Trial Master File Reference Model

General Meeting

21 September 2020

Agenda

- Welcome
- Update on Membership
- Update on Initiatives
- Virtual Inspections
  - Presentations
  - Panel for Q&A
- Next Meeting

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Membership … Since last meeting*…

- 21 new project team members (groups.io) – current total 339
- 1163 Mailing List Subscribers** (tmfrefmodel.com)
- LinkedIn group – 3,158 members (98 new members)
- For details on these different groups and how to get involved, see http://tmfrefmodel.com/join

* 27th July 2020

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

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TMF RM Active Initiatives

TMF Tools:

- Real-World Studies Document Index Provides a proposed Document Index for use on real-world studies, based on the TMF Reference Model for clinical trials (v1.0 Approved 29-July-2020) NEW
- Industry Guidance: Electronic Communications Guidance from the TMF Reference Model Project on the management of trial-related electronic communications (aka email) (v1.0 Approved 29-July-2020) NEW

Initiative	Deliverables / Activity
Sub-artifacts	• A super-set of sub-artifacts for Companies to select and customise • Removal of the 'Alternative Name' column – any unique names have been added as sub-artifacts • With CCB
Devices	• Updated artifacts and sub-artifacts specific to Device studies • Being finalised
Exchange Mechanism	• An extension of the TMF RM which focuses on the transfer of content, metadata, audit trail and eSig information

We will be assessing for new initiatives …..

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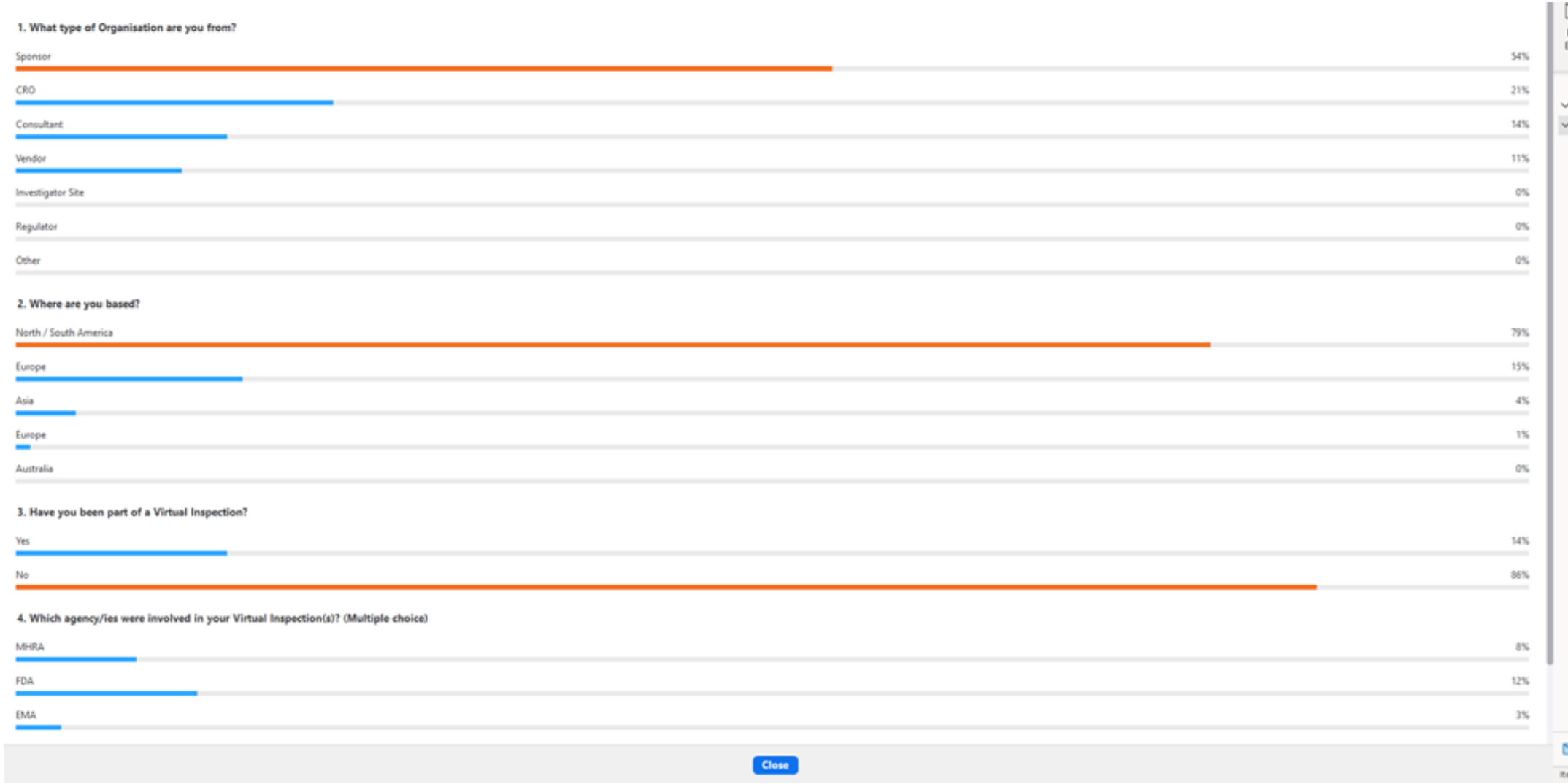
Virtual Inspections

Polls



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MHRA: Will Virtual Inspections continue?

- As of September in-line with the MHRA announcements (https://mhrainspectorate.blog.gov.uk/2020/07/23/mhra-planning-for-return-to-on-site-good-practice-gxp-inspections/) they are starting to do on-site inspections, but they will continue to make use of remote inspections where it is appropriate in a hybrid type model for GCP. Of course, any restrictions imposed by the government may require a review of any inspection plans at short notice.

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Overall thoughts

- Virtual inspections won't affect the basic requirements
- Virtual inspections have been around for a while – accelerated by the pandemic
- Most virtual inspections have been at Sponsor or CRO, not at sites (although it is starting)
- Most virtual inspections have been in the eTMF, not in an archive system

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Considerations for the Preparing for Remote Inspections by Health Authorities

Lisa Mulcahy

Is the Concept of Remote Inspections New?

Let's go back a time, way back, maybe 2012, when eTMF systems were starting to be consistently implemented to manage TMFs, Health Authorities, especially UK and EU, were seeing the value of the eTMF system as a tool that could be accessed prior to and after inspections.

Some of the reasons were:

1) Growing comfort with eTMF systems

2) Consistent TMF taxonomy and architecture through the utilization of the TMF RM

3) Growing comfort to go directly into sponsor system(s) without navigators

4) Shrinking budgets for inspections

Remote Inspection Preparations

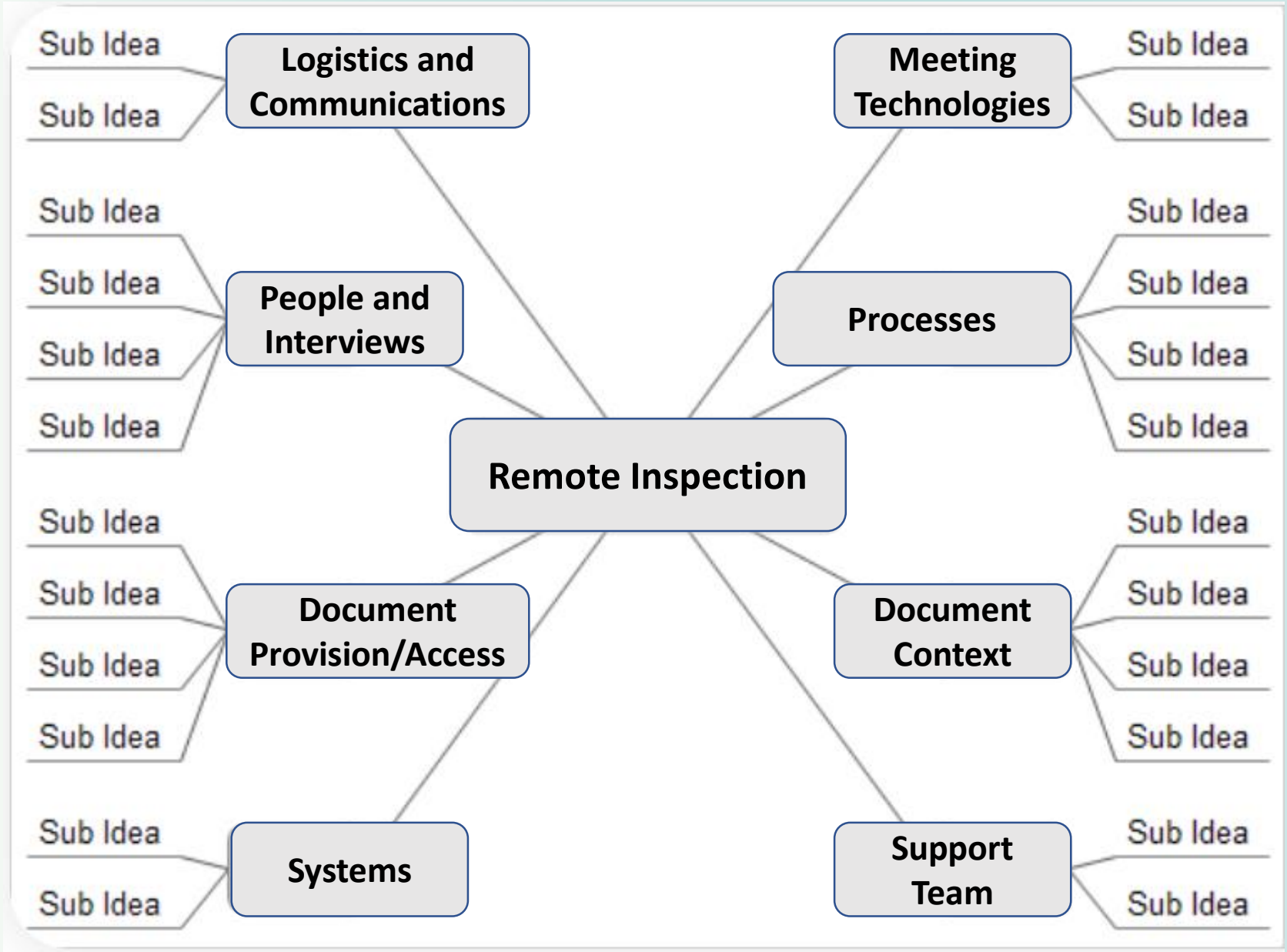
1) Start with a plan

2) Translate plan to process

3) Plan for the inspector's access to documentation that may be in multiple systems; system support and consideration for provisioned document

4) Impact to the people involved: preparation, pre-inspection, during

5) Conduct of the mock inspection

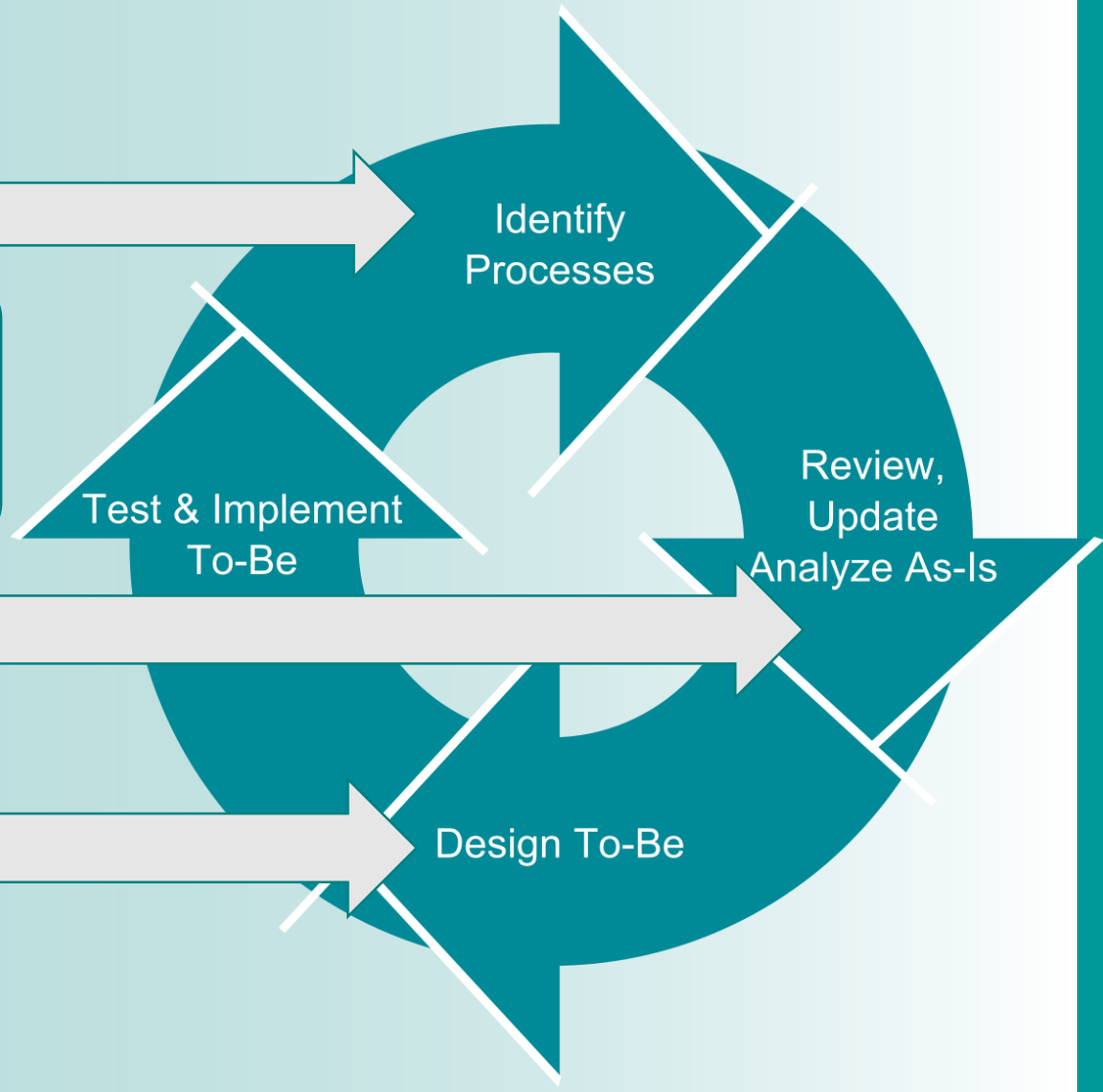


Start with a Plan - Build a Spider Diagram or a Mind Map

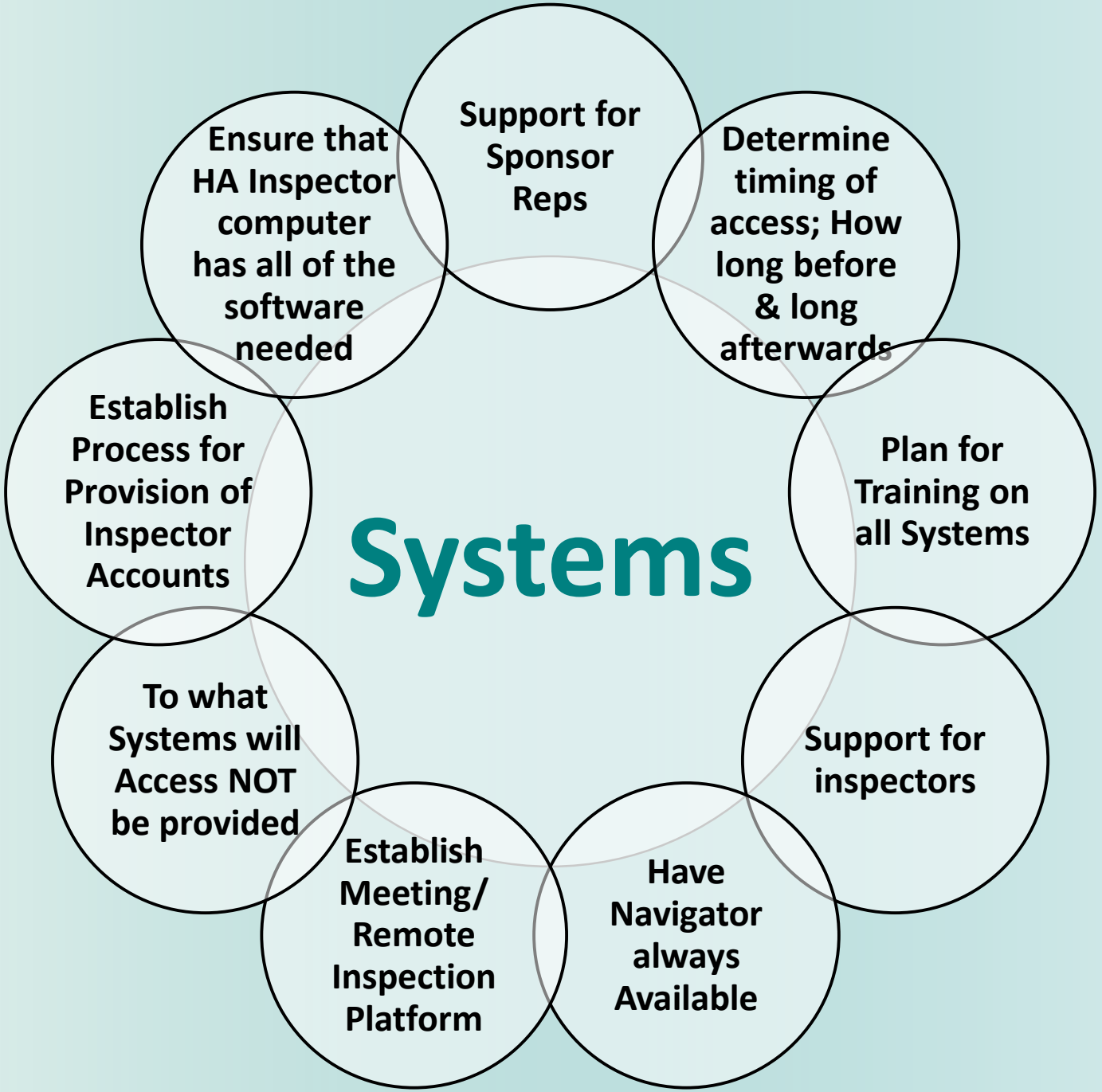
Translate Plan to Process

Start by listing all applicable procedural document in place. Compare your remote inspection plan to determine the already established processes for conduct of inspections, provision of content in scope, etc..

Review and decide which need to be updated and any new ones that need to be created. Align back to the plan to make sure all parts of the process are defined in a quality system. This is not the time to take your time in review and approval.



Business Process Reengineering Cycle


Systems
Support for Sponsor Reps
Determine timing of access; How long before & long afterwards
Plan for Training on all Systems
Support for inspectors
Have Navigator always Available
Establish Meeting/ Remote Inspection Platform
To what Systems will Access NOT be provided
Establish Process for Provision of Inspector Accounts
Ensure that HA Inspector computer has all of the software needed

Sincerest Thanks and References

Thanks to my trusted colleagues

- **Autolus Limited, Daiichi Sankyo, Just in Time GCP, Pfizer**

References

- **EMA Guidance on remote GCP inspections during the COVID19 pandemic**
  - https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-remote-gcp-inspections-during-covid-19-pandemic_en.pdf
- **Hosting A Virtual FDA Inspection: Advice From Former FDA Investigator And Investigations Director Ricki Chas**
  - https://govzilla.com/blog/2020/07/pharma-medical-devices-hosting-a-virtual-fda-inspection-advice-from-former-fda-investigator-and-investigations-director-ricki-chase/
- **MHRA Blog - GCP Inspections: Expectations and the dos and don'ts for hosting**
  - https://mhrainspectorate.blog.gov.uk/2020/03/10/gcp-inspections-expectations-and-the-dos-and-donts-for-hosting/
- **MHRA remote inspection: What you should know**
  - https://www.ideagen.com/company/blog/mhra-remote-inspection-what-you-should-know
- **Preparing For A Virtual FDA Inspection: Advice From Former FDA Investigator And Investigations Director Ricki Chase**
  - https://govzilla.com/blog/2020/07/pharma-medical-devices-preparing-for-a-virtual-fda-inspection-advice-from-former-fda-investigator-and-investigations-director-ricki-chase/

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EMA Remote Inspections – Technical Requirements

Paul Fenton

TECHNICAL REQUIREMENTS – EMA

The reference is: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-remote-gcp-inspections-during-covid-19-pandemic_en.pdf

As mentioned above, inspectors should explore the technical capabilities of the situation / setting at the inspectee as well as the capabilities at their own location / agency. Usually, there are certain restrictions imposed by the regulatory agencies' IT departments on the use of additional software, devices, applications and access to cloud computing services as well as file transfer protocols for downloading documents that could affect the planned inspection

- Make sure that you identify all systems that may be inspected
- Ensure that the inspection team can access them
- Have a back up plan in case they can't…

TECHNICAL REQUIREMENTS – EMA

Ideally, a video streaming system, embedded video conferencing or interactive tool for managing questions, queries and decisions, document sharing, or intuitive inspectors viewing tool, would facilitate all involved parties' work and avoid disruptions, overlapping of activities and optimise resources and time invested. A chat / instant-messaging platform should also be considered, in case of sound interferences.

- Plan how you will use tools to conduct the inspection
- Do some dry runs and make sure the inspection team knows how to use these applications
- Longer term, work with your vendors to integrate these types of communication tools

TECHNICAL REQUIREMENTS – EMA

Any recording (audio / video / screenshots) during the inspection process should be notified and agreed upfront between all involved parties.

- Decide on what needs to be recorded, if anything
- Ensure you have an agreement with the inspector

TECHNICAL REQUIREMENTS – EMA

It is the inspectors' expectation to be able to review the eTMF (related) audit trails, activity logs and metadata in order to reconstruct its management since its deployment. Completeness, quality and timeliness of the retrieval of documents from the eTMF are therefore important during a remote inspection. Moreover, inspectors should be enabled to use export / save functions to retrieve documents from the eTMF. This could be provided through a sharing document platform or other media like email or a secure system after the applicable Quality Assurance (QA) checks by the document owner / subject matter experts have been performed.

- Ensure that the inspector can easily find and understand audit trails and activity logs
- Make sure that all metadata is complete and correct
- Ensure that the inspector can download and save records, keep a log of this

TECHNICAL REQUIREMENTS – EMA

It is recommended to use an electronic document request form that can be shared among the inspectee and the inspection team. The inspection team may request the inspectee to keep track of all requests and provide a regular update of the electronic document created.

- Try and implement an electronic request form or log
- This could be available directly in your eTMF application
- Work with your vendors to improve and integrate this into your eTMF application if not available

TECHNICAL REQUIREMENTS – EMA

It is important that sponsors / CROs provide remote technical support for inspectors, that the eTMF is robust and capable to support a remote inspection even if the eTMF is decentralised and managed from different locations and its content spread across different systems. It is important that inspectors can still gain access to (or via) a centralised system with one or several connected systems.

- This may be challenging with todays systems that tend not to be connected
- Work with your vendors to find a way of being able to link to other systems
- Maybe consider SSO for authentication
- In the future we should look to build federated systems

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MHRA: Will the be any changes to Inspections post Brexit?

- There will be no change to the risk based GCP inspection programme and therefore GCP Inspections will continue after the transition period ends. The only changes will relate to the involvement of EMA requested inspection in relation to centralised licensing applications, as this will cease unless there is any deal agreed as per current negotiations.

Feedback on Differences and Challenges

- Inspector training done remotely – Not same opportunity as when you are in the room and can navigate the TMF – It has to be done remotely through Webex and because the inspector access and view in the system may be different from yours you have to guide them as they navigate the system from their end
- Inspector account credentials to be provided through secured/protected email
- Logistics for interviews and follow up especially when you have study team members and inspectors all over the world
- Coordination for preparation and QC of the requests – May take longer than when you are on site because you don't have the study team, inspection team on site.
- The communication, chat between the inspector room and control room is the same as if you would be on site. The using usual communication channels Webex, Zoom or TEAMs are used. However, it is important to check connectivity and video capability upfront. Would recommend a dry run prior to the inspection.
- In a virtual context, planning, coordination, testing, communication are more important than ever!

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Technology Advice for Virtual Inspections

- A few technology items from our remote HC inspection in case folks are prepping for one in the time of COVID: We used SharePoint for doc. request mgmt., MS Teams for interviews (they wanted video for everything), utilized a central tracker for document request which was then loaded to SharePoint and had a Teams Channel linking to the SharePoint for doc. requests, scribe notes (OneNote), etc....also be aware of your Teams Chat and who has access as that's an ongoing thread.

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Mock Inspection Experience

- We've done virtual mock inspections with FDA and EMA ex-inspectors. Our QA team had a few practice runs to get the virtual front and back rooms set up, and they had a numbering system for the requests with corresponding numbered shared folders for our responses. At the end of each day QA did a check to see what was still open. Other than the logistics of it is felt 'normal', and the eTMF was key to the whole thing, as ever.
- Advice is to test the virtual rooms a couple of times, dry runs really helped as the technology was new for all of us. Some of the back room folks and QC'ers were inundated with many chat channels
- The FDA inspector spent far more time in the eTMF

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PMDA Case Study for a CRO

- We experienced a remote GCP inspection by Japan PMDA. As remote inspections at investigator sites are not considered to be feasible, PMDA requires the sponsor and CRO to prepare documents which reflects the implementation of clinical site management. For instance, generally, PMDA verify informed consent forms at the clinical site, but instead of that, they request us to prepare the template of informed consent forms created by the clinical investigator and monitoring activity reports including the subjects' consent date.
- PMDA's remote GCP inspection is divided into two rounds. Firstly, they verify documents uploaded to the cloud system and it takes 10 business days. Secondly, the following day, they make online interviews based on the findings to the sponsor and CRO.
- For the 1st round, we had to digitized a lot of documents as the studies are based paper TMF. However, the 2nd round took less than three hours, whereas traditional interviews used to take a day.
- According to the latest announcement, the remote GCP inspection will be carried on until the end of March 2021.

TMF-related events coming up*

Events page on website (under Resources menu)

- VIRTUAL FierceLive / Questex / Exl European TMF Summit, 2nd to 6th November
- Electronic Trial Master File Forum, New Jersey & Virtual, 26-27 Oct
- AGxP San Antonio, TX - 8-11 November
- IQPC TMF & GCP Inspection Readiness, Bruges, Belgium RE-SCHEDULED TO APRIL 2021

* COVID-19 dependent

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TMF RM General Meetings

- <26th October>
- 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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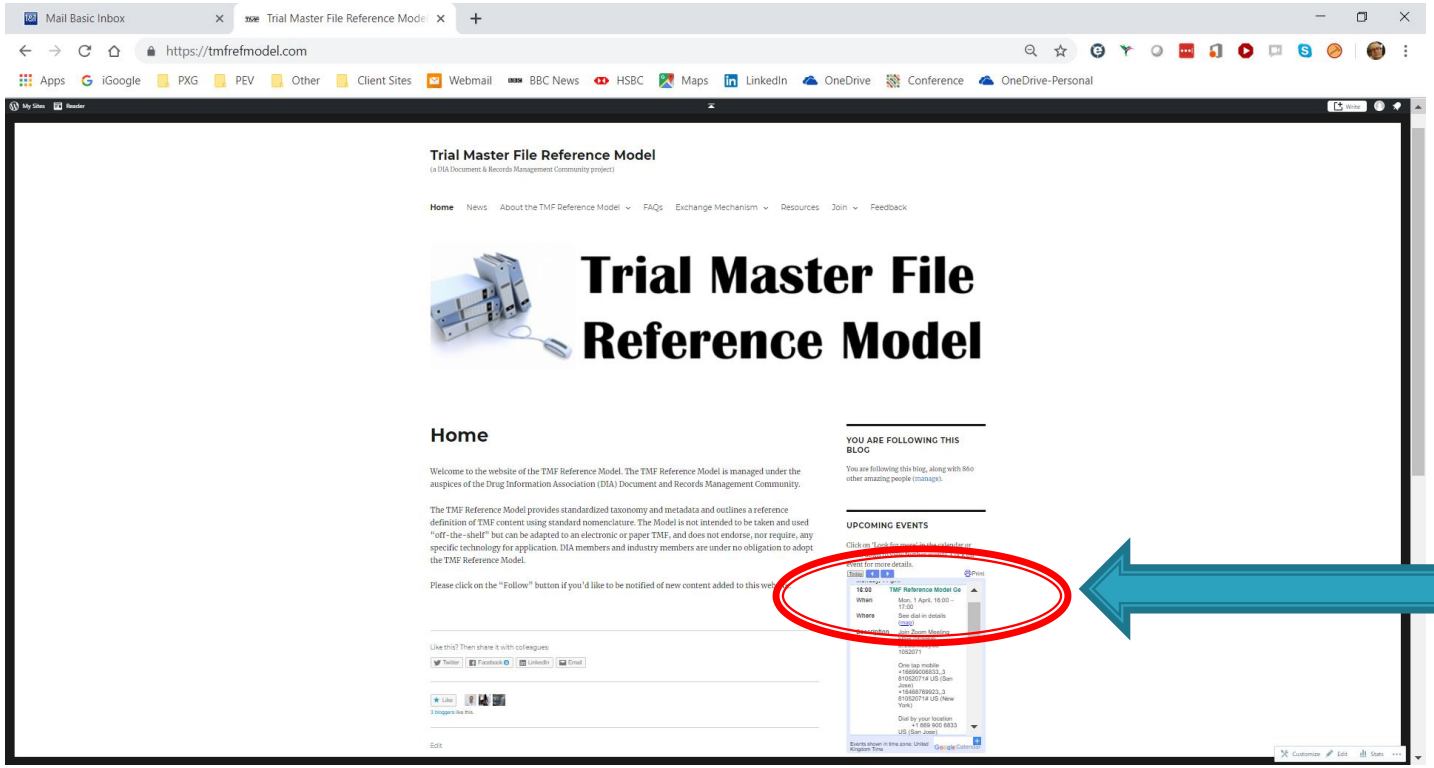
Meeting details

- 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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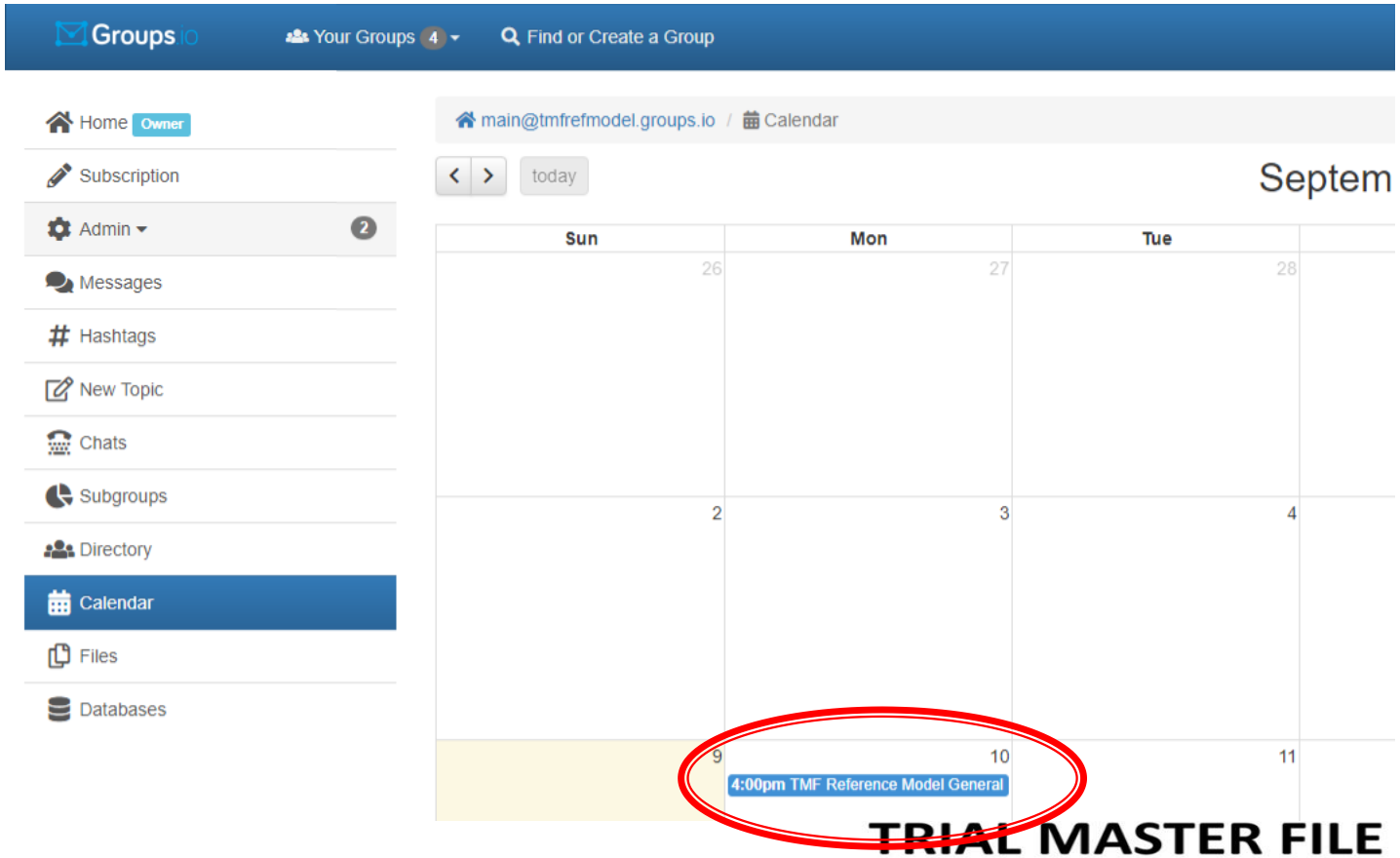
Meeting details

- 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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