Enhancing Data Integrity by Applying Edit Checks to Your TMF

Presented by:
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Meet the Speakers

Christina Mantzioros

Title: Head, Clinical Solutions Strategy

Organization: Montrium

With a mandate to bridge the gap between clinical research, technical development, and business applications, Christina plays a vital role as Montrium's Head of Clinical Solutions Strategy. Her experience in the pharmaceutical industry and passion for technology help Montrium in building the next generation of eTMF. Christina is currently participating in the Data Standards / Exchange Mechanism Standard Working Group, a workstream part of the CDSIC TMF Reference Model. In the years prior to joining Montrium, Christina worked in clinical project management roles in both academic and private sector clinical research organizations.

Todd Georgieff

Title: Clinical Operations Consulting

Todd has been working in Drug Development for more than 30 years. He has extensive experience in global clinical operations and has also held leadership roles in many large process improvement, technology, and organizational change initiatives. In the past few years, Todd has been working on projects relating to the digitization of clinical research, both at Roche and Genentech and in several cross-industry collaborations. These include TransCelerate's Digital Data Flow initiative, leading the Precision Cancer Consortium Clinical Trial Patient Matching workstream, participating in the Decentralized Trials Research Alliance, and several others. Many of these initiatives aim to make drug development more efficient and sustainable and to help our industry "break the document paradigm."

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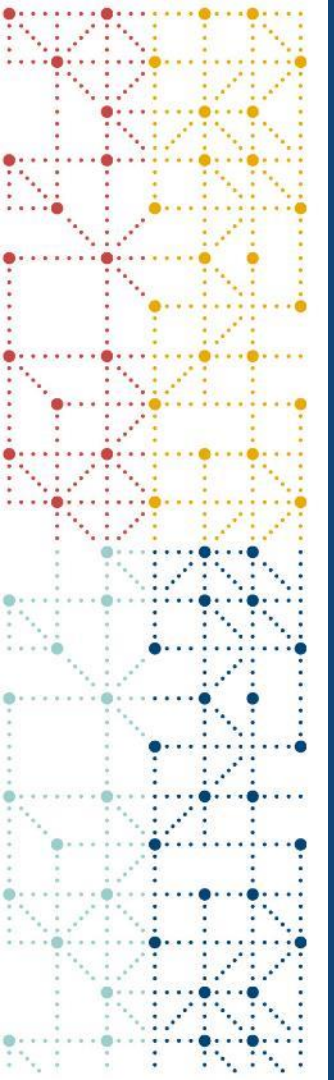
- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The author(s) have no real or apparent conflicts of interest to report.*



Introduction

Why did the trial master file go to therapy?

…Because it had too many unresolved issues!

Introduction

Today, we tend to focus mostly on filing documents. While the quality of the individual documents is important, the **eTMF should also be logical in its content.**

By applying clinical data management type techniques similar to what we use in EDC, we can run logical checks (going forward, referred to as **TMF edit checks**), on our eTMF artifacts and metadata to ensure that it tells an **accurate story**

This approach will allow us to **embed confidence** in the quality of our TMF in addition to the quality of the artifacts themselves

Objective

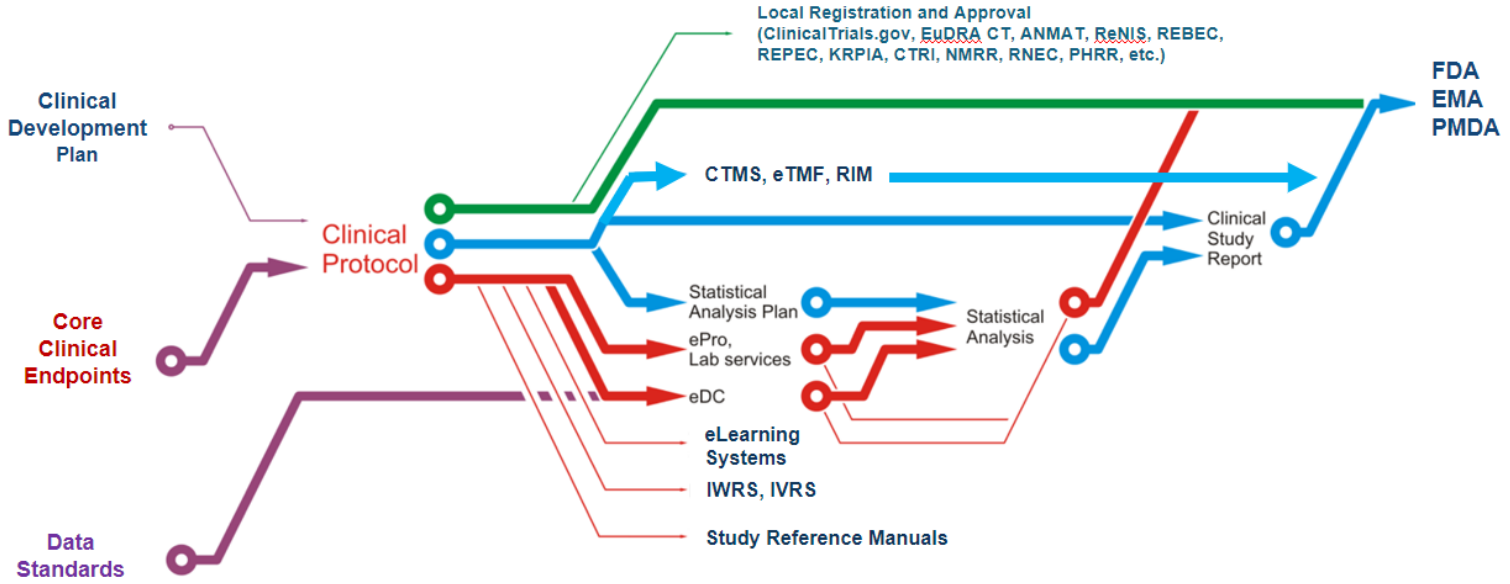
To explain how the principles of Clinical Data Management can be applied to eTMF, including **edit checks** that can detect **anomalies** and create **queries** that will contribute to **proactively maintaining a state of inspection readiness.**

Clinical Trials Involve Several Types of "DATA"

Trial plans and specifications	Study Protocol Monitoring Plans, Pharmacy Manual, Laboratory Manual Standard Operating Procedures
Study observations and clinical data	**EDC data, Laboratories, Images, eCOA**
Study operational and performance data	Recruitment information, country and site information, budgets
Regulatory and trial oversight data	Health Authority and Ethics Submissions and Approvals Monitoring Visit Reports Safety Updates

→ Clinical Data Management approaches usually apply here

The Clinical Trial Information Flow



From: Evans D. CDISC Clinical Trial Information Flow. CDISC Japan Interchange, Tokyo, Jul 10-11, 2023 and CDISC China Interchange, Beijing, Aug 25-26, 2023.

Clinical Data Management Principles

- Clinical Data Management (CDM) is the process of collecting, verifying, "cleaning" and managing all study participant data in compliance with the study protocol and regulatory standards
- Study Data Managers follow defined processes to ensure data are complete, logical and reliable
- The CDM function is a critical partner in the execution of clinical trials:
  - Identify the data types and sources of all data to be collected, according to the study protocol
  - Develop a strategy for data collection or acquisition, including design of data collection forms or other formats
  - Ensure data are collected, accessible and ready to be used for downstream processes (study analysis and reporting)
  - Apply standards (e.g., CDASH, SDTM, ODM, ADaM) to ensure that data can be transmitted and properly interpreted

What are edit checks?

What are edit checks?

Edit checks are essentially logic checks on data that are collected

Edit checks can be univariate or multivariate, and can include:

- RANGE CHECKS
- CONSISTENCY CHECKS
- MANUAL CHECKS (for logic)

Fall into different categories, such as:

- COMPLETENESS: was the data collected, or is it missing
- CORRECTNESS: is the data reported as expected – does the date look like a date?
- LOGICAL CONSISTENCY: does the data "make sense" in the context of the trial, or other data collected?

Edit checks specifications can be pre-defined and can be pre-programmed as data collection systems (like EDC) are configured

Edit check example 1

- Missing or Ambiguous Data
  - Physical Exam

Organ/System	Normal	Abnormal	If "abnormal" specify:
Ear-Nose-Throat	X		
Respiratory		X	
Neurological	X		

Is the comment missing, or should the evaluation of have been "Normal?"

Edit check example 2

- Illogical or Missing Data
  - Concomitant Medication

Medication	Dose	Start	Stop	Indication
Prednisone	5mg	2/15/2022		Exacerbation of asthma

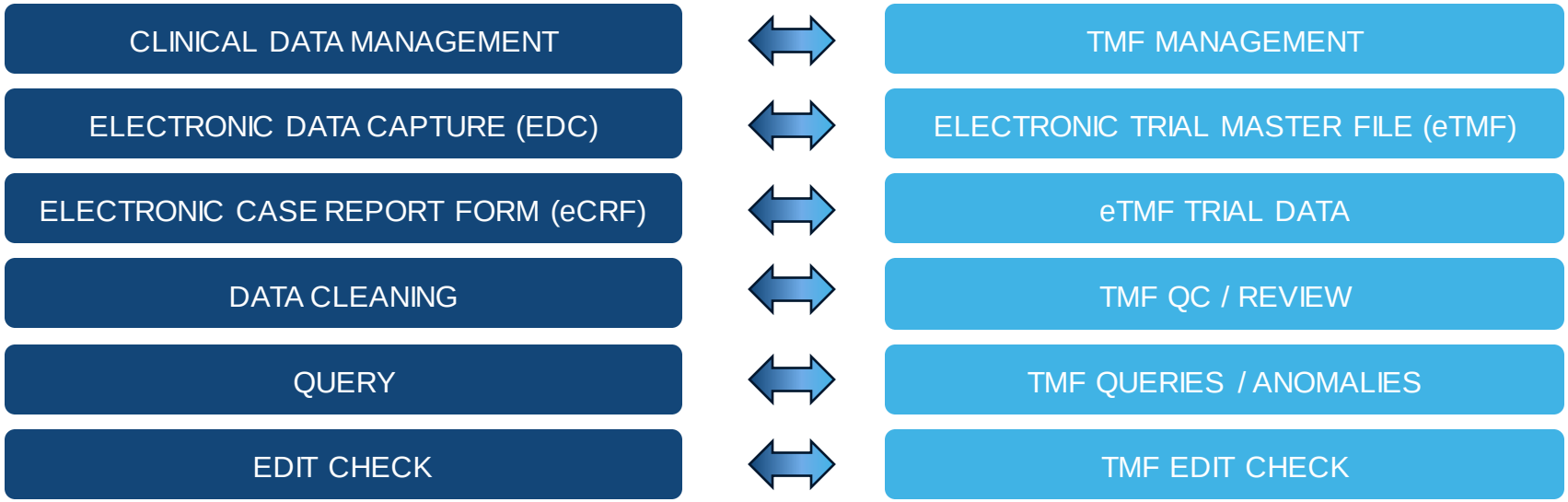
  - Adverse Event

Event	Severity	Onset	Stop	Relationship to Treatment?

"Exacerbation of asthma" should be captured as an Adverse Event

Application of edit checks to the TMF

Parallels CDM and EDC to TMF and eTMF



eTMF as an active data management tool

- It's not just about documents anymore...
- More and more systems are being used in GxP environments
- Activities are documented more and more in the form of data
- There is a strong focus from the regulators on data and data integrity

Levels of check complexity

Level 1 – Artifact Presence

Easily automated, all data that is necessary to complete the check is more likely to be housed in the eTMF system itself

e.g., For each qualified site, verify that the site start-up package is complete.

- Completeness
- Timeliness

Level 2 – Cross-reference

Slightly more complex check that cross-references several artifacts and their metadata

e.g., For every site staff member, verify that there is evidence of training on the study training plan prior to or on site initiation.

- Completeness
- Timeliness
- Logic

Level 3 – Content

Most complex check, involves reading the content of an artifact (either electronic or a scan of a wet ink document) to complete the check

e.g., For every person listed as site staff on the delegation log, ensure that there are valid CVs and licenses available.

- Completeness
- Timeliness
- Quality
- Logic

Today's Limitations (and Tomorrow's Opportunities)

TMF RM Sub-artifacts

Inconsistency and variability of sub-artifacts that contain critical information or metadata

ISF documents

Many critical site documents are not currently maintained in digital form (e.g., site delegation log)

Lack of digital documents and forms

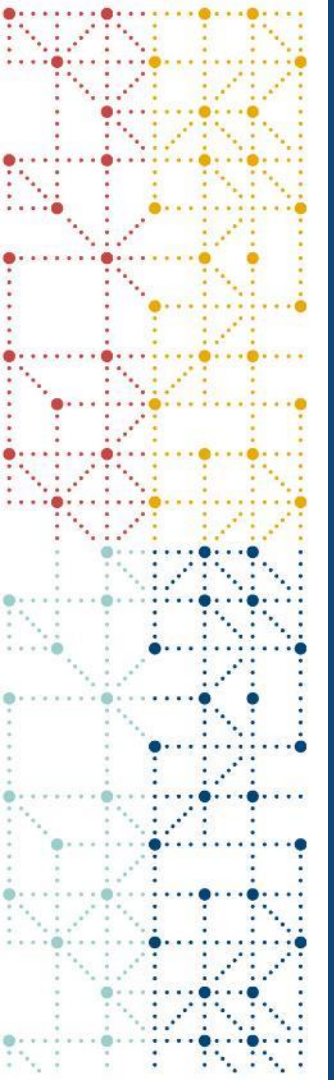
A lot of information is found in content of documents

Other systems holding TMF relevant content

Other clinical systems may hold the authoritative source

How might we achieve this

- Development of standard edit checks that apply to the vast majority of protocols
  Industry initiative? A conformance rules engine against TMF-RM is aligned with other CDISC initiatives
- Prioritize high risk areas (that can be identified from observations collected via inspection agencies) or areas with significant volume
- Use of AI/ML to extract artifact content and metadata
- Develop digital forms and documents similar to what we use in EDC to better exploit artifact content
- Continue the work to allow for better interoperability and exchange across electronic systems



Practical Examples

Example – Site Activation

- An artifact that signifies an important study event has occurred is uploaded to the eTMF. For example, the IP Release to a specific site indicates that the site is now “active” for recruitment of patients for that clinical trial.

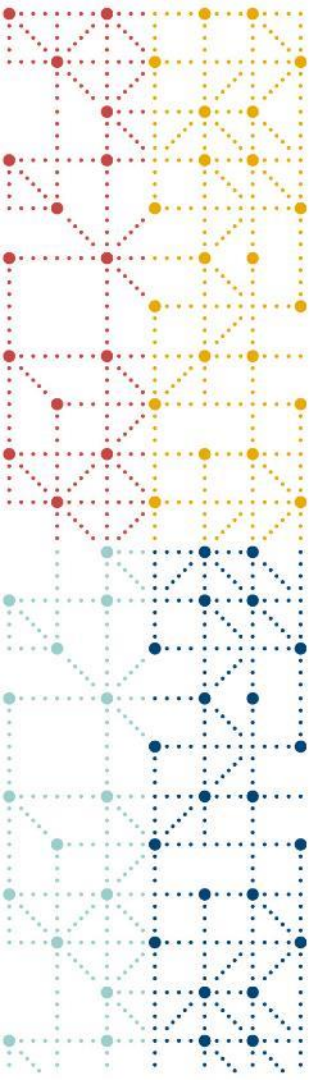
An edit check could be configured that would verify that the other site essential documents (such as a Protocol signature page, Ethics Approval and a signed Clinical Trial Agreement) are also present in that site’s file

An edit check could also query the metadata of those documents to ensure they are complete, and that they pre-date the IP Release

Example – Site Monitoring

- A site monitoring visit date is captured in the system or in a source system.
- An SOP for Site Monitoring states that monitoring visit reports should be finalized within 10 business days and this parameter is captured in your eTMF.
- Your study configuration also required you to define a timeliness parameter (delay to upload documents to the eTMF).
- Monitoring Visit Date + Monitoring Visit Report Finalization Timeline + Timeliness Parameter = Deadline for MVR to be uploaded in eTMF

An edit check can verify whether an MVR is present based on the above calculation and if not, issue a query related to timeliness, requesting the MVR to be uploaded or to provide a justification if it is not available



Conclusion

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Clinical Data Management (CDM) processes, including **Edit Checks could be applied to eTMF management and oversight**

Employing Edit Checks would potentially result in **increased TMF compliance, greater quality compliance**, and would be **more efficient** than our current, manual oversight processes

Application of CDM processes could transform eTMF maintenance activities from a resource-intensive filing requirement to a **real time, value-added activity to proactively maintain a state of compliance and inspection readiness**

Thank You!