



GOOD CLINICAL PRACTICE

Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples.

CONTENTS	PAGE
1. Foreword.....	3
2. Introduction.....	3
3. Glossary of terms	4
4. Guidance for Good Clinical Practice (GCP) Laboratories	8
4.1. Organisation.....	8
4.2. Personnel.....	8
4.3. Serious Breaches	9
4.4. Contracts and Agreements.....	9
4.5. Study conduct.....	10
4.6. Requests for additional work	11
4.7. Sub-contracting laboratory analysis	11
4.8. Patient safety.....	12
4.9. Informed consent.....	12
4.10. Sample receipt and chain of custody	13
4.11. Method validation.....	14
4.12. Repeat analysis	14
4.13. Data recording.....	14
4.14. Reporting	14
4.15. Facilities	15
4.16. Equipment maintenance.....	15
4.17. Computerised systems.....	15
4.18. Quality Assurance (QA) processes.....	17
4.19. Quality Control (QC)	18
4.20. Standard Operating Procedures (SOPs) and facility policies	19
4.21. Blinding/unblinding	19
4.22. Retention of data.....	20
4.23. Preparation and distribution of clinical kits.....	21
5. References.....	21

1. Foreword

The Medicines for Human Use (Clinical Trials) Regulations 2004 (the Regulations) regulate the conduct of clinical trials in the United Kingdom. The regulations relate to persons or organisations that participate in any aspect of a human clinical trial including organisations that analyse or evaluate samples collected as part of a clinical trial. The purpose of this guidance document is to provide such facilities with information that will help them develop and maintain quality systems which will comply with the Regulations. It will also provide information on the expectations of the MHRA's inspectors who may be assigned to inspect facilities that perform work in support of human clinical trials.

2. Introduction

The transposition of the EU Clinical Trials Directive 2001/20/EC into UK law (The Medicines for Human Use (Clinical Trials) Regulations 2004, Statutory Instrument 2004 No.1031, as amended) provides provision for the inspection of laboratories that perform the analysis or evaluation of samples collected as part of a clinical trial. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has responsibility for monitoring such laboratories for compliance with these Regulations. Compliance is assessed by inspections which will be performed approximately every two years. However, it is important to note that the frequency of inspections may increase or decrease in line with the MHRA's risk assessment process depending on the level of compliance maintained by the laboratory.

The analysis of samples collected from healthy volunteers and patients 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.

3. Glossary of terms

“**Amendment to the clinical trial authorisation**” means an amendment to:

- (i) the terms of the request for authorisation to conduct that trial or the application for an ethics committee opinion in relation to that trial,
- (ii) the protocol for that trial, or
- (iii) the other particulars or documents accompanying that request for authorisation or application for ethics committee approval

“Substantial **amendment** to the clinical trial authorisation” means an amendment to the clinical trial authorisation which is likely to affect to a significant degree:

- (i) the safety or physical or mental integrity of the subjects of the trial,
- (ii) the scientific value of the trial,
- (iii) the conduct or management of the trial, or
- (iv) the quality of safety of any investigational medicinal product used in the trial.

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

“**Chief Investigator**” means

- (a) in relation to a clinical trial conducted at a single trial site, the investigator for that site, or
- (b) in relation to a clinical trial conducted at more than one trial site, the authorised health professional, whether or not he is an investigator at any particular site, who takes primary responsibility for the conduct of the trial.

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

“**Clinical Protocol**” is a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial.

“**Clinical Trial**” means any investigation in human subjects, other than a non-interventional trial, intended

- (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products,
- (b) to identify any adverse reactions to one or more such products, or
- (c) to study absorption, distribution, metabolism and excretion of one or more such products, with the object of ascertaining the safety or efficacy of those products.

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

“**Clinical Trials Regulations**” - means Statutory Instrument 2004:1031 (as amended). Part 1 Regulation 2 contains interpretations and definitions of key phrases used within the Regulations, it is recommended these terms are referred to when reading the regulations and

developing systems and procedures to assure the quality of clinical laboratory procedures and data.

“**Schedule 1**” of the Clinical Trials Regulations SI 2004:1031, as amended, contains information relating to the conditions and principles of good clinical practice applicable to all trials, and the protection of clinical trial subjects.

“**Subject**” means, in relation to a clinical trial, an individual, whether a patient or not, who participates in a clinical trial –

(i) as a recipient of an investigational medicinal product or of some other treatment or product, or

(ii) without receiving any treatment or product, as a control.

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

“**Declaration of Helsinki**” means the Declaration of Helsinki adopted by the World Medical Assembly in June 1964, and subsequent amendments as referenced in Directive 2005/28/EC, Chapter 2, Article 3.

“**EU Directive**” means Directive 2001/20/EC of the European Parliament and the Council of 4th 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 and Commission Directive 2005/28/EC 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 and importation of such products.

Part 1, Regulation 2 of the Clinical Trials Regulations: “**conducting a clinical trial**” includes –

Carrying out any test or analysis –

(i) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of the investigational medicinal products administered in the course of the trial,

(ii) to identify any adverse reactions to those products, or

(iii) to study absorption, distribution, metabolism and excretion of those products,

but does not include any activity undertaken prior to the commencement of the trial which consists of making such preparations for the trial as are necessary or expedient;

“**Good Clinical Practice**” (**GCP**) means a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and data reporting of clinical trials that provides assurance that the data and the reported results are credible and accurate, and that the rights, integrity, and confidentiality of the trial subjects are protected.

“**Investigational Medicinal Product**” means a pharmaceutical from an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has marketing authorisation, but is for the purposes of the trial:

(i) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation;

(ii) used for an indication, not included in the summary of product characteristics under the authorisation for that product, or

(iii) used to gain further information about the form of that product as authorised under the authorisation.

“Laboratory” means a facility that conducts manipulation, 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.

“Laboratory management” is the individual(s) having control 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 underpin work for a number of clinical trials. Study-specific terms, conditions, details, roles and responsibilities are then further defined in other documented agreements.

“Principal Investigator” means, in relation to a clinical trial, the authorised health professional responsible for the conduct of that trial at a trial site, and if the trial is conducted by a team of health professionals at a trial site, the principal investigator is the leader responsible for that team.

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

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

“Quality assurance processes” are defined as the activities employed by an organisation to ensure that regulatory requirements are met and internal standards maintained. These activities are documented, established and managed in a systematic and visible manner, with a clear focus on prevention. Quality Assurance activities should be performed by staff who are not directly involved with the analysis of clinical samples.

“Source Data” All information in original records and certified copies of original records of clinical findings, observations, 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” Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

“Serious Breach” is a breach which is likely to affect to a significant degree:

- (i) the safety of physical or mental integrity of the subjects of the trial; or
- (ii) the scientific value of the trial.

Regulation 29A of The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) states that the sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:

(i) the conditions and principles of good clinical practice in connection with that trial;
or
(ii) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25,
within 7 days of becoming aware of that breach.

“Sponsor” in relation to a clinical trial means, the individual(s) who takes responsibility for the initiation, management, and financing (or arranging the financing) of that 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”.

4. Guidance for Good Clinical Practice (GCP) Laboratories

4.1. 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 and scientific analysis.

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

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

Care should be taken not to confuse terminology. For example, a principal investigator has a specific meaning in the context of a clinical trial (see glossary of terms) or a GLP study. Consequently, this title should be avoided when describing the position held by a scientist responsible for conducting laboratory analysis.

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 Trials Regulations, the clinical protocol and any associated work instruction.

The named individual(s) is responsible for reporting the results of the analysis or evaluation and any deviations from the work instruction or clinical protocol to the sponsor or their representative.

If any serious breaches of GCP are identified they must be reported to the sponsor or their representative immediately. In some circumstances it may be necessary for laboratory personnel to report serious breaches directly to the MHRA. The laboratory should maintain a documented procedure to describe the actions that would be taken in the event of a serious breach.

Prior to the initiation of any analysis, the persons designated as "laboratory management" should make provision to ensure that sufficient resources are available to conduct the analysis in accordance with the clinical protocol, work instructions and associated methods.

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.

4.2. 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.

The Clinical Trials Regulations state that "No person shall conduct a clinical trial other than in accordance with the conditions and principles of good clinical practice" (SI2004:1031 as amended, Part 4 Regulation 28). It therefore follows, that 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 statutory regulations and associated guidance documents.

Laboratory personnel must 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 clinical 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, signed and dated to ensure the information they contain is up to date and remains relevant.

4.3. Serious Breaches

It is the responsibility of the sponsor of a clinical trial to notify the licensing authority in writing of any serious breach of the conditions and principles of GCP or of the clinical protocol. If the laboratory becomes aware of circumstances that may potentially constitute a breach, the relevant information must be communicated to the sponsor or, if appropriate, directly to the MHRA. For example, in cases where fraudulent activity is suspected.

An effective mechanism should be established to ensure the reporting of incidents that may constitute a “serious breach” is performed in a timely manner.

4.4. 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 sponsor, 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 delegated representative) and laboratory management.

Contracts and agreements between the laboratory and the sponsoring organisation should not conflict with the requirements outlined in the clinical protocol or work instruction. It is advisable to review the contract, the relevant sections of the clinical 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 must be taken to ensure that any study-specific

schedules or appendices are not over-riden 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 a company or individual that provides a service linked to the analysis or evaluation of clinical trial samples. These agreements will 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.

4.5. Study conduct

Clinical analyses performed in the UK must be conducted in accordance with the current Clinical Trials Regulations, EU Directives, applicable Commission guidance and the Declaration of Helsinki.

Under most circumstances the laboratory will be provided with a copy of the full clinical 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 have been contracted to perform.

The laboratory should be able to verify with the sponsor that the clinical protocol (or part thereof) 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 relevant amendments to the clinical protocol are supplied to the analytical laboratory.

Prior to the initiation of sample analysis or evaluation, it is often necessary to prepare a work instruction detailing the methods and 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 protocol or the contract.

The exact nature of a work instruction is not stipulated in the Clinical Trials Regulations and consequently these documents may take a number of different forms. However, care should be taken to ensure that the work instruction contains sufficient detail for the analyst to perform their duties and to allow the reconstruction of techniques used to perform the analysis or evaluation. Checks should be made to ensure that the work instruction does not contradict other documents associated with the laboratory analysis or evaluation, such as the contract and the clinical protocol.

It is critical that the work instruction only includes work that is covered by the informed consent given by the trial subjects.

If a work instruction is produced by the contract laboratory it must be agreed with the sponsor or their representative prior to the initiation of the work. Verification of this agreement should be documented. Once a work instruction has been agreed it should not be amended without the agreement of the sponsor or their representative. This process will enable the sponsor or their representative to determine if changes to the work instruction constitute a substantial or non-substantial amendment to the clinical protocol.

All analysis or evaluation of clinical trial samples must be performed in accordance with the clinical protocol. Consequently, a check should be made to ensure that the work instructions do not conflict with or exceed the requirements detailed in the clinical protocol. If a full clinical protocol has not been provided by the sponsor, it would be appropriate for the sponsor to

confirm that they have reviewed the work instruction and it does not exceed or contradict the requirements set out in the full clinical 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 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. Additionally, it will also allow them to determine if the deviation constitutes a serious breach as described in the Clinical Trials Regulations.

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 confidentiality, patient consent or patient safety, appropriate procedures should be implemented to ensure the issue is reported to the study sponsor or their representative immediately.

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 must be available to confirm that the conduct of the analysis is performed in a manner which assures its quality.

4.6. Requests for additional work

Laboratories should not perform any work that is not detailed in the original work instructions, contract/agreement or clinical protocol (whichever is applicable). 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 a documented assurance from the sponsor that the additional work does not conflict with the requirements of the clinical protocol or compromise the informed consent given by the trial subjects.

It should be noted that patient 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 work instruction or the contract. The sponsor should notify the MHRA and relevant ethics committee of urgent safety measures within 3 days from the date the measures are taken. Laboratories should maintain a documented policy detailing how they would address this type of situation.

4.7. 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 its initiation. Particular attention should be paid to staff training.

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

A contract or service level agreement must 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 responsibilities 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 protocol, work instruction or the contract between the analytical laboratory and the study sponsor.

4.8. Patient safety

The safety of trial 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 study sponsor, or their representative, to ensure that any issues that may impact on patient 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 clinical protocol or work instructions.

The need to expedite the reporting of results should always be considered and discussed with the study 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 these ranges are exceeded a mechanism must be established to communicate this information to the study sponsor or their representative 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 and the sponsor, or their representative, 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.

4.9. Informed consent

Prior to the initiation of a clinical study, informed consent must be obtained from all trial subjects or their legal representatives. The principal investigator is responsible for ensuring that the subjects enrolled on a study (and/or their legal representatives) have been provided with an appropriate level of information concerning the nature of the trial and that consent has been obtained. However, all laboratory personnel that perform work in support of clinical trials must exercise due diligence to ensure that the work they have been contracted to conduct is covered by the consent given by the trial subjects. Mechanisms implemented to address this concern may include a review of the approved clinical protocol, or a documented dialogue with the sponsor to confirm that the consent process covers the work that will be undertaken by the laboratory. It may also be appropriate to include a clause in the contractual agreement between the sponsor and the laboratory which stipulates the need for informed consent to cover any laboratory analysis or evaluation.

There should be a mechanism to ensure that the laboratory is informed in a timely manner if consent is withdrawn to ensure that no further data is generated or collected. While the responsibility for providing this information primarily resides with the sponsor, the clinical laboratory must 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.

4.10. Sample receipt and chain of custody

Samples should be transported in such a way that their integrity and viability remains unaffected. If samples are transferred from the trial centre to the laboratory at ambient temperature particular attention should be paid to the time the samples remain in transit and the climatic conditions at the time of 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. Best practice would include the use of data loggers to monitor temperature during 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 should be notified promptly.

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 study sponsor or their representative should be contacted in order to investigate and resolve the issues. It is imperative that samples are not analysed until their identity is confirmed. Policies for dealing with missing, unexpected or poorly labelled samples should be documented.

Each sample received at the laboratory should be appropriately and uniquely identified. A robust mechanism to track the movement of each sample from arrival to analysis or evaluation should be implemented and maintained.

It is strongly 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 should be examined to ensure that its label does not display information which may identify the trial subject. If information is recorded on the label which may compromise the trial subject's right to privacy, it should be masked or deleted. 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 personal details should be masked and a unique identifier assigned to the sample by the laboratory.

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

The required sample storage conditions should be included in the work instruction or associated study documentation. These conditions must be monitored 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 parameters 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.

4.11. 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.

Relevant storage stability data must be available if samples are to be stored for extended periods of time prior to analysis.

Routine system suitability tests 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. For example, where the laboratory is blinded it is especially important that the presence of carry over is assessed.

***Leading edge research analysis". For example - the identification of potential PD markers in specific patient groups where the method is validated as part of the clinical trial.*

4.12. Repeat analysis

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

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 must be documented.

4.13. 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, manipulated and stored or archived electronically, it is strongly recommended that (where possible) an electronic audit trail is maintained. 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.

4.14. Reporting

The way in which data will be reported should be agreed with the sponsor 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 as a hard paper copy or electronically. Which ever method is used it is advisable to ensure that full data sets have been received, especially if results are sent using, for example, e-mail attachments or internet portals.

Draft 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 study reports or other supporting documentation that the analysis or evaluation of samples has been performed in compliance with the Clinical Trials Regulations.

4.15. 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.

4.16. 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. It is good practice to document any such tests and retain the records 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).

Where appropriate, laboratory equipment should be subject to regular calibration. Calibration frequency will be determined by management or their representatives and should be designed to ensure that all equipment remains fit for purpose.

If routine maintenance or calibration of equipment is undertaken by laboratory personnel, it should be performed in accordance with standard operating procedures or the manufacturer's manuals.

4.17. Computerised systems

All computerised systems used for the capture, processing, manipulation, reporting and storage of data should be developed, validated and maintained in ways which ensure the validity, integrity and security of the data. It is recommended that the following points are 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. It is good practice to perform validation 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. It may be appropriate to document this information 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 source data. Source data may take a number of forms including electronic primary source data or paper hard copies. Source data must always be archived and be sufficiently detailed to ensure it can be used to reconstruct

the analysis, and any subsequent manipulation of data performed, 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.

4.18. Quality Assurance (QA) processes

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

The Clinical Trials Regulations require that; “the necessary procedures to assure the quality of every aspect of a trial be complied with and that all clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of the trial subjects remains protected”. 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 studies 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 Clinical Trials Regulations 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 clinical 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 resource 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:

- i. 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.
- ii. 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.
- iii. The audit of technical procedures and methodologies used to conduct the analysis or evaluation of clinical trial samples.
- iv. Audits performed to assess the conduct of routine and repetitive processes which are common to all trials such as; sample receipt, temperature monitoring, pipette and balance calibration 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.
- v. 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 in accordance with the clinical protocol, 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 Principal or Chief 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.

4.19. Quality Control (QC)

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 mis-reporting of data or may compromise other key trial functions.

4.20. 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 organised, 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 study data and non study specific records.
- Quality assurance and quality control functions.
- Clinical kit preparation.

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.

4.21. 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 it is likely to constitute a serious breach of the GCP regulations and may invalidate the trial results.

The study 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 must exercise due diligence to ensure they do not inadvertently compromise the blinding process.

In situations where samples from blinded studies are supplied to a laboratory without an unblinding code, there is little danger that the laboratory will be in a position to compromise the blinding process. However, it is still important that data is only sent to an established point of contact at the sponsoring organisation.

It is not uncommon for analytical laboratories to be asked to unblind studies so that analysis is not performed on samples collected from trial subjects that 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 compromise the integrity of the trial.

If laboratories are supplied with the codes necessary to unblind trial samples this information should be stored securely and only be accessed by authorised laboratory personnel.

4.22. Retention of data

Prior to the initiation of experimental work the laboratory should agree with sponsor who will take responsible for archiving study data.

If the sponsor requests that data is returned to them on completion of the work, the laboratory should retain copies of the data for one inspection cycle in order to allow the laboratory to demonstrate that they are operating in compliance with the GCP regulations.

Archive facilities should be available for the secure storage of clinical trial 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 must be secure to prevent unauthorised access to the retained materials.

Non study 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 a clinical studies and also provide evidence of compliance, with the GCP regulations, during statutory 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, robust 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
- The shelf-life of the storage medium where appropriate (CD-ROM, DVD, floppy disks etc.)
- QC checks following data migration to a secure server or other storage medium.

4.23. 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.

5. References

European Directive 2001/20/EC

European Directive 2005/28/EC

The Medicines for Human Use (Clinical Trials) Regulations 2004, Statutory Instrument 2004 No.1031.

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, Statutory Instrument 2006 No. 1928.

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, Statutory Instrument 2006 No. 2984.

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2008, Statutory Instrument 2008 No. 941.

The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009, Statutory Instrument 2009 No. 1164.