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A Case Example of the Review of Audit Trails in GCP Inspections

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Background

- A sponsor submitted a NDA for a new molecular entity
- The drug was the first targeted treatment for a serious disorder
- The OND review division requested data audit inspections of the sponsor, CRO, and several clinical investigators

Sponsor Inspection

- During the sponsor inspection, we found that a majority of the data for the pivotal study was handled by a single electronic database (EDCα), which had been set up for the sponsor by the CRO
- This database contained all the study eCRFs
- The audit trails for EDCα were adequate for reconstructing the conduct of the study

Primary Efficacy Endpoint Data

- However, the primary efficacy endpoint data were handled by a vendor, who had a separate database (EDCβ), also set up the CRO
- The logic behind this separate database was apparently to help protect the study blind
- This second database was also reviewed during the sponsor inspection

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Problem with the Audit Trails

- In particular, we reviewed the audit trails for this second database (EDCβ) that handled the primary efficacy endpoint data
- Audit trails for approximately half the subjects appeared to be adequate
- However, for the other half of the subjects, the audit trails all:
  - Started with the same individual
  - On the same date
  - With no reason given

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What is Going On? (1/3)

- We brought the issues with the audit trails in the primary efficacy endpoint database (EDCβ) to the sponsor's attention
- The explanation was the following: it turns outs that during the first half of the study, the vendor had used their own database (EDCΔ) to capture the primary efficacy endpoint data
- This initial vendor database (EDCΔ) had not been disclosed to the FDA at the beginning of the sponsor inspection

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What is Going On? (2/3)

- Halfway through the study, during an audit of the vendor, the sponsor had recognized that the initial vendor database (EDCΔ) was not Part 11 compliant
- The CRO therefore quickly had created a new database for the vendor (EDCβ) to handle the primary efficacy endpoint data
- The primary efficacy endpoint data for the first half of the study then had been transferred to the new vendor database (from EDCΔ to EDCβ)

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What is Going On? (3/3)

- The audit trails, however, if they ever existed, had not been transferred
- Therefore, for these subjects, the audit trails in EDCβ all:
  - Started with the same individual *[the person conducting the transfer]*
  - On the same date *[date of transfer]*
  - With no reason given *[some reason should still have been given]*
- We were told there was no way to recover the audit trails from the initial vendor database (EDCΔ)

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Implications

- We were therefore unable to reconstruct the conduct of the study with respect to the handling of the primary efficacy endpoint data for approx. half of the subjects
- Did this mean that we needed to recommend to the FDA review division that they throw out the data for half of the subjects?
  - In this case, the study might no longer be positive due to loss of statistical power
- It is true that FDA had verified the primary efficacy endpoint data during the clinical investigator inspections, but this was only for a small percentage of the total subjects

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Were there any other options?

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Salvaging the Data

- For a subset of clinical sites, those with the most known or suspected GCP issues, we asked the sponsor to provide certified copies of the paper source records for the primary efficacy endpoint
- Due to the nature of this composite endpoint, this request ended up being thousands of pages
- Several dedicated OSI/FDA reviewers spent many hours each auditing the source records by comparing them to the data line listings provided by the sponsor
- Only very minor discrepancies were found

Outcome

- As a result, the application was able to move forward, and the drug was approved
- The patients with this disorder who were eagerly awaiting the approval of this first targeted treatment were able to receive the drug in a timely manner
- However, if the source data for the primary efficacy endpoint had been electronic, as is the case with many trials nowadays, there might have been no way to salvage the data

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