

**European Forum for
Good Clinical Practice**

Audit Working Party

**The Role of the
Quality Assurance Unit**



'where science & ethics meet'

This guideline is published as an EFGCP publication, intended to contribute to the development of best practices in ethics and science in health research. To receive additional copies or further information on EFGCP publications and activities, please visit www.efgcp.be or contact info@efgcp.be.

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The Role of the Quality Assurance Unit

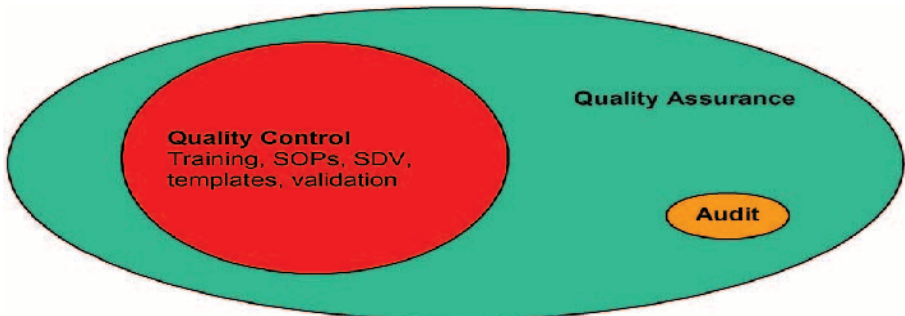
For a new Quality Assurance Unit (QAU), with responsibility for auditing clinical trials, the choice of which activities to prioritise can be bewildering. There will be many pressures from colleagues in other areas of the organisation who will be asking for help, and the QA unit's resources will have to be allocated carefully in order to maximise their effectiveness. This may mean that not all of the roles in this document can be conducted by all units. For small units in particular, the focus should be heavily on auditing, rather than other activities.

1. What is Quality Assurance?

The global guideline for good clinical practice is accepted to be the ICH E6 document. This defines Quality Assurance as “all those 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 and the applicable requirements.”

For those in the UK, the MHRA definition of Quality Assurance is as follows: “It is the sum total of the organised arrangements made with the object of ensuring that medicinal products or services are of the quality required for their intended purpose.”

While many groups which audit, provide advice and assist with inspection facilitation have the name “Clinical Quality Assurance”, this term is slightly misleading as all members of the organisation are responsible for quality. The quality level of the work is set when the work is done, and cannot be increased retrospectively during an audit. Consider the following diagram:



The diagram shows that Quality Assurance encompasses all of the Quality Control activities as well as auditing. It is not audit by itself. Furthermore, the number of staff performing QC is huge in comparison with those performing audit. From this it is clear that the responsibility for quality can only lie with the staff conducting the work initially. In this explanation of QA, the term is synonymous with the Quality Management System – the totality of documents, processes, reporting relationships etc, which describe what is to be done; how it is to be recorded, checked and audited; who is to do the role and what training they require.

Having covered the formal definition of QA, we will now move on to the accepted use of it. In this document the Quality Assurance Unit is understood to be conducting audits, and providing advice and consultation. In common with most existing QAUs, it has no QC responsibilities.

2. Introduction

This guideline has been written by experienced Clinical Quality Assurance professionals in the hope that it will help those starting such a unit 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. The guide is written at a high level, and refers to the activities which are appropriate for a new QAU, rather than giving detail on how to conduct those activities. Those who require more detail on conducting audits are recommended to review the ENGAGE guideline, available from the EFGCP.

Some principles for QA are set out in the ICH E6 guide to GCP. One of these is that the auditors must be independent of those conducting the work. This is important in order that deviations can be identified in an objective way, and that the reporting of these deviations can be done without fear or favour. Being independent of the system being reviewed, auditors will have no preconceptions.

It is essential for a QAU (of any type) that management support must be strongly visible from day 1. Without this, of the three competing elements time, cost and quality, quality will always be the one to suffer. As the QAU is forming, meetings with senior managers should take place to ensure they fully appreciate the need for quality, that they will resource the unit adequately, and that they will support QA on the occasions when

QA gives them unwelcome but necessary information. These meetings with, and support from, the highest level of senior management will help to send the right message across the rest of the organisation.

The document uses terminology relating to medicinal product. For some organisations there is the added complexity of working with medical devices too. Legislation and guidance on medical devices differs somewhat from that regarding medicinal products, but the principles are largely the same. Members of a QAU involved in this area will need to become familiar with the specific legislation relating to devices.

3. Positioning of QA and organisational interactions

There is a hierarchy of quality assessment:

- Self-check
- Departmental QC
- Independent audit

As explained above, those responsible for the work conduct their own checks and this is defined as quality control. In some organisations there is an internal audit function with responsibility for assessing all risks (eg financial, commercial, intellectual property) across every process (going beyond just GCP), and these “corporate” auditors often give reports to board level.

It is very important to establish which level of risk the QAU is expected to address. This document concentrates primarily on the GCP compliance auditing level, but the same principles would apply to auditing other business risks.

Neither the ICH nor the MHRA definitions 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 organisation 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

Since QA professionals are experts in GCP, it is appropriate for QA to provide advice and interpretation of regulations and guidelines. Assuring quality is achieved in part through audit, which requires QA to be independent from the functions/processes being audited i.e. not involved in the processes. Giving advice is considered to be outside of the process since there is no mandate for the advice to be followed, therefore QA retains its independence. Ultimately the client must accept the responsibility for their actions and that they own the quality of the process.

It is a good idea, when giving written advice, to give the context of the advice where possible (ie re-stating the issue as it was presented). This will help to avoid advice being applied out of context in a different situation, or clients giving only part of the scenario in the hope of getting the advice they really want.

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.

Quality Assurance staff must strive to find an appropriate balance between advising and evaluating to remain as independent as possible. In some cases they may believe there is only one correct approach and will advise accordingly. In other situations any advice is only a suggestion and it is clear there may be alternatives. Where alternatives exist, these should be provided as well as the impact of each of these alternatives if possible. When there is flexibility in the solution the customer should consider the recommendation and weigh it against other ideas, as they may identify superior solutions. Ultimately, clear communication is necessary to convey the nature of the QA advice, whether it is seen as the only way to proceed or one of several ways.

QA may be involved in helping a client determine an efficient and compliant process, and the question is sometimes asked whether they can still review the process. In general the QA team can also assess later

on whether the process is actually being followed, whether the expected documentation and records provide adequate evidence, and whether staff are trained. If the QA team is large enough, different staff may be involved in the advising and assessing roles. QA can be of real business benefit by being involved in business process discussions, because of their familiarity with the regulations and guidelines, and their opportunity to identify best practice across many parts of the organisation.

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.

4. Training

Members of the QAU will become familiar with the organisation'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 organisation to the deviations they are finding, in the hope that the quality level may be raised across the board.

A way of maximising the uptake of the QA message is for the auditors to support the organisation's existing training programme, or to put slots into the schedule of department meetings. For a new unit this will serve the dual purpose of helping everyone to learn from the audit of comparatively few staff, and it will raise awareness of the existence of the unit.

In a setting where audits have not previously been performed, many potential auditees will be nervous of the process. The image of the nit-picking, hostile auditor of many years ago has not completely disappeared. For those presenting the face of the new QAU therefore, it will be critically important to be seen as positive and helpful. Once a

collaborative, trusting environment is created, client groups will openly raise problem issues and concerns with the QAU, rather than attempting to cover them up, and everyone gains as a result.

When presenting audit findings it is important to be non-judgmental, and if the audience is of mixed client groups, it would be wise to focus on the process and remove anything which might identify the auditee specifically. Where there is the potential of comparisons being drawn, or staff learning of the findings of other departments, consideration should be given to having multiple close-out meetings. Findings should be presented as process observations rather than targeted at an individual. This has the added benefit of making management responsible for corrections. The trust that was so carefully built can be destroyed if clients feel their issues become public property.

It is very important that the audit findings are not used to grade the performance of any group. The temptation to hide issues and argue for a downgrading of issues will be very strong in this case. This is an area where the QAU must stand firm and employ the support of senior management.

A QAU may be asked to present on regulations and guidelines, and this can be a valuable way to help others achieve compliance. Bear in mind it is resource intensive, so while the unit may lead the operation, it would be wise to spread the load around the clients and ask each to review one section of the regulation in question and be prepared to present as the in-house expert on it. This lessens the workload on QA and helps the clients to learn the regulations in depth.

QA will probably want to present to the clients at some point on fraud and scientific misconduct. This is an emotive topic, and plenty of preparation is required. There are several good reference books on the subject which could be consulted. The aim should be to clarify the organisation's policy on pursuing fraud, to give some indicators of fraud and scientific misconduct which staff can look out for, and to emphasise that, while fraud is a reality, the chances of meeting it are not high. Misconduct should be clarified – it encompasses a wide range of misdemeanours, but becomes fraud when there is an intention to deceive.

If the organisation 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 organisation needs focussed, remedial training.

5. Auditing

The following sections give high-level guidance on auditing processes. More detail can be found in the ENGAGE guideline.

5.1. 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.

5.1.1. Documents

Protocol audit and database audits are now conducted less frequently than before, as they are recognised as a QC function. They may be performed retrospectively as part of a “systems” audit, focussed on the quality control aspects of the document production. (see below). 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 organisation:

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

5. 1. 2. 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
- enrolment
- 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

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 organisation 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 include the following, among others. For more detail, see the ENGAGE auditing guideline, available on the EFGCP website.

- 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: $\sqrt{(n+1)}$, 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

5. 1. 3. Other study-related audits

Some organisations conduct study safety audits, following safety data through its processing stages.

5. 2. 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.

Prioritise 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.

5. 3. Role of QA in vendor (service provider) audits

Audits can take place before a contract has been awarded to a vendor, or once the work is being conducted.

In a pre-contract audit (sometimes called an evaluation), QA may participate as part of a team. Representatives of the relevant client departments should attend (eg data management will assess processes being contracted out in their own area) and if there is an outsourcing department, they will probably lead the team. QA may assess only the audit function of the service provider, or they may review the whole quality management system (including training and SOPs as well). The final decision on the use of the vendor should not be decided by QA, but by the functional group.

The contract with the vendor should determine whether the sponsor organisation, vendor, or both will conduct audits of the work carried out.

Vendors should be selected for audit on a risk basis, e.g. based on impact on efficacy parameters, or volume of work contracted to the vendor (e.g. one provider for all IVRS). A programme for vendor audits should be created for discussion with the client groups, to confirm that QA resource is addressing the vendors of greatest risk to the organisation.

It is normal in a vendor audit to make some findings relating to the vendor, and some concerning the sponsoring organisation. The sponsor findings are not usually shared with the vendor, so separate reports are created for the sponsor (with all findings) and the vendor (with only those relevant).

Evaluations need to be conducted by the group responsible for conducting the work, irrespective of whether QA can participate in the evaluation. For example, data management staff must conduct the review for a data management vendor.

For audits of safety-related vendors, more information may be found in the EFGCP guideline of pharmacovigilance audits, available from the EFGCP website.

6. Role of QA in regulatory inspections

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

6.1. 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 files, training files 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.

6. 2. 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.

6. 3. 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 utilise 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.

7. Safety-related activities

7.1. 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 organisation 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 organisation. 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 organisation. Support from specialised 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.

7.2. Product Complaint review

Not many GCP QAUs are involved in complaint review unless the complaint includes a medical event, e.g. colour changes in tablets causing headache, which may either be reported to the manufacturer or the PV department or to both in parallel. Note that a medical event can include lack of efficacy. The pure technical complaints (ie with

no medical event) are normally a function of specialist groups or the GMP QA team.

For the complaint review process a documented interface between the GCP QAU and the GMP QAU is important. There should be regular reconciliation processes between the GMP and PV departments. The interface between the product complaints department and the medical information department is very important. Audits conducted jointly by the GMP QAU and GCP QAU are beneficial to cover this process in its entirety.

8. Post approval studies

This is a term used for later stage studies, where a licence has been applied for, or granted in some areas. These are often therefore larger studies, and may not be used for product registration (as the licence has already been applied for). They may also be requested by regulatory authorities as a condition of initial approval.

The audit will be planned on to a risk basis taking into account the population exposure and safety profile of the product. The inclusion criteria may be much wider and exclusion criteria less strict compared to the earlier studies to allow fast inclusion of a large number of patients. If an organisation is performing these studies, it would be a wise decision for the QAU to discuss what standards are being applied, whether the processes are the same as for earlier phase or not, and use this basis to determine how many, audits to conduct. It will usually be a much smaller proportion than for earlier phase work, due to the increased numbers of sites and patients. To avoid 'double-standards' however it is important to clearly convey the message within the organisation that GCP-principles need to be applied whenever patients are included in research projects and that therefore the audit programme needs to cover all phases of studies involving human subjects. If resources are limited it might be an option to use contract auditors to cover such large studies.

Sometimes post-approval studies can be safety-related, and in these cases the audit focus should be firmly on the pharmacovigilance aspects of the study. This may require a change in audit conduct from the standard site audit process.

9. Interfaces of GCP QAU with other GxP-QAUs

As for the PV QA activities it might be advisable to contract such audits to specialised consultants if in-house resources and/or knowledge are not sufficient. This applies to the sponsor's own computer systems as well as to audits of computerised systems used by CROs e.g. for Data Management and Statistical Analysis and third-party vendors on behalf of the sponsor.

Depending on the size and structure of the organisation conducting studies and its departments and the history of the QAU function, different areas may be covered by clinical QA. The availability (or non-availability) of other GxP QA units, e.g. GMP, GLP, IT will have an influence on the remit to be covered by the clinical QAU in addition to the essential clinical development activities. This is discussed by area below. Whether these fall in the remit of a given clinical QA unit and to which extent needs to be clearly defined and decided on a case by case basis and will vary between organisations.

As a principle, it is however important for a comprehensive and adequate Quality Management system to ensure that all interfaces are covered and no unattended gaps between the different responsible QA units remain. It is understood that the provision of such a comprehensive Quality Management system is a management responsibility and cannot be achieved by one of the QA units alone. However, the individual QAUs are responsible to raise management's attention to potential gaps in the overall Quality Management system and request corrective actions.

9.1. 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 computerised 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.

9. 2. GMP interface related to IMPs

Annex 13 to Volume 4 of GMP details the principles and requirements for GMP compliant manufacturing of IMPs. While the QA activities of the specific manufacturing processes fall within GMP-QA's responsibility, some of the later, study specific steps such as labelling/re-labelling, shipment to (including IVRS) and receipt and storage at intermediate warehouses and investigator sites may fall under the remit of Clinical QA. As in other interface areas between the different GxP-QA groups it is essential to have clearly defined areas of responsibilities for each QAU and processes covering such interfaces.

Joint audits (GMPQA/Clinical QA) may be beneficial for mutual training and understanding of the different audit functions as well as to ensure full compliance of the processes applied. This can include QP release of IMPs e.g. in phase I units.

It is important to review temperature monitoring of the investigational product, especially for cold chain material, but increasingly questions

are being asked about storage of product at >30C as well. These aspects may therefore be encountered during site audits.

9. 3. GLP interface related to human biological samples

Clinical laboratories analysing human samples are normally not GLP-certified, and if they are, it is because they also analyse 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 speciality laboratories (e.g. those analysing 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 specialised external laboratory, or laboratory internal to the organisation, 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.

10. SOPs

For large organisations 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 organisations, 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.

11. Potential Other Activities

A successful QA unit will have built close relationships with its clients, and earned a reputation for wise interpretation of GCP legislation and guidance, and for pointing the way towards process improvement. Very soon, other potential client groups will want to benefit from this resource, and it is essential for the QA unit to determine where they can help, and where they should not. The following is a brief discussion of some of these potential groups.

When organisations in-licence a product from outside, there is a careful review of the external company and its product. Depending on the resources and experience of the organisation buying the rights, the QAU may be asked to participate in what is called a “due-diligence” review. The risk to the organisation can be high, so often it would be appropriate for the QAU to be involved in this area, even if it draws resource from the audit programme.

Inappropriate promotion of medicines, and improper inducements to investigators, are frequently in the media and are a risk to the reputation of any organisation. These areas are covered by legislation other than GCP. It may be decided that it is an area that the QAU will cover, but it would be wise to obtain additional resource to cover it, or it will inevitably reduce the GCP coverage.

Disclosure of clinical trial data is an emerging risk which has not usually been part of the role of the QAU. High profile cases regarding lack of timely disclosure have resulted in damage to reputations and are cited in product liability cases.

Finally, the area of Health Economics is one that is on the increase – determining the economic benefits to justify the use of a drug or treatment regimen. Therefore there are often studies performed to determine if those taking a drug/regimen are using the local health system less than before, or avoiding the need for other prescription drugs. These studies may be determined to be within, or outside, the scope of the QAU, depending on resource.

12. Acknowledgements

This guide was compiled by Paul Strickland, with contributions from Graeme Downes, Birthe Nielsen, Brunhilde Schneider, Ian Thompson, Kate Wallace and the support of the EFGCP Audit Working Party.



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