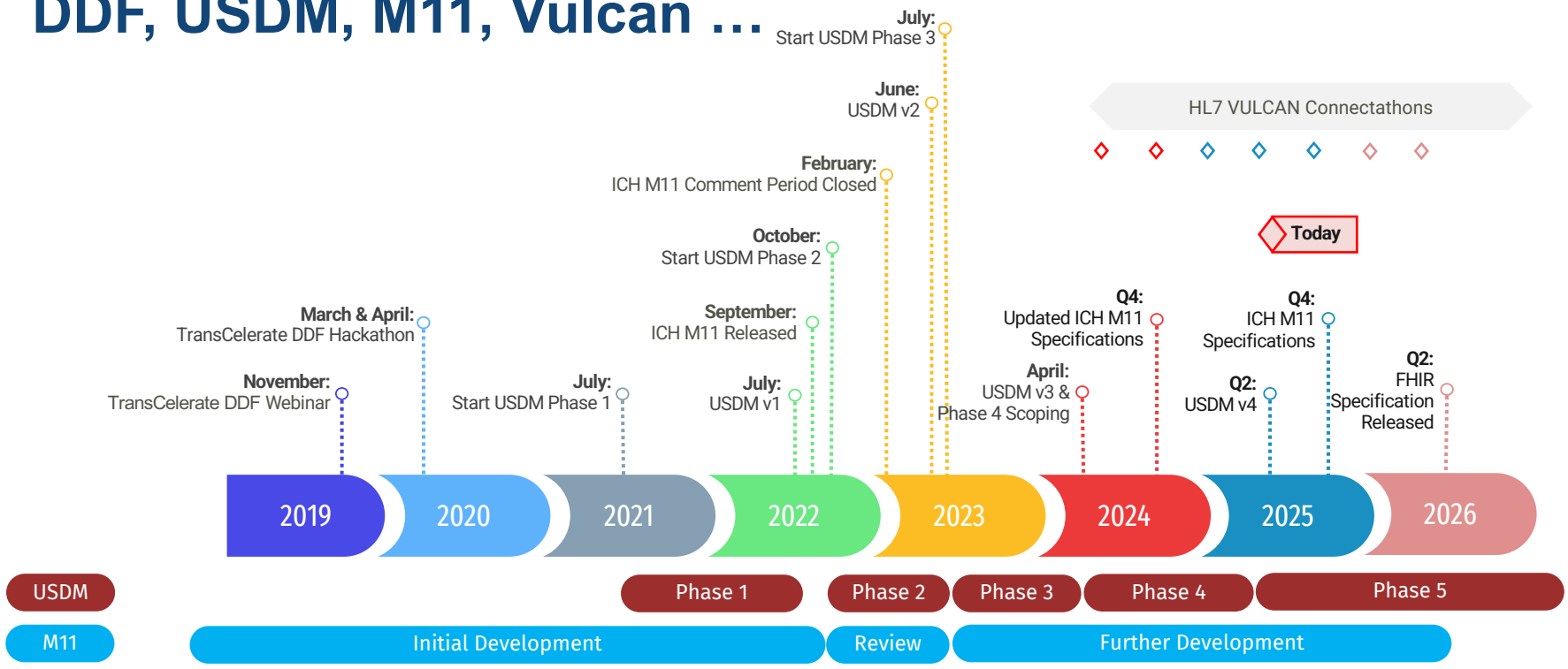
Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*
- *On contract to CDISC for the DDF work*

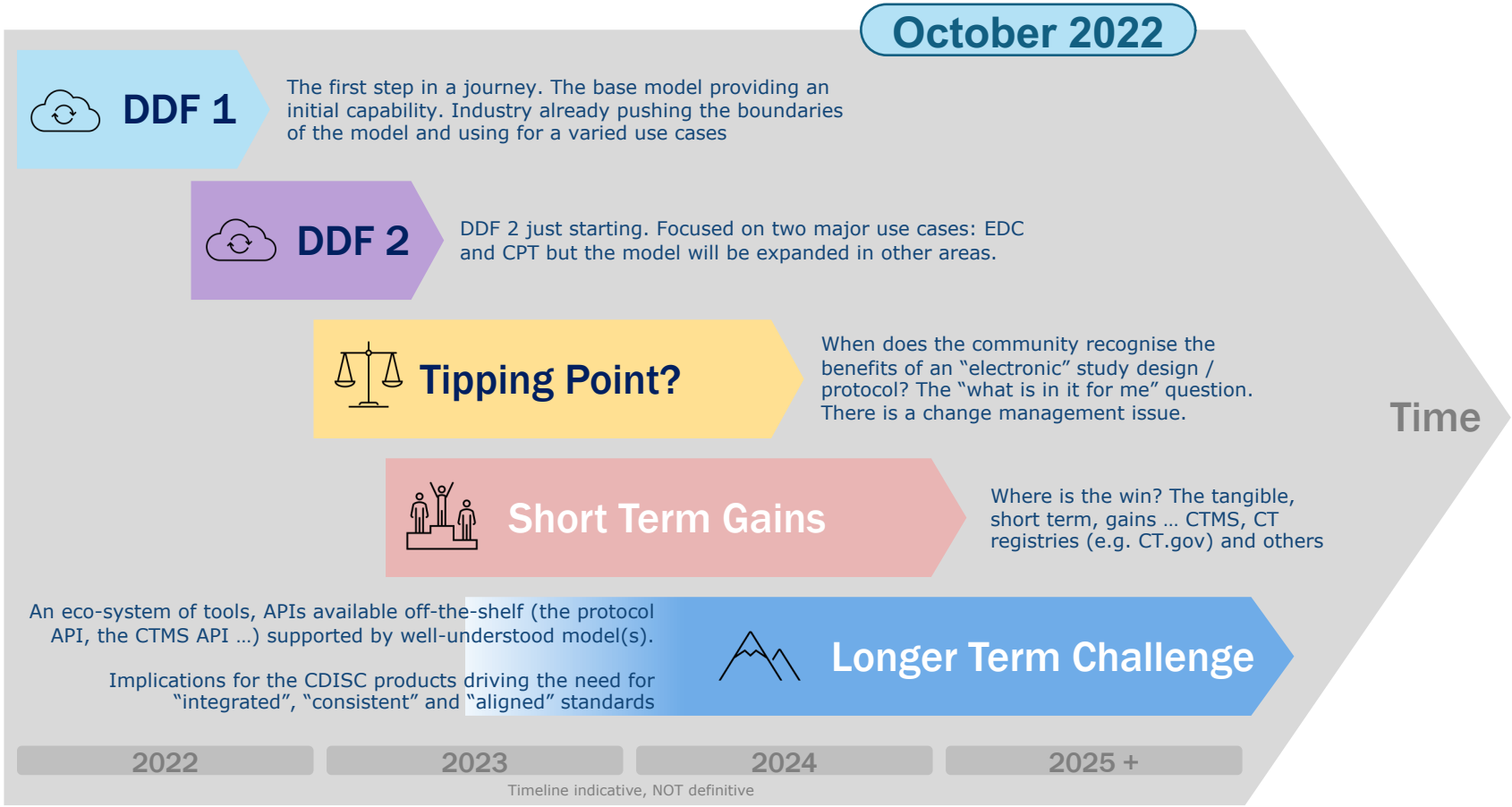
Agenda

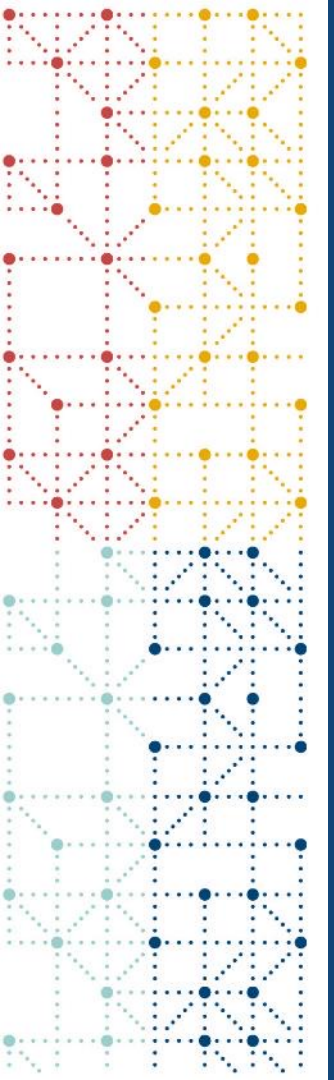
1. Digital Data Flow Project and USDM
2. ICH M11
3. USDM, M11, and HL7 UDP
4. precisionFDA and PRISM
5. And next …

DDF, USDM, M11, Vulcan …



Acronyms
DDF: Digital Data Flow
USDM: Unified Study Definitions Model
ICH: International Council for Harmonisation
M11: Clinical electronic Structured Harmonised Protocol (CeSHarP)


October 2022
DDF 1
The first step in a journey. The base model providing an initial capability. Industry already pushing the boundaries of the model and using for a varied use cases
DDF 2
DDF 2 just starting. Focused on two major use cases: EDC and CPT but the model will be expanded in other areas.
Tipping Point?
When does the community recognise the benefits of an "electronic" study design / protocol? The "what is in it for me" question. There is a change management issue.
Time
Short Term Gains
Where is the win? The tangible, short term, gains … CTMS, CT registries (e.g. CT.gov) and others
An eco-system of tools, APIs available off-the-shelf (the protocol API, the CTMS API …) supported by well-understood model(s).
Implications for the CDISC products driving the need for "integrated", "consistent" and "aligned" standards
Longer Term Challenge
2022
2023
2024
2025 +
Timeline indicative, NOT definitive



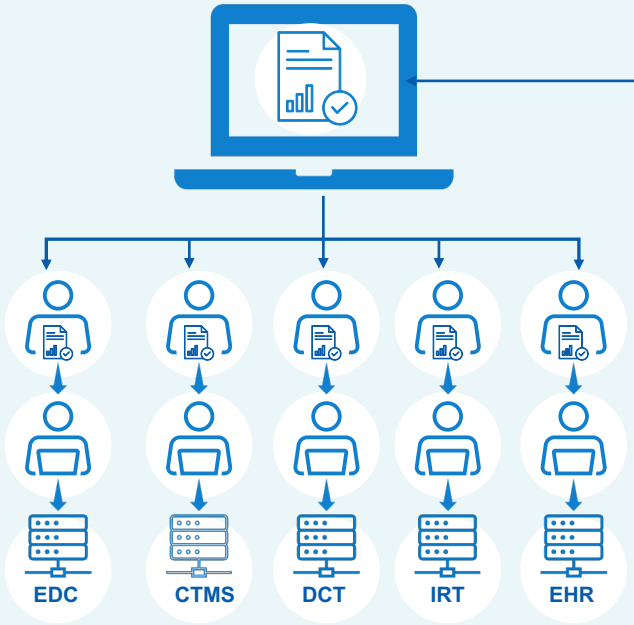
Unified Study Definitions Model (USDM)

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

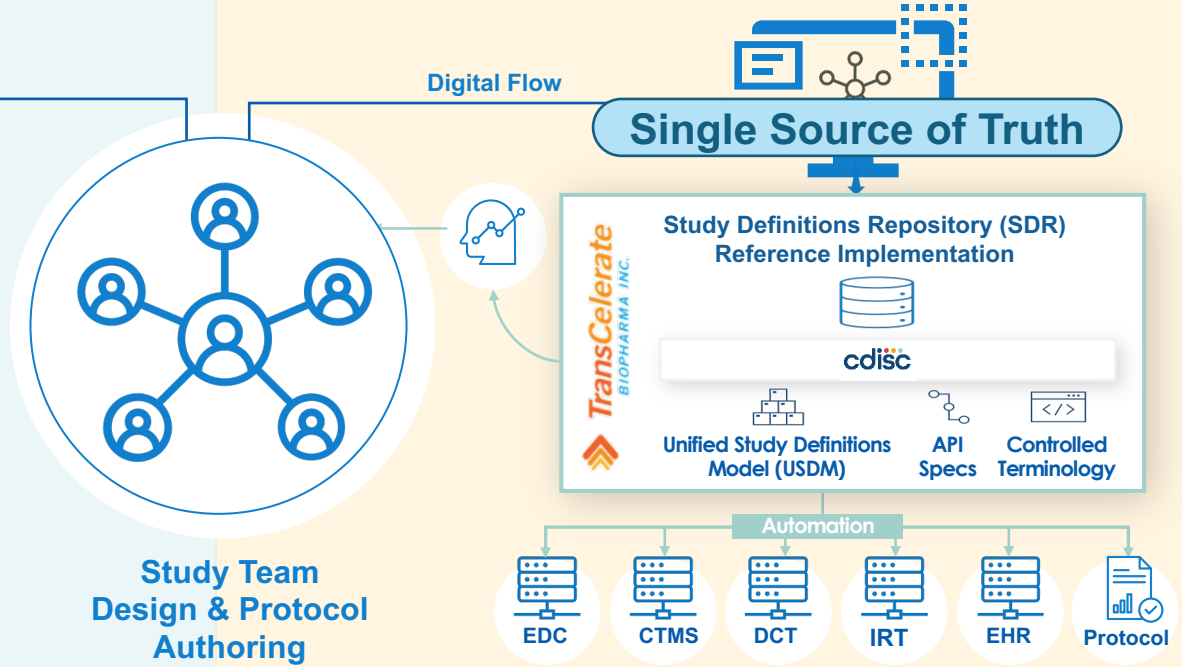
TransCelerate Digital Data Flow (DDF) Ambition

Write Once, Read Many

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



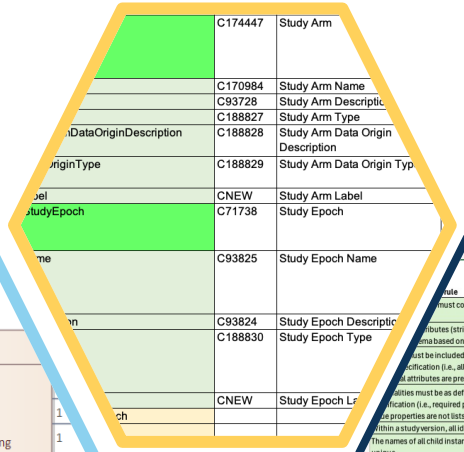
TOMORROW: Digital paradigm for protocol creation, with fully automated data flow and interoperability between systems



The USDM Standard

CDISC Controlled Terminology

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

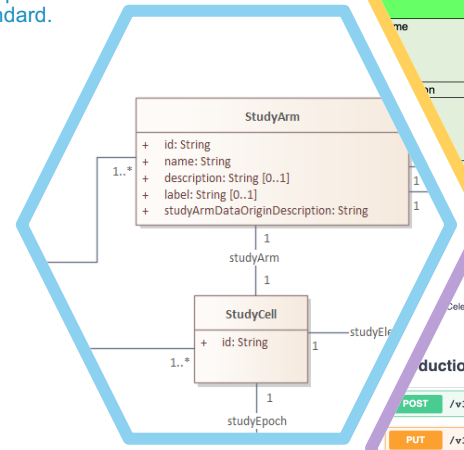


Examples

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

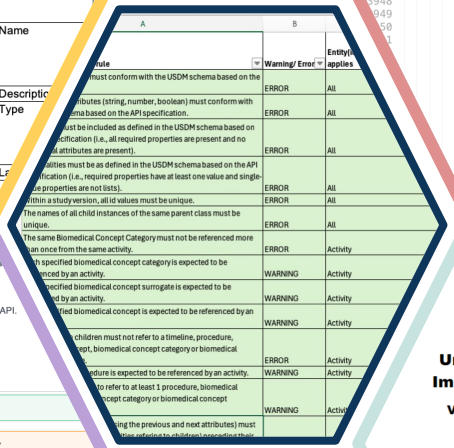
Logical Model

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

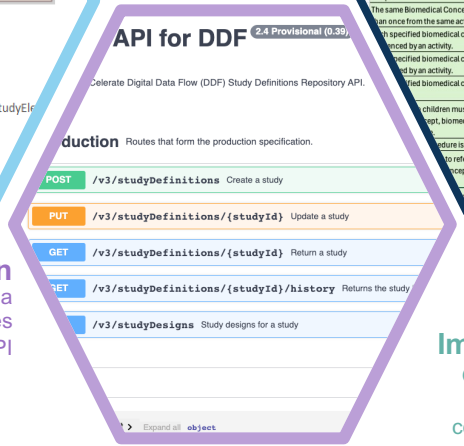


CORE Rules

Specification of the rules that define USDM compliance

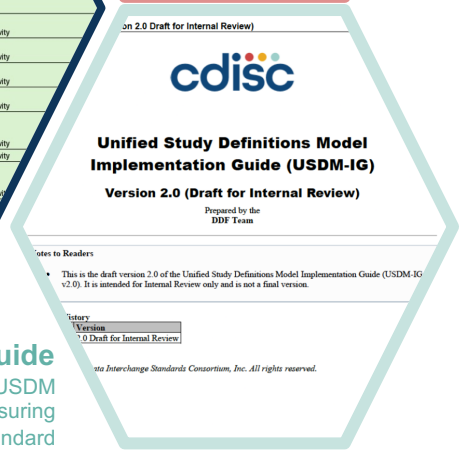


API for DDF



API Specification

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

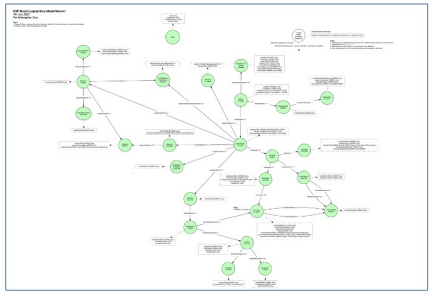


Implementation Guide

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

CDISC DDF / USDM, Phases One to Four

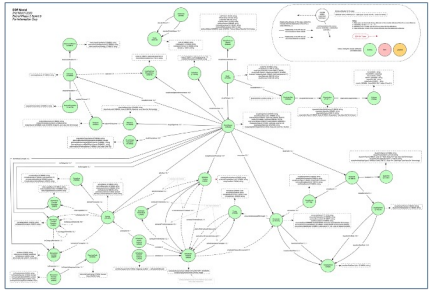
Phase One



25 Classes

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

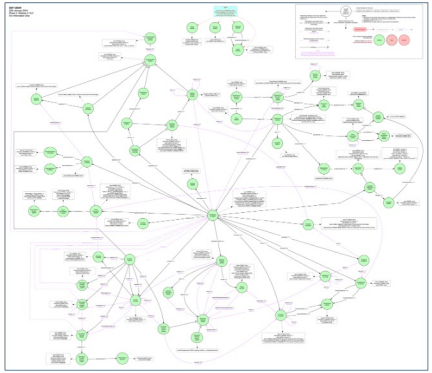
Phase Two



35 Classes

- 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

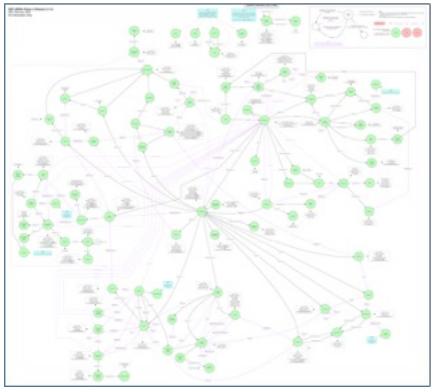
Phase Three



58 Classes

- 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

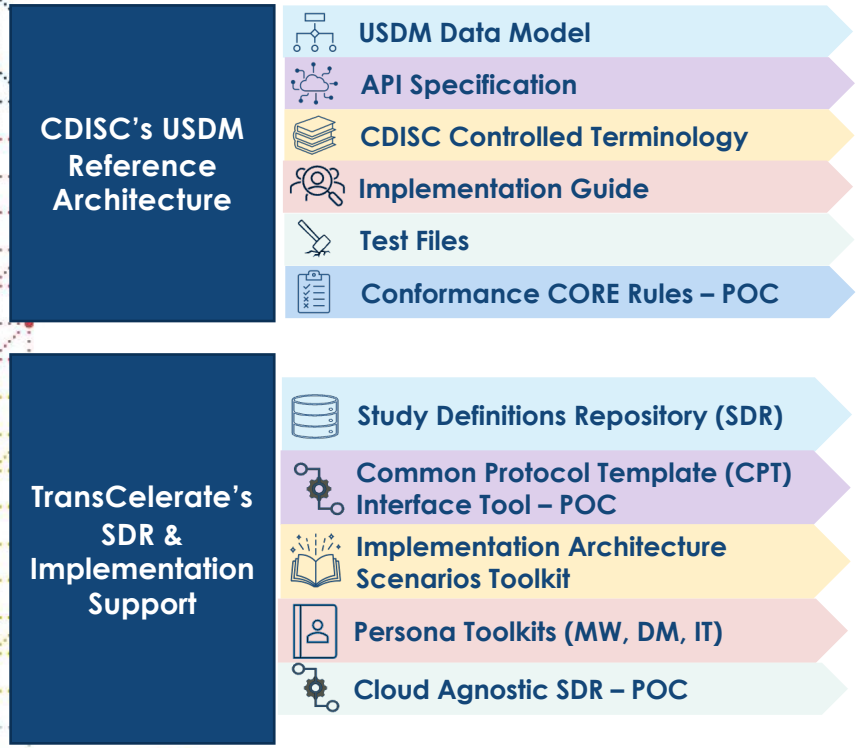
Phase Four



89 Classes

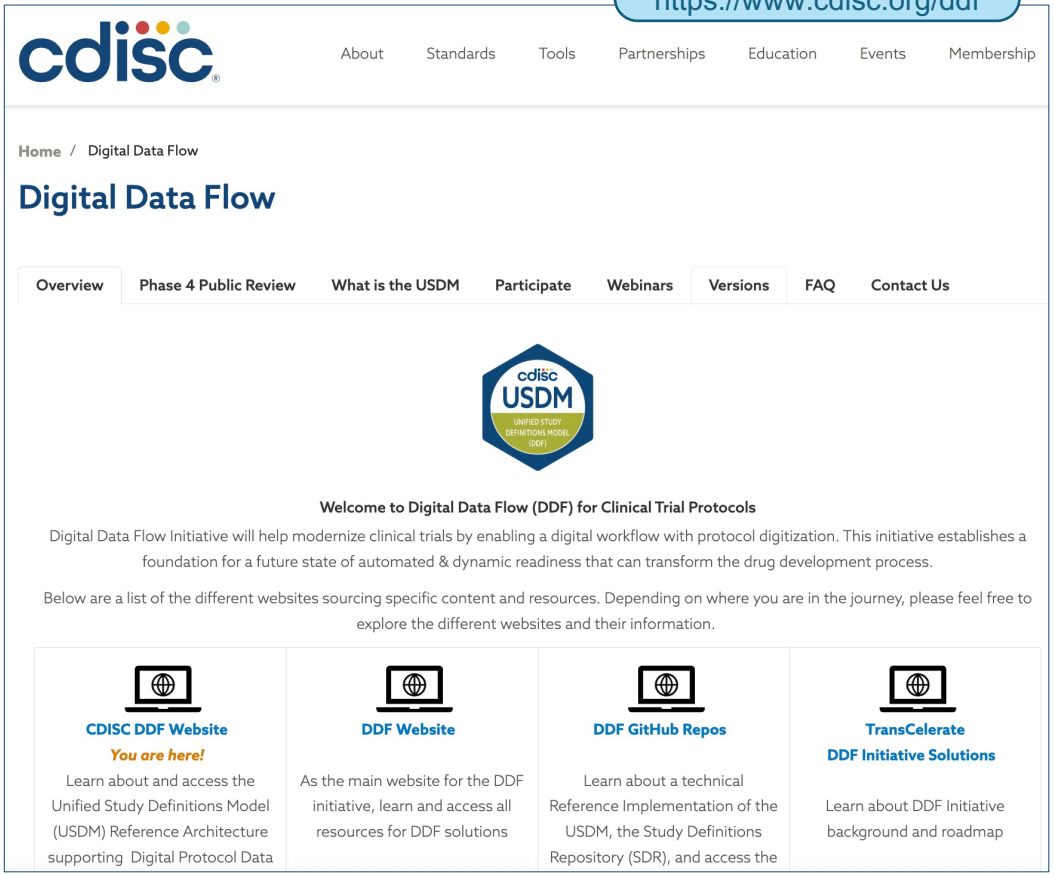
- Aligned with ICH M11
- Support for complex studies, interventional & observational studies, and medical devices
- Maximise content re-use and support for multiple document templates
- Extension mechanism to provide flexibility

DDF Evolution: Phases One to Four



DDF Web Page

https://www.cdisc.org/ddf

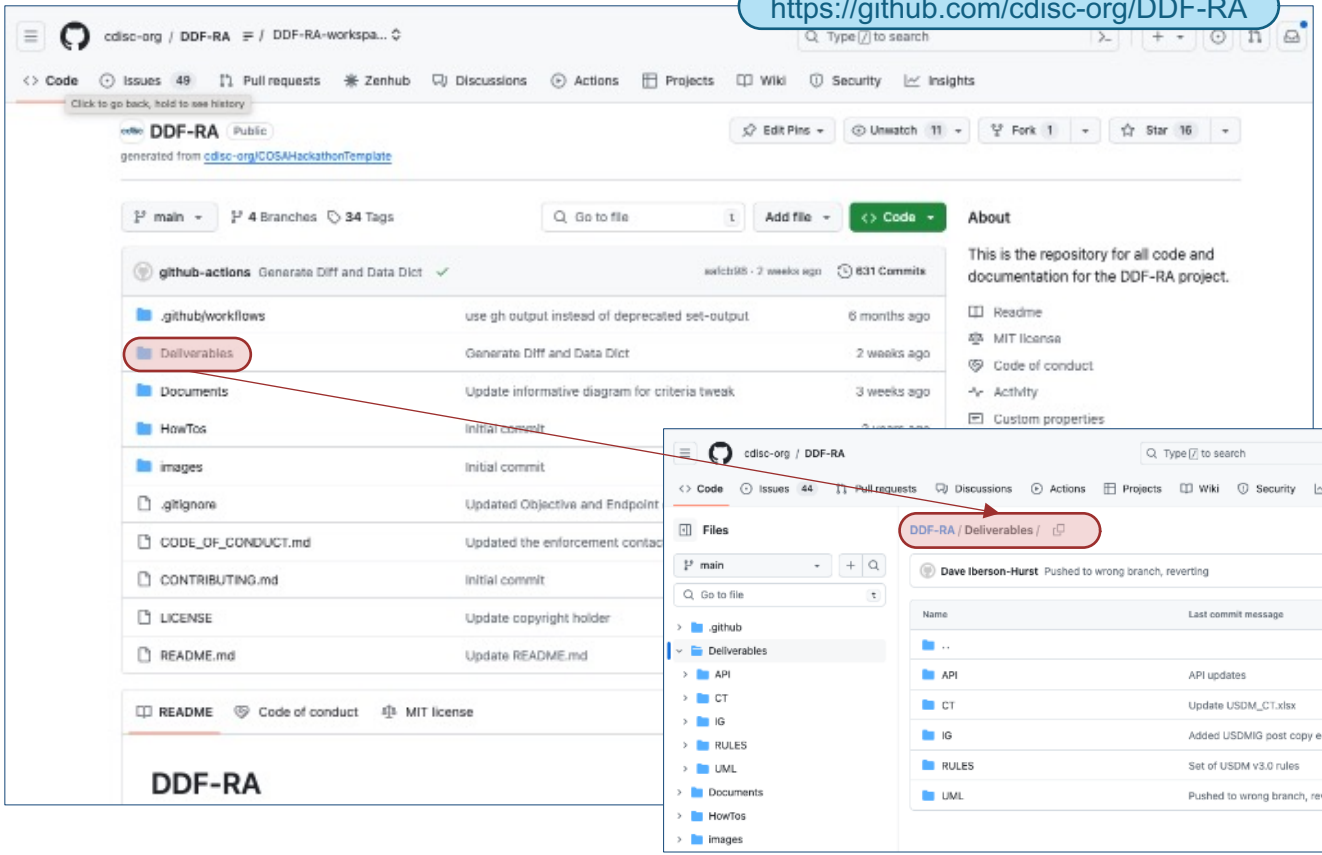


CDISC DDF

Scan Me

DDF-RA (USDM) GitHub

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



CDISC GitHUb

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USDM in Action
Use Cases Supporting the DDF Vision

Use Cases

Retrospective

Protocol 'Store'

Past Protocols
The storage of past sponsor protocols in to support a variety of use cases such as:

- Therapeutic area specific content
- Standard inclusion and exclusion criteria.
- Libraries of objectives, endpoints and estimands.
- Asses the past to prevent protocol amendments.
- General search across the library

Prospective

Study Design

Protocol Authoring
Support the authoring of new protocols including complex studies such as Master, Umbrella etc.

This would include analyzing previous protocol information to inform design choices (see Protocol Store).

Writing associated SAP, Informed Consent, Monitoring Plan, Drug Plan etc via content reuse.

Study Build
Build of the study based on the protocol I including all detailed procedures and assessments to allow for immediate deployment.

Feasibility & Cost
Support study feasibility and complexity evaluations.

Determine the cost of the study including such items as vendor and CRO costs and support the laboratory RFP process

Regulatory Authority
Approval for the execution of the study including IND, CTA etc and discussions with regulatory authorities

Stakeholder Views
Tailored views for stakeholders such as IRB and ethic committees.

Study Start-up

Deployment
Deployment of the study across the enterprise using the USDM to support electronic configuration rather than manual data entry including Data collection systems (incl. EDC), CTMS, IRT, Data transmission specifications and more

TMF
Linking the protocol to the specification of milestones and essential documents

Data Collection Strategy
Ensure all data that is needed for analysis is collected. Remove unnecessary procedures & data collection to reduce trial cost and patient burden.

Trial Registries
Registration of the study with registries such as CT.gov, CTIS etc.

Training
Provision of training materials to those involved in the study including sites

Site Support
Provision of tailored information to sites regarding study execution.

Study Execution

Amendments
Support the amendment process with the ability to indicate the precise changes to the user community.

Ensure fewer amendments (see Protocol Store).

Subject Information
Provision of improved information to subjects regarding study execution, improve expectation management.

Drug & Study Materials
Assist in the planning and provision of study drug, materials and supplies

Subject Recruitment
Support the identification of subjects to help improve subject recruitment to the study. Help support EHR participation identification.

Analysis & Reporting

Automation
Provide a solid foundation for the automation of analysis and reporting outputs such as TLFs and CSRs.

SDTM
Creation of 'T' domains. Auto generation of data domains

ADaM
Use the protocol statistical metadata to assist in the derivation of analysis datasets

Statistical Analysis Plan
Use the protocol as the initial source of the SAP to ensure consistency with objectives, endpoints, estimands

Regulatory Submission

Submission
Preparation of the submission by the sponsor

Regulatory Review
Review of the submission by the regulatory authority and discussions / questions with the sponsor

Statistical and Safety Review
Support the comparison of data by arm or study design.

Allow for the verification of planned (protocol) data versus actual (study data) captured data

Across The Lifecycle

Dashboards
The display of protocol related information sourced from one or more protocols in ways which have not been achievable before

Comparison
Compare and verify differences across versions and similar protocols

Unified Study Definitions Model (USDM)

Study Details
The overall study, its various versions, identifiers and associated governance. Also includes the amendments made to the study

Study High Level Design
The single or set of study designs making up the study detailing the epochs, arms etc.

Study Science
The detailed description of the study science: the populations and the associated inclusion and exclusion criteria, the indications being studied, the interventions being used and the objectives, endpoints and the associated estimands.

Detailed Study Logic
A precise definition of the study logic including support for the Schedule of Activities.

Unstructured Content
The ability to support one or more document presentations of the USDM content including the ICH M11 protocol template, sponsor templates and other documents.

Procedures and Biomedical Concepts
The detail around the procedures and observations to be performed as part of the detailed study designs.

Controlled Terms
The controlled terminology needed to define the semantics within the model. Managed in the same manner as all CDISC CT and aligned with the M11 template standard.

Use Cases

Scan Me

NOTE: The use cases presented are illustrative and the list is not intended to be exhaustive.

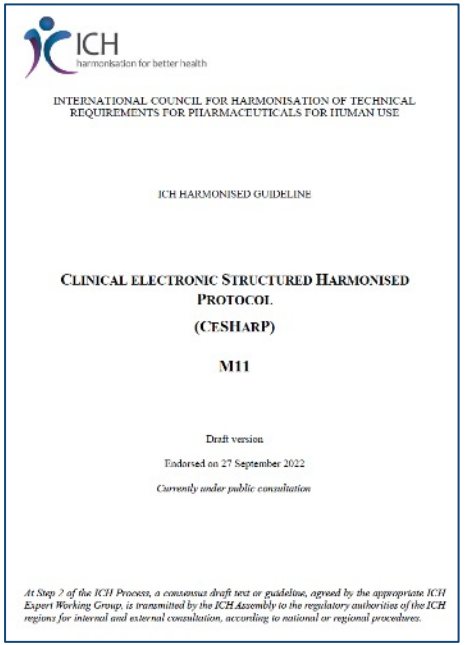
Version 5, 24th October 2024. Prepared by D Iberson-Hurst for the TransCelerate 'DDF in Action' day.
With thanks to Rob Ferendo (TransCelerate), Bill Illis (Novartos), Jasmine Kestemont (Argenx), Kirsten Langendorf (d4k), Mary Lynn Mercado (Novartis), Lissa Morgan (Amgen), Johannes Ullander (d4k) and Peter Van Reusel (CDISC)

ICH M11

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

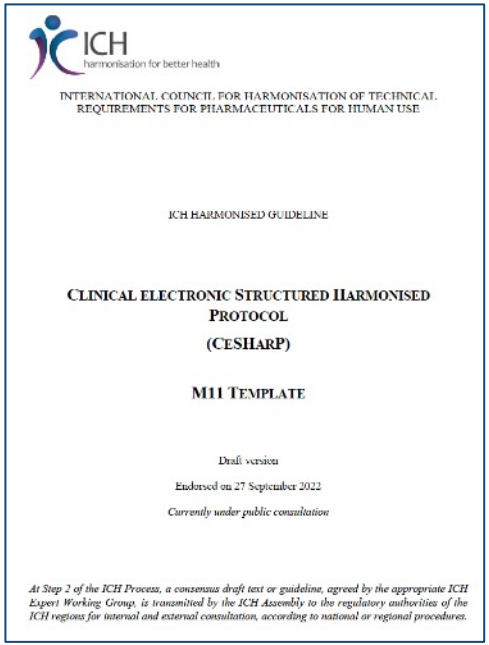
Draft version

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

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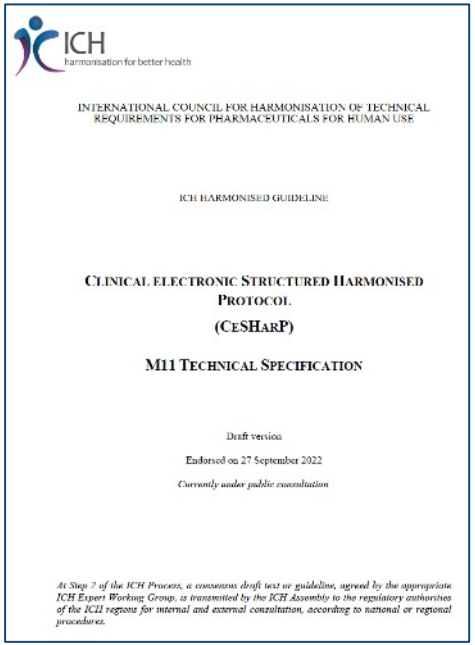
Provides the written format for the Interventional Clinical Trial Protocol Template



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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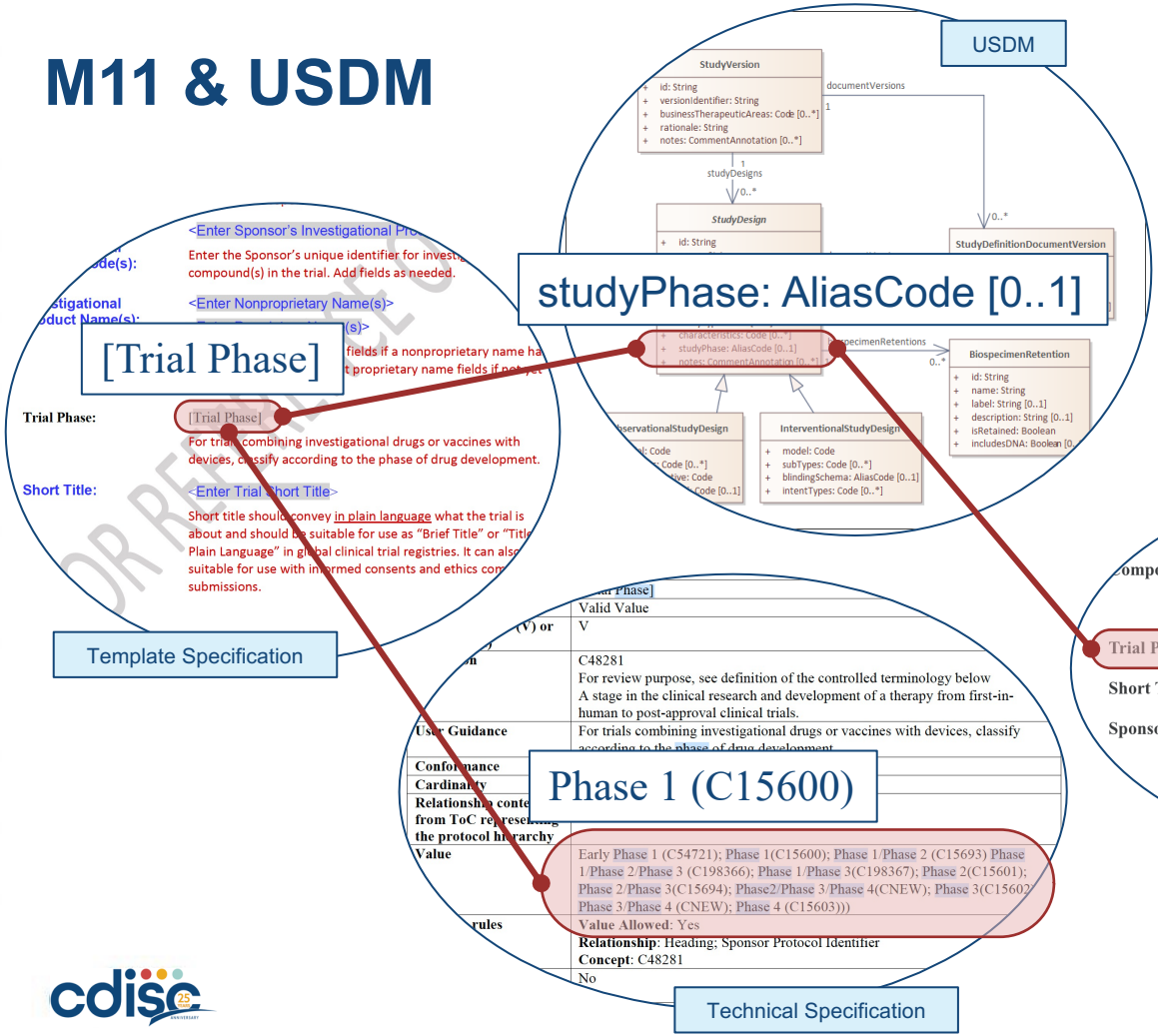
Provides the technical representation aligned with the guideline and protocol template

M11 & USDM



The graphic shows the links between the Trial Phase field that is defined as part of the M11 Title Page to the M11 Technical Specification, on to the USDM and onwards to an implementation of USDM and M11

- *A StudyDesgn has a studyPhase*
- *studyPhase is an AliasCode*
- *AliasCode can store:*
  - *a single standard code (CDISC Trial Phase Response, C66737) using the Code class*
  - *And zero or more other alias codes (e.g. a sponsor phase code) using the Code class to provide flexibility*

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.
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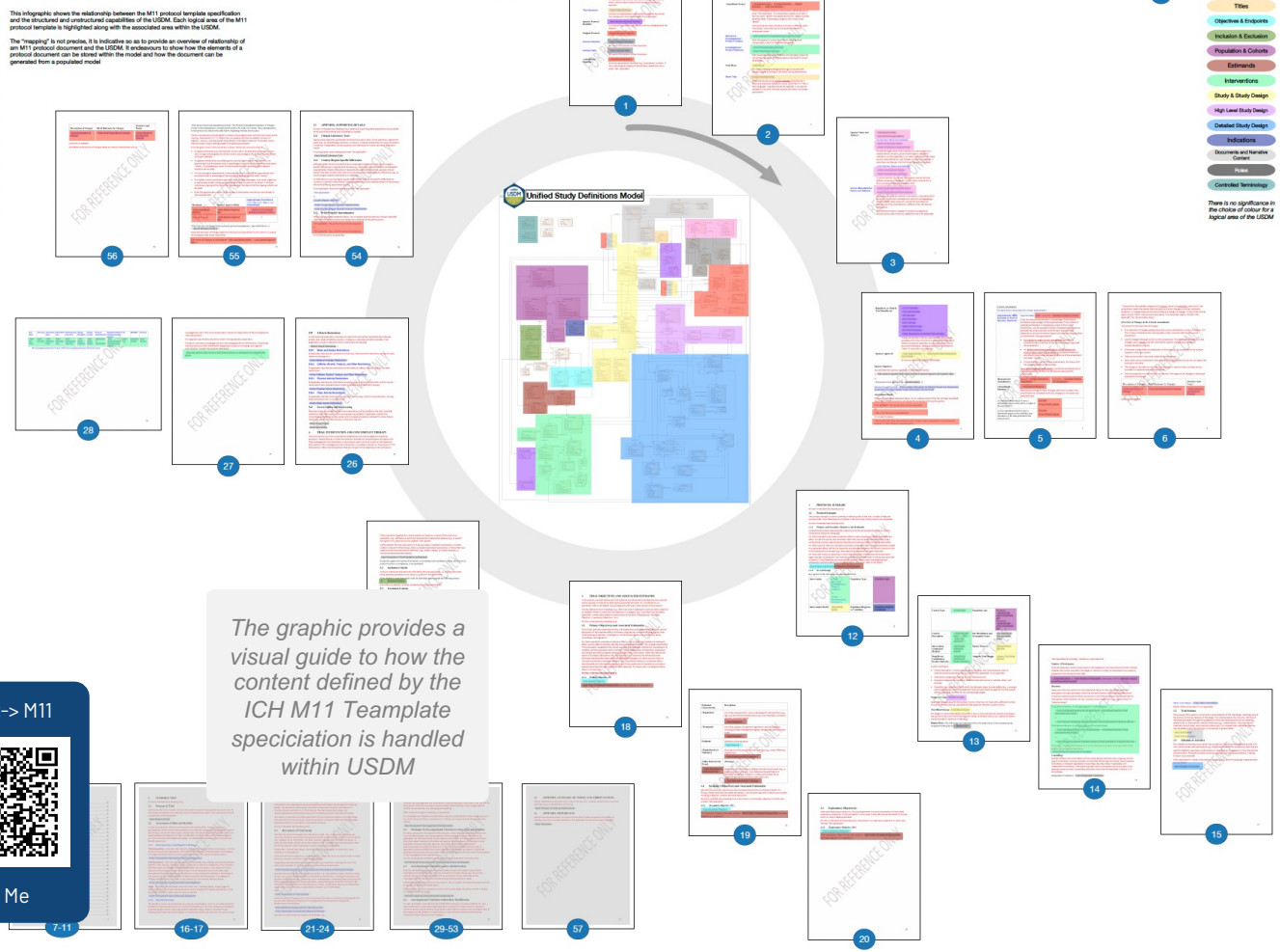
cdisc

ICH harmonisation for better health



The graphic provides a visual guide to how the content defined by the ICH M11 Teamplate speciciation is handled within USDM

USDM <-> M11

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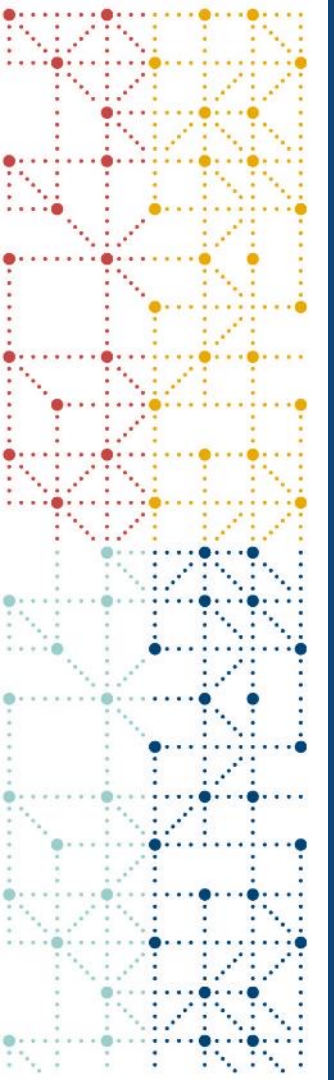
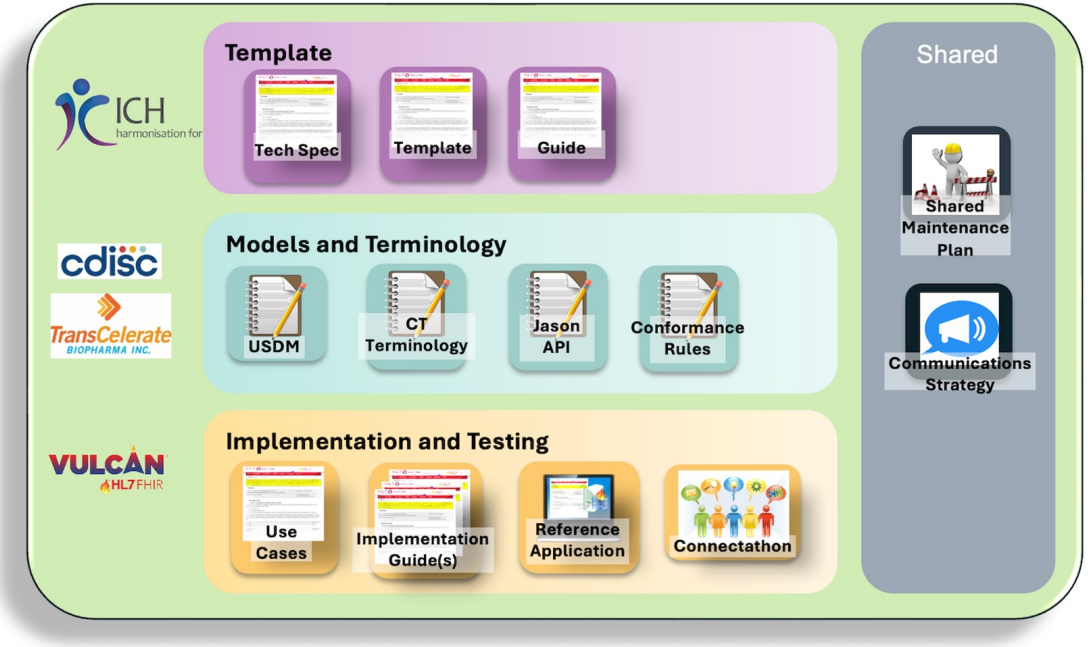


USDM, M11, and the HL7 UDP

Utilizing the Digital Protocol

UDP is an Umbrella Project with many Use Cases

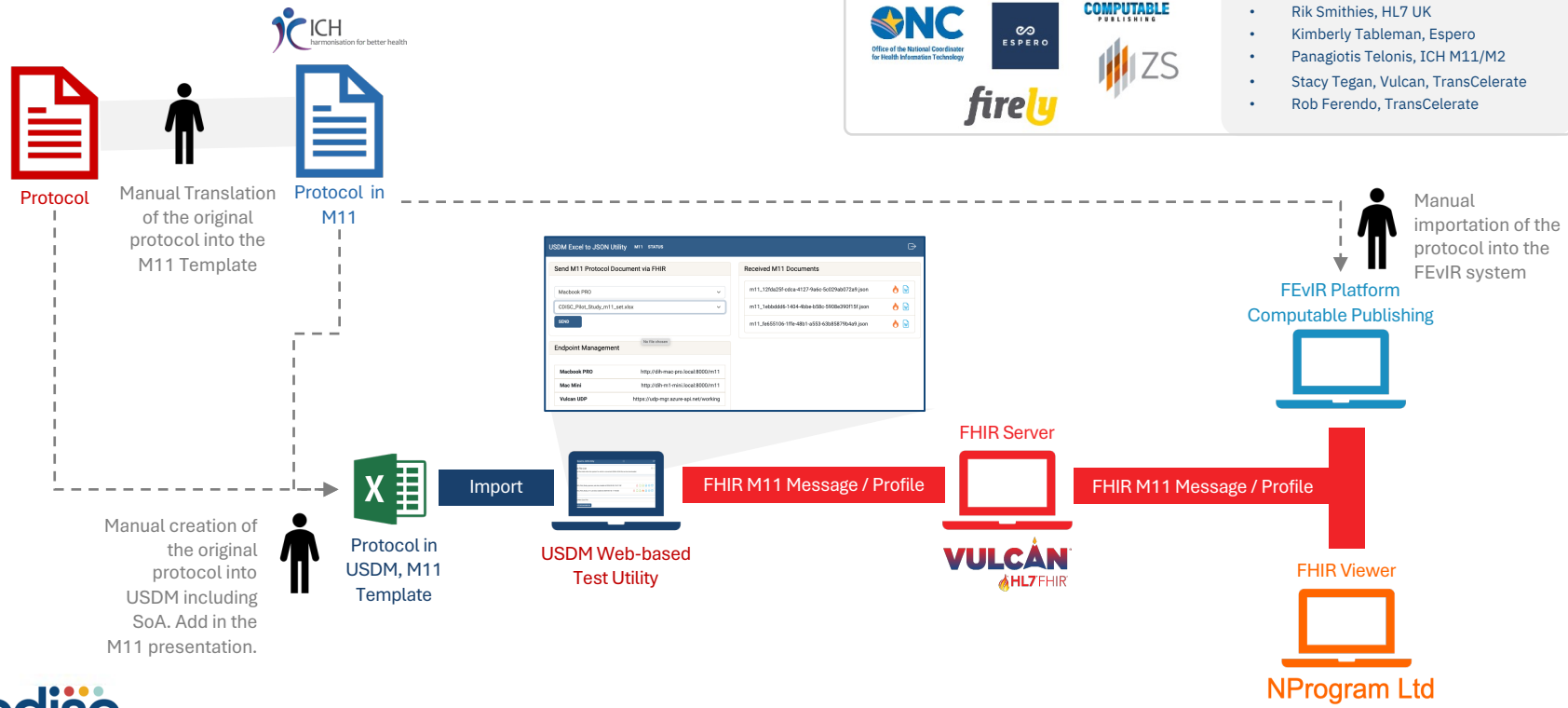


- Inputs:
  - ICH M11 template
  - ICH M11 technical specification
  - Models, definitions
- FHIR will carry CDISC CT and USDM content
- The technical specification can be used to develop other Implementation Guides

HL7 FHIR Connectathon

Dallas, May 2024

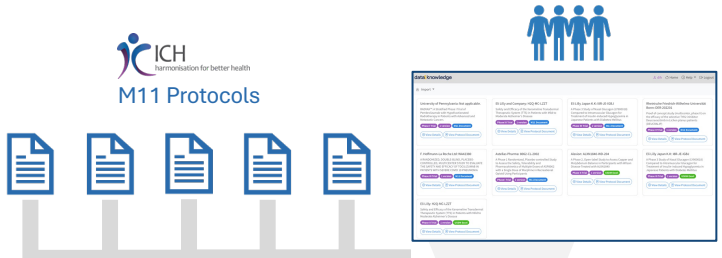
- Brian Alper, Computable Publishing
- Matt Elrod, ONC
- Hugh Glover, Vulcan ***TRACK LEAD***
- Dave Iberson-Hurst, CDISC
- Dan Newingham, ZS Associates
- Jimita Parekh, ICH M11/M2
- Khalid Shahin, Computable Publishing
- Rik Smithies, HL7 UK
- Kimberly Tableman, Espero
- Panagiotis Telonis, ICH M11/M2
- Stacy Tegan, Vulcan, TransCelerate
- Rob Ferendo, TransCelerate



HL7 FHIR Connectathon

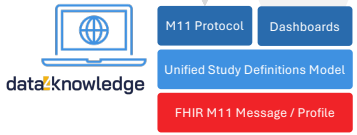
Atlanta, September 2024

- Brian Alper, Computable Publishing
- Hugh Glover, Vulcan *TRACK LEAD*
- Dave Iberson-Hurst, CDISC
- Khalid Shahin, Computable Publishing
- Rik Smithies, HL7 UK
- Stacy Tegan, Vulcan, TransCelerate
- Rob Ferendo, TransCelerate
- Mary Lynn Mercado, Novartis
- Enam Rahman, TransCelerate
- Mihoko Okada, Idial



"Sponsor" 1

- M11 '.docx' → USDM → FHIR

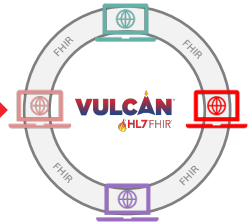


M11 Protocol | Dashboards

Unified Study Definitions Model

FHIR M11 Message / Profile

FHIR M11 Message / Profile



FHIR M11 Message / Profile

FHIR Viewer

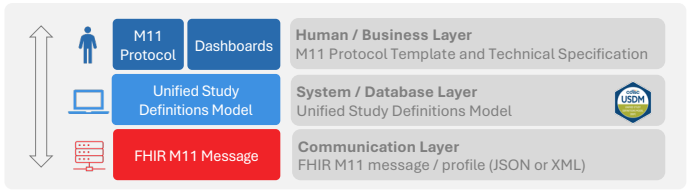
NProgram Ltd

"Regulator" 2

- FHIR → USDM → M11 Presentation

Structure parts of the M11 Template:

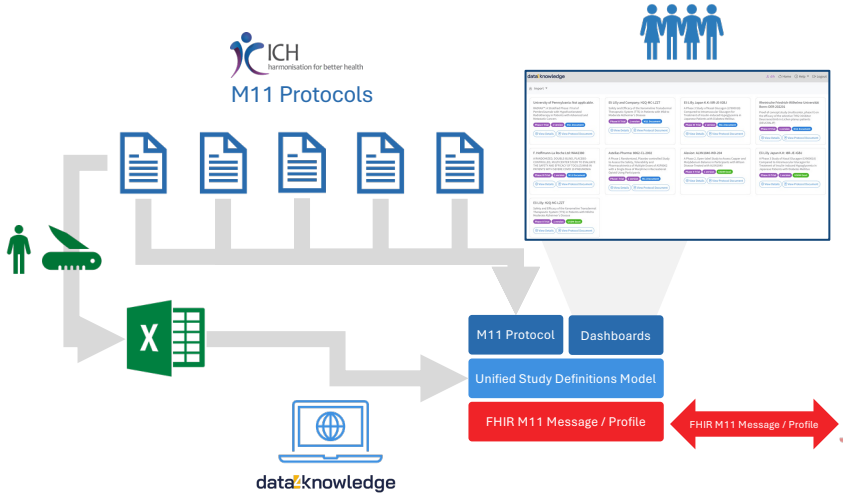
- *Title Page*
- *Inclusion / Exclusion*
- *Estimands, Objectives and Endpoints*
- *Amendments*

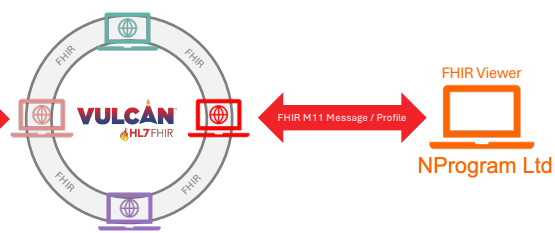


HL7 FHIR Connectathon

Virtual, January 2025

- Hugh Glover, Vulcan TRACK LEAD
- Rob Ferendo, TransCelerate
- Patrick Genyn, fhir4pharma
- Dave Iberson-Hurst, CDISC
- Geoff Low, Medidata
- Keiko Ota, Osaka Metropolitan University Hospital
- Rik Smithies, HL7 UK
- Stacy Tegan, TransCelerate, Vulcan





Structure the SoA

- *Visits*
- *Activities*
- *Timing*

"Sponsor" 1

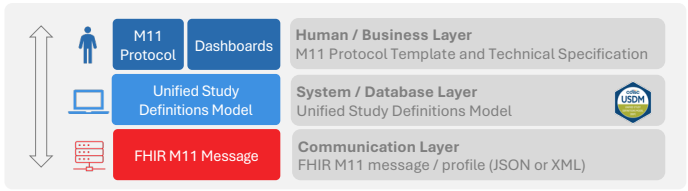
- M11 '.docx' → USDM → FHIR M11
- USDM '.xlsx' → USDM → FHIR SoA

"Regulator" 2

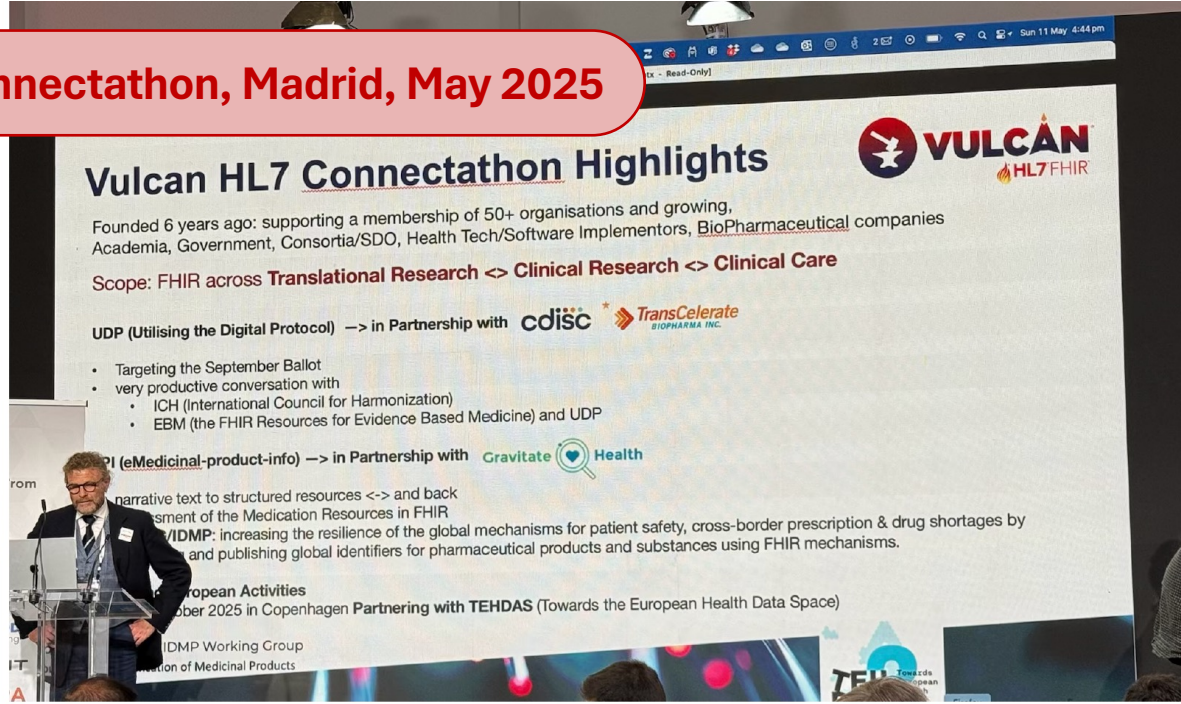
- FHIR → M11 Presentation

"Operational Environment" 3

- FHIR → SoA Presentation

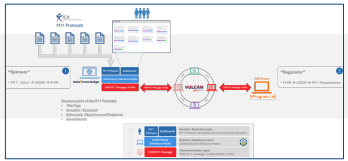


HL7 Connectathon, Madrid, May 2025

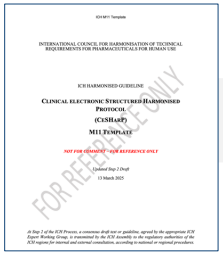


HL7 FHIR Connectathon

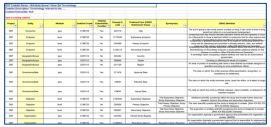
Madrid, May 2025



Dallas & Atlanta Connectathons



ICH M11 Template & Technical Specifications

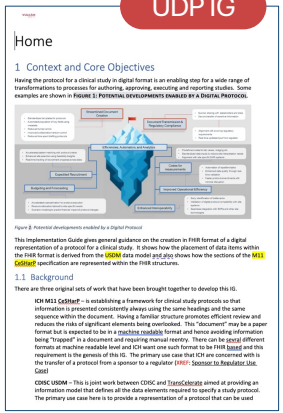


ICH M11 and CDISC USDM share the same CT

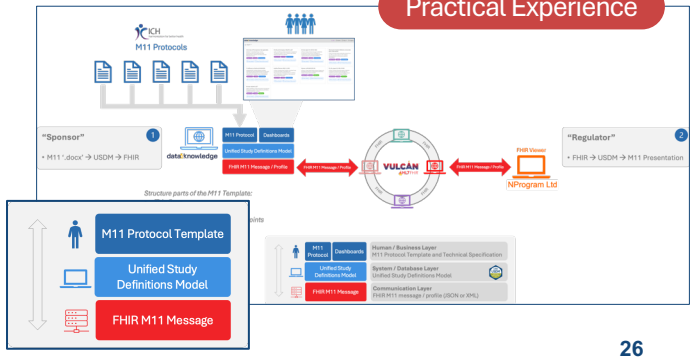
Controlled Terms

CDISC USDM
Logical Model

UDP IG



Practical Experience



ICH M11 Work Plan

Next ICH Assembly meetings

13 - 14 May 2025 in Madrid, Spain

18 - 19 November 2025 in Singapore

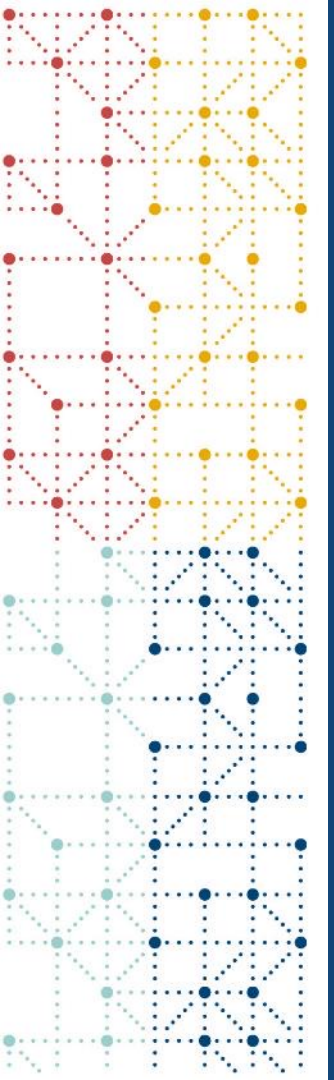
1.c. Future anticipated key milestones

Expected future completion date	Milestone
Oct. 2024	• *Regional Party Review of the Updated Guideline, Template, and Technical Specification* • *Clinical Data Interchange Standards Consortium (CDISC) Public Review of the M11 terms, definitions, and valid values*
Dec 2024	• *Adjudication of review comments* • *Updated Guideline, Template and Technical Specification*
Mar. 2025	*Regional Public Consultation Period on Technical Specification*
Jun 2025	*Adjudication of Public Comments on the Technical Specification*
Sep 2025	*Updated Guideline, Template and Technical Specification*
Oct. 2025	*Step 3 Sign-off Guideline, Template and Technical Specification*
Nov. 2025	*Step 4 adoption of Guideline, Template and Technical Specification*
Nov. 2025	*Final versioned training materials*
Feb 2026	*Step 2 (Testing) of the ICH Technical Implementation Guide for Fast Healthcare Interoperability Resources (FHIR)*
May 2026	*Step 4 adoption of ICH Technical Implementation Guide for FHIR*

Today

Release

FHIR IG



precisionFDA and PRISM

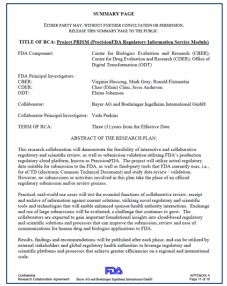
PROJECT PRISM

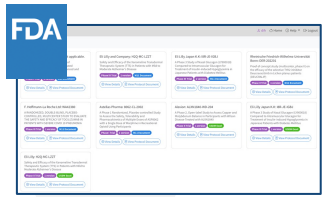
A Regulatory Cloud Collaborative Initiative

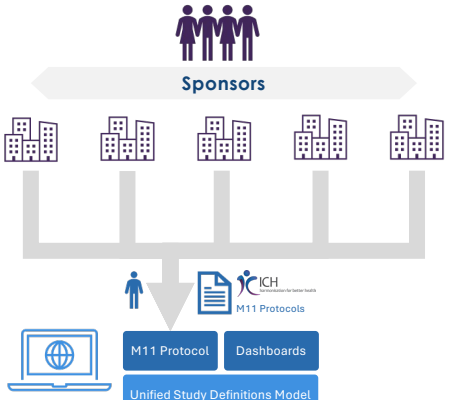
precisionFDA Regulatory Information Service Module
FDA-Industry Research Collaboration Agreement
(Public-Private Partnership)

Boehringer Ingelheim · BAYER · EMD SERONO · Takeda · Bristol Myers Squibb

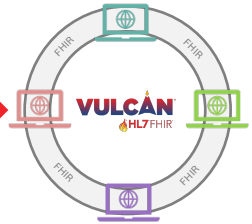
TransCelerate BIOPHARMA INC. · cdisc



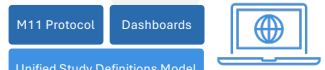




FHIR M11 Message / Profile



FHIR M11 Message / Profile

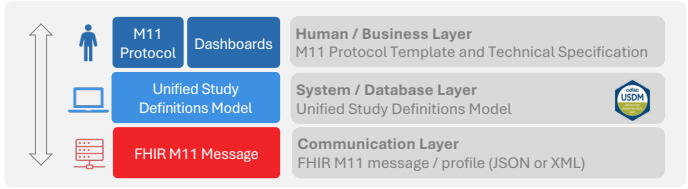


Sponsor 1

- M11 '.docx' → USDM → FHIR
- Try and make it easy, "a few clicks"

FDA 2

- FHIR → USDM → M11 Presentation
- Dashboards, what is possible?



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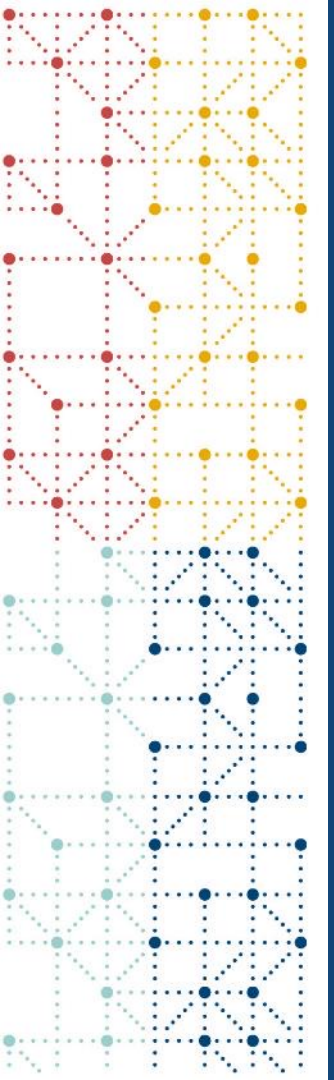
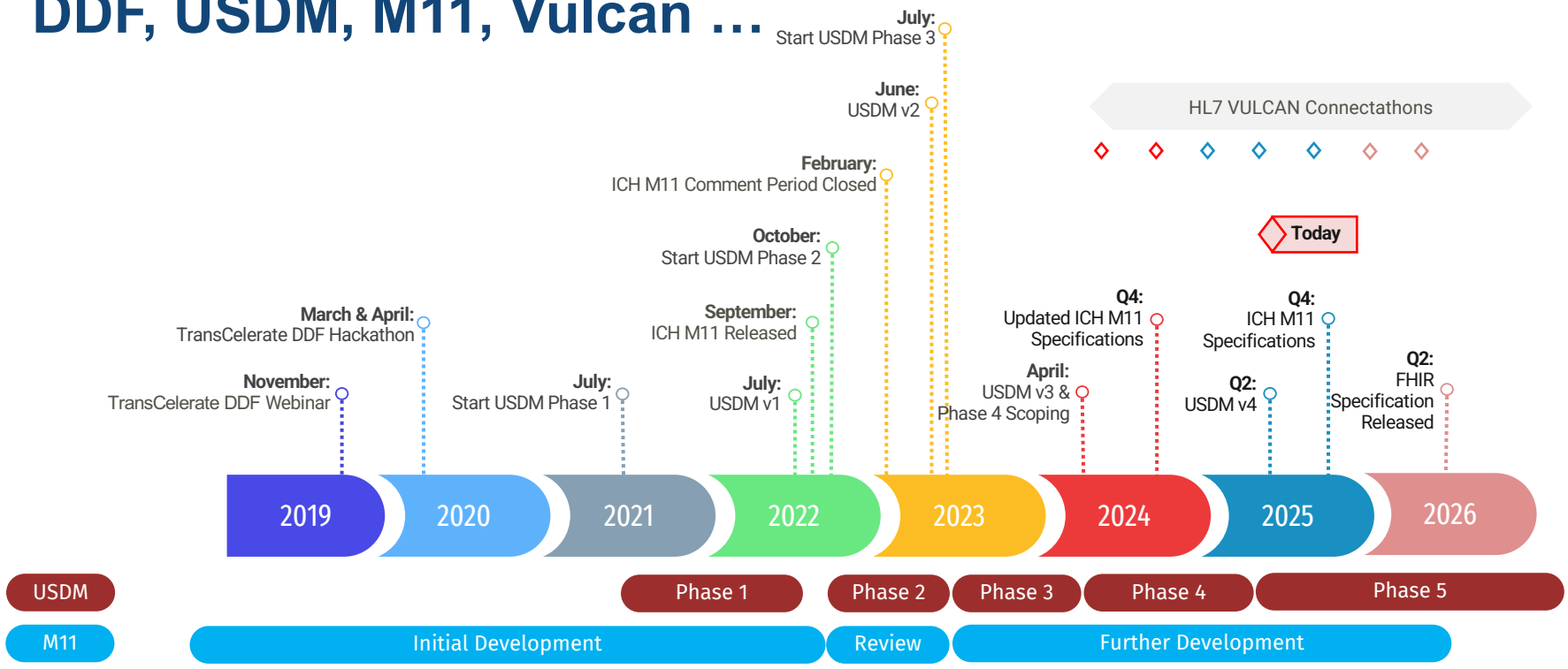


And next …

DDF, USDM, M11, Vulcan …

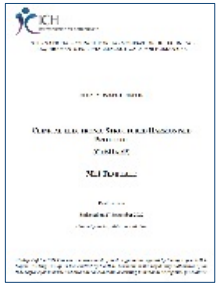


Acronyms
DDF: Digital Data Flow
USDM: Unified Study Definitions Model
ICH: International Council for Harmonisation
M11: Clinical electronic Structured Harmonised Protocol (CeSHarP)

And next …

ICH & M11 Specifications
Align when final public version released

ICH harmonisation for better health



cdisc 360i

USDM Phase 5
Stability. The foundation for CDISC 360i. Scoping ongoing.

PROJECT PRISM
A Regulatory Cloud Collaborative Initiative

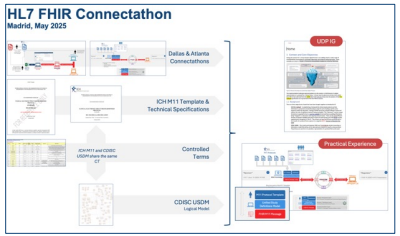
precisionFDA Regulatory Information Service Module
FDA-Industry Research Collaboration Agreement
(Public-Private Partnership)

FDA & PRISM
Working with FDA to pilot first electronic 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.

VULCAN~UDP



EMA, M11 & CTIS
Working with EMA to align USDM with CTIS

TransCelerate & Adoption
Sponsor and vendors working with USDM. Latest adoption will be visible at the TransCelerate 'Mission Possible' days in September

TransCelerate BIOPHARMA INC.

cdisc 25

October 2022

DDF 1

The first step in a journey. The base model providing an initial capability. Industry already pushing the boundaries of the model and using for a varied use cases

DDF 2

DDF 2 just starting. Focused on two major use cases: EDC and CPT but the model will be expanded in other areas.

Tipping Point?

When does the community recognise the benefits of an "electronic" study design / protocol? The "what is in it for me" question. There is a change management issue.

Short Term Gains

Where is the win? The tangible, short term, gains … CTMS, CT registries (e.g. CT.gov) and others

Longer Term Challenge

An eco-system of tools, APIs available off-the-shelf (the protocol API, the CTMS API …) supported by well-understood model(s).

Implications for the CDISC products driving the need for "integrated", "consistent" and "aligned" standards

Time

2022 | 2023 | 2024 | 2025 | 2026

Timeline indicative, NOT definitive

cdisc 360i

Thank You!

HL7 Connectathon, Atlanta, Sept 2024, College Football Hall of Fame

CDISC Team:

- Dave IH
- Richard Marshall
- Erin Muhlbradt
- John Owen
- Berber Snoeijer
- Craig Zwickl

Contacts:

Dave IH: diberson-hurst@cdisc.org
John Owen: jowen@cdisc.org

J Owen Email
Scan Me

DIH Email
Scan Me

DIH LinkedIn
Scan Me