



Trial Master File Reference Model

The TMF Reference Model and the Exchange Mechanism Standard

Boston, June 26th 2018

Presenters

- ▶ Karen Roy
 - Chair of the TMF Reference Model Steering Committee
 - Chief Strategy Officer, Phlexglobal

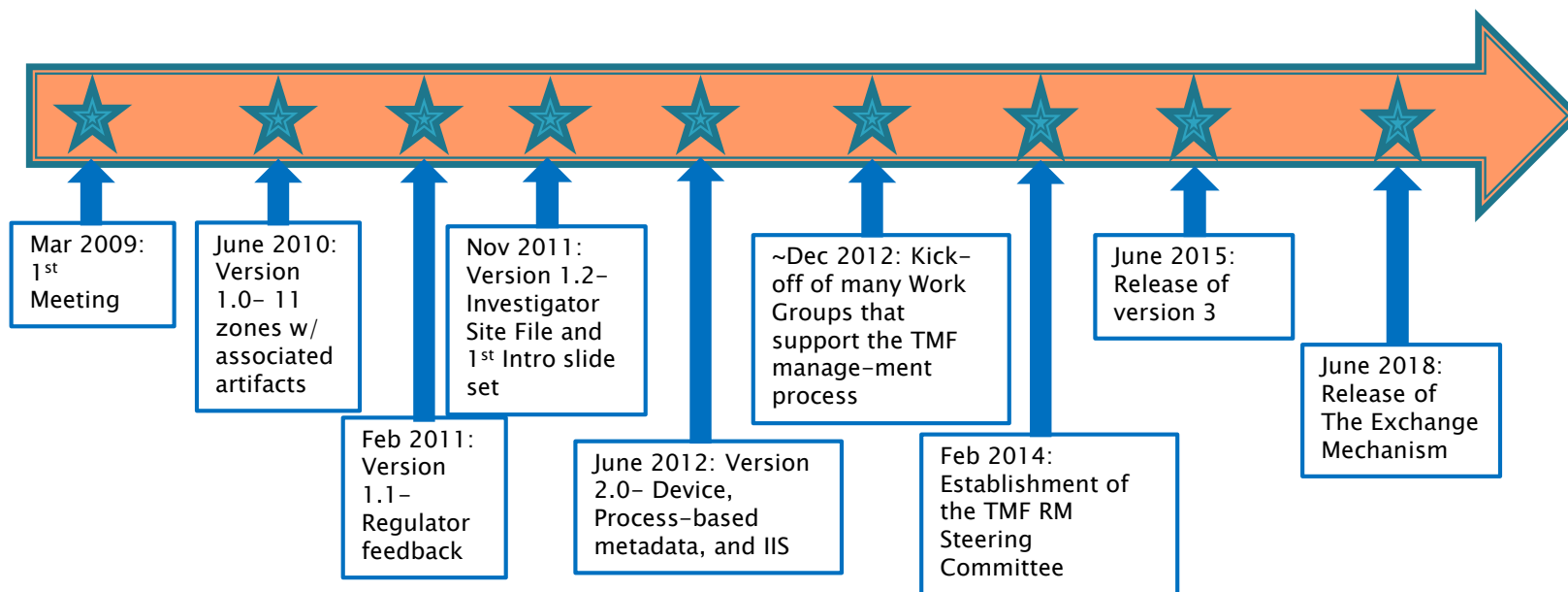
- ▶ Paul Fenton
 - Co-chair of the TMF Reference Model Exchange Mechanism
 - CEO, Montrium

- ▶ Ken Keefer
 - Project Lead of the TMF Reference Model Exchange Mechanism
 - Principal Consultant, Keefer Consulting Inc.

- ▶ Elvin Thalund
 - Co-chair of the TMF Reference Model Exchange Mechanism
 - Senior Director, Industry Strategy, goBalto

History of the TMF Reference Model

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



Purpose of the TMF RM

Standard Contents

Industry opinion on
what is kept in a TMF

Standard Naming

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

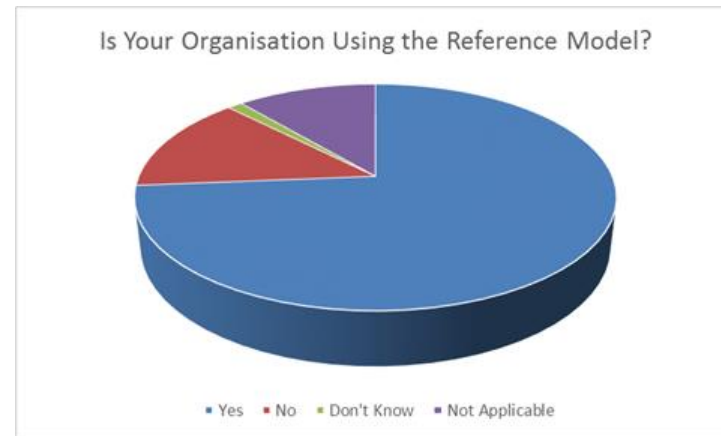
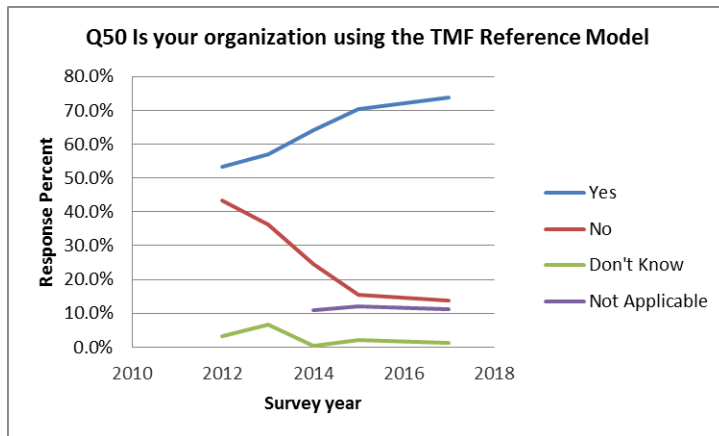
Standard Structure

To support paper and
electronic systems

Standard Metadata

For eTMFs, minimum
metadata at system
and artifact level

Usage of the TMF RM



Source: DIA Annual Ref Model Survey 2017

Management of the TMF RM

- ▶ 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

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%

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)



Trial Master File Reference Model

Overview of the Standard

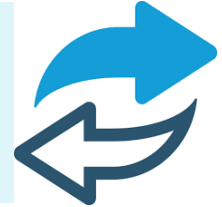
Paul Fenton

Where we have come from

- ▶ Prior to the TMF RM, organization of TMF content was a free for all
- ▶ Since then we have seen massive uptake of the TMF RM across the industry and globally
- ▶ The TMF RM provides us with structure and a certain level of 'standardization'
- ▶ Focus is still very much on the organization of the artifacts rather than describing artifacts through metadata
- ▶ This is a challenge for systems....enter the eTMF-EMS

What is the eTMF–EMS

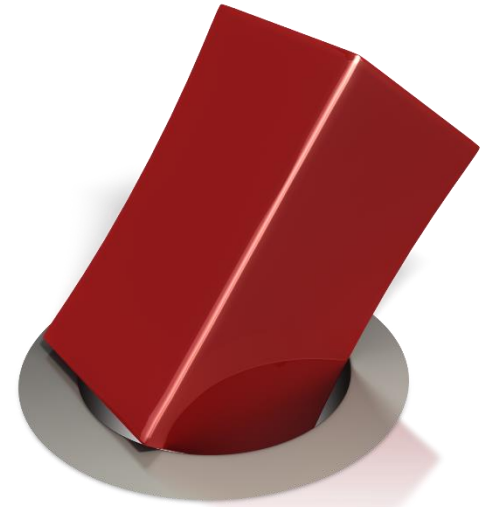
Electronic Trial Master File – Exchange Mechanism Standard



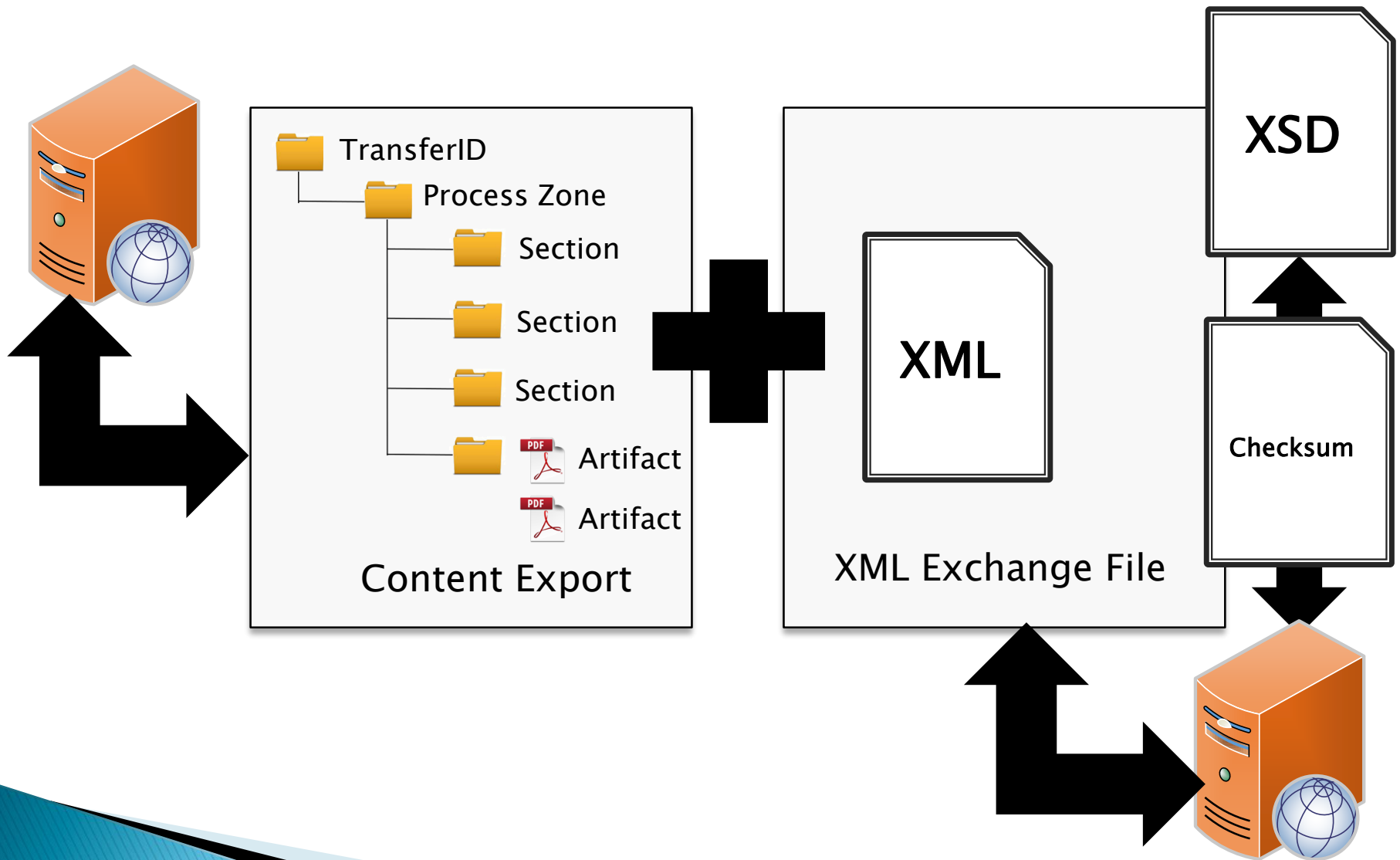
- ▶ An extension of the TMF RM which focuses on the transfer of content, metadata, audit trail and eSig information
- ▶ A TMF metadata standard
- ▶ A mechanism for exchanging TMF content between systems
- ▶ A method for describing TMF artifacts which is comprehensible by both humans and machines

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** back 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**



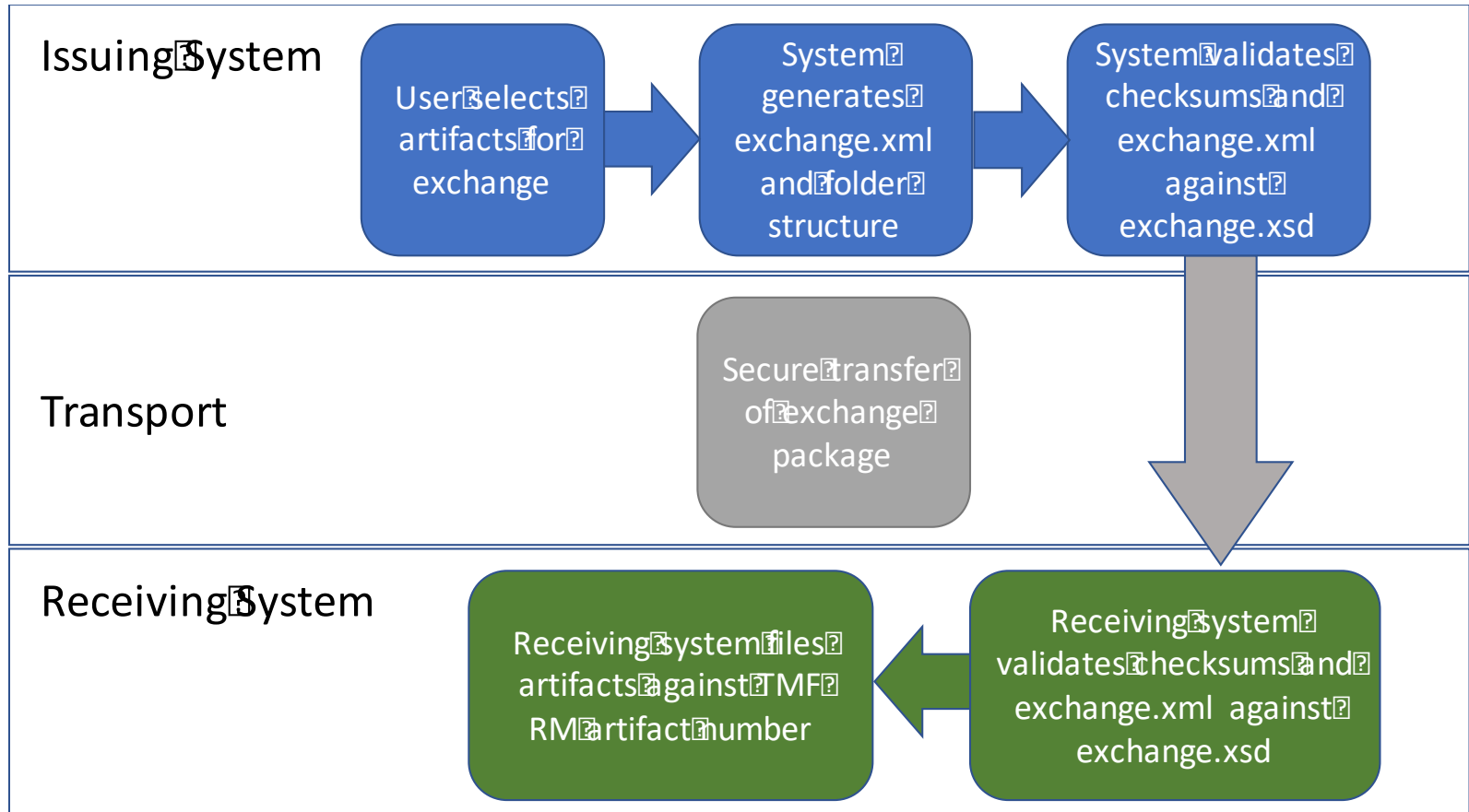
How it works



How could it 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**

Process flow



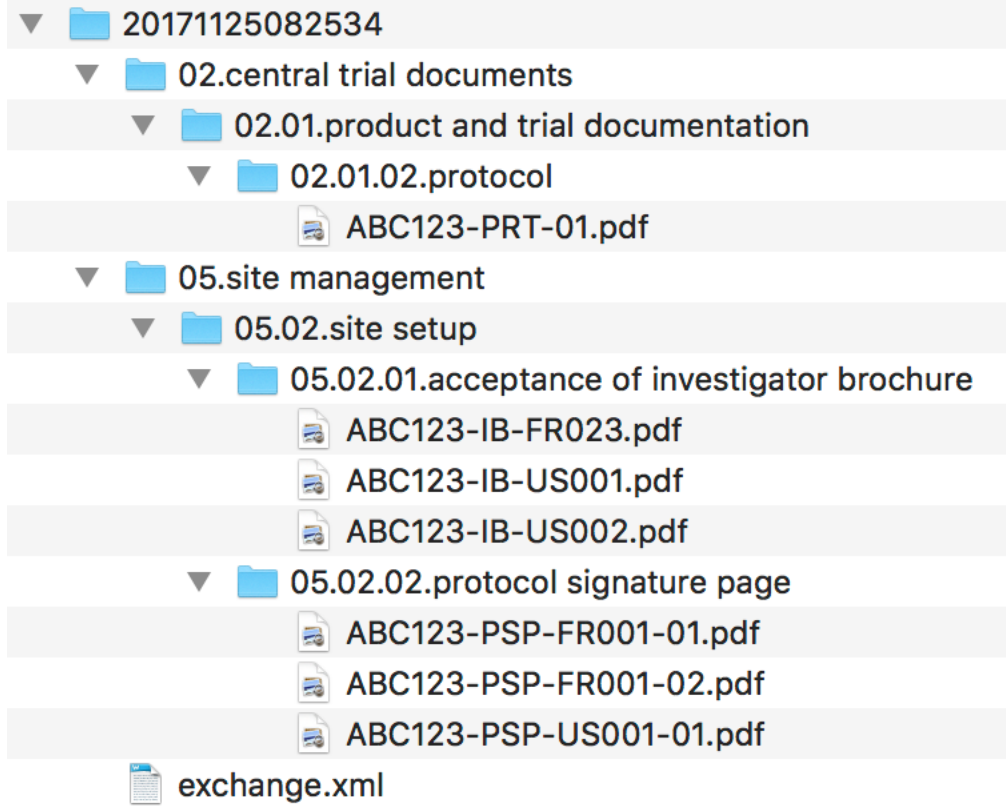
How does it link to the RM

- ▶ The eTMF–EMS is linked to the RM through the following cross references:
 - Artifact Number i.e. 01.01.01
 - Unique ID i.e. 001
 - RM version number
- ▶ When an artifact is exchanged it must be cross referenced with the above information
- ▶ This allows the receiving system to properly identify and file it within it RM based structure

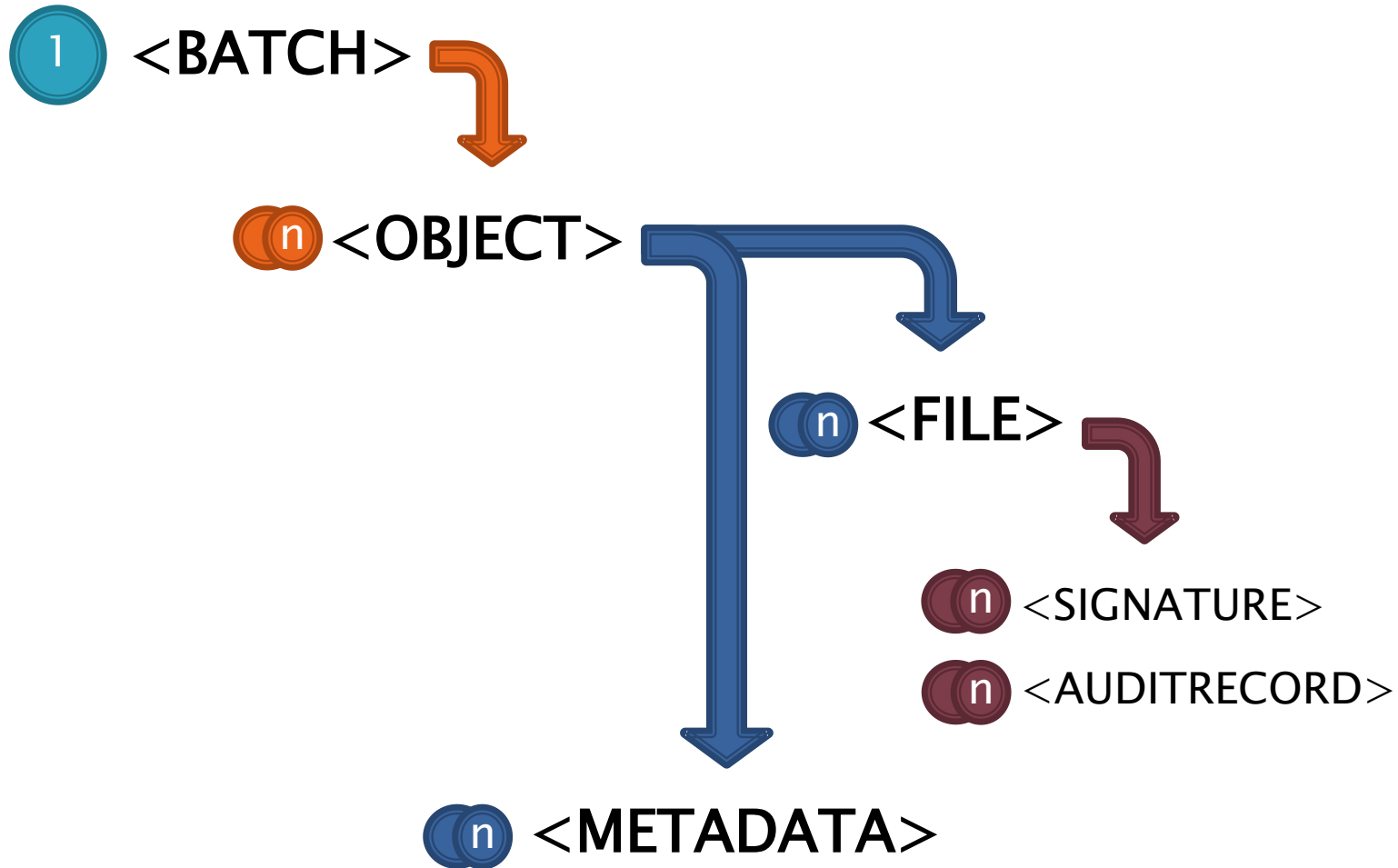
Exchange Agreements

- ▶ 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

Folder Structure



exchange.xml Hierarchy



Sample Exchange File

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    <OBJECTLEVEL>Site</OBJECTLEVEL>
    <COUNTRYID>USA</COUNTRYID>
    <SITESYSTEMID>US204</SITESYSTEMID>
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    <ARTIFACTCODE>05.02.01</ARTIFACTCODE>
    <PERSONNAME>John Smith</PERSONNAME>
    <ORGANIZATIONNAME>St.Mary's Hospital</ORGANIZATIONNAME>
    <OBJECTLANGUAGE>EN</OBJECTLANGUAGE>
    <TRANSLATION>No</TRANSLATION>
    <OBJECTVERSION>1.0</OBJECTVERSION>
    <OBJECTVERSIONSTATE>Current</OBJECTVERSIONSTATE>
  ▼<OBJECTTITLE>
    Acceptance of Investigator Brochure Annex for Site US-204
  </OBJECTTITLE>
  <SUBARTIFACT>Signed IB Annex</SUBARTIFACT>
  <OBJECTCOPY>Yes</OBJECTCOPY>
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  </CONTENTURL>
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  </SIGNATURE>
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  </AUDITRECORD>
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</OBJECT>
</BATCH>
```



Trial Master File Reference Model

Project Overview and Next Steps

Ken Keefer

The eTMF–EMS Project

- ▶ Scope
- ▶ Objectives
- ▶ Constraints and Assumptions
- ▶ Risks
- ▶ Milestones
- ▶ Organization
- ▶ Status and Plans

Scope

- ▶ Version 1
- ▶ Review and testing
- ▶ Ratification of standard
- ▶ eTMF Vendors
- ▶ Business cases

Version 1 Scenarios

- ▶ Full study or defined portion of a study
 - A transfer of a completed TMF
 - A one-time transfer of an active TMF
 - Multiple transfers of an active TMF

Project Objectives

▶ General

- Obtain Steering Committee ratification
- Gain industry acceptance and commitment

▶ Specific

- Review Specification and XML
- Ensure no conflict with work of other subgroups
- Align with vendor product offerings
- Meet business needs

Meeting Business Needs

- ▶ Sponsors and CROs
 - Develop business scenarios and standard data sets
- ▶ Vendors
 - Develop product features to consume and/or generate standard data sets
 - Test business scenarios

Constraints and Assumptions

- ▶ Volunteer full-time work responsibilities
- ▶ Time estimates accurate and realistic

Risks

- ▶ Diversity and number of stakeholders
 - Significant rework
 - Managing scope
 - Knowledge transfer
- ▶ Competing standards

Milestones

Milestone	Projected Completion
Review EMS Version 0.5	2018 Q2
Obtain SC Ratification of Version 1.0	2018 Q2
Publish Version 1.0	2018 Q2
Test EMS Version 1.0	2019 Q1
Clarify use cases supported by Version 1.0	2019 Q1
Identify use cases for future versions	2019 Q1
Obtain SC Ratification of Version 1.1	2019 Q1
Publish Version 1.1	2019 Q1

The eTMF-EMS Subgroup

- ▶ Approximately 25 members from pharma, CROs, vendors and consultants
- ▶ Overseen by the TMF RM steering committee
- ▶ Active 2.5 years
- ▶ Meets weekly

Accomplishments

- ▶ Charter approved by Steering Committee
- ▶ Specification and XML developed
- ▶ Review by industry volunteers
 - Sponsors and CROs
 - eTMF vendors
- ▶ Ratification by Steering Committee
- ▶ Version 1.0 Released

What's Next?

- ▶ Reorganize team for testing
- ▶ Develop eTMF system interfaces
- ▶ Build schema to validate files
- ▶ Identify pilots for implementation
- ▶ Build on version 1.0
- ▶ Ratification by ICH?

Communication

- ▶ Online Q&A sessions
- ▶ FAQs on TMF RM website
- ▶ Targeted team meetings
- ▶ Groups.io



Trial Master File Reference Model

Case Study – IRB and Study Start-up

Elvin Thalund

IRB/EC to Vendor Approvals – What is the TMF RM EMS?

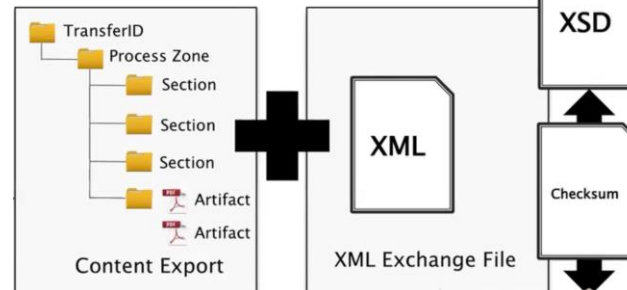
IRB Approvals – IRB
feature

Study Startup – Vendor
feature



IRB Approval
export to

NEW
TMF RM
Exchange
Mechanism
standard



[tmfrefmodel.com/
ems/](http://tmfrefmodel.com/ems/)



IRB Approval
import from

TRIAL MASTER FILE
TMF
REFERENCE MODEL

IRB/EC to Vendor Approvals – Why use the TMF RM EMS?

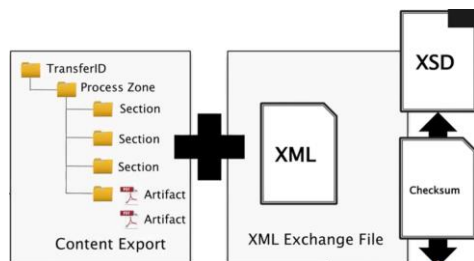
- One implementation for all studies
- One solution for all Vendors
- Clear separation of responsibilities
 - IRB generate out to one format in TMF RM standard and can use same data format and mapping for all implementations
 - Vendors convert TMF RM standard into customer model for subsequent processing
- Can become an official implementation recognized the TMF RM and available in github for opensource implementation
- <https://github.com/TmfRef/exchange-framework/>

IRB/EC to Vendor Submissions - EVENTID="IRB-RECEIVED"



IRB
Submissions

IRB
Submissions



Artifact #	Artifact name
04.01.01	IRB or IEC Submission
04.02.01	Other Submissions
04.03.01	Notification to IRB or IEC of Safety Information
04.03.02	IRB or IEC Progress Report
04.03.03	IRB or IEC Notification of Trial Termination
04.04.01	Relevant Communications
04.04.04	Filenote

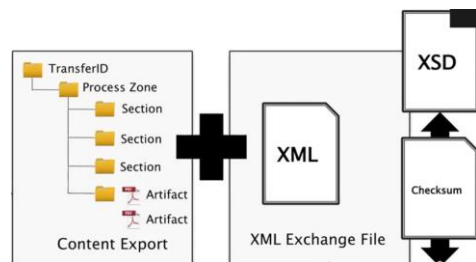


TRIAL MASTER FILE
TMF
REFERENCE MODEL

IRB/EC to Vendor Approvals and other documentation - EVENTID="IRB-SENT"



IRB
Approvals



IRB
Approvals

Artifact #	Artifact name
04.01.02	IRB or IEC Approval
04.01.03	IRB or IEC Composition
04.01.04	IRB or IEC Documentation of Non-Voting Status
04.01.05	IRB or IEC Compliance Documentation
04.02.02	Other Approvals
04.04.01	Relevant Communications
04.04.04	Filenote



TRIAL MASTER FILE
TMF
REFERENCE MODEL

Vendor to IRB/EC Submissions – <BATCH> - EVENTID="IRB-RECEIVED"

<BATCH

xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
xsi:noNamespaceSchemaLocation="TmfReferenceModelExchange.xsd"

STUDYSYSTEMID="ATEM0025"

STUDYID="ATEM-0025"

EVENTID="IRB-RECEIVED"

TRANSFERSOURCEID="CRO101"

TRANSFERID="20180616151025"

SPECIFICATIONID="ABC-0235"

TMFRMVERSION="3.0">

Vendor to IRB/EC Submissions – <OBJECT> - Site Information Questionnaire

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</OBJECT>

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IRB/EC to Vendor – <BATCH> - EVENTID="IRB-SEND"

<BATCH

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xsi:noNamespaceSchemaLocation="TmfReferenceModelExchange.xsd"

STUDYSYSTEMID="ATEM0025"

STUDYID="ATEM-0025"

EVENTID="IRB-SEND"

TRANSFERSOURCEID="IRB101"

TRANSFERID="20180626140025"

SPECIFICATIONID="ABC-0235"

TMFRMVERSION="3.0">

IRB/EC to Vendor Submissions – <OBJECT> - IRB Board Roster

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    <CONTENTURL>04/04.01/04.01.03.IRB or IEC Composition/Super IRB Board Roster 01Jul2018.pdf</CONTENTURL>
    <FILEDESCRIPTION>Record</FILEDESCRIPTION>
  </FILE>

</OBJECT>

</BATCH>
```

IRB/EC TMF RM EMS – Mapping requirements

- In the case of IRB/EC communication there are in some cases where one form can be used for different types of communication
- To track/file this on a desired level it requires coding and related mapping. Here is an example template for this mapping

Event ID	Artifact #	Artifact name	Sub Artifact (Form-Type)	Definition
IRB-RECEIVED	04.01.01	IRB or IEC Submission	F-103	
IRB-RECEIVED	04.02.01	Other Submissions		
IRB-RECEIVED	04.03.01	Notification to IRB or IEC of Safety Information		
IRB-RECEIVED	04.03.02	IRB or IEC Progress Report		
IRB-RECEIVED	04.03.03	IRB or IEC Notification of Trial Termination		
IRB-RECEIVED	04.04.01	Relevant Communications		
IRB-RECEIVED	04.04.04	Filenote		
IRB-RECEIVED	04.01.02	IRB or IEC Approval		
IRB-SENT	04.01.03	IRB or IEC Composition		
IRB-SENT	04.01.04	IRB or IEC Documentation of Non-Voting Status		
IRB-SENT	04.01.05	IRB or IEC Compliance Documentation		
IRB-SENT	04.02.02	Other Approvals		
IRB-SENT	04.04.01	Relevant Communications		
IRB-SENT	04.04.04	Filenote		

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>