York Foundation Trust R&D Unit
Standard Operating Procedure
R&D/S04

Breaches of GCP or the Study Protocol

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and/or Q-Pulse for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive versions of all R&D Unit SOPs appear online. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the R&D Unit's website: www.northyorksresearch.nhs.uk/sops.html and/or Q-Pulse

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Author:	Deborah Phillips
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Approved by:	Name/Position:	Lydia Harris, Head of R&D
	Signature:	Signed copy held by R&D Unit
	Date:	12th July 2017
	Name/Position:	Sarah Sheath, SOP Controller
	Signature:	Signed copy held by R&D Unit
	Date:	12th July 2017

This SOP will normally be reviewed every 3 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of significant changes
1.0	6th February 2009	
2.0	28th September 2009	Updated to include R&D Lead for Sponsoring Trust in assessment of severity of breach. New template used. In hosted studies, Investigator to notify R&D Unit when serious breach occurs at one of Alliance Trusts.
3.0	6th November 2009	Update to MHRA email address for reporting of serious breaches. More notification examples added.
4.0	21st November 2011	Addition of NRES requirements; change to SOP Controller; inclusion of requirements for non-CTIMP studies.
5.0	22nd April 2013	Updated following MHRA inspection to include Trust's responsibility to assess suspected serious breaches occurring on hosted studies. Fax number updated. Alliance reference removed. Head of R&D reference removed.
6.0	17th December 2015	Minor updates to R&D personnel responsibilities
7.0	14th August 2017	Slight change to title

Contents

1 Introduction, Background and Purpose

"Serious Breach" is a particularly significant concept for clinical trials of investigational medicinal products (CTIMPs). This is because there are specific legal obligations to identify and report them contained in the UK Clinical Trial Regulations (see Regulation 29A).

In addition, in York Teaching Hospital NHS Foundation Trust all studies, CTIMP and non-CTIMP, should be run to GCP-equivalent standards to ensure consistent practice and scientific quality.

Breaches should, therefore, be recorded for all studies and suspected serious breaches should be reported to the Sponsor. For non-CTIMPs they should, in addition, be reported to the Research Ethics Committee (REC); for CTIMPs they should also be reported to the REC and to the Medicines and Healthcare Products Regulatory Agency (MHRA).

2 Who Should Use This SOP

This SOP is relevant to all individuals involved in research studies taking place within York Teaching Hospital NHS Foundation Trust (the Trust) or in any other organisation that has a current contract with the Trust for use of its SOPs.

3 When this SOP Should be Used

The procedure described in this SOP should be followed when a breach of GCP or the study protocol is identified in:

(i) a research study sponsored by York Teaching Hospital NHS Foundation Trust;

(ii) a co-sponsored study where the sponsorship agreement states that York Teaching Hospital NHS Foundation Trust SOPs will be followed;

(iii) a research study hosted, but not sponsored, by York Teaching Hospital NHS Foundation Trust.

4 Procedure(s)

4.1 Identification of GCP or Protocol Breaches

What is a breach?

Research studies must be run in accordance with GCP and the Protocol

Protocol and GCP breaches may occur in research studies. Breaches are deviations from GCP or the study procedures as documented in the protocol, regulatory applications or local procedures.

Breaches can be serious or non-serious in nature. Not every deviation from the protocol represents a serious breach that must be reported to the regulatory authorities – the majority are technical deviations that do not result in

harm to the study subjects or significantly affect the scientific value of the reported results of the study. Breaches of this type, while they must be documented, are not serious breaches or reportable.

What is defined as a 'serious' breach?

This is a breach which is likely to effect to a significant degree:

(i) the safety or physical or mental integrity of the subjects; or

(ii) the scientific value of the study.

The breach may be of the conditions and principles of good clinical practice; or of the Protocol relating to that trial.

4.2 Documentation of ALL breaches

When identified, ALL breaches of GCP or protocol must be clearly and systematically documented, in order for appropriate corrective and preventative actions to be taken.

In York Teaching Hospital NHS Foundation Trust it is expected that any breaches (including non-serious breaches) should be documented and as a minimum recorded on the Protocol/GCP Deviations Log (R&D/F119) and in an explanatory file note (if appropriate). Breaches that may potentially be 'serious' require further action and should be notified using 'Suspected Serious Breach Notification to Sponsor Form' (R&D/F05), as detailed below.

Documentation of the breach should include as a minimum:

1. full details of the breach
2. the date and time of its occurrence
3. any remedial action undertaken
4. assessment by the CI or PI (or delegated individual) as to whether the breach is serious (include signature, date and time)

For Trust sponsored studies, the study monitor will review all breaches and associated documentation during monitoring visits. The monitor will assess whether each breach has been adequately identified and documented and will make an independent assessment of the severity of the breach. If the monitor notes a pattern of repetition of non-serious breaches this may amount to a quality control failure and become serious and reportable for that reason. The monitor will therefore scrutinise not only individual breaches but also the overall quality of management within the trial. All breaches and quality control failures will be reported fully in the monitoring report prepared for the Sponsor.

Studies hosted by York Teaching Hospital NHS Foundation Trust may be subject to auditing by the Trust. During this process all breaches will be assessed as described in the previous paragraph.

All breaches that occur during the course of a research study must be considered when the study report is written as they may have an impact on the analysis or interpretation of the data and they may need including in the study report (refer also to R&D/S27).

4.3 Reporting Procedures for Trust Sponsored Studies only

4.3.1 Notifying the Trust of a Breach that *may* be Serious [note: If there is ANY concern that a breach may be serious then the following should apply]

A breach in a Trust sponsored or co-sponsored study that is detected by any member of the research team or by the study monitor during a monitoring visit and assessed as possibly serious MUST be reported by the individual identifying the breach to the R&D Unit within 24 hours of the breach being identified.

The completed 'Suspected Serious Breach Notification to Sponsor Form' (see section 5) must be faxed to the R&D Unit on 01904 725700. [If the R&D Unit fax is unavailable for any reason then the notification may be emailed to research.governance@york.nhs.uk as this email address is checked every working day.] A member of the R&D Unit will acknowledge receipt of the notification of breach by noon of the next working day. Acknowledgement will be faxed to the fax number from which the breach was notified unless an alternative method of acknowledgement has been agreed with the R&D Unit in writing. It is the responsibility of the reporting individual to contact the R&D Unit immediately if no acknowledgement is received.

4.3.2 Trust Sponsor Assessment of Suspected Serious Breach

Upon receipt of a fax notifying a suspected serious breach the R&D Unit personnel receiving the notification will immediately inform the Head of R&D. If the Head of R&D is not available the notification will go to one of the following, in this order: (1) Research Advisor, (2) Research QA Manager, (3) Clinical Lead for Research in the Trust.

The Head of R&D (or alternate as above) will, unless there is urgent need for reporting that precludes this, consult the reporting individual, CI/PI, medical expert(s) named for the study (if applicable), and the R&D Clinical Lead for the Trust to determine whether and how the breach impacts on:

(i) the safety or physical or mental integrity of the study participants, or

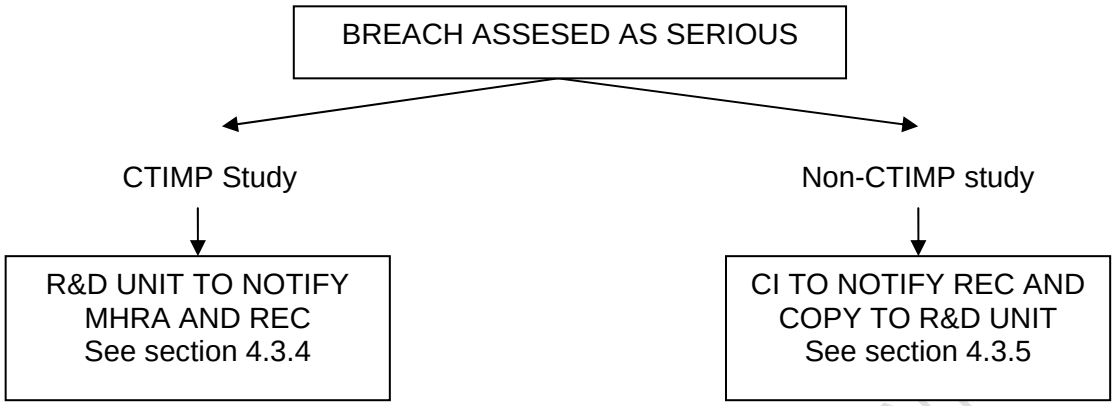
(ii) the scientific value of the study.

Contact details for the medical expert for the study (where applicable) will be retained in the Sponsor File.

The Head of R&D (or alternate as above) will reach a decision, on behalf of the Trust, as to whether the breach is serious in nature. This judgement depends on a variety of factors e.g. the design of the study, 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. This assessment must be undertaken urgently and documented in the Sponsor File and a copy retained in the R&D Unit central 'Suspected Breaches Folder' for ease of reference.

[Note: For CTIMP studies, if the potential for a breach to have significant impact on the scientific value of the trial is unclear, the MHRA should be contacted to discuss the issue.]

4.3.3 Notifying a Breach that has been assessed as Serious



Serious breaches occurring on CTIMP studies must be notified within specific timescales to both the MHRA and REC by the Trial Sponsor (see 4.3.4). For Trust sponsored studies the Head of R&D will nominate a 'Sponsor Representative' (who will normally be a member of the R&D Unit) to take on this role.

Serious breaches occurring on non-CTIMP studies only require reporting to the REC and responsibility for this notification is delegated by the Sponsor to the CI (see 4.3.5).

4.3.4 Notification for CTIMP studies only

If the R&D Unit (on behalf of the Trust) obtains clear and unequivocal evidence that a serious breach has occurred in a CTIMP study (as defined in Regulation 29A), then the nominated Sponsor Representative must notify the MHRA and REC within 7 days of receiving notification. The Sponsor Representative will also be responsible for investigating the serious breach and take additional appropriate corrective action simultaneously or after notification.

A template form for notifications of serious breaches to the MHRA is available from http://www.northyorksresearch.nhs.uk/sops.html (see section 5).

The completed notification form should be sent to both:

- the MHRA by email (GCP.SeriousBreaches@mhra.gsi.gov.uk)
- the REC by email

An acknowledgement of receipt should be requested and proof of sending should be filed by the Sponsor.

Note: If thought necessary then the MHRA Inspectorate may initially be contacted by telephone to discuss the breach but a written notification follow-up must also be submitted within 7 days of the R&D Unit becoming aware of the breach.

The Sponsor Representative must 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.).

For further advice refer to 'Guidance for the Notification of Serious Breaches of GCP or the trial protocol' available on the MHRA website.

4.3.5 Notifying for non-CTIMP studies

For non-CTIMP studies, the Serious Breach Notification to the REC Form (see section 5) should be completed by the Chief Investigator (or delegated other) and submitted to the REC, copied to the R&D Unit.

4.3.6 Following Regulatory Authority notification

Following the initial notification of serious breach to the MHRA and/or the REC, the R&D Unit, on behalf of the Sponsor, will perform a further review of the breach and prepare a report for consideration by the R&D Clinical Lead for the Trust and the R&D Group. Appropriate corrective actions will be implemented and any further information on the breach notified to the MHRA and/or REC.

Copies of all correspondence relating the breach will be securely retained by the R&D Unit in the central 'Breaches Folder'. Cross referencing file notes will be placed into the relevant study Sponsor Files. Where it is deemed appropriate, documentation may be copied across to the Sponsor file for archiving.

The R&D QA Manager (or alternate) will undertake a review of all suspected serious breaches occurring within the Trust (including both sponsored and hosted studies) every 6 months as a minimum. This review will aim to identify any pattern of related breaches that need to be addressed by the Sponsor or reported to the Regulatory Authorities. This review will be documented in the 'Breaches Folder' and copies of any resulting notifications also filed here.

4.4 Breaches in Externally Sponsored Studies Hosted by the Trust

In externally sponsored studies hosted by the Trust, all suspected serious breaches should be notified directly to the study sponsor contact person. In addition, and at the same time, the Head of R&D (or delegate) must also be notified that a suspected serious breach has occurred within the Trust.

This notification must be faxed to the R&D Unit on 01904 725700. [If the R&D Unit fax is unavailable for any reason then the notification may be emailed to research.governance@york.nhs.uk as this email address is checked every working day.] The notification can be the same notification that is sent to the study Sponsor or R&D/F05 may be used for this purpose. A member of the R&D Unit will acknowledge receipt of the faxed/or emailed notification of breach by noon of the next working day. Acknowledgement will be made to the fax number/email from which the breach was notified. It is the responsibility of the reporting individual to contact the R&D Unit immediately if no acknowledgement is received.

The Head of R&D (or alternate) will determine whether and how the breach impacts on:

(i) the safety or physical or mental integrity of the study participants, or

(ii) the scientific value of the study.

The Head of R&D (or alternate as above) will reach a decision, on behalf of the Trust, as to whether the breach is considered to be serious in nature.

The CI/PI will be responsible for ensuring that the R&D Unit is notified of the Sponsor assessment of the reported suspected serious breach as soon as this is confirmed.

In situations where there may be disagreement between the investigator and/or R&D Unit and an external Sponsor over the assessment of a breach then the Trust will exercise due diligence and give consideration as to whether it has a responsibility to direct report to the Regulatory Authorities. This decision will be made by the Head of R&D (or delegate) and documented in the R&D Unit central 'Breaches Folder' for ease of reference. A cross referencing file note should be placed in the Investigator Site File.

All serious breaches occurring on studies hosted by the Trust and notified to the Head of R&D will be reported to the R&D Group for consideration.

All non-serious breaches should be documented as described in section 4.2 unless Sponsor specific instructions exist.

5 Related SOPs and Documents

R&D/F05	Suspected Serious Breach Notification to Sponsor Form (All Studies)
R&D/F06	Serious Breach Notification Form – to MHRA and REC (CTIMPs only) (for Sponsor use)
R&D/F81	Serious Breach Notification Form – to REC (non-CTIMPs only) (for Investigator use)
R&D/F119	Protocol/GCP Deviations Log
R&D/S08	Monitoring of Trust Sponsored Research Studies
R&D/S71	Auditing of Research Studies and Processes
R&S/S28	Quality Assurance
R&D/S12	Receiving and Acknowledging Safety Notifications to the R&D Unit

APPENDIX

FOR A TRUST SPONSORED STUDY			
Is the breach serious?	NO	YES	DON'T KNOW
	Document in Protocol/GCP Deviations Log (R&D/F119) and explanatory file note (if appropriate). Include: - full details of the breach - the date and time of its occurrence - any remedial action undertaken - assessment by the CI or PI (or delegated individual) as to whether the breach is serious (include signature, date and time)	Fax a completed 'Suspected Serious Breach Notification to Sponsor Form' to the R&D Unit on 01904 725700/or email to reseach.governance@york.nhs.uk Assist with any assessment/ investigation by the R&D Unit with urgency.	Proceed as if 'YES'
FOR A HOSTED STUDY			
Is the breach serious?	NO	YES	DON'T KNOW
	Consider whether the Sponsor has any specific instructions for being notified. As a minimum, document in Protocol/GCP Deviations Log (R&D/F119) and explanatory file note (if appropriate).	Notify Sponsor as soon as aware. Notify R&D Unit also. Fax a completed 'Suspected Serious Breach Notification to Sponsor Form' to the R&D Unit on 01904 725700./or email research.governance@york.nhs.uk Assist with any assessment/ investigation by the Sponsor and/or R&D Unit with urgency. Notify the R&D Unit of the Sponsor's assessment of the breach.	Proceed as if 'YES'