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Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples

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Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples

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1. Executive summary

The purpose of this reflection paper[i] is to provide laboratories that perform the analysis or evaluation of human samples collected as part of a clinical trial, with information that will help them develop and maintain quality systems which will comply with relevant European Union Directives, national regulations and associated guidance documents. It will also provide information on the expectations of the inspectors who may be assigned by national monitoring authorities to inspect facilities that perform work in support of human clinical trials.

2. Introduction

Clinical analyses should be conducted in accordance with relevant EU Directives, applicable guidance and the Declaration of Helsinki[ii].

Article 15 of EU Clinical Trials Directive 2001/20/EC[iii] provides provision for the inspection of laboratories that perform the analysis or evaluation of samples collected as part of a clinical trial and expects Member States to appoint inspectors to verify compliance with good clinical practice.

The analysis of samples collected from subjects participating in clinical trials forms a key part of the clinical trials process. Sample analysis or evaluation provides important data on a range of endpoints which is used, for example, to assess the pharmacokinetic profile of investigational medicinal products and to monitor their safety and efficacy. Consequently, it is essential that sample analysis or evaluation is performed to an acceptable standard which will ensure patient safety is not compromised and that data is reliable and accurately reported.

In the absence of any comprehensive guidance, from regulatory and monitoring authorities, for laboratories that perform the analysis or evaluation of clinical trial samples, some clinical laboratories have applied the principles of Good Laboratory Practice (GLP). There are some aspects of GLP that will be applicable to clinical sample analysis. However, it should be noted that the scope of GLP is designed for non clinical studies and consequently does not take into account issues that may impact on the safety and rights of clinical trial subjects. This reflection paper addresses these specific issues, in addition to providing information on the organisation, conduct and monitoring of laboratory work.

3. Scope

The nature and purpose of laboratory work conducted as part of a clinical trial is extremely broad. Laboratories perform a wide range of activities which provide data that is used to monitor trial subject safety, assess pharmacokinetic parameters and to measure end points. Consequently, because of the diverse nature of laboratory work associated with clinical trials, it is very difficult to provide guidance which is wholly applicable in all situations. It is acknowledged that the recommendations set out in the paper may not be applicable in their entirety to some laboratories. The paper is primarily aimed at contract research organisations, sponsors laboratories and non commercial laboratories that are involved in the production of data that is used to assess end points of safety and efficacy. The paper is not specifically designed for laboratories that perform routine clinical chemistry or gather data which will be used for purposes not directly linked to the primary objectives of the trial. However, it should be noted that there is a requirement for all laboratories that perform work in support of clinical trials to implement appropriate measures to assure the quality and integrity of the data they produce and to exercise due diligence to ensure that the trial subjects rights are not compromised.

This reflection paper is designed to complement existing quality systems where they exist. Inspectors are encouraged to consider the scope and focus of existing quality systems before performing a laboratory inspection in order to avoid duplication of effort.

The information detailed in this reflection paper is applicable to all laboratories that generate data which will be used in dossiers submitted to EU/EEA regulatory authorities as part of a clinical trials application or marketing authorisation. The reflection paper is also applicable to investigator initiated trials.

This paper does not apply to non-interventional trials.

4. Legal basis

This document is a reflection paper (reference to guideline on guidelines) of the GCP Inspectors Working Group. The paper is intended to cover the conduct of analysis or evaluation of clinical samples collected as part of a human clinical trial. It is applicable to all clinical trials that are conducted as part of a Marketing Authorisation Application which will be submitted to EU/EEA regulatory authorities. The paper has its basis in Directive 2001/20/EC and Directive 2005/28/EC[iv], and in the Note for guidance on good clinical practice (CPMP/ICH/135/95)[v].

5. Definitions

“Analyst” means the person(s) that perform the analysis or evaluation of samples collected as part of a clinical trial.

“Archivist” means the person responsible for the management of the archive.

“Clinical Kit” means the necessary components required to collect clinical trial samples prior to their analysis or evaluation in a laboratory.

“Computerised System” is a system (consisting of one or more hardware components and associated software) that is involved with the direct or indirect capture, processing, reporting and storage of data. Examples include: a programmable analytical instrument or a personal computer linked to a laboratory information management system.

“Clinical trial samples” means any biological sample collected from a participant of a clinical trial as required by the protocol. Samples may include but are not limited to: blood, plasma, serum, urine, faeces, tissues and cells.

“Laboratory” means a facility that conducts the analysis or evaluation of samples collected as part of a clinical trial; such analysis or evaluation may include the generation of pharmacokinetic data, safety data, primary efficacy data, histopathology data or data used to support any other stated end point. Laboratories may be: independent contract research organisations, part of the sponsor’s organisation or part of a hospital or academic institution.

“Laboratory management” is the individual(s) having the authority and formal responsibility for the organisation and functioning of a laboratory in which work that forms part of a clinical trial is conducted.

“Master service level agreement” is an overarching contract of general terms & conditions between two parties, such as a laboratory and a sponsoring organisation, which may be used to support work for a number of clinical trials. Trial-specific terms, conditions, details, roles and responsibilities are then further defined in other documented agreements.

“Non-interventional trial” a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study.

“Quality Assurance personnel” (QA) means, the individual(s) who are responsible for maintaining the laboratories quality assurance processes. (see “Quality Assurance processes”).

“Quality assurance processes” All those planned and systematic actions that are established to ensure that the trial is performed and data are generated, documented (recorded), and reported in compliance with Good Clinical Practice and the applicable regulatory requirement(s).

“Quality Control” (QC) means a formal process for the systematic checking of processes and data to ensure accuracy.

“Source Data” is equivalent to the term “raw data” used by many GLP compliant laboratories. Both terms mean, all information in original records and certified copies of original records of clinical findings, observation, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

“Source Documents” means, original documents, data, and records.

“Sponsors representative” means an individual(s) appointed by the sponsor who will act on their behalf with respect to activities undertaken as part of a clinical trial.

“Validation of a computerised system” is a documented process that demonstrates that a computerised system is suitable for its intended purpose.

“Work instruction” is a written plan which will include, but is not limited to, the purpose of the analysis and the methodology that will be used to perform the analysis. This may also be referred to as an “analytical protocol” or an “analytical plan”.

In addition to the above definitions, reference should be made to the definitions provided in the Note for guidance on good clinical practice.

6. Reflection paper for laboratories that perform the analysis or evaluation of clinical trials samples

6.1. Organisation

Roles and responsibilities within a laboratory should be established and documented prior to the initiation of analytical work. These will include but not be limited to identifying personnel that are responsible for laboratory management, quality assurance, scientific analysis, reporting and archiving.

It is the responsibility of laboratory management to ensure that laboratory personnel are appropriately trained and qualified to perform the roles and responsibilities assigned to them.

Laboratory management should ensure that each individual involved in the analysis of clinical trial samples has a current job description detailing the individual’s role and responsibilities within the laboratory.

Laboratory management should ensure that there is a Quality Assurance programme with designated personnel and ensure that the quality assurance responsibility is being performed in accordance with regulatory requirements.

The analysis or evaluation of clinical trial samples should be overseen by a named individual(s) who assumes responsibility for the conduct and reporting of the work. This individual(s) should ensure that all laboratory work is performed in compliance with the clinical trial protocol, clinical trial protocol amendments, the contract, any associated work instruction and standard operating procedures.

Prior to the initiation of any analysis, the persons designated as “laboratory management” should make provision to ensure that sufficient resources are available for the timely and proper conduct of the analysis in accordance with the clinical trial protocol, work instructions, associated methods and standard operating procedures.

Prior to the initiation of analytical work, lines of communication should be established and documented between the sponsor or their representative and the individual who is responsible for coordinating the laboratory analysis. It is particularly important that laboratory personnel know to whom they should report anomalous results which may impact on trial subject safety.

6.2. Personnel

Procedures and systems should be implemented to ensure that individuals involved in the organisation and conduct of the analysis or evaluation of samples collected as part of a clinical trial are appropriately educated, experienced and trained. Laboratory personnel should be fully aware of their roles and responsibilities with respect to the analysis or evaluation they are performing.

All staff involved in the analysis or evaluation of clinical trial samples should receive GCP training commensurate with their roles and responsibilities.

It is appropriate for laboratory staff to receive periodic GCP refresher training. Such training is especially important following changes to regulations and associated guidance documents.

Laboratory personnel should receive an appropriate level of technical training prior to their participation in the analysis or evaluation of clinical trial samples. Specifically, laboratory management should ensure that staff are competent to perform the techniques required by the protocol, work instructions or associated methods.

A record of training should be maintained for each individual involved in the analysis or evaluation of clinical trial samples. Laboratory management should ensure a copy of this information is retained when staff leave the organisation.

If an individual has relevant experience that has been gained through previous employment, they should maintain a record of this experience in addition to a record of training provided by their current employer.

It is recommended that training records are periodically reviewed by laboratory management to ensure the information they contain is up to date and remains relevant. This review should be documented.

6.3. Contracts and Agreements

The analysis or evaluation of clinical trial samples may be organised in a number of different ways depending on the requirements of the clinical trial protocol, the type of data that is being generated, the volume of samples that are received and the time lines within which data is required. In all

circumstances the analysis should be organised and conducted in such a way that the findings are transparent and stand up to retrospective verification.

Contractual agreements between relevant parties should be in place prior to the initiation of any work. This will usually take the form of a legally binding contract which is signed by the sponsor (or their representative) and laboratory management.

Contracts and agreements between the laboratory and the sponsor should not conflict with the requirements outlined in the clinical trial protocol or work instruction. It is advisable to review the contract, the relevant sections of the clinical trial protocol and (where applicable) the work instruction prior to the initiation of laboratory analysis or evaluation in order to ensure that the documents are not contradictory and that their requirements are not incompatible. It is also appropriate to ensure these agreements comply with local legal regulatory and ethical requirements, and again that there are no conflicting terms.

If a laboratory performs analysis or evaluation of samples associated with more than one clinical trial for the same sponsor, it may be appropriate to conduct the work under a master service level agreement. In such circumstances it is important to ensure that the terms and conditions stipulated in the master service level agreement are applicable to all the work conducted for the sponsor in question. Care should be taken to ensure that any trial specific schedules or appendices are not over-ridden by the terms of the master service level agreement.

The laboratory's quality system should include a documented procedure for the drafting, agreement, review and revision of contracts. All contracts and agreements, including master service level agreements, should be subject to periodic review to ensure that they remain up to date and relevant. In cases where the contract is provided by the sponsor, the laboratory's quality system should include procedures for agreement and review of contracts.

There is an expectation that a contract or agreement will be implemented between the laboratory and any company or individual that provides a service linked to the analysis or evaluation of clinical trial samples. These agreements should stipulate the nature of the service(s) provided. Examples may include companies that provide maintenance services for analytical equipment through to scientific experts who are contracted to read pathology slides.

A formal contract is not required in situations where the laboratory is part of the sponsor organisation. However, a service level agreement or other internal policy documents, which detail the roles and responsibilities of both parties (including lines of communication and timelines), should be in place prior to the initiation of any work. Service level agreements or policy documents should be subject to periodic review.

6.4. Trial conduct

Under most circumstances the laboratory will be provided with a copy of the full clinical trial protocol (and amendments). As a minimum the laboratory should be provided with the sections of the clinical protocol which are relevant to the work that they are contracted to perform.

The laboratory should be able to verify with the sponsor that the protocol (or part there of) provided is current and has not been subject to amendments.

A mechanism should be agreed with the sponsor or their representative to ensure that any amendments to the clinical protocol that are relevant to the work of the laboratory are supplied accordingly.

Prior to the initiation of sample analysis or evaluation, it is often necessary to prepare a work instruction detailing the procedures which will be used to conduct the analysis or evaluation. Exceptions will include situations where all the relevant information is detailed in the clinical trial protocol, in the contract or in SOPs.

Work instructions and SOPs may take a number of different forms. However, care should be taken to ensure that they contain sufficient detail for the analyst to perform their duties and to allow the reconstruction of techniques used to perform the analysis or evaluation of samples. Checks should be made to ensure that they do not contradict other documents associated with the laboratory analysis or evaluation, such as the contract and the clinical trial protocol.

It is critical that the work instructions only include work that is covered by the clinical trial protocol.

All analysis or evaluation of clinical trial samples must be performed in accordance with the clinical trial protocol. If a full protocol has not been provided by the sponsor, it would be appropriate for the sponsor to confirm that they have reviewed the work instruction, or where applicable, SOPs and they do not exceed or contradict the requirements set out in the clinical trial protocol.

Appropriate procedures should be implemented to ensure effective and timely communication with the sponsor or their representative, regarding any serious deviations from the work instruction, clinical trial protocol or contract/agreement. Timely reporting will ensure that the sponsor or their representative are able to determine the significance and impact of the deviation on the safety and well being of the trial subjects and on the integrity and reliability of the trial data.

The impact of any deviations from the laboratory's standard operating procedures or documented policies should be assessed and documented. Where there is potential for a deviation to impact on the integrity or reliability of the trial data, patient or subject confidentiality, consent or safety, appropriate procedures should be implemented to ensure the issue is reported immediately to the sponsor or their representative and, if appropriate, to the investigator.

Regardless of the way in which clinical analysis is organised and performed, activities should be driven by documented policies or procedures. In all cases sufficient documentation should be available to confirm that the conduct of the analysis is performed in a manner which assures its quality.

This section also applies to laboratories that are part of the sponsor organisation. It will always be necessary to ensure that agreed lines of communication are established between the laboratory and the department in the company that is acting as sponsor and that the laboratory is provided with an appropriate level of information.

6.5. Requests for additional work

Laboratories should not perform any work on clinical trial samples that is not specified in the clinical trial protocol. If additional work is requested by the sponsor or their representative all relevant documentation must be amended prior to the initiation of the additional analysis or evaluation. The laboratory should seek assurance from the sponsor that the additional work does not conflict with the requirements of the clinical trial protocol, compromise the informed consent given by the trial subjects or impact on the ethics committee approval and/or the authorisation given by the competent authority.

It should be noted that patient/subject safety is of primary importance. Consequently, if unscheduled analysis or evaluation is required for urgent clinical reasons, for example, as a result of adverse events, then it should not be delayed because it is not stipulated in the clinical trial protocol, the work instruction or the contract. Laboratories should maintain a documented policy detailing how they would address this type of situation.

6.6. Sub-contracting laboratory analysis

If analysis or evaluation of clinical trial samples is sub-contracted to another laboratory, the ability of the sub-contractor to perform the work must be assessed prior to its initiation. Particular attention should be paid to staff training.

Before placing work with a sub-contractor, the sponsor, or their representative, should be informed and, if necessary, the contract with the sponsor amended.

A contract or service level agreement should be implemented between the two laboratories prior to the initiation of any work. Any such contract or service level agreement should clearly state roles and delegated tasks and the scope and nature of the work that will be undertaken by the sub-contractor. Care should be taken to ensure that contracts do not conflict with the requirements of the clinical trial protocol, work instruction or the contract between the analytical laboratory and the sponsor.

6.7. Patient/subject safety

The safety of trial patients or subjects takes precedence over any other aspect of the trial. Consequently, prior to the initiation of laboratory work, lines of communication should be established with the sponsor, or their representative, and with the investigators, to ensure that any issues that may impact on patient/subject safety are reported without delay. These may include, but are not limited to, the reporting of unexpected or out of range results and significant deviations from the protocol or work instructions.

The need to expedite the reporting of results should always be considered and discussed with the sponsor or their representative prior to the initiation of any laboratory work.

Under most circumstances normal ranges should be established for safety tests prior to the start of analysis. If clinically significant deviations from these ranges are recorded, a mechanism should be in place to communicate this information to the sponsor or their representative and to the investigator as quickly as possible.

It is always appropriate to consider the need to expedite the reporting of results regardless of the nature of analysis or evaluation that is being conducted. For example, anomalous results or unexpected values associated with pharmacokinetic analysis may indicate incorrect dosing or marked differences in a subject's ability to metabolise an investigational medicinal product which may potentially have safety implications.

In all cases, results and observations should be reviewed by an appropriately qualified person to identify any anomalous or out of specification data. This review should be performed in a timely manner.

In situations where the clinical laboratory, the sponsor, or their representative, and the investigators are operating in different time zones or in countries with different (public) holiday allocations, consideration should be given to how the laboratory would expedite the reporting of issues that may impact on patient safety or well being. In such situations the laboratory should consider the implementation of an agreed and tested out of hours communication policy.

6.8. Informed consent

There should be a mechanism to ensure that the laboratory is informed in a timely manner of what actions to implement if consent is withdrawn. While the responsibility for providing this information primarily resides with the sponsor, the laboratory should exercise due diligence. It is therefore

recommended that these factors be considered and documented in the contractual agreement or other relevant documentation prior to the initiation of any analytical work.

6.9. Sample labelling, receipt, storage and chain of custody

The clinical trial samples should be labelled in such a way as to allow their unequivocal identification. A mechanism to track the movement of each sample from arrival to analysis or evaluation should be implemented and maintained.

Samples should be transported in such a way that their integrity and viability remains unaffected. This requirement should apply to all samples whether they are being transported over long distances or between different departments within the same organisation. Particular attention should be paid to the following: the time samples remain in transit, temperature monitoring during transit and, if not refrigerated or frozen, the climatic conditions samples are exposed to during transit.

Where there is a requirement for samples to be refrigerated or frozen during transportation, measures should be taken to positively confirm that the samples were maintained at an appropriate temperature for the duration of time they were in transit.

All samples received by the laboratory should be assessed on arrival to check their physical integrity. If samples have been compromised in transit the sponsor or their representative, or the investigator, should be notified promptly.

Date and time of receipt should be recorded and reported back to the sponsor or their representative, or the investigator to enable them to track clinical trial samples and ensure that they are handled in compliance with the requirements of the clinical trial protocol.

On receipt, laboratory staff should ensure that all samples are accounted for, this process should be documented. If samples are poorly labelled, missing or if unexpected samples are received, the sponsor or their representative, or the investigator, should be contacted in order to investigate and resolve the issues. In most cases samples should not be analysed until their identity is confirmed. However, if a delay in analysis is likely to compromise the integrity of the sample as a result of instability etc. the sample should be analysed and the result quarantined until the sample's identity has been established. If the identity of the sample can not be established the results should not be reported. Policies describing the process of receipt of samples and for dealing with missing, unexpected or poorly labelled samples should be documented.

It is recommended that sample receipt is subject to regular quality control checks. Additionally, it is advisable to include an audit of the sample receipt processes as part of the QA programme to ensure it is performed in accordance with laboratory policy. Failure to monitor the receipt and accurate "booking in" of samples may have a significant impact on the integrity of data produced by the laboratory.

On arrival, or prior to processing, each sample and requisition form should be examined to ensure that its label does not display information which reveals the full identity of the trial subject. If information is recorded on the label which compromises the trial subject's right to privacy, it should be masked. Care should be taken not to obliterate other information which may be needed to identify the sample during analysis or evaluation.

It would not be appropriate to permanently delete information on a label if there was no other way of identifying the sample. In such cases the trial subject's full personal details should be masked and a unique identifier assigned to the sample by the laboratory.

The above paragraphs may not be applicable in situations where samples remain within the confines of a hospital where local procedures ensure the confidentiality of trial subjects. However, care must always be taken to ensure the requirements of the clinical protocol are followed and blinding is not compromised.

The sponsor or their representative and/or the investigator should be notified of all instances of inappropriate labelling of clinical trial samples as soon as is practically possible.

The required sample storage conditions as specified by the clinical trial protocol should be included in the work instruction or associated documentation. Laboratory staff should monitor storage conditions in order to provide evidence that the samples have been stored in a way that ensures they remain fit for purpose.

Refrigerators or freezers used for the storage of clinical samples should be monitored to ensure they are operating within acceptable parameters. Procedures should be implemented to ensure that prompt action is taken if the acceptable limits are breached. Evidence of monitoring and action taken in the event of any excursions from the specified ranges should be documented and retained. Equipment used to monitor temperature should be subject to periodic calibration.

Adequate provision should be made to ensure that laboratories have sufficient spare capacity for the storage of chilled and frozen samples, should a refrigerator or freezer malfunction.

6.10. Method validation

In all but exceptional circumstances*, analysis should be performed using appropriately validated methods with defined acceptance criteria where appropriate. The validation of methods should be documented and, on completion, this documentation should be archived. The recommendations made in this paper which relate to equipment, personnel and facilities will apply to method validation studies.

Relevant storage stability data must be available if samples are to be stored prior to analysis.

Routine system suitability tests, such as the analysis of quality control (QC) samples, should be considered and included in the analytical methodology as required. It is important that analytical factors that may potentially affect clinical trial results are considered.

** Where the validation of a method is one of the clinical trial objectives.*

6.11. Repeat analysis

Acceptance criteria for each method of analysis and the circumstances that allow repeat analysis should be clearly defined and documented.

Repeat analyses should only be undertaken in accordance with a documented policy. Such a policy may be detailed in a standard operating procedure, or if there are specific requirements for a particular trial, this information may form part of the contract or work instruction. It is never acceptable to selectively report data; consequently, the rationale for performing the repeat analysis and the reason for the selection of the data points that will be reported should be transparent and should be documented.

6.12. Data recording

All data should be recorded directly, promptly, accurately, and legibly. It should be possible to determine the date on which the analysis or evaluation was performed and the identity of the person who conducted the work.

It is good practice to implement a quality control procedure to ensure that all data generated in a laboratory during the course of a trial is accurate and complete.

Any change to the data should be made so as not to obscure the previous entry. If data is generated, recorded, modified, corrected and stored or archived electronically, it is recommended that an audit trail is electronically maintained rather than manually, whenever possible. The reason for any changes to the data should be justified and the justification documented. It should be possible to determine who made the change, when the change was made and for what reason.

6.13. Reporting

The way in which data will be reported and the number of reports that will be generated should be agreed with the sponsor or their representative prior to initiation of the work. This agreement should be documented in the contract or the work instructions.

Depending on the circumstances, it is acceptable to report data in a number of different ways. These may include, a report which contains data, interpretation of results and conclusions or alternatively, the results of clinical analysis may simply be supplied as electronic source data or printouts from the analytical equipment used to perform the testing. Regardless of how data is reported it must be accurate and complete.

Data may be sent to the sponsor or their representative and to the investigator as hard paper copy or electronically. Whichever method is used, it is recommended that the means by which data are transferred are checked to ensure that the data sets sent have been received in their entirety, especially if results are sent using, for example, e-mail attachments or internet portals.

Interim datasets or reports which are used to make either patient-specific or trial-related decisions should be retained so that the basis upon which the decisions were made can be verified.

It is appropriate to indicate in trial reports or other supporting documentation that the analysis or evaluation of samples has been performed in compliance with the relevant national and international regulations and guidance.

6.14. Facilities

Laboratories which conduct work in support of a clinical trial should be of suitable size, construction and location to meet the requirements of the work being performed.

The design of the facility should provide an adequate degree of separation of different activities to assure the proper conduct of the work.

In order to maintain sample integrity, consideration should be given to arrangements for sample receipt, tracking and storage. It is essential that adequate and appropriate storage conditions are maintained that will protect sample integrity and prevent cross-contamination.

Facility personnel should ensure that appropriate procedures are in place for waste storage, collection and disposal. Procedures for decontaminating laboratories and their equipment should be considered where relevant.

6.15. Equipment maintenance

All equipment used to conduct clinical analysis should be fit for its intended purpose. As a minimum, equipment should be regularly maintained by suitably qualified persons and any maintenance documented.

Prior to use, analytical equipment should be subject to an appropriate level of user acceptance testing, by a suitably qualified person to demonstrate that the equipment is fit for its intended purpose. Any such tests should be documented and the records retained as long as the trial records to which the sample analyses relate (i.e. it may be necessary to retain the records beyond the decommissioning and retirement of the equipment).

Apparatus should be periodically inspected, cleaned, maintained and calibrated according to standard operating procedures or the manufacturer's manuals. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement. Calibration frequency will be determined by management or their representatives and should be designed to ensure that all equipment remains fit for purpose.

6.16. Computerised systems

All computerised systems used for the capture, processing, reporting and storage of data should be developed, validated and maintained in ways which ensure the validity, integrity and security of the data. The following points should be considered in relation to the use of computerised systems:

A responsible person should be identified who will act as the administrator for each computerised system.

Prior to use, all computerised systems should be subject to an appropriate level of validation. The primary aim of any validation process will be to demonstrate that the computerised system is fit for its intended purpose and can produce reliable and reproducible data. The scope of the validation should be linked to the level of functionality that will be utilised. Validation should be performed in accordance with a documented plan. All key aspects of the validation process should be documented and on completion, results should be assessed by a suitably qualified person. When a computerised system is deemed fit for use the decision should be documented and authorised by laboratory management or their designated representative. Any limitations of the system should be clearly described in laboratory procedures.

For each computerised system, the components (e.g. hardware and software) which constitute the system should be clearly defined. This information should be documented with the associated validation package.

If additional functionality is utilised which is beyond the scope of the original validation the need to perform additional validation must be considered and, in most cases, will be required.

If additional computerised systems are interfaced with an existing laboratory information management system (LIMS) the impact of the new equipment on the functionality of the LIMS should be assessed.

Following changes to computer software such as a system upgrade, or the installation of "patches", the need to re-validate the computerised system should be determined. It may be appropriate to perform a documented risk assessment which will determine what level of re-validation is required. Following any re-validation activities, if it is deemed that the computerised system remains fit for use this decision should be documented and authorised by laboratory management or their designated representative.

If a computerised system has been in use for some time, but has never been subject to any formal validation, a retrospective assessment of its suitability should be performed. The scope of any retrospective validation will vary, but should always be justified and documented.

If the validation of a computerised system has been performed at a remote location it will usually be necessary for laboratory management or their designated representative to review the validation records to confirm that the system is fit for purpose. In most situations, an appropriate level of validation should be performed to ensure that the system operates appropriately, following its installation in the laboratory. This assessment should be documented and retained.

On completion, all records associated with the validation of a computerised system should be archived.

Computerised systems should be sited in appropriate locations. Consideration should be given to environmental conditions and other external factors which may adversely impact on the systems performance.

Disaster recovery procedures should be considered for all computerised systems. In most cases it will be necessary to maintain documented policies which will describe the procedures that would be followed in the event of a system failure. Such procedures may, for example, describe the measures that would be taken to recover data.

Laboratory policies should clearly define what constitutes a source document. Source documents may take a number of forms including electronic primary source data or paper hard copies. Source documents must always be archived and be sufficiently detailed to ensure they can be used to reconstruct the analysis, and any subsequent operation performed on the data, during or after the analysis.

Access to computerised systems should be controlled. The identity of those with specific access rights to computerised systems should be documented and subject to periodic review to ensure that the access restrictions remain current and appropriate.

6.17. Quality Assurance (QA) processes

The following recommendation on quality assurance is provided to assist in the development of quality systems and to provide examples of best practice.

Commission Directive 2005/28/EC requires that; “the necessary procedures to secure the quality of every aspect of the trials shall be complied with”. Consequently, quality systems should be developed which include in-process quality control procedures and independent quality assurance audits designed to ensure data integrity and safeguard patient safety and confidentiality.

It is strongly recommended that facilities assess and document their approach to the implementation of quality assurance processes. Factors to consider in this assessment include, but are not limited to, the nature of the work performed, the number of trials conducted (or samples analysed) and the resources available to support the laboratory’s operations.

The frequency, duration and content of quality assurance checks will vary depending on the nature of the work conducted by the laboratory. However, QA programmes should always be designed to assure compliance with the relevant European Union Directives, associated guidance and the facility’s internal policies and SOPs.

Quality assurance processes should be developed to ensure that:

- Patient safety and confidentiality are not compromised.

- The analysis or evaluation of clinical trial samples is conducted in accordance with the principles of GCP.
- Analysis or evaluation of samples is performed in accordance with the protocol and, where applicable, the contract/agreement, the work instruction and associated methods.
- The laboratories policies and SOPs are adhered to.
- Trial data is recorded and reported accurately, legibly, completely and in a timely manner.
- Trial data is archived.

Laboratories may appoint dedicated quality assurance personnel or alternatively resources may be drawn from other areas of the organisation. However, it would be inappropriate for members of the organisation who are directly involved in generating trial data to be involved in a quality assurance programme. Consequently, before appointing quality assurance personnel, consideration should be given to any potential conflict of interest which may undermine their effectiveness or the independence of quality assurance processes.

Quality assurance personnel should be appropriately qualified and trained to perform the tasks assigned to them. A record of their qualifications and relevant experience should be maintained.

It is recommended that quality assurance activities include, but are not limited to the following:

1. Regular facility audits to ensure that the laboratory and associated equipment used to conduct analysis or evaluation of clinical trial samples remain fit for purpose.
2. Periodic review of the laboratory's quality systems, including control of standard operating procedures and/or laboratory policies, archiving and the maintenance of training records.
3. The audit of technical procedures and methodologies used to conduct the analysis or evaluation of clinical trial samples.
4. The audit of critical analytical phases if not covered by (3).
5. Audits performed to assess the conduct of routine and repetitive processes which are common to all trials such as; sample receipt, sample storage, temperature monitoring, pipette and balance controls, and cleaning procedures. The most robust audit schedules will ensure that all key functions, personnel and procedures are reviewed over the course of one audit cycle.
6. The audit of documentation generated during the validation of computerised systems or analytical equipment.

It would be appropriate for quality assurance personnel to review completed data sets and reports before they are sent to the sponsor to confirm that the analysis or evaluation of the clinical trial samples has been conducted and reported in accordance with the protocol, the contract/agreement, the work instruction and in compliance with the principles of GCP.

Quality assurance personnel should report audit findings to both laboratory management and other relevant personnel within agreed timelines. Quality assurance departments will usually take responsibility for monitoring the progress of corrective and preventative actions (CAPA) identified during audits. It is appropriate to implement a process for escalating the requirement to perform corrective actions should quality assurance personnel encounter delays or resistance from those concerned. Escalation policies should be agreed with, and supported by, laboratory management if they are to be effective.

A mechanism for informing the sponsor and the concerned investigator or coordinating investigator (as appropriate) of significant deviations (those that may impact on data integrity, patient safety etc.) should be agreed prior to the initiation of laboratory work.

Quality assurance personnel will normally require the underlying cause of a deficiency to be addressed as well as the specific deficiency itself. The most effective quality assurance programmes will include a documented CAPA procedure.

All routine quality assurance activities should be documented in standard operating procedures or laboratory policies.

A system should be implemented to ensure that the quality assurance personnel are working in accordance with their own procedures and in compliance with the principles of GCP.

6.18. Quality Control (QC)

The requirement for peer review and quality control checks prior to the acceptance and release of results should be established.

The requirement for internal quality controls and/or participation in external quality schemes (for the more standard assay/tests) should be considered and implemented if applicable.

The accuracy of data and/or specific processes, such as clinical kit preparation, should be subject to an appropriate level of quality control checks. The frequency and nature of these checks will vary depending on individual circumstances, but in all cases should be designed to minimise the risk of mistakes which could lead to the misreporting of data or may compromise other key trial functions.

6.19. Standard Operating Procedures (SOPs) and facility policies

A laboratory should have written procedures that are designed to underpin the quality and integrity of the data it generates. It is expected that these procedures will be periodically reviewed and authorised by an appropriately qualified person. Revisions to procedures should be controlled, documented and authorised. If new procedures are issued, or existing ones reviewed, the need to provide additional training should be considered and where appropriate addressed and documented.

Standard operating procedures or documented policies should cover all key activities; examples include, but are not limited to the following:

- The preparation and review of contracts and agreements.
- The way in which the analysis or evaluation of clinical trial samples is performed and reported.
- Issues linked to patient safety and confidentiality such as expedited reporting of results, issues associated with unblinding and blinding samples and procedures for dealing with the receipt of unexpected, unscheduled or poorly labelled samples.
- Procedures for the receipt, storage and processing of samples and reference materials.
- Policies that control the installation, validation, calibration, maintenance and servicing of apparatus, equipment and computerised systems.
- The retention of trial data and non trial-specific records.
- Quality assurance and quality control functions.
- Clinical kit preparation.

- Staff training.

Each area of the laboratory should have access to the procedures relevant to the activities being conducted within that area. Published text books, analytical methods and manuals may be used to supplement procedures written by the laboratory. However, consideration should be given to the retention of these documents for historical reconstruction and verification purposes.

6.20. Blinding/unblinding

In many cases clinical trials will be blinded. Maintaining the integrity of the blinding process is an essential part of conducting a clinical trial. If the blinding is compromised the validity of the trial may be put at risk.

The sponsor is responsible for ensuring that appropriate measures are implemented to ensure blinded individuals are not party to information which will compromise the blinding. Laboratories that perform the analysis or evaluation of clinical trial samples should exercise due diligence to ensure they do not inadvertently compromise the blinding process.

In situations where samples from blinded trials are supplied to a laboratory and the data generated by the laboratory may unblind the trial, it is important that data is only sent to an established point of contact.

It is not uncommon for analytical laboratories to be asked to unblind trials so that analysis is not performed on samples collected from trial subjects who have been given a placebo treatment. In such cases, it is imperative that the laboratory has a documented policy (ies) detailing how results will be communicated to the sponsor or their representative. Such policies may cover the reblinding of samples and safeguards that have been implemented to ensure that unblinded results are not disseminated in a manner that may comprise the integrity of the trial.

If laboratories are supplied with the codes necessary to unblind trial samples, the sponsor or its representative should ensure that the unblinding procedures are discussed and agreed with the laboratory personnel. This information should be stored securely and only be accessed by authorised laboratory personnel.

6.21. Retention of data

Documents should be retained in accordance with the requirements of GCP and national legislation.

Facilities should be available for the secure storage of clinical trial data (including source data). Facilities should be suitably designed and constructed to accommodate the types of material that will be archived. Archive design and environmental conditions should protect contents from untimely deterioration and should safeguard the confidentiality of any trial participants.

Archives may take a number of different forms including a building or room specifically designated for the retention of trial materials, a fireproof safe or lockable cabinet. All archive facilities should be secure to prevent unauthorised access to the retained materials.

Non trial-specific data such as equipment validation and maintenance records, staff training records, quality assurance reports, SOPs etc. should be retained in a secure archive to facilitate the reconstruction of clinical trials and also provide evidence of compliance, with the GCP regulations, during regulatory inspections.

Access to the archive should be restricted to designated member(s) of staff. In most instances a dedicated archivist will be appointed. Personnel responsible for the archive will normally not be

involved with the generation of data or supporting records that are passed into their care. In small organisations where separation of responsibilities is not possible, mechanisms should be adopted which ensure that the integrity of records is not compromised.

Procedures for the removal of material from the archive and its subsequent return should be documented.

If materials are removed from the archive they should be returned in a timely manner. On their return adequate checks should be performed to verify that all loaned material has been accounted for.

Requirements for the archiving of electronic records are the same as those for other record types. However there are a number of specific issues which should be considered such as:

- Long-term access to, and readability of, electronic information (data format)
- The shelf-life of the storage medium where appropriate (CD-ROM, DVD, server etc.)
- QC checks following data migration to a secure server or other storage medium.

6.22. Preparation and distribution of clinical kits

It is not uncommon for analytical laboratories to prepare and distribute clinical kits used for the collection of trial samples. If such activities are undertaken the following points should be considered.

A documented agreement should be implemented between the sponsor and the laboratory which includes: information on the content of each kit, shipment details (destination names and address) and the number of kits required.

Areas designated for the preparation of clinical kits should be fit for purpose. They should be large enough to allow a clear separation of activities and environmental conditions should be monitored.

Kit components must be stored in conditions that assure the integrity of any active ingredients. Particular attention should be paid to expiry dates.

Kit preparation must be subject to an acceptable level of quality control monitoring which will ensure that each kit contains the correct components and that associated labelling is accurate and readable.

The laboratory must make appropriate provision for the resupply of clinical kits at short notice.

7. Relevant References

[i] Guideline on guidelines: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004011.pdf

[ii] The Declaration of Helsinki adopted by the World Medical Assembly

[iii] Directive 2001/20/EC of the European parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

[iv] Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

[v] Note for guidance on good clinical practice (CPMP/ICH/135/95)