

A decorative graphic consisting of numerous overlapping circles of various sizes and colors, including purple, pink, blue, and grey, scattered across the page. The circles are of different diameters and are layered, creating a sense of depth and movement. The colors are vibrant and modern.

EMA Clinical Laboratory Guidance - Key points and Clarifications

PAUL STEWART

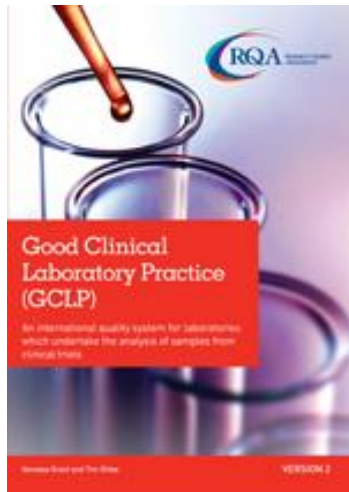
Framework

Labs generate data that are used to make decisions on the safety and efficacy of medicinal products; consequently, it is of paramount importance that the data are reliable.

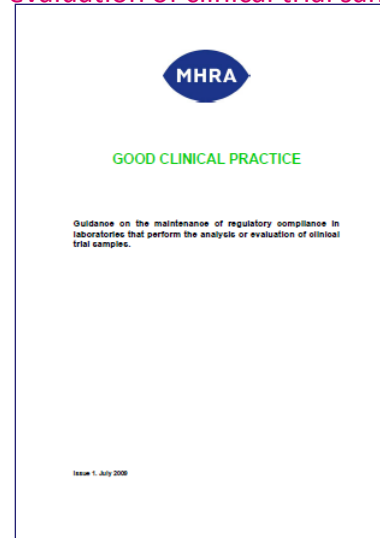
Regulations are not particularly informative in terms of laboratory conduct and was historically difficult to apply GCP principles to the analysis of clinical trial samples.

Guidance for organisations conducting laboratory work:

Good Clinical Laboratory Practice (RQA/ BARQA)



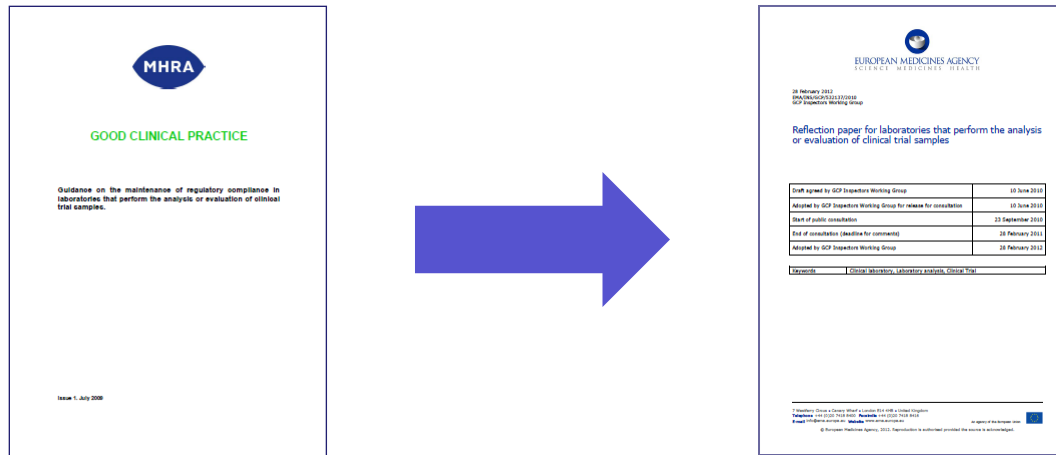
MHRA Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples. July 2009



Introduction

MHRA Guidance now transposed into the following:

- European medicines agency (EMA) reflection papers for laboratories that perform the analysis or evaluation of clinical trial samples (EMA/INS/GCP/532137/2010)
- EMA guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1)
- ICH Topic Q (r1) – ‘Validation of analytical procedures’ (CPMP/ICH/381/95)



Analyses must be performed in accordance with the clinical protocol, good clinical practice (GCP) and the laboratory's internal quality system.

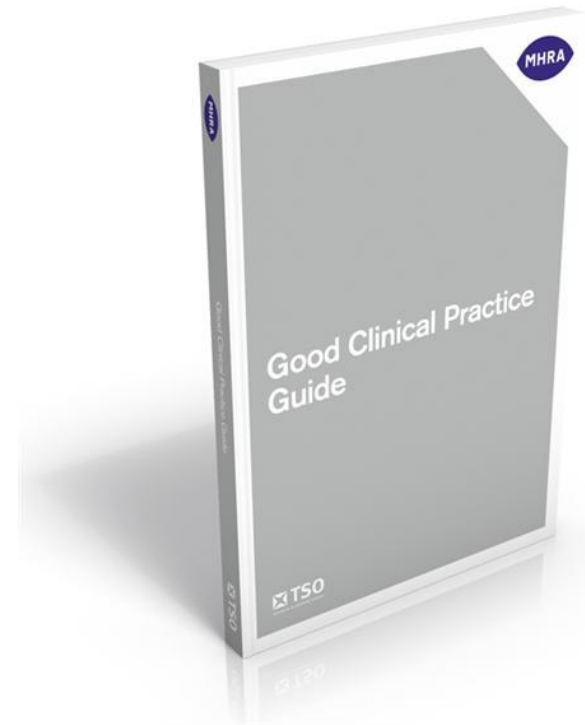
MHRA GCP Guide - “The Grey Guide”

- Sponsor Oversight
 - Clinical Trial Authorisations
 - Ethical Review
 - Key Trial Documentation
 - Pharmacovigilance for Clinical Trials
 - Investigational Medicinal Products
 - Monitoring
 - Data Management
 - Statistics
 - Trial Master File and Archiving
 - Investigator Sites
 - Phase I Clinical Trials
 - **Clinical Trial Samples - Analysis and Evaluation**
 - **Quality Systems**
- **Annex 1: Introduction to GCP Inspections**
 - Annex 2: Relevant legislation and guidance
 - Annex 3: Advanced Therapy Investigational Medicinal Product Trials
 - Annex 4: Considerations for the use of electronic systems in clinical trial management



MHRA GCP Guide - “The Grey Guide”

- **MUST** - Regulatory Requirements (mandatory)
 - Number coded-reference to legislation
- **SHOULD** - Guidance
- **RECOMMENDED** - Good practice





**ORGANISATION OF
LABORATORY WORK - IN
ADVANCE**



1

Laboratory Personnel

Roles and responsibilities within a laboratory should be established and documented prior to the initiation of analytical work.

A Responsible analyst with relevant expertise should be appointed.

Lab personnel must have an adequate understanding of specific GCP requirements.

- Specifically trial subject safety, consent and confidentiality

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

GCP refresher training -frequency not specified in the regs

- Should be outlined in SOPs.

Especially important following changes to regulations /guidance , roles, long absences etc.

Contracts, Protocol and Work Instructions

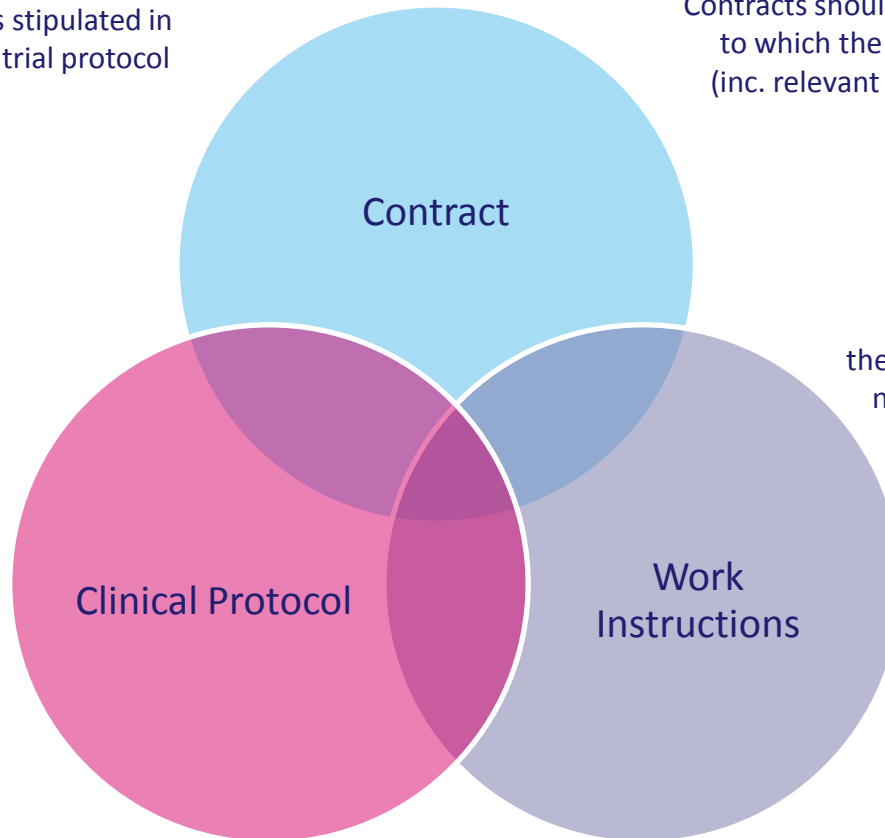
Essential that work carried out is stipulated in the necessary Contracts, clinical trial protocol and relevant work instructions.

Contracts should identify the standards to which the work will be conducted (inc. relevant regulations/ guidelines)

There must be consistency between these documents and this should be verified by both parties.

The Sponsor should ensure that version of the protocol (or part thereof) provided is current and has not been subject to amendments.

A mechanism should be agreed with the sponsor to ensure relevant amendments to the clinical protocol are supplied to the lab accordingly and in a timely fashion.



Deviations that impact patient welfare etc in particular must be conveyed to the Sponsor.

Work should not deviate from these without prior approval from the Sponsor (issues of consent may result)

Communication

Data generated in the laboratory influence key decisions made during the conduct of a clinical trial. Interim analyses or dose-escalation trials will rely on analytical data to determine exposure or required safety tests

Clinical chemistry may flag safety concerns requiring the investigator's immediate attention.

Therefore clear rapid communication channels are essential.

Lines of communication between the lab / sponsor /trial site should established/ tested prior to the initiation of any work. Particularly in instances where there are differing time zones.

Both parties should agree:

- Expedited reporting requirements (contract)
- Normal analytical parameters
- Procedure for deviations to instructions/protocol/contract



Method Validation

Data integrity best demonstrated by a robust, reliable reproducible analytical method i.e. validated.

- Full validation- no previously established technique.
- Partial validation verifying an existing technique
- Reproducibility assay

CT samples may exceptionally be used to validate methods (i.e. biomarker development)

Regulatory and ethical approval must be in place for this

- Validation of method is one of the trial objectives

Method should be validated prior to undertaking sample analysis

- Parallel validation is risky- problems may invalidate the samples
- Retrospective validation (i.e. LTS, general stability) should be avoided

Assess on a case by case basis

- Primary vs research endpoints.





DURING ANALYSIS

2

Transport / Receipt of Clinical Samples

Sample integrity is essential for the generation of valid and reliable results.

Due diligence is necessary and the responsibility of all involved parties.

- **Chain** of custody

Lab responsible for verifying that received samples have not exceeded the stipulated handling conditions (temperature, timelines)

- Confirm that samples arrived in an appropriate condition.

Document appropriately -results may be affected by a temperature excursion.



Sample Identification and Storage

Anomalous samples

- Additional to inventory/ clinical protocol, odd appearance

Be mindful of **Patient identifiers**

Monitoring of refrigerators and freezers to identify any temperature

Refrigerators often subject to significant fluctuation.

Storage conditions (electronically or manually) should be monitored equipment.

Retain evidence

Contingency in the event of a refrigerator or freezer failing.

Separate storage for backup samples.



Data Recording

Traceability is essential for data integrity

Data must be recorded accurately, legibly and promptly

(QC) checks should be performed to confirm the accuracy of the data that have been generated and subsequently transcribed into the report.

Any QC checks must be documented and retained.

Any change to the data must not obscure the previous entry.

E data- electronic audit trail should be maintained.

Justifications for any changes to the data must be documented

- What/ Who/When/Why.

Repeat Analysis

Is routinely necessary where:

- Internal controls fail
- Analytical equipment malfunctions

Less clear instances when repeat analysis may be required:

- Higher/ lower concentrations than expected
- Sample from a control group shows the presence of drug

Acceptance criteria / justification for section should be defined to prevent selective reporting of results.

Instances of repeat analysis must be clearly documented and retained CSR and TMF for transparency.





THE TRIAL SUBJECT



3

Patient Safety Considerations

The safety of trial subjects are of primary concern during the conduct of any clinical trials. Labs may have an important role in identifying adverse reactions to IMPs

- Expedited reporting may be necessary where laboratory is responsible for:
Assessing safety end-points (that may indicate organ damage for example)
- Generating data that are needed to determine dose adjustment
- Anomalous results must always be conveyed to Sponsor
- Must be reported as quickly as possible
- If in doubt - **escalate**



Consent

Laboratories must only perform work that is detailed in the clinical protocol, a work instruction or the contract.

Exceeding these / additional analysis may be in breach of patient consent.

Analytical kits – tread carefully

- Analysis of additional parameters to those identified in the protocol (and consented to by subjects.
- Must ensure that these unauthorised results are not captured, retained or reported.

Analyses that are not specified in relevant documentation must not be performed without explicit permission from the Sponsor.

Similarly for unexpected samples

- **Except** if there are safety implications (i.e. AE at site)

Amendments to agreement/ work instructions/ clinical protocol may be required.

Labs expected to show due diligence in ensuring consent has been given. How is this done?

Withdrawal of consent must be reported to the lab by the Sponsor, to ensure that no further data are collected or generated from the sample .

Confidentiality

The trial subjects' right to confidentiality (i.e. patient welfare) must always be considered by the lab.

Samples or associated documentation can sometimes contain information that identifies a trial subject.

Emails from site with patient identifiers must be managed appropriately and pragmatically

Measures must be taken to ensure the information is masked and not disseminated further .

Sponsor must be informed of all instances.

Consider on how this is documented (email, telephone)



Serious Breaches

Serious breach –one which is likely to effect to a significant degree:

- The safety or physical /mental integrity of trial subjects
- The scientific value of the trial.

Examples of these include:

- Identification of fraudulent activity such as inappropriate data manipulation
- Serious deviations from the clinical protocol /work plan that are likely to affect the integrity or interpretation of data.

Labs must show due diligence here to ensure GCP principles are maintained

- Not all Sponsors are aware of UK SB legislation.

If a deviation is suspected to be a serious breach:

- Inform the Sponsor of your suspicion.
- Follow up to ensure this has been reported appropriately.
- Inform the MHRA if unsatisfied – ultimate duty of care to patient/s.





**LABORATORY FACILITIES
AND EQUIPMENT**



4

Equipment Maintenance

Analytical instruments and general laboratory equipment should be subject to periodic calibration by appropriately qualified technicians.

If maintenance is performed by laboratory staff they should have an appropriate level of technical training.

Calibration also needs to be appropriate and should encompass all conditions required (i.e. analytical weight range of balances)



Computerised Systems

Organisations should subject all computerised systems used within the laboratory to an appropriate level of validation within their systems.

Systems may comprise:

- Bespoke systems developed exclusively for an organisation (more in depth validation)
- Commercially available / “off the shelf” (less rigorous validation)

Never assume a system is fit for purpose based on others experience

Consider what the system is intended to do

- Does it generate clinical trial data?

Based on internal assessment and justification





**QUALITY WITHIN THE
LABORATORY**



5

Quality Control

Representative sample of any manual calculations/ manipulations should be checked.

Spreadsheets are commonly used to perform calculations and unless such spreadsheets are validated, locked and version-controlled.

QC checks should be performed- especially of input data.

Other activities that will require QC checks include:

- Manual integration of chromatograms
- Recording of samples received
- Production of sample collection kits



Quality Assurance

QA staff must be appropriately trained and familiar with the processes they audit .

QA must be independent of analytical processes with separate reporting lines (where possible)

This is not always possible however!

- It may not be practical to employ dedicated staff to perform the QA function.
- Laboratory management may draw on resource from other areas of their operation.
- However, care should be taken to ensure the above



QA- Purpose

QA is NOT QC

Not solely reliant on reconciliation of reported vs raw/ source data

Assures compliance with:

- GCP
- Clinical Trial Protocol
- Contract
- Work Instructions
- Relevant Procedures

By means of relevant and appropriate auditing.

- Processes, systems and documentation related to analysis

QA- What to Audit

Specific focus on GCP - patient safety, welfare and data integrity:

<p>Sample receipt discrepancies</p> <ul style="list-style-type: none">• Additional samples• Patient IDs	<p>Anomalous results</p> <ul style="list-style-type: none">• Unexpectedly high/ low• Outliers• Positive controls
<p>Sample handling/ management</p> <ul style="list-style-type: none">• Sample integrity• Analysed within validated parameters	<p>Data integrity</p> <ul style="list-style-type: none">• Modification• Interpretation• Security• Traceability



ANY QUESTIONS?



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