Towards a more data driven TMF: Integration of the TMF Reference Model with Digital Data Flow, ICH M11 and other CDISC standards

Nick Hargaden, Director Clinical Trial Systems and Operations, Moderna

Paul Fenton, CEO, Montrium

Meet the Speakers

Nick Hargaden

Title: Director, Clinical Trial Systems and Operations

Organization: Clinical Development Operations, Moderna

Business owner for eTMF and CTMS applications. Global head of TMF Operations managing in house and vendor teams. 25 years in application of computerized systems to speed drug development and improve quality including IRT, TMF, RBQM, eCOA.

https://www.linkedin.com/in/nickhargaden

Paul Fenton

Title: Founder and Chief Executive Officer

Organization: Montrium

25 year experience in clinical computerized systems. Longstanding Member of the TMF Reference Model Steering Committee. Chair of the CDISC TMF Standards Working Group.

https://www.linkedin.com/in/paul-fenton-360b531/

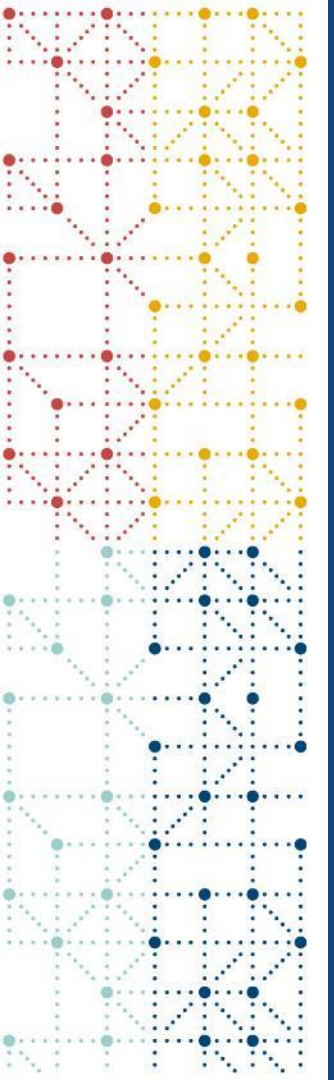
Disclaimer and Disclosures

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

- *The author(s) have no real or apparent conflicts of interest to report.*

Agenda

1. From Documents to Digital Assets
2. The Data Driven Approach to TMF
3. Benefits of a Data Driven Approach
4. Conclusions and Next Steps



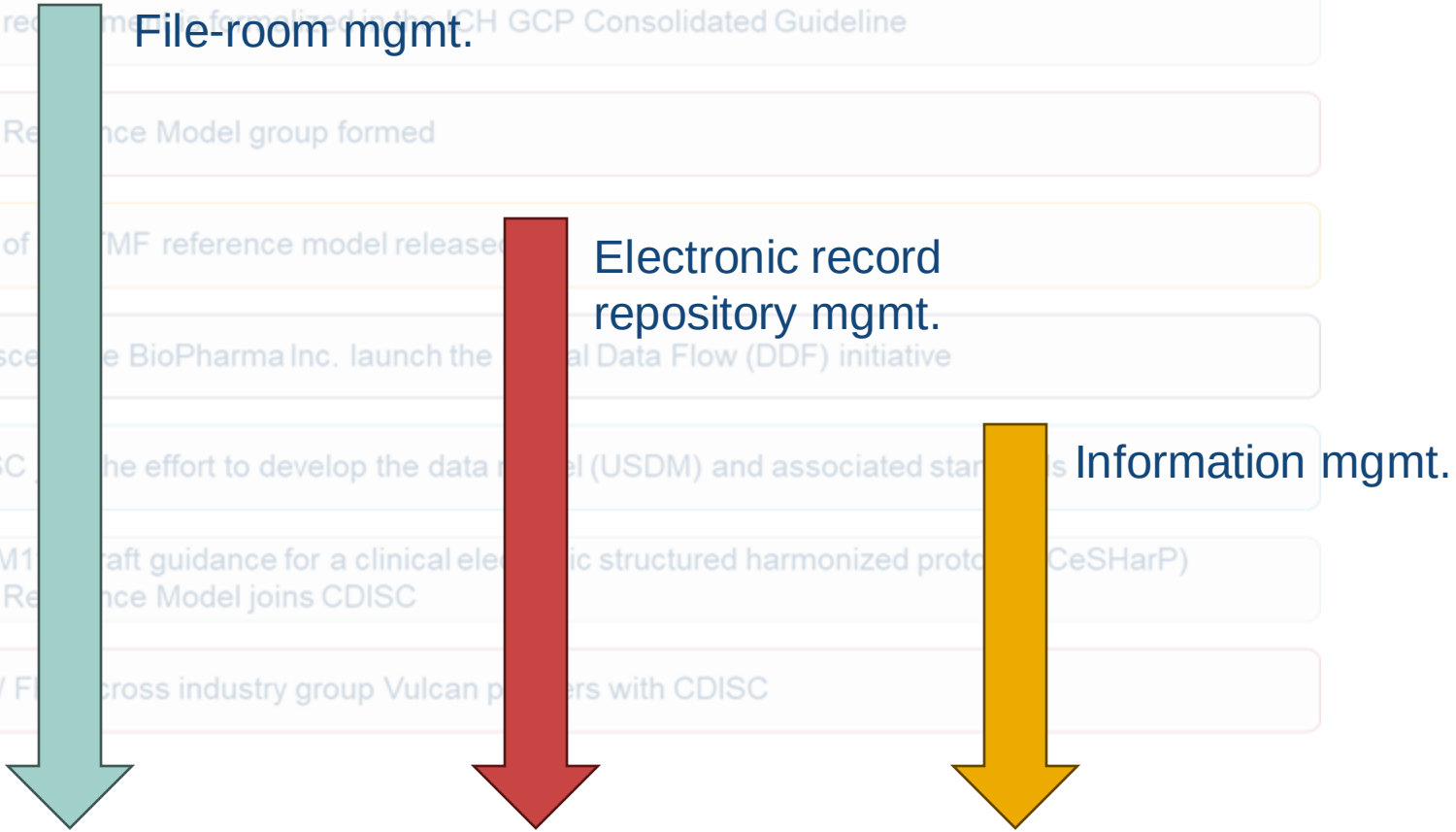
From Documents to Digital Assets

Current and future state of TMF as an information management discipline

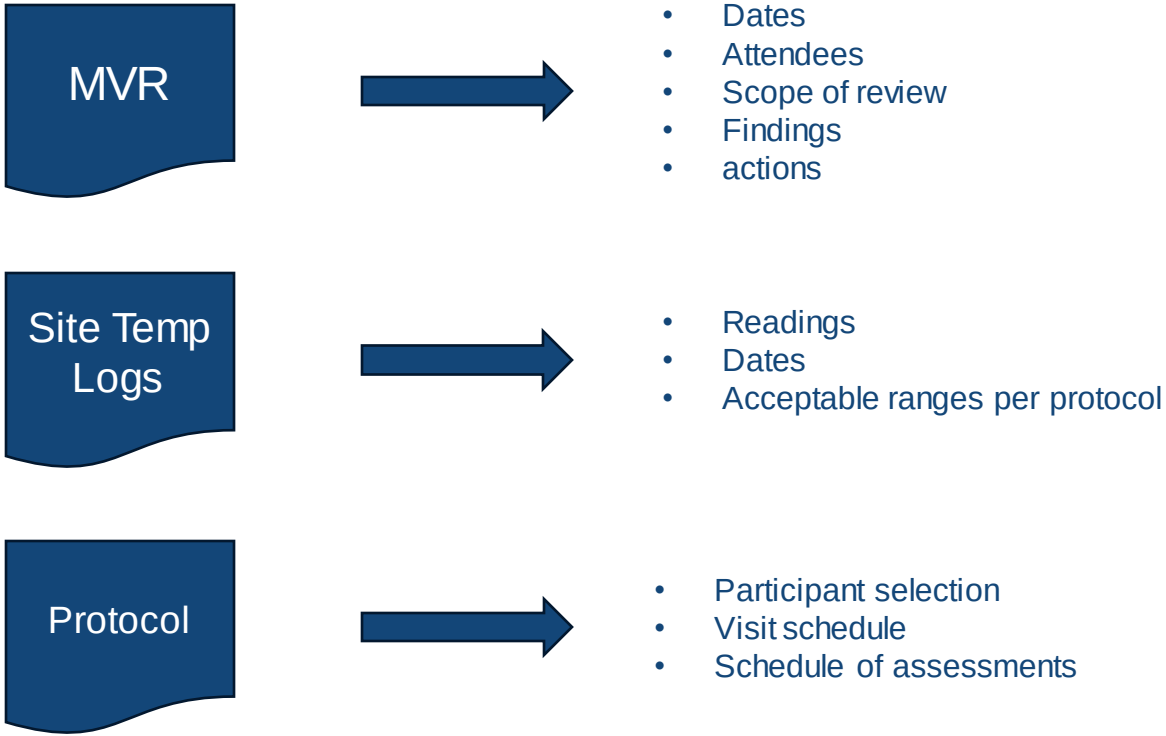
A brief history

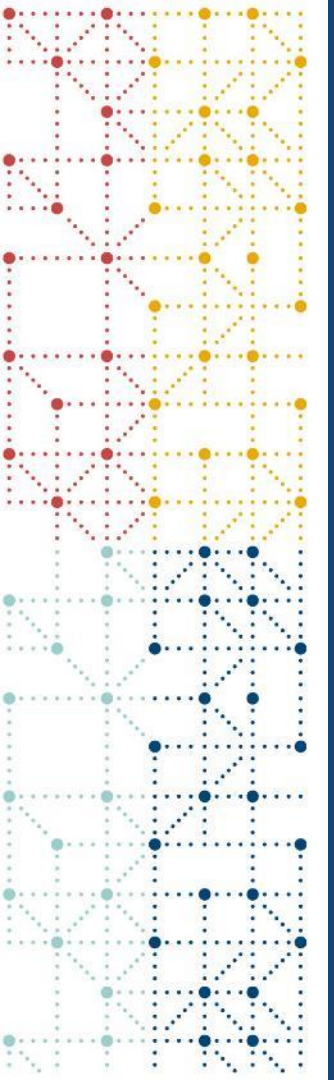
1996	• TMF requirement is formalized in the ICH GCP Consolidated Guideline
2004	• V1 of Study Data Tabulation Model (SDTM) is released by CDISC
2009	• TMF Reference Model group formed
2010	• V1.0 of the TMF reference model released
2018	• Transcelerate BioPharma Inc. launch the Digital Data Flow (DDF) initiative • TMF Reference Model EMS v1.0. released
2021	• CDISC joins the DDF effort to develop the data model (USDM) and associated standards
2022	• ICH M11 - draft guidance for a clinical electronic structured harmonized protocol (CeSHarP) • TMF Reference Model joins CDISC
2023	• HL7 / FHIR cross industry group Vulcan partners with CDISC

A brief history



Digital Assets and the TMF - Examples





The Data Driven Approach

Initiatives and application to eTMF systems

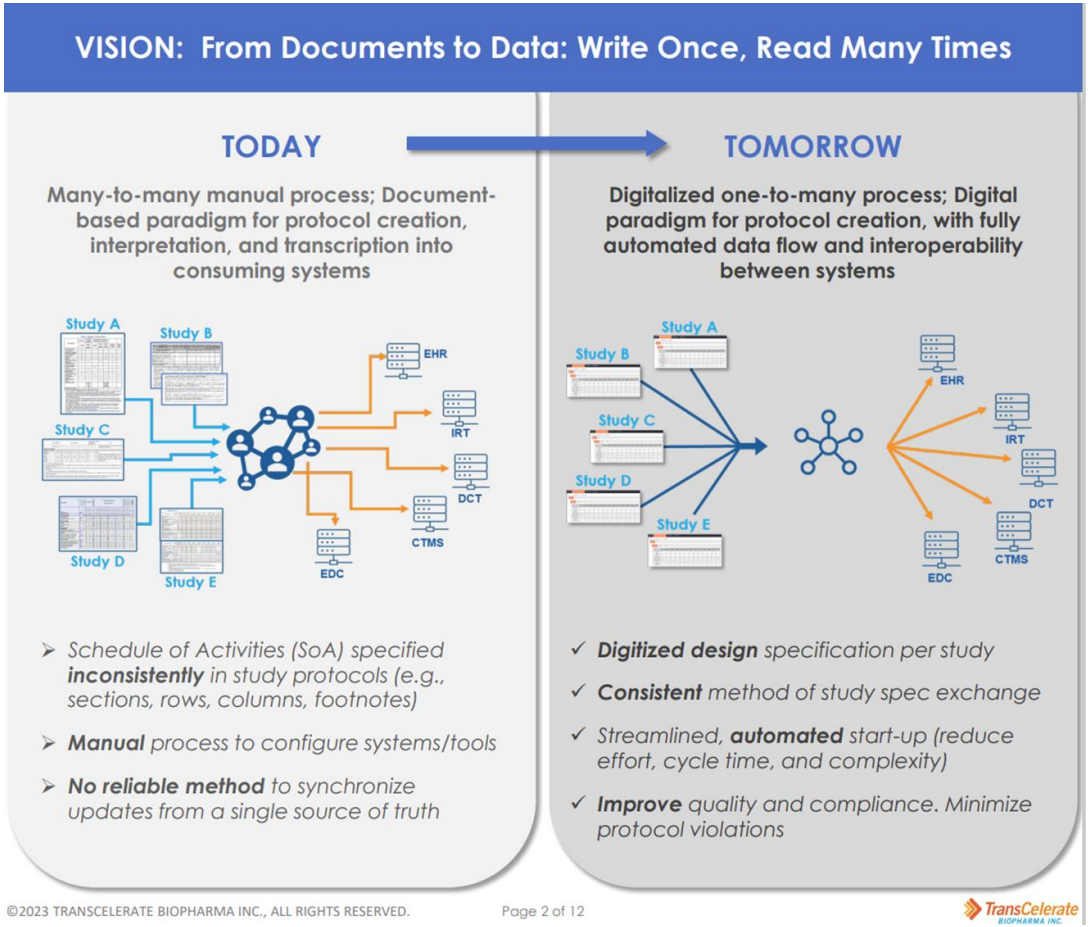
ICH M11: Clinical electronic Structured Harmonised Protocol (CeSHarP)

- Regulator driven guideline for a structured protocol standard that allows for digitization
- Standardizes content and format for trial information such as names, addresses, phase, amendment history and description, trial population, storage and handling information, blinding information, safety and AE information
- Tools will be used to develop and maintain the digital protocol
- No more word documents!

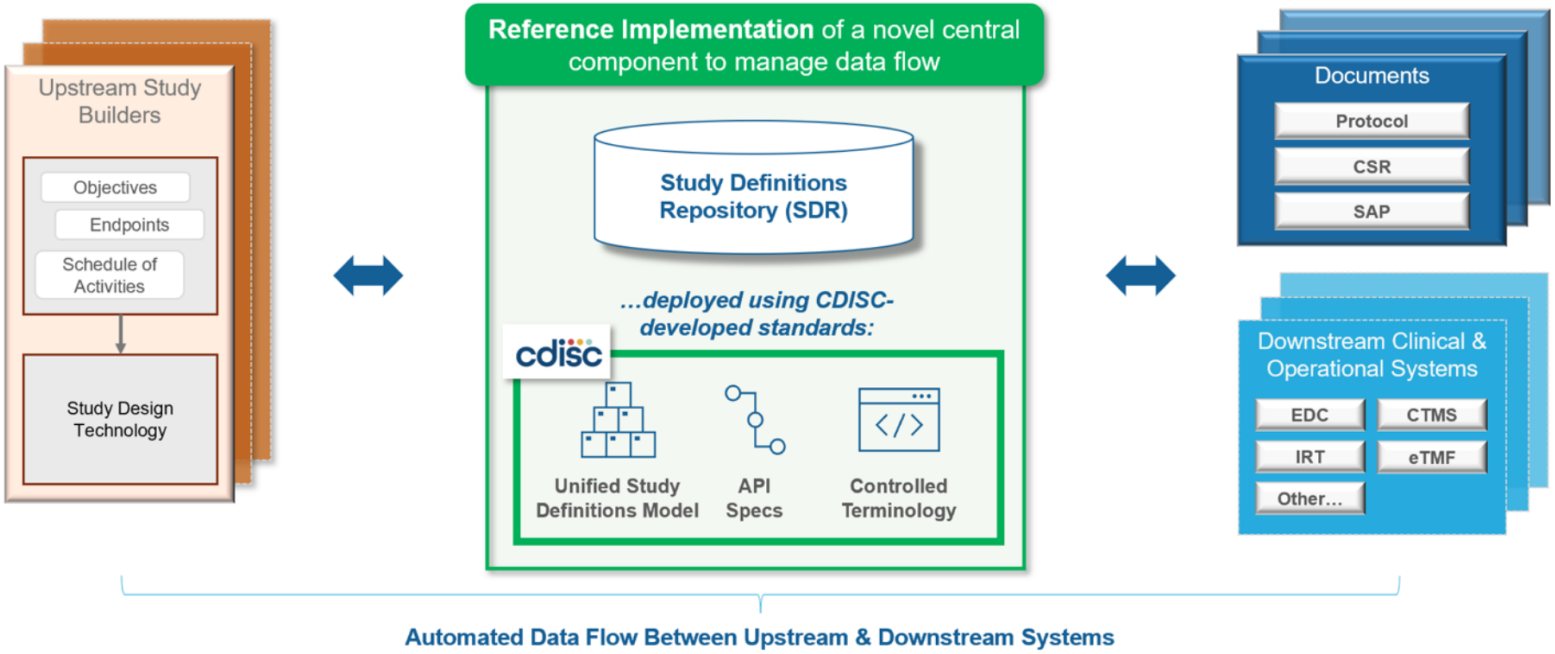
Term (Variable)	Committees
Data Type	List
Topic, Value or Header	D
Definition	
User Guidance	
Conformance	Required/Multiple
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Trial Design
Relationship (reference to high level conceptual model)	
Value	No, Data Monitoring Committee
Business rules	**Value Allowed:** Yes **Relationship:** n/a **Concept:** n/a
Duplicate field in other sections	

Digital Data Flow

- Digital data flow (DDF) aims to distribute digital protocol information to downstream systems
- This way each system is using the same version of the protocol design
- This information can be used to configure each clinical system and maintain the configuration as the protocol evolves
- Eventually systems will also be able to exchange information using DDF and associated standards



Unified Study Definition Model (USDM) & Study Definitions Repository (SDR)



NCI EVS – CDISC Controlled Terminology

- National Cancer Institute has partnered with CDISC to develop a controlled terminology library for all standards
- Controlled Terminology is composed of standard terms, code-lists, synonyms and definitions
- It allows us to easily understand what a particular data point is and to standardize on each data points nomenclature
- By using standard terms, we can better empower interoperability between systems and organizations and help ensure harmonization across all process zones of the reference model

NIH NATIONAL CANCER INSTITUTE Enterprise Vocabulary Services

	Term	Submission Value	Synonyms	Definition	
	C142451	protocol	clinical protocol; study protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments. NOTE: Present usage can refer to any of three distinct entities: 1) the plan (i.e., content) of a protocol, 2) the protocol document, and 3) a series of tests or treatments (as in oncology). [ICH E6 Glossary]	Clinical Trial Protocol

Dashboard
Expand All
Filter Products

Data Collection
Data Tabulation
SDTM v2.0
SDTM v1.8
SDTM v1.7
SDTM v1.6
SDTM v1.5
SDTM v1.4
SDTM v1.3
SDTM v1.2
SDTMIG v3.4
SDTMIG-MD v1.1
SDTMIG v3.3
SDTMIG-AP v1.0
SDTMIG v3.2
SDTMIG-MD v1.0
SDTMIG v3.1.3
SDTMIG v3.1.2
SENDIG v3.1.1
SENDIG-AR v1.0
SENDIG-DART v1.1
SENDIG v3.1
SENDIG v3.0
Data Analysis
QRS Instruments
Terminology

SDTMIG v3.4

Status Final
Effective Date 2021-11-29
Implements SDTM v2.0

Export
- Comma-Separated Values (CSV)
- Microsoft® Excel® (XLSX)
- Diff Report in Microsoft® Excel® (XLSX)

Classes

General Observations | Interventions | Events | Findings | Findings About | Special-Purpose | Trial Design | Study Reference | Relationship

Data Sets

TA | TD | TE | TI | TM | TS | TV

Trial Design TA

Name Trial Arms
Structure One record per planned Element per Arm

Description A trial design domain that contains each planned arm in the trial.
Status Final

Trial Arms

Filter results

	Ordinal ↑	Name	Label	Description	Data Type	Role	Core	Code List	Described Value Domain	Implements	Value List
	1	STUDYID	Study Identifier	Unique identifier for a study.	Char	Identifier	Req			STUDYID	
	2	DOMAIN	Domain Abbreviation	Two-character abbreviation for the domain.	Char	Identifier	Req			DOMAIN	"TA"
	3	ARMCD	Planned Arm Code	ARMCD is limited to 20 characters and does not have special character restrictions. The maximum length of ARMCD is longer than that for other "short" variables to accommodate the kind of values that are likely to be needed for crossover trials. For example, if ARMCD values for a 7-period crossover were constructed using 2-character abbreviations for each treatment and separating hyphens, the length of ARMCD values would be 20.	Char	Topic	Req			ARMCD	
	4	ARM	Description of Planned Arm	Name given to an arm or treatment group.	Char	Synonym Qualifier	Req			ARM	
	5	TAETORD	Planned Order of Element within Arm	Number that gives the order of the element within the arm.	Num	Timing	Req			TAETORD	
	6	ETCD	Element Code	ETCD (the companion to ELEMENT) is limited to 8 characters and does not have special character restrictions. These values should be short for ease of use in programming, but it is not expected that ETCD will need to serve as a variable name.	Char	Record Qualifier	Req			ETCD	
	7	ELEMENT	Description of Element	The name of the element. The same element may occur more than once within an arm.	Char	Synonym Qualifier	Perm			ELEMENT	
	8	TABRANCH	Branch	Condition subject met, at a "branch" in the trial design at the end of this element, to be included in this arm (e.g., "Randomization to DRUG X").	Char	Rule	Exp			TABRANCH	
	9	TATRANS	Transition Rule	If the trial design allows a subject to transition to an element other than the next element in sequence, then the conditions for transitioning to those other elements, and the alternative element sequences, are specified in this rule (e.g., "Responders go to washout").	Char	Rule	Exp			TATRANS	

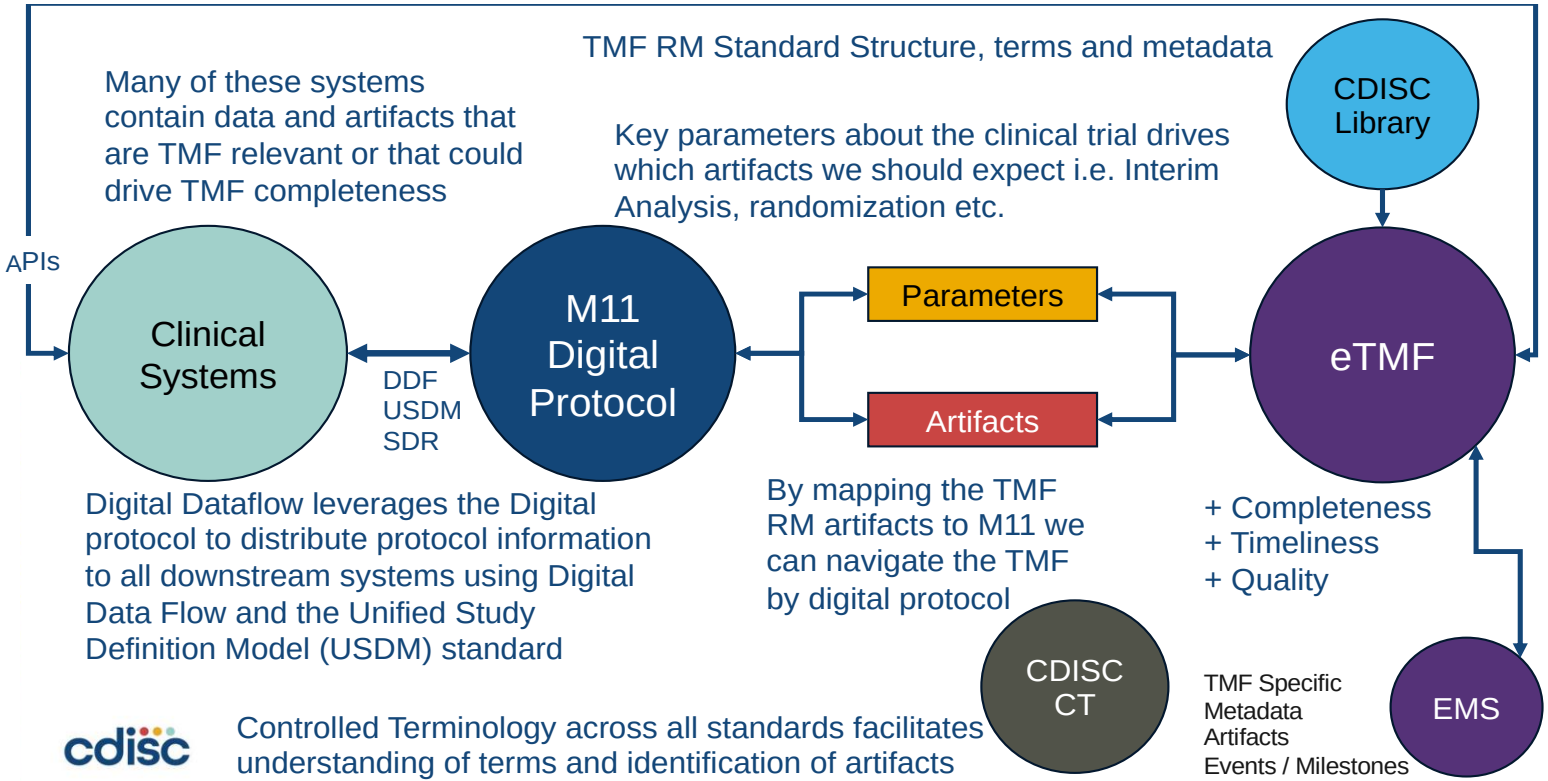
CDISC TMF Exchange Mechanism Standard (EMS)

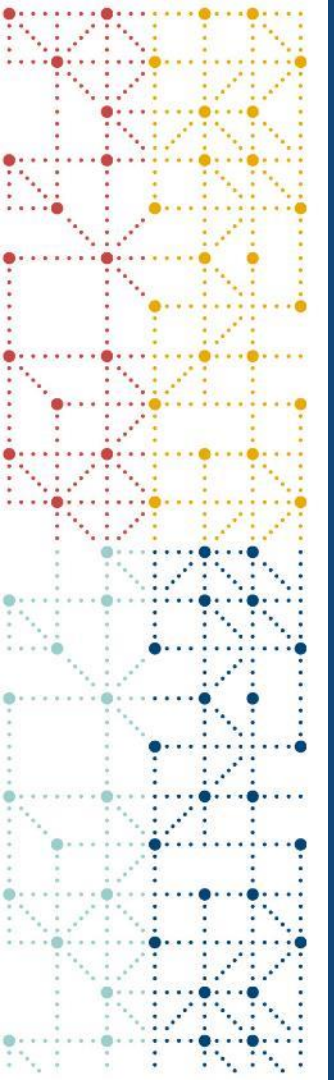
Standard developed specifically for TMF interoperability and artifact exchange

Is composed on a standard set of metadata and a mechanism for cross referencing files and and providing an inventory of what needs to be exchanged between two systems or organizations

Initial focus was on the transfer of files, but could also be used to transfer data points and study event information

The Data Driven Approach





Benefits of a Data Driven Approach

Implications and opportunities for the TMF community

Opportunities

Configuration

- Use the digital protocol to configure expected trial level elements such as countries, sites, events, milestones, and document lists in eTMF.

Synchronization

- Automatic exchange of records data between systems using standard formats (e.g. RIM to eTMF).
- Exchange of event data and EDL automation.

Completeness

- Remove the fundamental challenge of distributed filing, using synchronization.
- Create a comprehensive overview of trial status in eTMF.

Opportunities

Navigation and telling the story

- Completeness ≠ a clear story
- Digital protocol as TMF TOC?
- ChatGPT for TMF – "asking your TMF questions"

Contribute to trial health

- Sending TMF insights to other systems
- e.g. in risk mgmt. applications help create clusters of information for the assessment of trial events and drive proactive signal detection in risk based quality mgmt. (RBQM).

TMF as oversight tool

- Holistic TMF could be a true oversight tool for clinical teams and sponsor quality functions throughout the trial, not just in inspection.
- TMF as a window into what is happening, as it happens

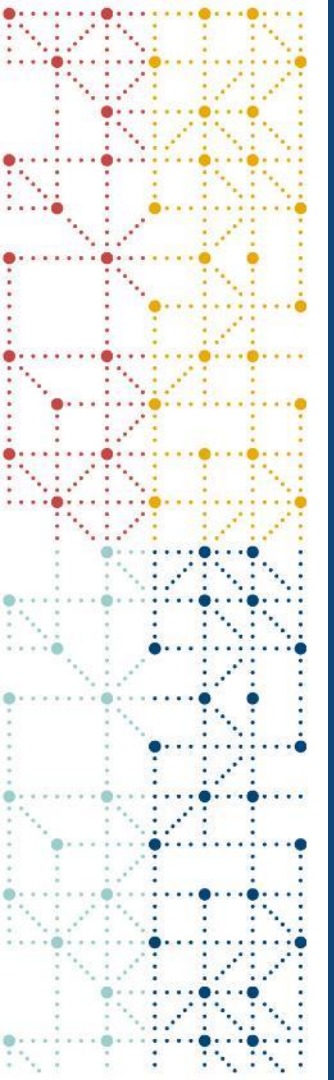
Potential Benefits

Our industry is transitioning to a data driven paradigm

- Less reliance on document rendition of computerized activities
- Process transformation (cf. paper to eCRF change in data mgmt.)
- Vendor and sponsor agnostic data standards

The TMF is an extraordinary but under-utilized resource of rich information about trial conduct.

- The record repository model limits the TMF to the role of inspection support
- An information management model could facilitate a move to a true trial oversight tool and information hub



Next Steps

Ongoing work and call to contribute

What's Next

Two TMF community papers will be released:

Available soon: A white paper outlining the current and future state of the data driven approach to clinical trial management and its implications for business processes and the TMF community.

In Q3: a technical specification detailing the potential application of USDM to the reference model and how to align the exchange mechanism standard.

Thank You!

Special thanks to Aaron Grant, VP Solutions Consulting, Phlexglobal