TMF Inspection Readiness

From Chaos to Calm

Just in Time GCP®

TMF WEEK 2022

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Just in Time GCP

- Over 15 years of experience in the clinical research industry
- Coordinates TMF management activities and works with clients to analyze, develop, and implement processes that support business use of electronic clinical systems
- Career also includes work in study participant outreach/recruitment, media planning/creation/buying and medical writing

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Let's set the Scenario

- You're being inspected. What's next? We'll discuss streamlined, stepwise strategies to move your team from chaos to calm.

- We will explore how to assess your inspection readiness:

  - Risk-based tools and approaches
  - Consider timeline and resource constraints
  - Engage functional groups in inspection preparedness

What does Inspection Readiness mean?

- Ensuring the **People, Processes** and **Evidence** of trial conduct are present for regulatory review

  - Do you have the evidence that……
    - What you said you were going to do is present in the documentation and data you have
  - Can you identify issues that might make it difficult to tell the story of the study? Can you explain them?
    - Patient safety - Data integrity - Operational
  - Make a plan
    - Storyboards
    - CAPA's

Roadblocks you will encounter

Lack of support due to competing priorities

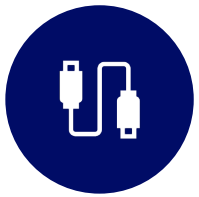
Defining TMF completeness and document filing location

CRO processes vs. Sponsor processes

Different perceptions around the importance of the TMF

Lack of training and emphasis on quality documentation

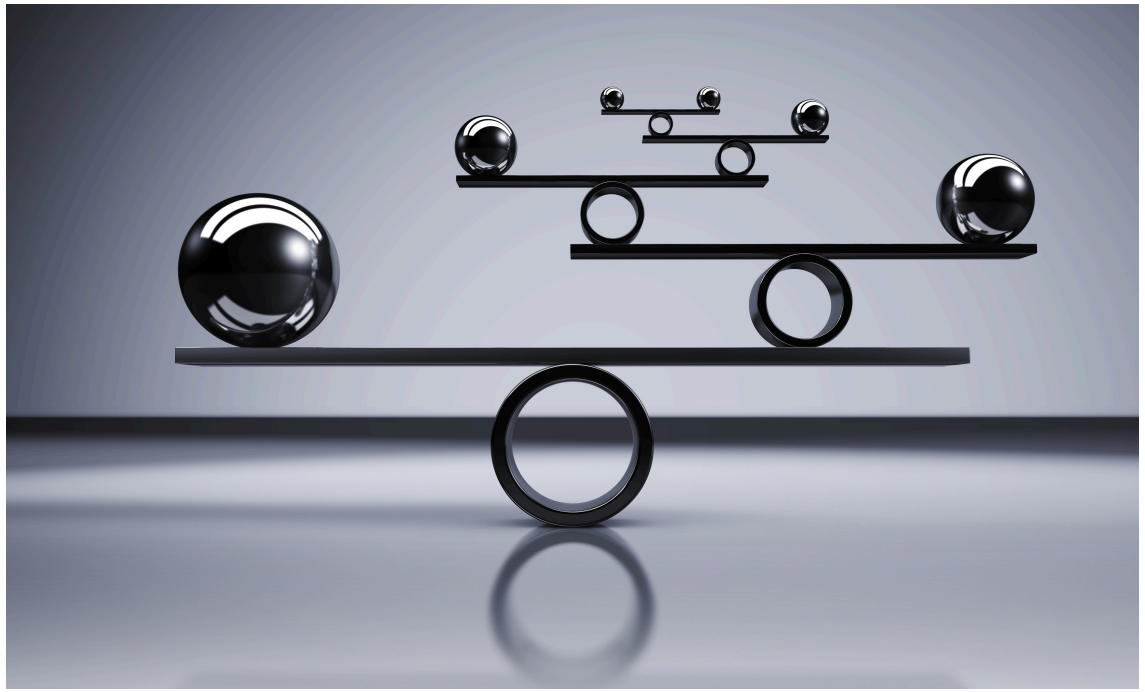
Changing Regulatory landscape



Multiple systems and system owners

How to assess your current inspection readiness state

- ✓ Quality
- ✓ Timeliness
- ✓ Completeness



Are Your Documents TMF Inspection Ready?

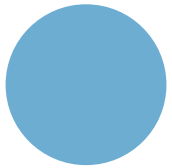
Study Team Staff

✓ Check all Curriculum Vitae's and training documents are filed for all CRO staff including handover if applicable.

Core

- ❑ Curriculum Vitae
- ❑ Handover form (if applicable)
- ❑ Training*

**For eTraining, a report can be generated and filed*

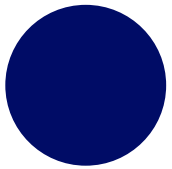


Investigational Product (IP)

✓ Check all relevant documents and records associated with the Investigational Product are approved (if applicable) and filed.

Country / Site

- ❑ Shipment & Receipt Forms
- ❑ IVRS (if applicable)
- ❑ Storage Records
- ❑ Thermometer Calibration
- ❑ Storage Calibration (refrigerator)
- ❑ Accountability Logs
- ❑ Return/Destruction Documentation
- ❑ IP Release Form

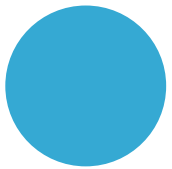


Lab

✓ Check all documentation available for **each lab** involved in the study are up-to-date, approved (if applicable) and filed.

Core / Country / Site

- ❑ Storage records
- ❑ Equipment calibration Temp/Refrigerator
- ❑ Reference Ranges
- ❑ Inventory log (if applicable)
- ❑ Certification / Accreditation
- ❑ Lab Head CV Local/Central



Patient

✓ Cross check to ensure that **patient identification** information is kept **confidential.**

✓ Cross check all documents to verify information matches *(i.e. number of randomized patients matches number of subjects visited at a site*.)

Site

- ❑ Screening log
- ❑ Subject Visits log
- ❑ Randomization log
- ❑ SAE Logs*
- ❑ SAE Site Reports*

**Check SAE logs against the SAE Site Reports*

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Clues from your eTMF

- Non-final status documents:
  - QC Rejected
  - In Progress
  - Other
- Expected documents lists and other reporting tools
  - Do outcomes align with study expectations

- Do you perform Completeness Reviews throughout your studies?
  - Yes - regular cadence
  - Yes - with no set cadence
  - No reviews performed

~Poll Question~

Clues from prior Completeness and/or Inspection Readiness Reviews

- Were queries resolved?
- What trends were observed?

- Are there areas where things didn't add up overall?
- Avoid reliance on Notes to File

- GCP compliance issues?
- Data integrity issues?
- Patient safety issues?

Would you give a contractor plans/specs, then never return until your house was built?

Absolutely not!

Oversight is key, but…

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Where's the Evidence?

- What SOP's did we follow?
  - Can we verify that we did?
- Did our vendors/CRO train all study team members assigned?
  - Is this filed in the TMF (or where is it filed)?
- Did we conduct Oversight?
  - Does our internal study team know what activities they were responsible for and is the evidence filed?
- Did we document deviations and changes?
- Did we follow regulatory requirements for reporting?

Conduct a through review of your TMF documentation

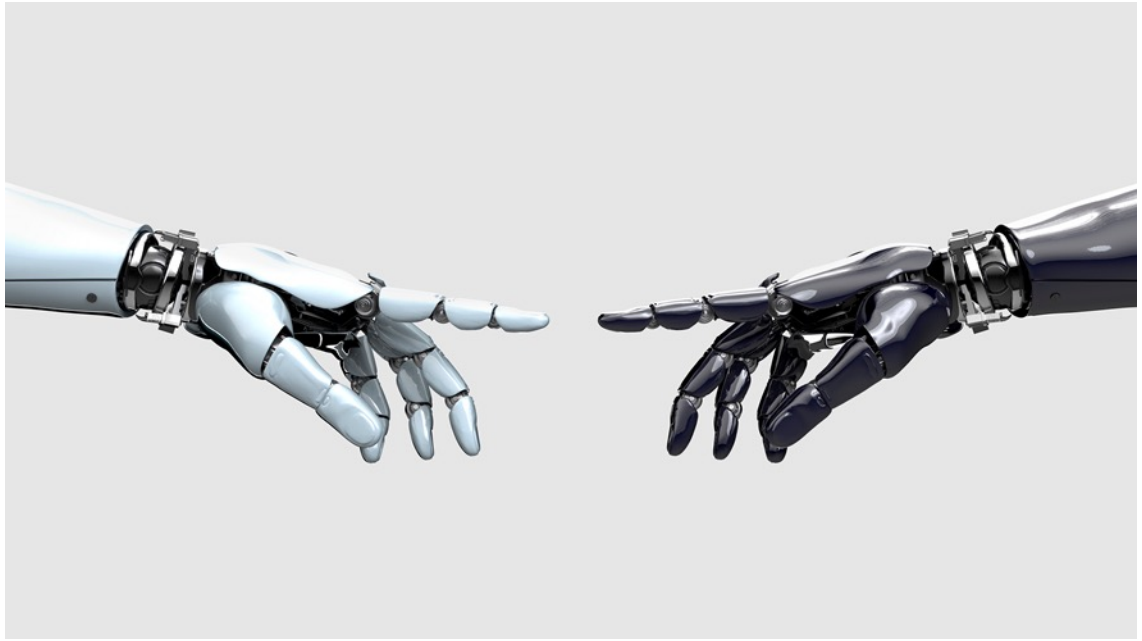
- What did you say you were going to do?
  - Review: Study Plans, Agreements, TORO, TMF Plan, Monitoring, Oversight
- Review your TMF Map:
  - Are all filing locations accurate? Review expected vs. not expected content
- Leverage metrics
  - Example: PDs can help target high risk sites. Where are misfiled / missing documents?
- Try to follow the trail:
  - Can you retrace activities and verify documentation is filed in the TMF?
  - Example: When you find a deviation →
    - Can you trace the activities?
    - Do you have data?
    - Does it provide reasonable evidence of resolution of documented deviations or issues identified?

Tools and approaches to make best use of your time and resources moving forward

Time, Resources, Knowledge

- Leverage technology
  - Use the tools within in the eTMF and other systems
    - Dashboards
    - System Reports
    - Audit Trails and Metadata
- Partner with a vendor
  - Leverage Knowledge & Experience
  - Leverage resources (especially in tight timelines)
  - Objectivity
  - Allows for maximizing your own team members

Strategies to engage functional groups in inspection preparedness



Get Functional Group Buy-In

- Help them understand how their TMF content connects to inspection readiness.
- Help them understand their risks.
- Engage them in managing their risks.

What Next

Act

- Document what you can't find or what you think is missing
- Follow-up with study team members and your CRO
- Develop a plan for addressing the deficiencies
- Track activities and progress
- Update and maintain storyboards
- Open CAPA's, but also ensure any already open are addressed

The Why behind Storyboarding

- Understanding where you have risk
  - Helping outline the story of the trial
  - Tracking trends and events which may lead to inspection questions or findings
    - End of study is typically too late to identify and remediate issues, but you need to conduct due diligence to determine impact on the overall health of the study
    - How will you respond to questions during the inspection
  - Allows you to address questions about risk and what was done to mitigate it.
  - Goes to oversight of areas that have risk and why
  - Develop a strategy for addressing gaps and identified issues

CAPA Tips

Root Cause (RC)

Regulators do not accept ‘Human error’ or ‘People’ as a Root Cause.

Use the following categories to structure an RC statement:

- Environment
- Inadequate Process
- Lack of Process
- Machine / Equipment
- Materials
- Non-Adherence to Process
- Other

Corrective Action / Preventative Action (CAPA) Plan

Corrective Action (CA) Fixes the Past

Preventative Action (PA) Fixes the Future

- Matches the RC
- Retraining is rarely a sufficient PA and may not even be an acceptable PA, except where RC is Non-adherence to process

Response

If you receive a finding:

Response may not be needed (only brief acknowledgement). Use chronological approach to challenge a finding or explain the investigations into the Root Cause.

- Shared findings should include a Root Cause with Corrective or Preventative Actions for each party.
- Corrective or Preventative Actions may not **both** be applicable, unless you are challenging the finding.

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Get Organized and Foster Accountability

- Specific actions, assignments and timelines = accountability

Action / Activity	Owner(s)	Due	Status / ddmmmyyyy
Action 1	**Insert Name**	**Insert Date**	**Requested ddmmmyyyy**
Action 2	**Insert Name**	**Insert Date**	**Complete ddmmmyyyy**
Action 3	**Insert Name**	**Insert Date**	**In Progress ddmmmyyyy**

- How do you support sites during inspections?
  - Sponsor availability during inspection
  - Sponsor supports inspection readiness
  - No sponsor support provided – CRO expected to support
  - I don’t know how/if we support sites during inspections

~Poll Question~

Remote Inspection Considerations

- Will a collaborative site be required to share documents in real time?
- Availability of staff considering when inspection activities will take place.
- Timing of provision of documents if inspector can't locate a document.
- TMF Map and Storyboards increasingly important to explain.

Let's Recap...

- Make a plan and get others involved
  - Check your documentation and data
    - Has everything been filed correctly?
    - Can you access all the necessary systems?
    - Can you grant access to an inspector?
    - Have a back-up plan for access incase of system issues.
  - Storyboards
    - Is everyone on board with what happened throughout the trial?
    - How are you going to explain the gaps or anomalies that you are aware of?
  - CAPA's
    - Did you open any CAPA's?
    - Have you addressed/closed the CAPA's?
  - Be proactive!
    - Ongoing oversight, completeness reviews, TMF health checks

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Thank You!