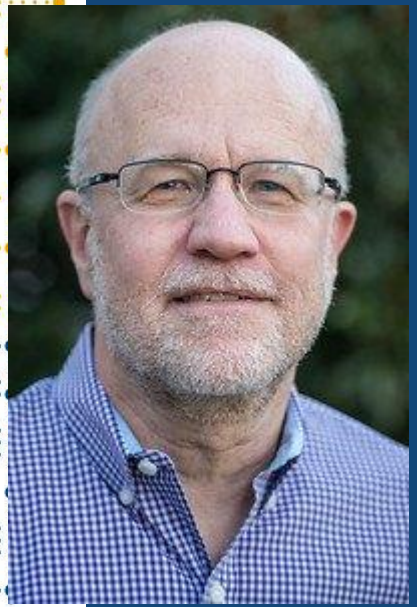
ICH M11, What Does this Really Mean to TMF?

Presented by William Illis, Novartis & TransCelerate

Meet the Speaker



Bill Illis

Workstream Lead, DDF
TransCelerate Biopharma
&
Executive Director, Technology & Scientific Computing
Advanced Quantitative Sciences
Novartis

Bill is all in on innovating the way clinical trials work for the benefit of patients worldwide. For the past several years he has led the Digital Data Flow initiative at the pharmaceutical industry consortium, TransCelerate. Recognizing the foundational nature of clinical trial protocols, this work is centered removing analog inefficiencies by building transformative industry-wide interoperability through the development and adoption of digital protocol standards in collaboration with CDISC.

Focused on sustainable and impactful innovation Bill has over 25 years of industry experience leading the design and implementation of impactful changes in teams, line functions and enterprise programs in the areas across healthcare R&D

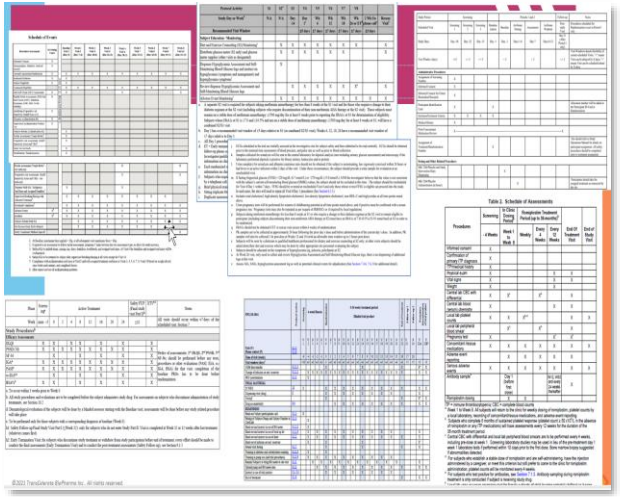
Disclaimer and Disclosures

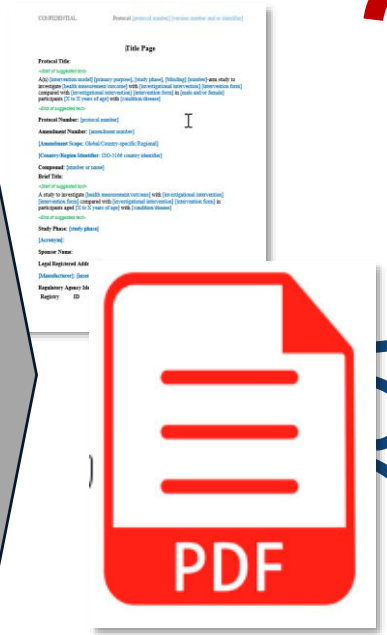
- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

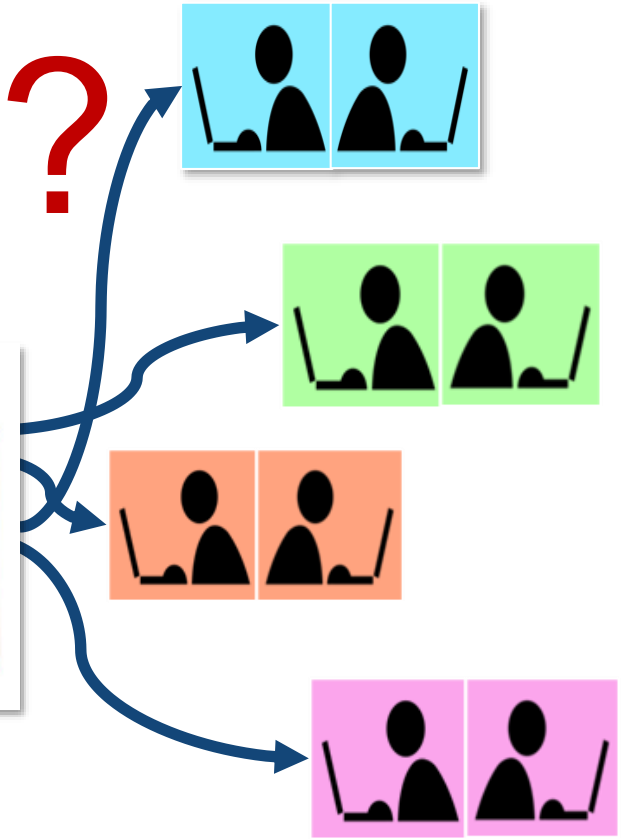
Agenda

Clinical Study Protocols

Broken...



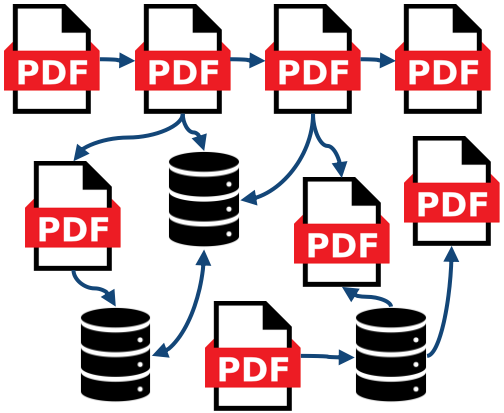




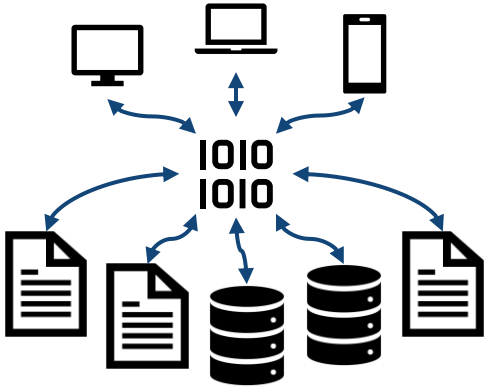
Why Digital Data Flow? – The Vision

Break the Document Paradigm

From document-first



To data-first



ICH M11 / (CeSHarP)
Clinical electronic Structured Harmonized Protocols

Protocols

- Important document that describes the processes and procedures directing the conduct and analysis of a clinical study
- **Format and core content** of study protocols vary from sponsor to sponsor, making interpretation difficult for its users (Medical Writers, monitors, Study Sites, Regulators, ethicists…)
- Regulators receive protocols in many different formats

Problem

- No internationally harmonized standard template for the format and content to support **consistency** across sponsors and **exchange of protocol information.**
- Lack of harmonisation contributes to **inefficiencies** and **difficulties** in reviewing and assessing clinical protocols by regulators, sponsors, ethical oversight bodies, investigators, and other stakeholders.

Source: ICH M11: A Critical Enabler for Clinical Trial Transformation, EMA, Noemi Manet, 21-May-2025

M11 Deliverables

Guideline

Provides background, purpose, and scope as a guideline


ICH

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

Template

Provides written format for the Interventional Clinical Trial Protocol Template


ICH

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

Technical Specifications

Provides technical representation aligned with the guideline and template


ICH

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

Guideline

- Explains the need, outlines development

Template

- Specifies headers, common text, instructions, data fields, and terminologies.

Technical Specification

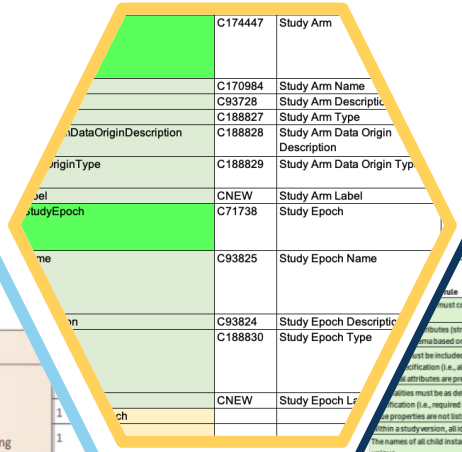
- open, nonproprietary standard to enable electronic exchange of clinical protocol information

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

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 Descriptic
	C188827	Study Arm Type
DataOriginDescription	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 Descriptic
	C188830	Study Epoch Type
	CNEW	Study Epoch La
ch		

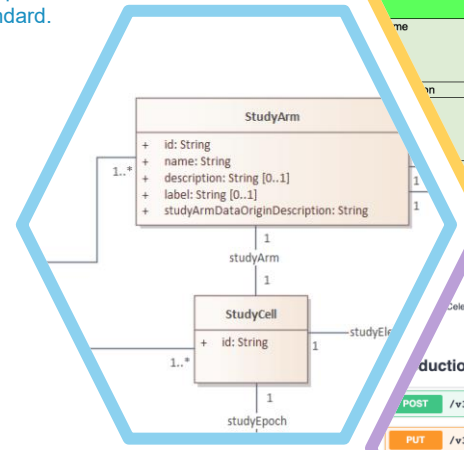
Examples

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-
```

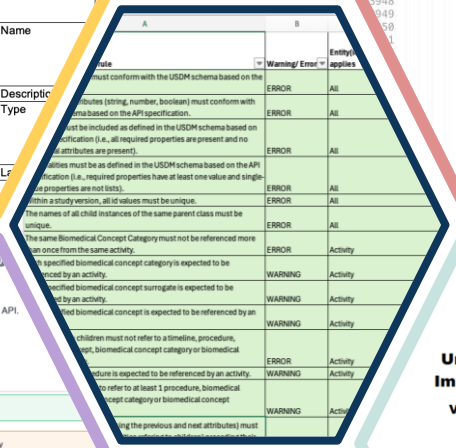

Logical Model

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



CORE Rules

Specification of the rules that define USDM compliance



Rule	Warning/ Error	Entity 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
st 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 ification (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
specified biomedical concept category is expected to be nced by an activity.	WARNING	Activity
ecified biomedical concept surrogate is expected to be d 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, pt, biomedical concept category or biomedical	ERROR	Activity
dure is expected to be referenced by an activity.	WARNING	Activity
o refer to at least 1 procedure, biomedical cept category or biomedical concept	WARNING	Activ
ing the previous and next attributes] must		

API for DDF

2.4 Provisional (0.39)

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

duction Routes that form the production specification.

POST	/v3/studyDefinitions	Create a study
PUT	/v3/studyDefinitions/{studyId}	Update a study
GET	/v3/studyDefinitions/{studyId}	Return a study
ET	/v3/studyDefinitions/{studyId}/history	Returns the study
	/v3/studyDesigns	Study designs for a study

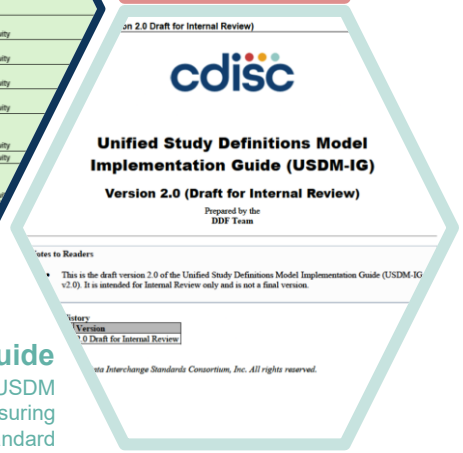
Expand all object

API Specification

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

Implementation Guide

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



on 2.0 Draft for Internal Review)

cdisc

Unified Study Definitions Model Implementation Guide (USDM-IG)

Version 2.0 (Draft for Internal Review)

Prepared by the DDF Team

otes to Readers

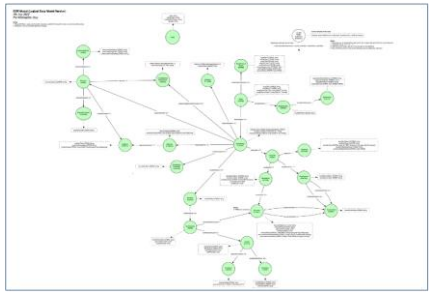
- This is the draft version 2.0 of the Unified Study Definitions Model Implementation Guide (USDM-IG v2.0). It is intended for Internal Review only and is not a final version.

Version
2.0 Draft for Internal Review

ata Interchange Standards Consortium, Inc. All rights reserved.

CDISC DDF / USDM, Phases One to Four

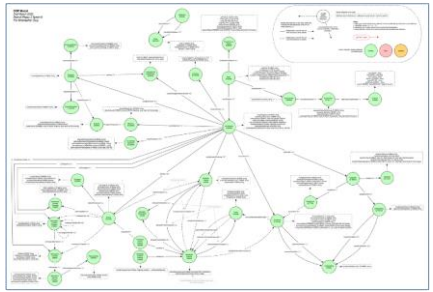
Phase One



25 Classes

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

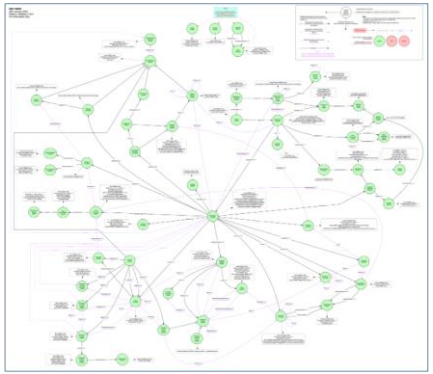
Phase Two



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

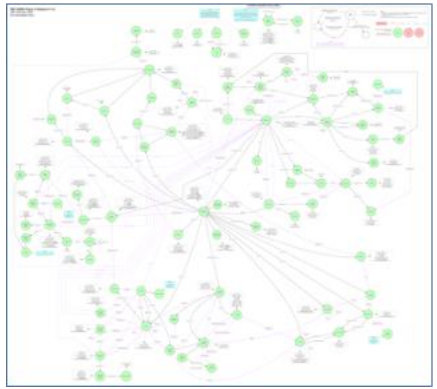
Phase Three



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



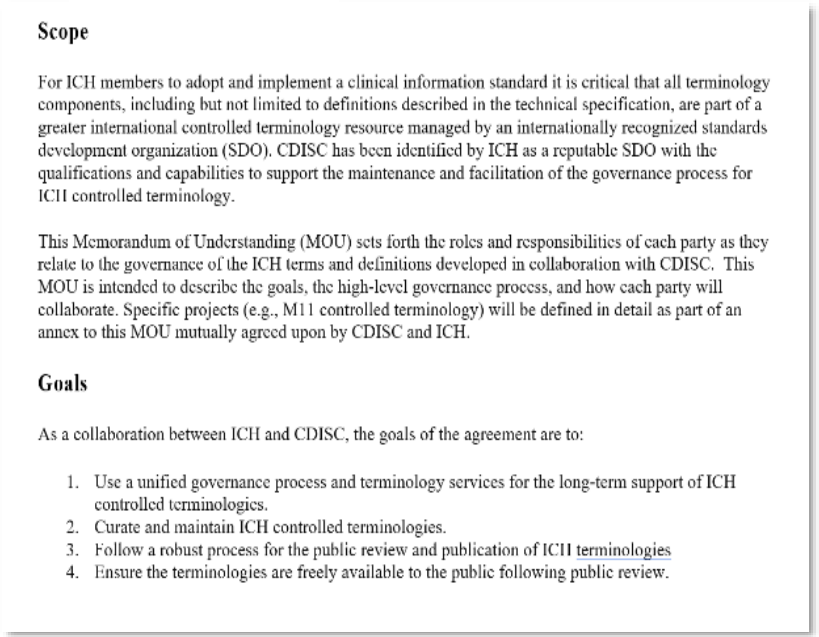
89 Classes

- **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

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
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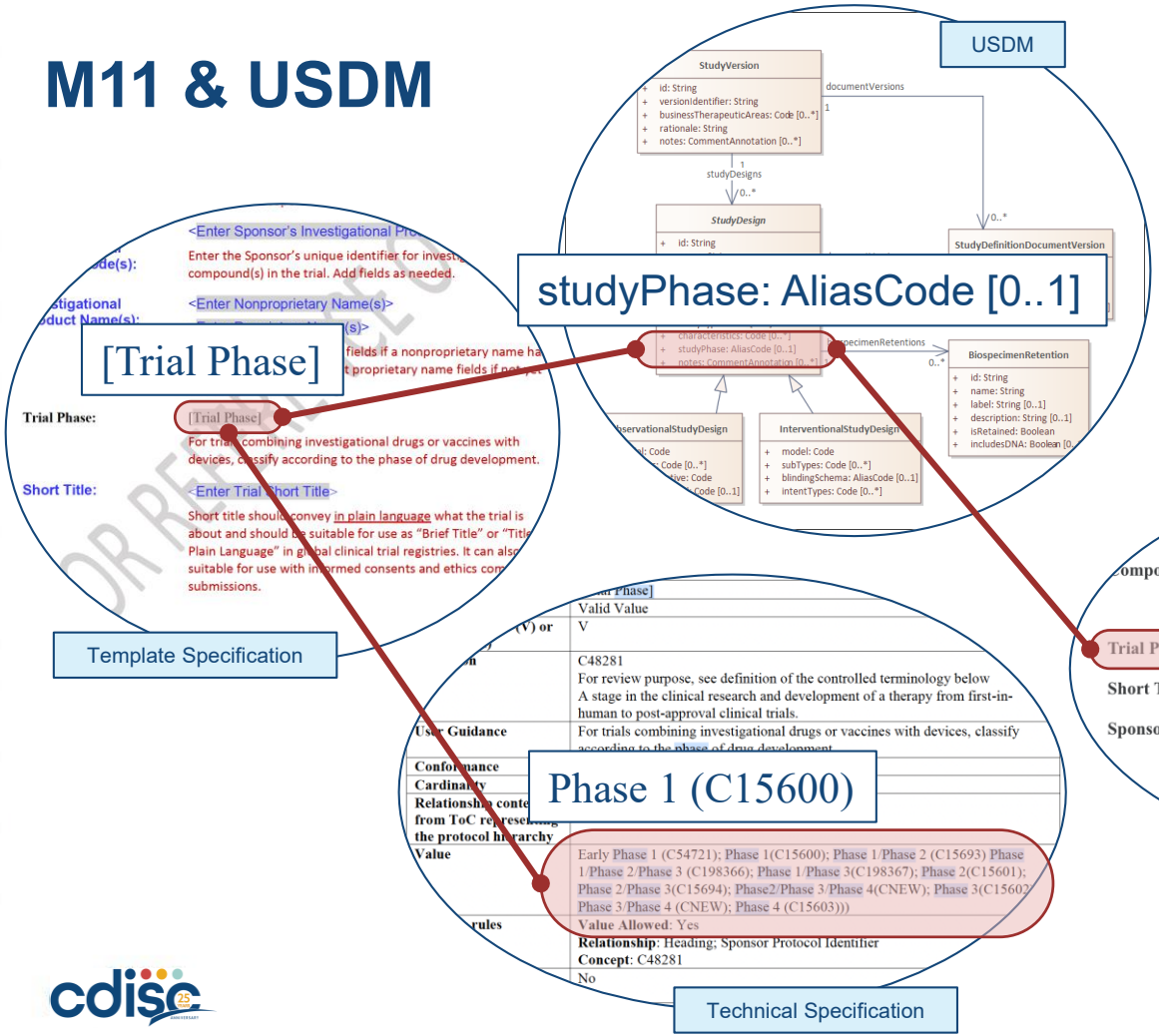
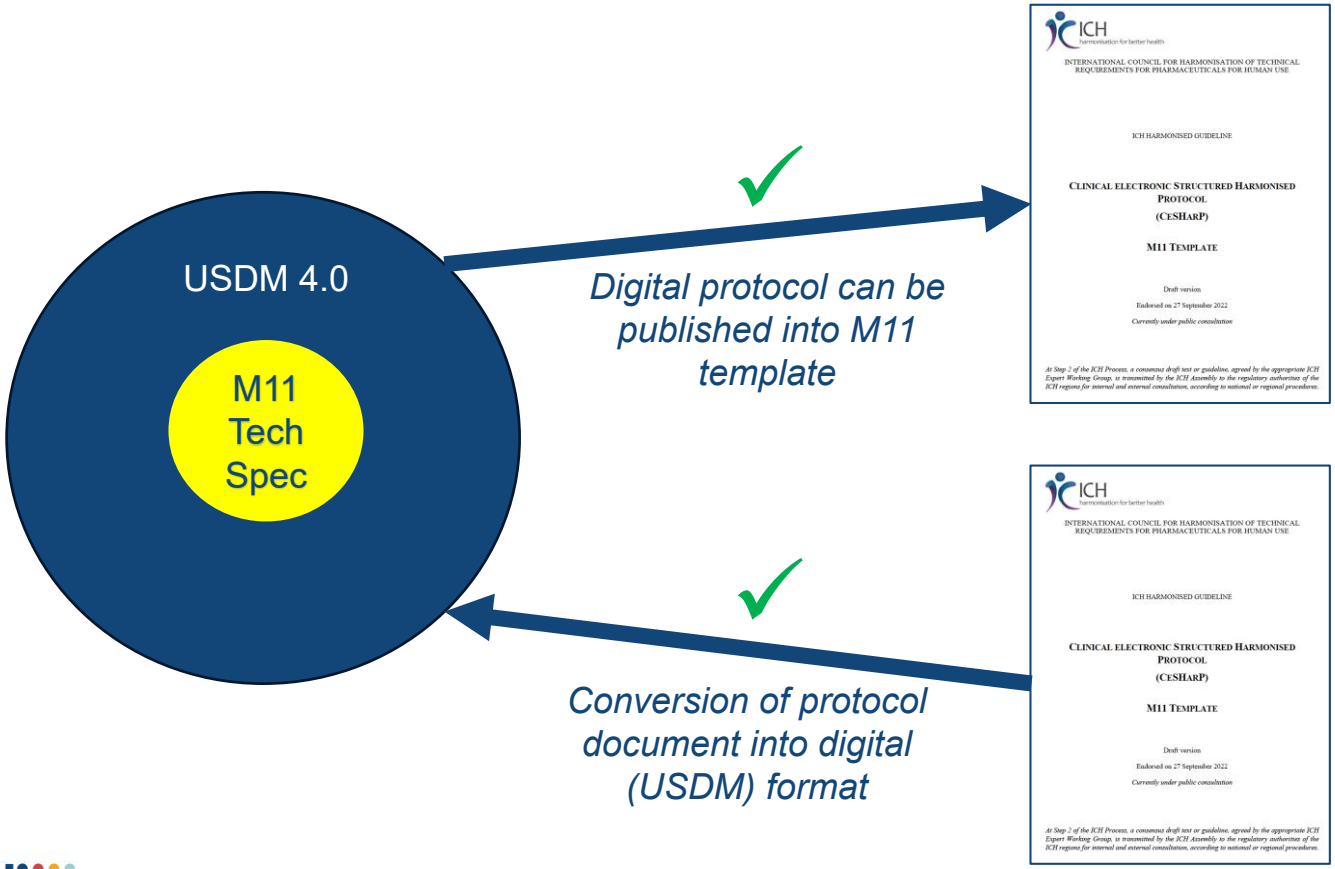
M11 & USDM

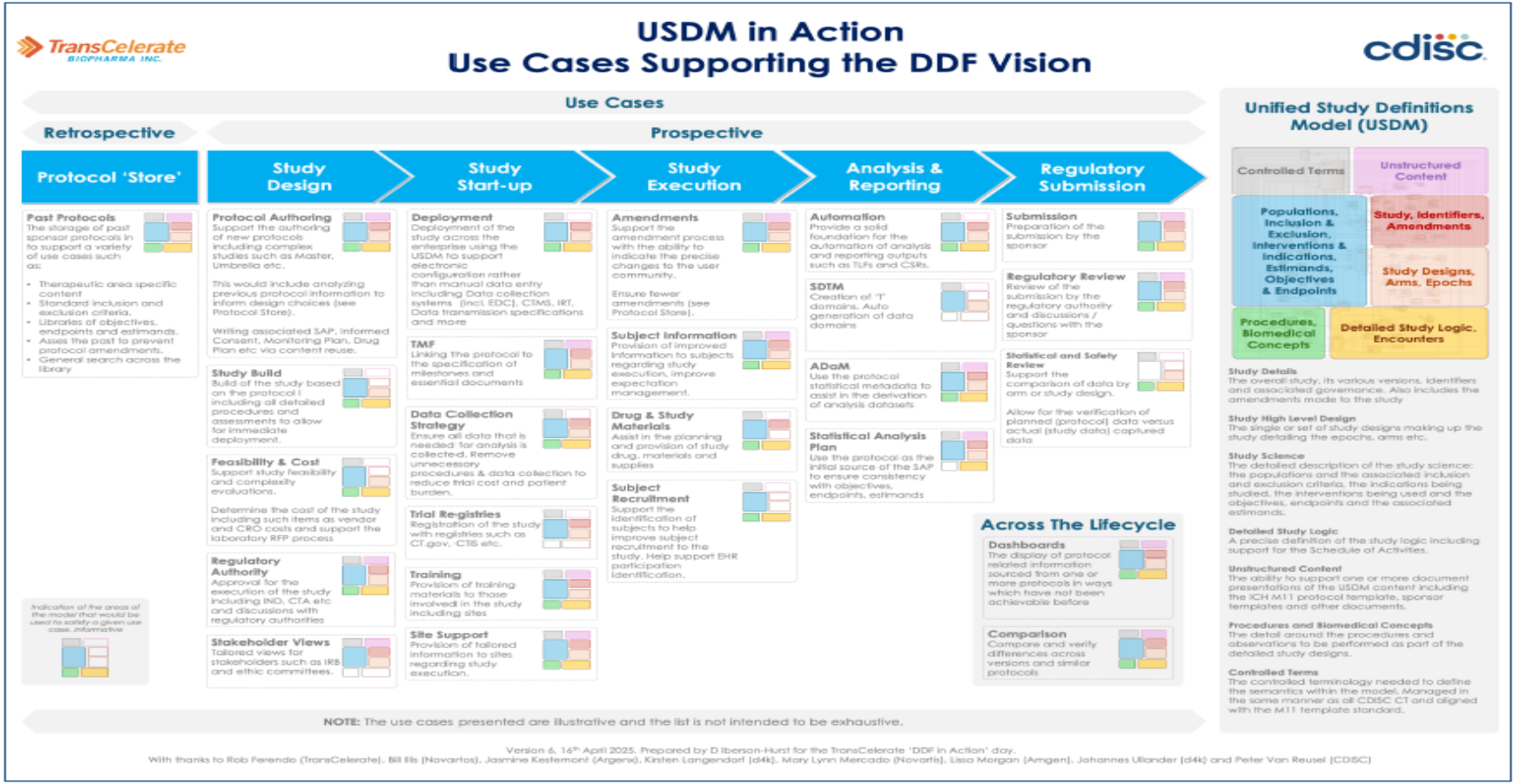


The graphic shows the links between the Trial Phase field that is defined as part of the M11 Title Page to the M11 Technical Specification, on to the USDM and onwards to an implementation of USDM and M11

- *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 M11 and USDM





Source: https://github.com/data4knowledge/usdm_m11_resources/blob/main/documents/infographics/use%20cases.png, (Dave Iberson-Hurst)

USDM in Action
Use Cases Supporting the DDF Vision

TransCelerate BIOPHARMA INC.

cdisc

Use Cases

Retrospective

Prospective

Protocol 'Store'	Study Design	Study Start-up	Study Execution	Analysis & Reporting	Regulatory Submission

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.
- Assess the past to prevent protocol amendments.
- General search across the library

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 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.

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

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

Amendments
Support the amendment process with the ability to identify impacts

Automation
Provide a solid foundation for the

Submission
Preparation of the submission by the sponsor

Regulatory Review

Data Collection Strategy
Ensure all data that is needed for analysis is

Indication of the areas of the model that would be used to satisfy a given use case. Informative

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.

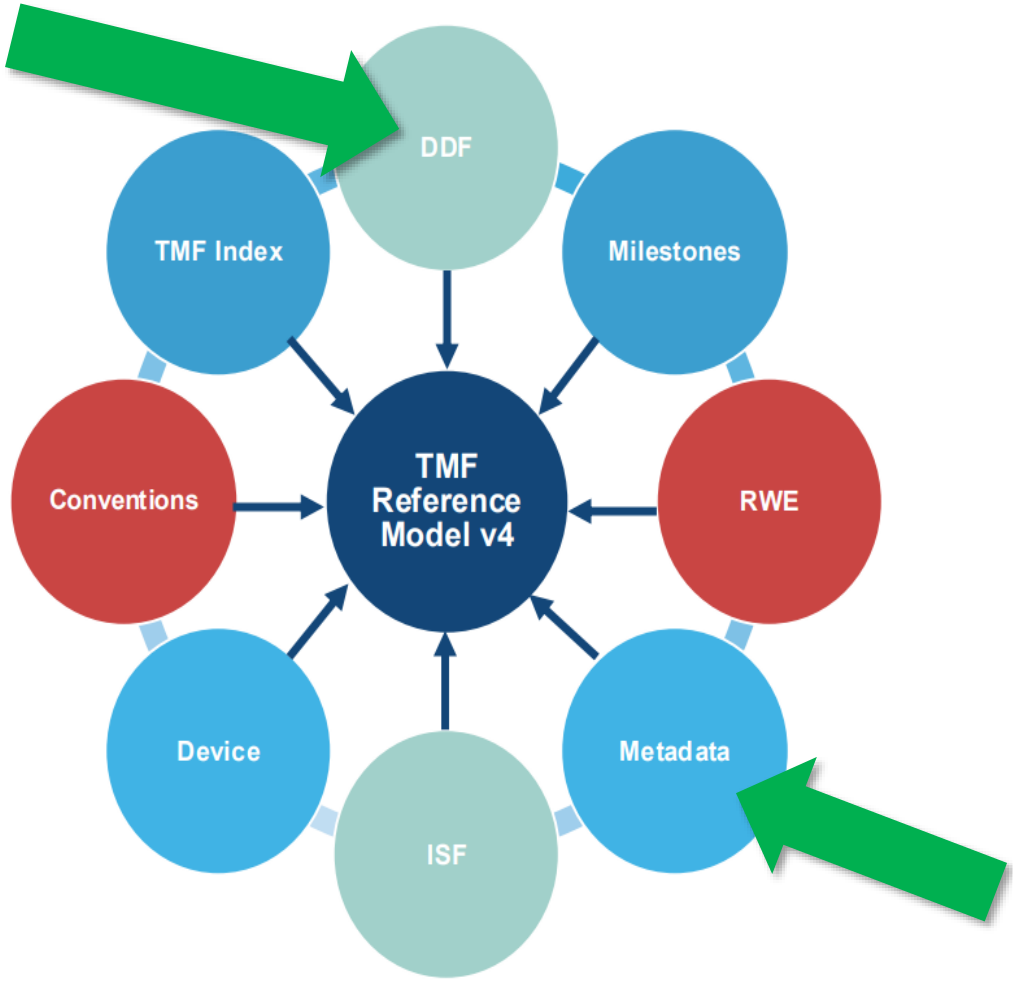
Procedures and Biomedical Concepts
The detail around the procedures and observations to be performed as part of the detailed study designs.

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 6, 16th April 2025. Prepared by D Iberson-Hurst for the TransCelerate 'DDF in Action' day.
With thanks to Rob Ferendo (TransCelerate), Bill Ells (Novartis), Jasmine Kestemont (Argenx), Kirsten Langendorf (d4k), Mary Lynn Mercado (Novartis), Lisa Morgan (Amgen), Johannes Ulander (d4k) and Peter Van Reusel (CDISC)

A vision for the Future:

TMF Reference Model v4



TMF RM V4 Guiding Principles

- **We don't make change for the sake of making change.** There needs to be strong justification for a change that is driven by these Guiding Principles and that considers **digital systems**
- Create consistency across TMF RM V4 to facilitate future migration of content and align with our **goal of interoperability**
- Where practical, Zone & Section content is organized by the functional area that supports those records.
- Build for the **digital future**
- Align with industry and regulation
- Construct a Standard that ensures universal industry adoption
- Adapt the RM to a structure that has unique **Record Types as core elements**

Conventions Driving Structure of TMF RM V4

- **Terminology Standardization** for Records and Documentation
  - Where relevant, the term **"document" should be replaced with "record"**
  - Keep the term "documentation" when it makes sense.
- Naming Conventions and Acronyms
  - Align Record Group names with ICH E6 R3 terms where possible, and Record Types with **Industry-standard names** including acronyms (i.e., Statistical Analysis plan = SAP)
  - If the Record Type name is repetitive to the Record Group, Zone or Section name, consider removing the repetitive aspect
- Creation of new Record Types
  - When the Record Type content is fundamentally different than any other record type consider creating a new record type

M11 and TMF (1)

ICH M11	***standardizes what and how the protocol is written***
TMF	***standardizes where and how that protocol and its supporting evidence are filed***

M11/USDM and TMF (2)

ICH M11/ USDM

- *defines structure and data elements of the protocol*
- *detailing headings, variables, conformance rules*
- *ensures controlled terms for protocol content and amendments.*

TMF

- *defines how clinical trial documents are organized and classified*
- *detailing artifacts, zones, sections, and associated metadata*
- *ensures completeness and inspection readiness.*

M11, USDM and TMF Mapping (Examples)

ICH M11 (Step 2, Draft)	USDM v4 (Class / Attribute)	TMF v3.3.1 Artifact/Section
"Study Identifier(s)" (e.g., EU CT, IND, IDE, jRCT, NCT, WHO/UTN), sponsor, version, amendments	Study & Identification (StudyIdentifier, Organization, StudyVersion, StudyAmendmens)	Trial Information (Protocol / Study Information, Versioning / Amendments)
Section Heading "Schedule of Activities"	Schedule of Activities (Activity, ScheduleTimeline, Procedures, BiomedicalConcept)	Protocol document / Schedule of Assessments sub-artifact

M11/USDM and TMF Implementation Considerations

- Establish a **controlled vocabulary** to align M11 and protocol data elements with eTMF metadata fields (e.g., version, effective date, amendment number, primary reason for change).
- Define **filing rules** that distinguish global vs. local protocol artifacts and ensure version control e.g. “Country/Region-Specific Differences, addenda, local approvals.
- **Automate capture** of M11/USDM identifiers and amendment summaries into eTMF to reduce manual entry and errors.
- **Maintain cross-references** between protocol, approvals, registries, and site communications for end-to-end traceability.

Working Toward a Digital Future

Vision

Together a coherent, compliant chain from protocol authoring through approvals to inspection-ready documentation.

Thank You!

Digital Protocol Resources

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