



THE WORLDWIDE LEADER IN PHARMACEUTICAL SERVICES



RG03

Database/Biostatistics Audits – from the Auditor's Perspective

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Database and Biostatistics Audits:

1. What is an audit and how is it conducted?
2. The regulatory framework
3. Techniques used by the auditor when reviewing key topics:
 - Staff Records
 - Standard Operating Procedures (SOPs)
 - Project-specific plans
 - Management of records
 - Security
 - Validation

What is an audit?

ICH Good Clinical Practice (GCP):

“A **systematic** and **independent** examination of trial related activities and documents to determine whether the evaluated ... activities were conducted, and the data recorded, analysed and accurately reported in accordance with the protocol, sponsor SOPs, GCP and applicable regulatory requirements.”

Systematic =>

The audit should be conducted according to an established process

... BUT that process should be reasonably flexible

Independent =>

The auditee should not be in a position to influence the audit findings

... BUT auditors need to be approachable

How is an audit conducted?

ICH Good Clinical Practice (GCP):

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What the auditor examines:	To provide:
CVs, job descriptions and training records	Assurances that staff are qualified to perform each activity
SOPs and project-specific plans	Assurances that each activity is conducted consistently and in line with regulations
Records generated during the activity	Evidence that SOPs/plans were actually followed

How is an audit conducted?

The conduct of the audit will typically depend on:

1. The scope of the audit

2. The time available:

A common approach is to:

- Review all activities at a high-level



Examples:

- Database Setup Audits
- Database Lock Audits
- Statistical Analysis Audits
- Study Report Audits
- Process Audits

- Review in detail a subset of documentation generated by some or all activities, perhaps for the same sample of data



The Regulatory Framework for a Database or Biostatistics Audit

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ICH Guidelines:

- Good Clinical Practice (E6)
- Statistical Principles for Clinical Trials (E9)

FDA Regulations:

- Electronic Records and Electronic Signatures (21 CFR Part 11)

FDA Guidance Documents:

- Computerized Systems Used in Clinical Investigations, May 2007
- 21 CFR Part 11 – Scope and Application, August 2003

The Regulatory Framework for a Database or Biostatistics Audit

ICH GCP:

- Section 2.8: Each individual involved in conducting a trial should be **qualified** by education, training and experience to perform his or her respective tasks.
- Section 2.10: All clinical trial information should be recorded, handled and stored in a way that allows its **accurate** reporting, interpretation and verification.
- Section 5.5.3: When using electronic data handling and/or remote electronic trial data systems, the sponsor should:
 - Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (**i.e. validation**).
 - Maintain **SOPs** for using these systems.
 - Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).
 - Maintain a **security** system that prevents unauthorized access to the data.
 - Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).
 - Maintain adequate backup of the data.
 - Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

Key Audit Topic: Staff Records

What the auditor reviews:	Why:
CVs	To assess the qualifications and experience of staff
Job Descriptions	To confirm that staff have been assigned specific responsibilities and are aware of them
Training Plans and Records	To assess the training planned or undertaken for: - Computer systems - Regulatory requirements - SOPs - Project-specific plans - Staff transitions
Training Material	To assess the quality of the training

Are records up-to-date and signed?

Key Audit Topic: SOPs and Project-Specific Plans



The auditor assesses SOPs and plans for:

- **Compliance with regulatory, protocol and contractual requirements**
- **Consistency with each other**
- **Internal consistency**

Are they also up-to-date?

Have key SOPs/plans been approved by key individuals?

Key Audit Topic: Records Management & Programming Standards

Records Management:

- Naming conventions
- Version control
- Headers and footers
- Filing practices
- Archiving plans

Every page should include:

- Name of document
- Author
- Date
- Version number
- Page n of nn

Programming standards:

- Version control of programs
- Use of headers, comments, naming conventions, indentation within programming code
- Separation of development, test and production environments
- Storage of code

Can documents and programs be understood/updated by others?

The auditor assesses:

- **Physical security of locations where documents or data are stored**
- **Logical security of data, programs and systems**

- **How is access approved, granted, revoked?**
- **What permissions are there?**
- **How is access limited to only those who need it?**
- **Is training provided before access?**

Key Audit Topic: Validation

The FDA defines validation as:

“Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.”

Expectations for each new program or change to a program:

- Specification
- Test plan
- Test results that include:
 - Who executed the test
 - When the test was executed
 - What the test outcome was
 - Objective evidence
- Review/QC records
- Formal release

Test data, code walk-throughs, proc compares

Paper or electronic

Documents
can be
combined

Data Management programs/systems that require validation include:

- The clinical database
- The edit checks
- Database listings for performing QC, SAE reconciliation, coding etc.
- Imports of non-CRF data
- Exports of CRF data

Biostatistics programs that require validation include:

- Programs to produce derived datasets
- Programs to produce tables, figures and listings

Key Audit Topic: Validation

The auditor may pay particular attention to:

The specification:

- Includes all requirements?
- Completed before programming begins?
- Can be understood by the programmers?

Test results and objective evidence:

- Have all requirements been met?

Release Document:

- Sign-off by appropriate reviewers?
- All validation activities completed?

Also, has the impact of changes been assessed?

In order to be assured that regulatory requirements have been complied with, the auditor would typically review the following for each Data Management or Biostatistics activity:

- 1. Is there an SOP and/or plan that describes the proposed activity?**
- 2. Are staff qualified/trained to perform the activity?**
- 3. Has documentation been generated to support the performed activity?**

Questions?

