Data Management in Clinical Research

The ECRIN Data Centre Certification Programme

Christine Toneatti, ECRIN Quality and risk manager, Secretary of Independent Certification Board, International Auditor
Agenda

- Introduction - Some basics about audit assessments
- ECRIN Data Centres Certification Programme
- Auditors versus Auditees: which challenges!
Extensive experience in the development and implementation of a QMS (GLP, GCP, GPvP, GcLP, ISO 9001:2015, ISO 27001:2013; ISO 19011, ISO 17025, ISO 15189, ICH Q8, Q9 and Q10, Non-regulated research)

Perform international audits (as lead auditor) (Europe, US, China).

Prepare and coordinate inspections by governmental agencies (MHRA GCP and PhV, ANSM GCP and Micro-Organisms and Toxins, UK Human Tissue Agency, Veterinary Inspections, Federal Agency for Medicine and Health Products GMP Belgium, PK studies Teijin/PMDA)

Coordinate and perform GCP, GLP, Data Integrity, Medical Devices regulation, ISO 9001:2015 trainings.

Extensive experience in quality project development and management in Human Research.

Basic audit terminology

- **Audit**: systematic, independent and documented process for obtaining **audit evidence** and evaluating it objectively to determine the extent to which the **audit criteria** are fulfilled.

- **Audit criteria**: set of policies, procedures or requirements used as a reference against which **audit evidence** is compared.

- **Audit evidence**: records, statements of fact or other information which are relevant to the **audit criteria** and verifiable.

- **Source**: Guidelines for auditing management systems (ISO 19011:2011)
Audit is required in GxPs Human research environment

- **Audit**: A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

- The sponsor is responsible for implementing and maintaining quality assurance

- *Source: ICH GCP E6 (R2) 2016, adopted EMA June 2017*
Common Auditing Classification

- **First Party Internal audit** is an ongoing internal process of assessing that the operations are in place, procedures in use and performance is effective.
- **Second Party External audit** is an independent internal process assessment in the form of audit activities, trending of data, and reviews of exceptions and deviations. This provides objective evidence that the overall set of operations for key activities is effective. This activity should be performed a person or group independent of the activity being assessed.
- **Third Party External Audit** is an independent external assessment in the form of audit activities. This provides objective evidence that the overall management of operations is effective and compliant. Third party audits are conducted by independent auditing organizations, such as regulators or those providing certification customers, or by other persons on their behalf.

Monitoring can be conducted in many ways including but not limited to workplace observation of tasks, checklist activity assessment, and desktop review of data or documentation.
The program identifies non-commercial clinical trials units in Europe that have demonstrated they can provide safe, secure, compliant and efficient management of clinical research data. It does so by testing the units for compliance with published ECRIN data standards, using an on-site audit of the unit’s data management activities and of the IT infrastructure used to support those activities.
ECRIN Data Centres Certification Program

**Objective**

CTUs from ECRIN member and observer countries will be selected for audit within National Clinical Research Networks (ECRIN's scientific partners) and after assessment of their application by the ECRIN Independent Certification Board (ICB).
DM Centre certification Programme
Model Overview -5 components

Developed by an ECRIN expert group. Regularly updated. Available in the public domain.
ECRIN resource: Approx. 12 experts for each review, held approximately every 2 years.

Perform independent audits of applicants CTU for certification, CAPA review, re-audit, certification renewal audit.
ECRIN resource: Approx. 8 – 12 auditors with expertise in clinical trials IT, DM or QM.

Objective and independent assessment of the audits results to decide for certification.
ECRIN resource: A chair and 6 independent expert members, Meet 2 to 4 times a year.

Managing the certification programme (annual calls, organising audits and audit teams, organising ICB meetings, supervising reporting, maintaining auditors’ expertise and capacity, etc.)
ECRIN resource: 1 secretary

Development and maintenance of programme procedures, templates, and supporting tools for audit observations tracking, grading, and reporting.
ECRIN resource: ECRIN IT developer and programmer
ECRIN Data Centre Certification process

1. ECRIN sends out a call to Centres.
2. Centres receive applications.
3. ECRIN passes applications to ICB.
4. ICB prioritizes and arranges audits.
5. Audit reports are considered by ICB.
6. ICB makes a certification decision.
7. ECRIN establishes an agreement on ECRIN usage, listing certified data centres.
8. Audits take place.

Introduction - Basics about Audit assessment
Auditors versus Auditees - which challenges!
Conclusion
ECRIN Data Centre Certification Independent Board

- Are independent experts
- Up to 3 meetings / year
- Assessment can lead to 4 options:
  - Award certification;
  - Recommend CAPA written evidence;
  - Recommend re-audit to examine compliance;
  - Withhold certification.

<table>
<thead>
<tr>
<th>name</th>
<th>institution</th>
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<tbody>
<tr>
<td>Rita Veloso Mendes</td>
<td>Administração Regional De Saúde De Lisboa E Vale Do Tejo, I.P., Lisboa, Portugal</td>
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<td>secretary)</td>
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### ECRIN Data Centre Certification

**11 External Auditors**

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<tr>
<th>Name</th>
<th>Country</th>
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<tr>
<td>Michael Wittenberg, Christian Ruckes</td>
<td>Germany</td>
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<tr>
<td>Michael Faherty</td>
<td>Ireland</td>
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<td>Catherine Cornu</td>
<td>France</td>
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<td>Christine Toneatti</td>
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<td>Nancy de Debremaeker</td>
<td>Luxemburg</td>
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<td>Steve Canham</td>
<td>UK</td>
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<tr>
<td>Marta Pavia</td>
<td>Spain</td>
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<tr>
<td>Carlos Domingues</td>
<td>Portugal</td>
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<tr>
<td>Synove Otterbech</td>
<td>Switzerland</td>
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<tr>
<td>Regina Grossmann</td>
<td>Switzerland</td>
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- Expert in the audited domain: IT, DM, GCP and auditing practice
- Trained by ECRIN in the DM standards
- Auditor team: At least one **native speaker**; A mix of auditor experiences. Ideally – one DM, one IT, one QA.
DM Centre certification Program – 2018 achievements

ECRIN DM standards v4.0, April 2018 revised
https://zenodo.org/record/1240941#.W9F9_HszaUk

100% of 2018 audit plan completed: 3 initial Data centers audits (Leipzig, Oslo, Paris) – 1 Data center re-audit (Roma OPBG) – 3 CAPA reviews (Dresden, Heidelberg, OPBG Roma) - Postponing on request of Data Centers of 1 initial and 2 re-audits (Basel, BCN, Madrid) – 2 ICB meetings. 3 certifications (Dresden, Heidelberg, Roma OPBG)

5 programme presentations performed in 2018, (National Network Germany, France, UK – CORBEL project – Japanese ARO annual meeting)
Programme new features: readiness procedure; formalized CAPA review; Auditors qualification matrix; Automation of recommendations for improvement in Database.

Asia(pilot program in Japan): 2 Data centers initial audits (Kobe and Nagoya) - Training of 3 Japanese auditors
ECRIN Data Centre Certification Applications

ECRIN DM Certification Program
Mapping of Applications Country
(21 in total)

Germany: 7
France: 4
Italy: 4
Portugal: 1
Spain: 2
Norway: 1
Switzerland: 1
**ECRIN Data Centre Certification**  
**Certified Data Centers**

**TOTAL Certified as of October 2018**

- Germany; 5; 46%
- France; 2; 18%
- Italy; 3; 27%
- Portugal; 1; 9%
- Other: 0%

- Germany
- France
- Italy
- Portugal
- Spain
- Hungary
- Norway
- Switzerland
- Czech Republic

- 32 audits of CTUs (since 2011 - initial and re-audits including Japan)
- 3 units certified at the first attempt.
- 5 units certified on CAPA review
- 4 units certified after re-audit (1 unit required re-audit and CAPA)
- 3 units are under evaluation (CAPA review, pending ICB review)
- Certification has lapsed for 2 units
ECRIN Data Centre Certification Value and challenges

Model effectiveness

based on the broad acceptance of the standards associated to a robust process for ensuring that certified entities conform to them.

Model sustainability challenges

- The maintenance of capacity and high qualification of the auditors,
- The maintenance and consolidation of ICB expertise with an active ICB member involvement.
- The program automation and controlled documents adaption requiring regular developments of new processes, functionalities and tools to face an evolving environment and the user and stakeholders needs.
Expanding the model to other countries

2017
Collaboration with Eastern countries (Singapore, Japan, South Korea and Taiwan):
• DM standards translated into Japanese,
• Auditor theoretical training,
• On the job audit participation as observers.

2018
• Pilot one-off audit programme in two Japanese DM centres (Nagoya, and Kobe).
• Presentation of the program at ARO annual workshop at Fukuoka
Adaptation of the expectations of evidence to the regulatory environment

In Japan and in the US, **Difference of oversight of registration trials** (J-GCP regulated – Approved by FDA/PMDA) versus **non-registration trials** (regulated by public notice “ethical guideline for clinical studies)

WHEN

In Europe, no difference in oversight (Directive 2001/20/CE, Regulation 536/2014)

IT03.02: Commitment to data protection:

The centre and its staff can demonstrate compliance with and commitment to all relevant data protection legislation, including the provision of related training programmes.

Europe: **EU General Data Protection Regulation** (GDPR May 2018)

Japan: **Personal Information Protection Law**
AUDITOR view:

**Common issues** encountered with e clinical data – **General** *

- **Lack or weak contractual arrangements** with external parties (IT) not reflecting the organization of services and respective role and **responsibilities** (long term archiving – data protection – ability to maintain and reconstruct one study).

- **Insufficient qualification records** or loss of involved individuals profiles, qualification, and training records when one company is purchased by another. **Contractual arrangements shall be in place to keep training and qualification records.**

*Source: ECRIN DM center audit results (2018) - EMA GCP Inspectors’ group meeting with interested parties on topics regarding electronic archiving of study data and related subjects – (May 2018)
Lack or unclear oversight of IT infrastructure: clearly differentiate the role and responsibilities of IT department and DM centres, so that everyone is clear what they are expected to do in any context,

- Clarify the information flows needed to guarantee that sponsors of trials, through the academic units, can retain **oversight of the infrastructure(s) they are using**.
- **Loss of audit trails or part of audit trails information.** Audit trails must allow for viewing when individuals logs in and logs out from one system.
- **IT Vendor are not trained enough in GCP specific requirements.** Vendors may not be fully aware of the particular security and GCP compliance requirements of clinical trial systems.
AUDITOR view: Common issues encountered with e clinical data - DM

• **Loss of data context and structure (metadata)** if the whole lifecycle of the trial is missing because i.e. only partial files are produced then it is considered a critical finding for EMA GCP inspectors (caution: dynamic versus static files).

• In case **Clinical Trial interim analysis** is part of a registration dossier: *need to know who extracted what and when in order to be able to reconstruct the trial at time of interim analysis.*

• **Incorporating Data Standards** (inter-operability of systems for data meta-analyses - Easier re-use of existing eCRFs for data capture). Increased use of data standards (e.g. from CDISC) in the commercial sector for submission files, but relatively low in non-commercial environments. As a minimum, any CDMS system used should provide good support of CDISC standards.

• **Long term data processing and data sharing**: currently, there is no solution for long term archiving datasets under proprietary format. Generic format for long term archiving is required.
AUDITOR view: overall challenges

- Many standards to go through during the audit: totally focus during the audit.
- Not easy to understand the organization of data center which is in general part of much bigger and complicated organizational structure.
- Every question must be resolved before the close out meeting.
“The Department of Clinical Research Support (CTU) at the Oslo University Hospital indeed considers an ECRIN Data management certification to be a valuable target. The communication before and during the audit was clear, and the auditors were very competent in all areas of IT and data management. Their thorough and supportive approach fosters learning during all steps of the audit, and made the process very valuable to us.”

Cecilie Moe, Head of section data management CTU, Jon Borgaard, Head of CTU, Research Support Services, Oslo University Hospital
AUDITEE challenges

A complete commitment to certification is required from Top Management:

• Allocate resource for coordination
• Allocate resource for preparation, i.e. update the current procedures/documents, develop new procedures/documents
AUDITEE challenges: external parties lack of oversight

- **Coordination with external parties**, i.e IT team who usually provide support for infrastructure, IT team who develops/maintain DM systems, or any other team who is not belonging to the data centre but work closely or provide services to data centre
- **External parties** not necessarily have in place **contract or clear agreement with data centre**: especially when external party has same umbrella, i.e. university hospital
- Data center responsible person does not necessarily know their procedures, their terms/conditions (IT systems)
AUDITEE challenges: Data Management

- Data protection/privacy: data centre has **no data privacy officer role**
- **Issue escalation**: no clear procedure, not easy to describe
- Training Standard: role, training program are managed according to the parent organisation i.e. university hospital, consequently not necessarily clear job description, or not easy to modify the training plan to be compliant with ECRIN standards
CONCLUSION
AUDIT IS A VERY USEFUL AND EFFICIENT TOOL

Plan
Objectives
Ressources
Communication

Do / Perform
Process, Products,
Activities, Services

Check
Measure,
Analyse,
Audits

ACT
RE(Act)
CAPA (Corrective and Preventive Actions)

CHECK

DO

PLAN

CONCLUSION - Basics about Audit assessment
ECRIN Data Centres Certification
Auditors versus Auditees - which challenges!

ECRIN - EUROPEAN CLINICAL RESEARCH INFRASTRUCTURE NETWORK
CONCLUSION AND KEY MESSAGES

- Audits include different levels, actors, practice which shall be defined as fit-for-purpose in one organization
- Are mandatory in some research environments (GxP - ISO)
- Provide added value such as
  - Increased customer satisfaction and trust,
  - Cost effectiveness and risk anticipation
  - Increased efficiency, reliability and compliance
THANK YOU – YOUR QUESTIONS?
YOUR QUESTIONS?

1. Question(s) on the new data challenges
   • EU GDPR application and conflicts to Swiss regulations (including Humanforschungesetz)
     • Territorial scope of GDPR, apply to all companies processing personal data of data subjects residing in the EU, regardless of the company’s location.
     • Lawful bases for data processing
     • Need for integrating in law the GDPR requirements for research: Swiss Federal Data Protection Act revision expected by end 2018
1. Question(s) on the new data challenges
   • Archiving & Security:
     • Original medium for data acquisition (paper, electronic files of static or dynamic nature) shall determine the suitable format and process for archiving;
     • Archives and archiving process shall be managed in a dynamic cycle embedding a risk based approach: archives shall evolve from dynamic files to datasets with metadata, then to flat PDF/A files.
     • Migration from one to another format shall be managed over time and be driven by risk-based approach (there is no way to maintain datasets in original format for 25 years without migrating the data).
     • Generic format for long term archiving is required. Oracle formats for example are not maintainable for long term archiving.

*Source : ECRIN DM center audit results (2018) - EMA GCP Inspectors’ group meeting with interested parties on topics regarding electronic archiving of study data and related subjects – (May 2018)
2. Question(s) on clinical trial data management and data center certification
   • Integration of electronic patient records:
     • It shall be clear for inspection: who acquire the data? When? For which purpose? Did you get consent?
     • Source data are data acquired in the database not the data acquired on individual’s own device when using them (E.g. ePRO).

*Source : ECRIN DM center audit results (2018) - EMA GCP Inspectors’ group meeting with interested parties on topics regarding electronic archiving of study data and related subjects – (May 2018)
YOUR QUESTIONS?

2. Question(s) on clinical trial data management and data center certification
   • Real added value of the certification? long-term costs (tools, human resources...):
     • Get practical guidance to managing high-quality data management services for clinical trials
     • Get recommendations for improvements
     • Being granted with a certificate of DM/IT high data quality management (Increased customer satisfaction and trust)
     • Comply with ICH GCP E6 (R2) requirements of audit readiness and regular assessment of methods and process for improvement
     • Direct business efforts where risks are anticipated (Cost effectiveness)
     • Provide your customers with an increased efficiency, reliability and compliance
     • Programme cost is monitored and balanced.