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# How to Apply the Golden Rule of Research to Your Trial Master File


Based on a
web panel discussion
presented by
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# Introduction

The Trial Master File (TMF) is the foundation of every clinical trial, and a strong foundation is essential to the overall health and stability of any clinical trial. The Golden Rule in clinical research (which also applies to the TMF) is,

**"If it's not written down, it didn't happen."**

# The ICH GCP

The International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

Since its inception in 1990, ICH has gradually evolved to respond to the increasingly global face of drug development. ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner.

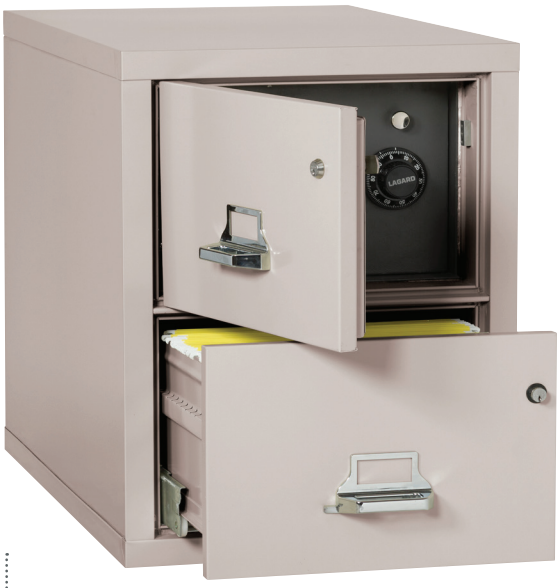
**ICH GCP (Good Clinical Practice) is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected.**

**The Trial Master File (TMF) is one of the most important deliverables of a clinical trial because it is the basis for inspection.** ICH GCP Release 2 states that Essential Documents are those documents that individually and collectively permit the evaluation and the conduct of a trial and the

quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. If you do not have the documentation, it did not happen.

# Good Document Practice

## Good document practice, abbreviated GDP or GDocP, describes the standards by which documents are created and maintained.



ICH GCP (R2) requires that documents meet ALCOA criteria. They must be:

- **Attributable** — It should be clear who has documented the data
- **Legible** — They should be readable with identifiable signatures
- **Contemporaneous** — The information should be documented in the correct timeframe along with the flow of events. If a clinical observation cannot be documented when made, chronology should be recorded. Acceptable amount of delay should be defined and justified
- **Original** — Documents should be the first copy made by the appropriate person. If not the original, it should be an exact copy
- **Accurate** — Consistent and faithful representation of facts

These simple principles should be part of your data lifecycle, GDP and data integrity initiatives.

Documents and data should also be:

- **Enduring**
- **Available and Accessible**
- **Complete**
- **Consistent**
- **Credible**
- **Corroborated**

ICH provides additional guidance on good clinical practice and good documentation practice in sections E6—1.51, 1.52 and 2.10.

- **ICH E6—1.51 Source Data** — Includes all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)
- **ICH E6—1.52 Source Documents** — Original documents, data and records
- **ICH E6—2.10** — All clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification

# Electronic Source Data

## The FDA goes into further detail with respect to good documentation practices in GCP.

In 21 CFR part 11, which is currently being updated, the FDA defines what they expect in regards to **electronic records, electronic signatures, and electronic source data** generated at the clinical trial site. The updates to 21 CFR part 11 are to ensure that adequate controls are in place to ensure the reliability and confidentiality of data, and to ensure that electronic signatures are controlled. Additionally, ICH E8 states that **electronic source data and source documentation must meet the same fundamental elements of data quality** (attributable, legible, contemporaneous, original and accurate) as are expected of paper records and must comply with all applicable statutory and regulatory requirements.

# Record Keeping and Retention

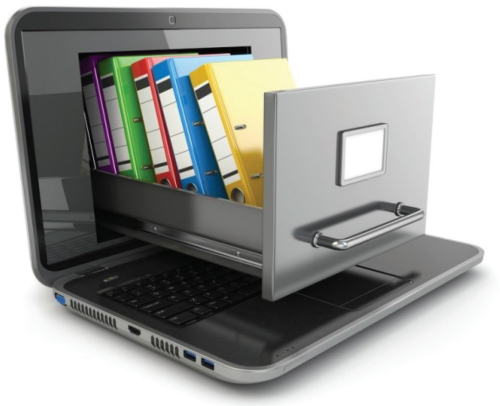
## The FDA also provides information on record keeping and retention and the inspection of sponsor records.

21 CFR 312 subpart D discusses the responsibilities of the sponsors and investigators concerning record keeping and retention. 21 CFR 58.130 subpart E discusses the conduct of non-clinical laboratory studies and describes how data are recorded and corrected. Finally, 21 CFR 812 subpart G discusses how the investigator should maintain accurate, complete and current records, again using ALCOA principles.

The EMA has similar guidelines stating that the information from clinical trials should be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified.

# Ensuring Compliance

## One of the ways to ensure TMF compliance throughout the lifecycle of a clinical trial is to build in quality by design.



That means that everything you do—your standard operating procedures, your work instructions, your job aides—are done in accordance with good clinical practices principles, ALCOA standards, and signature requirements. **Think about quality each step of the way and the result will always be a quality document.**

Secondly, train, train, train. All TMF stakeholders should receive adequate training on proper documentation practices and understand their responsibilities. **Everyone should understand documentation requirements, how to apply the ALCOA principle and the consequences of non-compliance.**

Lastly, consider signatures. Often, when documents require signatures from multiple people, each person will sign a copy

of the document and multiple copies of that document will end up in the TMF. Consider if you require that signature. **ICH only requires signatures on the following five document types:**

- **Protocols and amendments**
- **Agreements and contracts**
- **Completed consent forms**
- **Completed case report forms**
- **CRF correction signature sheet/signature log**

Additionally, the MHRA has stated in the GCP Guide that signatures on documents are recommended only where it adds value. If you are not adding value with a signature, don't require it.

# Notes to File (NTFs)

## Notes to File are widely overused and often unnecessary.

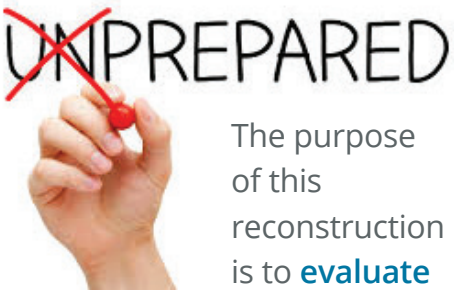
**A best practice for Notes To File is to stop writing them.** Chances are you are writing and processing too many of them and they are not adding any value to the quality of your TMF.

How can you avoid Notes To File? First, **perform ongoing content QC**. Look at the content of documents rather than just that the document is present. Identify gaps in the TMF in real-time, because correcting for discrepancies later is difficult and time-consuming. Performing ongoing content QC increases the likelihood of locating missing documentation. **Often, you do not need a Note To File; you actually require an SOP deviation.** It is important to make the judgment call and understand if a Note To File is necessary. Alternatively, is this something that needs to be included in the Decision Log?

# Inspection Readiness

## What does it mean to be inspection-ready?

It means that you are prepared for an inspector to come in and **reconstruct the clinical trial conduct via a thorough review of any and all documentation, data, and metadata** that is included as part of your TMF.




The purpose of this reconstruction is to **evaluate compliance with all the suitable legislation, regulations and with GCP.** More importantly, it allows them to confirm that your **patient rights and safety have been protected** and that the **data that you have produced in your clinical trial is reliable**.

Inspection readiness is something that should be thought about on the very first day of a clinical trial. It means that your organization and **your study team have an understanding of and are always following Good Clinical Practices and Good Document Practices**. It means following your company's established SOPs and processes, and understanding and documenting your TMF structure and any expected content.

# Metrics

## How do you measure your TMF's health so that you can control performance and eventually make the required improvements? The answer is TMF metrics.

"Measurement is the first step that leads to control and eventually to improvement. If you can't measure something, you can't understand it. If you can't understand it, you can't control it. If you can't control it, you can't improve it."

—James Harrington,
Former IBM Quality Expert

**TMF metrics are a means of monitoring and measuring your TMF health. It is important to keep in mind that TMF metrics really are not a one-size-fits-all solution.** You will see variation depending on your TMF format, such as whether you are working in a paper or electronic format. If electronic, it could depend on the system that is being used and its functionality. For instance, the metrics used for a paper TMF are often going to have to be much simpler and may not require much manual manipulation of the data.

## 3 Key Metrics for TMF Health

1. **Timeliness** — Of document filing post finalization or document finalization in an eTMF
2. **Quality** — Measure of whether document content, metadata and indexing are complete and accurate
3. **Completeness** — Assessment of whether the TMF contains all expected documents at the current point in the study

**Timeliness is a measurement of the time between when a document is finalized and when it gets filed in the TMF.** This timeframe should be minimized to ensure that you are maintaining a contemporaneous TMF. As documents are finalized, they should immediately be filed within the TMF. If you delay between finalizing the document and when it is filed, you risk having gaps which can later lead to inconclusive documentation.

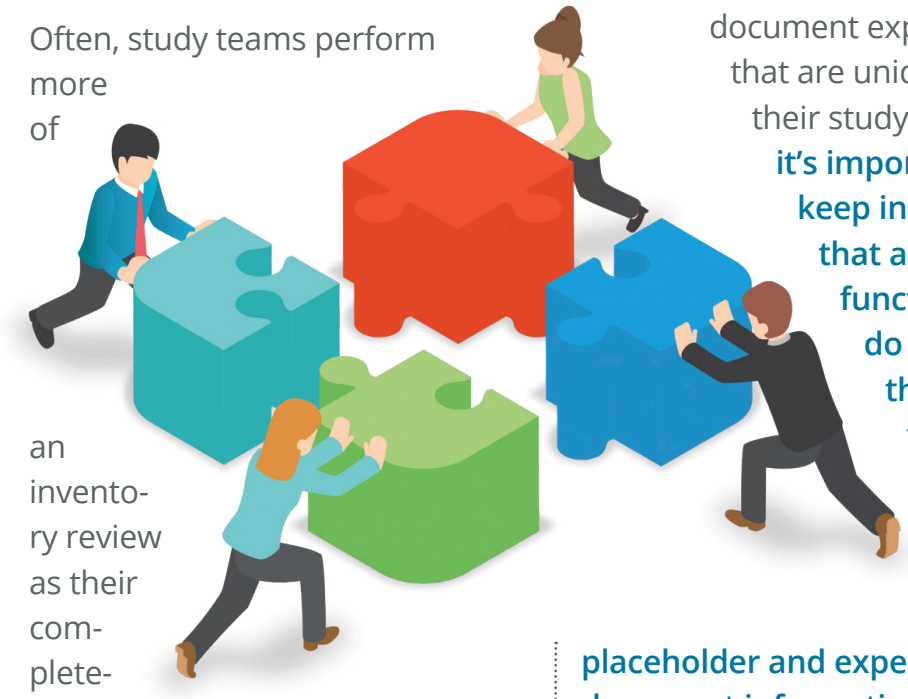
Timeliness may also be a measurement of the time between when a document is submitted to any TMF platform and when it's available and viewable in the system. This type of metric can **help to identify any bottlenecks or other issues within the TMF submission process**.

**Quality is a measurement of whether a document's content, metadata and indexing are all complete and accurate.** If the document is required to have signatures, does it have them? Is it versioned correctly? Has the metadata been applied appropriately so that the

document is named in accordance with the organization's naming conventions? Is the document in the correct location within the TMF?

Lastly, evaluate TMF completeness. This is an **assessment of whether the TMF contains all the expected documents at that current point in the study**. This metric is often the most challenging to measure because it requires an understanding and knowledge of the study events and milestones to know what documents are expected to be there at a particular point in time.

Often, study teams perform more of an inventory review as their completeness assessment, but that **can run the risk of merely looking at what's present and not what should be present**. This approach may identify some missing documentation, but miss others. For instance, if you have version one, two and four of a document then it is clear that version three is missing. However, what if versions five and six were missing? There would be no way to know you needed those additional versions.



Some eTMF platforms have developed functionality to support a completeness assessment, such as employing document placeholders, or expected document listings where teams can indicate some of those document expectations that are unique for their study. However, **it's important to keep in mind that all of these functionalities do not replace the need for study teams to keep that placeholder and expected document information up to date**. Those systems are only as good as how well they are maintained.

# Accountability

## We have established that we can use TMF metrics as a gauge of overall TMF health, but what if running those metrics exposes issues?

How do we ensure that those issues are resolved promptly? **For that, we need to ensure that there is clear accountability for all TMF tasks. It should start at your organization's SOPs and processes and with the TMF plan.** All of those documents should have clearly defined roles and responsibilities. Then, it is important to **ensure that everyone who is involved with the TMF understands their unique role and responsibilities**. There should be mandatory training on the organization's TMF processes. If you are utilizing any TMF platform, training on that system that is tailored to each user's role should also be required prior to the user being granted access to the system.

In addition, **ensure that you have clearly defined thresholds for escalation.** If you hit those thresholds, an escalation is required. It should be very clear who is responsible for responding to that escalation and also for ensuring that any issues are addressed or remediated as appropriate.

A similar approach should be taken when performing TMF QC. **Ensure that QC is tracked and any identified discrepancies are clearly documented.** Identify who is responsible for ensuring that each QC issue identified is followed through to completion and resolved.

# Summary


## The golden rule of research dictates how we should view clinical trial documentation and highlights the importance of having that documentation filed promptly to ensure continued inspection readiness.

The regulations govern proper clinical documentation. Not following GDP or GDocP will almost certainly result in inspection findings.

**Organizations should promote a quality by design approach and ensure that document creation and collection practices reflect GDP/ GDocP principles.**

Finally, organizations should ensure that **document stakeholders are accountable and clear on what their roles and responsibilities are** when it comes to TMF management.

TMF health can and certainly should be measured on an ongoing basis to ensure that any issues or trends that may be identified can be addressed in real time.

# Q&A

**Q** **If you've identified gaps or issues within your TMF, what can you do as opposed to using Note to Files?**

**A** The best way to avoid Note to Files is performing in-depth TMF quality control on an ongoing basis. A periodic thorough review of the TMF will help document owners and organizations identify TMF gaps. A best practice is performing these QCs every quarter. Once the QCs are performed, follow up and get discrepancies remediated in a timely manner. The longer you wait, the harder it is to get something resolved.

**Q** **Can documents with wet ink signatures be scanned and filed electronically to represent the original document in the eTMF?**

**A** The key is whether there's a process in place for certifying copies and originals. If your organization does have a process to create certified copies, it's certainly acceptable to scan documents with wet ink signatures and to incorporate those into your eTMF. Most organizations tend to take a more conservative approach and still retain those wet ink original documents, but there's certainly no reason they can't be placed into the eTMF. Note: Local regulations should be taken into account when making a decision about wet ink signatures; some countries may require retaining those documents.

**Q** **How do you measure timeliness when using a paper TMF?**

**A** The best way is to attach a transmittal cover sheet to all documents and capture when the document was submitted to be filed. Then, the received date can be compared with the document date to see how long it has taken between when that document was finalized and when it was actually submitted to the TMF for filing.

**Q** **How do you determine where to file documents that do not have a specific artifact?**

**A** There will always be documents that don't necessarily fit squarely within the structure and don't necessarily align with the specific artifact. It is incredibly important

that organizations using the TMF Reference Model out of the box without any customization, take the structure and make modifications to it as needed. If you have document types that you know your organization is going to generate that aren't necessarily reflected on that standard TMF Reference Model, make sure that you add them in where it makes the most sense. Then, document that on your organization's specific index so that documents that were not specifically called out on that template will be called out on your organization template, and then filed consistently by all the teams who would be using that template. Select a place that makes the most sense and ensure that there is consistency within the study teams and across all the teams within your organization.

**Q** **How do you determine document expectations for artifacts when the number of documents might not be known, for instance the number of monitoring reports you might have?**

**A** For that type of documentation, it's important to track for completeness. Keep trackers and logs of the ongoing study event. Ensure that you have an up-to-date tracker (i.e. Site Visit Log) so that you would know in real time if you looked at that log or that listing, how many reports you would expect, and as a result of that, how many confirmation letters and follow up letters must go out. We oftentimes refer to this type of information as story boarding information. It's a type of information and study history that you can use to reconstruct the trial and to determine document expectations.

**Q** **Do you have any recommendations on how to ensure reliable maintenance and archiving of the ISF?**

**A** This goes back to clearly defining roles and responsibilities and providing training to ensure that you have clearly documented expectations for all of your investigator sites and that they are trained on what document expectations. And, an ongoing QC with monitors to ensure that the ISF is being maintained appropriately and then having those conversations with your investigators about archiving (depending on the region, the archiving period may be up to 25 years).

# About the Panelists

## Sholeh Ehdaivand

### Principal Consultant and President, LMK Clinical Research

Sholeh is an internationally known TMF Subject Matter Expert with over 15 successful years of experience in the Clinical Research Industry. Her expertise and knowledge in all areas of study management and operational aspects of the clinical trial and document management processes has made her a leader and trusted expert.

Her experience includes the TMF Reference Model Subject Matter Expert, eTMF management, domestic and international pharmaceutical and biological clinical trials, clinical trial management, site selection, vendor relations, electronic document management, regulatory submissions, quality control processes and implementation and regulatory inspection preparation and participation.

## Jackie Morrill

### Director of Clinical Operations, LMK Clinical Research

Jackie Morrill is a Lean Six Sigma Green Belt certified clinical research professional with nearly a decade of experience in clinical trial coordination and process improvement within the healthcare, biotech, and pharmaceutical industries.

In recent years, her dedicated focus has been on all things Trial Master File (TMF). Her experience includes oversight of electronic TMF (eTMF) implementation, coordination of a large migration project to move 20+ studies from a paper and/or hybrid TMF to an eTMF, development of a robust metrics and training program, a complete overhaul of TMF QC processes, and extensive inspection readiness preparation for FDA, MHRA, and PDMA inspections.

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