Trial Master File Reference Model

Presentation to ICH M2 Expert Working Group

10 April 2018

Presenters

- Karen Roy
  - Chair of the TMF Reference Model Steering Committee
  - Co-founder of the TMF Reference Model with Lisa Mulcahy
  - Chief Strategy Officer, Phlexglobal

- Paul Fenton
  - Co-chair of the TMF Reference Model Exchange Mechanism
  - CEO, Montrium

Agenda

- Origins of the TMF Reference Model Concept
- Why is a TMF Reference Model needed?
- Why should it be used?
- How has it been developed?
- The Exchange Mechanism
- What about OASIS?
- How is the TMF Reference Model governed?
- Who is involved and what is the current usage?
- What does it look like?
- Change Control
- Past and current activities and deliverables
- What is the future?

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Origins of the TMF Reference Model Concept

DIA DEVELOP INNOVATE ADVANCE

DIA Communities

Document & Records Management Community

- EDM Reference Model

- Gap in Electronic Document Management (EDM) Reference Model identified for non-submission TMF documents
- EDM scope is regulatory submissions:
  - Large proportion of TMF not accounted for….
  - But minimal guidance available for TMF content
  - Hence the creation of the TMF Reference Model

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Why a TMF Reference Model?

- ICH GCP Section 8.2 – 8.4
- "The minimum list of essential documents – those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.
- ICH GCP does **not** provide a comprehensive contents list for the TMF
  - Examples of missing documentation:
    - Electronic systems
    - Data management and statistical methodology
    - Safety monitoring

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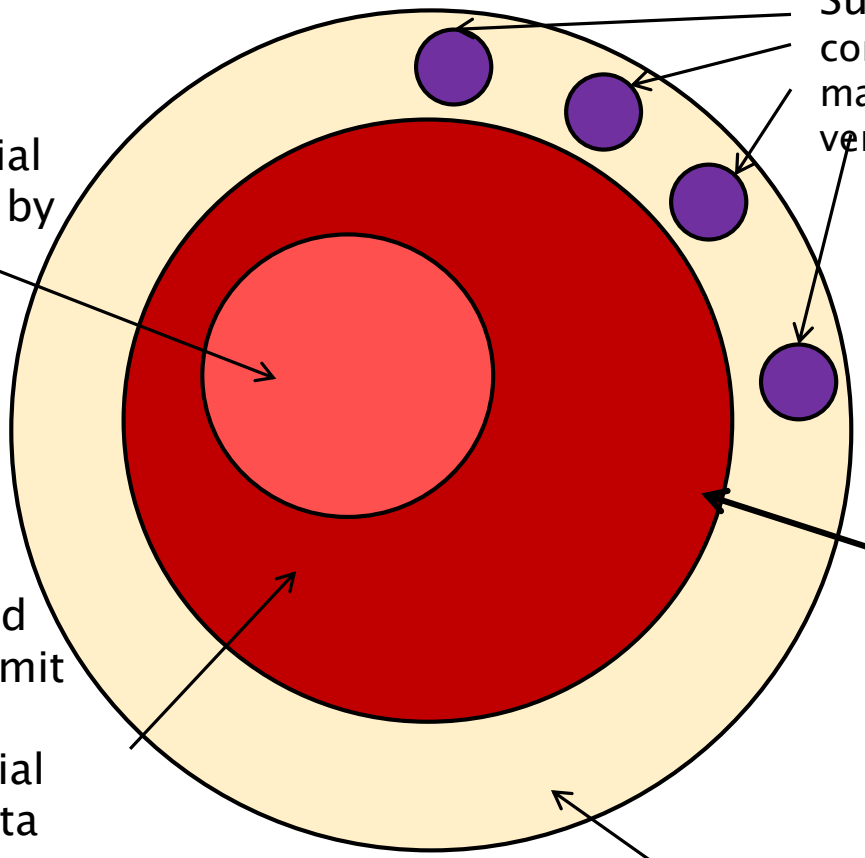
Defining the TMF Reference Model



Minimum list of essential documents, as defined by ICH GCP, Chapter 8

Supporting files e.g. computer SDLC files; GMP manufacturing files; vendor selection files

Usually considered outside the scope of the TMF

The Trial Master File

Other trial-related records that "permit evaluation of the conduct of the trial and quality of data produced"

Other business records

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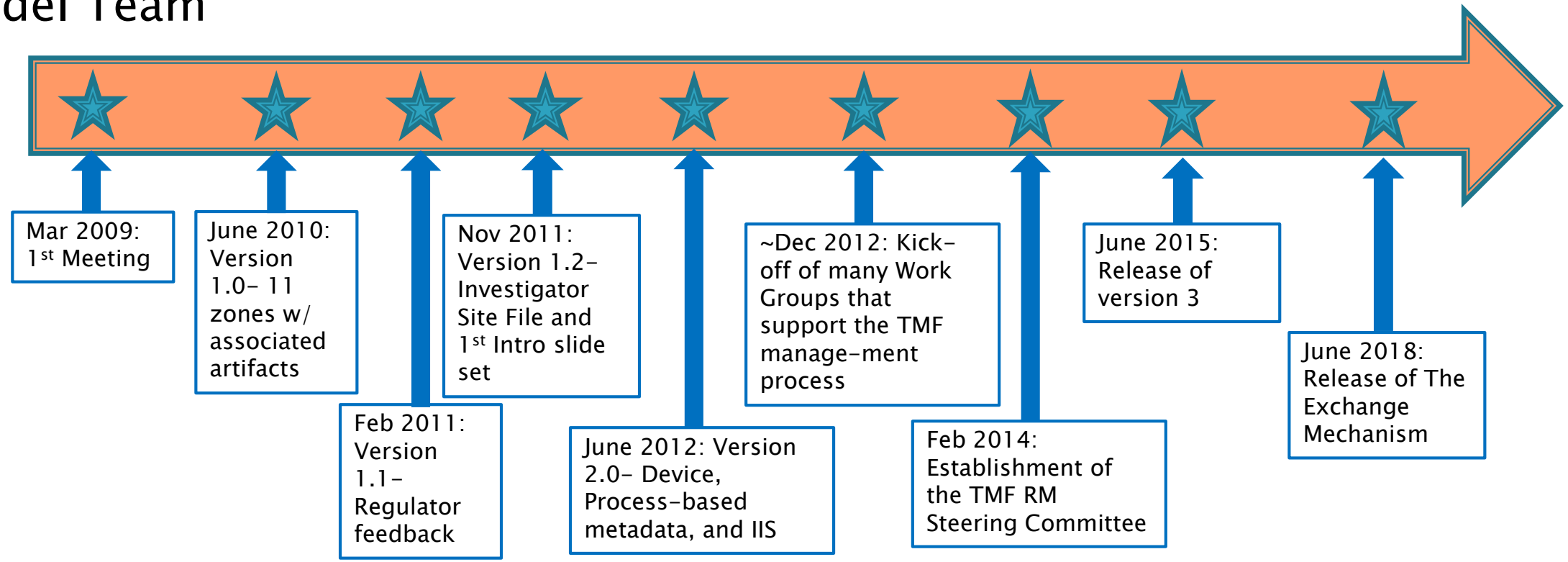
Benefits Gained by Implementation

- Standardizes company content and structure and limits company customization
  - We all follow the same regulatory requirements
  - Inspectors are the same across companies
  - Company-specific requirements are often driven by tradition, legacy or personal opinion
- Simplifies engagement of CROs and other third parties
- Simplifies consolidation of disparate documents into a single TMF structure (in real time, at defined trial events and/or at study end)

About the TMF RM

- Created through a group of DIA (Drug Information Association) volunteers and maintained through an extended TMF Reference Model Team



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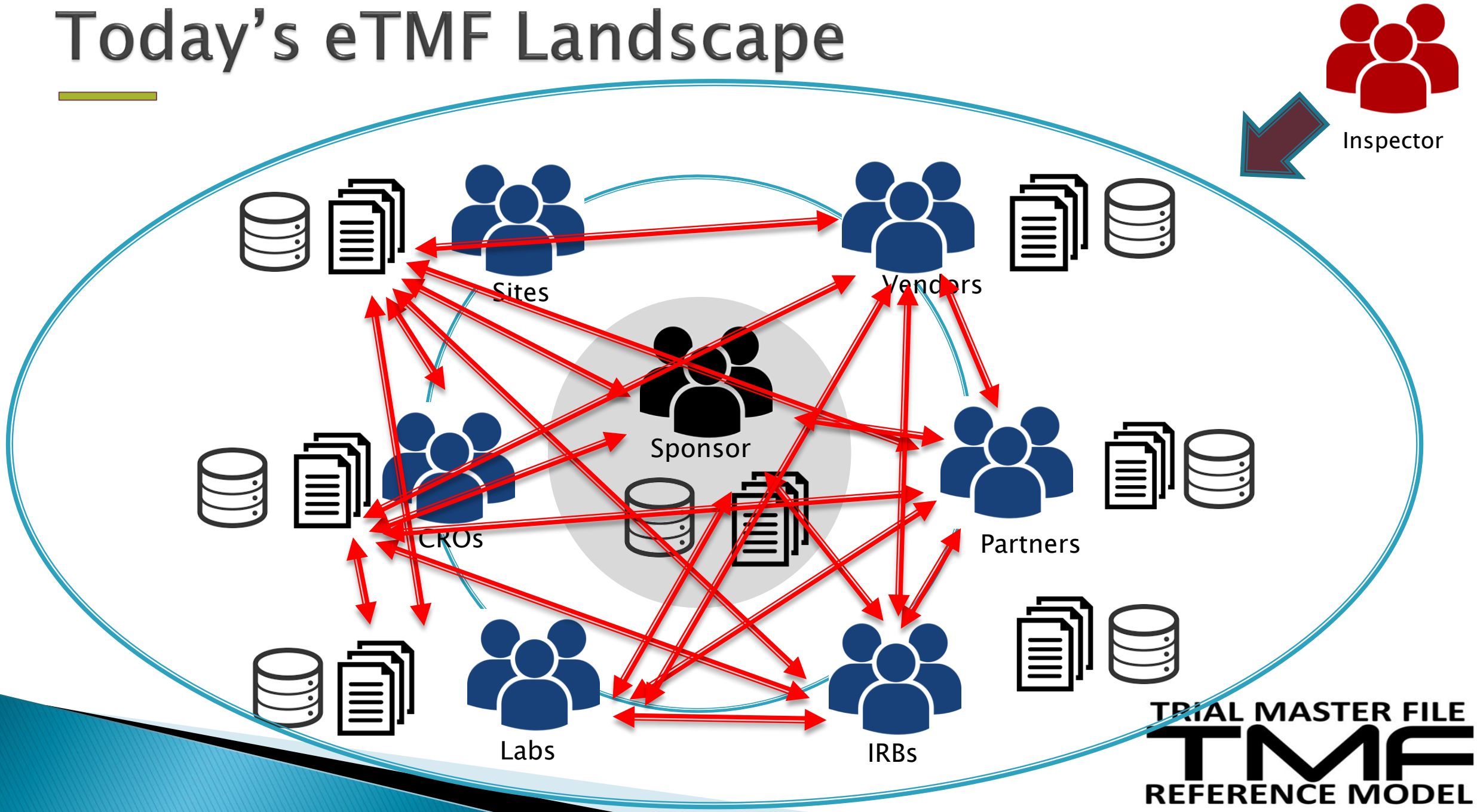
Today's eTMF Landscape



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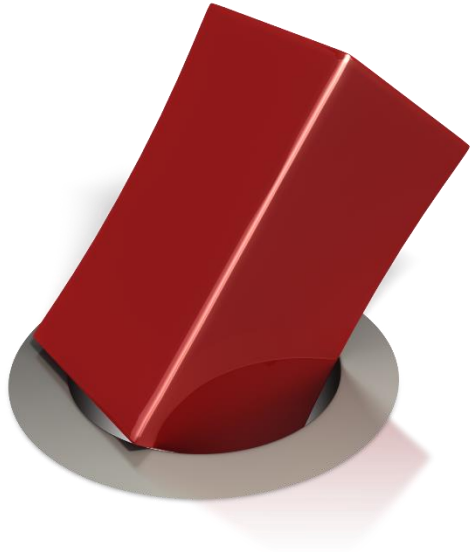
TMF
REFERENCE MODEL

eTMF-EMS What are we trying to solve

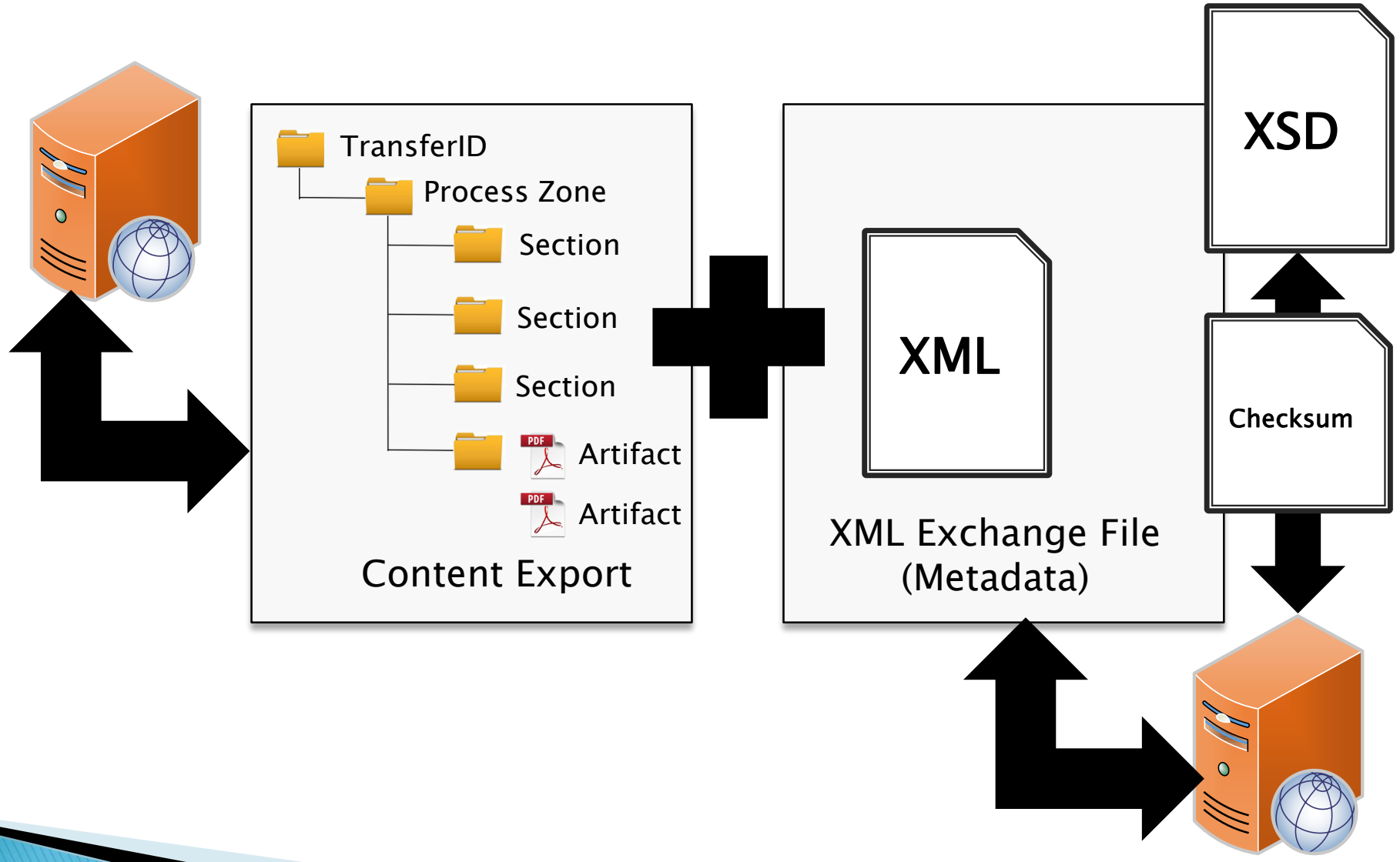
- More and more electronic systems are being used to manage TMF
- Most systems use the **TMF RM** to **organize artifacts**
- At the **end of the study** the TMF needs to be **transferred** to the sponsor
- This often requires a **significant amount of mapping** and manipulation to be able to import the content
- **Solution: A transport protocol which facilitates exchange of eTMF content…The eTMF Exchange Mechanism Standard (eTMF-EMS)**



eTMF-EMS

- Exchange Mechanism
  - XML standard to support data transfer between eTMF systems
  - Group established 2 years ago to develop standard
- Modelled on eCTD
- Reviewing feedback on draft specification
  - Technology review – eTMF Vendors
  - Business review – Sponsors / CROs
  - Anticipate April completion
- Expected release date of v1 – June 2018
- Exchange Road-test underway

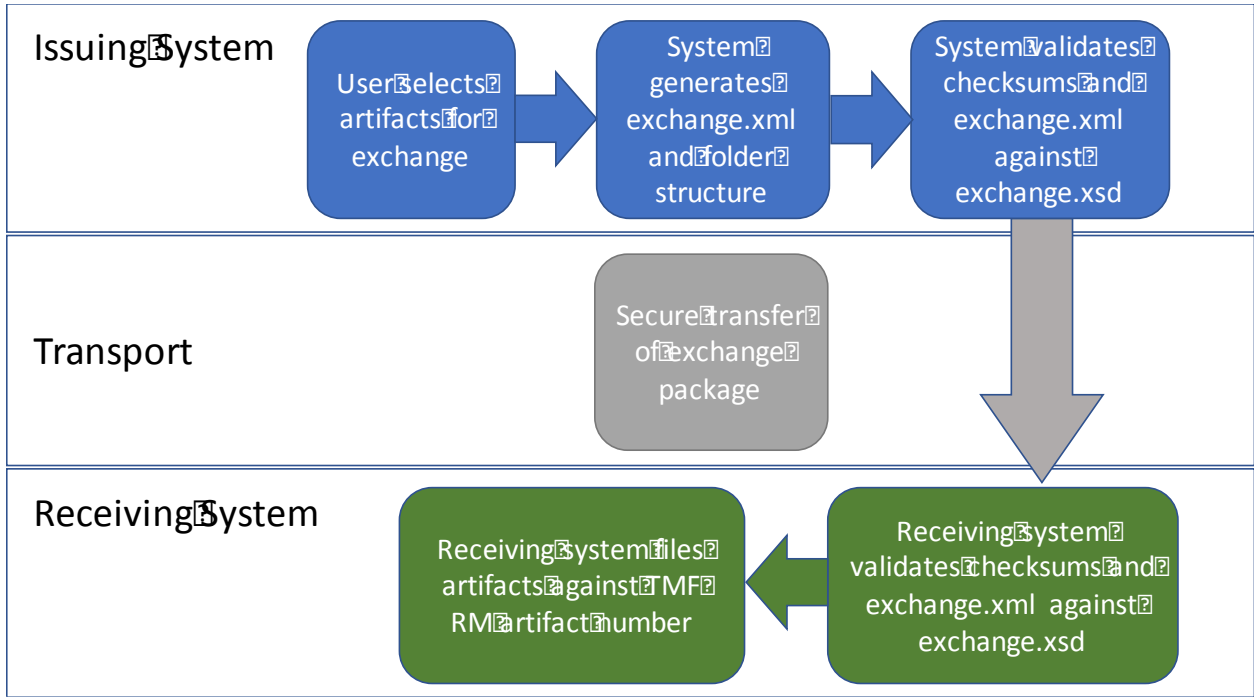
How the eTMF-EMS works



How could the eTMF-EMS be used?

- **Final eTMF transfer** to sponsor from CRO for archiving
- **Interim transfer of eTMF content** to central eTMF or other trial management system
- **Migration of eTMF** content following **merger and acquisition**
- **Migration of eTMF** content following **upgrade** or change of eTMF system
- **Long term archiving** of eTMF content and associated metadata

EMS Process flow



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Exchange Agreements

- Standard is flexible and does not cover every detail
- Exchange Agreements between 2 parties allows context specific information to be defined including:
  - Identification of exchanging parties
  - Identification of computerized systems
  - Identification of version(s) of the TMF Reference Model being used
  - Method of transfer and verification
  - Frequency of transfer
  - Convention on updates and modifications
  - Type of artifacts being transferred i.e. Data Management documents, entire TMF etc.
  - Folder structure specification (e.g. TransferID > Process Zone > Section)
  - Organization specific sub-artifact definitions
  - Organization specific non-standard metadata definitions
  - Organization specific data conventions

What about Oasis?

- The OASIS eTMF initiative was developed specifically for exchange of electronic TMF documents
- It was initially based loosely on the TMF Reference model but changed to become the OASIS Reference Model
- There has been minimal uptake of this Model and its associated exchange – the OASIS initiative was closed resulting in an approved specification but no OASIS standard
- The TMF Reference Model now has the Exchange mechanism to facilitate transfers of documents

Management of the TMF Reference Model

- Governed under a formal charter
- 14 member Steering Committee
  - Chair
  - Membership secretary
  - Meeting secretary
- Independent website www.tmfrefmodel.com
  - Resources include Charter, deliverables, meeting slides, educational links, useful information and links
- Change Control Board

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Steering Committee from 1st April 2018

- Karen Roy, Phlexglobal, Chairperson of SC, Co-chair of the TMF RM
- Lisa Mulcahy, Mulcahy Consulting – Co-chair of the TMF RM
- Eldin Rammell, Rammell Consulting, Membership secretary
- Allison Varjavandi, Astellas, Meeting secretary
- Marie-Christine Poisson, Pfizer
- Jamie Toth, Daiichi-Sankyo
- Fran Ross, Paragon
- Kathy Clark, IQVIA
- Scott McCullough, CRO
- Todd Tullis, Veeva
- Wendy Trimboli, Eisai
- Paul Fenton, Montrium
- David Ives, Vertex
- Russell Joyce, Heath Barrowcliff Consulting

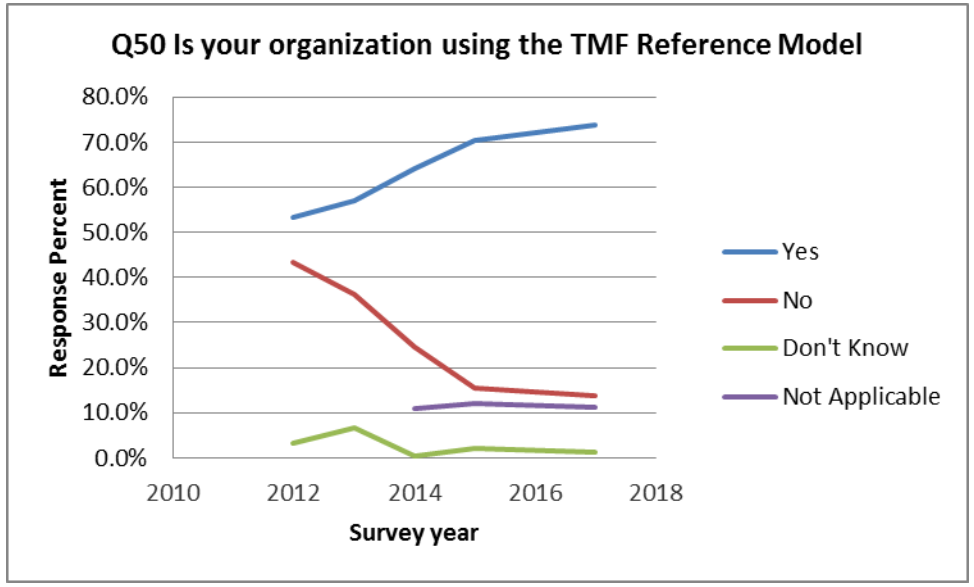
Members

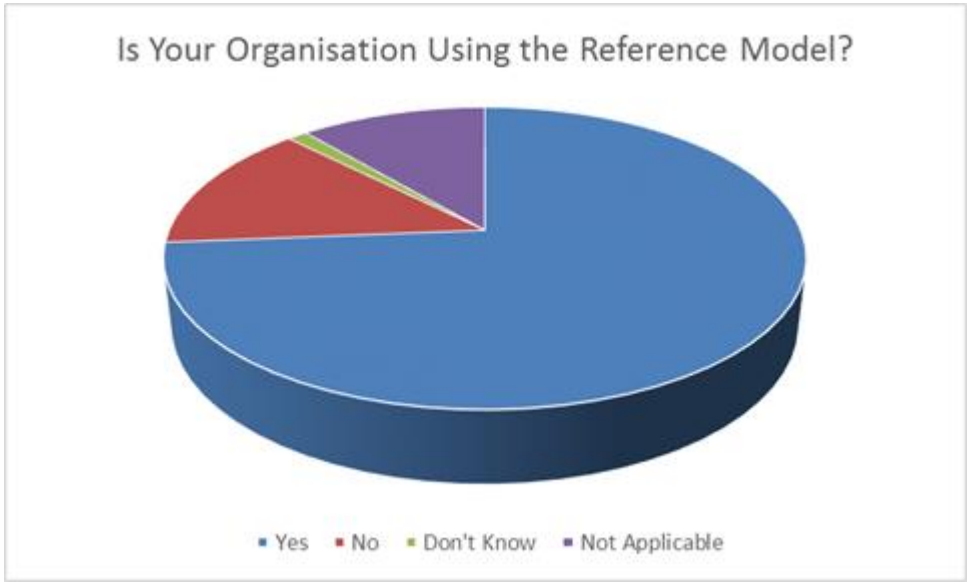
- Core TMF Reference Model Project (i.e. active on a team): 260
- Subscribers (involved in meetings etc): 708
- Yahoo!Groups Discussion Board: 540
- LinkedIn Group: 2,463
- Historical data

Africa	0.5%
Asia-Pac	5.6%
Europe	21.2%
Middle East	0.3%
North America	57.8%
South America	0.2%
Unknown	14.4%

Agency	0.5%
Clinical Research	2.8%
Consultant	8.8%
CRO	18.0%
Site	0.1%
Lab	0.1%
Non-profit	1.7%
Retired	0.1%
Services vendor	5.2%
Sponsor	53.0%
System vendor	9.8%

Usage of the Reference Model





Source: DIA Annual Ref Model Survey 2017

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Purpose of the TMF Reference Model

Standard Contents

Industry opinion on what is kept in a TMF

Standard Naming

Based on ICH E6 Sect. 8 & industry-accepted terminology

Standard Structure

To support paper and electronic systems

Standard Metadata

For eTMFs, minimum metadata at system and artifact level

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Purpose – Standard Contents

Standard Contents

Industry opinion on what is kept in a TMF

- Expands minimum list of documents found in ICH GCP
- Consistent interpretation, based on peer opinion and regulator feedback
- Avoids scope creep for TMF

Purpose – Standard Naming

Standard Naming

Based on ICH E6 Sect. 8 & industry-accepted terminology

- Avoids one artifact being referred to using different terms within an organisation and between organisations
- Avoids company-specific terms

Purpose – Standard Structure

Standard Structure

To support paper and electronic systems

- Facilitates consistent filing and rapid retrieval
- Helpful when responsibility for maintaining different sections of the TMF is distributed across several parties e.g. sponsor, CRO, consultants

Purpose – Standard Metadata

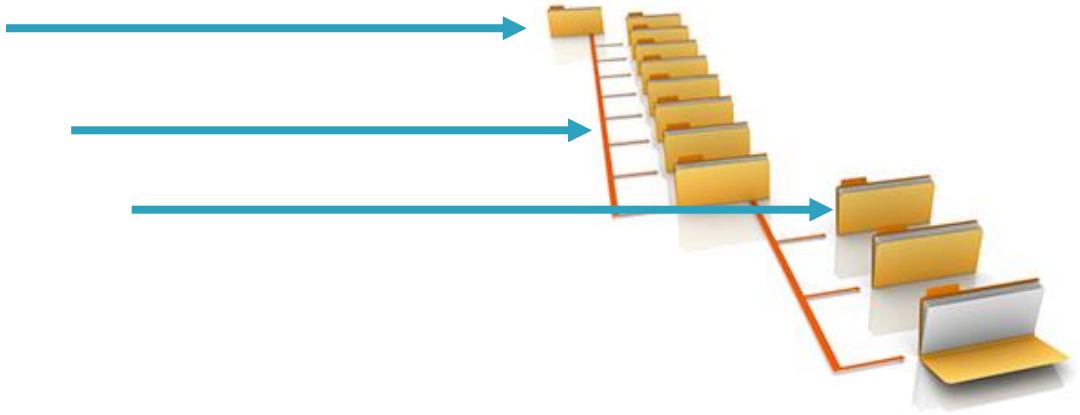
Standard Metadata

For eTMFs, minimum metadata at system and artifact level

- Encourages adoption of good practices to facilitate document retrieval
- Encourages consistency across the industry for exchange of content

Structure and Content of the Model

- Data held in a simple Excel spreadsheet
  - Easy for non-technical people to use!
- Hierarchical structure
  - 11 Zones
  - 48 Sections
  - 249 ***Artifacts***



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TMF Reference Model Zones

11 Zones
Trial Management
Central Trial Documents
Regulatory
IRB or IEC and other Approvals
Site Management
IP and Trial Supplies
Safety Reporting
Central and Local Testing
Third Parties
Data Management
Statistics

TMF Reference Model — TMF RM Website

Zone #	Zone Name	Section #	Section Name	Artifac	Artifact name	Alternate names (artifact also commonly known	
09	Third parties	09.01	Third Party Oversight	09.01.03	Ongoing Third Party Oversight		To conf meet al
09	Third parties	09.02	Third Party Set-up	09.02.01	Confidentiality Agreement		To conf be prev contrac
09	Third parties	09.02	Third Party Set-up	09.02.02	Vendor Selection		To iden parties selecti
09	Third parties	09.02	Third Party Set-up	09.02.03	Contractual Agreement	Scope of Work Project Work Order(s) Change Order(s) Financial Agreement Contract Service Agreement Letter of Agreement Letter of Intent Authorization to Proceed	To docu that del obligati descrip
09	Third parties	09.03	General	09.03.01	Relevant Communications	Correspondence	Zone-sp not spe include
09	Third parties	09.03	General	09.03.02	Tracking Information		Zone-sp the cou
09	Third parties	09.03	General	09.03.03	Meeting Material		Agenda internal signific and any
09	Third parties	09.03	General	09.03.04	Filenote	Note to File	To docu
10	Data Management	10.01	Data Management Oversight	10.01.01	Data Management Plan	Data Management Operational Plan Data Handling Manual Data Processing Plan Technology Plan	To iden compila limited Databa
10	Data Management	10.02	Data Capture	10.02.01	CRF Completion Requirements	CRF Completion Guidelines	To prov comple

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TMF Reference Model Sections

- The contents of each zone are grouped into sections
- Each section includes content that is relevant to a specified activity
- Sections are helpful for classification and searching

TMF Reference Model — TMF RM Website

Zone #	Zone Name	Section #	Section Name	Artifac	Artifact name	Alternate names (artifact also commonly known	
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TMF Artifacts

- Could include data files, documents, media, digitised content
- Could be 1 document or multiple documents
- Includes associated records e.g. approvals, translations, checklists, QC records, amendments

Artifac	Artifact name	Alternate names (artifact also commonly known	Definition / Purpose
09.01.03	Ongoing Third Party Oversight		To confirm throughout the duration of a study that a third party continues to meet all relevant criteria to fulfill a contractual obligation.
09.02.01	Confidentiality Agreement		To confirm by written legal agreement that key information between parties will be prevented from being inappropriately disclosed. May be included in another contractual agreement.
09.02.02	Vendor Selection		To identify how a third party was selected. May include details of other third parties short-listed, master vendor list and any assessments carried out prior to selection.
09.02.03	Contractual Agreement	Scope of Work Project Work Order(s) Change Order(s)	To document by a written dated signed agreement between two or more parties that defines any arrangements on delegation and distribution of tasks and obligations (including financial obligations); critical components include service

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Artifact Definition

- A description to explain the content of an artifact and/or the use and purpose of the artifact
- Assists with ensuring a common interpretation of the model
- Aligned with ICH definitions

Artifact name	Alternate names (artifact also commonly known	Definition / Purpose
Filenote	Note to File	To document any decision or to clarify any information relating to this zone.
Data Management Plan	Data Management Operational Plan Data Handling Manual Data Processing Plan Technology Plan	To identify the overall strategy for data management process for the study; a compilation of documents that may include amendments/appendices but are not limited to: Completion Guidelines, Data Quality Plan, CRF Design Document, Database (build) Specification, Entry Guidelines, Database Testing..
CRF Completion Requirements	CRF Completion Guidelines	To provide detailed instructions on how data points on each CRF are to be completed; how to enter on paper and if EDC, how to enter data into the system.
Annotated CRF		To assign variable names and attributes to the fields on the CRF and to link the

ICH Code

- Reference to the ICH GCP Guidelines
- Notice that other sections beyond E6 Section 8 are quoted
- Includes indirect as well as direct references

Zone #	Zone Name	Section #	Section Name	Artifac	Artifact name	Core or Recommended for inclusion	ICH Coc
08	Central and Local Testing	08.02	Sample Documentation	08.02.02	Shipment Records	Recommended	8.2.15 8.3.8
08	Central and Local Testing	08.02	Sample Documentation	08.02.03	Sample Storage Condition Log	Recommended	8.2.14
08	Central and Local Testing	08.02	Sample Documentation	08.02.04	Sample Import or Export Documentation	Core	8.2.15 8.3.8
08	Central and Local Testing	08.02	Sample Documentation	08.02.05	Record of Retained Samples	Core	8.3.25
08	Central and Local Testing	08.03	General	08.03.01	Relevant Communications	Core	8.3.11

Sub-artifacts

- When an artifact name does not explicitly refer to a single kind of record (e.g. Meeting Material), sub-artifacts provide a means to list all company-specific records that are expected for a given artifact.
- Only examples are provided in the model but expected to be overridden as part of adopting the Reference Model for a company.
- Current subgroup activity to refine

Zone #	Zone Name	Section #	Section Name	Artifact	Artifact name	Sub-artifacts (examples of document types different from the artifact provided, overwrite with your company-specific record
01	Trial Management	01.03	Trial Committee	01.03.03	Committee Output	Committee Correspondence Committee Data Package Committee Minutes Committee Report
01	Trial Management	01.04	Meetings	01.04.01	Kick-off Meeting Material	Agenda Minutes Attendance Sheet Presentation Materials Questions and Answers Recording
01	Trial Management	01.04	Meetings	01.04.04	Trial Team Evidence of Training	Attendance Sheet Training Report Recording

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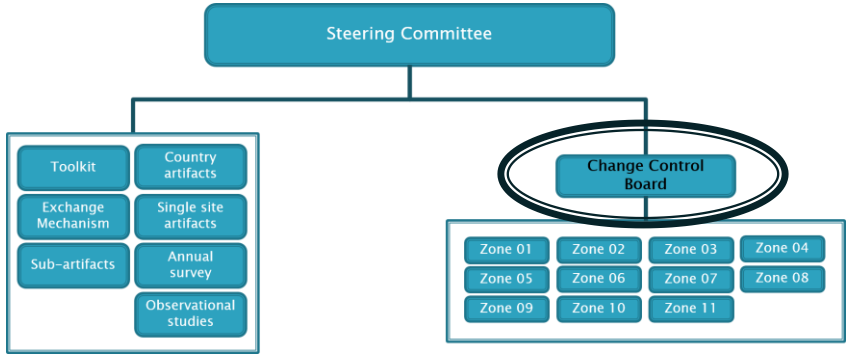
Change Control Board



- **Change Control Board Structure**
  - 15 members
  - Kelley Robinson, Pfizer: Chair
  - Joanne Malia, Regeneron: Deputy Chair
- **Deliverables to Date**
  - Meeting twice a month since October 2017
  - Created and finalized: Change Control Procedure, RACI and CR Tracker
  - Reviewed and categorized all current change requests
  - Triaging all change requests to Zone Teams

Version Control

- Maintenance release e.g. v3.0.1
  - e.g. minor typographic changes, clarification, sub-artifacts
- Minor release e.g. v3.1
  - Substantial change in content but no compatibility issues e.g. additional optional column (milestones)
- Major release e.g. v4.0
  - Change likely to have compatibility issues with prior version e.g. addition/removal of artifacts

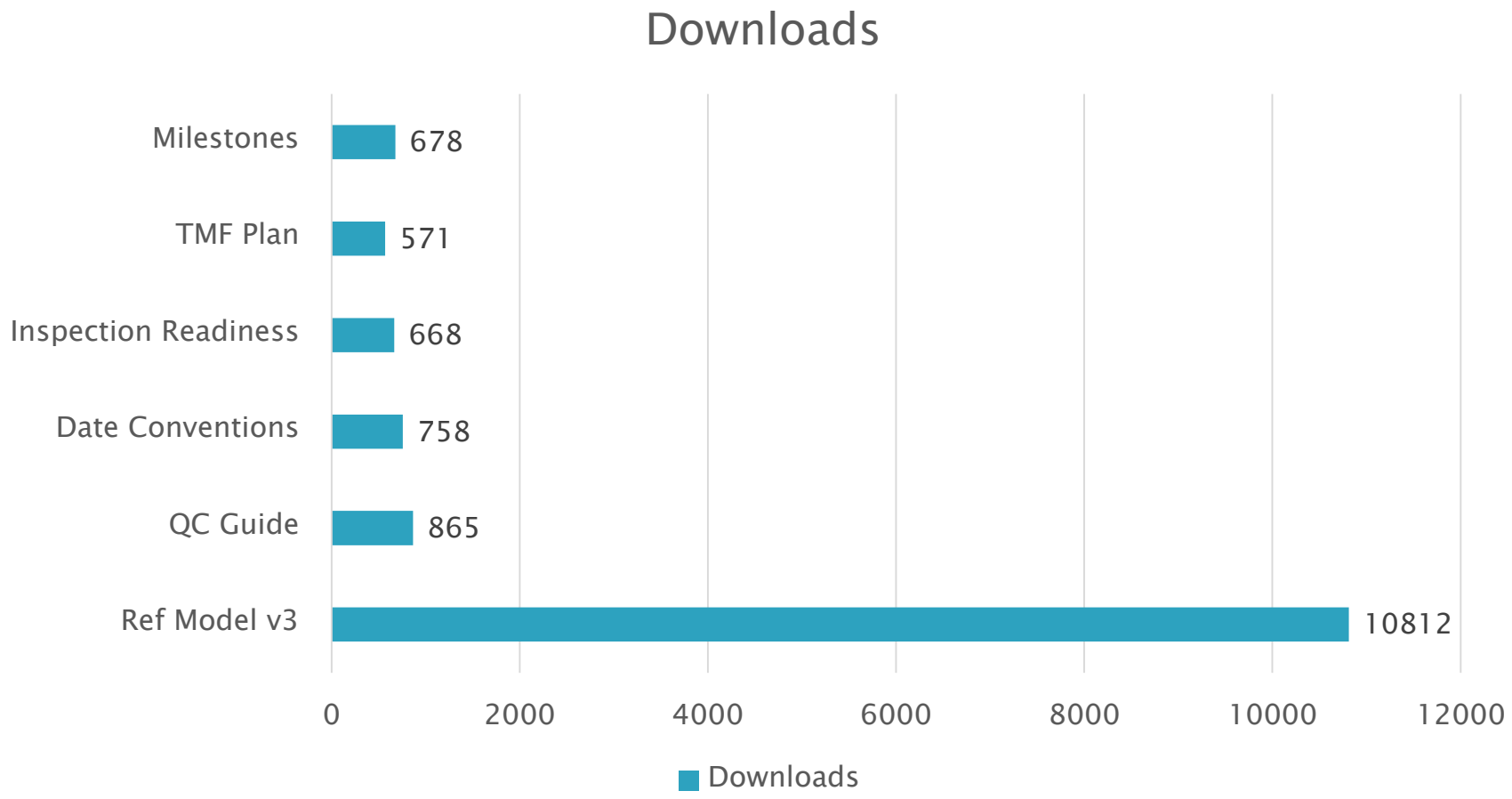
Deliverables to Date

TMF Tools:

- TMF Reference Model User Guide: Introduction to the model, understanding its structure, and how to use it (v1.0 Approved 16-March-2018) **NEW**
- TMF Reference Model Implementation Guidance: Provides a framework for implementing the model in your organization (v1.0 Approved 14-March-2018) **NEW**
- TMF Plan Template: Suggested structure and outline for a Trial Master File Plan (v1.0 Approved 23-February 2018) **NEW**
- TMF Plan Template Feedback: Click on LINK to provide feedback on the TMF Plan **NEW**
- Milestones / Events: Suggested latest milestones or events by which each artifact should be filed (v1.1 Approved 31-January-2018) **REVISED**
- Date Conventions: Suggested date convention to use for each artifact (Approved 15-Feb-2017)
- Date Conventions Guidance: Guidance notes to be used with Date Conventions spreadsheet (Approved 15-Feb-2017)
- TMF Quality Control: Toolkit to help prepare a TMF quality control programme (Approved 12-Oct-2016)
- TMF Quality Control Presentation: Powerpoint slides presented to group meeting November 7, 2016
- Inspection Readiness: Toolkit to help prepare TMF for regulatory inspections (Approved 09-Nov-2016)
- Inspection Readiness Presentation: Powerpoint slides presented to group meeting January 9, 2017
- eTMF Selection – Request for Proposal Template (co-authored by Scientific Archivists Group, TMF Reference Model and Pocket EDMS, March 2017
- Inspection FAQs: Common inspection questions with answers, and regulatory resource list (Approved 15-Mar-2017)

- Metrics 101 – How to Implement a TMF Metrics Program (PDF File)
- Metrics 101 – How to Implement a TMF Metrics Program (PPT File)
- Metrics Definitions – Recommended Metrics for your TMF Metrics Program (XLS File)

File downloads since Mar 30, 2017



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Ongoing Subgroup Activities

Group	Aim
Metadata	To standardise the metadata collected – integrated into the Exchange Mechanism
Sub-artifacts	To standardise the subartifacts in the TMF RM
Country specific artifacts	Guide for country specific artifacts required (with links to relevant websites)
Device Studies	Device specific artifacts
JGCP	Mapping to Japanese GCP documents

The Future of the TMF Reference Model

- Change Control Board for the minor and major changes
- Be recognized by regulators
- Be referenced in regulations including ICH
- Further thoughts?

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QUESTIONS?

Join the TMF Reference Model Yahoo! Discussion Group

https://groups.yahoo.com/neo/groups/tmfrefmodel/info

- Knowledge sharing
- Networking
- Too Much Fun!

Join the TMF Reference Model Project Team

http://tmfrefmodel.com/join

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Trial Master File Reference Model

Thank You!