South Eastern Health and Social Care Trust

Standard Operating Procedure (SOP)
Research and Development Office

Title of SOP:	Recording and Reporting Deviations, Violations, Potential Serious Breaches, Serious Breaches and Urgent Safety Measures
SOP Number:	23
Version Number:	2.1
Supercedes:	2.0
Effective date:	August 2013
Review date:	August 2015

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Date:	07 February 2014

Version History:

Version No.	Date	Author	Reason for Change
1.0	Sept 2007	Katrina Hughes	N/A
2.0	Aug 2011	Alison Murphy	Revise title and document to include procedures for protocol deviations, violations and urgent safety measures. Updated to reflect new SOP format.
201	Feb 2014	Alison Murphy	Section 8. Page 10. Contact Details for CI reporting Serious Breaches. Email address updated.

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1. INTRODUCTION

Regulation 29 'Conduct of trial in accordance with clinical trial authorisation' of the UK regulations (SI 2004/1031) and 'The Medicines for Human Use (Clinical Trials) Regulations 2004' stipulate that all 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.

Under the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 it is now a requirement that serious breaches of GCP or the trial protocol are reported to the Medicines and Healthcare products Regulatory Agency (MHRA). The amended regulations state:

(1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

- the conditions and principles of GCP in connection with that trial: or
- 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 -

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial".

These stipulations were incorporated into the regulation to:

(1) Enhance the safety of trial subjects/patients by seeking to ensure that the licensing authority is promptly informed of such serious breaches, in order to take appropriate action in response to the breach and/or,

(2) To take the information regarding serious breaches into account when assessing future applications for clinical trial authorisation, and applications for marketing authorisation, which include data from trials affected by serious breaches.

It is the responsibility of the trial sponsor or a person legally authorised by the sponsor to carry out the notification procedure within 7 days of becoming aware of the breach.

2. OBJECTIVE

This objective of this SOP is to describe the process for the recording, reporting and notification of protocol and/or GCP deviations, violations, potential serious breaches, serious breaches and urgent safety measures.

3. SCOPE

This SOP applies to all Clinical Trials of Investigational Medicinal Products (CTIMPs) and other research studies carried out in the South Eastern Health & Social Care Trust.

4. PROTOCOL DEVIATIONS

A deviation is usually an un-intended departure from the expected conduct of the trial and is often classified as non-serious or minor in nature e.g. a protocol visit date deviation (a common deviation) 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 or as delegated and the CI/PI made aware. It is the responsibility of the CI/PI to train their trial staff on the trial protocol requirements and this training must be documented and filed in the Trial Master File (TMF) or Investigator Site File (ISF).

It is recognised that minor deviations from approved clinical trial protocols and GCP occur commonly in research studies/trials. 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.

4.1 Recording and Reporting of Protocol Deviations

Protocol deviations should be documented in the case report form for the trial or in a file note in the TMF/ISF, in order for appropriate corrective and preventative actions to be taken. In addition, these deviations should be included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data.

They do not need to be reported to the Trust Research Office or the MHRA.

5.0 PROTOCOL AND/OR GCP VIOLATIONS

A minor violation is a violation that does not impact on subjects' safety or compromise the integrity of study data. Example of this may be,

- Missing original signed consent form (only photocopy present).

Violations may impact on the subjects' safety or affect the integrity of the study data. Examples of this include, but are not limited to,

- Failure to obtain informed consent (ie 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 a SAE/R/SUSAR
- IMP dispensing/dosing error

5.1 Recording and Reporting Protocol and/or GCP Violations

If a violation is deemed minor in nature then these cases should be documented in the CRF and a file note written where necessary in the TMF/ISF. In addition these deviations should be included and considered (where applicable) when the clinical study report is produced, as they may have an impact on the analysis of the data.

Any violations that may impact on the subjects' safety or affect the integrity of the study, identified in Trust sponsored studies, must be reported to the Trust Research Office by emailing the Research Manager, as soon as possible, (this may also constitute a potential serious breach of GCP and/or protocol and will require further reporting in accordance with this SOP).

6.0 SERIOUS BREACHES OF THE PROTOCOL AND/OR GCP FOR CTIMPS

The MHRA define a serious breach as:

- Any serious breach of:

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

  (b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25.

- 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 (this should be relevant to trial subjects in the UK); or

  (b) 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 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.

6.1 Recording and Reporting Serious Breaches

It is the responsibility of the Chief Investigator and Principal Investigator(s) to continually monitor the conduct of the clinical trial; this may be delegated to a suitably qualified or experienced member of the research team or sub-contracted to an appropriately qualified party. In addition South Eastern Health and Social Care Trust and its partner Universities or Trusts may audit the trial as part of their Quality Assurance procedures.

Any breaches identified in Trust sponsored studies either through monitoring, audit or by other means must be reported to the Trust Research Office within **one** working day of the breach being identified and confirmed.

Initial reporting to the Trust Research Office should be carried out using the dedicated email address (see section 8) and should include:

1. Name of Chief Investigator and Principal Investigator at the site where the breach occurred.
2. Full title of the clinical trial
3. An explanation of how the breach was identified
4. Details of the breach
5. Details of any initial corrective actions
6. Assessment of the impact the breach will have on the trial subjects/patients and/or scientific integrity.

6.1.1 Assessment of a Serious Breach

Upon receipt of an initial breach report, the Research Manager or Associate Medical Director (Research) will discuss the issue with the Chief/Principal Investigator to identify which section of GCP or the protocol has been breached and how the breach impacts on subject/participant safety and/or the scientific integrity of the trial.

It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial. This assessment should be documented. The appropriateness of the decisions taken by the Sponsor may be examined during MHRA inspections.

The Research Office may contact the MHRA to discuss the issue if it is unclear about the potential for a breach to have significant impact on the scientific value of the trial.

If assessment deems the breach to be serious the Research Manager or Associate Medical Director (Research) will meet with the Chief/Principal Investigator and the study team to discuss the breach and compile evidence to support notification to the MHRA.

The Research Manager or Associate Medical Director (Research) will work with the Chief/Principal Investigator to identify the extent of the breach and to initiate any Urgent Safety Measures that may be required.

6.1.2 Initial Notification of Breach to MHRA

The Research Manager will collate all available information and complete the Notification of Serious Breaches of GCP or the Trial Protocol Form.

The form will be submitted via e-mail to the MHRA within the 7 day reporting period defined in regulation. The form will be sent to:

GCP.SeriousBreaches@mhra.gsi.gov.uk

The Research Manager will also consider if there are any other 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 to the Defective Medicines Report Centre if the breach involves defective medicines or IMP recall etc.)

6.1.3 Provision of additional information to the MHRA

It is not necessary to wait for all the required information to report to the MHRA; updates are acceptable. If investigations or corrective and preventative action is ongoing at the time of reporting the serious breach, plans with projected times for completion should be indicated. If this is the case the initial report should indicate when these are expected to be completed and what follow up reports will be provided to the MHRA and when.

Once the initial notification has been submitted to the MHRA, the Trust Research Office will review the breach in full to identify the extent of the breach and the Research Manager will forward all new information to the MHRA.

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

- Be clearly identified as a follow up report
- Identify the unique GCP identification allocated when the initial report was acknowledged
- Be forwarded to the inspector dealing with the initial notification directly or via the MHRA serious breaches mailbox

The MHRA may request additional information such as a copy of the protocol, ethics application, SOP's etc. The Research Manager will liaise with the study team to obtain additional documents and submit them to the MHRA.

6.1.4 Planning and Implementing Corrective Action

The Research Manager will work with the CI to devise a formal plan of corrective action to address the breach. The corrective action plan will be submitted to the MHRA on their request.

Depending on the initial assessment of seriousness and impact, the Trust Research Office may carry out a full audit of the trial and general trial management systems and procedures.

The Trust Research Office may publish general information on the breach, in an anonymised form, to educate and inform researchers about errors that can occur in the trial process and to facilitate an open environment for reporting such occurrences.

6.2 Non Trust Sponsored Studies

Any breaches identified in studies not sponsored by the Trust, that occurred on the Trust site, should be reported to the Trust Research Office by emailing the Research Manager with the details of the breach. There is no set time period for reporting to the research office but should be as soon as practically possible. SOPs of the study sponsor should be followed regarding reporting requirements to the sponsor.

7.0 URGENT SAFETY MEASURES

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 measures to protect clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately'.

7.1 Recording and Reporting Urgent Safety Measures

When the CI/PI becomes aware of information that necessitates immediate change in study procedure to protect clinical trial subjects from any immediate hazard to their health and safety they 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.

The CI should report the urgent safety measure to the Trust Research Office immediately, using the dedicated email address (see section 8).

The Research Office will notify the MHRA and the main REC providing full details of the information they have received and the decision making process leading to the implementation of the urgent safety measure within 3 days.

The notification should include a covering letter detailing the measures taken, the reason for them and the medical assessor contacted and any supporting documentation.

The notification to the MHRA should be

- sent by email to (clintrialhelpline@mhra.gsi.gov.uk) marked 'Urgent Safety Measure' and
- sent as PDF documents on disk to: Information Processing Unit, Area 6, Medicines & Healthcare products Regulatory Agency, 151 Buckingham Palace Road, Victoria, London. SW1W 9SZ.

7.2 Non Trust Sponsored Studies

Urgent safety measures taken in studies not sponsored by the Trust, that impact on the conduct of the study in the Trust, should be reported to the Trust Research Office through the normal amendment process but should be implemented immediately as required/instructed by the study sponsor.

8. CONTACT DETAILS FOR CI REPORTING SERIOUS BREACHES OR URGENT SAFETY MEASURES TO THE TRUST RESEARCH OFFICE

For the reporting of Serious Breaches or Urgent Safety Measures please contact the Research Office **for Trust Sponsored studies** using the email addresses below.

Paul.Carlin@setrust.hscni.net copying in Marion.Fay@setrust.hscni.net

9. REGULATIONS, GUIDELINES, REFERENCES, SOP LINKS ETC

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 Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol Version 2 15/10/09

10. APPENDICES

10.1 Appendix 1 – Serious Breaches Notification Examples

Appendix 1 – Serious Breaches Notification Examples

Notified by:	Issue:	Would MHRA have expected this case to be notified?
Sponsor	Dosing error. Ethics Committee & MHRA informed. The Sponsor stated there were no serious consequences to subjects or data.	No, if there was no significant impact on the integrity of trial subjects or on scientific validity of the trial.
Sponsor	Patient Information Leaflet and Informed Consent updated. At one trial site this was not relayed to the patients until approximately 2-3 months after approval. *More information on the potential consequences of the delay should have been provided.*	Possibly not. If this was not a systematic or persistent problem and if no harm to trial subjects resulted form the delay. Yes, if there was a significant impact on the integrity of trial subjects.
Sponsor	Visit date deviation. A common deviation in clinical trials.	No. Minor protocol deviation, which does not meet the criteria for notification.
Contractor	Investigator failed to report a single SAE as defined in the protocol (re-training provided)	No, if it did not result in this or other trial subjects being put at risk, and if it was not a systematic or persistent problem. In some circumstances, failure to report a SUSAR could have a significant impact on trial subjects. Sufficient information should be provided for the impact to be assessed.
Identified during inspection prior to the current requirement to report serious breaches	Investigator site failed to reduce or stop trial medication, in response to certain laboratory parameters, as required by the protocol. This occurred with several patients over a one year period, despite identification by the monitor of the first two occasions. Patients were put at increased risk of thrombosis.	Yes, under the current requirements, this should have been reported as a serious breach.
Sponsor	Becomes aware of fraud at investigator site in the UK, which does not affect the overall scientific value of the Sponsor's trial or the integrity of trial subjects in the UK. However, the Sponsor is aware that the fraudster was involved in trials being sponsored by other organisations.	Although, in this situation, not a legal requirement under 29A, MHRA encourages voluntary reporting of all fraud cases in the UK, because MHRA will wish to establish the impact on the other trials in case subject integrity or the scientific value of those trials was compromised.