Breach of Protocol or Good Clinical Practice	
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Position	Chief Investigator/R & D Committee member
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1.0	1.1	Dr Sarah Pountain	19th February 2010	Update of contact details

Contents

1 Background

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

This SOP describes the process for reporting/documenting a breach of protocol or GCP during the Stroke Oxygen Study, sponsored by North Staffordshire Combined Healthcare NHS Trust. The new requirement was implemented in UK legislation in order 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.

3 Definitions

- 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.

4 Scope and responsibilities

This SOP is to be used by the Chief Investigator and Principal Investigators of the Stoke Oxygen Study.

4.1 Sponsor

- The Sponsor is responsible for ensuring that arrangements are in place to ensure that any serious breach of protocol of GCP is reported to MHRA within the required timeframes.

4.2 Chief Investigator

- The Chief Investigator is responsible for notifying 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, **within 7 days** of becoming aware of that breach.

4.3 Principal Investigator

- The Principal Investigator is responsible for ensuring that non-serious breaches are recorded using the 'Breach of Protocol or Good Clinical Practice reporting (R&D-RF-SOS-003)' and attached to the CRFs.

- The Principal Investigator is responsible for ensuring that serious breaches are recorded using the 'Breach of Protocol or Good Clinical Practice reporting (R&D-RF-SOS-003)' and sent to the Chief Investigator and Study Manager **immediately**.

5 Procedures for reporting a Serious Breach of GCP or Trial Protocol

5.1 Reporting a serious breach – Principal Investigator

If you feel that there has been a potential breach in protocol or GCP then you must complete the 'Breach of Protocol or Good Clinical Practice reporting (R&D-RF-SOS-003)' available from the SOS website.

If it is decided that the breach is a **potentially serious** breach this form should then be emailed to christine.roffe@northstaffs.nhs.uk (Chief Investigator) AND sarah.pountain@northstaffs.nhs.uk (SOS Study Manager) or faxed to 0300 123 0894 (office hours) **immediately**.

If it is decided that the breach is **a non-serious** breach this form should be attached to the CRF.

Please note:
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 by filling in the reporting form and attaching to the case report form.

5.2 Reporting a serious breach –Chief Investigator

1] The Chief Investigator must notify the MHRA of a serious breach **immediately** by telephone:
01707 299130

2] The Chief Investigator must then notify the MHRA of a serious breach in writing **within 7 days** of becoming aware of the breach

The template form for notifications of serious breaches to the MHRA , attached in Appendix 3, should be filled in and emailed to GCP-PV.Inspectors@mhra.gsi.gov.uk marked 'Serious Breach' or posted to GCP Inspectorate, MHRA, 18-103, Market Towers, 1 Nine Elms Lane, London, SW8 5NQ.

Alternatively the form can be sent by post or fax to any of the three MHRA Inspectorate offices. Current office addresses can be found on the MHRA web site. For example,

Welwyn Garden City, Medicines Inspectorate, 2 Falcon Way, Welwyn Garden City, Hertfordshire, AL7 1TW
Fax: 01707 376649

5.3 Identifying serious breaches

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. 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.

What needs to be reported?

- Any serious breach of:

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

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

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.

It is the responsibility of the Chief Investigator to assess the impact of the breach on the scientific value of the trial. This assessment should be documented and the appropriateness of the decisions taken by the Chief Investigator may be examined during MHRA inspections. If the Chief Investigator is unclear about the potential for a breach to have significant impact on the scientific value of the trial, the Chief Investigator should contact the MHRA to discuss the issue.

Examples illustrating breaches classified as serious or non-serious are given in appendix 1. A selection of notifications that have been received to date are shown in appendix 2.

5.4 Potential actions by the MHRA

Upon receipt of a serious breach notification, the MHRA will log and review the notification, and a variety of actions may be taken, depending on the nature of the breach and its potential impact e.g.

- Acknowledgement of receipt, but no immediate action e.g. if appropriate action has already been taken by the sponsor. The case may be examined during future MHRA inspections.
- Request for additional information from and investigation by, the Sponsor. If insufficient information is provided in the initial notification to assess the impact of the breach, follow-up information will be requested.
- Sharing of information with other concerned parties, in accordance with the regulations and applicable agreements e.g. to concerned Ethics Committees, other competent authorities, MHRA Clinical Trials Unit.
- Investigation by the MHRA, for example, triggered inspection(s).
- Implementation of urgent safety measures, where appropriate.
- Suspension or termination of a clinical trial authorisation, where appropriate.
- Referral for enforcement action e.g. infringement notices, criminal investigation.
- Referral to professional bodies e.g. the General Medical Council.

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.

7 Approval signature: Do not use this SOP unless it has been signed below

As a member of the R & D Committee I authorise the use of this SOP.

SOP Reference: R&D-SOP-SOS-002

Version Number: 1.1

Name Prof Christine Roffe Position Chief Investigator

Signed  Date 9.4.2010

Appendix 1: Notification Examples

Examples illustrating breaches classified as serious or non-serious (this is not an exhaustive list):

1. A breach of GCP or the protocol leading to the death, hospitalisation or permanent disability of a trial subject in the UK. Please note, not every serious adverse event (SAE) or suspected unexpected serious adverse reaction (SUSAR) would routinely be classified as a serious breach, but SAEs/SUSARs resulting from a breach of the conditions and principles of GCP or a breach of the protocol may constitute a serious breach. Submission of a serious breach notification to the MHRA Inspectorate does not obviate the requirement for a SUSAR report, where applicable, to be submitted to the concerned competent authorities e.g. via the EudraVigilance database.

2. Proof of fraud relating to clinical trial records or data, if the fraud is likely to have a significant impact on the integrity of trial subjects or the scientific value of the data.

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

   If clinical trial fraud is identified at a non-UK trial site, for a trial 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 trial subjects in the UK or on the overall scientific value of the trial. A site refers to any site involved in the trial e.g. CRO or other contracted organisation and not solely to investigator sites.

3. Persistent or systematic non-compliance with GCP or the protocol that has a significant impact on the integrity of trial subjects in the UK or on the scientific value of the trial. For example, 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. Another example would be of an investigator repeatedly failing to reduce or stop the dose of an IMP in response to a trigger (e.g. abnormal laboratory results) defined in the protocol.

4. Failure to control investigational medicinal product(s) such that trial subjects or the public in the UK are put at significant risk or the scientific value of the trial is compromised. If a serious breach occurs due to an IMP defect, a drug defect report may need to be submitted to the MHRA Defective Medicines Reporting Centre (DMRC), in addition to the serious breach notification.

5. Failure to report adverse events, serious adverse events or SUSARs in accordance with the legislation, such that trial subjects, or the public, in the UK are put at significant risk e.g. inadequate safety reporting in dose escalation studies may have an impact on the decision to escalate to the next dose level.

6. For trials that are on-going in the UK, should serious breaches that occur at non-UK sites be reported?

   Example:

   a. A serious breach is identified at an investigator site in Mexico. The breach has a significant impact on the integrity of trial subjects at the Mexican site and is likely to have a significant impact on the integrity of trial subjects in the UK. For example, 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. Notify the MHRA of the serious breach (other concerned competent authorities may also need to be informed).

      In relation to the example quoted, an urgent safety measure (USM) may need to be implemented to address the cause of the breach. If, in order to address the cause of a serious breach, a USM is implemented at UK sites, to amend the conduct of the trial or suspend the trial, a USM notification should be sent by the Sponsor to the MHRA Clinical Trials Unit within 3 days from the date the measures are taken (in accordance with Regulation 30), in addition to the serious breach notification to the MHRA Inspectorate.

   b. A serious breach is identified at an investigator site in Mexico, which is likely to affect to a significant degree the overall scientific value of the trial. Notify the MHRA of the serious breach (other concerned competent authorities may also need to be informed).

Please see Appendix III for a selection of notifications that have been received to date that may help the Chief Investigator when deciding whether to submit a notification of a serious breach.

This is not an exhaustive list. Other types of serious breaches may occur and it is the responsibility as Chief Investigator to assess the information and ensure appropriate reporting.

It is also the responsibility of the Chief Investigator to take appropriate corrective and preventative actions in response to the serious breach, and to document these actions.

Appendix 2: Examples of notifications that have been received to date by MHRA

Notification Examples

Notified by:	Issue:	Would MHRA have expected this case to be notified?
Sponsor	Dosing error. Ethics Committee & MHRA informed. Subjects withdrawn. The sponsor stated that 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 from 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.

Appendix 3: Notification Form (for Chief Investigator use only)

Notification of Serious Breach of Good Clinical Practice or the Trial Protocol

(Ref: UK Statutory Instrument 2006:1928, Regulation 29A)

Your Name:	Your Organisation:
Your Contact Details:	Date Breach Identified by Sponsor:
Details of Individual or Organisation committing breach:	Details of related study (e.g. study title, EudraCT No) if applicable:
Please give details of the breach. Where possible, please include your rationale (e.g. patient safety / data integrity issue and relevant legislation if known). (continue on additional sheets if required)	

Please give details of action taken: (continue on additional sheets if required)

FOR MHRA USE ONLY:

Date Received:	GCP Ref Number:

Please forward this notification to GCP-PV.Inspectors@mhra.gsi.gov.uk OR GCP Inspectorate, MHRA, 18-103, Market Towers, 1 Nine Elms Lane, London, SW8 5NQ.