The TransCelerate / CDISC Digital Data Flow Project: Practical Electronic Study Designs

Dave Iberson-Hurst, CDISC DDF / USDM product Owner

Version 3

Meet the Speaker

Dave Iberson-Hurst

Title: **Partner**

Organization: **d4k, Copenhagen**

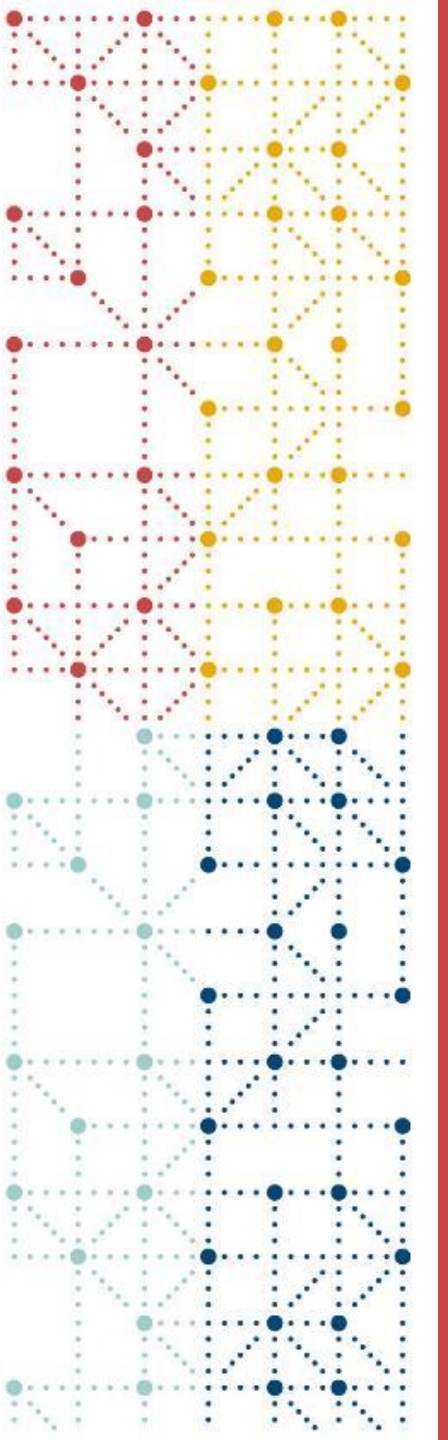
Dave has over 40 years' experience across several industries with the last 20 years spent in the pharmaceutical industry combining his technology and software development experience with clinical data standards.

During this time, he has 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 for the Digital Data Flow project.

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. Drivers for Adoption
3. Current Adoption
4. Resources
5. What’s Next
6. Summary

2003 Dublin (not an interchange)
2004 Brussels
2005 Paris
2006 Berlin
2007 Montreux
2008 Copenhagen
2009 Budapest
2010 London
2011 Brussels
2012 Stockholm
2013 Bad Nauheim (Frankfurt)
2014 Paris
2015 Basel
2016 Vienna
2017 London
2018 Berlin
2019 Amsterdam
2020 Virtual
2021 Virtual
2022 Virtual
2023 Copenhagen
2024 Berlin

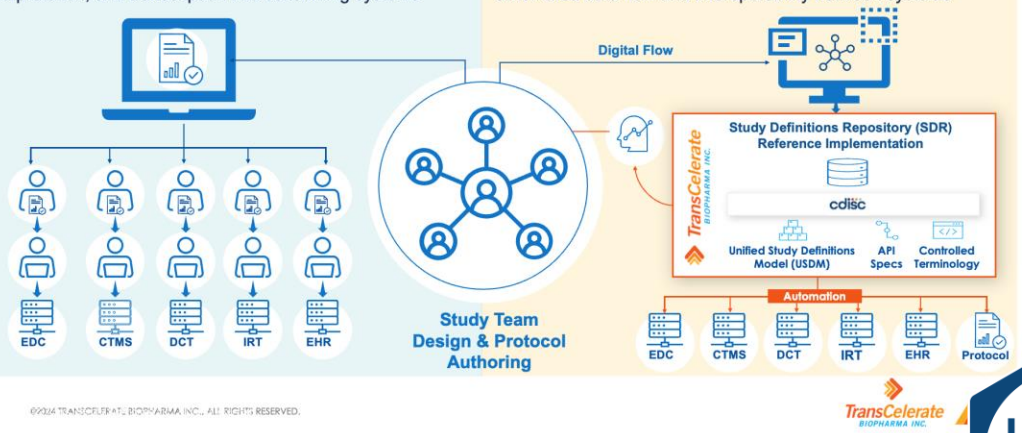
https://www.transceleratebiopharmainc.com/assets/digital-data-flow-solutions/

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



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The USDM Standard

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

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

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

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

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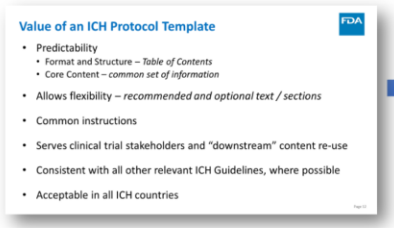
cdisc USDM UNIFIED STUDY DEFINITIONS MODEL (DDF)

Value of an *Electronic* ICH Protocol Template

FDA



Value of an ICH Protocol Template

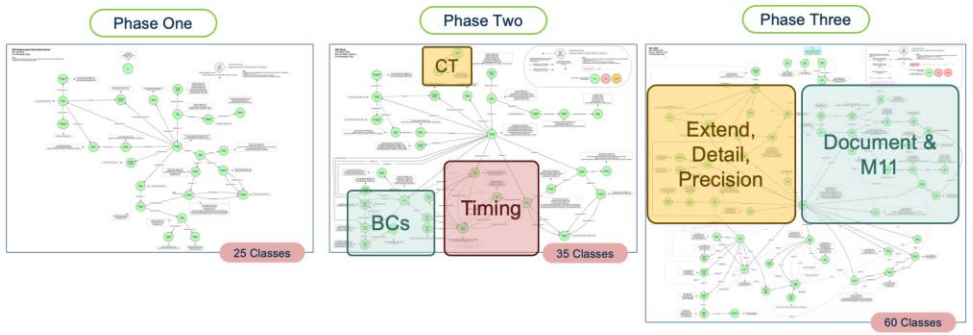
- Predictability
  - Format and Structure – *Table of Contents*
  - Core Content – *common set of information*
- Allows flexibility – *recommended and optional text / sections*
- Common instructions
- Serves clinical trial stakeholders and "downstream" content re-use
- Consistent with all other relevant ICH Guidelines, where possible
- Acceptable in all ICH countries

Protocol will be data-driven . . .

- **Tailored User Experience**
  - Task or role-based views of the content
  - Personal views– *have the information served up the way you want it*
- **Collaboration**
  - Multi-sponsor development programs
  - Regulator to Regulator Reviews
- **Downstream Automation**
  - Clinical Trial Registries
  - Data Capture
  - Statistical Analysis Plan
  - Clinical Study Report
  - Other Protocols
- **Future**
  - Capability to compare / contrast trial designs across sponsor submissions
  - Perform "what / if" scenarios on trial design, arms, interventions, etc.

Page 14

CDISC DDF / 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) & BCs
- The protocol document 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

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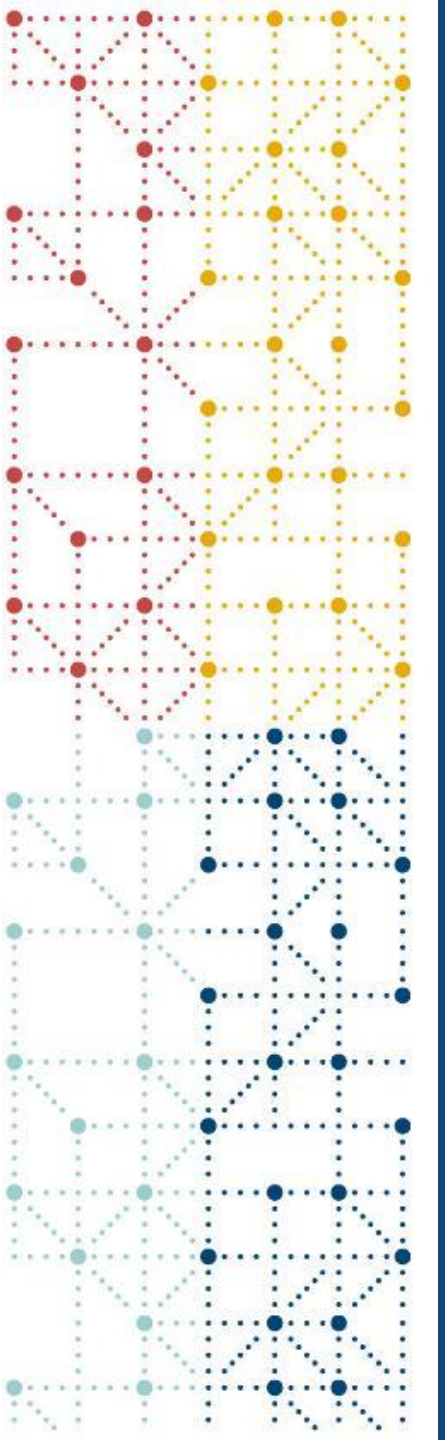
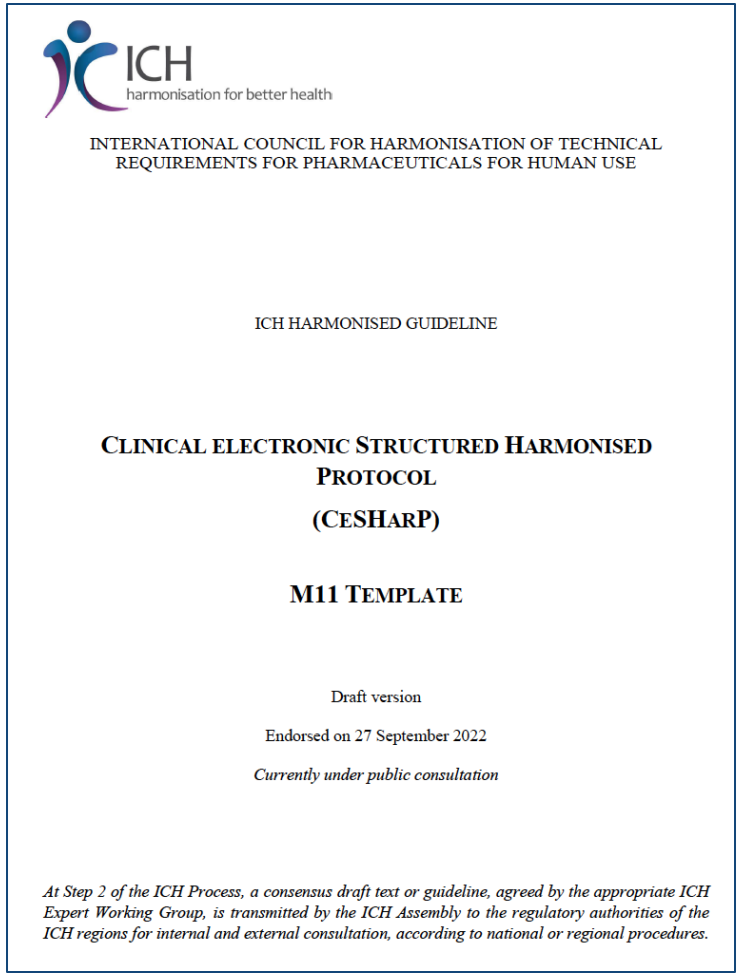


Drivers for Adoption

ICH CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL (CeSHarP)

ICH harmonisation for better health

Founding Regulatory Members	Founding Industry Members	Standing Regulatory Members	Regulatory Members	Industry Members
• EC, Europe (EMA) • FDA, United States • MHLW / PMDA, Japan	• EFPIA • JPMA • PhRMA	• Health Canada, Canada • Swissmedic, Switzerland	• ANVISA, Brazil • COFEPRIS, Mexico • EDA, Egypt • HSA, Singapore • MFDS, Republic of Korea • MHRA, UK • NMPA, China • SFDA, Saudi Arabia • TFDA, Chinese Taipei • TITCK, Türkiye	• BIO • Global Self-Care Federation • IGBA



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 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.

Example Use Cases I

Authoring

Protocol authoring and sharing including the providing a **tailored user experience.**

Provide a solid foundation for study execution

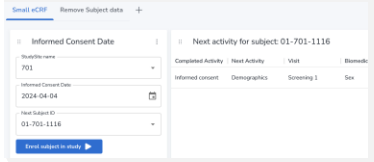
A standard for protocol information re-use during and after study execution

Regulatory

Automate or ease the process of providing protocols and protocol information to regulators and clinical trial registries

Data Capture

The use of detailed study design information to ease the configuration data capture systems



Insights

Use of protocol information to gain insights into past performance to improve future outputs and processes

Subject Impact

Use of protocol information to assess impact on subjects such as subject burden, time and risk

There are many use cases, these are just a few examples

Example Use Cases 2

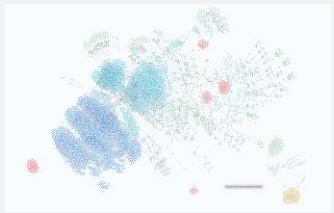
SDTM T Domains

Use of protocol information to generate SDTM trial design domains

Can also read trial design domains to assist in rebuilding studies

SDTM Data

Use of the detailed study design information available within USDM to provide a solid foundation for the automated generation of SDTM data domains



aCRF

Use of the detailed study design to create an annotated Case Report Form for the study

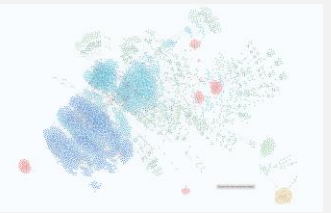
Define.xml

<ODM>

Use of the detailed study design to create a define.xml for the study

Data Decay

Use of the detailed study design information available within USDM to provide a framework for ingesting old study data



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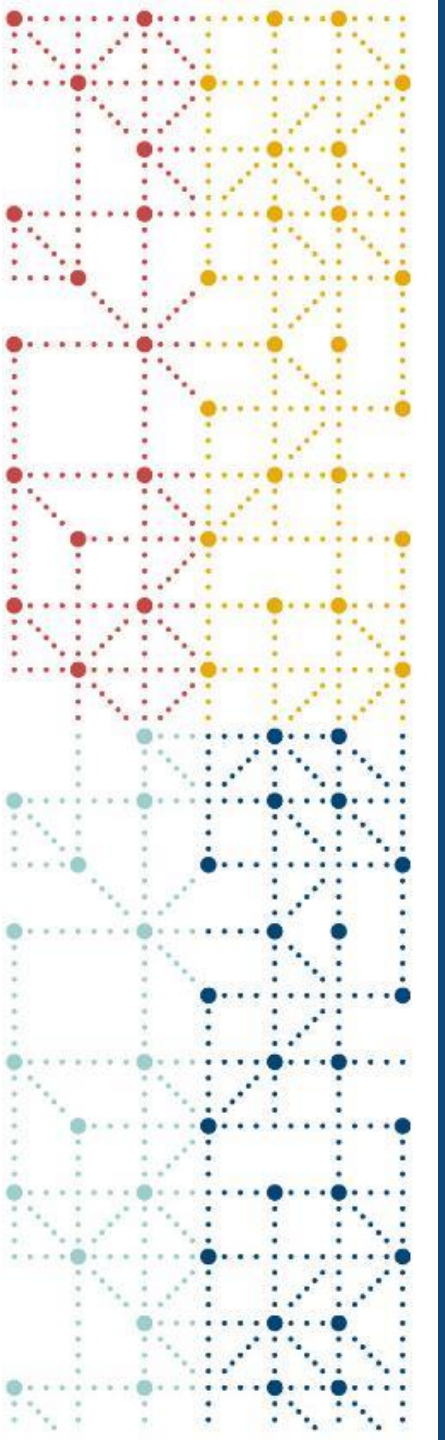


Current Adoption

Discovery Day (September 2023)

USDM Data Mining Application

Sponsor working with CDISC to develop a retrospective use case

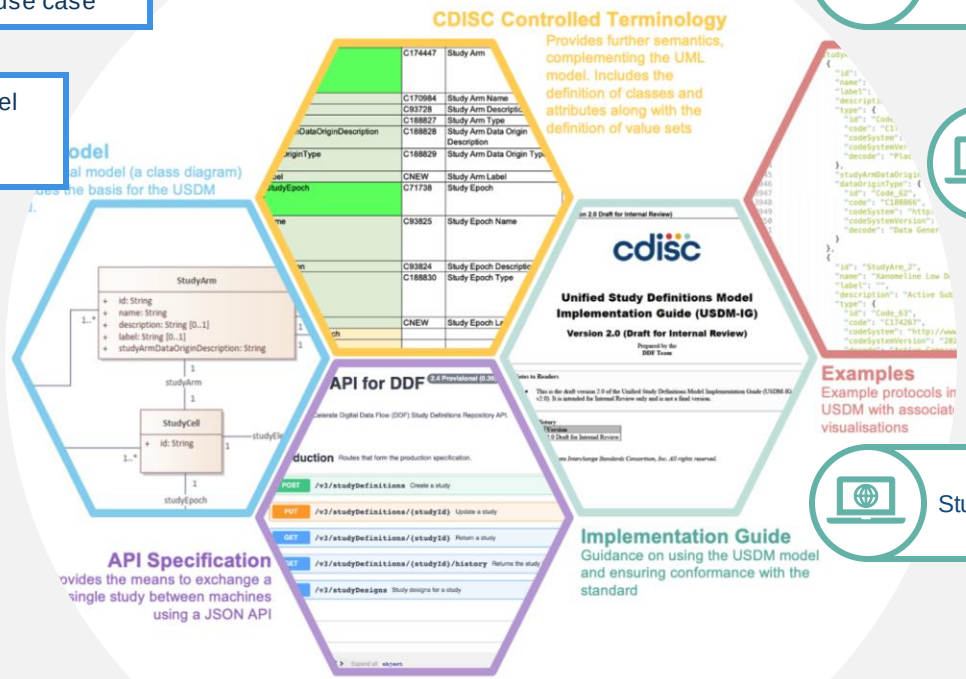
Sponsor is using the model for retrospective data ingestion

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

Study Build Application

Study Build & EDC Configuration

Study Build Application



Retrospective Studies

Prospective Studies

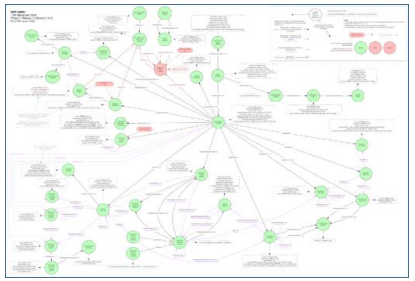
The "footnote conundrum"

- *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*

Population of USDM from old protocols

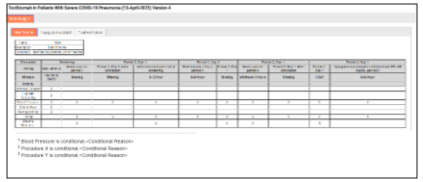
Open Study Builder Study Build Application

DDF Initiative encompasses technical delivery, change management, and industry engagement



Unified Study Definitions Model (USDM) Reference Architecture

TransCelerate's Study Definitions Repository (SDR)



Digital Data Flow Initiative

Suite of DDF Adoption Resources, Videos & Change Management Tools

Continued Industry Collaboration between TransCelerate, CDISC ICH, and HL7

Growing Solution Collaboration Forum (SCF)*

*Company logos illustrate current involvement and are not used to imply endorsement of specific vendors for DDF or to identify a comprehensive list of all actual or potential future participants in DDF.

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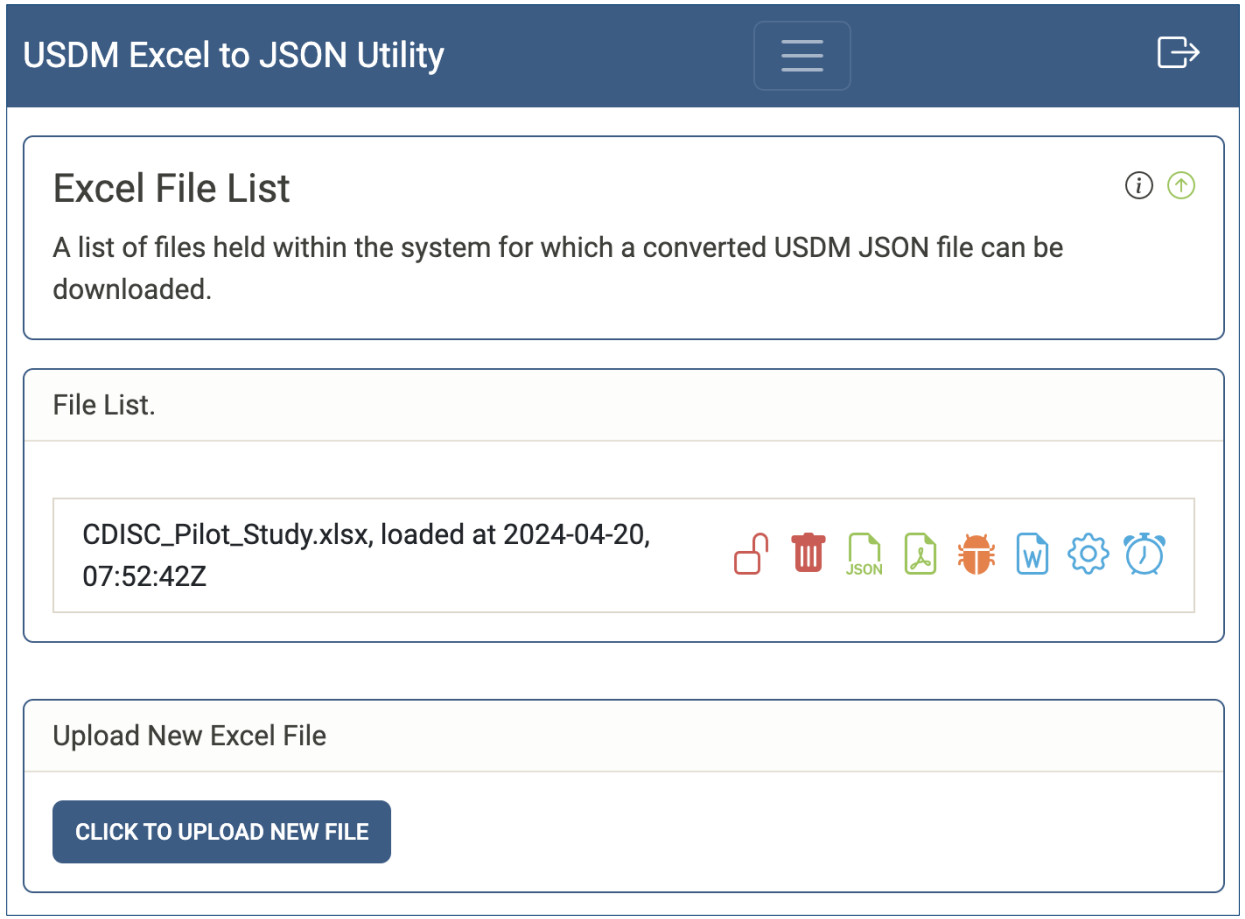
Team Testing

- Three full protocols have been “converted” into USDM
- Another protocol is ready to be upgraded from an earlier USDM version
- Another complex protocol has been provided by a Transcelerate member company
- Also have LZZT in M11 format which could be placed into USDM format
- Add aim to get 7-10 protocols “converted”
- Each takes approximately three days to “convert”



Team Testing – Use Cases

- What do I wish to structure?
  - SoA
  - Inclusion & Exclusion Criteria
  - Objectives & Endpoints
  - Amendments
  - Interventions
  - Populations
  - … *and more*
- What are the use case(s) for the resulting structured protocols?
  - Use in new protocols
  - Learning from mistakes (e.g. amendments)
  - Searching old studies
  - *…etc*
- Doing a few protocols manually teaches you a lot, allows you to think about the mechanics and aims of any automated process

USDM Training, Berlin, April 2024

	Screening	Screening	Treatment One	Treatment One	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Three	Follow Up
	Screening 1	Screening 2	Baseline	Week 2	Week 4	Week 6	Week 8	Week 8	Week 12	Week 12	Week 16	Week 16	Week 20	Week 20	Week 24	Week 24	Week 26
Study drug record , Medications dispensed, Medications returned			X	X	X	X	X		X		X		X		X	X	4.4 days	-3..3 days
TTS Acceptability Survey																X		
ADAS-Cog	X[2]		X				X				X				X			
CIBIC+	X[3]		X				X				X				X			
DAD	X[4]		X				X				X				X			
NPI-X	X[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
																		X

1 Performed if patient is an insulin-dependent diabetic

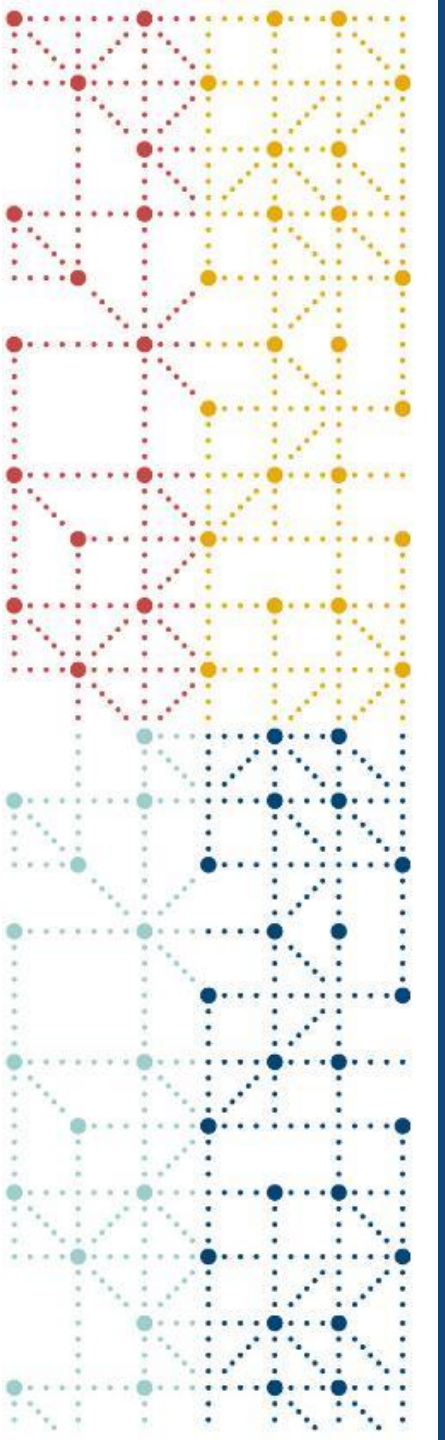
2 Practice only - It is recommended that a sampling of the CIBIC+, ADAS-Cog, DAD, and NPI-X be administered at Visit 1. Data from this sampling would not be considered as study data and would not be collected.

3 Practice only - It is recommended that a sampling of the CIBIC+, ADAS-Cog, DAD, and NPI-X be administered at Visit 1. Data from this sampling would not be considered as study data and would not be collected.

4 Practice only - It is recommended that a sampling of the CIBIC+, ADAS-Cog, DAD, and NPI-X be administered at Visit 1. Data from this sampling would not be considered as study data and would not be collected.

5 Practice only - It is recommended that a sampling of the CIBIC+, ADAS-Cog, DAD, and NPI-X be administered at Visit 1. Data from this sampling would not be considered as study data and would not be collected.

This relates to existing protocols being digitized (retrospective use case) not the authoring of new protocols



Resources

Example Resources – CDISC

https://www.cdisc.org/ddf

Digital Data Flow

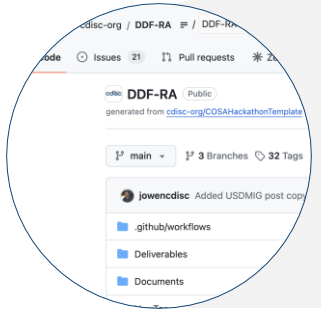
Overview | What is the USDM | Participate | Webinar | Versions | FAQ | Contact Us

Welcome to Digital Data Flow (DDF) for Clinical Trial Protocols

Digital Data Flow Initiative will help modernize clinical trials by enabling a digital workflow with protocol digitization. This initiative establishes a foundation for a future state of automated & dynamic readiness that can transform the drug development process.

Below are a list of the different websites sourcing specific content and resources. Depending on where you are in the journey, please feel free to explore the different websites and their information.

CDISC DDF Website	DDF Website	DDF GitHub	Transcelerate DDF Initiative Solutions
You are here! Learn about the Unified Study Definitions Model (USDM) Reference Architecture supporting Protocol Standards	As the main website for DDF, learn and access all resources supporting DDF	Learn about and access the Study Definitions Repository Reference Implementation	Learn about DDF background and initiative roadmap
Target Audience: Those interested in data standards	**Target Audience:** All those interested in implementing DDF Solutions	**Target Audience:** Those interested in SDR development	**Target Audience:** All those generally interested



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

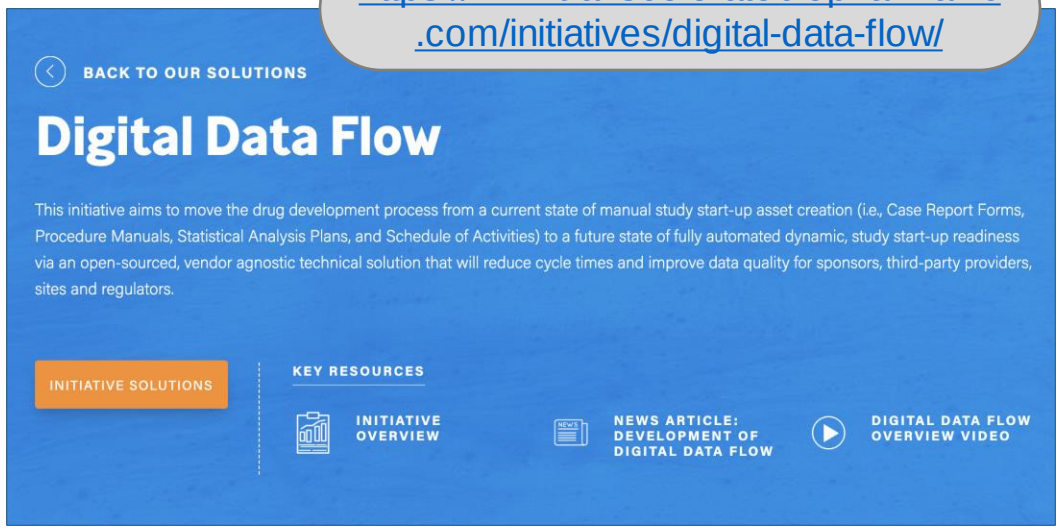
https://pypi.org/project/usdm/

Web-based version of the USDM test tooling.

https://usdm-service.fly.dev/

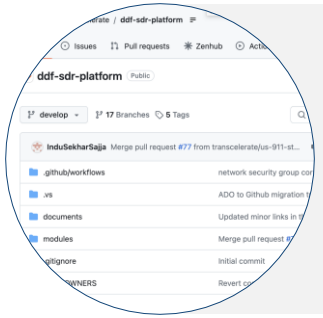
Example Resources – TransCelerate

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



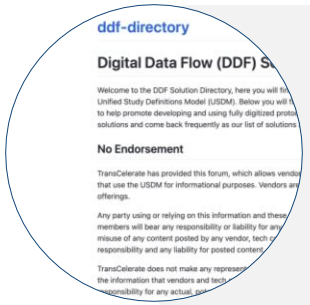
TransCelerate web page holding.a significant number of DDF and USDM resources including the persona guides

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

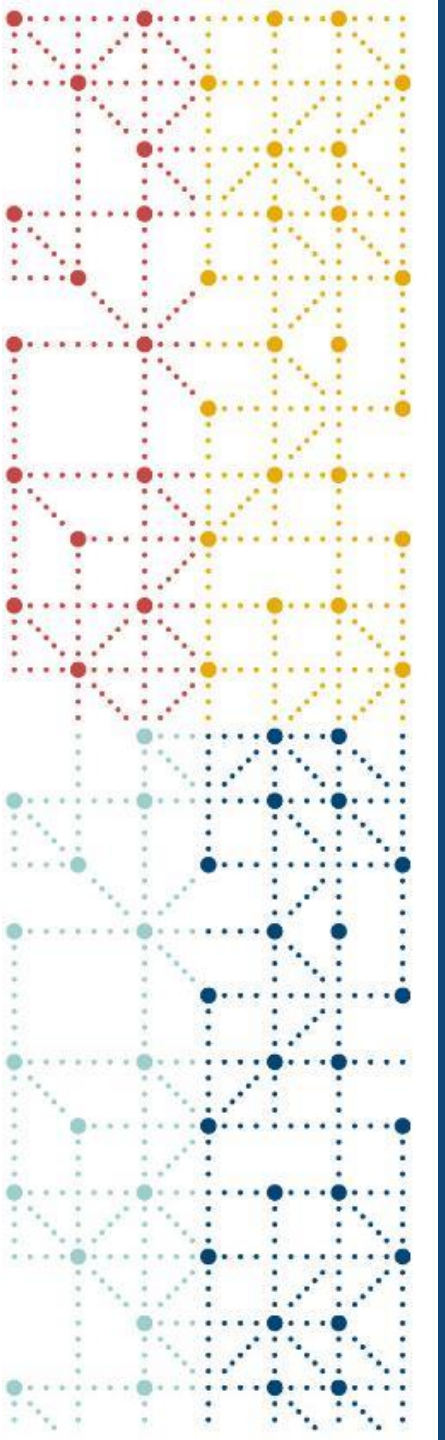


Github housing the source for the Study Definition Repository (SDR) Reference Implementation of the USDM

https://github.com/transcelerate/ddf-sdr-platform

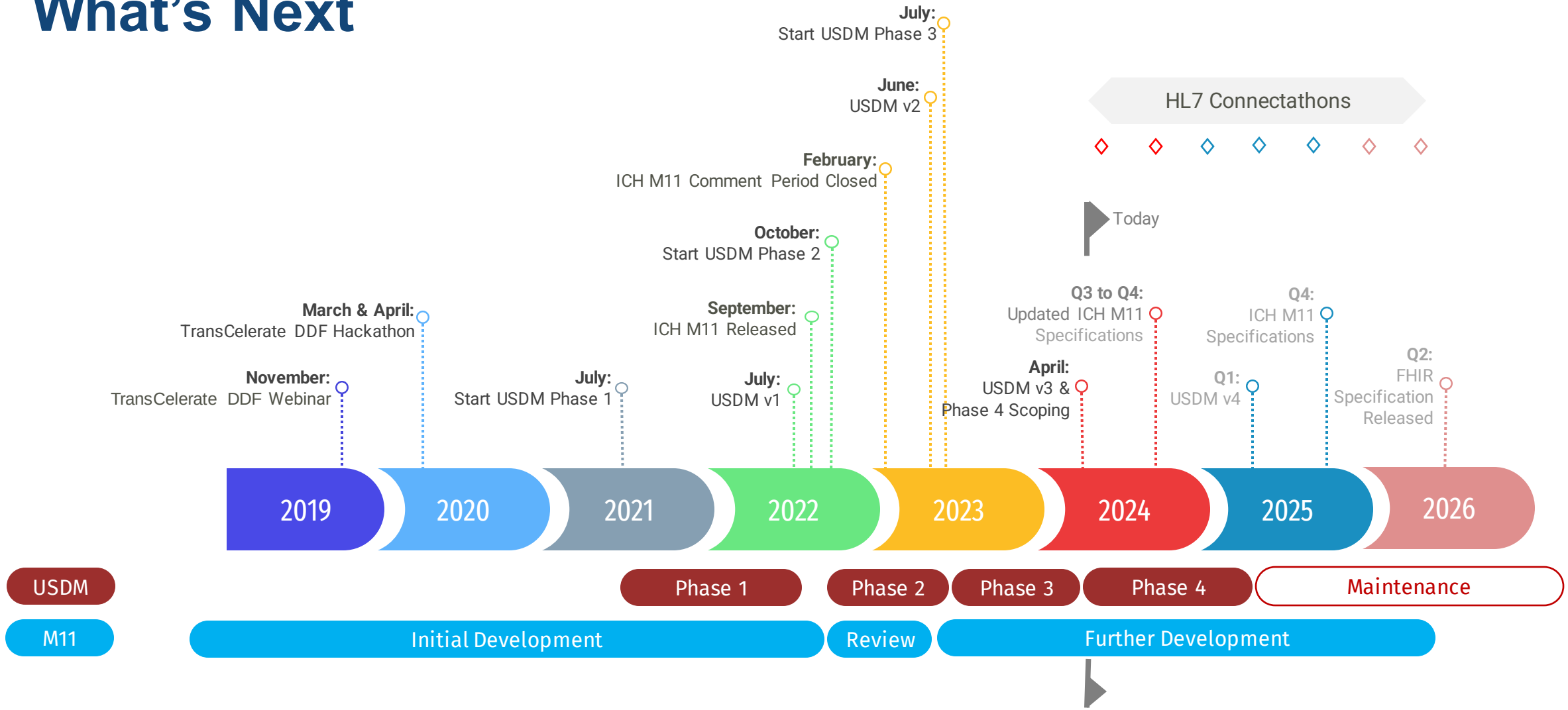


DDF solutions directory. A growing list of self-reported solutions which utilize and follow the DDF Unified Study Definitions Model (USDM)
https://transcelerate.github.io/ddf-directory/directory/directory.html



What’s Next

What's Next

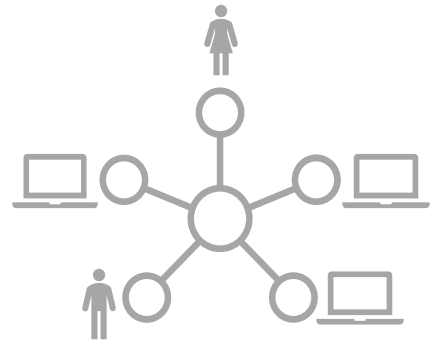


DDF: Digital Data Flow
USDM: Unified Study Definitions Model
ICH: International Council for Harmonisation
M11: Clinical electronic Structured Harmonised Protocol (ceSHarP)

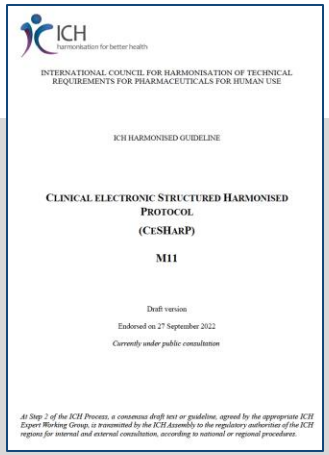
Phase Four Focus

1. **USDM Enhancements** Further IDMP Alignment, M11 amendments and versions, complex studies designs such as multiphase seamless designs, additional trial registration mappings, and statistical / estimands enhancements
2. Continued alignment of USDM with ICH M11
3. Participation in the Utilizing the Digital Protocol (UDP) project with TransCelerate, ICH and HL7 Vulcan
4. Continue development of USDM Conformance Rules to support USDM v3.0 and v4.0
5. Continue support and development of test data and test tools
6. Development of training and, education materials in conjunction with TransCelerate's Change and Engagement team to foster adoption of DDF

CDISC and ICH Technical Development



ICH M11 Specifications


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

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CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL
(CESHARP)
M11 TECHNICAL SPECIFICATION

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USDM

Existing Formats (e.g. CTRs)

DDF/USDM

HL7 FHIR

PDF

DOCX

XML, JSON

Exchange

Protocol information exchanged seamlessly between humans and machines allowing for ease of creation and consumption.

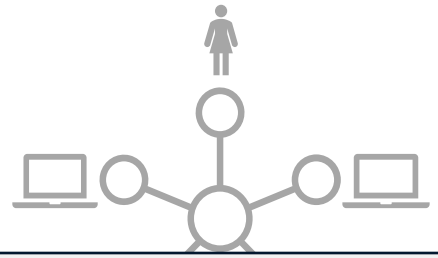
USDM

A logical view of a protocol and study design information for use across the pharmaceutical enterprise

Transport

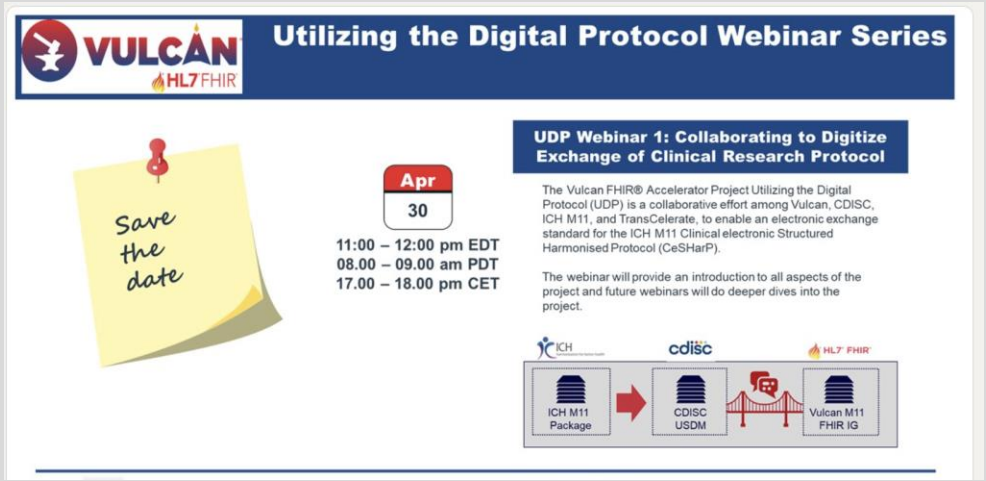
Transported between machines using existing and new formats such as DDF/USDM and FHIR (serialised as JSON or XML) with the ability to render the entire document into a human-readable form.

CDISC and ICH Technical Development



ICH M11 Specifications

April 30th, 5-6pm CET



https://www.linkedin.com/events/7186665509034110976/

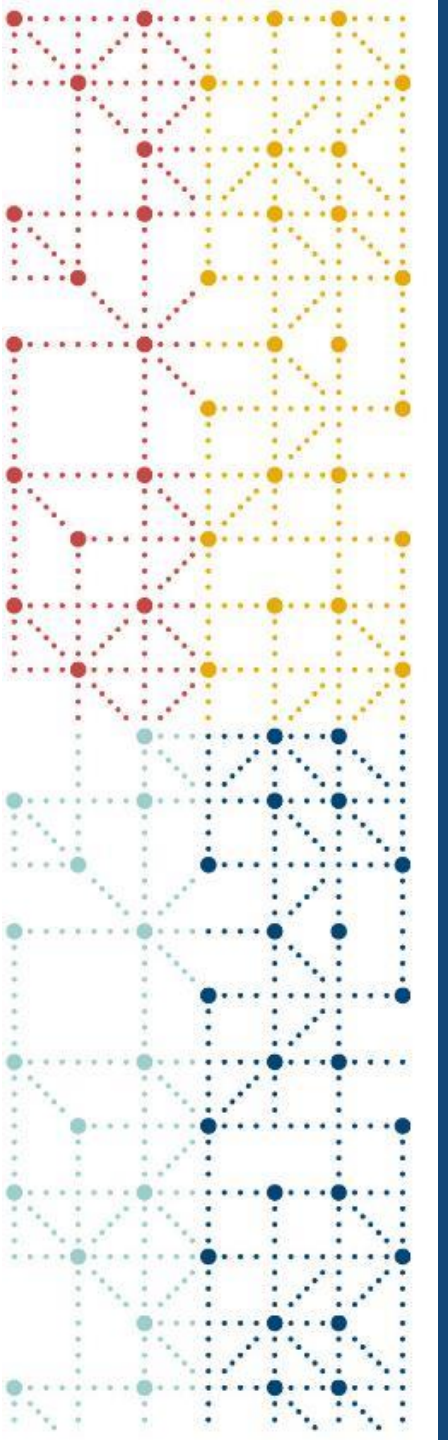
June 25th, 3-4pm CET

Details TBA

Formats
(e.g. CTRs)

XML, JSON

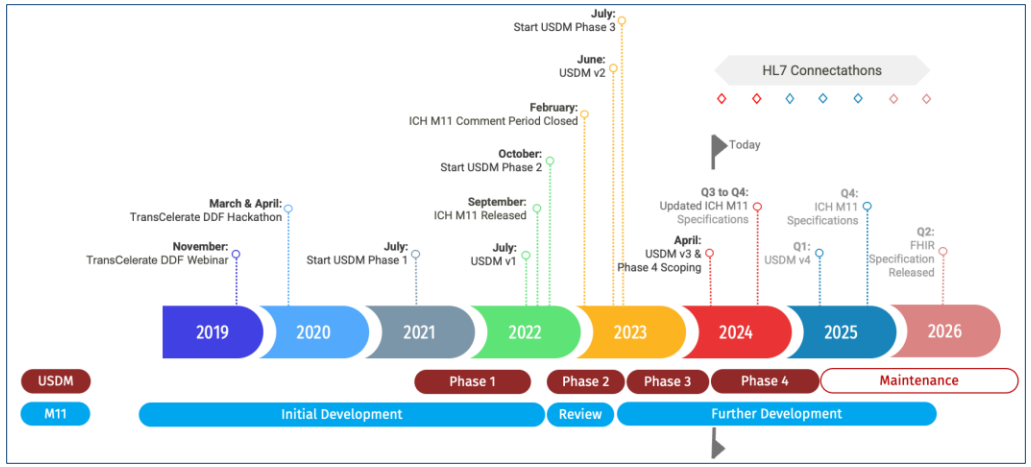
or XML) with the ability to render the entire document into a human-readable form.



Summary

Summary

- A demonstrable & implementable logical model capable of structuring and holding an entire protocol
- The model supports any protocol format, in particular:
  - Sponsor template(s)
  - TCB CPT template
  - ICH M11 template
- Initial proof-of-concept of CORE rules validating USDM content
- Collaboration with ICH M11, EMA and FDA working together on the HL7 Vulcan FHIR Utilizing the Digital Protocol (UDP) project
- Sponsors and vendors have started to pilot and implement
- Phase 4 commencing



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