MRC Clinical Trials Unit

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UCL

SERIOUS BREACH, RESEARCH FRAUD OR FINANCIAL IRREGULARITY

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The following symbols may be used in this SOP:

Indicates a link to a related document

Indicates instructions to document trial-specific processes elsewhere

Throughout this document 'MRC CTU' will be used to refer to the MRC Clinical Trials Unit at UCL (MRC CTU at UCL).

1 BACKGROUND AND RATIONALE

1.1 DEFINITIONS

Research Fraud - Intentional distortion of the research process by fabrication of data, text, hypothesis, or methods from another researcher's manuscript form or publication; or distortion of the research process in other ways.

Financial irregularity – is taken to include (but is not limited to)

Fraud
Intentional deception with intent to make a gain or to cause a loss, or to expose another to the risk of loss. It can be perpetrated for the benefit of or the detriment to UCL and can be committed by persons outside as well as inside UCL.

The Fraud Act 2006 provides for a general criminal offence of fraud, with three ways of committing it: by false representation (with the intention of making a gain or causing a loss or risk to another); by failing to disclose information to another person where there is a legal duty to disclose such information; and by dishonestly abusing one's position. The Act also makes it an offence for any person, by any dishonest act, to obtain services for which payment is required, with the intent to avoid payment.

Corruption
The offering, giving, soliciting, or acceptance of an inducement or reward which may influence the action of any person.

Misconduct - fabrication, falsification, plagiarism or deception in proposing, carrying out or reporting results of research and deliberate, dangerous or negligent deviations from accepted practice in carrying out research. It includes failure to follow established protocols if this failure results in unreasonable risk or harm to humans, other vertebrates or the environment and facilitating of misconduct in research by collusion in, or concealment of, such actions by other. It does not include honest error or honest differences in the design, execution, interpretation or judgement in evaluating research methods or results or misconduct (including gross misconduct) unrelated to the research process.

Serious breach - For the purpose of this SOP the definition of a serious breach is that given in the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument (SI) 2004/1031], as amended by SI 2006/1928. It is also defined in the EU Clinical trial regulation 536/2014.

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice in connection with that trial which is likely to affect to a significant degree

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

1.2 LEGAL REQUIREMENTS

It is a legal requirement[1] in the UK for a sponsor (or sponsor's representative) to notify the regulatory authority in writing of any serious breaches of Good Clinical Practice (GCP) and/or the Protocol within 7 days of becoming aware of the breach.

For further details on the notification process of CTIMPS and non CTIMPS please refer to current MHRA and HRA webpages.

The consequences of research fraud or misconduct on human health and clinical practice can be very great and every effort should be taken to avoid its occurrence in research.

Examples of types of fraud in a clinical trial or study include:

- Deliberately attempting to deceive when making a research proposal
- Fabricated patient(s)
- Patient exists, but data attributed are fabricated
- Fabricated data elements
- Fabricated qualifications
- Financial irregularities

Although not a legal requirement under Regulation 29A, the Medicines for Healthcare Regulatory Agency (MHRA) GCP Inspectorate encourages the reporting of all confirmed instances of clinical research fraud occurring at sites in the UK, which the Sponsor becomes aware of. The reason for this is that, although fraud at one particular site may not have a significant impact on scientific value or subject integrity for that particular trial or study, the MHRA would wish to assess the impact on other studies or subjects/patients at that site.

If clinical research fraud is identified at a non-UK site, for a study that is also being conducted in the UK, a serious breach notification should be submitted to MHRA if the fraud is likely to have a significant impact on the integrity of participants in the UK or on the overall scientific value of the trial/study. A site refers to any site involved in the trial or study, for example, a CRO or other contracted organisation and not solely to investigator sites (such as laboratories analysing samples from UK patients/subjects).

[1] Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928, contains a requirement for the notification of "serious breaches" of GCP or the trial protocol.

2 PURPOSE

The purpose of this SOP is:

- To outline the procedure to be followed by MRC CTU staff if a potential breach of the study protocol or the principles of GCP is suspected or has been identified.
- Define the roles and responsibilities of the Trial/Study team for identifying, assessing and reporting potential breaches to the MHRA, including the handling of misconduct and fraud within trials coordinated by the MRC CTU;
- Describe the responsibilities of the Research Governance Committee (RGC) in relation to the investigation of breaches that might be considered serious and the oversight of any remedial actions.
- Outline the procedure for reporting any suspected serious breach, research fraud or financial irregularity to the sponsor and regulatory authorities.

3 RESPONSIBILITY AND ROLES

The following table lists the roles relevant to this SOP and a brief summary of their responsibilities. Full details of responsilbity is listed in the main text of the SOP.

This SOP will be circulated for Read and Understand to all appropriate roles identified in the training matrix.

ROLE	RESPONSIBILITIES
All MRC CTU Staff	▪ All staff are responsible for reporting observations of suspected research misconduct or fraud and for ensuring onward reporting in accordance with this SOP
Trial Management Team (TMT)	▪ Responsible for reporting potential serious breaches, fraud/misconduct and other important issues to the RGC. ▪ Assessment of extent and impact of the issues identified and whether immediate remedial action is required. ▪ Informing relevant stakeholders of any serious or potential breaches ▪ Development, implementation and documentation of Corrective and Preventative Action plans (CAPA) ▪ Reporting serious and potential serious breaches to the REC and regulators. ▪ Providing RGC or RGC2 with follow-up information on issues, until satisfactory resolution.
Research Governance Committee (RGC) Secretariat	▪ Acknowledging notification forms submitted to the RGC ▪ Forwarding notifications to RGC members
Research Governance Committee (RGC) Chair/Deputy	▪ Initial review of notifications submitted to RGC ▪ Convening meeting (or email discussion) of RGC members to discuss notifications
Research Governance Committee (RGC)	▪ Initial review of notifications submitted to RGC ▪ Oversight of investigations to determine whether or not the breach fulfills criteria for onward reporting as a potential serious breach ▪ Overall responsibility for determining if an issue is a potential Serious Breach and what onward reporting is required. ▪ Ensuring that any regulatory reporting timelines are met for events deemed serious breaches. ▪ Responsible for ensuring that relevant organisations and study sponsors are notified of serious breaches. ▪ Follow-up of CAPAs
Research Governance Implementation Group (RGC2)	▪ Responsible for taking forward investigations on wider implications of reported serious breaches ▪ Work with the RGC to disseminate information widely and develop necessary action plans for unit-wide issues. ▪ Follow-up of CAPAs

4 PROCEDURES

- If a member of staff suspects that something has occurred in a study that consitutes a important/systematic breach of the protocol or GCP, they should bring it to the attention of senior staff within **one business day**.

  This would normally be the relevant Project Lead and/or Clinical Project Manager but where that is not practical or appropriate, it should be brought to the attention of the relevant Programme Leader, Head of Trial and Study Management, ICTM r Director. The Chief Investigator should also be informed.

- If there is any possibility that a serious breach of GCP or the protocol has taken place it must be referred to the RGC within **one business day**. mrcctu.rgc_secretary@ucl.ac.uk

- If there is any possibility that there is evidence of fraud/misconduct it must be referred within **one business day** to the RGC. This may include financial fraud identified by ICTM Finance Staff.

Notifications should be submitted using the **Notification to RGC of Possible Serious Breach Form** which should be completed as far as possible and sent by email to the RGC Secretariat with a copy to the RGC group email address.

Complete the **Notification to RGC of Possible Serious Breach Form** available on SOPbox

In parallel the TMT should make an immediate assessment of the extent and impact of the issue and decide whether any immediate action should be taken i.e. an Urgent Safety measure or temporary halt in recruitment. They should assess whether any immediate actions to safeguard participants at other sites are required and take the necessary action.

For example, if the breach resulted from misinterpretation of the protocol leading to an error with the dose of IMP administered to the participants, it should be clarified with all sites immediately.

For further details on how to implement an Urgent Safety Measure please refer to **Urgent Safety Measures SOP**

For further details on how to implement a temporary halt or unplanned cease to recruitment please refer to **Trial Closure and Reporting SOP**

4.1 RECOGNISING POTENTIAL SERIOUS BREACHES

The TMT should take in to account the following when determining if an issue may be a potential Serious Breach and therefore subject to expedited reporting to RGC.

Any serious breach of:

a) The conditions and principles of good clinical practice in connection with that trial or study (as defined in UK legislation); or

b) The protocol relating to that trial or study, as amended from time to time in accordance with regulations 22 to 25[2].

For the purposes of the regulation, a "serious breach" is a breach which is likely to affect to a **significant** degree:

a) The safety or physical or mental integrity of the subjects of the trial/study (this should be relevant to trial/study subjects in the UK); or

b) The scientific value of the trial/study.

   For example, persistent or systematic non-compliance with GCP or the protocol e.g., widespread and uncontrolled use of protocol waivers affecting eligibility criteria, which leads to harm to trial subjects in the UK or which has a significant impact on the scientific value of the trial

The judgement on whether a breach is likely to have a significant impact on the scientific value of the trial or study depends on a variety of factors, for example, the design of the trial or study, the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, the impact of excluding the data from the analysis etc.

The RGC maintain overall responsibility for determining if an incident is a potential Serious Breach and what onward reporting is required and therefore if in doubt the incident should be referred to the RGC immediately

4.1.1 STUDIES WITH UK AND NON-UK SITES

In studies with UK and International sites a serious breach occurring in a non-UK site should be reported to the MHRA if it is likely to have a significant impact on the integrity of the participants in the UK.

For example, a serious breach is identified at an investigator site in Mexico. The breach has a significant impact on the safety of trial subjects at the Mexican site and is likely to have a significant impact on the safety of trial subjects in the UK. The cause of the breach is such that the breach may occur at other trial sites, e.g., death of a subject due to incorrect administration of IMP resulting from erroneous reconstitution instructions in the protocol.

[2] The Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument (SI) 2004/1031], as amended by SI 2006/1928

4.2 RECOGNISING POTENTIAL FRAUD

The oversight of clinical trial conduct and central monitoring of study data by MRC CTU staff when data are received, checked and entered on to the database, and by statisticians at the time of analyses, enables staff to look for any signs of potential fraudulent data within a trial or study. The threshold of acceptability will vary between trials or studies.

Examples of potential concern may include:

- Unusual patterns of data collected e.g., Out of range data items, none/little variability on repeated measures variables
- Inability to confirm patient existence e.g., unable to trace via NHS Digital flagging.
- Financial irregularities detected in expense claims

Where a case of potential fraud in suspected, this should be reported to the RGC in the same timelines as described below.

4.3 RESEARCH GOVERNANCE COMMITTEE (RGC)

- On receipt of a completed notification form the RGC Secretariat will acknowledge the notification and forward all information to RGC committee members **within 2 business day**.

- The RGC Chair/delegate will review and determine if the report warrants immediate dicussion (i.e potential serious breach). If so the RGC Chair/or deputy will convene a meeting or email discussion with members of the committee to review the notification and determine whether the issue fulfils criteria for onward reporting as a potential serious breach within **2 business days**.

The RGC will consider the possible impact of the breach/misconduct/fraud on:

a) the safety or physical or mental integrity of the study participants, and

b) the scientific value of the study.

Investigation of the issue may be required to determine whether or not it meets the criteria for onward reporting as a potential serious breach. The RGC will oversee the investigation and will nominate a senior member of staff to lead it and an RGC contact for the investigation.

The RGC have guidelines in place to ensure review of potential breaches is performed in a uniform way and these guidelines are outlined in the RGC charter.

The RGC will ensure that the TMT inform any relevant organisations of any serious breach. Depending on the nature of the event and the specifics of the study, these may include, but not be limited to:

- The Sponsor
- UCL (when UCL is sponsor) – via the UCL Sponsor Oversight Committee quarterly
- Competent Authority (MHRA in UK)
- Research Ethics Committee (REC)
- Organisation responsible for a clinical site (e.g., the R&D Department in the Trust) and the site PI

- The employer of the person suspected of any misconduct
- Funder
- Trial Steering Committee

The RGC (via RGC Implementation Group (RGC2)) should ensure that issues that may be relevant to other studies that emerge from review of potential serious breach reports are communicated to staff groups within the MRC CTU at UCL and ICTM. This will allow other trials to assess whether their systems and process are adequate to mitigate the risk of similar breaches. RGC2 will be responsible for taking forward investigations on wider implications of reported serious breaches.

4.4 NOTIFICATION TO REGULATORY AUTHORITIES AND RESEARCH ETHICS COMMITTEES

4.4.1 STUDIES WITHIN THE SCOPE OF THE SI

If the study concerned is within the scope of the SI and if, after preliminary investigation, the issue is deemed to be a potential serious breach, it must be reported to the MHRA and Research Ethics Committee (REC) within 7 days of when the RGC has come to the view that it is a potential serious breach (even if not yet fully investigated).

Notification of the competent authority and REC should not be delayed pending detailed investigation of the event, rather investigation and notification of the relevant organisations should be concurrent.

The notification should follow the instructions provided on the MHRA and HRA websites.

For notifications to MHRA & REC use the **Notification of serious breaches of GCP or trial protocol form** available from the MHRA website.

For further details on the notification process of CTIMPS and non-CTIMPS please see current MHRA and HRA webpages.

4.4.2 STUDIES OUTSIDE THE SCOPE OF THE SI

If the study concerned is NOT within the scope of the SI (e.g. non-CTIMPs or studies conducted wholly outside of the UK) and if, after preliminary investigation, the issue is deemed to be a potential serious breach (according to the SI definition); it should be reported to the National Research Ethics Committee (REC).

For notification of serious breaches use the **Notification of serious breach form to REC (Non-CTIMP/Non-UK) form** available in SOPbox.

4.4.3 STUDIES WHERE UCL ARE NOT SPONSOR

Where MRC/UCL are not the Sponsor of the study/trial a Sponsor may have separate processes for notification in place that need to be acknowledged. The RGC and TMT will make sure that the Sponsor is informed of the potential breach and their responsibility to inform the regulatory authorities. A copy of the Sponsor's letter to the regulatory authorities will be requested.

4.5 CORRECTIVE AND PREVENTIVE ACTIONS

For every potential breach of the protocol or GCP reported to RGC, the Trial Management Group should develop, implement and document a corrective and preventive action plan (CAPA). For any breach that is potentially serious, the plan should be approved by the RGC, either by email or at the next meeting, and noted in the minutes of the RGC meeting. This does not preclude the TMT taking

immediate actions to correct the problem. CAPA will be followed-up by RGC 2 /RGC until completion.

Please refer to the **Template Corrective and Preventive Action Plan**

The RGC should be provided with follow-up information until the issue has been satisfactorily resolved.

5 RELATED DOCUMENTS

For further information on this topic, see also:

UCL specific processes

- http://www.ucl.ac.uk/finance/policies-procedures/fraud-policy
- http://www.ucl.ac.uk/srs/governance-and-committees/resgov

MRC specific processes

- http://www.mrc.ac.uk/documents/pdf/mrc-code-of-conduct/

Tools and Template documents (available in SOPbox)

- MRC_CTU_TT_0062_3.0_ **Notification to RGC of Possible Serious Breach Form**
- MRC_CTU_TT_0404_1.0_Template Corrective and Preventive Action
- MRC_CTU_TT_0403_1.0_Notification of serious breach form to REC (Non-CTIMPNon-UK)

Regulatory documents

- Statutory instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004.
- Statutory Instrument 2006/1928: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.
- MHRA GCP Guide 2012