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Agreed by the QA Focus Group

SOP Number **003**

SOP Title **Safety Reporting for CTIMPs**

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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

Investigational Medicinal Product (IMP)

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. This includes products with a marketing authorisation but used or formulated/packaged in different way from the authorised form, used for an unauthorised indication, or used to gain further information about the authorised form.

Reference Safety Information (RSI)

The information used for assessing whether an adverse reaction is **expected**. This is contained in a specified section of either the IMP Investigator's Brochure (IB) or 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 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. 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.

Causality

This is a medical assessment of whether the adverse event is likely to be related to the trial IMP

Adverse Reaction (AR)

Any untoward and unintended response in a participant to an 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.*

Serious Adverse Reaction (SAR)

An adverse event that is both serious and, in the opinion of the reporting Investigator, believed to be an untoward and unintended response in a participant, which is related to an IMP.

Expectedness

This is an assessment based on knowledge of the adverse reaction and the list of expected adverse reactions listed in the Reference Safety Information.
NOTE: *This does not need to be performed by a medically qualified member of staff*.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

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.

Development Safety Update Report (DSUR)

A legally required, annual safety report submitted to the Regulatory Agency, 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 CI, within their other delegated accountabilities, is responsible for informing PIs of relevant safety issues.

Principal Investigator (PI)

The 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.

Assessment of Causality
A registered medically qualified doctor (or when appropriate, a registered qualified dentist) 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.

Assessment of Expectedness
This will include the assessment of whether the event is **expected** according to the version of the IMP Reference Safety Information that is Sponsor and Regulatory Agency approved at the moment of occurrence of the event.

In accordance with ICH E2A guidance, SARs which add significant information on the specificity or severity of an event listed in the RSI should be considered unexpected (see Appendix B for examples).

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

Pregnancy is not, in itself an SAE. On trials where pregnancy is an exclusion criterion, any pregnancy that occurs during IMP administration should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of "serious" at section 4 above and be reported as a serious adverse event. A process should be in place at trial start to ensure this follow up is possible. Pregnancies and outcomes will be included in annually produced safety reports.

6.6 Reporting Timescales for SUSARs

All SUSARs during the course of a trial must be reported to the relevant Regulatory Agency 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 by an appropriately delegated person. The processing of this unblinding should be carefully considered especially when the CI and PI are the same person.

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 Updates to SmPC and IBs

It is a legalislative requirement that the IB be reviewed at least annually. During this review period, any change to the RSI or risk /benefit of the trial is considered a substantial amendment.

For trials that have a SmPC, a periodic review of the SmPC should be undertaken during the trial (in line with section 6.1 and 6.7) and documented in the TMF. If the CI/safety oversight body decide it is appropriate to implement the new SmPC, any change to the RSI or risk/benefit of the trial is considered a substantial amendment.

For updated IBs/SmPCs necessitating a substantial amendment, the amendment must be approved before they can be implemented in the trial. The timing of this amendment should be considered with regards to the DSUR reporting window, see Appendix C.

If an updated IB or SmPC does not involve changes to the RSI, benefit:risk ratio or any other safety information (e.g. clinical or toxicology), this will be considered a non-substantial amendment and the updated document can be implemented without an application to the MHRA. However, this updated document version may still require an amendment submission to other parties (e.g., the REC, and where applicable the HRA) should be detailed in the DSUR with an explanation that the RSI remained unchanged, and informed at the next substantial amendment to the MHRA. There should be a clear change control procedure documented in the TMF for RSI updates during the trial and a tracking process which can demonstrate when the RSI was approved by the Regulatory Agency (and each relevant competent authority) and implemented by those making the expectedness assessment for the trial.

See University of Oxford Core SOP 11 – Registration, applications, amendments and reporting.

6.9 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 Regulatory Agency, REC, any relevant organisations and the Investigators at site within 3 days. A protocol amendment must be submitted subsequently. See University of Oxford Core SOP 010 – Urgent Safety Measures.

6.10 Periodic Safety Reporting

In addition to the expedited reporting required for SUSARs, Sponsors are required to submit a safety report to the Regulatory Agency and the Research Ethics Committee, once a year throughout the clinical trial (or on request) in the form of the DSUR with one exception listed below.

The Sponsor or delegate must ensure that the DSUR is submitted within 60 days of the anniversary of the first approval by a Regulatory Agency 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. For assessment of SARs in the DSUR, the RSI that was Sponsor and Regulatory Agency approved at the start of the safety reporting period must be used.

For CTIMPs that are not part of a multi-study development programme and authorised under the Notification scheme (Type A trials) by the MHRA, the Health Research Authority (HRA) Annual Progress Report (APR) form should be used as a template for the DSUR, and should include a list of all SARs in Section 6. The cover letter must state that this is an APR in lieu of a full DSUR, and include the EudraCT number and Clinical Trial Authorisation reference number.

7. RELATED DOCUMENTS

Appendix A (Flow Diagram of collecting and reporting Adverse Events)
Appendix B (Examples of 'suspected' SARs considered 'unexpected' because of specificity and/or severity)
Appendix C (Example of IB RSI update following DSUR reporting period)
University of Oxford Core SOP 011 - Registration, Applications, Amendments and Reporting
University of Oxford 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)

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)

CTRG documents for safety reporting https://researchsupport.admin.ox.ac.uk/ctrg/resources

Reference Safety Information Q&A document from the Clinical Trial Facilitation Group http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf

HRA Annual Progress Reports https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/

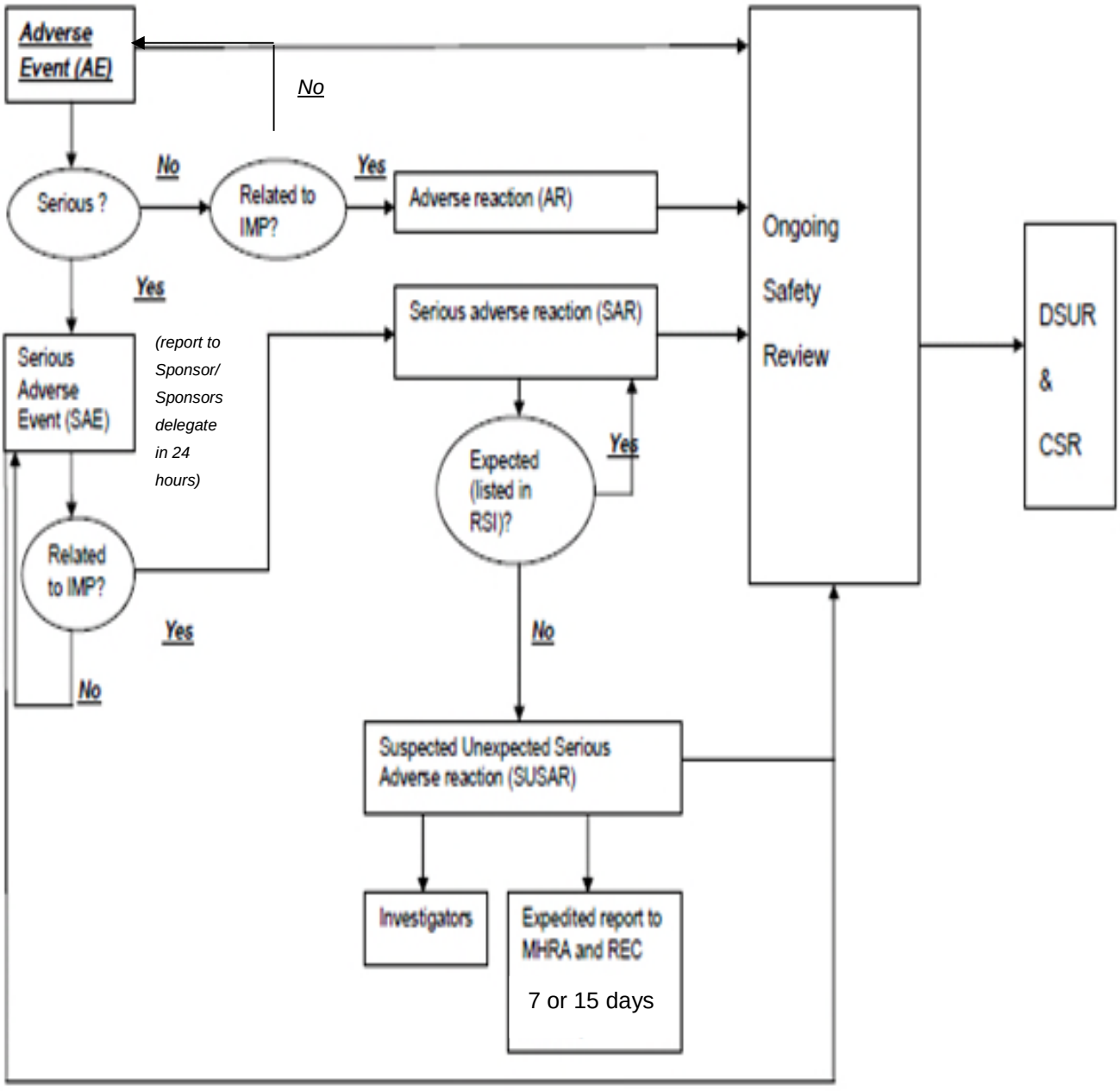
MHRA RSI clinical trial part III blog
https://mhrainspectorate.blog.gov.uk/2021/02/05/reference-safety-information-rsi-for-clinical-trials-part-iii/

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	27 Jul 2017	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
4.0	See page 1	Definitions added; more detail provided on AE/SAE assessments, pregnancy, unblinding considerations and periodic reporting; RSI use/information; addition of new Related Documents, References and Appendices	3.0

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

Adapted from Reference 'MHRA Good Clinical Practice Guide 2012'



APPENDIX B (EXAMPLES OF 'SUSPECTED' SARS CONSIDERED 'UNEXPECTED' BECAUSE OF SPECIFICTY AND/OR SEVERITY)

Reference 'Reference Safety Information Q&A document from the Clinical Trial Facilitation Group'

Listed SAR in RSI	'Suspected' SAR in individual Case Reports	Unexpected due to specificity or severity
Acute renal failure	Interstitial nephritis	Specificity
Hepatitis	Fulminant hepatitis	Severity
Cerebral vascular accident	Cerebral thromboembolism	Specificity
Exfoliative dermatitis	Stevens-Johnson Syndrome	Severity and Specificity
Transient increase in liver function tests	Increased liver function tests persisting for several months	Severity
Hypertension	Hypertensive crisis	Severity
Herpes Zoster	Multi-dermal herpes zoster	Severity
Sepsis	Septic shock	Severity
Supraventricular Cardiac Arrhythmia	Atrial fibrillation	Specificity

APPENDIX C (EXAMPLE OF IB RSI UPDATE FOLLOWING DSUR REPORTING PERIOD)

Further information in q12 & 13 of reference 'CTFG Q&A document – Reference Safety Information'