ARTIC PC Recording and Reporting of Deviations, Violations, Potential Serious breaches, Serious breaches and Urgent Safety Measures SOP

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Revision History

Version	Revision	Date
1	New document	

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Definitions and abbreviations

Centre	The University department supporting recruitment to the trial. In this trial the lead Centre is the University of Southampton and the specific department is Aldermoor Health Centre. The coordinating Centres are the Universities of Bristol, Oxford and Cardiff.
CCF	Coordinating Centre File, a file similar to the TMF held by the centres supporting the trial

	which holds all the information relevant to that centre.
CI	Chief Investigator is in overall charge of the project.
Closed site	Site where any site closure procedures have been completed and where all outstanding action points have been completed.
Closed trial	Trial where any trial closure procedures have been completed and where all outstanding action points have been completed.
CRF	Case Report Form, the form that collects all the data about participants.
CTA	Clinical Trials Authority
CTIMP	Controlled Trial of an Investigational Medicinal Product.
CTU	Clinical Trials Unit, a supporting unit often within a University.
doi	Digital object identifier
DL	Development Lead (SOP); anyone with previous experience of the procedure / completing the procedure being described, who will take the lead in drafting the SOP or delegating specific section of the SOP to the appropriate person.
DG	Development Group (SOP); A group of approximately 2-4 personnel who are responsible for helping develop, maintain and improve the SOP system, consists of other suitably experienced members.
DM	Data Manager, an individual with responsibility for ensuring data is captured in an ethical manner and a useable format.
GCP	Good Clinical Practice, the regulations that govern the practice of researchers.
GMP	Good Manufacturing Practice, of IMP.
IMP	Investigational Medicinal Product
ISF	Investigator Site File, a file held by a Local Investigator containing all information they need to safely conduct the project.

LI	Local Investigator, the individual with responsibility for the conduct of the study at their site. In a CTIMP this has to be a medically qualified doctor or pharmacist.
MHRA	Medicines Healthcare Regulatory Authority
PI	Principal Investigator, an Individual responsible for the safe and ethically conduct of the study, often leading a centre in academic research.
PMC	Primary Medical Care
S(T)A	Study (Trial) Administrator a member of staff from the Centre.
S(T)C	Study (Trial) coordinator a senior member of staff who may have delegated tasks
S(T)M	Study (Trial Manager) a senior member of staff from the Centre who will have delegated tasks to run the project.
SOP	Standard Operating Procedure, specifies what should be done, when, where and by whom
Site	Primary care Centre that recruits into the study or trial
Sponsor	The University of Southampton
TMF	Trial Master File, a file containing all relevant information about the running of the project.
WPD	Working Practice Document, a guide to good practice

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1.Purpose

The purpose of this SOP is describe to specifies the overall process and procedure for Investigators and the Research and Integrity (RIG) department to follow for a University of Southampton (UoS) sponsored clinical trial in the event of a protocol and/or GCP deviation. Criteria to follow are outlined in order to assess the impact of the deviation in light of the definition of a potential serious breach and /or an urgent safety measure.

This SOP describes the procedure for the Investigator to record the event and notify the RIG and/or the MHRA/REC and for the Sponsor (or their delegate) to report to the MHRA and/or REC as and when necessary.

2. Background

Regulation 29 "Conduct of trial in accordance with clinical trial authorisation etc." of the UK regulations (SI 2004/1031) 'The Medicines for Human Use (Clinical Trials) Regulations 2004' stipulates that all Clinical Trials of Investigational Medicinal Products (CTIMPs) must be conducted in accordance with a protocol that has been approved by a Research Ethics Committee (REC) and the Competent Authority (MHRA in the UK).

It is the Sponsor's responsibility to oversee the conduct of all CTIMPs and to ensure compliance with the approved protocol and prevailing UK regulations.

The Investigator/Institution should only conduct the trial in accordance with the **approved protocol** unless an urgent safety measure must be taken, according to SI 2004/1031 under Regulation 30 and in section 3.1.3 below.

The Investigator, or person designated by the Investigator (in the trial delegation log), should **document and explain any deviation** from the approved protocol.

Definitions used throughout this document

2.1 Protocol Deviation**:** A deviation is usually an **un-intended** departure from the expected conduct of the trial (protocol, SOPs)e.g. a protocol visit date deviation (a common deviation in clinical trials) which does not need to be reported to the sponsor. These events will be identified by the trial team during trial conduct and must be continually monitored by the CI/PI and site team.

It is recognised that minor deviations from approved clinical trial protocols and GCP occur commonly in CTIMPs. Not every deviation from the protocol will result in a serious breach. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial (see MHRA "Guidance for the notification of serious breaches of GCP or the trial protocol", document version 2.0). These cases should be **documented in the CRF or in a file note** and *appropriate corrective and preventative action taken in order to ensure they do not recur.* Please use the CRF and the PI's **Log of (Protocol and/or GCP) Deviations/ Violations/ "Potential Serious breaches"/"Serious breaches"/"Urgent Safety Measures"** provided by the JBRU to the PIs to record each case during trial conduct**.**

2.2 Violations**: A violation can occur when there is a consistent variation in practice from trial protocol, SOPs. A violation can be classified as major if there is a significant occurrence which affects participant safety or integrity of the research.** You are required to report to the sponsor any violations that may impact on the subjects' safety or affects the integrity of the study data.

Examples of this include but are not limited to;

- Failure to obtain informed consent (i.e. no documentation in source data or an Informed Consent form)
- Enrolment of subjects that do not meet the inclusion/exclusion criteria
- Undertaking a trial procedure not approved by the REC and/or the MHRA (unless for immediate safety reasons)
- Failure to report an SAE/R/SUSAR to the RIG
- IMP dispensing/dosing error

Minor Violation - a violation that does not impact on subjects' safety or compromise the integrity of study data. Examples of this maybe;

Missing original signed consent form (only photocopy present).

2.3 Serious Breaches of the protocol and/or GCP

Please consider whether the violation that has occurred on site meets the following definitions. These cases must be reported to the RIG office as soon as the Investigator has become aware of the event.

Under Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [SI 2004/1031], as amended by SI 2006/1928, there is a requirement for the notification of "serious breaches" of GCP and/or the trial protocol:

*"**29A.** (1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of -*

*(a**) the conditions and principles of GCP** in connection with that trial; or*

*(b**) the protocol** relating to that trial, as amended from time to time in*

*accordance with regulations 22 to 25, **within 7 days** of becoming aware*

of that breach.

*(2) For the purposes of this regulation, a "serious breach" is a breach which is **likely** to effect 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".

2.4 Urgent Safety Measures (Implementing a Protocol Deviation under an emergency)

The Investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects **without** prior approval from the REC/MHRA. This is defined as an Urgent Safety Measure under UK Regulation 30:

"The sponsor and investigator may take appropriate urgent safety measure to protect clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately". However, in order to meet the legal timelines **the investigator must inform the MHRA and the RIG (in parallel) in writing immediately and within 3 days.**

See section 6.13 below for the REPORTING procedures.

3. Scope

This SOP details the process (for Investigators and for the RIG regarding UCL sponsored clinical trials) to follow for the recording and reporting of CTIMP protocol deviations and violations. It describes what consideration must be taken into account to assess whether the deviations and violations also meet the definition of a potential serious breach or urgent safety measure and the reporting requirements.

4. Responsible personnel

The Investigator has the responsibility to record and report any violations to the RIG within the agreed timeframes and in accordance with this SOP if these are deemed a potential serious breach/urgent safety measure. Deviations need only be documented on site, in the CRF and on the PI's Log of (Protocol and/ or GCP) Deviations/Violations/"Potential Serious breaches"/"Serious breaches"/"Urgent Safety Measures" and file noted where required. Any corrective and preventative action should also be documented and retained in the site file.

The RIG and/or investigator must report serious breaches to the competent authority within the regulatory timelines and consider the following actions:

Receipt and Assessment (i.e. assessment of deviations/violations by RIG/delegate, isolated/systematic incident, patient(s) harmed or put at risk/data credibility etc.)

- Investigation
- Corrective and Preventative Action (CAPA)
- Reporting to competent authority
- Compliance with 7-day reporting timescale.

If the Investigator is unsure whether a deviation or violation is a potential serious breach then please notify the RIG and trial teams as soon as possible and provide as much information as possible.

The RIG and trial teams should assess the impact of the breach on the scientific value of the trial; this can be carried out in conjunction with the PI/CI. If a potential serious breach is identified by a member of the RIG or trial teams, the QA manager should also be alerted as soon as possible with a further discussion with the CI/PI in order to clarify the situation and take appropriate corrective and preventative action. The RIG or trial team would then inform the competent authority and REC of the serious breach.

The regulatory timeline will only commence once the RIG and trial teams has been notified of an event and has assessed the event as being a serious breach.

5. Procedure

Please check that this version of the SOP is the latest by going onto the ? Research governance and PCPS Sharepoint site.

5.1 Identification of deviations, violations and potential serious breaches

The judgment on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors e.g. the design of the trial, 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.

In addition, it is important that site notifies the RIG team and trial team of what corrective and preventative action has been taken (CAPA) in order to devise a formal plan of corrective and preventative action.

5.1.1 Deviations

Recording: Recorded in the case report form, deviations and violations log and file noted if necessary.

Reporting: minor deviations are not required to be notified to the sponsor. Where a deviation is reoccurring and may result in identification of a serious breach, this should be notified to the sponsor.

Escalation: Corrective and preventative actions should be implemented for deviations.

It is recommended that reoccurring deviations be discussed at any trial meetings and if required detailed in the clinical study report.

6.1.2 Violations

Recording: Recorded in the case report form, deviations and violations log and file noted if necessary.

Reporting: Violations of GCP, protocol and regulations must be notified to the sponsor within 3 calendar days of becoming aware of that violation.

Escalation: Corrective and preventative actions should be implemented for violations.

If the violation is determined to be a potential serious breach (as defined by UK clinical trials regulation 29A) then this would be reported to the competent authority and REC within regulatory timelines.

It is recommended that reoccurring violations be discussed at any trial meetings and if required detailed in the clinical study report.

If the deviation/violation is identified at RIG, the case must be discussed with the QA manager as soon as possible and senior management notified if that person is not available.

A violation may constitute the RIG to undertake a triggered monitoring visit. All major violations must be resolved to conclusion. Depending on the nature of the violation it may constitute a Serious Breach of GCP and further follow up and reporting maybe required by the RIG in line with current regulations.

5.2 Procedure for notifying the RIG team of a POTENTIAL serious breach

5.2.1. Site team to complete the "Notification of Serious Breaches of GCP or Trial Protocol form (see Appendix 1) " all available details pertaining to the breach should be documented on the form.

5.2.2. Completed Notification of Serious Breaches of GCP form to be sent to the RIG team (compliance oversight advisor, sponsor regulatory advisor)

5.2.3. RIG to assess and collate information relating to the potential serious breach and report to the competant authority within 7 calendar days.

5.2.4. Violation / serious breach to be noted on the Log of (Protocol and/ or GCP) Deviations/Violations/"Potential Serious breaches"/"Serious breaches"/"Urgent Safety Measures

In addition the PI must log the "Potential serious breach" in the PI's Log of (Protocol and/ or GCP) Deviations/Violations/"Potential Serious breaches"/"Serious breaches"/"Urgent Safety Measures".

5.3 Assessment by the RIG team

RIG to discuss potential serious breach internally through:

Discussion with appropriate team members (e.g., sponsor regulatory advisor, senior pharmacovigilance coordinator, trial manager)

Assess which relevant GCP, regulatory or protocol section the breach was identified in.

Evaluate whether the breach fulfils the competent authority (MHRA) definition of a serious breach. The RIG team may seek clarification from the MHRA on a potential serious breach by contacting the GCP inspectorate (email). Phone conversations with the MHRA are discouraged, because it is crucial that a clear trial of what information is passed on to the MHRA and received from the MHRA needs to be maintained. **In doubt, best is to send the case as a POTENTIAL serious breach, detail the information at hand and request the MHRA to assess the event.**

Compile all supporting documentation pertaining to the breach and submit to the MHRA within 7 days of assessing the event as a serious breach.

NB: In addition, the RIG or trial team might have to submit a substantial amendment/ urgent safety measure report if necessary.

Organisations should also consider if there are any relevant MHRA units that require to be notified to comply with other legislation e.g. notification to the Clinical Trials Unit (CTU) if the breach constitutes an Urgent Safety Measure or if a substantial amendment is required due to a temporary halt in the study or the Defective medicines Report Centre if the breach involves defective medicines or IMP recall etc. and/or if the REC needs to be notified.

If the sponsor obtains clear and unequivocal evidence that a serious breach has occurred the default position should be for the RIG or trial team to notify the MHRA first, within 7 days, investigate and take action simultaneously or after notification. In this case, the RIG or trial team should not wait to obtain all of the details of the breach prior to notification.

Should a deviation or violation occur that relates to more than one site only one report should be made and filed in the applicable section of the ISF.

5.4 Corrective and Preventative Actions (CAPA):

The RIG and the CI/PI must agree on the appropriate corrective and preventative action to be taken and this should be documented and detailed within the body of the notification report.

5.5 Notification to the MHRA:

The completed form should be sent to the GCP Inspectorate **within 7 days** of the RIG team having assessed an event as a serious breach. It is not necessary to wait until all the information is obtained, updates to the report are acceptable. In such cases, plans should be indicated with projected timelines for completion on follow up reports.

The completed form (Appendix 1) should be emailed to:

GCP.SeriousBreaches@mhra.gsi.gov.uk

Alternatively, if this is not possible, notifications may also be sent by fax or post to any of the three MHRA Inspectorate offices as per the MHRA website.

In cases where an external organisation is obliged contractually to report serious breaches on behalf of RIG, all regulatory timelines remain applicable (notification within 7 days to MHRA of becoming aware of serious breach).

The RIG staff member reporting the serious breach must update the "JBRU Log of "Potential Serious breaches"/"Serious breaches" reported by the PI/CI/Lab to the JBRU on UCL

sponsored CTIMPs on the S:drive. If a "potential serious breach" is investigated but does not become a serious breach, it should be logged as a "Potential serious breach".

The log must be reviewed periodically to help identify any trends, in particular those relating to recurrent findings that may require additional training or monitoring visits to site.

5.6 Follow up reports:

Follow up reports should be made in writing (the serious breaches form can also be used for this) and should ideally:

Be clearly identified as a follow up report

Identify the unique GCP ID allocated when the initial report was acknowledged by the MHRA

Be forwarded to the initial inspector dealing with the case

5.7 Escalation and dissemination process:

Internally:

The line manager(s) of the Investigator from the site where the breach took place must be notified of the "notification of serious breach" having been sent to the MHRA and be informed of what CAPA is in place. The line manager(s) of these organisations will have to inform their QA and senior management if necessary and according to their own SOPs.

The serious breach might be notified to the Safety Committee, the Clinical Trial Strategic Committee, and the Research Governance Committee as deemed appropriate.

The R&D Department of the site where the serious breach took place must be informed of what CAPA is in place.

Externally:

This will be dependent on the nature of the breach and may include other sites and pharmacies affected, other MHRA departments, Ethics Committees etc.

The breach should be circulated to relevant staff for inclusion of relevant information in to the study report or publication. Serious breaches relating to investigator sites/Laboratories

etc. should also be made available to those selecting sites for studies .i.e. careful assessment should be made before using a non-compliant site in future studies.

5.8 Further actions:

Until the serious breach has been fully resolved and given the amount of resources diverted from the RIG to process/address serious breaches, **the RIG will not be carrying out any activities on trials that the CI may have in set up at their discretion**.

UoS reserves the right to withdraw sponsorship for the trial as and when necessary.

6. Notification of an Urgent Safety Measure

(SI 2004/1031, Regulation 30 page 31) by a site

The CI/PI should phone the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor **immediately** once an urgent safety measure was taken at a site. An email must be written by the PI/CI to the MHRA person spoken to on the phone, to summarize the information exchanged and the advice provided by the MHRA person. The MHRA person should be requested to confirm that the email's content (info provided and advice given) is correct.

The CI/PI must then notify the MHRA, the MREC and RIG (a monitor and a Trial coordinator should be emailed) in writing, of the measure taken and the reason for the measure **within 3 days.** Depending on the local R&D site letter, the local R&D Department might need to be informed.

If a substantial amendment is required, the investigator must inform the sponsor and a notification of substantial amendment submitted to the REC and competent authority.

The substantial amendment form

(http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/11_an2_14-2005.pdf) should include a covering letter detailing the measures taken, the reason for them and the medical assessor contacted; a Notification of Amendment form and supporting documentation.

The urgent safety measure notification should be:

1. Faxed to the Clinical Trials Unit on **020 7084 2443** or sent by e-mail to clintrialhelpline@mhra.gsi.gov.uk) **marked 'Urgent Safety Measure'** and
2. Sent as PDF documents on disk to: Information Processing Unit, Area 6, Medicines and Healthcare products Regulatory Agency, Market Towers, 1 Nine Elms Lane, London. SW8 5NQ

The PI should copy this notification and file it in his ISF. The PI should be logging this event into the **PI's Log of (Protocol and/ or GCP) Deviations/Violations/"Potential Serious breaches"/"Serious breaches"/"Urgent Safety Measures".**

N.B. The recently amended regulation (SI2009/1164) to the Medicines for Human Use (Clinical Trials) Regulations 2004 to allow for notice of urgent safety measures (taken in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety and the circumstances giving rise to those measures) to be given **as soon as possible** to the licensing authority and an ethics committee established under Part 2 of those Regulations during a period in which a disease is pandemic and is a serious risk to human health or potentially a serious risk to human health. See http://www.opsi.gov.uk/si/si2009/uksi_20091164_en