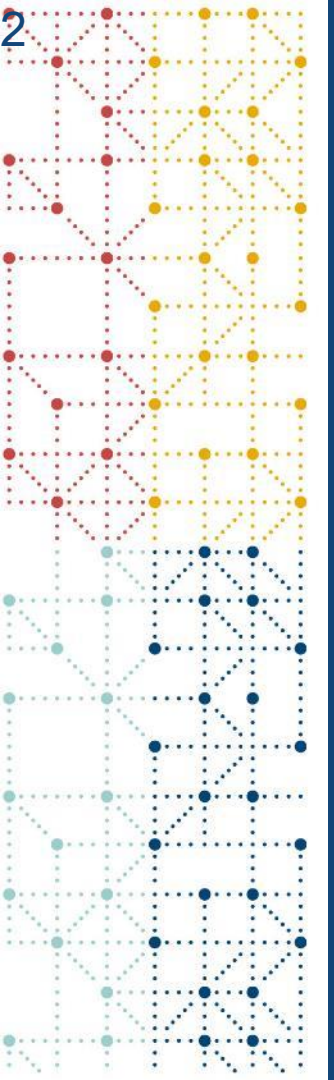
The TMF Reference Model
General Meeting September 2025

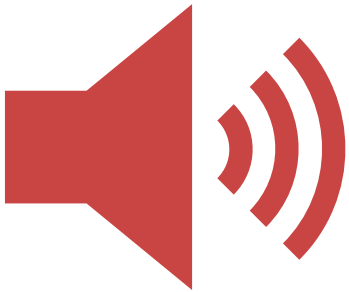
Presenters:

- Paul (Fenton) Carter, CEO, Montrium; Chair, TMF Reference Model Steering Committee
- Jamie Toth, Sr. Director, Global Trial Master File Management & Records, BeOne Medicines; Incoming Chair Elect, TMF Reference Model Steering Committee
- Yuto Kanda, Veeva Vault Clinical Support Manager, Chugai Pharmaceutical Co.
- Lisa Mulcahy, Mulcahy Consulting LLC, TMF Reference Model Steering Committee Member
- Lisa Grim, Program Manager, Patient Safety & Pharmacovigilance, Sanofi
- Jo Oliver, TMF Study Owner, Pfizer
- Curran Murphy, Head of Clinical Business Operations, Blueprint Medicines



Housekeeping

Housekeeping

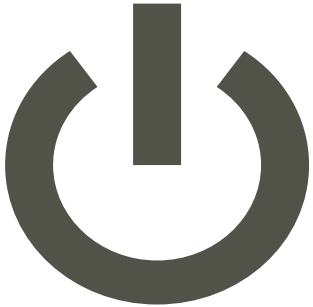


You will remain on **mute**

Housekeeping

Submit questions at any time via the Questions tool on your Teams app

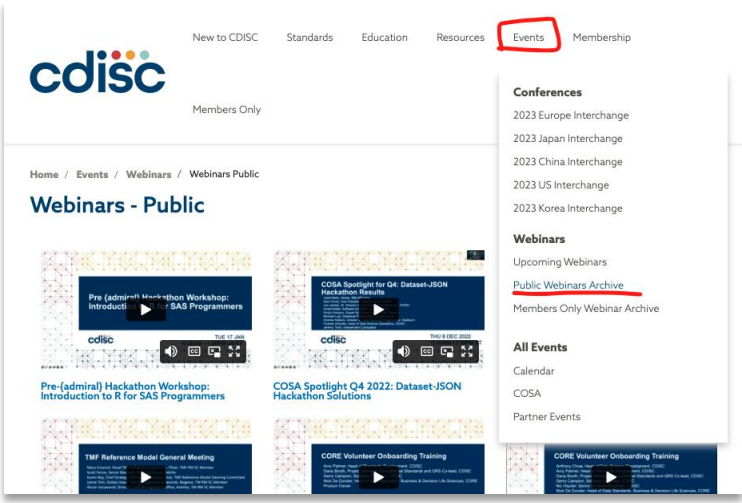
Housekeeping



Audio Issues?

First, close and restart your Teams App
Second, check your local internet connection strength

Housekeeping

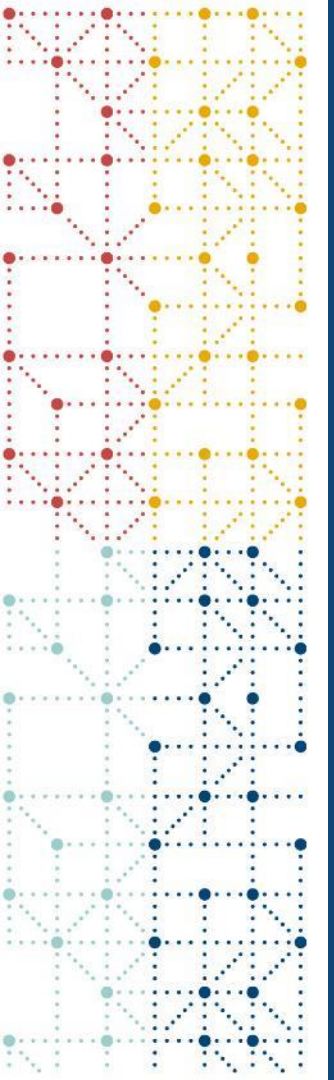


Webinar Recording

A recording of this webinar will be available in the Public Webinar Archive on the CDISC website.

Agenda

1. Announcements & Housekeeping
2. Events & Interchange
3. Community Update
4. TMF v4 Update
   - Triage Committee
   - ICH E6 R3
   - EU CTR
   - Vendors & Metadata
   - (In-Vitro) Device
   - Computerized Systems
   - RWE
5. ISF Initiative
6. Education Committee
7. Risk Initiative



Announcements

Paul (Fenton) Carter, CEO, Montrium; Chair, TMF Reference Model Steering Committee

Thank you JP

Welcome Suzanne

Presentation to EMA

- Good Clinical Practice Inspectors' Working Group (GCP IWG) will be held in Amsterdam on November 24th 2025
- The agenda will focus on:
  - **Essential records:** what to keep and what not to keep
  - **Computerised and AI systems:** risk-proportionality: scaling risks without tipping the scales
- Donna Dorozinsky and Paul Carter will be presenting during the meeting on the work being done for V4 and the vision for the TMF RM
- This will also be an opportunity for us to connect with EU regulators and create visibility for the new standard within the GCP IWG

Check out the updated Website!

[Trial Master File Reference Model | CDISC]

Go to https://www.cdisc.org/tmf

New landing page and content is better organized for ease of navigation!

Events & Interchange Update

Jamie Toth, Sr. Director, Global Trial Master File Management & Records, BeOne Medicines; Incoming Chair Elect, TMF Reference Model Steering Committee


2025
CDISC + TMF
US INTERCHANGE
NASHVILLE
CONFERENCE & EXPO: 13-14 OCTOBER | TRAININGS: 15-17 OCTOBER

US Interchange Update, Part I

- Registration Today = 322
  - 122 TMF
  - 191 CDISC
  - Register Here
  - Significant discounts for CDISC Members and groups of 10+ people!
- Sponsors & Exhibitors Today = 22
  - 10 TMF Exhibitors
  - 11 CDISC Exhibitors
  - 1 Sponsor-Only
  - Last Chance on Booth Spaces – only a few spots remaining! Sign Up Here

US Interchange Update, Part II

Conference Highlights:

- Two (2) Keynote Presentations
  - **Dr. Peter Émbi**, Professor of Biomedical Informatics and Medicine, Vanderbilt University Medical Center, presenting “AI in Clinical Research - Balancing Innovation with Ethics and Oversight”
  - **Sarah Dolan**, Ambassador, Davis Phinney Foundation; Member, FDA PCNS Advisory Committee; Member, Critical Path to Parkinson's Endpoints Team, presenting “Lemons or Lemonade - One Perspective of Living with Young Onset Parkinson’s Disease”
- Join us for deep insights into the future of TMF, specifically **TMF v4 and ICH E6 (R3).**
- Visit our **Poster Session** and the **TMF Vendor Community** during all breaks and lunches.
- Level up your TMF knowledge by joining a TMF course! **Two (2) TMF trainings** will be offered during the Interchange week:
  - Fundamentals of the TMF Reference Model
  - The Critical Role of Data Managers, Biostatisticians, and Programmers in Achieving TMF Excellence
  - Sign Up for Training Here

All Aboard for the Evening Networking Event!

After the first day of the Main Conference on 13 October, join us aboard the iconic *General Jackson Showboat*, enjoy a Southern-style dinner, live entertainment, and stunning views of the Nashville skyline.

Note: *The Evening Event is free for Main Conference attendees, but space is limited. Be sure to select this option during registration.*

Upcoming Opportunities

- 2025 Japan Academic Workshop
  - Fully virtual event
  - Full Agenda Online
  - Sponsorship Opportunities
  - View webpage here
- 2026 CDISC+TMF Europe Interchange
  - The Interchange will be held in Milan, Italy at the stylish new Quark Hotel Milano
  - 20-21 May: Main Conference
  - 18, 19, 22 May: CDISC Training
  - Sponsorship Opportunities and Call for Abstracts will be announced in October.
  - To submit early interest, please reach out to events@cdisc.org.

Poll Question!

Do you plan to attend the Nashville conference?

A. Yes

B. No

Poll Question!

Do you plan to attend the CDISC+TMF Interchange in May in Milan?

A. Yes

B. No

Poll Question!

If you attended a CDISC+TMF Interchange in the past, how effective do you find the current Events & Interchange sessions in addressing your needs and providing valuable insights?

A. I have yet to attend a CDISC+TMF Interchange
B. I find the sessions very effective
C. The sessions are somewhat effective, but there's room for improvement

Community Update

Yuto Kanda, Veeva Vault Clinical Support Manager, Chugai Pharmaceutical Co.

Poll Question!

What additional topics or updates would you like to see included in future Community Updates to better support your work?

A. I would like to see more updates on industry trends and best practices.

B. More case studies and success stories would be helpful.

C. I think we should focus on more technical updates and resources.

Poll Question!

Are there other regional communities that you think we should start?

A. APAC
B. Latin America
C. Europe
D. Other

Update from TMFers community in Japan 1/2

- **We successfully finished our 1st F2F workshop on 24June**
- **Topics Covered**
  - ✓ICH-E6 (R3) vs TMF
  - ✓Sponsor-CRO collaboration
  - ✓TMF RM
  - ✓Oversight
  - ✓Completeness
  - ✓AI/Tech optimization

- **Next F2F will be on 3Dec2025**
- **Idea example raised for next time ;**

EDL, risk-based TMF management, invitation to foreign speakers….

Update from TMFers community in Japan 2/2

- Currently we **have almost 30 members**,
and **we are growing… especially in Academia.**
  - We've got many new members from 3 Japanese hospitals
  - They are not only interested in ISF RM, but also in TMF RM
  - **@JP TMFers, please contact me if you are interested :)**
    メンバー募集中です！

- **We've launched Linkedin Community for JP TMFers.**
@JP TMFers, let's sign up to join us !

- **Yuto and Miyuki will be speaking more about us in Nashville on13Oct,**
See you there !

14:00 - 14:30	**The Japanese TMF Community** Yuto Kanda, Chugai Pharmaceutical Co., Ltd.; Miyuki Taguchi, Inseption

TMF v4 Updates

Paul (Fenton) Carter, CEO, Montrium; Chair, TMF Reference Model Steering Committee

Poll Question!

How prepared do you feel for the transition to TMF v4, and what resources or support would help you the most during this process?

A. I feel well-prepared for the transition and don't need additional support.

B. I feel somewhat prepared but would benefit from additional resources and training.

C. I don’t feel prepared at all and would need comprehensive support & guidance

Poll Question!

How well do you understand the implications of the EU CTR on your current processes, and what further information or training would be beneficial?

A. I have a good understanding of the implications and feel confident in my knowledge.

B. I have a basic understanding but would benefit from additional training or resources.

C. I am not familiar with the EU CTR and would need comprehensive training to understand its impact.

Poll Question!

What challenges do you foresee in implementing the new ICH E6 R3 guidelines, and how can we address them collectively?

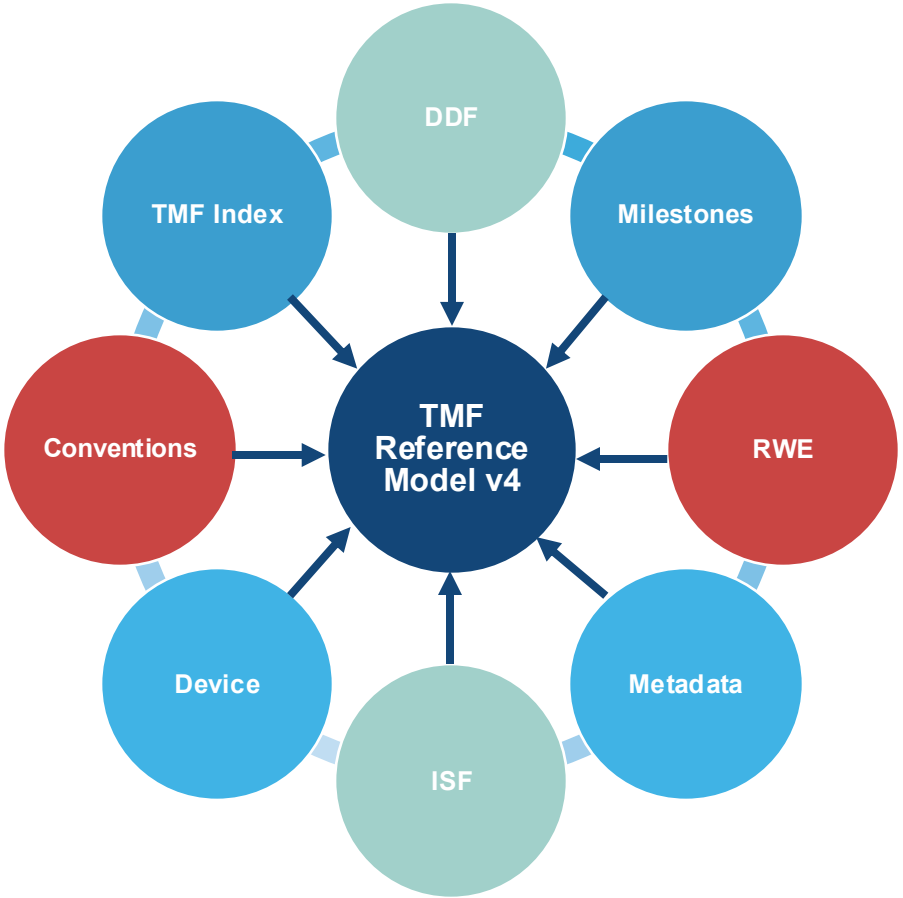
A. I foresee challenges in aligning our current processes with the new guidelines. We could address this by organizing workshops and training sessions.

B. The main challenge will be ensuring everyone is on the same page. Regular team meetings and clear communication will help.

C. I don't anticipate any major challenges, but having a dedicated support team would be beneficial.

A vision for the Future:

TMF Reference Model v4



Where Are We Today?

V4 Kick-off
Sept 2024

Community Feedback Sept through March

Working Groups (Vendor, CSV, ICH E6 R3, Metadata, ISF, Device, RWE, Oct 2024

Triage Committee
Nov 2024

Zone Team Review
July 2025

Key Operational Decisions Endorsed by the SC

Endorsements to Date

Reference Model Structure

- Retaining the Hierarchy of Zone, Section, Record Group, and Record Type with Unique IDs
  - Retain concept of numbering associated with Artifacts (now
- Retaining Trial, Country, Site designation
- Program level records will be managed by each vendor individually but will not be part of V4.
- Artifacts & Sub-artifacts have been renamed to Record Group & Record Type
- Record Types will become part of the Standard
- Intentional focus right now away from Record Groups to Record Types – Working groups are focusing on Record Types that will drive V4

Guiding Principles & Conventions Driving TMF RM V4 Refresh

July, 2025

Existing CDISC Guiding Principles

- Develop standards of the highest quality that allow *all* researchers to leverage and share information from individuals and studies around the world.
- Facilitate the ability for implementers of CDISC standards to effectively structure and analyze data so that it is easily interpreted, understood, and navigated by regulatory reviewers.
- Ensure the standards are developed in a manner that emphasizes content, structure and quality, transcending implementation strategy and platform.
- Convene a global, multidisciplinary, cross-functional community of members, volunteers and stakeholders from across the research spectrum to develop consensus-based standards.
- Collaborate, and partner with, fellow thought leaders and organizations on key initiatives to foster efforts to advance standards and semantics.
- Accomplish CDISC goals without promoting any individual vendor or organization.

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

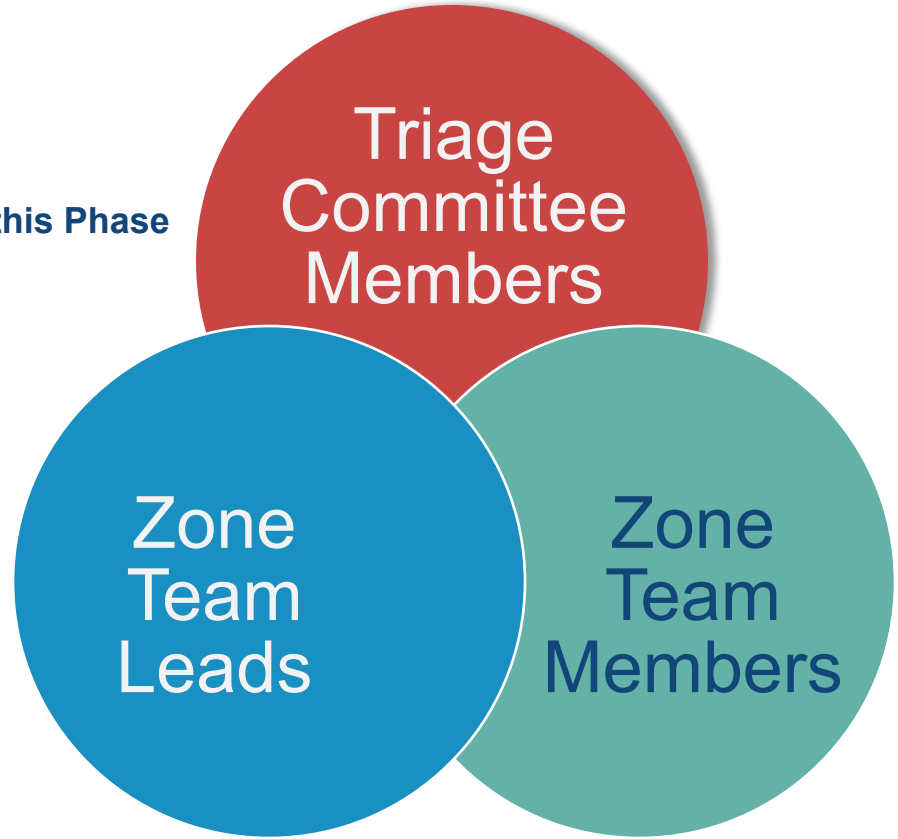
Next Steps

- Zone Teams are currently reviewing Community Feedback
- Triage review of outputs from ICH E6 R3 & CSV
- Ongoing meetings with other Working Groups

v4 Subgroup: TMF Triage Committee

Lisa Mulcahy, Mulcahy Consulting LLC, TMF Reference Model Steering Committee Member

Key Contributors During this Phase



Zone Team Lead and Triage Committee Lead table

Zone #	Zone Team Lead	Zone Team Lead email	Triage Committee Lead	Triage Committee email
1	TBD	To be determined	Jessica Vicari	jessica.vicari@sagerx.com
2	Joanne Bilmazes	jbilmazes@yahoo.com	Sarah Hitching	sarah.hitching@hedianrm.com
3	Abida Zameer	To be determined	Kathie Clark	kathleen_p_clark@yahoo.com
4	TBD	ramya.iyer@regeneron.com	Marion Mays	mmays@jerionconsulting.com
5	Rebecca Reel	rebecca.reel@biogen.com	Liz Farrell	liz.farrell@agios.com
6	TBD	To be determined	Vittoria Sparacio	vittoria.sparacio@novartis.com
7	Katie Kelly	katie@praxismedicines.com	Jackie Morrill	Jackie.morrill@apogeetherapeutics.com
8	Karen Hue	hueconsultantltd@gmail.com	Curran Murphy	CMurphy@blueprintmedicines.com
9	Courtney Igne	cmigne@mgh.harvard.edu	Steph Viscomi	steph.viscomi@apellis.com
10	Luciana Giodini	l.giodini.interim@chiesi.com	Anne-Noelle Charles	anne-noelle.q.charles@gsk.com
11	Yen Phan	yen.phan@codlad.com	David Ives	david.ives@novartis.com
Device	Joanne Bilmazes	jbilmazes@yahoo.com	Jo Oliver	Jo.Oliver@pfizer.com

Zone Triage Committee Member & Zone Team Lead - A Partnership During Reviews for TMF RM V4

TMF RM SC

TMF RM V4 MC

Triage Committee

Zone Triage Committee Members

Zone Team Leads

Partnership

*Feedback Waves:
Community, Workgroups: EUCTR, ICH GCP R3, CSV, Metadata, Device, ISFv2, and RWEv2 … then Community & Public Reviews

Zone Team Lead Receives Triaged Input* to Consider from Zone Triage Committee Member

Zone Team Lead Coordinates and Leads Zone Team Reviews

Zone Team Lead Captures Feedback on Worksheet

Zone Team Lead Prepares Draft of Zone Record Groups and Record Types for CCB

Zone Triage Committee Member
1) Support Project Updates to Zone Teams 2) Filters Up Questions to Triage Committee and TMF RM V4 MC. 3) Facilitates Cross Zone Consistency and Alignment

Full Revision Process

v4 Subgroup: ICH E6 R3

Dawn Niccum, Executive VP, QA, inSeption Group, TMF Reference Model Steering Committee Member

Team

Leads: Donna Dorozinsky and Dawn Niccum

- Beatriz Sevilla-Jensen
- Kelly Torfs
- Erika (Lingying) Fu
- Jackie (Tingting) Fu
- Marcella Coelho
- Jennifer Christofferson
- Iris (Yixuan) Wang
- Jennifer Escobar
- Kimberly Swint
- Amruta Patil
- Vanessa Gonzalez Vivero
- Pam Giltner Delea

Goals of Subgroup

- Evaluate ICH E6 R3 (all sections – not just Appendix C)
  - Identify current artifacts that align with update
  - Identify additional record groups/types to include in V4 of the RM
- Focus of Key Areas
  - Oversight
  - Risk Based Approaches
  - Quality by Design
  - Service Providers
- Out of Scope: Computer System Validation

Outputs

- Identified approximately 50 new potential record types
  - Examples:
    - Evidence of Risk Review
    - Oversight Plan
    - Regulatory Notification of Quality Issues
- Completed review of all sections by the end of July
- New record types currently being reviewed by Triage Committee
- Overall group noted that evidence of completion of key areas were not currently well represented

v4 Subgroup: Vendor Update

Aaron Grant, Head of Innovation, Just in Time GCP

Vendor Group has been meeting since Jan

Key Goals

- Facilitate vendor understanding of the changes in V4
- Gather vendor input to ensure the model aligns with practical needs
- Support smooth adoption and implementation of V4 across vendor platforms and services

Outputs:

- Provided feedback and recommendations to technical changes in reference model structure
- Provide a harmonized minimum harmonized metadata suggestion for wider v4 team

Next: Assemble Metadata Team

Cross-functional representation from across the industry:

- Large, medium, and small sponsors
- CRO representatives
- Vendor representatives

Purpose

- Provide a collaborative forum for input across different stakeholders
- Advance vendor team outputs by shaping metadata standards for V4

Goals

- Define metadata rules for V4
  - Establish clear principles governing metadata structure, consistency, and usability.
  - Ensure compatibility across systems and processes.

v4 Subgroup: CSV Update

Jennifer Arters, Principal Consultant, Epista

Working Group Objectives

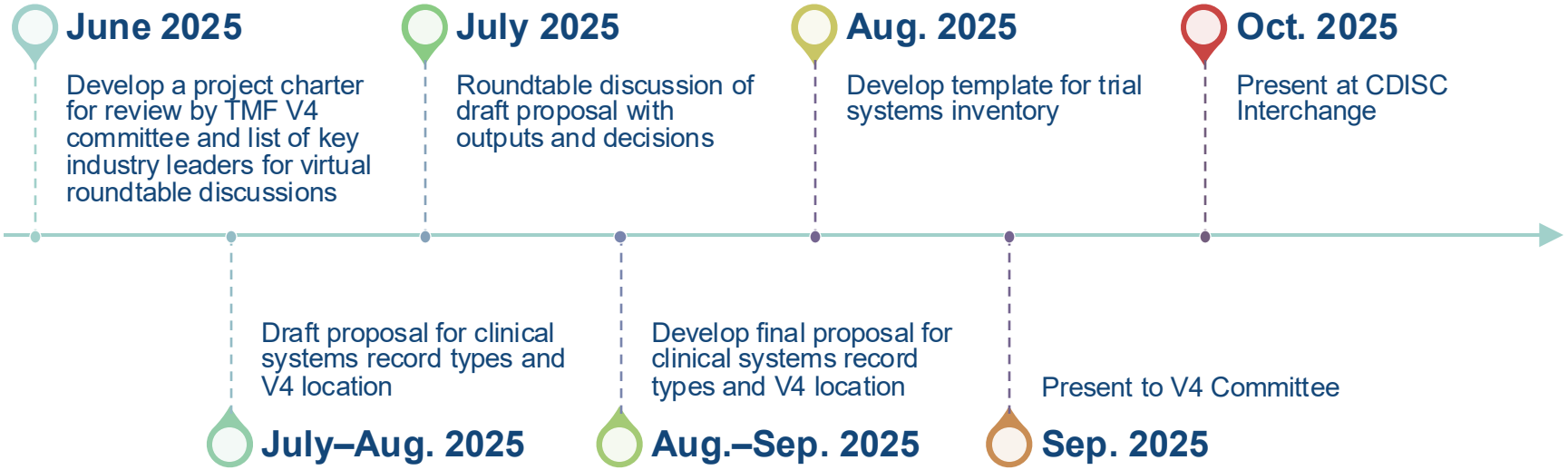
Problem Statement:

- TMF Reference Model *3.x* calls out limited record types for storing computerized system records, only for specific systems (EDC, IRT, ePRO). There is little industry guidance on what the appropriate content should be to facilitate oversight and inspection readiness.
- Perceived widespread issue that Service Providers and Sponsors cannot easily provide a detailed list with information on critical / high risk systems in use.

Business Need:

- Guidance for systems in scope and out of scope.
- What to file (core record types) including evolving use of audit trails for operational oversight.
- Filing zone and core metadata guidance.
- Report / tool to inventory trial systems to facilitate inspection readiness and support.

Method and Deliverables



Solution

TMF RM

- Separate zone for trial related computerized system records.
- Move existing system records out of their zones.
- Inventory template and guidance

Record Group Sets

- System Requirements
  - URS, FRS, Tech Design Doc, Edit Check Plan, DB Spec, Integration Spec, Data Migration Plan
- User Acceptance Testing
  - UAT Scripts (fully executed), UAT Issue Tracking, Trace Matrix
- Validation
  - Val Plan, Val Cert, Val Report
- System Release Documentation
  - Impact Assessment, Change Control Form, Release Cert or Equivalent, Release Notes, System Approval
- System Training
  - System User Manual, User Training Manual, Evidence of System Training
- User Access Management
  - User Account Report, System Security Matrices

Core metadata

- Includes system types
  - Core systems with extensible list of options
- Associated Functional Area
- Owner e.g., Service Provider/Sponsor etc.
- System category e.g., trial, enterprise, service provider, other

Core Record Types and Metadata

System Requirements	Systems: IRT, eCOA, eTMF, CTMS, Site Portal, etc.
User Acceptance Testing	Systems: IRT, eCOA, eTMF, CTMS, Site Portal, etc.
Validation	Systems: IRT, eCOA, eTMF, CTMS, Site Portal, etc.
System Release Documentation	Systems: IRT, eCOA, eTMF, CTMS, Site Portal, etc.
System Training	Systems: IRT, eCOA, eTMF, CTMS, Site Portal, etc.
User Access Management	Systems: IRT, eCOA, eTMF, CTMS, Site Portal, etc.

Software Supplier/Vendor	Type of System (i.e. eTMF, eISF, eCRF, IRT, PV system, CTMS, QMS, etc.)	Off the shelf or in-house developed?	eSystem Validation Status	System Status	Integrated to other system?	System Owner (i.e. Company/Persons Name/Department)	Trial (built/configured/validated trial specific releases of the eSystem)	Company Version/Release (i.e. IRT V2; updated screening call questions to add pregnancy check)	Vendor Version
Veeva	eTMF	OTS	Validated	Active	No	ABC Inc. IT Jane Doe	ABC_123	N/A	23R2
							XYZ_123	N/A	24R1
							EFG_123	N/A	20R1

System Inventory List

Project Charter: CDISC TMF Reference Model v 4.0 - Clinical Trial Computerized Systems Records

Project Name	CDISC Proposal for Clinical Trial Computerized Systems Record		**Project Leads**	Jennifer Arters, Jennifer Peacock
Project Start & End Date	End Q1-2025	End Q4-2025	**Project Sponsor**	CDISC

Goal	Define recommended clinical systems record types, metadata and location in V4 structure inclusive of clinical system validation, configurations, and commonly requested record types such as user access reviews, training/manuals, and a trial system list.
Scope/ Objectives	In scope activities include (1) Proposal development for CDISC leadership review, (2) Conduct virtual roundtables with industry leaders to challenge proposal, (3) Present final proposal to V4 Steering Committee, (4) Present approved proposal and System List Template at CDISC + TMF US Interchange
Deliverables	1. Project charter 2. Draft proposal for clinical systems record types and V4 location 3. List of key industry leaders for virtual roundtable discussions 4. Roundtable discussion of draft proposal with outputs and decisions 5. Final proposal for clinical systems record types and V4 location 6. Template for trial systems inventory

Members / Resource Needs	**Dependencies/ Processes or Systems Impacted**
Core project team 1. Jennifer Arters, Epista Life Science 2. Jennifer Peacock, Biogen 3. Nick Hargaden, Merus	1. Dependency: External stakeholders (Large & small Pharma, CROs, vendors) 2. Processes: Clinical System Validation, TMF Management 3. Systems: eTMF

Additional stakeholders

The following stakeholders will be included as the project progresses:

1. TMF Ref Model V4 Committee
2. External stakeholders (Large & small Pharma, CROs, vendors)
3. TMF Ref Model Triage Committee

Milestones *(may be in parallel with each other and not distinct)*	**Date**
Identify core team members and initiate KOM for the workstream	13 June 2025
Establish charter, project plans and define key deliverables	25 June 2025
Provide workstream charter for CDISC Leadership review	3 July 2025
Conduct Roundtable Discussions	July 2025
TMF Ref Model Triage Committee	8 Sept. 2025
Final Proposal Presentation at CDISC + TMF US Interchange	13-14 October 2025

Workstream risks	**Impact / Probability**		**Mitigation**
Alignment with other functions requirements, e.g. IT, Quality	H	H	Recommend Zone 10 team review as EDC is pre-existing in V3 and most impacted.
Change management/adoption	H	L	Part of V4 broader project. Recommend to develop supporting guidance
Resource Availability	H	M	Recommend if possible that final proposal still be open to zone review after Nashville presentation.

v4 Subgroup: Medical Device Update

Jo Oliver, TMF Study Owner, Pfizer

Definitions

In-Vitro

Refers to processes or reactions conducted outside a living organism, typically in a controlled environment like a test tube or culture dish.

**Pharmaceuticals are In Vivio; "in the body"*

IVD

In Vitro Diagnostics Medical Device are tests done on samples such as blood or tissue that have been taken from the human body.

These tests can detect diseases or other conditions and can be used to monitor a person's overall health to help cure, treat, or prevent diseases.

IVDR

The In Vitro Diagnostic Medical Devices Regulation (IVDR, EU 2017/746) is a European Union regulation that sets higher standards for the quality and safety of in vitro diagnostic devices, aiming to harmonize requirements across EU member state.

Seeking approval for an IVD alone or as a CDx.

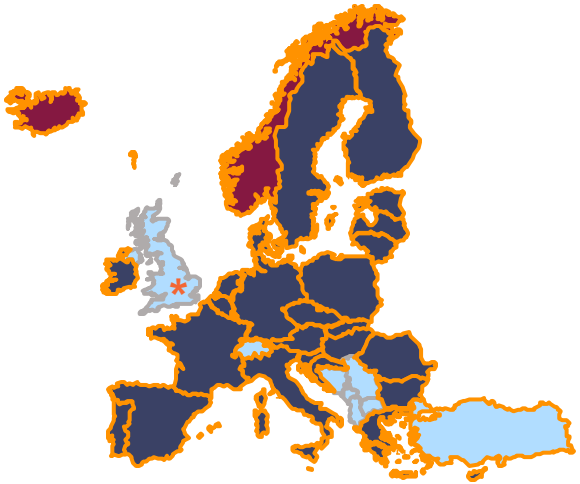
Clinical Trial (CT): a research study where people are given specific treatments to see how these treatments affect their health. *I.e., Pharmaceuticals

Clinical Performance Study (CPS): evaluates the performance of a medical device, especially in vitro diagnostic devices (IVDs), by systematically assessing its effectiveness and reliability.

Diagnostic Study (Dx): research or clinical evaluation designed to assess how well and IVD device can detect, measure, or monitor a specific condition, disease, or biomarker using samples taken outside the body.

Introduction to IVDR *(In-Vitro* Diagnostic Medical Devices Regulations)

A European Regulation



- European Union
- Non-EU European Economic Area Countries
- Non-EU countries
- Countries Recognising IVDR

*UK will recognize CE- mark until 2030

IVDR: In-Vitro Diagnostic Medical Devices Regulation
REGULATION (EU) 2017/**746** OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 **on *in vitro* diagnostic medical devices** and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

- officially came into effect on May 26, 2022

What is regulated under IVDR?

- All aspects of IVD manufacturing, marketing and vigilance
- All aspects of IVD development (analytical and **clinical performance** of IVDs)
- Other uses of IVDs presenting potential risks to the patients
- Guidance MDCG Guidance - how to implement IVDR.

Out of IVDR scope: medical devices (MDs), general laboratory products and products for research use only

Combined Trials (IVD +IMP): Separate Submissions and Approvals Required

Sponsorship must be identified for any CPS involving in vitro diagnostic devices.

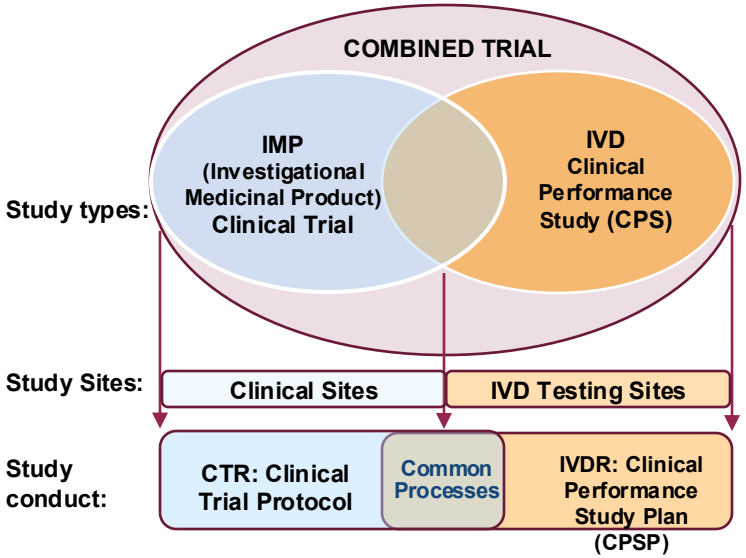
According to IVDR What Does This Mean?

Sponsor: the individual, company, institution, or organization that takes responsibility for the initiation, management, and financing of a clinical performance study.

- The sponsor must be **identified in the study documentation**, including the **performance study application**.
- The sponsor is responsible for ensuring that the study complies with **ethical and regulatory requirements**, including:
  - Submitting the study to **competent authorities** and **ethics committees**
  - Ensuring **informed consent** is obtained
  - Managing **adverse event reporting**
  - Maintaining **study records and data integrity**

*Where a **clinical trial sponsor assigns a medical purpose to an assay** in the context of the clinical trial the clinical trial sponsor may assume the role of a manufacturer under the IVDR. In this role, it is up to the clinical trial sponsor to determine **the regulatory status** of the assay **based on the planned use** in the clinical trial.*

Assay: a laboratory technique used to measure, analyze, or detect the presence, quantity, or activity of a substance within a sample.



*MDCG 2022-10 Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)

**Clinical Trials Regulation (EU) No 536/2014

Planned Use of the IVD

IVD test used as a research only

- Provides information on a therapeutic's mode of action
- Provides information used for stratification of patients in arms of a clinical trial
- Provides information used for endpoint analysis in a clinical trial

Notification Study

IVD test used to determine patient care

- Identifies patients at increased risk of serious adverse reactions as a result of treatment
- Provides information concerning a pathological process or state
- Identifies before treatment patients most likely to benefit from a drug
- Provides information used for monitoring of patients in a clinical trial and deciding treatment discontinuation
- Provides information used for defining therapeutic measures in a clinical trial

Authorization Study

Not shared with CT Sites ← **Test Results** → **Go back to CT Sites**

Notification

CPS: Minimal to No Patient Risk

Non-Interventional

Retrospective Testing

No Enrollment Impact; IVD development using left-over samples

- **Filing Documents:** Simple Dossier
- Approval not required before CT can begin
- IVD testing can begin by country approval.

Authorization

CPS: Patient Risk

Interventional

Prospective Testing

Enrollment Impact; CDx development

- **Filing Documents:** Complex Dossier
- Approval of CPS required before CT begins
- IVD testing can begin by country once CPS & CT Approved

Impact on Clinical Trials

Impact On	Why	How
1. Increased Regulatory Scrutiny	Under IVDR, IVDs used in clinical trials must now undergo **more rigorous performance evaluation and clinical evidence requirements**. This includes:	•Demonstrating **scientific validity**, **analytical performance**, and **clinical performance**. •Submitting detailed **performance study plans** and **investigator brochures**. •Involving **Notified Bodies** for higher-risk devices, which was not required under the previous IVDD.
2. Impact on Clinical Trial Design	Clinical trials involving IVDs must now:	•Align with **Regulation (EU) 536/2014** (Clinical Trials Regulation or CTR) when diagnostics are used to stratify or select patients. •Include **performance studies** for IVDs, which are distinct from traditional drug trials but must still meet ethical and scientific standards •EUDAMED European database on medical devices
3. Delays and Operational Complexity	The IVDR has introduced **longer timelines** and **more complex approval pathways**, especially for:	•**Multi-country trials**, where coordination between national competent authorities is required. •Trials involving **combined CPS**, which now need dual compliance with both IVDR and CTR
4. Fragmentation and Harmonization Challenges	Despite the EU's goal of harmonization, implementation of IVDR has led to:	•**Regulatory fragmentation** across Member States. •Calls for **targeted legislative updates** to streamline processes and reduce administrative burden
5. Strategic Shifts in Clinical Research	To adapt, stakeholders are:	•Launching initiatives like **ACT-EU** and **MedEthicsEU** to improve coordination. •Advocating for **simplified policy implementation** and **greater investment** in regulatory infrastructure •September 2025 Pilot: joint EU-CTR & IVDR Submissions

When clinical trials require biomarker testing, they may use an IVD that is not yet approved or not approved for use.

Conclusion and Future of IVDR

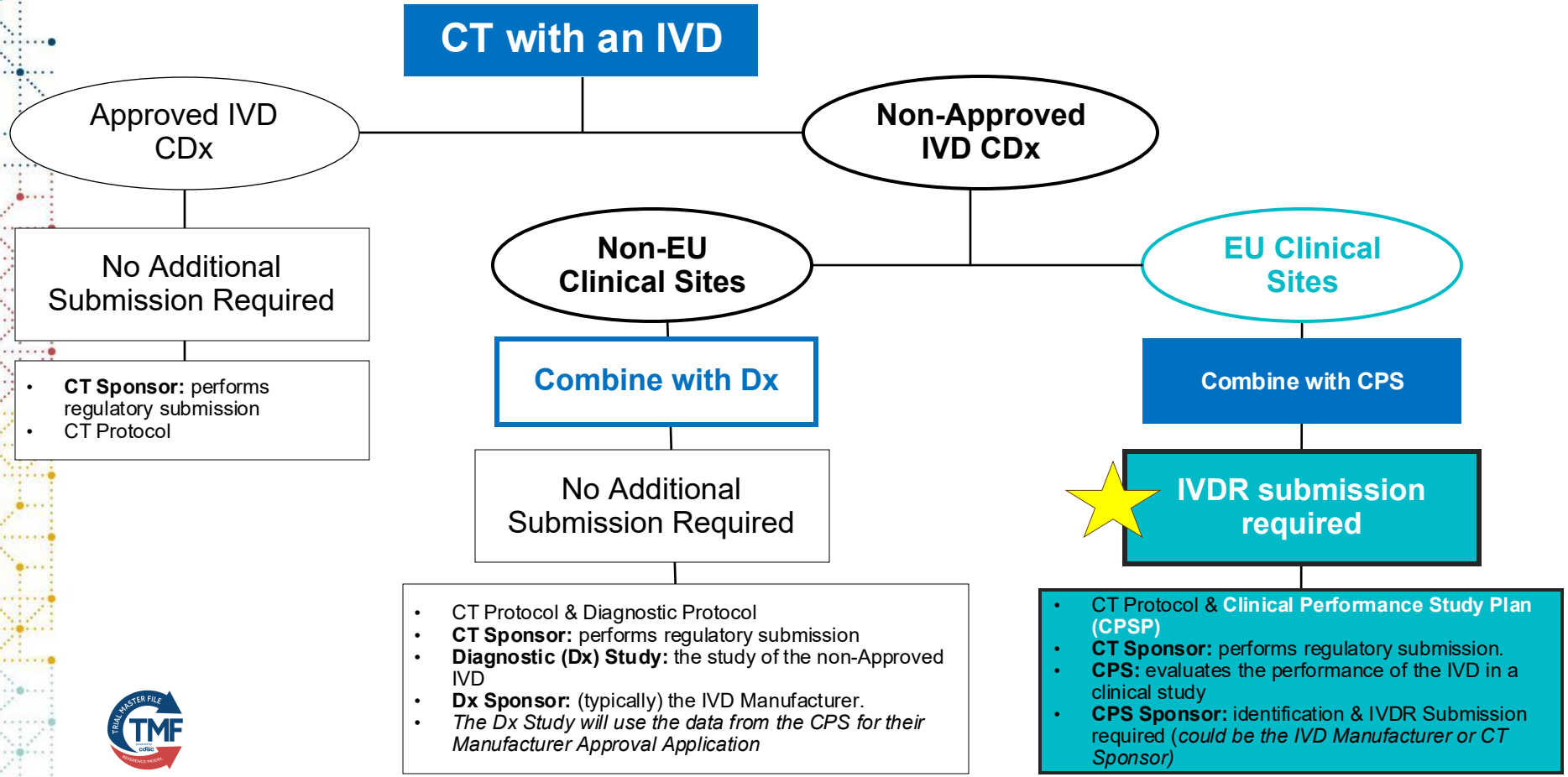
- **IVDR** represents a significant evolution in diagnostic regulations.
- **IVDR** is an EU Regulation that requires its own Submission & Approval
- Minimum of **three study types** are affected by IVDR; Clinical Trials, Clinical Performance Studies, & Diagnostic Studies.
- Ongoing training and education for manufacturers and CT Sponsors is vital.
- Future updates will refine the regulatory framework.

Future Impacts for TMF Reference Model version 4.0

- Device Zone Team is being Created & will include In-Vitro Diagnostic representatives.
- **How the IVD is used** for the CPS determines what Submission Type to IVDR is needed
  - Authorization
  - Notification
- **Submission Type & TMF** impacts
  - Required documents for filing in TMF (Countries have different submission requirements)
  - Timing of Inspection Readiness Activities
- Regulation states **"combined"**: Combined TMFs vs. Separate TMFs & Study Ids.
  - **(Problem)** Separate TMF for **IVDR** vs. **(Recommendation)** Combine CPS with the study that is Sponsored by the same Organization; i.e., CT & CPS filed together when Sponsored by same.
  - **(Problem)** Separate Study id for submissions (CT & CPS) vs. **(Recommendation)** use same study id.
    - September 2025 Pilot: joint EU-CTR & IVDR Submissions

Resources

How CT, Dx, & CPS Interact



Resources

- How to Implement IVDR: Guidance - MDCG endorsed documents and other guidance
- Regulation (EU) 2017/746 on In Vitro Diagnostic Medical Devices & Repealing Directive 98/79/EC and Commission Decision 2010/227/EU
- MDCG 2022-10 - Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746

v4 Subgroup: EU CTR

Curran Murphy, Head of Clinical Business Operations, Blueprint Medicines

Martina Duvel, Systems Excellence Project Leader, Bayer

Working Group Approach

Problem Statement:

- Working under the European Clinical Trial Regulation (EU CTR) requires only a limited number of dedicated new records which require TMF filing. However, the transparency rules and the specifics for working in the Clinical Trial Information System (CTIS) and the EU registries are affecting document management in the frame of trial submissions and reporting and need to be considered for impact on v4 of the TMF Reference Model (RM)

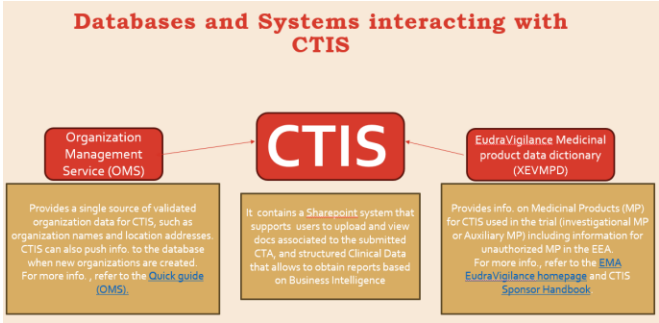
Methodology and Deliverable

- Comparison of records to be submitted under EU CTR with record types listed in the current version of the RM to identify gaps
- Checking the workflows in CTIS (submission, approval, notification, reporting, publishing of information) for documentation requirements
- Create a sheet listing proposed new record types and comments for consideration for the Triage Committee and use by the Zone Teams

EU CTR Background

Directive 2001/20/EC	Regulation (EU) No. 536/2014
• Since May 2014	• Effective 31st Jan 2022 with CTIS go-live
• Aim to harmonize across EU	• Single submission to EMA portal for EC & NCA
• Still lots of deviating requirements by NCAs	• Joint review by NCA
• Separate EC procedures	• One decision per MS
• Local submissions	• Central submission

EC = Ethic Committee
NCA = National Competent Authority
MS = Member State
CTIS: Clinical Trial Information System



Goals of EU CTR

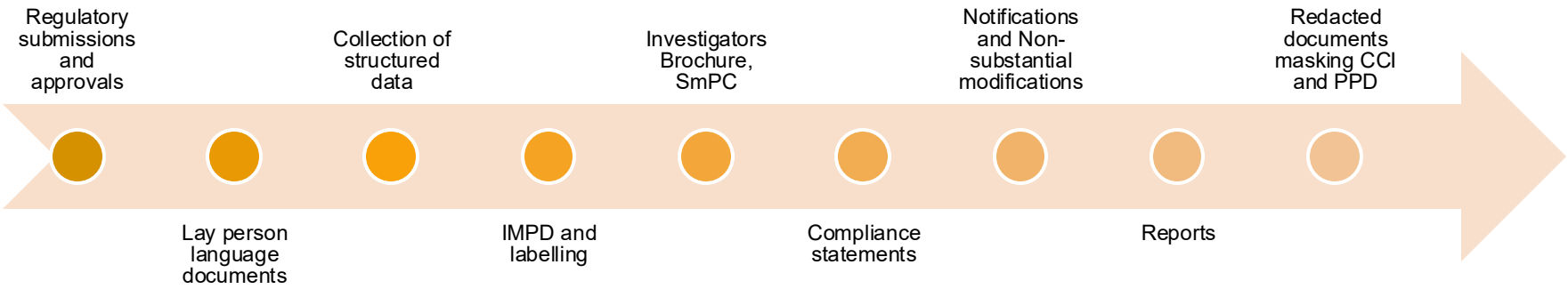
Harmonization
- Single EU submission of clinical trial applications and approval via single Clinical Trial Information System (CTIS)

Transparency
- Relevant information submitted via CTIS will be made publicly available

Patient Centricity
- Lay language documents required

EU CTR and TMF Filing

Filing of EU CTR Specific Records to be Considered



EU CTR General Considerations for TMF Filing

Filing of Submissions	•CTIS does not provide acknowledgement of receipt: screen shot, content list, or pdf of application may work as "Evidence of Submission" •Need of filing all submitted records in the TMF? •Filing of RFI and responses
Structured data	•Recommended to keep these as record •Registration information from SPOR / OMS to be filed separately?
Approvals	•Conclusions will come on study level and per country •Approval per country
Ethics Committees	•Lack of detailed information on EC involved •Only list of country contacts and general list of country ECs available
Masking of CCI and PPD in published records	•Redacted versions as separate record type or meta data?
New records requiring filing recommendation	•Compliance statements •Results reports •Lay language records

v4 Subgroup: RWE

Lisa Grim, Program Manager, Patient Safety & Pharmacovigilance, Sanofi

Project Overview: RWE 2.0 Study Master File Review

Purpose:
The project objectives, responsibilities, and deliverables is a revision of the CDISC TMF Reference Model Real World Evidence (RWE) Study Master File Index, originally published in 2020.

Why Now:
Five years since its initial release, the RWE SMF Index requires an update to ensure alignment with current industry standards, regulatory frameworks, and practical use cases.

Objectives:

- Incorporate lived-experience feedback from users of the original index
- Reflect the diversity of RWE study categories
- Embed best practices for pragmatic application
- Align with evolving regulatory and industry guidance

Deliverables:

- **Revised RWE SMF Index (RWE 2.0):**
  A clarified, user-friendly index tailored to various RWE study types to promote broader adoption
- **Release Notes:**
  A formal document from the Change Control Board detailing all modifications made to the index

Outcome:
A universally relatable and practical RWE SMF Index that supports efficient, standards-compliant work across real-world evidence studies.

RWE 2.0 Project – Quarterly Business Review (Q3 2025)

Project Highlights

- ✅ Team Site Setup: Live with project referentials
- ✅ Onboarding: SMEs with RWE & TMF RM expertise
- ✅ RASCI Model: Roles and responsibilities agreed
- ✅ Kick-Off: Held on **August 29, 2025**

Team Structure

- 🌍 Time Zones: EST | PST | GMT | GST | IST
- 🕒 Monthly Syncs: 1-hour meetings
- 🔄 Independent Work: Role-specific hours

Progress & Deliverables

- 📄 User Requirement Specification:
  - Study group use cases, terminology traceable to RWD DI 1.0, TMF RM, and evolving standards

Project Goal

🗂️ Deliver a Study Master File (SMF) Index

User-friendly

Fit-for-purpose

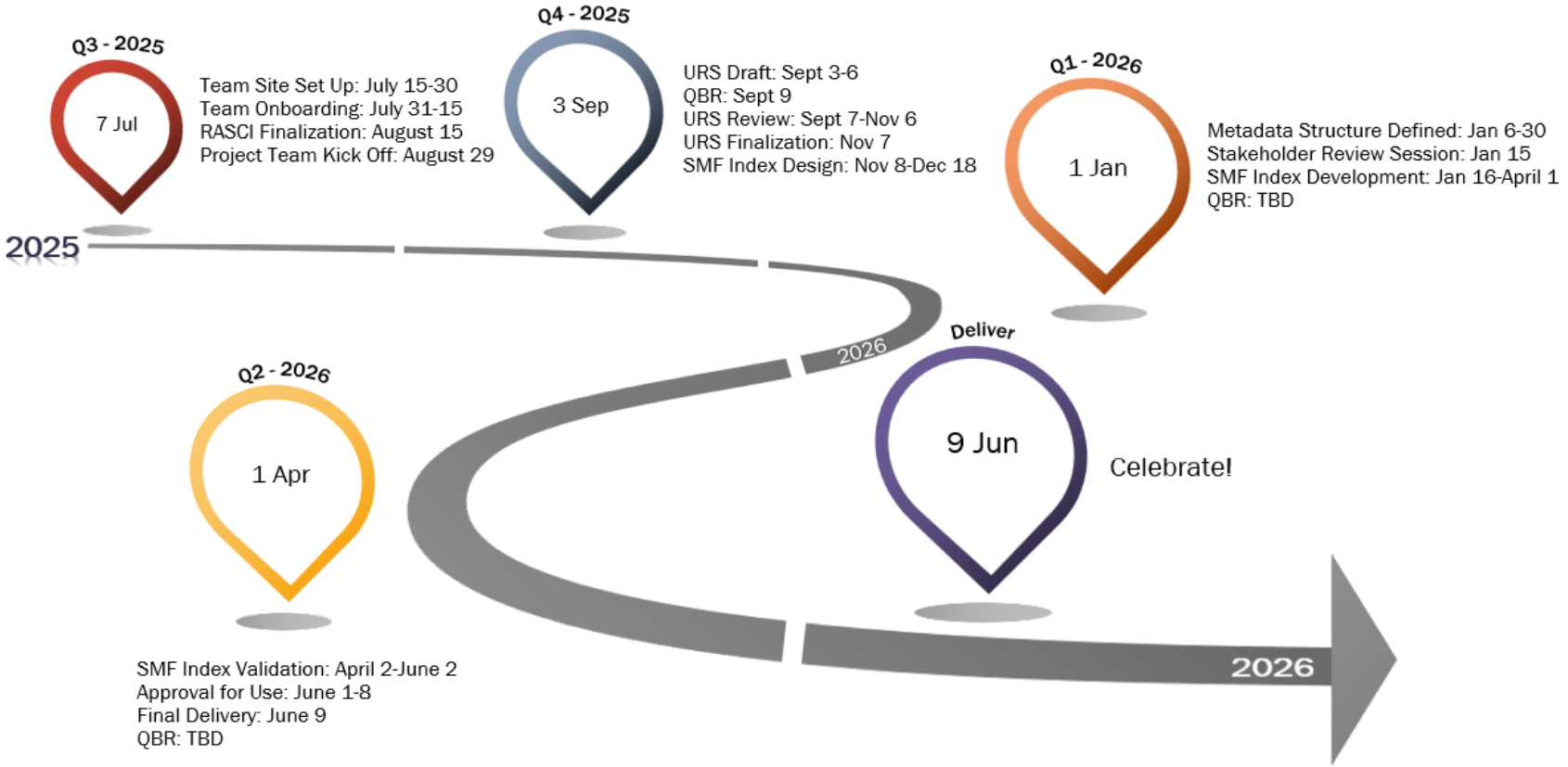
Standards-compliant

Enables efficient workflows

Next Quarter Objectives (Q1 2026)

🧩 Finalize SMF Index Framework Design
📊 Define Metadata Structure & Traceability Matrix
🛠️ Align with evolving standards (RWD DI 1.0, TMF RM, ICH)
🤝 Conduct stakeholder review sessions
🗓️ Maintain monthly team cadence and role-based deliverables

On track for **Q2 2026** delivery



ISF Initiative

Jamie Toth, Sr. Director, Global Trial Master File Management & Records, BeOne Medicines; TMF RM SC Member and Incoming Chair Elect

ISF Reference Model Release 1.0

The Investigator Site File (ISF) structure was made available for public review in early July!

This structure standardizes document organization at the site level, improving efficiency, collaboration, and compliance and is aligned to the TMF RM 3.3.1.

Public Review closed 05-Sep-2025.

The team has been reviewing the comments every 2 weeks as they have come in.

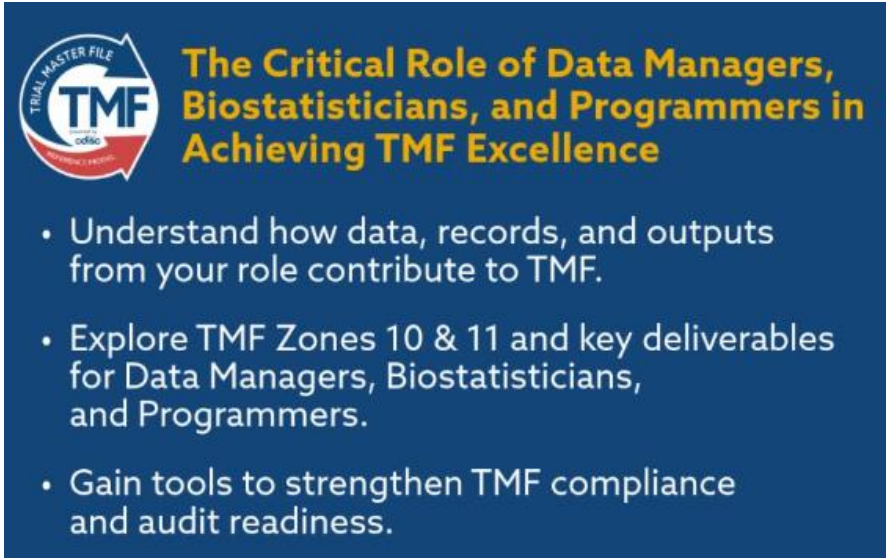
25 forms submitted with xxx comments – we do have comments from vendors, sponsor companies, sites,…. We will be reviewing the feedback and making updates and are prepping next steps, including webinars and trainings.

Education Committee

Dawn Niccum, EVP, QA & Compliance, inSeption Group, TMF RM SC Member

Courses at TMF Interchange

15 Oct



Courses in Development

- Introduction to the TMF Record Quality Check Process – Recorded Training, coming soon
- TMF Risk Management
- Investigator Site File
- Advanced TMF Training
- Expansion of The Critical Role of Data Managers, Biostatisticians, and Programmers in Achieving TMF Excellence to a Full Day Course

Risk Initiative

Sarah Hitching, Director, Hedian Records Management Ltd

UPDATE

White Paper is Available:

Link: 2025-05-30_TMF_Risk_Initiative_White_Paper_v1.1_0.pdf

Tool is Available:

Link: CDISC TMF Risk Initiative Tool - V1 - 05May2025.xlsx

A few questions / comments have been received – please continue sending those in!

Training is being finalized.

Thank You!!!