# Trial Master File Reference Model

## General Meeting

19th July 2021

# Agenda

- Membership
- Zone Team Update
- ICH E6 R3 Update
- Draft EMA guidelines – what is new?
- eSignatures – is 21CFRpart 11 compliance always needed?
- The Challenges of signing a 1572
- Upcoming TMF Meetings
- Next Meeting

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# Membership

- 323 project team members (groups.io)
- 1,517 Mailing List Subscribers** (tmfrefmodel.com)
- 3,628 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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# Trial Master File Reference Model

Zone Teams Refresh

19 Jul 2021

Kelley Robinson

JP Miceli

# Zone Team Liaison: JP Miceli

20 years experience in the pharma and biotech industry, 16 of them dedicated solely to working with the TMF

Joined the TMF RM group in early 2010 prior to release of the first version of the Model

Member of the TMF RM CCB since 2018

Currently a member of Zone 1 group, and the Lead for Zone 7

# Zone Team Liaison

- Leadership Role on the CCB
- Responsible for coordinating periodic meetings with the zone team leads and members to update them on CCB activities
- Point of contact for zone changes (e.g., change in zone lead)
- Responsible for following up with zone teams to ensure requests are reviewed timely
- Reports back to the CCB on any updates/concerns to the zone teams
- Reports back to the CCB and SC on zone team activity as needed

# Zone Teams

- Responsible for contributing to the TMF Reference model by:
  - Reviewing submitted change requests and providing feedback
  - Reviewing the artifacts within the zone for relevancy and suggesting updates based on new regulatory guidance. Includes:
    - Reviewing artifacts for consistency
    - Identifying the need for new artifacts and sub-artifacts
    - Reviewing milestones and ICH references
    - Suggesting updates to definitions

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# Zone Team Member Responsibilities and Qualifications

Willingness to commit to reviewing change requests and reviewing artifacts within the zone for possible updates

Active participation within the zone and commitment to reviewing requests within the specified timeframe

Open to anyone with an interest and contributing to the TMF Reference Model

Expertise in TMF or within the zone area preferred

# Zone Team Lead Responsibilities and Qualifications

- Committed to lead the zone team by facilitating the review of change requests and artifacts within the zone.
- Single Point of contact for the zone with the CCB
- Not a current member of the Steering Committee.
  Not a current member of the Change Control Board (if possible)
- Expertise with the zone area preferred
- Experience with the TMF Reference Model
- Approved by the CCB

# Zone Team Lead Vacancies

- To be considered as a zone team lead or to nominate someone as a zone team lead, please email JP Miceli at jmiceli@advancedclinical.com

- Zone Team Leads are needed for:
  - Zone 2: Central Trial Documents
  - Zone 3: Regulatory
  - Zone 4: IRB or IEC and Other Approvals
  - Zone 6: IP and Trial Supplies
  - Zone 7: Safety Reporting
  - Zone 8: Central and Local Testing
  - Zone 9: Third Parties
  - Zone 10: Data Management
  - Device Group:  review changes across all zones for impact to Device process

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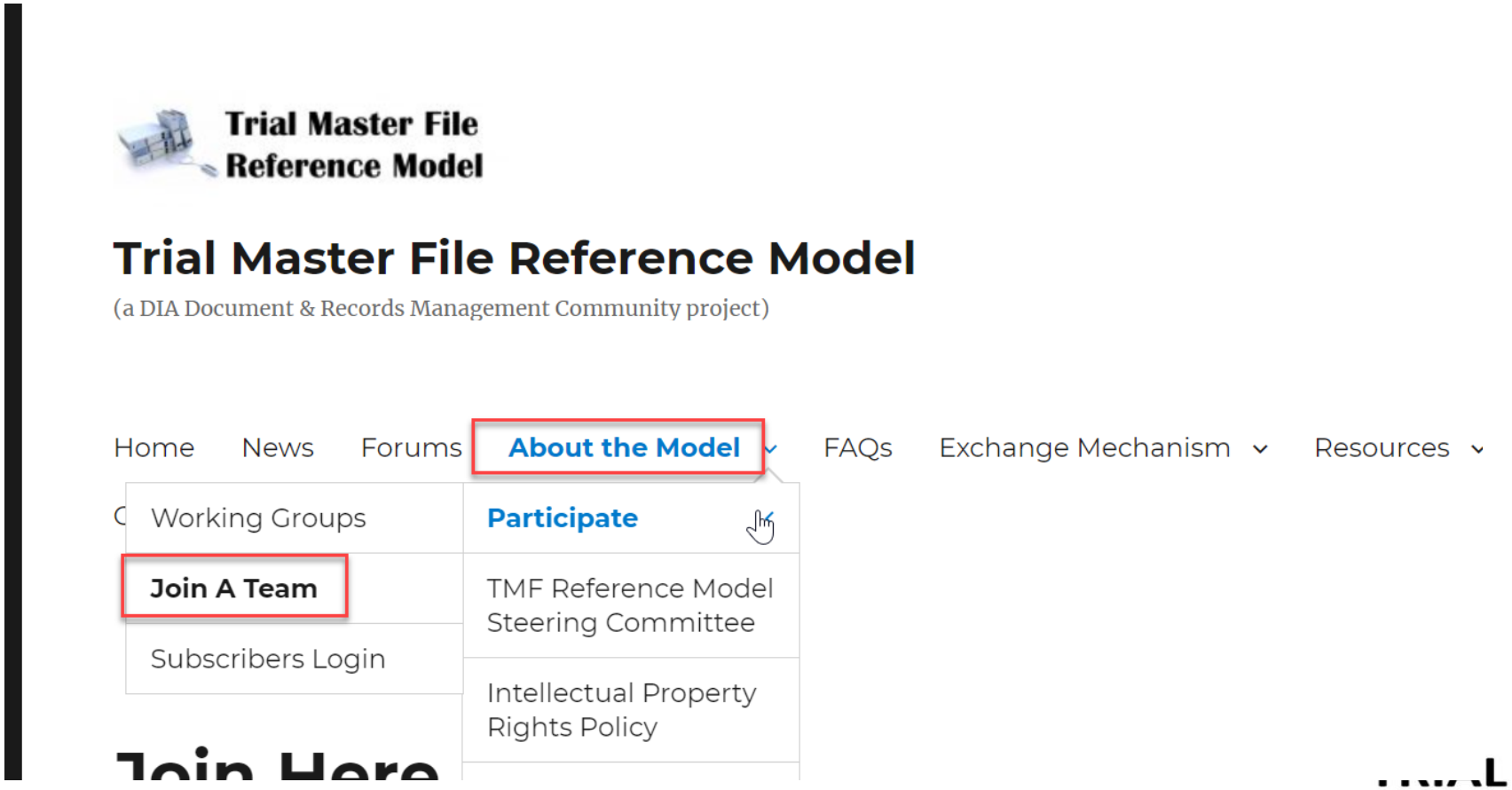
# How to Join a Zone Team

From the TMF Reference Model homepage select About the Model > Participate > Join a Team



# How to Join a Zone Team

The zone teams use groups.io as a collaboration platform so you will need to go to our GROUPS.IO portal page. Joining the project happens in two stages:

Sign up to groups.io

At the bottom of the screen click on 'Apply for Membership'

You need to reply to the email to validate your subscription request. Following validation, you will receive an automated email welcoming you to groups.io. Do **not** re-apply if you are already a member

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# How to Join a Zone Team

Within 4 weeks join one or more sub-teams:

Navigate to the GROUPS.IO portal page At the bottom of the screen click on ‘Apply for Membership’

When you have identified a zone team that you wish to join, just click on the link/button “Apply For Membership In This Group” and login. You will now see a menu option headed “**Subgroups**“.

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# No specific update on ICH E6R3

- Link to CTTI E6R3 **project**:
  - https://www.ctti-clinicaltrials.org/projects/informing-update-ich-e6
- Link to CTTI's webinar **overview and recordings**:
  - https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/meeting_report_of_key_themes_and_comments_june_2020_-_final_09152020.pdf
- Link to CTTI's webinar **coverage/synopsis**:
  - https://www.ctti-clinicaltrials.org/briefing-room/meetings/ich-e6-guideline-good-clinical-practice-stakeholder-engagement

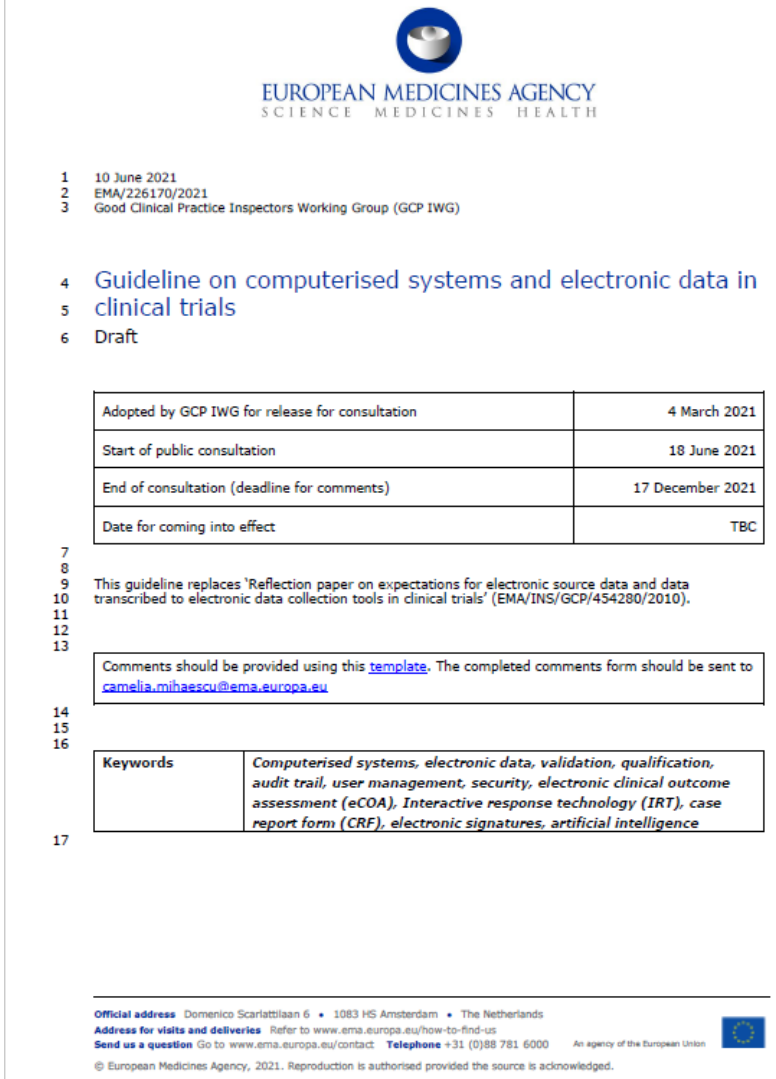
# Trial Master File Reference Model

## EMA Draft Guideline on Computerized Systems and Electronic Data in Clinical Trials: An Overview

Gillian Gittens, Director, eClinical Strategy & Solutions, Trial Interactive

# Purpose of the Guidance

- Changes in trial and data types have meant an increased use of computerised systems
- Need to provide guidance reflective of changes
- ‘Reflection Paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials’ published 2010 needed updating



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 June 2021
EMA/226170/2021
Good Clinical Practice Inspectors Working Group (GCP IWG)

Guideline on computerised systems and electronic data in clinical trials
Draft

| | |
|---|---|
| Adopted by GCP IWG for release for consultation | 4 March 2021 |
| Start of public consultation | 18 June 2021 |
| End of consultation (deadline for comments) | 17 December 2021 |
| Date for coming into effect | TBC |

This guideline replaces ‘Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials’ (EMA/INS/GCP/454280/2010).

Comments should be provided using this template. The completed comments form should be sent to camelia.mihaescu@ema.europa.eu

| | |
|---|---|
| **Keywords** | ***Computerised systems, electronic data, validation, qualification, audit trail, user management, security, electronic clinical outcome assessment (eCOA), Interactive response technology (IRT), case report form (CRF), electronic signatures, artificial intelligence*** |

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# Scope of the Guidance

- Scope is all computerised systems, (including instruments, software and services) used in clinical trials in the creation/capture of electronic clinical data and to the control of other processes
- Includes eTMF!
- Advises of a risk based approach to CSV

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# Definitions of Note

- Artificial intelligence, Machine Learning and Deep Learning
- Dynamic file formats and static file formats
- Good Documentation Practice
- ALCOA++

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# Principles of Guidance

- Data integrity
- Responsibilities
- Electronic data
- Source data
- ALCOA++
- Criticality & risks
- Performing data capture
- Electronic signatures
- Data protection
- Validation
- Direct access

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# Also of Note…

- Decommissioning of systems
- Contracts with Vendors
- CSV and requirements documentation
- User access
- Security

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# Link to Download:

- https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-computerised-systems-electronic-data-clinical-trials_en.pdf

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# Update on applicability of 21CFR11 to third-party vendors

Eldin Rammell, Head of Quality Assurance, Phlexglobal

# A potted history

- 1994 FDA published proposed rules in Federal Register and received 49 comments
- 1997 Final rule published….. resulting in much confusion!
- 1999 Compliance Policy Guide (CPG) published
- 2002 Risk-based approaches emerge
- 2003 FDA withdraws CPG & issues Guidance for Industry
- 2007 FDA finalizes Use of Computerized Systems in Clinical Investigations
- 2011 EU Annex 11
- 2016 FDA draft guidance on data integrity

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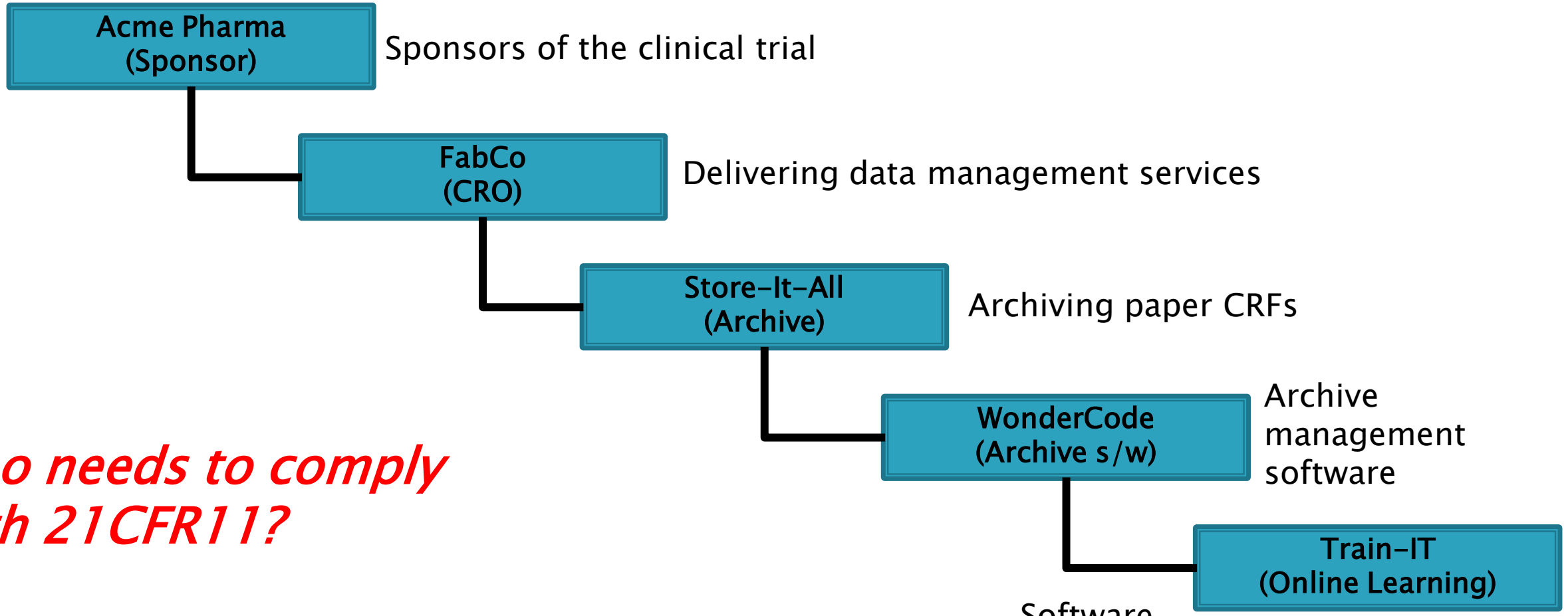
# So what's the problem?




***Who needs to comply with 21CFR11?***

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# Straight from the horse's mouth

- Are sub-contractors and other third parties also expected to comply with 21CFR11, even though their records are never submitted to the FDA and are extremely unlikely to ever be reviewed by the FDA?
  - For example, commercial s/w developer selling eTMF solution. Are electronic validation records, training records, electronically signed SOPs etc required to comply with 21CFR11?

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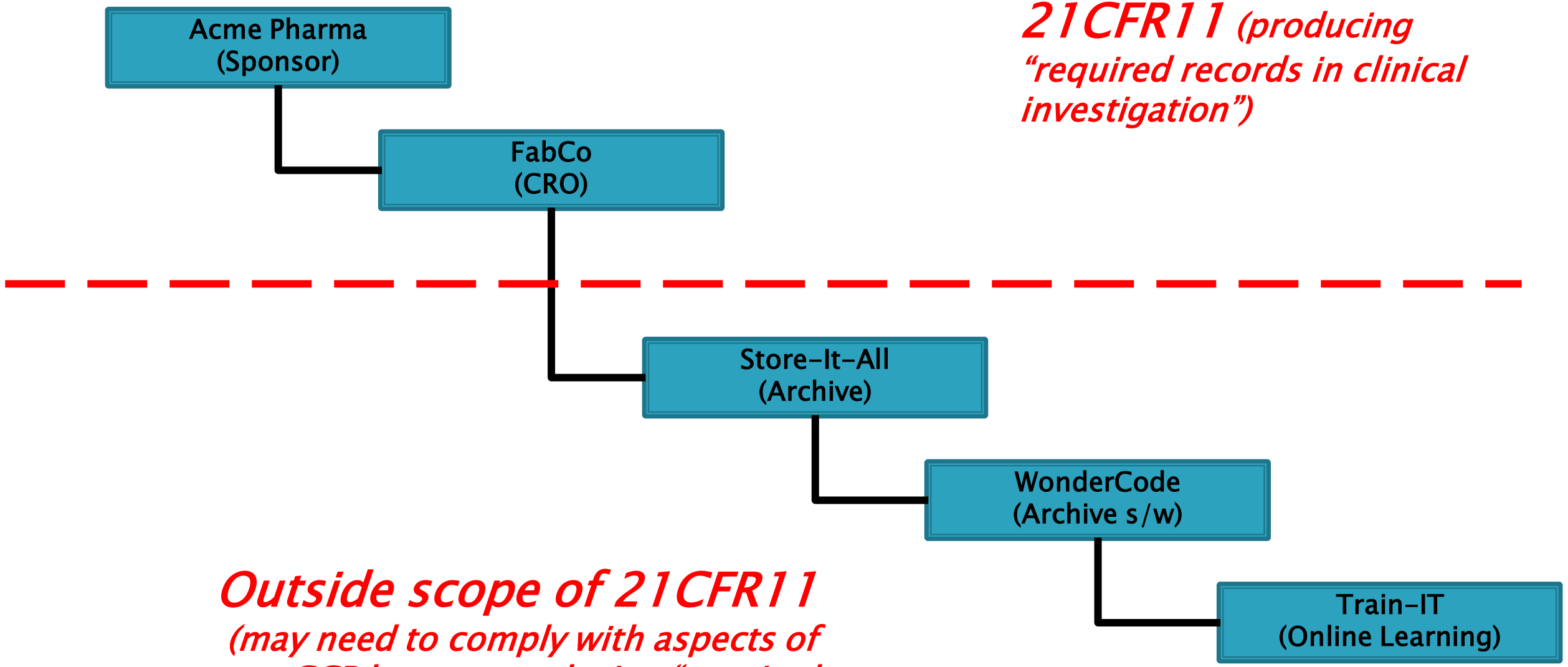
# FDA Response

- Electronic systems used to produce required records in clinical investigations (e.g. eTMF) are required to comply with 21CFR11. The responsibility for compliance is not the subcontractor or third-party vendor's responsibility, but the sponsor's to ensure the systems they use are reliable for regulatory purposes.
- With respect to subcontractors or third-party vendors, SOPs, validation documentation, training records and other documents that are part of an internal quality management system are generally not regarded as required records of clinical investigations. These documents would not be subject to 21CFR11, including electronic signature requirements.




***Within scope of 21CFR11*** *(producing "required records in clinical investigation")*

***Outside scope of 21CFR11***
*(may need to comply with aspects of GCP but not producing "required records")*

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# The Challenges of signing a 1572 (RAPS)

For an IND sponsor who would like to enrol global sites for their clinical trial, especially in countries with recommendations to not sign Form FDA 1572, there are several options:

- 1. Exclude ex-US sites from the IND.
- 2. Request a waiver for the 1572 (i.e., Section 9 Commitments) for ex-US investigators.
- 3. Collect unsigned 1572s from investigators.
- 4. Continue collecting 1572s from all ex-US investigators

# TMF-related events coming up*

**Events page on website (under Resources menu)*

- HSRAA, Virtual, September 2021
- Fierce TMF Summit, NEW ORLEANS, October 2021
- Clinical Document World, New Jersey, November 2021

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# TMF RM General Meetings

- <13th September>
- 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

**(be prepared to work! – we can't do this without YOU)**

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

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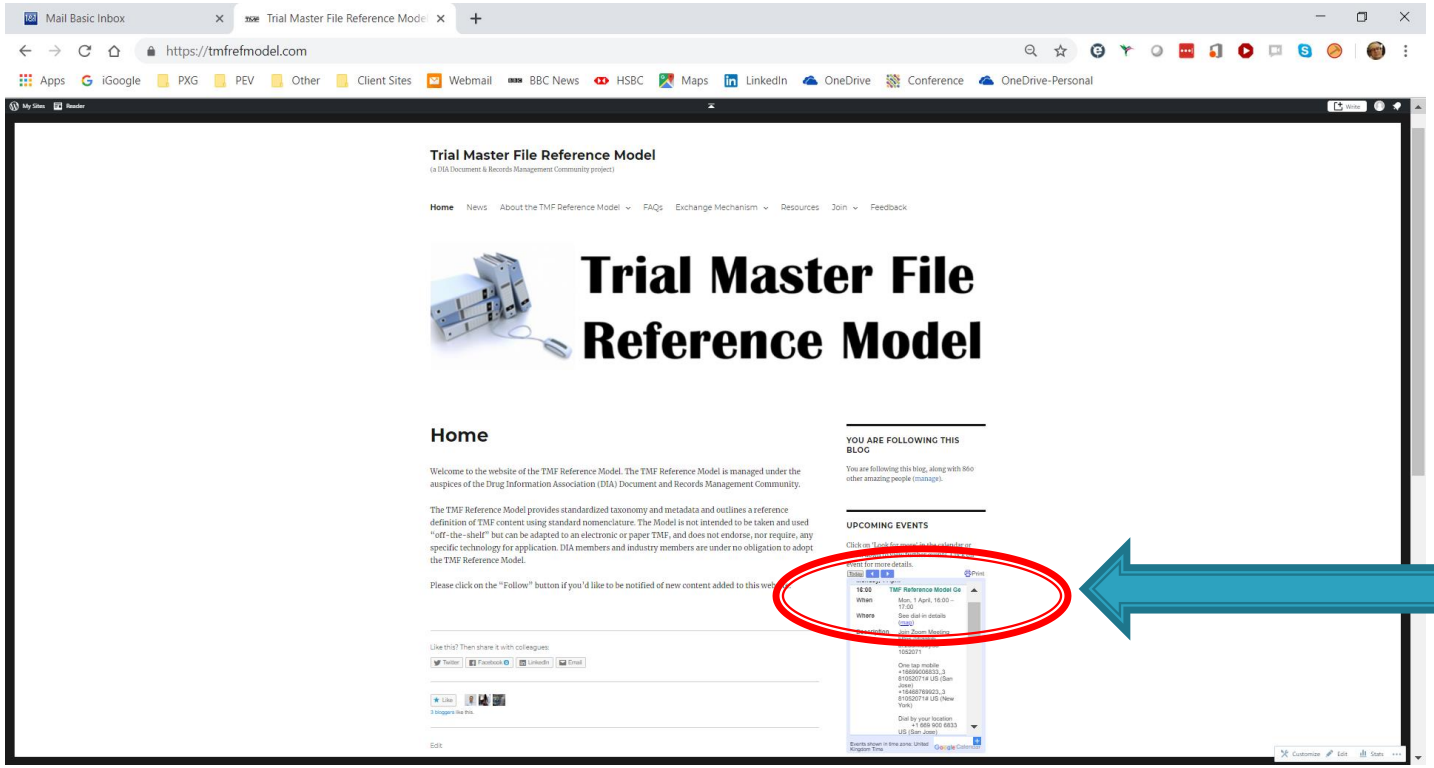
# Meeting details

- 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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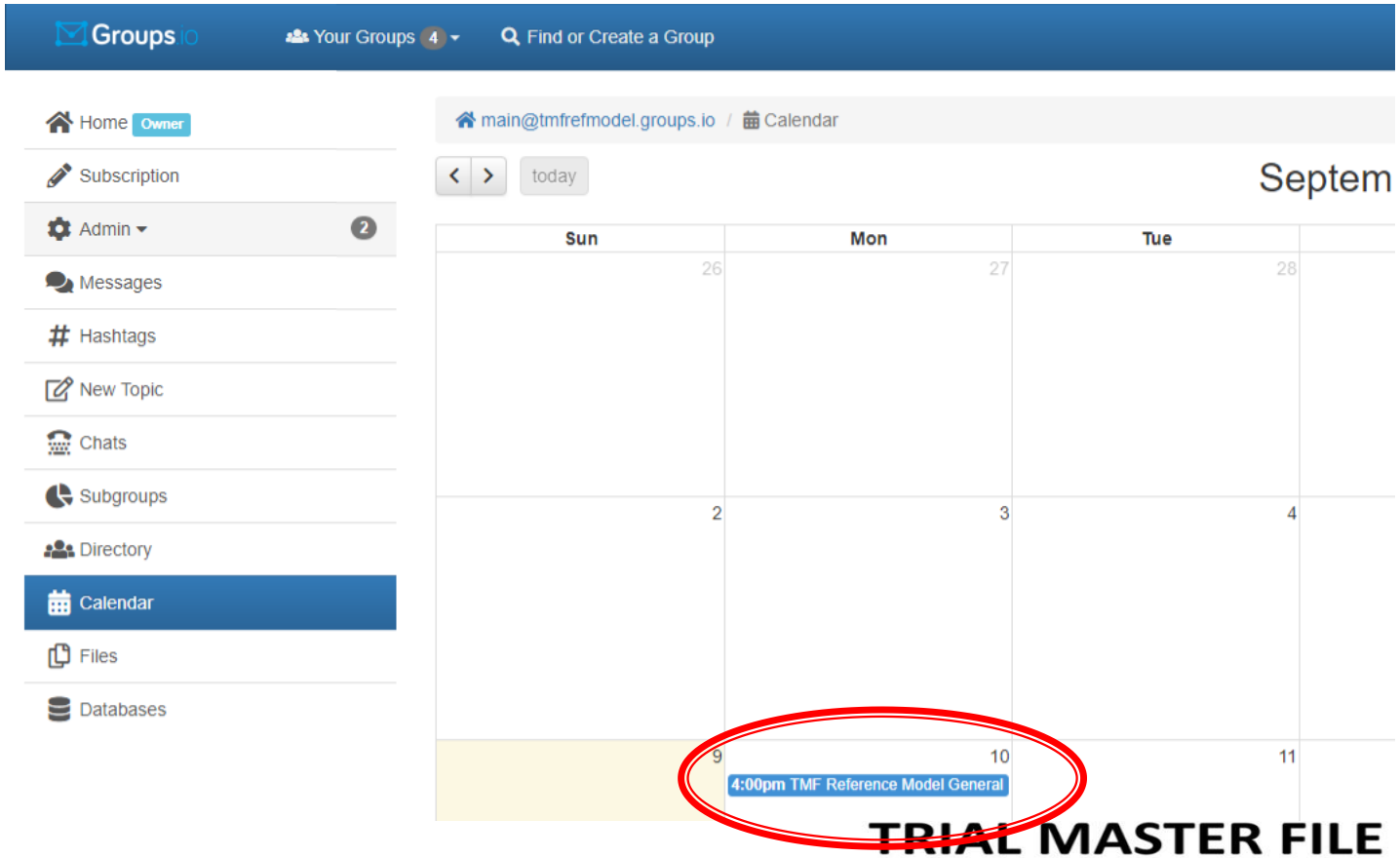
# Meeting details

- 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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