Accelerating end to end automation with Digital Protocol

John Owen, Head, PMO, CDISC

PHUSE SDE, London, 10th February 2025

Meet the Speaker

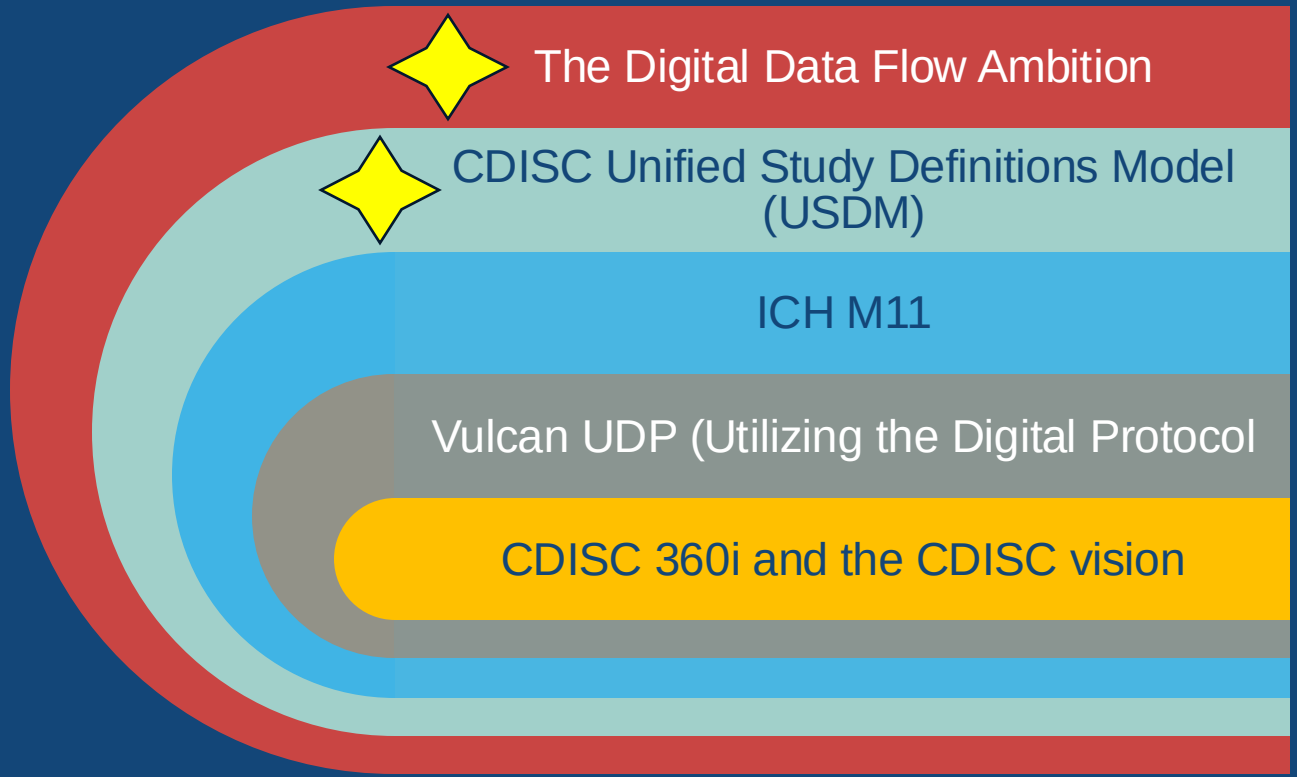
John Owen

Title: Head, PMO
Organization: CDISC

John Owen has worked with CDISC for over 9-years. After supporting the project management of various Therapeutic Area User Guides, John now also works in identifying and growing CDISC's development activities to advance standards across a wide range of therapeutic areas and heads up the CDISC Project Management Office.

John graduated from The University of Wales, Collage of Cardiff with a Bachelors Degree in Biology.

Working within the pharmaceutical industry in clinical data management, clinical programming, and standards development roles for the past 30 years.

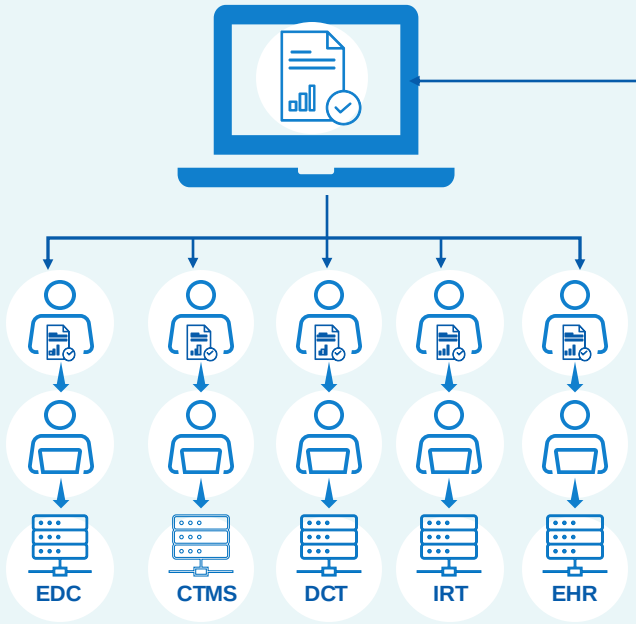

The Digital Data Flow Ambition
CDISC Unified Study Definitions Model (USDM)
ICH M11
Vulcan UDP (Utilizing the Digital Protocol
CDISC 360i and the CDISC vision

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

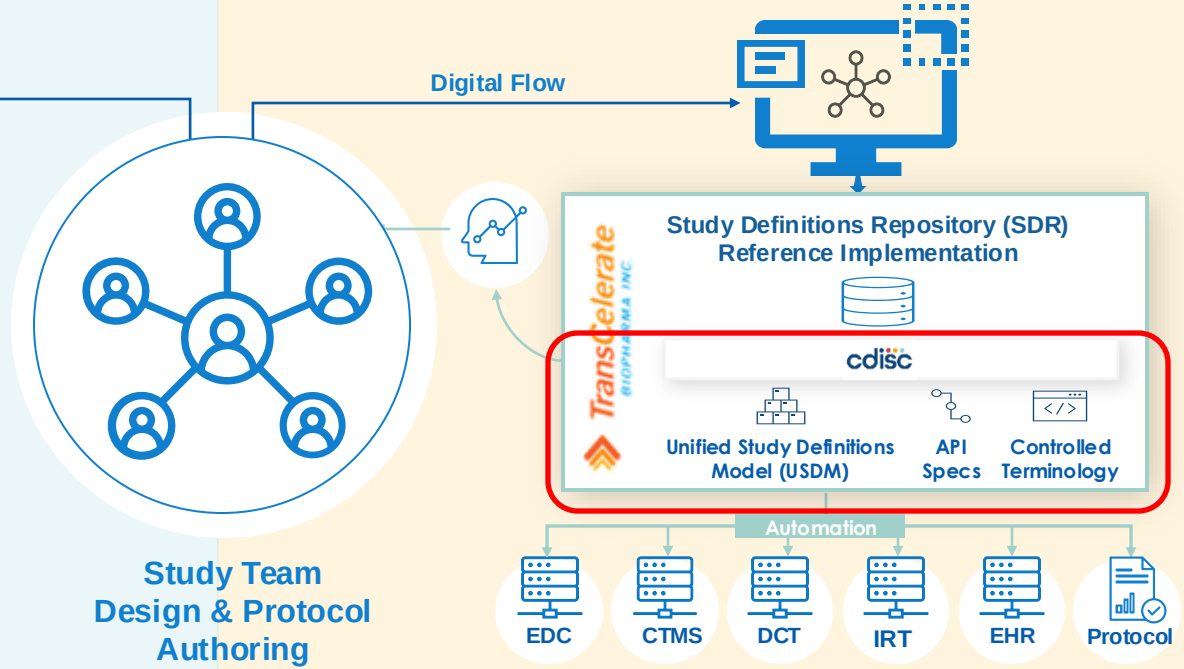
TransCelerate Digital Data Flow (DDF) Ambition

Write Once, Read Many

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



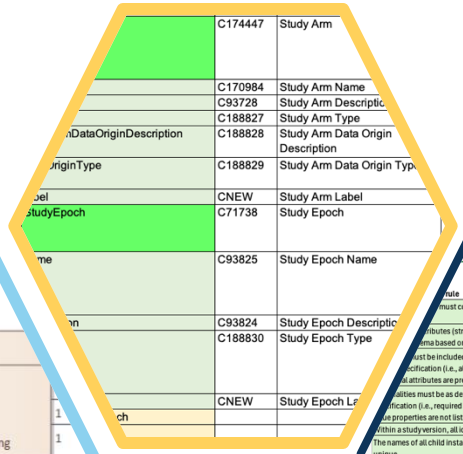
TOMORROW: Digital paradigm for protocol creation, with fully automated data flow and interoperability between systems



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		

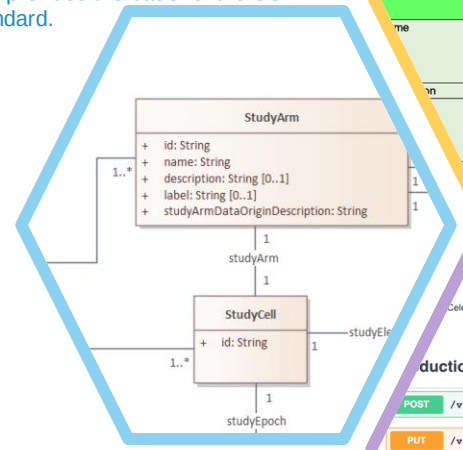
Examples

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-
```

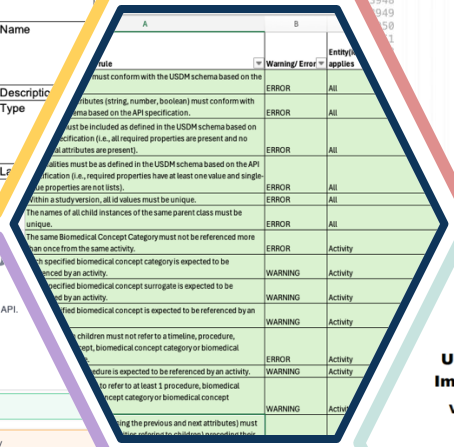
Logical Model

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



CORE Rules

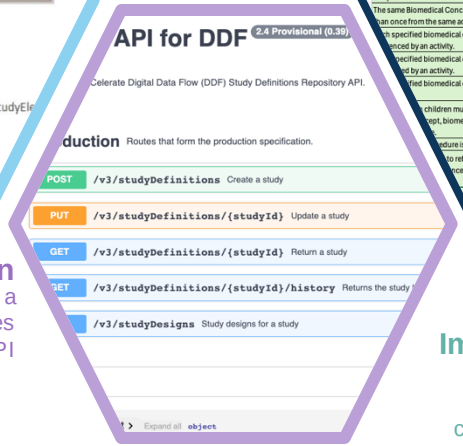
Specification of the rules that define USDM compliance



	A	B	
	ule	Warning/ Error	Entity(applies
	must conform with the USDM schema based on the	ERROR	All
	ibutes (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 cification (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 fication (i.e., required properties have at least one value and single- e 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
	ecified biomedical concept surrogate is expected to be ed by an activity.	WARNING	Activity
	ied 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
	edure 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		

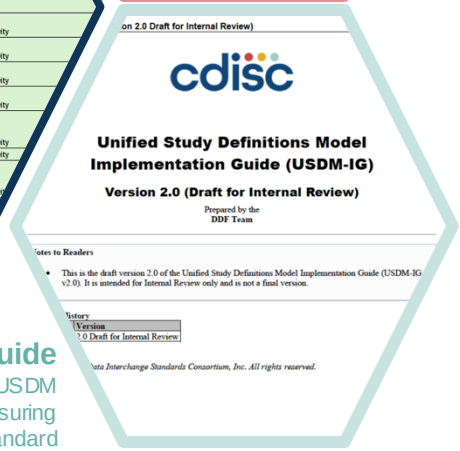
API Specification

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

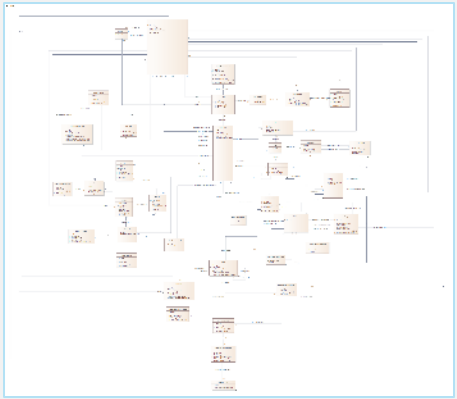


Implementation Guide

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



USDM Content



Controlled Terms

Study, Identifiers, Amendments

Estimands

Populations

Inclusion & Exclusion

Interventions & Indications

Objectives & Endpoints

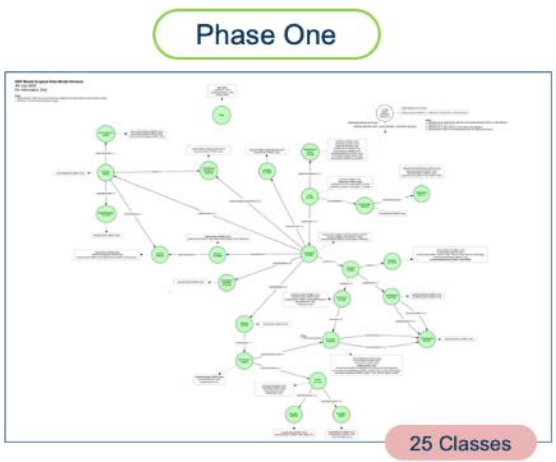
Unstructured Content

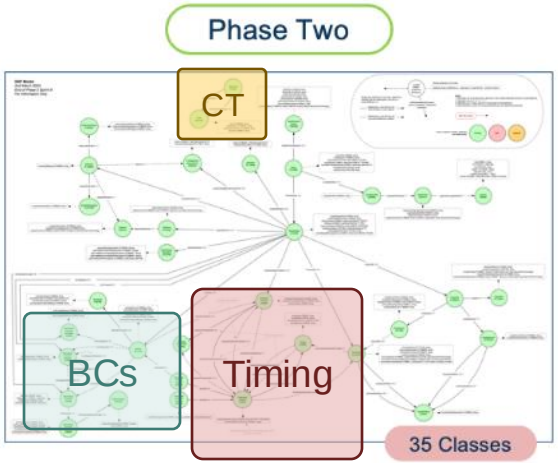
Study Designs, Arms, Epochs

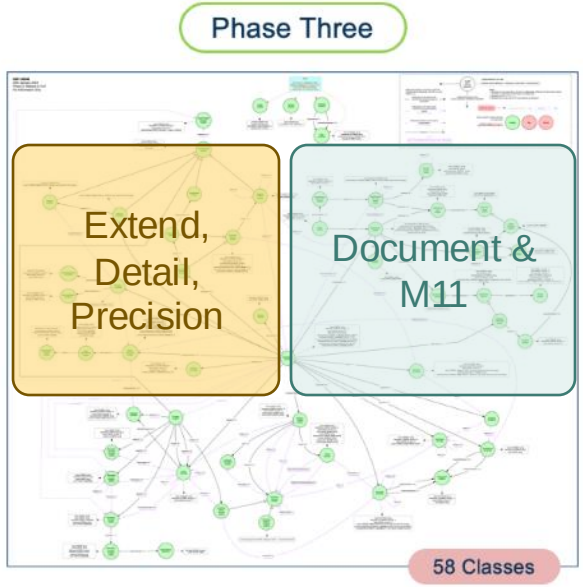
Detailed Study Logic, Encounters

Procedures, Biomedical Concepts

CDISC USDM: Phases One, Two and Three







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

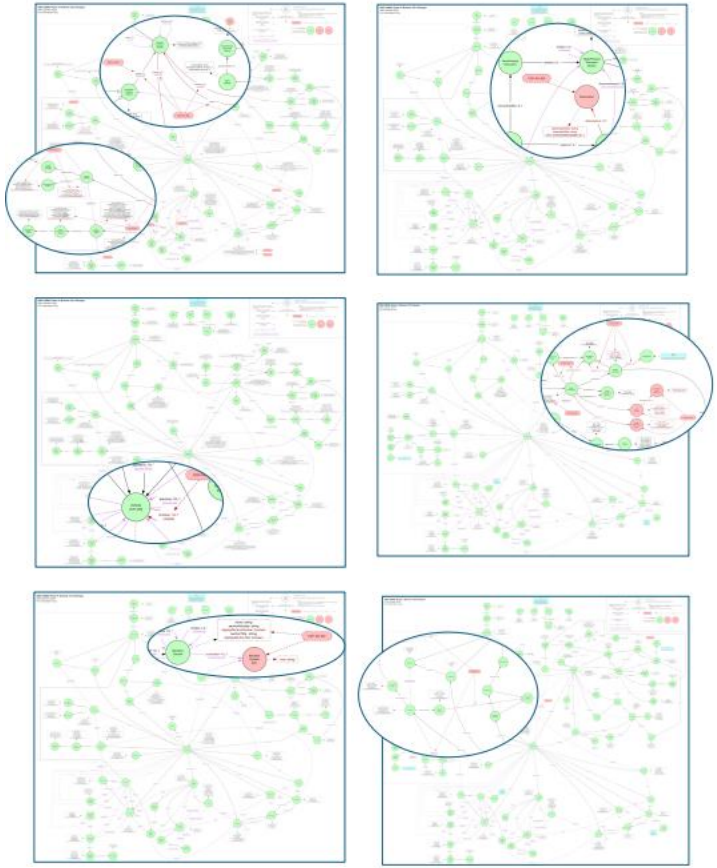
- Focused on the structured elements of the protocol, e.g. the Schedule of Activities (SoA) & Biomedical Concepts (BCs)
- The protocol document is still an external entity

- 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

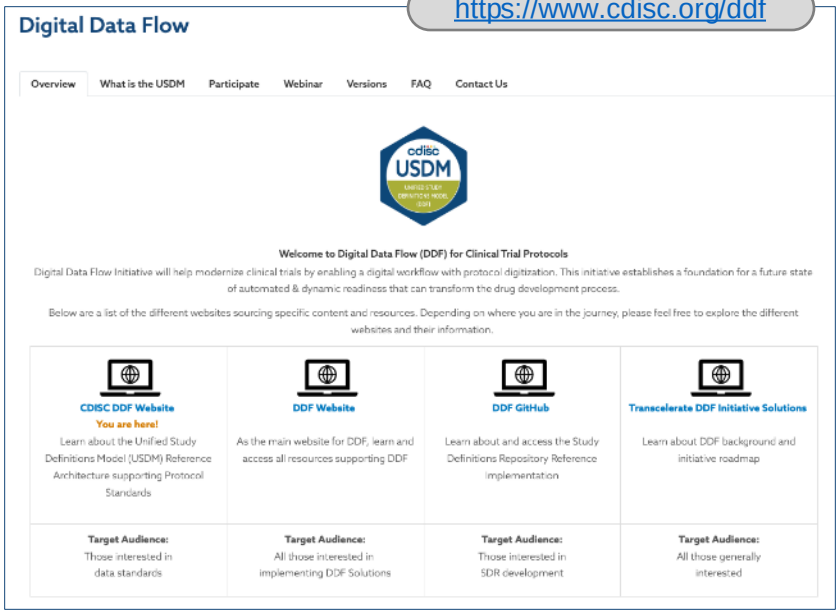
- More focus on refinement rather than new content
- Need to pay attention to backward compatibility
- Maximum alignment with ICH M11
- Conformance Rules now part of the standard

- 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



Example Resources – CDISC

https://www.cdisc.org/ddf

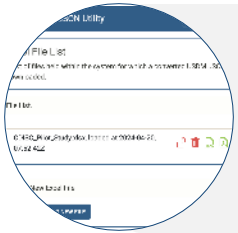


CDISC Github housing the USDM deliverables (model, CT, API etc) along with examples of protocols placed into USDM.

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/

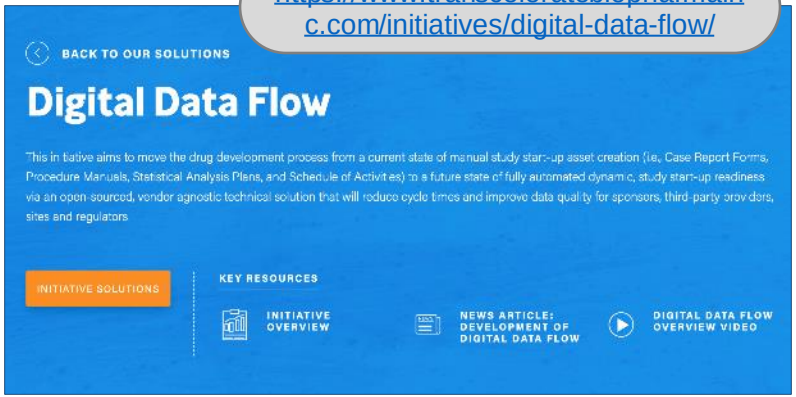


Web-based version of the USDM test tooling.

g
U: PHUSE
P: learning_usdm

Example Resources – TransCelerate

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

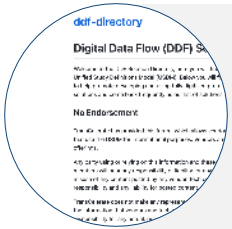


TransCelerate web page holding a significant number of DDF and USDM resources including the persona guides

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

USDM in Action
Use Cases Supporting the DDF Vision

TransCelerate BIOPHARMA INC.

cdisc

cdisc USDM UNIFIED STUDY DEFINITIONS MODEL (DDF)

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

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

Unified Study Definitions Model (USDM)

- Controlled Terms
- Unstructured Content
- Populations, Inclusion & Exclusion, Interventions & Indications, Estimands, Objectives & Endpoints
- Study, Identifiers, Amendments
- Study Designs, Arms, Epochs
- Procedures, Biomedical Concepts
- Detailed Study Logic, Encounters

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.

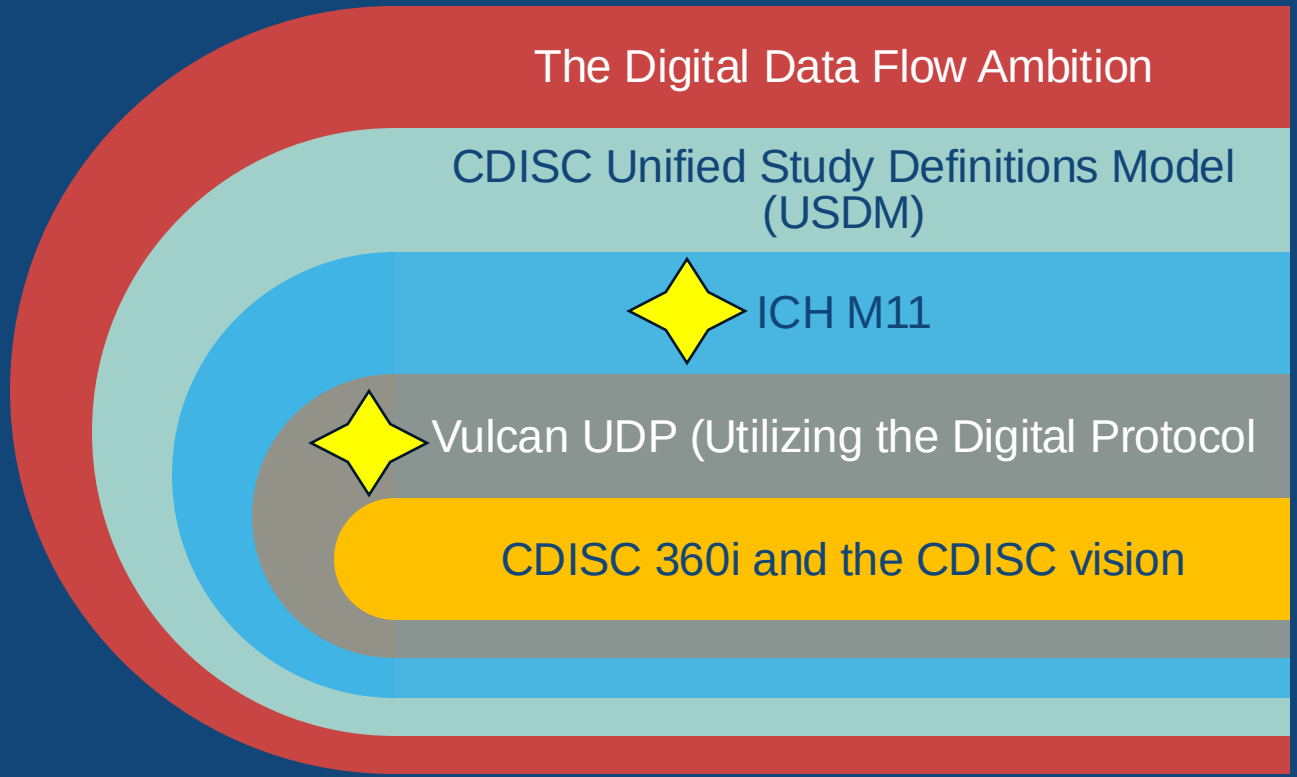
Unstructured Content
The ability to support one or more document presentations of the USDM content including the ICH M11 protocol template, sponsor templates and other documents.

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.

Version 5, 24th October 2024

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)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CDISC M2/M11 Engagement

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

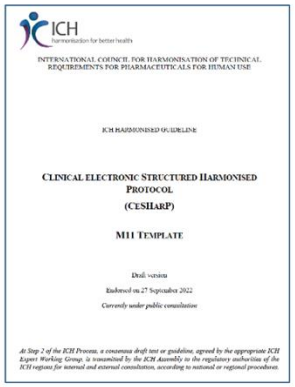
Draft version

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

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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 cons

At Step 2 of the ICH Process, a consensus draft text or ICH Expert Working Group, is transmitted by the ICH A of the ICH regions for internal and external consultat procedures.

Provides the technical re aligned with the guideline template

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.

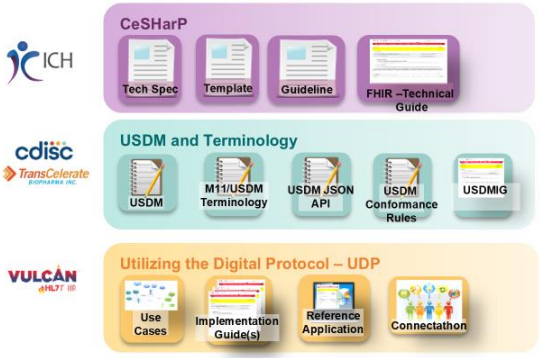
Goals

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.

cdisc ICH harmonisation for better health

ICH M11 and Vulcan Utilizing Digital Protocol (UDP)



Inputs:

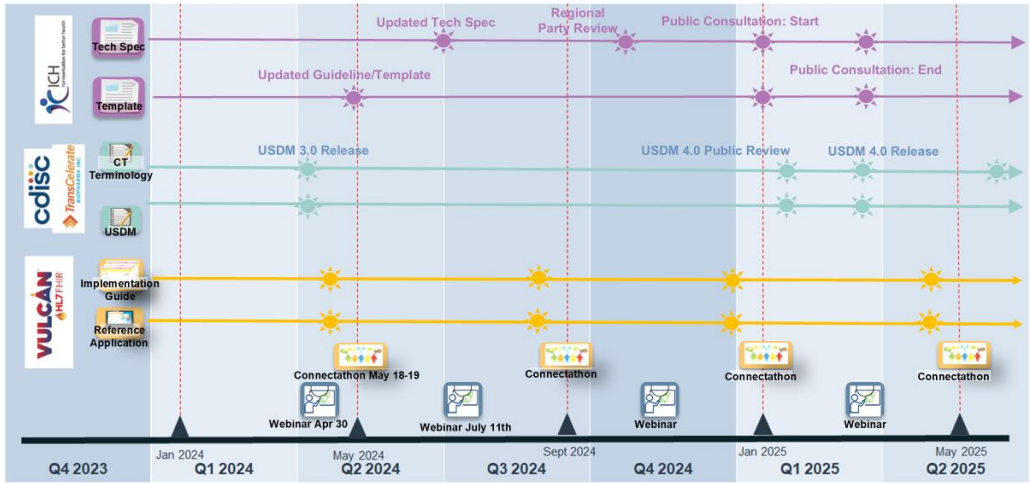
- ICH M11 template
- ICH M11 technical specification
- Models, definitions

FHIR will carry CDISC CT and USDM content

The technical specification can be used to develop other Implementation Guides

VULCAN ~UDP

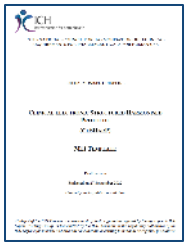
Timelines

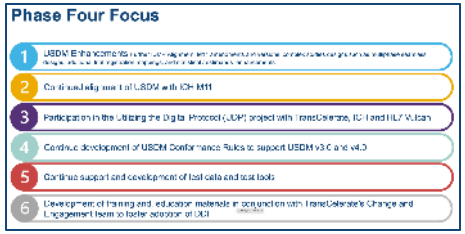


VULCAN

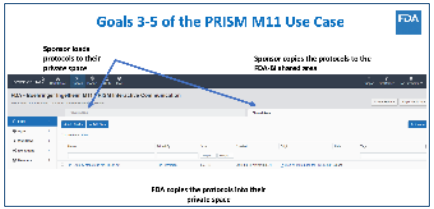
Status

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





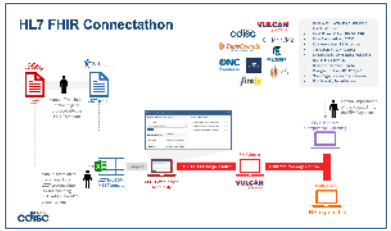
USDM Phase 4
Refine, improve, adopt



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

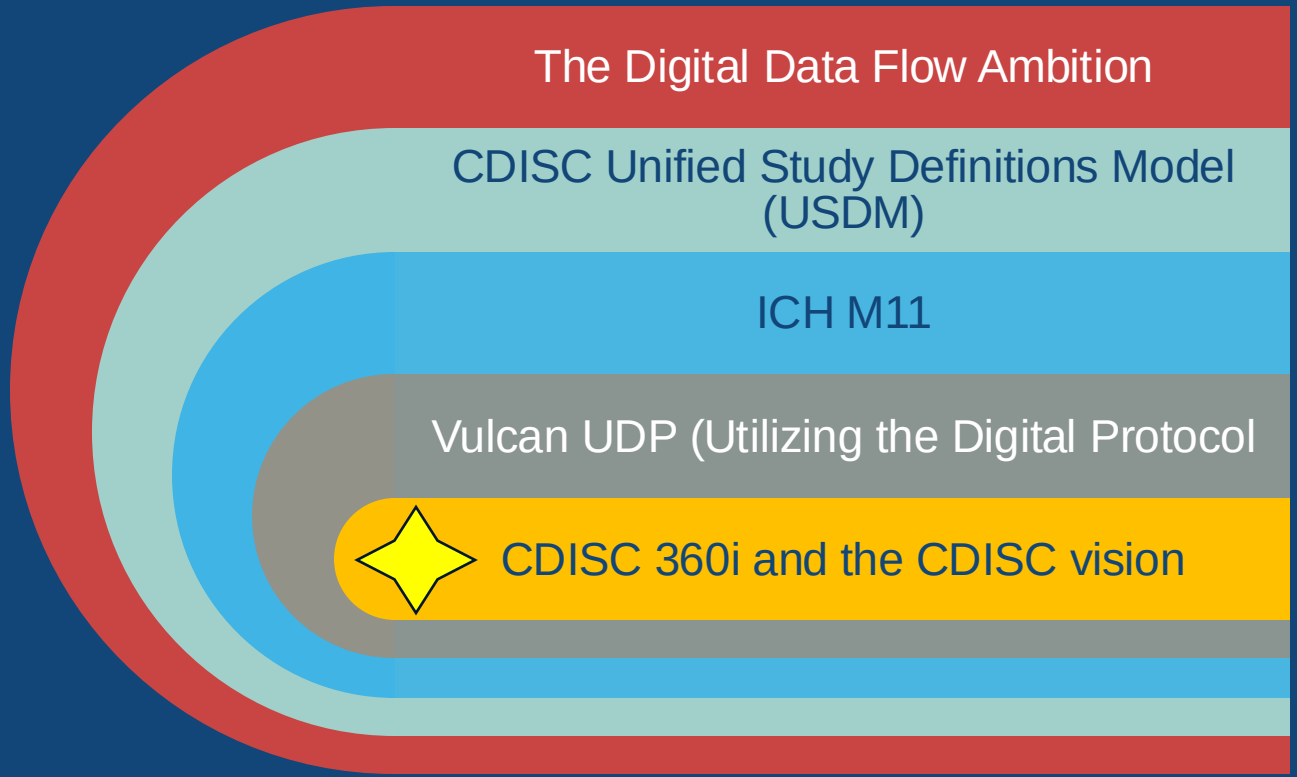
cdisc USDM
UNIFIED STUDY DEFINITIONS MODEL (DDF)

HL7 Vulcan & UDP
Working with HL7 Vulcan to build FHIR message to support exchange of USDM / M11 content.



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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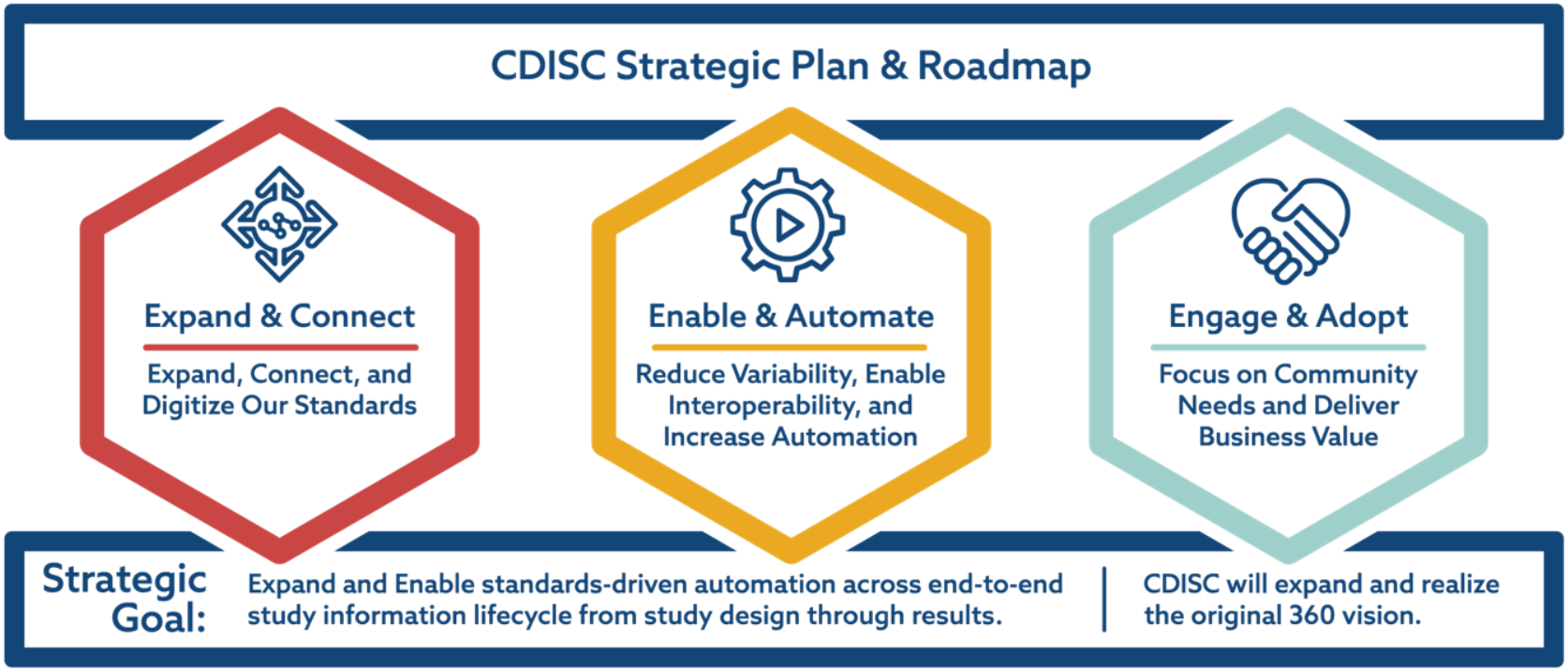
Realizing the CDISC Mission



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

360i Study Package

Metadata	Data	Software	Demonstration
• Publish a complete study metadata package that covers the full study data pipeline from study design through TLFs.	• Publish the complete set of raw datasets for the test study to execute the automated study data pipeline.	• Publish a pre-configured set of open-source software tools that consume the study metadata and data to execute the study design using the test data.	• Execute the study build and data pipeline automation in a Connectathon event to demonstrate generating analysis results from a study design.

Description of the End State

- 360i has published a complete preconfigured study package
- All the components defined in metadata from study design to submission
- Test data for the study
- Software to execute the study data pipeline to generate analysis results

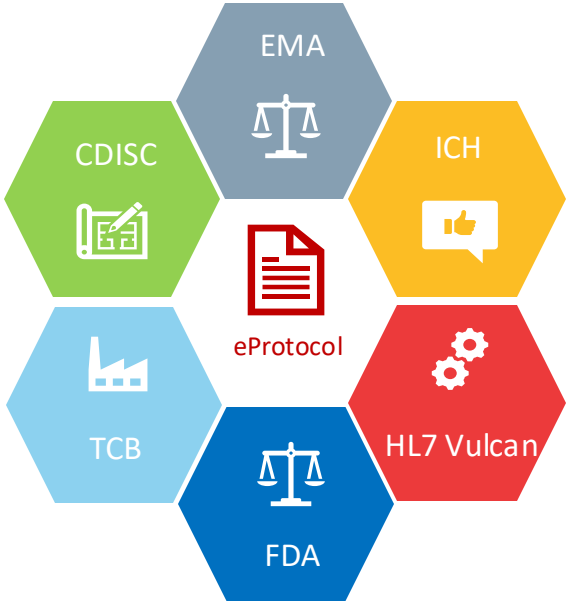
360i Webinar

Date: 18 February 2025

Time: , 4:00-5:30pm UK

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!