acdm

association for **clinical data management**

Getting started with Audit Trail Review in Clinical Trial data: An Essential Guide

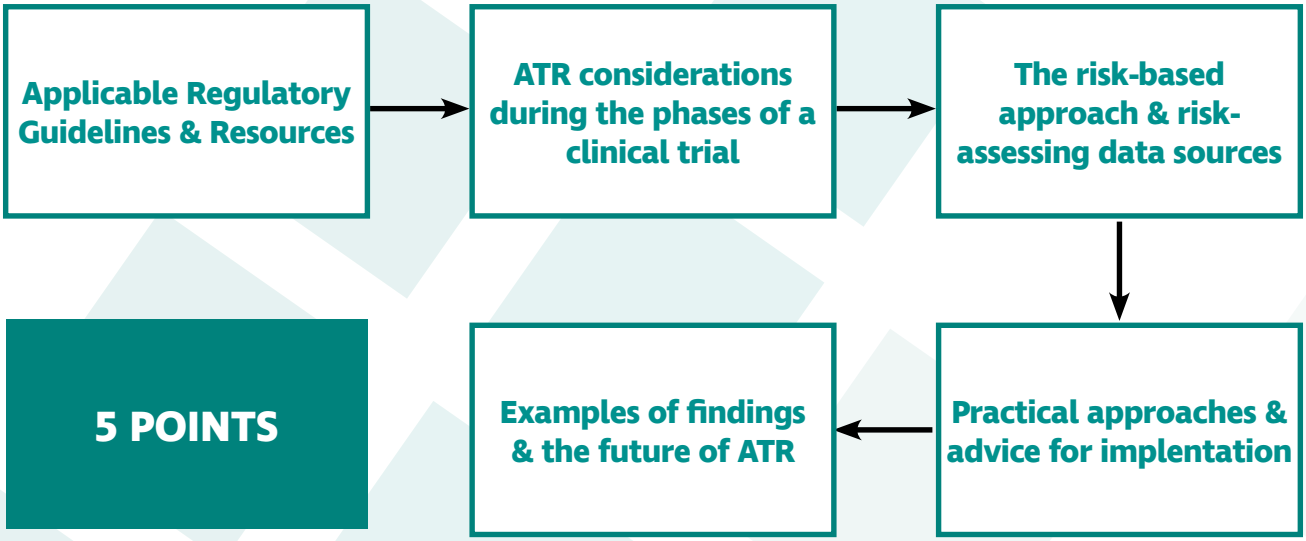
Authors: Jennifer Logue Nielsen, Angela Paterson, Uwe Lahr, Rich Davies, Martin Miller

Contributors: Frank Jensen, Silvia Perez, Simone Schopper

Date/Version: 16SEP2024, V1.0

Getting started with Audit Trail Review in Clinical Trial data: An Essential Guide

Disclaimer: The information presented in the paper draws upon the combined understanding and knowledge of the Association of Clinical Data Management (ACDM) Audit Trail Review (ATR) Expert Group on this topic and is provided as an aid to understanding the environment around audit trail review in clinical research. These recommendations are the opinion of the authors and do not necessarily reflect the position of individual companies. Readers should assess the content and recommendations considering their own knowledge, organisational needs and experience as well as interpretation of relevant guidance and regulations.



In clinical research, the integrity and reliability of the data are paramount. The Audit Trail Review (ATR) process serves as an important tool to ensure that the data collected during clinical trials is complete, accurate, and consistent and in accordance with ALCOA principles (attributable, legible, contemporaneous, original, accurate).

With the finalisation of European Medicines Agency's (EMA) Guideline on computerised systems and electronic data in clinical trials in March of 2023, regulatory expectations around Audit Trial Review in clinical research have been set. By reviewing audit trails and metadata where appropriate, research organisations can identify and address any discrepancies or anomalies in the data, thereby safeguarding the reliability of the trial's outcomes. In addition, because audit trails and their metadata show the journey of the data and all actions performed along the way, including the source, changes, reasons changed and the date and time of the action, Clinical Data Management (CDM) can trace the data back to the source of truth and can measure the integrity of the clinical data they are managing.

Audit trails and metadata can generate a vast amount of data, and developing a process to perform a review of this data can be complex and confusing. Therefore, we have developed this document to outline the essential aspects of ATR. Drawing upon the collective expertise of the ACDM ATR Expert Group, we have devised suggestions and recommendations for how organisations can get started with this complex process.

This paper will describe the various use case categories where ATR can be effectively applied, such as system access, data changes, data collection, reporting, and device concerns. It emphasises the importance of a risk-based approach and aligning ATR with existing processes and tools to enhance efficiency and effectiveness. We share examples of findings and operational insights into the process. In addition, vendor and Contract Research Organisation (CRO) perspectives on ATR will be explored, and future directions in the ATR space will be addressed.

Note: there are two common types of ATR; trial-level ATR, and system-level ATR. This paper will focus on trial-level ATR, which involves review of the audit trail generated for the clinical data collected as part of the clinical trial. System-level ATR involves reviewing the audit trail for clinical systems used to collect the clinical data and is usually performed by the organisation's system owners and not clinical data mangers. System-level ATR would be employed to review for potential misuse of GxP systems used in clinical trials, e.g. review the audit logs to identify viruses/malware, security breaches, configuration changes, etc. For more information relating to system-level ATR, we would recommend reaching out to the GxP system owners.

General recommendations to organisations getting started with ATR

Now that you are ready to implement an ATR process, how can you get started? Below are our recommendations and suggestions on where to start:

1. Perform a thorough Impact assessment of applicable guidelines

The applicable guidelines which will inform the implementation of the ATR process in your organisation are: Medicines and Healthcare products Regulatory Agency's (MHRA) **Guidance on GxP data integrity**, EMA's **Guideline on computerised systems and electronic data in clinical trials** and the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use **(ICH) E6 R3** (which is currently in draft at time of writing). These guidelines should be reviewed and understood before embarking on your ATR implementation. They also need to be read in the context of your organisation and the types of clinical data being collected. It is important to interpret the guidance and consolidate it with your current processes.

Section 6.13 of the MHRA **Guidance on GxP data integrity**, published in March 2018, discusses audit trail review, and states that "Routine data review should include a documented audit trail review where this is determined by a risk assessment... Reviewers should have sufficient knowledge and system access to review relevant audit trails, raw data and metadata." ATR should therefore be treated like all other data reviews which are included in the Data Management (DM) and Risk-Based Quality Management (RBQM) processes.

In addition, Section 6.15 of the MHRA guidance describes that a procedure should be in place for data review and approval, and that a risk-based review of relevant metadata should be included. Recommendations around documentation of review are also included in this section, explaining how to file and archive the evidence of ATR.

It is worth noting that ATR is mentioned in the Food and Drug Administration (FDA) guidance Data Integrity and Compliance with Drug CGMP, also published in 2018, which discusses the use of audit trail review from the Good Manufacturing Process (GMP) perspective. In the GMP space, like the clinical space, audit trail review is an expectation to ensure that the robustness and reliability of the manufacturing practice: "Your approach to audit trail review and the frequency with which you conduct it should ensure that CGRP requirements are met, appropriate controls are implemented, and the reliability of the review is proven."

EMA's **Guideline on computerised systems and electronic data in clinical trials**, published March 2023, provides useful over-arching guidance, including focusing on critical data and taking a risk-based approach. This guideline is in line with the recommendations in the earlier MHRA paper, with sections 6.2.1, and 6.2.2 discussing audit trail review. It is important to note section 6 advises that: "Electronic source data, including the audit trail should be directly accessible by investigators, monitors, auditors, and inspectors without compromising the confidentiality of participants' identities". This re-iterates the need to consider data privacy rules in your implementation of ATR at a trial-level.

The EMA guideline also states, "The scope of this guideline is computerised systems, (including instruments, software and 'as a service') used in the creation/capture of electronic clinical data and to the control of other processes with the potential to affect participant protection and reliability of trial data, in the conduct of a clinical trial of investigational medicinal products (IMPs)". Therefore, ATR may not always be required for every clinical trial or project. For example, projects which do not have an IMP may not use an electronic data capture (EDC) for their data capture and therefore an audit trail will not be generated. Also, for projects where data is obtained via a registry review, it would not be necessary to perform an ATR, as it is a non-interventional trial. However, for projects where an IMP is being studied, all the data sources should be part of the assessment to determine if they are in scope for ATR. For example, if EDC is being utilised, review of the system generated audit trail would usually be in scope based on the guidance. The decision to implement or not implement ATR for a clinical study should always be documented as part of the project's risk assessment process, along with the reason it is or is not applicable.

Note that the EMA guideline stipulates that all systems used to create or capture clinical data are in scope of ATR, however, it may be that there is no added value in data management performing ATR on the data generated by a specific system. For example, external lab data audit trail may not be accessible and therefore CDM are unable to perform the ATR on this data; this should be documented as a consideration during the risk-assessment.

Finally, the current draft of **ICH E6 R3** guideline, due to be finalised later in 2024, mentions audit trail review as a piece of metadata review. Section 4.2.2 describes the approach for implementing, evaluating, accessing, managing and reviewing relevant metadata. Section 4.2.2 (c) describes how audit trails and logs should be decipherable and facilitate analysis. Section 4.2.3 expands on themes seen in the previous guidance, stating that "Procedures for review of trial-specific data, audit trails and other relevant metadata should be in place. It should be a planned activity, and the extent and nature should be adapted to the individual trial and adjusted based on experience during the trial." This guideline reinforces the view of ATR being incorporated into the existing data review cycles and the current RBQM processes within the organisation. It is interesting to note that the inclusion of metadata review in ICH E6 R3 will increase harmonisation across regions around this process because it applies to the US, the EU, and Japan, making it easier for data managers to harmonise their ATR process.

2. Consult the SCDM Audit Trail Review, a key tool to ensure data integrity paper

The Society for Clinical Data Management (SCDM) paper **Audit Trail Review, a key tool to ensure data integrity** is a good place to start when implementing audit trail review in your organisation. This paper details potential objectives of ATR and describes in detail five Use Case Categories:

- System Access
- Data Changes
- Data Collection
- Reporting
- Device Concerns

After reviewing the paper in detail, assess the use cases provided and determine if they are covered by existing processes. If an existing process covers the use case, ATR may not be needed. If the use case is not covered by other processes, or using ATR would provide an additional useful mitigation, it will be within the scope of your ATR process, along with any other applicable use cases.

The SCDM paper mentions that: 'All data types and systems used to generate and manage those data, should be considered in scope of ATR.... Need for ATR should be evaluated for all data supporting clinical development, patient safety, product quality and regulatory compliance using justifiable risk-based approaches.' This guidance confirms that ATR should be considered in relation to all data sources for the project, each data source being risk assessed to determine if ATR is an appropriate control/mitigation. In addition, EMA's **Guideline on computerised systems and electronic data in clinical trials** also refers to ATR being applied to critical data.

By focusing on critical data when setting up your ATR process initially, the scope of ATR can be contained and will be more manageable to conduct.

3. Incorporate ATR into existing processes and tools

Audit Trail Review can be built into each stage of the clinical project; trial sourcing and setup, trial conduct, and closeout/archiving

Prospective ATR involves planned reviews of audit trail metadata to identify potential issues with data integrity, data quality or data processes.

Retrospective ATR involves reviews of audit trail metadata when issues have been identified and the root cause analysis can be investigated via ATR.
Prospective ATR may be employed as a mitigation for any data quality/data integrity risks to the project, or it may be employed during maintenance as a regular process review, for example, to ensure system access is appropriate for all users and no changes have been made by unauthorised users.

For every study a general risk assessment based on the study protocol is required and a Risk Assessment Categorization Tool (RACT) is recommended. Based on the risk score, suitable mitigation actions are defined. In cases where ATR could help identify if a risk becomes an issue, it can be used as a mitigation action.

To easily identify if the audit trail of the system under review can provide the required information, an initial assessment of ATR capabilities should exist. It should be performed for each GxP relevant system. If such a system does not provide a machine-readable audit trail it may not be applicable to use it.

Mitigation action shall include review cycles. In this scenario, the ATR is covered in the RBQM process. For each use case, an initial risk should be added to RACT.

Overleaf is an example of how the RACT could be completed for risks where ATR is the most appropriate mitigation strategy.

Risk Statement	Risk Category	Project Phase	Impact Description	Probability Score	Impact Score	Detectability Score	Overall Risk Score	Risk Decision	Risk Mitigation & Control Measure	Risk Owner
Data fields remain editable until DB Lock. Therefore, it is possible for the site to modify the primary data multiple times.	Data Integrity	Maintenance	Variables related to project endpoints which have large number of changes are an indication that the data has not been correctly transcribed and can call into question to accuracy of the data being entered.					Mitigate	Implement KRI for volume of changes to Primary Endpoint Variables via Audit Trail Report.	RBQM Manager
Sites need to centrifuge the blood samples for x mins, y mins after blood draw as per protocol. The start and end times of centrifuge need to be recorded in EDC to ensure processing is completed as per protocol. There is a risk that this will not be collected correctly at the time of processing the sample.	Process	Maintenance	If site does not process sample as per protocol, the sample will not be able to be analysed and project will be missing critical data for results. If length of time sample is centrifuged is not reported correctly, samples may be tested but provide inaccurate results.					Mitigate	Review of the user-name, date and time en-tered for the for start and end times of centrifuge variables to identify where this data is not entered contempora-neously.	RBQM Manager

The organisation will need to determine who is the process owner, and this will depend on the organisation's set-up. What we have seen thus far is that Data Management are usually involved, especially in relation to EDC systems, and often other systems like eCOA/ePRO (electronic clinical outcome assessments and electronic patient reported outcomes). System owners may need to take the responsibility, depending on the system.

In the future, we would like to see audit trail review become a more centralised process, embedded within the RBQM function. However, at present there are challenges to overcome to make this realistic. For example, the audit trail metadata needs to be able to be easily accessed, consumed, and analysed for it to be useful to a central team. This is one of the main current challenges when trying to scale up the ATR process; organising the multiple heterogenous audit trail data sources into a manageable format that can be interrogated, displayed, and compared.

What follows are additional considerations for the different phases of the clinical trial:

Sourcing Phase
Emphasise the importance of considering audit trail requirements from the beginning. For organisations with an Internal Audit function, ensure that your audit teams are aware of any requirements you may have around audit trails when they are auditing vendors/Contract Research Organisations (CRO). This will enable them to ask upfront about your requirements. For Sponsor organisations, if a CRO will be auditing a vendor, determine how you will ensure that the CRO Audit team is aware of your requirements. For vendors being contracted by the CRO, consider adding text around audit trails and audit trail review into contracts with CROs.

Ensure that ATR requirements are met by educating internal stakeholders on requirements around audit trails and audit trail review. Determine how much particular skill areas need to know about ATR at this stage and how you can go about this.

When it comes to external data vendors, in our experience there are differing levels of what vendors know and what they can supply regarding audit trails and audit trail review. If a vendor is not able to meet your requirements, you will need to consider the purpose of the data in the trial and consider any mitigations to cover the risk. It may be that the organisation chooses not to go with a vendor if they cannot produce a GxP compliant audit trail for their computerised systems and cannot guarantee the integrity of their data.

At the Request for Proposal (RfP) stage, ensure your requirements for audit trails and ATR for vendor and CRO systems, as well as any third-party systems, are described in the request for proposal. When Bid Defence meetings are held, ensure the trial teams responsible for making the decision are aware of requirements, including the selection of digital health technologies.

Start-up Phase
During the Start-up phase of the project, the specifics around ATR for the trial will be agreed upon. How ATR will be implemented should also be considered during this stage of the project. Below are the tasks which are often required during project start up.

Consider providing the contracted Vendors or CROs a generic document describing the ATR requirements, detailing why the review should be performed and how each review should be conducted. It is recommended that such a document would describe findings and learnings from previous trials. If the sponsor is performing ATR in-house, this document should be shared with the study team responsible for the project.

CROs or Sponsors may have a master list of checks/visualisation for different systems based on vendor processes; this could be a template with a list of standard visualisation/checks and whether they will be used with a particular data source and the rationalisation around this. If visualisations are available, this may make implementing the ATR easier from a set-up perspective; however, it should be noted that, from a risk-mitigation perspective, it will not cover all possible risk scenarios. Therefore, it is important to perform a complete risk assessment of the project to identify any gaps where ATR needs to be implemented and a standard report/check/visual is not available. On the other hand, standard visualisations are useful to set up, as these can help the organisation learn what their data is telling them, and usually leads to further identification of use cases for future trials.

Create the "ATR Plan". The ATR Plan can be a stand-alone document or a part of existing documentation, such as the Data Management Plan or the Data Review Plan, depending on organisational needs. The project Risk Assessment will document general risks which can be mitigated/identified via ATR, while the ATR Plan will detail the specific reviews to be applied to which metadata collected in the trial. All the data sources in the clinical trial should be risk-assessed for the need for Audit Trail Review and the ATR plan should include the rationale if not performing ATR on a data source. A description of the review and the frequency should be described for data sources where ATR will be performed. This is in line with the SCDM ATR paper where it is stated that 'ATR techniques and frequencies should be based on data criticality and associated risks.

Determine any KRI thresholds or simple statistics, such as standard deviation, to be used in the trial. These may be more applicable when ensuring the number of changes to critical data items is not excessive. Vendor RBQM systems may also have functionality around this. For example, CluePoints has a 'Time Similarity Test' for identifying unusual grouping patterns in time-orientated data, that can be used for detecting issues in ePRO data. Not all scenarios will need statistics though.

Additionally, consider if it would add value to visualise cycle times via audit trails. For example, if you want to ensure Investigators are accessing the EDC database and reviewing and approving eCRFs regularly, this could be done via visualisation to identify patterns and trends. Other cycle times can also be visualised, depending on the user actions in the audit trail.

Consider how you will document your review; will you use existing templates or systems, or will you create specific templates specific to the ATR process? Again, this will depend on organisational needs and set-up. Additionally, consider creating standard text for the ATR Plan for some data types that are used across multiple clinical trials. You could also have project-level templates for ATR at the compound level, again based on the organisational need.

In this phase, you should also consider how you will implement ATR for the data sources in scope. This could be the setup of visualisation for the metadata. As the audit trail data quantity is a level of magnitude higher than the clinical data, additional considerations around (long-term) data storage will be needed. This is especially true in large studies, where the file size of the audit trail may exceed size limits for loading into a visualisation platform, and strategies to mitigate this may be needed. Further considerations would be needed around the validation level of visualisation built in-house.

Audit trail data can be uploaded into applications such as Spotfire, Qlik Sense, or Power BI to create visualisations, or SAS to create listings. Commercially available RBQM solutions such as CluePoints also provide capabilities for ATR alongside the wider support for detecting risk from clinical and operational data. In addition, we see vendors implementing reports and functionality around audit trail review into their systems.

Finally, consider training needs at the study site in relation to audit trails. Per the EMA Guideline, section 6.2.2, the Investigator should receive an introduction on how to navigate the audit trail of their own data to be able to review changes. Audit trail reviewers should always be trained in the system and be familiar with the data/study.

Conduct Phase
In the conduct phase, the review of the data will be performed as specified in the plan.

Determine how you will follow-up on any findings. In general, decisions should not be made on any anomalies or discrepancies found via visualisation; further follow-up should first be performed using the clinical data and associated documentation. You may need to consult with the monitors or speak with an internal QA function. Root cause analysis should be performed and corrective and preventative actions may be needed, depending on the finding.

In relation to the reasons for data changes, it may be found that the data is changing because queries are being raised and influencing the site to change the data. Alternatively, it could be that a site user had opened the incorrect participant's casebook and changed the wrong data. Data may be changed for any number of reasons; therefore, it is necessary to follow-up consulting the clinical data and associated documentation before any action is taken.

Consider if a CTMS or another clinical system would be useful for documentation of results and follow-up. If ATR is part of the RBQM for the project, the findings from ATR can be included for discussion within the RBQM cross-functional meetings.

It is recommended to document the results for each round of review, if done more than once. We have seen this done in multiple ways: Documenting review in a specific report, documentation via already existing documentation, for instance, via data cleaning meeting documentation, or documentation via the trial risk-log—again this will depend on the setup within your own organisation. The result of the review should describe the outcome of the review and the remediation actions to correct any potential finding detected. This result also serves as supportive documentation for any inspections as it provides evidence the ATR process was conducted. If it wasn't documented, it didn't happen.

Based on the review and the findings, the process for ATR may need to be modified/adapted to better suit the trial. Consider reviewing the process throughout the conduct phase to ensure that reviews planned at the beginning remain relevant. You may need to include additional reviews that were not planned at the beginning of the trial but are deemed necessary after one or more review rounds.

Closeout and Archival
During closeout and archival, you will finalise the review, learn from the results, and archive your documentation.

Before decommissioning and closure of the system, ensure the audit trail does not have any records after database lock. If there are, this will need to be investigated.

Finalise the report of your review and perform analysis and trending on the findings. Trending can occur on the study, program, compound level, or on the data/system type. Consider how trends and learnings will be reported within the organisation and how to feed the trends discovered back into the overall process and use cases.

Finally, consider any actions related to future audit or inspection. Consider facilitating any future audit or inspection by creating documentation that will allow any auditors or inspectors to quickly get an overview of the metadata. Such a document would explain the format and general structure of the audit trail/metadata, describe any columns that are not self-evident, or other relevant information. Be aware that inspectors may request access to systems.

4. Risk-assess the Metadata for all data sources

After looking at the overall risk-assessment and identifying general risks where ATR could be a useful mitigation, you should risk-assess data sources in detail.

ALL data sources, internal and external, should be risk-assessed for the need for ATR in a clinical trial. This is important to document, and it provides evidence that ATR has been considered from the beginning in a proactive manner. The documented ATR risk assessment can be made available to auditors/inspectors if required.

Audit trails should include the data changes (previous and current value), who made the changes, when the changes were made, and the reason for the change. Metadata related to primary and secondary endpoints and other critical data should always be considered for audit trail review. However, it may not always be possible/practical to implement ATR.

For example, lab data parameter values are often not changeable, only updates to header fields/ subject identifiers are possible, and this is documented during the reconciliation process. If data cannot be updated, and subject identifier changes are tracked via reconciliation, reviews of the audit trail, if available from the vendor, may give little meaning, as the lab values themselves cannot be updated.

Furthermore, ATR may not be required on project data that is generated by wearable devices, if a risk assessment of the metadata shows that potential data issues are identified via other means. For example, the wearable device tech owner could have controls built into their system which identifies inconsistencies in the data collection, e.g., if no data has been generated for certain amount of time, dramatic changes in the data that is being produced for the individual wearer, etc.

When performing the risk assessment of the metadata for ATR, it is not only necessary to consider how the data will be obtained, but also to consider the criticality of the data to the outcome of the project. Clinical research projects can generate vast amounts of data and it is not possible (or efficient) to review every data point's journey from its source to its final destination.

For example, if the wearable device tech owner's systems do not have checks in place to identify anomalies in the data, and the data generated from these devices is not a part of the project's primary or secondary endpoints or is exploratory data, ATR may not be needed for this data. These rationales should be included in the risk-assessment so any future auditors/inspectors can understand the decisions you made for each data source.

Additionally, data may be integrated directly into EDC or a Clinical Data Warehouse (CDW) from the central lab, interactive response technology (IRT) vendor or other external data source and therefore the metadata might only show the date and time of the import, and the program name used to complete the import, rather than the full audit trail. In such instances, ATR would not be required as the integration will be set up to only allow the data to be imported if it meets the required criteria. If an import fails, the required team members will be alerted and the log will be reviewed as to why the data was unable to be imported; thus, negating the need for ATR on this data source. Instead, ATR may be performed in the original system, before export and integration into a downstream system, if appropriate.

It is also worth noting that some systems which are in scope for ATR, may be owned by other parts of the organisation outside of clinical development/data management, e.g. the IRT system used in the trial. In this instance, a coordinated effort will need to be made across the systems/stakeholders in a trial for the risk-assessment for ATR and may require education and training around regulatory expectations for metadata review/audit trail review in other parts of the organisation. For larger organisations, this could mean multiple processes around audit trail review in different part of the organisation.

5. Data privacy concerns and redaction

It is important to consider data privacy and redaction in relation to audits and inspections.

As ATR is a regulatory expectation, **external auditors** may request to see the documentation of what has been reviewed on a trial level. As the audit trail for some data types may contain sensitive data such as user names, it is recommended to redact such content to be compliant with GDPR. One method of redaction is creating an internal and external version of documents. The external version would have redacted data and/or masking of user names. In case a system ATR is a topic of sponsor audit, consider if the study identifier or other variables should also be redacted if the database contains data from multiple sponsors.

In cases of **regulatory inspection**, redaction is not likely to be accepted as inspectors would expect to see the data you have, and additionally, they may request access to systems.

It may be necessary to contact your organisation's data privacy office/expert for more guidance around privacy concerns.

6. Unblinding considerations

When risk-assessing your data sources, first consider the unblinding potential for your data sources and then consider who will review the data and whether their role is blinded or unblinded in the trial. As stated in the paper Audit Trail Review: A Key Tool to Ensure Data Integrity, "Reviewers' roles need to be considered when making audit trail reports available".

For example, if an IRT system is used for a blinded trial, ATR may be used to determine if any changes have been made to randomisation data. It is important for blinded team members to remain blinded to the treatment arms assigned to the participants in the trial. In addition, some types of lab data may also be unblinding and if ATR is in scope for this data, blinding considerations need to be carefully applied. Consider possibilities around removing or masking any columns from an audit trail or having unblinded roles review these audit trails.

7. Invest time in learning what your audit trails will tell you from the beginning

There can be a steep learning curve with audit trail review - reviewers may not be experienced in reviewing metadata and it can be difficult to figure out exactly what to review, how to review it and how to visualise the data contained in audit trails.

Using the risk-based approach allows you to focus your review on data sources which are important to the success of the individual clinical trial. Review of all metadata in a trial is neither feasible or desirable, so focusing on what matters will allow the organisation to learn and refine their processes more efficiently.

Before implementation of a process, it is necessary to understand the structure of the metadata generated by the data sources and what it contains as it will inform the organisation on implementation of the ATR process and help identify any upskilling requirements for those performing the review.

It is often necessary to invest in training and up-skilling of the reviewers who will devise and perform the audit trail reviews. They may need training in the review method, the platform used to visualise the data, and how to perform data interrogation, for example.

After implementing an ATR process, take time to thoroughly examine the metadata provided with the systems' audit trails and learn what it can tell you. Learn which variables denote the previous and current values, where it is documented when the changes were made, which time zone is the timestamp local to, and how to determine the number of times a datapoint has been changed. This part of the process will be greatly facilitated by visualisation of audit trials through an analytical platform.

The necessity of understanding what the audit trail is telling you cannot be understated. It will be difficult to further refine and improve your process without spending time with this step. However, as you gain experience and become more familiar with your (meta)data, you WILL notice anomalies, inconsistencies, irregularities, or red flags in the audit trail. The findings you discover will provide you with more use cases, and this will allow you to refine your review and interrogation of the audit trail in future trials, improving the process and building in efficiencies.

8. Start small and build up over time

Depending on the resourcing available, consider a stepwise approach over time. Pick a use case or two that would add the most value to your organisation's data.

Many organisations employing EDC for the collection of their study data will already be performing audit trail review for the System Access use case. At a minimum, the review will include which users have access to the system, which sites/subjects' data they can access and the role the user has been assigned. The purpose of such review is to ensure that the user has the appropriate access for their role on the project and they are not able to perform any tasks in the system which they are not trained for. ATR for system access can also flag any users who have access and have not logged into the system for a long period of time; this can indicate users who are no longer involved in the study and should have their access revoked. ATR for system access is also useful to flag where Principal Investigators (PIs) have not activated their accounts and thus flag that they are not regularly reviewing their patients' data, or that they will not have access to sign the forms prior to any interim or full database lock.

If the same EDC is being employed for multiple projects in the organisation, it may be possible to develop standard checks/visualisation for ATR. We have seen organisations develop some standard visualisation around data changes to primary endpoints and key safety data, for example. And while most EDC systems have reports around cycle times, visualising them in an analytical platform as part of an ATR process can make ongoing identification of lagging cycle times more detectable. For example, you could create a visualisation around EDC users with site roles that have data changes at more than one site, which is typically not expected behaviour.

Every trial and the associated risks are different, so ATR will never be a one size fits all approach. On the other hand, you must start somewhere and producing a few standard visualisations could be a first step. Afterall, doing something, even if it is not perfect, is better than doing nothing at all. The route your ATR process development takes may vary as you go along, as you find new methods, new tools to support and identify efficiencies. Therefore, it's important to begin as soon as you can, learning and modifying the ATR as you go.

The goal is proactive and planned review of all audit trails in the scope of ATR as specified within the risk-assessment, which is adjustable based on the results of the review.

Keep in mind that a stepwise approach may not meet regulatory requirements or cover all risk scenarios.

9. Examples of findings and use cases from audit trail review

System	Finding	Action taken
EDC with real-world data (RWD) collection	RWD Collection project required data to be anonymised; the site could not associate subject ID with actual patient data. Sites were required to enter the data from the patient records on the same day, as it was not possible to link the subject ID generated in EDC with the actual health record of the patient for returning to data entry. ATR was applied to ensure sites adhered to the process and all data for one subject ID was entered on the same day and within reasonable time frame (approx. 15mins).	Use case
EDC	ATR was used as a tool to ensure sites adhered to the process for data anonymisation.	Use case
Various	Can help identify data that should not have been collected, for example data collected after the last protocol defined visit/ assessment.	Use case
Various	Investigating data changes made by the sites without a discrepancy and/or data change request.	Use Case -- high numbers of changes can indicate a need for re-training.
eCOA	Low confidence in the accuracy/robustness of site entered data. eCOA data captured at one site was captured in a matter of minutes versus the typical 20-minute duration of sites within the wider trial.	The data from the site was not used.
eCOAs	Improperly inactivated eCOAs via review of data changes in the eCOA/ePRO platform.	Reactivated eCOAs where appropriate.
eDiary	eDiary not being inactivated on time, leading to data collection past the last scheduled visit/assessment in the study.	Additional data was then deleted because of this finding.
ePRO	Misconfiguration of data collection systems. Data was detected as being entered by a site user rather than a patient.	Correction of user role and data update as needed.
ePRO	ePRO data fabricated by site staff. A high proportion of ePRO patients were seen to complete episodic diaries at a similar time. The site had omitted to distribute the diaries to the patients and on discovering their mistake, fabricated the patient results at the end of their working day.	The site was excluded from the trial

9. Examples of findings and use cases from audit trail review

EDC	Sites had to aliquot the blood samples before sending to central lab. The samples had to be centrifuged within a specific timeframe. Times of collection and processing were collected in EDC. Upon review, one site entered times which were outside of the window and when queried, updated the times as per the expectations. Reviewing the Audit Trail showed same individual updating the times in EDC and site audit confirmed times of the sample processing were not routinely captured in the source data and the team member was fabricating the processing time.	Data potentially unusable
EDC	Background processes in the coding module adding lines to the audit trail for the EDC system after DBL, which was unexpected behaviour.	No impact on data, but alerted team to investigate the process around coding updates
EDC	High numbers of cancelled queries in the EDC system due to improperly firing edit-checks on an outsourced study.	Alerted Sponsor Data Manager to investigate
EDC	Mandatory forms in EDC being inactivated in error for some screen-fail subjects.	Forms reactivated so mandatory data entry could occur.
EDC	ATR helped identify "professional subjects" who would enrol in the same study at different sites.	Data potentially unusable
EDC	ATR identified a site user had updated subject data at another site.	Correction of access and update/ verification of data at the incorrect site.
EDC	It was detected that an Investigator was signing case report forms at multiple sites, when they should only have access to their own site.	Correction of access for the Investigator and verification of entry and re-signature of data at the incorrect sites.
EDC	A study had on-site monitoring, with 100% source data verification (SDV). Dates of SDV were found in the audit trail that did not correlate with a site visit or monitoring report.	Re-SDV by another monitor, improved training and oversight of monitors.
Various	System error generating duplicates identified via inspection of the audit trail.	Error corrected and duplicates removed.
Various	Ensuring that key safety variables that are updated over the course of the study, for example, the question I wish I was dead from yes to no, are verified and properly documented.	Follow-up via Monitor/CRA

10. Vendor and CRO Concerns:

Sponsors, being ultimately responsible for data integrity and reliability of the results from the data, need to determine the appropriate level of ATR and provide CROs/Vendors with an ATR Plan and guidelines for maintaining independence in those performing the review.

Going back to a previous point, the sponsor must understand their audit trails and potentially provide use cases, depending on the data source, before asking CROs or Vendors to perform ATR. The sponsor should ensure that the CRO/Vendor has an independent function/process around ATR. This could be a separate QA function performing the review independent of those involved in creating the data or performing data management. Our experience is that it can be quite challenging to find CROs and/or Vendors to do this review on behalf of the sponsor organisation. Sponsors need to be prepared to do it in-house.

If a CRO or vendor is doing the review, it is important the sponsor be informed of the results on an ongoing basis so any necessary follow-up can occur. The sponsor should ensure that reviews are being performed correctly and meet sponsor expectations.

Technology vendors have an opportunity to support and facilitate ATR by ensuring access to the relevant data captured by their solutions. This can be in the form of providing access to the raw audit trail content such that it can be utilised by downstream analytics, and by introducing easily consumable ATR reports from within their own solutions. Such reports need not be complicated to introduce but should cover simple risk scenarios relevant to the given system.

For instance, if an EDC solution tracks the date a user became trained, it is relatively simple to report on any users who may have manipulated data before they were trained. This confirms if the user enablement and training process has been implemented effectively.

Archived audit trails should be in a format which is searchable and dynamic (not only in .pdf) to facilitate analysis, but our experience is that audit trails can be vastly different in format and contents, which is a hindrance to scaling up this process. More industry dialog is needed on the state of metadata in the industry and what is needed to facilitate metadata review.

What could the future look like for Audit Trail Review?

Clearly, Artificial Intelligence and Machine Learning need further investigation. The ability to detect complex scenarios within enormous data volumes would seem to be an ideal target for the application of machine learning and artificial intelligence. Developing machine learning solutions to identify robust and reliable issues from audit trial data will require temporary hurdles to be overcome, but the promise is there that this kind of solution could become a real value-add to remove complexity and burden from users responsible for performing ATR. In addition, AI will aid in the efficiency of detection of data issues across clinical trials, for example, a program of clinical trials for a specific compound.

One challenge in developing a model capable of predicting issues from audit trail data is that it will require an appropriate volume of training data and connected output scenarios. Large datasets will be needed for training these AI/ML models, which means that more industry collaboration is needed to gather and share enough data and findings to train the model. In addition, variations in the structure and format of audit trail data may complicate the generation of transferable models for predication, although AI/ML is better placed to deal with those variations than other approaches. While an AI/ML approach to detecting risk from audit trail data might be 'a' future scenario, it might not be accessible to all or appropriate for all kinds of scenarios. Statistical monitoring and data visualization approaches are valid and accessible in the near-term. Variations in audit trail structure complicate the use of audit trail data and more standardization would be a welcome future state to aid consumption and interrogation, regardless of the technical approaches being implemented. However, with the progress of and pace of machine learning, it is hoped that such challenges can be overcome to create viable and helpful solutions in this space.

However, with the progress of and pace of machine learning, it is hoped that such challenges can be overcome to create viable and helpful solutions in this space.

We should also maintain our focus on why we are doing audit trail and metadata review. Not only is it a way of looking at data changes, finding errors, detecting fraud, and ensuring data integrity, but it is also a tool for maintaining oversight of the trial process. Via visualisation of cycle times, identifying training needs at sites, and determining system design improvements through review of audit trails and metadata, the clinical trial process is improved, not only for the benefit the sponsor, but also for the benefit of the sites, and ultimately the patients.

In conclusion, the Audit Trail Review process ensures the integrity and reliability of data in clinical research. By implementing ATR, organisations can identify and address issues, safeguarding the validity of trial outcomes. This paper has outlined the key aspects of ATR, including regulatory guidelines, use cases/examples of findings, and risk-based approaches.

As ATR can be complex, a stepwise approach, starting with high-impact use cases, is often useful. Continuous learning and adaptation of the organisational process will enhance the effectiveness of ATR, ultimately contributing to the quality and integrity of clinical trial data.

www.acdmglobal.org