CDISC TMF Reference Model - the benefits of becoming a standard for long term records retention and clinical trial reconstruction

Presented by Karen Roy and Paul Fenton

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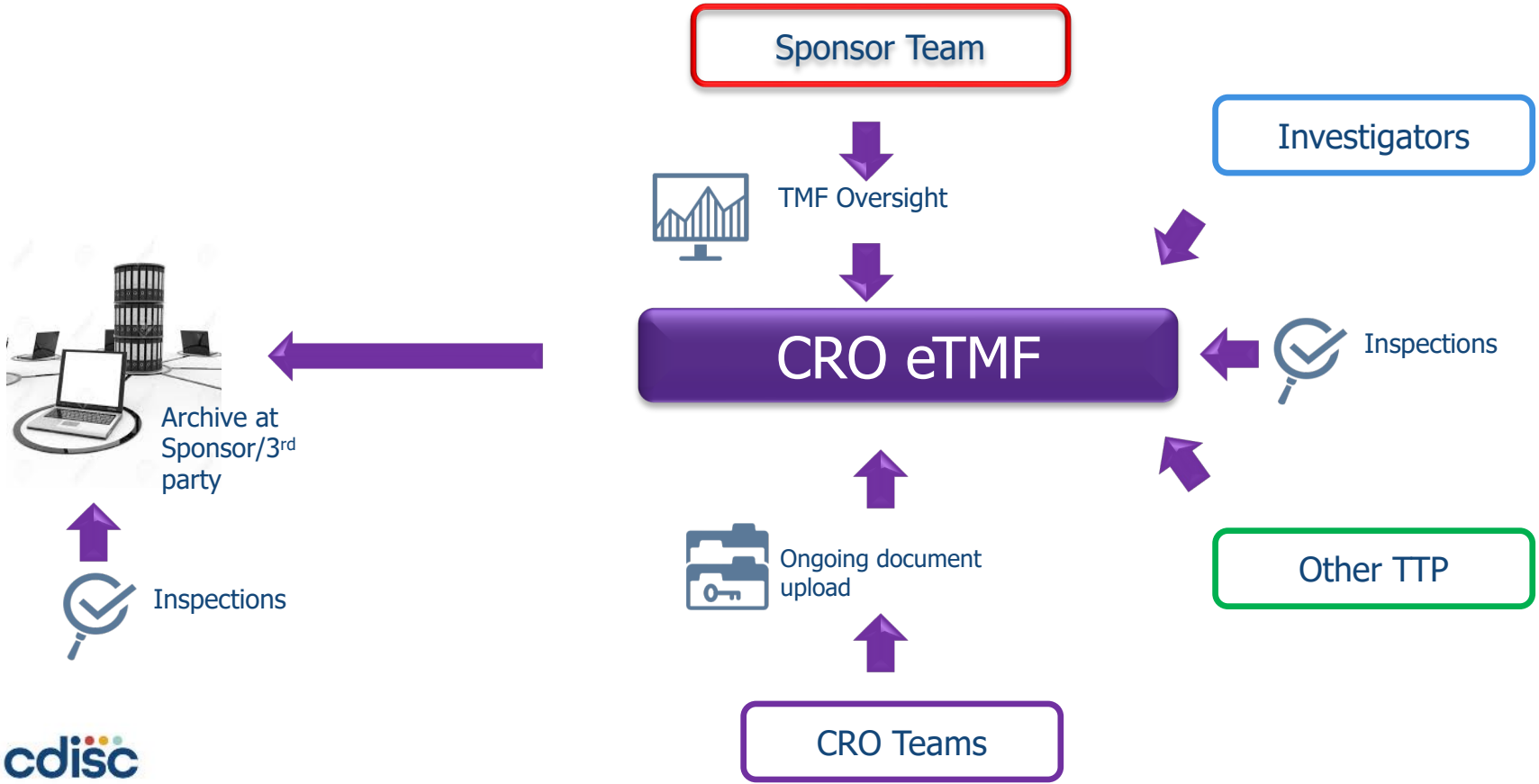
TMF is challenging…..
TMF archiving is even more challenging

- How do we know if our TMF is complete and free of quality issues?
- How can we ensure that we can still tell an accurate story of what happened in a trial many years down the road?
- How can we ensure that the TMF is still retrievable and navigable as clinical trial standards evolve over the next 25 years?
- How do we overcome the challenge of TMF relevant records being held in many other systems and organisations?

The Complex Transfers with Multiple Systems



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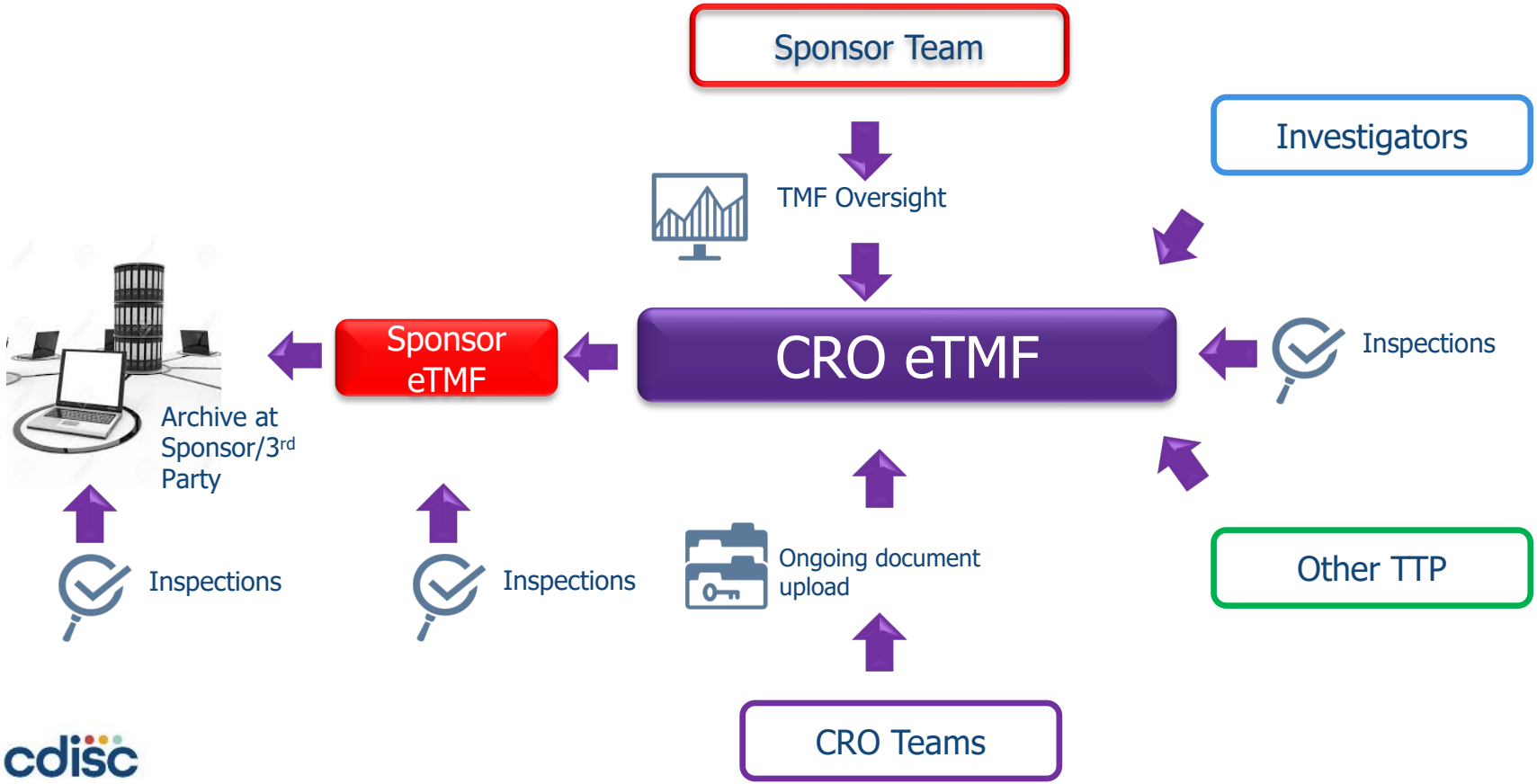

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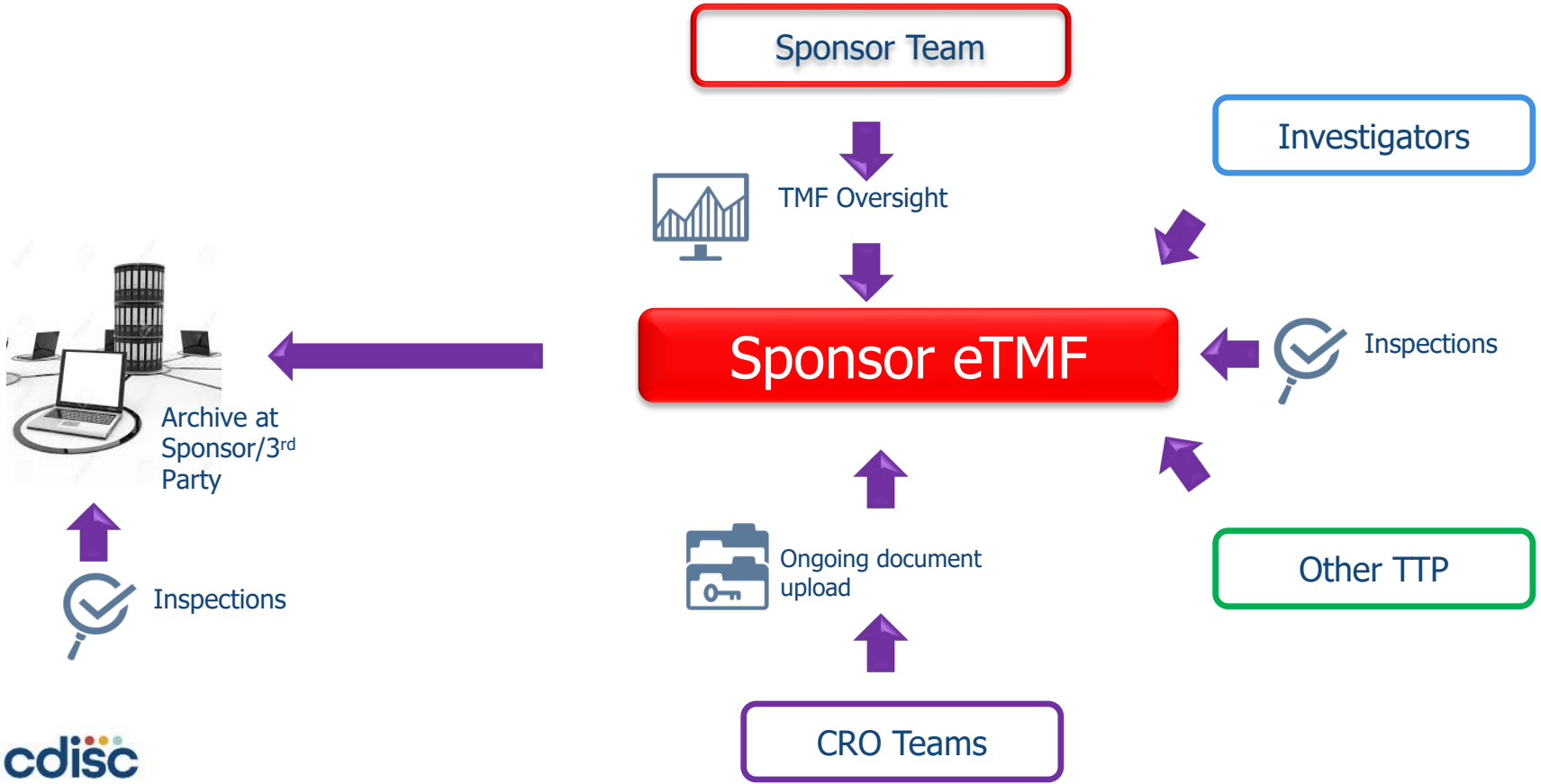

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We don’t have all the answers but standardisation is key to meeting these challenges

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First a little history....

Development of the TMF Reference Model

DIA DEVELOP INNOVATE ADVANCE

Document & Records Management Community

2009 to 2010

Initial meeting in 2009 with first version being released in 2010

2011 to 2013

Multiple releases including Regulator feedback, Investigator Site Files, Devices, Process based metadata. Workgroups established

Separated from DIA

2014 to 2021

Formalization with a Steering Committee. **Release of the Exchange Mechanism Specification** and Version 3

2022 onwards

Forward to Compliance

TRIAL MASTER FILE TMF powered by cdisc REFERENCE MODEL

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Why Join CDISC?

***Mission**: To develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare*

GLOBAL NON-PROFIT CLINICAL RESEARCH STANDARDS DEVELOPMENT ORGANISATION WITH 40+ STAFF

RECOGNITION BY REGULATORY AGENCIES

ABILITY TO EXTEND THE TMF METADATA AND PROVIDE IN MACHINE READABLE FORMAT

FRAMEWORK FOR STANDARDS DEVELOPMENT LIFECYCLE

EDUCATION TEAM FOR CERTIFIED TRAINING

MARKETING AND EVENTS

STANDARDS TO REMAIN FREELY AVAILABLE

CDISC Standards Development

- Consensus-based standards development
- Standards for clinical and translational research
- Standards are freely available at www.cdisc.org
- IP Policy ensures open standards
- Ongoing global research support in the Americas, Europe, Japan, China, India, Korea and other regions
- Standards and supporting documents available in English, Japanese, and Chinese.

Alliances and Collaborations

New Partnerships 2021 - onward

Academic Institutions	Consortia	Platform Providers	Gov Vendors
University of Texas San Antonio	BioPharmaceutical Statistics Leaders Consortium	OpenClinica	Digital Infuzion
University of Heidelberg	Clinical Data Privacy Consortium	REDCap	Embleema
University of Michigan	Learning Health Community	Vivli	
University of Oxford	Pharmaceutical Data Standards Leaders		
	CodeX HL7 Accelerator		
	GA4GH		

Transforming the TMF Reference Model into a standard

What Are Clinical Data Standards?

- Clinical data standards refer to a set of agreed-upon rules, formats, and guidelines for collecting, storing, and exchanging clinical information.

- These standards are crucial in healthcare and medical research because they ensure that data is consistent, reliable, and can be effectively shared and compared across different systems, studies, and organizations.

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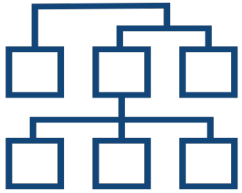
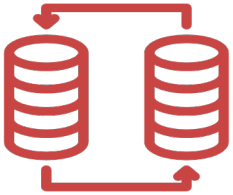
What Can We Standardize?



Models



Data Exchange

Terminology

Process

Identifiers

Data Types

Data Formats

Data Collection

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Where is the TMF Reference Model at today?

- The reference model itself is an Excel spreadsheet
- We need to be able to better map the TMF RM to other standard and models
- We need to expand the reference model in terms of metadata
- We have developed an initial standard for eTMF Interchange: the EMS (Exchange Mechanism Standard)
- We are already embarking on our CDISC journey to standardisation!

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TMF Standards Sub-Group

- Established in December 2022
- Will oversee the move of the TMF Reference Model from a de-facto standard to a formal standard
- 4 Initiatives:
  - Migration of TMF RM to CDISC Library
  - Evolution of EMS/Interoperability
  - TMF RM Standard Alignment and Management
  - Development of Controlled Terminology and alignment with ICH M11

TMF RM Standard Alignment and Integration

- The CDISC vision is for TMF to be full integrated into the standards landscape
- As DDF and ICH M11 standards evolve, we will align and integrate the CDISC TMF RM Standard
- We have initiated a project with the NCI-EVS team to develop and align controlled terminology for TMF

Migration of TMF RM to CDISC Library

- We want to move away from a Spreadsheet to a more dynamic format
- The CDISC library is a database where all CDISC standards are mapped and managed
- We will be able to search the library to find information on specific artifacts
- We should also be able to extract the model in Excel format
- Advantages to moving to the library include:
  - Ability to expand the RM (metadata)
  - Better control changes and version history
  - Allow clinical systems (including eTMFs) to query the library through APIs
  - More easily map to other models and standards
  - Define sub-models for different types of trials

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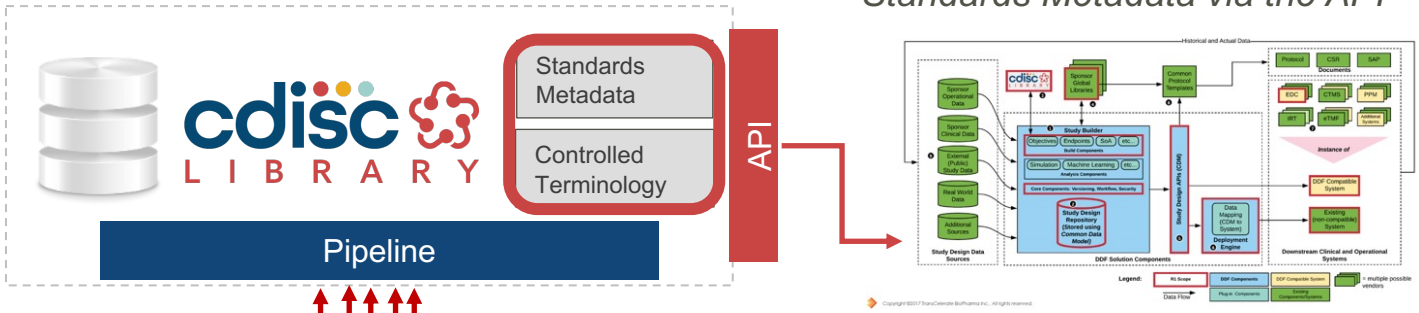
CDISC Library: Standards as a Service

Software Applications Consume Standards Metadata via the API

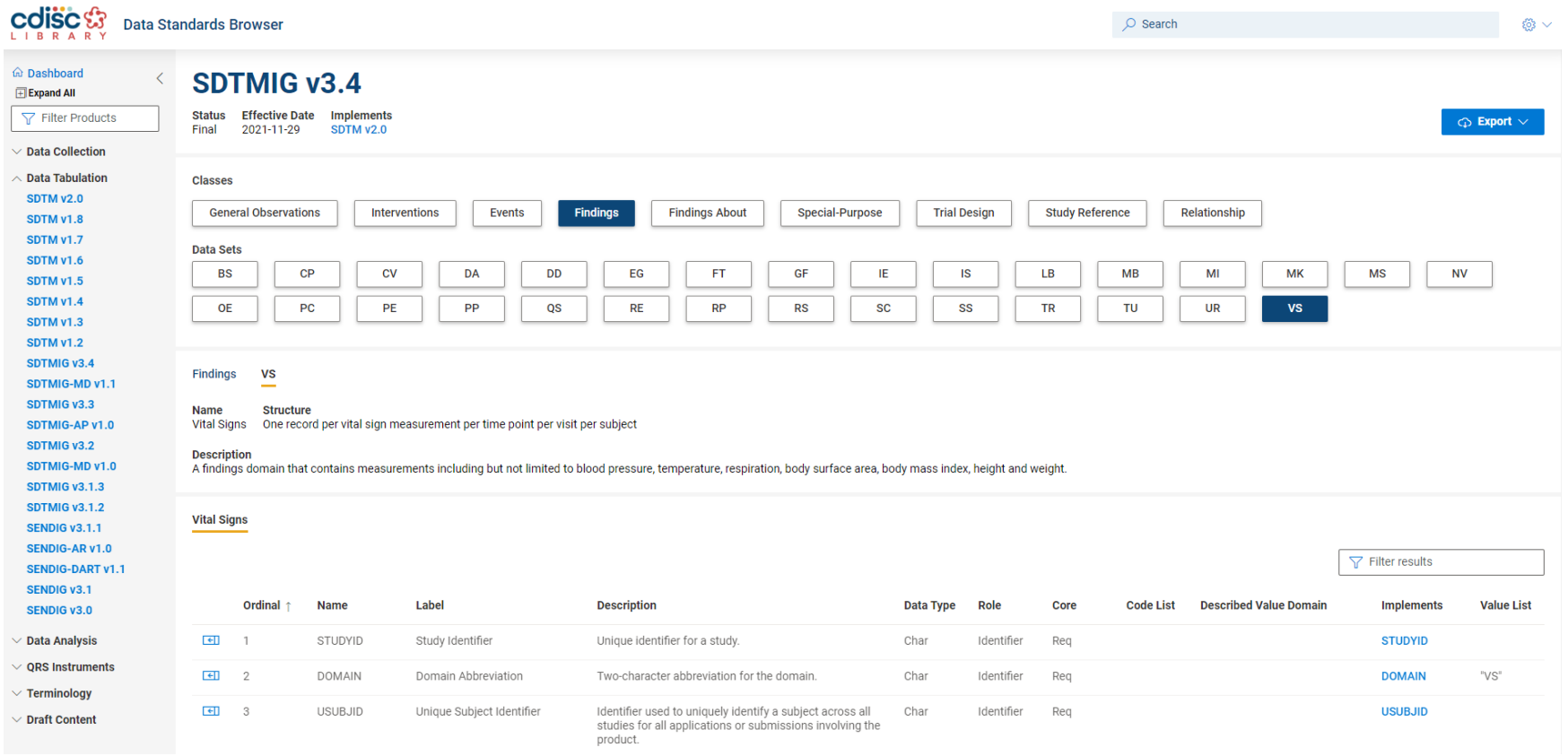


Executable Conformance Rules

Biomedical Concepts	Codelist Subsets	Dataset Specializations	Implementation Guide Text	Standards Mappings
Analysis Results Standard	TAUG Metadata	Derivations and Mappings	Machine-readable Examples	Draft Standards Metadata
Tables, Listings, and Figures	QRS Metadata	Trial Master File Reference Model	CRF Collection	Diff Content Between Versions

REST architecture principles at work

CDISC Library Data Standards Browser



CDISC Library TMF Use Cases

- Ability to maintain of all versions of the RM in a controlled state
- Ability to consult the TMF by searching for artifacts or artifact attributes
- Ability to map to other models i.e. RWS, ISF etc.
- Ability to define relationships between artifacts (clustering)
- Ability to expand TMF RM metadata standard (in collaboration with NCI initiative)
- Ability to provide TMF RM structure and metadata programmatically to systems
- Ability to develop study-type TMF structures based on study design parameters
- Ability to develop rules for TMF structure and metadata validation through CORE?
- Others?

Controlled Terminology Better Support the RM and the Exchange of TMF Content

Create Clear Standards and Formalize the model with regulatory authorities

- Concept coding at Zone, Section and Artifact levels – unique and permanent tracking for each TMF concept at each level.
- Definition proofing: clearly, consistently and meaningfully defined individual concepts (instead of plain language description now used by the reference model).
- Standardized TMF concepts will help to better support the Refence Model itself, which will further help to formalize the TMF-RM with regulatory agencies.
- Terminology analysis and placement influences RM modeling and structuring – users will have a better understanding of where to add and place a new or existing artifact.

Enhance the Trial Master File Exchange Mechanism Standard

- Codified artifacts and metadata standards will be used in the “exchange.xml” to support the automatic transfer of TMF content between sponsors, CROs and other stakeholders in the eTMF-EMS.
- Enhance communication among sponsors, partners, and CROs.

Maintain community engagement

- From the start: controlled terminology is made by their users: need to be clear, consistent, practical and useful.
- To the end: user community governance and quality assurance through public outreach, review and commenting.

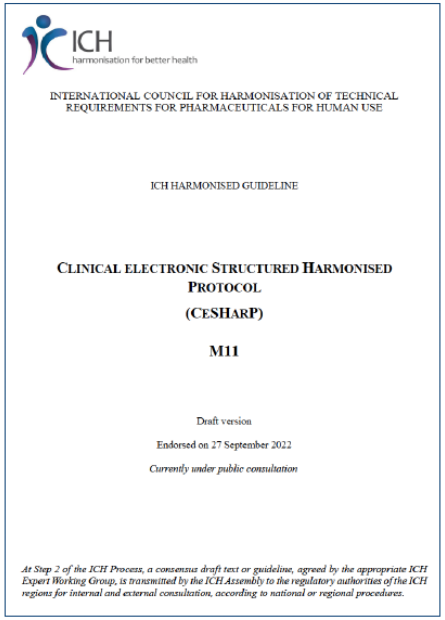
Imported into the CDISC Library

- Searching for specific artifacts, mapping relationships between artifacts.
- Control changes and version history.
- Retrieve versioned reference model and TMF terminology from the library.
- Create views of content and metadata for various types of trials.

M11 Is …

ICH CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL (CeSHarP)

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



ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

(CESHARP)

M11

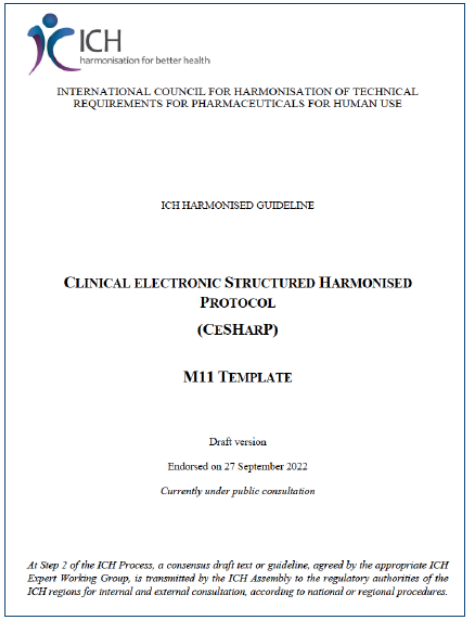
Draft version

Endorsed on 27 September 2022

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

Provides background, purpose, and scope as a guideline



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M11 TEMPLATE

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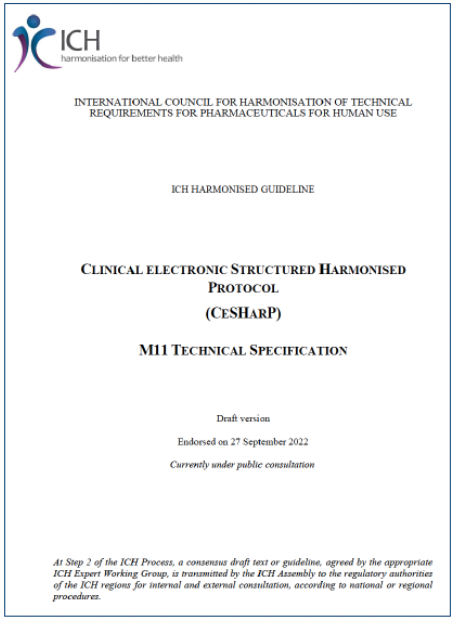
Provides the written format for the Interventional Clinical Trial Protocol Template



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(CESHARP)

M11 TECHNICAL SPECIFICATION

Draft version

Endorsed on 27 September 2022

Currently under public consultation

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Provides the technical representation aligned with the guideline and protocol template

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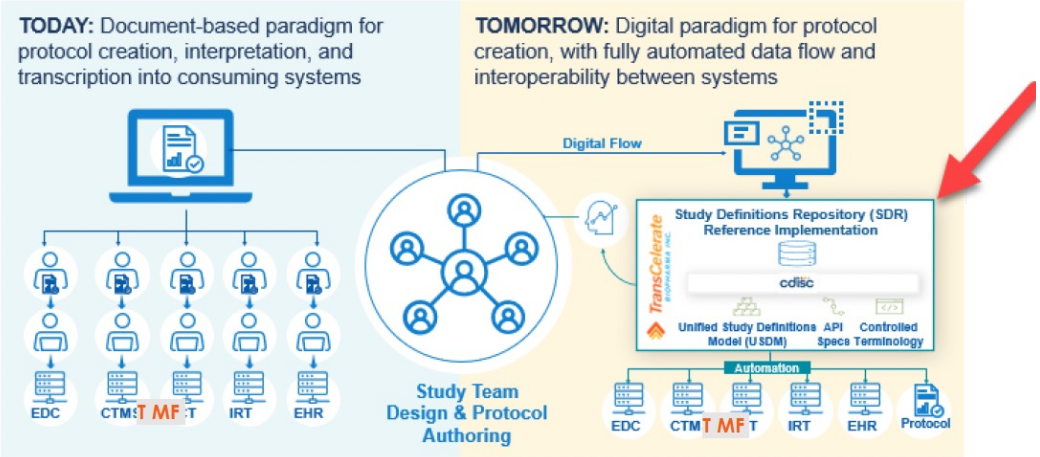
Digital Data Flow Ambition

Digital - standard representation of study protocol
- ✓ structured
- ✓ machine readable
- ✓ executable

Data Flow – industry-wide interoperability
- ✓ exchange of data
- ✓ non-cooperating organizations
- ✓ minimal effort

Documents to Data / Write Once, Read Many



Eliminate non-value added activities, work smarter not harder
Enable automation of downstream study startup and conduct processes
For all stakeholders

TransCelerate BIOPHARMA INC.

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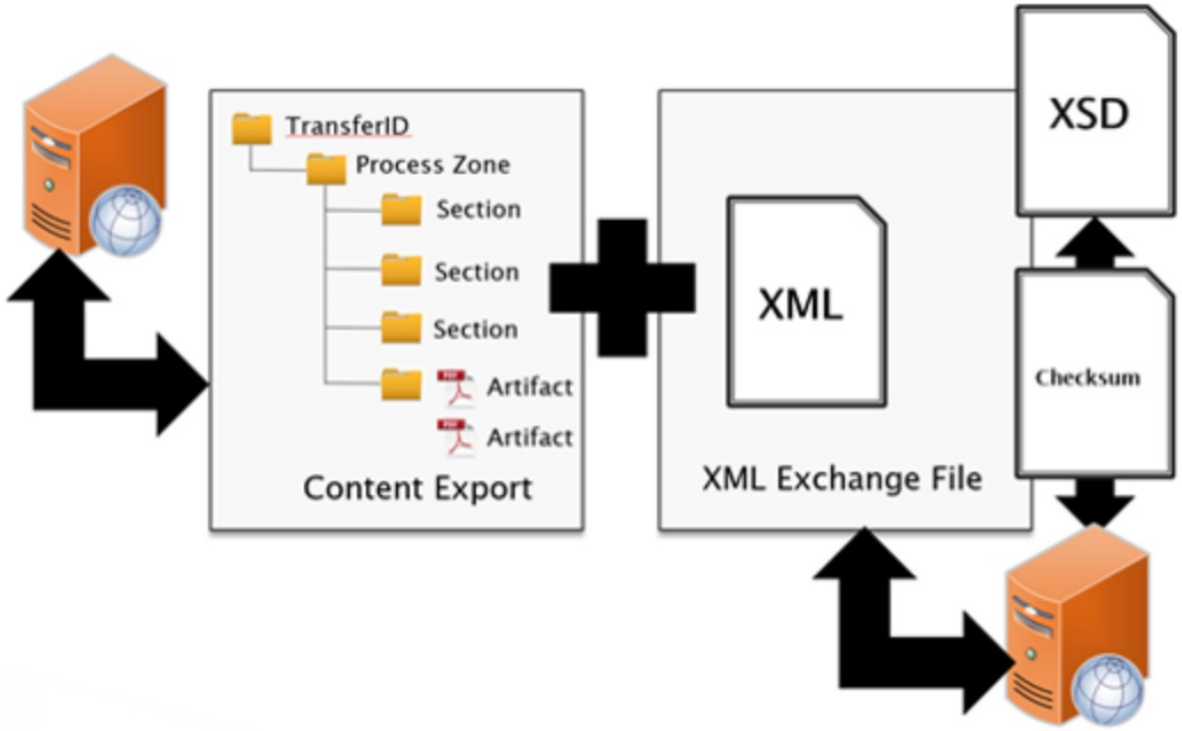
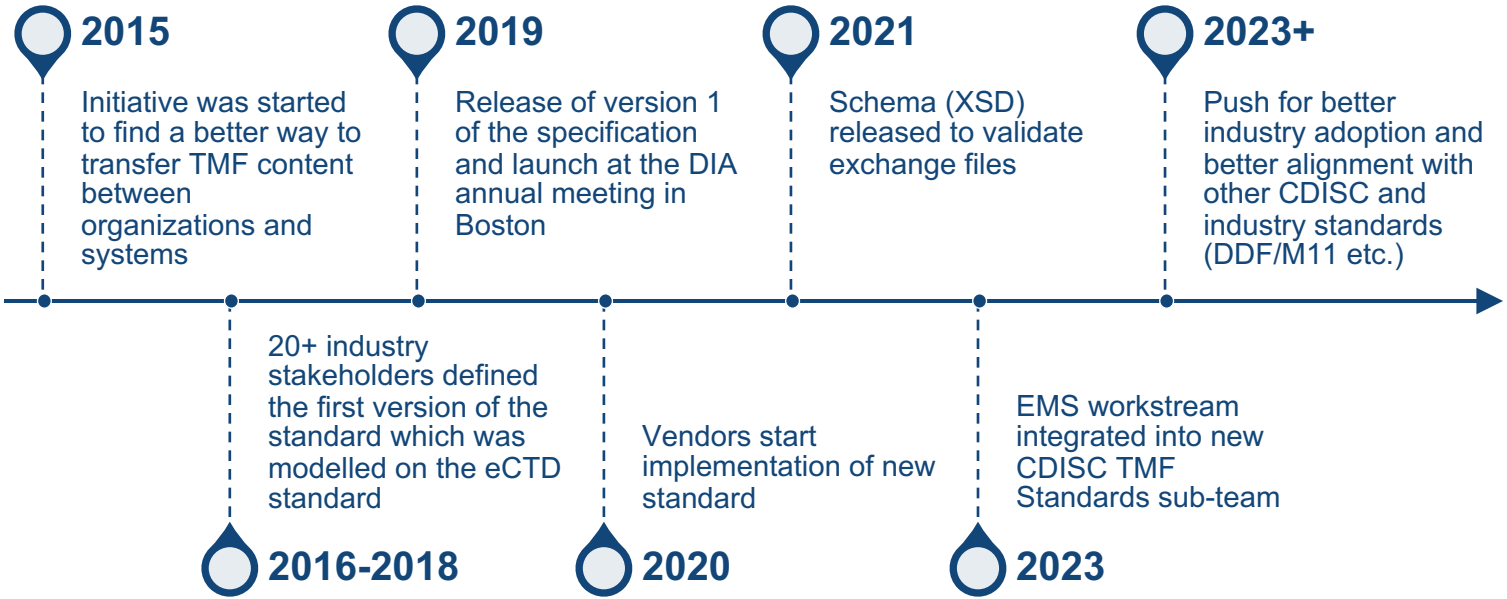
Source: Rob DiCicco, TransCelerate Biopharma Inc.

eTMF Exchange Mechanism Standard V1



History of EMS



Evolution of EMS / Interoperability

- EMS has been developed, and some vendors are adopting it, but has yet to be reduced to practice in a significant way
- A new workstream has been put together to start to align the EMS to USDM in preparation for integration with DDF
- More modern data formats are also being evaluated to make it easier to integrate into modern computerized systems
- The workstream will also look at aligning/defining terminology with CDISC CT
- Audit trail metadata will also be updated
- The output of the updated standard will be published in the library

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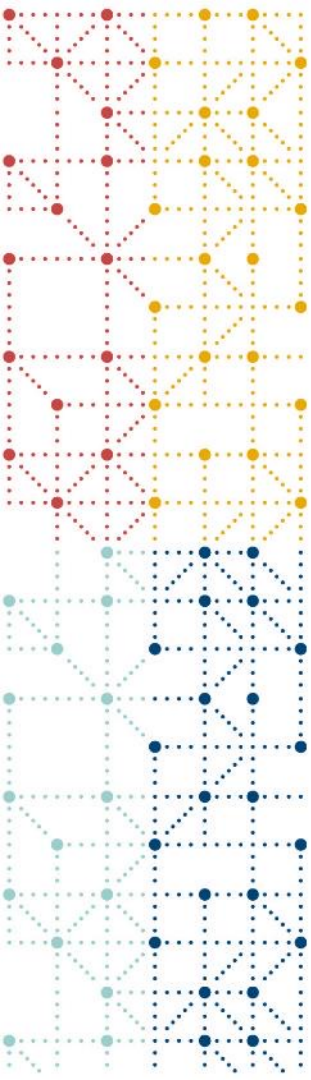

Long Term Retention

Meeting the EU Directive's Requirements for Archiving

"The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities"

"The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the period"

- Trend is to reduce the number of transfers:
  - Increasing use of Sponsor eTMF
  - eTMFs supporting long term retention with archivist access
  - Integration focus with groups such as CRISI
- Standardisation significantly reduces transfer effort

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Mindset Change around On-line vs Off-line archiving

- ”Archiving” the completed studies in the on-line system facilitates leveraging historical eTMF data to manage different aspects of our clinical development
  - Identify which artifacts are required to document specific processes and events which will improve completeness
  - Calculation of risk scores so that we can focus our oversight on high-risk areas
  - Navigate using the latest standards provided by the CDISC library (or the original version of the reference model used to index the TMF ☺)
  - Facilitate completeness and quality assessment for Inspection (it does happen!)

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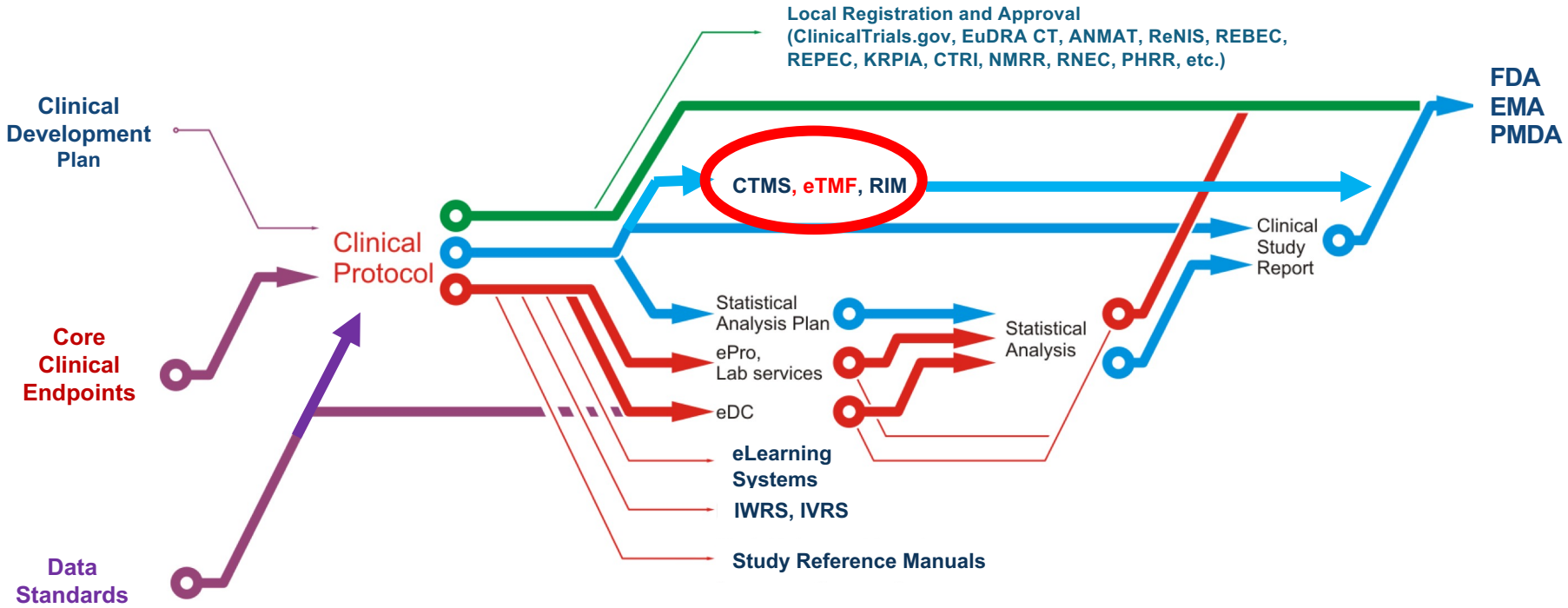
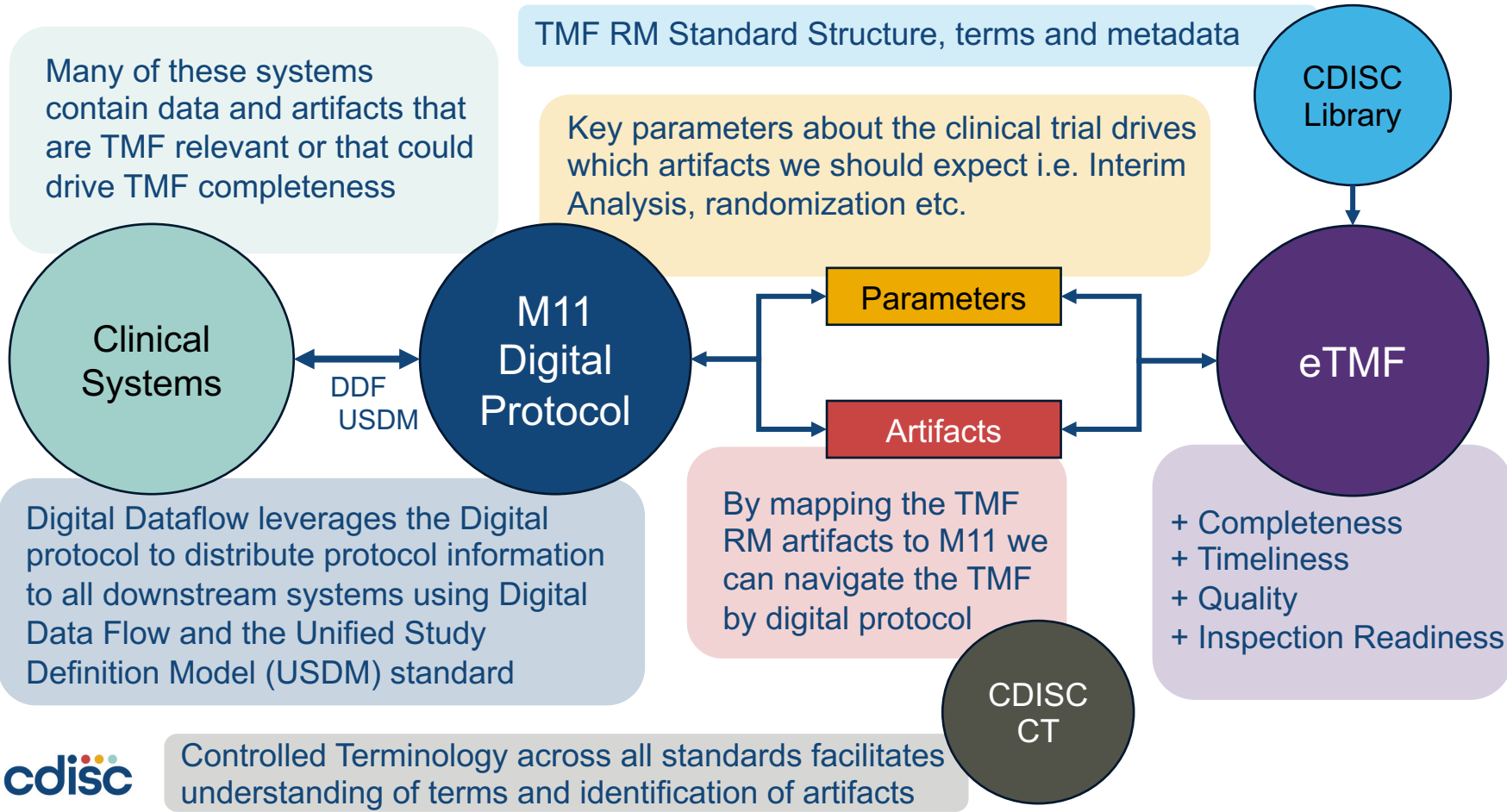
The Future State

The Clinical Trial Information Flow



Using M11 and DDF to facilitate completeness and long-term retention



Conclusion

- Better interoperability and digital flow of information across systems will allow us to better gauge completeness and create stronger links to records contained within other systems
- Standardization of the reference model and maintenance of the reference model in the CDISC library will help us ensure the long term retrievability of eTMFs
- The application of CDISC controlled terminology to the reference model will ensure consistency not only within the reference model but also with other clinical systems
- ICH M11 digital protocols will allow us to better drive eTMF expected artifacts through trial design parameters and allow us to navigate the TMF by study protocol
- Standardization will ultimately help us achieve more effective long-term retention, retreivability and traceability of records within our TMFs and also make them future proof
- They will also allow us to start to unlock the goldmine of information that our TMFs contain to help us build more intelligent eTMF systems

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Thank you!

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