



2023
US
INTERCHANGE
FALLS CHURCH, VA | 18-19 OCTOBER



Digital Data Flow, Phase 3: The USDM meets M11

Dave Iberson-Hurst, CDISC Product Owner
18 Oct 2023, Version 3



Meet the Speaker

Dave Iberson-Hurst

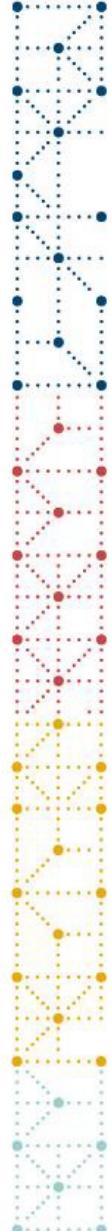
Title: Partner

Organization: d4k, Copenhagen

Dave has over 40 years' experience across several industries with the last 20 years spent in the pharmaceutical industry combining his technology and software development experience with clinical data standards.

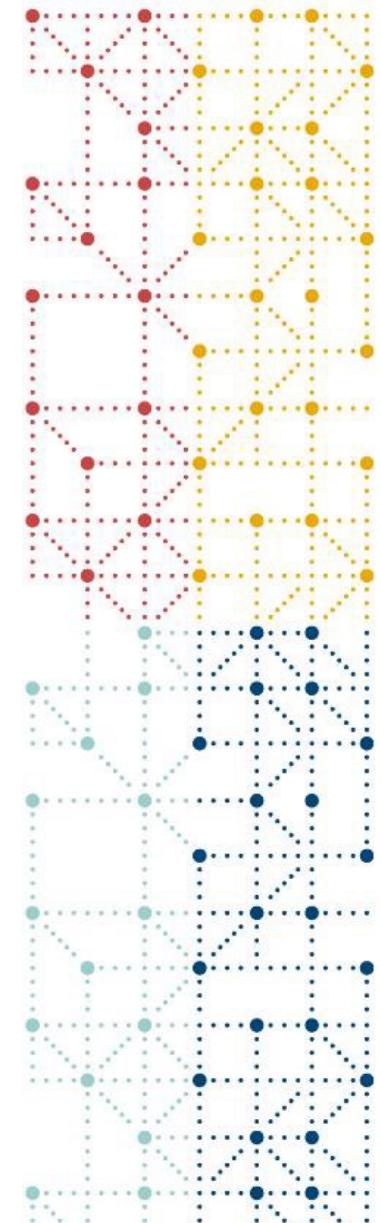
During this time, he has worked on, and led, several CDISC teams, co-led CDISC's eSource initiative (eSDI) and presented in many forums in Europe, the US, and elsewhere across the globe. He has worked closely with the FDA, EMA, HL7, ISO, and other standards organizations and was a member of CDISC's Blue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

He is a partner at data4knowledge in Copenhagen and is focused on getting greater value and utility from clinical trial data.



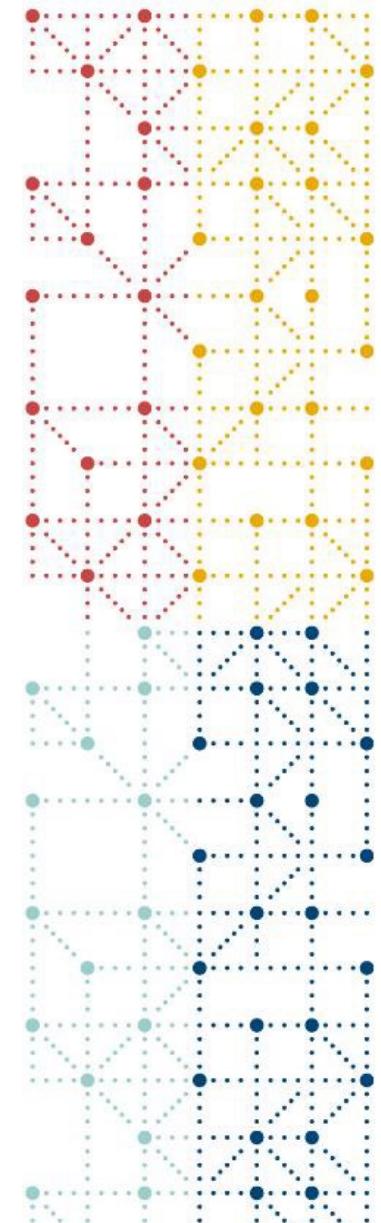
Disclaimer and Disclosures

- *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*



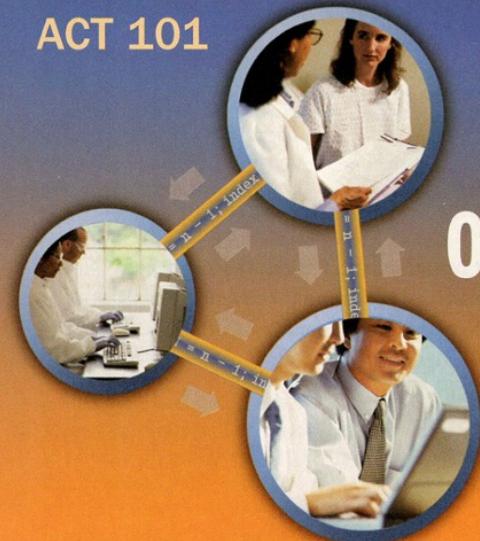
Agenda

1. Introduction
2. Digital Data Flow – The Project
3. Use Cases
4. Phase Three: USDM Meets M11
5. Summary



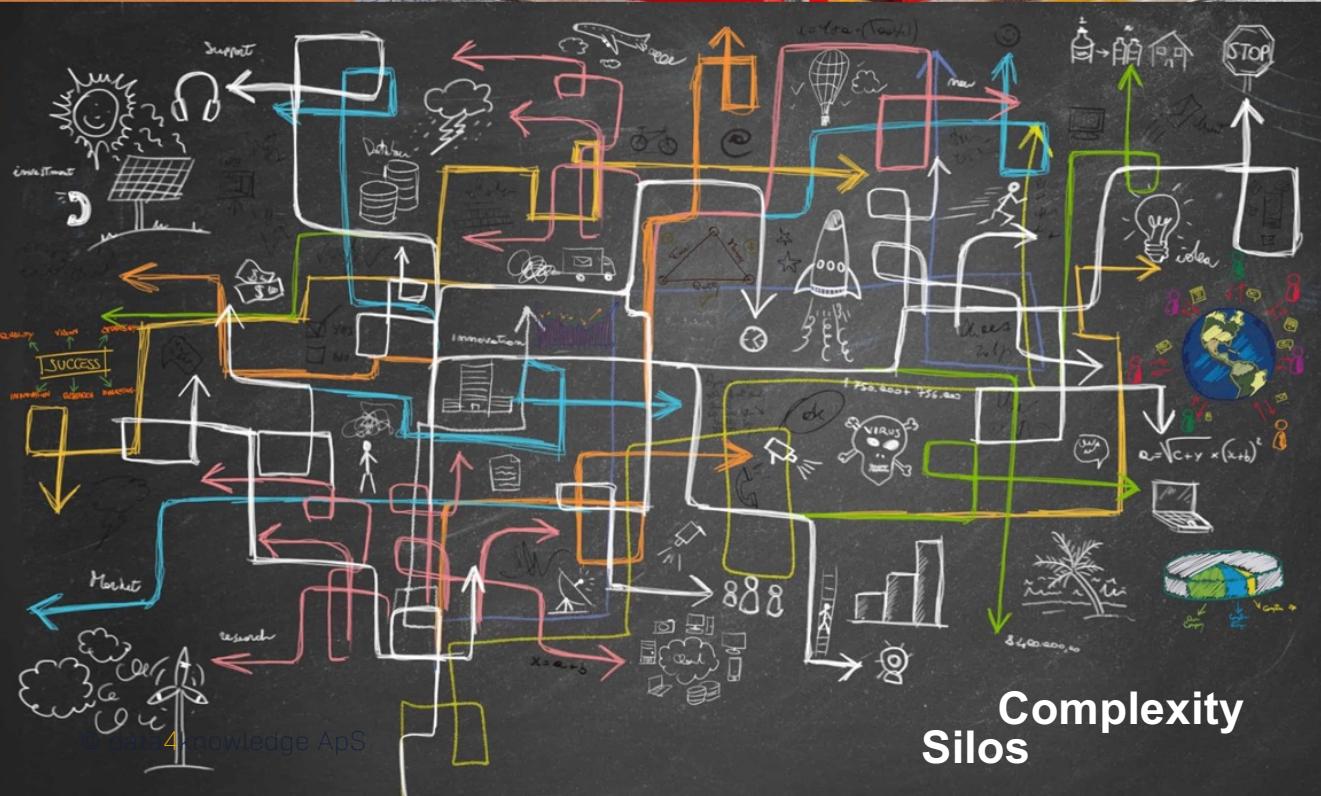
Introduction

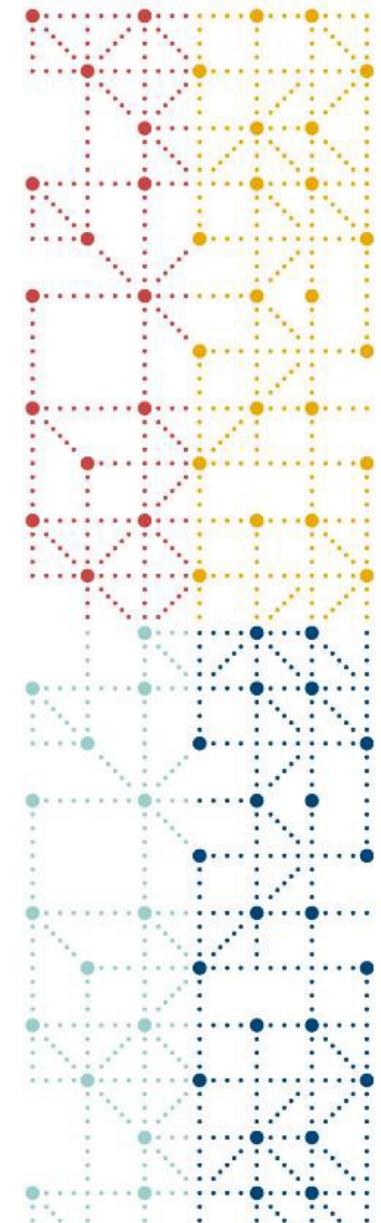
ACT 101



The CDISC Operational Data Model: Ready to Roll?

Dave Iberson-Hurst



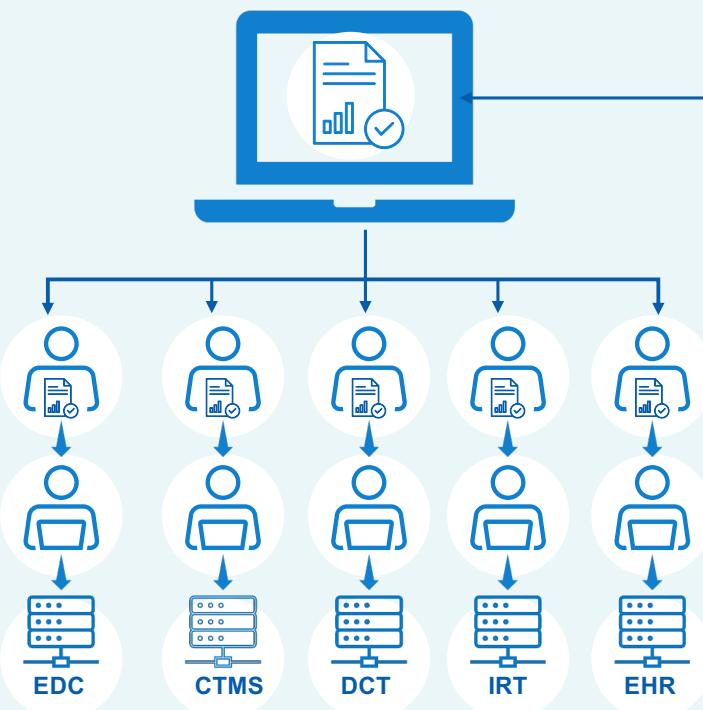


Digital Data Flow - The Project

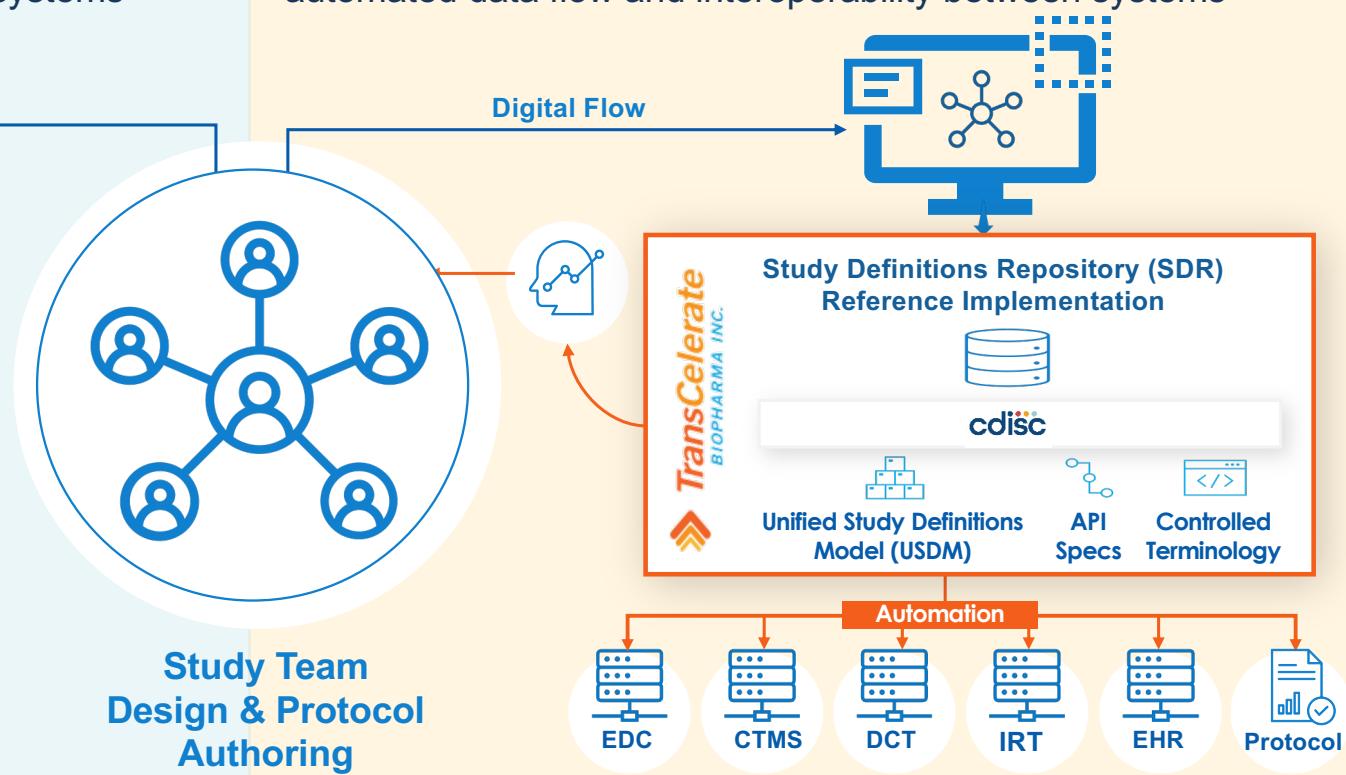
TransCelarate Digital Data Flow (DDF) Ambition

Write Once, Read Many

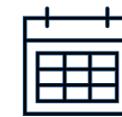
TODAY: Document-based paradigm for protocol creation, interpretation, and transcription into consuming systems



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



CDISC DDF Phase One



July 2021 – July 2022



Unified Study Definitions Model (USDM) Class Diagram

The UML class diagram (normative) as well as SQL Data Dictionary, Entity Relationship Diagram and example JSON output (informative)



Application Programming Interface (API) Specification

The API definition (normative) in JSON and HTML forms



CDISC Controlled Terminology

The controlled terminology (normative) developed for the project. Provided in an Excel format so as to be easily searched and filtered.



Reference Architecture Conformance Tests

Provided by the functionality provided by tools such as SwaggerHub and Postman



Essential Users Stories

The User Stories. PDF document



Architecture Principles

The architectural principles developed by the project. PDF Document



Supporting Materials

A set of informational materials in PDF format to help understand the deliverables being reviewed. PDF documents or references.



V1.0.0

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

9

CDISC DDF Phase Two



Oct 2022 – June 2023



Unified Study Definitions Model (USDM) Class Diagram

The UML class diagram (normative) as well as SQL Data Dictionary, Entity Relationship Diagram and example JSON output (informative)



Application Programming Interface (API) Specification

The API definition (normative) in JSON and HTML forms



CDISC Controlled Terminology

The controlled terminology (normative) developed for the project. Provided in an Excel format so as to be easily searched and filtered.



Test Files

Examples of USDM JSON files



Implementation Guide

Improved explanation of the model and its use, examples etc



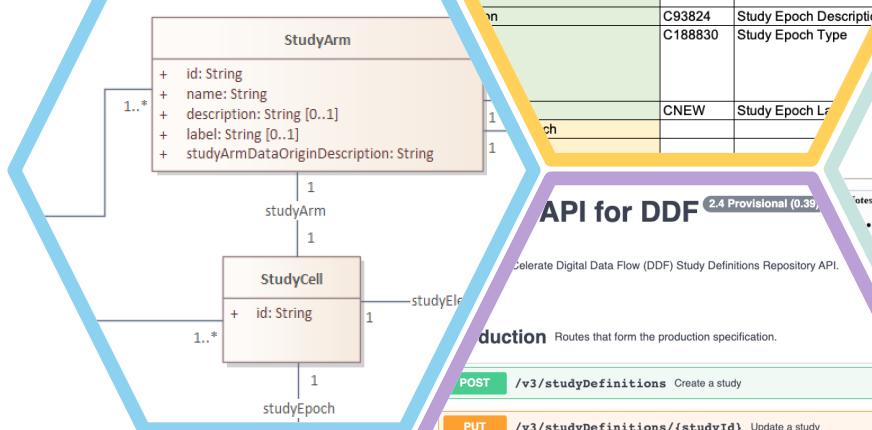
V2.0.0
<https://github.com/cdisc-org/DDF-RA>

10

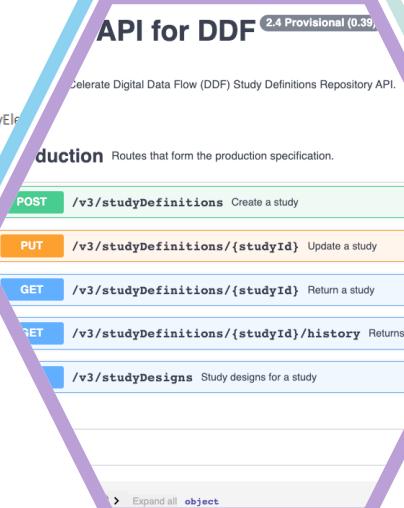
The USDM Standard

Logical Model

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



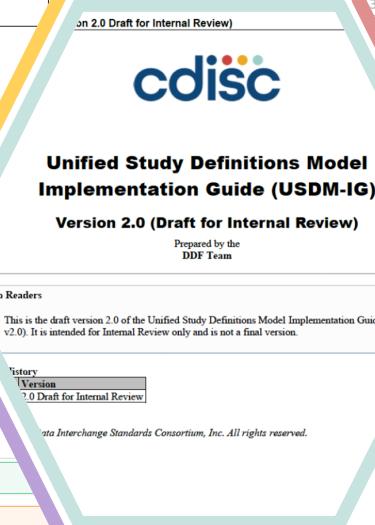
API Specification
Provides the means to exchange a single study between machines using a JSON API



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 Description
C188827	Study Arm Type
C188828	Study Arm Data Origin Description
C188829	Study Arm Data Origin Type
CNEW	Study Arm Label
C71738	Study Epoch
C93825	Study Epoch Name
C93824	Study Epoch Description
C188830	Study Epoch Type



```
studyArms: [
  {
    "id": "StudyArm_1",
    "name": "Placebo",
    "label": "...",
    "description": "Placebo",
    "type": {
      "id": "Code_61",
      "code": "C174268",
      "codeSystem": "http://www.cdisc.org",
      "codeSystemVersion": "2022-12-16",
      "decode": "Placebo Comparator Arm"
    },
    "studyArmDataOriginDescription": "Data collected from the study design or protocol",
    "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.org",
      "codeSystemVersion": "2022-12-16",
      "decode": "Active Comparator"
    }
  }
]
```

Examples

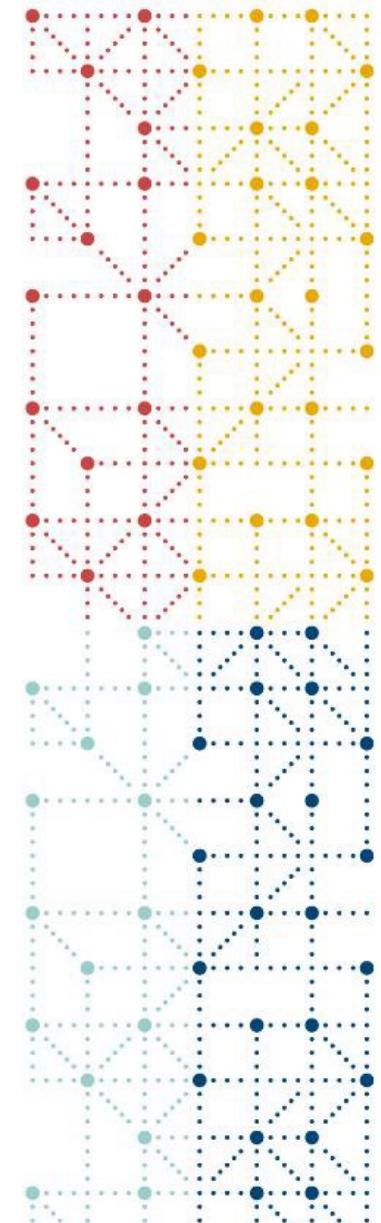
Example protocols implemented in the USDM with associated JSON files and visualisations

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

Choices ...

- Recreate the current world or look for something better?
- How radical do we wish to be?
- Don't just want to recreate the "paper world"
- Align with existing CDISC standards but not be constrained by them
- Don't reinvent the wheel
- Don't constrain implementations
- The project exposes the complexity of our world

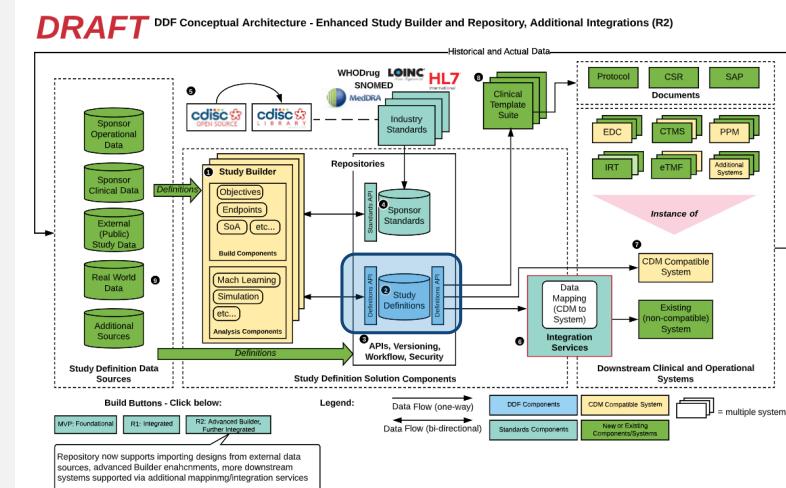




Use Cases

Use Cases: USDM with BCs allows for ...

Data Capture	Automate the setup of data capture systems ,incl. RWE, and capture the data.	CTMS, TMF ...	The provision of protocol information to down stream systems needing "study" information.
SoA	Use the study design to build the FHIR SoA message.	Query	Having multiple studies that have a common structure allows for data export and query across the set of studies
Data Import	Import data from a variety of sources . Can be re-exported thus allowing for conversion across versions.	SDTM	Automate the generation of SDTM datasets using the study design and BCs, including the "T" Domains
Common Protocol Template (CPT)	Generation of the CPT from a study design.		
Data Decay	Re-import data using the USDM as a framework to rebuild a study design & data using the SDTM Trial Design Domains.		
Scoring	The "scoring" of a study for such purposes as site impact, subject impact, environmental impact etc.		
Feasibility	The use of the design to determine study feasibility including subject recruitment. A study data template.		
CT Registry	The provision of study information to a CT registry.		
FAIR Data	The use of the design to aid Findability, Accessibility, Interoperability, and Reusability.		



Plus many more ...



USDM Adoption

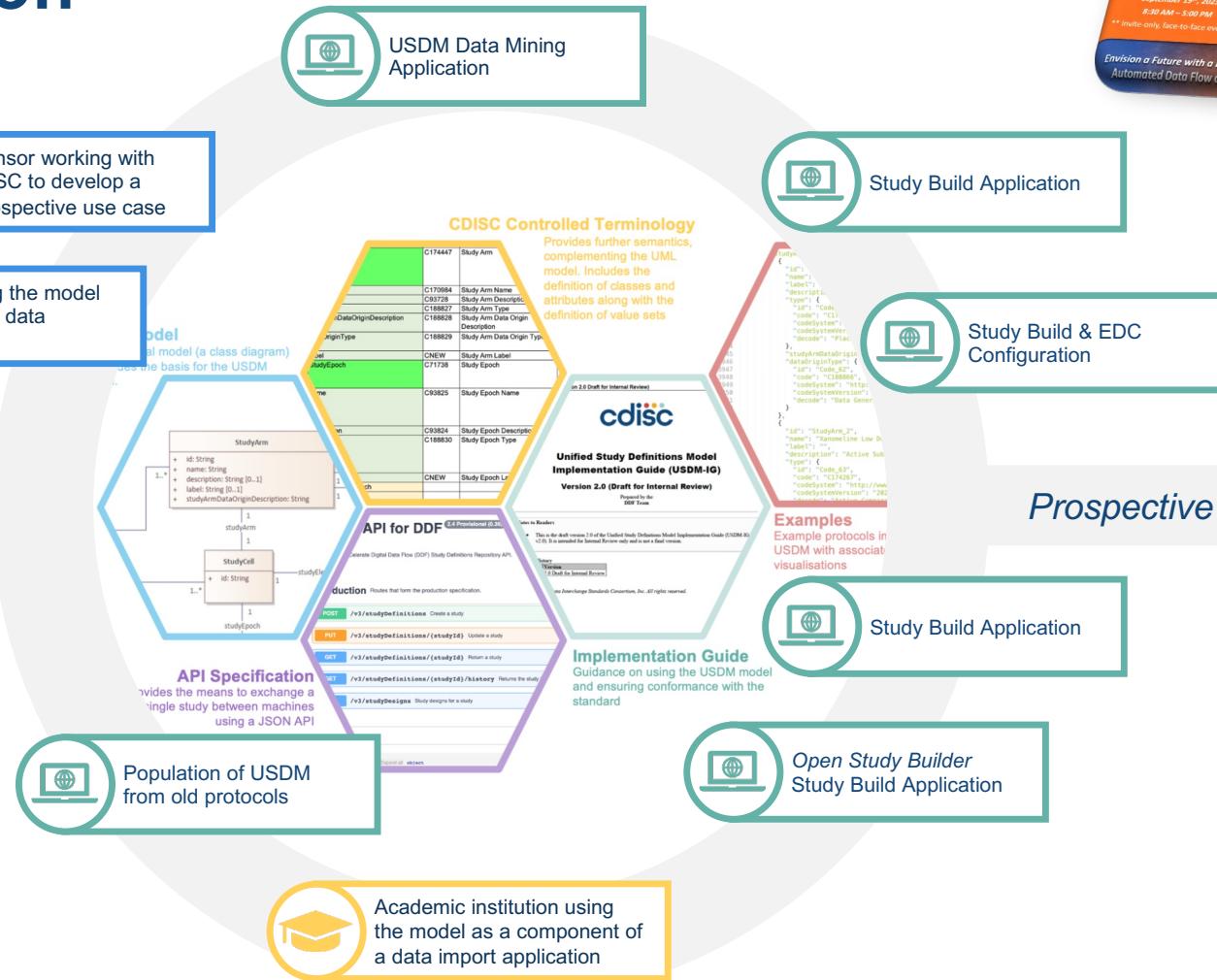


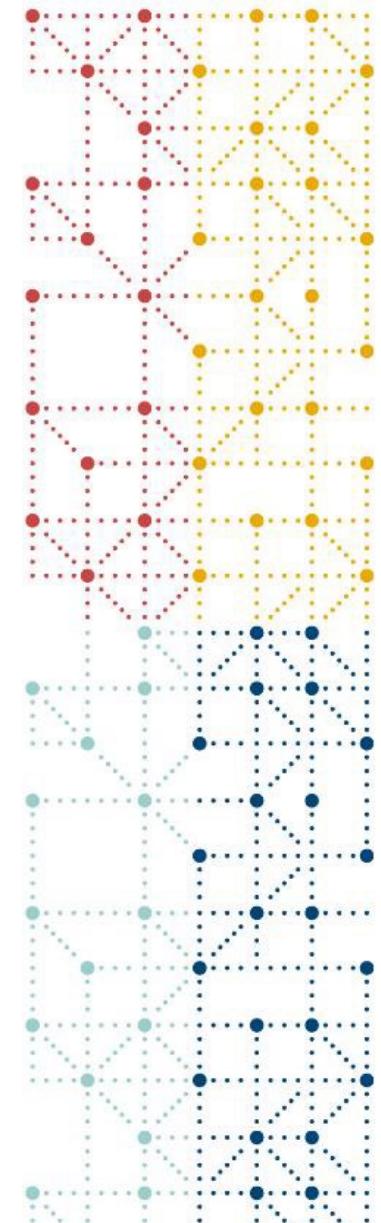
Retrospective has a lower risk as a first point of entry into using USDM

Retrospective Studies

The “footnote conundrum”

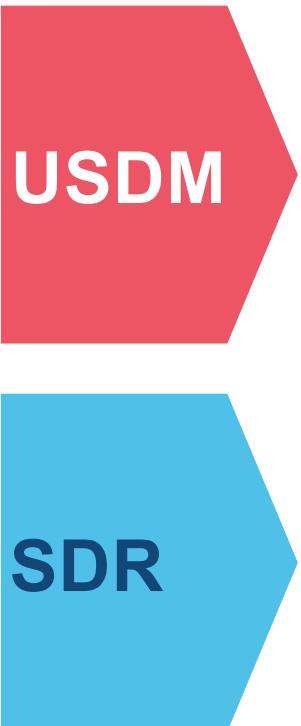
- Retrospective study re-creation brings a few challenges
- We are not constrained by the “2D” paper world. USDM enables an “improved” reconstruction.
- Sponsors need to consider their “philosophy”, their approach to “reconstruction” of protocols





Phase Three: USDM Meets M11

Next Steps – Phase Three



Slide from May 2023

1

- Baseline model for specifying a study in digital format
- Model supports use of a CRF link to specify which forms to use in EDC.
- Handles simple study designs

2

- Improved support for complex study designs with a fully specified digitized Schedule of Activities (SoA)
- Model supports the identification of the appropriate CRFs for data collection to enable automated, faster configuration via use of Biomedical Concepts
- Improved CPT alignment
- Initial 'T' Domain support

3

Focus for Phase 3 is currently being determined. Current expectations are:

- Expand ability to handle increasingly complex studies
- ICH M11 & CPT alignment

M11 Is ...

ICH CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL (CeSHarP)

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



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



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

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



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

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

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

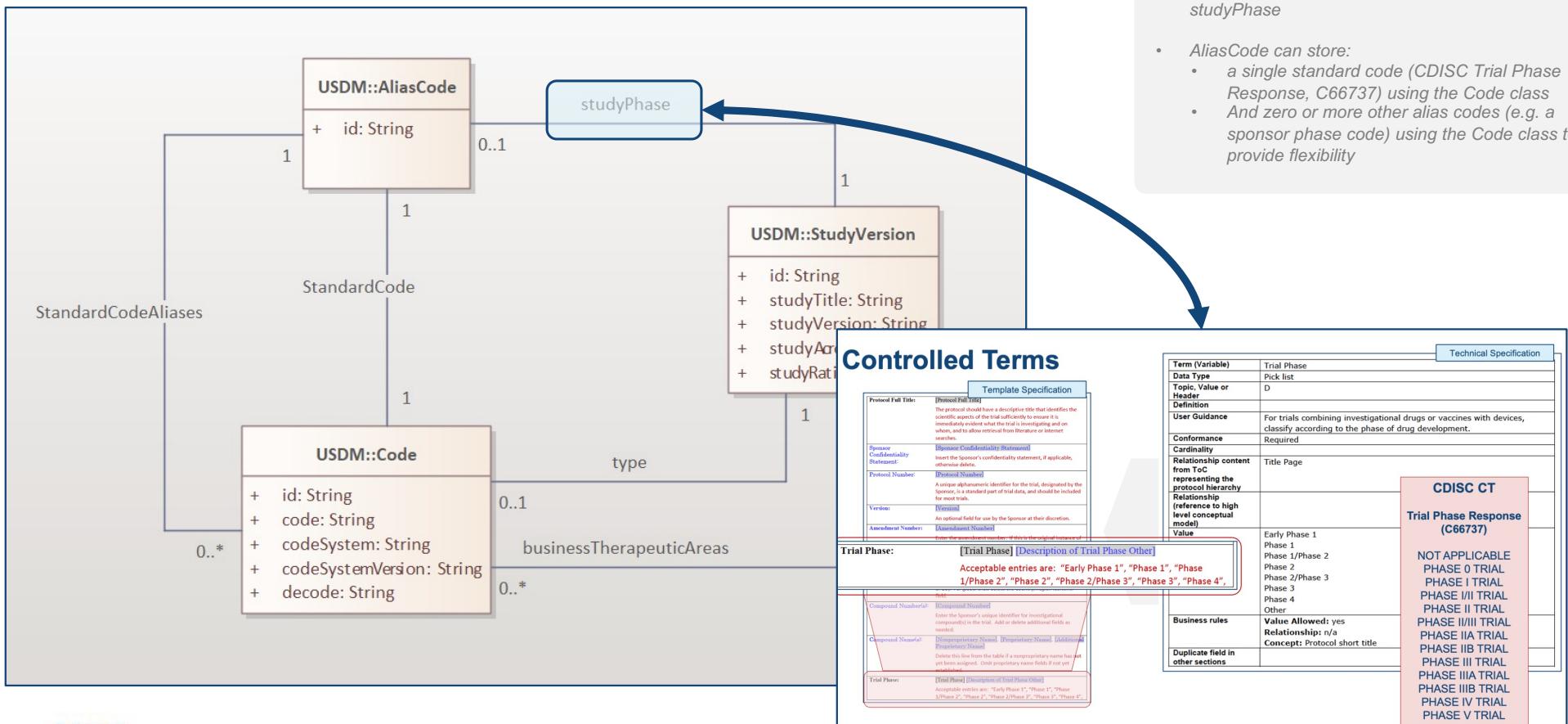
Template Specification	
Protocol Full Title:	[Protocol Full Title] The protocol should have a descriptive title that identifies the scientific aspects of the trial sufficiently to ensure it is immediately evident what the trial is investigating and on whom, and to allow retrieval from literature or internet searches.
Sponsor Confidentiality Statement:	[Sponsor Confidentiality Statement] Insert the Sponsor's confidentiality statement, if applicable, otherwise delete.
Protocol Number:	[Protocol Number] A unique alphanumeric identifier for the trial, designated by the Sponsor, is a standard part of trial data, and should be included for most trials.
Version:	[Version] An optional field for use by the Sponsor at their discretion.
Amendment Number:	[Amendment Number] Enter the amendment number, if this is the original instance of
Trial Phase: [Trial Phase] [Description of Trial Phase Other] Acceptable entries are: "Early Phase 1", "Phase 1", "Phase 1/Phase 2", "Phase 2", "Phase 2/Phase 3", "Phase 3", "Phase 4",	
Compound Number(s):	[Compound Number] Enter the Sponsor's unique identifier for investigational compound(s) in the trial. Add or delete additional fields as needed.
Compound Name(s):	[Nonproprietary Name], [Proprietary Name], [Additional Proprietary Name] Delete this line from the table if a nonproprietary name has not yet been assigned. Omit proprietary name fields if not yet established.
Trial Phase:	[Trial Phase] [Description of Trial Phase Other] Acceptable entries are: "Early Phase 1", "Phase 1", "Phase 1/Phase 2", "Phase 2", "Phase 2/Phase 3", "Phase 3", "Phase 4".

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

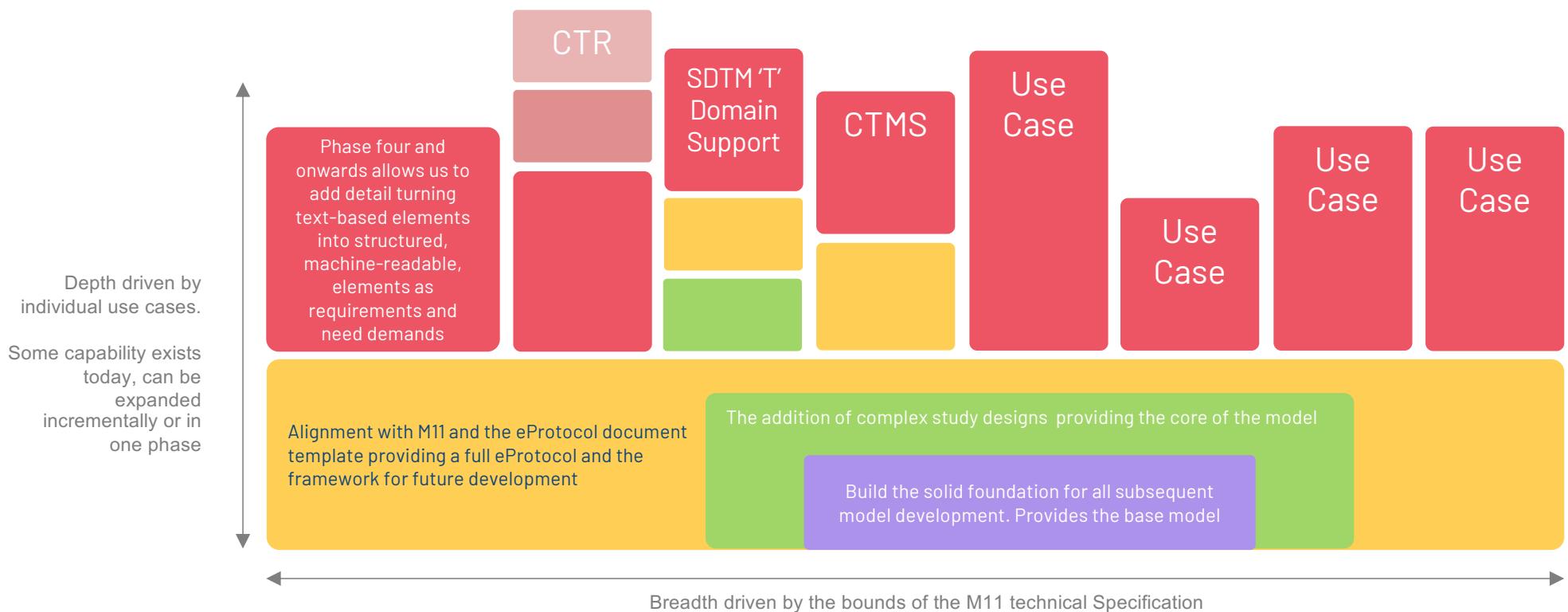
CDISC CT
Trial Phase Response (C66737)

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

Put Into Context ... the USDM

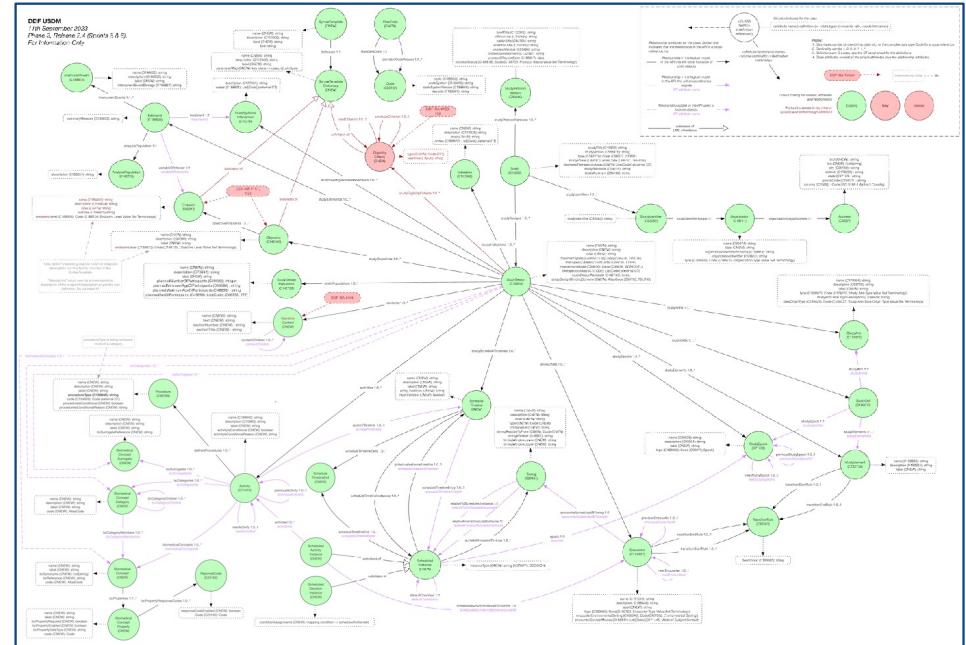


Breadth versus Depth



Shift of Focus

- Phases One & Two
 - Focused on the structured elements of the protocol, e.g. the Schedule of Activities (SoA)
 - The protocol document was an external entity into which the structured content could be exported
- Phase Three
 - Now contains structured and unstructured elements
 - The entire protocol document is held within the USDM
 - Allows for the protocol document to be generated from the model



M11 Template Example Document

- First attempt to create a protocol document from the USDM, both structured [non-narrative] and unstructured [narrative text] content.
- Functionality has been added to the Excel test data tool
- More work is needed, this is very much a first draft



The screenshot shows a section of a protocol document titled "5 TRIAL POPULATION". The page includes a red diagonal stamp with the text "VERY DRAFT". At the top right, there is a link "Document doesn't look right? We'll help you out!" and a "DOCUMENT" button. The section is divided into three subsections: "5.1 Selection of Trial Population", "5.2 Rationale for Trial Population", and "5.3 Inclusion Criteria".

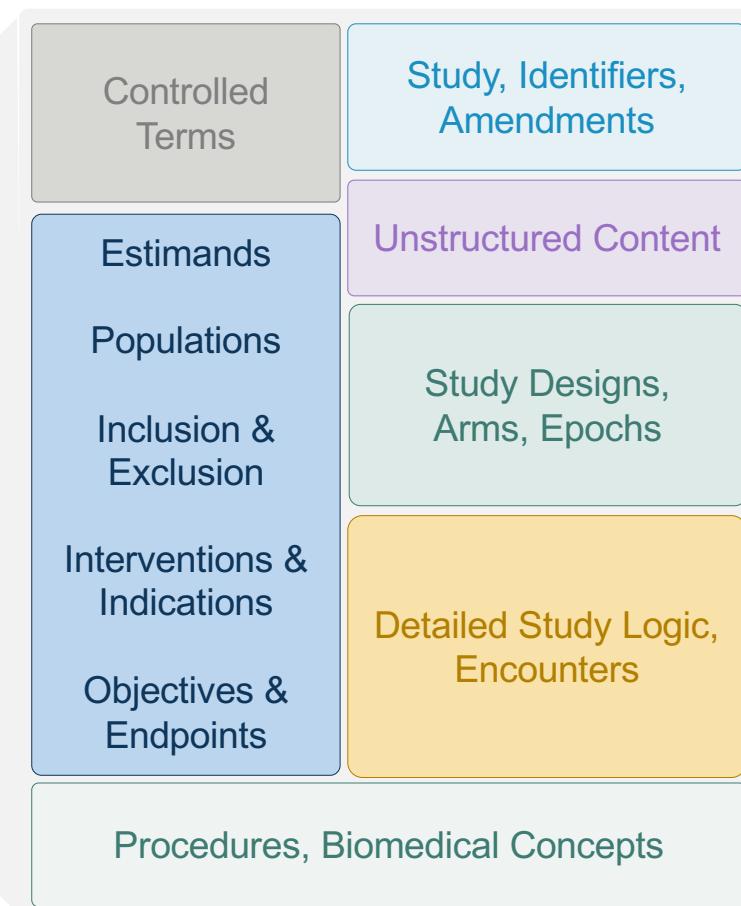
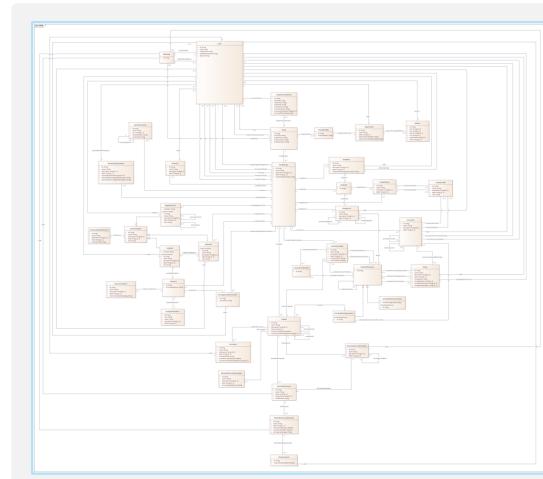
5.3 Inclusion Criteria

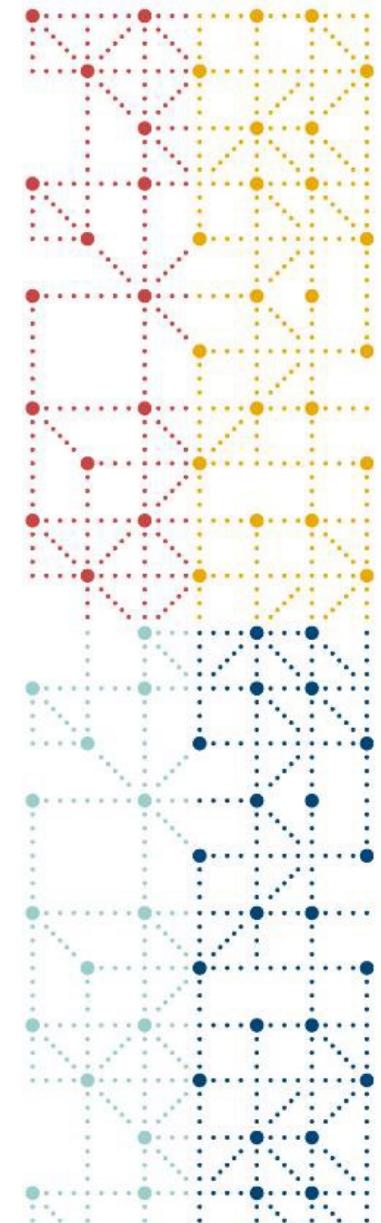
Patients may be included in the study only if they meet all the following criteria:

- [1] Males and postmenopausal females at least 50 years of age.
- [2] Diagnosis of probable AD as defined by National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) guidelines (Attachment LZZT.7).
- [3] MMSE score of 10 to 23.
- [4] Hachinski Ischemic Scale score of ≤4 (Attachment LZZT.8).
- [5] CNS imaging (CT scan or MRI of brain) compatible with AD within past 1 year. The following findings are incompatible with AD:
 - a. Large vessel strokes
 1. Any definite area of encephalomalacia consistent with ischemic necrosis in any cerebral artery territory.
 2. Large, confluent areas of encephalomalacia in parieto-occipital or frontal regions consistent with watershed infarcts. The above are exclusionary. Exceptions are made for small areas of cortical asymmetry which may represent a small cortical stroke or a focal area of atrophy provided there is no abnormal signal intensity in the immediately underlying parenchyma. Only one such questionable area allowed per scan, and size is restricted to ≤1cm in frontal/parietal/temporal cortices and ≤2 cm in occipital cortex.
 - b. Small vessel ischemia
 1. Lacunar infarct is defined as an area of abnormal intensity seen on CT scan or on both T1 and T2 weighted MRI images in the basal ganglia, thalamus or deep white matter which is ≤1 cm in maximal diameter. A maximum of one lacune is allowed per scan.
 2. Leukoariosis or leukoencephalopathy is regarded as an abnormality seen on T2 but not T1 weighted MRIs, or on CT. This is accepted if mild or moderate in extent, meaning involvement of less than 25% of cortical white matter.

USDM Summary

- Structured content along with the ability to hold unstructured content





Summary

M11 & The CDISC Project

Phase Three Timeline

- January 2024
 - Phase 3 development sprints complete
- February 2024
 - Phase 3 public review
- April 2024
 - Version 3 USDM published

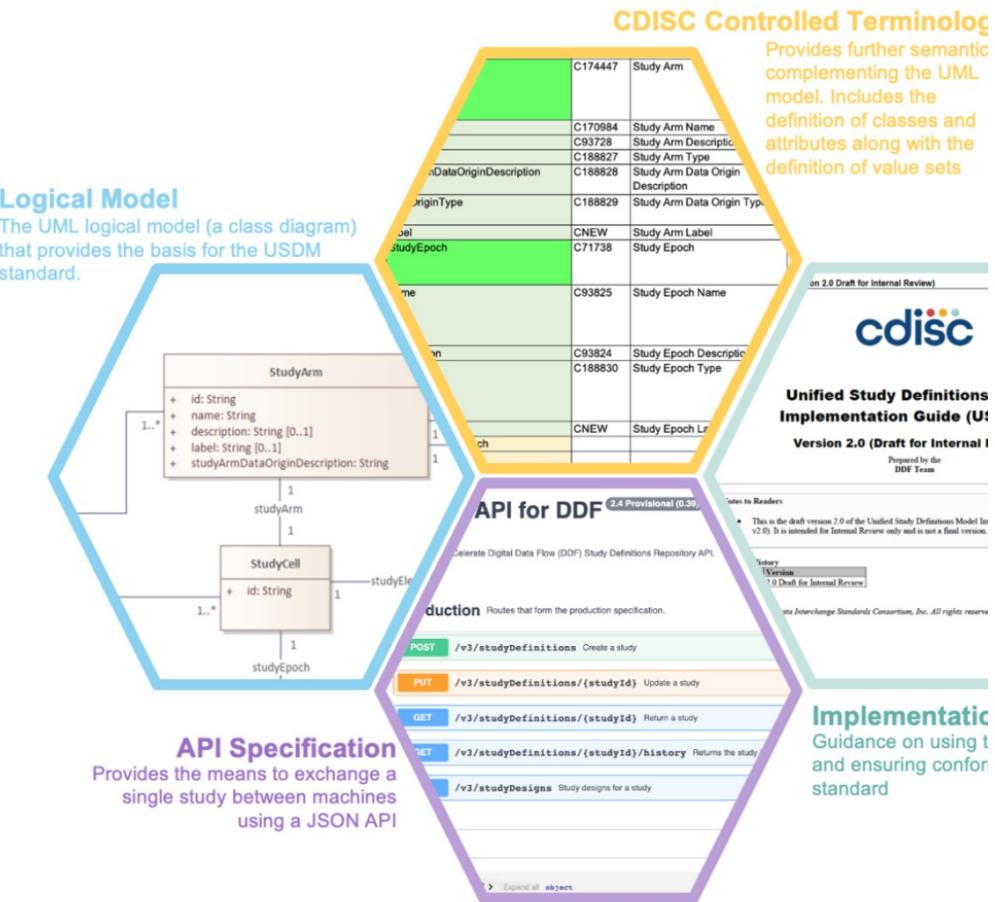
Dates may be adjusted to align with ICH M11 publication dates.

M11 next version expected early in 2024 with formal release towards the end of 2024



Summary

- We are “understanding” the complexity
- We can start to remove the silos and join the dots
- Digital Data Flow / Unified Study Definitions Model (DDF/USDM) fills an important gap
- USDM is but one building block, but an important one
- USDM alignment with ICH M11 will be an important step forward
- Can support various use cases, the prospective versus the retrospective
- We are only limited by our imagination



Thank You

Contacts:

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

Link:

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

Team:

- Gerry Campion
- Drew Mills
- Erin Muhlbradt
- John Owen
- Jared Schreibman
- Berber Snoeijer
- Craig Zwickl

PHUSE EU Connect, Sunday 5th November

Hands-on Workshop

Mastering USDM Standards with an
Interactive Demo and Hands-on Workshop

