Trial Master File Reference Model

General Meeting

1st March 2021

Agenda

- Introduction
- Release of TMF RM 3.2.1 – Joanne Malia
- MHRA GCP Inspection Report – Kathie Clark
- BIMO Report – Karen Roy
- Progress on the EMS Survey – Ken Keefer, Elvin Thalund & Paul Fenton
- Upcoming TMF Meetings
- Next Meeting

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Membership …

- 307 project team members (groups.io)
- 1,377 Mailing List Subscribers** (tmfrefmodel.com)
- 3,429 members of LinkedIn group
- For details on these different groups and how to get involved, see http://tmfrefmodel.com/join

** Make sure webadmin@tmfrefmodel.com is on your email whitelist

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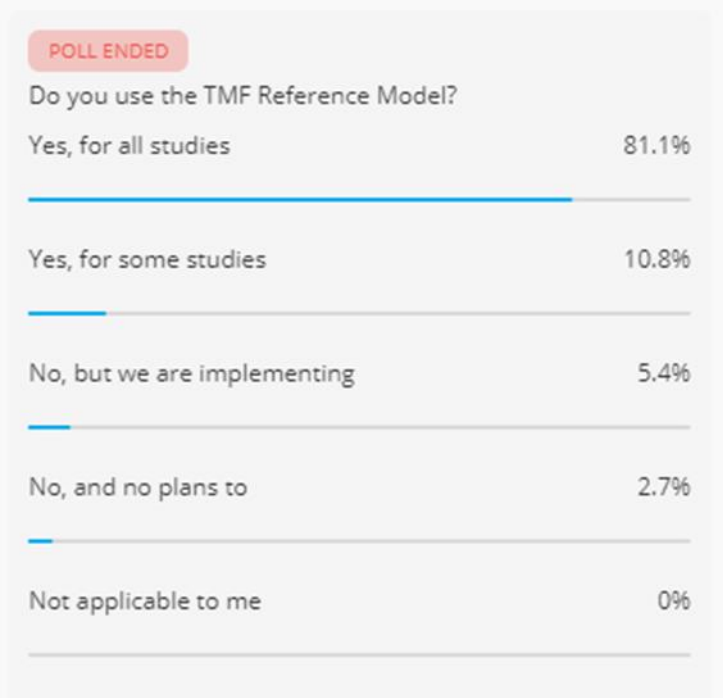
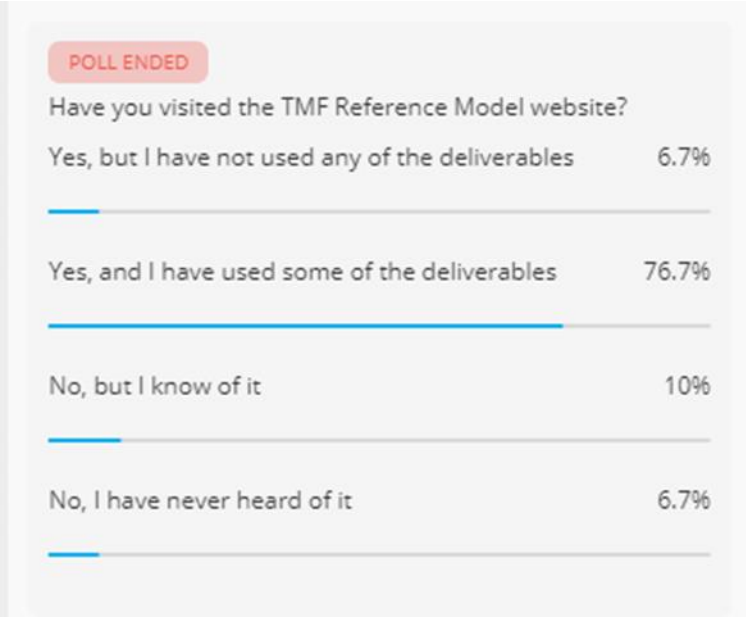
Clinical Document World Polls





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Trial Master File Reference Model

TMF Reference Model Version 3.2.1

Joanne Malia

General

- An inconsistency within the sub-artifacts has been raised as in some cases it appears that the sub-artifacts refer to individual documents whereas others may refer to general "buckets" of sub-artifacts along with individual documents.
- The TMF Reference Model is a model and should be modified as needed by the companies using the model. It is recommended that companies need to select the sub-artifacts they want and may need to modify them to make them more applicable to their organization.

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Changes in Version 3.2.1

Artifact Number	Artifact Name	Change
01.01.11	Debarment Statement	Trial level milestone updated to 02 Clinical Infrastructure Ready
01.03.01	Committee Process	Removed strike through
01.01.08	Monitoring Plan	Milestone added - 03 Site Live /Ready /Open for Enrolment
10.05.02	Tracking information	X added to country column
2.1.10	Report of Prior Investigations	RPI spelled out as Report of Prior Investigations
2.2.3	Informed Consent Form	Removed duplicate summary of change
3.1.2	Regulatory Authority Decision	Corrected wording to “conditional approval”

Trial Master File Reference Model

MHRA and BIMO Inspection Reporting

Kathie Clark and Karen Roy

MHRA GCP Inspection Report

- On February 12, 2021, The UK Medicines & Healthcare Products Regulatory Agency (MHRA) published their annual GCP INSPECTIONS METRICS REPORT
  - This report covered the period from 1 April 2018 to 31 March 2019
  - Typical that it is considerably delayed in publication

- The report provides excellent insight into MHRA's compliance concerns
  - In this edition, there were a number of detailed findings related to the Trial Master File

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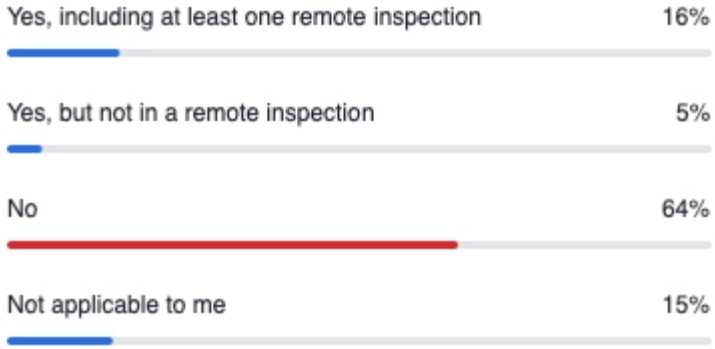
1. Have you participated in a health authority TMF inspection in the last year?



2. What do you feel is the single most important area for inspectors?

3. If you have experienced an inspection, what should you have done a better job on?

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Inspection Summary

08

Sponsor Inspections

- 7 total Critical Findings
- 2 Critical Findings **related to TMF**

11

CRO Inspections

- 6 total Critical Findings
- 1 Critical Finding **related to TMF**

11

Non Commercial Entities

- 3 total Critical Findings
- 1 Critical Finding (indirectly) **related to TMF**

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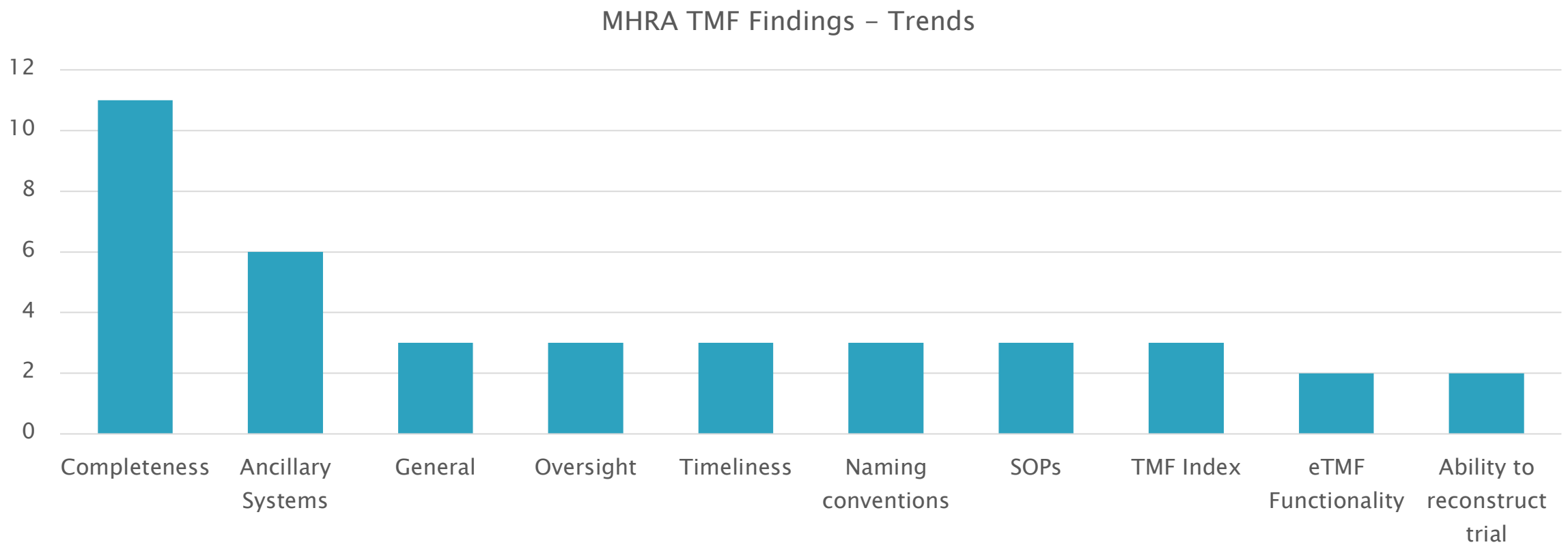
TMF Findings

The report contained a total of 33 individual observations related to eTMF



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Trend 1: TMF Completeness

- Numerous observations related to the completeness of the TMF
- In some cases, completeness was lacking because the scope of the TMF did not include all essential documents, especially if not stored in the core eTMF
- Other observations could be traced to failure to file required documents and lack of oversight in including completeness.

Trend 2: Ancillary Systems

- This area showed increased focus by MHRA
- Observations included failure to define ancillary systems as containing TMF content, lack of control and oversight, and failure to define the system of record in TMF SOPs and indices
- As a result, this area is tightly coupled with completeness issues

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Trend 3: Naming Conventions

- Inspectors should be able to rely on consistent naming conventions to identify documents and understand their contents without having to open documents
  - Documents could not readily be located due to file naming conventions
  - Inconsistencies with naming conventions
  - Document descriptions were not reflective of the contents and thus documents had to be opened to identify what they were
  - Misnamed documents

Trend 4: “Shadow TMF”

- One trial had a paper TMF defined, yet all documents required to reconstruct trial activities and compliance with the quality system were not filed in this paper TMF but rather kept in alternative electronic systems/locations.
- The paper TMF was used as a document archive rather than a working TMF and trial team members did not have access to the paper TMF, but instead used an electronic “shadow TMF”
- Upon review, it was found that there were a large number of documents in the “shadow TMF” which were not filed in the paper TMF.

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One Surprise…

"A number of "Data" files were classified as non-essential and filed outside the eTMF, this included SAE data listings. Such data files, however, were essential for demonstrating key safety processes and sponsor oversight and thus should have been held in the eTMF."

Inspection Finding 2018-2019

MHRA Presentation 2016

Sense Check

Is it sensible to convert everything to a pdf or move files into the eTMF system or can long term retention (archive) and direct access be maintained in current system?

For example:

- Output of a MVR pdf from the CTMS
- Printing of data to a pdf
- Moving SAS files (datasets, programs) into the eTMF

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Wrap-Up and Poll Question

- This presentation was just a brief overview – organizations should review the detailed findings and create their own action plans
- As findings are from inspections over one year ago, we have a polling question on how much you think recent trends on remote inspections changes the relevance of this information

For more, see
https://en.ennov.com/blog/mhra-trial-master-file-tmf-gcp-inspection-findings-trends-and-takeaways/

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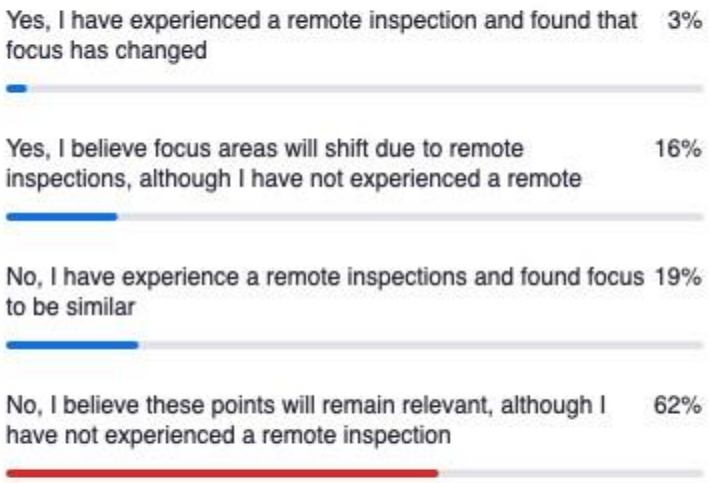
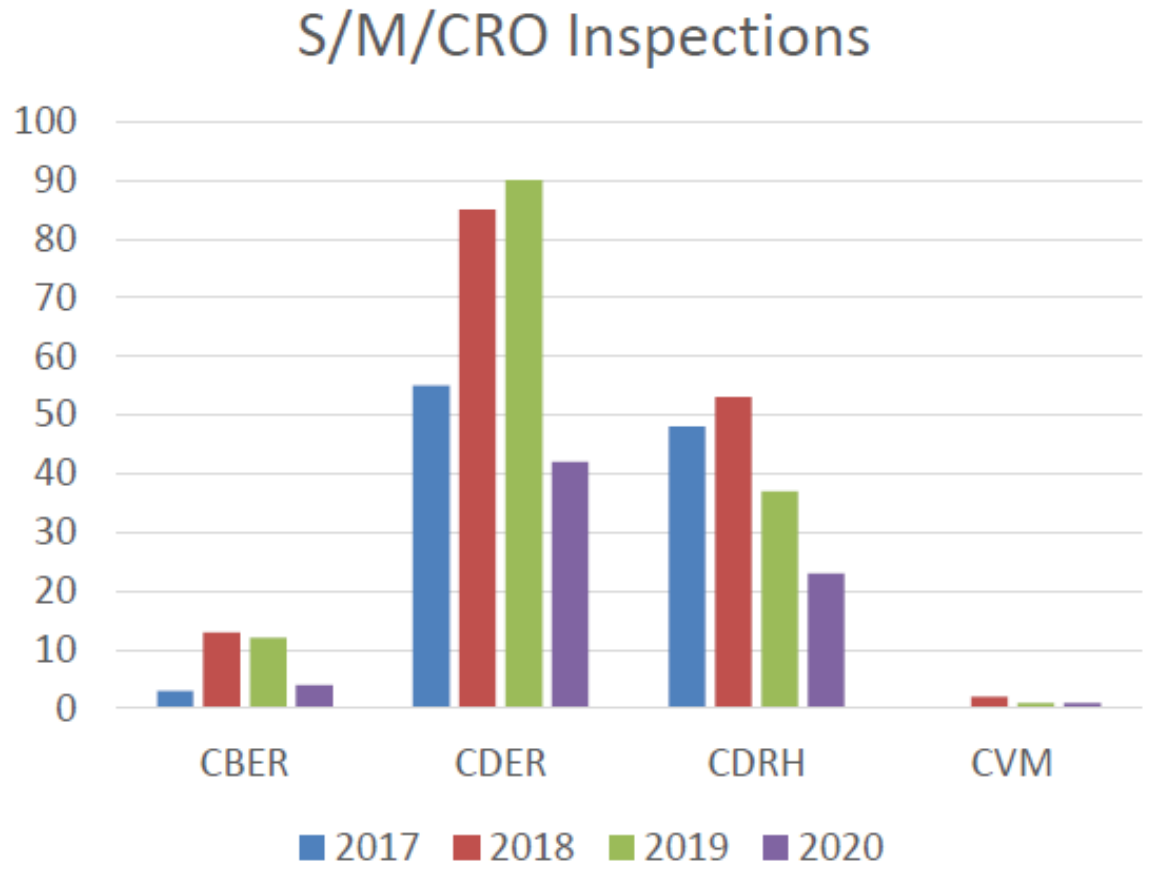
1. Since many inspections have been conducted remotely in the past 12 months due to COVID-19, do you think these inspections findings have become less relevant?



Bioresearch Monitoring (BIMO) Fiscal Year 2020 Metrics

- Due to the COVID-19 pandemic, FDA paused on-site surveillance inspections in March 2020 to protect the safety of their staff and stakeholders.
- BIMO introduced Remote Regulatory Assessments (RRA), which were voluntary remote evaluations of data and processes conducted via video teleconference. RRAs are evaluations and will not receive an inspection classification.
- The Remote Record Review (RRR) is an alternative to inspection involving a voluntary interaction with a site of interest. Records from the site are evaluated by Center staff, which are followed by a series of remote video and teleconference meetings with the site of interest to discuss questions, concerns and findings.

Sponsor/Monitor/Contract Research Organization Inspections by Center FY 2017–2020*



Due to the COVID-19 pandemic, RRAs (not reflected here) were conducted.

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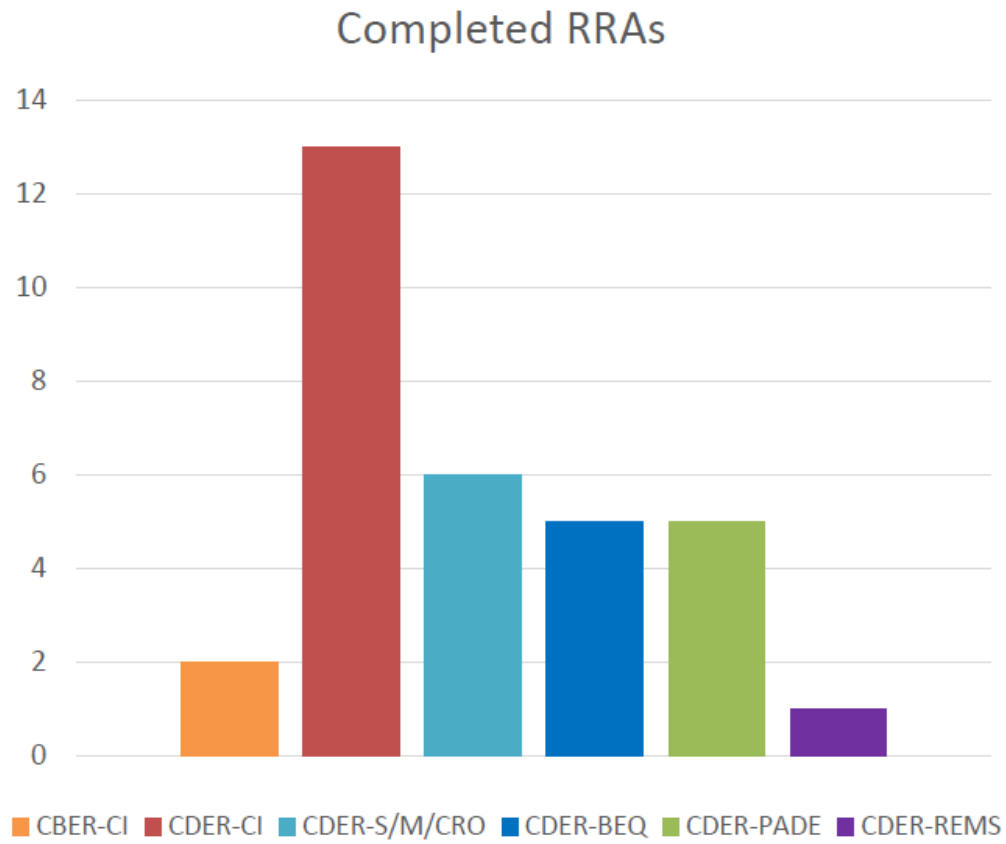
Remote Regulatory Assessments Completed during FY20 COVID-19 Pandemic



Center	Program area	2020
CBER	Clinical Investigator	2
CDER	Clinical Investigator	13
CDER	Sponsor/Monitor/Contract Research Organization	6
CDER	Bioavailability/Bioequivalence	5
CDER	Postmarketing Adverse Drug Experience	5
CDER	Risk Evaluation Mitigation Strategies	1

Common Sponsor/Monitor/Contract Research Organization Inspectional Observations

- Failure to maintain and/or retain adequate records in accordance with 21CFR312.57; accountability for the investigational product; Investigator Statement (FormFDA1572); Financial disclosures.

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Exchange Mechanism Standard Survey Results

Ken Keefer, Elvin Thalund and Paul Fenton

Background and Objectives

- The Exchange Mechanism Standard (EMS)
  - A common approach for exchanging documents between systems and organizations
  - Open to TMF stakeholders across the industry
  - Saves time to set up document exchanges
  - Supports interim exchanges to keep TMF current
- Purpose of Survey
  - Prioritize critical use cases
  - Identify collaboration opportunities
  - Advance industry-wide EMS adoption

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Methodology

- Target Audience
  - Invitations to participate emailed to TMF Reference Model subscribers
  - Announcements posted to LinkedIn groups
    - TMF Reference Model
    - TMF Exchange Mechanism
    - Electronic Trial Master File
    - CTMS – Clinical Trial Management Systems
    - Clinical Trial Management System (CTMS)
- Online questionnaire
- 4 months duration (Oct 26, 2020 – Feb 22, 2021)

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Types of Questions

- Respondent information
- Use cases of interest
  - Select 1 to 3 use cases
  - 8 listed
  - Option to enter a use case not listed
- Plans for implementation and barriers
- Perceived value of each selected use case

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Respondents

Organization Type	Number of Respondents
Sponsor	62
CRO	39
eTMF Vendor	17
Consulting services	9
Clinical Research Site	3
Software (not eTMF)	3
IT or integration services provider	2
Respondents not providing Organization Type	3
Total	138

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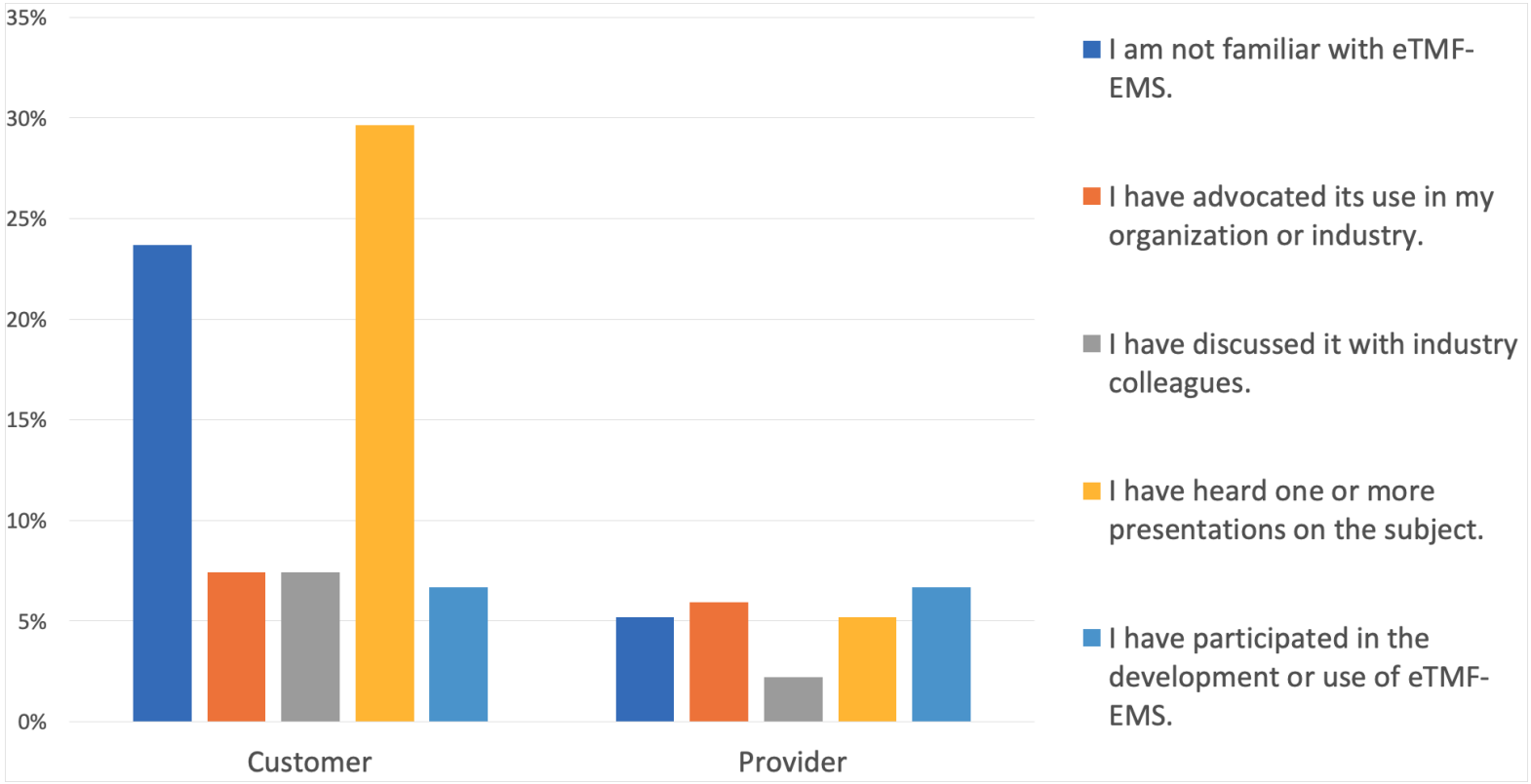
Could training help?



	No knowledge	Some knowledge	Total
Sponsors	30	32	62

30% are not familiar with the EMS

- 24% of these are customers
- 5% are providers

What would you say the biggest barriers are to using the EMS standard for TMF interchange?

48% of sponsors: "I don't know how to implement it".

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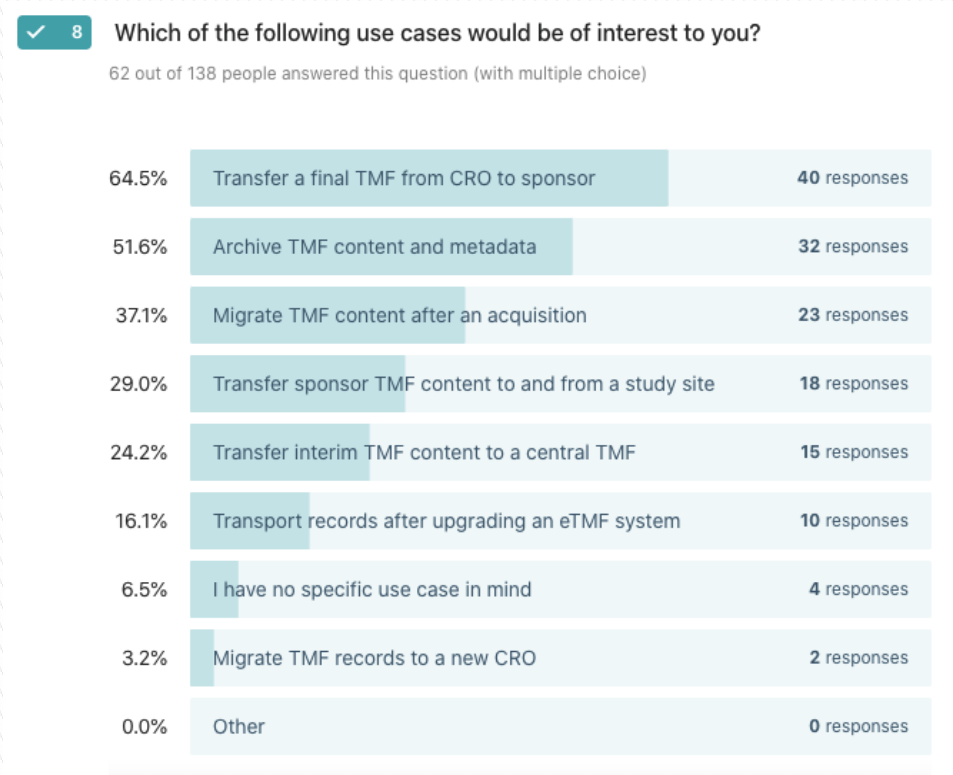
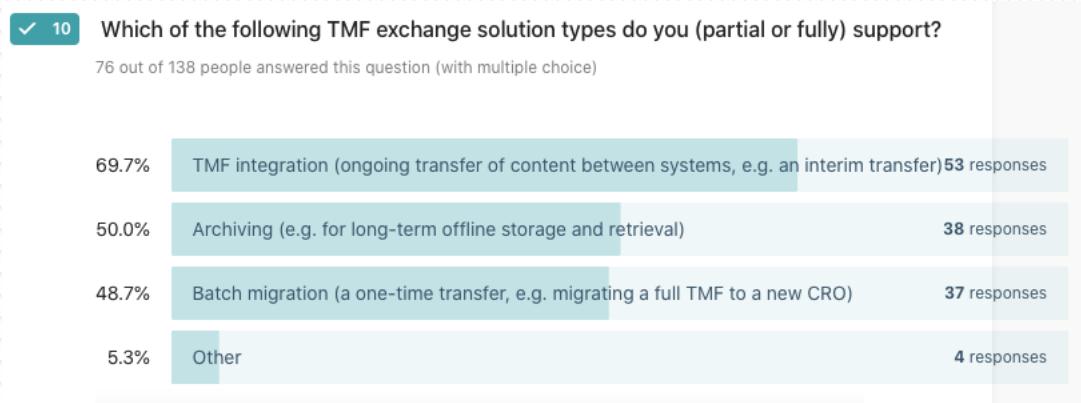
Focus by Customers and Providers





Use case ranking by Customers

Solution type ranking by Provider

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How does Customers requests align with current provider solutions?

	Solution Type	23 – Solution Type: TMF integration (ongoing transfer of content between systems, e.g. an interim transfer)	24 – Solution Type: Batch migration (a one-time transfer, e.g. migrating a full TMF to a new CRO)	25 – Solution Type: Archiving (e.g. for long-term offline storage and retrieval)
Use Case		53	37	38
14 – Transfer interim TMF content to a central TMF	15	15/53		
15 – Migrate TMF records to a new CRO	2		2/37	
16 – Transfer a final TMF from CRO to sponsor	40		40/37	
17 – Archive TMF content and metadata	32			32/38
18 – Migrate TMF content after an acquisition	23		23/37	
19 – Transport records after upgrading an eTMF system	10		10/37	
20 – Transfer Sponsor TMF content to and from a Study Site	18	18/53		
21 – I have no specific use case in mind	4			
22 – Others	0			
Total customer support for solution type	144	33	75	32

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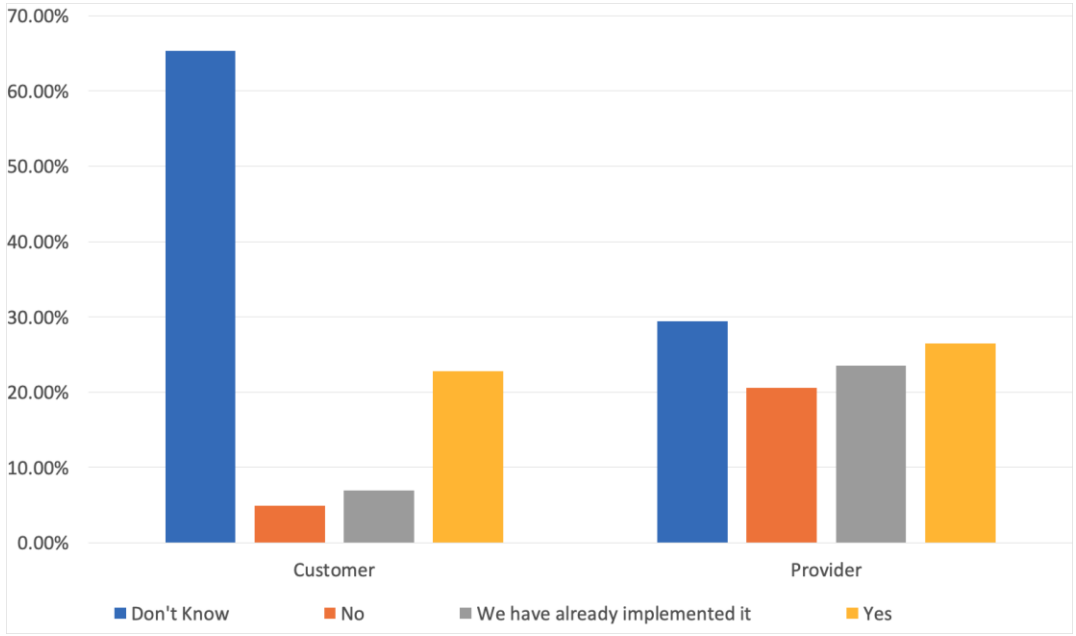
Conclusions – Sponsors need to drive adoption

- The majority of respondents were aware or were familiar with the EMS
- Almost half of sponsor and CROs indicated they did not know how to implement it
- 56% of respondents didn't know if they were going to implement EMS and 34.8% of responded had or plan to implement the standard
- When it came to vendors, 35% indicated that their customers were not asking for the EMS, and 31% indicated they did not know how to develop it
- This suggests that we need to do more to educate both sponsors/CROs as well as vendors on how the EMS could be implemented
- It is also imperative that sponsors/CROs take more ownership of the model and work with vendors to get it implemented
- Over 90% of vendors felt that the use of the EMS for interim/final transfer would bring value to their customers and give them competitive edge

Do you plan on (partial or fully) implementing the eTMF-EMS?



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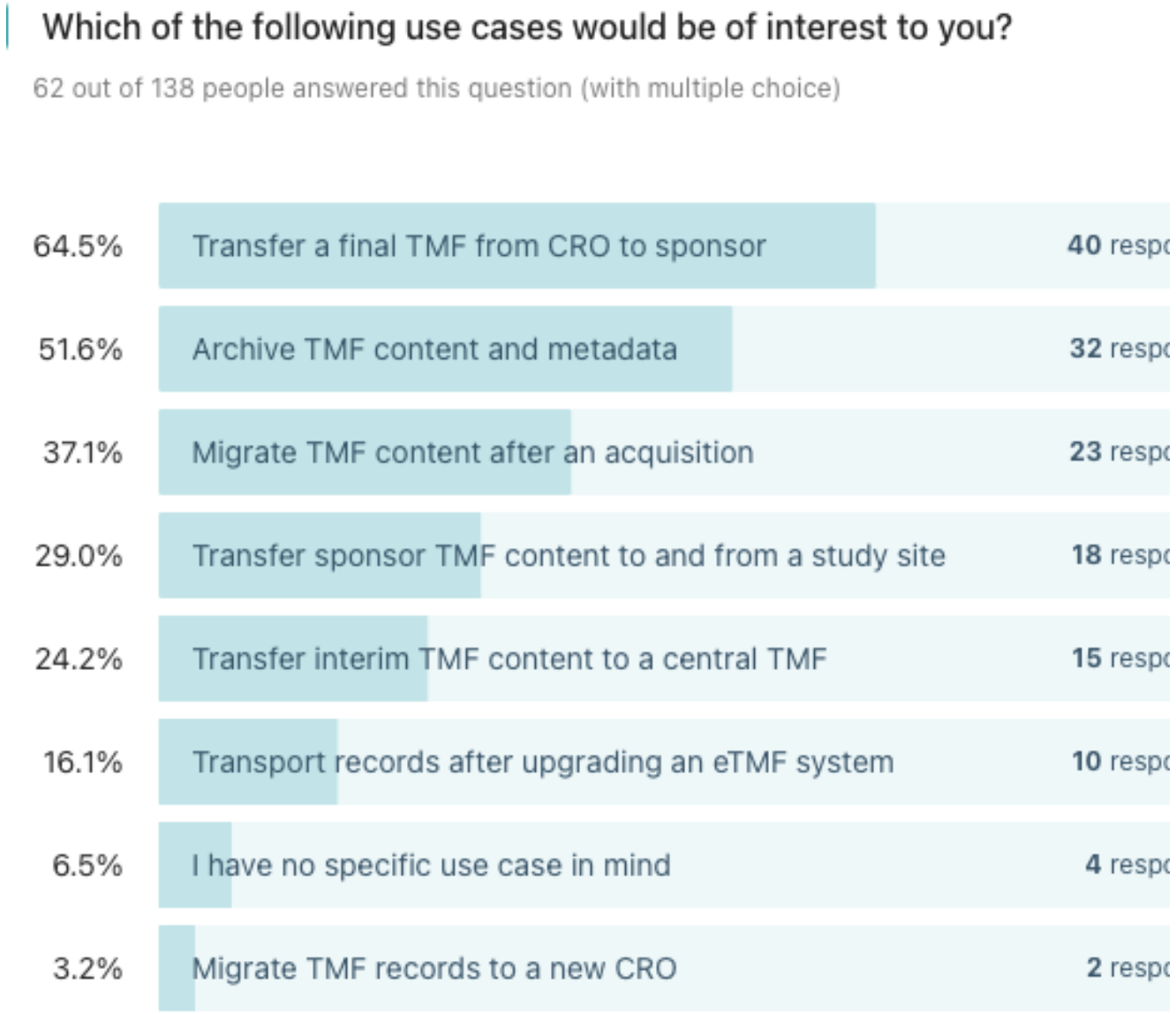
Conclusions – Clear use cases emerge

- 64.5% of sponsor organizations are interested in using the EMS for final transfers – majority of transfers currently done manually
- Over half are interested in using it for archiving – Majority of vendors provide extracts to sponsors and only 34% of sponsors use their eTMF to archive content
- 64% of vendor respondents felt that the EMS could be a useful standard for archiving of the eTMF
- 1/3 were interested in using the EMS for Sponsor-Site interactions – only 33% of sponsors/CROs use a portal to transfer content



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Actions and Initiatives (All)

- Try and involve decision makers from companies in the initiative to improve buy in
- Restart working groups to educate and strategize on implementation
- Prepare integrated implementation guides for sponsors/CROs/vendors
- Setup a working group to define a clear set of requirements that can be used by all stakeholders
- Evaluate the top five most popular use cases and define an action plan for reviewing the standard based on these use cases
- Assign business and vendor leads for each use case to work on implementation guides and participate in working groups

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EMS Roadmap

Standard

Current EMS Specification

Industry Leadership Engagement, Education & Support

Sponsor/CRO Leadership

Vendor Leadership

Leads and Working Groups

Archiving

Transfers

Indexing

Sponsor-Site

Requirements

Deliverables

Implementation Guides & Requirements

Updated EMS Specification

Desired Outcome

SOLUTION DEVELOMENT & INDUSTRY ADOPTION

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Next Steps

- Distribution of full survey results towards the end of March
- Webinar to present more detailed analysis of survey results will be given
- Reach out to form the leadership committee and working groups

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TMF-related events coming up*

Events page on website (under Resources menu)

- Clinical Document World, Inspection Readiness, Virtual, May 2021
- HSRAA, Virtual, September 2021
- Fierce TMF Summit, In Person, October 2021
- Clinical Document World, New Jersey, November 2021

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TMF RM General Meetings

- <19th April>
- Add to your calendar NOW or download the calendar file (.ics file) from our homepage
- Outlook Meeting Request no longer distributed

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QUESTIONS?

Join the TMF Reference Model Discussion Group
https://tmfrefmodel.com/register

- Knowledge sharing
- Networking
- Too Much Fun!

Join the TMF Reference Model Project Team
(but be prepared to work!)
https://tmfrefmodel.groups.io/g/main

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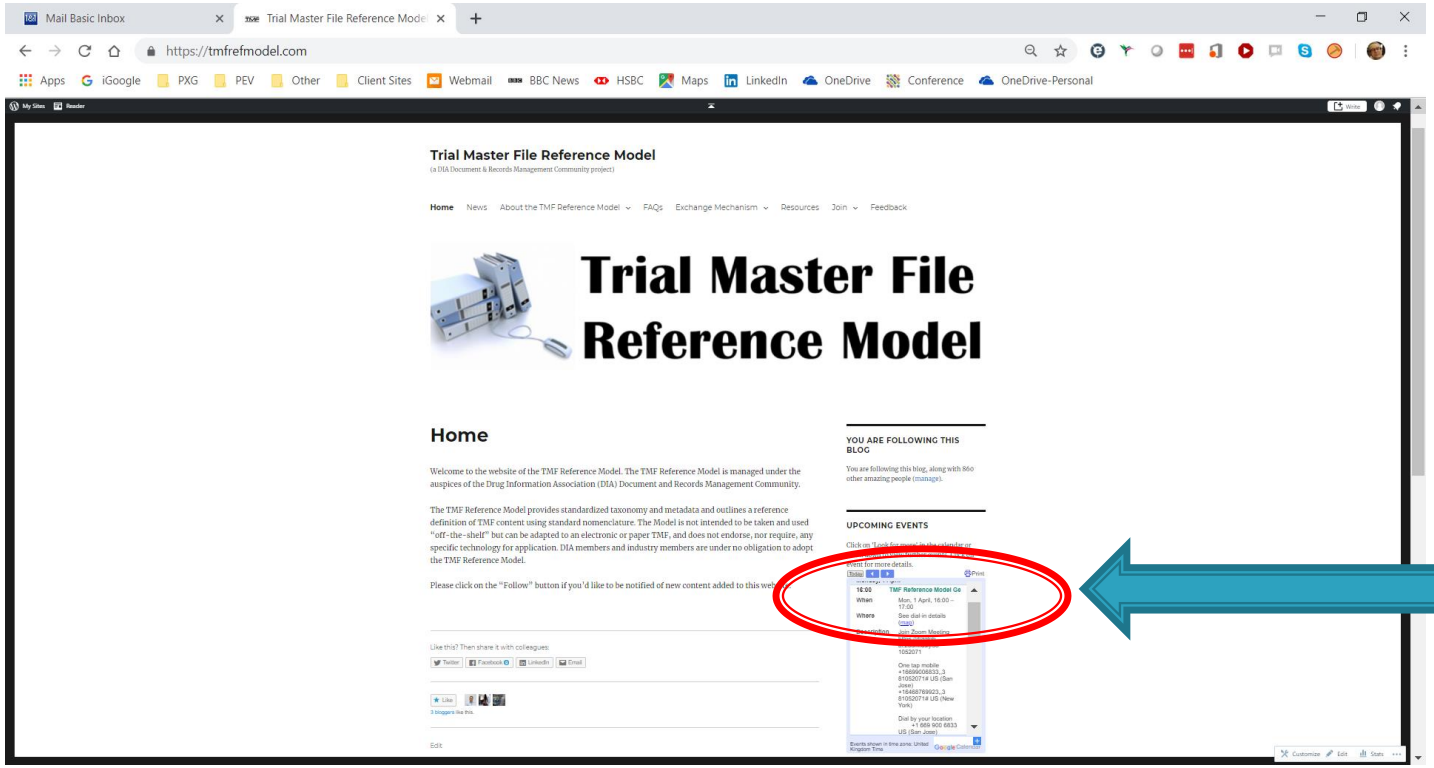
Meeting details

- Wondering where to find details of the next meeting?



On TMF Reference Model website, click on calendar to see meeting details. Click 'Copy to my calendar' to add to your Outlook / Google calendar.

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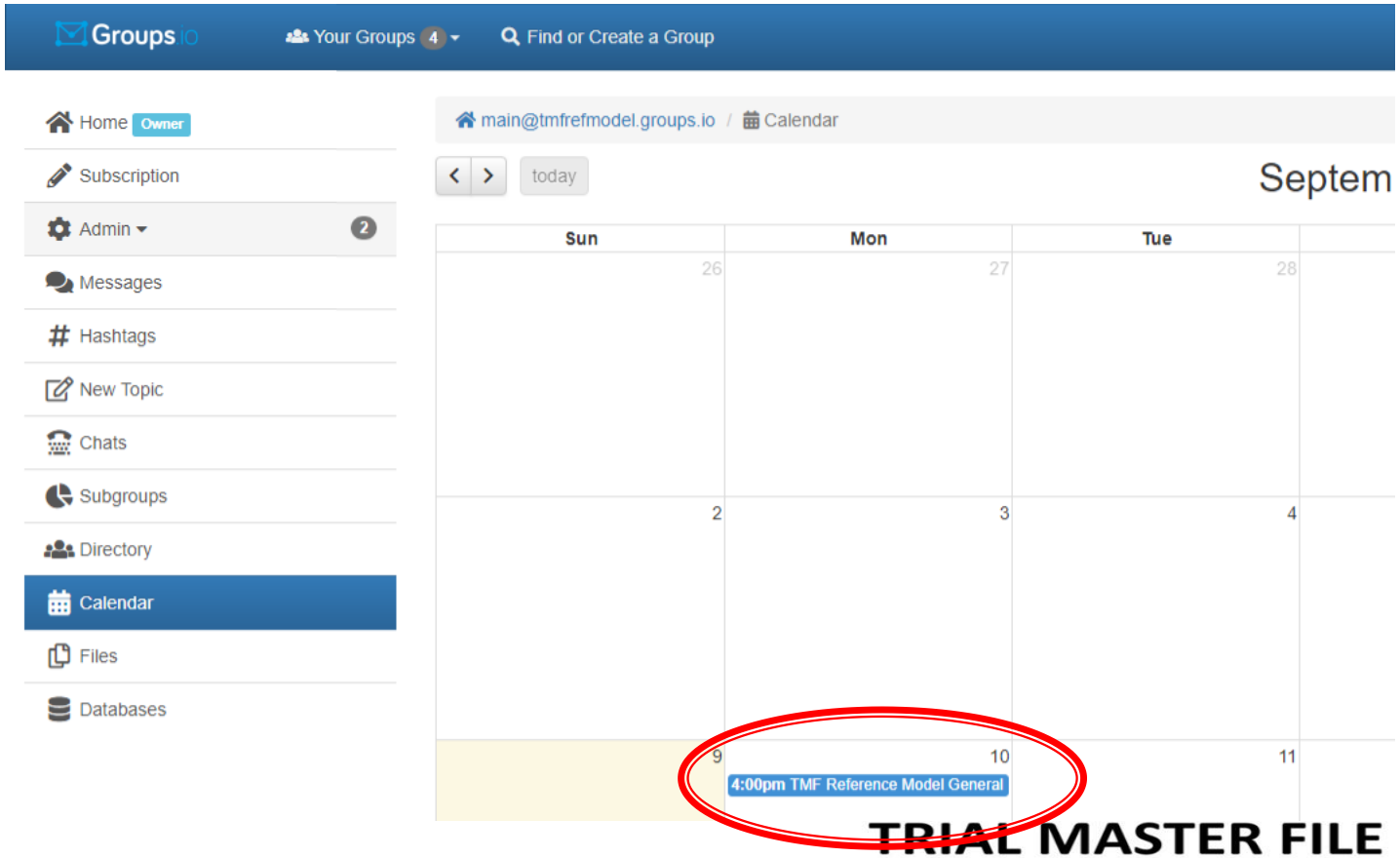
Meeting details

- Wondering where to find details of the next meeting?

On Groups.io, click on Calendar to show group calendar. Click on an event to see dial-in details

https://tmfrefmodel.groups.io/g/**main**/



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