Recording, Managing and Reporting Adverse Events in the UK

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Author: Gisela Barreto

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<tr>
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1. PURPOSE

This SOP describes the process for recording, managing and reporting Adverse Events for Imperial College Academic Health Science Centre (AHSC) sponsored studies of both Investigational Medicinal Products (IMPs) and non-IMPs in the UK, but the principles are relevant for all clinical trials.

2. INTRODUCTION

It is essential that all adverse events which occur during the course of study participants’ involvement in a research project are appropriately recorded and reported in order to ensure their continuing safety.

The Medicines for Human Use (Clinical Trials) Regulations 2004 and the Department of Health’s Research Governance Framework for Health and Social Care set out specific requirements for the managing of adverse events (AE). Of particular importance is the assessment of any event for causality and expectedness.

Consequently, AEs can be classified into different categories (further explanations are given in section 2.1.)

1. Adverse Event
2. Adverse Reaction
3. Serious Adverse Event/Reaction
4. Suspected Serious Adverse Reaction
5. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Each type of AE is subject to different reporting requirements.

It is important that this SOP is followed as failure to report incidents, or deal with incidents adequately, can result in regulatory approval being withdrawn from an individual project, or, in extreme cases, from all research carried out by the Chief Investigator (CI) or Principal Investigator (PI).

2.1 Definitions

2.1.1 Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

Comment: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

2.1.2 Adverse Reaction (AR)
All untoward and unintended responses to an IMP related to any dose administered.

Comment: All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to the IMP qualify as adverse reactions.

2.1.3 Serious Adverse Event/Reaction (SAE/SAR)
Any adverse event or adverse reaction that at any dose:
• results in death
• is life-threatening
• requires hospitalisation, or prolongation of existing inpatients’ hospitalisation.
• results in persistent or significant disability or incapacity
• is a congenital anomaly or birth defect
• other important medical event

Comments: Life-threatening, in the definition of an SAE or SAR, refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Should a study participant become pregnant whilst undertaking a clinical trial of an investigational medicinal product (CTIMP), or aid in the conception of a child whilst they are participating in a CTIMP, the pregnancy and resulting child should be followed up for a period of no less than 18 months to verify whether a congenital anomaly or birth defect is present. This will be subject to guidance from the relevant pharmaceutical company. Preganacies and outcome will be included in the Annual Safety Reports. The Chief Investigator (CI) will report any pregnancy occurring on a Clinical trial via the SAE form to the JRCO.

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious”, which is based on patient/event outcome or action criteria.

2.1.4 Suspected Serious Adverse Reaction (SSAR)
Any adverse reaction that is classed as serious and which is consistent with the information about the IMP listed in the Summary of Product Characteristics (SmPC) or Investigator Brochure (IB). For IMPs used within their Marketing Authorisation (MA), the SmPC must be in the Trial Maser File (TMF) and provided to the clinical trial pharmacist. The CI is responsible for ensuring the SmPC is reviewed at least annually and any changes to the Reference Safety information (RSI) should be notified to the clinical trial pharmacist. Current SmPCs can be accessed at www.medicines.org.uk

2.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse reaction that is classed as serious and is suspected to be caused by the IMP that is not consistent with the information about the IMP in either the SmPC or IB, i.e. it is suspected and unexpected. The RSI includes a list of medical events defining which reactions are expected for the IMP being administered to clinical trial subjects, and therefore do not require expedited reporting to the Competent Authority. For reactions to be excluded from expedited regulatory reporting they must be listed in the RSI or clearly defined in the current approved version of the protocol. Any change to the RSI is a change to the Risk/Benefit and requires a substantial amendment be submitted and approved by the MHRA before it is implemented in the trial. It is the CI’s responsibility to ensure the amendment is submitted to the MHRA. Only then an updated SmPC/IB should be added to the TMF and used by the CI/PI as reference for safety reporting (SUSARs).

The trial protocol should include a list of known side effects for each drug in the study. This should be checked with each serious adverse event that occurs in terms of expectedness. If
the event is not listed as expected, or has occurred in a more serious form than anticipated, this should be considered a SUSAR.

2.2 Responsibilities
There are a number of responsibilities when managing adverse events. Below is a list of responsibilities for both the Investigator and the Sponsor (for Imperial College AHSC sponsored studies, the Joint Research Compliance Office (JRCO) will act on behalf of the Sponsor).

The CI has overall responsibility for the conduct of the study. In a multi-site study, the CI has coordinating responsibility for reporting adverse events to the Medicines and Healthcare products Regulatory Agency (MHRA) and to the relevant Research Ethics Committee (REC).

The Principal Investigator (PI) has responsibility for the research at a local site where the study involves specified procedures requiring site-specific assessment. There should be one PI for each research site. In the case of a single-site study, the CI and the PI should be the same person. The PI is responsible for informing the CI, or the coordinating research team, of all adverse events that occur at their site following the guidelines below.

Any CI/PI who has agreed to undertake duties for pharmacovigilance delegated by the Sponsor must undertake both Investigator’s and Sponsor’s responsibilities as described throughout this document.

2.2.1 Investigator’s Responsibilities
1. PI to report all SAEs and SUSARs within agreed timelines to the CI (see section 3.3)
2. CI to report all SAEs within agreed timelines to Sponsor
3. CI to report SUSARs within agreed timelines to Sponsor, MHRA, REC and relevant NHS Trust Research and Development Office (R&D) (see section 3.3)
4. Provide the Sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety within the agreed timeframes specified in the protocol.
5. Assess each event for causality and seriousness between the IMP and/or concomitant therapy and the adverse event.
6. Supply the Sponsor, MHRA, REC and relevant NHS Trust R&D with any supplementary information they request.

2.2.2 Sponsor’s Responsibilities
1. *Ongoing safety evaluation of any IMP(s), including trend analyses.
2. *Promptly notify all Investigators, REC(s) and MHRA, of any findings that may affect the health of subjects. This may include informing investigators using the same IMP in different studies.
3. *Keep detailed written reports of all AEs reported by PIs and performing an evaluation with respect to seriousness, causality and expectedness.
4. *Report all relevant safety information to the relevant REC and MHRA.
5. *Report all SUSARs to the MHRA, REC and relevant NHS Trust R&D in concerned Member States associated with comparator product(s) and Marketing Authorisation (MA) holder(s), within given timelines.
6. *Break treatment codes before submitting expedited reports to MHRA and REC for specific subjects, even if the Investigator has not broken the code. (Note: A system for maintaining blinding for the CI/PI and trial staff may need to be agreed in advance).
7. *Submit the annual safety report to Sponsor, MHRA and REC.
8. Encourage the setup of Independent Data Monitoring Committees (IDMC) for phase III clinical trials that have high morbidity/mortality and describe their function in the protocol.
9. Ensure written SOPs and systems are in place to ensure quality standards and contractual agreements are met.
10. Register users for pharmacovigilance data entry with the European Medicines Evaluation Agency (EMEA) if required.

*Note: Where Imperial College AHSC is Sponsor for a study, responsibilities 1-7 are delegated to the Chief Investigator. Correspondence for Imperial College AHSC sponsored studies should be sent to the Joint Research Compliance Office (JRCO).

3. PROCEDURES

3.1 Study Planning
All protocols should list known side effects and adverse reactions contained within the manufacturer’s product information. This should be written in agreement with the relevant drug/device company where applicable. Rare/very rare events may or may not be included depending on individual study requirements.

A detailed explanation of SAE reporting procedures should also be included in the protocol.

A generic SAE reporting form is available in Appendix 1. This form can be amended to create a study specific form following consultation with the JRCO.

3.1.1 Which AE to Record?
The CI can decide how to record and report adverse events, whether expected or not. Adverse events are usually described on case report forms (CRFs), unless they are classified as serious, in which case, these should be reported on a specific SAE form (see Appendix 1 for an example). It should be clearly stated in the study protocol and the local SOP what will be recorded and how the reporting is to be managed.

It may be decided that all, or only some, non-serious AEs are to be recorded. Whatever option is chosen, it must be consistent with the purpose of the trial and any toxicity and efficacy end points.

3.1.2 Which SAE to Report?
The management and reporting arrangements for SAEs should be in place for all trials. Agreements at the beginning of the trial should be made for such SAEs that can be defined as disease-related and therefore not subject to expedited reporting. The procedures for managing and reporting SAEs must be clearly defined in the protocol.

It is recommended that an Independent Data Monitoring Committee (IDMC) is appointed in order to review safety data regularly throughout the trial and when necessary, recommend to the Sponsor whether to continue, modify or terminate the trial. Again, this procedure must be defined in the protocol.

As with all recording and reporting, subject confidentiality and adherence to the Data Protection Act (2018) must be maintained on all reports.

3.2 During the Trial
Each AE must be evaluated for seriousness (see 2.1.3), causality, and expectedness. The responsibility for this evaluation can be shared between the CI and PIs. It may be most appropriate for the treating PI at each local site to evaluate each event, before reporting it to the CI. It must be stated in the clinical trial protocol and the local SOP who will take responsibility for the assessment and reporting of such events to the Sponsor and CI simultaneously. As expedited reporting may be
required, this SOP assumes that responsibility of initial assessment and reporting to the CI lies with the PI.

Flowcharts in Appendix 2 are designed to enable Investigators/research personnel to assess AEs and SAEs should they occur during the trial and decide if the event requires further expedited reporting by the CI.

3.2.1 Causality
Adverse reactions should be assessed for causality. The definitions below can be used.

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>There is no evidence of any causal relationship</td>
</tr>
<tr>
<td>Unlikely</td>
<td>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 medication). There is another reasonable explanation for the event (e.g. the patient’s clinical condition, other concomitant treatment).</td>
</tr>
<tr>
<td>Possible*</td>
<td>There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments).</td>
</tr>
<tr>
<td>Probable*</td>
<td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely.</td>
</tr>
<tr>
<td>Definitely*</td>
<td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td>
</tr>
<tr>
<td>Not assessable</td>
<td>There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.</td>
</tr>
</tbody>
</table>

* If the AE is serious and unexpected, the possible, probable and definitely related should be notified to the MHRA, the relevant REC and the Sponsor as SUSARS.

If different causality definitions are specified in the protocol, it must be clear which definitions constitute a ‘related’ event.

3.3 Reporting Guidelines –Clinical Trials of Investigational Medicinal Products (CTIMPS)

Once the CI/PI has evaluated the AE in terms of seriousness, causality and expectedness, the following guidelines should be followed.

3.3.1 AEs
AEs that are not considered serious should be included in the patient notes and on the relevant case report forms (CRFs). The completed form should be filed along with the other CRFs for the study and a copy provided to the Sponsor as agreed.

3.3.2 SAEs
If the AE is assessed as serious, the PI must report the event to the CI immediately or within 24 hours of being made aware of the event (other than those SAEs identified in the protocol as not requiring immediate reporting). The initial report can be made verbally but must be promptly followed with a detailed, written report. The PI must record the event with his assessment of seriousness, (along with causality, expectedness and severity) on a trial SAE form provided by the CI (see Appendix 1). The PI should ensure that follow-up information is provided when available. Where supporting documents are sent with this form, these must be anonymised. Where the information available is incomplete at that time, as much
information as can be ascertained should be sent to ensure timely reporting, with additional information provided as soon as it is known. Additional information received for an event (follow-up or corrections to the original event data) needs to be detailed on a new Serious Adverse Event Reporting Form.

**Follow-up of adverse events**

All adverse events must be followed-up until symptoms cease or the condition becomes stable. The Adverse Event Record Sheet requires a judgement on outcome, rating the adverse event as resolved (1), resolved with sequelae (2), persisting (3), worsened (4), fatal (5), or not assessable (6).

**Providing contact details for adverse event reporting**

Participants should be advised to contact the PI to report any unexpected occurrence or effect that they think might be related to the study medication. In addition to the participants themselves, pharmacy staff and other healthcare professionals responsible for the clinical care of the participant may notice suspected adverse events/reactions. It is essential that contact details for the study team are provided to anyone who may be in a position to recognise any change in the participant’s behaviour or functioning, abnormal test results or untoward medical occurrences that may be related to the study medication. The most appropriate local contact details for a member of the study team must be included on the GP Letter.

The CI should include all SSAR's and SUSAR's in the annual safety report (see section 3.5).

The **PI/CI must send all SAE reports to the Joint Research Compliance Office, Imperial College AHSC immediately or within 24 hours after becoming aware of the event at the below address:**

JRCO.CTIMP.TEAM@imperial.ac.uk

Local research governance procedures at each site, e.g. NHS Trust, should also be followed.

### 3.3.3 SUSARs

Any AE that the PI evaluates as serious, is suspected of having a causal relationship to the trial medication and is unexpected, will require expedited reporting to the JRCO, MHRA, REC and to other organisations as required under the terms of the individual contracts (e.g.: relevant pharmaceutical companies, NHS Trusts).

If the CI, or Trial Management Group if appropriate, is not in agreement with the “expectedness” decision of the PI, the CI cannot overrule the PI’s decision. Both opinions should be recorded on the SAE form.

SUSARs should be reported following the timelines in section 3.3.3.1. via the e-SUSAR electronic reporting system outlined in section 3.3.4. **Appendix 5** contains the covering document required for the main REC (CTIMPs Safety Report form).

The minimum data required for reporting SUSARs to the MHRA and REC are:

i) The suspected Investigational Medicinal Product (IMP)

ii) Subject trial Identification

iii) An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship

iv) An identifiable reporting source

#### 3.3.3.1 Timeframes for expedited reporting

**Fatal/life threatening SUSARs**

The CI must inform the JRCO, MHRA, REC, and relevant pharmaceutical companies (if required under the terms of the contract) of fatal or life threatening SUSARs as soon
as possible, but no later than 7 calendar days after the CI has first knowledge of the minimum criteria for expedited reporting. In each case, relevant follow-up information should be sought and a report completed as soon as possible. This should be sent within an additional 8 calendar days.

Non-fatal and non-life threatening SUSARs
The CI must report all other SUSARs and safety issues to the JRCO, MHRA, REC, and relevant pharmaceutical companies (if required under the terms of the contract) as soon as possible, but no later than 15 calendar days after the CI has first knowledge of the minimum criteria for expedited reporting. Further relevant information should be given as soon as possible.

3.3.4 Urgent Safety Measures
The Chief and Principal Investigators have the authority to deviate from the protocol if doing so relates to the immediate safety of a participant, where continuing to follow protocol would put that participant at risk. This is classed as an urgent safety measure and must be reported to the JRCO, MHRA and REC within three calendar days of the occurrence. This may be reported verbally in the first instance but must be supported by a written report as soon as information is available. Please refer to JRO/SOP/037

3.3.5 e-SUSAR Reporting
Once a trial has received MHRA approval the JRCO will generate an e-SUSAR account which will be identified by trial title, CI and EudraCT number.

The JRCO will require the contact details of the person(s) responsible for entering the data onto the e-SUSAR system so that user accounts can be generated. Each user will only be given permission to access those trials they have responsibility for.

The Trial details are automatically populated in the report by first selecting the trial for which the report is to be made. The form guides the user through a series of steps collecting information on the Trial Subject, the Reaction and the IMP (Suspect Drug). The user’s details are also automatically populated into the report and are defined by their account information.

Prior to submission, a summary of the data collected is presented and the user has the option to amend any details. The user also has the option to download a full report in either PDF format or as XML. Institutions may find these reports useful for informing Ethics Committees.

As well as creating and submitting new reports, users can submit follow-up reports, edit previously created but as yet not submitted reports and create and submit copy reports based on previous reports.

Once a report has been submitted it cannot be altered and any amendments will need to be included in follow-up reports.

For trials where the AHSC is acting as Legal Representative for a non-EU organisation, the sponsor has the option to register their organisation as an administrator for the e-SUSAR system, or access the system via the AHSC account if the data are being entered by an AHSC staff member.

3.3.6 Unblinding
Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. It is important that the details of the unblinding process are included in the trial protocol.
For blinded trials involving a placebo and an active drug, seriousness, causality and expectedness should be evaluated as though the patient was on active drug. Cases that are considered serious, unexpected and possibly, probably or definitely related (i.e. possible SUSARs) would have to be unblinded. Only those events occurring among patients on the active drug (unless thought to be due to the excipient in the placebo) should be considered to be SUSARs requiring reporting to the MHRA, RECs and JRCO. It may be that individuals who are not directly involved in the management of the trial could perform unblinding.

For blinded trials involving two active drugs, the person responsible for the evaluation for causality and expectedness might be able to state that if the patient were on drug A the event would be causal and/or unexpected, but if on drug B it would be expected. If the event were unexpected for either of the active drugs, the case should be unblinded by the individual charged with unblinding, who would then classify the event accordingly. An IDMC has access to semi-blinded or unblinded data and can oversee the assessment of emerging risks, such as an increase in frequency or severity of adverse events. The committee’s assessments are carried out without disclosure to the trial team. They may recommend protocol amendments, or termination of the study, if they detect serious safety issues. In addition, the chairman of an IDMC might be able to play a role in unblinding individual reports of SUSARs for expedited reporting (if this could be managed within the requisite timeframes) and SSARs for annual reports.

3.3.7 Reporting to PIs involved in Study
All PIs within the trial concerned must also be informed of the SUSAR, although this does not have to be within the 7/15-day deadline. All PIs should be sent a summary of SUSARs approximately every 3 months. This timeframe may vary between trials depending on the rates of recruitment and/or SUSARs.

If the CI is informed of SUSARs from other trials using the IMP by a pharmaceutical company, the CI should inform PIs as above.

3.4 Reporting Guidelines – Non-IMP Studies

If a research participant experiences a SAE you should report this to the relevant Research Ethics Committee and the Joint Research Compliance Office, Imperial College AHSC, where in the opinion of the chief investigator the event was:

- ‘related’: that is, it resulted from administration of any of the research procedures; and
- ‘unexpected’: that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the CI becoming aware of the event, using the form in Appendix 3. The form should be completed in typescript and signed by the chief investigator.

Reports of double-blind studies should be unblinded.

3.5 Annual Reports

For IMP clinical trials please refer to JRO/SOP/035 – Developmental Safety Update Reports. These replace the previous Annual Safety Report system for MHRA regulated trials.

3.6 Adverse Event Reporting for International Trials

Clinical trials that involve sites outside of the UK must follow the requirements of the countries in which the trial is taking place.
The procedures for reporting relevant events onwards to regulatory and ethics committees should be included in any agreements between international groups performing the trial. The protocol and/or study specific SOP should specify procedures for both the timing and format of reports of SUSARs in sites outside the EU.

### 3.6.1 Reporting SUSARs to the Ethics committee
The reporting requirements of the main ethics committee responsible for the trial in each country should be established prior to the start of the study. These requirements will vary, therefore it should be detailed in the protocol/study specific SOP which SUSARs will need to be reported and where they should be sent e.g. the UK RECs evaluate UK SUSARs only.

### 3.6.2 Reporting SUSARs to the Competent Authorities
For trials taking place within the EU, the CI must ensure that all SUSARs are reported to the competent authority for each country in which the trial is taking place.

For trials where Imperial College AHSC is Sponsor, but where all sites are outside the EU, there is no requirement to report SUSARs to the MHRA. The reporting requirements of the authorities in the participating countries must be complied with.

### 3.6.3 Annual Safety Reports/Developmental Safety Update Reports
An annual safety report should be submitted to the main REC and competent authority in each EU country that has a site participating in the trial (see section 3.5). This should include all SSARs and SUSARs occurring in all countries participating in the trial.

The requirements for countries outside the EU should be included in the protocol/study specific SOP. Annual reporting should take place as required.

### 3.7 Trend Analyses
The CI, in conjunction with the pharmaceutical company providing the IMP for the study, should conduct regular trend analyses and signal detection to determine the continued safety of the drug within the study. This is normally done post-marketing of the drug thus the company may request information to complete their dossier and submit their periodic safety update report (DSUR).

### 4. REFERENCES

Data Protection Act (2018)

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use

Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)

The Medicines for Human Use (Clinical Trials) Regulations 2004 Part 5
http://www.opsi.gov.uk/si/si2004/20041031.htm#32

National Research Ethics Service guidance on safety reporting
5. APPENDICES

All templates and forms are available on the JRO website:
http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice

http://www.ct-toolkit.ac.uk/routemap/pharmacovigilance/
5.1 Appendix 1: Sample SAE Form

**<Study title>**

### Serious Adverse Event Reporting Form

**EudraCT number:**

Please email the SAE form to the JRCO CTIMP Inbox at [jrco.ctimp.team@imperial.ac.uk](mailto:jrco.ctimp.team@imperial.ac.uk) within 24h of notification of event

<table>
<thead>
<tr>
<th>Patient Initials:</th>
<th>Patient Study No:</th>
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<table>
<thead>
<tr>
<th>Treating Clinician:</th>
<th>Hospital/Site:</th>
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#### Type of Report

- **Trial Arm**
  - 1 = First
  - 2 = Interim
  - 3 = Final

- **Sex**
  - 1 = Male
  - 2 = Female

<table>
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<tr>
<th>Height</th>
<th>Weight</th>
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<tbody>
<tr>
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<td>kg</td>
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#### Date of last trial treatment given prior to SAE

<table>
<thead>
<tr>
<th>d</th>
<th>d</th>
<th>m</th>
<th>m</th>
<th>m</th>
<th>y</th>
</tr>
</thead>
</table>

#### Was the trial treatment given at full protocol dose prior to event?

- 0 = No, specify
- 1 = Yes

#### Why was the event serious? (choose most serious)

1. Resulted in death
2. Life-threatening
3. Required inpatient hospitalisation or prolongation of existing hospitalisation
4. Resulted in persistent or significant disability/incapacity
5. Resulted in congenital anomaly/birth defect
6. Other medically important event

#### Where did the SAE take place?

1. Hospital
2. Out-patient clinic
3. Home
4. Nursing home
5. Hospice
6. Other, specify

#### Briefly describe SAE (include relevant symptoms, body site, and relevant lab tests, treatments received)

continue on a separate sheet if necessary

#### Details of SAE

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>Duration of SAE</th>
<th>SAE Status</th>
<th>Expectedness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td>(dd mmm yy)</td>
<td>1 = Resolved</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Resolved with sequelae</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = Persisting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 = Worsened</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 = Fatal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 = Not assessable</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Expected*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Unexpected</td>
<td></td>
</tr>
</tbody>
</table>

---

*SOP Ref: JRO/SOP/001
V9.0 29 Aug 2018
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### Name

<table>
<thead>
<tr>
<th>Date of Onset</th>
<th>Date Resolved</th>
<th>or tick box if ongoing</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
</table>

*Was the event one of the recognised undesirable effects of the trial medication?*

**RSI version used to assess (IB/SmPC)**

---

### Trial Treatment

<table>
<thead>
<tr>
<th>Trial drugs patient was receiving when SAE started</th>
<th>Total Daily Dose</th>
<th>Start Date of Most Recent Cycle (dd mmm yy)</th>
<th>Currently Ongoing?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0= no 1=Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End Date (dd mmm yy)</th>
<th>Causal relationship to event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1= Definitely</td>
</tr>
<tr>
<td></td>
<td>2= Probably</td>
</tr>
<tr>
<td></td>
<td>3= Possibly</td>
</tr>
<tr>
<td></td>
<td>4= Unlikely</td>
</tr>
<tr>
<td></td>
<td>5= Not related</td>
</tr>
<tr>
<td></td>
<td>6= Not assessable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Action Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>0= None</td>
</tr>
<tr>
<td>1= Dose reduction</td>
</tr>
<tr>
<td>2= Treatment delayed</td>
</tr>
<tr>
<td>3= Treatment delayed and reduced</td>
</tr>
<tr>
<td>4= Treatment permanently stopped</td>
</tr>
</tbody>
</table>

---

### Other treatments at time of event

*include concomitant medication, radiotherapy, surgery, palliative care, continue on a separate sheet if necessary. Exclude any therapy given for management of SAE*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Daily Dose</th>
<th>Route of Administration</th>
<th>Start Date (dd mmm yy)</th>
<th>Currently Ongoing?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1=Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2= Intravenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3= Subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4= Other, specify</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End Date (dd mmm yy)</th>
<th>Action Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0= None</td>
</tr>
<tr>
<td></td>
<td>1= Dose reduction</td>
</tr>
<tr>
<td></td>
<td>2= Treatment delayed</td>
</tr>
<tr>
<td></td>
<td>3= Treatment delayed and reduced</td>
</tr>
<tr>
<td></td>
<td>4= Treatment permanently stopped</td>
</tr>
</tbody>
</table>
Other relevant information to facilitate assessment
(Include medical history, drug or alcohol abuse, family history, findings from special investigations)

Was this event expected in view of the patient’s clinical history?

☐ 0 = No
☐ 1 = Yes

Additional Information:

Signature
Authorised Health Professional  

Contact telephone no:

Print name

Date of report dd/mm/yy

SITES TO COMPLETE

Was SAE drug related? Yes ☐ No ☐

Was event unexpected? Yes ☐ No ☐

Was the event a SUSAR? Yes ☐ No ☐

Date site aware dd/mm/yy

Date reported to CI dd/mm/yy

Date reported to Sponsor dd/mm/yy

Form completed by xxx (staff signature)

Comments:

Date dd/mm/yy
5.2 Appendix 2: Flowchart for Reporting and Assessing Adverse Events in CTIMPs sponsored by Imperial College

Safety Reporting Overview

 Serious Adverse Event

- Serious
  - Serious Adverse Event
    - Related to IMP
      - Serious Adverse Reaction
    - Not related to IMP
      - Serious Adverse Event

- Not serious
  - Adverse Event
    - Related to IMP
      - Adverse Reaction
    - Not related to IMP
      - Adverse Event

Expectedness

- Expected
  - Suspected Unexpected Serious Adverse Reaction
    - Report to Sponsor Immediately
    - Include in Annual Safety Report

- Not Expected
  - SAE
    - Record in notes + CRF + SAE form
      - Report to Sponsor Immediately
      - Include in Annual Safety Report

Causality

- Related to IMP
  - SSAR
  - Record in notes + CRF + SAE form
    - Report to Sponsor Immediately
    - Include in Annual Safety Report

- Not related to IMP
  - AR
  - AE
    - Record in notes + CRF

Expedited Reporting!

- Record in notes + CRF + SAE form
- Report to Sponsor Immediately
- Report to MHRA & EC (7/14 days)
- Include in Annual Safety Report

* Unless identified in the protocol as not requiring immediate reporting
5.3 Appendix 3: SAE Reporting Form for non-IMP studies

This form can also be found on: http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/

**Health Research Authority**

REPORT OF SERIOUS ADVERSE EVENT (SAE)
(For all studies except clinical trials of investigational medicinal products)

*The Chief Investigator should report any SAE that is both related to the research procedures and is unexpected. Send the report to the Research Ethics Committee that gave a favourable opinion of the research within 15 days of the CI becoming aware of the event.*

### 1. Details of Chief Investigator

<table>
<thead>
<tr>
<th>Name:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
</tr>
<tr>
<td>Telephone:</td>
</tr>
<tr>
<td>Email:</td>
</tr>
<tr>
<td>Fax:</td>
</tr>
</tbody>
</table>

### 2. Details of study

<table>
<thead>
<tr>
<th>Full title of study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of main REC:</td>
</tr>
<tr>
<td>Main REC reference number:</td>
</tr>
<tr>
<td>Research sponsor:</td>
</tr>
<tr>
<td>Sponsor’s reference for this report:</td>
</tr>
<tr>
<td>(if applicable)</td>
</tr>
</tbody>
</table>

### 3. Type of event

*Please categorise this event, ticking all appropriate options:*

<table>
<thead>
<tr>
<th>Death</th>
<th>Life threatening</th>
<th>Hospitalisation or prolongation of existing hospitalization</th>
</tr>
</thead>
</table>
Persistent or significant disability or incapacity

Congenital anomaly or birth defect

Other

4. Circumstances of event

Date of SAE:

Location:

Describe the circumstances of the event:

(Attach copy of detailed report if necessary)

What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?

5. Declaration

Signature of Chief Investigator:

Print name:

Date of submission:

6. Acknowledgement of receipt by main REC (please insert name):

The [ ] Research Ethics Committee acknowledges receipt of the above.

Signed:

Name:

Position on REC:

Date:
Signed original to be sent back to Chief Investigator (or other person submitting report)

Copy to be kept for information by main REC.

5.4 Appendix 4: MHRA Addresses

Developmental Safety Update Reports should be provided to the MHRA using CESP (https://cespportal.hma.eu/Account/Login?ReturnUrl=%2f). The same guidance for submitting clinical trials applications via CESP applies, but please select regulatory activity G0042 - Development Safety Update Reports.

eSubmission Guidance: Guidance has been published on the structure and format of electronic submissions for both human & veterinary medicinal product submissions and can be access at: http://esubmission.ema.europa.eu
5.4  – Appendix 5 – CTIMPs Safety Report Form

Copies of all safety information supplied to MHRA must also be emailed to the main Research Ethics Committee, accompanied by a CTIMPs Safety Report form. This form can also be found at: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

SAFETY REPORT TO RESEARCH ETHICS COMMITTEE

Please indicate which type(s) of safety report you wish to notify with this cover sheet (tick all that apply). Use a separate sheet for notifications relating to different trials. Please send by email to the main REC for the trial concerned together with enclosures. For further guidance see: http://www.hra.nhs.uk/research-community/during-your-research-project/safety-reporting/

1. Expedited report(s) of SUSAR in the UK
   Notify only Suspected Unexpected Serious Adverse Reactions occurring in the concerned trial at a UK site. SUSAR reports must follow the ICH E2B format.

2. Annual safety report / DSUR
   ASRS MUST FOLLOW THE ICH E2F FORMAT FOR DEVELOPMENT SAFETY UPDATE REPORTS (DSUR). INCLUDE A GLOBAL LIST OF ALL SSARS (SUSPECTED SERIOUS ADVERSE REACTIONS) RELATED TO THE IMP AND OCCURRING IN THE REPORTING PERIOD.

3. OTHER
   For example, report of Data Monitoring Committee or other safety review.

<table>
<thead>
<tr>
<th>Full title of study:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EudraCT number:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research sponsor:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of Chief Investigator:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>
**Name of main REC:**

**Main REC reference number:**

### Contact details for person making this notification

<table>
<thead>
<tr>
<th>Name:</th>
<th>Address:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone:</td>
<td>Fax:</td>
</tr>
<tr>
<td>Email:</td>
<td>Date of this notification:</td>
</tr>
</tbody>
</table>

### List of enclosed documents

Please list each report submitted with this notification (insert extra rows in table as required).

1. **Expedited SUSARs (UK only)**

<table>
<thead>
<tr>
<th>Sponsor’s report no. / reference</th>
<th>Trial site</th>
<th>Date SUSAR first reported to sponsor</th>
<th>Is this a 7 or 15 day report?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Other reports**

<table>
<thead>
<tr>
<th>Type of report</th>
<th>Date of report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SOP Ref: JRO/SOP/001
Final v7.0 18/02/15

© Imperial College of Science, Technology and Medicine
Acknowledgement of receipt by main REC (please insert name):

The [ ] Research Ethics Committee acknowledges receipt of the above.

Signed:  

Name:  

Position on REC:  

Date:  

Signed original to be sent back only to the sponsor (or other person submitting the report).

Copy to be kept for information by main REC.