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EMA Perspective on eSource, RWD and

Opinion on eSource/DDC

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Check of electronic source data in clinical trials – why is it important?

GCP inspectors check that patient safety is maintained and that data are reliable in clinical trials.

A considerable number of critical deviations are currently given when inspecting clinical trials used as support for marketing authorisation applications or important healthcare decisions

Critical deviations:

– Conditions, practices or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data.

Impact:

– problems with getting marketing authorisations (serious delays and rejections),

– withdrawal of or corrections to publications etc.

– Participant safety and rights can be violated

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Legal requirements and guidance regarding electronic systems in clinical trials

– EU legislation

   – DIRECTIVE 2001/20/EC (Clinical Trial directive)

   – DIRECTIVE 2005/28/EC (GCP directive)

   – REGULATION (EU) No 536/2014 (Clinical Trial regulation), comes into application in ???

– Local/national legislation about implementation of directives

– ICH GCP E6 (R2, 2017 – R3 is being drafted and will contain text on pragmatic trials, use of RWD etc.)

– Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials **(NB! in the process of being reviewed, expanded and upgraded to guidance)**

– EU guidelines and Q&As (e.g. on the content, management and archiving of the clinical TMF (2018))

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Typical deviation areas related to e-source/DDC

– Lack of fitness for purpose of data collection tools

  – Poor design, not involving researchers and patients

  – Poor specification/requirements and inadequate testing

– Unclear definitions of source data

– Inadequate metadata (including audit trail)

– Inappropriate data correction procedures

– Lack of central data and metadata overview (including centralised monitoring)

– Inadequate user management

– Insufficient IT security

– Breach of data protection

– …and so many more!

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Inspection deviation, review of metadata example 1

Review of audit trail data revealed that primary efficacy data was not entered directly into the application by sites as described in the protocol. The sponsor/monitor had not discovered that alternative source data should exist. Discrepancies were detected when the inspectors retrieved the 'true' source data and verified against these.

Impact: errors in primary efficacy data

Classification: major and requiring follow up by sponsors to determine whether this could be happening at other sites as well

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Inspection deviation, review of metadata, example 2

The sponsor/CRO had not reviewed the audit trail and had missed important non-compliance, which was evident when reviewing metadata.

Inspector review of the ePRO (patient diary) audit trail demonstrated that ePROs were accessed and data entered during an unreasonable short period compared to the expected time when considering the procedures that were to be performed with the trial subjects while entering data.

Impact and classifications either major or critical depending on the data, the amount etc.

Review of metadata (e.g. audit trail, event logs etc.)

More and more trial data are collected electronically and entered directly in systems. Consequently review of metadata will be of higher importance.

Expectations from GCP inspectors are that:

– investigators have uninterrupted access to patient data

– that sponsors receive data and metadata from vendors/CROs (e.g. on ePROs, lab data etc.) on an ongoing basis and that data are reviewed to identify potential issues regarding e.g. data quality, completeness of data, irregularities etc.

– Procedures for risk based audit trail reviews are in place. The need for audit trail review should be defined on a trial level. Audit trail data is likely to be requested by GCP inspectors (usually export to excel)

– Awareness should be raised on receiving all relevant data from vendors and in relevant formats – also suitable for long-term archiving

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Inspection deviation access rights, example 3

Granting and revoking procedures for site staff was initiated and maintained by on-site monitors who applied for accesses to various databases for site staff based on their roles.

In this trial there was a division of staff into blinded and unblinded staff. Monitors had not been appropriately trained in the importance of this and numerous inappropriate accesses were granted resulting in blinded staff becoming unblinded.

Impact: the trial was considered by assessors of the MAA to be single-blind instead of double-blind

Classification: critical

Inspection deviation access rights, example 4

No regular review of users was performed. User management consisted of routine procedures for granting and revoking accesses. By inspectors' review it could be seen that several staff members, which were previously working in the safety department but at the time of the inspection had changed department, still had access to the safety database.

Impact: Safety staff have access to e.g. unblinded SUSARs, therefore other staff with inappropriate access to the safety database is a risk of inappropriate unblinding.

Classification: major or critical

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