ICH E6 R3 and the TMF

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Meet the Speaker

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Dr. Torsten Stemmler earned his PhD in Biology (Neurobiology and Psychophysics) from the University of Bremen, Germany, in 2011. Following his doctoral studies, he pursued postdoctoral research at RWTH Aachen, focusing on visual perception. His career took a dynamic turn when he retrained as a Data Manager, developing database solutions at the University Hospital Aachen. In 2017, he brought his expertise to the Federal Institute for Drugs and Medical Devices, where he serves as a GCP Inspector, ensuring compliance with Good Clinical Practice standards.

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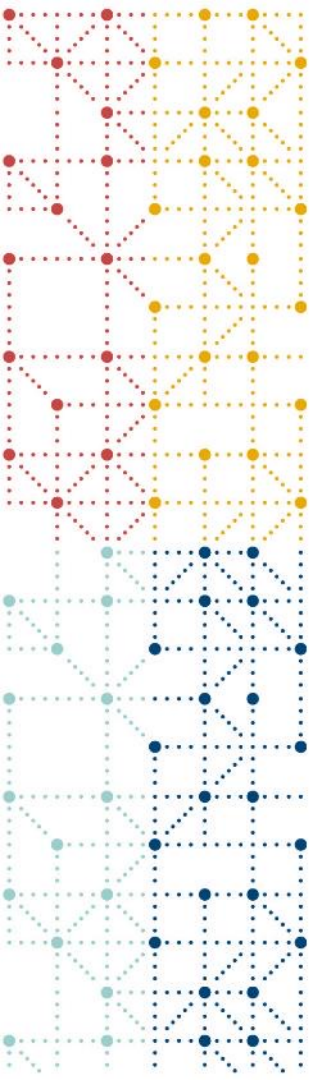
ICH E6 R3 and the Trial Master File

1. Setting the Scene
2. Investigator Site File
3. Trial Master File
4. Essential Records
5. Essential Question



Setting the scene

“You don’t just follow compliance—you decode it, you master it, you see beyond the numbers and reports. Welcome to the real world”

What is a Record in Clinical Trials?

"Original documents or data (which includes relevant metadata) or certified copies of the original documents or data, irrespective of the media used. […]" - ICH E6 R3 Source Records

Key Characteristics

- **Records are defined by the information they hold -** Their value comes from the data they document, not just their physical or digital existence.
- **Records exist in any format -** Whether physical, digital, or certified copies, their purpose remains the same: preserving trial integrity.
- **Records are only complete with metadata -** Contextual details such as timestamps, authorship, and version history ensure traceability and usability.

The Purpose of Record Keeping

"*[…] These essential records should be available to regulatory authorities, monitors, auditors and IRBs/IECs (as appropriate) upon request to enable appropriate evaluation of the trial conduct in order to ensure the reliability of trial results*." - ICH E6 R3 9.5

Key Reasons for Maintaining Records

- **Ensuring Trial Integrity -** Records serve as the foundation for verifying trial design, conduct, and outcomes.
- **Regulatory Compliance & Oversight -** Enables audits, inspections, and ethical review processes.
- **Data Reliability & Traceability -** Essential records provide context, ensure accuracy, and protect against errors or bias.

Investigator Site File

“Every protocol, every deviation, every decision - it’s all recorded in the Site File. And once you see it, there’s no turning back.”

Investigator - Defining & Maintaining Source Records

Maintaining Adequate Source Records *"The investigator/institution should maintain adequate source records that include pertinent observations on each of the trial participants under their responsibility. […]"* - ICH E6 R3 2.12.2

Ensuring Record Integrity & Traceability "*Source records should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source records should be traceable, should not obscure the original entry and should be explained if necessary (via an audit trail).*" - ICH E6 R3 2.12.2

Defining & Managing Source Records "*The investigator should define what is considered to be a source record(s), the methods of data capture and their location prior to starting the trial and should update this definition when needed.*" - ICH E6 R3 2.12.2

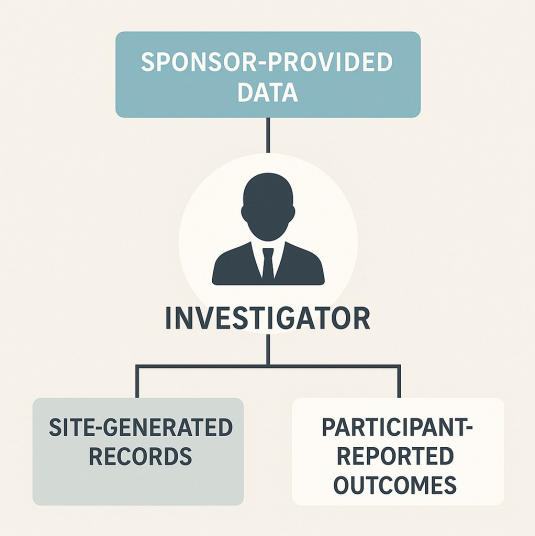
Investigator - Retention of Essential Records

Regulatory Retention Requirements *"The investigator/institution should retain the essential records for the required retention period in accordance with applicable regulatory requirements or until the sponsor informs the investigator/institution that these records are no longer needed, whichever is the longest. […]"* - ICH E6 R3 2.12.12

Ensuring Availability & Security *"[…] The investigator/institution should take measures to ensure availability, accessibility and readability and to prevent unauthorized access and accidental or premature destruction of these records."*
- ICH E6 R3 2.12.12

Continuity in Record Management *"The investigator/institution should keep the sponsor informed of the name of the person responsible for maintaining the essential records during the retention period; for example, when the investigator site closes or an investigator leaves the site."* - ICH E6 R3 2.12.13

Investigator - Responsibilities for Record Access



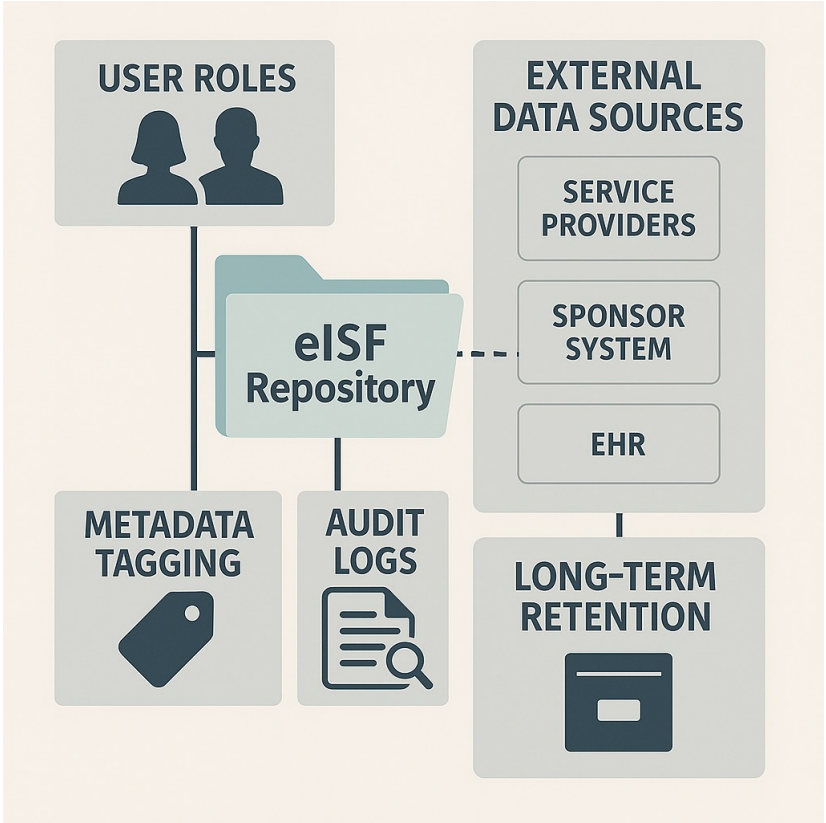
Investigator Access & Review of Data *"The investigator should be provided with timely access to data by the sponsor […] and be responsible for the timely review of data, including relevant data from external sources that can have an impact on participant eligibility, treatment, or safety […]."* - ICH E6 R3 2.12.3

Ensuring Secure Record Access *"The investigator/institution should take measures to ensure availability, accessibility, and readability and to prevent unauthorized access and accidental or premature destruction of these records."* - ICH E6 R3 2.12.12

Investigator - Defining an Electronic Investigator Site File (eISF)

The electronic Investigator Site File (eISF) should be structured to ensure compliance, accessibility, security, and traceability.

- Controlled Access & Permissions
- Audit Trails for Traceability
- Security & Data Protection
- Standardized Record Definition



Investigator - The Power of Standardized Record Definition

"The investigator should define what is considered to be a source record(s), the methods of data capture and their location prior to starting the trial and should update this definition when needed." - ICH E6 R3 2.12.2

How Standardization Enhances Clinical Trial Integrity

Creates a Clear & Reliable Framework

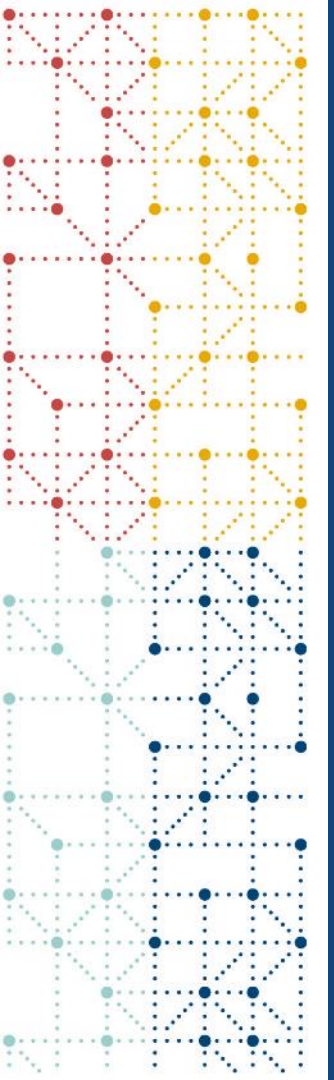
Standardized records provide a clear foundation for documenting patient data, ensuring consistency at site.

Strengthens Trust & Compliance

A well-defined record system ensures every data point is accurate, attributable, and complete, reinforcing confidence in trial results.

Optimizes Efficiency & Accessibility

Standardization allows faster data retrieval, streamlined audits, and seamless regulatory review, keeping the trial process smooth and transparent.



Trial Master File

“The Trial Master File is the Oracle - it holds the answers, but only if you know how to read them.”

Sponsor - Agreements & Record Arrangements

Retention Commitment in Agreements "*The sponsor should retain appropriate essential records for the required retention period in accordance with applicable regulatory requirements or until the sponsor informs the investigator/institution or, where applicable, the service provider that these records are no longer needed, whichever is longest*. […]" - ICH E6 R3 3.6.3 (c)

Ensuring Direct Access & Oversight *"To permit monitoring and auditing by sponsors, inspections by regulatory authorities (domestic and foreign) and, in accordance with applicable regulatory requirements, review by IRBs/IECs, including providing direct access to source records and facilities, including to those of service providers."*
- ICH E6 R3 3.6.3 (d)

Data Ownership & Transfer Responsibilities *"[…] The sponsor should report to the appropriate authority(ies) any transfer of ownership of the essential records as required by applicable regulatory requirement(s). The sponsor should also inform the investigator if sponsorship of the trial changes."* - ICH E6 R3 3.16.3 (c)

Sponsor - Monitoring Essential Records

Remote & Secure Access for Monitoring *"Monitoring may include remote and secure, direct read-only access to source records, other data acquisition tools, and essential record retention systems."* - ICH E6 R3 3.11.4.1 (c)

Investigator Record Management Confirmation *"Confirming that the investigator is maintaining the essential records."* - ICH E6 R3 3.11.4.5.2 (c)

Retention & Final Accountability Checks *"Confirming the arrangement for the retention of essential records and the final accountability of the investigational product (e.g., return and destruction or alternative disposition) during site close-out activity."*

- ICH E6 R3 3.11.4.5.2 (j)

The sponsor should ensure the ISF remains compliant, accessible, and inspection-ready throughout the trial. Monitoring activities confirm investigators maintain essential records and follow regulatory requirements. Before site close-out, the sponsor verifies proper record retention and security for long-term compliance.

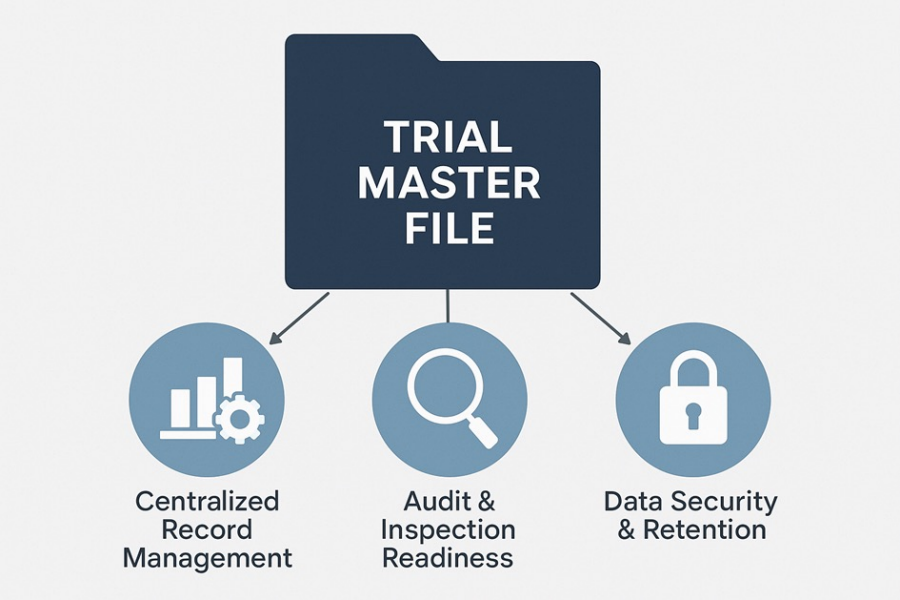
Sponsor - The Trial Master File

Essential Record Retention & Accessibility *"The sponsor should retain appropriate essential records pertaining to the trial in accordance with applicable regulatory requirements."* - ICH E6 R3 3.16.3 (a)

Structured Document Repositories *"These essential records should be maintained in or referred to from repositories held by the sponsor and by the investigator/institution for their respective records."* - ICH E6 R3 C.2.3

Ensuring Compliance & Traceability *"The storage system(s) used during the trial and for archiving should provide for appropriate identification, version history, search and retrieval of trial records."* - ICH E6 R3 C.2.4

Sponsor - TMF Supports Trial Integrity



- **Centralized Record Management**
  The TMF serves as the official repository for sponsor-generated and maintained trial documents.
- **Audit & Inspection Readiness**
  Ensures essential records are organized, traceable, and accessible for regulatory review.
- **Data Security & Retention**
  Protects trial documentation with controlled access, version control, and long-term archiving protocols.

Essential Records

“Essential record management is not just organization. It is structure. It is discipline. And most importantly - it is control.”

Essential Records - Identifiability & Version Control

"Records should be identifiable and version controlled (when appropriate) and should include authors, reviewers and approvers as appropriate, along with date and signature (electronic or physical), where necessary" - ICH E6 R3 C.2.1

Essential records should be clearly identifiable, version-controlled when applicable, and include

- Author names
- Reviewer & approver details
- Date & signature (electronic or physical)

Implementation Example - A digital Trial Master File (TMF) ensures version tracking with audit logs, allowing regulators to verify document authenticity and approval timelines.

Essential Records - Access & Management for Delegated Activities

"For activities that are transferred or delegated to service providers by the sponsor or investigator/institution, respectively, arrangements should be made for the access and management of the essential records throughout the trial and for their retention following completion of the trial." - ICH E6 R3 C.2.2

If trial activities are transferred or delegated to service providers, sponsors or investigators should

- Define access rights in agreements
- Maintain oversight of essential records
- Ensure retention even after trial completion

Implementation Example - A service provider providing centralized imaging analysis should be required, via contract, to ensure stored radiological data is transferred or remains accessible.

Essential Records - Storage System Requirements

"The sponsor and investigator/institution should maintain a record of where essential records are located, including source records. The storage system(s) used during the trial and for archiving ([…]) should provide for appropriate identification, version history, search and retrieval of trial records." - ICH E6 R3 C.2.4

Storage systems (digital or physical) should provide

- Identification & version history
- Search & retrieval functionalities
- Secure long-term archival

Implementation Example - An electronic TMF (eTMF) uses metadata tagging and revision history to provide secure document retrieval while preserving historical versions for compliance.

Essential Records - Timely Record Collection & Filing

"The sponsor and investigator/institution should ensure that the essential records are collected and filed in a timely manner, which can greatly assist in the successful management of a trial. Some essential records should generally be in place prior to the start of the trial and may be subsequently updated during the trial." - ICH E6 R3 C.2.5

Essential documents should be generated and filed promptly to avoid gaps in compliance. Some key records should

- Exist before trial initiation (protocols, approvals)
- Be updated throughout the trial (monitoring logs, amendments)
- Be created at the end of the trial

Implementation Example - Investigator site communication records should be captured in real-time to ensure documentation of trial is inspection ready.

Essential Records - Record Ownership Responsibility

"The sponsor and investigator/institution should ensure the retention of the essential records required to fulfil their responsibility. The original records should generally be retained by the responsible party who generated them." - ICH E6 R3 C.2.7

The original record generator is responsible for record retention

- Investigators retain clinical source data
- Sponsors retain trial-specific oversight records

Implementation Example - A data analysis report created by the sponsor remains with the TMF, while patient records stay within the investigator's Site File.

Essential Records - Shared Record Access Between Sponsor & Investigator

"In order to fulfil their responsibilities in the conduct of the trial, the sponsor and investigator/institution may need access to or copies of one another's relevant essential records before and during the conduct of the trial. At the end of the trial, each party should retain their essential records ([…]). The record location may vary during the trial depending on the nature of the record. [..]" - ICH E6 R3 C.2.8

During a trial

- Investigators may need access to sponsor-generated documents
- Sponsors may need copies of investigator records for oversight

Implementation Example - Suspected Unexpected Serious Adverse Reaction (SUSAR) reports from the sponsor are shared with investigators via a secure portal.

Essential Records - Exclusive Sponsor & Investigator Records

"Some records are typically maintained and retained only by the sponsor (e.g., those related solely to sponsor activities such as data analysis) or only by the investigator/institution (e.g., those that contain confidential participant information). Some records may be retained by the sponsor and/or the investigator/institution."
- ICH E6 R3 C.2.10

"Careful consideration should be given to the sharing of records when there are blinding considerations and when the records are subject to applicable data protection legislation." - ICH E6 R3 C.2.11

- **Some records are solely retained by sponsors (e.g., statistical analysis)**
- **Others remain only with investigators (e.g., confidential patient data)**

Implementation Example - Randomization logs may be retained only by the sponsor to maintain blinding, while patient health records remain exclusively in investigator control.

Essential Question

“What to Keep or Not to Keep.”

Essential Question - Understanding the Structure of Appendix C

"The assessment of whether a record is essential and has to be retained should take into account the criteria below. Such assessment, whilst important, is not required to be documented. A structured content list for storage repository(ies) may be used to prospectively identify essential records." - ICH E6 R3 C.3.1

The ICH E6 R3 guideline assigns 26 categories (a–bb) to essential records, providing a structured framework for ensuring compliance and oversight.

"The secret of getting ahead is getting started. The secret of getting started is breaking your complex overwhelming tasks into small manageable ones, and then starting on the first one." – Mark Twain

Essential Question - TMF Reference Model

The TMF Reference Model is structured into zones that correspond with essential records outlined in Appendix C.3.1 (a - bb).

Zone 1 - Trial Management

Oversight, monitoring, and general trial execution

(r) Sponsor oversight of site selection, monitoring, auditing, and corrective actions.

(p) Documents proving that service providers are qualified for delegated activities.

(e) Agreements between parties, including financial contracts and insurance.

(l) Documentation ensuring sponsor personnel are qualified for their responsibilities.

Essential Question - TMF Reference Model

Zone 2 - Central Trial Documents

Core documents required for trial structure and integrity

(b) Trial-specific procedures or plans (protocols, amendments).

(i) Signed authorization from sponsor/investigator confirming review or approval.

(d) Records verifying trial procedures (e.g., database lock checklist).

(aa) Source records substantiating participant existence and trial data integrity.(*ISF)

Essential Question - TMF Reference Model

Zone 3 - Regulatory

Approval submissions and regulatory compliance

(a) Regulatory submissions and issued decisions from IRB/IEC or authorities.

(f) Compliance with regulatory approval requirements.

(g) Committee composition, correspondence, and decisions affecting trial approvals.

Zone 4 - IRB/IEC and Other Approvals

Ethics and Institutional Review Board (IRB) oversight

(c) IRB/IEC submissions, amendments, and correspondence.

(k) Documents confirming informed consent processes and approval.

Essential Question - TMF Reference Model

Zone 5 - Site Management

Site feasibility, investigator delegation, and operational oversight

(m) Investigator and delegated staff qualifications for trial activities.

(z) Participant recruitment, screening, and consent management.

(h) Validation of trial-specific computerized systems and assessment of non-trial systems.

(j) Signature authentication of staff undertaking trial-related activities

Essential Question - TMF Reference Model

Zone 6 - Investigational Product (IP) and Trial Supplies

Handling, storage, shipment, and accountability of investigational products

(u) Investigational product details and labeling documentation.

(v) Shipment, storage, packaging, dispensing, randomization, and blinding details.

(w) Accountability from manufacturer release to administration and return/destruction.

(x) Information verifying the identity and quality of investigational products.

Essential Question - TMF Reference Model

Zone 7 - Safety Reporting

Adverse events, risk management, and compliance

(o) Documents detailing oversight of trial participant safety.

(bb) Security breach management to protect participant data integrity.

(o) Sponsor and investigator oversight of participant safety, including safety reporting.

Zone 8 - Centralized and Local Testing

Laboratory tests, imaging, and sample handling

(t) Collection, processing, and retention/destruction of biological samples.

(q) Validation of laboratory activities and trial-specific tests.

(n) Trial data and metadata required for evaluation.

Essential Question - TMF Reference Model

Zone 9 - Third Parties

External service providers and collaborations

(p) Documentation proving service providers are qualified for delegated activities.

(e) Contracts and agreements between investigators, sponsors, and third-party providers.

Zone 10 - Data Management

Ensuring structured data processing and integrity

(s) Compliance with protocol for data management, statistical analysis, and reporting.

Essential Question - TMF Reference Model

Zone 11 - Statistics

Statistical analysis, reporting, and randomization procedures

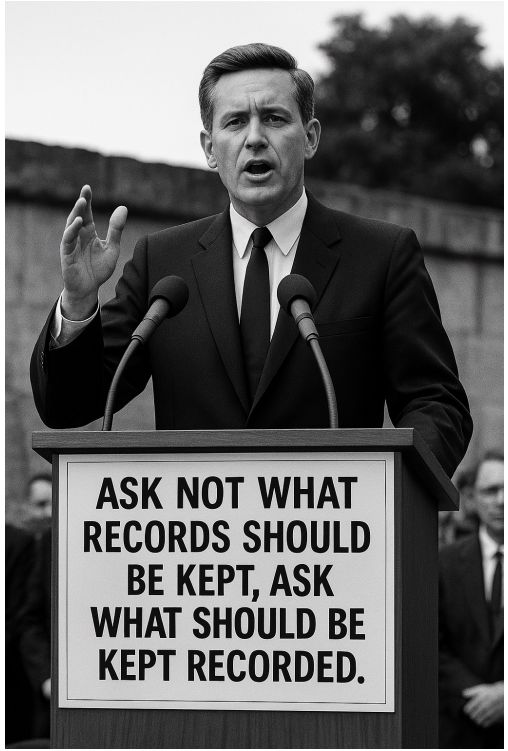
(y) Documentation related to unblinding processes and activities.

(s) Statistical analysis documentation for trial results.

This mapping exercise shows that Appendix C3.1 categories (a to bb) can be aligned with TMF zones for efficient document organisation, regulatory compliance, and data integrity.

However, the question remains, what to keep or not to keep?

Bonus Round


ASK NOT WHAT
RECORDS SHOULD
BE KEPT, ASK
WHAT SHOULD BE
KEPT RECORDED.

The Five "W" Questions for Documentation Triage

WHAT information may be clutter?

Start by identifying information.

WHY is this information relevant to the trial?

Identify the purpose and significance of each intended record.

WHO needs access to this information?

Define the stakeholders who rely on these information.

WHEN should the information be recorded and retained?

Determine the timing for documentation and storage.

WHERE should this information be recorded?

Locate the record and ensure it is kept in a secure and accessible.

Records & Reality: Navigating the TMF Matrix

- **Introducing ICH E6 R2 & Essential Records** – Highlighting the changes of ICH E6 R3 and emphasizing the critical role of essential records in maintaining compliance and transparency.
- **Integrating Appendix C into the TMF Reference Model** – Demonstrating how Appendix C aligns within the Trial Master File framework, ensuring a structured and efficient documentation approach.
- **Identifying Relevant Information** – Providing practical strategies to determine which records truly matter, balancing documentation requirements with efficiency and clarity.

Record What Matters, Keep What's Essential.

As Albert Einstein once said, 'Not everything that can be counted counts, and not everything that counts can be counted.' True documentation excellence isn't about keeping everything—it's about safeguarding the right data, decisions, and compliance records with precision and purpose.

Thank You!