The quality assurance of clinical trial data

In this special report, Dr Julie Meeson of J3i Quality Management Systems Ltd provides an insight into auditing clinical data at the study site and audits of data management activities, data analysis and the study report.

Auditing clinical data at the study site

The definition of quality assurance (QA) in the ICH GCP guidelines is all encompassing, covering all aspects of the clinical trial including data generation, documentation and reporting activities. This article describes how data collected at the study site can be formally audited as part of a QA programme and offers practical tips.

Part of a typical site audit involves assuring that the data generated at the site are accurate, credible and verifiable. Source document verification, performed during routine monitoring visits, forms the quality control (QC). During the site audit, the adequacy and effectiveness of this QC step are evaluated.

When preparing for a site audit, the auditor should consider the following:

- what data will be reviewed? The options include a systematic assessment of all the study data or a focus on the key efficacy and safety data. One commonly applied approach is to assess one or two patients entirely in order to detect systematic erroneous data issues, and then to focus on the key safety and efficacy criteria for the majority of the data review.
- how many patients will be reviewed during the audit? Sampling techniques vary, but most sponsors use a non-statistical sample size of $\sqrt{n} + 1$ (where $n$ is the number of patients at the site) or 10% of the patients recruited at the site. Whatever the data sample size, it is important that any subsequent audit observations can...
be substantiated and their impact assessed based on the frequency of the observation in the sample reviewed.

- which patients’ data will be reviewed? Status reports and other monitoring outputs can assist in patient selection prior to the on-site audit. However, some flexibility in the choice of patients is needed in order to respond to the outcome of other parts of the audit (eg. inconsistencies detected in drug accountability or problems in the patient recruitment log).

**Audit worksheets**

Prior to the site audit it is useful to prepare data audit worksheets. These can be developed to be protocol specific, capturing key study details (eg. visit periods, disallowed medications) as part of the worksheet information. They will assist the auditor in the data review process, making the audit more efficient to conduct as well as adding consistency when different auditors conduct site audits for the same study.

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The data worksheets should also be used to record data discrepancies, noting the nature of the data issues and enabling accurate reporting of the audit findings. The information recorded should clearly indicate whether the issue is related to
- a discrepancy between the information in the source data and the CRF
- missing information, where the CRF lacked a piece of information recorded in the source data (eg. an adverse event in the patient notes that was absent from the CRF)
- unsubstantiated data, where data in the CRF could not be substantiated by the source data (eg. onset date for a disease condition).

**Site audit report**

The audit findings that arise from the on-site data review process are usually incorporated into a site audit report, along with other issues noted during the site audit. The auditor needs to ensure that the exact nature of the data issue is communicated, together with its potential impact. This requires an assessment to be made using information about the type of data issue, its frequency and the systematic nature of its occurrence.

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The auditor also needs to explain whether the issue represents errors in the data submitted in the CRF or inadequacies with the source data held at the site. If the auditor makes a judgement that any of the data issues potentially affect the overall validity, reliability and/or acceptability of the data from the site, this should be brought to the attention of the relevant management at the sponsor company and communicated in the audit report.

**Data management audits**

**Audits of data management activities can be conducted at any stage of the data management processes, from immediately after database set-up through to the database finalisation and reporting processes.**

Audits can be organised on a by-study basis – where the processes and products reviewed during the audit are limited to one study – or conducted as process audits, when the focus of the audit is on the underlying processes, and data from several studies are included. Both approaches are useful to draw conclusions about the validity of the data management processes and the resultant data.

**Database set-up, approval and access control audit**

The objective of a database set-up, approval and access control audit is to ensure that the database has been
adequately validated and tested prior to use, and that there is a formal release mechanism. Another objective is to confirm that access to the data is controlled and documented. Such an audit is typically conducted early in the study, just after the first data entry has taken place. The value of this type of audit is that it will highlight any weaknesses in the database set-up activities and supportive documentation, as well as any data access security issues. Deficiencies can therefore be corrected at an early stage, improving the ongoing conduct of the study.

**Data entry accuracy audit**

The objective of a data entry accuracy audit is to assure that the data in the database accurately reflect those submitted in the CRF and that the activities are routinely controlled. The simplest way to approach this audit is to compare systematically a sample of CRF data with data in the database. There are various approaches to selecting the data to be reviewed during the audit, including some statistically based sampling methodologies (Sullivan *et al*, *Drug Information Journal* 1997, Vol 31, p 647–653). However, most sponsors use a non-statistical-based methodology and focus on the key efficacy and safety criteria.

What is important is that the audit confirms whether the data within the database are an accurate reflection of the data collected in the CRFs. The audit can be conducted at any stage after sufficient data entry has been performed to select a data sample. It can also be repeated at intervals to ensure that accuracy of data entry is maintained.

It is expected that the operational group responsible for the data entry process will be performing systematic QC checks and that documentation relating to these checks will be available to the auditor. It is useful to include a review of the QC records within the scope of the audit.

**Data handling validity audit**

The key objective of a data handling validity audit is to ensure that the data handling standards applied to the study are appropriate and documented, thus ensuring the validity of the data. This typically involves reviewing data management study documentation to ensure that it has been developed and maintained in accordance with company requirements, and that its content complies with GCP. The final stage is to audit a sample of data to confirm that the documented data management practices were complied with.

This type of audit can be conducted partway through the study, when the documentation should all be in place and sufficient CRFs have been through the data management process. Alternatively, it can be conducted as an end-of-study audit when all data management activities are complete.

**Finalisation of the clinical database audit**

Several unique activities take place at the database finalisation stage that are critical to the data for the overall study. The key objective of an audit at this point is to confirm that the activities involved in finalising the database have been adequately controlled and conducted in accordance with a data management plan.

“It is expected that the documentation relating to systematic QC checks will be available to the auditor.”

Good preparation is needed for this type of audit. Information should be collected about the finalisation activities planned, as well as the sequence of these activities relative to each other and to the proposed audit. For example, if there will be external data imports (e.g. from central laboratories or any other external supplier) into the final database/analysis datasets, the audit needs to be timed to allow a review of this process after it has taken place. Similarly, if end-of-study QC reviews are to be performed, the audit should be timed to occur after the completion of these reviews, to allow an assessment of their adequacy and the appropriateness of any QC follow-up actions.

**Database ‘lock’ or ‘freeze’ audits**

The objective of a database ‘lock’/‘freeze’ audit is to confirm that changes to study data have not been made after database lock/freeze has been declared. This audit should be performed after database lock/freeze has occurred and access rights should be reviewed to determine the levels of access (e.g. read-only access, change access) for all users.

A review of the audit trail should also be conducted to confirm that no changes have been made to the study data after the database lock/freeze time point. It is useful to conduct this type of audit as a systems audit across several databases that have been locked/frozen to assure the consistency of these processes.
Data analysis and clinical study report audits

Many auditors feel uncomfortable auditing the data analysis stage of a study, because they fear that they lack the expertise required to audit a specialist area such as statistics. However, conducting process-based audits, together with auditing the associated documentation and the outputs, is an effective way to audit this area.

As many clinical study reports (CSRs) are integrated reports, combining the statistical report and the clinical report, a statistical analysis audit may be most effective if combined with a CSR audit. This article describes how these audits can be performed and offers practical tips.

Statistical analysis audits

The following areas should be taken into consideration during statistical analysis audits:

- The statistical analyses must be in accordance with what was planned and formally documented in the protocol and any Statistical Analysis Plan (SAP). If the statistical analyses have deviated from the plan (eg. with respect to the population groupings or the key efficacy/safety criteria in the outputs) then this is an important audit observation. Analysis plans commonly evolve during a study (often as a result of recruitment or treatment issues) and the protocol/SAP may not be formally amended to reflect the updated intentions of the statistical analyses. By reading the SAP and then comparing what was planned against the output of the analyses, it should be assured that the output reflects what was planned in the protocol/SAP.

- To determine which patients are included in the per protocol analysis population, there is usually a review of patients who did not follow the protocol, ie. who had protocol violations/deviations. It is important to assure during an audit of this area that the rules for exclusion of patients were described in the SAP, and that the review of the affected patients was conducted prior to the unblinding of data. The audit should confirm that patient grouping remained consistent after the identity of patient treatment was known: if changes were made after the treatment identity was known, this may have introduced bias into the study results that may jeopardise the validity of the study. This is an easy process-based check to perform that needs no expert statistical skills.

- Statistical programming, like any other operational activities, should have had adequate QC. The audit of statistical programming should assess whether adequate QC controls are described within the functional SOPs and whether they were followed. Many sponsors routinely use independent programmers to repeat or review the complex statistical programming activities. The auditor should check that these QC activities have been performed and that the relevant evidence (documentation, approvals and programmes) has been retained.

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CSR audits

The objective of a CSR audit is to confirm that the report accurately describes the conduct and results of the study. As always, there should have been adequate QC checks performed as part of the CSR production process. However, if these have not taken place, there is a risk that the audit may be misused as a QC review step. There are a number of ways to reduce the likelihood of this occurring:

- communicate the expectation that QC is performed as part of the CSR production process, and that the CSR audit is an independent activity to confirm the quality of the end product. Reviewing the QC documentation as part of the audit, with audit citations made for any process or documentation inadequacies, can also be effective.

- conduct the CSR audit after all the peer reviews and updates have occurred and the report is deemed ready for approval by management.
This will prevent any audit findings from being downgraded to issues that would have been addressed prior to approval.

- ensure that the audit methodology is based on sampling parts of the report being reviewed. Then clearly state in the audit report that the findings do not necessarily represent all the issues in the entire report, but represent those detected during the audit, which was based on a sampling method.
- have a defined process available to stop the audit and return a CSR to the responsible operational group if the audit shows the CSR to be clearly substandard.

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The areas that should be covered during a CSR audit include those listed above for statistical analysis audits, as well as the following:

- compliance with internal SOPs and external standards (eg. ICH E3)
- confirm that the study description in the CSR reflects the protocol and all amendments. To assure this the auditor needs to reference external information held in the Trial Master Files and/or study tracking systems within the sponsor company.
- check that the report includes reference to significant protocol violations and matters not well described in the protocol
- review the content of the CSR synopsis to assure it is consistent with the text of the report (especially the conclusion section), as well as the summary tables and any relevant listings. Qualitative as well as quantitative statements should be fully substantiated by the study data.
- check that the Table of Contents for the CSR is consistent and corresponds to the report itself. The tables and listings referenced in the CSR text should be reviewed to assure accurate referencing. Any errors of this nature found during the CSR audit should be cited as an inadequate/ineffective QC process.
review the tables incorporated into the CSR text and ensure that they are consistent with relevant tables and listings in the appendices.

- review the written text for a selection of the report – the sample chosen often focuses on the key efficacy and safety sections, together with any areas known to have caused issues within the study or likely to cause issues within the company. A sample of the numbers and population totals cited in the CSR should be checked back to the summary tables and/or listings in the appendices.

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- a sample of patients reported in the patient narratives section (eg. patients with serious adverse events (SAEs) or other significant study events) should be selected and the data cited in the narratives checked back to the listings. The identity of the patient’s treatment reported in the patient narrative should also be confirmed in the patient treatment list.

- overall consistency between SAEs reported in the SAE section of the CSR (including the relevant tables/listings) and the safety database/regulatory reports should be assured.

- a sample of SAE data should be selected from the CSR and compared with the safety database/regulatory reports submitted for the patients. There should be overall consistency in the key patient data cited in both reports.

- any serious and/or outstanding quality issues that occurred during the conduct of the study should have been described in the report. As some of these compliance/quality issues may have arisen during other independent audits of the study, it is useful to review all previous audit reports whilst preparing for a CSR audit.

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- to summarise and make readers aware of relevant articles and information in other publications, press releases and information on the Internet
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