MHRA
Regulating Medicines and Medical Devices

Is GLP an appropriate standard for laboratories that analyse samples from human clinical trials?

A European perspective

Dr. Andrew J Gray – Head UK GLPMA

Medicines and Healthcare Products Regulatory Agency

Analysis of samples from human clinical trials

GLP is an established quality standard which can under-pin the quality of non-clinical studies.

Focus –

Documentation – study plan/final report

Data integrity – quality assurance audits

Reconstruction – recording and storage of data

Why it's not just GLP

- **GLP** – EU Directive 2004/9/EC and Directive 2004/10/EC
- EC Directives transposed into national law:
  - UK Regulations SI 3106 as amended by SI 994 , 2004
  - Compliance with the principles of GLP is a legal requirement for test facilities that undertake health and environmental safety studies that will be submitted to regulatory authorities for the purposes of risk assessment
  - Does not include clinical studies… GLP is limited to pre-clinical

- **GCP** - EU Clinical Trials Directive 2001/20/EC was transposed into UK law:
  - The Medicines for Human Use (Clinical Trials) Regulations 2004 (the Regulations) have regulated clinical trials in the UK since they came into force on the 1 May 2004.
  - The regulations relate to persons or organisations that participate in any aspect of a human clinical trial, including the laboratories that are responsible for the analysis of clinical samples.

Why it's not just GLP

- **GLP doesn't:**
  - Consider the subject

- **GCP does include:**
  - Safety
  - Confidentiality
  - Consent
  - Ethics

Points to consider.

GCP for Clinical Laboratories

- Contracts and Agreements
- Safety
- Confidentiality
- Consent

Example findings and expectations

Why is GCP relevant to laboratories that perform clinical analysis?

- Subjects in clinical trials have certain rights and these rights extend to the way that clinical samples are taken, processed and reported.

Good Clinical Practice is about the SUBJECT as well as quality science

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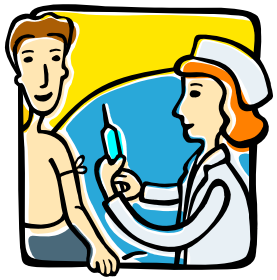

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Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples

Contracts and Agreements

- A contract and/or agreement should be in place prior to initiation of work conducted at the Clinical Laboratory

- There should be a policy or procedure detailing the requirements, for example:
  - Expectations in terms of content
  - Signatories
  - Review and update procedures

- Letters of intent

- Master Service Agreement

Contracts and Agreements

- **Key elements:**
  - Has the contract been agreed with the relevant parties?
  - Define roles and responsibilities (including communication channels).
  - Patient confidentiality and consent considered?
  - Define the standard to which the work will be performed.
  - Are the procedures to be followed defined?
  - Outline requirement to receive the clinical protocol (and any subsequent amendments).

Patient Safety

EU 2005/28/EC
"The rights, safety and well being of the trial subjects shall prevail over the interests of science and society".

UK Statutory Instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended).
"The rights, safety and well-being of the trial subjects are the most important considerations & shall prevail over interests of science and society".

Declaration of Helsinki adopted in 1964
"In medical research…considerations related to the well-being of the subject should take precedence over the interests of science and society".

Expedited Reporting

- When is it necessary?
- Who should do it?
- What are the minimum expectations?

- Roles and responsibilities.
- Data review.
- Lines of communication.

Common Findings – Expedited Reporting

- No consideration given to expedited reporting of data.
- The laboratory is contracted to perform the analysis, not to interpret the results!
- Expedited reporting is not necessary as the dosing was performed several weeks ago!

Subject Confidentiality

EU Directive 2001/20/EC
"the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with Directive 95/46/EC are safeguarded"

EU Directive 2005/28/EC
"All clinical trial information shall be recorded, handled, and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected".

Statutory Instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended).
"The rights of each subject to physical and mental integrity, to privacy and to the protection of data concerning him in accordance with the Data Protection Act 1998 are safeguarded"

Common Findings - Subject Confidentiality

- No documented procedure to deal with subject identifiers coming in-house.
- Evidence of subject identifiers coming in-house
- Identifiers are processed and distributed around the laboratory (or externally)
- Identifiers may be stored long term on samples tubes and/or entered onto a database

Informed Consent

EU Directive 2001/20/EC

Definition: "decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent"

Statutory Instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended).

"The conditions and principles of Part 3 apply"

Part 3:

"The subject has given his informed consent to taking part in the study."

ICH GCP (For example, Section 2.9)

"Freely given informed consent should be obtained from every subject prior to clinical trial participation".

Expectations – Informed Consent

- Laboratory should exercise due diligence.

- There should be procedures to describe how to deal with:
  - unexpected/unscheduled samples
  - incorrectly labelled samples

- The laboratory should consider implications of, for example, automatic analysers where a spectrum of measurements may be obtained

- Additional work or research should not be performed unless consent has been obtained.

Blinding

The legislation requires that the protocol is followed.

If the study is blinded then the integrity of the blind must be maintained (the protocol should specify who will be unblinded)

If…

…the laboratory are blinded, and are not provided with the randomisation codes, then there is usually no issue.

However……..

Blinding

…Laboratories are often unblinded:

- PK analysis is often performed unblinded to prevent costly analysis of samples that do not contain the drug substance.
- Analysts may be provided with the randomisation list.
- Care must be taken in the storage of the codes.

Summary

- There are many aspects of GLP that can be applied to GCP laboratory work
- Understanding of specific GCP requirements for clinical laboratories is important – (subjects rights)
- A Laboratory is a crucial part of the process and plays an important role in ensuring patient safety and well being.

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