Standard Operating Procedure:

Reportable Issues

# Purpose:

The purpose of this standard operating procedure (SOP) is to describe the process for ensuring any issues that may impact on participant safety or data integrity are reported without delay. These may include, but are not limited to, the reporting of unexpected or out-of-range results and significant deviations from the protocol or analytical plan.

# Scope:

The SOP is applicable to all University of Birmingham (UoB) staff and laboratories performing analyses that contribute to the (primary, secondary and/or exploratory) endpoints of 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:

The analysis of CTIMP samples can provide vital information that informs the assessment of new drugs and treatments, and it can also provide valuable information relating to a participant’s health. Where there are deviations in laboratory procedures or equipment failures (such as freezers used for sample storage) these may directly impact on the integrity of the clinical trial samples or subsequent trial data. Where these issues are not recognised and reported, they could affect both the participants enrolled on the trial and the trial conclusions which drive future clinical care.

The reporting of anomalous or out-of-range results beyond the scope of experimental analyses must also be considered. For example, unexpected values associated with pharmacokinetic analysis may indicate incorrect dosing or a patient’s inability to metabolise an investigational medicinal product, which may have serious safety implications for the patient.

The laboratory must plan to address these situations in its documented procedures. Trial-specific reportable issues and a process for reporting them should be defined, so that in the event of their occurrence they can be dealt with swiftly to minimise the risks to both participant and data.

# Procedure:

1. The LAL (or delegate) will create a documented procedure detailing what constitutes a reportable issue (see UoB-CRL-QCD-024 Reportable Issues). Reportable issues are those issues that may impact on participant safety or data integrity and can include (but is not limited to) those listed below.

* Anomalous or out-of-range results that are of clinical significance to the patient or indicate incorrect dosing.
* Deviations from the analytical plan, clinical trial protocol and/or contract/agreement which could impact on the integrity of trial samples or data.
* Equipment failure, to include refrigerators or freezers where samples are stored, and equipment used in the analysis of samples which could impact on the integrity of trial samples or data.
* Extra analyses or evaluations requested based on urgent clinical reasons.

1. The LAL (or delegate) will create a documented procedure detailing the steps to be taken following detection and up-escalation (where appropriate) of a reportable issue (see UoB-CRL-QCD-024 Reportable Issues). This will include (but will not be limited to) those aspects listed below.

* Who will assess the impact of the reportable issue.
* A communication plan to ensure laboratory staff know whom to contact when reporting reportable issues to the sponsor’s representative (if externally sponsored) or trial team (or their representative) if UoB sponsored.
* Where there is potential to impact on the integrity or reliability of the trial data, participant confidentiality, consent or safety, the issue must be reported immediately to the sponsor or their representative and, if appropriate, to the recruiting investigator.
* Where the reportable issue also constitutes a ‘serious breach’ see also UoB-DBS-SOP-001 Deviations and Serious Breach Reporting.

1. The LAL (or delegate) will follow the documented procedure for issue reporting where a reportable issue is noted and retain all documented evidence and relevant correspondence (see UoB-CRL-QCD-024 Reportable Issues).

# List of expected outputs:

* A documented procedure defining what constitutes a reportable issue (see UoB-CRL-QCD-024 Reportable Issues).
* A documented procedure defining the procedures to be followed following the occurrence of a reportable issue (see UoB-CRL-QCD-024 Reportable Issues).
* Evidence of the laboratory’s procedures being followed, where reportable issues have arisen (see UoB-CRL-QCD-024 Reportable Issues).

# Related documents:

* UoB-CRL-QCD-024 Reportable Issues
* UoB-CRL-SOP-001 Laboratory Set Up and Management
* UoB-CRL-SOP-002 Laboratory Facilities
* UoB-CRL-SOP-003 Sample Management
* UoB-CRL-SOP-004 Laboratory Analysis
* UoB-CRL-SOP-006 External Laboratory Set-up and Oversight
* UoB-DSB-SOP-001 Deviations and Serious Breach Reporting

Note the UoB QMS documents can be found on the [CRCT website](mailto:CRCT%20website). 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 |
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| CTIMP | Clinical trial of an investigational medicinal product. |
| 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) | Referred to as ‘Laboratory Manager’ and ‘Analytical Manager’ in the *Reflection paper for laboratories that perform the analyses or evaluation of clinical trial samples (2012), European Medical Agency*.  The individual(s) having the authority and formal responsibility for the organisation and functioning of a laboratory where work that forms part of a clinical trial is conducted.  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’s team. |
| Reportable issue | Either a deviation from the laboratory’s documented policies, work instructions, clinical trial protocol, contract or any comparable documents or equipment failures (for example, refrigerators, freezers or centrifuges), which may compromise the integrity of the sample or the quality of the data. |
| Serious breach | A 'serious breach' is a breach that is likely to affect to a significant degree: the safety or physical or mental integrity of the participants; or the scientific value of the trial. |
| SOP | Standard operating procedure. |
| Trial team | Chief investigator (CI) and their team of individuals taking on CI duties relating to the trial management. Individuals may include co-investigator, trial coordinator, trial administrator and/or data manager. |
| UoB | University of Birmingham. |

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