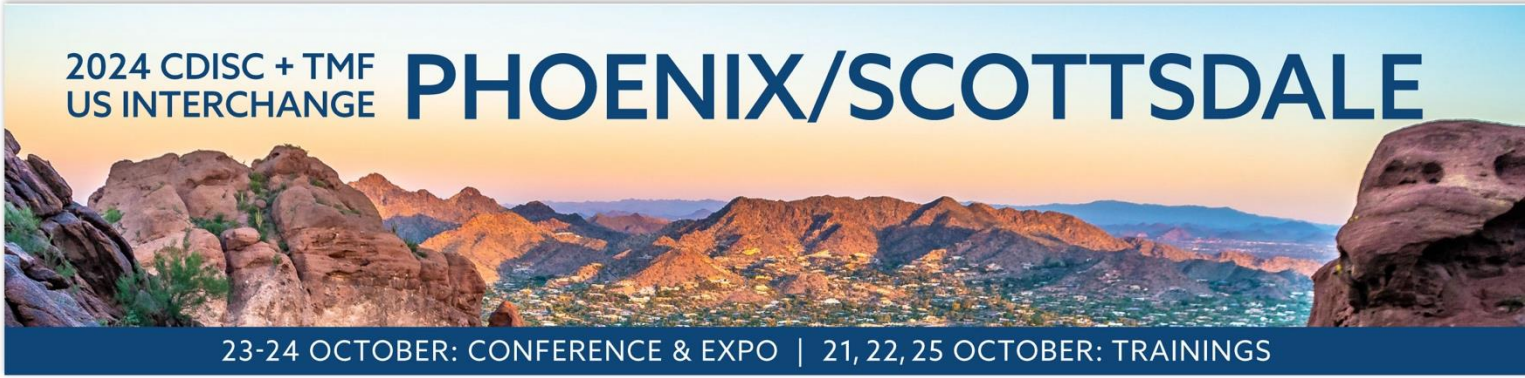

How to use the TMF Index as an Auditing Tool

Presented by Pam Dellea-Giltner, President PDG Clinical Consulting LLC.

Meet the Speaker

Pam Dellea-Giltner

Title: President

Organization: PDG Clinical Consulting LLC.

Pam Dellea-Giltner started her involvement in Clinical Research in 1991 working in pharma in various positions including Clinical Quality Auditing, Phase IV Clinical Research, Health Outcomes Research, and Medical Affairs in several therapeutic areas. She held positions in both small and large CRO's then decided to become an independent consultant in 2015. Clinical Quality Auditing has become her focus with experience in multiple areas. In addition to conducting training presentations at SQA Quality College and Global meetings, she is vice chair of the Quality Assurance Consulting Specialty (QACS) section along with being an active member of several SQA committees. Pam received a BS in Pharmacology, MBA in Pharmaceutical Marketing and received her RQAP-GCP certification in 2021.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The author has no real or apparent conflicts of interest to report.*

Agenda

1. Definitions / Regulations
2. Planning the Audit
3. Characteristics of the Audit
4. Auditing Techniques
5. Tips for Success
6. Questions
7. References

Definitions and Regulations

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21CFR Part § 312.58 Inspection of sponsor's records and reports

ICH E6 (R2) – Section 8.0 Essential Documents

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Planning the Audit

Planning the TMF Audit

- Having an **Audit Plan** is the key to success
- Sets the expectations for all parties for what is to be reviewed

Several types of TMF Audits

- Internal Process Audit
- Audit Trail Audit
- Document Audit

TMF Audit Plan

- Important to establish the scope of the audit between the sponsor and auditor.
- Confirm exact number of files to be reviewed i.e., Trial, Country and Site Level Files.
- Verify what is to be reviewed: Audit, QC, selected folders, selected documents.
- Identify the breath and depth of the documentation to be reviewed
- Request for study specific documents
- Timelines for completion and write up of the audit

Characteristics of the TMF Audit

Characteristics of the Audit

The TMF Reference Model *should* provide a wealth of information on the what, when, and where documents are to be filed:

What?

- Core – if a record exists, it must be filed in the TMF
- Recommended – record does not need to exist, but if created or collected, it should be filed in the TMF.

When?

Milestones

- First country approval, Site Live/Open for enrollment, Close out visit

Where?

Filed into which location:

- Trial, Country, Site

Characteristics of the Audit

Missing Documents

- Example – there were 5 versions of the protocol, the expectation would be 5 sponsor signed protocols in the Trial Folders, 5 IRB approvals for each of the versions in the IRB approval folders, 5 signed Protocol Signature page and possibly 5 ICF master versions.

Duplication of Documents

- Multiple copies of the same document in the same file or the same document filed across several different folders.

Document and Page Legibility

- Are all the pages within a document present, legible and complete.

Missing Signatures

- Reviewing documents that require PI/Sponsor signatures.

Naming Conventions

- The TMF plan should outline the conventions for naming documents.

Characteristics of the Audit

Qualification Records

- Cross check PI/Sub I qualifications with FDA Form1572

Study – Specific Training Records

- Training records for all study staff or only selected staff?

Laboratory Documentation

- Central laboratory(ies) documentation present: (Trial or Country Level folders) and Local Labs (Site Level Folders)?

Study Management

- Are all the site documents filed as per the TMF Reference Model?

Monitoring

- Are all the monitoring documents filed?

Auditing Techniques

Auditing Techniques

- Access and Training on the TMF system
- How to review the files in a logical way
- Note taking during the audit
- Documenting observations

Access and Training

- Plan to take all training before the start of the audit
- May need to complete system training in order to get access to the system
- Ensure you know how to navigate within the system
- Request a live training with the TMF Coordinator

How to Review the TMF in a Logical Way

- Sponsor or company SOP may dictate the information to be captured
- Use the TMF Reference Model excel spreadsheet
- Filter columns for the pertinent information
- Add columns for Audit Notes, Empty Folders and Audit Observations
- Notes should be detailed enough to be able to cross check documents
- Have any sponsor listings of expected documents available for reference

Select Required Artifacts	Zone		Section		Artifact #			Sub-artifacts			File Name
Selected Artifacts (X or NO)	Zone #	Zone Name	Section #	Section Name	Artifact #	Artifact name	Alternate names (artifact also commonly known as)	Sub-artifacts (Yes Or No)	Sub-artifacts (examples of document types different from the artifact provided, overwrite with your company-specific records)	Artifacts/ Sub-Artifacts	Current File Artifact/ Sub-Artifact Name (Organization)
X	01	Trial Management	01.01	Trial Oversight	01.01.01	Trial Master File Plan	Records Management Plan Central File Maintenance Plan Filing instructions Filing and archive plan	Yes		Trial Master File Plan	Trial Master File Plan
X	01	Trial Management	01.01	Trial Oversight	01.01.02	Trial Management Plan	Project Management Plan Clinical Development Plan	Yes		Trial Management Plan	Trial Management Plan
X	01	Trial Management	01.01	Trial Oversight	01.01.03	Quality Plan		Yes		Quality Plan	Quality Plan
X	01	Trial Management	01.01	Trial Oversight	01.01.03			Yes	Quality Report	Quality Report	Quality Report
X	01	Trial Management	01.01	Trial Oversight	01.01.04	List of SOPs Current During Trial		Yes		List of SOPs Current During Trial	List of SOPs Current During Trial
X	01	Trial Management	01.01	Trial Oversight	01.01.04			Yes	SOP Deviations	SOP Deviations	SOP Deviations
X	01	Trial Management	01.01	Trial Oversight	01.01.05	Operational Procedure Manual	Study Reference Manual Work Instruction Manual of Procedures	No		Operational Procedure Manual	Operational Procedure Manual
X	01	Trial Management	01.01	Trial Oversight	01.01.06	Recruitment Plan		No		Recruitment Plan	Recruitment Plan
X	01	Trial Management	01.01	Trial Oversight	01.01.07	Communication Plan		No		Communication Plan	Communication Plan
X	01	Trial Management	01.01	Trial Oversight	01.01.08	Monitoring Plan		No		Monitoring Plan	Monitoring Plan
X	01	Trial Management	01.01	Trial Oversight	01.01.09	Medical Monitoring Plan		No		Medical Monitoring Plan	Medical Monitoring Plan
X	01	Trial Management	01.01	Trial Oversight	01.01.11	Debarment Statement	Restricted Party Lists	No		Debarment Statement	Debarment Statement
X	01	Trial Management	01.01	Trial Oversight	01.01.13	Investigator Newsletter		No		Investigator Newsletter	Investigator Newsletter
X	01	Trial Management	01.01	Trial Oversight	01.01.14	Audit Certificate		Yes		Audit Certificate	Audit Certificate
X	01	Trial Management	01.01	Trial Oversight	01.01.14			Yes	List of audits	List of audits	List of audits
X	01	Trial Management	01.01	Trial Oversight	01.01.15	Filenote Master List	Note to File Master List	No		Filenote Master List	Filenote Master List
X	01	Trial Management	01.01	Trial Oversight	01.01.16	Risk Management Plan	Risk Assessment	No		Risk Management Plan	Risk Management Plan
X	01	Trial Management	01.01	Trial Oversight	01.01.17	Vendor Management Plan		No		Vendor Management Plan	Vendor Management Plan
X	01	Trial Management	01.01	Trial Oversight	01.01.18	Roles and Responsibility Matrix	Task Ownership Matrix RACI	No		Roles and Responsibility Matrix	Roles and Responsibility Matrix
X	01	Trial Management	01.01	Trial Oversight	01.01.19	Transfer of Regulatory Obligations		No		Transfer of Regulatory Obligations	Transfer of Regulatory Obligations
X	01	Trial Management	01.01	Trial Oversight	01.01.20	Operational Oversight		Yes		Operational Oversight	Operational Oversight
X	01	Trial Management	01.02	Trial Team	01.02.01	Trial Team Details	Trial Team Members List Team Structure Team Roster	Yes		Trial Team Details	Trial Team Details
X	01	Trial Management	01.02	Trial Team	01.02.02	Trial Team Curriculum Vitae		No		Trial Team Curriculum Vitae	Trial Team Curriculum Vitae
X	01	Trial Management	01.03	Trial Committee	01.03.01	Committee Process	Committee Charter	Yes		Committee Process	Committee Process
X	01	Trial Management	01.03	Trial Committee	01.03.02	Committee Member List		No		Committee Member List	Committee Member List
X	01	Trial Management	01.03	Trial Committee	01.03.03	Committee Output		Yes		Committee Output	Committee Output

DIA (3.0)

Ready Filter Mode

100%

9:01 AM
8/31/2021

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	D	E	F	G	T	U	V	AF	AG	AH
1	Section		Artifact #		Level					
2	Section #	Section Name	Artifact #	Artifact name	Study	Country	Site	Audit Notes	Empty Folders	Audit Observations
234	05.01	Site Selection	05.01.01	Site Contact Details			X			
235	05.01	Site Selection	05.01.02	Confidentiality Agreement			X			
236	05.01	Site Selection	05.01.03	Feasibility Documentation	X		X			
238	05.01	Site Selection	05.01.04	Pre Trial Monitoring Report			X			
239	05.01	Site Selection	05.01.04				X			
240	05.01	Site Selection	05.01.04				X			
241	05.01	Site Selection	05.01.05	Sites Evaluated but not Selected	X					
242	05.02	Site Set-up	05.02.01	Acceptance of Investigator Brochure			X			
243	05.02	Site Set-up	05.02.02	Protocol Signature Page			X			
244	05.02	Site Set-up	05.02.03	Protocol Amendment Signature Page			X			
542										
543										

Audit Observations

- Format may vary on how audit observations are captured.
- Capturing a link to the exact folder where the observation was seen

Ob #	Section Number	Section Name	Artifact #	Artifact Name	Audit Observation	Response
1						
2						

	D	E	F	G	T	U	V
1	Section		Artifact #		Level		
2	Section #	Section Name	Artifact #	Artifact name	Study	Country	Site
234	05.01	Site Selection	05.01.01	Site Contact Details			X
235	05.01	Site Selection	05.01.02	Confidentiality Agreement			X
236	05.01	Site Selection	05.01.03	Feasibility Documentation	X		X
238	05.01	Site Selection	05.01.04	Pre Trial Monitoring Report			X
239	05.01	Site Selection	05.01.04				X
240	05.01	Site Selection	05.01.04				X
241	05.01	Site Selection	05.01.05	Sites Evaluated but not Selected	X		
242	05.02	Site Set-up	05.02.01	Acceptance of Investigator Brochure			X
243	05.02	Site Set-up	05.02.02	Protocol Signature Page			X
244	05.02	Site Set-up	05.02.03	Protocol Amendment Signature Page			X
542							
543							

Audit Observations

Ob #	Section Number	Section Name	Artifact #	Artifact Name	Audit Observation	Response
1	05.01	Site Selection	05.01.04	Pre-Trial Monitoring Report		
2						

Example of Audit Notes

	D	E	F	G	V	AF	AG	AH
1	Section		Artifact #		Level			
2	Section #	Section Name	Artifact #	Artifact name	Site	Audit Notes	Empty Folders	Audit Observations
234	05.01	Site Selection	05.01.01	Site Contact Details	X	Present in folder		
235	05.01	Site Selection	05.01.02	Confidentiality Agreement	X	CDA - 15Dec2019		Document is corrupt and can not be opened
236	05.01	Site Selection	05.01.03	Feasibility Documentation	X	Questionniaire 15Nov2019		
238	05.01	Site Selection	05.01.04	Pre Trial Monitoring Report	X	Missing	X	No pretrial monitoring report in folder
240	05.02	Site Set-up	05.02.01	Acceptance of Investigator Brochure	X	V1 15Dec19, V3 15Nov20,		No IB V2 in file
241	05.02	Site Set-up	05.02.02	Protocol Signature Page	X	Original 05Jan2020		Protocol Signature page is blank, no PI signature
242	05.02	Site Set-up	05.02.03	Protocol Amendment Signature Page	X	V1 06Mar2020		
540								

Ob #	Section Number	Section Name	Artifact #	Artifact Name	Audit Observation	Response
1	05.01	Site Selection	05.01.02	Confidentiality Agreement	Document is corrupt and can not be opened	
2	05.01	Site Selection	05.01.04	Pre-Trial Monitoring Report	Folder is empty	
3	05.02.01	Site Set Up	05.02.01	Acceptance of Investigator Brochure	No IB V2 dated 15Jun2020 in file	
4	05.02.02	Site Set Up	05.02.02	Protocol Signature Page	Protocol signature on original dated 05Jan2020 is blank.	

Audit Summary with Audit Observations

- Audit Report to summarize all of audit observations
- Group/summarize findings and assign criticality
- Attach all audit observations (Trial, County, Site level)

- Conclusion Statement – Is the TMF Inspectable?

Tips for Success

Tips for Success

- Ensure finalized Audit Plan is clear to all parties before starting
- Request all relevant sponsor documents to be provided before starting the audit
- Ensure understanding of the Reference Model utilized
- Obtain training or a live demonstration for the eTMF system
- Ensure you are using a method of capturing audit observations that works for you
- If there are big issues across several files, it may be time for a conversation with the sponsor/client before you keep going
- Ask for clarification if needed!!

Q & A

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Thank You!

References

- FDA 21 CFR Part §312.58: Inspection of sponsor's records and reports
- E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6 (R1); Guidance for Industry – [ICH E6R2] – Section 8.0 Essential Documents
- FDA Compliance Program for Bioresearch Monitoring (#7348.810)
- Trial Master File Reference Model: CDISC TMF Reference Model https://www.cdisc.org/tmf
  - TMF Reference Model – User Guide, Implementation Guide, Reference Model, Plan Template