Academic and Clinical Central Office for Research and Development

STANDARD OPERATING PROCEDURE FOR MANAGEMENT OF DEVIATIONS, VIOLATIONS AND URGENT SAFETY MEASURES

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DATE: 29th July 2010

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DATE APPROVED: 2nd August 2010

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DATE APPROVED: 29th July 2010

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(QA Group, ACCORD)

DATE RELEASED: 29th July 2010

1. PURPOSE

To describe the process of identifying, documenting and reporting deviations, violations and Urgent Safety Measures in Clinical Trials of Investigational Medicinal Products (CTIMPs) that are sponsored or co-sponsored by NHS Lothian (NHSL) and/or the University of Edinburgh (UoE).

2. APPLICABILITY

All researchers undertaking CTIMPs sponsored or co-sponsored by NHSL and/or UoE.

All members of the Academic and Clinical Central Office for Research and Development (ACCORD) who manage, coordinate or advise on clinical research sponsored or co-sponsored by NHSL and/or UoE.

3. POLICY

It is policy that researchers adhere to the protocol at all times (the only exception is when a deviation is required for the safety of a participant – see urgent safety measures section 4.1.3). It is the responsibility of the Principal Investigator that the trial is run in accordance to the trial protocol and to the principles of ICH GCP.

Deviations from the trial protocol or trial documents as approved by the main Research Ethics Committee (REC) and the Competent Authority (CA) or deviations from other information relating to the conduct of the trial, or deviations from ICH GCP may affect the safety or physical or mental integrity of trial participants or the scientific value of the trial.

Urgent safety measures may be required to protect trial participants from any immediate hazard to their health and safety.

Deviations, violations and urgent safety measures must be recorded in such a way that their impact on the trial can be independently assessed during conduct, reconstruction and reporting of the trial. Where there have been deviations from the protocol, full detail must be recorded which includes the corrective and preventative actions to avoid this occurring again.

4. PROCEDURE

4.1 Definitions

4.1.1 Deviation

Any departure from the approved protocol, trial documents or any other information relating to the conduct of the trial that does not result in harm to the trial participants or significantly affect the scientific value of the trial data.

Examples of deviations may include, but are not limited to:

- A protocol visit date deviation outside the study visit window;
- Isolated incident of a missed or incomplete study procedure (e.g. lab test);
- Isolated incident of a missed or incomplete study evaluation (e.g. exam).

4.1.2 Violation

Any departure from the approved protocol, trial documents or any other information relating to the conduct of the trial which may affect the safety or physical or mental integrity of the trial participants or the scientific value of the trial data.

Examples of violations may include, but are not limited to:

- Failure to obtain informed consent (i.e. no documentary evidence);
- Enrolment of participants that do not meet the inclusion/exclusion criteria;
- Undertaking a trial procedure not approved by the main REC, CA or local NHS R&D department (unless for immediate safety reasons);
- Failure to report adverse events, serious adverse events or SUSARs in accordance with the legislation, such that trial participants, or the public are put at significant risk;
- Investigational Medicinal Product(s) dispensing, labelling or dosing error.

4.1.3 Urgent Safety Measure

Investigators may implement a deviation from, or a change of the protocol only in a case to eliminate an immediate hazard to trial participants without prior approval from the main REC, CA and local NHS R&D department. This is defined as an urgent safety measure and must be reported to the main REC, CA, local NHS R&D department(s) and ACCORD immediately.

4.2 Recording Deviations and Violations

4.2.1 It is the responsibility of Investigators to identify deviations or violations as they occur.

4.2.2 A Log of Deviations, Violations and Urgent Safety Measures (Attachment 1) must be maintained.

4.2.3 A Deviation/Violation Form (Attachment 2) must be completed to assess if the departure is a deviation or a violation.

4.2.4 Deviation/Violation Forms and the Log of Deviations, Violations and Urgent Safety Measures are essential documents and must be stored in the Investigator Site File (ISF).

4.2.5 Responsibility for completing the form and maintaining the log may be delegated to named persons on the Study Delegation Log.

4.2.6 The forms and log will be checked at monitoring visits.

4.2.7 Forms leading to identification of a violation must be submitted to ACCORD.

4.2.8 The log must be provided to ACCORD at the end of trial and will be included in the QA check of the end of trial report.

4.3 Reporting Violations

4.3.1 If a departure is assessed as a violation, a copy of the Deviation/Violation Form must be submitted to ACCORD within 3 days of becoming aware of the violation.

4.3.2 A copy of the completed Deviation/Violation Form must be filed in the ISF.

4.3.3 ACCORD will file a copy of the Deviation/Violation Form in the Trial Master File (TMF).

4.3.4 A violation may trigger a monitoring visit.

4.3.5 The Sponsor may assess a violation as a Serious Breach and further assessment, escalation and notification may be required according to

ACCORD SOP25 Escalation and Notification of Serious Breaches of GCP or the Trial Protocol.

4.4 Recording and Reporting Urgent Safety Measures

4.4.1 Investigators may implement a deviation from, or a change of the protocol to eliminate an immediate hazard to trial participants without prior approval from the main REC and CA. This is defined as an urgent safety measure and must be reported to the main REC, CA, local NHS R&D department(s) and ACCORD.

4.4.2 The Investigator is responsible for deciding on the appropriate action required to protect participant safety, but where possible the decision to implement an urgent safety measure should be discussed with a co-Investigator or member of the Data Monitoring Committee (DMC). Such discussions should be documented in the ISF and passed to ACCORD if requested.

4.4.3 The Investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately when an urgent safety measure is taken at a site.

4.4.4 The Investigator must then notify the MHRA, the main REC, local NHS R&D department(s) and ACCORD in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

4.4.5 During a period in which a disease is pandemic and is a serious risk to human health or potentially a serious risk to human health, notification must be provided to the MHRA, main REC, local NHS R&D department(s) and ACCORD as soon as possible.

4.4.6 The substantial amendment must include a covering letter detailing the measures taken, the reason for them and the medical assessor initially contacted; a Notification of Amendment Form (Attachment 3); and supporting documentation.

4.4.7 The template Urgent Safety Measure Form (Attachment 4) may be used to ensure the information required in a covering letter is included.

4.4.8 The Notification of Amendment Form, covering letter and supporting documentation must be:

1. Faxed to the Clinical Trials Unit on 020 7084 2443 or sent by email to clintrialhelpline@mhra.gsi.gov.uk marked urgent safety measure; and
2. Sent as PDF documents on disc to Information Processing Unit, Area 6, Medicines and Healthcare Products Regulatory Agency, Market Towers, 1 Nine Elms Lane, London, SW8 5NQ; and
3. Faxed to the ACCORD Research Governance & QA Office on **+44 (0)131 242 9447** or sent by email to researchgovernance@ed.ac.uk marked urgent safety measure; and
4. Sent to the relevant main REC by fax or email, marked urgent safety measure; and
5. Sent to the local NHS R&D department(s), marked urgent safety measure.

4.4.9 A copy of the notification must be filed in the ISF.

4.4.10 ACCORD will file a copy of the notification in the TMF.

5. ATTACHMENTS

1. ACCORD template Log of Deviations, Violations, Serious Breaches and Urgent Safety Measures
2. ACCORD template Deviation/Violation Form

3. Notification of Amendment Form
4. Urgent Safety Measure Form

6. RELEVANT DOCUMENTS

1. ACCORD SOP 25 "SOP for Escalation and Notification of Serious Breaches of GCP or the Trial Protocol".

2. ACCORD SOP 11 "SOP for Identifying, Recording and Reporting Adverse Events for Trials of Investigational Medicinal Products".

7. DEFINITIONS

ACCORD	**Academic and Clinical Central Office for Research and Development**
CA	**Competent Authority**
CI	**Chief Investigator**
CTIMP	**Clinical Trial of an Investigational Medicinal Product:** A drug trial falling within the scope of the EU Clinical Trials Directive (2001) and the Medicines for Human Use (Clinical Trials) Regulations (2004) and amendments thereto.
GCP	**Good Clinical Practice**
ISF	**Investigator Site File**
MHRA	**Medicines and Healthcare products Regulatory Agency**
NHSL	**NHS Lothian**
PI	**Principal Investigator**
REC	**Research Ethics Committee**
SOP	**Standard Operating Procedure**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TMF	**Trial Master File**
UoE	**University of Edinburgh**

8. REFERENCES

The Medicines for Human Use (Clinical Trials) Regulations 2004, (SI 2004 No. 1031) and any relevant amendments.

DOCUMENT HISTORY

Version Number:	Edited by (job title):	Effective Date:	Details of editions made:
2.0	Marise Bucukoglu (Clinical Trials & Research Governance Manager)	06/08/2010	Remove major and minor violations to simplify classification. Administrative changes.
1.0	Marise Bucukoglu (Clinical Trials & Research Governance Manager)	04/03/2010	New

ATTACHMENT 1

Log of Deviations/Violations/Urgent Safety Measures

Study Title	
EudraCT Number	
Principal Investigator	
Site name and address	

Date added to log	**Event date**	**Participant number**	**Is this a** 1. Deviation 2. Violation 3. Urgent safety measure	**Site Corrective Actions**	**Site Preventative Actions** (e.g. protocol amended, trial halted)	**Violation** Date reported to ACCORD	**Urgent Safety Measure** Date reported to the MHRA, REC, NHS R&D department(s) and ACCORD

ATTACHMENT 2

DEVIATION/VIOLATION REPORT FORM

DO NOT SEND IDENTIFIABLE DATA WITH THIS FORM*

1. REPORT DETAILS	
EudraCT number	
REC number	
Trial title	
Centre number	
Country reported from	
Participant number	
Participant initials	
2. DETAILS OF DEVIATION	
Date occurred	
Description	
Reason for deviation	

3. ASSESSMENT		
Does the deviation have an impact on:		
Safety of participant	**Yes** ☐ **No** ☐	**Details**
Integrity of trial data	**Yes** ☐ **No** ☐	**Details**

If yes to either of the above, deviation is considered as a violation and the following sections should be completed:

4. ACTIONS TAKEN		
Date		
	Corrective action	
	Preventative action	
	Reported to ACCORD within 3 days of becoming aware of violation **Fax +44 (0)131 242 9447**	

DEVIATION/VIOLATION REPORT FORM

DO NOT SEND IDENTIFIABLE DATA WITH THIS FORM*

5. INFORMATION SOURCE	
Name, address and telephone number of PI	
Date of report	
PI signature	

FOR ACCORD USE ONLY		
Date report form received		
Does the violation have a <u>significant</u> impact on:		
Safety of participant	**Yes** ☐ **No** ☐	**Details**
Integrity of trial data	**Yes** ☐ **No** ☐	**Details**
If yes to either of the above, violation may be considered as a <u>serious breach</u> and the following sections should be completed:		
ACTIONS TAKEN		

Date		
	Initial notification to MHRA within 7 days of becoming aware of serious breach **Email** GCP-PV.inspectors@mhra.gsi.gov.uk	

Signed on behalf of the University of Edinburgh	Signed on behalf of NHS Lothian
Refer to ACCORD SOP25 Escalation and Notification of Serious Breaches of GCP or the Trial Protocol for further procedures and documentation.	

ATTACHMENT 3

NOTIFICATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY

For official use:

Date of receiving the request:	Grounds for non acceptance/ negative opinion: ❑ Date:
Date of start of procedure:	Authorisation/ positive opinion: ❑ Date:
Competent authority registration number of the trial: Ethics committee registration number of the trial:	Withdrawal of amendment application ❑ Date:

To be filled in by the applicant:
This form is to be used both for a request to the Competent Authority for authorisation of a **substantial** amendment and to an Ethics Committee for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.

A TYPE OF NOTIFICATION

A.1 Member State in which the substantial amendment is being submitted:	
A.2 Notification for authorisation to the competent authority:	☐
A.3 Notification for an opinion to the ethics committee:	☐
A.4 Notification for information only[1]:	☐
A.4.1 To the competent authority	☐
A.4.2 To the Ethics committee	☐

B TRIAL IDENTIFICATION *(When the amendment concerns more than one trial, repeat this form as necessary.)*

B.1 Does the substantial amendment concern several trials involving the same IMP?	yes ☐ no ☐
B.1.1 If yes repeat this section as necessary.	

B.2 EudraCT number:
B.3 Full title of the trial :
B.4 Sponsor's protocol code number, version, and date:

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1	**Sponsor**
C.1.1	Organisation:
C.1.2	Name of person to contact:
C.1.3	Address :

[1] For substantial amendments to information that only the CA has previously assessed (e.g. quality data in most of the MS), the sponsor should not only submit the amendment to the CA but also inform the ethics committee that they have made the notification indicating that it is "for information only". Similarly, the sponsor should inform the CA of any notification of a substantial amendment to information which was previously only assessed by the ethics committee (e.g. facilities for the trial).

C.1.4	Telephone number :
C.1.5	Fax number :
C.1.6	e-mail:

C.2	**Legal representative[2] of the sponsor in the Community for the purpose of this trial (if different from the sponsor)**
C.2.1	Organisation:
C.2.2	Name of person to contact:
C.2.3	Address :
C.2.4	Telephone number :
C.2.5	Fax number :
C.2.6	e-mail:

D APPLICANT IDENTIFICATION, (please tick the appropriate box)

D.1	**Request for the competent authority**	
D.1.1	Sponsor	☐
D.1.2	Legal representative of the sponsor	☐
D.1.3	Person or organisation authorised by the sponsor to make the application.	☐
D.1.4	Complete below:	
D.1.4.1	Organisation :	
D.1.4.2	Name of person to contact :	
D.1.5	Address :	
D.1.5.1	Telephone number :	
D.1.5.2	Fax number :	
D.1.5.3	E-mail	

D.2	**Request for the Ethics Committee**	
D.2.1	Sponsor	☐
D.2.2	Legal representative of the sponsor	☐
D.2.3	Person or organisation authorised by the sponsor to make the application.	☐
D.2.4	Investigator in charge of the application if applicable[3]:	
	• Co-ordinating investigator (for multicentre trial)	☐
	• Principal investigator (for single centre trial):	☐
D.2.5	Complete below	
D.2.5.1	Organisation :	
D.2.5.2	Name :	
D.2.5.3	Address :	
D.2.5.4	Telephone number :	
D.2.5.5	Fax number :	
D.2.6	E-mail :	

[2] As stated in Article 19 of Directive 2001/20/EC.
[3] According to national legislation.

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1	**Sponsor's substantial amendment code number, version, date for the clinical trial concerned:**

E.2	**Type of substantial amendment**	
E.2.1	**Amendment to information in the CT application form**	yes ☐ no ☐
E.2.2	**Amendment to the protocol**	yes ☐ no ☐
E.2.3	**Amendment to other documents appended to the initial application form**	yes ☐ no ☐
E.2.3.1	If yes specify:	
E.2.4	**Amendment to other documents or information:**	yes ☐ no ☐
E.2.4.1	If yes specify:	
E.2.5	**This amendment concerns mainly urgent safety measures already implemented**	yes ☐ no ☐
E.2.6	**This amendment is to notify a temporary halt of the trial**	yes ☐ no ☐
E.2.7	**This amendment is to request the restart of the trial**	yes ☐ no ☐

E.3	**Reasons for the substantial amendment:**	
E.3.1	**Changes in safety or integrity of trial subjects**	yes ☐ no ☐
E.3.2	**Changes in interpretation of scientific documents/value of the trial**	yes ☐ no ☐
E.3.3	**Changes in quality of IMP(s)**	yes ☐ no ☐
E.3.4	**Changes in conduct or management of the trial**	yes ☐ no ☐
E.3.5	**Change or addition of principal investigator(s), co-ordinating investigator**	yes ☐ no ☐
E.3.6	**Change of sponsor, legal representative, applicant**	yes ☐ no ☐
E.3.7	**Change/addition of site(s)**	yes ☐ no ☐
E.3.8	**Change in transfer of major trial related duties**	yes ☐ no ☐
E.3.8.1	**If yes, specify:**	
E.3.9	**Other change**	yes ☐ no ☐
E.3.9.1	**If yes, specify:**	
E.3.10	**Other case**	yes ☐ no ☐
E.3.10.1	**If yes, specify**	

E.4	**Information on temporary halt of trial**	
E.4.1	**Date of temporary halt** (YYYY/MM/DD)	
E.4.2	**Recruitment has been stopped**	yes ☐ no ☐
E.4.3	**Treatment has been stopped**	yes ☐ no ☐
E.4.4	Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment	
E.4.5	**What is (are) the reason(s) for the temporary halt?**	
E.4.5.1	Safety	yes ☐ no ☐
E.4.5.2	Lack of efficacy	yes ☐ no ☐
E.4.5.3	Other	yes ☐ no ☐
E.4.5.3.1	If yes to other, specify :	
E.4.6	**Briefly describe (free text)**:	

- Justification for a temporary halt of the trial
- The proposed management of patients receiving treatment at time of the halt *(free text):*
- The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product *(free text):*

F REASONS FOR SUBSTANTIAL AMENDMENT *(one or two sentences):*

G BRIEF DESCRIPTION OF THE CHANGES *(free text)***:**

H CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN THE MEMBER STATE CONCERNED BY THIS AMENDMENT

H.1 Type of change
H.1.1 **Addition of a new site**
H.1.1.1 **Principal investigator** (provide details below)
H.1.1.1.1 Given name
H.1.1.1.2 Middle name (if applicable)
H.1.1.1.3 Family name
H.1.1.1.4 Qualifications (MD……..)
H.1.1.1.5 Professional address
H.1.2 **Removal of an existing site**
H.1.2.1 **Principal investigator** (provide details below)
H.1.2.1.1 Given name
H.1.2.1.2 Middle name (if applicable)
H.1.2.1.3 Family name
H.1.2.1.4 Qualifications (MD……..)
H.1.2.1.5 Professional address
H.1.3 **Change of co-ordinating investigator** (provide details below of the new coordinating investigator)
H.1.3.1 Given name
H.1.3.2 Middle name
H.1.3.3 Family name
H.1.3.4 Qualification (MD…….)
H.1.3.5 Professional address
H.1.3.6 Indicate the name of the previous co-ordinating investigator:
H.1.4 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)
H.1.4.1 Given name
H.1.4.2 Middle name
H.1.4.3 Family name
H.1.4.4 Qualifications (MD……..)
H.1.4.5 Professional address
H.1.4.6 Indicate the name of the previous principal investigator:

I CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

I.1 Change of e-mail contact for feedback on application*	
I.2 Change to request to receive an .xml copy of CTA data	yes ☐ no ☐
I.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT?	yes ☐ no ☐
I.2.1.1 If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses):	
I.2.2 Do you want to receive this via password protected link(s)[4]?	yes ☐ no ☐
If you answer no to question I.2.2 the .xml file will be transmitted by less secure e-mail link(s)	
I.2.3 Do you want to stop messages to an email for which they were previously requested?	yes ☐ no ☐
I.2.3.1 If yes provide the e-mail address(es) to which feedback should no longer be sent:	
(*This will only come into effect from the time at which the request is processed in EudraCT).	

J LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM

Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

J.1 Covering letter stating the type of amendment and the reason(s)	☐
J.2 Summary of the proposed amendment	☐
J.3 List of modified documents (identity, version, date)	☐
J.4 If applicable, pages with previous and new wording	☐
J.5 Supportive information	☐
J.6 Revised .xml file and copy of initial application form with amended data highlighted	☐
J.7 Comments on any novel aspect of the amendment if any :	

[4] This requires a EudraLink account. (See www.eudract.emea.eu.int for details)

K SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

K.1 I hereby confirm that/ confirm on behalf of the sponsor that (delete which is not applicable)

- The above information given on this request is correct;
- The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and
- It is reasonable for the proposed amendment to be undertaken.

K.2 APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY(as stated in section C.1):☐
K.2.1 Signature [5]:
K.2.2 Print name :
K.2.3 Date :

K.3 APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE (as stated in section C.2): ☐
K.3.1 Signature [6]:
K.3.2 Print name:
K.3.3 Date :

[5] On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.
[6] On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.

ATTACHMENT 4

NOTIFICATION OF URGENT SAFETY MEASURE FORM

(To be completed by the Chief Investigator)

WITHIN 3 DAYS OF TAKING AN URGENT SAFETY MEASURE:

Complete this form and a Notification of Amendment form. Provide with any supporting documentation as follows:

- Fax to the MHRA Clinical Trials Unit on 020 7084 2443 or send by email to clintrialhelpline@mhra.gsi.gov.uk.
- Send as PDF documents on disc to Information Processing Unit, Area 6, Medicines and Healthcare Products Regulatory Agency, Market Towers, 1 Nine Elms Lane, London, SW8 5NQ.
- Send to the relevant main REC by fax or email.
- Send to the local NHS R&D department(s).
- Fax to the ACCORD Research Governance & QA Office on **+44 (0)131 242 9447** or send by email to researchgovernance@ed.ac.uk.

Retain copies of all documentation in the ISF. ACCORD will file a copy in the TMF.

1. CHIEF INVESTIGATOR DETAILS	
Name	
Address	
Telephone	
Email	
Fax	
Ensure contact details are where the Chief Investigator can be contacted to discuss the urgent safety measure.	
2. DETAILS OF STUDY	
EudraCT number	
REC number	
Trial title	

NOTIFICATION OF URGENT SAFETY MEASURE FORM

(To be completed by the Chief Investigator)

3. DETAILS OF URGENT SAFETY MEASURE	
Date implemented	
Name of MHRA Medical Assessor contacted	
Circumstances giving rise to urgent safety measure	
Measures taken	
Additional notes	
CI signature	
CI name	
Date	