The University of Nottingham	**Sponsor Standard Operating Procedure**

Title: **TRIAL INITIATION**

SOP ref: TA008 **Version and date: 2.0 26th November 2010** **Superseded version and date:** **1.0 5th November 2008**	**Effective from date :** **13th December 2010** **Review cycle: 2 yrs after effective date**

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Signature:	**Date :**

Document history:	**Modification to previous version:**
1. v1.0 5th November 2008	1. Addition of responsibility for SOP training in section 2.2 2. Addition of SOP compliance form to section 3. 3. Change to web link in section 3. 4. Addition of sections 4.12.2 and 4.13.2 detailing SOP training. 5. Addition of monitoring duties to appendix A.

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1. PURPOSE and SCOPE

PURPOSE:
To provide instruction for the setting up of a new clinical trial at a site, obtaining local approvals, training of trial staff, the procedures and documentation required before trial commencement and subsequent record maintenance.

SCOPE:
Applicable to all clinical trials under the jurisdiction of the Department of Health Research Governance Framework, 2005; and/or the Medicines for Human Use (Clinical Trials) Regulations, SI 2004, 1031.

2. NOTES

2.1 The processes outlined in this SOP are to occur after national ethics committee and regulatory approvals have been sought. No trial shall commence at any site* before these approvals are given. Training and appointment of staff in anticipation of the trial commencing may occur but no participants may be recruited and no trial interventions may be given at a particular site until the national and individual local approvals are in place, trial agreements have been signed, trial staff are appropriately trained and all resources to carry out the trial at the site are in place.

2.2 The Chief Investigator has overall responsibility for the conduct of the trial, ensuring trial staffs are aware of and their adherence to Sponsor Standard Operating Procedures, GCP and the maintenance of records. For multi-site trials the Principal Investigator at each site is delegated the responsibility for the local trial conduct and management at that site under supervision of the CI. This includes appointment of trial staff, formal delegation of their duties and training in Sponsor SOPs.

2.3 It is the responsibility of the Chief Investigator to provide initial training in aspects of the trial and its management to each participating site. The local PI will then be responsible for ensuring that newly appointed trial staff are given appropriate training to carry out their trial duties.

2.4 It is the responsibility of the Chief Investigator to obtain local NHS Trust R&D or host organisation approval in order to conduct the trial at their site. This will be according to locally defined procedures.

2.5 It is the responsibility of the Principal Investigator to obtain, where necessary, National Research Ethics Service Site Specific Assessment and local NHS Trust R&D or host organisation approvals in order to conduct the trial at their Site. The latter two will be according to locally defined procedures.

2.6 For international trials the UK Chief Investigator (CI) shall consult with the appropriate international study committee (if any) or collaborators and agree a strategy for the provision of trial training and obtaining local approvals in order to carry out the trial.

* Site is defined as a participating organisation and sub-divisions thereof where recruitment of participants takes place and/or trial interventions are given.

3. CROSS REFERENCES

3.1 Ethics Application — SOP TA006

3.2 Sponsor / Chief Investigator clinical trial agreement

http://www.nottingham.ac.uk/ris/local/research-strategy-and-policy/research-agreements.php

3.3 Sponsor / Participating Site / Principal Investigator non-commercial trial agreement

http://www.nottingham.ac.uk/ris/local/research-strategy-and-policy/research-agreements.php

3.4	(Attendance at) Investigator Training	RF1 TA008
3.5	Site Responsibility (Delegation) Log	RF2 TA008
3.6	SOP Compliance Form	RF3 TA008
3.7	Document Control	SOP QA004
3.8	Trial Master File / Trial Site File: Set Up and Maintenance	SOP TA010
3.9	Trial Monitoring	SOP TA012
3.10	Delegated Trial Related Duties	Appendix A

4. PROCEDURE

The Chief Investigator shall:

4.1 Where required, obtain NRES Site Specific Assessment and NHS Trust R&D approval (as per SOP TA006, Ethics Application) for the trial at their site. The latter may be according to local procedures.
Where the site is not an NHS Trust permissions must be sought according to the requirement of the host organisation.

4.2 Agree to and sign the Sponsor/Chief Investigator clinical trial agreement between the CI and Sponsor. Two copies are required - one to be retained by the Sponsor and the other for retention in the Trial Master File.

4.3 Ensure that the following trial related duties are covered by delegation as appropriate to suitably qualified and experienced staff. Delegation is to be authorised by the CI and documented on RF2 TA008, Site Responsibility Log:

4.3.1 Document control and dissemination of trial related documents, including but not limited to the protocol, information sheets, consent forms, Case Report Forms, delegation log, subject recruitment log, Serious Adverse Event reporting form and any others as appropriate. Document control shall be according to SOP QA004.

4.3.2 The setting up and maintenance of a Trial Master File as per SOP TA010, Trial Master File / Trial Site File: Set Up and Maintenance.

4.3.3 Appropriate monitoring procedures are in place as per SOP TA012, Trial Monitoring, or according to the trial protocol.

4.3.4 For trials of Investigational Medical Products or Devices that procurement, storage, distribution, accounting and return of the product is managed according to the trial protocol and that appropriate records are retained. These must demonstrate a full audit trail of the product.

For multi-site trials:

4.4 Confirm suitability of the facilities and appoint through agreement a Principal Investigator at each participating site.

Note: Suitability and availability of facilities is assessed as part of the NRES Site Specific Assessment and R&D review at each site. The possibility of participating is usually determined before the ethics and regulatory applications.

4.5 Ensure that a non-commercial trial agreement between the PI, participating site and the Sponsor is disseminated to each site. Three original agreements are signed and two returned - one to the Sponsor and the other for retention in the Trial Master File, the third to be retained by the participating site.

4.6 Lead and instigate appropriate training in trial related procedures and responsibilities for their own and each participating site – see section 4.11.

The Principal Investigator shall:

4.7 Where required, obtain NRES Site Specific Assessment (as per SOP TA006, Ethics Application) and NHS Trust R&D or host organisation approvals for the trial at their site. The latter may be according to local procedures.
Where the site is not an NHS Trust permissions must be sought according to the requirement of the host organisation.

4.8 Ensure that there are appropriate medical, paramedical and clerical/data management staff to support the trial. Ensure that there are proper physical location and facilities to undertake the trial. Sign (themselves) and ensure that officials of the host organisation agree to and sign the non-commercial trial agreement. Copies are retained as given in 4.5. A (photo)copy may also be retained for the Trial Site File.

4.9 Ensure that the following trial related duties are covered, by delegation as appropriate to suitably qualified and experienced staff. Delegation is to be authorised by the PI and documented on RF2 TA008, Site Responsibility (Delegation) Log. Use the example codes given in Appendix A to identify the duties on this form.

4.9.1 Local document control and dissemination of trial related documents, including but not limited to the protocol, information sheets, consent forms, Case Report Forms, delegation log, recruitment log, Serious Adverse Event reporting form and any others as appropriate. Document control shall be according to SOP QA004.

4.9.2 The setting up and maintenance of a Trial Site File as per SOP TA010, Trial Master File / Trial Site File: Set Up and Maintenance.

4.9.3 Appropriate local monitoring procedures are in place as per SOP TA012, Trial Monitoring, or according to the trial protocol.

4.9.4 For trials of Investigational Medical Products or Devices that local procurement, storage, distribution, accounting and return of the product is managed according to the trial protocol and that appropriate records are retained. These must demonstrate a full audit trail of the product.

4.10 Participate in any trial training initiated by the Chief Investigator and take subsequent responsibility for the ongoing training of all staffs participating within any of the trial's activities.

Trial Training

The **Chief Investigator** shall:

4.11 Arrange for and deliver trial specific training to all staff likely to be involved in the trial. This must occur for the staff at both the Chief Investigator's site and all participating

sites. The CI may delegate the responsibility for training at each participating site to the local Principal Investigator, after assuring that each PI is appropriately trained.

4.12 Training sessions should cover key aspects of the protocol and address logistical and resource implications for the trial. A signed record should be maintained of training sessions and attendees. Record local training sessions on RF1 TA008, Investigator Training form, and file in the Trial Master File.

4.12.1 Regular updates should occur to provide training for new members of staff and to give direction in the event of any amendments to the trial regime and / or documentation. All training sessions should be recorded on RF1 TA008, Investigator Training form.

4.12.2 Ensure that all personnel engaged in trial related duties are aware of, have read and understood and agree to abide by the Sponsor SOPs as relevant to their role in the trial. All staff to sign the SOP Compliance Form, RF3 TA008, and this retained in the Trial Master File.

The **Principal Investigator** shall:

4.13 Arrange and deliver trial specific training to all local staff likely to be involved in the trial. Training sessions should cover key aspects of the trial and local logistical arrangements. Particular attention should be given to the reporting of safety incidents.

4.13.1 Regular updates should occur to provide training for new members of staff and to give direction in the event of any amendments to the trial regime and / or documentation. All training sessions should be recorded on RF1 TA008, Investigator Training form.

4.13.2 Ensure that all personnel engaged in trial related duties are aware of, have read and understood and agree to abide by the Sponsor SOPs as relevant to their role in the trial. All staff to sign the SOP Compliance Form, RF3 TA008 and this retained in the Trial Site File.

Appendix A — Delegated Trial Related Duties

The following trial related duties may be delegated and authorised as such by the Principal Investigator. Overall responsibility remains that of the PI and shall not be delegated but day-to-day practice, documentation and administration of the activity may be delegated to suitably qualified trial staffs.

A. Overall responsibility for study at Site and responsible for local financial management where appropriate	L. Completion and return of CRFs, including electronic entries
B. Medical care and supervision of trial patients	M. Authorisation of CRFs
C. Obtain local ethics committee and R&D approvals and communication of subsequent amendments	N. Respond to data queries
D. Ensuring all staff delegated to work on the trial are adequately informed as to the protocol requirements and trained in study procedures	O. Prescription of and administration of IMP
E. Delegation and authorisation of study related duties	P. Be familiar with IMP safety data and disseminate to staff
F. Act as document controller for trial related documents	Q. Ensure IMP accountability
G. Set up and maintenance of Site File	R. Documentation of adverse events and timely SAE reporting
H. Implementation of subject recruitment strategy and obtaining informed consent	S. Adhere to CI recommendations in response to SAEs
I. Screening of potential subjects	T. Collection of trial related biological samples
J. Obtaining consent and signing of consent forms (as appropriate to local policy & practice)	U. Initiation (training) of new trial personnel
K. Randomisation (allocation of trial intervention)	V. Prepare and be available for audit and inspections
	W. Archiving of trial data
	X. Responsibility for data monitoring.
	Others as locally applicable or trial specific (list):
	Y.
	Z.

The University of Nottingham	**Sponsor Standard Operating Procedure**

Title: **SERIOUS ADVERSE EVENT REPORTING**

SOP ref: **TA014**	**Effective from date :**
Version and date: **2.0 5th August 2010**	**1st September 2010**
Superseded version and date: **N/A**	**Review cycle:** **2 yrs after effective date**

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Signature:	**Date :**

Document history:	**Modification to previous version:**
1. Version 1.0, November 2008, superseded.	1. Instruction for eSUSAR reporting added, 2.3.1.1 2. In step 4.5.1 instruction to complete CIOMS form removed. 3. In step 4.5.2 notification address removed. 4. Instruction to inform the Sponsor added to 4.5.3. Order of steps 4.5.3 to 4.5.5 altered accordingly.

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1. PURPOSE and SCOPE

PURPOSE:
To describe the procedures for the reporting of Serious Adverse Events (SAEs) that may occur in clinical trials, in compliance with all applicable government directives, UK legislation and European guidance and directive documents.

SCOPE:
This SOP is applicable to all researchers conducting clinical trials that are governed by the Medicines for Human Use (Clinical Trials) Regulations, SI 2004, 1031 and/or the Department of Health Research Governance Framework, 2005.

2. NOTES

2.1 The definition of an SAE as given in the Medicines for Human Use (Clinical Trials) Regulations, SI 2004, 1031, shall be adopted within all clinical study protocols:

"A Serious adverse event, serious adverse reaction or unexpected serious adverse reaction means any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- results in death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect."

2.2 Subject to 2.1, the protocol shall make clear distinction between those events that may be expected because of known effects of the treatment given and the level at which they may be expected, and those events that are outside of these criteria and therefore require reporting as an SAE.
In the event of uncertainty or lack of clear distinction all SAEs must be reported.
Similarly, in the event of uncertainty of causality the SAE shall be assumed to be related to the treatment given and assessed accordingly.

2.3 SAEs must be reported **immediately** of knowledge of the event (but see section 4.2)

Clinical Trials of IMPs:

2.3.1 All Suspected Unexpected Serious Adverse Reactions (**SUSARs**) occurring in the trial at any of the participating sites, including outside the UK must be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) within **seven days** of knowledge of the event and any follow-up information and reports within a **further eight days**.

2.3.1.1 Reporting is electronic via the eSUSAR website. In order to be able to access this website and report for the University of Nottingham you must be allocated an account. Contact the Research Governance Team for this to be set up.

2.3.2 SUSARs occurring in the UK must be reported to the Research Ethics Committee (REC) for the trial within the same time-frames.
Non-UK SUSARs do not need to be reported to the REC but must be reported within the member state concerned according to local legislation.

2.3.3 SUSARs must be reported immediately to the Sponsor. Although the Sponsor delegates the responsibility of reporting to the MHRA, REC and other investigators

as required to the Chief Investigator or nominated deputy, the Sponsor shall be kept informed and be sent copies of all documentation relating to the SUSAR.

2.3.4 All SAEs and SARs (both non-SUSAR) should be reported to the Chief Investigator and any further reporting to the trial specific Data Monitoring Committees or any other group according to the protocol.

Non-IMP Clinical Trials:

2.3.5 SAEs for non-IMP trials deemed to be directly related to, or an unexpected result of, the trial procedure or treatment, require expedited reporting to the REC that gave a favourable opinion for the trial. Reporting should be within 7 days of knowledge of the event, with any follow-up information within a further 8 days.

2.3.6 All SAEs including those not deemed directly related to the trial treatment or procedures should be reported to the Chief Investigator and any further reporting to the trial specific Data Monitoring Committees or any other group according to the protocol.

2.4 Assessment of seriousness and any requirement for expedited reporting is the overall responsibility of the Chief Investigator. This duty may not be delegated. A deputy must be nominated.

2.4.1 The Chief Investigator and/or any investigator and the treating doctor must take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

2.4.2 If such measures are taken these should be reported immediately to the Chief Investigator who shall **inform the Sponsor** and any Principal Investigators no later than 3 days from the date the measures are taken. Where appropriate (the event is related to an Investigational Medicinal Product or directly to the trial procedures), the Chief Investigator shall give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

2.4.3 Events that lead to the suspension of the trial are classed as a substantial amendment and must therefore be notified to the MHRA and REC within fifteen days of the trial being suspended. See SOP TA013, Protocol Amendments.

2.5 For international trials the UK Chief Investigator (CI) has overall responsibility for safety assessment for the trial and will report to the appropriate international study committee and national competent authorities and ethics committees as required.

2.6 It is the responsibility of the local investigator in any UK NHS Trust to comply with the reporting guidelines for that NHS Trust.

3. CROSS REFERENCES

3.1 Statutory Instrument 2004 No.1031, The Medicines for Human Use (Clinical Trials) Regulations 2004, part 5.
3.2 The EU Directive, 2001/20/EC, April 2004, articles 16, 17 and 18.
3.3 Protocol Amendments — SOP TA013
3.4 SAE reporting form — RF1 TA014
3.5 Annual and Safety Reporting — WI1 TA014

4. PROCEDURE

4.1 All clinical and trials staff at the locations where the trial is conducted are responsible for identifying Serious Adverse Events (SAEs). The Principal Investigator must ensure that appropriate procedures are in place locally to provide assurance that SAEs are recognised and that staff are appropriately trained to fulfil the reporting requirements.

4.2 Trial staff are obliged, immediately upon knowledge of a serious event, to notify the Chief Investigator. In practice this should be within 24 hours of event onset or of the event being assessed as serious.

4.3 Notification shall be according to the procedure stipulated in the trial protocol or by using the standard SAE Reporting Form, RF1 TA014.

4.3.1 In the first instance a verbal report may be given e.g. telephone, in order to discuss the event and make provision for patient safety and any emergency measures necessary. The Principal Investigator in consultation with the Chief Investigator and other clinical colleagues as needed, must determine seriousness and causality of the event as soon as possible and define as such on form RF1 TA014.

4.3.2 RF1 TA014 must be signed by the local Principal Investigator or deputy and sent to the Chief Investigator immediately (fax or email – use a scanned signature if using this route) for corroboration and authorisation. Retain a copy locally in the Trial Site File (TSF).

The **Chief Investigator** shall:

4.4 Assess the event for seriousness, severity, causality and relatedness to any IMP or trial treatment and record this assessment on RF1 TA014 with an authorising signature.

4.4.1 If the event is deemed unrelated to the Investigational Medicinal Product or the trial procedures no further expedited safety reporting is required regardless of outcome. Return* a completed copy of the RF1 TA014 form to the Principal Investigator for inclusion in the Trial Site File. Retain the original form in the Trial Master File (TMF). *fax a photocopy or email an electronic copy using a scanned signature for authorisation

4.4.2 Ensure that the appropriate Case Report Form for the trial is completed and ensure the event is recorded according to the protocol.

Note: In the event of the CI or a deputy not being available for initial consultation regarding the severity and causality of the event then the PI shall take responsibility for the assessment, record as such on RF1 TA014, and take appropriate action depending on the assessment. In this instance the CI must be informed as soon as possible. The CI may then amend accordingly. Records of all amendments must be retained in both the TSF and TMFs.

Clinical Trials of IMPs:

4.5 In the event of an SAE being deemed a **SUSAR** the Chief Investigator must:

4.5.1 Report the SUSAR to the MHRA using the eSUSAR website:

https://esusar.mhra.gov.uk/

Note: For this you will need an account allocated by the University's eSUSAR Administrators - the Research Governance Team. Ensure that this is set up before the trial commences.

4.5.2 Login and click on 'report'. Select your trial then follow the on-screen instructions to add the SUSAR report and subsequently any additional information as it becomes available.

4.5.2.1 The eSUSAR website may also be used to report SUSARs originating in other EEA Member States to the MHRA. However, reporting to other EEA Member State Competent Authorities must be carried out in accordance with each individual Member State's requirements.

4.5.3 Inform the Sponsor: Download a PDF of the eSUSAR report and send via email to sponsor@nottingham.ac.uk. Add your contact details and any relevant supporting information to the email.

4.5.4 Inform the REC that approved the study. Use the REC reporting form and a covering letter:

http://www.nres.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=7660

A PDF of the eSUSAR report may also be submitted to the REC in addition to the REC form.

4.5.5 Inform any other trial committee or organisation that needs to be informed according to the trial protocol.

Non-IMP Clinical Trials:

4.6 In the event of an SAE being deemed directly related to *and* an unexpected result of any trial treatment or procedure the Chief Investigator must:

4.6.1 Within 7 days inform the REC that approved the study. Use the REC reporting form and a covering letter:

http://www.nres.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=311

Any follow-up information should be submitted within a further 8 days.

4.6.2 Inform any other trial committee or organisation that needs to be informed according to the trial protocol.

4.6.3 Inform the Sponsor.

All clinical trials:

4.7 The Chief Investigator / Principal Investigator shall send a copy of *all* subsequent correspondence to the Sponsor.

4.8 Copies of all correspondence and forms must be retained in the TSF and TMF and all SAE events reported in the annual safety and progress reports required by the MHRA and REC. See Work Instruction, WI1 TA014, Annual and Safety Reporting.

5. FLOW CHART

Not applicable.

The University of Nottingham	**Sponsor Standard Operating Procedure**

Title: **SERIOUS GCP BREACH REPORTING**

SOP ref: **TA016**	**Effective from date :**
Version and date: **1.0 30th March 2011**	**13th April 2011**
Superseded version and date: **N/A**	**Review cycle:** **2 yrs after effective date**

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Document history:	**Modification to previous version:**
1.	1.

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1. PURPOSE and SCOPE

PURPOSE:
To describe the procedures for the reporting of serious GCP breaches that may occur in clinical trials of investigational medicinal products, in compliance with all applicable government directives, UK legislation and European guidance and directive documents.

SCOPE:
This SOP is applicable to all researchers conducting clinical trials that are governed by the Medicines for Human Use (Clinical Trials) Regulations, SI 2004, 1031, its subsequent amendments and/or the Department of Health Research Governance Framework, 2005.

2. NOTES

2.1 The definition of a serious GCP breach as given in the Medicines for Human Use (Clinical Trials) Amendment Regulations, SI 2006, 1928, shall be adopted within all clinical study protocols:

"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."

2.2 "The Sponsor of a clinical trial (*of an investigational medicinal product*) shall notify the licensing authority (*MHRA*) 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 form time to time in accordance with regulations 22 to 25,
within 7 days of becoming aware of that breach."

2.2.1 In practice it is the Chief Investigator whom shall have responsibility for the reporting. The Sponsor must be kept informed at all stages. See 2.5

2.3 Subject to 2.2 the protocol shall make clear distinction between protocol violations or deviations and serious GCP breaches. A protocol violation or deviation is a change or departure from the clinical trial protocol and/or GCP that does not result in harm to the trial subjects or significantly affect the scientific value of the trial. Such deviations should be documented (e.g. in a case report form for the trial or trial master file) in order for appropriate corrective and preventative actions to be taken.

2.4 Serious GCP breaches occurring in the UK must be reported to the Research Ethics Committee (REC) for the trial within the same time-frames.
Non-UK breaches do not need to be reported to the REC but must be reported within the member state concerned according to local legislation.

2.5 Serious GCP breaches must be reported immediately to the Sponsor. Although the Sponsor delegates the responsibility of reporting to the MHRA, REC and other investigators as required to the Chief Investigator or nominated deputy, the Sponsor shall be kept informed and be sent copies of all documentation relating to the breach.

2.5.1 Reporting of the breach to the Trial Steering Committee and Independent Data Monitoring Committee may also be appropriate depending on the nature of the breach.

2.6 Assessment of seriousness and any requirement for expedited reporting is the overall responsibility of the Chief Investigator. This duty may not be delegated. A deputy must be nominated.

2.6.1 The Chief Investigator and/or any investigator and the treating doctor must take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

2.6.2 If such measures are taken these should be reported immediately to the Chief Investigator who shall **inform the Sponsor** and any Principal Investigators no later than 3 days from the date the measures are taken. Where appropriate (the event is related to an Investigational Medicinal Product or directly to the trial procedures), the Chief Investigator shall give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

2.6.3 Events that lead to the suspension of the trial are classed as a substantial amendment and must therefore be notified to the MHRA and REC within fifteen days of the trial being suspended. See SOP TA013, Protocol Amendments.

2.7 For international trials the UK Chief Investigator (CI) has overall responsibility for safety assessment for the trial and will report to the appropriate international study committee and national competent authorities and ethics committees as required.

2.8 It is the responsibility of the local investigator in any UK NHS Trust to comply with the reporting guidelines for that NHS Trust.

3. CROSS REFERENCES

3.1 Statutory Instrument 2004 No.1031, The Medicines for Human Use (Clinical Trials) Regulations 2004.
3.2 Statutory Instrument 2006 No.1928: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
3.3 Protocol Amendments SOP TA013

4. PROCEDURE

4.1 All clinical and trials staff at the locations where the trial is conducted are responsible for identifying serious GCP breaches The Principal Investigator must ensure that appropriate procedures are in place locally to provide assurance that such breaches are recognised and that staff are appropriately trained to fulfil the reporting requirements.

4.2 Trial staff are obliged, immediately upon knowledge of the event, to notify their Principal Investigator. In practice this should be within 24 hours of event onset of the event being suspected of being a serious GCP breach.

4.3 The Principal Investigator shall notify the Chief Investigator immediately of knowledge of the event. Notification shall be by writing a GCP Breach Report. This should follow the MHRA guideline and include the following:

Name of reporter
Name of the organization (University of Nottingham)
Contact details of the reporter
Study identifiers: title, Sponsor's reference, EudraCT number, CTA number

Date the breach was identified
Details of the individual or organization committing the breach (i.e. where it happened and by whom)
Details of the breach
Action taken

4.3.1 In the first instance a verbal report may be given e.g. telephone, in order to discuss the event and make provision for patient safety and any emergency measures necessary. The Principal Investigator in consultation with the Chief Investigator and other colleagues as needed, must determine seriousness and causality of the event as soon as possible and define as such on the GCP breach report.

4.3.2 The initial report must be signed by the local Principal Investigator or deputy and sent to the Chief Investigator immediately (fax or email – use a scanned signature if using this route) for corroboration and authorisation. Retain a copy locally in the Trial Site File (TSF).

Note: In the event of the CI or a deputy not being available for initial consultation regarding the severity and causality of the event then the PI shall take responsibility for the assessment and take appropriate action depending on the assessment. In this instance the CI must be informed as soon as possible.

The **Chief Investigator** shall:

4.4 Assess the event for seriousness, causality and impact on the trial conduct and continuation.

4.4.1 If the event is deemed not serious then that decision shall be recorded on the GCP breach report and authorised by signature. No further expedited reporting is required.

4.4.2 If the event is deemed a serious GCP breach the CI shall corroborate the report and send either that report or a completed new one with further details to the MHRA:

GCP-PV.Inspectors@mhra.gsi.gov.uk

4.4.2.1 Inform the Sponsor: via telephone or email to sponsor@nottingham.ac.uk. Add your contact details and any relevant supporting information to the email.

4.4.3 The Chief Investigator or Sponsor may initially contact the MHRA Inspectorate by telephone to discuss the breach and follow up with a written notification within 7 days of the Sponsor becoming aware of the breach.

4.4.4 Inform the REC that approved the study. Send a copy of the GCP breach report with a covering letter.

4.4.5 Amend the trial protocol as necessary following SOP TA013, Protocol Amendments, citing the reason for the amendment as following the actions taken to correct a serious GCP breach.

4.4.6 Inform any other trial committee or organisation that needs to be informed according to the trial protocol or as appropriate.

4.4.7 Retain all copies of all documentation in the Trial Master File (TMF).

MHRA response

4.5 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:

4.5.1 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.
4.5.2 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.
4.5.3 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.
4.5.4 Investigation by the MHRA, for example, triggered inspection(s).
4.5.5 Implementation of urgent safety measures, where appropriate.
4.5.6 Suspension or termination of a clinical trial authorisation, where appropriate.
4.5.7 Referral for enforcement action e.g. infringement notices, criminal investigation.
4.5.8 Referral to professional bodies e.g. the General Medical Council.

4.8 Copies of all correspondence to and from the MHRA must be retained in the TMF. Where further information and/or action is requested by the MHRA the Sponsor shall be included in the response and kept informed at all stages.

5. FLOW CHART

Not applicable.