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AGENDA

Introduction
Welcome
What is a Trial Master File (TMF)

International Council for Harmonization (ICH)
Good Clinical Practice (GCP)(R2)
Section 8 Essential Documents

Trial Master File Reference Model
Drug Information Association (DIA)
2009

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INTRODUCTION

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- 10 Volunteers (FAQ)
- 17 Volunteers (Master File)

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WHAT SHOULD YOU KNOW ABOUT THE TRIAL MASTER FILE:

a refresher for paper or electronic

Georgetown University | Howard University
MedStar Health Research Institute | Oak Ridge National Laboratory | Washington DC Veterans Affairs Medical Center

Trial Master File (TMF)

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Site Master File (SMF)

Who has access?

Ten (10) Quick Facts

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1. What is a Trial Master File (TMS)?

Collection of documentation that allows the conduct of the clinical trial, the integrity of data, and the compliance of the trial with GCP. Documentation should be sufficient to adequately reconstruct trial activities.

2. Is a TMF always required?

Yes. The TMF forms the basis for an inspection to confirm compliance with regulatory requirements. The sponsor Trial Master File (TMF) and the investigator Site Master File (SMF) are regarded as comprising the entire TMF.

3. Can the sponsor TMF and investigator SMF be combined?

It is essential to segregate the master files that are held by the sponsor of the trial from those of the investigator. This requirement is due to subject confidentiality. For example, the sponsor must not have documents such as a signed informed consent.

4. How should the TMF be organized?

The organization of a sponsor file can become complex when the trial is multi-country or multi-center. The recommended approach is global, country, and investigator site. Documents are stored in reverse chronological order with the newest documents placed in the front of each section.

5. Is an TMF SOP and standard indices required?

The use of a formal procedure and a standard indexing system when sponsoring several trials is recommended as it facilitates compliance, audits, and inspections.

Ten (10) Quick Facts

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6. How should the TMF be stored?

The TMF is a repository of all information necessary to reconstruct a clinical trial and its security and maintenance is important. Who should access the TMF to add or remove documents is also important.

7. What is essential documentation?

- Documentation that enables both the conduct of the clinical trial and the quality of the data.
- Documentation that shows whether the trial is, or has been, conducted in accordance with the Good Clinical Practice (GCP) directive.

8. Can management of the TMF be sub-contracted by the sponsor when using a CRO?

Yes, the management of the TMF can be sub-contracted. The complexity of the TMF is increased by the use of a CRO. Therefore, it is suggested that there is some type of plan to clarify the management of the TMF. The sponsor must still maintain an adequate level of oversight.

9. Should the TMF be kept up to date?

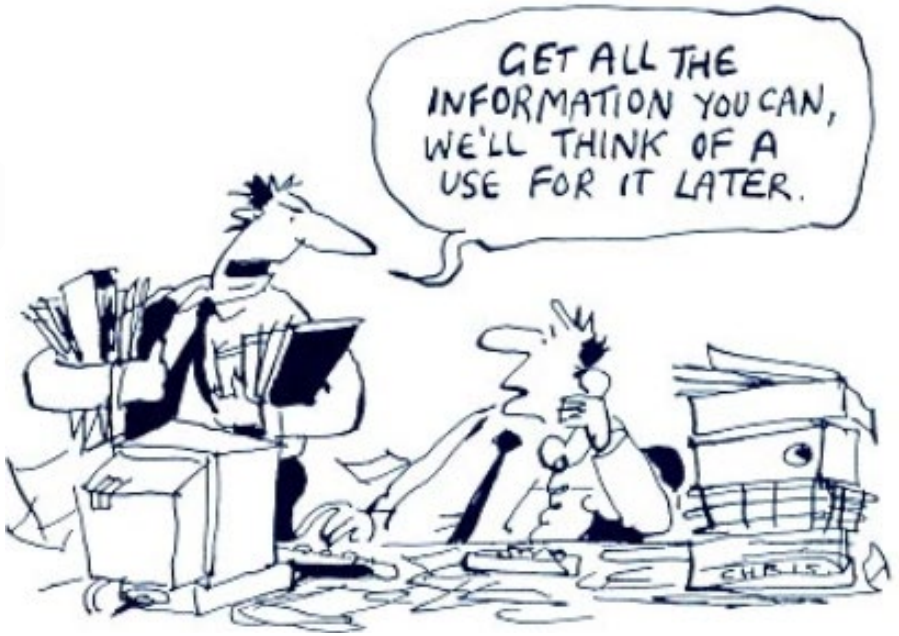
The TMF must be kept up to date, with documents placed in the TMF in a timely manner. This assists in the successful management of a trial by the investigator, sponsor, and monitor.

10. How to deal with correspondence?

Correspondence is an important component when reconstructing the trial conduct. Only relevant correspondence that is necessary for reconstruction of key activities and decisions or that contains other significant information must be retained.

What is relevant study documentation?

1. Subject directed communication that reconstructs the activities and decisions that were carried out during the clinical trial need to be included in the TMF.
2. Documents of trivial nature and are not business critical or have little or no value as a record of compliance (e.g., email directions to a clinical site, email with potential site visit dates).
3. Budget, payment, and other contractual or financial communications should be filed separately from the regulatory binder and should not be part of the patient's legal medical record.



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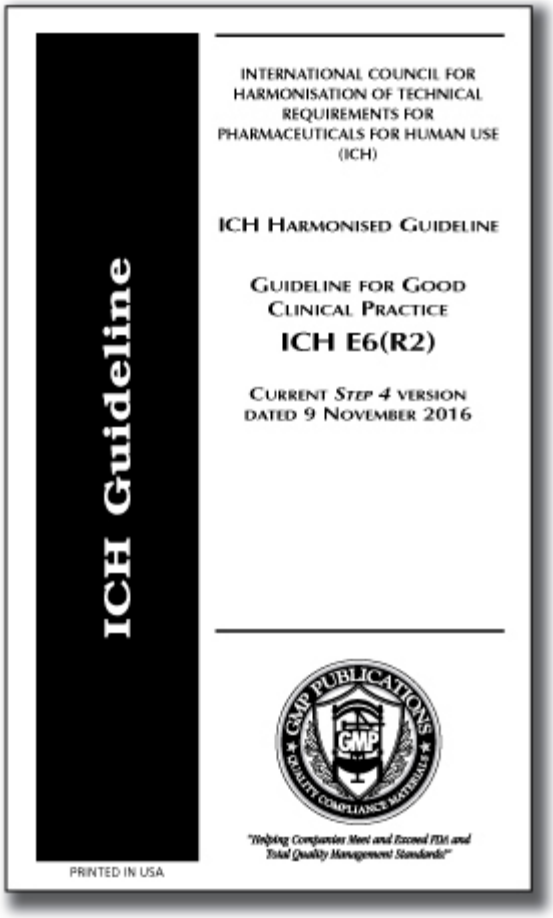
GOOD CLINICAL PRACTICE

Section 8 Essential Documentation

What is the ICH Guideline?



The ICH-GCP guidelines are used in clinical trials throughout the world with the main aim of protecting and preserving human rights.

As a founding regulatory member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

Sections of ICH E6 (GCP)

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ICH GCP Sections

- Chapter 1 - Glossary
- Chapter 2 - Principles of ICH GCP
- Chapter 3 - Institutional Review Board
- Chapter 4 - Investigator
- Chapter 5 - Sponsor
- Chapter 6 - Protocol and Amendments
- Chapter 7 - Investigator's Brochure
- Chapter 8 - Essential Documents

ICH E6 Section 8

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 Introduction
8.2 Before the Clinical Phase of the Trial Commences
8.3 During the Clinical Conduct of the Trial
8.4 After Completion or Termination of the Trial

ICH E6 Section 8

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8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.1	INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	INFORMATION GIVEN TO TRIAL SUBJECT - INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	X	X
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X

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Let's Look at Our Master Files

ICH E6 Section 8

Although ICH E6 Section 8 provides guidance regarding the minimum essential documents required to be on file during the various phases of the trial, there are many additional documents, datasets, and data that are generated during a trial that are not defined in Section 8.

This leaves an organization with the task of defining their own structure/inventory of files that they were going to maintain to comply with applicable regulatory requirements.

SOURCE: Trial Master File Reference Model User Guide Version 2

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Trial Master File

Reference Model

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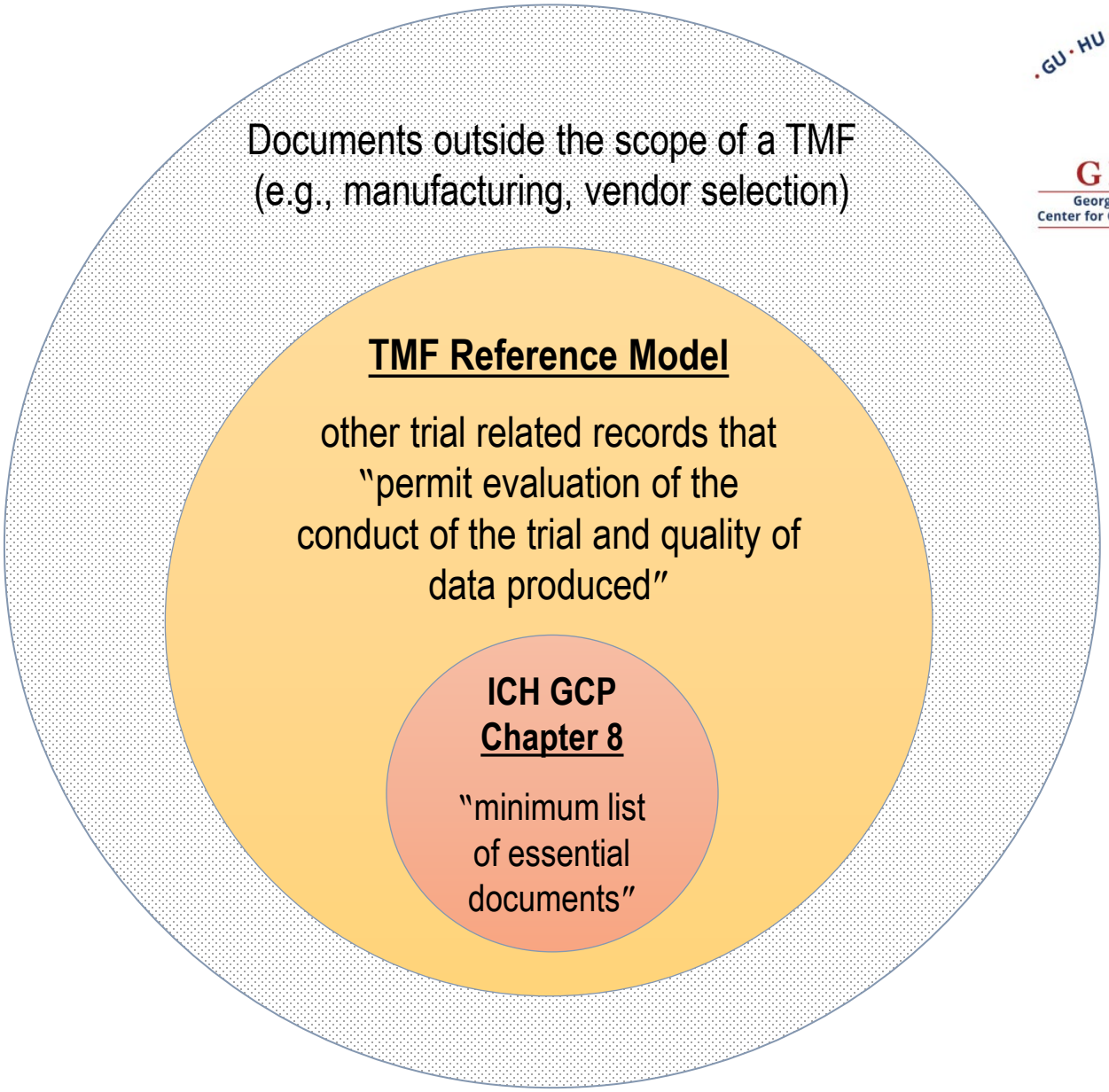
raise your hands if you are familiar with the

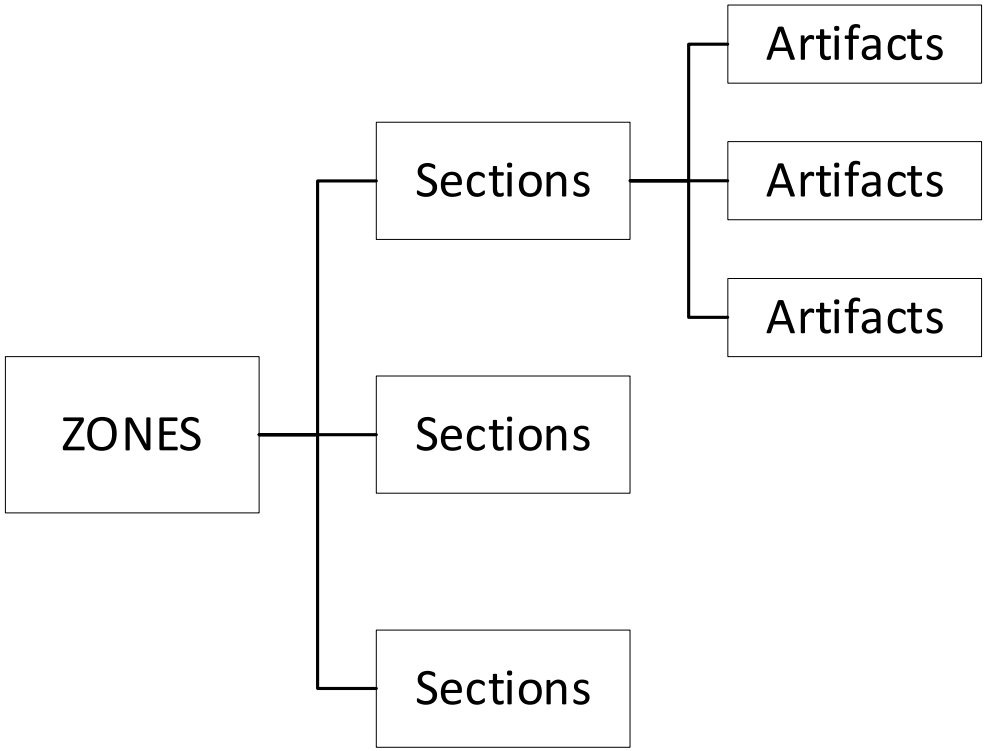
History of TMF Reference Model

2009	2010	2012	2015	2020
Reference Model Working Group was formed by the Drug Information Association (DIA). Volunteer effort with pharma, device, CROs, healthcare, academia	Version 1 TMF Reference Model was published as a single unified interpretation of the regulations and best practices	Version 2 released and includes additional details Investigator Site Files, Investigator Initiated Studies, Process-Based Metadata, and Device studies	Version 3 refined the Artifacts and Zones, introduced sub-artifact facilitation and provided an improved presentation layer	Version 3.2.0 added "recommended sub-artifacts" and features a super-set of 612 customizable sub-artifacts to replace previous sub-artifacts


Documents outside the scope of a TMF
(e.g., manufacturing, vendor selection)
TMF Reference Model
other trial related records that "permit evaluation of the conduct of the trial and quality of data produced"
ICH GCP
Chapter 8
"minimum list of essential documents"

What is the TMF Reference Model?

The TMF Reference Model is an industry-adopted reference structure for the TMF that takes the form of an index



Eleven (11) Zones

Zone 1 - Trial Management

Zone 2 - Central Trial Documents

Zone 3 - Regulatory

Zone 4 - IRB/IEC

Zone 5 - Site Management

Zone 6 - Investigation Product and Trial Supplies

Zone 7 - Safety Reporting

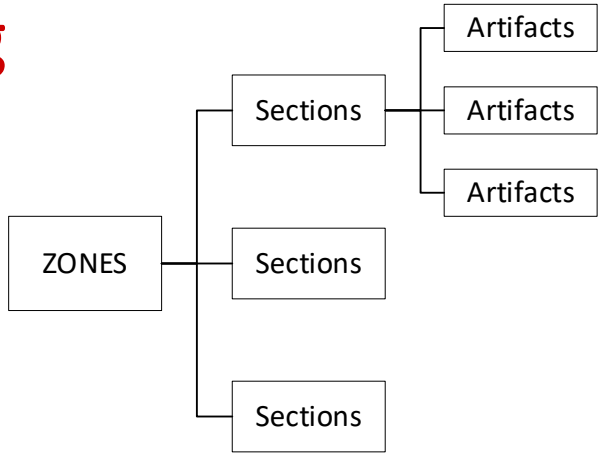
Zone 8 - Centralized and Local Testing

Zone 9 - Third Parties

Zone 10 - Data Management

Zone 11 - Statistics

TMF Numbering



2 Central Documents

2.1 Product and Trial Documentation

2.1.1 Investigator's Brochure
2.1.1 Protocol
2.1.3 Protocol Synopsis

ZONE

Section

Artifacts

TMF Reference Model in Excel

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	A	B	C	D	E	F	G	H
1	**TMF Reference Model**						TMF RM Website	**Version 3.2.1**
2								
3	**Zone**	**Zone Name**	**Section #**	**Section Name**	**Artifact**	**Artifact name**	**Definition / Purpose**	**Recommended Subartifacts - Documents/documentation recommended to be filed to the artifact.**
4	01	Trial Management	01.01	Trial Oversight	01.01.01	Trial Master File Plan	To describe how records for the trial will be managed and stored during and after the trial, including study-specific processes and documentation for archiving and destruction. To include TMF filing structure to be used. May include TMF content list, filing structure and chain of custody records. Artifact can include any evidence of plan execution including, but not limited to: plan, reports, checklists, etc.	Document Transfer Documentation Evidence of Quality Review Request to Lock TMF Trial Master File Plan Trial Master File Index Trial Master File Report

ZONE Section Artifact Definition/Purpose Sub-artifacts

TMF Reference Model in Excel

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Zone #	Zone Name	Sectic	Section Name	Artifact #	Artifact name	Sponsor Document	Investigator Document
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.01	Investigator's Brochure	X	X
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.02	Protocol	X	X
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.03	Protocol Synopsis	X	NO
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.04	Protocol Amendment	X	X
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.05	Financial Disclosure Summary	X	NO

TMF Reference Model in Excel

Zone #	Zone Name	Section #	Section Name	Artifact #	Artifact name	TMF Level: Trial Level Document	TMF Level: Country/ Region Level Docume	TMF Level: Site Level Documen
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.01	Investigator's Brochure	X	X	
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.02	Protocol	X	X	X
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.03	Protocol Synopsis	X	X	
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.04	Protocol Amendment	X	X	X
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.05	Financial Disclosure Summary	X	X	X

Glossary

Item	Description
Artifact	Records or documents which one would expect to find in a TMF, at both Sponsor and Investigator site. It is important to note that artifact "progeny records" such as approval/signature pages, amended records or translation documentation are not typically called out uniquely as they belong filed with their related artifact.
Recommended Sub-artifact	A fully-customisable list of company-specific records that an organization might expect to file under a given artifact
Paper TMF / eTMF	Paper TMF usually presented according to Trial, Country and Site levels. Electronic TMFs denote level using metadata. For single country, combine Trial and Country.
Core	If created or collected, the artifact must be in the TMF as dictated by either the ICH Guidelines, regulations, or by consensus of the TMF Reference Model group.
Recommended	The artifact does not have to be produced, but if it is created or collected, it is required to be in the TMF if not housed elsewhere.
Drafts	Drafts to be excluded unless specifically submitted for approval
Central and Local Testing	Centralized and local testing zone is intended for all specialty testing vendors, on a global study level, a country level or a site level and should be modified based on the testing utilized.
ISF	X refers to an artifact that is always part of the ISF; NO refers to one that usually is not - please note there may be some targeted exceptions based on local criteria (i.e. countries).
IIS	For IIS, M is Mandatory, D is dependant upon the type of study being undertaken, R is recommended

Zone	Definition of Zone Contents
01 - Trial Management	Records related to the general design, management and oversight of the study; includes information about the trial team; project management and tracking; committees and charters, and training.
02 - Central Trial Documents	Includes the IB, Protocol, and Amendments, Sample CRF, ICF, and the CSR, as well as any ancillary documents directly related to the above. Capture study documents that are related to the protocol, key subject documentation such as the ICF, questionnaire, diary, participation card and clinical study reports including pharmacokinetics in accordance with applicable regulatory standards
03 - Regulatory	Records related to Regulatory Submissions and Approvals (to/from Health Authorities), Regulatory Filing and Registration Information, and Regulatory Notifications specific to the clinical trial.
04 - IRB / IEC and other	Official communications and exchanges with IRB's/IECs, including central, national, regional and local. Includes records related to IRB/IEC

... | Ver 3.2.0 Markup | Model Overview | Milestones_Events & Description | **Instructions and Glossary** | Computer System Validation

Filter

1. Filter by Zone Number/Name, Section Number/Name, or Artifact Number/Name narrow down your view to only those selected zones, sections or artifacts.

Zone #	Zone Name	Section #	Section Name	Artifact #	Artifact name
01	Trial Management	01.01	Trial Oversight	01.01.01	Trial Master File Plan

Artifact State

Determine artifact state upfront

- Paper or electronic
- Location

2 Central Documents

2.1 Product and Trial Documentation

2.1.1 Investigator's Brochure → Electronic Box
2.1.1 Protocol → Electronic Box
2.1.3 Protocol Synopsis → Electronic Box

-or-

2.1.1 Investigator's Brochure → Paper Binder, MWHC, Suite 3-1822
2.1.1 Protocol → Paper Binder, MWHC, Suite 3-1822
2.1.3 Protocol Synopsis → Paper Binder, MWHC, Suite 3-1822

Summary

- The Trial/Site Master file refers to a repository of documents that collectively can be used by monitors, auditors, sponsors and inspectors to demonstrate that a clinical trial has been conducted in compliance with Good Clinical Practice (GCP) and the approved protocol.

- The Trial/Site Master file is a requirement under Good Clinical Practice (GCP).

- The Trial/Site Master File permits the study to be independently recreated from study records.

TMF Reference Model

https://tmfrefmodel.com/

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Thank You!