Trial Master File Reference Model

General Meeting

14 May 2018

Agenda

- Welcome
- Steering Committee Update
- TMF RM Community
- ICH Presentation
- Exchange mechanism
- Other Subgroup activity update
- Framework for the Destruction of Paper
- HSRAA MHRA Presentation
- Upcoming Industry meetings

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Steering Committee Update

- Voting Results
  - Kathie Clark, IQVIA, USA (Vendor)
  - David Ives, Vertex, USA (BioPharma)*
  - Russell Joyce, Heath Barrowcliff Consulting, UK (Consultant)*

  - *New Members

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TMF RM Community in numbers

- Project Team Members: 229[1]
  - Please join a team!
- Subscribers (join from website homepage): 716[2]
- Discussion Board (Yahoo! Groups): 548[2]
  - Eight discussion topics since last meeting
- LinkedIn Group: 2,525
  - Six discussion topics since last meeting

[1] Inactive members dropped out since last meeting

[2] Approx. 10 new subscribers each month

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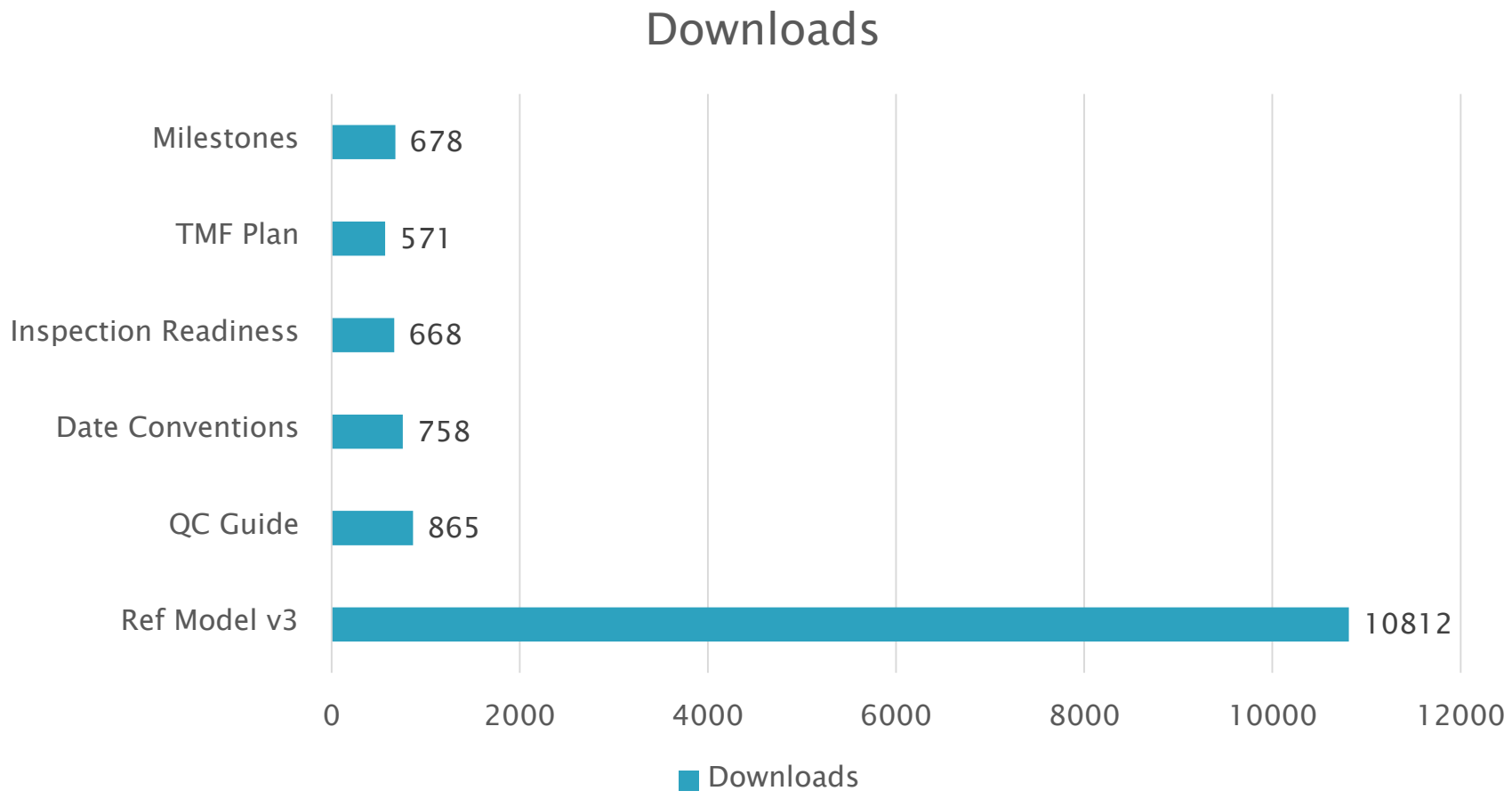
File downloads since Mar 30, 2017



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ICH Presentation to ICH M2 Expert working Group

- 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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ICH Q & A

- Overall feedback from regulators?
  - Generally positive feedback. Regulators not permitted to "approve" the Reference Model. Considered by regulators to be a helpful tool.
- Is there a common validation tool that will be used?
  - A combination. XSD is used to validate the form of XML that is being transferred. Also other tests on the content are completed by either the sending or receiving system…. to be completed by vendors. Intention to keep EMS flexible and simple.
- Is EMS extensible?
  - Yes, EMS has standards for tags but also allows for non-standard values e.g. name of manufacturer. Also, if same tags are being used frequently, they can be brought into standard in the future.
- How to handle eSignatures?
  - As a group, we define the scope of activities and this is generally limited to content and structure. We don't specify standards for eSigs as it is out of scope. However, within the EMS eSigs are accommodated. Metadata tags cover parameters for eSigs, based on CDISC tags. For digital signatures (with certificate), the signature is embedded within the artifact so no additional metadata required.

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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Trial Master File Reference Model

eTMF-EMS – Towards a First Industry Standard

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

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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

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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

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Who is involved?

- The eTMF-EMS subgroup is composed of around 25 members from pharma, CROs, vendors and consultants
- The group is overseen by the TMF RM steering committee
- Group has been active for around 2.5 years and meets weekly
- Significant interest and support from industry

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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

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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

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Where are we at?

- Specification has been developed and reviewed by industry
- Specification will be shortly submitted to the TMF RM SC for ratification
- Release of v1.0. of the specification will be in June 2018 at DIA Annual Meeting

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What's next

- Vendors need to develop interfaces within eTMF systems to generate and import exchange files
- The schema needs to be built to be able to validate files
- Sponsors and CROs need to work with vendors to identify pilots for the implementation of the eTMF-EMS
- We need to build on v1 and continue to evolve the standard
- Possible ratification by ICH?

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eTMF Exchange Mechanism Standard, Version 1
Review, Testing, and Ratification

- Progress to date:
  - Specification drafted by the eTMF-EMS subgroup
  - Review by vendors, sponsors, and CROs
  - Updates and submission to SC for ratification
- What is next?
  - Sponsor and CROs to create business scenarios, test cases, and test data
  - Vendors to develop code and test
  - SC to ratify Version 1.1
- Submit your questions and become involved!
  https://tmfrefmodel.com/ems/

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Activity Other Subgroups

Group	Lead
Observational Studies	Russell Joyce
Sub-artifacts	Karin Schneider
Country specific artifacts	Eleanor Hewes
Device Studies	Melonie Warfel
J-GCP	Sub group
Change Control Board	Kelley Robinson / Joanne Malia

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Observational Studies (Russell)

- **Using term Non-Interventional Study as defined by Art 2 (c) 2001/20/EC & EMA**
  - The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
  - The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
  - No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data
- **Structure**
  - 15 members (6 active)
  - Chairman: Russell Joyce, Heath Barrowcliff Consulting
  - De Facto Co-Chairman: Stuart McCully, CHCUK
- **Progress to Date**
  - Currently meeting fortnightly
  - NIS TMF to be a modification of TMF Ref Model
  - Determining documentary requirements arising from EU & US regulatory requirements
  - Drafting NIS glossary of terms

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Devices (Melonie)

- 10 Members
- Small group – reviewing the Zones and documenting recommendations as a team
- Zone 1 meeting May 24th 11:00-12:00 EST
- Meetings scheduled every 4th Thursday through end of year
- Depending on how long it takes per Zone we may increase time per meeting or add a meetings to speed process
- If interested please join the group!

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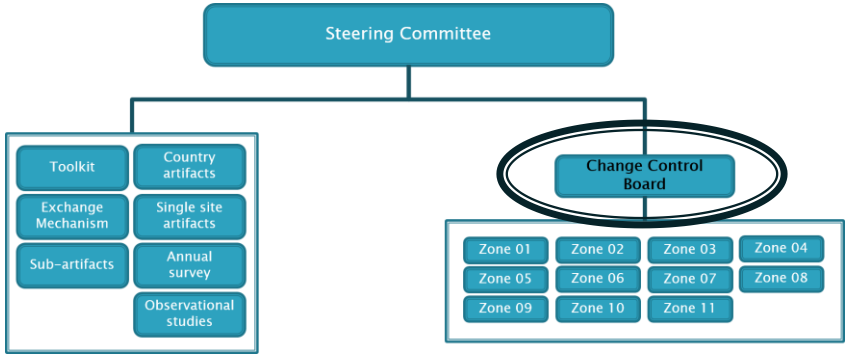
Change Control Board



- **Change Control Board Structure**
  - 15 members – no additional members needed
  - Kelley Robinson, Pfizer: Chair
  - Joanne Malia, Regeneron: Deputy Chair
  - Gift Chareka, UCSF: Exchange Team Liaison
  - Eldin Rammell: Steering Committee Liaison
- **Deliverables to Date**
  - Currently meeting once a month
  - Change requests have been sent to Zone teams
  - Eight recommendations have been submitted to the Steering Committee for final review. ~ 12 more to be sent by the end of the month.
  - Submit requests here: https://tmfrefmodel.com/feedback

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Framework for the Destruction of Paper

Project Summary

-Review, Assess, and Update the current recommendations and provide a new version of the framework. Organized/Supported by DIA DRM Community.

-70 volunteers, about 50% are active. If interested to join project, we always utilize anyone in a variety of ways at any point. **Need Legal team members**

To get yourself involved or to refer your legal colleagues contact Lisa Mulcahy at mulcahyconsulting@comcast.net

Deliverables of the Project

- Survey conducted March-April 2018 – Top Line results compiled
- Updated Framework
-Toolkit for Implementation – team kicking off in May; goes through October

Publication and presentation plan in development to support the communication of the deliverables.

Tracking to the Timeline

Expect all current parameters to be reviewed by end of June.

July-August will be to address question, ensure consistency, update glossary, revise opening and acknowledgement pages

Published framework on track for 4Q18

Good work being done in these first months. Fresh eyes (reviewers) of the full draft document needed in Aug/Sept.

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HSRAA Meeting – MHRA Findings on Archiving

- Unable to construct Sponsor and Vendor involvement in a study
- Not all electronic data / documents returned to Sponsor at the end of a study. Do they have to be returned?
- Differing archive processes for data / documents from different aspects of the TMF
- Electronic media in a safe which had to be hammered open ☺

- *Guidance being drafted on expectations for CROs when data is returned to a Sponsor or systems remain at Vendor*

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MHRA StEM Meeting and Other Feedback

- Rise in eTMF non-compliance principally because eTMF has made it harder to inspect than paper TMF e.g. access not arranged in advance, index difficult to navigate / not aligned with paper documents, not up-to-date, difficult to find documents and data.
- Phillip Moeller from Danish Medicines Agency said that the TMF guidance will be available in 2019. Gabrielle Schwartz, Andy Fisher and Phillip started working on the feedback recently.
- Joint NHS Health Research Authority (HRA) / MHRA statement on eConsent coming in June 2018

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eTMF Conferences coming up

- EXL TMF Institute, Boston, July 11-12, 2018 http://tmfsummit.com/institute
- IQPC, TMF and Inspection Readiness, 24th to 27th September, Amsterdam https://trialmasterfile.iqpc.co.uk/
- EXL TMF Summit, London, 15th to 17th October http://tmfsummit.com/europe
- DIA Clinical and Regulatory Operational Excellence, Barcelona, 28th to 29th November 2018, Abstracts are open. http://www.diaglobal.org/en/conference-listing/meetings/2018/11/edm-2018-clinical-and-regulatory-operational-excellence-forum

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TMF RM General Meetings

- 10-Sept
- Add to your calendar NOW or download the calendar file (.ics file) when you receive the meeting notification from MailChimp
- Outlook Meeting Request no longer distributed

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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
(but be prepared to work!)
http://tmfrefmodel.com/join

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