Hull and East Yorkshire Hospitals NHS
NHS Trust

R&D Department

Notification of serious breaches of GCP or the trial protocol at HEYHT

When this document is viewed as a paper copy, the reader is responsible for checking that it is the most recent version.

The current version is available on the HEY internet Research & Development site
Click on GCP SOPs for HEY-sponsored CTIMPs
http://www.hey.nhs.uk/rd

Or the HEY intranet Research & Development site
Click on GCP SOPs
http://intranet/rd/

This SOP should be read in conjunction with policy CP129:
MANAGING HAZARDS AND INCIDENTS: REPORTING, INVESTIGATION AND ANALYSIS

SOP reference no:	**R&D GCP SOP 17**
Author:	**J Illingworth / J Pacynko**
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Date first approved:	**27.10.10**
Target audience:	**Research staff, R&D staff, pharmacy clinical trials staff**
Distribution:	**R&D internet and itranet site**
Signed off by R&D Director:	**Professor Nick Stafford**
Signature:	***Signed and dated copy kept in R&D***
Date:	
Signed off by R&D Manager:	**James Illingworth**
Signature:	***Signed and dated copy kept in R&D***
Date:	

This page should detail the version history for this SOP and the main changes corresponding to the versions.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 27.10.10		Original SOP approved by R&D Committee on 27.10.10.
Version 2, 26.01.15	J Pacynko	Web links up-dated. Page 5 and 6 in red type – recording of protocol deviations in CRFs, file notes and the protocol deviation form for the trial.

Please note

- **For definitions of acronyms refer to Appendix 2 of Management of SOPs.**
- **Refer to Appendix 3 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.**
- **Contact either the R&D QA Manager or Monitor for access to documents referred to in this SOP which are only available on the Trust's Y: drive in GCP SOPs & forms.**

1. PURPOSE, SCOPE and WHO SHOULD USE THIS SOP

- This SOP describes the process for declaration and notification of serious breaches of Good Clinical Practice (GCP) or the approved trial protocol.

- This SOP applies to all clinical trials using investigational medicinal products (CTIMPs) sponsored by Hull and East Yorkshire Hospitals NHS Trust (HEY).

- This SOP should be used by all staff involved with HEY sponsored CTIMPs for example, R&D staff, chief/principal investigators, co-investiagators or sub-investigators, research nurses, trial managers, trial co-ordinators, data managers, research staff, pharmacy staff, laboratory staff (list not exhaustive).

2. INTRODUCTION AND BACKGROUND

The EU GCP Directive 2005/28/EC was transposed into UK law as the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 on the 29th August 2006.

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). The amended regulation 29A states that:

Regulation 29A: Notification of serious breaches

(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.

These stipulations were incorporated into regulation 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. PROCEDURES

3.1 Responsibilities and timelines

- Any major deviations or breaches of the study should be notified by telephone or in person to the HEY R&D Manager, QA Manager, Monitor or Office **within 24 hours** of the deviation or breach being identified. If you are unsure whether a serious breach has occurred please discuss with the R&D Manager or Monitor by telephone or in person.

- It is the responsibility of the trial sponsor to assess whether a deviation or breach of the study is serious and therefore should be reported to the MHRA.

- It is the responsibility of the trial sponsor or a person legally authorised by the sponsor to notify the MHRA **within 7 days** of becoming aware of the serious breach.

- It is the responsibility of the sponsor to assess the impact of the breach on the scientific value of the trial.

- It is the investigators responsibility to notify R&D of protocol deviations and to record deviations in patients case report forms (CRFs) if applicable. At the end of each study visit in the CRF, there is a reminder to record any protocol deviations in the Protocol Deviations Log at the end of the CRF.

- The R&D monitor will ensure that the Protocol Deviations Form for the study is up-dated after monitoring visits.

- It is the responsibility of the investigator to include and consider any protocol deviations or breaches in the clinical study report at the end of the study, as they may have an impact on the analysis of the data.

3.2 Deviation or serious breach?

Deviations from clinical trial protocols and GCP can occur in clinical trials. Most of these deviations do not result in harm to the trial subjects or significantly affect the scientific value of the results of the trial.

Protocol deviations, and actions taken, will be documented in patients CRFs (if applicable) and in the Protocol Deviation Form for the study and explained in File Notes kept in the Trial Master File. The actions taken should be corrective and preventative.

The decision on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors including 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 (list not exhaustive).

3.3 Monitoring

Hull & East Yorkshire Hospitals NHS Trust will monitor and may audit clinical trials as part of its Quality Assurance procedures.

The R&D clinical trial monitor will review all deviations during monitoring visits. The monitor will assess whether each deviation has been adequately identified and documented and will make an independent assessment of the severity of the deviation. If the trial monitor notes a pattern of repetition of deviations this may become a serious breach and reportable for that reason. The monitor will assess individual deviations and also the overall quality of their management within the trial.

All deviations and serious breaches will be recorded on the Protocol Deviations Form for the study and will be recorded in the monitoring visit report. Frequently the monitor will be involved in preparing File Notes to fully document protocol deviations.

3.4 Information required by sponsor

The following information is required from the person reporting the suspected breach:

1. Name of Chief/Principal Investigator
2. R&D number
3. Title of the clinical trial
3. An explanation of how the breach was identified
4. Details of the breach
5. Date and time of breach
6. Number of study patients in the trial at the time of the breach
7. Which patients were affected by the breach.
8. Details of any initial corrective and preventative actions
9. Assessment of the impact the breach will have on the safety of trial study patients and scientific integrity of the trial.

With this information, the R&D manager, QA manager or monitor will complete the R&D form: Initial Review of Serious Breach of GCP or Trial Protocol in ***Appendix 1.***

3.5 Sponsor assessment of a Serious Breach

An investigation panel will be convened usually to include the R&D Director, R&D Manager, QA Manager and R&D Monitor.

The R&D Manager will discuss the issues with the Chief/Principal Investigator to identify which section of GCP or the protocol has been breached and how the breach impacts on subject safety and/or the scientific integrity of the trial.

The investigation panel will decide whether a breach is serious.

Examples of serious breaches can be found in the MHRA's Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol – Appendix II
http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con060111.pdf

The decision may require telephoning the MHRA to speak to an MHRA inspector for advice. The telephone conversation and outcome will be recorded on the R&D form: Initial Review of Serious Breach of GCP or Trial Protocol.

The investigation panel will decide if the trial should by temporarily halted. If this is so a letter will be sent from the R&D Director to the Chief/Principal Investigator. See ***Appendix 2*** for the letter template.

As per the letter, the investigation panel will meet with the Chief/Principal Investigator and the study team to discuss the serious breach and compile the facts for notification to the MHRA. The panel will work with the Chief/Principal Investigator to identify the extent of the serious breach and to initiate any safety measures that may be required.

The R&D Manager, QA Manager or Monitor will notify the Ethics Committee, who gave the favourable opinion for the trial, of the serious breach.

3.6 Temporary halt of a trial

Should the decision be to suspend the study until the breach has been investigated, a Notification of Amendment form will be completed by the R&D Manager (or nominated deputy) according to the instructions on the MHRA website at the link below.
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm#l12

Instructions taken from the MHRA link:
When a sponsor halts a trial temporarily, he should notify the MHRA and Ethics Committees immediately and at least within 15 days from when the trial is temporarily halted. The notification should be made as a substantial amendment using the Notification of Amendment form and clearly explain what has been halted (for example stopping recruitment and/or interrupting treatment of subjects already included) and the reasons for the temporary halt.

Substantial amendments relating to temporary halts should be submitted as PDF documents on disk to: Information Processing Unit, Area 6, Medicines & Healthcare products Regulatory Agency, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ.

To restart a trial that has been temporarily halted, the sponsor should make the request as a substantial amendment using the Notification of Amendment form and providing evidence that it is safe to restart the trial.

If a sponsor decides not to recommence a temporarily halted trial, the MHRA and Ethics Committees should be notified within 15 days of his decision, using the End of Trial Declaration form and including a brief explanation of the reasons for ending the trial.
The Chief/Principal Investigator will complete the End of Trial Declaration form on behalf of the sponsor.

3.7 Initial Notification of Breach to MHRA

The R&D Manager (or nominated deputy) will complete the Notification of Serious Breach of GCP or Trial Protocol form (***Appendix 4***).

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

GCP.SeriousBreaches@mhra.gsi.gov.uk

The R&D Manager (or nominated deputy) will be the contact person for all correspondence with the MHRA.

A copy of the Notification of Serious Breach form will also be sent to the Ethics Committee.

3.8 Provision of follow-up investigation report to the MHRA

Once the initial notification ***(Appendix 4)*** has been submitted to the MHRA, the serious breach investigation panel will review the breach in full to identify the extent of the breach.

In conjunction with the Chief/Principal Investigator, the serious breach investigation panel will compile an investigation report for submission to the MHRA (***see Appendix 5 for report template***).

The R&D Director and R&D Manager (or Medical Director) will review the investigation report and submit to the MHRA after confirmation by the Chief/Principal Investigator (signed and dated) that the content is accurate and true. A copy of this report will be sent to the Ethics Committee.

The MHRA may request additional information such as a copy of the protocol, ethics application, drug stability data, SOPs etc. The R&D Manager will liaise with the study team to obtain additional documents and submit them to the MHRA.

3.9 Planning and Implementing Corrective and Preventative Action

The serious breach investigation panel will work with the study team to devise a formal plan of corrective and preventative actions to address the breach. The corrective action plan will be submitted to the MHRA as part of the investigation report. Monitoring of the action plan will be undertaken by the R&D Department and most likely by the MHRA during any future GCP inspections.

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

4. DISSEMINATION AND IMPLEMENTATION

As part of the dissemination process, the R&D Department may send anonymised information regarding the breach to:

- Heads of appropriate departments for circulation amongst staff
- HEY staff that have signed up to receive R&D corporate emails.
- The appropriate internal research governance forum/committee.

Dissemination and implementation of this SOP will conform to the process outlined in R&D SOP 01 Management of SOPs.

5. 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.
http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con060111.pdf

Appendix 1: Initial Review of Serious Breach of GCP or trial protocol

R&D Number:	**Short Study Title:**				
Principal Investigator (PI) at HEYHT:			**Sponsor:**	**Funding Organisation:**	
Has the PI assessed the seriousness of the breach?	☐ Yes	☐ No	Has recruitment at this site ceased immediately?	☐ Yes	☐ No
Date of suspected GCP/ trial protocol breach : / /			Time of suspected GCP/ trial protocol breach : :		
Does the suspected breach relate to: ☐ Patient/participant safety ☐ Scientific validity of the data			Estimated number of participants affected by the breach:		

Details of how suspected breach was identified and overview of the GCP or trial protocol breach:

Details of decision of whether breach is serious: *details of telephone call to MHRA, date trial suspended (if applicable) etc*

Corrective and Preventative actions undertaken to date:			
R&D Staff member completing this form.			
Name:	**Signature:**	**Date:** / /	**Time:** :

Appendix 2

Research & Development Department
Office 13 2nd Floor Daisy Building
Castle Hill Hospital

[Insert date]
[Insert recipient address]

Dear [Insert name(s)]

Re: [Insert research title and reference number]

As a result of an issue relating to the above trial being brought to my attention, I have to inform you that, effective from today, recruitment into this trial is suspended pending the result of our investigations. Patients already recruited should continue as per protocol.

The issues of concern are:

1. [Insert list of known issues at time of writing the letter]

A serious breach investigation panel has been convened to include the following members:

- [Insert name] Research & Development Manager
- [Insert name] QA Manager
- [Insert name] Director of R&D
- [Insert name] R&D Clinical Trials Monitor
- [Insert other members as appropriate]

The initial Terms of Reference of the Investigation Panel are:

- To establish the events leading to the incident and identify the root cause(s).
- To review the overall current trial management to ensure compliance with the study protocol and Good Clinical Practice (GCP).
- To consider other events which may be relevant to the investigation.
- To identify educational/training requirements in relation to the incident.
- To make recommendations and form an action plan outlining corrective and preventative actions that have been, and will be, implemented.
- [Amend as appropriate]

A member of the panel will be in contact shortly to arrange an initial meeting to discuss the issues. I would hope that the concerns raised can be resolved quickly to ensure minimal disruption to the research. The incident has been given the unique identifier [insert reference number].

Please don't hesitate to contact any of the panel members for further information at this time. Thank you for your continue co-operation.

Yours sincerely
[Insert name] Director of Research & Development

FOR MHRA USE ONLY:	
GCP Unique ID:	
Triaging Inspector	

Appendix 3

Notification of Serious Breach of Good Clinical Practice or Trial Protocol

(Ref: UK Statutory Instrument 2004/1031 Regulation 29A, as amended by 2006/1928)

Please forward this notification to **GCP.SeriousBreaches@mhra.gsi.gov.uk** OR MHRA, Block 14, First Floor, 14F A06/07, FERA (The Food and Environment Research Agency), Sand Hutton, York YO41 1LZ

Your Name:		**Your Organisation:**
Your Contact Details:		**Date Breach Identified by Sponsor:**
		Date Breach Notified to MHRA:
Details of Individual or Organisation committing breach:		**Details of related study** (if applicable)**:** (e.g. EudraCT No, CTA number, study title)
Report: Tick appropriately	**Initial Report** ☐	**Follow-up Report** ☐

Please give details of the breach

Potential impact to patient safety and/or data credibility:

- ☐ Patient safety
- ☐ Patient confidentiality
- ☐ Approval Issues
- ☐ IMP
- ☐ Scientific value / data credibility
- ☐ NA/None
- ☐ Other Non-compliances (specify)

Background:

(continue on additional sheets if required)

Other relevant information:

(i.e. study status, site(s), ethics, trust, CRO /sponsor details etc.)

(continue on additional sheets if required)

Please give details of the action taken:

This should include: Any investigations by your organisation, details of investigations by other organisations (e.g. CRO/ethics/trust), the results and outcomes of the investigations (if known or details of when they will be available/submitted), how it will be reported in the final report/publication, the corrective & preventative action implemented to ensure the breach does not occur again.

(continue on additional sheets if required)

Actual impact to patient safety and/or data credibility:

☐ Patient safety	☐ Scientific value / data credibility
☐ Patient confidentiality	☐ NA/None
☐ Approval Issues	☐ Other Non-compliances (specify)
☐ IMP	

Appendix 4

Hull and East Yorkshire Hospitals NHS Trust

R&D Department

Serious Breaches of GCP or the Trial Protocol: Internal Investigation Report Template

When this document is viewed as a paper copy, the reader is responsible for checking that it is the most recent version.
The current version is available in the SOP section of the Research and Development site of the HEY intranet.

This page should detail the version history for this Template and the main changes corresponding to the versions.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, (add approved date)		Original template approved by R&D Committee on (add date)

Hull and East Yorkshire Hospitals NHS Trust

RESEARCH & DEVELOPMENT NOTIFICATION OF SERIOUS BREACH REPORT (TRIAL insert identifier)

[INSERT MONTH AND YEAR]

SERIOUS BREACH REPORT [INSERT MONTH AND YEAR]
Hull & East Yorkshire Hospitals NHS Trust Internal Investigation Report

CONTENTS **PAGE**

SUMMARY OF TRIAL (insert trial identifier)

Title:	
MREC:	
Eudract number	
Chief Investigator	
Funder:	
Sponsor:	
Date ReDA number assigned:	
Date of Ethics Approval:	
Date of Trust Approval:	
Method:	
Pre-study monitoring visit:	
Additional study monitoring visit:	
First patient recruited:	
Total number of patients recruited to date:	
Pharmacy issues:	
Outcome:	
Trial Design issues:	
Outcome:	
Version control/management issues: **[add issues columns as applicable]**	

1. PURPOSE OF THE REPORT

To summarise and present the findings established by the Hull and East Yorkshire Hospitals NHS Trust Research and Development Department following an investigation by the serious breach investigation panel into [insert one sentence summary of issue].

2. INVESTIGATION (incident/investigation/findings/recommendations)

Terms of Reference [amend as appropriate]

- To establish the events leading to the incident and identify the root cause(s).
- To review the overall current trial management to ensure compliance with the study protocol and Good Clinical Practice (GCP).
- To consider other events which may be relevant to the investigation.
- To identify educational/training requirements in relation to the incident.
- To make recommendations and form an action plan outlining corrective and preventative actions that have been, and will be, implemented.

Investigation Panel [others co-opted as necessary]

- [Insert name] Research & Development Manager
- [Insert name] QA Manager
- [Insert name] Director of R&D
- [Insert name] R&D Clinical Trials Monitor
- [Insert other members as appropriate]

Sources of data [examples below – amend as applicable]

- Incident reports (Datix)
- Interviews with key staff
- Initial stability data from the manufacturer
- Ethics correspondence including protocol versions approved
- Pharmacy records (*See Appendix 1 for table of supply information*)
- Drug accountability forms.

3. TIMELINE

[Insert brief overview of timelines and key milestones from initial notification to submission to MHRA]

The Trust has gathered sources of information and held discussions with key personnel involved in order to establish the facts surrounding the incident and to ensure that corrective and preventative actions can be put in place immediately.

(See Appendix 2 for detailed chronology of events and actions taken in the Trust).

4. KEY ISSUES

[Insert number] key issues were identified in need of further investigation as part of the Trusts declaration of a serious breach:

- [insert each issue heading]:

  [Insert summary paragraph for each key issue identified]

(See Appendix 4 for table documenting protocol version history [add as applicable]).

5. KEY CONTRIBUTING FACTORS

- [insert each contributing factor heading – should be one heading for each key issue above]:

  [Insert summary paragraph (or bullet points)for each contributing factor identified]

6. ROOT CAUSES

The investigation identified the following root causes precipitating this declaration of a serious breach to the MHRA:

- The failure of [list each identified root cause – there will usually be 2 or 3 root causes]

7. IMPACT ON PATIENT SAFETY & SCIENTIFIC VALIDITY

[Insert summary sentence of why there may be impact on patient safety and or scientific validity].The investigation has ascertained the following impact of this in relation to patient outcome:

- [list each impact]

As part of establishing the impact on outcome, in terms of patient safety the Trust [insert what action taken in this regard]

The Trust acknowledges its duty of care to inform the patients [insert details if applicable]. Patients will be notified following consultation with the Trust Communications Department [insert details if applicable].

It may be that the unauthorised shift in methodology away from the approved protocol, further compounded by the [insert details if applicable], limits the use of the data collected. The [insert details if applicable] significantly affects the scientific validity of the data preventing true comparison in the treatments.

8. RECOMMENDATIONS

As a matter of priority, the Trust Pharmacy Department [if applicable] should:

- [list all agreed actions]
- Implement and monitor all corrective and preventative actions taken to date and ongoing. (*See Appendix 3 for details of corrective and preventative actions taken by [insert]*).

As a matter of priority, the Trust Research and Development Department [if applicable] should:

- [list all agreed actions]
- Implement and monitor all corrective and preventative actions taken to date and ongoing. (*See Appendix 3 for details of corrective and preventative actions taken by [insert]*).

9. RISK ASSESSMENT

It should be noted that, [insert details of risk assessment]

10. LIKELIHOOD OF RECURRENCE

The recommendations and the associated corrective and preventative measures should minimise the risk of recurrence.

11. SHARING LESSONS

An anonymous case-study pulling out the lessons that can be learnt will be disseminated to all known researchers, the Research and Development Committee and the Trust Patient Quality, Safety Experience Committee (PQSE). The key issues will also be anonymised and included in the bi-monthly R&D Newsletter.

12. DISSEMINATION

The report will be disseminated to the following:[add others as applicable]

- MHRA
- Local Ethics Committee
- Chief Pharmacist
- Chief Investigator
- Medical Director
- General Manager – Clinical Governance

13. DECLARATION

Chief Investigator/Principal Investigator:

I declare that the content of the serious breach investigation report is, to the best of my knowledge, a true and accurate account.

Signed..... Date.....

Director of R&D (or nominated investigation panel lead):

I declare that the content of the serious breach investigation report is, to the best of my knowledge, a true and accurate account.

Signed..... Date.....

Appendices 1 – 5
[amend as applicable]

Table of patients [Example only - amend as applicable]

Study no.	Initials	Hospital Site	Treatment	Date dispensed	Results (outcome)	Comments

CHH = Castle Hill Hospital HRI = Hull Royal Infirmary

Table completed [insert date].

NOTIFICATION OF SERIOUS BREACH TIMELINE AND ACTIONS TAKEN BY R&D (insert trial identifier) **Appendix 2**

Date	Action taken	Comments/ongoing corrective and preventative actions.

CORRECTIVE AND PREVENTATIVE ACTIONS TAKEN /TO BE TAKEN [example – amend as applicable] **Appendix 3**

Trust R&D Department:		
	Action	**Date/Evidence**
1		
2		
3		
4		
5		
Trust Pharmacy		
	Action	**Date/Evidence**
1		
2		
3		
4		
5		
Chief Investigator		
	Action	**Date/Evidence**
1		

Appendix 4

Clinical Trial [insert title] (insert identifier)
Protocol versions [amend as applicable]

Version	Date of EC favourable opinion	Comments

Appendix 5

Stability Data

[Insert manufacturer stability data as applicable]