Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

Non-Compliance and Management of Serious Breaches

SOP History	*CSUH 01/027*
SOP Number	*C125 (Replaces A105)*
Created	*STH Research Department (EW)*
Reviewed	
Superseded	*NA*
Version	*1.0*
Date	*05 November 2013*
Related SOPs	*A103, For Cause Audit,* *A104 Protocol Amendments,* *B131 Monitoring of STH sponsored IMP studies* *C106 Misconduct and Fraud*
Approved by	*Research Manager*

Standard Operating Procedure
Non-compliance and Management of Serious Breaches

This SOP has been produced in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, ICH GCP and Research Governance Framework 2005. This SOP will outline the procedure when protocol non-compliance has occurred.

Background
Where there is poor compliance with the protocol or with GCP the regulatory authorities can reject the data, patient safety can be compromised and indemnity may not apply.

It is the responsibility of the sponsor to ensure compliance with the study protocol and with GCP. It is essential to record non-compliances throughout the course of a study and to determine their causes. In doing so avoidable non-compliances can be identified easily and measures put in place to prevent repetition. Unavoidable non-compliances may indicate previously unanticipated problems with the study design and if identified early, steps can be put in place to change the protocol by way of a substantial amendment to ensure it is fit for purpose.

Possible sources of non-compliance should be considered by the CI, other members of the research team, and the Sponsor as the protocol is being written. This is part of the process of risk assessment and risk mitigation. The protocol should have in place measures to reduce the incidence of protocol non-compliance and to provide robust parameters within which the study must be conducted. Examples include:

- Explicit, robust and realistic inclusion/ exclusion criteria
- Explicit detail regarding prohibited medication
- Explicit detail regarding the correct procedures for and timing of tests
- Explicit statements to clarify realistic and achievable study visit windows
- Carefully worded participant information to reduce the incidence of the participant failing to comply with study requirements.

STH sponsored CTIMPs undergo a risk assessment process during the protocol development phase. STH Research Department Guidance for Writing Protocols requires investigators to consider where they can add detail to their study protocol to mitigate against risk, including the risk of non-compliance. SOP C118 describes the process for risk assessing the protocol during the study authorisation process.

An STH Protocol Non Compliance Form is available to aid study teams in the reporting of protocol non-compliance.

Definitions

1. Non-Compliance
Non-compliance is any failure to comply with GCP or the current study protocol as approved by Ethics Committee, any relevant Regulatory Authority, sponsor and STH Research Department. Non-compliances are often technical deviations which do not have a significant impact on the safety or physical or mental integrity of the subjects of the trial or the scientific value of the trial. More serious non-compliance may constitute research fraud or misconduct or may constitute a serious breach of the trial protocol or GCP.

2. Serious Breach
A “serious breach” is a serious non-compliance with the protocol or with GCP **which is likely to affect to a significant degree**:

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

Governance Requirements for Serious Breaches

i. CTIMP Studies

A serious breach must be reported by the Sponsor to any relevant Regulatory Authority and the relevant Ethics Committee within 7 days of the sponsor becoming aware of the breach. This is a legal requirement for CTIMPs under the Medicines for Human Use (Clinical Trials) Regulations.

ii. Non-CTIMP Studies

For non-CTIMP studies NRES SOPs require investigators to report serious breaches to the relevant Ethics Committee within 7 days of becoming aware of the breach.

Procedure

A. STH Sponsored Studies not using a CTU/CRO for full project management

1. Reporting of non-compliance

1.1 The Principal Investigator (PI) or other member of the research team identifies that a non-compliance with either GCP or the protocol has occurred.

1.1.1 The member of the research team identifying the non-compliance informs the PI of the non-compliance.

1.2 The PI or delegate records the non-compliance on the STH Non-Compliance Form and makes an initial assessment of whether the non-compliance may constitute a serious breach

1.3 Where the PI or delegate suspects that the non-compliance may constitute a serious breach the PI or delegate reports the non-compliance to their STH R&D Coordinator within 24 hours of becoming aware by faxing the non-compliance form to the Research Department

1.4 The R&D Coordinator notifies the QA Lead and Research Manager immediately of the potential Serious Breach and logs the receipt on the Research Department database

1.5 Where the non-compliance is not considered to be a serious breach the PI or delegate forwards the non-compliance form to the STH R&D Coordinator either by email or by post.

1.5.1 The R&D Coordinator logs receipt of the non-compliance form on the Research Department database.

1.5.2 The R&D Coordinator reviews the non-compliance form, taking advice from the QA Lead, Research Manager or delegate where necessary to decide whether the non-compliance could constitute a serious breach.

1.5.3 If the R&D Coordinator suspects that a Serious Breach may have occurred the R&D Coordinator reports their concerns immediately to the QA Lead or Research Manager

1.6 Non-compliances may also be detected by the Research Department during Monitoring Visits or For Cause Audits. In this case non-compliances will be recorded as findings on the Monitoring Report. If, as a result of the monitoring visit the R&D Coordinator conducting the visit suspects that a serious breach may have occurred the R&D Coordinator reports their concerns immediately to the QA Lead or Research Manager as described in SOP B131.

1.6.1 A serious breach may also be detected during review of the Monitoring Visit Report by the QA Lead or delegate. If the QA Lead or delegate suspects that a serious breach may have occurred the QA Lead or delegate reports their concerns immediately to the Research Manager as described in SOP B131

1.7 The Research Manager and/or QA Lead liaises with the PI or delegate as necessary to collect further information on the non-compliance.

1.8 The Research Manager and/or QA Lead liaises with the Director of R&D or delegate, and/or the study CI as appropriate to determine whether the non-compliance constitutes a serious breach

2. Where the sponsor (STH) categorises the non-compliance as non-serious

2.1 The R&D Coordinator determines whether any remedial action is required, taking advice from the QA Lead or Research Manager where necessary; action may include training in designated areas and/or amendment to the study protocol.

2.2 Where remedial action is required, the R&D Coordinator or QA Lead informs the PI in writing by letter or email copying in the Research Manager and or Director of R&D as appropriate outlining the remedial action required and a time frame for completing the actions.

2.3 Cessation of further recruitment may be required until remedial action is complete. For a CTIMP, if a temporary halt in recruitment or study suspension is deemed necessary this will be reported to the Ethics Committee and Regulatory Authority by way of substantial amendment within 15 days.

2.4 The R&D Coordinator ensures that all remedial action is completed satisfactorily within the specified time frame.

2.5 Where remedial action is not completed satisfactorily within the specified timeframe the R&D Coordinator reports the matter to the QA Lead and/or Research Manager.

2.5.1 The QA Lead or Research Manager re-reviews the non-compliance to determine whether the unresolved issue now constitutes a Serious Breach.

2.5.2 The QA Lead or Research Manager takes further actions to pursue resolution of the non-compliance as appropriate on a case by case basis.

2.5.2.1 If necessary, a for cause audit may be undertaken. In addition for cause audit of other studies conducted by the study team may be undertaken, and/or authorisation of new studies may be delayed until conditions are met

2.6 When conditions are met, a decision will be taken by the QA Lead or Research Manager as to whether more frequent monitoring than originally planned trial is required. If necessary, For Cause Audit of other studies conducted by the study team may be undertaken.

3. Where the study is a CTIMP and the sponsor (STH) categorises the non-compliance as a Serious Breach

3.1 The Research Manager or delegate immediately informs the CRO Director, Director of R&D, Medical Director, Chief Investigator and Clinical Director of relevant directorate(s) of the serious breach. Where the PI holds a substantive contract with another institution relevant persons at the employing institution are also informed. Where the serious breach has taken place at a non-STH site the Research Manager also informs the Director of R&D from that site (or R&D contact listed in the study agreement) of the Serious Breach.

3.2 The Research Manager or delegate reports the breach to the Ethics Committee and the Regulatory Authority within 7 days of the Serious Breach being confirmed.

3.3 The Research Manager liaises with the CRO Director, the Director of R&D and the QA Lead as appropriate to decide:

3.3.1 whether a For-Cause Audit or investigation of Research Misconduct should be undertaken.

3.3.2 whether temporary cessation of further recruitment or suspension of the study at the trial site is required.

3.3.3 what remedial action is required as a result of the breach.

3.3.4 whether audit of other studies conducted by the study team should be undertaken, and/or authorisation of new studies should be delayed until actions/conditions are met.

3.4 If a temporary halt in recruitment or study suspension is deemed necessary this will be reported to the Ethics Committee and Regulatory Authority within 15 days by way of substantial amendment.

3.5 The relevant Regulatory Authority and Ethics Committee each reviews the breach and informs the Sponsor and Investigator of any action required including suspension or termination of the study.

3.6 The Research Manager or delegate ensures that all remedial action/conditions required of the PI by the STH R&D Department, Ethics Committee and applicable Regulatory Authority is completed satisfactorily.

3.7 The Research Manager or delegate tracks the serious breach until conclusion, ensuring related correspondence is filed in the R&D Master File.

3.8 When actions/conditions are met, the Research Manager will confirm that any study suspension may be lifted. This must be done by way of substantial amendment to the Ethics Committee and Regulatory Authority. The substantial amendment must be approved by the Ethics Committee, Regulatory Authority and Research Department before the study recommences. The Research Manager with the QA Lead will also determine whether more frequent monitoring than originally planned is required.

4. Where the study is a non-CTIMP and the sponsor (STH) categorises the non-compliance as a Serious Breach

4.1 The Research Manager or delegate immediately informs the CRO Director, Director of R&D, Medical Director, Chief Investigator and Clinical Director of relevant directorate(s) of the serious breach. Where the serious breach has taken place at a non-STH site the Research Manager also informs the Director of R&D from that site (or R&D contact listed in the study agreement) of the serious breach.

4.2 Per NRES SOPs the CI reports the serious breach to the relevant Ethics Committee within 7 days of becoming aware of the breach. The Research Manager or delegate ensures that the CI is aware of the obligation and that the obligation is fulfilled.

4.3 The relevant Ethics Committee reviews the breach and informs the Sponsor and Investigator of any action required including suspension or termination of the study.

4.4 The Research Manager liaises with the CRO Director, the Director of R&D and the QA Lead as appropriate to decide:

4.4.1 whether a For-Cause Audit or investigation of Research Misconduct should be undertaken.

4.4.2 whether temporary cessation of further recruitment or suspension of the study at the trial site is required.

4.4.3 what remedial action is required as a result of the breach.

4.4.4 whether audit of other studies conducted by the study team will be undertaken, and/or authorisation of new studies should be delayed until actions/conditions are met.

4.5 The Research Manager or delegate ensures that all remedial actions/conditions required of the PI by the STH R&D Department and Ethics is completed satisfactorily.

4.6 The Research Manager or delegate tracks the serious breach until conclusion, ensuring related correspondence is stored in the study specific PST.

4.7 When actions/conditions are met, the Research Manager will confirm that any study suspension may be lifted. The Research Manager with the QA Lead will also determine whether more frequent monitoring than originally planned is required.

B. STH Sponsored Studies using a CTU/CRO for full project management

5. For studies using a CTU/CRO for full project management, detection, reporting and tracking of non-compliance, and assessment and reporting of Serious Breaches will be carried out in accordance with the CTRU/CRO's own SOPs and any study specific SOPs.

5.1 The division of responsibility for assessing and reporting Serious Breaches will be defined in the study specific agreement between the CTU/CRO and STH as sponsor.

5.2 Where CTU/CRO or study specific SOPs do not cover any aspect of management of non-compliance or Serious Breaches then this SOP will be followed.

5.3 Where management of non-compliance or Serious Breaches is not delegated to the CTU/CRO then this SOP will be followed.

C. Studies with an external sponsor

6. Reporting of non-compliance externally Sponsored studies

6.1 The Principal Investigator (PI) or other member of the research team identifies that a non-compliance with either GCP or the protocol has occurred.

6.1.1 The member of the research team identifying the non-compliance informs the PI of the non-compliance.

6.2 The PI or delegate records the non-compliance on the non-compliance form provided by the Sponsor or on the STH Non Compliance Form if no Sponsor form has been provided. The PI of delegate makes an initial assessment of whether the non-compliance may constitute a serious breach.

6.3 Where the PI or delegate suspects that the non-compliance may constitute a serious breach the PI or delegate reports the non-compliance to the Sponsor and to their STH R&D Coordinator within 24 hours of becoming aware.

6.4 Where the PI or delegate does not suspect that a serious breach has occurred the PI or delegate reports the non-compliance to the Sponsor using the procedure required by the study Sponsor

6.5 The Sponsor requests further information and makes an evaluation of whether the non-compliance constitutes a serious breach.

7. Where the sponsor categorises the non-compliance as non-serious

7.1 The PI or delegate undertakes the action required (e.g. patient withdrawn or continues) by the sponsor in accordance with the sponsor's SOPs.

7.2 If the PI or delegate had previously reported the non-compliance to STH R&D department as a possible serious breach then the PI or delegate informs the R&D Department of the sponsor decision

8. Where the sponsor categorises the non-compliance as a Serious Breach

8.1 As per the NRES SOPS and, where relevant, the Medicines for Human Use (Clinical Trials) Regulations, the Sponsor/CI is responsible for informing the relevant Ethics Committee and any relevant Regulatory Authority within 7 days of becoming aware of the serious breach.

8.2 The PI informs the R&D Coordinator of the sponsor decision immediately.

8.3 The R&D Coordinator notifies the Research Manager immediately and logs the Serious Breach on the Research Department database.

8.4 The Research Manager or delegate immediately informs the CRO Director, Director of R&D, Medical Director, Chief Investigator and Clinical Director of relevant directorate(s) of the serious breach. Where the PI holds a substantive contract with another institution, relevant persons at the employing institution are also informed.

8.5 The Research Manager liaises with the CRO Director, the Director of R&D and the QA Lead as appropriate to decide:

8.5.1 whether a for cause audit or investigation of Research Misconduct should be undertaken.

8.5.2 whether audit of other studies conducted by the study team will be undertaken, and/or authorisation of new studies should be delayed until actions/conditions are met

8.6 If the sponsor deems it necessary, temporary halt to further recruitment or suspension of the study at STH may be required. The sponsor is responsible for informing the Ethics Committee and any relevant Regulatory Authority within any relevant timelines if such a suspension is required.

8.7 The PI keeps the Research Department informed of all communication with and outcomes of the reviews conducted by the sponsor, Ethics Committee and any relevant Regulatory Authorities.

8.8 The sponsor is responsible for ensuring that all remedial actions/conditions required of the PI by the sponsor, Ethics Committee and any relevant Regulatory Authority is completed satisfactorily.

8.9 The Research Manager or delegate tracks the serious breach until conclusion, storing related correspondence in the study specific PST.

Appendix - Associated Documents

	Document	Research Department Network Location	Website	Database	Created by
1	Protocol non-compliance form	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	AL
2	MHRA Guidance for the notification of serious breaches of GCP or the trial protocol	NA	NA	NA	MHRA