Queen's University Belfast

Research and Enterprise

Standard Operating Procedure

Research Governance

Title:	**Audit of Laboratories to Good Clinical Practice Standards**		
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Revision Log

Previous Version number	Date of Review/Modification	Reason for Review/Modification	New Version Number

1. Purpose

This Standard Operating Procedure (SOP) outlines the procedure for implementing Good Clinical Practice (GCP) standards published by the Medicines and Healthcare Products Regulatory Agency (MHRA) in University labs. This procedure will be developed and subject to expedited review in place of the two year standard. This is deemed necessary as translational research is an area where substantial investment by the University and modernisation of labs for a number of Centres is planned.

2. Introduction

Until recently Regulatory Authorities have dedicated limited resource to assessing GCP compliance in laboratories. In 2009 the MHRA published regulatory guidance on the topic titled 'GCP for laboratories' and this document details the expectations the University must apply (Reference 1). The EMA has also published a reflection paper on this topic in 2012 and from this point Regulators have been increasingly interested in labs processing human samples from CTIMPs (Reference 2). The MHRA has provided greater resource to determine compliance to GCP standards and developed a dedicated inspection programme. This has focused on Good Laboratory Practice (GLP) labs that also provide GCP analytical services. The University is more likely to be inspected against these standards during routine GCP inspection in its role as a Sponsor/co-Sponsor of Clinical Trials of Investigational Medicinal Products (CTIMPs). At present the University does not have any labs operating to GCP standards. However this is only a legal expectation for analysis of human samples from CTIMPs providing information on primary end-points. For testing procedures outside of this, potential risk to the University can be reduced by implementing a proportionate level of GCP. This approach will also be taken for testing that is seen as early experimental work. The MHRA example presented is "the identification of potential PD markers in specific patient groups where the method is validated as part of the clinical trial".

3. Scope

This procedure applies to any stage of analytical testing of human samples originating in a CTIMP that are not providing information on primary end-points unless seen as early experimental work. Primary end-point testing and safety testing should always be conducted to full GCP. This procedure will assess all analytical testing of human samples from CTIMPs. This includes the clinical assessment of participants, for example ECG and blood pressure readings. A diagram indicating the increasing regulatory burden is presented in Appendix 1.

4. Responsibilities

4.1 Chief Investigator

Overall responsibility for all elements of research activity, including the compliance of laboratory testing to GCP is the Chief Investigator (CI). Were the CI is not a University employee a lead QUB researcher should be identified as the local PI. The risks of not complying with GCP are not just about failing to meet regulatory expectations. They could also include:

(i) Breach of contract and litigation;
(ii) Patient safety;
(iii) Integrity of study findings;
(iv) Reputational for the University and the Individual;
(v) Action under the Research Misconduct Regulations.

The CI should inform Research Governance at the earliest opportunity that they plan to conduct lab work on human samples from a CTIMP. The CI should accommodate an audit of the appropriate lab if required according to the procedure detailed below.

The CI is also responsible for resolving any audit findings that arise before testing is carried out on University premises.

It is the responsibility of Research Governance to conduct an audit of the laboratory if required within one month or later if requested by the CI. An audit report should be provided within two weeks of the audit. Due to the technical nature of this topic Research Governance are required to provide guidance or sign-post on a suitable resolution to any finding.

5. Procedure

5.1 Notice of GCP analysis study

When a researcher confirms with Research Governance that they wish to analyse human samples from a CTIMP a meeting will be set-up to determine the details of the proposed work. This meeting will be conducted within 2 weeks of Research Governance being made aware of the study or later if agreed with the CI.

5.2 Completion of the screening form

The screening form will be completed by the CI/lead QUB researcher with help from the Research Governance representative (Appendix 2). There are four actions that may arise after the review of this form:

(i) No further action required from Research Governance - It has been determined that there is no need to comply with any aspect of GCP for labs. A copy of the form will be provided to the CI/lead QUB researcher. The original will be stored in a folder within the Research Governance Office.

(ii) Guidance should be provided to the CI/lead QUB researcher - This could be for various reasons such as the lab is not suitable for participant safety testing of samples from a CTIMP. A copy of the form will be provided to the CI/lead QUB researcher. The original will be stored in a folder within the Research Governance Office.

(iii) An audit of the laboratory facility is recommended - The proposed work should be conducted to a proportionate level of GCP and is suitable to be conducted in a University lab. Research Governance will conduct an audit of the laboratory if required within one month or later if requested by the CI. An audit report should be provided within two weeks of the audit. The audit process is detailed in section 5.3.

(iv) Further clarification of the testing should be requested from the Sponsor – this could be for a variety of reasons, for example, to clarify why a certain type of test must be contractually conducted to GCP and will the Universities approach of applying 'proportionate' GCP be acceptable. All communication regarding this issue with the Sponsor should be held in the Research Governance Office along with any related documentation such as contracts.

5.3 Audit Procedure

Research Governance will conduct an audit of the laboratory if determined using the screening form within one month or later if requested by the CI. The audit will be

conducted using the audit checklist (Appendix 3) and the Risk/Compliance tool (Appendix 4).

Using the Risk: Compliance tool the facility will be:

(i) 'Approved' for the analysis of human samples obtained from a CTIMP.
(ii) Conditionally 'approved' for the analysis of human samples obtained from a CTIMP.
(iii) Deemed not appropriate or requiring substantial measures to increase GCP compliance.

The CI/lead QUB Investigator will be sent a copy of the audit report along with the suitability of the lab to conduct the proposed work. A certificate will be issued for the type of testing the lab has been assessed for and this will reduce the need to re-audit for each study. The certificate will be initially valid for a period of one year in-line with industry QA requirements.

6. References

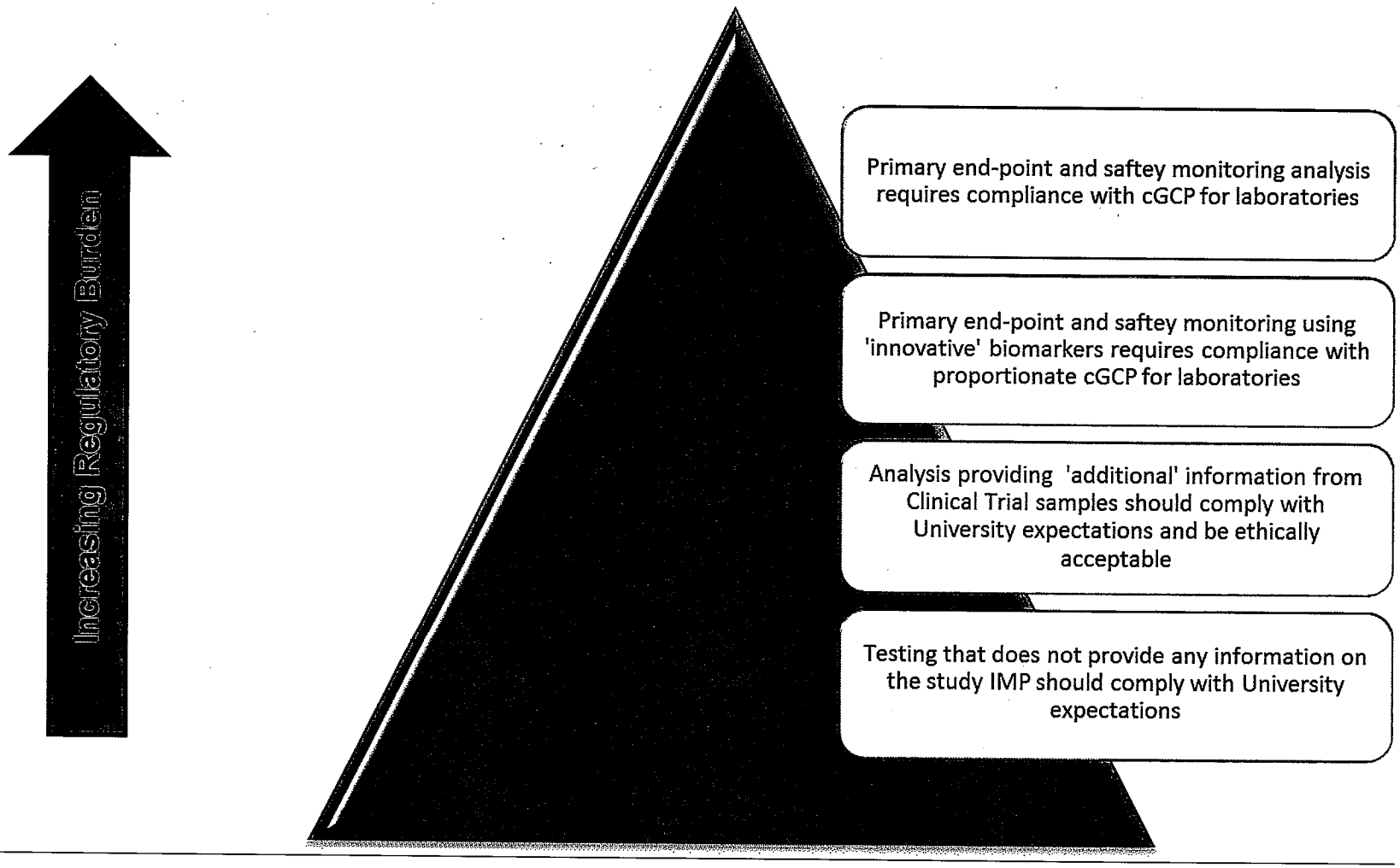
MHRA guidance document GCP for Labs (last accessed October 2013)

http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con051910.pdf

EMA Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples (last accessed October 2013)

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127124.pdf

GCP for Laboratories



QUEEN'S UNIVERSITY BELFAST

Analytical Analysis of Human Samples from Clinical Trials of Investigational Medicinal Product (CTIMP)

Please sign, date, and return this form to:

Research Governance (researchgovernance@qub.ac.uk)

Attention: To be completed and signed by the Chief Investigator/ Lead QUB Researcher

Scope

The analysis of human samples from CTIMPs is regulated by the MHRA. This applies to all processes in the analytical testing of human samples, for example, storage of samples. Please read the following statements and indicate what is relevant to your study.

CTIMPs within the University are audited internally and externally by the MHRA. Failure to comply with regulatory expectations in laboratories may lead to action by the MHRA, recent examples of this have ranged from the removal of the Clinical Trial Authorisation to custodial sentences.

Type of testing involved:

Yes | No	Primary end-point and safety monitoring analysis that requires compliance with cGCP for laboratories
Yes | No	Primary end-point and safety monitoring using 'innovative' biomarkers that requires compliance with proportionate cGCP for laboratories
Yes | No	Analysis providing additional information from clinical trial samples that should comply with University expectations and be ethically acceptable
Yes | No	Testing that does not provide any information on the study IMP should comply with University expectations
Yes | No	Other (please provide details):

Guidance sought to date:

Yes | No I have received guidance from the MHRA

Yes | No I have contracted an independent Regulatory / GxP consultant

Yes | No I have contacted the lead sponsor and asked their advice

Please provide further details if you have already sought guidance:

Please note: This form will remain on file and could be held in archive indefinitely. As the Chief Investigator it is legally your responsibility to ensure that CTIMPs are conducted in accordance with GCP. The MHRA have determined that laboratory analysis of human samples from CTIMPs is an important aspect of GCP.

Chief Investigators/ Lead QUB Researcher's Name (please print):_____

Position held at the University: _____

Date:_____

[Research Governance Use Only]

The following further action is recommended:

Yes | No No further input is required from Research Governance

Yes | No Guidance should be provided to the Chief Investigator

Yes | No An audit of the laboratory facility is recommended

Yes | No Further clarification of the testing should be requested from the Sponsor

Please provide further details if required:

Audit Checklist

The following categories should be rated for compliance with the legislation.

1 = not compliant, 2 = some aspects of compliance, 3 = compliance in key areas, 4 = compliant with GCP and 5 = exceeds compliance

Requirement	Compliance Level	Notes
Organisation		
Organogram		
Job descriptions		
Capacity planning		
Serious GCP breaches reporting procedure		
Resources		
Communication with the Sponsor		
Personnel		
Training record		
Appropriate GCP training		
Contracts and Agreements		
Contracting policy		
Contracts in place for all active studies		
Practice reflects contracts		
Service contracts in place eg equipment maintenance		
Study Conduct		
Clinical protocol available and controlled		
Work instructions		
Deviation procedures		
Patient safety procedures		
Additional work controls		

Sub-contracting procedure		
Informed Consent, including withdrawal procedure		
Sample receipt and chain of custody		
Transit procedures		
Control of transit conditions		
Control of storage conditions		
Receipt checks and process		
Cataloguing of samples		
Confidentiality		
Sponsor Incident reports		
Back-up cold storage		
Analytical processes		
Method Validation		
Repeat Analysis		
Data recording		
Reporting		
Facilities and Equipment		
Suitable design		
Degree of separation		
Cross-contamination		
Waste disposal procedures		
Equipment maintenance		
Computerised Systems		
Validation package and user testing		
Revalidation		
Control of hardware		

Disaster recovery plan for IT systems		
Source data		
Access control		
Quality Assurance (QA)		
Suitable processes in place		
Frequency and duration of QA checks is appropriate		
Documented checks for essential activities		
Appropriate QA staff		
QA staff training		
Study Audits		
QMS audit		
Audit of computer systems		
'Key' task audit		
Procedural Audit		
CAPA system		
QA reporting process		
Quality Control (QC)		
Checks on specific processes		
QMS		
Contracts and agreements		
Analytical procedures		
Patient issues		
Supply-chain		
Validation, qualification, calibration and maintenance		
Retention of data		

QA and QC functions		
Archival of data and QMS		
Blinding/unblinding		
Clinical kits		

Audit outcome:

After audit and review of the risks using the Risk: Compliance Tool the following determination has been made: (delete as appropriate):

- 'Approved' for the analysis of human samples obtained from a CTIMP.
- Conditionally 'approved' for the analysis of human samples obtained from a CTIMP.
- Deemed not appropriate or requiring substantial measures to increase GCP compliance.

{Further information to be provided}

Auditor 1: **Auditor 2:**

Date: **Date:**

RISK: COMPLIANCE TOOL

This tool is to assess the risk involved in a particular analytical test and weigh it against the level of compliance in the associated laboratory. This form should be filled in prior to conducting the audit. The CI/lead QUB researcher should be involved in this process as they are the expert in the use of the particular technique within the University. The information provided should be confirmed by the signature of the CI/lead QUB researcher on this form.

Description of the test in lay terms:

Significance of the test in the CTIMP:

Consequences of incorrect analysis of samples:

Signature of CI/lead QUB researcher:_____ Date: _____

Audit requirements and areas of importance:

Signature of Auditor_____Date:_____