

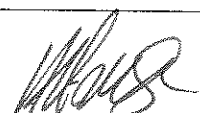


SOP Number            003  
SOP Title                Safety Reporting for CTIMPs

	Name	Title	Signature	Date
<b>Author</b> on behalf of the QA Focus Group	Clare Riddle	Senior QA and Compliance Manager, Clinical Trials and Research Governance		27 JUNE 2017
<b>Reviewer</b> on behalf of the QA Focus Group	Elaine Chick	Deputy Head of Clinical Trials and Research Governance		27 JUNE 2017
<b>Authoriser</b>	Heather House	Head of Clinical Trials and Research Governance		27/06/2017

Agreed by QA Focus Group	27 JUNE 2017
Effective Date	27 JULY 2017 <sup>17</sup>
Review Date	26 JULY 2020 <sup>17</sup>

## 1. PURPOSE

This purpose of this SOP is to describe the responsibilities and processes related to the collection, reviewing and reporting of Adverse Events (AEs) originating from Clinical Trials of Investigational Medicinal Products (CTIMPs) in accordance with regulatory requirements in the UK and internationally.

## 2. INTRODUCTION

It is a legal requirement that organisations which take on the role of Sponsor of clinical trials must have systems in place for pharmacovigilance.

To comply with the regulations, those taking on pharmacovigilance responsibilities must ensure that the necessary quality standards are observed in documentation of cases, data collection, validation, evaluation, archiving and reporting of adverse events in the clinical trial.

## 3. SCOPE

The scope of this procedure is for all CTIMPs sponsored by the University of Oxford, but may also be used for other CTIMPs at the discretion of the unit.

## 4. DEFINITIONS

### Reference Safety Information (RSI)

The information used for assessing whether an adverse reaction is expected. This is contained in either the Investigator's Brochure (IB) or in the Summary of Product Characteristics (SmPC).

### Investigator's Brochure (IB)

A document containing a summary of the clinical and non-clinical data relating to an Investigational Medicinal Product (IMP) that is relevant to the study of the product in human subjects.

### Summary of Product Characteristics (SmPC)

Describes the properties and conditions for use of a particular licensed medical product, and is the basis of information for health professionals on how to use the medical product safely and effectively. It includes the composition, pharmaceutical form and strength, approved indications, side effects, warnings and precautions for use, shelf life, storage conditions and the name of the Marketing Authorisation (MA) holder.

### Adverse Event (AE)

Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

### Adverse Reaction (AR)

Any untoward and unintended response in a participant to an Investigational Medicinal Product (IMP) which is related to any dose administered to that participant.

### **Serious Adverse Event (SAE)**

Any adverse event that:

- Results in death,
- Is life-threatening,

*NOTE: The term "life-threatening" in the definition of "serious" 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 it were more severe.*

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events.

*NOTE: May be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.*

### **SAE Report Form**

A form for collecting and reporting SAEs, which consists of a minimum set of reporting requirements. For example and instructions, please see CTRG website.

### **Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information.

### **Development Safety Update Report (DSUR)**

A legally required, annual safety report submitted to the Competent Authority, the Research Ethics Committee (REC), and other parties as applicable.

The DSUR should take into account all new available safety information received during the reporting period for all trials with the same IMP and sponsored by the same organisation.

### **Clinical Study Report (CSR)**

The final document containing information on conduct, results and interpretation of the trial.

## **5. RESPONSIBILITIES**

### **Sponsor**

The Sponsor has overall responsibility for the ongoing safety evaluation within the trial. Accountability for certain functions may be formally delegated in writing, where appropriate, to the Chief Investigator (CI) and/or the unit.

### **Chief Investigator (CI)**

The Chief Investigator (CI), within their other delegated accountabilities, is responsible for informing PIs of relevant safety issues.

### **Principal Investigator (PI)**

The Principal Investigator (PI) has responsibility for safety reporting at their trial site. The PI is responsible for informing the CI, or the unit, of all SAEs that occur at their site in line with site agreements and the study protocol. Additionally, the PI is responsible for informing the Site Study Team of relevant safety issues.

### **Site Study Team**

Members of the Site Study Team have responsibility for safety reporting as defined in the protocol.

### **Safety Oversight Body**

According to the level of risk identified in the study protocol,

- an Independent Data Monitoring Committee (IDMC), and/or
- a specifically convened Study Safety Group, and/or
- an appointed Medical Safety Monitor

may be established to assess the safety data to recommend to the CI and Sponsor whether to continue, to modify or to terminate a trial. This review procedure will be defined in the protocol, terms of reference or charter.

## **6. SPECIFIC PROCEDURE (see APPENDIX A: Flow diagram)**

### **6.1 Risk-Adapted Approaches**

Using a risk-adapted approach within protocol design enables safety reporting requirements to be tailored to reflect the amount of safety data available on a specific IMP, and the alignment of the use of the IMP relative to normal clinical care. For example, where the IMP is used as part of normal clinical care, at the standard dose and dosing period, and where assessment of safety is not an objective, non-serious adverse events may not be required to be collected or reported. Alternatively, the period of collection of serious and non-serious adverse events may be shorter than the participant's involvement, if this can be justified.

Some patient populations may be expected to have a high number of serious adverse events occurring that are easily foreseeable, and so may not require immediate reporting.

Wherever there is a planned adaptation from full reporting of AEs and SAEs, this should be clearly outlined and justified within the protocol, together with follow-up requirements.

### **6.2 Identification, Assessment and Recording of AEs**

The process for identifying and recording adverse events will follow the specific requirements of the protocol.

#### **Seriousness**

Each reported AE must be assessed for seriousness according to the definitions above.

#### **Causality**

A medically qualified individual at the study site must assess the causality of an AE or SAE, and this assessment cannot subsequently be downgraded by others.

#### **Severity**

Severity of each AE must be assessed according to the protocol.

The term '**severe**' should not be confused with '**serious**'.

### 6.3 Reporting Process for SAEs

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported on the SAE Reporting Form to the Sponsor or delegate within 24 hours of Site Study Team becoming aware of the event being defined as serious.

### 6.4 Review of SAEs

For each trial, the processes for receipt, acknowledgement, and review of reported SAEs must be in place. This will include the assessment of **expectedness** using the Reference Safety Information current at the time of the event.

Review of SAEs should be timely, taking into account the reporting time for a potential SUSAR. Additional and further requested information will be reported on the SAE Report Form and returned to the sponsor or delegate.

### 6.5 Pregnancy Safety Reporting

Any pregnancy that occurs during IMP administration, whilst not necessarily an adverse event, requires monitoring and follow-up to full pregnancy term. Pregnancies and outcomes will be included in annually produced safety reports. Each pregnancy will be followed up until outcome of the pregnancy is known.

### 6.6 Reporting Timescales for SUSARs

All SUSARs during the course of a trial must be reported to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARs, this must be done **no later than 7 calendar days** after the Sponsor or delegate is first aware of the event. Any additional relevant information must be reported **within 8 calendar days** of the initial report. All other SUSARs must be reported within **15 calendar days**.

Treatment codes must be un-blinded for specific participants.

Principal Investigators must be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current study.

### 6.7 On-going Safety Evaluation of IMPs

According to the level of risk, ongoing evaluation of safety will be reviewed by the safety oversight body defined in the protocol.

### 6.8 Urgent Safety Measures

Where there is any immediate hazard to patient health and safety requiring urgent safety measures, these measures should be taken **immediately**. The Sponsor or delegate must notify the relevant Competent Authority, REC, any relevant organisations and the Investigators at site within 3 days. A protocol amendment must be submitted subsequently.

### 6.9 Periodic Safety Reporting

In addition to the expedited reporting required for SUSARs, Sponsors are required to submit a safety report to the Competent Authority and the Research Ethics Committee, once a year throughout the clinical trial (or on request) in the form of the DSUR.

The Sponsor or delegate must ensure that the DSUR is submitted within 60 days of the anniversary of the first approval by a Competent Authority for the Sponsor to use the IMP in a clinical trial. The DSUR must be in a standard format and include headings defined by the ICH guideline E2F.

**7. RELATED DOCUMENTS**

Appendix A (Flow Diagram)  
Core SOP 010 - Urgent Safety Measures

**8. REFERENCES**

ICH Harmonised Tripartite Guideline for Development Safety Update Report E2F (2010)  
EU Clinical Trials Directive (2001/20/EC)

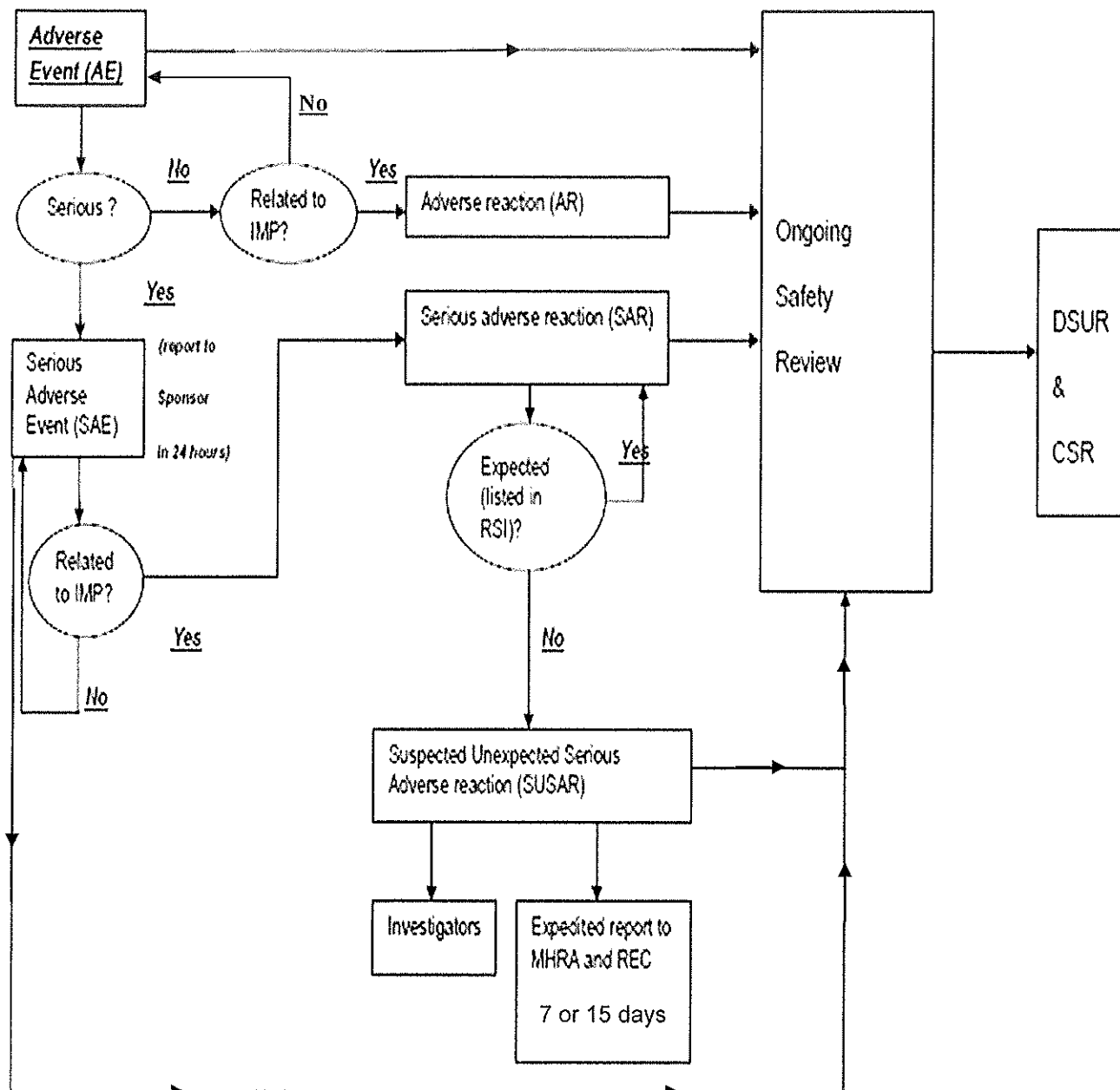
Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [E2A] (CPMP/ICH/377/95)

Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT3' 2011/C 172/01)

**9. CHANGE HISTORY**

Version No.	Effective Date	Significant Changes	Previous Version No.
1.1	01 Jan 2014	Updated into new Core SOP template Minor editorial changes for clarification	1.0
2.0	24 Jun 2014	SOP text unchanged. Version number updated only.	1.1
3.0	See page 1	Update to scope and front page in line with changes to SOP template. Minor editorial changes to section 6.1 and the flowchart in appendix A.	2.0

**10. APPENDIX A (FLOW DIAGRAM OF COLLECTION AND REPORTING OF ADVERSE EVENTS).**



Reference MHRA Good Clinical Practice Guide 2012