UKCRC Registered Clinical Trials Units

Guidance for CTUs Assessing the Suitability of Laboratories Processing/Analysing Clinical Trial Samples

UK CLINICAL RESEARCH COLLABORATION

igniting our potential

UKCRC Registered CTUs Network

Guidance for CTUs Assessing the Suitability of Laboratories Processing/Analysing Clinical Trial Samples[1]

([1] Referred to as samples in this document)

This guidance document has been developed by the UKCRC Registered CTUs Laboratory work stream[2] (as part of the Quality Assurance operational group) to provide general guidance for CTUs assessing the suitability of laboratories processing and or analysing samples used in clinical trials and should be used in conjunction with the UKCRC Laboratory Assessment Questionnaire. This guidance covers:

- The laboratory where the work will be done *(laboratory facilities, personnel, contractual arrangements, organisation roles and responsibilities, equipment, IT systems and quality management systems)*
- Sample management *(receipt, processing, reporting, method validation, sample and data storage, QA and QC processes and preparation of sample kits).*

[2]*The laboratory work stream comprises both QA representatives and laboratory leads.*

1. Introduction

Sample processing and/or analysis contributes significantly to research data, including important safety information and trial outcomes. It is therefore essential that any samples collected as part of an approved clinical trial, are processed/analysed in accordance with the trial protocol, and in compliance with Good Clinical Practice (GCP), applicable regulations and associated guidance. (For International Trials refer to that countries guidance).

Laboratories may also work to other regulations or guidelines such as Good Laboratory Practice (GLP), Good Clinical Laboratory Practice (GCLP) and ISO15189:2012, however, when processing and analysing clinical research samples, it is GCP that applies.

GCP requires that records are retained to demonstrate that sample processing/analysis meet the requirements of the trial protocol, therefore documented evidence should be available for review by the CTU, the Sponsor or regulatory bodies.

Processing/analysis of samples in accordance with GCP is described in:

- The EMA reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples (2012)
- The MHRA Good Clinical Practice Guide, Chapter 13 (2012)

Formal assessment of laboratories can be carried out using the UKCRC Self-Assessment Questionnaire developed by the laboratory work stream for assessing regulatory compliance in laboratories that perform processing, storage and analysis or evaluation of samples.

The template can be modified in advance to ensure it is specific for the proposed work that the laboratory will be carrying out. The UKCRC template questionnaire is available at www.ukcrc-ctu.org.uk

2. Oversight Requirements

1. The sponsor/CTU must have the same confidence in results generated from the analysis of samples, as it would for any other type of trial data.
2. How this is achieved will depend on the level of oversight required by the sponsor/CTU, the quality systems in place for the laboratory/facility used, and sponsor/CTU review of the questionnaire
3. The following examples of laboratory facilities are not mutually exclusive, and the aim of this guidance document is to outline measures that the CTU can implement to assure the quality of laboratory results.

3. All Facilities

1. It is expected that formal contracts or agreements are put in place. For laboratories within the same legal entity where a formal contract is not required, a description of roles, responsibilities and requirements should be agreed that covers the planned work this can be in the form of:
    - A memorandum of understanding
    - A service level agreement
    - Other, depending on local policies.
2. Laboratory facilities/systems must meet the requirements of the trial protocol and GCP.
3. Accreditation may not be sufficient to ensure compliance with specific GCP requirements of the protocol.
4. It is recommended that a review of the services and systems provided by each laboratory/facility is performed at least once, by completion of the UKCRC self-assessment questionnaire.

A. Sample processing and/or storage only

1. Samples processed and stored before shipping to a specialist laboratory for analysis. This may take place in clinical research facilities, sample handling rooms or clinical areas, as well as established laboratories.
2. Sample processing may involve but is not limited to:
    - Centrifugation
    - Aliquoting
    - Labelling
    - Histological techniques
    - Storage in preparation for batch analysis
    - Transport
3. The accuracy of these processes is vital to the integrity of the final analysis and as such must be subject to the same oversight as samples analysed for clinical care or research endpoints.

B. Samples analysed as part of routine clinical care

1. Samples collected and analysed as part of routine clinical care may also contribute to the trial dataset. Typically, an NHS Pathology laboratory with UKAS accreditation for the analysis described in their lab manual.
2. Samples analysed using standard clinical assays in a laboratory with a functional, audited quality system. Typically, a commercial Clinical Research Organisation often with ISO accreditation. These samples are normally analysed using standard assays to:
    - Determine eligibility
    - Monitor ongoing safety
    - Identify trial endpoints
    - Stratification (This would require additional oversight with reference to In-Vitro Diagnostic Device (IVDD)and medical device legislation)
3. CTUs should ensure there is a GCP representative in these laboratories who understands clinical trial protocols and the GCP requirements governing patient identifiable data, consent, blinding, reporting and retention of records.
4. If novel techniques are used the trial specific section of the questionnaire should be used to clarify the processes involved, including any validation of assays.

C. Samples analysed for clinical trial purposes only

1. Samples collected and analysed for trial objectives only.

2. Typically, an academic institution, although NHS laboratories can be used according to the protocol and local agreements.
3. If novel techniques are used the trial specific section of the questionnaire should be used to clarify the processes involved, including any validation of assays.

4. Use of the laboratory questionnaire

1. The UKCRC Laboratory Questionnaire template has been designed to capture and document all the aspects of sample management/analysis.
2. The template can be tailored for protocol specific requirements.
3. The questionnaire should be reviewed by the CTU and sections which are not applicable deleted. The questionnaire should be filled out by a suitably qualified member of the laboratory staff and reviewed according to CTU local procedures, typically the coordinator and a member(s) of CTU staff with relevant laboratory and QA experience (e.g. a lab group).
4. The facility should be able to comply with the regulations and guidelines that apply to clinical trial protocols.
5. The questionnaire consists of two sections. It may be helpful for the CTU to assist the laboratory to complete the form.

   Section A

   Section A is populated by all facilities. It is recommended that the trial team populate the requirements for the trial in the laboratory service box and that the laboratory/facility populate the services they offer in the same box.

   Section A covers Contact details, Laboratory facilities. Quality Assurance, Personnel, Contracts and Agreements, Sample management and storage, Trial conduct, Equipment, Data handling, Record keeping (both hard copy and electronic documentation and records).

   Section B

   Section B should be populated with section A by facilities providing analysis for trial endpoints and exploratory work. This covers the additional requirements for laboratories performing analysis. Methodology, repeat analysis, validation and quality control, reporting of results, management of blinded trials, preparation of kits and also a section to record any additional trial specific information.

5. Additional Oversight

1. A risk-based approach may be taken when considering how the questionnaire is reviewed. Refer to appendix 1 for an example.
2. For new laboratories or new trials using a laboratory previously used by the CTU, if no significant issues have been raised, completion and review of the self-assessment questionnaire may be sufficient. This should be documented according to local procedures.
3. If concerns are identified on review of the questionnaire, that may impact on the outcome of the trial, consideration must be given to escalating the level of oversight previously undertaken.
4. Examples that may indicate enhanced oversight is required, note this is not an exhaustive list:
    - A completed questionnaire that demonstrates risks that need to be managed, e.g. a lack of appropriate quality management system / processes
    - A poorly completed questionnaire
    - Sample labelling issues (e.g. inclusion of patient identifiable data, incorrect labelling or sample traceability concerns
    - Potential for delays in expedited reporting, that may constitute a serious breach
5. Additional support from the CTU may include:
    - Conducting a laboratory audit
    - Increased monitoring of samples and oversight of the work of the laboratory
    - Providing template documentation
    - Training
6. Clear lines of responsibility and communication must be in place to allow review of concerns by the CTU and escalation of potential breaches to the CTU/sponsor.
7. Local procedures (CTU SOPs, laboratory manuals etc.) and agreements should define reporting requirements including laboratory quality assurance and approval processes.
8. Exploratory work may not be specified in the protocol, which may have limitations (such as a specific disease class or time frame). This work comes under the UK Policy framework for health and social care, where the research is part of an ethically approved study. CTUs should determine the level of oversight they require in this case.
9. The CTU must ensure that samples are only processed according to the consent provided and the ethical approval granted. This may be for use in another ethically approved study, transfer to a licensed tissue bank (*this transfer would be an appropriate activity to monitor to ensure all samples are reconciled),* or destruction, once the trial is complete.

6. Summary

1. The CTU must have confidence that the processing/analysis of clinical trial samples has been in accordance with the trial protocol, good clinical practice and applicable regulations and guidance.
2. The level of oversight will depend on how well the quality systems are established within the laboratory.
3. Established systems, such as those used to analyse routine clinical samples may only require a low level of oversight that can be directed to GCP specific requirements. This decision must be based on an appropriate risk assessment of the work requested and the supporting systems in place.
4. If a novel assay is being performed, or a new laboratory used, additional oversight must be considered.
5. Oversight may be focused at the start of the trial (ensuring quality systems are in place) with further action undertaken if concerns arise during the trial.
6. Some information may be gathered centrally by the CTU to identify concerns.
7. It is important to maintain good communication with the laboratory.
8. A clear understanding of the requirements for sample analysis and or processing and reporting must be in place.
9. It is recommended that laboratories have a senior member of staff with an understanding of research trial protocols and GCP.

Other relevant documents:

- UKCRC Guidance and Training Requirements for Laboratories Processing and or Analysing Research Samples
- UKCRC Flowchart for the Oversight of laboratories By CTUs
- UKCRC Self-Assessment Questionnaire for assessing regulatory compliance in laboratories that perform the storage and analysis or evaluation of research samples
- UKCRC Internal Audit Prioritisation Guidance

This guidance document has been developed by the UKCRC Registered CTUs QA sub-group:

Sara Yeats	Southampton Clinical Trials Unit
Carolyn Sexton	Cambridge Clinical Trials Unit
Roisin Beehag	CR UK & University College London Cancer Trials Centre
Sophie Perry	Institute of Cancer Research
Louise Swinburne	Newcastle Clinical Trials Unit, University of Newcastle

Fiona Parker	Oxford Clinical Trials Research Unit, University of Oxford
Helen Evans	Leeds Institute of Clinical Trials Research, University of Leeds
Lisa Flaherty	University of Liverpool
Joanna Black	Oxford Clinical Trials Research Unit, University of Oxford
Valerie Godfrey	Tayside Medical Science Centre, University of Dundee
Nicola Jenkins	Centre for Trials Research, University of Cardiff
Simon Kerridge	Oxford Primary Care and Vaccines Collaborative Clinical Trials Unit

Reviewed by

Jason Wakelin-Smith Expert GCP Inspector, Medicines and Healthcare products Regulatory Agency

References

Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples (Ref. EMA/INS/GCP/532137/2010, EMA, 2012)

Good Clinical Practice Guide (Chapter 13, MHRA, 2012)

Guideline on the Investigation of Bioequivalence (Ref. CPMP/EWP/QWP/1401/98, EMA 2010)

ICH Harmonised Guideline Bioanalytical Method Validation and Study Sample Analysis M10 Final version Adopted on 24 May 2022

Appendix 1 – An example of taking a risk-based approach when assessing questionnaire responses

Perspectives of Severity		Likelihood					Outcome		
		1	2	3	4	5	Score	Interpretation	Audit/ Inspection Schedule
GCP/business risk	Scientific/clinical impact	Nil/Negligible: Routine test, repetitive task qualified personnel GCP/CPAS	Possible: Routine test, (QMS not GCP/CPAS)	Expect several GCP breaches: Novel activity / activity occurs infrequently or changed recently / QMS GCP/CPAS	Frequent: Novel activity / activity occurs infrequently or changed recently / QMS not GCP/CPAS	Certain: Novel Activity/ New or No QC Process / Academic lab uncontrolled.	1 to 6	Low level of compliance risk	12 month review / annual report on trial progress as per communication plan?
Critical: Participant rights/safety & data integrity	Primary endpoint/crucial to trial clinical decision making/novel assay	5	10	15	20	25	8 to 15	Medium level of compliance risk	6 months update and self reporting of issues?
High	Secondary endpoint, potential direct clincial value	4	8	12	16	20	16 to 25	High level of compliance risk	Contact monthly
Moderate	other complex/high impact readout crucial to success of trial	3	6	9	12	15			
Minor	Exploratory, not validated, no direct clinical impact	2	4	6	8	10			
Low	Diagnostic standard or well validated research technique	1	2	3	4	5			