



Audit Trail Review  
Jennifer Logue Nielsen, ACDM ATR DMEG  
04MAR2024

# ATR @ACDM –Agenda

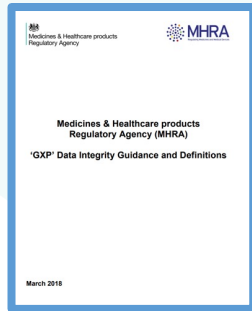
- ATR Landscape 2024
- Getting started with ATR?
- DMEG activities/summary



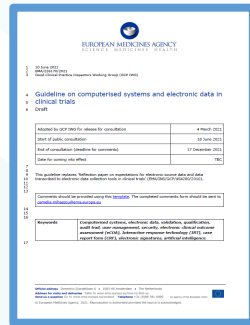
**acdm24**   
 Copenhagen  
3<sup>rd</sup>-5<sup>th</sup> March

# The ATR Landscape 2024

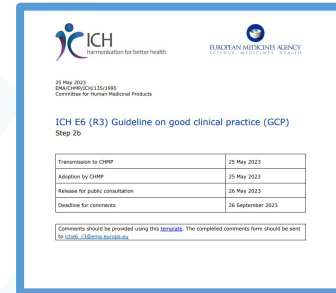
# Audit Trail (AT) where have we been, where are we at?



March 2018, MHRA GxP Data Integrity Guidance



June 2021, DRAFT EMA Guidance on electronic systems



May 2023, DRAFT ICH E6 (R3) Guideline on GCP



Jan. 2024, Hot Topic: ATR



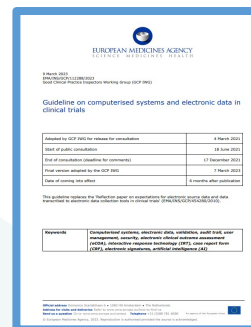
Mar 2018

March 2024

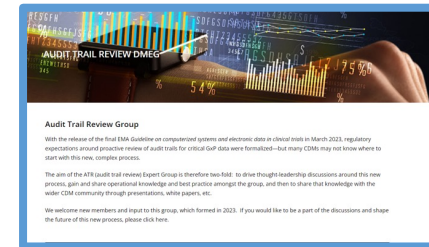
October 2020, ATR paper released



March 2023, FINAL EMA Guidance on electronic systems



August 2023, ACDM ATR EG formed



# Insights around ATR from the DKMA dialogue session, June 2023, Copenhagen

## 1. Risk Assessment

- Need to risk-assess and document all data sources in a clinical trial—important document from an inspection standpoint

## 2. ATR vs. Metadata review

- ATR is more than just looking at data changes
- Draft ICH E6 R3 highlights that not only Audit trail should be reviewed but also metadata for trending, systems improvement, etc.

## 3. Vendors

- Maintaining oversight if done by a vendor
- Vendors—think about Audit trail from the beginning, put in contracts, get audit trail from vendor or ensure retention contractually

Getting started with ATR?

# Disclaimer

- The information presented in the slides draws upon the combined understanding and knowledge of the ACDM ATR EG and is provided as a tool to understanding the environment around audit trail review in clinical research data. These recommendations are the opinion of the authors and do not necessarily reflect the position of individual companies.
- Readers should assess the content considering their own knowledge, organizational needs and experience as well as their interpretation of relevant guidance and regulations.

# General advice about ATR

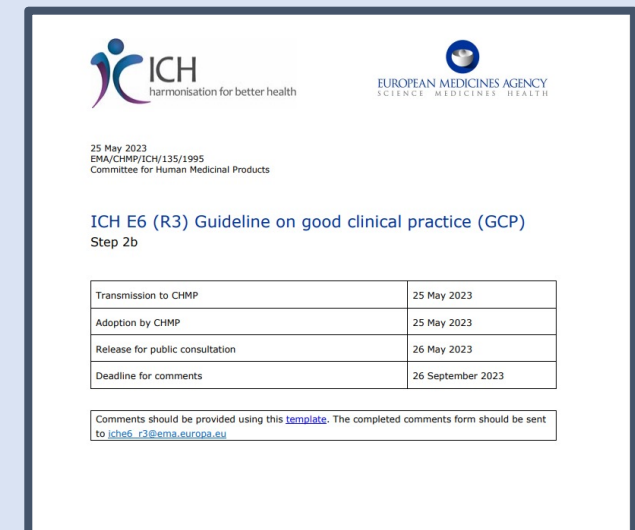
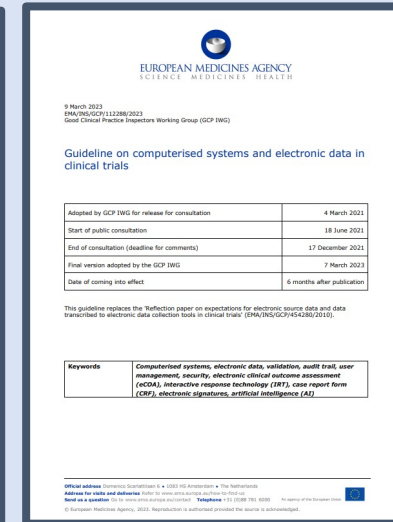
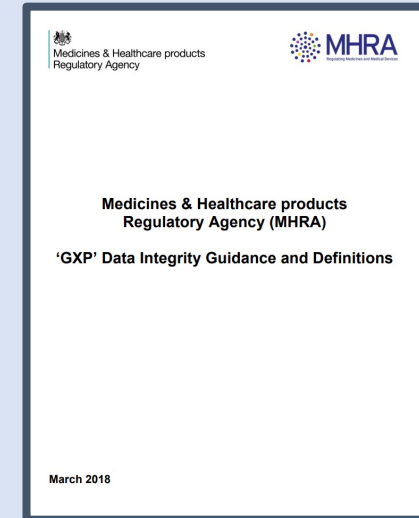
- Invest time in learning what your audit trail will tell you.
- Risk-assess all data sources for the trial on the need for ATR
- Have a process for ongoing review of audit trails, which is tied in to the overall risk assessment for the trial
- Possible starting point: 'standard checks' relating to primary endpoints/key safety data (critical data)
- Focus on the value-add and nice to have vs must-have (via your IA of Guidelines)
- Anything is better than nothing!

# Getting Started: Do a thorough Impact Assessment of the applicable guidelines

- **MHRA Data Integrity Guidance (2018)**
  - Multiple sections, see 6.13
- **EMA Guidance (2023, Final):**
  - See section 6, 6.2.1, and 6.2.2
- **ICH GCP E6 (R3, draft):**
  - Greater harmonization—ICH e6 applies to the US, EU and Japan
  - 4.2.2 Relevant Metadata, Including Audit Trails
  - 4.2.3 Review of Data and Metadata
  - Final March – Sept. 2024

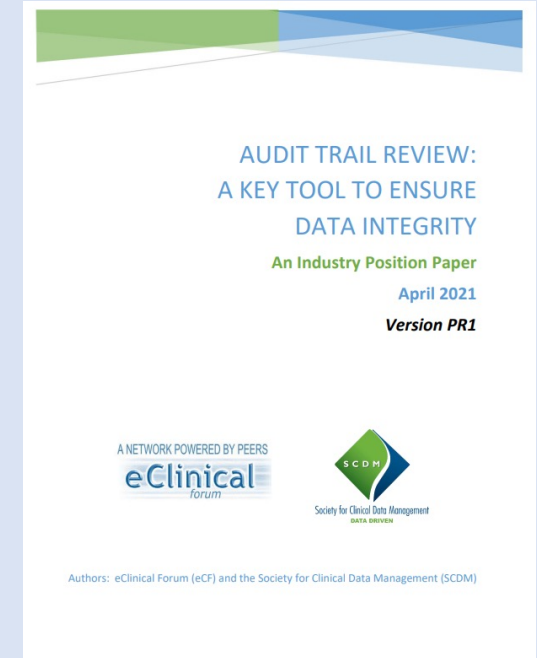
## MHRA IN 2018:

*“There should be a procedure that describes the process for review and approval of data. Data review should also include a risk-based review of relevant metadata, including relevant audit trails”*



# Read the Industry Paper on ATR and assess at the use cases

- Assess uses cases, determine which are not covered by other processes
- If not covered by other processes → may be in scope for ATR



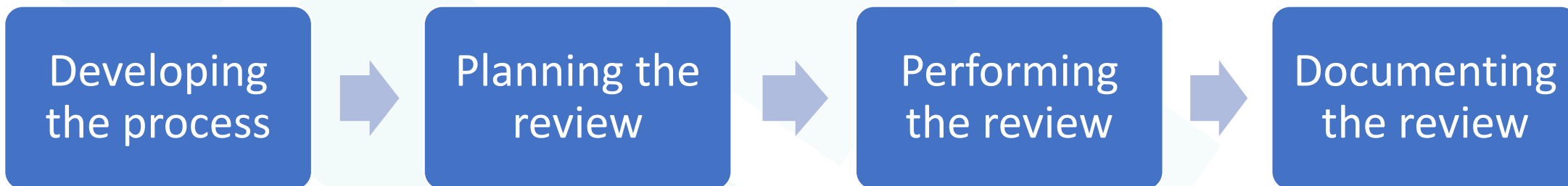
Defines data integrity risks where ATR could be used as a primary tool for investigation:

System access, Data Changes, Data Collection, Reporting, Device Concerns

[Audit trail review: a Key tool to ensure data integrity \(scdm.org\)](https://www.scdm.org)

Use Case Category 2: Changes					
2.1: Incomplete data- data deleted	Data item deleted without query or explanation (e.g., removed AEs impacting analysis and label)	EDC, IRT, eCOA	audit trail in source system(s)	Vendor	Report (listing, dashboard) for inactivation or deletion at field-, form-, record-, or patient-level
	Mass deletes or changes/updates by system non-user (e.g., IT admin super user role)				
	Frequent deletions within a subject record or by a user				
	Record- or patient level-deleted data				
2.2: Changes to inclusion/exclusion (I/E) criteria, primary efficacy, key secondary	Any changes to I/E criteria or eligibility scoring by authorized user could impact patient safety by enrolling ineligible patient	EDC, IRT, eCOA	audit trail in source system(s)	Vendor	Interactive dashboard or listing of all changes to any records used in I/E criteria, eligibility scoring or primary efficacy, key secondary efficacy, safety or critical data.

# Developing an ATR process at the trial-level and the questions to ask



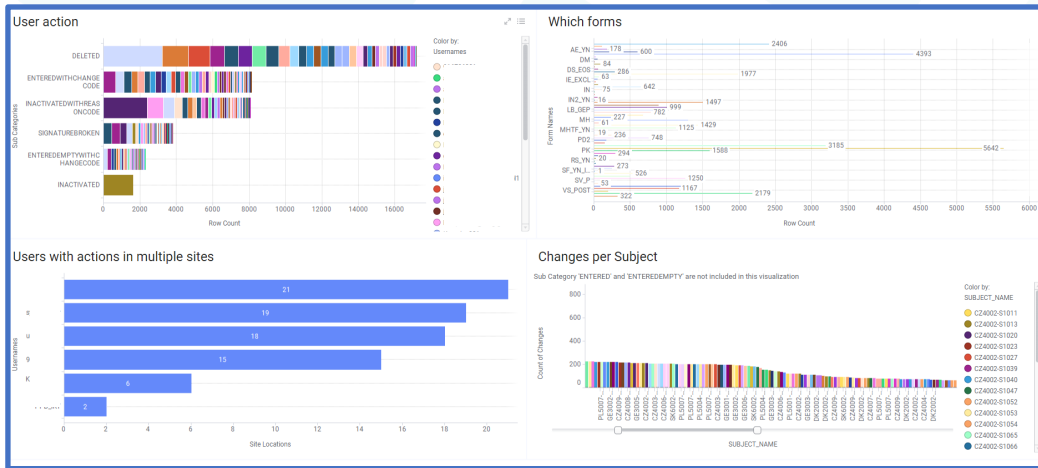
1. How will you review the audit trail? And what role(s) will review?
2. What is the level of your process?
3. Internal vs. External (vendor) data

1. How will you risk-assess the data in the trial?
2. Where will you document the risk-assessment?
3. Frequency, timing of review (i.e. trial phase)
4. Mitigations

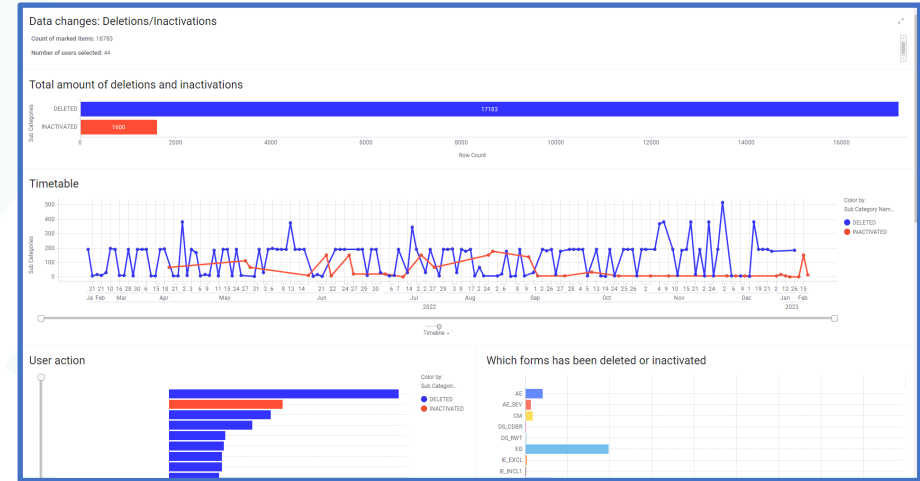
1. Will you include standard data visualizations?
2. Details on the how
3. Documenting learnings from review

1. Where will you document the results?
2. Considerations around documenting results

# Visualizing audit trails



Data Changes – trends



Deletions and Inactivations -- trends

Sponsors: What is your audit trail data going to tell you? How will you review? What will you then ask it?

You have to dig into the data....



# ATR considerations in different study phases

# Sourcing Phase - Consider ATs/ATR from the very beginning



**Ensure Internal Audit teams are aware of ATR requirements when auditing vendors/CROs**

*In cases where the CRO audits a vendor, how will you ensure that the CRO is asking about audit trails/ATR?*

**Ensure your requirements for ATR for vendor/CRO systems, and any 3rd party systems are described**

*Consider describing audit trail/ATR requirements in documentation sent to CROs at RfP stage*

**Trial teams who pick vendors/CROs/ technologies should be aware of ATR considerations when picking vendors**

**Contract with CROs should have text about looking at vendor capabilities with audit trail, when the vendor is contracted by the CRO**



Considerations at this stage:

- 1. Differing levels of understanding** among vendors, and what they can supply in terms of audit trail and ATR—best to discuss as early in the process as possible.
- 2. Educating internal stakeholders** in the outsourcing process around audit trails ATR—what do other skill areas know about ATR? How much should they know?
- 3. Who should perform the review (if needed)?** What will you do if a vendor cannot or will not perform ATR? Will you not use them? Do it yourself? Will you mitigate? How will you mitigate?

# Startup Phase – Plan for ATR



## General Sponsor Requirements

Consider creating a generic document on ATs/ ATR as Guidance for vendors/CROs to explain the why and how

## What should be checked?

Consider having a master list of checks for different systems and pick and choose based on vendor processes

*Example—template with a list of checks and what the vendor is doing, i.e. checking ATR via a report, etc.*

## Make the 'ATR Plan', aka risk-assessment

What will you check for data sources? What is the method, frequency, etc.

How will ATR be documented? Whose templates will you use?

*For example, an ATR Plan trial-level template which can cover internal and external systems, and additionally, mitigations if ATR is not possible*

## Implement ATR

Implement the method, consider overall study timelines

What is the level of UAT needed by the reviewer per study, if any?

Considerations at this stage:

1. **Differing levels of vendor/CRO preparedness.** Costs/educational effort in having the vendor/CRO perform ATR, vs. doing it yourself (less time, less expense)—if you can get the audit trail
2. How does ATR fit into your process landscape?

# Conduct Phase – Perform and Document ATR



Reviewers must be trained in the system and familiar with the data

No decisions to be made based on ATR alone—all findings require follow-up.

Consider including simple checks, for example, visualizing users that have changes at more than one site (should only be sponsor/CRO), or that there are no changes after DBL in the audit trail.

What will you find?

*Example—ATR Report template to document findings, document follow-up/mitigation and corrective and preventative actions, if applicable. Or a system.*

How will you follow-up on any findings during ATR?

*Where and how will you document follow-up?*

Check the number of lines in the audit trail before DBL

Considerations at this stage:

1. **Developing internal competencies** around data visualization tools, data review, and understanding audit trails.
2. Follow-up will likely go through the monitor, consider if the CTMS can be used for issue tracking/resolution (or an RBQM system).
3. Additional roles not a part of the core study team, such as Compliance or QA, may need to be consulted during follow-up on findings.

# Closeout Phase – Document and Archive ATR



Ensure your audit trail has not changed since DBL – unless you have unlocked

Finalize the report, trend on issues in the study, are there any insights to be gained? As you gain more experience trend by study, program, type of system/data, etc.

Archive of documentation of ATR in the eTMF for the study; Archive ATs\*

*For example, documentation will be filed in the DM section of the eTMF by the reviewer. Where will you archive ATs?*

You are ready for that Inspection! How can you improve the process next time? What are the learnings?

Considerations at this stage:

1. What sort of trending will be performed on the findings and how?
2. How will trends be reported? To whom?
3. **As per the SCDM ATR Document (Apr2021), the archived ATRs should not only be stored in .pdf, but should be added to final archives in file formats that can be read with basic text editors, e.g. SAS, xml, csv, etc.**
4. What have you learned over the entire process that can fed back into Shared Best Practice?



# Focus Group Activities/Summary

Jennifer

# Future Plans for the Focus Group



## Driving ATR Forward

### Operational Insights around ATR

Making the move from theory to actual practice and how to get there, see more on next slide



### Looking into audit trails across clinical systems

Is there a need for more standardization of metadata?



### Keeping the conversation going

Thought leadership through presentation, dialogue and knowledge sharing



# Work in Progress



How to start, commonly seen use cases → Where to start if you are new to ATR



Suggestions for a minimum level of ATR (must-have vs nice-to-have) →  
Addressing the needs and challenges of smaller organizations



Process guidance and process text suggestions → Per EMA, procedures for ATR  
should be in place



Learnings and Best Practice → Breaking down barriers to wider adoption

# The ACDM ATR Expert Group

- See [Audit Trial Review DMEG » ACDM \(acdmglobal.org\)](https://acdmglobal.org)
- Just getting started –much more to come
- Collaborative groups are needed to collate industry knowledge and can help shape the future of the space
- We welcome new members!

**Audit Trail Review Group**










With the release of the final CDMS Guideline on computerized systems and electronic data in clinical trials, in March 2023, regulatory expectations around proactive review of audit trails for critical GCP data were formalised—but many CDMS may not know where to start with this new, complex process.

The aim of the ATR (audit trail review) Expert Group is therefore two-fold: to drive thought-leadership discussions around this new process, gain and share operational knowledge and best practice amongst the group, and then to share that knowledge with the wider CDMS community through presentations, white papers, etc.

We welcome new members and input to this group, which formed in 2023. If you would like to be a part of the discussions and shape the future of this new process, please click here.

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**Audit Trail Review Group members**

	<b>Jennifer Nielsen</b> (Chair) Senior Specialist, Clinical Data Management   Lundbeck <a href="#">Click to view biography</a>
	<b>Svein Bergsjon</b> Co-Founder   Vector <a href="#">Click to view biography</a>
	<b>Rob Davies</b> VP, Quality System   CapForm <a href="#">Click to view biography</a>
	
	<b>Tanya du Plessis</b> Chief Data Strategist and Solutions Officer   Soforum <a href="#">Click to view biography</a>
	
	<b>Alex Franklin</b> Project D&I Director - Immuno-Oncology   GSK <a href="#">Click to view biography</a>
	
	<b>Amy Neubauer</b> Director, Global Clinical Data Management Operational Excellence   Alkerm <a href="#">Click to view biography</a>

Thank-you!

Contact the ATR ACDM DMEG:  
[jnni@lundbeck.com](mailto:jnni@lundbeck.com)



# Backup slides



# EMAs (FINAL) Guideline on computerised systems and electronic data in clinical trials March 2023 still mentions audit trail

- 6 ‘Electronic source data, including the audit trail should be directly accessible by investigators, monitors, auditors, and inspectors without compromising the confidentiality of participants’ identities’
- 6.2.1 Audit trails should be visible at data-point level in the live system, and it should be possible to export the entire audit trail as a dynamic data file to allow for the identification of systematic patterns or concerns in data across trial participants, sites, etc
- 6.2.2 Procedures for risk-based trial specific audit trail reviews should be in place and performance of data review should be generally documented. Data review should focus on critical data. Data review should be proactive and ongoing review is expected unless justified.

EUROPEAN MEDICINES AGENCY  
SCIENCE · MEDICINES · HEALTH

9 March 2023  
EMA/INS/GCP/112288/2023  
Good Clinical Practice Inspectors Working Group (GCP IWG)

Guideline on computerised systems and electronic data in clinical trials

Adopted by GCP IWG for release for consultation	4 March 2021
Start of public consultation	18 June 2021
End of consultation (deadline for comments)	17 December 2021
Final version adopted by the GCP IWG	7 March 2023
Date of coming into effect	6 months after publication

This guideline replaces the 'Reflection paper on expectations for **electronic source data** and data transcribed to electronic data collection tools in clinical trials' (EMA/INS/GCP/454280/2010).

**WHY ATR (6.2.2)?** ‘Data review can be used to (among others) identify missing data, detect signs of data manipulation, identify abnormal data/outliers and data entered at unexpected or inconsistent hours and dates (individual data points, trial participants, sites), identify incorrect processing of data (e.g. non-automatic calculations), detect unauthorised accesses, detect device or system malfunction and detect if additional training is needed for trial participants /site staff etc. Audit trail review can also be used to detect situations where direct data capture has been defined in the protocol but where this is not taking place as described.’

# ICH E6 R3 draft talks about metadata review/ATR

## 4.2.2 Relevant Metadata, Including Audit Trails

The approach used by the responsible party for implementing, evaluating, accessing, managing and reviewing relevant metadata associated with critical data should entail:

- (a) Evaluating the system for the types and content of metadata available to ensure that:
  - (i) computerised systems maintain logs of user account creation, changes to user roles and permissions and user access;
  - (ii) systems are designed to permit data changes in such a way that the initial data entry and any subsequent changes or deletions are documented, including, where appropriate, using a risk-based evaluation, the reason for the change if it is not implicit;
  - (iii) systems record and maintain workflow actions in addition to direct data entry/changes into the system.
- (b) Ensuring that audit trails, reports and logs are not disabled or modified except in rare circumstances and only if a log of such action and justification is maintained;
- (c) Ensuring that audit trails and logs are decipherable and can facilitate analysis;
- (d) Ensuring that the automatic capture of date and time of data entries or transfer using data acquisition tools are unambiguous (e.g., coordinated universal time (UTC));
- (e) Determining which of the identified metadata require review and retention.

## 4.2.3 Review of Data and Metadata

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.