STANDARD OPERATING PROCEDURE

SOP 210

Managing Protocol and Regulatory Non-Compliance including Serious Breaches

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1 ABBREVIATIONS

CAPA	Corrective and Preventative Action plan
CI	Chief Investigator
CRF	Case Record Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
HRA	Health Research Authority
ICH	International Conference for Harmonisation
ISF	Investigator Site File
JRO	Joint Research Office
MHRA	Medicines and Healthcare products Regulatory Agency
NNUH	Norfolk and Norwich University Hospital
PI	Principal Investigator
R&D	Research & Development at NNUH
REC	Research Ethics Committee
RIN	Research and Innovation Services at UEA
SOP	Standard Operating Procedure
TMF	Trial Master File
UEA	University of East Anglia

2 INTRODUCTION

The aim of this SOP is to describe the processes to be followed for identifying, recording and reporting cases of non-compliance with the trial protocol, SOPs, GCP and/or regulatory requirements for studies sponsored by the University of East Anglia (UEA) or the Norfolk and Norwich University Hospital (NNUH). This includes discovery of a course of action or event, which may constitute either a minor non-compliance, a major non-compliance or a serious breach from the approved protocol, SOPs, GCP and/or regulatory requirements.

It is the Sponsor's responsibility to ensure that research is undertaken in compliance with the approved protocol and SOPs and in accordance with GCP and regulatory requirements.

These procedures will ensure that appropriate action is taken for the protection of patients, maintenance of trial integrity, and compliance with legal requirements and any applicable regulatory guidance.

3 SCOPE

This SOP applies to all healthcare research sponsored by NNUH or UEA which falls within the scope of the UK policy framework for health and social care research. Where additional legislation applies - for example the Medicines for Human Use (Clinical Trials) Regulations 2004 (and amendments) or the Medical Devices Regulations 2002 - required procedures will be indicated. It is the responsibility of the local PI to ensure that

study specific SOPs can be operated without conflicting with this SOP and in accordance with all organisational policies related to research.

4 DEFINITIONS

Minor non-compliance is a departure from one or more of the protocol, SOP, GCP or regulatory requirements that have been identified retrospectively, which is neither critical or major and so **not** likely to effect to a significant degree:

- The safety or physical or mental integrity of the trial participant
- The scientific value of the trial

Major non-compliance is a significant and unjustified departure from the protocol, SOP, GCP or regulatory requirements that may not have developed into a critical issue but may have the potential to do so unless addressed. Where there are a number of instances of minor non-compliance within a single area of responsibility, this indicates a systematic quality assurance failure and so should be collectively treated as major non-compliance.

Serious Breach, as defined by the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, is a significant and unjustified departure from the protocol, SOP, GCP or regulatory requirements that has been identified retrospectively, which **is** likely to effect to a significant degree:

- The safety or physical or mental integrity of the trial participant
- The scientific value of the trial

Where there are a number of instances of major non-compliance within a single area of responsibility, this indicates a systematic quality assurance failure and so should be collectively treated as a serious breach.
Additionally, serious breaches include where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported major non-compliances and/or where the Trial Master File does not comply with the regulations, is not readily available or accessible or is incomplete to an extent that it impedes or obstructs inspection.

5 PROCEDURE & RESPONSIBILITIES

- The CI/PI is responsible for identifying any breach of protocol or GCP, documenting all breaches using the "**Form for Protocol and Regulatory Non-Compliance Including Serious Breaches"** (available from the NNUH SOP website), saving them in the ISF and reporting all breaches to the JRO. All breaches assessed as serious should be notified to the JRO using the "**Form for Protocol and Regulatory Non-Compliance Including Serious Breaches"** (available from the NNUH SOP website) **within 24 hours** of the breach being identified. The CI/PI is also responsible for developing and implementing the corrective and preventative action plan (CAPA) for instances of non-compliance that are not serious breaches. The CI/PI is responsible for developing the CAPA with members of the JRO if the issue is assessed as a serious breach and ensuring that this is submitted to the appropriate offices in accordance with this SOP.

The CI/PI must also ensure that any action recommended by the relevant review body/ies is undertaken. Every team member has a responsibility to inform the CI/PI and sponsor of a potential serious breach.

- On receipt of the completed form, the sponsor is responsible for working with the CI/PI and study team to assess the non-compliance, developing the CAPA if a serious breach, and supporting its implementation. The sponsor is responsible for reporting serious breaches to the REC (and to the MHRA if a CTIMP or Medical Device Trial) within 7 days of being notified, and to the Joint Research Governance Committee.

If the Chief Investigator is unsure whether a non-compliance is a potential serious breach they should notify the Sponsor as soon as possible and provide all available information.

- If the safety or physical or mental integrity of the trial participant has been affected by the non-compliance or serious breach, then the procedure for reporting an Adverse Event or Serious Adverse Event will also need to be followed (SOP 205, SOP 206 & SOP 230).

- These serious breaches and any other instances of non-compliance should be included and considered when the clinical study report is produced (SOP 340), as they may have an impact on the analysis of the data.

6. REFERENCES

- MHRA**:** Guidance for Notification of Serious Breaches of GCP or the Trial Protocol
- UK policy framework for health and social care research Medical Devices Regulations 2002
- Medicines for Human Use (Clinical Trials) Regulations 2004
- www.hra.nhs.uk

7. RELATED DOCUMENTS

- SOP 205 Identifying, Recording and Reporting Adverse Events for Clinical Trials
- SOP 206 Identifying, Recording and Reporting Adverse Events for Healthcare Research Studies that are not CTIMPS
- SOP 230 Urgent Safety Measures
- SOP 320 Developing a Research Protocol
- SOP 340 Clinical Trial Reporting

- **Form for Protocol and Regulatory Non-Compliance Including Serious Breaches** available from the NNUH internet webpage

8. LIST OF APPENDICES

Appendix 1: Change Control, Revision and Review Sheet

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Revision Form: SOP 210				
Version No	Change Date	Reason for Change		
1.1	31/01/2011	SOP updated to reflect UEA/NNUH joint working arrangements.	Reviewer:	**Signature and Date:**
2.0	01/01/2014	SOP updated to reflect changes to NNUH staffing and change of SOP title from "Protocol Violations" to "Breaches of Good Clinical Practice or the Trial Protocol". Procedure for reporting breaches revised to include the implementing of a Corrective and Preventative Action Plan and recording breaches in the Trial Master File. Combining of SOP control and revision sheets.	Reviewer:	**Signature and Date:**
3.0	01/12/2014	SOP updated to clarify that all breaches must be recorded and the form saved in the Investigator/Trial Master File. The Form for recording and reporting breaches has been created as a separate document and removed from the SOP. Responsibilities and procedure sections expanded and the relationship to reporting results made in the introduction section.	Reviewer: Sue Steel Contracts Manager (UEA)	**Signature and Date:** 11/11/2014 (authorized by email)
4.0	19/12/2017	Major amendments to presentation of definitions and procedures to follow to improve clarity and usability, especially the procedures to be followed for serious breaches and non-serious instances of non-compliance.	Reviewer: SOP focus group	**Signature and Date:** 19/12/2017 *SOP focus group*

		Addition of reference websites and a change to the Research Governance Framework.		