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White Paper

Completeness, Quality and Timeliness: A Deep Dive

Introduction

Beginning in 2013 with the seminal approach developed for TMF Management by Pfizer[1], organizations managing Trial Master File have relied on the key metrics of Completeness, Quality and Timeliness in understanding the health of their TMFs. Most modern electronic Trial Master Files (eTMFs) provide reports or dashboards displaying these metrics.

However, there are no standard definitions for these metrics, and they may provide an incomplete or misleading picture of TMF health. For example, metrics may be distorted by an incomplete picture of what is needed in eTMF or when, manipulated by eTMF users, or insufficiently granular to provide actionable information.

This paper will examine the Key Performance Indicators (KPIs) of Completeness, Quality and Timeliness in more detail in order to assist organizations in improving the quality and understanding of these metrics and their roles in risk management, continuous process improvement, and compliance.

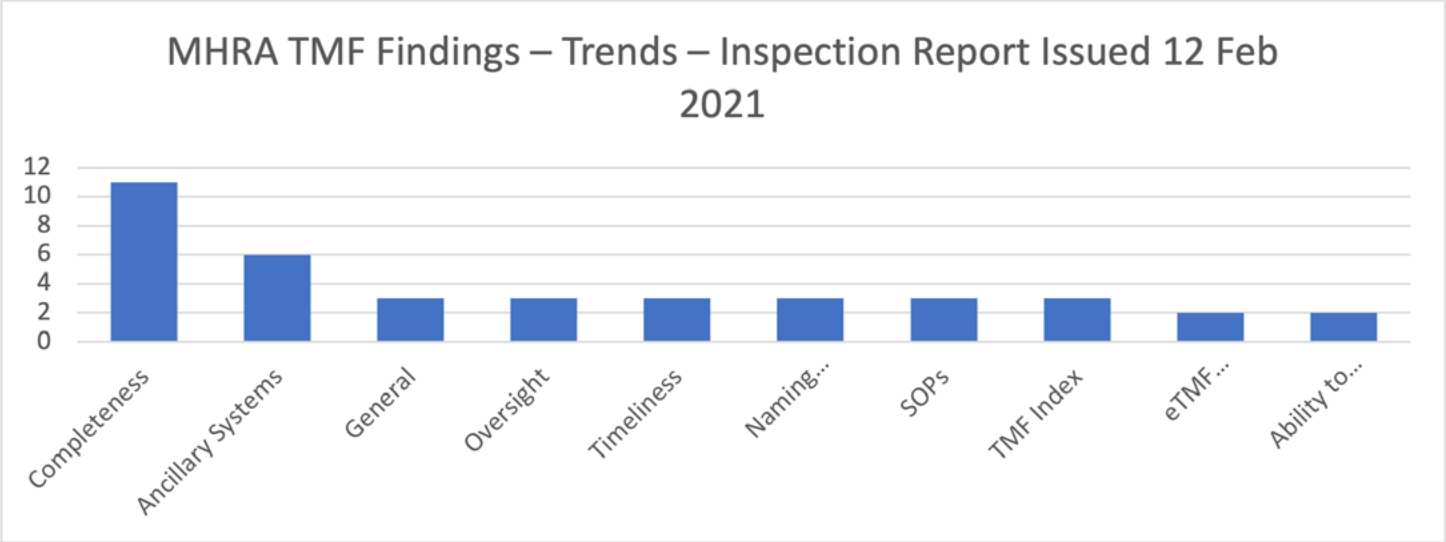
TMF Completeness

While TMF Completeness is a term often used by both health authorities and industry, no formal definition exists. Completeness as a metric is most useful as a snapshot in time during an ongoing trial, as it's expected that before the TMF is locked, all required documents will be present. That doesn't mean that the locked TMF is 100% complete, but rather that the sponsor or CRO managing the TMF is unaware that some required documents are missing.

For this paper, TMF Completeness is defined as **the percentage of documents that are due by today's date that have been received and finalized in the eTMF.**

TMF completeness is important for obvious reasons: without a complete set of documentation, a health authority cannot assess data integrity, ensure that the rights of trial subjects have been respected, or reconstruct the trial. Completeness is also important to sponsor and CRO associates who need documents to provide oversight or perform other trial activities.

Completeness is the most common Health Authority inspection finding during inspections including the Trial Master File. The UK's Medicines & Healthcare products Regulatory Agency recently published inspection findings[2] summarized in the Ennov blog article MHRA Trial Master File (TMF) GCP Inspection Findings: Trends and Takeaways.



Despite the importance of ensuring completeness, it remains a challenge for many organizations. In considering whether completeness problems are due to information being unknown or in fact being unknowable, several aspects of the TMF must be considered:

- What is the quality of TMF planning?
- Are accurate due dates assigned to expected documents?
- Are documents managed in a location or system other than the primary eTMF available?

How Good is Your Planning?

Modern eTMFs track completeness using a set of planned documents or placeholders (also called expected documents). These are generated in a variety of ways using tools such as templates and wizards that plan documents that will be needed throughout the course of the trial. However, planning is an inexact science. Common problems include:

- Planning unnecessary documents (for example, documents not needed for open label or single arm trials).
- Failing to plan documents needed for investigators, committees, labs, and other individual or institutional participants.
- Failing to plan at sufficient granularity (for example, planning only a single document when in fact a number of documents are needed). Often this is related to the consent of TMF Reference Model "sub-artifacts" which describe in more granular detail the contents of the eTMF. Not all eTMFs support this concept.
- Failing to name placeholders in such a way that it's clear to uses what is expected.

Consider the example of a trial kick-off meeting. This example shows the TMF Reference Model artifact and sub-artifacts for this meeting, and asks what is planned in the eTMF.

01.04.01 Kick-off Meeting Material Agenda, presentation materials and other documentation made available for attendees of the trial kick-off meeting, including attendance sheets.

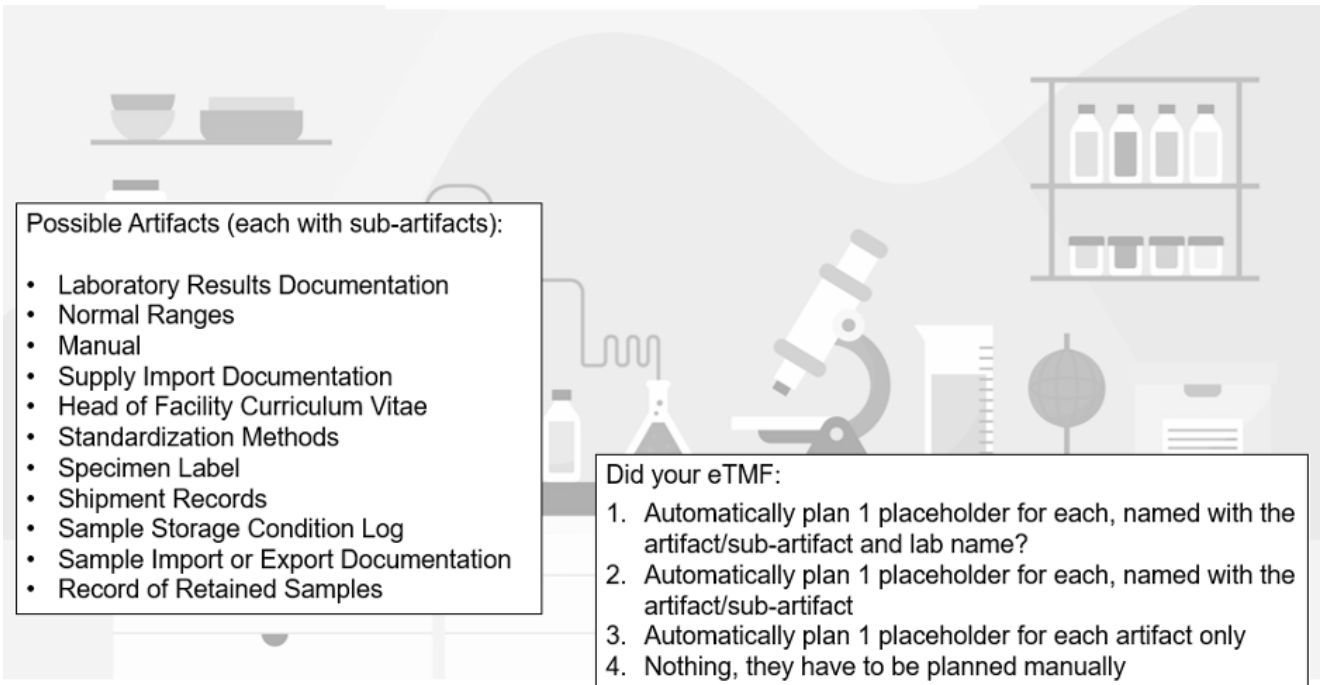
- Kick-off Meeting Agenda
- Kick-off Meeting Attendance Sheet
- Kick-off Meeting Presentation Materials
- Kick-off Meeting Minutes

Did your eTMF:

1. Automatically plan 1 placeholder for each sub-artifact, named with the sub-artifact
2. Automatically plan 4 placeholders named “Kick Off Meeting Materials”
3. Automatically plan a single placeholder for “Kick Off Meeting Materials”
4. Nothing, they have to be planned manually
5. Something else

In this case, the most accurate answer would be number 1: the best planning would create four placeholders named clearly with what was expected (artifact plus sub-artifact).

A second example envisions the planning done when a new laboratory is added some time after a trial is underway. This would generally result in the need for a set of documents.



Possible Artifacts (each with sub-artifacts):

- Laboratory Results Documentation
- Normal Ranges
- Manual
- Supply Import Documentation
- Head of Facility Curriculum Vitae
- Standardization Methods
- Specimen Label
- Shipment Records
- Sample Storage Condition Log
- Sample Import or Export Documentation
- Record of Retained Samples

Did your eTMF:

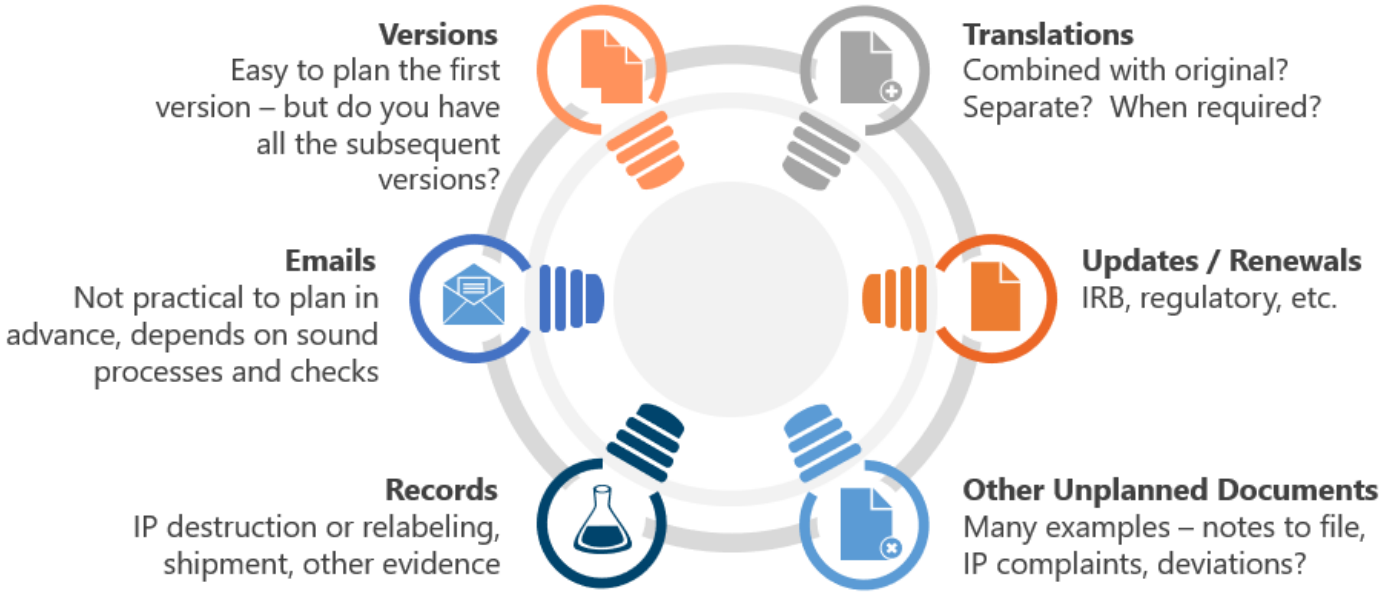
1. Automatically plan 1 placeholder for each, named with the artifact/sub-artifact and lab name?
2. Automatically plan 1 placeholder for each, named with the artifact/sub-artifact
3. Automatically plan 1 placeholder for each artifact only
4. Nothing, they have to be planned manually
5. Something else

Some systems would not automatically plan any placeholders for the new lab. In this case, a manual process must be in place to ensure that the documents are planned or collected. Again, the best outcome would be to automatically plan the entire set of documents that are needed.

Looking at these examples, it's clear that the quality of planning depends on good eTMF technology supplemented by manual processes filling in any gaps. Without this, a true picture of expected documents is not available and completeness will most likely be very inaccurate.

Unplanned Documents

Many documents in eTMF are not planned in advance. Common examples appear below.



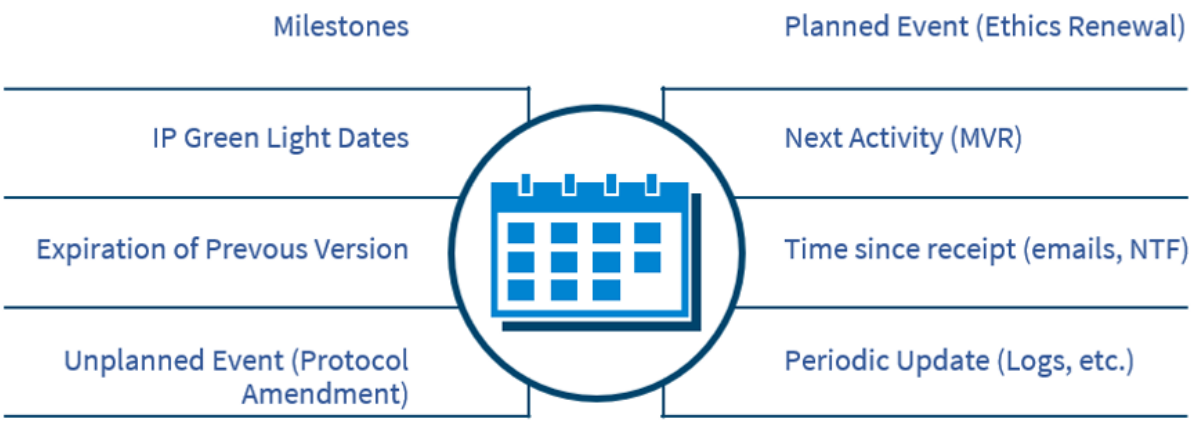
Missing unplanned documents create a significant amount of completeness problems. In the future, artificial intelligence and more automated integration of systems may help to identify and address these types of completeness problems. Currently, manual processes are needed that focus on identifying and collecting unplanned documents. Example include:

- Periodic processes where document owners or departments review documents that may not have been submitted to the eTMF (correspondence, updated versions of plans, etc.)
- High quality training that reinforce the need to submit these types of documents promptly to eTMF
- Comparisons with historical records (for example, if TMFs are typically 25% correspondence and a recent TMF is only 10%)

Sources of Due Dates

Modern eTMFs determine completeness based on what documents are due at any point in a trial (not just at the end). This is important to assessments of completeness for on an ongoing trial – for example on day 1 of a trial, the Clinical Study Report is neither missing nor overdue.

But how do you determine when documents are "due"? Due dates are often assigned based on associated study, country or site milestones. But in fact, there can be many sources for due dates. The figure below shows common examples.

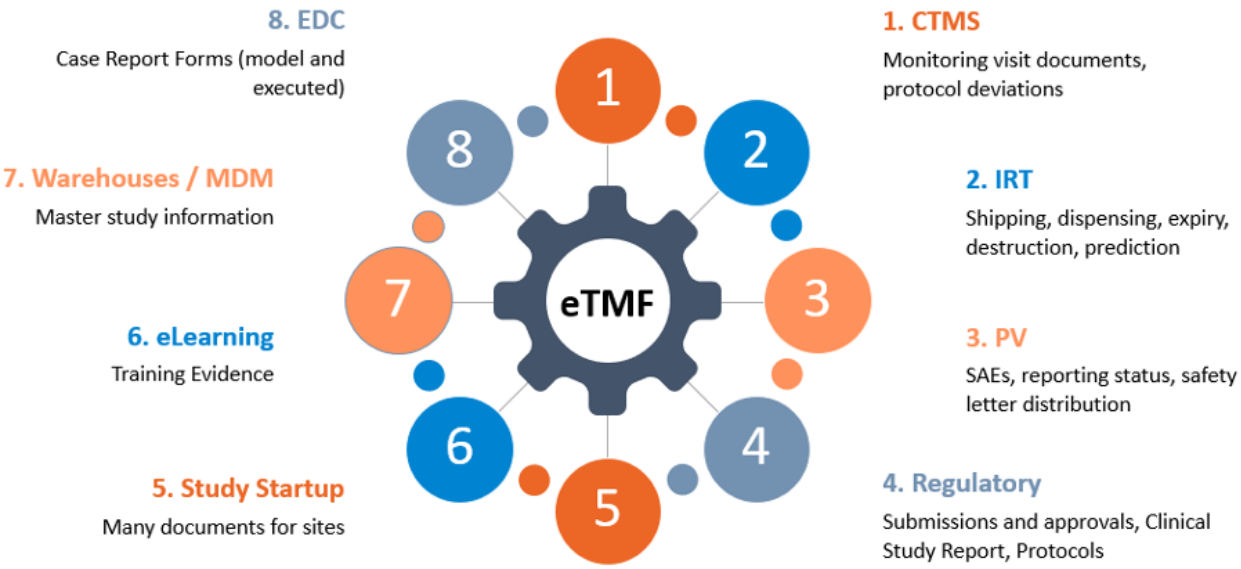


If due dates are not assigned, or are not accurate, TMF completeness estimates will also be inaccurate.

Records Stored Outside the Primary eTMF

Health Authorities do not require that all records are stored in the primary eTMF. It may not be practical to unify or integrate all electronic systems containing content that is part of the TMF. For records that are primarily data, the best solution may be to retain them in repositories where they can be treated as live data.

The figure below gives examples of TMF records that may be retained in other repositories. However, thisdoes not place these records outside the scope of a GCP inspection.



It's difficult to get a complete picture of TMF completeness when documents are distributed across multiple repositories. Best practices for addressing this issue include:

1. Documenting the system of record for every type of document (artifact) in the TMF
2. Establishing a role or department that is responsible for ensuring the completeness of each artifact
3. Documenting, following and auditing procedures for ensuring compliance

TMF Quality

TMF Quality is generally measured as the percentage of documents that are finalized without requiring rework related to issues with indexing (assigning metadata) or content. The name of this KPI is somewhat misleading, as it's assumed that all problems identified with TMF documents are ultimately resolved before documents are finalized. It also by definition only reports on issues that were identified – not the issues that were missed, which ultimately reduce TMF Quality.

Therefore, the purpose of the metric – unlike the underlying activity – is really process improvement. With information about the nature and prevalence of problems found during the Quality Control (QC) process, steps can be taken to reduce the occurrence of these problems.

Another way to look at Quality metrics is to map issues to resulting risk. In fact, the North Carolina Translational and Clinical Science Institute defines Quality as the absence of errors that matter to decision-making. (Institute, 2015) Using this definition, an organization can take a fresh look at both the Quality Control process and the resulting metrics to determine if they are actually detecting errors that matter – and ignoring errors that don't matter.

> "Quality" in clinical trials is defined as the absence of errors that matter to decision making—that is, **errors which have a meaningful impact on the safety of trial participants or credibility of the results** (and thereby the care of future patients).
>
> -- North Carolina Translational and Clinical Sciences Institute's Clinical Trials Transformation Initiative (CTTI)

Critical to Quality Factors: QC Focus

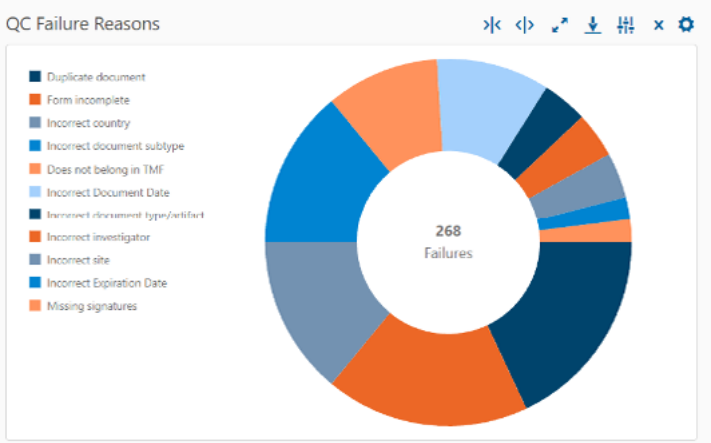
In order to map Quality Control issues or findings to risk, consider the impact of each type of issue. Some examples in the table below show the impact of common findings and also examine the effort required during QC to identify the error. To the extent possible, these issues should be avoided at the source: the document submitter.

Category	Impact	Severity	Effort (Doc Specialist)
Taxonomy – Artifact Type (Subtype)	Misfiled documents extremely difficult to find	High	Moderate
Indexing – Study/ Country/Site	Misfiled documents extremely difficult to find	High	Low
Indexing – Document Date	Difficult to reconstruct trial	Moderate	Low
Content Correctness and Completeness	Document not usable	High	Very high/ impossible
Scan Quality	Portions of document may be incomplete/difficult to read	Low	Moderate to high

Using an analysis such as this, a set of improvements can be made such as reinforcing training for submitters on ensuring documents are submission-ready, or eliminating QC checks that don't add significant value.

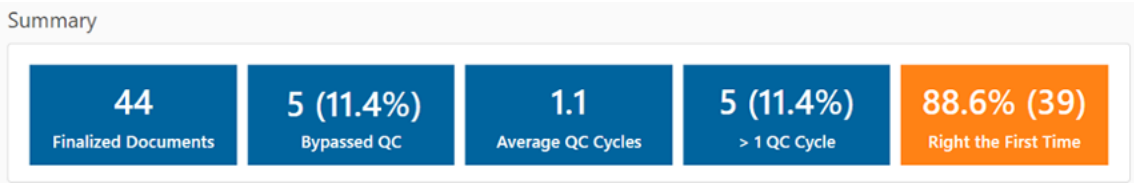
Quality Metrics

Quality metrics can provide valuable information for ongoing process improvement. Some examples include:



- **QC Failures by Category/Failure Reason.** This shows which failure reasons are the most com mon, pointing to the need for training and work instruction updates.
- **Average Number of Cycles.** This provides an indication of how often more than one rework cycle is needed, which may highlight misunderstandings or inattention to detail
- **Failures by Submitter.** This information, which should be available only to authorized users, can identify individuals who are careless or poorly trained.
- **Failures by Document Specialist.** This information can identify Document Specialists (users who perform QC) who fail an infinitely high or low number of documents, possibly indicating excessive "pickiness" in the first case or poor work quality in the second.
- **Outliers by Doc Type, Study, etc.** This can assist in identifying problematic document types (for example those often confused with others), teams with problematic leadership, and so on.

Summaries often provide a quick way to identify problems.



TMF Timeliness

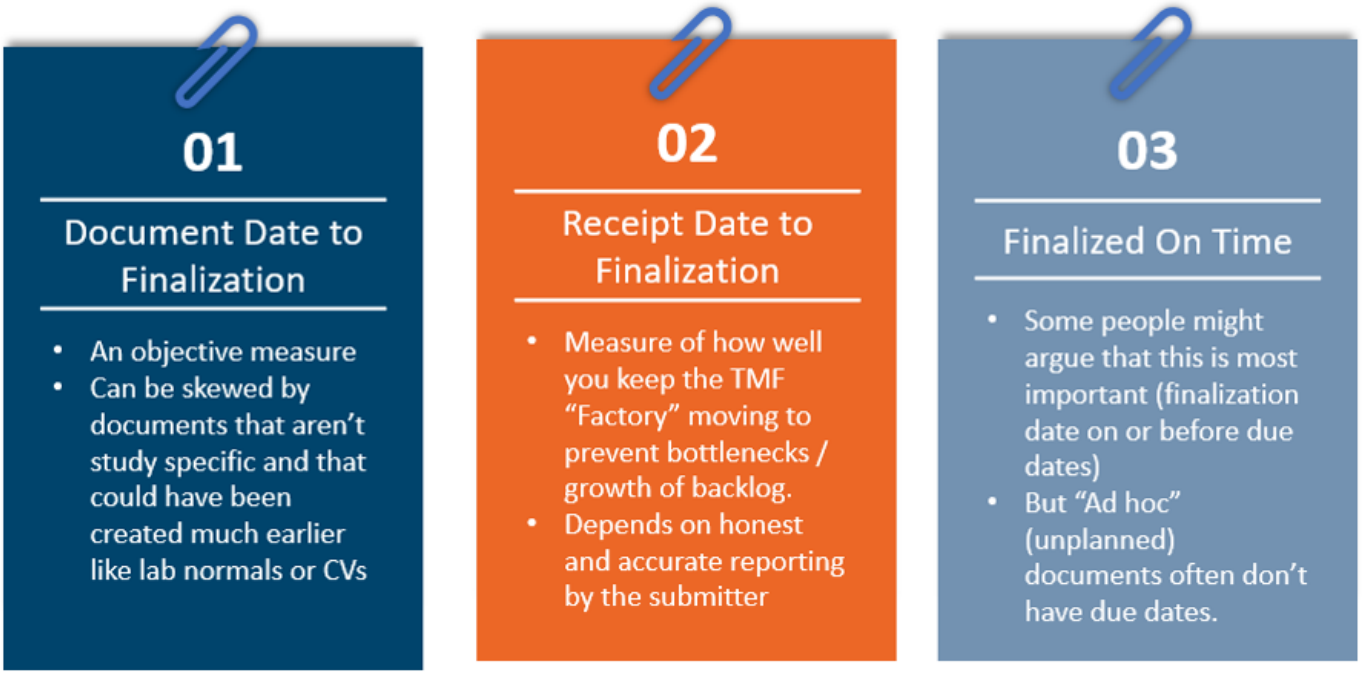
Once again, there is no single or standard definition of TMF Timeliness. MHRA Good Clinical Practices (Medicines and Healthcare products Regulatory Agency, 2012) provide some insight by emphasizing that:

> Documentation in the TMF that is ***relied upon for subsequent activities should therefore be in the TMF before these activities take place***; for example, monitoring visits rely on the information in the previous report, so the previous report should be completed and filed in the TMF prior to the next visit.
>
> -- MHRA GCP

- The TMF must be kept up to date, with documents placed in the TMF in a timely manner
- Documentation must be in place before activities that rely upon it take place
- The TMF must be kept up to date so that the organization's ability to manage and oversee the trial is not impaired.

However, there are a number of ways that timeliness of filing can be measured, each with its own advantages and disadvantages. The figure below defines the three primary ways of measuring timeliness. The following definitions apply:

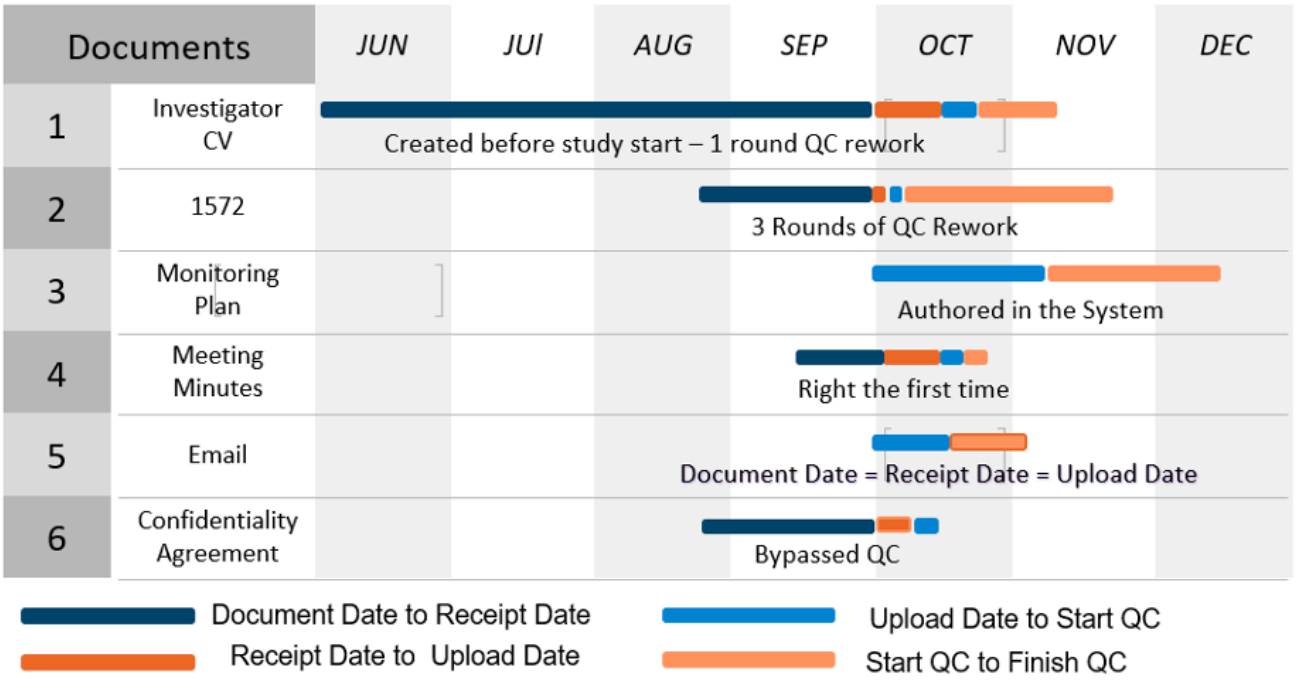
- Document Date is the key date recorded in the document content (such as an approval date, signature date or effective date)
- Receipt Date is the date a submitter received the document for upload into the eTMF



With the Document Date to Finalization and Receipt Date to Finalization methods, elapsed time can be compared to a threshold value to serve as a KPI. With the third method, a percentage of finalized on time is computed.

Timeliness Examples

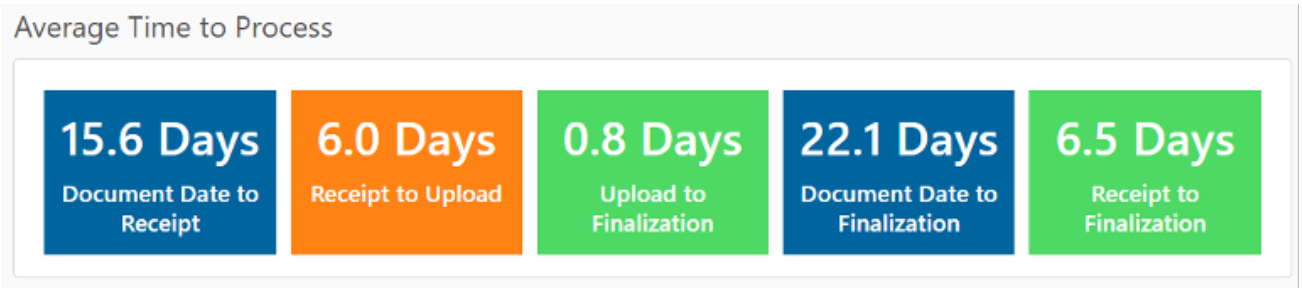
The examples below illustrate the difficulties in applying timeliness metrics across a body of TMF documents. In this example, a group of six documents, all initially available on 1 October, are examined.



- Document 1 shows that downside of measuring timeliness based on document date.
- Document 3 is an authored document and has different lifecycle stages. Should it be excluded from metrics? Measured in some other way?
- Document 5 is an email that is automatically filed in the eTMF upon being sent due to an integration. Therefore, Document Date = Receipt Date = Upload Date.
- Document 6 bypassed QC due to a risk-based sampling process, so metrics need to reflect this.

The Timeliness Toolkit

Since no measure of timeliness is perfect, so having a variety of information helps to identify risk and inform improvements. Timeliness dashboards should identify outliers, support drill down for investigation, allow KPI thresholds to be set, and allow metrics to be associated with volume (for example, if a specific document type takes 180 days from receipt to finalization but there are only two instances of that type). Some examples follow.



Top 5 Longest to Process by Artifact

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ARTIFACT	AVG DAYS RECEIPT TO FINALIZ...	NUMBER
01.01.04 List of SOPs Current During Trial	17.0 Days	8
03.01.01 Regulatory Submission	15.0 Days	25
06.04.01 IP Storage Condition Documentation	15.0 Days	122
02.01.01 Investigator's Brochure	14.0 Days	1
01.04.01 Kick-off Meeting Material	8.0 Days	1222

Beyond Outliers

Those responsible for specific artifacts or functional areas should have access to graphical or tabular data to understand how components of the process are functioning. In this example, a user can understand the time for each component of the lifecycle for each artifact in the TMF.

Average Time to Process by Artifact/Section/Zone

Artifact Section Zone

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ARTIFACT	AVG DAYS RECEIPT TO FINALIZATI...	AVG DAYS RECEIPT TO UPLO...	AVG DAYS UPLOAD TO FINALIZAT...	NUMBER OF VALUES
01.01.01 Trial Master File Plan	2.5 Days	2.2 Days	0.1 Days	11
01.01.02 Trial Management Plan	0.0 Days	0.0 Days	0.0 Days	1
01.01.04 List of SOPs Current During Trial	17.0 Days	16.1 Days	0.8 Days	8
01.02.01 Trial Team Details	3.0 Days	3.0 Days	0.0 Days	1
01.04.01 Kick-off Meeting Material	8.0 Days	7.0 Days	0.0 Days	1
02.01.01 Investigator's Brochure	14.0 Days	14.0 Days	0.0 Days	1
03.01.01 Regulatory Submission	15.0 Days	15.0 Days	0.0 Days	1

Summary

This paper has examined some of the complications behind the use of single metrics for completeness, quality and timeliness. Some issues have clear solutions, but others may require considerable investigation, analysis or process improvement to address. Some organizations may not have the resources to invest to optimize processes and data. Some guiding principles can help to achieve progress even with limited resources.

1. **TMF will never be perfect.** Focus on Critical to Quality factors, risk, and process improvement.
2. **There's no single right way to calculate or use metrics.** Make sure that the metrics you (or your system) produces actually support your objectives.
3. **Data is Power.** Having a complete set of metrics will allow you to learn about and improve your processes

4. **Avoid misunderstandings and misuse.** Insist on clarity for how each metric is gathered, analyzed and used.

5. **Examine tradeoffs.** Keep in mind that focusing on a single metric may degrade other metrics – for example, extensive focus on quality may impact timeliness or completeness.

References

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