Paper RG03

Database/Biostatistics Audits - from the Auditor's Perspective

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ABSTRACT

This paper discusses areas of Data Management and Biostatistics audits that are of particular relevance to Database and Statistical Programmers. The paper outlines the regulatory framework for Data Management and Biostatistics audits and the techniques that may be employed by the auditor when reviewing some key topics: Staff Records, Standard Operating Procedures (SOPs) and Project-Specific Plans, Records Management, Security, and Validation.

INTRODUCTION

ICH GCP defines an audit as a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data recorded, analysed and accurately reported in accordance with the protocol, sponsor SOPs, Good Clinical Practice (GCP) and applicable regulatory requirements.

Examples of audits that typically involve Database and/or Statistical Programmers include:
- Database setup audits, which focus on the setup of the clinical database and the processes for managing the data;
- Database lock audits, which focus on the reliability of the data collected;
- Statistical analysis audits, which focus on the methods used to analyse the data;
- Study report audits, which focus on the presentation of the conclusions drawn from the statistical analysis.

During these types of audits, the auditor may examine:
- The data itself;
- The records associated with the data;
- The processes for recording, analysing and reporting the data;
- The qualifications, training and experience of the staff performing these processes.

It is worth remembering that an audit can also be an opportunity for the auditees to learn about regulatory requirements and best practices and to identify process improvements. This

can be facilitated by an open dialogue between the auditor and auditees. Nevertheless, the auditor's independence is paramount.

REGULATORY FRAMEWORK

The following regulatory requirements are applicable to Data Management and Biostatistics audits:

- ICH Guideline for Good Clinical Practice (E6)
- ICH Guideline on Statistical Principals for Clinical Trials (E9)
- FDA Regulation on Electronic Records and Electronic Signatures (21 CFR Part 11)

The FDA has also published guidance documents on:

- Computerized Systems Used in Clinical Investigations, May 2007
- Part 11, Electronic Records; Electronic Signatures – Scope and Application, August 2003

Which aspects of these regulatory requirements are particularly relevant to Data Management and Biostatistics audits?

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).

21 CFR Part 11:

IV Section 11.10 Controls for closed systems: Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following: (a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

CONDUCTING A DATA MANAGEMENT OR BIOSTATISTICS AUDIT

How does the auditor assess compliance with regulatory requirements?

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

1. CVs, Job Descriptions and Training Records. These provide assurances that staff are qualified to perform the activity.
2. Applicable SOPs and plans. These provide assurances that the activity is conducted in a consistent manner and in line with regulatory requirements.
3. Documents and records generated during the activity. These provide assurances and/or evidence that applicable SOPs and plans were actually followed.

Ideally, this documentation should 'speak for itself'. However, interviews with staff are usually also required to clarify what has been reviewed in the documentation and to support the auditor's assessment.

How is a Data Management or Biostatistics audit actually conducted?

The conduct of an audit will depend on the scope of the audit and the time available. However, typically, it is impossible for the auditor to review all trial-related activities and documentation. Therefore, a common approach is to:

- Review at a high level each trial-related activity within the audit's scope. This may involve questioning staff about the activity and reviewing SOPs/plans. By doing this, the auditor can be reasonably assured that each activity was conducted appropriately.
- Review in detail a subset of documentation generated by some or all activities, perhaps for the same sample of data. For example, during a Biostatistics audit, the auditor may select a particular value as presented in a table, figure or listing and trace it's generation back through:
    - The program that produced it;
    - Any derived datasets;
    - Any programs to create those derived datasets;
    - The raw datasets received from Data Management;
    - The statistical analysis planned for the data.
    - Validation/QC/peer review records relating to the above;

  During a Data Management audit, the auditor may further trace the value back to CRF or non-CRF data and also review:

- How the data was tracked, entered/imported and maintained secure;
- How the data was 'cleaned' e.g. by means of edit checks and self-evident corrections;
- How the data was QC'ed, coded, and reconciled with other data;
- How the data was locked and transferred to Biostatistics.

What areas are reviewed during a Data Management or Biostatistics Audit that are particularly relevant to the activities of a Database or Statistical Programmer?

1. Staff Records:

During a Data Management or Biostatistics audit, the auditor would review:
- CVs in order to assess the qualifications and experience of personnel.
- Job descriptions in order to confirm that personnel have been assigned specific responsibilities and are aware of them.
- Training records in order to assess the training already undertaken by personnel and training plans in order to assess the training due to be undertaken. The auditor would expect to see training records relating to:
  - Computer systems being used;
  - Relevant regulatory requirements e.g. ICH GCP;
  - SOPs;
  - Project-specific plans;
  - Staff transitions.

It is important that staff records are maintained reasonably up to date and, at the very least, job descriptions (or equivalent documents such as the employee contracts) should be signed by their owners in order to provide assurances that responsibilities are understood.

2. Standard Operating Procedures (SOPs) and Project-Specific Plans:

During a Data Management or Biostatistics audit, the auditor would assess SOPs and plans for:
- Compliance with regulatory requirements, protocol requirements and, if applicable, contractual requirements.
- Consistency with each other.

It is particularly important that SOPs and plans are maintained up-to-date and that documented approvals of key documents by key individuals are in place e.g.:
- Management approval of SOPs.
- The Biostatistician's approval of the Edit Checks Specification.

3. Records Management and Programming Standards:

During a Data Management or Biostatistics audit, the auditor would assess documentation practices, including:
- Naming conventions;

- Version control;
- Headers and footers;
- Filing practices;
- Archiving plans.

It is important to include on every page of a document its name, author, date and version number as well as the page number and total number of pages.

The auditor may also assess programming standards including:

- Version control of programs (both draft and final);
- The use of headers, comments, naming conventions and indentation within programming code;
- The separation of development, test and production environments;
- The storage of source code.

Documents, records and programs should be prepared in such a way that they are easy to understand and update by individuals other than their authors.

4. Security:

During a Data Management or Biostatistics audit, the auditor would assess both the physical security of any locations where documents and data are stored and the logical security of data, programs and systems.

Programmers often play a key role in administering access to computer systems. The auditor may review processes and records relating to:

- Approving, granting and revoking access rights;
- The permissions associated with different access rights;
- Limiting access to only those who need access;
- The provision of training prior to granting access.

5. 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.”

Apart from being a regulatory requirement, validation (including validation documentation) provides assurances that a program consistently does what it is supposed to do and can be easily maintained and/or upgraded.

During a Data Management or Biostatistics audit, the auditor would expect to see, at a minimum, the following validation documentation for each new program or change to an existing program:

- A specification.
- A test plan.
- Documented test results that indicate, for each test:

  - Who executed the test;
  - When the test was executed;
  - What the outcome of the test was – if the outcome was not as expected, then further details should be recorded including a description of the unexpected outcome and what actions were taken to address it, including any retests;
  - Objective evidence of the above.
- Review/QC records relating to each of the above.
- A formal release into production.

However, there are different ways of presenting this validation documentation. For example:
- Some documents can be combined e.g. in the case of edit checks, it is common to combine the specification, test plan and test results in a single spreadsheet;
- Objective evidence is often held electronically (e.g. within a database) rather than as printouts.
- Tests can be executed in numerous ways, including:
  - Inputting test data;
  - Code walk-throughs;
  - Proc Compares.

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.

The auditor may pay particular attention to the following key validation documents:
- The specification: It describes the requirements of the system or program. It should specify all requirements before programming begins as updating requirements (e.g. relating to an electronic CRF) can be costly and introduce delays. It is also important that the specified requirements are understood by the programmers. Therefore, requirements should be written in 'plain' English to avoid misunderstandings. This is particularly important in the context of dual programming where there is a risk that both programmers make the same misunderstanding.
- The test records and associated objective evidence: These provide evidence that the requirements of the system or program have been met. Where there are many requirements and/or many tests, then a formal mechanism should be in place for tracing tests back to requirements.
- The release document: It indicates the formal release of the program or system into production. The auditor would expect to see sign-off by appropriate reviewers of the validation documentation and that all validation activities have been completed by the time of the release.

Changes to existing progams/systems usually also require validation. It is also important that the impact of changes are assessed e.g. updating the design of fields within a clinical database may mean that related edit checks also need to be updated.

CONCLUSION

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?

Each of these questions should be considered when preparing for an audit or inspection.

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