

## STANDARD OPERATING PROCEDURE:

### Notification of Serious Breaches of GCP in Clinical Trials

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| <b>SOP SUMMARY</b>   |  |                 |
| This Standard Operating Procedure (SOP) describes procedures for identifying and reporting serious breaches of GCP in clinical trials.   |  |                 |
| <b>The Trust monitors the implementation of and compliance with this policy in the following ways:</b>   |  |                 |
| Monitoring of implementation and compliance with this procedure will be undertaken by the Executive Medical Director, Research manager, Research lead, R&D department staff and R&D group. |  |                 |
| <b>Services</b>  | <b>Applicable</b>  | <b>Comments</b> |
| Trustwide  | ✓  |                 |
| Essex MH&LD  |  |                 |
| CHS  |  |                 |

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### 1. BACKGROUND

This Standard Operating Procedure (SOP) describes procedures for identifying and reporting serious breaches of GCP in clinical trials.

The EU GCP Directive 2005/28/EC was transposed into UK law as the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, together with the Medicines for Human Use (Clinical Trials) Regulations 2004. Under the amendment 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), Research Ethics Committee (REC) and the Trust R&D Department. The amended regulations state:

“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”.

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.

Examples of serious breaches 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 JBRU
- IMP dispensing/dosing error

Please also refer to Appendix 1 for examples of notifications to the MHRA.

Deviations from clinical trial protocols and GCP occur commonly in clinical trials. 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. These cases should be documented e.g. in the case report form for the trial

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or trial master file, 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. However, not every deviation from the protocol needs to be reported to the MHRA as a serious breach. The reporting procedures for protocol violation/deviation are usually defined in the clinical trial protocol.

It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial. Anyone who is unsure whether a breach has occurred can contact the R&D Office to discuss the situation and clarify whether a breach is classed as serious (examples of possible serious breaches can be found in Appendix 1).

### **2. PURPOSE**

- To outline procedures for identifying a potential serious breach of GCP or protocol violation.
- To describe the process for notification of serious breaches of GCP or the approved trial protocol.
- To ensure appropriate assessments are carried out by relevant parties and fully documented.
- To outline the role of the R&D Office in assessing the reported serious breaches and the escalation process.

### **3. APPLICABLE TO**

Any employee involved with clinical research including, Chief Investigators (CI), Principal Investigators (PI), Consultants, clinical trial pharmacists, research managers, statisticians, research nurses, trial coordinators and data managers.

### **4. RESPONSIBILITIES**

All researchers must ensure all possible serious breaches are reported to the Chief Investigator immediately or as per protocol. For multicentre trials, any reported events by participating sites to the study coordinator should be notified to the CI.

The Chief Investigator or delegated individual of the study shall ensure that any reported possible serious breaches are reported as per protocol and SOPs.

For sponsored multicentre trials, the process for identifying breaches should be provided to all participating sites at study set up. The sponsor should also ensure that adequate procedures are in place as part of the routine monitoring processes to identify potential GCP breaches.

For any possible serious breaches reported to the R&D Office, R&D staff will ensure that they are assessed immediately, and that appropriate recommendations are made to the Chief Investigator.

The R&D Office and the Chief Investigator shall ensure that all reported serious breaches are reported to the MHRA within 7 days, and that any relevant follow up

information is provided ASAP.

### 5. PROCEDURE

#### 5.1 Identifying and Notifying Sponsor of a Serious Breach

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 (e.g. coordinating centre).

If a possible protocol violation and/or GCP breach has been identified, the CI should carry out an assessment to confirm if the event affects the safety, physical or mental integrity of the trial subject or the scientific value of the trial. If yes, this should be treated as a possible Serious Breach and should be investigated further. Immediate reporting to R&D Office is also required. However, if the event only relates to a protocol violation, then record the event as per protocol requirements.

Any potential serious breaches of GCP identified either through monitoring, audit or by other means must be reported to the R&D Office within 24 hours of the breach being identified by the study. For multicentre trials, the clock starts either when the event has been identified by the sponsor or when the event has been reported to the CI by the participating site.

For sponsored multicentre trials, the process for identifying breaches should be provided to all participating sites at study set up. The Sponsor should also ensure that adequate procedures are in place as part of the routine monitoring processes to identify potential GCP breaches.

If a possible breach has been reported by a PI at a participating site or identified by the Sponsor as part of the routine monitoring process, this SOP should be followed to conduct the necessary assessment and reporting required by the sponsor.

#### 5.2 Assessment of a Serious Breach

Upon receipt of an initial breach report, the R&D office will discuss the issue with the Chief Investigator or delegated individual to identify which section of GCP or the protocol has been breached and how the breach impacts the subject/participant safety and/or the scientific integrity of the trial.

The R&D office will meet with the study team to discuss the breach and compile evidence to support notification to the MHRA. This will then be sent to the CI and related departments e.g. pharmacy, for approval prior to submission to the MHRA.

The R&D office will work with the study team to identify the extent of the breach and to initiate any Urgent Safety Measures that may be required.

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### 5.3 Initial Notification of Breach to the MHRA

The R&D office will collate all available information and assist with completion of 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 the regulations.

Complete the notification of serious breaches of GCP or the trial protocol form [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/633795/Notification\\_of\\_serious\\_breaches\\_of\\_GCP\\_or\\_the\\_trial\\_protocol\\_form.doc](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/633795/Notification_of_serious_breaches_of_GCP_or_the_trial_protocol_form.doc) and send it to [GCP.SeriousBreaches@mhra.gov.uk](mailto:GCP.SeriousBreaches@mhra.gov.uk)

Further guidance on reporting serious breaches to MHRA is available at [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/404588/GCP\\_serious\\_breaches\\_guide.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/404588/GCP_serious_breaches_guide.pdf)

### 5.4 Provision of Additional Information to the MHRA

Once the initial notification has been submitted to the MHRA, the R&D Office will review the breach in full to identify the extent of the breach and continue to update the MHRA with new information.

The Chief Investigator/R&D Office will compile a project report for submission to the MHRA. The project report will include:

- 1) Full title of trial, ethics approval number, EudraCT number, version number, date of Commencement
- 2) Name of Chief Investigator
- 3) List of sites
- 4) Number of subjects recruited
- 5) Brief description of the trial
- 6) Summary of the breach including rationale
- 7) Summary of actions taken
- 8) Assessment of the impact of the breach to subject/participant safety
- 9) Assessment of the scientific integrity of trial
- 10) Statement from Chief Investigator (if not the person completing the report)

If the incident involves other departments such as pharmacy, then departmental specific (e.g. pharmacy) assessments for point 8 and 9 should be performed. For the assessment of scientific integrity of the trial, the CI of the study should liaise with the named statistician on the trial to complete the data integrity assessment and provide supporting documentation.

The R&D Office will review the project report. The MHRA may request additional information such as a copy of the protocol, ethics application, SOPs etc.

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### 5.5 Other Reporting Requirements and Implementing Corrective and Preventative Action

Any possible serious breach that occurs may also require reporting to the Trust's risk management team. The R&D Office shall make recommendations to the study team about where further reporting requirements apply.

The breach may also require reporting to the Ethics committee if it is in breach of the ethical conditions of study approval.

The R&D Office will work with the study team to devise a formal plan of corrective and preventative action to address the breach. This should be submitted to the MHRA in the final report being submitted to the MHRA.

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

## 6. REFERENCES

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.

Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol, MHRA.

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)

The Medicines for Human Use (Clinical Trials) Amended Regulations 2006 (SI 2006/1928)

The Medicines for Human Use (Clinical Trials) Amended Regulations 2009 (SI 2009/1164)

King's College London, Joint Clinical Trials Office, SOP on *Serious Breaches of Good Clinical Practice or Trial Protocol*, final version 1.0 dated 4th July 2008.

## 7. APPENDICES

### APPENDIX 1: MHRA Serious Breach Examples

| Notifier | Breach  | Is it considered a Serious Breach?  |
|----------|---|---|
| Sponsor  | Dosing error. Ethics Committee & MHRA informed. Subjects withdrawn. The sponsor stated that there were no serious consequences to subjects or data. | No<br>As no significant impact on the integrity of trial subjects or on scientific validity of the trial. |

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| 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. <i>More information on the potential consequences of the delay should have been provided.</i>  | Possibly not. If this was not a systematic or persistent problem and if no harm to trial subjects resulted from the delay. Yes, if there was a significant impact on the integrity of trial subjects (e.g. there was key safety information not relayed to subjects in a timely manner etc.).   |
| Sponsor                         | Visit date deviation.<br><i>A common deviation in clinical trials.</i>   | No<br>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 and context should be provided for the impact to be assessed adequately. |
| Identified during an Inspection | 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.  |
| Sponsor                         | Became aware of fraud at an investigator site in the UK, which did 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 investigator site was also 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 need to establish the impact on the other trials in case subject integrity or the scientific value of those trials was compromised.   |

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| Sponsor | IMP temperature excursions reported. | No, if the excursions had been managed appropriately (i.e. IMP moved to Alternative location/quarantined as necessary and it was identified by qualified personnel that there was no impact on stability of the product and therefore no impact on patient safety/data integrity).<br>Yes, if this went unmanaged and subjects were dosed with the IMP were found to have become unstable and this resulted in harm or potential harm to subjects |
|---------|--------------------------------------|---|