MANAGEMENT OF ELECTRONIC TRIAL MASTER FILES AND ESSENTIAL DOCUMENTS IN PHARMA AND CROS

26 August 2016
Combined CRCS – CRP Forum
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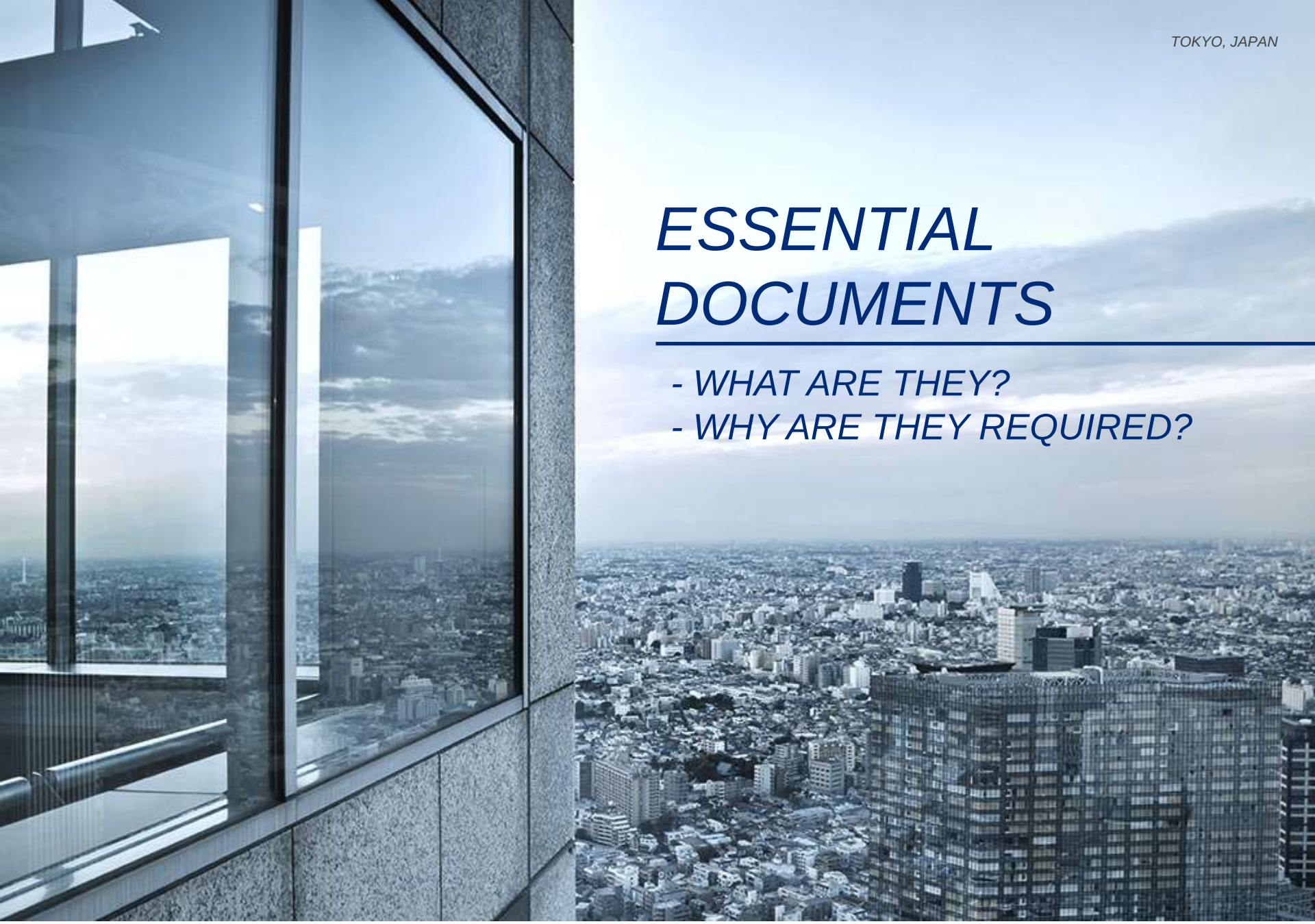
AGENDA

- **Essential Documents**
- What are they?
- Why are they required?

- **Trial Master Files**
- What are they?
- It’s evolution to electronic TMF
- Electronic TMF
- Benefits of eTMF

- **Management of Electronic Trial Master Files (eTMF)**
- eTMF Requirements
- Typical eTMF File Structure
- Process Flow
- Maintenance
- Delivery to client



ESSENTIAL DOCUMENTS

- WHAT ARE THEY?
- WHY ARE THEY REQUIRED?

ESSENTIAL DOCUMENTS – WHAT ARE THEY?

- **The GCP definition of essential documents states that essential documents—either individually or collectively—are intended to permit the evaluation of the conduct of a study and of the quality of the data produced.**

- **GCP guidelines categorize essential documents according to the three trial stages during which the documents are normally generated:**

- Before a trial starts (GCP 8.2)

- During a trial (GCP 8.3)

- At trial termination or completion (GCP 8.4)

ESSENTIAL DOCUMENTS – BEFORE A TRIAL STARTS (GCP 8.2)

Title of Document	Investigator/ Institution	Sponsor
8.2.1 Investigator's Brochure	X	X
8.2.2 Signed protocol and amendments, if any, and sample Case Report Form (CRF)	X	X
8.2.3 Information given to trial subject - informed consent form , any other written information, advertisement for subject recruitment (if used)	X	X
8.2.4 Financial aspects of the trial	X	X
8.2.5 Insurance statement	X	X
8.2.6 Signed agreement between involved parties	X	X
8.2.7 Dated, documented approval of the MCRC and/or EC (as appropriate)	X	X
8.2.8 EC composition	X	X (Where required)
8.2.9 EC, MCRC and the Ministry of Health authorisation / approval / notification of protocol (where required)	X (Where required)	X (Where required)
8.2.10 Curriculum vitae and/or other relevant documents, evidencing qualifications of investigator(s) and sub-investigator(s)	X	X

ESSENTIAL DOCUMENTS – BEFORE A TRIAL STARTS (GCP 8.2)

Title of Document	Investigator/ Institution	Sponsor
8.2.11 Normal value(s) / range(s) for medical / laboratory / technical procedure(s) and / or test(s) included in the protocol	X	X
8.2.12 Medical / laboratory / technical procedures / tests	X (Where required)	X
8.2.13 Sample of label(s) attached to investigational product container(s)	Not Required	X
8.2.14 Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	X	X
8.2.15 Shipping records for investigational product(s) and trial-related materials	X	X
8.2.16 Certificate(s) of Analysis of investigational product(s) shipped	Not Required	X
8.2.17 Decoding procedures for blinded trials	X	X (third party, e.g. pharmacy if applicable)
8.2.18 Master randomisation list	Not Required	X (third party if applicable)
8.2.19 Pre-trial monitoring report	Not Required	X
8.2.20 Trial initiation monitoring report	X	X

ESSENTIAL DOCUMENTS – DURING A TRIAL (GCP 8.3)

Title of Document	Investigator/ Institution	Sponsor
8.3.1 Investigator's Brochure updates	X	X
8.3.2 Any revision to: - protocol / amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	X	X
8.3.3 Dated, documented approval of the MCRC and/or the EC (as appropriate) of the following: - protocol amendment(s) - revision(s) of: - informed consent form - any other written information to be provided to the subject - advertisement for subject recruitment (if used) - any other documents given approval - continuing review of trial (where required)	X	X
8.3.4 EC, MCRC and the Ministry of Health authorisations / approvals / notifications where required for: - protocol amendment(s) and other documents	X (where required)	X
8.3.5 Curriculum vitae for new investigator(s) and/or sub-investigator(s)	X	X
8.3.6 Updates to normal value(s) / range(s) for medical / laboratory / technical procedure(s) / test(s) included in the protocol	X	X
8.3.7 Updates of medical / laboratory / technical procedures / tests	X (where required)	X

ESSENTIAL DOCUMENTS – DURING A TRIAL (GCP 8.3)

Title of Document	Investigator/ Institution	Sponsor
8.3.8 Documentation of investigational product(s) and trial-related materials shipment	X	X
8.3.9 Certificate(s) of analysis for new batches of investigational products	Not Required	X
8.3.10 Monitoring visit reports	Not Required	X
8.3.11 Relevant communications other than site visits - letters - meeting notes - notes of telephone calls	X	X
8.3.12 Signed informed consent forms	X	Not Allowed
8.3.13 Source documents	X	Not Allowed
8.3.14 Signed, dated and completed Case Report Forms (CRF)	X (copy)	X (original)
8.3.15 Documentation of CRF corrections	X (copy)	X (original)
8.3.16 Notification by originating investigator to sponsor of serious adverse events and related reports	X	X

ESSENTIAL DOCUMENTS – DURING A TRIAL (GCP 8.3)

Title of Document	Investigator/ Institution	Sponsor
8.3.17 Notification by sponsor and/or investigator, where applicable, to the Ministry of Health and MCRC and EC(s) of unexpected serious adverse drug reactions and of other safety information	X (where required)	X
8.3.18 Notification by sponsor to investigators of safety information	X	X
8.3.19 Interim or annual reports to the MCRC, the EC and the Ministry of Health	X	X (where required)
8.3.20 Subject screening log	X	X (where required)
8.3.21 Subject identification code list	X	Not Allowed
8.3.22 Subject enrolment log	X	Not Required
8.3.23 Investigational products accountability at the site	X	X
8.3.24 Signature sheet	X	X
8.3.25 Record of retained body fluids / tissue samples (if any	X	X

ESSENTIAL DOCUMENTS – AT TRIAL TERMINATION OR COMPLETION (GCP 8.4)

Title of Document	Investigator/ Institution	Sponsor
8.4.1 Investigational product(s) accountability at site	X	X
8.4.2 Documentation of investigational product destruction	X (if destroyed at site)	X
8.4.3 Completed subject identification code list	X	Not Allowed
8.4.4 Audit certificate (if available)	Not Required	X
8.4.5 Final trial close-out monitoring report	Not Required	X
8.4.6 Treatment allocation and decoding documentation	Not Required	X
8.4.7 Final report by investigator to the MCRC and EC where required, and where applicable, to the Ministry of Health	X	Not Mandatory
8.4.8 Clinical study report	X (if applicable)	X

ESSENTIAL DOCUMENTS – WHY ARE THEY REQUIRED?

During all stages of a trial, essential documents:

- **Demonstrate investigator compliance (and that of sponsors and monitors, when applicable) with all applicable regulatory requirements**
- **Assist in the successful management of the trial**
- **Provide a detailed record of actions to assist in the monitoring or audit of the trial.**

The GCP guidelines also describe the purpose of each essential document and whether it should be filed in the investigator's files, the sponsor's files, or both.

Please note that GCP guidelines allow for some documents to be combined as long as the individual elements of the stipulated documents are identifiable.

TRIAL MASTER FILES (TMF)

- WHAT ARE THEY?
- IT'S EVOLUTION TO ELECTRONIC TMF
- ELECTRONIC TMF
- BENEFITS OF ETMF

TRIAL MASTER FILES – WHAT ARE THEY?

- To comply with regulatory requirements surrounding clinical trials, every organization involved in regulated clinical trials must maintain and store certain 'essential documents' related to the clinical trial

- Depending on the regulatory jurisdiction, this information is typically stored in the Trial Master Files (TMFs).

- According to GCP, TMFs should be established at the beginning of the trial, both at the investigator / institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator / institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

- The TMF has historically been composed primarily of paper documents, images and media captured centrally in physical file cabinets.

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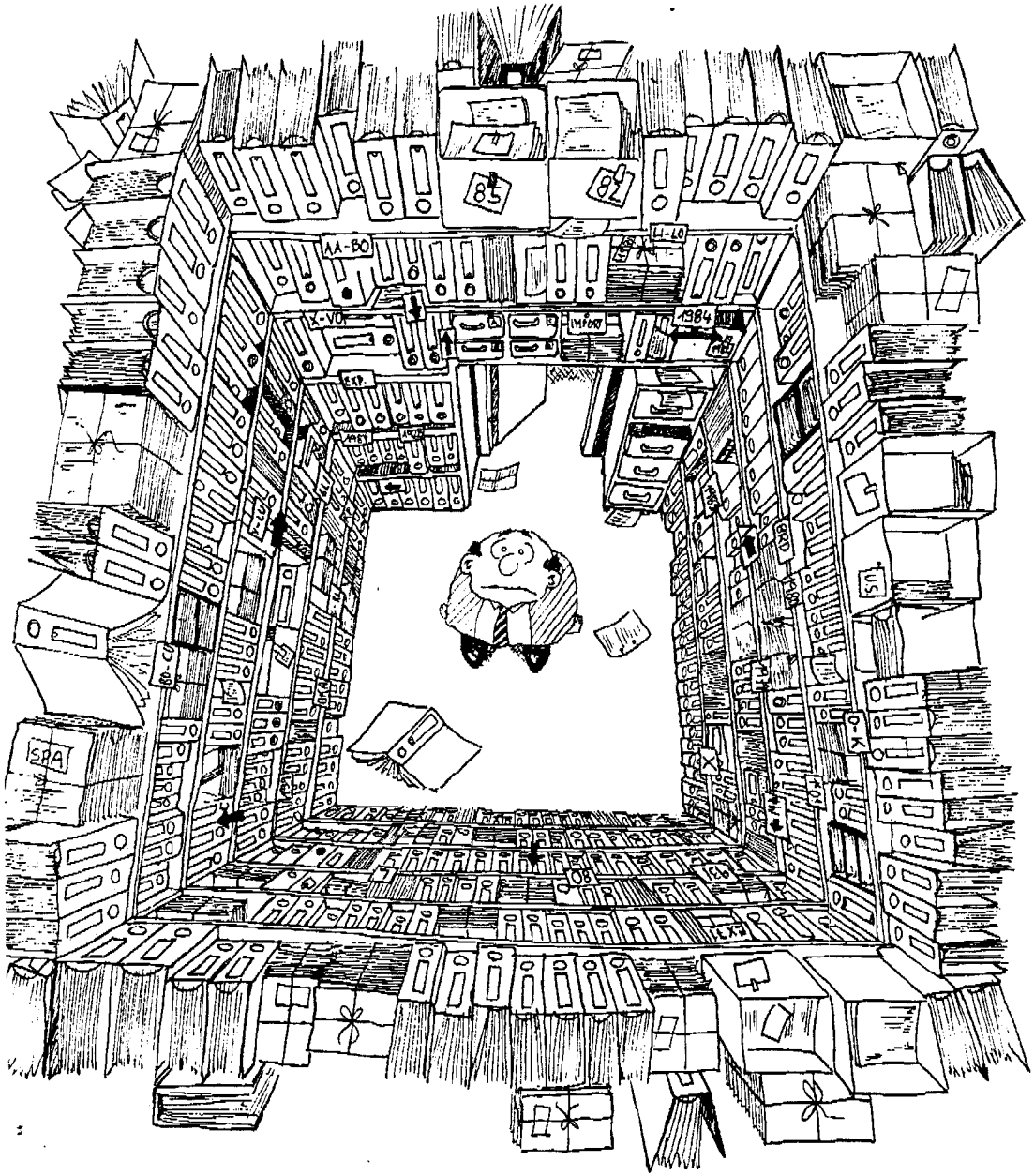

"No, you can't have my old file cabinet. I'm using it as a paperweight for all the stuff I'm too lazy to file!"

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EVOLUTION OF TRIAL MASTER FILES

In order to lower costs and to expedite the clinical trials approval processes:

- U.S. Food and Drug Administration (FDA) created regulation CFR 21 Part 11 which supports the use of electronic records, digital media and digital signatures in clinical trials.

As a result this regulation, US organizations involved in U.S. clinical trials can move from a paper-based TMF to an electronic TMF (eTMF), and still be in compliance with FDA regulatory policies

- European Medicines Agency (EMA) has issued policies that support the use of digital signatures in clinical trials.

- In clinical trials and healthcare, enterprises with manual paper-based systems are seeking to transition to automated electronic enterprise content management (ECM) systems to ensure higher levels of regulatory compliance for reduced business risk**.**

ELECTRONIC TRIAL MASTER FILES

- **a formalized means of organizing and storing documents, images and other digital content for pharmaceutical clinical trials that may be required for compliance with government regulatory agencies.**
- **The term eTMF encompasses strategies, methods and tools used throughout the lifecycle of the clinical trial regulated content.**
- **An eTMF system consists of software and hardware that facilitates the management of regulated clinical trial content.**

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DEFINITION OF ETMF

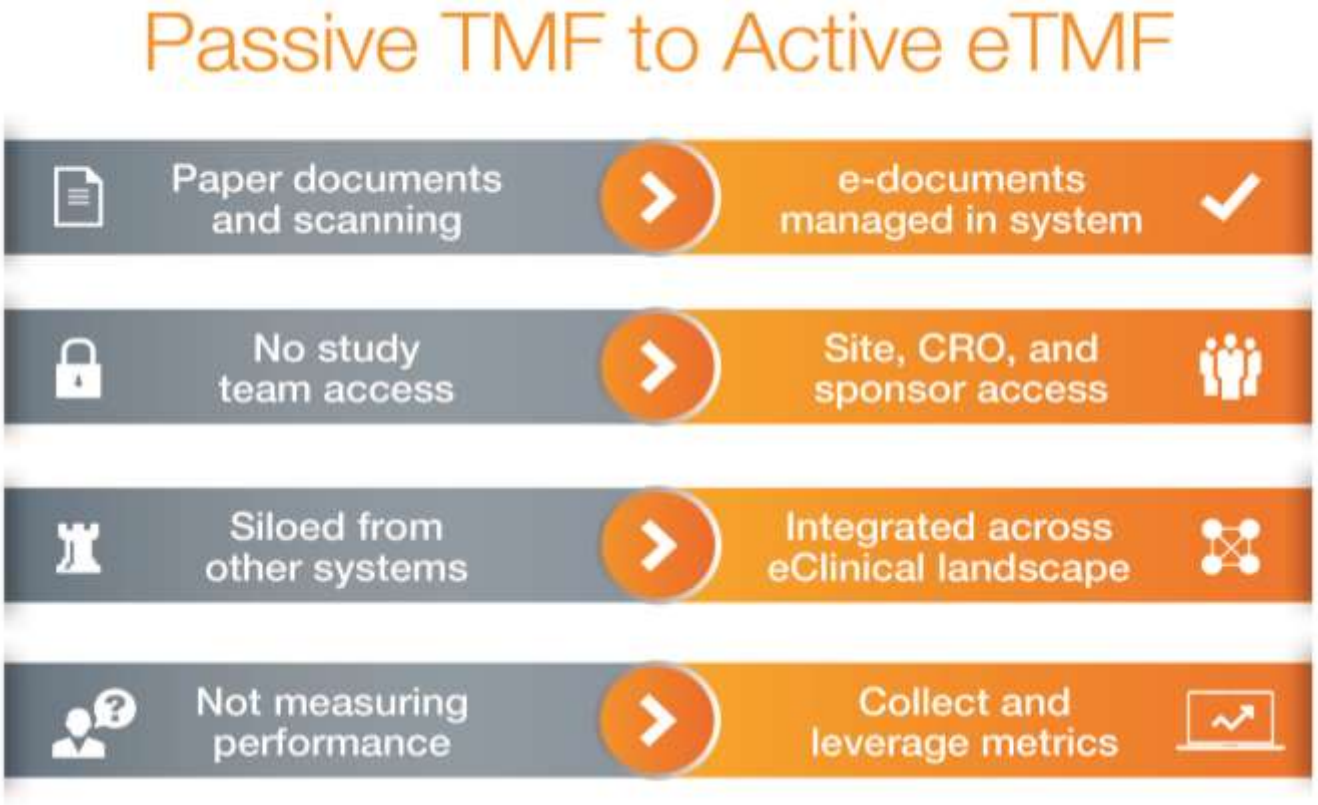
- **The definition of what comprises an eTMF is defined by the regulatory agency with jurisdiction over the clinical trial.**

- **In Europe, the EMA has recently defined an eTMF as follows: 'An eTMF can contain digital documents in their original format, potentially with digital signatures, or records that have been converted from another format, such as paper documents that have been converted to digital images, which may contain wet-ink signatures. The metadata applied to documents is recommended be formally defined to ensure consistency across all documents.'**

- **As of 29 Oct 2015, there are no formal US FDA requirement for the use of an eTMF system in a clinical trial. However, if a clinical trial elects to store trial master file 'essential documents' in electronic format, then the eTMF system used to store those files is subject to regulatory controls specified under FDA Title 21 CFR Part 11.**

BENEFITS OF ETMF

Cost savings $$$
Environmental Friendly
Real time tracking and viewing of documents
Increased TMF/SOP compliance
Reduced business risk



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"I mentioned 'Paperitis.' Apparently, that disease scares the staff."

MANAGEMENT OF ETMF

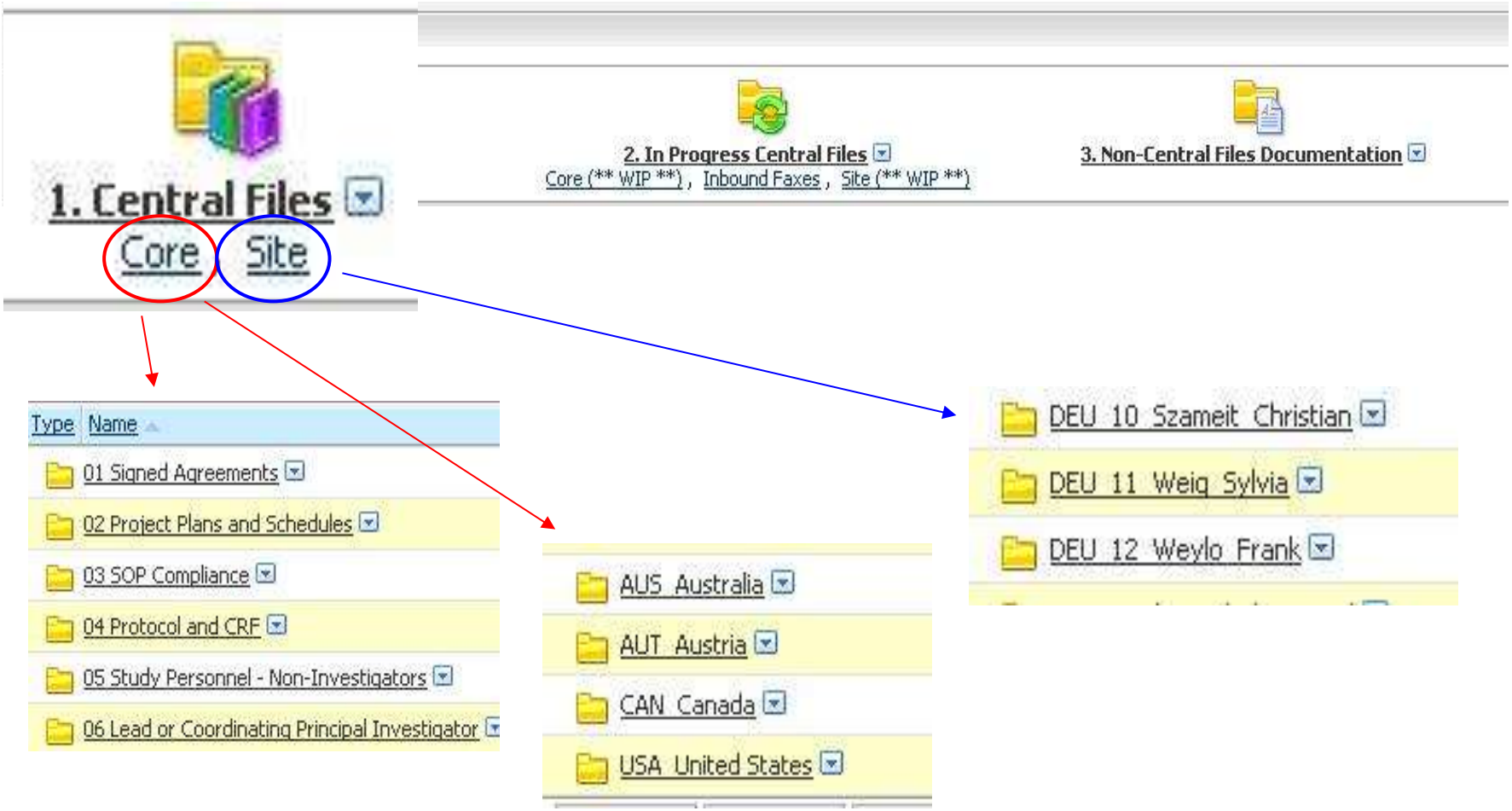
- ETMF REQUIREMENTS
- TYPICAL ETMF FILE STRUCTURE
- PROCESS FLOW
- MAINTENANCE
- DELIVERY TO CLIENT

REQUIRED COMPONENTS OF AN ETMF SYSTEM

With respect to the FDA, the required components, controls and policies for an eTMF used in US based clinical trials follow US FDA CFR 21 Part 11 requirements. Systems used to store electronic records or documents are generally subject to the following controls and requirements:

- Limiting system access to authorized individuals
- Use of operational system checks
- Use of authority checks
- Use of device checks
- Determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- Establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- Appropriate controls over systems documentation
- Controls for open systems corresponding to controls for closed systems bulleted above
- Requirements related to electronic signatures
- Record Audit trail (timestamping of records)
- Record export to a portable format such as PDF or XML
- Validation of the system

TYPICAL ETMF FILE STRUCTURE



ELECTRONIC TRIAL MASTER FILING – PROCESS FLOW
A SET OF INTEGRATED APPLICATIONS AND WORKFLOWS

Investigator Site

Collection, scanning and uploading of essential documents by Pharma/ CRO Representatives

Pharma/ CRO Representatives QC/ Review /Finalize documents

Pharma/ CRO Representatives

Document e-Signing

Electronic Trial Master Files

Export

- HTML
- XML
- PDF
- Audit Trail

Finalized Site Reports/ Visit follow-up letters

Clinical Trial Management System

MAINTENANCE OF ETMF

- Diligent eTMF maintenance drives compliance and quality of essential documents collection.

- Maintenance of eTMF are typically governed by **Guidance/Manuals** drawn up by Pharma/CROs which are in line with their SOPs.

Included in these documents are typically the following:

- TMF structure
- Folders, Sub-folders
- Description of required contents in each folder
- Naming convention of TMF files

- Handing of Wet ink Documents
- Location of TMF wet ink hub
- How documents should be sent, its frequency
- Labelling instructions

- Quality Checks
- Requirements
- Frequency

MAINTENANCE OF ETMF

- **Periodic Quality checks by designated QC Checker to cover:**
  - Inventory QC
    - To verify the presence of expected documents
    - To opened and review documents as part of the verification.
  - Basic QC
    - Checks to confirm document completeness, consistency, accuracy and that project specific quality standards are met.

- **Ongoing Quality Check process by designated Project Team members to cover:**
  - QC follow-up activities – deficiencies noted by QC checker will be made known to document owner
  - ‘QC done’ attribute available in eTMF, ready for move to CF?
  - Verification Report – Confirming key documents are in place

MAINTENANCE OF ETMF

The **features/ interfaces of eTMF support** Pharma/CROs to ensure compliance to maintenance requirements

- **eTMF reports are utilized to obtain real-time inventory of the TMF**

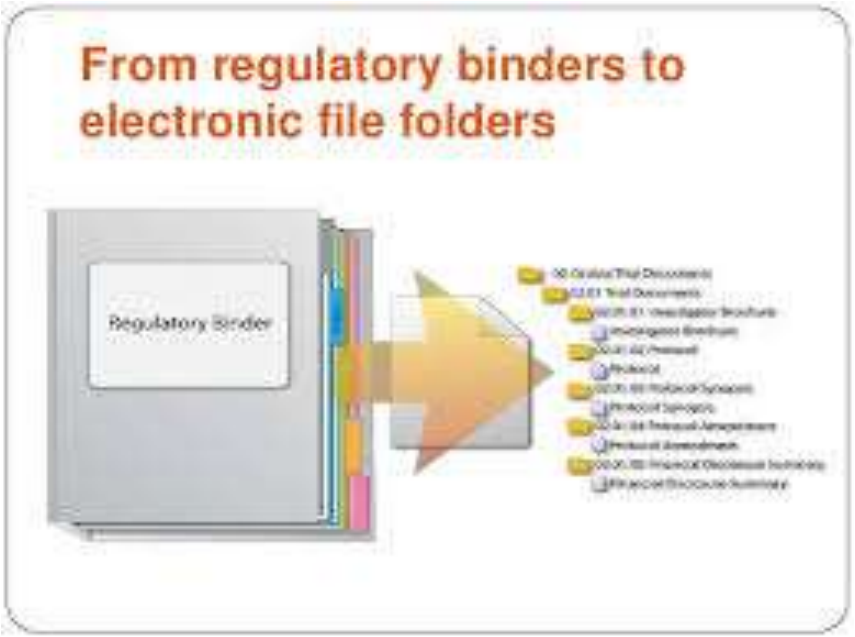
  Reports can be run on selected sections of eTMF: Central Files, Work in Progress (WIP), Core, Core Country, Site Level, all sites in one country etc. for:

  - Total number of document in CF or WIP
  - List of documents filled
  - List of empty sections

- **CTMS interfaces and automatic migration of specific documents allows Timely submission to TMF**
  - Automatic uploads of Visit reports, Contact reports finalized in CTMS
  - Site-Start-up portals where documents are uploaded for review/QC, once approval obtained, documents are uploaded into eTMF. For example, Site personnel documents, Ethics approvals, ICFs, Confidentiality Agreement, etc.
  - Actual Monitoring Visit date entered in CTMS, Visit entered as completed. CTMS-eTMF interface tracks compliance of eTMF maintenance - MV Confirmation/FU letter uploaded?

- **Consistent file naming convention used on all electronic documents**
  - Facilitates document transfer to sponsor specific folder structure

DELIVERY TO CLIENT - BOTH ELECTRONIC AND WET INK FILES



- Most essential documents are stored electronically in eTMF
- Depending on Pharma/CRO's SOP, some wet-ink originals as specified in SOP Index will be kept as paper documents.
- At the end of the study, should the study be managed by a CRO, all eTMF electronic files will be exported along with the complete audit trail for archiving by the Pharma company. Wet-ink originals will also be provided to the Pharma company.

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