Queen's University Belfast

Research and Enterprise

Standard Operating Procedure
Research Governance

Title:	**Reporting and Managing Research Related Adverse Events**		
SOP Reference Number:	QUB-ADRE-006	Date prepared	9 July 2008
Version Number:	Final v 5.0	Revision Date	07 September 2016
Effective Date:	01 October 2016	Review Date:	August 2018

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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	Final v 1.0
Final v 1.0	10/11/10	Annual Review/ Update following MHRA GCP Inspection	Final v 2.0
Final v 2.0	10/08/2012	Periodic Review	Final v 3.0
Final v 3.0	21/10/2014	Periodic Review	Final v 4.0
Final v 4.0	07/09/2016	Periodic Review	Final v 5.0

1. Purpose

This Standard Operating Procedure (SOP) sets out the procedure for reporting and managing adverse events of both Investigational Medicinal Products (IMPs) and non-IMP research studies in the UK, where Queen's University Belfast is the sponsor, or co-sponsor.

The primary focus of this SOP is for clinical trials of IMPs (CT-IMPs) but it is relevant for any research involving human participants.

2. Introduction

The Medicines for Human Use (Clinical Trials) Regulations 2004, and subsequent amendments and the Department of Health and Social Services Research Governance Framework, February 2007 state specific requirements for the management of:

- Adverse Events (AEs);
- Adverse Drug Reactions (ADRs);
- Serious Adverse Events / Serious Adverse Reactions (SAEs/SARs);
- Suspected Serious Adverse Reactions (SSARs);
- Suspected Unexpected Serious Adverse Reactions (SUSARs).

Each type of Adverse Event, categorised above, is subject to different reporting requirements. This SOP will outline the requirements for each. In addition, adverse event and near miss reporting should also be undertaken in accordance with the host Trust's policy, if applicable, on reporting and the management of accidents, incidents and near misses. It is the researcher's responsibility to familiarise themselves with the relevant Trust's incident policies.

2.1 Definitions

2.1.1 Adverse Event (AE)

An adverse event is an untoward medical occurrence (regardless of seriousness, causality or expectedness) in a patient or clinical trial subject who has been administered a medicinal product. An AE does not necessarily have a causal relationship with this treatment.

2.1.2 Adverse Drug Reactions (ADR)

Any untoward and unintended responses to an IMP related to any dose administered.

2.1.3 Serious Adverse Event / Serious Adverse Reaction (SAE/SAR)

A serious adverse event or reaction is one that:

- Results in death;
- Is life-threatening i.e. it is the opinion of the investigator that the subject was at risk of death at the time of the event;
- Requires hospitalisation, or the period of hospitalisation is prolonged – regardless of the length of stay;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Requires medical or surgical intervention in order to prevent permanent damage or impairment of a body function.

Medical judgement should be exercised when deciding whether the occurrence is an adverse event (AE) or adverse reaction (AR).

2.1.4 Suspected Serious Adverse Reactions (SSAR)
Any adverse reaction that is classed as serious **and is** consistent with the information known about the IMP, which should be listed in the Investigator Brochure or is in the summary of the product characteristics for that particular product.

2.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse reaction, which is suspected to have been caused by the IMP, that is classed as serious **and is not** consistent with the information known about the IMP.

2.1.6 Near Miss
An unplanned event that does not cause injury, damage or ill health but could do so.

2.1.7 Severity
The severity, or intensity, of an adverse reaction is classified as mild, moderate or severe and explained further in 5.2.3. It should be noted that the severity and seriousness of an adverse reaction are not the same thing. Seriousness is based on the patient/event outcome, for example those items listed in 2.1.3.

2.1.8 Causality
A reasonable causal relationship with the trial medication.

2.1.9 Expectedness of an Adverse Reaction
A reaction which is a recognised adverse effect of the medication, is deemed expected, otherwise it is deemed unexpected?
Expected: Consistent with the toxicity of the Investigational Medicinal Product (IMP) listed in the Summary of the Product Characteristics or Investigator's Brochure.
Unexpected: Not consistent with the toxicity of the IMP listed in the Summary of the Product Characteristics or Investigator's Brochure.

2.1.10 Expedited
Expedited is a term used to identify which reports need to be reported immediately and in no case later than 15 calendar days from receipt to the relevant competent authorities.

3. Scope

This SOP applies to all studies where the University is acting in the capacity of Sponsor, or Co-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 Chief Investigator

The Chief Investigator (CI) has overall responsibility for the conduct of the study. He/she must:

- Report all serious adverse events immediately to the Sponsor (unless specified in the protocol or investigator's brochure as not requiring expedited reporting);
- Report all adverse events identified in the protocol as being critical to the evaluation of the trial safety to the trial Sponsor;

- Supply the Sponsor and the Research Ethics Committee (REC) with any additional information requested;
- Adhere to the Trust's accident/incident policy and report near misses to the Trust's research office;
- To ensure that the study has been correctly entered on the Universities Human Subjects Database.

4.2 Site Principal Investigator(s)

In the case of a multi-centre study the CI should delegate to the Site Principal Investigator (SPI) the appropriate responsibilities for managing and reporting adverse incidents on a given site. The Study Delegation Log (SOP-QUB-ADRE-005) should be completed as necessary.

4.3 All Researchers

On discovery of an adverse event, the research team member must record and notify the SPI or CI, whichever appropriate, of all adverse events not stated in the protocol or investigator's brochure as being exempt from the recording process.

At each trial visit the researcher in contact with the research subject must seek information to ascertain if any serious and/or non-serious adverse events have occurred since their last visit.

4.4 Sponsor

The University as Sponsor will ensure that robust Pharmacovigilance processes are in place for each regulated study. As stated below these functions are delegated to the Chief Investigator and could involve the use of external organisations. Therefore the process may vary slightly between studies, but oversight will be maintained by the Sponsor with at least:

- Reporting of all suspected unexpected serious adverse reactions (SUSARs) to the main REC and MHRA in an expedited manner;
- Providing an annual safety report to the main REC and MHRA;
- Informing all PIs of SUSARs that occur in relation to an investigational medical product used in that trial (relevant in the case of multi-centre trials).

N.B. Where Queen's University Belfast is sponsoring the study, pharmacovigilance and safety reporting functions of the Sponsor are delegated to the Chief Investigator. However it is necessary that the University as Sponsor is content with the pharmacovigilance provision in place and has co-operation and access to all procedures when requested.

5. Procedure

5.1 Protocol Development

Before initiating a clinical trial, the CI should ensure that the protocol lists known side effects and adverse reactions that are contained within the manufacturer's product information. Then careful consideration should be given to the following:

- The process for collecting, recording, assessing and reporting AEs;
- Which AEs should be recorded (see paragraph 5.2);
- Which SAEs should be reported (see paragraph 5.2).

The CI may decide that all, or only some, non-serious AEs are to be recorded. The decision made must be consistent with the purpose of the trial and any toxicity and efficacy end points.

5.2 Collecting, recording, assessing and reporting SAEs

The procedures for collecting, recording, assessing and reporting SAEs should be detailed in the trial protocol. There should be agreement as to which are defined as disease-related and are therefore not subject to expedited reporting. In addition, the protocol should specify which AE data will be recorded on a Case Report Form (CRF (SOP QUB-ADRE-007)) and when a specific SAE form will be used.

5.2.1 Collecting

Collecting information from all research subjects should be undertaken at each trial visit to identify if any serious and/or non-serious adverse events have occurred since their last visit. Researchers should also consider other potential sources of information about AEs:

- Information on source documents;
- Information in data collection forms (e.g. diary cards, quality of life forms etc);
- Missed and/or unscheduled visits, dropouts or withdrawals;
- Use of concomitant medications/devices;
- Abnormal clinical laboratory data.

5.2.2 Recording

All AEs (serious and non-serious) must be recorded by the researcher, unless the protocol / investigator's brochure states otherwise. This information will provide the basis of the annual safety report required by the MHRA and/or REC, as appropriate.

The AE record should include a description, the start date, duration and outcome. It should also contain an assessment of its seriousness, relatedness, expectedness, severity, actions and be legibly signed.

The AE should be recorded in the research participant's medical notes (or other relevant source data if not medical notes).

The researcher must also comply with the accident/incident/near miss recording system of the host NHS/HSC Trust, as appropriate.

5.2.3 Assessing

Each AE should be assessed to determine the seriousness, as outlined in 2.1.3, severity, expectedness (discussed in 2.1.9) and causality.

Severity:

The clinical lead should use their judgement to determine how severe or intense the AE was:

Mild	There was mild awareness of the event but it was easily tolerated, it required no treatment and did not interfere with the research participant's everyday activities.
Moderate	There was discomfort enough to cause some interference with the research participant's daily activities.

Severe	The AE prevented the research participant's normal daily activities.

Causality:

Not related	The AE is definitely not associated with the administration of the study medication/device.
Unlikely	The temporal association to the administration of the study medication/device is likely to have had another cause.
Possible*	There is a reasonable temporal sequence from the administration of the study medication/device but the event could have been due to another, equally likely cause.
Probable*	There is a reasonable temporal sequence from the administration of the study medication/device and it abates once discontinued. The event is more likely to be explained by the product than any other cause.
Definitely*	There is a reasonable temporal sequence from the administration of the study medication/device which abates once discontinued and is confirmed on repeat exposure.

**where the event is assessed as possible, probable or definitely related, the event is an AR.*

SUSAR:
An event that is assessed as being 'serious', 'possible, probable or definitely related' and is 'unexpected' is defined as a SUSAR and will require expedited reporting to the MHRA / Research Ethics Committee.

5.2.4 Reporting

If the SAE is considered serious, not disease-related and has been specified in the protocol as not requiring recording, the researcher must report the event to the CI immediately, or within 24 hours of being made aware of it. This initial report may be verbal but it must be followed up promptly with a detailed, written report taking into consideration his/her assessment of the seriousness, along with causality, expectedness and severity on a SAE form. Guidance for the reporting of SAEs is provided by the Health Research Authority:
http://www.hra.nhs.uk/research-community/during-your-research-project/safety-reporting/

The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses.

For blinded clinical trials, the blind should be maintained unless it is felt necessary to be broken in the interest of subject safety. The blind should be broken for all SUSARs before they are reported to the MHRA for that specific subject. In the case of QUB sponsored projects the un-blinding should be carried out by individuals who are not involved in the day to day management of data.

The CI for all QUB sponsored studies will assume all Pharmacovigilance functions that are stated in the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" Therefore the CI is responsible for ensuring that SAEs are reported to the MHRA, REC, or other relevant organisations.

The CI, or in the case of a site specific study the SPI, is responsible for ensuring that all adverse incidents/near misses which involve NHS/HSC patients, staff or facilities, are reported in accordance with the relevant NHS/HSC Trust incident reporting procedure.

All ARs related to an IMP that are both serious and unexpected (i.e. a SUSAR) are subject to expedited reporting, as defined in 2.1.10 above.

- **Minimum criteria for expedited reporting of SUSARs to MHRA and REC**

  For regulatory purposes, initial expedited reports should be submitted as soon as the following minimum criteria are met:
  i. The suspected IMP is identified;
  ii. Trial subject is identified;
  iii. An AE assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship;
  iv. An identifiable reporting source.

  The 7 or 15 day reporting clock does not start until the Sponsor can confirm that the event fulfils the criteria listed above.

- **Submission to the Research Ethics Committee**

  Complete the Health Research Authority Safety Report Form and submit it to the relevant REC along with a full SUSAR report:
  http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/

  There is no prescribed format for the SUSAR report. Therefore, the CI will need to prepare a report to complement the NRES SAE form. Subsequently the SUSAR report, which may be in the form of a letter, should include:
  i. Patient trial number;
  ii. Age in years;
  iii. Sex;
  iv. Suspected drugs to include generic name, daily dose regime, routes of administration;
  v. Reported causal relationship;
  vi. Concomitant drug(s) and relevant history.

- **Submission to the MHRA**

  Reporting of SUSARSs should be completed via the eSUSAR website. There is no need for Sponsors to dual report to the European Medicines Agency's (EMA's) EudraVigilance Clinical Trial Module (EVCTM). As the MHRA will forward all reported SUSARs this would result in duplication within the EVCTM. If in doubt as to whether the online reporting system was fully functional ensure that the MHRA receive a report by email/paper-based system.

  However, no matter what the format used, it is important that the basic information identified in European Commission detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use is included in the report.

- **Informing Investigators**

  Investigators should be informed of any SUSARs that occur in relation to any IMP in that trial. The CI and Sponsor should agree the frequency and format of the SUSAR information to be sent to investigators.

- **Annual Reports**

  One year following the granting of a Clinical Trials Authorisation (CTA), and thereafter annually, the CI should compile an annual safety report, consisting of a list of all SSARs which have occurred during that year in relation to the trial, including those reactions relating to any IMP used as a placebo or as a reference in the trial, and for each IMP being tested. Where the trial is a multicentre trial the line listing should include SSARs which have occurred at other sites in the UK or elsewhere (Refer to SOP-QUB-ADRE-013).

  - The CI should send the information, detailed in SOP-QUB-ADRE-013 to the:
    i. MHRA;
    ii. Sponsor;
    iii. REC that granted approval;
    iv. Competent Authorities (equivalent to the MHRA) of any European Economic Area State, other than the UK, in which the trial is being conducted.

  - Quarterly safety reports to the REC area also required where:
    i. The Sponsor is responsible for other trials of the IMP, whether in the UK or internationally;
    ii. One or more SUSARs have occurred during the quarterly reporting period in these trials.

6. References

Health Research Authority, Safety Reporting for CTIMPs and Non-CTIMPs (last accessed October 2014);
http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/

European Commission, April 2006. Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use;

Imperial College London: SOP for Recording, Managing and Reporting Adverse Events in the UK;

Cardiff University: SOP for Managing and Reporting Research related Adverse Events in Clinical Trials of an Investigational Medicinal Product IMP.