Standard Operating Procedure:

Laboratory Analysis

# Purpose

The purpose of this standard operating procedure (SOP) is to describe procedures which will ensure that the analysis or evaluation of clinical trial samples are performed to Good Clinical Practice (GCP) in the laboratory standard ensuring that patient safety is not compromised, that data is reliable and accurately reported, and in accordance with applicable law, and with established policies at the University of Birmingham (UoB).

# Scope

The SOP is applicable to all UoB staff and laboratories performing analyses that contribute to the (primary, secondary and/or exploratory) endpoints of all clinical trials of investigational medicinal products (CTIMPs) whether these are sponsored by the UoB or sponsored/co-sponsored by another institution.

# Implementation plan

This SOP will be implemented in line with this document’s effective date.

# Stakeholders

* Laboratory academic lead (LAL)

# Background and rationale

To ensure that samples are being analysed correctly, careful consideration needs to be given to the whole process of analysis; particularly regarding selecting the correct assay, confirming it is fit for use and that acceptance criteria are clear and defined. Assay validation is key to this process, however there will be exceptional circumstances where the validation of the method is one of the clinical trial’s objectives.

The use of computerised systems to support clinical trials, including data collection, treatment allocation and trial management, is becoming increasingly common. Data integrity, reliability and robustness therefore also depends on the computer systems being validated and deemed fit for purpose.

# Procedure

## Assay validation

1. The LAL (or delegate) will create assay validation plans for each assay that contributes to the trial. See quality control document (QCD) Assay Validation (UoB-CRL-QCD-020) and the QCD Assay Validation Flow Cytometry (UoB-CRL-QCD-026).
2. The LAL (or delegate) will implement the validation plan and produce a validation report; see the QCD Assay Validation (UoB-CRL-QCD-020). It will be documented that an assay is fit for use before the assay is used to analyse clinical trial samples.

* Cross-validation will be required if new batches of control/reagents become necessary.

## Computerised systems’ validation

1. Where computerised systems are used to generate trial data the LAL (or delegate) will develop a validation plan for each computerised system to demonstrate that each computer system is fit for its intended purpose and can produce reliable and reproducible data. See the QCD Computerised System Validation Plan (UoB-CRL-QCD-021). The validation plan will include (but not be limited to):

* components of the computerised system (the hardware and software)
* any limitations of the system
* where raw data is generated, stored or manipulated.

1. The LAL (or delegate) will implement the computerised-system validation plan and produce a computerised-system validation report. See the QCD Computerised System Validation Plan (UoB-CRL-QCD-021

* The LAL (or delegate) will review the computerised-system validation report to determine if the computerised system is fit for use.
* The LAL (or delegate) will document that the computerised system is fit for use before it is used in the generation of clinical trial data.
* Where further functionality is required of the computerised system (beyond the scope of the original validation) the LAL (or delegate) will implement further validation.

1. The LAL (or delegate) will confirm that following changes to the computerised system, such as upgrades or the installation of “patches”, the system remains fit for purpose.

* A risk-assessment will be performed by a suitable qualified person to determine the level of re-validation required and this process will be documented.
* Where re-validation has confirmed that the computerised system is fit for purpose it will be recorded by the LAL (or delegate).

1. The LAL (or delegate) will perform a retrospective validation of computerised systems that are already in use (but were not subject to a documented validation plan prior to their use) and document the process.
2. Where a computer system’s validation has been performed by the computer system’s vendor, the LAL (or delegate) will ensure that the following are documented in a written agreement or contract. See the QCD Laboratory Contracts and Agreements Checklist (UoB-CRL-QCD-004) and*the* Compliance Review SOP (UoB-CPR-SOP-001) for more information.

* The arrangements between the vendor and Sponsor regarding validation.
* Provisions for access to validation/test documentation.
* Provision for the Sponsor and/or regulatory authorities to perform audits and/or inspections of the vendor.

## Analytical plan

1. The LAL (or delegate) will create an analytical plan detailing how to conduct each assay, unless sufficient detail is present in the clinical trial protocol. See the QCD Analytical Plan (UoB-CRL-QCD-022). The analytical plan will include those aspects listed below.

* Contain sufficient detail to allow an analyst to perform their duties and to allow the reconstruction of the assay performed.
* Only include work covered by the clinical trial protocol.
* Detail the appropriate quality control (QC) samples/experimental controls to be included, the equipment and reagents to be used for each assay and the type and number of samples to be analysed.
* Where source data will be stored, including back-up arrangements for digital data.

1. The LAL (or delegate) will capture the need to record the date the analysis was performed, the identity of the analyst, the specific pieces of equipment used, batch/lot numbers of reagents and that all key steps in the analysis were followed.

* This may be achieved, for example, by the creation and use of trial specific work sheets.

1. The LAL (or delegate) will define (in the analytical plan) when repeat analysis is acceptable. See the QCD Analytical Plan (UoB-CRL-QCD-022). The procedure will include (but not be limited to):

* the rationale for performing any repeat analysis
* the identity of reanalysed samples
* the need to justify which data points are selected and reported
* the need to document the steps followed for each incidence of repeat analysis.

1. The LAL (or delegate) will check that the analytical plan does not contradict the clinical trial protocol, any contracts or memoranda of understanding. See the QCD Analytical Plan (UoB-CRL-QCD-022). Evidence of these checks being performed will be retained.

## Data Integrity and quality control

1. The LAL (or delegate) will introduce methods to ensure a full audit trail is achievable.

* Where computer systems do not allow for attributable log-ins other methods will be employed to capture user information; for example, a version-controlled paper-based method may be employed to capture user activity.
* Where errors have occurred and changes need to be made to data, they will be made in such a way as to not obscure the original, the change will be initialled and dated by the individual making the change. Correction fluid will not be used.

1. The LAL (or delegate) will introduce methods to maintain the integrity of all analytical standards and reagents which will include those aspects listed below.

* Storing all analytical standards and reagents at the correct temperature and ensuring temperature is monitored, as described in the Laboratory Facilities SOP (UoB-CRL-SOP-002).
* Recording batch numbers of all analytical standards and reagents used throughout the trial.

1. The LAL (or delegate) will assess the need to quality check data at any step that poses a particular risk to data integrity, e.g. transfer, copying, and transcription. See the Data Management SOP (UoB-CRT-DMA-SOP-001).

## Data reporting

1. The LAL (or delegate) will ensure that data has been quality checked before release and that the process has been documented. See the QCD *Review and Release of Results (UoB-CRL-QCD-023)*.
2. The LAL (or delegate) will report data in the way that has been agreed. See the Laboratory Set-up and Management SOP (UoB-CRL-SOP-001).

* Where appropriate this will be included in contracts or memoranda of understanding between the laboratory and CI (where UoB sponsored) or sponsor (where externally sponsored). See the Laboratory Set-up and Management SOP (UoB-CRL-SOP-001).
* Careful consideration should be given to the method of data transfer. Data encryption should be used where any personal identifiers or confidential information are included in the transferred data set.

1. The LAL (or delegate) will appropriately file all data sets required to allow reconstruction of the interim and final analyses and subsequent reporting, and subsequent archiving. See the Archiving SOP (UoB-ARC-SOP-001) and the Laboratory Set Up and Management SOP (UoB-CRL-SOP-001).

# List of expected outputs

* Assay validation plans for each assay. See the QCD Assay Validation (UoB-CRL-QCD-020).
* Evidence of assay validations being performed and the production of assay validation reports. See the QCD Assay Validation (UoB-CRL-QCD-020).
* Evidence that assay validation reports for each assay have been reviewed and a decision made as to whether the assay is fit for use before any clinical trial analysis has occurred. See the QCD Assay Validation (UoB-CRL-QCD-020).

Evidence of cross validation where necessary. See the QCD Assay Validation (UoB-CRL-QCD-020).

* Computerised system validation plans for each computerised system. See the QCD Computerised System Validation Plan (UoB-CRL-QCD-021).
* Evidence of computerised system validations being performed and the production of computerised system validation reports. See the QCD Computerised System Validation Plan (UoB-CRL-QCD-021).
* Evidence that computerised system validation reports for each computerised system have been reviewed and a decision made as to whether the computerised system is fit for use before being used in the clinical trial. See the QCD Computerised System Validation Plan (UoB-CRL-QCD-021).
* Evidence of re-validation of computerised systems where further functionality is required of the computerised system. See the QCD Computerised System Validation Plan (UoB-CRL-QCD-021).
* Evidence of re-validation of computerised systems following the installation of ‘patches’ or upgrades. See the QCD Computerised System Validation Plan (UoB-CRL-QCD-021).
* Evidence of retrospective validation of computerised systems already in use that were not subject to initial validation. See the QCD Computerised System Validation Plan (UoB-CRL-QCD-021).
* A documented procedure to be followed in the event of repeat analysis being necessary and evidence of its implementation, where necessary. See the QCD Analytical Plan (UoB-CRL-QCD-022).
* Analytical plans for all assays and evidence of their implementation. See the QCD Analytical Plan (UoB-CRL-QCD-022).
* Evidence that Analytical Plans have been checked against the clinical trial protocol and any contracts or agreements. See the QCD Analytical Plan (UoB-CRL-QCD-022).
* A complete audit trail for all data produced.
* Evidence that the data is being reported as agreed. See the Laboratory Set Up and Management SOP (UoB-CRL-SOP-001).
* Evidence that any reported data has been quality checked. See the QCD *Review and Release of Results (UoB-CRL-QCD-023)* and*the* Data Management SOP (UoB-CRT-DMA-SOP-001).
* Data sets required to allow reconstruction of the interim and final analyses and subsequent reporting are appropriately filed and subsequently archived. See the Archiving SOP (UoB-ARC-SOP-001) and the Laboratory Set Up and Management SOP (UoB-CRL-SOP-001).

# Related documents

* UoB-ARC-SOP-001 Archiving
* UoB-CPR-SOP-001 Compliance Review
* UoB-CRL-QCD-004 Laboratory Contracts and Agreements Checklist
* UoB-CRL-QCD-020 Assay Validation
* UoB-CRL-QCD-021 Computerised System Validation Plan
* UoB-CRL-QCD-022 Analytical Plan
* UoB-CRL-QCD-023 Review and Release of Results
* UoB-CRL-QCD-026 Assay Validation Flow Cytometry *(under development)*
* UoB-CRL-SOP-001 Laboratory Set Up and Management
* UoB-CRL-SOP-002 Laboratory Facilities
* UoB-CRL-SOP-003 Sample Management
* UoB-CRL-SOP-005 Reportable Issues
* UoB-CRL-SOP-006 External Laboratory Set-up and Oversight
* UoB-CRT-DMA-SOP-001 Data Management

UoB QMS documents can be found on the [CRCT website](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/index.aspx). Internal work instructions can be obtained from the CRCT ([crct@contacts.bham.ac.uk](mailto:crct@contacts.bham.ac.uk)) and/or from the RGT ([researchgovernance@contacts.bham.ac.uk](mailto:researchgovernance@contacts.bham.ac.uk)).

# References and frameworks

* ‘GXP’ Data Integrity Guidance and Definitions (2018), Medicines & Healthcare products Regulatory Agency (MHRA):

<https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf>

* Reflection paper for laboratories that perform the analyses or evaluation of clinical trial samples (2012), European Medical Agency: [www.ema.europa.eu/docs/en\_GB/document\_library/Regulatory\_and\_procedural\_guideline/2012/05/WC500127124.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127124.pdf)
* The Human Tissue Act (2004): <http://www.legislation.gov.uk/ukpga/2004/30/contents>
* The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments: <http://www.legislation.gov.uk/uksi/2004/1031/contents/made>

# Abbreviations and definitions

| Term | Description |
| --- | --- |
| Analyst | The person(s) who performs the analysis or evaluation of clinical trial samples. |
| Analytical plan | This is a written plan that will include the purpose of the analysis and the methodology that will be used to perform the analysis. Also described as a “work instruction” or “analytical protocol” in the *Reflection paper for laboratories that perform the analyses or evaluation of clinical trial samples (2012), European Medical Agency*. It is expected that this role will be assigned to the principal investigator of the laboratory and that they will in turn delegate some of the responsibilities to other members of the laboratory’s team. |
| Assay | An assay is an investigative procedure in a laboratory, for qualitatively assessing or quantitatively measuring the presence, amount, or functional activity of a target entity (for example, a hormone, gene or metabolite). |
| Assay validation | Assay validation is a documented process that demonstrates that an assay is suitable for its intended purpose. |
| Computerised system validation | The process of documenting that a computer system meets a set of defined system requirements. |
| Laboratory | A facility that conducts manipulation, analysis or evaluation of samples collected as part of a clinical trial; such analysis or evaluation may include the generation of pharmacokinetic or pharmacodynamic data, safety data, primary efficacy data, histopathology data or data used to support any other stated primary, secondary or exploratory end point. |
| Laboratory academic lead (LAL) | At the University of Birmingham the LAL takes on the responsibility of the ‘Lab Manager’ and the ‘Analytical Manager’ as described in the *Reflection paper for laboratories that perform the analyses or evaluation of clinical trial samples (2012), European Medical Agency*. It is expected that this role will be assigned to the principal investigator of the laboratory and that they will in turn delegate some of the duties to other members of the laboratory team. |

See also the [Glossary of Terms](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/Glossary-of-Terms.aspx).