Introduction to Good Clinical Laboratory Practice

Contents

1. Contents
2. Introduction
3. Good Clinical Practice
   1. Good Clinical Practice
4. More Than GCP
5. Good Laboratory Practice
   1. Good Laboratory Practice
6. GCP vs GLP
7. Good Clinical Laboratory Practice
   1. Good Clinical Laboratory Practice
   2. Knowledge Check
8. Principles of GCLP
   1. Organisation and Personnel
   2. Facilities
   3. Equipment, materials and reagents
   4. Standard Operating Procedures
   5. Planning of the work
   6. Sub-contracting
   7. Trial Materials
   8. Conduct of the work
   9. Reporting Results
10. Quality Control and Quality Audit
11. Storage and Retention of Records
12. Confidentiality, Blinding & Participant Safety
13. Knowledge Check
9. Implementation of GCLP
   1. Clinical Trial Protocol
   2. Analytical Plan
   3. Visit-specific Kit
   4. Kits and Instructions to Investigator Sites
   5. Sample Collection
   6. Sample Transport
   7. Sample Reception
   8. Sample Analysis
   9. Report
10. Sample Storage
11. Archive
12. Knowledge Check
10. Summary
11. Quiz

Introduction
What is Good Clinical Practice?

'A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected'. *ICH GCP 1.24*

Good Clinical Practice

The principles of GCP are concerned with the safety, rights and well-being of participants and the validity and quality of the research data. The ICH Guideline for Good Clinical Practice (ICH Topic E6) of 1996 (from here onward, this Guideline will be referred to as ICH GCP) is based on thirteen principles that cover the following major areas of clinical studies:

- Institutional Review Board/Independent Ethics Committee
- Investigator
- Sponsor
- Clinical trial protocol and Protocol Amendments
- Investigator Brochure
- Essential Documents for the Conduct of a clinical trial

In some regions, such as Europe and the USA, the requirements of the ICH-GCP guidelines are embedded in their legislation. However, even though this requirement is limited to specific studies, such as intervention trials with investigational medicinal products, trial sponsors and many other organisations (e.g. funding agencies, publishers) request that studies
are **conducted according to GCP principles** to ensure a consistent ‘standard’. Everyone working in clinical research should be aware of their **local and national GCP requirements** and all **regulatory requirements**.

Below is a list of bodies that compile national laws, regulations, and guidelines for clinical research:


2. The CRA Training Institute, *‘Countries that follow ICH-GCP Guidelines for Clinical Trials’*: [http://www.crtinstitute.org/ICH-GCP%20countries.pdf](http://www.crtinstitute.org/ICH-GCP%20countries.pdf)

3. Global Health Technologies Coalition, *‘Database for regulatory requirements’*: [https://www.ghtcoalition.org/home](https://www.ghtcoalition.org/home)

**Note:** Alternative guidelines such as *Good Research Practice (2002)* will not be covered in this introductory module.

### Good Clinical Practice

GCP provides a standard for **designing, conducting, recording** and **reporting clinical trials** but does not cover the specifics for **laboratories and the analysis of samples** from **clinical trials**. GCP **does not define the standards laboratories should follow**, and the only guidance provided in ICH GCP for clinical laboratories is summarised in the table below:

<table>
<thead>
<tr>
<th>ICH Section/Title</th>
<th>GCP Reference/Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.13 Principles of ICH GCP</td>
<td>'Systems with Procedures that assure the quality of every aspect of the trial should be implemented'</td>
</tr>
</tbody>
</table>
| 8.2.11 Essential Documents for the Conduct of a Clinical Trial - before the clinical phase of the trial commences | **Title of Document:** Normal Values(s)/Range(s) for Medical/Laboratory/Technical Procedure(s) and/or Test(s) included in the protocol  
**Purpose:** 'To document normal values and/or ranges of the tests' |
| 8.2.12 Essential Documents for the Conduct of a Clinical Trial - before the clinical phase of the trial commences | **Title of Document:** Medical/Laboratory/Technical Procedures/Tests Certification or accreditation or established quality control and/or external quality assessment or other validation (where required)  
**Purpose:** 'To document competence of facility to perform required test(s), and support reliability of results' |
| 8.3.6 Essential Documents for the Conduct of a Clinical Trial - during the clinical conduct of the trial | **Title of Document:** 'Updates to Normal Value(s)/Range(s) for Medical/Laboratory/Technical Procedure(s) and/or Test(s) included in the protocol'  
**Purpose:** 'To document normal values and ranges that are
What is Good Laboratory Practice?

‘A quality system concerned with the organisational process and conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported’. OECD 1998 GLP Guidelines

The requirements of GLP cover the following main aspects of a laboratory:

- **Resources**: Organization, personnel, facilities, equipment and maintenance
- **Rules**: Protocols and written procedures
- **Characterisation**: Test items and systems
- **Results**: Raw data, final report, and archiving
- **Quality Assurance**: Monitoring of research processes

GLP assures regulatory authorities that the data submitted from non-clinical studies are a true reflection of the results obtained during a study; however, GLP guidelines are only applicable to the analysis of samples from non-clinical studies.
Good Laboratory Practice

Current published directives for GLP (FDA, OECD, WHO, EMA) do not specify criteria for the conduct of laboratory tests that support human or clinical efficacy trials and refer specifically to a quality system that is concerned with the processes and conditions under which non-clinical (pre-clinical) safety studies are conducted. GLP principles in their regulatory sense apply only to studies on pharmaceuticals that:

- Are non-clinical
- Are intended to be submitted to a national registration authority for the purposes of registering or licensing a product

GLP is not directly concerned with the scientific design of the study but rather the appropriate conduct of the study to a defined plan. Therefore, the use of GLP alone as guidance for a clinical trial laboratory is not ideal because:

- The GLP regulations do not apply to testing of clinical samples
- GLP does not cover all aspects of the clinical analytical process

GCP vs GLP

Let’s recap:

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that ensures accurate and credible data while protecting the rights, safety and well-being of participants.

GLP is a quality system concerned with the organisational process and conditions under which non-clinical laboratory studies are planned, performed, monitored, recorded, archived and reported.

There is a clear requirement for a hybrid between GCP and GLP, a standard to complement GCP for the testing of clinical samples within a clinical trial laboratory. Good Clinical Laboratory Practice (GCLP) provides this complementary laboratory standard:

What is GCLP?

‘GCLP applies those standards established under GLP which are relevant to the analyses of samples from a clinical trial, whilst at the same time ensuring that the purpose and objectives of the GCP regulations are satisfied. In so doing, the reliability and integrity of data generated
Good Clinical Laboratory Practice

GCLP is a set of guidelines first introduced by the British Association of Research Quality Assurance (BARQA) in 2003 to describe the application of those GLP principles that are relevant to the analyses of samples from clinical trials while ensuring the purpose and objectives of the GCP principles are maintained.

In 2009 BARQA GCLP Version 1 was published in full by the World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases (TDR). More recently in 2012 the Research Quality Association (RQA(formally BARQA)) published a revision of the original GCLP; RQA GCLP Version 2. The Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health in collaboration with the Global Government and Public Health Services Laboratory (PPD) have also produced a separate version of GCLP; DIADS Guidelines for GCLP Standards (2013).

The BARQA-GCLP guidelines and the DIADS Guidelines for GCLP Standards offer very similar guidance but they differ slightly in four elements for optimal management of clinical laboratory operations: training, auditing, assay validation, and proficiency testing. (Sarzotti-Kelsoe et al. (2009)

GCLP was designed in response to laboratories requesting a definition as to the standards expected in the analysis of samples from clinical trials and provides a framework for organisations regarding facilities, systems and procedures to ensure the reliability, quality and integrity of the work and results to satisfy GCP expectations.

Good Clinical Laboratory Practice

GCLP covers the entire laboratory involvement within a trial and not just what happens within the laboratory. It focuses on the accuracy in the performance of an individual measurement but also considers the integrity of the sample prior to analysis. GCLP also covers method validation to ensure the methods are fit for the purpose for which it is intended.

The main benefits for trial laboratories that comply with GCLP include:

- Ensuring the quality, reliability, consistency and integrity of the laboratory data.
- Comparability of laboratory data across different laboratories
- Archiving records to enable the documented reconstruction of the study after the study has been completed
- Uniformity of the performance of specific functions across all laboratories worldwide
- Efficiently managed resources and minimised waste
- Confidence in the abilities of the laboratory and personnel involved

Note: Laboratory accreditation is not covered in this module. To gain accreditation a laboratory must be fully compliant with either of the relevant standards set out by the International Organization for Standardization (ISO):

Knowledge Check

Are the following statements True or False?

1. GCP is concerned with the safety, rights and well-being of participants BUT NOT the validity and quality of research data.
   - ○ True
   - ○ False

2. Studies conducted according to GCP principles ensure a consistent ‘standard’ between clinical trials but does not define the standards laboratories should follow.
   - ○ True
   - ○ False

3. GLP guidelines are ONLY applicable to the analysis of samples from non-clinical studies and do not cover all aspects of the clinical analytical process.
   - ○ True
   - ○ False

4. GCLP guidelines have replaced both GLP and GCP guidelines for all laboratories conducting research.
   - ○ True
   - ○ False

5. GCLP covers the entire laboratory involvement within a clinical trial and ensures the purposes and objectives of GCP principles are maintained.
   - ○ True
   - ○ False

Submit

Principles of GCLP

The following are the key principles of GCLP as defined by BARQA Version 1:

1. Organisation and Personnel
2. Facilities
3. Equipment, materials and reagents
4. Standard Operating Procedures
5. Planning of the work
6. Sub-contracting
7. Trial materials
8. Conduct of the work
9. Reporting results
10. Quality Control
11. Quality Audit
12. Storage and Retention of Records
13. Confidentiality
The following are additional key principles defined by RQA GCLP Version 2:

14. Blinding
15. Participant safety

GCLP guidelines provide the minimum requirements for each of the key principles to ‘ensure that the requirements of GCP applicable to the analysis of clinical samples are met’ (RQA GCLP 2012). For this introductory GCLP module we will now summarise each of these principles.

Organisation and Personnel

Organisation and personnel is the first key principle of GCLP and is critical to the implementation of GCLP within a clinical trial laboratory. Each laboratory may be organised in slightly different ways but should consist of laboratory management, an analytical project manager and laboratory staff. GCLP guidelines specify the responsibilities for each area.

Laboratory Management Responsibilities:

Laboratory management are responsible for ensuring that GCLP principles are adhered to in their facility whilst ensuring overall compliance with GCP. Management must ensure that all staff involved in laboratory related functions, operate according to GCLP. RQA GCLP 2012

Responsibilities of the laboratory management include ensuring that:

- a suitable quality management system is in place and executed appropriately; this should include Quality Control (QC) and Quality Audit
- appropriate document control and record archiving procedures are established and followed by staff.
- appropriate facilities, equipment and materials are available to conduct the trial.

Analytical Project Manager Responsibilities:

Overall conduct and reporting of the analyses performed by the laboratory is the responsibility of the analytical project manager. These responsibilities include ensuring that:

- prior to initiation of the work, the analytical plan is agreed upon by dated signature
- the procedures specified in the analytical plan are followed, and that authorisation for any modification is obtained and documented together with the reasons for change
- all results of the analyses are fully documented and accurately reported
- the analytical report, if issued, is signed and dated to indicate acceptance of responsibility for the validity of the results
- When analytical results are issued, the results are only issued under the dated signature of an authorised signatory
- after completion of the analyses, the analytical plan, analytical report and/or analytical results, raw data and any supporting study documentation are archived and retained

In the absence of an analytical project manager the laboratory management will assume these responsibilities.

Laboratory Staff Responsibilities:

All laboratory staff should be aware of the principles of GCLP and GCP and how to apply the guidelines to their day to day work. Laboratory staff must ‘follow the instructions given in the clinical trial protocol, analytical plans and Standard Operating Procedures (SOPs)’. Laboratory staff are responsible for the quality of their data which should be
recorded promptly, accurately and in compliance with GCLP. <i>RQA GCLP 2012</i>

Facilities

Control of facility areas is a key aspect of ensuring compliance and the quality of the work being conducted in a clinical trial laboratory.

Laboratories:
In order to minimize any disturbances that might interfere with the validity of the trial or its results the laboratory should be ofisksite size, construction and location to meet the requirements of the trial’. There must be adequate size and space for the volume of work with sufficient separation and security in place to assure sample integrity. The laboratory should have appropriate areas for the storage of samples and supplies to avoid contamination or mix up. <i>RQA GCLP 2012</i>

Archive Facilities:
Designated storage areas for the safe and secure archival, storage and retrieval of data, reports, and samples should be provided. Security measures for this area must be in place and must be adequate to ‘prevent the unauthorised access to the retained materials’. Suitable archive facilities can be provided by a third party if required. <i>RQA GCLP 2012</i>

Waste Disposal:
The handling and disposal of waste generated during the performance of a trial should be carried out in a manner that is consistent with local regulatory requirements’. <i>RQA GCLP 2012/WHO GCLP 2009</i>

Equipment, materials and reagents

Equipment:
Laboratory equipment should be:

- suitably located
- appropriately designed
- of adequate capacity

Periodic inspections, cleaning, routine and preventative maintenance, calibration and repair should be carried out as appropriate, and this must be recorded and retained. A service schedule should be in place for all relevant equipment. Equipment used should be ‘demonstrably fit for purpose’ and only operated by suitably qualified and trained individuals. <i>RQA GCLP 2012/WHO GCLP 2009</i>

Materials:
‘Materials used in the analysis of trial samples should be demonstrably fit for purpose and appropriately stored’. <i>RQA GCLP 2012/WHO GCLP 2009</i>

Reagents:
‘Reagents should be suitably labelled and indicate the identity, concentration, specific storage instructions and stability. Stability information may include the preparation date and earliest expiration date’. <i>RQA GCLP 2012/WHO GCLP 2009</i>

Standard Operating Procedures
What is a Standard Operating Procedure (SOP)?

‘Detailed, written instructions to achieve uniformity of the performance of a specific function’.

ICH GCP 1.55

The careful preparation and document control of SOPs are vital to the planning and execution of a clinical trial. Documented SOPs approved by the laboratory management should be available to:

- establish step by step standard procedures which will ensure quality and integrity of the data
- communicate these procedures to those who will make use of them and to reinforce training
- provide a permanent record of the methodology employed during the trial

SOPs should be periodically reviewed and an up to date list of current SOPs (including version numbers) should be maintained. Laboratory staff should have immediate access to relevant SOPs for the activities being performed. The diagram below provides some examples of processes that should be described in written SOPs:

All laboratory personnel are responsible for complying with the instructions given in each SOP and must document and communicate any deviation from SOP instructions to the laboratory management. The laboratory management must ensure that each SOP is understood and followed by the relevant laboratory staff. Where required the Laboratory management should provide training for the activities outlined in the SOPs.

Planning of the work

Prior to the initiation of the work for each specific trial the laboratory should produce a written analytical plan that describes the work to be performed by the laboratory. The analytical plan is often also referred to as the laboratory manual. ‘This plan should be an exact reflection of the requirements detailed in the clinical protocol and only include work that is covered by the informed consent given by the trial subjects’.

RQA GCLP 2012
The analytical plan should be:

- agreed, signed and dated by the sponsor and laboratory manager
- made available to the staff involved in that work
- retained as part of the laboratory records for the trial

The plan may be:

- a controlled document or
- form part of the contractual agreement with the sponsor or
- be contained within the clinical protocol

All changes, modifications or revisions to the agreed analytical plan should be documented, including justification(s), and be agreed to by the dated signature of the analytical project manager and the sponsor. ‘Copies of all such amendments should be maintained with the original analytical plan’. 

The analytical plan should contain enough detail to provide clear instruction to the laboratory staff undertaking the work. At a minimum it should include the following:

- **Identification of the work** – title, nature and purpose of the work.
- **Information concerning the sponsor and the laboratory** – name, address and contact details of the sponsor, investigator and laboratory.
- **Dates** – date of agreement to the analytical plan and proposed starting and completion dates for the laboratory work.
- **Analytical Process** – methods to be used including analytical design, methods, materials and conditions, type and frequency of analysis etc. Preparation and shipment of materials used for sample collection.
- **Records** – list of the records to be retained and archive location.
- **Quality Audit** – quality audits to be performed to assure the quality and integrity of the data and the accuracy of the reported results.

**Sub-contracting**

Sub-contracting of analytical or other study related work by the laboratory can only take place with the prior approval of the sponsor. For all sub-contracted work the laboratory management should gain assurance that work will be carried out in accordance with GCP, GCLP and any trial requirements. The laboratory management is responsible to the sponsor for this sub-contracted work.

‘The agreement for sub-contracted work (contract/service level agreement and/or analytical plan) should clearly specify the role and responsibilities, the detail of the analyses to be performed and the retention of trial data’. 

**Trial Materials**

Facilities, systems and procedures outlined in the Analytical Plan must be in place for the receipt, handling, storage, retrieval, transport, disposal and general management of trial materials/samples to ensure their integrity and validity. All trial materials/samples must be accurately identifiable and traceable at all times whether in transit or in storage for the duration of the trial. Detailed records must be maintained and retained for all samples/materials to allow a full examination of where they have been and how they have been stored over the lifetime of the trial.
All procedures for receipt, chain of custody, logistics and disposal of trial materials/samples should be outlined in the Analytical Plan and subject to quality control procedures to confirm conformance with defined requirements. 

RQA GCLP 2012

Conduct of the work

WHO GCLP 2009 states that all ‘work should be conducted in accordance with the Trial Protocol and the Analytical Plan’ and all the data produced must be recorded:

- directly,
- promptly,
- accurately,
- legibly

The data produced (including any changes to the data) should be signed or initialled and dated and this can be done manually or using a computer system. When choosing and utilising a computer system for the trial there are many considerations to take into account. RQA GCLP 2012 specifies the following:

- The computer system used should be appropriately validated and demonstrably fit for purpose
- The system needs to be well maintained throughout the trial.
- When used to receive, capture, process or report data the system should be developed, tested and operated within the established guidelines/laws.
- Procedures should be outlined to ensure system security including establishing a data audit trail
- Computer access should be limited to authorised personnel only
- Data retained electronically should be adequately backed up to ensure the data can always be accessed/retrieved

The analytical method used should be selected to ensure it is suitable and will provide reliable results. Such methods should be validated to ensure results generated are accurate and reproducible’ (RQA GCLP 2012). Decisions about the most appropriate choice of method(s) to use should be based on current guidelines, regulations and the expectations of the sponsor. According to RQA GCLP 2012 the methods used in sample analysis should always be:

- documented
- validated
- controlled
- approved

The laboratory should retain records demonstrating the validity and suitability of all analytical methods. Analytical methods should remain unchanged throughout the duration of the trial; however, if changes are required they must be approved by the sponsor, documented and revalidated.

Once the methods are validated and the trial is underway the samples should be analysed and reported within a set timeframe and in accordance with the relevant SOPs, the clinical protocol and the analytical plan, taking into account local legalisation and standards of practice for safety.

Reporting Results
Both BARQA based guidelines (*RQA GCLP 2012* & *WHO GCLP 2009*) state that analytical results from a clinical study can be reported in two ways:

1. **Analytical Report**: a formal report which may be issued on completion of the work detailed in the analytical plan, including (*RQA GCLP 2012 [p.21]*):
   1. ‘Identification of the analytical work by a descriptive title and identification number
   2. The clinical trial number
   3. Name and address of the sponsor
   4. Name and address of the laboratory that carried out the work and any laboratory that conducted sub-contracted work
   5. Name of the analytical project manager
   6. The start and completion dates of the laboratory work
   7. Identification of any quality audit activities
   8. Description of methods and materials used including data manipulation techniques and any statistical methods used
   9. Presentation of the results
   10. All information and data required by the analytical plan
   11. The location[s] where the analytical plan, any specimens required to be retained, data and the final analytical report are to be archived.

2. **Analytical Results**: a document(s) containing just the results which is usually issued rapidly on completion of sample analysis on a given day, including but not necessarily limited to the following (*RQA GCLP 2012 [p.22]*):
   1. ‘Identification of the analytical work by its unique identification/trial number
   2. Identity of the sponsor
   3. Identity of the laboratory that performed the analysis, including any sub-contracted assays
   4. The investigator to whom the results are directed
   5. Presentation of the results’

The information from these reports provide a detailed formal breakdown of the work undertaken and an accurate record of the results from all sample analyses carried out on any given day of the trial. Therefore, all reports should be submitted to a quality control review to verify the accuracy of the information, and copies should be provided to the Sponsor and the Investigator, and a copy should be retained at the trial facility.

The reports may be used to make fundamental decisions on the treatment of the participants and they may also be used by Regulators, Sponsors and Investigators in relation to the investigational medicinal product and its possible safety and efficacy for use in humans. Consequently, it is very important that the information contained within the report is accurate and reliable.

**Quality Control and Quality Audit**

What is Quality Control (QC)?
‘The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.’ *ICH GCP 1.47*
Laboratory **Quality Control** procedures should be in place to guarantee the **quality and accuracy** of all work throughout the **lifetime of the study** (i.e. within/between batch acceptance criteria, defined analytical performance criteria) Where appropriate, **membership to external accreditation/performance/proficiency schemes** can demonstrate the competency of the laboratory performing the work.

**What is a Quality Audit?**

'A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor’s standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).’ *ICH GCP 1.6*

Audits should be carried out by **competent individuals** who are **independent of the work** being audited. Independent audits by external experts may also be utilised. Independent laboratory audits aim to examine **how the trial is being conducted** and checks the **study's compliance** with the trial protocol, analytical plan, SOPs and GCLP guidelines. The following should be audited at intervals following a prearranged programme:

- Facilities
- Systems
- Equipment
- Procedures
- Analytical procedures
- Trial methods
- Standard operating procedures
- Quality control procedures
- Data recording
- Personnel records
- Trial documentation and reports
- Archive process
- Overall compliance with GCP

Audit results should be **documented** and any **recommendations for changes/improvements** should be acted on within a reasonable timeframe. The progress of these changes should be monitored to ensure compliance and upon ‘the satisfactory completion of an audit, an **audit certificate should be produced**, which identifies the activities audited, and an indication of the compliance of those activities with the guidelines’. *WHO GCLP 2009*

**Storage and Retention of Records**

One of the primary objectives of an organisation’s GCLP compliance program is that it should be possible for a regulatory inspector to **reconstruct a study from the records retained**. The storage and retention of trial records and laboratory records are required by regulatory authorities for a **specified retention period** and should be stored and maintained in such a way that the **trial can be recreated** from them. The trial sponsor is responsible for meeting this requirement and clear specifications of **how**, **where** and for **how long** the records are to be **stored and maintained** should be laid down in the analytical plan. All records should be stored **securely and confidentially**.

The RQA Guidelines for GCLP (2012) state that **trial records** should include the following:

1. The clinical protocol, analytical methods used and analytical plan
2. Procedural and processing data
To ensure that the laboratory performing analyses/testing for a clinical trial is compliant with the relevant regulatory requirements, the following laboratory records are recommended for retention:

- Personnel/training records
- Equipment records (QA/QC, calibration and maintenance)
- SOPs / Control documents
- Data processing records
- Organisation charts / site plans
- Computer validation records
- Method development / validation
- Temperature monitoring records (i.e. Fridge / freezer/ room temperature records)
- Analytical records
- QA records

‘Samples and specimens should be retained as required by GCP, the clinical protocol and analytical plan but only as long as the quality of the sample permits evaluation’. RQA GCLP 2012

Electronic records for both the trial and the laboratory should be stored in a format which is easily retrievable and legible. Backup procedures are essential to prevent the loss of any data.

Confidentiality, Blinding & Participant Safety

Confidentiality:

Protecting the confidentiality of trial participants is a requirement of Good Clinical Practice, the Declaration of Helsinki and the trial protocol. Procedures need to be established to ensure that participant confidentiality is respected and maintained at every stage of the study, i.e from the collection of data up to the reporting of results. It is also a requirement that the sponsor’s proprietary information is not divulged to any unauthorised individual.

Blinding:

‘The laboratory should be aware of any blinding and unblinding conditions that apply to a trial and take care not to inadvertently unblind a trial. Particular care should be taken in reporting results to ensure unblinding does not occur. The sponsor should be informed of any event, either accidental or arising as a result of an investigation, which may compromise study blinding.’ RQA GCLP 2012 [p.28]

Participant safety:

Ensuring the safety of trial participants is paramount in any study and processes should be put in place in collaboration with the trial sponsor prior to the start of laboratory work to establish:

- Any issues which may have a negative effect on the safety of trial participants
- A clear reporting procedure, ensuring that any safety issue is reported promptly. Such issues ‘may include, but is not limited to, the reporting of unexpected or out of range
Knowledge Check

Are the following statements True or False?

1. The laboratory manager must ensure EVERY staff member of the laboratory is qualified, competent and trained to perform EVERY laboratory procedure for the entire trial.
   - True
   - False

2. Your SOP requires you to calibrate/verify the laboratories digital balance; by use of check weights, every morning before use. This is to ensure the balance is fit for purpose.
   - True
   - False

3. The Analytical plan is replaced by SOPs once the trial has begun.
   - True
   - False

4. The analytical report and analytical results provide a detailed breakdown of the work undertaken and an accurate record of the results from sample analysis on any given day of the trial.
   - True
   - False

5. Quality Control procedures guarantee the quality and accuracy of all laboratory work conducted during the trial whereas Quality Audits ensure all trial related activities comply with the trial protocol, analytical plan, SOPs and GCLP guidelines.
   - True
   - False

6. There are participant specimens stored in the -80 freezer in your laboratory but the study has finished. These samples MUST be destroyed immediately.
   - True
   - False

Submit

Implementation of GCLP

GCLP applies to and should be implemented across the entire clinical trial sample testing process. The diagram below is an example of the different processes involved in the conduct of a clinical trial and also shows who is responsible for each process:
GCLP guidelines use the term ‘investigator site’ for the site location where participant visits occur and study samples are collected. Other terminologies such as ‘research site’ or ‘trial site’ are also commonly used instead of ‘investigator site’. The laboratory and investigator site may be at the same location or at different locations entirely; however, the processes and flow of the implementation of GCLP as outlined in this module remain the same.

The next sections will explain the clinical trial process based on the example above and highlight how GCLP should be implemented at each of the above steps. The implementation of GCLP in low- and middle-income countries (LMIC) can be difficult due to a lack of resources but the processes and principles involved in its implementation remain the same.

Clinical Trial Protocol

Clinical Trial Protocol:

‘The clinical trial protocol approved by the sponsor which describes all activities which make up the clinical trial: its objectives, design, methodology, statistical considerations and organisation’. **ROA GCLP 2012**

An approved clinical trial protocol is required by GCP for all clinical trials and is classified as an essential document for a clinical trial (click here for an example of an approved clinical trial protocol). The development of the trial protocol is the responsibility of the sponsor and they must ensure it is provided to all trial staff including laboratory staff.

The protocol is ‘a document that describes the
The protocol must be followed by the laboratory, but it does not describe all the details of the analytical procedures. Therefore, an analytical plan is required to provide the laboratory with more ‘in depth’ information to ensure the appropriate analysis of participant samples.

Once the clinical trial protocol is in place the process of laboratory selection begins. This process ensures that the most suitable laboratories are used for the trial. The selection process includes the proposal of laboratories, laboratory assessment, and pre-qualification (e.g. if required testing is not already conducted at the laboratory) final selection and training.

Analytical Plan

Analytical Plan:
‘A formal authorised document that describes all aspects of the work to be performed by the trial facility’. WHO GCLP 2009

Prior to the initiation of the work the laboratory should produce a written analytical plan (also referred to as the ‘laboratory manual’) At a minimum the analytical plan should describe:

- Identification of the work
- Information concerning the sponsor and the laboratory
- Dates
- Analytical Processes
- Records
- Quality Audit
- Parameters, analysis requested at each visit
- Kits, specimens, supplies
- Transport and shipping instructions
- Test methods
- Reference ranges, analytic measurement ranges, reporting units, conversion factors
- Warning and alert limits
- Reporting requirements
- Storage of samples/specimens
- Archiving instructions

The sponsor usually works with the laboratory to produce the analytical plan because ultimately the analytical plan is the responsibility of the sponsor. The analytical plan is an exact reflection of the laboratory specific steps outlined in the trial protocol but provides additional information for the laboratory outlining each phase of laboratory testing:
Visit-specific Kit

The visit-specific kits are part of the **pre-analytical phase of laboratory testing** and are the **responsibility of the laboratory**. Laboratory staff should prepare all **visit-specific kits** that are to be sent to the investigator sites for the **collection of participant samples**. Preparation of these kits can be delegated to other study staff, but the laboratory remains responsible for the correct preparation of each visit-specific kit. Each kit must include the **equipment and materials** necessary to ensure that:

**The correct samples are collected at each specific study visit**
- e.g. the initial study visit may require blood and urine samples but a follow-up visit three months later may require only bloods

**The correct number of samples are taken at each visit**
- e.g. the initial study visit may require three whole blood samples and two urine samples but a follow-up visit three months later may require only one blood sample

**The correct collection materials are used**
- e.g. the initial study visit may require three blood samples; two of which are taken into a collection tube containing anti-coagulant (e.g. Lithium Heparin) and the third into a tube with a clotting agent

**The correct specimen labelling and identification process are adhered to**
- i.e. each sample needs to be labelled appropriately to enable correct identification of samples upon receipt at the laboratory
Laboratory Requisition Forms can be included in the kits and should provide a list of all the samples to be taken, the type of collection tubes to be used and tests required for each visit.

Kits and Instructions to Investigator Sites

Adequate instructions must be provided for the study staff at the investigator sites outlining the collection of samples as detailed in the analytical plan. Study staff should have access to the relevant SOPs but additional information can be provided in the form of a laboratory instruction leaflet which could incorporate images and flow diagrams to ensure samples are collected appropriately. It is the responsibility of the laboratory to ensure that adequate instructions are provided at each investigator site. It is essential that samples are effectively labelled as outlined in the analytical plan so that participant samples can be tracked from initial collection at the investigator sites all the way through to analysis and storage.

The laboratory must keep track of all the materials sent to each investigator site whereas the study staff at the investigator site are responsible for keeping track of the expiry and amount of materials on site. Re-call, re-supply and/or disposal of materials can occur at any time during a study and requires excellent communication between all the different teams involved.

Sample Collection

Sample collection is the responsibility of the investigator sites and is usually performed by study clinicians and study nurses using the visit-specific kit provided by the laboratory. The collection and preparation of each study sample must be performed according to the analytical plan using the relevant SOP to ensure that reliable results are obtained by the laboratory staff during analysis in the laboratory. For reliable results to be obtained during analysis the collection and preparation of samples is vital to ensure:
**The correct type and number of samples are taken**
- The analysis to be performed at the central laboratory may differ for each study visit

**The correct volume/mass are collected for each sample**
- An individual sample may be used for several laboratory tests and each will require an aliquot of specific volume/mass

**The correct collection tubes are used**
- Collection tubes can contain various additives such as preservatives or anti-coagulants and the tubes used for collection are directly related to the laboratory tests to be carried out

**Each sample is appropriately and uniquely labelled**
- This will enable laboratory staff to correctly identify, analyse and store each participant sample.

**The correct preparation methods are used for each sample**
- Certain samples may require centrifugation, separation and/or aliquoting.

**The correct timeframes are adhered to**
- Time from sample collection to refrigeration, sample preparation, testing and/or storage may affect certain analytes in the samples that are to be analysed

**Each sample is stored under the correct conditions**
- Certain samples may require refrigeration whereas others may requiring freezing, the storage conditions may depend on the type of test to be performed

**The correct documentation is collected and sent to the laboratory**
- A properly completed requisition form may be required for each sample/participant

**Sample Transport**
SOPs are required for the safe and secure transfer or transport of samples from the investigator sites to the laboratories. Sample transport is usually the responsibility of the investigator sites but it could also be the responsibility of the laboratory depending on who is arranging the transport. Samples are classed as infectious substances (a form of biological hazard) by the United Nations (UN) because ‘regardless of the presumed infection status of the patient, specimens of human and animal origin should be packaged and transported in such a way as to protect those engaged in transportation from the risk of infection’ ([WHO, Transport of Infectious Substances, 2017](http://who.int/transport_of_infectious_substances/)). Therefore they need to be packaged, labelled and shipped in accordance with local, national and international regulations (e.g. [International Air Transport Association, Dangerous Goods Regulations, 2015](http://www.iata.org)). There should be specific SOPs (or specific sections within SOP) outlining the different transport procedures specific to the method of transport required:

- Transport of samples within the investigator site (e.g. on a trolley)
- Transport of samples to a distant laboratory (e.g. by motorised vehicle)
- Shipment of samples across international borders (e.g. by aeroplane)

Shipment of samples should be appropriately scheduled and notification should be sent to the laboratory regarding the expected delivery, including all documentation of transport (i.e. samples and transportation conditions). A chain of custody should be accurately documented and should include information about:

- Who was responsible for preparing the shipment
- The number and type of specimens being transported
- When the shipment left the investigator site
- How the samples were transported
- The conditions under which the samples were transported (i.e. frozen/refrigerated)
- All shipment logs

Sample Reception

Reception of study samples at the laboratories is performed by laboratory staff and is the last
Laboratory staff are responsible for:

- **Registration of all specimens** at the laboratory so that each sample can be processed accordingly and tracked throughout the laboratory. Samples are often registered using a **Laboratory Information Management System (LIMS)** which will automatically (in the absence of a LIMS, registration of samples can occur manually):
  - assign a unique identification number/code to each sample
  - assign laboratory tests to each sample
  - assign storage locations for each sample/aliquot

- **Verification** of volume/mass, number of specimens and adequacy (e.g. haemolysis, correct tube)

- **Ensuring** that samples requiring temperature monitoring are processed under the correct conditions and recorded appropriately.

- **Acceptance or rejection of specimens** for testing based on criteria pre-defined in the laboratory SOPs

- **Generation** of data clarification forms (DCF) or data query forms (DQF) with appropriate data or sample quality queries

- **Preparation of samples** for analysis and storage, this could include:
  - Centrifugation
  - Separation
  - Aliquoting
  - Dilution/concentrating
  - Slide preparation

- Ensuring that all aliquoted samples are **appropriately labelled** to enable accurate identification and traceability to primary/source sample.

- Ensuring the **correct samples/aliquots** are **sent for analysis** (or storage)

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**Sample Analysis**

Sample analysis is the **responsibility of the laboratory** and should be performed by **appropriately trained and competent laboratory staff**. This is the **analytical phase of laboratory testing** with the laboratory tests for each sample being performed as outlined in the analytical plan. **Participant samples can only be analysed for the tests consented to during the informed consent process**. The **methodology** for each test required for each type of sample should also be outlined in the analytical plan.
To ensure suitability for the testing required the **methodology, systems, equipment, reagents** and **materials** involved in the analysis of study samples must be demonstrably fit for purpose. This will also ensure the accuracy, precision, consistency and reliability of the results obtained. Demonstrating that something is fit for purpose can be achieved through **validation** which is defined as follows:

**Validation**

‘Action or process of proving that a procedure, process, system, equipment, or method used works as expected and achieves the intended results’. *Westgard Basic Method Validation 2008*

The process of validation usually includes testing for **accuracy**, **precision** and **consistency**. Such testing should be documented and recorded. If for any reason a method, system, equipment, reagent or material cannot be validated (e.g. certain immunology assays or qualitative assays) then it should undergo **qualification**.

**Qualification**

‘a set of actions used to provide documented evidence that any piece of equipment, critical material or reagent used works reliably as intended or as specified and leads to the expected results'. *WHO guidelines on good manufacturing practices for blood establishments 2003*

‘Qualification is part of validation, but the individual qualification steps alone do not constitute process validation’ (*ICH GMP, 2000*)

Each sample must be analysed as specified in the analytical plan using the relevant study SOPs. The **verification of results** obtained from laboratory analysis should include:

- **Internal and external quality control measures**
  - e.g the use of *Between Batch* and *Within Batch* quality control samples that contain a known range of analytes similar in range to the analytes being tested in the study samples

- **Repeat analysis** of study samples. This may be required if the quality control measures are not met
  - e.g if *Within Batch* quality control samples are outside the pre-defined reference ranges

**Report**
Once sample analysis is complete and \textbf{all results are reviewed and verified} it is the \textbf{responsibility of the laboratory} to \textbf{report all the results} obtained from study samples to the \textbf{study team according to the analytical plan}. This is the \textbf{Post-Analytical Phase} of laboratory testing and includes:

- Reporting of \textbf{all laboratory results} for each study sample
- Reporting of \textbf{results that are outside} the pre-defined \textbf{acceptable /normal range} for the participant population (e.g. abnormal chemistry results)
- Reporting of expedited results (e.g. upon request from the study team or in response to abnormal test results)
- Responsibilities for various tasks in the reporting process (e.g. who performed the sample analysis, who was responsible for validation of results)
- The \textbf{date, time and location} of all sample analyses
- Description of \textbf{report flow} from laboratories

\textbf{Traceability of data} is essential and all raw result data needs to be \textbf{traceable back to the participant}. This is why care should be taken to \textbf{appropriately label and track all study samples}. This applies to all sub-contracted work.

\textbf{Sample Storage}
As part of the Post-Analytical Phase of laboratory testing it is the responsibility of the laboratory to appropriately store study samples as outlined in the analytical plan. Study samples should be stored under the appropriate conditions (e.g. 2°C – 8°C) and the storage conditions should be continuously monitored for the entire duration of storage. This can be achieved using an electronic monitoring system or a manual system of checking and logging temperatures (if using a manual checking system, weekends and holidays must be covered).

The location of each stored sample should be recorded so that retrieval is possible at any point during the pre-determined duration of storage outlined in the clinical trial protocol (The allocation of sample storage positions usually occurs during sample receipt via the LIMS or alternative registration system. This enables samples to be easily retrieved if/when required for further testing). The pre-determined duration of storage must adhere to national requirements and in order to store samples for longer than the period outlined in the trial protocol, consent must be obtained from participants.

‘Samples and specimens should be retained as required by GCP, but only as long as the quality of the sample permits evaluation’. RQA GCLP 2012

Archive
The responsibility for archiving depends on what document is being archived, who is responsible for that document and where it is archived. Therefore, it could be the responsibility of the sponsor, investigator site staff, laboratory staff and/or other designated staff.

All trial records and laboratory records should be archived including: raw data, sample results and reports, equipment documents, QC results and reports, QA records, requisition forms, protocols, relevant SOPs, shipping lists and relevant biological specimens. ICH GCP guidelines specify that ‘essential documentation be retained by the investigator/institution for a period of at least 2 years after the last of approval of a marketing application or longer if required by regulation or by an agreement with the sponsor. ICH GCP 4.9.5

Archiving can take place at the study facility or at a separate archiving facility provided that access to archives are restricted, designated to individuals with appropriate training (i.e. archive manager) and meet the minimum requirements of GCP, GCLP and national requirements. The archiving period for study samples is pre-determined by the protocol and should adhere to national requirements.

The ultimate purpose of the GCLP requirements for record retention is to enable the reconstruction of a clinical trial should this be required at any stage in the regulatory process.

Knowledge Check

Are the following statements True or False?

1. The laboratory is responsible for sending materials to the investigator sites, but once delivered, the materials are the responsibility of the investigator site.
   - True
   - False

2. It is not important to notify the laboratory of the number of samples being transported from the investigator site to the laboratory.
   - True
   - False

3. Investigator site staff must ensure that a unique identification number/code is assigned to
each participant specimen so they do not need to be re-labelled for analysis upon receipt at the laboratory.

- True
- False

4. The analytical plan states that blood and urine samples should be analysed for each participant. Participant X provided both samples but did not consent to urine sample analysis during the informed consent process. Only blood analysis should be performed for participant X.

- True
- False

5. The laboratory should report only verified results to the study team.

- True
- False

6. The laboratory is responsible for archiving ALL trial records and laboratory records.

- True
- False

Summary

- GCLP is a **hybrid between GCP and GLP** providing a complimentary laboratory standard regarding facilities, systems and procedures to ensure the reliability, quality and integrity of the work, analysis and results of **clinical samples within a clinical trial laboratory**.

- GCLP covers the **entire laboratory involvement within a trial** and the benefits of GCLP compliance include:
  - Study data that is of high quality, reliable, consistent and credible.
  - Comparability of study data
  - Allowing for reconstruction of the study
  - Uniformity of the performance of specific functions across all laboratories worldwide
  - Efficiently managed resources and minimised waste
  - Confidence in the abilities of the laboratory and personnel involved

- GCLP guidelines outline the **key principles of GCLP and specifies the minimum requirements for each principle** to ensure that the requirements of GCP applicable to the analysis of clinical samples are met

- GCLP needs to be **interpreted and implemented in your own laboratory** across the **whole clinical trial process** including all phases of laboratory testing i.e:
  - pre-analytical
  - analytical
  - post-analytical

Quiz

1. GCP provides extended guidelines in most aspects of clinical trials but provides very little
Which of the following laboratory guidance is offered by GCP? (please select all that apply)

- Normal values and/or ranges of the tests should be available
- Certification or accreditation or established quality control and/or external quality assessment should be in place
- Systems with Procedures that assure the quality of every aspect of the trial should be implemented

2. In the 1990s, the Organisation for Economic Co-operation and Development (OECD) established GLP to ensure quality management controls of non-clinical tests between countries in which of the following aspects? (please select all that apply)

- Consistency
- Reliability
- Reproducibility
- Quality
- Integrity

3. GCLP is a hybrid between GCP and GLP providing a complimentary laboratory standard for the testing of non-clinical samples within a clinical trial laboratory:

- True
- False

4. The benefits of being a GCLP compliant laboratory include which of the following? (Please select all that apply)

- Confidence in the abilities of the laboratory and personnel involved
- Inefficiently managed resources and maximised waste
- Ensuring the quality, reliability, consistency and integrity of the study data
- Comparability of study data with non-GCLP compliant laboratories
- Record keeping to enable the documented reconstruction of the study after the study has been completed

5. Responsibilities of the laboratory management DO NOT include ensuring that:

- A sufficient number of suitably qualified, competent and trained staff are available
- A suitable quality system is in place and executed appropriately
- Raw data is recorded promptly, accurately and in compliance with GCLP
- Appropriate document control procedures are established
- Appropriate facilities, equipment and materials are available to conduct the trial

6. In order to minimise any disturbances that might interfere with the validity of the trial or its results, the laboratory should be which of the following?

- Suitably sized
- Suitably constructed
- Suitably located
- Sufficiently secure
- All of the above

7. To ensure compliance and quality of the work being conducted in a clinical trial, laboratory equipment should be:

- Suitably located
- Appropriately designed
- Of adequate capacity
8. Which of the following statements are true? SOPS which include detailed, written instructions to achieve uniformity of the performance of a specific function are needed for the following including:

- Equipment use and maintenance
- Data collection and records
- Methods to be used, and control of those methods
- All of the above

9. An Analytical Plan is a formal document describing all aspects of the work performed by the trial facility?

- True
- False

10. The trial facility may sub-contract work without prior approval from the Sponsor.

- True
- False

11. Detailed records must be maintained and retained for all samples/materials to allow a full examination of where they have been and how they have been stored over the lifetime of the trial. Therefore, materials/samples must be accurately identifiable and ________ at all times whether in transit or storage?

- Traceable
- Retrievable
- Reportable
- Storable

12. The methods used in sample analysis should always be:

- Documented
- Validated
- Controlled
- Approved
- All of the above

13. Which of the following statements are NOT true? The analytical Results document(s) containing the daily laboratory results should include:

- Identification of the analytical work by its unique identification/ trial number
- Identity of the sponsor
- Identity of the laboratory that performed the analysis, including any sub-contracted assays
- Identity of participants

14. A quality audit is a systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor’s standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

- True
- False
15. Which of the following statements is NOT true? To ensure that the laboratory used in the study is compliant with the regulatory authority, the following laboratory records are recommended for retention, including:

- Personnel/training/equipment records
- SOPs and control documents
- Method development, validation and QA records
- Temperature monitoring records
- Analytical records
- Unsecured data processing records

16. The laboratory should be aware of any blinding and unblinding conditions that apply to a trial and take care in reporting results to ensure unblinding does not occur. The sponsor should be informed of any event, either accidental or arising as a result of an investigation, which may compromise study blinding.

- True
- False

17. The Analytical Plan does NOT contain information on which of the following?

- Quality Audit
- Reference ranges
- Laboratory staff details
- Archiving Instructions

18. Laboratory staff involved in conducting a clinical trial should prepare visit-specific kits that are to be sent to the research sites during the Post-Analytical Phase to ensure the proper collection of participant samples.

- True
- False

19. The Analytical Plan should contain detailed instructions for sample collection and sample transport.

- True
- False

20. Prior to sample analysis, samples processed for receipt must have adequate volume/mass, the correct number of specimens and be adequate for analysis. Improper preparation of samples, labeling, and aliquotting are types of issues that could lead to sample rejection or sample quality queries.

- True
- False

21. According to GCLP which of the following statements are true?

- Sample storage and archiving study documentation are the responsibility of the sponsor
- Sample storage is the responsibility of the laboratory whereas the responsibility for archiving study documentation depends on what is being archived
- Sample storage is the responsibility of the laboratory whereas the sponsor is responsible for archiving study documentation
- Sample storage and archiving study documentation are the responsibility of the laboratory