Safety Reporting
Part 1: For Clinical Trials of Investigational Medicinal Products (CTIMPs)

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Version 1.5	**26 February 2014**	Biennial review: Web links updated. Addition of information on safety reporting for international trials.
Version 1.4	**1 December 2011**	Update to annual safety reporting requirements. Additional information re: blinding and pregnancy in clinical trials
Version 1.3	**1 September 2010**	Addition of information re: new MHRA electronic SUSAR reporting system (section 3.3.4.1)
Version 1.2	**29 January 2010**	Biennial review. Web page links & CTCAE version number updated.
Version 1.1	**25 January 2008**	Format change. Clarification of reporting process.
Version 1.0	**March 2006**	

Safety Reporting Part 1 – for Clinical Trials of Investigational Medicinal Products (CTIMPs)

1. Purpose

The purpose of this Standard Operating Procedure (SOP) is to define adverse event terminology and to detail reporting requirements; both to whom adverse events must be reported and the time-scale involved.

2. Background

The accurate and timely reporting of adverse events (AEs) is a legal requirement of the Medicines for Human Use (Clinical Trials) Regulations (2004) for all Clinical Trials of Investigational Medicinal Products (CTIMPs). These regulations enact the EU Clinical Trials Directive of 2001. Failure to comply with the regulations is a criminal offence.

This document covers adverse events that occur during clinical trials of investigational medicinal products. Clinical studies involving only licensed medical devices, food supplements or other non-medicinal therapies (such as surgical/physiotherapy interventions) are not covered by the Directive, but still require that adverse events are managed according to Good Clinical Practice (GCP). For these studies, see Part 2 of this SOP 'Safety Reporting; For trials other than CTIMPs'.

You are advised to refer to the University of Warwick's Research Code of Conduct: http://www2.warwick.ac.uk/services/rss/researchgovernance_ethics/research_code_of_practice/

3. Procedure

3.1 Who?

This procedure applies to all WMS staff involved in clinical trials of investigational medicinal products. All staff must ensure that they are familiar with the definitions of adverse events and serious adverse events contained within this document, and the reporting timescales required by law.

All staff that come into contact with trial participants have a responsibility to note any adverse events mentioned by participants, and ensure that they are recorded/reported in line with this document.

The Chief Investigator (CI) is responsible for the reporting of relevant adverse events to the Sponsor. SAEs must be reported immediately to the Sponsor.

The Sponsor is responsible for the assessment and recording of adverse events and the expedited reporting of certain adverse events to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee, as detailed in this document. If Warwick Clinical Trials Unit (WCTU) has taken on responsibility for pharmacovigilance in a trial, the procedures set out in SOP 17 part 3 entitled 'Safety Reporting Process at WCTU' will be followed.

A list of all adverse events must be sent to the Data Monitoring Committee (DMC), as specified in the protocol.

3.2 When?

At each visit, or study assessment, adverse events that might have occurred since the previous visit or assessment should be elicited from the participant. This includes events from the time the participant signed the informed consent until the end point of the trial as defined in the protocol (this is often stated as 28 days after the last clinic visit or dose of investigational medicinal product IMP). Any worsening of concomitant illness or new illness must be recorded as adverse events at each visit.

3.3 How?

This document provides definitions for the different types of adverse events and the timelines set for reporting to the Sponsor, MHRA and ethics committee.

The proposed procedures for assessing, recording, notifying and reporting of adverse events should be agreed for each trial, detailed in the trial protocol and approved by the main Research Ethics Committee (REC), the DMC and the MHRA during the Clinical Trial Authorisation (CTA) assessment.

The protocol for the clinical trial will state the mechanism by which participants will be asked about any adverse events they may have experienced.

3.3.1 Definitions

3.3.1.1 Adverse Event (AE)

An AE is: "Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product, which does not necessarily have a causal relationship with this treatment".

> Comment:
> An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding or ECG result), symptom, or disease that occurs during the time a participant is taking an investigational medicinal product, *whether or not* it is considered to be related to the investigational medicinal product.

The following do not need to be recorded as adverse events, if they are recorded as medical history/concomitant illness at the start of the trial:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the participant has signed the informed consent
- Pre-existing conditions found as a result of screening procedures

3.3.1.2 Adverse Reaction (AR)

An AR is: "All untoward and unintended responses to an investigational medicinal product related to any dose administered".

Comment:
This is an adverse event for which there is reason to suspect that it may be *caused* by the medicinal product.

3.3.1.3 Unexpected Adverse Reaction (UAR)
An UAR is: "An adverse reaction, the nature or severity of which is not consistent with the applicable product information." (i.e. investigator's brochure for an unapproved investigational product or summary of product characteristics for an authorised product).

3.3.1.4 Serious Adverse Event or Serious Adverse Reaction (SAE or SAR)
An SAE or SAR is: Any untoward medical occurrence or effect that at any dose:

1. Results in death,
2. Is life-threatening,
3. Requires hospitalisation or prolongation of existing inpatients´ hospitalisation,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly or birth defect,
6. Requires medical intervention to prevent one of the above, or is otherwise considered medically significant by the investigator.

Comment:
Some other adverse events/reactions may also count as *serious* reactions. Those events that do not immediately fall into one of the above categories, but that *jeopardise* the participant, or require intervention to *prevent* one of the outcomes listed above, should also be considered serious.

Important note: "*Serious*" and "*severe*" are not synonymous. "*Serious*" refers to a specific definition for the outcome of an event (see above), whilst "*severe*" refers to the intensity of a reaction (e.g. mild, moderate, severe). For example, it is possible to have a "severe" headache, but the headache itself is not a "serious" reaction.

The term *'life-threatening'* in the definition of a serious adverse event refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which, hypothetically, might have caused death if more severe.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

3.3.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)
A SUSAR is: "A suspected serious adverse reaction that is also unexpected" i.e. the nature or severity of the event is not consistent with the applicable product information (i.e. investigator's brochure for an unapproved investigational product or summary of product characteristics for an authorised product).

Comment:
A SUSAR is therefore a reaction suspected of having a causal relationship with the IMP which has not previously been documented.

3.3.2 Severity grading: for the purposes of grading the severity of an adverse reaction, the National Cancer Institute Common Terminology Criteria (version 4: active as of 10/1/2009) may be used. This is a descriptive terminology that provides a grading (severity) scale of 1 (mild AE) to 5 (death related to AE) with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild AE
Grade 2 Moderate AE
Grade 3 Severe AE
Grade 4 Life-threatening or disabling AE
Grade 5 Death related to AE

Full details of the clinical descriptions may be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Other organisations e.g. World Health Organisation also provide severity scales for AE reporting which may be used to define the severity of an event.

3.3.3 Pregnancy
A trial participant (or the wife/partner of a male participant) must be advised to notify the Investigator immediately if she becomes pregnant during the trial. The Investigator must then report any pregnancy to the Sponsor (or delegate). Any pregnancy must be followed up and any complications recorded as an adverse event. If the infant has a congenital anomaly/birth defect, this must be reported and followed up as a serious adverse event.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive method. Guidance on suitable contraceptive methods can be found at:
http://www2.warwick.ac.uk/fac/med/research/ctu/process/setup/imp/

3.3.4 Blinded Trials
Where possible, the blind should be maintained. However, if a SAE is deemed to be a SUSAR (related and unexpected), the treatment code for the participant concerned should be broken before reporting the event to the MHRA and REC. The breaking of the code should be recorded along with the reasons on the Case Report Form (CRF) and any other documentation.
If after unblinding the product administered to the participant is the **placebo** then this will not usually satisfy the criteria for a SUSAR and therefore will not require expedited reporting. It is the Sponsor's responsibility to report such cases at their discretion. The reaction may be a hypersensitive response to an excipient compound in the formulation of the placebo.

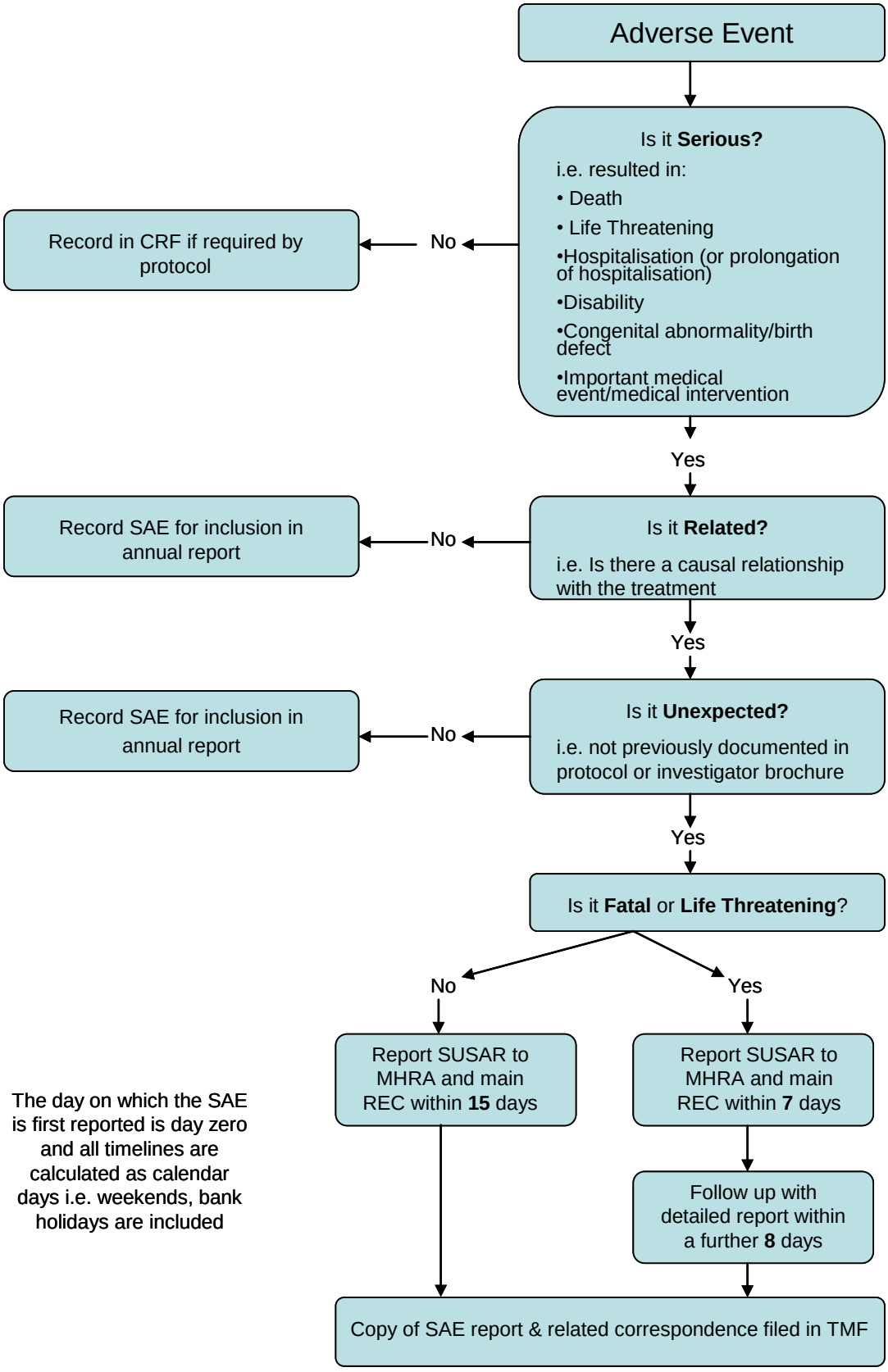
3.3.5 Reporting Requirements

Recording and reporting requirements will be dependent upon the assessment of seriousness, causality and expectedness as detailed in Flowchart 1 below:

Causality assessments should be undertaken initially by the Investigator at site.
See Appendix 1 for more detailed explanations of the terms 'Related' and 'Expected'.

The CI/Sponsor is not permitted to downgrade an Investigator's PI's causality assessment. Any difference in opinion should be provided with the report.

Flowchart 1:



The day on which the SAE is first reported is day zero and all timelines are calculated as calendar days i.e. weekends, bank holidays are included

3.3.5.1 Defining SAEs that require immediate reporting

Principal Investigators (PIs) must report all SAEs immediately (within 24 hours of first knowledge of the event) to the CI, unless the SAE is one which the protocol defines as not requiring immediate reporting. The CI is then responsible for ensuring that events are reported to the sponsor, ethics committee and MHRA according to requirements.

See Appendix 2 for further details of CI and Sponsor responsibilities.

Reports of SAEs to the CI (or delegated recipient) will normally be in either the CIOMS-1 format which is widely accepted as the standard within the pharmaceutical industry or by faxing a trial specific SAE report form (which is usually found in the participant's CRF booklet).

SUSARs must be unblinded and reported to the REC and MHRA within set timelines of 7 days for a fatal or life threatening event and within 15 days for all other events.

The standard covering form and further information on reporting to the Ethics Committee can be found at: http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-research-ethics-committee-rec-ctimp-safety-report-form/

From 1 September 2010, SUSAR reports originating from UK trial sites must be submitted via the MHRA's eSUSAR electronic reporting system: http://esusar.mhra.gov.uk/. The site can also be used to maintain a record of reports that have been submitted for each of the Institution's clinical trials and a pdf output can be used to report to the Ethics Committee.

The University of Warwick has registered details of the Institution and nominated a representative from the Research Support Services department as the main Administrator of the eSUSAR system. For each CTIMP sponsored by the University (or co-sponsored and including the responsibility for pharmacovigilance), the CI should identify a member of the trial team to register on the system and report any SUSARs that occur. WCTU QA Manager will also register as a system user for all trials in which WCTU is responsible for pharmacovigilance.

For more information, visit the MHRA safety reporting web pages:
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

SUSAR reports received from international CTIMPs involving trial sites within the European Economic Area (EEA) should be reported according to the timelines detailed above via the European Medicines Agency's EudraVigilance reporting system EVWEB: http://eudravigilance.ema.europa.eu/highres.htm

The University of Warwick is registered to use the EudraVigilance system and individuals responsible for safety reporting from international trials must be trained and registered, as a unique username and password are required to access the system.

Safety reports submitted via this system are known as Individual Case Safety Reports (ICSRs).

3.3.5.2 Defining SAEs that do not require immediate reporting

Some SAEs do not need to be reported immediately to the sponsor, MHRA and ethics committee. The protocol should define those serious adverse events that do not need to be reported immediately. These include:

- SAEs which are *serious but expected*, and those reactions that are considered *unrelated* to the investigational medicinal product (whether expected or not). It is for the Chief Investigator and/or Sponsor to decide whether or not each individual serious adverse event requires expedited reporting.

- SAEs that form an outcome for the trial. Details of such events must be included in the safety analysis and form part of the annual Development Safety Update Report to the MHRA (and main ethics committee; see SOP 6 'Ethics Approvals and Communications' for more details). Examples include; death from progression of the disease under study where this forms an outcome for the study or hospitalisation for an event which forms an outcome for the study.

List of abbreviations used

AE/AR	Adverse Event /Adverse Reaction
CI	Chief Investigator
CIOMS	Council for International Organisations of Medical Sciences
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
GCP	Good Clinical Practice
ICSR	Individual Case Safety Report
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
NRES	National Research Ethics Service
PI	Principal Investigator
SAE/SAR	Serious Adverse Event/Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAR	Unexpected Adverse Reaction
WCTU	Warwick Clinical Trials Unit

Appendix 1: Causality Assessment

The **relationship** between the administration of an IMP in a trial and a Serious Adverse Event should be categorised as below.

Relationship to IMP	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial drug). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurred within a reasonable time after administration of the trial drug). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

The **expectedness** of a SAE should be determined according to the reference documents as defined in the trial protocol i.e. Investigator Brochure (IB) for unlicensed products or Summary of medicinal Product Characteristics (SmPC) for licensed products. The reference documents should be regularly checked via the link below to ensure that the current version is in use and filed in the TMF.
http://www.medicines.org.uk/EMC/default.aspx

Expected	The reaction has previously been identified and described in the Protocol and/or reference documents
Unexpected	The reaction has NOT been previously described in the protocol or reference documents

Appendix 2: Specific responsibilities of Chief Investigator and Sponsor in detail

1 Chief Investigator

1.1 A Chief Investigator must report any **serious adverse event** immediately to the **sponsor,** either orally or in writing. Following the immediate report of a serious adverse event, the Chief Investigator must make a detailed written report on the event.

1.2 This does not apply to serious adverse events specified in the protocol or the investigator's brochure as not requiring immediate reporting.

1.3 **Adverse events and/or laboratory abnormalities** (that are not classified as serious adverse events) that are identified in the protocol as critical to evaluations of the safety of the trial must also be reported to the sponsor. Such requirements, including the time periods for such reporting, should be specified in the protocol.

1.4 All reports of AEs or SAEs must identify the participant only by the unique trial number, not by name.

1.5 Additional information may be requested by the sponsor and ethics committee for all AEs or SAEs that consist of, or result in a death of a participant.

2 Sponsor (or Chief Investigator / trial team for trials where the University of Warwick is the Sponsor)

2.1 The sponsor must keep detailed **records of all adverse events** reported by Chief Investigators. These records may be requested by the MHRA.

2.2 The sponsor must **evaluate** all adverse events reported to him to decide upon their **seriousness**, **causality** and **expectedness**.

2.3 All **suspected unexpected serious adverse reactions (SUSARs)** must be:

(a) recorded; and

(b) reported as soon as possible (see below) to—

(i) the competent authorities by entering data into the EU database (EUDRAVigilance) or by informing the MHRA,

(ii) the competent authorities of any EEA State, other than the United Kingdom, in which the trial is being conducted, and

(iii) the relevant ethics committee.

SUSARs that are **fatal or life-threatening** must be reported within 7 calendar days of the sponsor first becoming aware of the reaction, with a more detailed report sent within a further 8 calendar days.

SUSARs which are not fatal or life-threatening must be reported within 15 calendar days of the sponsor first becoming aware of the reaction.

Reports of SUSARs in double-blind trials should be unblinded.

2.4 The sponsor must send the MHRA and ethics committee an **annual list of SAEs** and a **safety report**. This must include a list of all suspected SAEs related to each investigational medicinal product tested in clinical trials for which he is the sponsor, and a report on the safety of the participants of those trials.

2.5 All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the sponsor should be provided with the report.

2.6 Other safety issues also qualify for expedited reporting to the MHRA and ethics committee where they might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product administration or in the overall conduct of the trial, for instance:

- single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. a fatal outcome),
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important, i.e. trend analysis
- post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the sponsor,
- new event relating to the conduct of the trial or the development of the investigational medicinal product likely to affect the safety of the participants, such as :
  - a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
  - a significant hazard to the participant population such as lack of efficacy of an investigational medicinal product used for the treatment of a life-threatening disease,
  - a major safety finding from a newly completed animal study (such as carcinogenicity).