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Increasing Quality of the TMF Through Risk Based QC

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Dawn Niccum

Title: Executive Vice President, QA & Compliance

Organization: inSeption Group

Dawn is recognized for her expertise in building TMF in a document management system from the ground up (including metrics and QC checks). She is a member of the CDISC TMF Reference Model Steering Committee and Chair of the Education Committee. She has extensive experience and strength in establishing trial master file structures and streamlined approaches to reduce risk. She has presented as a Subject Matter Expert at numerous conferences on the importance of TMF inspection readiness.

Carol Radwanski

Title: Associate Director, TMF Services

Organization: Just in Time, GCP

Carol is the Associate Director of TMF Services at Just in Time, GCP. Her 9+ years of TMF experience began with supporting Phase 1 clinical trials. Most recently her focus has been on supporting TMF activities across various portfolios and ensuring the overall health of the TMF. Her responsibilities include QC support and management, migrations, training, audit prep and assistance, staff management, and development of standardized processes.

What Is the Trial Master File (TMF)?

Records which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

ICH GCP

The TMF is the collection of records that are created and maintained throughout the course of the conduct of a study that allows for the evaluation of:

- The conduct of the clinical trial
- The integrity of the trial data
- The safety of the study participants
- The compliance of the trial with Good Clinical Practice (GCP)

What is Record Quality Check (QC)

- Process of checking and verifying that documents meet the quality criteria before they are filed. Ensures that product quality is maintained or improved.
- Records should be checked for quality prior to uploading by the Functional Area (record owner) into the eTMF to ensure:
  - Completeness
  - Final
  - Signed, if applicable
  - Formatting
  - No PHI is present
  - Relevant to the study
  - Not a duplicate
  - Legible
- Proper filing and metadata applied and ensure that they meet the ALCOA+ Principles


Contemporaneous
Legible
Original
Attributable
Accurate
ALCOA++
PRINCIPLES
Available
Traceable
Enduring
Complete
Consistent

BusinessTools

Used to ensure consistency in the TMF record management process... leads to the parameters by which the TMF records are QC'd and filed

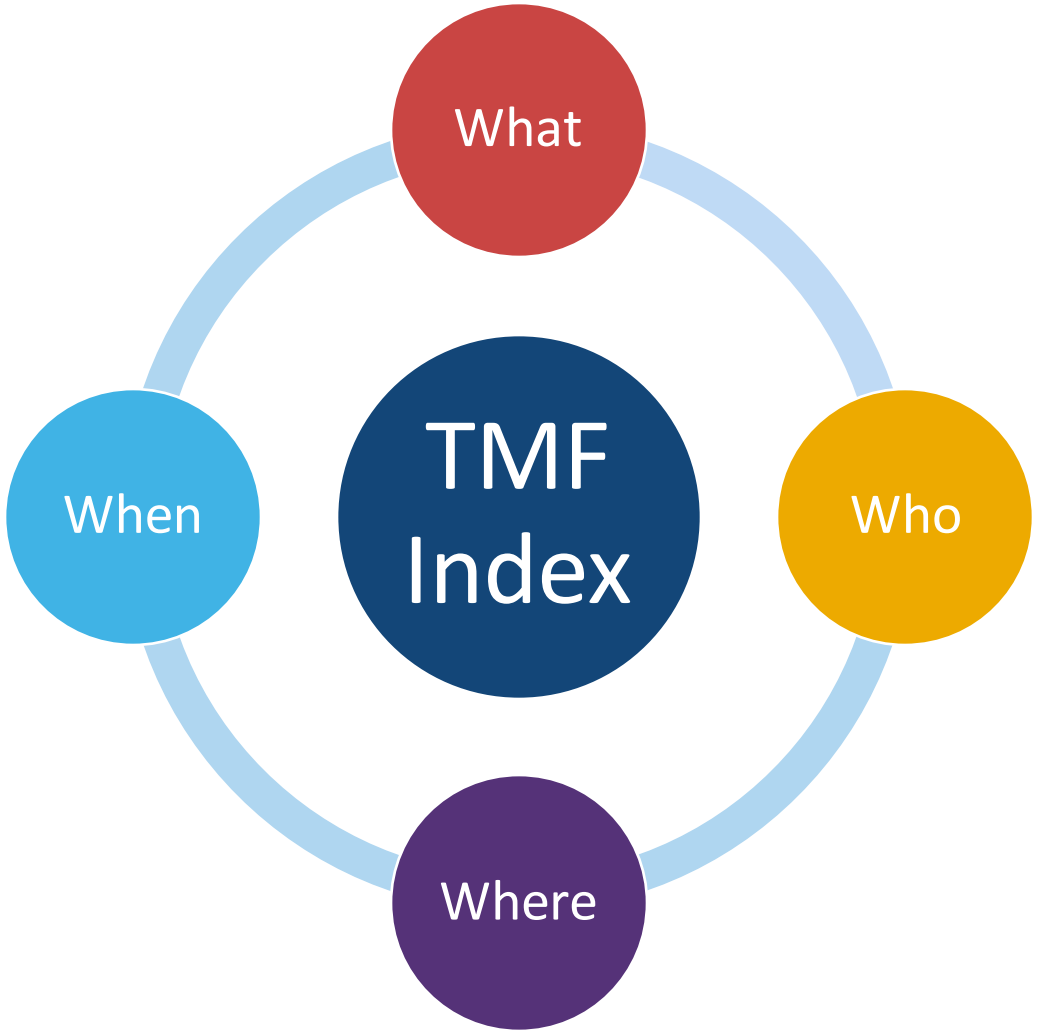
- **TMF Index**
  - Standardized listing of a company's TMF using standard naming conventions and filing level at which the record will be created and collected. Lists the location, ownership and how the record will be managed throughout the study.
- **TMF Plan**
  - Describes how records for the trial will be managed and stored during and after the trial, including study-specific processes and documentation for archiving and destruction.
- **Business Rules**
  - Formal/Informal process related record to assist users in the management of their owned or delegated TMF record. An example is "Naming Conventions for TMF Records"

TMF Index

A roadmap for your TMF.

- What records are expected
- Who is responsible for creating/ collecting/filing the records
- **Where the records are filed**
- When the records are expected
- ***Standardization for filing, naming, and dating conventions**

A tool for regulatory inspectors



Screenshot of TMF Ref Model Index

TMF Reference Model	TMF RM Website	Version 3.2.0	2-Nov-20	X: applicable; NO* : Not applicable *There may be some targeted exceptions based on local criteria (i.e. countries)

												TMF Artifacts (Non-device)		TMF Artifacts (Device)		TMF Level		
Zone #	Zone Nam	Section #	Section Nam	Artifact	Artifact name	Definition / Purpose	Recommended Subartifacts - Documents/documentation recommended to be filed to the artifact.	Core or Recommended for inclusion	ICH Co	Artifact name in v1.3 EDM Referenc e Mod	Unique ID Numbe	Sponsor Docume	Investigator Docume	Sponsor Docum	Investigator Docume	Trial Level Document	Trial Level MILESTONE /EVEN	Dating Conventio
01	Trial Manage ment	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	Recommended	5.5.7		001	X	NO	X	NO	X	02 Clinical Infrastructur e Ready	Version Date
01	Trial Manage ment	01.01	Trial Oversight	01.01.02	Trial Management Plan	To describe overall strategy for timelines, management and conduct of the trial and typically makes reference to other artifacts. Artifact can include details on contingency plan covering details for site start up planning.	Clinical Development Plan Project Management Plan Trial Management Plan	Recommended	2.2		002	X	NO	X	NO	X	01 First Country RA Approval	Version Date
01	Trial Manage ment	01.01	Trial Oversight	01.01.03	Quality Plan	To describe the operational techniques and activities undertaken within the quality management system to verify that the requirements for quality of the trial-related activities have been fulfilled. Relevant parts may include, but not be limited to, a plan written for internal oversight of study quality management, an audit plan, data verification steps; also includes escalation in the event of a quality issue being identified and all corrective and preventative actions determined. Artifact can include any evidence of plan execution including, but not limited to: plan, reports, checklists, etc.	Quality Documentation Quality Plan Quality Report	Recommended	5.1		003	X	NO	X	NO	X	02 Clinical Infrastructur e Ready	Version Date
01	Trial Manage ment	01.01	Trial Oversight	01.01.04	List of SOPs Current During Trial	To document which standard operating procedures (SOPs) and which versions were in effect for the duration of the trial and trial-specific procedures created for the trial. To include sponsor and third party SOPs. This artifact does not include the SOPs themselves. May include SOP waivers to document and describe study-specific deviation from a named SOP or working procedure and the rationale for the deviation, when applicable.	List of SOPs Current During Trial SOP Waivers SOP Deviations	Core	5.1.1		004	X	NO	X	NO	X	02 Clinical Infrastructur e Ready	Document Date
01	Trial Manage ment	01.01	Trial Oversight	01.01.05	Operational Procedure Manual	To describe trial-related processes not covered by formal standard operating procedures. Includes manuals given to sites for ISFs and vendor study-specific manuals as well as any study related tools provided to investigator sites not subject to IRB/IEC approval. Artifact can include any evidence of plan execution including, but not limited to: plan, reports, checklists.	Operational Procedure Manual	Recommended	5.1.1		005	X	X	X	X	X	02 Clinical Infrastructur e Ready	Version Date

Ensuring TMF Quality with Risk-Based Approach

What exactly is a risk-based approach?

- Identifying and assessing potential risks early in the process, allowing organizations to take proactive measures to mitigate these risks before they escalate into quality issues.
- Focuses on the critical areas (essential documents) of the TMF (essential records) of the TMF (i.e. the ones that matter)
- Can also be defined by an organization's risk tolerance (i.e. what they are comfortable with)

Establish what is critical

Align with regulatory expectations

Identify which records and/or the amount of records percentage of what you should check

Align the scope of Periodic Quality Review with RBA

Define how often the Quality Oversight Review is performed and by whom

Evaluate if risk appropriate, and modify as needed

Ensuring TMF Quality with Risk-Based Approach

What Risk-Based Approach Is Not

No oversight of the QC Process

Waiting until the end of the study to perform any review activities

Thinking that having an eTMF and processes eliminates the need for Quality Control

Randomly not reviewing records without a justification

Misaligned with the company's comfort level with risk

Quality

"...All clinical trial information shall be recorded, processed, handled... in such a way that it can be accurately reported, interpreted and verified..."

EU Regulation Article 56

" Quality control should be applied to each stage of data handling to ensure all data are reliable and have been processed correctly."

ICH E6(R2), 5.1.3

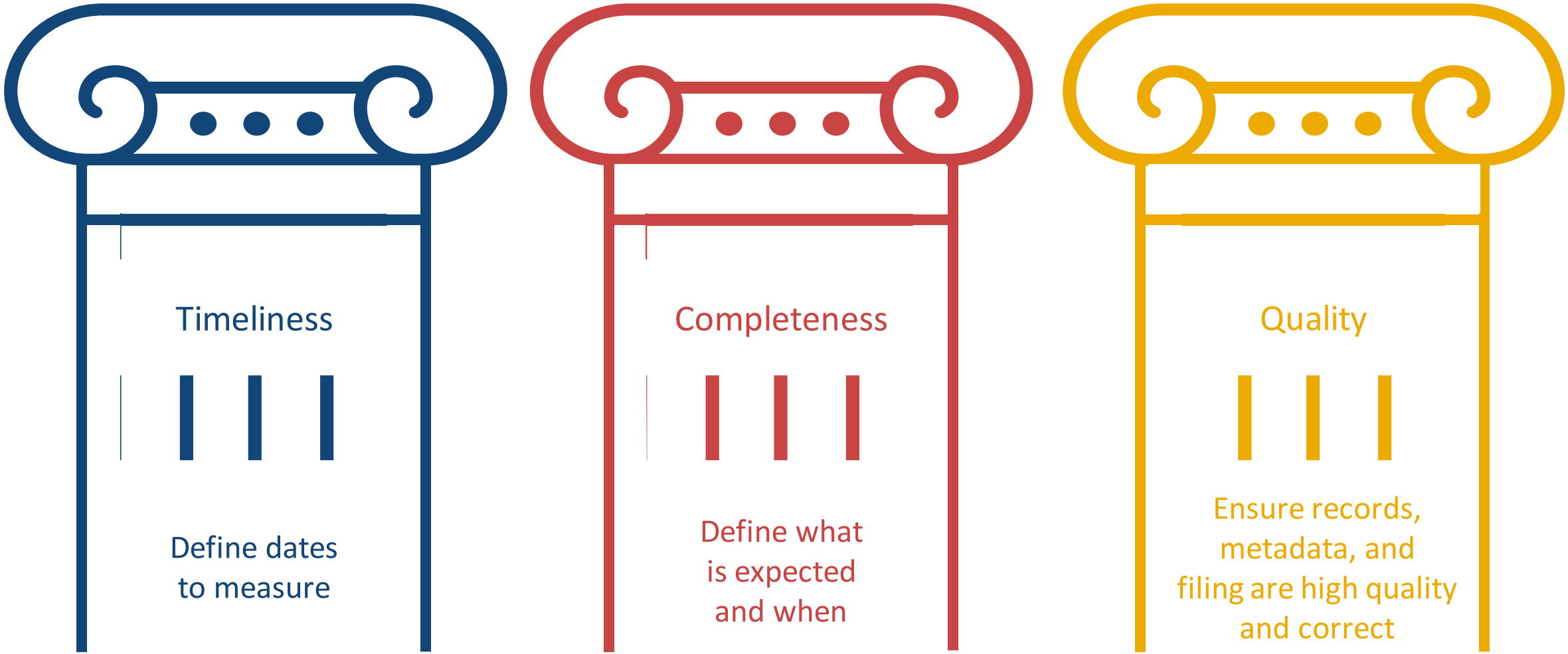
The data integrity of TMF records

Consistency of record filing location and naming

Part of inspection readiness of TMF

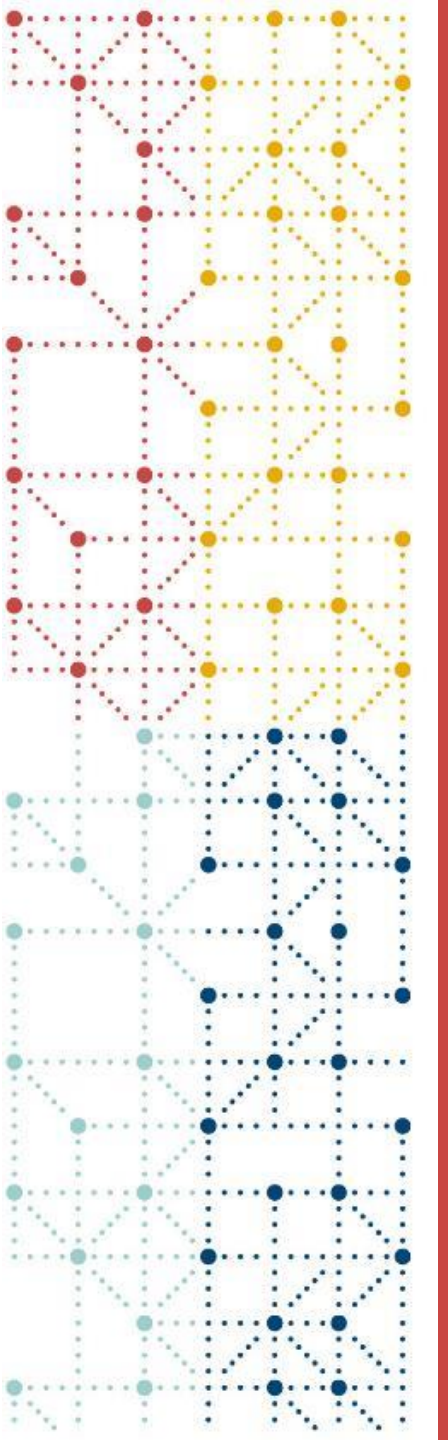
Driving Quality

Part 1: Using Pillars of TMF Health



How does Quality Control impact Periodic reviews?

By performing periodic reviews, you are focused on building a TMF based on Quality by Design from the start!
Having quality records in the TMF ensures that the TMF is Inspection Ready at all times, and it is able to tell the story of the study when filing is accurate and consistent



Risk Process

Identify Critical Processes & Data

- Data Integrity
- Human Subject Protection
- End Points
- IP Administration or Management

Identify Risks

- Potential areas for failure

Risk Process (Based on ICH E6, Section 5)

Mitigate & Control

- Risk acceptance
- Eliminate Risk
- Identify early to prevent large issues

Risk Process (Based on ICH E6, Section 5)

Communicate Risks

- Document the approach to risk in TMF Plan
- Train on the plan
- Share metrics

Risk Process (Based on ICH E6, Section 5)

Document!

- Update the plan
- Document review

References and Resources

- Introduction to the TMF Ref Model
- ALCOA
- CDISC Resources
- Fundamentals of TMF
- EMA Guidances