



Quality Management Requirements for Clinical Trials: Implications for Sample Handling

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Quality Management Requirements for Clinical Trials: Implications for Sample Handling

1. The Regulatory Requirements
2. Putting the Regulations into Practice
3. Focus on Sample Handling
4. Examples of Sample Handling for Biomarker Assays



The Regulations: EU Directive and UK Statutory Instruments on Clinical Trials

EU DIRECTIVE 2001/20/EC

“The implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use”



‘clinical trial’: any investigation in human subjects intended to discover or verify the clinical, **pharmacological and/or other pharmacodynamic** effects of one or more investigational medicinal product

STATUTORY INSTRUMENTS

2004 No. 1031 MEDICINES

The Medicines for Human Use
(Clinical Trials) Regulations 2004

2006 No. 1928 MEDICINES The Medicines for Human Use
(Clinical Trials) Amendment

2006 No. 2984 MEDICINES The Medicines for Human Use
(Clinical Trials) Amendment (No.2)

2008 No. 941 MEDICINES The Medicines for Human Use
(Clinical Trials) and Blood
Safety and Quality (Amendment)

2009 No. 1164 MEDICINES The Medicines for Human Use
(Miscellaneous Amendments)

<http://www.opsi.gov.uk/stat.htm>



Regulatory Requirement on Laboratories

Medicines and Healthcare Products Regulatory Agency (MHRA) GCP Symposium 20-21 January 2010

“... the sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of GCP are satisfied and adhered to.” [Part 4, 28(2)]. As per part 4, 28(5) this also applies to those delegated duties by the sponsor.

“The necessary procedures to secure the quality of every aspect of the trial shall be complied with.” [Schedule 1, Part 2(4)].

ICH Guideline for Good Clinical Practice (GCP)

- 2.13 *Systems with procedures that assure the quality of every aspect of the trial should be implemented*

- 8.2.12 *Essential Documents: Medical/Laboratory/Technical procedures/Tests-certification or accreditation or established quality control and /or external quality assessment or other validation (where required)*



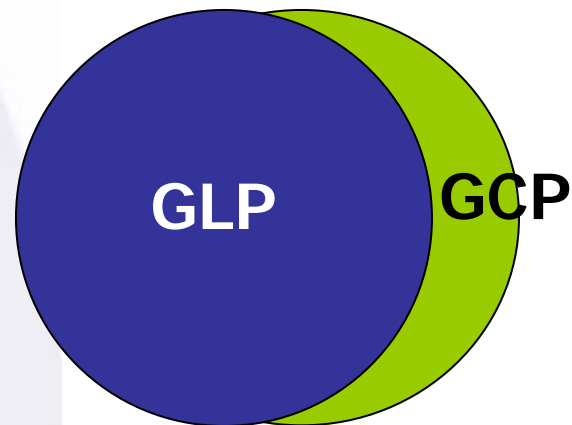
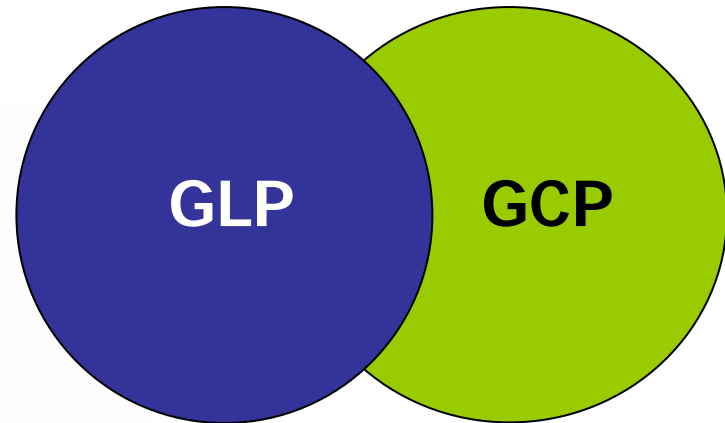
Do the Clinical Trials Regulations Apply to Me?

1. If your laboratory receives, processes, stores, analyses or archives any sample/specimen collected from a subject entered into a clinical trial
2. If your laboratory conducts mathematical or statistical analyses or performs scientific interpretation of data derived from clinical trials

The answer is yes!



GCLP Formulated by BARQA in 2003 to Fill a Regulatory Gap





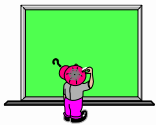
The Scope of a Quality System such as GLP/GCLP



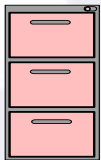
Study Director-In control



C of A and Stable



Signed Off



Bomb Proof



Data Paper/Computer Trail



QA - Independent



Trained Staff



F for P



SOPS
Singing from the
Same Sheet



Chain of Custody

Planning
Personnel
Facilities
Apparatus/Reagents
Method Validation
Analytical Plan
SOPs
Patient Samples
Sample Analysis
Data Trail
Auditing
Analytical Report
Archiving



MHRA Finally Publish “Guidance for Laboratories that Perform the Analysis or Evaluation of Clinical Trial Samples”

July 2009



GOOD CLINICAL PRACTICE for LABORATORIES



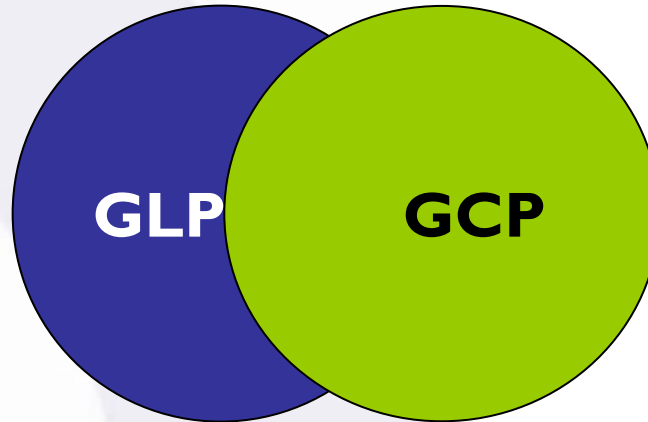
GOOD CLINICAL LABORATORY PRACTICE (GCLP)



<http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPracticeforClinicalLaboratories/index.htm>



Guidance on the Maintenance of Regulatory Compliance in Laboratories that Perform the Analysis or Evaluation of Clinical Trial Samples





The Scope of MHRA GCP for Laboratories – In Totality

- 4.1. Organisation
- 4.2. Personnel
- 4.3. **Serious Breaches**
- 4.4. **Contracts and Agreements**
- 4.5. Study conduct
- 4.6. **Requests for additional work**
- 4.7. Sub-contracting laboratory analysis
- 4.8. **Patient safety**
- 4.9. **Informed consent**
- 4.10. Sample receipt and chain of custody
- 4.11. Method validation
- 4.12. **Repeat analysis**
- 4.13. Data recording
- 4.14. Reporting
- 4.15. Facilities
- 4.16. Equipment maintenance
- 4.17. **Computerised systems**
- 4.18. Quality Assurance (QA) processes
- 4.19. Quality Control (QC)
- 4.20. Standard Operating Procedures (SOPs) and facility policies
- 4.21. **Blinding/ unblinding**
- 4.22. Retention of data
- 4.23. Preparation and distribution of clinical kits



The Scope of MHRA GCP for Laboratories – In Essence

Compliance to
The Regulations

Patient Centred



Quality
Assurance

Data Integrity

GCP
Approvals



Sample
Collection



Sample
Analysis



Data Audit
Trail



The GCP Regulations that Now Apply to Laboratories - I

Compliance to
The Regulations



Quality
Assurance

1. All laboratory/biobank staff must receive GCP training commensurate with their roles and responsibilities
2. If the laboratory becomes aware of a potential serious breach to the clinical trials regulations, they must contact the sponsor or, if appropriate, directly to the MHRA
3. Contractual agreements - signed by the sponsor and laboratory/biobank management - should be drawn up prior to the initiation of the laboratory work
4. The laboratory should be provided with the most up to date version of the protocol (and any relevant amendments) or at least the sections relevant to the work that they have been contracted to perform
5. The laboratory should seek assurance from the sponsor that additional work does not conflict with the clinical protocol or compromise the informed consent



The GCP Regulations that Now Apply to Laboratories - II

Compliance to
The Regulations



Quality
Assurance

1. 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
2. The MHRA place great store in sample tracking. Thus, full sample tracking must be conducted from receipt, to log in, through tracking (and temperature monitoring), during analysis and finally to archiving, dispatch or disposal
3. To comply with GCP, patient samples must be anonymized prior to being sent to the lab, therefore each sample should be examined to ensure that its label does not display information which may identify the trial subject
4. Procedures should be in place to deal with issues linked to patient safety and confidentiality, unblinding and blinding samples and for dealing with the receipt of unscheduled or poorly labelled samples
5. Laboratories must exercise due diligence to ensure they do not inadvertently compromise the blinding process



Focus on Sample Handling

National Academy of Clinical Biochemistry Laboratory Medicine

Quality Requirements

Errors Reported in Laboratory Tests

Pre-Analytical Phase

30-75%

Analytical Phase

13-31%

“The majority of pre-analytical errors for tumor markers are attributable to simple specimen-handling errors, such as inappropriate timing and incorrect specimen identification.....the occurrence of which should be minimized by good laboratory practice and effective auditing procedures.”

Clinical Chemistry 2008 Volume 54 Part 8; e1-e10



Focus on Sample Handling

Frozen

Frozen Samples – Low risk ?

Positive confirmation that they are frozen on arrival

Issues: Instructions to top up dry ice

Chilled !!

Chilled Samples

Need verification that samples have been transported under appropriate conditions.

What condition do they arrive in?

Are cold blocks still cold?

Procedure for dealing with samples at ambient temperature.

Ambient !!!

Ambient conditions/potential issues

How long have the samples been in transit?

What temp. have they been exposed to and for how long?

Clear policy on when it is or isn't appropriate to report data

How are these issues communicated to the sponsor



Focus on Sample Handling

Can the integrity of the sample be confirmed?

Some points to consider

Reconciliation of samples received with those expected

How can QA and QC checks be used to ensure the process is robust

Processes for dealing with the receipt of unexpected samples

Unexpected and not labelled samples

Don't analyse until sample ID has been established

Exceptions:
Failure to analyse immediately could/will lead to the loss of data

Analyse and quarantine results until sample ID is established



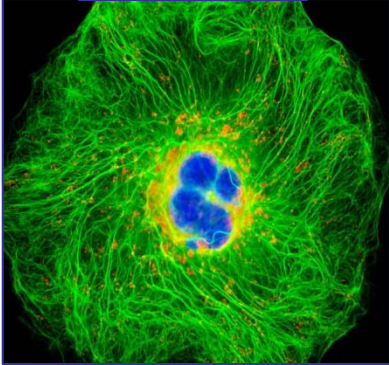
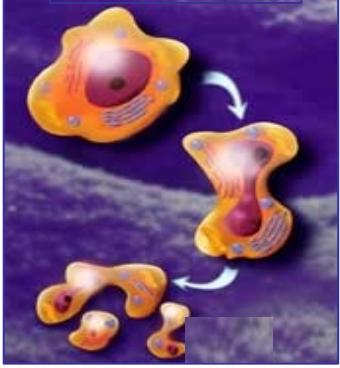
Sample Logging and Tracking Throughout the Analysis Cycle

1. Examine Each Sample Upon Arrival
2. Comment on Condition/Labelling
3. Uniquely Identify Individual Samples
4. Automated ID and Bar Code Generation (optional)
5. Define Storage Location
6. Log Sample Details
7. Monitor Storage Temperature
8. Have Backup Procedure in case of Freezer Malfunction
9. Record Details of Analysis
10. Sample Verification During Analysis by Scanning Barcodes
11. Track Sample to Disposal

Based of PICR CEP SOPs: ST/002; ST/003; ST/004; ST/008; QA/003; QA/014 and QA/023



The M30 and M65 ELISAs Detect Different Forms of Cytokeratin18 (CK18) as Biomarkers of Cell Death

Death Process	Drug induced disassembly of the i-Filaments (IF) and recruitment to the soluble pool	Caspase cleavage of the IF to facilitate collapse of the highly rigid cytoskeleton
Schematic	<p style="text-align: center;">Necrosis</p> 	<p style="text-align: center;">Apoptosis</p> 
Component Released	Intact CK18	Soluble CK18 Fragments
Detected By	M65	M30 and M65



Importance of Sample Handling for Biomarker Assays – M30 and M65 ELISA as a Paradigm

1. M30 and M65 produce quantitative biomarker data
2. These data are correlated to either drug action (Pharmacological Biomarkers); Drug effect (Predictive Biomarkers) or Disease outcome (Prognostic Biomarkers)
3. Three years of effort went into validating these assay in order to produce reliable data with clinical trials samples
4. However, there are a number of sample handling issues that can affect the validity of the results

Cummings et al British J Cancer 2005 92; 532-538
Cummings et al Cancer Chem Pharmacol 2007 60; 921-924

Cummings et al British J Cancer 2006 95; 42-48
Greystoke et al Annal Oncol 2008 19; 990-995



Importance of Sample Handling for Biomarker Assays – M30 and M65 ELISA as a Paradigm

1. A 4-hr delay in processing blood to separate plasma – results in an artefactual 50% increase in the value measured by the M30 assay
2. Serum versus plasma give rise to different values (20% lower in plasma) and also have different stability profiles
3. Long terms storage of samples even at -80°C for more than 3 months before analysis results in marked instability in the M30 assay but not the M65
4. Plasma and sera samples exhibit non-dilution linearity if values are off scale and samples require dilution
5. Duplicate analysis of plasma samples give rise to much greater variability than with serum

Cummings et al British J Cancer 2005 92; 532-538
Cummings et al Cancer Chem Pharmacol 2007 60; 921-924

Cummings et al British J Cancer 2006 95; 42-48
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Summary -I

1. QA cannot offer a guarantee of sample integrity, but can reduce uncertainty, dependent on the level of QA implemented
2. Therefore when considering how much QA to implement, try to evaluate the level of risk you are willing to accept, as well as a cost/benefit analysis
3. Focus on ensuring that samples are labelled correctly, uniquely identified and anonymized
4. Here, good lines of communication between the trials centre and the laboratory/biobank is essential
5. QA audits should be conducted at the trial centre, where possible, to ensure procedures are being followed
6. Particular focus should be paid to sample stability issues – with the onus being on the laboratory to provide appropriate guidance



Summary - II

1. SOPs for sample handling should be written and document controlled such that lab and clinic have identical copies
2. Mistakes happen but it is essential that any deviations from procedures are recorded and sent back to the laboratory, as a priority
3. Equal attention should be paid to equipment maintenance (e.g. centrifuges) and staff training in sample processing techniques at the trials centre as in the laboratory
4. Remember that each different sample type and biomarker assay are likely to have individual sample handling requirements