UKCRC Registered Clinical Trials Units

Guidance for CTUs on Assessing the Suitability of Laboratories Processing Research Samples

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This guidance document has been developed by the UKCRC Registered CTUs Laboratory work stream (as part of the Quality Assurance operational group) and provides general guidance to CTUs on appropriate levels of oversight required for laboratories processing research samples. The laboratory work stream comprises both QA representatives and laboratory leads and has been developing templates and guidance on CTU oversight of laboratories, laboratory staff training and CTU training for auditing laboratories.

Guidance on research training requirements for laboratories is available as a separate document.

Background

Laboratory sample analysis contributes significantly to research data, including important safety information and study outcomes. It is therefore essential that research samples, that is any sample collected as part of a research protocol, are processed in accordance with the study protocol, and in compliance with Good Clinical Practice[1] (GCP) and applicable regulations and associated guidance.

The processing of research samples in accordance with Good Clinical Practice is described in detail in a number of guidance documents. For the purposes of guidance for UKCRC CTUs, the EMA Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples (2012) and the MHRA Good Clinical Practice Guide, Chapter 13 (2012) have been used as the primary sources of information (if applicable, refer to guidance on processing research samples from other sources/countries e.g. for international trials). These documents describe the systems and procedures required to ensure patient safety is not compromised and that the resulting sample analysis can be relied upon when assessing the overall conclusions of the research study. Specifically, the guidance covers both where the laboratory work will be done (laboratory facilities, personnel, contractual arrangements, organisation roles and responsibilities, equipment, IT systems and quality management systems) and also how the sample will be processed (receipt, processing, reporting, method validation, sample and data storage, QA and QC processes and sample kits). GCP requires that records are retained to demonstrate the facilities and sample processing meet the requirements of the study protocol, therefore documentation for the various aspects of the guidance described above should be available for review by the CTU or sponsor.

1. The processing and analysis of research samples collected as part of clinical trials or other research studies must comply with Good Clinical Practice. Laboratories may also work to other guidelines such as Good Laboratory Practice (GLP), Good Clinical Laboratory Practice (GCLP) and ISO 15189:2012, however, when processing and analysing clinical research samples, it is GCP that applies.

Oversight Requirements

The sponsor/CTU must have confidence in the results generated from the research samples, just as it would require for any other type of study data. How this confidence is achieved will depend on the role of the sample in the protocol objectives and the extent of any pre-existing quality systems for sample management. For example, samples may:

- be collected and analysed as part of routine clinical care, but may also contribute to the study dataset,
- be collected and analysed for study objectives only,
- may only be prepared and stored before shipping to a specialist laboratory
- be analysed using a standard clinical assay in laboratory with a functional, audited quality system
- be analysed using an exploratory/experimental assay

These examples are not mutually exclusive, and the aim of this guidance document is, therefore, to outline measures that the CTU can implement to assure the quality of the protocol defined laboratory results.

Samples processed for research data but analysis is equivalent to clinical care

Many research samples will be processed by local pathology laboratories to determine eligibility, monitor ongoing safety or to identify study endpoints, using standard assays that are also used to analyse non-research samples, as part of routine clinical care.

CTUs should ensure that existing systems for the processing of these samples meet the requirements of the study protocol. This may include:

- Ensuring that the same procedures will be used for the research sample, as for samples being analysed as part of routine clinical care. Assay details should be included in laboratory agreements or study plans/manuals and both the CTU and laboratory should ensure that any updates to study plans/manuals are agreed and implemented when required.
- The laboratory is accredited (CPA, UKAS etc.) with no outstanding non-compliances that could affect the integrity and analysis of the research sample. Lack of or conditional accreditation may not prevent use of the laboratory, however, may prompt further review by the CTU. It should be noted that accreditation demonstrates that a laboratory has the necessary systems in place to ensure that clinical samples are processed to a minimum standard at the time of inspection. There may be additional requirements for research samples, and therefore it is not recommended that accreditation status alone is used as evidence of laboratory quality.
- The laboratory report contains confirmation of accreditation status, reference ranges and identifies abnormal results. There should be a clear process to demonstrate approval of the provided laboratory report by a suitably qualified person (e.g. laboratory clinician, experienced Biomedical Scientist).
- There are approved, written procedures in place for processes that are specific both to research samples (e.g. sample identification and labelling, reporting of results and

sample storage) and for those that are used to process all samples (receipt, storage, analysis, reporting etc.).
- There is a senior laboratory contact with knowledge of the CTU's requirements for research sample processing and appropriate GCP training. The contact should have oversight of the work to be conducted and the ability to implement actions as required to ensure the appropriate management of research samples.

It is recommended that a review of the services and systems provided by laboratories processing such samples is performed at least once for each laboratory. A risk based approach may be taken for subsequent reviews if conducted (e.g. focusing on changes to laboratory systems, new protocol requirements or causes for concern). As a minimum, the laboratory should be able to comply with those aspects of the regulations and guidelines (see references) that apply to the study protocols used. Review may be performed by requesting each laboratory to complete a self-assessment questionnaire to provide the CTU with general information on the laboratory's facilities and quality systems. A template questionnaire has been developed by the laboratory work stream and is available at www.ukcrc-ctu.org.uk.

Samples processed only for research data, with no equivalent clinical care pathway

Where research samples are contributing to study endpoints and the assays performed are specific to the research environment (i.e. typically in academic or central laboratories and not also used as a routine clinical test), additional oversight to that described above will be required. This may include:

- Ensuring that the processing laboratory has a quality systems in place sufficient to meet the requirements of the protocol and intended activities. As described above, these are detailed in the EMA and MHRA guidance documents, but should include systems for document control, training, data handling, computer system validation (if applicable) and equipment maintenance. A risk based approach may be taken when considering how these systems are reviewed.
    - For established laboratories, where no significant issues have been raised previously, completion and review of a self-assessment questionnaire may be sufficient.
    - For new laboratories, or those where previous concerns have been identified, a laboratory GCP audit may need to be commissioned unless information can be obtained from previous audits which can be used to mitigate against potential concerns.
- Ensuring that specific approved procedures are in place for the processing of the research sample (including conducting the assay) and that training is provided in these procedures.
- Ensuring that appropriate, documented validation of the assay(s) and associated key items of equipment exists or will be carried out prior to sample analysis.
- Where available, the assay should be subject to internal or external QC and/or QA processes, ideally as part of a national EQA (External Quality Assurance) program or using commercial standards.
- There should be robust processes for the acquisition, review and transfer of analytical data and associated metadata (audit trails, supporting data and documentation).

- Consideration of risk based monitoring of the study samples, including review of processes and documentation listed above.

Exploratory Assays

The study protocol may include the processing of research samples for exploratory objectives that do not have a clear definition. It may not be possible to ensure that these objectives receive specific oversight. It is still important, however, to ensure that the samples are stored and analysed in accordance with the study protocol and the informed consent given, and that systems are in place to assure the integrity of the data. This can be achieved by:

- Ensuring quality systems are in place, so that aspects of the sample process that can be standardised are assured (e.g. equipment maintenance, training, use of QC samples, data management). This may form part of the general oversight of the laboratory as described above.
- Though the definition of the type of exploratory work may not be specific in the protocol, it may have limitations (such as a specific disease class or time frame). The CTU may need to ensure that these limitations are adhered to, and, that samples are not processed for exploratory work after the ethical approval for the study samples has expired (samples may be transferred to a tissue bank at the end of the study and this transfer would be an appropriate activity to review).

Additional Oversight

If concerns are identified that may impact on the outcome of the research study (such as poorly labelled samples identified by the laboratory or delays in expedited reporting), or that may constitute a serious breach (as defined by current clinical trials regulations), consideration must be given to escalating the level of oversight previously undertaken. This may include commissioning a GCP laboratory audit and the implementation of more detailed GCP monitoring of the research samples. In all cases, clear lines of responsibility and communication must be in place to allow review of concerns and potential breaches by the CTU/sponsor. Local procedures (CTU SOPs, laboratory manuals etc.) and agreements should define reporting requirements.

Summary

The CTU must have confidence that the processing of research samples has been in accordance with the study protocol, good clinical practice and applicable regulations and guidance. The level of oversight will depend on the role of the research sample within the protocol and on how well the quality systems are established within the laboratory. Established systems, such as those used to process routine clinical samples may only require a low level of oversight that can be directed to GCP specific requirements but this decision must be based on the appropriate risk assessment of the work to be undertaken and the supporting systems in place. If a novel assay is being performed, or a new laboratory used, then additional oversight must be considered.

Oversight may be focused at the start of the study (ensuring quality systems are in place) with further action undertaken if concerns arise during the study. Some information may be gathered centrally by the CTU to identify concerns. These may include delays in result reporting, inadequate reporting of abnormal results, or high levels of rejected samples and poor follow up of concerns raised.

It is important to maintain good communication with the laboratory. A clear understanding of the requirements for sample processing and reporting must be in place, and it is recommended that laboratories have a senior member of staff with an understanding of the laboratory requirements of the study protocol and of GCP.

A flowchart has also been developed by the laboratory work stream which provides an overview of the oversight requirements described above.

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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)