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7 Quality Assurance and Clinical Data Management

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INTRODUCTION

Ever since the finalisation of the International Conference of Harmonisation (ICH) GCP guideline in 1996, the implications have been very clear. No longer would the Regulatory Authorities be content to accept that the investigator site was the only target for high-quality standards in a clinical trial. The new proposal for a European Parliament and Council Directive on the implementation of Good Clinical Practice (97/0197 (COD))[1] describes the need for and importance of a clear paper trail for any clinical trial. In the same section on 'Verification of Compliance' the Directive describes the importance of the 'audit' of the study. In the many complex clinical trials being conducted today, the handling of clinical data outside the investigator site is of equal importance. In fact, some agencies, especially the Food and Drug Administration (FDA) have always taken an interest in the manner that clinical data were collected and analysed. The FDA *Compliance Program Guidance Manuals:* 'Clinical Investigators' (7348.810)[2] and 'Sponsors, Contract Research Organisations and Monitors' (7348.811)[3] require the Food and Drug Administration (FDA) Inspector to establish how the clinical data are going to be entered into the computer system and then analysed.

In any submission process, the clinical study report forms a vital part of the mechanism to get a new product onto the market. The development of the report commences not when the first medical writer prepares the title page but when the first entry takes place in the Case Report Form (CRF). Some may argue correctly that the process starts earlier when the protocol is developed, or when the CRF is designed and the staff at the investigator site are trained. All these processes require rigorous execution if the initial risks, however small, taken by the subject in a trial are to be justified. The role of the Quality Assurance (QA) group in this process is ensuring that the clinical data presented and interpreted in the clinical

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study report reflect a true picture of what took place in the trial. One of the main roles of the QA group is as an independent auditing group.

It is true that in the non-drug industry, the organisation that has a QA group may benefit by being more efficient, producing quality products or service. Frequently, the presence of a QA group is perceived as of marginal importance, certainly in the view of senior management. However, there is no doubt that the inclusion of quality in the culture of a company or organisation is a requirement of any operation conducting clinical trials. The last principle of ICH GCP requires that there are 'systems with procedures that assure the quality of every aspect of the trial'.

In order to form a clear picture of where QA fits into the clinical data management part of a clinical trial some definitions and comments are required for Quality Control (QC), QA, audit and the responsibilities of the QA group.

QUALITY CONTROL

The definition in the ICH GCP Guideline for QC is:

> The operational techniques and activities undertaken within the quality assurance system to verify the requirements for quality of the trial-related activities have been fulfilled[4].

This means that clinical data management must have documented evidence of what activities have been carried out throughout the trial to ensure the quality of the clinical data. QC tasks are the responsibility of the personnel handling the clinical data. In some cases, it is the actual group designated within clinical data management to conduct these tasks.

It must be remembered that QA auditing is not QC and the responsibility for fully checking transcription, calculations, interpretation and reporting must remain with operational clinical monitors and clinical data management personnel—'the experts'.

The QA group is responsible for taking 'snapshots' of the study at critical times and places. The information obtained will allow data management to extrapolate findings forming a picture of the quality and integrity of the data on which to base decisions.

QUALITY ASSURANCE

The definition given in the ICH GCP guideline for QA is:

> All those planned and systematic actions that are established to ensure that the trial is performed and the 'clinical' data are generated, documented

> (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s)[4].

This means in practical terms that clinical data management must have written procedures in place which will allow an independent group to audit against the actual processes taking place in the handling of clinical data. The documentation detailing what has happened during that trial should be present. The same group may have already reviewed the CRF, the protocol, and in some cases have trained the Investigator and his/her staff. The auditors may have visited the sites to audit the actual process of collecting clinical data by the Investigator and his/her staff.

Independent QA should be built into the clinical data management system and carried out concurrently with other clinical data management activities.

AUDIT

The definition in the ICH GCP guideline for an audit is:

> A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the 'clinical' data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s)[4].

All key aspects of an audit are covered by this definition. All audits should be defined by an audit plan and the main scope should be recorded in the resulting audit report. Normally, key questions will have been listed before the audit has commenced and the auditor should be encouraged to restrict his/her attention to the audit's scope. However, too much rigidness can create the 'tick list' mentality which allows the CRF to match the clinical database listings but does not note that its storage is under a leaking roof; that is a lack of flexibility in the auditing process can mean that serious deficiencies are missed or fail to be addressed. The European Network of GCP Auditors and other GCP Experts have published an *Optional Guideline for GCP Compliance and Quality Systems Auditing*[5] which provides a basis to conduct any audit.

THE QUALITY ASSURANCE GROUP

QA auditing is the responsibility of an independent group which reviews clinical data at defined times to assure that procedures have been followed in accordance with approved quality procedures and that the

quality of the clinical data is acceptable. The benefits of such a group auditing early in the process are that ambiguities or inconsistencies can be identified, documented and, more importantly, acted upon before impacting too heavily on the final product. This often results in making the documentation more user friendly and saves time or confusion during the study as well as assuring GCP is being complied with.

Historically the QA group spent its limited resources auditing at investigator sites with occasional audits 'in-house' to review the final report. In some cases, QA were undertaking a QC role and may have been seen and used as a safety net, involved only at the end of the process when it was too late to make a constructive difference to a project. In the past it was common for the QA group to audit prior to clinical database lock to provide a 'final seal of approval'. If problems were found at this stage, timelines would have to be extended, especially if there were queries which needed to be resolved at the investigator site.

The QA group should not hold up the clinical data flow; they should be auditing at intervals throughout the trial. At such audits they should be able to assure that procedures are adequate and are being followed. The task of the QC checks falls on the clinical data management personnel, since they are the operational personnel and know how the clinical data should be handled.

As already mentioned, it is beneficial for the QA group to be involved throughout the clinical trial process. The QA personnel should be consulted at the protocol and CRF design stage. This independent audit is essential to ensure that all possible pitfalls are avoided and GCP complied with. Auditors can then commence formal audits at the investigator sites when the clinical trial recruitment commences. The group can continue the auditing process on the clinical database in-house, completing a full review of the clinical data management process by auditing the handling of CRF data.

The QA group can use their broad experience to provide advice about the planned data management procedures. They can give an independent viewpoint, uninfluenced by other project concerns or pressures. In order for the group to be used to its fullest potential, regular audit reports should be issued to management. Such reports should highlight timeliness, completeness, reliability and consistency of the clinical data collected.

Regular audits of clinical data management systems (see section on Process Audits) may reduce accidental or deliberate corruption of the clinical data. It is important that audit findings are clear and precise so that they can be correctly followed up. This also ensures that future studies can benefit from changes incorporated into the process.

Another important factor in ensuring an error-free clinical trial is communication. Problems highlighted by audits of the clinical data

management and clinical monitoring groups, early in the process, can be communicated to them. This reduces the impact on the final product.

TRAINING OF THE QA PERSONNEL

Before we discuss in some detail what processes should be present, some consideration should be given to the auditing personnel and how they are trained.

The selection of QA personnel is difficult. Auditors should be meticulous, analytical, good communicators and good trainers. Communication can involve 'one to one' situations, but often the auditor needs to be able to address a group. In addition, they are required to be disciplined enough to audit with thoroughness clinical data listings and tables against CRFs, and the clinical study report against source documentation. All personnel must have a full knowledge of the many facets of the clinical trial process and GCP. Frequently, in large institutions, the personnel conducting in-house data management audits are personnel involved in the data management and so the audit is really a QC activity. In order for such an audit to be regarded as a QA activity it must be performed by an independent auditor.

The selected individual should never be made responsible for the conduct of an audit until they have been fully trained and have reached a level of confidence acceptable both to themselves and to their management. The training should be based on a series of training sessions, often attending the same sessions as site monitors and data management personnel, until they are fully familiar with the theory behind the clinical trial process. In addition, many specialised external courses, such as those organised by the Drug Information Association (DIA) and the British Association for Research Quality Assurance (BARQA), provide additional training in a wider field of QA.

However, the most important part of the training is that carried out with other experienced auditors either in mock audits or as an attendee at a real audit. New personnel should be trained using real listings, tables and clinical study reports, which have already been audited by an experienced auditor. This allows for a comparison to be made between the trainee auditor's findings and the experienced auditor's findings. For cost-conscious management, time taken to complete tasks will be longer with new personnel and should be budgeted for.

INVESTIGATOR SITE AUDITS

A full description of the events that take place at an investigator site audit is not within the scope of this chapter but does need to be considered

briefly. Considerable time is spent at the site establishing that correct documentation exists for regulatory and Independent Ethics Committee/ Institutional Review Board (IEC/IRB) approval for the site, that the consent has been obtained correctly from each patient and that the study drug has been supplied to the patients correctly. All these items are important for GCP compliance and for any successful submission and will also feature in the clinical study report. However, from the point of view of clinical data management, the following aspects are critical if the clinical data are to be suitable for successful analysis.

The CRF

The CRF should be carefully designed to answer the questions posed by the protocol and to allow the appropriate safety data to be collected and recorded. There should be a clear definition of all data variables (e.g. diseases, adverse events, efficacy endpoints). Clinical data management can help in this quest by reviewing the draft protocol and CRF in conjunction with QA. This is particularly important if new CRF modules are being used which are different from those previously used or there have been problems with the previous template. Auditors constantly note that some of the questions asked are not completed by the Investigator, either because this part of the test or examination was never done or because the Investigator feels that it is an inappropriate question. The designer, even if medically qualified, sitting at his/her desk away from the intensive care ward or general practitioner's surgery should determine before the study commences what is essential and also what would be 'nice' to have but is not essential. The designer should also remember that the clinical data will need to be read before being entered into a clinical database. It should be in a format that allows easy completion by both the Investigator and his/her staff and easy understanding by the data entry individuals. The statisticians may also wish to comment if the data are collected electronically by remote data entry and will require manipulation before analysis. A good reference point for the design of CRFs is Gill Lawrence's review on CRF design[6].

The Protocol

The protocol should be easily understood in order for it to be followed by the Investigator and his/her staff. In spite of ICH GCP (Section 6), many protocols still appear to have been put together by several committees, often appear to have been written for different indications and for a different country, and therefore are very difficult to understand. Frequently amendments are required because of poor preparation of the protocol rather than due to issues which arise during the conduct of the clinical

research. It may be a sensible approach to retrieve parts that have been well written and are relevant to the new study from a previous protocol but very careful editing is required. QA should always be part of the reviewing team. An experienced auditor will be familiar with the many pitfalls that will occur at the investigator site when a poorly designed protocol is used. When the protocol is badly written the resulting effect is the collection of poor-quality clinical data.

The Training of the Site Personnel

Training of site personnel is of paramount importance and should be done before a study commences. The Investigators' meeting, the pre-study visit and the initiation visit by the monitor will help prevent misunderstandings and ensure that the clinical data recorded in the CRF will provide the scientific information needed for regulatory submissions. Some pharmaceutical companies provide training in GCP to investigators and their staff in addition to any training that they may undergo for a specific protocol. Many investigators and their staff are prepared to give up their time for this type of training. QA should have a role in the training of site staff including the investigators. They should be present at the Investigators' meeting, and their audit findings from past and present studies should influence how clinical data management and clinical staff train the Investigator.

Source Data Verification

ICH GCP states that the definition for documentation is 'all records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken'. The monitor needs to ensure that there are source documents available and that the clinical data in the CRF match the source documents. At the beginning of the study, there should be clear guidance as to what source data will be required to be provided by the Investigator and this should be documented in the protocol. If the clinical data are not accurate and correct, there is little point in collecting the data. QA and, perhaps more importantly, inspectors from the regulatory authorities, will check that this process has taken place when site audits/inspections are conducted.

Monitors

These key staff should be well trained and given enough time and resource to ensure that the clinical data coming from the site are accurate and that

the CRF has been completed correctly. They will be ultimately responsible for ensuring that the investigator and the site staff are trained properly. CRFs arriving in-house which require queries to be generated and sent back to the site cause delays, expense and frustration on the part of clinical data management and often the investigational staff. The site personnel believe that they have answered all the questions until they find additional ones in the post, perhaps several months after the particular visit that has generated the query. In addition, there is always the temptation to answer the query in-house in spite of the need for the endorsement by the investigator (ICH GCP 4.9.3).

CLINICAL DATA MANAGEMENT AUDITS

Before a study starts the following items should be addressed:

- Review of relevant quality procedures
- Preparation of protocol
- Design and preparation of CRF
- Allocation of staff and responsibilities
- Establishment of data security requirements
- Adequate office space
- Validated computer systems
- Archives (both current and long term)

It is beneficial to address the above in a clinical data management plan which ensures the documenting of processes to be followed during the data management process. It also guarantees, if followed, that an audit trail will exist and thus the study can be recreated if required.

Audits of the clinical data management area often consist of five distinct types: study documentation, complete CRFs, key variables, tables, figures and listings, and clinical study report audits. Such audits are normally conducted in-house.

STUDY DOCUMENTATION AUDITS

Clinical trial data require documentation that supports the Sponsor's claims to the regulatory agency when it is submitted for drug licensing. In many organisations there exists one project file containing both clinical data management and clinical monitoring documents. Document review is carried out throughout clinical trial using the ICH GCP essential document checklist. The auditor's philosophy will always be 'if it is not documented, it did not happen'. Therefore documentation has to be accurate and give a

true picture of what happened during the clinical trial. In order for this to be the case the clinical data management team has to implement certain recorded checks throughout the life of the study. The clinical data management documentation will include the current protocol and its amendments, the receipt of the CRFs from the site, QC checklist for the data files, the preparation of the database, change control documents, unfreezing-refreezing file request forms, and the CVs, training records and job descriptions. Study documentation should be reviewed continuously throughout the clinical data management process. This is to ensure that there is a clear and concise record of the activities of the clinical data management group. The auditors are assuring that ICH GCP has been followed in parallel to ensuring that quality procedures are in place and being followed. This type of audit should not be seen as a filing exercise. It is important that at any time during the clinical trial there is documentation in place describing what has happened.

Such documentation is the primary record of all activities carried out by the clinical data management personnel in the execution of a study. Study documentation should be organised in such a way that it is accessible and easy to follow. If audits are started early in the process it can be ascertained quickly whether adequate documentation is being kept to give a true picture of what is happening in the process.

DATA AUDITS

The early audits by the QA group are conducted by reviewing study documentation so that if there are any missing areas the situation can either be resolved or the deviation documented. Above all, problems can be prevented from happening again.

CRFs should be reviewed by auditors early in the clinical data management process. Although driven by the clinical database, all documentation around the clinical data should be reviewed. The auditor is looking at the processes involved in getting the clinical data from the Investigator to the database. By doing this type of audit early in the process, the auditor can highlight any gaps in the QC activities and any GCP non-compliance, early enough for deficiencies to be corrected to reduce any impact on the final clinical database. This will also help towards producing a high-quality product and ensuring timelines are met.

The CRFs to be audited should be selected from different sites and countries so that the process of handling clinical data can be examined across the data sources. CRFs should be selected to cover all areas of the clinical data management process, that is, 'just data-entered', computer data validation checks completed, queries sent out, queries returned. This will give a true picture of how the data are being handled and whether

there is adequate documentation in place and adequate quality control procedures. The percentage of CRFs to be audited depends on the size and complexity of the study. A simple small study such as an asthma study with 50 patients and five sites would probably only need five CRFs to be audited in order to get a picture of how the clinical data are being handled. Whereas a larger, more complex study with 3000 patients and 100 sites may required 50+ CRFs to be audited.

The auditor should be provided with all the study-specific documentation such as the final signed protocol, and the final version of the clinical data handling conventions, including data entry guidelines. This will ensure that they do not raise unnecessary queries and also gives them the assurance that such documentation exists and is being followed. All audit findings should be written clearly and precisely so that the auditee understands completely what has been found. If at any time the auditor feels that they are finding too many ambiguities or mistakes then the audit should be curtailed and a senior member of the clinical data management team informed. A decision then needs to be made on whether there is a systematic breakdown of the process or whether no particular breakdown can be identified. It could result in all the clinical data needing to be re-reviewed. If this audit has been done early in the process then there should be plenty of time before database lock to correct process problems.

An audit of the key variables is an important exercise prior to database lock. Key variables are dictated by the protocol and the project statistician, not the auditor. They normally consist of safety and primary efficacy clinical data as a minimum. It is essential that those variables specified are also those identified by clinical data management. The audit should then take place on a similar size population as the CRF audit. The 100% checks should be completed as part of the quality control process and the audit should be assuring that this process has taken place. Often it is beneficial to pick some patients previously audited at the CRF stage to assure that the key variables have been consistently handled and that any problems identified have now been resolved. When auditing the key variables the procedure is similar to the CRF audit with the main emphasis being on a review of the process and the documentation.

Another aspect of clinical data review is coding and the world of coding is a complicated place. Rules need to be laid out early on and specifications clearly given to the coders. The dictionaries used frequently at the first level are in-house, the codes are then often broken down into COSTART and WHO-ART preferred terms. These dictionaries can be extremely constricting as often the verbatim term used by the Investigator does not match any of the terms found in them. It is hoped that in the future there will be a dictionary that is recognised worldwide, but this at present is still in a draft format.

When dealing with coding there should be a great deal of emphasis on quality control and those involved should understand the variables that they are coding and why they are coding at all. More and more companies are now adopting a policy of having a dedicated group of professionals who concentrate solely on coding. These personnel are usually medically trained and have a thorough understanding of the coding dictionaries. An important factor of having one central team performing the coding means that the coding is standardised and the clinical database is held in a central and uniform manner. The QA audit consists of a check to ensure that guidelines and quality control procedures are being followed.

It is now frequently the situation that coding is computer assisted and this has made coding easier on a practical level[7]. One of the main benefits is that looking up codes and later reference is easier. It also helps towards coding consistency as frequently referenced codes can easily be accessed.

Coding is used to provide a more effective way of analysing certain data collected. Codes can be used to present clinical data in a uniform and therefore easier way, but any misinterpretation of data meaning must be avoided. The existence of controlled guidelines and quality procedures and trained personnel prevents such misinterpretation. The QA audit can give the further assurance that the data can be regarded as a true representation of what the investigator collected on site. If many errors occur in the coding of clinical data, then this will affect the final clinical study report.

TABLES, FIGURES AND LISTINGS AUDITS

The process for the production of tables, listings and figures should also be audited early. This ensures that there are adequate documented quality control procedures in place and that they are being followed. As with the database audits, if problems can be found early on then changes can be implemented before there is an impact on the final product.

Final tables, figures and listings are audited by the QA group for programming, accuracy and also to ensure that the statistical analysis, as described in the protocol, has been followed. Often this results in a number 'crunching' exercise by the auditors. Documentation behind the production of the tables, figures and listings is also reviewed to ensure that validation has taken place and has been documented clearly. The main aims of such an audit are to provide assurance that the listings are a true reflection of the CRF, the tables are a true representation of the data found in the listings, and the figures are a true representation of the data found either in the tables or listings. The auditor is also looking to ensure that the programmers and statisticians are following documented procedures that adhere to ICH GCP, the final, signed protocol and statistical analysis plan.

A handover meeting should be held between the programmer, statistician and auditor to ensure there is no confusion regarding what tables, listings and figures are to be audited. A complete list should be provided to the auditor and if possible a cross-reference given between tables and listings, listings and figures, figures and tables. Often the same program is used to produce more than one table and it is helpful to the auditor if this information can also be made available to them. The auditor should have reviewed the protocol and statistical analysis plan prior to the audit in order to gain sufficient knowledge about the study. These documents are then reviewed throughout the audit to ensure that the final product exactly meets the requirements and to ensure the relevant quality procedures have been followed.

If a randomisation list is applicable, this is checked against the appropriate listing, also the procedures followed to break the randomisation code are reviewed. A complete CRF is checked against the listings to ensure that the programming is correct and that they truly represent what has been recorded by the investigator. All titles between tables, figures and listings are checked for consistency and accuracy with the statistical analysis plan.

All fields are checked for misspellings and any 'odd looking' values within a listing are investigated. This particularly applies to laboratory clinical data. All footnotes are reviewed for sense and suitability, and any flagged items are checked to ensure there is an explanatory footnote. Numbers are checked within the tables for accuracy. Checking should also be completed between tables and listings for such clinical data as adverse events and withdrawal details. As with clinical database audits the audit findings must be written clearly and precisely so that any resolutions required can be implemented.

CLINICAL STUDY REPORT AUDITS

The final clinical study report is audited to assure its integrity and accurate reflection of the clinical trial. All factual statements are checked against the medical writer's source and all documentation supplied is checked for its authenticity. The audit is also ensuring that the report is a true reflection of the study design outlined in the protocol. All numbers referred to from the tables and listings are checked for accuracy against the appropriate tables and listings. The process for auditing the report is similar to the tables, listings and figures audit in that the final, signed protocol and statistical analysis plan and quality procedures followed, are reviewed throughout the audit. After the report has been reviewed page by page for accuracy against source documentation, it is read thoroughly for general sense. The audit findings are again written clearly and

precisely so that the audience can understand them and take the appropriate action in a timely fashion.

ERROR METRICS

The *Concise Oxford English Dictionary*[8] definition of an effort is a 'mistake or the condition of being wrong in conduct or judgement'.

Many auditing groups create elaborate error metrics in order to give a statistical meaning to the problems they have found in clinical data. The usefulness of errors can only be established if there is some structure behind their meaning. It is possible to have a very high error rate but on investigation it can be seen that the errors only concern non-critical data and so to spend time on resolving them would be wasteful. If the definition for an error is not clearly established then it can lead to misunderstandings between auditors and clinical data management. The actual calculation of the errors also needs to be statistically acceptable. This is when a statistician's skills are very necessary and valuable.

It is more beneficial often to review errors for systematic problems. A pattern of clinical data entry errors or a high error rate can highlight certain process problems. If these are highlighted early in the clinical data collection then resolutions can be implemented before too much data is adversely affected. It cannot be repeated often enough that error rates are only useful if they mean the same to all personnel looking at them and if the error criteria are also clear.

AUDIT CERTIFICATES

ICH GCP states that an audit certificate is 'a declaration of confirmation by the auditor that an audit has taken place'. The auditor can never state that everything contained in the clinical database, tables, figures and listings or clinical study report is 100% accurate and that there are no errors existing. They can state that they have carried out audits and that as far as they can reasonably determine the clinical database, tables, listings and figures or clinical study report are a true reflection of what happened in that trial.

CLINICAL DATA MANAGEMENT TRAINING

The QA group can help an organisation to improve customer satisfaction and reduce costs by implementing a quality system. This puts more emphasis on the group's role in helping to provide the means to achieve continuous improvements in performance. QA and QC, as already stated,

are integral parts of the clinical trial process. It is essential that a proactive mechanism be implemented to promote high-quality clinical data acquisition and reporting. It is important that personnel working in clinical data management provide feedback on QC issues and are able to contribute to process improvement. This can only happen if these personnel are trained and kept up to date with procedures.

The QA group should be involved in training and should assure that adequate training takes place by performing regular documented audits. Through the auditing of training documentation and the processes the QA group can highlight any training needs to management to ensure that training requirements are met.

Auditors can be involved in quality procedure training, holding workshops to explain the importance of such procedures. They should also be involved in training in the principles of GCP. Often they are able to give examples of actual incidents which graphically describe the importance of GCP.

REGULATORY AUTHORITY INSPECTIONS

Frequently, the QA group are the hosts for the Inspections of the regulatory agencies. The request from the regulatory authority to inspect a specific project will usually be sent to the sponsor. In the case of international trials, this could be the local country office of the sponsor and the request requires to be relayed to the office where the data management has been carried out. The QA group will usually ensure that all the appropriate staff are prepared, that there is a room, ideally somewhat remote from the everyday business of the institute, and a photocopier, translator, and document collector available. Clear instructions should be given to the staff involved in the Inspection. Questions from the inspectors should be answered with honesty, with as much clarity as possible and without unrequested additional information.

If the support and training of QA has been effective, no surprises should come from the Inspectors' comments at the end of the Inspection. Previous audits by QA should have revealed most of the deficiencies. The frequently quoted deficiencies include the lack of original documents, protocol nonadherence and inability to identify staff involved in the Project. If problems are found, FDA inspectors will look in depth at the systems involved, including whether the computer system has been validated.

QUALITY SYSTEM

In the introduction we commented on the requirement of ICH GCP to have systems in place which 'assure the quality of every aspect of the trial' (ICH

GCP 2.13). Without some kind of quality management system it is difficult to envisage compliance with this GCP requirement.

TOTAL QUALITY MANAGEMENT (TQM)

TQM is an approach that can be used by the management of an organisation which is centred on quality. It ensures the involvement of all staff and aims at achieving long-term success by customer satisfaction, benefiting all members of the organisation, and society, and providing a mechanism for continuous improvement.

In all 'apparently' progressive organisations, various efforts are made to create a culture of 'quality' using some form of TQM. There is nothing new to the concept of implementation of the often considered mystic term of 'quality'. In 1951, Feigenbaum wrote a book on *Total Quality Control*[9]. In Japan, in the 1960s, the so-called 'quality circles' were developed to ensure the personal involvement of factory workers in quality management and problem solving. At the same time, in the US, the 'zero defect concept' was being applied to Pershing missiles, producing them without defects in the stipulated time.

The implication of TQM in clinical research is that QC will be carried out by all staff. If successful, QC should extend from the initial design to the final 'product', that is the clinical study report. QC should also extend to all aspects of the study, including the training of the individuals involved, the payment of staff and investigators, the quality of the paper used in the manufacturing of the CRF and all the essential but 'peripheral' tasks. However, until the rigour of ISO 9000 was established, TQM remained a vague concept to most ordinary members of staff.

ISO 9000

ISO 9000 is a series of quality management and quality assurance standards and guidelines. The series is written from the perspective of a service or product supplier. The standards have been designed for application to all industries but the relevant standard for GCP is that of ISO 9001 *Quality systems—Model for quality assurance in design, development, production, installation, and servicing*[10]. It provides the framework for a quality system which can assure that clinical data are handled in an error-free manner[11]. Such a system involves the training of study personnel, and comprehensive documentation of the operations and procedures that all personnel are following. Some describe the system as a bureaucratic nightmare, but this is only true when intelligence has not been applied to the standard. For example, ISO 9001 can encourage the design of concise CRFs since it

will prescribe both the appropriate checklist, and the need for the right people to review and approve the form. It will also prevent the CRF from being designed before a near-final draft of the protocol has been prepared.

The system should assign responsibility for different aspects of quality monitoring, and ensure periodic audits of the clinical database and procedures against source documents. It should also regularly report on details of clinical data quality that identify sources of errors and delays that limit accuracy and timelines of the production of a complete clinical database. There should also be provision for corrective actions to be implemented and the system should be revised or redesigned if deemed necessary.

PROCESS AUDITS

One of the features of any quality management system is that audit of processes should be performed, as well as those audits related to specific protocols. One could argue that to conduct any audit even specific to a protocol will involve auditing the process as well. This is often true but frequently the protocol-specific audit will not highlight a general deficiency. The process of clinical data entry may, in a protocol-specific audit, show that data have been successfully entered into the database. It will not necessarily show that the staff have no documented training and, worse still, that the computer system, of which the clinical data entry is part, has not been correctly validated. Process audits should be conducted on all clinical data management processes at least once a year and more often if changes are taking place or deficiencies have been highlighted.

REMOTE CLINICAL DATA ELECTRONIC CAPTURE

The role of QA in clinical data management has been described essentially for a paper system. Increasingly, various hard and software packages will allow clinical data to be transferred into the clinical database with limited involvement of human input. Personnel in QA will need to establish that the data, perhaps entered by the investigator or read by a scanner, cannot be changed by unauthorised personnel or without authorised documentation. An audit trail will need to be available as would be required for a paper-based system. The manner in which the data arrive at the database where the analysis will take place is open to numerous pitfalls. For example, the problems of laboratory data being merged into a second database illustrate the need to be vigilant. The validation of the computer system to be used for data collection will need to be addressed.

COMPUTER VALIDATION

Computer validation is a process which documents that a computer system reproducibly performs the functions it was designed to do[12]. To achieve sufficient comfort in any system to meet this criterion and to satisfy the regulatory authorities, it will not be sufficient to establish that the software has been properly written and tested. The FDA have suggested in their new draft *Guidance for Industry* document that a computer system is one that includes 'computer hardware, software, and associated documents that generate, collect, maintain, or transmit in digit form information related to the conduct of a clinical trial[13]. Validation must include the original requirements, any modifications made after the system was designed, the security of the system, and the training of computer staff. The records of the testing of the design are part of the validation documentation. Written procedures for the operation and maintenance of the system will need to be present and the auditor will need to be assured that a full change-control process is followed. Any vendor software must be checked to establish that it, too, has been validated. Visits by client auditors to the vendor supplier will become commonplace. In the past, in QA, it was rare to find a specialist in computer validation auditing but this cannot be the case in the future. Increasingly, the general auditor will not only be skilled in data management auditing but also will have experience of computer validation auditing. For larger QA groups, a specialist computer auditor will be part of the team.

THE FUTURE

Three aspects will dominate the future for the QA of clinical data management.

First, the impact of various remote clinical data entry systems, the use of scanners to read the written word, and paperless and computerised clinical data management, will serve to reduce some of the more tedious aspects of QC. It should also eliminate some of the human elements of transferring clinical data from paper to paper and from paper to computer. Electronic Signatures consisting of a computer data compilation of a series of symbols will act as a legally binding equivalent of the individual's handwritten signature. A new role for the QA group will develop since some QA activities will be reduced, but this will be countered by increased auditing requirements for computer validation processes, extending to the vendors of the software and hardware. Electronic packages will often be the final product being submitted to the regulatory authorities for submissions, and the resulting listings and tables will be subjected to vigorous interrogation by those authorities. Again, QA will need to be

present, reviewing clinical data, that will be more and more frequently online with the clinical data management staff and those preparing clinical study reports. The Assurance of Quality becomes even more important with the advent of harmonisation globally for submissions, since the contents of any clinical study report may be used internationally in marketing applications.

Second, all the indications for the future imply a preoccupation with cost containment in the drug industry. Governments, insurers and in many cases the patients will require new drugs at the minimum cost. Management will constantly seek to reduce expenditure and any quality system which does not reduce or abolish 'rework' does not ensure timelines are met, and is not in compliance with ICH GCP and other applicable guidelines/regulations will be far more exposed to scrutiny. Management may see its profit margins decline with the additional fear that the regulatory authorities will delay or stop the product reaching the market. Against this background, it can be predicted that QA will play an ever more important role in successful drug development.

Third, as a result of the above developments, the training of QA personnel will assume increasing importance and greater control of it will be instituted by both government and professional bodies. The authors envisage that for some of the QA processes only 'chartered' QA personnel will be eligible. These 'chartered' personnel will have undergone formal training in QA processes, acquired several years of experience and be subject to further examination by their peers before being 'chartered'.

CONCLUSION

QA is an essential part of the clinical data management process. The QA group has several tasks which include auditing, training and advising. It is essential that auditing is not restricted to the two areas of the investigator site audit and the final clinical study report but is conducted at other stages too. The auditor should not just be identifying non-compliance but should also be trying to influence decisions and processes before significant problems arise.

Training by the QA department of all members involved in the clinical trial process can benefit everyone, provided the selection and training of QA personnel is thorough and of a high standard.

Working together, clinical data management and QA groups can ensure that the final product is acceptable for submission.

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