Trial Master File Reference Model

General Meeting

30Mar2020

Agenda

- Welcome
- Membership Update
- On-line Forums
- Steering Committee Update
- Covid-19 and the TMF
- MHRA-FDA GCP Symposium Summary
- Upcoming Events

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Since last meeting*…

- 7 new project team members (groups.io) – current total 317
- 998 Mailing List Subscribers** (tmfrefmodel.com)
  - 27 new discussion topics posted (54 responses, 2,156 hits)
- LinkedIn group – 2,964 members (27 new members)
  - 7 new discussion topics posted
- For details on these different groups and how to get involved, see http://tmfrefmodel.com/join

- *Yahoo!Group Forum closed*
  - *Deletion scheduled for tomorrow (31-Mar)*

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

* 3 February 2020

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Online Forums

- https://tmfrefmodel.com/forums
- New forums, organized by subject / topic
  - Enables you to subscribe only to those topics you are interested in, rather than "all or nothing"
  - More topics to be added soon
- Daily digest
  - Each forum topic now shows "Include topics from this forum to the digest emails (edit settings)"
  - Click on link to add to your daily digest
  - Click on "Edit settings" to turn on/off your daily digest

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Steering Committee

- Five vacancies
- Eight nominations received
- Details: https://tmfrefmodel.com/category/news
- Voting for active members* opens at 5pm until Friday 10th April
- Sender: invitations@mail.electionbuddy.com

Nominees:

- Donatella Ballerini, Chiesi
- Donna Dorozinsky, Just In Time GCP
- Elvin Thalund, Oracle
- Mamoru Furuichi, Santen Pharmaceuticals
- Fran Ross, Advanced Clinical
- Jamie Toth, Daiichi Sankyo
- Lisa Mulcahy, Mulcahy Consulting
- Todd Tullis, Veeva Systems

* Registered on groups.io

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COVID-19 and the TMF

Agenda

Topic	Presenter
Introduction Polling Questions Health Authority Guidance Review	Kathie Clark Product Director, CTMS Ennov Software for Life
Impact on TMF/eTMF processes, validation activities, and quality systems	Lisa Mulcahy Owner and Principal Consultant Mulcahy Consulting, LLC
Impact on TMF Documentation	Sholeh Ehdaivand President and CEO LMK Clinical Research Consulting

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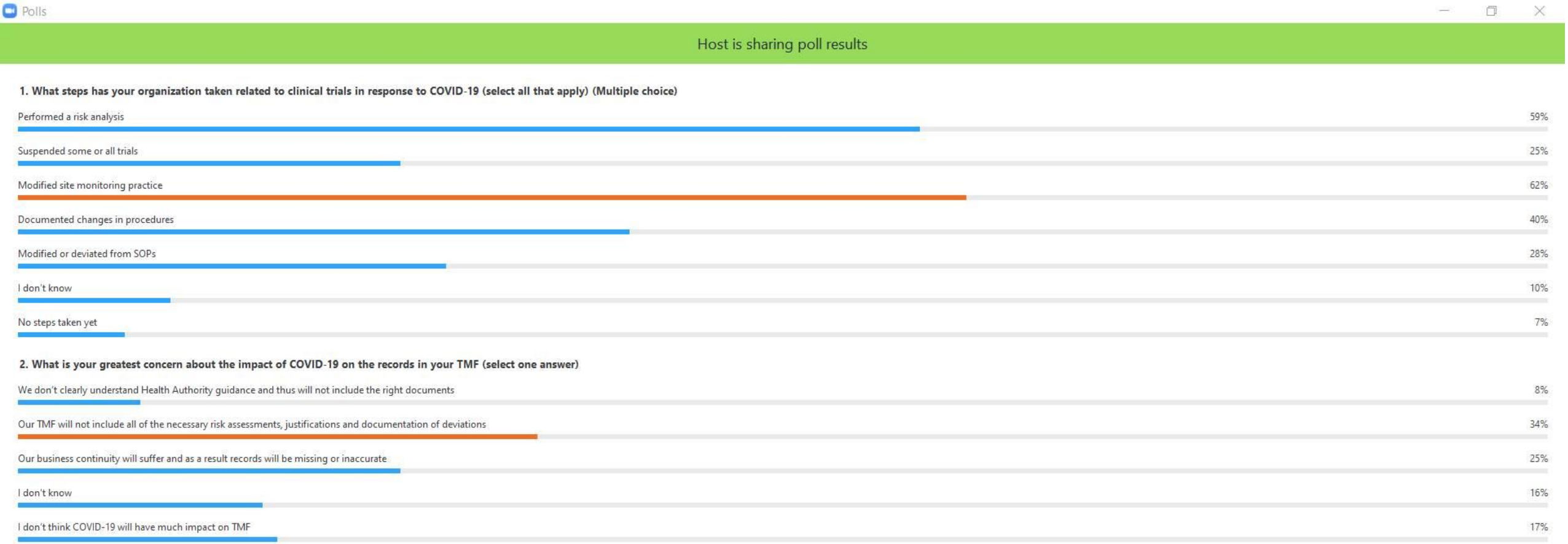
Overview

- Major Health Authorities have recently issued advisory or guidance documents on COVID-19 and Clinical Studies
- The TMF Reference Model Steering Committee (TMF RM SC) has prioritized review of guidance and considerations of impact
  - Though Kathie, Lisa, and Sholeh will lead the discussions, any one of the TMF SC members may be sharing their own experiences within their companies on the topics presented
- New for all of us:
  - We aren't providing advice on specific documents or practices in most case, but points to consider
  - Interested in continuing the dialog with our entire community to help all of us as well as the patients in our trials

Polls



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Health Authority Guidance Review

Kathie Clark

US Food and Drug Association

- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic
  - Safety Considerations → recruitment, monitoring, patient discontinuations → need to inform sponsors, sites, IRBs, patients
  - Urgent protocol changes should be discussed with IRBs & (if needed) FDA; **may be implemented without prior approval but must be reported**
  - Sponsors and clinical investigators should **document** how restrictions related to COVID-19 led to **changes in study contact or duration**
  - Changes in study visit schedules, missed visits, or patient discontinuation → **Missing info explained in CRF → CSR**
  - Alternate distribution methods for study drug may be considered; **accountability requirements remain in place**
  - **Consult with FDA review division** when amending data management and/or statistical analysis plans

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European Medicines Agency (EMA)

with HMA, GCP Inspectors Working Group, CTEG

Guidance on the Management of Clinical Trials during the COVID-19 pandemic & Points to consider: implications of COVID-19 on methodological aspects of ongoing clinical trials

- All decisions to adjust clinical trial conduct should be **based on a risk assessment** by the sponsor and reassessed as needed
- Sponsors are advised to **pre-plan** how systematic deviations resulting from the measures / individual decisions related to the COVID-19 pandemic are **captured**
- Need for urgent action means that urgent safety measures may be **taken and afterwards reported** to NCA and Ethics Committee ASAP
- Critical lab tests, imaging or other diagnostic tests could **be performed at a local site** if subject can't reach normal facility
- PI might need to delegate to a sub-I; **permanent changes must be reported** to NCA and Ethics Committee
- Prospective protocol waivers remain **unacceptable**
- Mark any contact with NCAs with **'COVID-19' in the subject field**

Health Canada

Management of clinical trials during the COVID-19 pandemic

- Halting recruitment or temporarily halting the trial **must be reported** in a clinical trial application notification (CTA-N)
- Increased protocol deviations expected; **document but do not report unless participants at risk**
- Direct shipment of IP to subjects may be acceptable; **records** respecting the shipment, receipt, disposition, return and destruction of the drug **must be complete and accurate**
- Processes may need to be changed: e.g., **consider an electronic alternative** in place of a wet ink signature

Medicines Healthcare products Regulatory Agency (MHRA)

Advice for Management of Clinical trials in relation to Coronavirus

- Conduct and document a **brief risk assessment**
- Certain oversight duties such as monitoring & QA might need to be **reassessed and alternative proportionate mechanisms used** (phone calls, video calls etc.) to ensure ongoing subject safety
- An **increase in protocol deviations** in relation to Coronavirus expected; reporting not needed unless of patients put at risk
- If your processes require wet-ink signatures, **consider alternative methods** of demonstrating approvals, such as email confirmation
- Prospective protocol waivers remain **unacceptable**
- **Also see** MHRA Good Practice (GxP) inspections during the COVID19 outbreak

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Additional Health Authority / Related Guidance

Not exhaustive – Check HA Guidance Frequently!

- Danish Medicines Agency (Lægemiddelstyrelsen): Extraordinary measures for clinical trials due to COVID-19
- Norwegian Medicines Agency (NoMA): Management of Clinical Trials in relation to covid-19
- UK NHS: COVID-19: Guidance for sponsors, sites and researchers (v2.2 26 March 2020)
- Italian Medicines Agency (L'Agenzia Italiana del Farmaco): Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency
- **Netherlands** Central Committee on Research Involving Human Subjects: **Recommendations for the conduct of clinical research at the time of restrictive measures due to the coronavirus**

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Impact on TMF/eTMF processes

Lisa Mulcahy

Impact on TMF/eTMF processes–
General

If documentation processes change, document the change.

Work with study teams to ensure a robust process is put in place to capture all the different types of TMF documentation changes that are occurring.

- Watch for the creation of NEW documentation when instead current documentation might be updated. Update study's TMF Inventory.
- Consider suggesting to the study team to maintain a centralized listing (tracker at 01.05.01?) to capture these processes impacted and the resultant new or changed TMF documentation (and its management).
  - When time to write the CSR, the impacts are centrally documented for review

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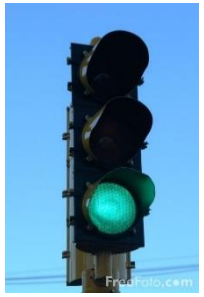
Impact on TMF/eTMF processes–
TMF Documentation Creation –



TMF Documents with Wet-ink component

Clarify the processes; document deviations

- Wet-ink signature pages that are scanned – Are all wet-ink partial signature papers to be collected and filed? What is the process for if they are not?
- Email approvals – Allowed? Do emails get associated/amended to the actual document being approved?
- Email decision/approval documentation needs to be in the TMF. Establish new/revised process for maintaining study decision log.

Authoring, Reviewing, Electronic Signatures and Approvals

Offer your organization web-based training sessions on how to author, review, and electronical approve and sign documentation in the eTMF system.

- Previously reluctant parties may now be open to accept this new way of working as not everyone has scanning equipment in their home office.

Personal phone pics of documents

Acceptable replacements for pdfs? Establish quality parameters.

Impact on TMF/eTMF processes-
Audit and Inspections

Inspections go forward but remote access requests are very likely to increase.

Has your company implemented processes for provision of remote access to eTMF and other TMF repositories… it's the other repositories that are likely the tricky part. Start the conversation if it the right time for your company.

Electronic copies of documentation may be requested

How will electronic copies be created and provided when a company/vendor/site is not open for physical presence? A process for creating, checking, tracking, and providing electronic copies to inspectors needs to be created.

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Impact on TMF/eTMF processes-
eTMF System Functionality, User Access, and Validation

System-related indicators

Consider if there are ways in the eTMF system to tag, note, capture additional information, or even add new sub-artifacts for newly created documentation.

Paper processes for User Access Requests

Many companies still might have a paper process for requesting access for users to a system such as eTMF. Consider changing process… no time like the make the process an author, review, e-sig or approval process

Validation and UAT documentation impacts

Creative alternatives to paper wet-ink documentation of activities such as electronic completion and e-signature

- Document, Document, Document new ways to confirm in UAT and Validation plans and reports

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Impact on TMF Documentation

Sholeh Ehdaivand

Clinical Process Change: Impact on TMF Documentation

- Protocol amendments (e.g. to adjust the patient visit schedule, etc.), ensure that the documentation of the amendments and associated documentation (e.g. protocol acceptance) are filed in the TMF.
- Cross-check other applicable documents and make revision/amendments as needed (e.g., Monitoring Plan). Ensure all updated documents are filed in the TMF.
- Closely monitor protocol deviations and ensure they are tracked and documented appropriately.

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Clinical Process Change: Impact on TMF Documentation

- Additional meetings (ad hoc and routine) should have the appropriate documentation (e.g., meeting agenda and minutes) filed in the TMF.
- The Decisions Log is your friend. Please do not default to Note-to-Files! It can be “easy” to do in this situation, but there are more suitable ways to document decisions
- If adjustments to your clinical program require new team members, ensure that your team roster, CVs, qualification documentation, training, Delegations of Duties log (or equivalent) are revised and filed in the TMF.

Clinical Process Change: Impact on TMF Documentation

- Communication with the IRB(s) – including submissions/approvals/decisions should be collected and filed in the TMF.
- Revisions are properly documented in the Clinical Study Report (CSR).

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Last Thoughts

All of these challenges will bring:

- Delay in getting TMF documents
- understand the type of documentation that will be generated to manage clinical operations during the pandemic to determine the filing
- New ways of working and collaborating
- More efficient ways of doing processes that have been done this way “forever”
- Electronic signatures and approvals instead of wet-ink
- Priority to get virtual TMF management and inspection processes in place

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Last Thoughts

- Focus on documentation and management of decisions in the TMF to support summary in the CSR
- Assessing risk during this time is vitally important
- As risk is assessed and action is taken, communicate to the appropriate Stakeholders and document along the way
- Remember that the TMF tells the “story” of the clinical trial, the documentation in your TMF will be used to reconstruct the trial. Ensure that your study is not missing any chapters!

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MHRA-FDA GCP Symposium London, 13-14 Feb 2020 Summary & Highlights

Wendy Trimboli, Sr. Director, Clinical Operations Process, Systems & Inspection Readiness

TMF General Meeting, 30 March 2020

wtrimboli@acadia-pharm.com

ACADIA® Pharmaceuticals

MHRA-FDA GCP Symposium – Overview & Purpose

- Regulatory agencies conduct Good Clinical Practice (GCP) inspections to assure the integrity of data generated in clinical trials and to confirm the protection of human research subjects, in addition to ensuring that clinical trials are conducted according to the applicable regulations.

- With the globalization of clinical trials, regulators have increased collaboration amongst themselves to evaluate the adequacy of clinical trial conduct to optimize regulatory resources and oversight.

- This event provided regulatory perspectives on the importance of sponsor oversight of clinical sites and laboratories, eSource including electronic health records, protocol deviations including the impact on clinical trials, and the challenges in ensuring data quality in novel clinical trial designs.

About 400 in-person attendees and Day 1 was streamed internationally

MHRA-FDA GCP Symposium – Day 1

Update on International Collaboration

Ni A. Khin, MD, Division Director, FDA, & Gail Francis, Expert Inspector, GCP, MHRA – FDA-MHRA International Good Clinical Practice Collaboration

Protocol Deviations: Identification, Impact, and Reporting

Jean Mulinde, Senior Advisor, FDA Violations and Deviations: Is Anyone Really Happy with Current Handling?
Jennifer Martin, Lead Senior GCP Inspector and Operations Manager, GCP, MHRA Management of Protocol Deviations: Identification, Classification, Use in Analysis
Julia Cho, Division Director, FDA Impact of Protocol Deviations on Bioequivalence Evaluations

- Understand how protocol deviations impact data reliability and subject safety when not properly identified, tracked, analyzed and reported
- Discuss challenges and opportunities in protocol deviation management
- Examine how current practices may impact data quality and ultimately the acceptability of study results for regulatory review

Challenges in Ensuring Data Quality in Novel Clinical Trials

Mandy Budwal-Jagait, Senior GCP Inspector and Michael McGuinness, GLP/GCP Inspector, MHRA Adaptive trials and dose escalation
Cheryl Grandinetti, Pharmacologist, FDA Considerations for the Design and Conduct of Decentralised Trials: Regulatory Perspectives

Sponsor Oversight: International Perspective

Stephen Vinter, Operations Manager, GLPMA & Laboratories Group, MHRA Key Considerations for Sponsorship of the Clinic and Laboratory
Kassa Ayalew, Branch Chief, FDA FDA Perspective on International Clinical Trials

E-Source including Electronic Health Records

Andy Fisher, Lead Senior GCP Inspector, MHRA Current Challenges with eSource (based on the EU experience)
Phillip Kronstein, Lead Medical Officer, FDA eSource: Practical Examples

***Panel Discussions**
***Opportunities to speak directly with FDA/MHRA Inspectors during breaks and lunch**

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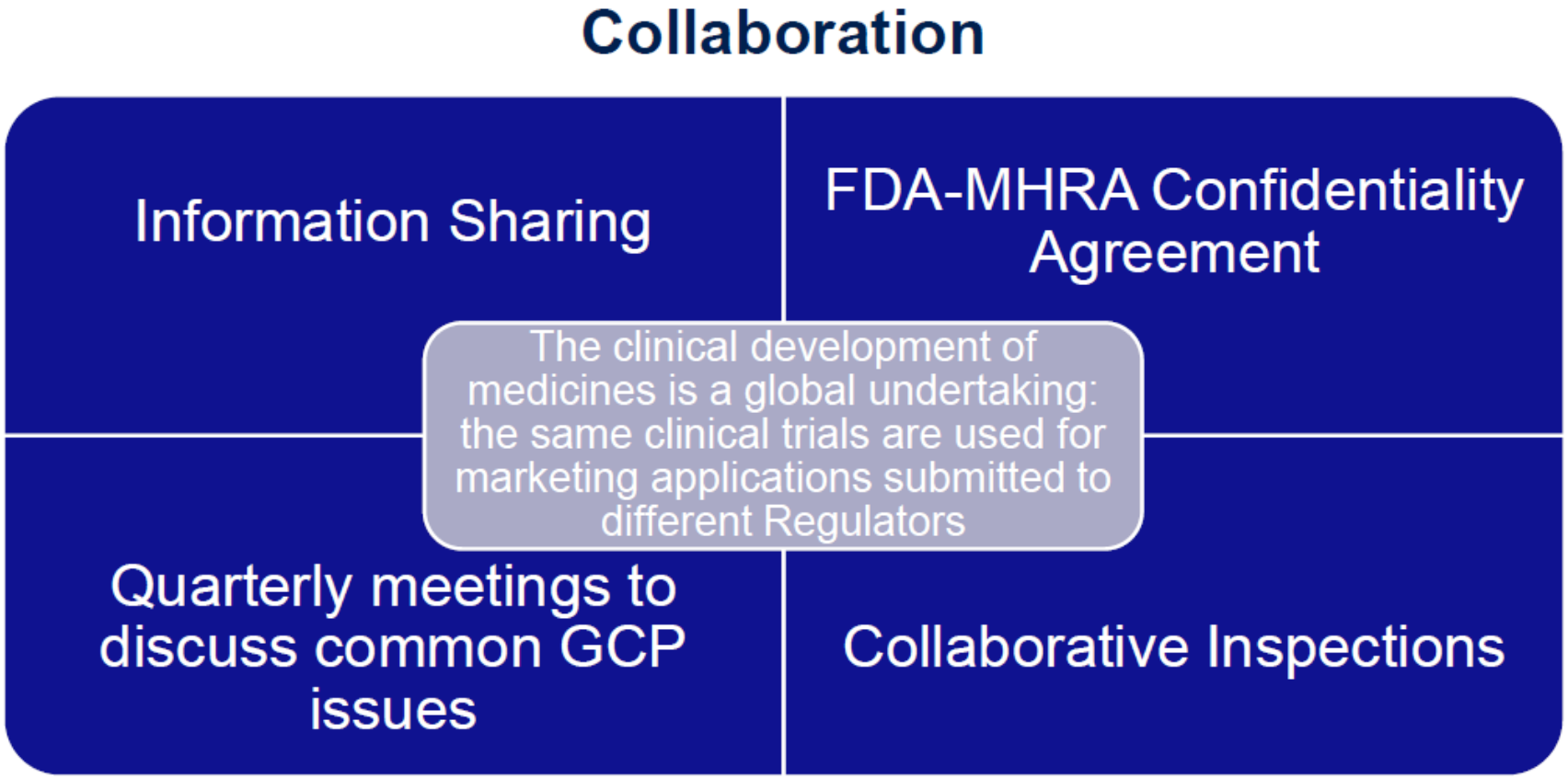
Update on International Collaboration



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Update on International Collaboration

Types of Collaborative Inspections

Joint: Both FDA and MHRA are on site at the same time or at an overlapping time conducting an inspection. MHRA and FDA follow their respective Agency's processes and procedures for performing inspections and produce an independent/separate inspection report in accordance with their respective Agency's policies and procedures

Observational: Either FDA or MHRA conduct a GCP inspection with observers from the non-inspecting authority (MHRA or FDA) present during the inspection

Parallel: MHRA and FDA conduct separate GCP inspections at different sites within an agreed parallel time, in support of the same investigational product clinical trial of interest

Sequential: When the submission timing of an application does not overlap sufficiently, the agency receiving the application first, and therefore initiating the GCP inspection, supports the planning of the inspection by the second agency

There have only been two Joint FDA-MHRA inspections to date.
1st was Jan 2019

Update on International Collaboration

Purpose of GCP Collaboration

- To characterise and compare GCP inspection findings from organisations inspected by both agencies
- To provide insight into similarities and differences between the GCP inspection findings of the two agencies
- To focus on GCP findings relevant to data reliability/integrity
- Share intelligence related to the conduct of clinical trials
- Sharing of expertise and provide training opportunities
- Shared understanding of technical/compliance issues

During panel discussion, it was noted that there were more similarities than differences. One difference that was specifically mentioned was TMF timely submission. An FDA inspector stated the FDA is not as concerned about timely submission as the MHRA.

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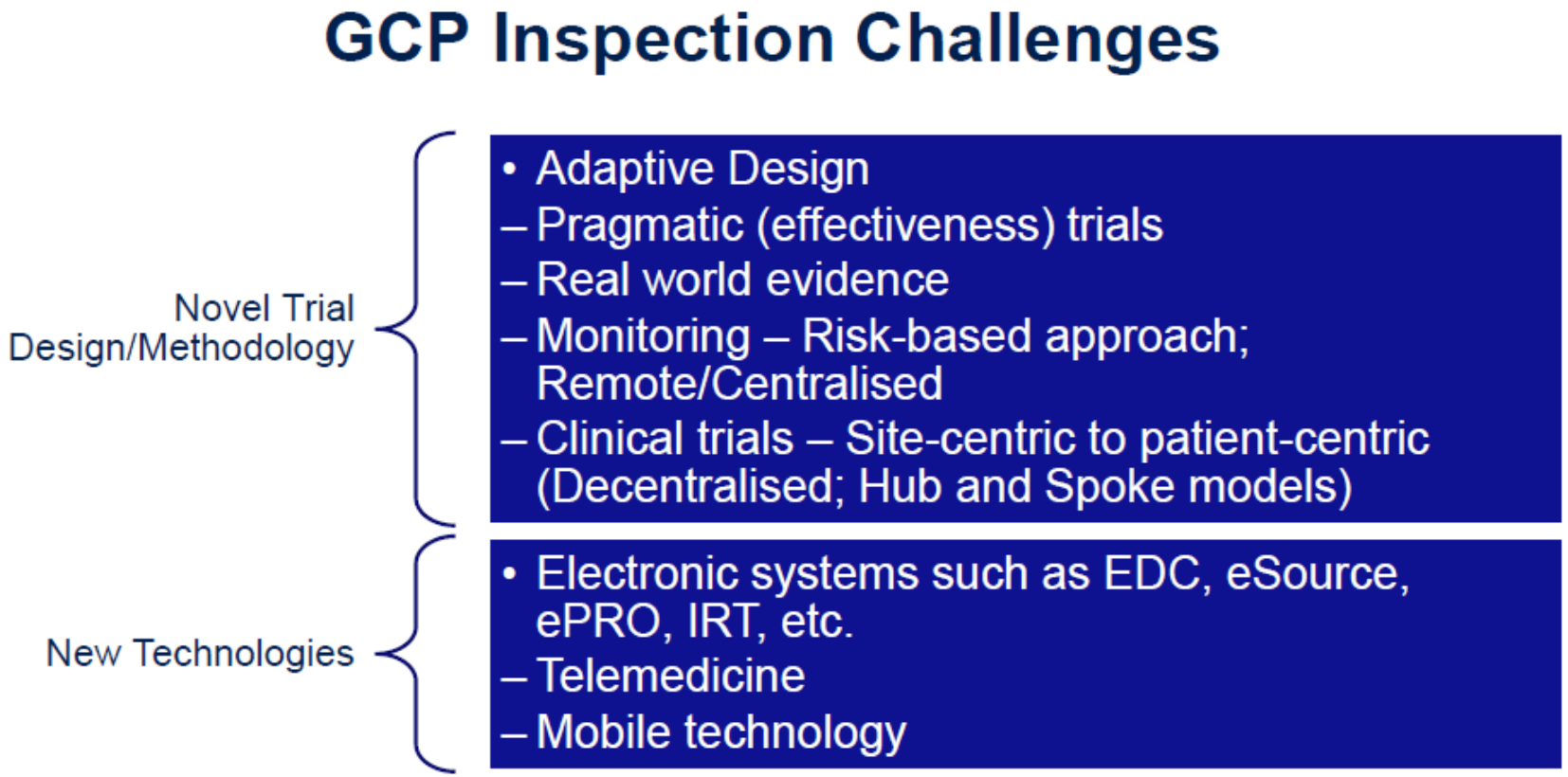
Update on International Collaboration



Update on International Collaboration

Moving Forward

- A closer look into common GCP inspection findings (similarities and differences) in order to determine how regulatory bodies may work more efficiently to coordinate inspection efforts, when possible
- Process improvement
- Look for opportunities to provide guidance and regulatory convergence related to common GCP issues, novel trial design/methodology and new technologies

Protocol Deviations: Identification, Impact, and Reporting

There is a need to more effectively and efficiently leverage “deviation” data to:

- Protect the rights, safety and welfare of our trial participants
- Ensure data from clinical trials of sufficient quality for stakeholders to make treatment, development, and regulatory decisions

Gaps remain in our ability to utilize deviation data:

Lack of clear definitions

- Protocol deviations
  - Site
  - Sponsor
  - Vendor
- Process deviations
- Data Standards (CDISC) – subject specific protocol deviations only; no controlled terminology; no standards for capture site level, sponsor level, vendor level, or process deviations as data

Tracking of protocol deviations in multiple systems and lack of system interoperability (EDC, CTMS, Vendor systems, spreadsheets, etc) result in limitations on ability to identify, track, analyze and report

Protocol Deviations: Identification, Impact, and Reporting

Regulatory Expectations

- Data and documentation on protocol and process deviations to:
  - Permit regulators to reconstruct the conduct of the study
  - To understand how you have determined “important” versus “non-important”
- Evidence that you are maintaining your oversight obligations (document of risk assessment(s) and your identification, tracking, and analysis of protocol and process deviations, also when indicated issue escalation, evaluation and resolution)
- MHRA serious breach reporting

Protocol Deviations: Identification, Impact, and Reporting

What does a good process look like?

- Identify ALL trial deviations
  - Protocol
  - GCP
  - SOPs/Trial procedures
- Record/log ALL identified deviations
  - Sponsor, CRO/Vendor, Investigator site
- Contemporaneous documentation of review and assessment
  - Who/ When/ Decision/ Outcome/ CAPA
- Circulations and Escalation
  - Regulatory notification (SB/USM)
  - Removal from statistical analysis
  - Inclusion in CSR 10.2 / Appendix 16.2.2

MHRA-FDA GCP Symposium – Day 2

Case Study Session 1

- **Bioanalytical approaches to mitigate issues identified during BE clinical site inspection**
- Arindam Dasgupta and Andrace Deyampert, FDA
- Emma Whale and Jason Wakelin-Smith, MHRA
- **GCP ePRO source data**
- Andy Fisher, Gail Francis, and Paula Walker, MHRA
- Phillip Kronstein and Rachel Skeete, FDA

Case Study Session 2

- **Laboratory audit trails**
- Jason Wakelin-Smith, Emma Whale and Michael McGuinness, MHRA
- Arindam Dasgupta and Julia Cho, FDA
- **Handling protocol deviations**
- Bei Yu, Ni Khin and Barbara Wright, FDA
- Mandy Budwal-Jagait and Hayley Dixey, MHRA
- Debbi Fox, Health Canada

MHRA-FDA GCP Symposium – Day 2 Handling Protocol Deviations

What questions will the inspectors have on the data?

- How are Deviations identified, recorded, reconciled and categorized? Where is this information located? Is there an SOP defining this?
- How was the Protocol Deviation listing put together? What sources were used to obtain this data? (CTMS, eCRF, etc)
- What about procedural deviations or other significant non-compliances which may be identified at the trial level (eg, in other departments, such as data management)?
- How do the deviations get into the CSR and what process is in place to ensure all the deviations are provided to the statistician for review? Is all of the documentation in the TMF and can it be reconstructed?

Inspection Preparation

- Map out all sources of deviations
- Review procedures for reporting and recording deviations
- Ensure you have listings of all the deviations identified
- Any data integrity concerns related to the conduct of this study?
- What impact assessment has been performed? Any impact on analysis?

MHRA-FDA GCP Symposium – Day 2 Handling Protocol Deviations (cont'd)

Common root causes:

- Failure to reconcile CTMS list with eCRF
- Inconsistent classification of same Protocol Deviations by CRAs
- Sponsor decision not to include in CSR not documented and no rationale
- Lack of oversight (CRO/Vendors)
- Failure to identify all sources of procotol deviations and GCP non-compliance

- Review across all departments and functional teams
- Quality Management System in place

Questions?

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TMF-related events coming up

- DIA, Washington, June 2020 – a few TMF sessions plus a 10 year birthday party! ITS STILL ON FOR NOW
- Clinical Documentation World, Philadelphia, PA September 9-11, 2020
- IQPC TMF Conference Bruges 14-17 Sep
- Exl TMF Summit London 19 – 21 Oct
- AGxP San Antonio, TX – 8-11 November

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TMF RM General Meetings

- <11th May>
- 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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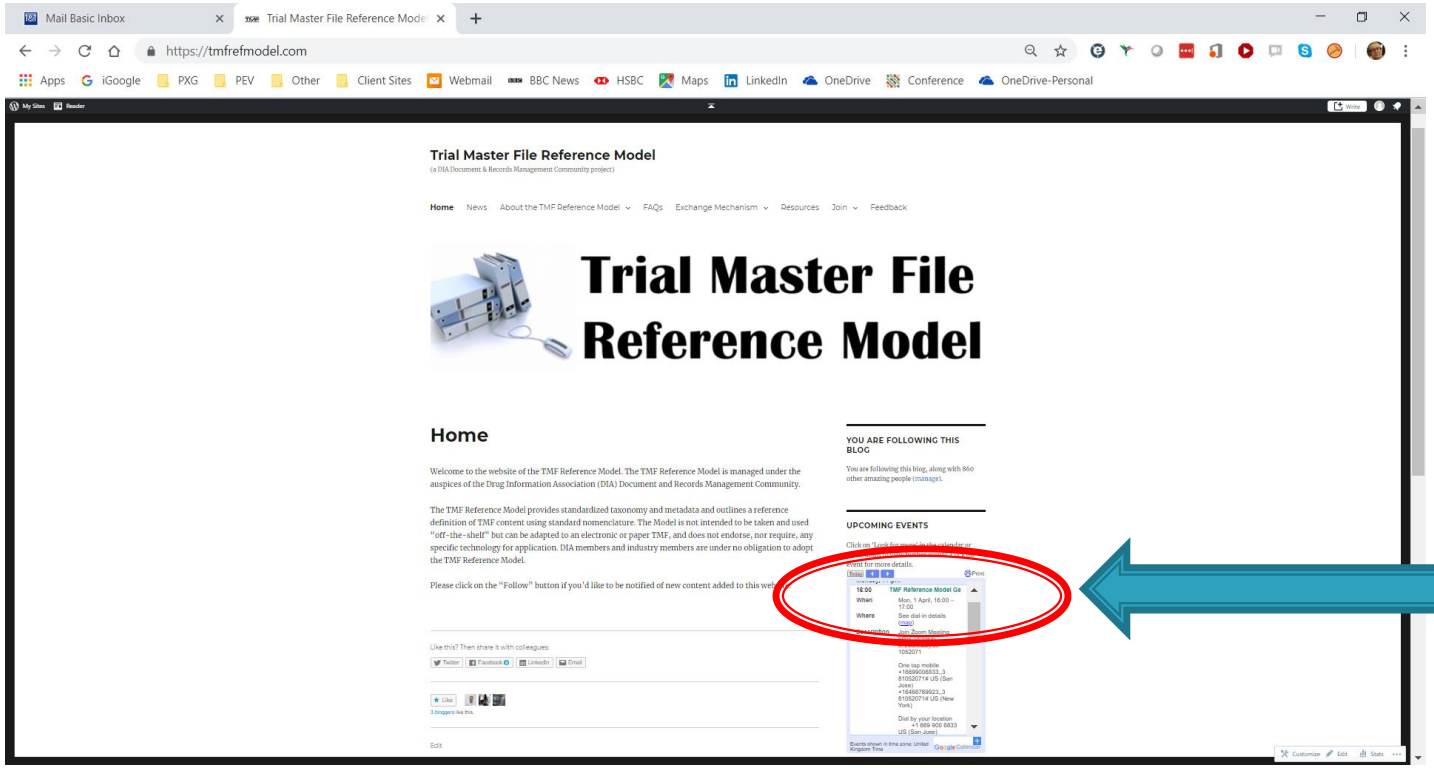
Meeting details

- 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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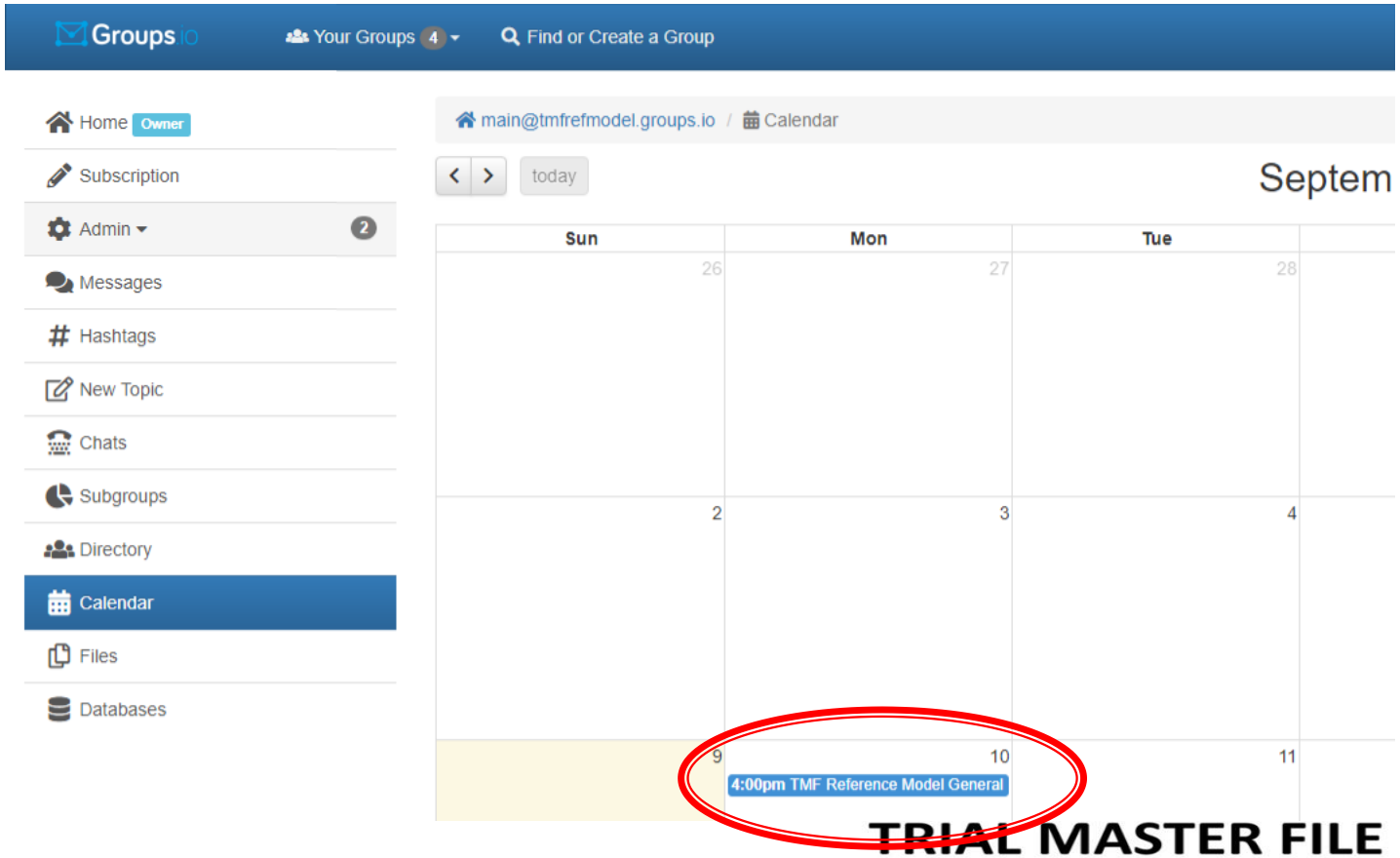
Meeting details

- 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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