Queen's University Belfast

Research and Enterprise

Standard Operating Procedure
Research Governance

Title:	Matters of Non-compliance with Study Protocol		
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* For all University sponsored research recorded as risk category level 4, including IMP studies
# For all other University sponsored research involving human participants

Revision Log

Previous Version number	Date of Review/Modification	Reason for Review/Modification	New Version Number
Final v 1.0	10/11/09	Annual Review	Draft v 2.0
Draft v 2.0	09/09/11	Annual Review/ Update following MHRA GCP Inspection	Final v 2.0
Final v 2.0	21/08/12	Periodic Review	Final v 3.0
Final v 3.0	06/10/2014	Periodic Review	Final v 4.0
Final v 4.0	18/01/2017	Periodic Review	Final v 5.0

1. Purpose

This Standard Operating Procedure (SOP) provides guidance for the actions to be taken in the event of non-compliance with the approved study protocol and/or Good Clinical Practice (GCP).

2. Introduction

Non-compliance with a study protocol may lead to regulatory authorities rejecting the data and/or may compromise patient safety. Under the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 the research Sponsor must ensure that researchers comply with the study protocol. It is a legal requirement that the University reports serious breaches and/or persistent events of non-compliance with the protocol and/or Good Clinical Practice (GCP) to the Medicines and Healthcare products Regulatory Agency (MHRA) (if applicable) and the Research Ethics Committee (REC).

The failure to comply with the final REC approved study protocol is classified as a breach of protocol. A breach may result from human error or purposeful misconduct and must be reported to the Sponsor who will onward report to the MHRA and REC.

A protocol deviation is less serious than non-compliance and is usually as a result of trying to address unforeseen circumstances. It is important that the study protocol defines the criteria for deviation and a breach.

A serious breach is one that is likely to significantly affect the:
- Safety or physical or mental integrity of the study's participants;
- Scientific value of the study;
- Conditions and principles of Good Clinical Practice (GCP) in connection with a study.

The judgement on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors e.g. 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. Notification examples can be found in Appendix 1.

3. Scope

This SOP applies to all studies where the University is acting in the capacity of Sponsor. It applies to all members of University staff; both academic and support staff as defined by Statute 1, including honorary staff and students.

4. Responsibilities

4.1 Sponsor

Where a breach has occurred, the sponsor must assess the impact of the breach on the scientific value of the trial and notify the regulatory authorities, i.e. the MHRA (if applicable) and main Research Ethics Committee (REC) as appropriate. Notification to the regulatory authorities must be within 7 days of becoming aware of the breach.

4.2 Chief Investigator (CI)

The Chief Investigator (CI) should monitor the conduct of the research study. In the event of the CI becoming aware of a breach of the protocol, GCP and/or SOPs the CI should notify the Research Governance Team immediately, but no later than 24 hours. The CI should facilitate any follow-up undertaken by the Research Governance Team.

4.3 Site Principal Investigator

In the event of a multi-centred trial the Site Principal Investigator (SPI) should monitor the conduct of the research study locally. In the event of the SPI becoming aware of a breach of the protocol, GCP and/or SOPs the SPI should immediately advise the CI, and notify the Research Governance Team, but no later than 24 hours.

4.4 Investigators/Members of the Research Team

All those involved in a research study have a responsibility to report to the Chief Investigator/Research Governance Team breaches in compliance with the study protocol, SOPs and/or GCP.

5. Procedure

5.1 Sponsor Notification

On becoming aware of a matter of non-compliance the CI should inform the Research Governance Team. This can be undertaken through email: (researchgovernance@qub.ac.uk), in person or by telephone. The CI should provide information on the study, including its title, the site where the matter of non-compliance occurred, the name of the SPI (if applicable) and give full details regarding the matter of non-compliance.

5.2 Assessing Non-compliance

The Research Governance Team will, in conjunction with the CI assess the breach and how it impacts on participant safety and/or scientific integrity. The facts surrounding the matter of non-compliance will be collated which may be through reviewing documentation and/or interviewing relevant staff.

In addition, the Research Governance Team will work with the CI to ensure that any urgent safety measures are implemented.

Once the facts are collated and assessed, the Research Governance Team and CI will decide if a serious breach has occurred. The Director of Research and Enterprise and/or Pro-Vice Chancellor for Research, Enterprise and Postgraduate Affairs will be consulted if a serious breach has occurred.

5.3 Notifying the regulatory authorities

Once a matter of non-compliance has been categorised as a serious breach, the Research Governance Team will notify the MHRA GCP Inspectorate using their email address GCP.SeriousBreaches@mhra.gov.uk and any other relevant units/organisations.

The Notification of Serious Breach template, attached as Appendix 2, will be used for notifications. Notification will occur within 7 days of the Sponsor becoming aware of the breach.

Further updates will be provided to the MHRA as and when information becomes available.

5.4 Review and Follow-up

Once the initial notification has been submitted a fuller review will be undertaken, if required. A report will be compiled providing a summary of the breach, the actions

taken, and the impact of the breach against participant safety, scientific integrity and risk to the University. A copy of the report will be submitted to the MHRA and the Research Governance Steering Group for their consideration.

6. References

MHRA Guidance for the Notification of Serious Breaches of GGP or the Trial Protocol (last accessed January 2017).
http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con060111.pdf

Notification of Serious Breach of Good Clinical practice or the Trial Protocol form (https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#report-a-serious-breach, last accessed January 2017)

7. Appendices

Appendix 1 Notification Examples

Notification Examples

(Extracted from MHRA Guidance for the notification of serious breaches of GCP or the trial protocol)

Notified by:	Issue:	Would MHRA have expected this case to be notified?
Sponsor	Dosing error. Ethics Committee & MHRA informed. Subjects withdrawn. The sponsor stated that there were no serious consequences to subjects or data.	No, if there was no significant impact on the integrity of trial subjects or on scientific validity of the trial.
Sponsor	Patient Information Leaflet and Informed Consent updated. At one trial site this was not relayed to the patients until approximately 2-3 months after approval. *More information on the potential consequences of the delay should have been provided.*	Possibly not. If this was not a systematic or persistent problem and if no harm to trial subjects resulted from the delay. Yes, if there was a significant impact on the integrity of trial subjects.
Sponsor	Visit date deviation. *A common deviation in clinical trials.*	No. Minor protocol deviation, which does not meet the criteria for notification.
Contractor	Investigator failed to report a single SAE as defined in the protocol (re-training provided).	No, if it did not result in this or other trial subjects being put at risk, and if it was not a systematic or persistent problem. In some circumstances, failure to report a SUSAR could have a significant impact on trial subjects. Sufficient information should be provided for the impact to be assessed.
Identified during inspection prior to the current requirement to report serious breaches	Investigator site failed to reduce or stop trial medication, in response to certain laboratory parameters, as required by the protocol. This occurred with several patients over a one year period, despite identification by the monitor of the first two occasions. Patients were put at increased risk of thrombosis.	Yes, under the current requirements, this should have been reported as a serious breach.

Sponsor	Becomes aware of fraud at investigator site in the UK, which does not affect the overall scientific value of the Sponsor's trial or the integrity of trial subjects in the UK. However, the Sponsor is aware that the fraudster was involved in trials being sponsored by other organisations.	Although, in this situation, not a legal requirement under 29A, MHRA encourages voluntary reporting of all fraud cases in the UK, because MHRA will wish to establish the impact on the other trials in case subject integrity or the scientific value of those trials was compromised.
Sponsor	IMP temperature excursions reported.	No, if the excursions had been managed appropriately (i.e. IMP moved to alternative location/quarantined as necessary and it was identified by qualified personnel that there was no impact on stability of the product and therefore no impact on patient safety/data integrity). Yes, if this went unmanaged and subjects were dosed with IMP found to have become unstable and this resulted in harm or potential harm to subjects.
Sponsor(s)	On two separate occasions sponsors identified issues with the same organisation. First with consenting issues and the second with potential fraud in recruitment and consenting. However, there was not unequivocal evidence of fraud at the time of reporting. One of the studies involved children.	Yes, this subsequently led to enforcement action against the organisation in question. MHRA
MHRA (CTU)	GCP Inspectorate notified that a substantial amendment had been submitted regarding changes to dosing on a first in human study, as a result of an SAE after dosing the initial subject. The sponsor had temporarily halted the trial and only after further investigation had assigned the SAE as unrelated. The sponsor had **not** notified the CTU of the "urgent safety measure" implemented or reported the SAE as a potential SUSAR.	Yes
CRO	A cohort had invalid blood samples as they were processed incorrectly. As a result one of the secondary endpoints could not be met. Therefore, a substantial amendment was required to recruit more subjects to meet the endpoint. Patients were dosed unnecessarily as a result of this error.	Yes

Sponsor	A pharmacy dispensing error resulted in a non-serious adverse event. The incident was investigated and the notification from the Sponsor confirmed that training had occurred and more robust procedures were being implemented by the site.	No, information provided by the Sponsor identified this as a single episode and the Sponsor supplied detailed corrective and preventative action. Yes, if it was persistent and systematic, occurring after the CAPA had been put in place by the Sponsor.
Identified During inspection.	A **potential** serious breach was identified, but not reported (i.e. documentation in the Sponsor's TMF identified that there may have been fraud at an investigator site, re-use of previous timepoint data in later timepoints). The Sponsor had investigated and the issue was subsequently found to be a genuine error not fraud.	No, on this occasion. *However, had this been identified as fraud impacting on the integrity of the data, then this serious breach would not have been notified within the regulatory timeframe (i.e. 7 day window).*
NRES	Destruction of investigator site files early (i.e. one study had only been completed a year earlier and one study was still ongoing.)	Yes
Sponsor	Concerns raised during monitoring visits about changes to source data for a number of patients in a trial, which subsequently made patients eligible with no explanation. An audit was carried out by the Sponsor and other changes to source data were noted without explanation, potentially impacting on data integrity. Follow-up reports sent to MHRA confirmed Sponsor concerns over procedures for approvals, consenting issues and data changes made to source without adequate written explanation.	Yes *Note: not all information provided in original notification and Sponsor provided follow-up updates.*
Member of public	Member of public received named invite to be a volunteer in clinical trials (no specific trial mentioned). However, she was not on the organisation's volunteer database and had not participated previously in a study. On further investigation by MHRA, the organisation had contracted the use of a mailshot organisation to send a generic mailshot to a list of people in relevant area over a certain age. This had been approved by the Ethics Committee.	No

Sponsor	A study patient attended A&E, who attempted to contact pharmacy (using the phone number on the patient's emergency card) in order to break the unblinding code. Unable to break code in a timely manner, and the patient decided to withdraw from the study feeling unhappy that the pharmacy was not available for emergency situations.	Yes, as this could have resulted in significant potential to harm to the subject if unblinding would have affected the course of treatment.
CRO	Patient safety compromised as, protocol not followed and, therefore, repeat ECGs were not conducted when required. Also potential stopping criteria missed due to inadequate QC of the interim clinical summary report for dose escalation.	Yes