Need for Re - Engineering Quality Assurance in Clinical trials

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Summary

The purpose of quality assurance is not to ensure that the data are 100% error-free. Its purpose is to ensure that the clinical trial results are reliable; that is the observed treatment effects are real and their estimated magnitude is unbiased. Quality Assurance activities in a clinical trial is a wide area to be covered and explaining each of every activities would not be possible within the article. The article briefly discusses the the possible errors during a clinical trial and the prevention of such errors by statistical approach and explains the Quality assurance activity in prevention of such errors before,during and after a Clinical Trial.

Key Words: Quality Assurance, Quality Assurance Unit(QAU), Audit, Inspections Standard operating Procedures (SOPs),

Introduction

Quality assurance in clinical trials is a world wide critical function. The term "Quality Assurance" has been defined by different regulatory guidelines in a different way but the extract of all the definitions is the same and it is a planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s)[1]. To ensure consistent quality in clinical trials, it is mandatory to make the quality assurance team an integral part of the whole process, from design to submission of reports. The regulatory guidelines such as the ICH, USFDA, WHO, CDSCO, EMEA and other guidelines gives the responsibility to the sponsor for implementing and maintaining quality assurance and quality control systems with written SOPs. SOPs play a crucial role in clinical quality assurance and it is therefore essential that they are understood and followed by all end-users in a clinical trial. If SOPs are not up to the regulatory requirements and not followed correctly, the validity of data generated is compromised, leading to warning letters being issued and

delays in the trial process. Auditors and inspectors see SOPs as essential and following them is crucial. This article briefly explains to promote quality assurance by identifying various methods for reducing important errors such as phantom participants, fabrication of data, entry of participants with major ineligibility criteria, randomization mix ups, and outcome measure mistakes. This review is presented for Clinical Quality Assurance professionals in the hope that it will help them to avoid some of the common pitfalls. It is for guidance only, based on what has worked for those who have been through the process before. It is hoped it will be of equal value to those in commercial and non-commercial research.

Types of Errors

During the conduct of clinical trials, two types of errors can occur and they are 'Random Errors' and 'Systematic Errors' , Random errors include measurement errors (such as assay precision,frequency of visits ect) errors due to slopiness (such as transcription errors). Systematic errors include design flaws(such as exclusion of patients with incomplete treatment or unequal schedule of visits); apart from but cannot be classified either to the two errors are Errors resulting from "falsified data" (Fraud) are always serious and must be dealt with accordingly; other errors may be serious or trivial. However, every clinical study must include procedures to avoid or minimize data errors. Most frauds have little impact on the trial results because: they introduce random but not systematic errors (i.e. noise but no bias) in the analyzes they affect secondary variables (e.g. eligibility criteria) their magnitude is too small to have an influence (one site and/or few patients)[2,3]

Prevention of Errors

Every clinical study must include procedures to avoid or minimize data errors. Several changes have occurred over the years which make attention to data error more of an issue. In the past, the typical multicenter study had a number of well-funded clinics, selected at least partly on the basis of research experience, and a well-funded coordinating center. These features facilitated understanding and implementation of the protocol and the scientific method used by the clinic investigators. Also, with larger clinic staffs, several staff were around to catch both types of errors. Today, for clinical trials in particular, there is a greater use of the so-called "large simple study" model. Here, almost any investigator with certain minimal qualifications enters participants, and payment is typically done on a per participant basis. As a consequence, there are many more investigators, there is less on-site monitoring, and each investigator may enroll fewer participants on average. Thus, the protocol may not be as well understood. Nevertheless, clinical trials and observational studies involve the collection of hundreds of thousands of data items. With care and appropriate (and sometimes costly) procedures, errors can be minimized, though not reduced to zero.

Statistical approaches to data checking

Humans are poor random number generators hence randomness can be checked through ' *Benford's law'* In 1972, Hal Varian suggested that this law could be used to detect possible fraud in lists of socio-economic data submitted in support of public planning decisions. Based on the plausible assumption that people who make up figures tend to distribute their digits fairly uniformly, a simple comparison of first-digit frequency distribution from the data with the expected distribution according to Benford's law ought to show up any anomalous results [4]. Plausible multivariate data are hard to fabricate. Clinical trial data are highly structured hence we can compare expected vs observed . Clinical trial data are rich in meaning hence we can test plausibility (e.g. dates). Fraud or gross errors usually occur at one center then we have to compare between centers.

Non-parametric approach

In multicentric trials, the distribution of all variables can be compared between each center and all others, through statistics for discrete variables, t-test to compare means of continuous variables F-test to compare variances, mutivariate test statistics for more than one variable etc.

Brute force approach

These tests can be applied automatically, without regard to meaning or plausibility, They yield very large number of center-specific statistics,Meta-statistics can be applied to these statistics to identify outlying centers[5].

Role of Quality Assurance

Quality Assurance Unit (QAU), with responsibility for auditing clinical trials, the choice of which activities to prioritise can be bewildering.

Positioning of QA and organisational interactions

There is a hierarchy of quality assessment:

- Self-check
- Departmental QC
- Independent audit

It is very important to establish which level of risk the QAU is expected to address. Neither the ICH nor the other regulatory bodies of Quality Assurance refer to the independence of the QAU. However section 5.19 of ICH GCP refers to the purpose of an audit as independent in nature and also refers to the requirement for independent auditors. Section 5.19.3(d) mentions preserving the independence of the QA function.

It is important (where possible) for the QAU to report independently of the areas of the organization which it audits. Conflicts may arise when the QAU has the same reporting line as those groups responsible for performing the operations that will be audited. If the same individual is responsible for managing an activity, they may not always believe that it is in their interest to investigate an issue raised by the QAU."Independent" can be defined as: Not involved in the day to day activities which are subject to QA activities Having a functional reporting line outside of the management of audited departments. QAU members should be aware of the potential for a conflict of interest. If this seems unavoidable in some circumstances, consideration should be given to contracting the audit out.

Risk management is a planning tool used to focus and prioritise the audit programme and individual plans. It is usually worth performing a formal, documented risk assessment – identifying possible risks (firstly on a high level, then decreasing towards the details) in the business, and quantifying them by assessing the likelihood of a failure, and the probable impact to the business if the failure took place. The advantage of assessing risks is that they can be ranked, with the highest risks taking the available QAU resource for audits. Should client groups then request other areas to be audited, the QAU can re-prioritise in the light of the new risks.

Training

Members of the QAU will become familiar with the organization's SOPs and other standards, and with GCP guidelines and regulations. They will become adept at interpreting these, particularly the grey areas, and this knowledge will often be sought out by the client groups. Auditors will also want to alert all areas of the organization to the deviations they are finding, in the hope that the quality level may be raised across the board.

If the organization has a training department, clearly QA will work closely with them. QA will want to participate in some of the arranged sessions to disseminate audit findings, and may be a resource to help in general GCP training. The training department should receive audit reports so they can help to identify the areas where the organization needs focused, remedial training.

Auditing

Role of QA in study-related audits This relates to those audits looking at a specific and therefore study related, site or document, rather than comparing processes across several sites or documents.

Documents

Protocol audit and database audits are now conducted less frequently than before, as they are recognized as a QC function. They may be performed retrospectively as part of a "systems" audit, focused on the quality control aspects of the document production. The majority of document audits are of Clinical Study Reports, and sometimes of submission dossiers. Other documents may be CRFs, informed consent documents and data handling plans. All documents for auditing must first be approved as final by the client department – this is because the quality control stages of the document are part of the assessment, so the document must be signed off, and at the end of its processing before the audit. This will require careful negotiation with the client to ensure the timing of the audit does not delay the use of the document unnecessarily.

Documents are audited against the relevant regulations and guidelines, and also the standards of the organization:

? Policies, SOPs, and other controlled documents
? Templates
? Related documents (eg CRFs are assessed against the relevant protocol for consistency)

Investigator sites

Investigator sites are selected for audit based on many risk factors including (but not limited to):

- importance of the medicinal product/device/study
- enrollment
- a concern from a client group
- geography (combining audits of nearby sites if practicable)
- avoiding previously audited investigators or monitors (unless there have been problems)
- a new therapeutic area
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The audit reviews how the sponsor has monitored the study at the site and always includes source document verification – an assessment of the source documentation against the data in the CRF to check for completeness and accuracy. This is an essential step as very few sponsor staff have access to this first stage of data collection.

The audit can range from one auditor for one day, to two auditors for three days. This will depend on the number of subjects recruited by the site and the size of the medical record (eg oncology records are much more voluminous than respiratory records), and also to what extent in-house preparation is possible. If at all possible, the monitor is present. The monitor is the familiar face of the organization for the investigator, should be familiar with the course of the study and location of documents, and the monitor will also gain from the insight into the study from an independent viewpoint. Consideration should be given to the reports of important issues which have already been identified by the monitor or the site staff. In this case it is essential to acknowledge the action of the monitor in the audit report, unless corrective action was not completed.

The main areas of focus for an investigator site audit includes the following,

Safety of subjects (have all adverse events been properly documented),Protocol compliance, including eligibility Existence of subjects and substantiation of data, Accuracy of data, SAEs, Use logic in planning your sample size, for example: ?(n+1), possibly a maximum of 10 subjects, include some early terminators, some completers, Adequacy of facilities,IMP accountability, Informed consent process,Investigator site file, Data privacy, Ethical aspects of the trial such as location, standard of care and post-trial treatment availability.

Other study-related audits

Some organizations conduct study safety audits, following safety data through its processing stages. Role of QA in systems audits Systems audits (also called process audits) review a single process across several studies, therapeutic areas or regions. The aim is to see where differences exist, how clear the SOPs covering the area are (if any), whether there is a best practice that should be adopted, and how effective any training in the process has been. These are resource-demanding audits for QA, but they are usually popular with the client groups. Competent staff should conduct these audits as the scope, duration and agreement with the client is critical. The client can learn a lot that will help them improve their processes, and it is the process and its guidance documents which is being assessed, rather than an individual.

The basic process is as follows:

Identify which systems/processes are in use by the business. Start at a high level and work down to a level of greater detail. Include system audits for newly implemented systems. Include resource for "triggered system audits" e.g. triggered by audit findings and inspection findings.

Prioritize the systems regarding the importance of the process for clinical development. Consider:

? Likelihood of a failure and the impact on the business if the system fails e.g. patient safety, data integrity, data availability, reputation

? Previous audit findings

? Changes in systems

Define core competencies for the audit team according to the system requirements specifications (ie the particular training the auditors will need in order to understand the system). There should be close interaction between auditors performing site, service provider and document audits and those conducting a system audit. Useful information can be exchanged in both directions. Solicit input on the systems audit programme from senior management of both QA and the client departments in order to fully understand the main areas of risk within the system. To aid discussion of the system to be audited, draw up a draft audit plan. Discuss and get input on the plan from the owner of the system.As findings are potentially across departments, agree on ownership for corrective action and implementation.

Role of QA in regulatory inspections

Often QA have an integral role in hosting and facilitating before, during and post regulatory inspection activities.

Pre-Inspection

As soon as a facility is informed of a forthcoming regulatory inspection the QA group generally has an important role in ensuring appropriate pre-inspection activities occur. This might involve identifying who will need to be involved in the inspection, providing coaching on what to expect during the inspection and how they should respond when asked questions. A QA pre-inspection audit of the area/study that is going to be inspected may be appropriate, if time permits, in order that study fi les, training fi les etc. can be checked for availability, completeness and adequacy. In addition, the logistical challenges of hosting an inspection should be considered and appropriate arrangements implemented. This may include a room for inspectors to work in, a 'back room' for confidential internal discussions and for requesting, logging and reviewing documents prior to passing them on to the inspectors. Adequate photocopying facilities, network connections and telecoms etc. should be available.

During Inspections

For inspections of third parties (CROs, investigators etc) QA may act as a facilitator providing assistance and guidance to site personnel. This role is especially valued when the CRO or study site have never previously undergone a regulatory inspection. For internal inspections of the sponsor, typically QA hosts the inspection. Working with local operational and quality management they will be responsible for scheduling inspection activities and ensuring the availability of required individuals. During inspections it is common for QA to sit in during the inspection interviews and record all key questions and any issues that arise. They ensure that all questions are directed to individuals sufficiently qualified and experienced to provide accurate answers. In addition, QA may also be responsible for ensuring the effective, efficient running of the 'back room', encouraging the maintenance of a calm and focused environment where the retrieval, review and copying of documents can be performed. In this role QA can also prepare interviewees prior to going into the inspection room and also debrief them immediately after they have been interviewed by the inspector to make sure the interviewees are satisfied with all of the responses they provided and for an early indication of potential issues.Other important functions that can be fulfilled by QA during the inspection process are the provision of daily summaries of inspection progress to senior management and the coordination of immediate corrective actions, if applicable.

Post Inspections

During the period immediately after an inspection QA may be involved in ensuring that any information requested during the inspection but that could not be provided at the time is sent to the inspectors as soon as possible. Once an inspection report is received, QA experience is often employed to review and interpret the inspection report. QA may be involved in the coordination and review of the responses to ensure they are provided in a timely fashion and that they fully address the concerns of the inspectors. Finally, QA can often utilize the inspection experience where lessons learnt during the inspection can be shared with, not only those directly involved in the actual inspection, but also with those other parts of the business that may not have been involved but who are also liable to GCP inspection.

Safety-related activities

PV QA groups, complaints review process Subject safety is the priority for everyone involved with clinical studies, and any issues in the area can have huge impact. It is therefore to be expected that in any risk-based audit programme, safety-related activities will be reviewed frequently by the QAU.

It is essential for the organization conducting clinical trials to have a good system of pharmacovigilance in place and to ensure comprehensive coverage of it by the QA unit. How this is achieved depends on the size and policy of the organization. Some will devote specialists to the subject, who can focus on the specific legislation to the exclusion of all else. Others will use generalist GCP auditors, so all will have a chance to learn of pharmacovigilance. There are arguments both ways – the safety reporting system is often very complex, yet every GCP auditor needs some understanding of it. It will be wise to invest time in regular systems (process) audits of pharmacovigilance operations within the organization. Support from specialized consultants should be sought at least in the beginning until competencies and knowledge in the QAU are adequately developed. Apart from the risks inherent in this area, the audit programme itself is often of interest to the regulatory authorities in terms of frequency, scope, competence and training of auditors.

Computer systems

ICH GCP guidelines require that sponsors use validated electronic data processing systems (5.5.3) for handling and processing clinical trial data. From inspection history both in the US and in Europe it is clear that regulatory agencies enforce this requirement during inspections to ensure data integrity and validity. It is therefore essential for sponsors to ensure appropriate systems and processes are in place and adequately documented to enable successful demonstration of the 'validation status' of GxP-relevant computer systems.

Involved QA units often play a dual role in this area. During the validation process QA may act as advisor to the validation team and may review the key milestone validation documents (user requirements, plan, testing protocol, SOPs). The second part of the QA involvement relates to the auditing of the implemented system(s) and the adherence to the related processes to maintain the system in the 'validated status'. This should ideally involve different individuals with specialist knowledge in the area Due to the increasing use of computerized systems at the investigator sites, e.g. to measure trial-related parameters but also to capture and maintain patients' source data, it is necessary for every clinical auditor to be able to evaluate the suitability (i.e. validation status) of such systems for the clinical trial. Basic knowledge of computer system validation principles and requirements is therefore necessary for every auditor performing clinical audits at trial sites. Although computer systems can appear intimidating to the uninitiated, the same principles apply to electronic documents as apply to paper. Look for security of the system, who can access it, a formal process for changes, and a systems inventory.

GLP interface related to human biological samples

Clinical laboratories analyzing human samples are normally not GLP certified, and if they are, it is because they also analyze samples from toxicological safety studies. These, however often do not use the same processes, staff and equipment as the clinical samples. Nevertheless, clinical safety and specialty laboratories (e.g. those analyzing PK samples or special trial relevant parameters) need to follow pre-defined quality standards, and should be audited to ensure compliance (e.g." Guideline for Auditing Clinical Laboratories" by EFGCP, 2005). Clinical laboratories associated with an investigator centre (even if used as a central laboratory for a whole study) fall under the remit of the clinical QA unit, potentially with support from a colleague experienced in computer system auditing. The auditing of more specialized external laboratory, or laboratory internal to the organization, may require however special scientific and/or methodological knowledge to ensure the audit is effective. As with GMP, it is essential to decide with the GLP QA group where the responsibility for auditing biosamples lies.

SOPs

For large organizations clinical QA should not be involved in the development and control of SOPs in the clinical and associated areas. Other mechanisms should be in place to incorporate new guidance text, new legislation and to implement corrective actions from audit trending and audit observations. QA may provide advice and consultancy. For smaller organizations, however, the QAU may be involved in the development of SOPs. The QAU should support SOP development to facilitate overall GCP and legal compliance without taking over the responsibility for actually writing or even approving the SOPs. The QAU should remain as independent as possible and act as reviewer for compliance issues. In cases where the owners of the processes are not able to write the clinical SOPs themselves, the QAU may help identifying competent contractors to develop the SOPs. In these cases the QAU may keep the role as SOP reviewer. The QAU may also be involved in the review process of other clinical documents such as protocols or clinical study reports. When this is done outside the audit programme, the role and responsibility of the QAU in the review process should be clearly defined, e.g. internal consistency, compliance issues. It is still not recommended that the QAU should formally approve operational documents (protocols, deviations or reports) as this would compromise their independence.

Implementation of Quality Assurance Systems

Implementation of an effective QA system relies on proper education of the entire trial site staff. and for this purpose all investigators, before he performs his job profile a government body like the DCGI should evaluate the investigators after giving proper training in GCP and to issue a GCP certificate. To fulfill GCP requirements, research support staff must have appropriate education and training for their particular roles in the trial process. GCP does not mandate certification of support staff (eg, clinical research associates [CRAs] and study coordinators), though providing evidence of the capabilities of these individuals to perform their job functions is desirable. Educational opportunities include training of personnel at the beginning of their employment to ensure they are familiar with the operations, policies, and procedures of their particular research site. Continuing education is also important as policies change or deficiencies are discovered and need to be corrected. Many individuals involved in clinical trials, including investigators, may not have received formal training in GCP and other regulations required for clinical research, and the investigators are ultimately responsible for the conduct of their clinical trials.

Conclusions

We lack evidence on the (cost-)effectiveness of current trial procedures, such as intensive monitoring and 100% source data verification A statistical approach to quality assurance could yield huge cost savings without compromising the reliability of the trial results. Quality assurance in clinical trials is in great need of re-engineering. More regulations such as GCP or ICH, useful as they are, will not achieve this goal.

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