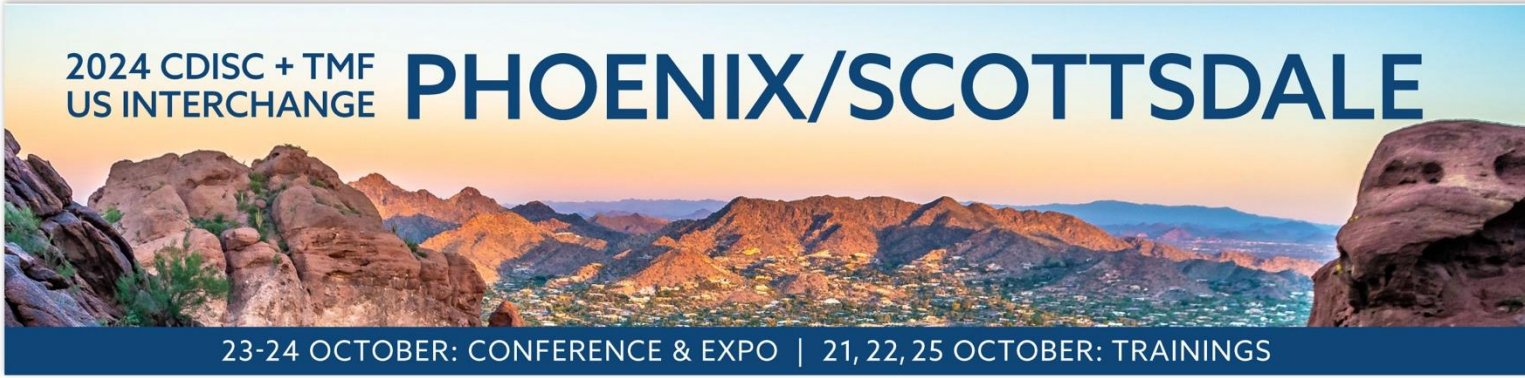

Unveiling the Secrets of eTMF Audit Trail Review

Nisi Nazim, Associate Director, Systems,
Global TMF Management & Records,
BeiGene

Meet the Speaker

Nisi Nazim

Title: Associate Director, Systems, Global TMF Management & Records

Organization: BeiGene

14 years' experience in the Clinical Systems domain responsible for delivering system enhancements and process improvements for the electronic Trial Master File (eTMF). Prior to BeiGene, at Daiichi Sankyo, has led integration project between eTMF and other systems including CTMS and was a core team member for the Master Data Management initiative and while with Accenture, contributed towards the implementation of various clinical systems for the some of the big pharmaceutical companies.

Disclaimer and Disclosures

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TMF NEWS

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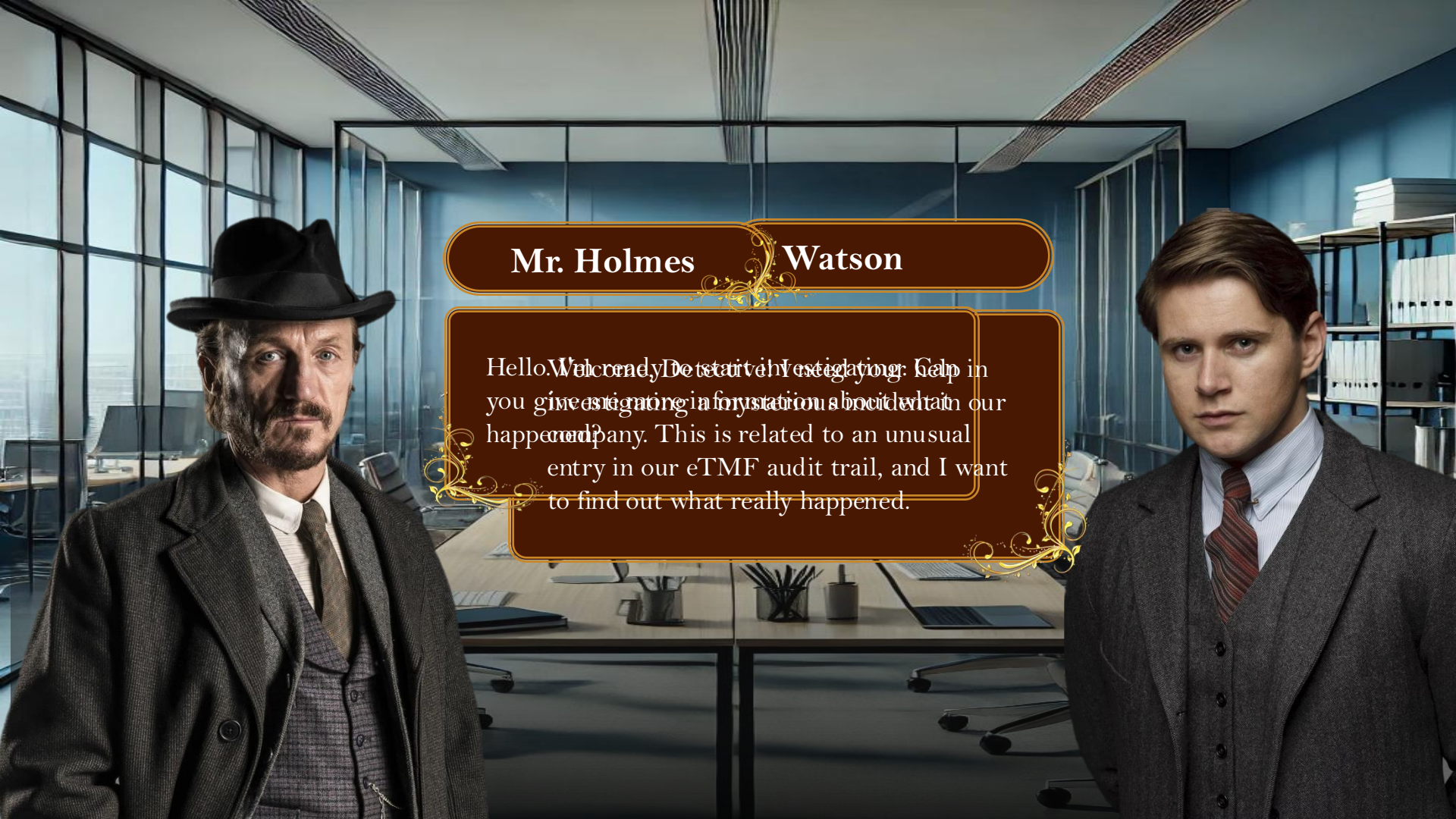
Only fresh news

founded 2009

A detective receives a call to investigate an unusual entry in the eTMF audit trail for a well-known pharmaceutical. The company was known to have robust procedures governing clinical systems including eTMF, but after observing several document deletions, everything turned out to be not so simple.

Upon arrival, the detective meets the core TMF Management team, R&D functions and IT, each of which are key stakeholders responsible for ensuring an inspection-ready TMF. And so, the investigation begins…


Mr. Holmes
Watson
Hello. Are you ready to start investigating?
Welcome, Detective! I need your help in investigating a mysterious incident in our company. This is related to an unusual entry in our eTMF audit trail, and I want to find out what really happened.
Welcome, Detective! I need your help in investigating a mysterious incident in our company. This is related to an unusual entry in our eTMF audit trail, and I want to find out what really happened.
Hello. Are you ready to start investigating? Can you give me information about what happened?

Introduction

Importance of Audit Trails in eTMF

Regulatory Compliance

Regulations mandate that all actions be documented and traceable.

Data Integrity and Authenticity

Audit trail entries are necessary for ensuring the integrity and authenticity of the eTMF data. They provide a record of all actions taken on the data, including any deletions, modifications, or additions.

Accountability

Audit Trail assigns accountability by tracking user actions.

Transparency

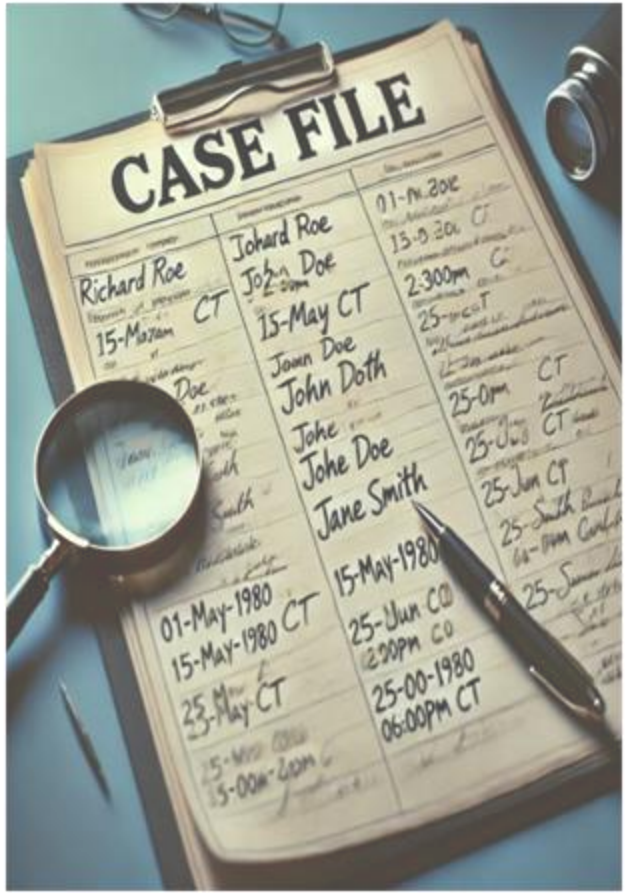
Audit Trail enhances transparency in the management of clinical trial documentation.

Error Tracking and Correction

Audit Trail can help trace back to the source of the problem.

Historical Record

Audit Trail provides historical record of all actions taken within the eTMF.



Clue #1: Understanding the Audit Trail

What is an Audit Trail?

An audit trail refers to the “who”, “what”, “when”, “where” and “why” of an activity on an electronic record.

Audit trails must be secure, computer-generated, time-stamped, incrementally, in chronological order and retained for a period that is required for the related electronic record.[1]

Audit trail must be stored in the system itself. Responsible party should be able to review and comprehend the audit trail and therefore the audit trail must be in a human-readable format. Audit trail must be available and should have the option to export as a data file for review.[2]

1 - U.S. FDA, Guidance for Industry - COMPUTERIZED SYSTEMS USED IN CLINICAL TRIALS April 1999

2 - EMA, Guideline on computerised systems and electronic data in clinical trials March 2023

Clue #2: The Purpose of Reviewing the Audit Trail

Per EMA guidelines, *procedures for risk-based trial specific audit trail reviews should be in place and performance of data review should be generally documented.* [3]

MHRA states that *Routine data review should include a documented audit trail review.* [4]

Per FDA guidance, *Audit trail and other information pertinent to use of the electronic system should be retained and be available for inspection.* [5]

Why review the Audit Trail?

- Compliance Verification
- Identifying Irregularities
- Ensuring Data Integrity
- Improving System Usage

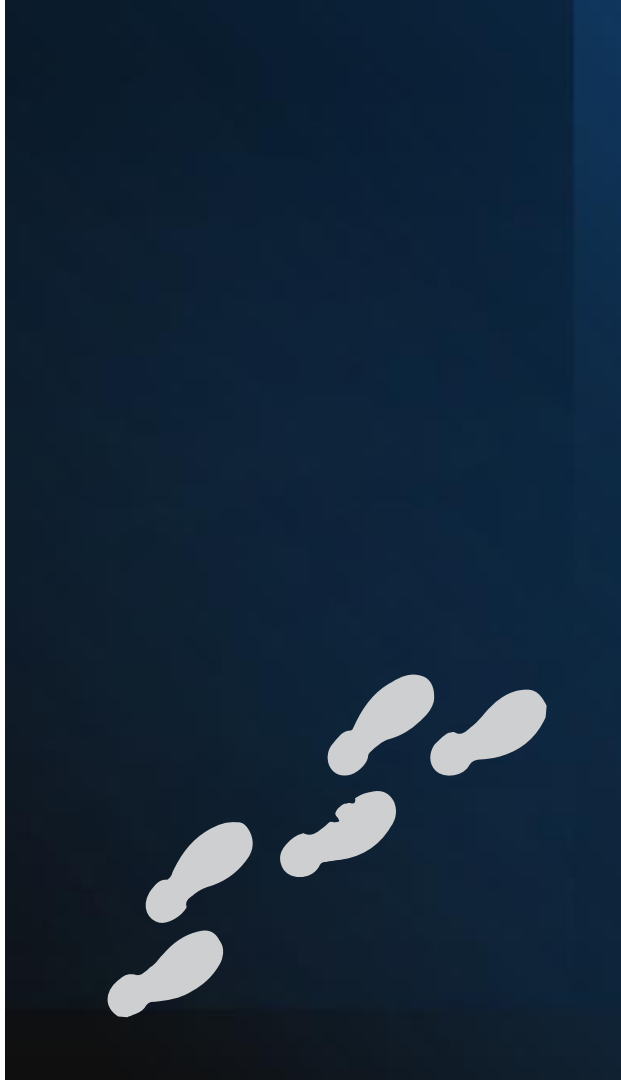
3 - *EMA, Guideline on computerised systems and electronic data in clinical trials March 2023*
4 - *MHRA, 'GXP' Data Integrity Guidance and Definitions March 2018*
5 - *FDA, Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers, October 2024*

Clue #3: What Are We Looking For?

Key Elements to Look For

1. User Activities
2. Change History
3. Access Logs
4. Document Status
5. Approval and Review Process
6. Compliance with Procedures
7. Audit Trail Integrity

Common Red Flags



The Red Herrings: Common Red Flags

1. Non-Compliance with Regulations
2. Unauthorized Access
3. Incomplete Documentation
4. Unapproved Changes
5. Inconsistent Status Updates
6. Inadequate User Activity Tracking
7. Unusual Patterns of Activity

Case Files: Regulatory Findings

EMA:

The sponsor did not identify and have a clear understanding of the content of the TMF(s).The eTMF was not properly maintained during the conduct of the trials and/or the audit trails were not complete. 6

Lack of procedure for period review of user accesses. 7

Lack of audit trail to reconstruct the course of events. 7

MHRA:

The audit trail provided from the eCRF system was not in a suitable format to aid review at a system level to identify what data changes were made, by whom and when in order to verify if the changes were authorised. 8

It was found that the audit trial was unreliable as it had not documented accurately the data changes made for primary endpoint data. 8

FDA:

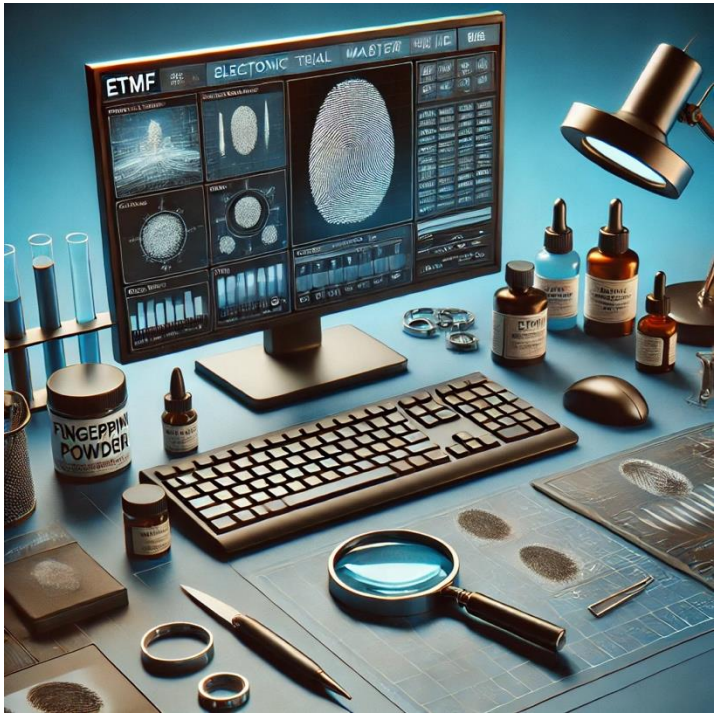
Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. 9

..software was not validated and lacked audit trails. 10

6 - EMA, Annual Report of the Good Clinical Practice (GCP) Inspectors' Working Group (IWG) 2022
7 - EMA, Annual Report of the Good Clinical Practice (GCP) Inspectors' Working Group (IWG) 2021
8 - MHRA, GCP Inspections Metrics Report March 2023
9 - FDA, Warning Letter, MARCS-CMS 630965, August 2022
10 - FDA, Warning Letter, MARCS-CMS 624415, May 2022

Audit Trail Review:
Process

Cracking the Case: Reviewing the Audit Trail



1. **Preparation**

Define objective, gather documentation and plan.

2. **Access the Audit Trail**

Audit trail are typically found under system settings or administration module.

3. **Review User Activities**

Examine user login / logout and check for any unusual actions.

4. **Examine Change History**

Review changes made to the document.

5. **Check Document Lifecycle**

Review the status changes of documents.

Cracking the Case: Reviewing the Audit Trail

6. Evaluate Audit Trail Integrity

Ensure that the audit trail itself is intact and has not been altered.

7. Identify and Document Findings

Document any issues, discrepancies, or anomalies found during the review.

8. Take Corrective Actions

Develop and implement corrective actions for any identified issues.

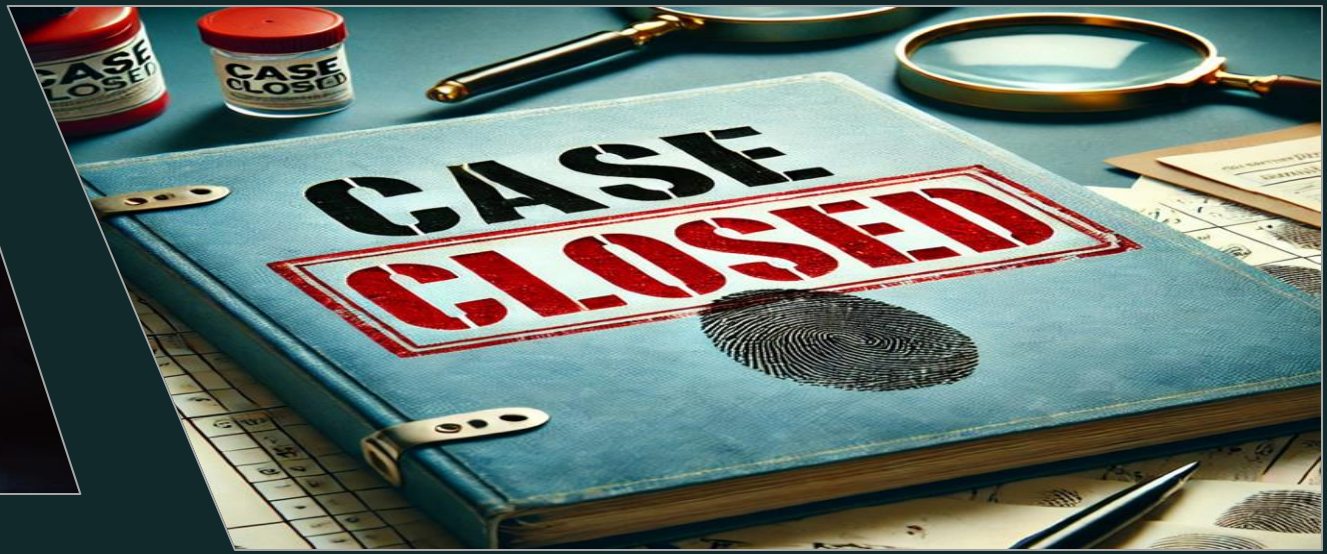
9. Follow-Up

Ensure that corrective actions have been implemented effectively.

10. Review Cycle

Set up a schedule for regular audit trail reviews to maintain ongoing compliance and system integrity.

Case Closed: Examples



Case Closed: Examples

Hypothetical Scenario

The audit trail for the electronic Trial Master File (eTMF) is being reviewed as part of the company's quality control process.

During the annual review of the eTMF audit trail, the TMF Specialist, notices something unusual: Several informed consent forms (ICFs) were updated and deleted in the system without proper justification.

The audit trail shows that the changes occurred after working hours and were not aligned with any specific planned activity. The user responsible for the deletion is listed as "admin_temp," a temporary administrator account created to manage system updates.

Case Closed: Examples

01 The Investigation Begins

❑ Interviews

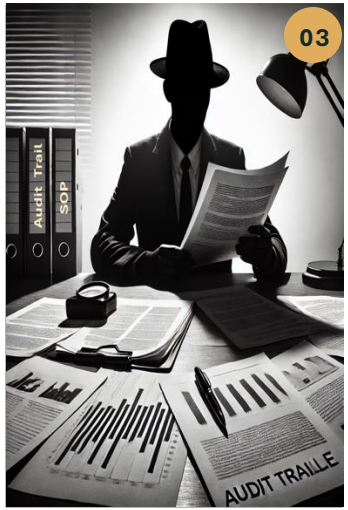
The IT department confirms that the "admin_temp" account was used to run routine system updates and that the account should have been deactivated immediately after the update.

❑ Escalation

The issue was escalated to Business leadership and QA. Team launches a deeper audit review to identity if other documents were affected.

02 Uncovering the Root Cause

The temporary admin account was improperly managed, remaining active longer than necessary.



04 Conclusion: Lessons Learned

Proper access controls are essential in preventing unauthorized actions.

Regular, automated monitoring of audit trail activity can help detect anomalies early.

Clear SOPs are crucial to maintaining the integrity of clinical trial data.

Establishing robust CAPAs ensures that similar incidents do not occur in the future.

03 Corrective Actions

❑ Recover Original Documents

Restored documents from backups

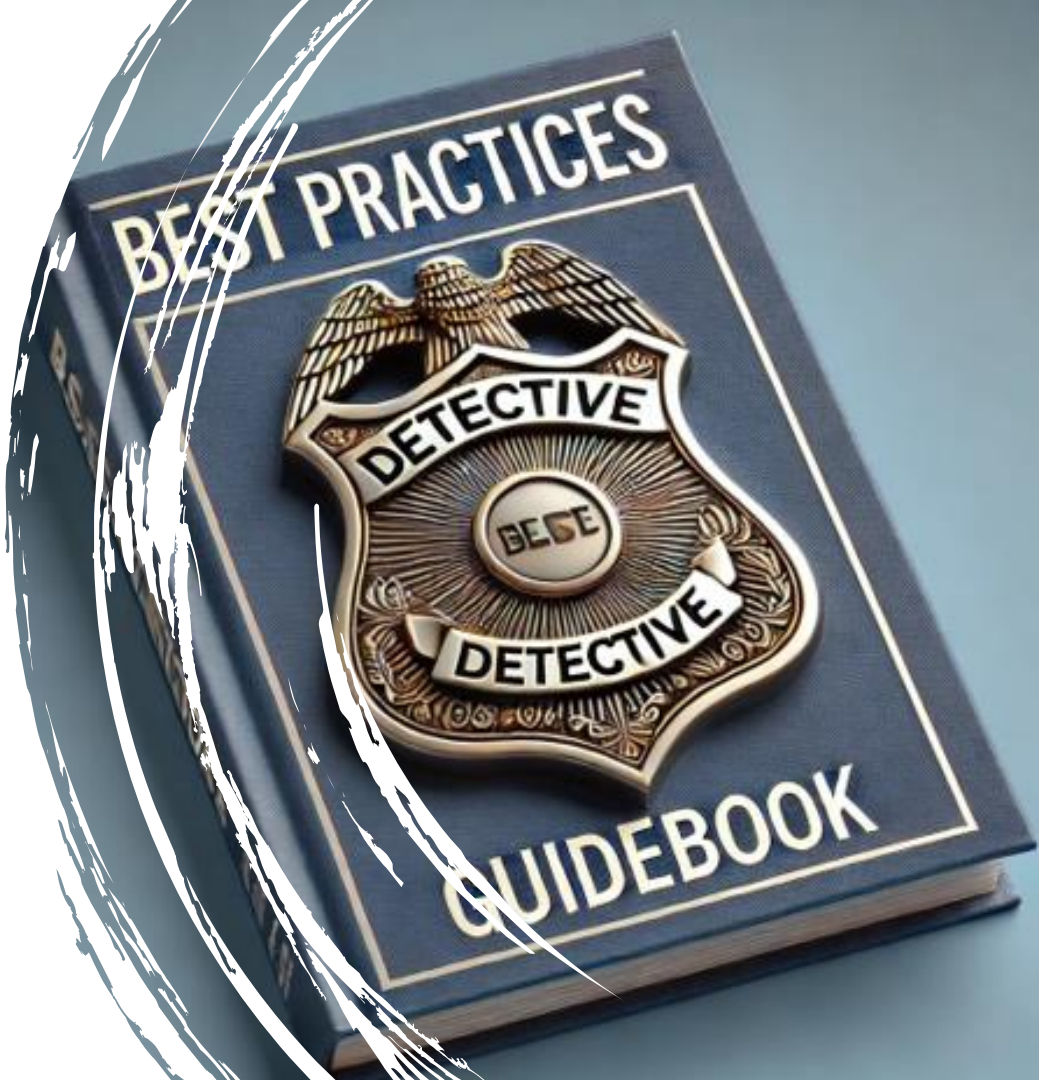
❑ Strengthen Access Controls

New SOPs implemented to ensure that all temporary admin accounts are deactivated immediately after updates.

❑ Continuous Monitoring

Quarterly audit trail reviews were made mandatory.

Best Practices for eTMF Audit Trail Review



The Investigator's Guide: Best Practices

Establish Clear Procedures

Create and document procedures for conducting audit trail reviews to ensure consistency and clarity.

Documentation and Reporting

Summarize the outcome of each review. Create detailed reports of findings, actions taken and recommendations.

Regular Reviews

Conduct reviews at regular intervals.

Maintain a Continuous Improvement Approach

Review and update procedures.

Tools of the Trade

Tools of the Trade

eTMF system with robust audit tracking capabilities

Audit Trail must be in a human-readable format and accessible at any time.

Efficient Search Techniques

Conduct efficient searches for an effective eTMF audit trail review. Include effective search strategies and techniques, such as keyword searches and filters, to quickly find relevant data.

Advanced Analytics and Visualization Tools

Use analytical tools to identify trends and graphical reports / dashboards to provide visual summary.

Looking Ahead: Tools of the Trade

Anomaly Detection

AI Algorithms can identify and detect deviations.

Automated Data Analysis

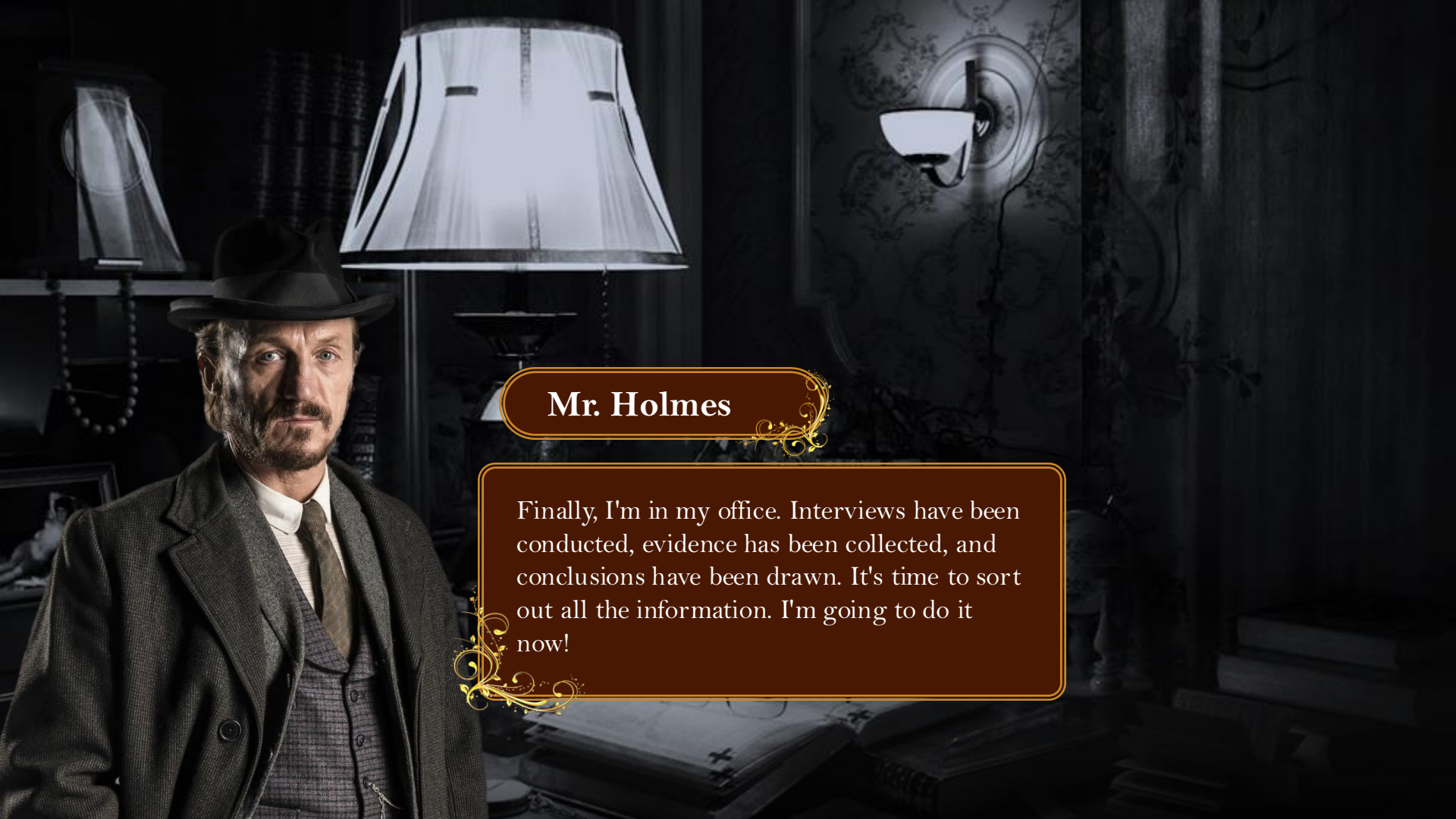
Analyze and extract key information from unstructured data.

Predictive Analytics

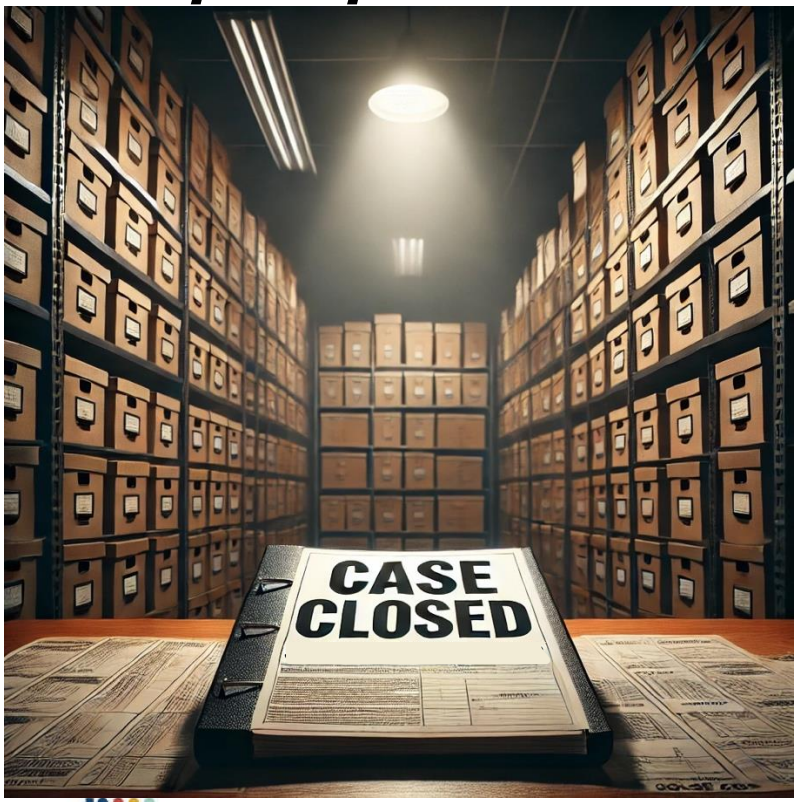
Use historical data to predict potential future risks.

Automated Review and Reporting

Generate summarized reports of audit trail reviews, highlighting key findings, trends, and issues .


Mr. Holmes
Finally, I'm in my office. Interviews have been conducted, evidence has been collected, and conclusions have been drawn. It's time to sort out all the information. I'm going to do it now!

The Mystery Solved



Reviewing the eTMF audit trail is essential for maintaining the integrity, security, and compliance of clinical trial documentation, ensuring that all processes are documented and traceable.

- Establish Clear Objectives
- Focus on High-Risk Areas
- Implement a Structured Process
- Review Key Elements Thoroughly
- Document and Report Findings
- Continuously Improve

Thank You!