HaaPACS

Pharma Auditing Consulting Services

Audits in Biostatistics & Programming

Background, Conduct & Common Findings

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PhUSE Single Event Day

Frankfurt am Main, Germany, 10 May 2016

Presentation Outline

- Definition and background of audits
- Auditing procedures
- Common findings
- Case studies

Background: QC vs. QA

- Quality Control
  - is performed routinely
  - with clearly defined scope according to standard operating procedures
  - by the study team
- Quality Assurance (e.g., audits)
  - is conducted on a sample basis
  - can have a broad scope of activities
  - by independent personnel

Background: Definition (ICH E6)

An audit is a

- Systematic and *independent* examination
- of study activities and documents

To determine whether

- activities were concluded
- and data recorded, analysed, and accurately reported

According to

- Protocol
- SOPs
- GCP
- Applicable regulatory requirements

Background: Auditing

- Examples of audits
  - System audit
  - Database audits
  - Independent verification of analysis results
  - Audit of Clinical Study Report or statistical reports
  - Vendor qualification
  - Per-cause audits
- Audit frequency
  - Every 1 to 3 years depending on criticality
  - Sufficient time should be planned for a thorough review
- The qualification of auditors, and experience about the subject matter are important
- Purpose is not blaming anyone, but verifying and improving quality

Audit Conduct

- Audit Plan and schedule
- Audit Conduct (typically on site)
  - Kick-off meeting
  - Conduct
    - Review of SOPs
    - Review of management & staff qualification
    - Interviews with personnel
    - Review of study files
    - Review of electronic files
    - Review of IT service management & computerised systems validation
    - Review of facilities
  - Close-out meeting
- Audit Report & Certificate
- Corrective and preventive actions (CAPAs)

Common findings

- Training & project management
  - Gaps in training or training evidence, study-specific training not done
  - Responsibilities, teams lists, deliverables not well defined
- SOPs
  - With gaps
  - Imprecise (e.g., passive formulations)
  - Allow exemptions from quality control
  - Are not trained or not followed
- Programming
  - QC standards below best practices
  - Version control & release of programs
- Filing & Archives
  - Missing evidence of Quality Control
  - Supportive documentation not included
  - Incomplete transfers CRO to sponsor

Example 1: System audit clinical study

Major finding:

- The QC levels of programming for a clinical study that required complex derivations for analysis datasets and efficacy endpoints were below best practices

Recommended CAPA:

- Perform retrospective QC prior to finalising the Study Report
- Independently verify the primary endpoint based on raw datasets

Example 1: Result

- The verification analysis of the primary endpoint resulted in discrepencies to the original analysis
- After further evaluation and QC, it was concluded that the verification analysis was correct
- Luckily, the verification analysis reached the primary endpoint but the original analysis did not

Example 2: Per-cause audit

A regulatory agency accused a trial sponsor having used „inappropriate statistical methodology“ because of additional analyses for primary endpoint presented in the clinical study report

- The pre-specified parametric analysis had failed
- An unplanned non-parametric analyses was significant

Example 2: Findings

- The protocol and SAP did not include a formal step to verify assumptions of the primary parametric model prior to unblinding, defining related actions
- The decision to perform the additional analysis was made in a meeting prior to unblinding, but the sponsor failed to document this properly in meeting minutes, Trial Master File, and study report
- The interpretation of the added analysis was not clearly described in the study report
- There was no version control of the statistical programs in place to clearly demonstrate if the additional analysis was programmed prior to or post unblinding

Example 2: Recommendations

Recommended preventive actions:

- Improve SOPs for protocol and SAP with respect to possible changes of the planned analysis under blind review
- Improve blind review process & documentation
- Improve program release & version control process

Recommended corrective actions:

- Further analyse details of the findings and prepare related file notes
- Clearly describe the added analysis in the Clinical Study Report (section: deviations from planned analyses)
- Clarify the intended interpretation of the added analyses. In view of the gaps in procedures for protocol, SAP, and blind review, a purely exploratory interpretation was recommended

Example 3: Case study

The paper study file at a CRO included a copy of the SAP but no other documents related to statistical analysis

What do you think?

- Is this a finding?
- Is this a problem?

Example 3: Answers

Without further review / information, one cannot finally conclude if this is a problem. Further review showed:

- There was a gap in SOPs to define appropriate Quality Control of programs.
- There neither was a formal concept of release and version control of programs
- There were no complete specifications of analysis datasets and TFLs in the SAP
- The QC actually performed was based on code review (only), not including double programming of critical or complex programs
- There was no evidence (paper or electronic) of code review
- There was some evidence of production output review

Critical finding because of a risk that study results may be erroneous, in view of insufficient QC (and/or insufficient evidence of QC)

Discussion