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Audit Trail Review Hot Topic Questions Answered

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Audit Trail Review Questions Answered

Context

In January 2024, the Audit Trail Review (ATR) Data Management Expert Group (DMEG) hosted an ACDM Hot Topic Session. Jennifer Logue Nielsen (Lundbeck and DMEG Chair), Martin Miller (Parexel), Richard Davies (CluePoints) and Catilina Nobre (AstraZeneca) led the session titled "Audit Trail Review: What do you need to know?".

Audit Trail Review (ATR) is now described in three regulatory guidances: the MHRA GxP Data Integrity Guidance from March 2018, the EMA Guideline on computerised systems and electronic data in clinical trials from March 2023 and in the draft ICH e6 (R3) guidance, released in May 2023. However, many in Data Management or other functions may not be aware of expectations around audit trail review or even where to start with this complex process.

This Hot Topic provided an overview of Audit Trail Review from a Sponsor, CRO and vendor perspective, including challenges and recent learnings.

The session was well attended by members of the ACDM, and due to time constraints, not all the questions in the Q&A could be addressed. The ATR DMEG decided to take these questions away to thoroughly answer as a group for ACDM members.

The group have compiled the following document with their answers.

Audit Trail Review Questions Answered

Q. Are there any known articles/paper explaining examples of ATR checks? I.e. what exactly to look for in the AT?

A: https://scdm.org/wp-content/uploads/2021/04/2021-eCF_SCDM-ATR-Industry-Position-Paper-Version-PR1-2.pdf

This paper describes 5 Use Case Categories:

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

Looking at the use cases in the paper is always a good start when deciding to implement audit trail review. Additionally, the EMA guidance on use of computerised systems provides useful over-arching guidance, such as focusing on critical data and taking a risk-based approach.

Q. When ATR is first presented, it feels like an extra 'thing' we don't have the resource to do. It would be useful to see how it fits within risk-based monitoring etc. rather than just an 'add-on'

A: We would suggest incorporating ATR into the existing processes and tools to the extent possible. When identifying risks for a trial, consider if ATR could be used to mitigate them. A risk you might consider mitigating via ATR could be high numbers of changes/deletions to your primary endpoint.

Q. When recording the reason for change to eCRF data: 1. Do you require this for all data fields, or just key endpoints? 2. Do you allow users to provide their own reason as free text, or do you provide users with a set of predetermined options to choose from? If so, what options do you allow?

A: Reason for change should be applied to all datapoints in the eCRF (the eCRF is a GxP system falling under 21CFR part 11). It will depend on which EDC system is being used as to how you can configure the reason; i.e. LOV or free text, or combination.

Audit Trail Review Questions Answered

Q. Any papers or metrics on the impact of ATR yet? How often are there issues discovered through this process? Is this a more efficient/cost effective way of picking up problems versus say an on-site monitoring visit? Would be good to have some evidence of what is good 'value' to add in terms of identifying high risk issues.

A: One of the challenges here in calculating ROI is that we need the industry to share their potentially negative scenarios that ultimately surfaced, so we can work backwards to calculate how much unnecessary cost and/or delay was accrued by not detecting the scenario sooner. What we can share today are the examples of operational challenges that have been detected by the use of proactive use of audit trail data in the data monitoring activities:

1. Misconfiguration of data collection systems. Data was detected as being entered by a site user rather than a patient, this was because the patient had been given the incorrect role when the ePRO system had been configured.

2. 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 trail. The data from the site was excluded.

3. 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, were fabricating the patient results at the end of their working day. The site was excluded from the trial.

4. RWD Collection project required data to be anonymised; site could not associate subject ID with actual patient data. Site 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).

5. Sites had to aliquot the blood samples before sending to central lab. The samples had to be centrifuged within 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 team member was fabricating the processing time.

6. Improperly inactivated eCOAs via review of data changes in the eCOA/ePRO platform.

7. Background processes in the coding module adding lines to the audit trail for the EDC system after DBL (not expected behavior).

8. 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.

9. High numbers of cancelled queries in the EDC system due to improperly firing edit-checks on an outsourced study (alerted Sponsor DM to investigate)

10. Mandatory forms in EDC being inactivated in error for some screen failure subjects.

Q. What do I need to consider in terms of GDPR? Usually plain site staff names are in there, which is personal data.

A: One approach is to record names and other identifiers in the audit trail (to fulfil GCP) but 'redact' them from any visualisations or exports. Be sure to redact for eTMF or any kind of export.

It also will depend on the system and the type of data is being collected, i.e., difference between a user name compared with full name and address.

With eCOA/ePRO – be very careful to identify places where potential personal data regarding **participants** might be located in audit trails in advance of any review and mitigate appropriately.

Q. How far are others going with the scope of audit trail review. A lot of critical data may come from 3rd party labs/niche labs. Are people looking into this?

A: From ICH_E6(R3): 'Acquired data from any source should be accompanied by relevant metadata'.

ICH_E6(R3) '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.'

Audit Trail Review Questions Answered

The ATR performed for a trial all goes back to the original risk-assessment. Some considerations around lab data might be:

1. Can actual lab values be updated, or is it only possible to update subject details, i.e. header information via the reconciliation process?
2. Is it possible to get an audit trail from the lab?
3. What is the criticality of the lab data being risked-assessed? The associated risk-level is clearly higher if the data source is a primary endpoint.

Q. Who are the most common owners of the ATR process?

A: To some degree, this would depend on your own set-up. What we have seen thus far, is that Data Management tends to be involved, especially in relation to EDC systems, and potentially other systems like eCOA/ePRO. System owners may need to take the responsibility, depending on the system.

Thinking longer term, we hope audit trail review can become a more centralised function. However, there are challenges to overcome to make this realistic, such as being able to easily access, consume and analyse the required data with a central team.

Q. What is the most interesting or project valuable finding that you have found from ATR activity?

A: Additional examples from those listed above are:

1. ATR helped identify “professional subjects” who would enrol in the same study at different sites.
2. ATR identified a site user had updated subject data at another site.

ATR was used as a tool to ensure sites adhered to the process for data anonymization.

Can help identify data that should not have been collected, for example data collected after the last protocol defined visit/assessment.

Audit Trail Review Questions Answered

Q. How do we ensure that proper independence and reported results between the audit trail data creators (Vendor/CRO) and Sponsor requesting the review.

A: Audit Trail data should follow the same ALCOA+ requirements as all clinical data generated during the trial. Audit trails and metadata help to tell the story of the data journey and therefore review of this data should be in line with the existing processes. Prospective audit trail review should form part of the Data Management Plans or other documentation depending on organization setup and be included in the trial risk assessment at study start-up.

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 is those performing the review. The sponsor should ensure that the 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.

Archived audit trails need to be in a format which is searchable and dynamic, not only in .pdf.

Finally, if the vendor cannot or will not perform ATR on a data source, what is your backup plan for reviewing this data?

Q. For those who already have this in place, how are the costs handled? Assume it may become std in contracts, but e.g. is it an out of scope on a contract currently?

A: We have seen ATR mostly done by the sponsor to this point, rather than a CRO or vendor, but this can depend on the system.

If a CRO or Vendor will perform ATR and it is not included as per original key risk process/ critical data review, etc., the Sponsor should define the scope of ATR required and conmod/ oos created accordingly.

Q. Is there any commercially available apps to monitor and analyse ATR?

A: Audit trail data can be uploaded into applications such as PowerBI or Spotfire 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.

Q. AT should be de-identifiable for inspection review? We are supposed to adhere to GDPR in this as well - what's your take on this with user ID's? What does need to be considered in terms of GDPR (audit trail data usually have site staff names and roles included)?

A: Consider redacting the Personal Identifier data in case of inspection.

ePRO –patient or site user names could be in the email address or data clarifications, be careful.

Q. How is the data in the ATR is monitored, by analysing visuals and user impression, or do you use statistical methods based on defined thresholds, like Stand Dev?

A: We believe it depends on what use case is being checked. If need to compare across sites the frequency PIs are accessing the EDC database, this could be done via visualisation to identify if a trend or if any site PIs are not logging into the database. However, if checking that the number of data changes for a certain critical data item is not excessive, you could define a KRI threshold or simple statistics like standard deviation to identify this. 'ATR techniques and frequencies should be based on data criticality and associated risks.' (SDTM Audit Trail Review: A Key Tool to Ensure Data Integrity, Apr2021)

There are statistical methods for identifying certain ATR scenarios. 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 for instance.

Q. What learning did you experience with regard to some data items with an unusual high rate of changes? I would expect re-training or other?

A: Root cause analysis should be performed to determine why the data items are being changed. Decisions would not be made on audit trail findings alone, and follow-up should be performed on any initial finding.

For example, in relation to data changes, it could be because queries are being raised and influencing the site to change the data, or it could be that site user had opened the incorrect participant's casebook and changed the original entries, then the data was changed back to reflect the correct participant's data (a normal data entry error). Once a root cause is established, a corrective and preventative action plan can be created, if required. Not all findings would require follow-up.

Q. Would you suggest that ATR has to look across all aspects of a clinical trial - potential fraud, data errors, process etc, as the scope could become huge?

A: SDTM Audit Trail Review: A Key Tool to Ensure Data Integrity, Apr2021: '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.' The EMA guidance document referenced above does refer to ATR being applied to critical data. Data Errors, Process problems or misconduct could all theoretically be the root cause outcomes of detecting an unusual pattern of activity with respect to critical data. By focusing on critical data, the scope of ATR can be contained and hopefully kept more manageable.

The risk-assessment of data sources in a trial for ATR is a key document is therefore a way to show your considerations on whether or not ATR is needed for a particular data source. When starting with ATR, it may be easier to limit the scope to 2-3 uses cases to develop experience and build up from there.

Q. Has anyone already thought to apply Machine Learning (ML) for detection of unusual settings in AT data? Or is this only feasible once variables are standardised?

A: For AI/ML models, the audit trail data will need to be in a standard format which can be interrogated. Large datasets are needed for training AI/ML models.

Q. Thoughts opinions on leveraging AI/ML to support ATR. Is this happening yet?

A: More sponsor/vendor collaboration is needed to gather enough data and findings to train the model.

Also, more standardization is likely needed for audit trial/metadata in a general sense—currently audit trails are quite heterogenous which can make compiling and analyzing/visualizing them difficult, let alone training an AI/ML model on standardized data.

We hope AI is the future!

Q. Do we need to have an audit trail for all types of studies? Sometimes we didn't use an EDC for collecting the data, and we didn't have an audit trail.

A: Great question. In the EMA Guidance, it 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)**".

If no audit trail was generated, because the process used did not generate an audit trail, then ATR cannot be performed. If audit trail is not present, but could have been, then this would likely be a critical audit finding. Look at clinical data instead.

External data should also have audit trails, but these are not always accessible in our experience.

Q. There needs to be considerations in audit trail review around maintaining study blinding if in place, especially if it's related to your critical data.

A: Absolutely! When risk-assessing your data sources, consider the unblinding potential for your data sources. Then consider who will review the data and whether their role is blinded or unblinded in the trial.

"Reviewers' roles need to be considered when making audit trail reports available" (SDTM Audit Trail Review: A Key Tool to Ensure Data Integrity, Apr2021).

Find out more about the ACDM ATR DMEG here.

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