STANDARD OPERATING PROCEDURE

Safety Reporting

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RESEARCH AND INNOVATION

R & I

BACKGROUND

Adverse Events (AEs) and Serious Adverse Events (SAEs) should be reported in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004 and also in compliance with ICH Good Clinical Practice guidance, and within any other conditions stipulated in the trial protocol or by the host Trust. It is the responsibility of the sponsor to ensure that events are reported appropriately to the competent authority (in the UK this is the Medicines and Healthcare Regulatory Agency – MHRA) and also the Health Research Authority (HRA) and Research Ethics Committee (REC) providing the favourable opinion for the trial.

The Regulations distinguish between Adverse Events (AEs), Adverse Reactions (ARs), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs), with differing reporting requirements for each type of event. This clarification is also included in all study protocols that require such reporting.

Definitions

Adverse event (AE): Any untoward medical occurrence in a trial patient which does not necessarily have a causal relationship with the treatment.

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death
- Is life-threatening*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability / incapacity or
- Is a congenital anomaly or birth defect

* Life-threatening in the definition of a serious adverse event refers to an event in which the subject 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 or were left untreated.

- An untoward medical occurrence that is otherwise considered medically significant to the investigator may also be reported as an SAE.
- Some sponsors may specify other events that should be reported as SAE although they do not fulfil any of the above criteria of SAE (this will be specifically identified in the study protocol)

Adverse Reaction (AR): All untoward and unintended responses to an investigational medical product related to any dose administered. Any event that could not be determined as definitely not caused by the IMP should be reported as an AR.

Serious Adverse Reaction (SAR): An adverse reaction resulting in serious outcomes as listed in SAEs. Seriousness is not the same as severity, as seriousness relates to the outcome of the event and not the intensity of the reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction is 'unexpected' if its nature and severity are not consistent with the medicinal product information (detailed in the Summary of Product Characteristics if a licensed product or in the Investigators Brochure if not yet licensed).

PURPOSE

To describe the procedure for identifying, recording and reporting adverse events in a clinical trial, including Clinical Trials of Medicinal Products (CTIMPs), Device trials and other interventional studies.

PROCEDURE

1. WHO?

The sponsor is responsible for ensuring all events are reported to the MHRA and the REC, however in many cases, this responsibility is delegated to the Chief Investigator (CI) or a Contract Research Organisation. Principal Investigators (PI) involved in hosted trials are responsible for ensuring that all events occurring at their site are reported appropriately to the sponsor or their delegate.

All staff and clinicians involved with managing trial patients should note adverse events that are reported by the patient and make them known to the appropriate study staff. Patients entered into clinical trials must be encouraged as part of the consent process to contact their clinician or research practitioner, e.g. Research Nurse at the time of an event occurring. It is important that if patients are admitted to other ward areas, that the trials staff are informed of the hospital admission as soon as possible.

The appropriate research staff should conduct study assessments, and ensure that all adverse events are identified for each patient as far as possible.

All staff involved with managing trial patients are responsible for ensuring that methods of pharmacovigilance are followed in accordance with this SOP.

2. WHEN?

At each visit or study assessment, adverse events that have occurred since the previous patient contact should be discussed with the patient. For source documentation verification, these events need to be detailed in the patient's medical notes including the start dates (if known) of the onset of the event as well as the date the event stopped or changed, if applicable. Adverse events ongoing on completion of the study should be followed up as required by the protocol and as clinically indicated. For some studies, telephone contact may be used between visits to ensure accurate timely collection of such events.

3. HOW?

Adequate pharmacovigilance procedures should be clearly documented in the protocol and it is advisable to have a formal SOP in place at the local site. All procedures and requirements outlined in the protocol should be followed. Awareness of procedures and documentation should form part of initiation to the study for staff involved.

Documenting events

The following should be documented as clearly as possible in accordance with the protocol:

- Time and date of start and stop of event (if the patient cannot remember, then as near as possible)

- Severity of event, this may be graded by using the toxicity criteria in the protocol. This is often mild, moderate or severe (guidance as to what defines each of these may be in the protocol)

- Action taken regarding study drug (if any) – these may include stopping study drug temporarily or permanently.

- Any treatment/medication given for the event, including the dates the treatment/medication was commenced and the date it was stopped / changed, if applicable.

- The event outcome

Complete collection of the necessary data relating to adverse events will ensure that source data is available to ensure complete and accurate Case Report Form completion and reporting of the adverse event adhering to the study protocol, Good Clinical Practice and appropriate regulations.

Assessing events

This is summarised in Appendix A. Individual adverse events should only be assessed by a medically qualified person integrally involved in the study i.e. the PI or delegated other and if applicable they should be reported to the sponsor or delegate for evaluation / clarification. Assessment of the event should include determination of:

1. Causality:
    - Is there a possible causal relationship between the investigational medicinal product(s) (IMP), concomitant therapy, device or intervention and the adverse event?
    - The causality assessment given by the PI should not be downgraded by the sponsor and if the sponsor disagrees with the PI's assessment, then the opinion of both the PI and sponsor should be provided in the report.

2. Seriousness, is it:
    - fatal
    - life-threatening
    - requiring inpatient hospitalisation or prolongation of existing hospitalisation
    - resulting in persistent or significant disability / incapacity
    - a congenital anomaly or birth defect
    - another event specified in the protocol to be reported as an SAE

3. Expectedness:
    - Is its nature and severity not consistent with the medicinal product information - detailed in the Summary of Product Characteristics if a licensed product or in the Investigators Brochure? Information on expectedness may also be detailed in the protocol.

An event is a SUSAR if it is unexpected, serious and is possibly related to the trial treatment (see Appendix A)

Reporting events

This is summarised in Appendix A.

Adverse Events are reported using study specific data collection tools e.g. Case Report Form or electronic Case Report Form. These will be sent to the Sponsor with other data relating to that patient contact. Adverse Event reports may be submitted to the MHRA and the REC by the sponsor or their delegate.

All SAEs, as defined by study specific protocols must be reported by the site ***immediately*** to the sponsor, except where the protocol does not require this. The immediate report to the sponsor can be brief, but must be followed up by a more detailed report. SAE reporting forms should be provided at study set up and all staff need to be familiar with the study specific requirements and documentation as part of their induction to the study. The procedure for how to report to the sponsor should be outlined in the protocol. SAEs should be reported by the Sponsor in quarterly annual safety reports to MHRA and REC and presented regularly at the trial safety monitoring committee, if applicable. These reports should be maintained in the site file.

All SUSARs should be reported by the site ***immediately*** to the Sponsor according to the protocol as for SAEs above. The Sponsor must report such events as per protocol and Clinical Trials Regulations to the MHRA and the REC.

Once it has been determined that an SAE / SUSAR was related to the clinical trial / intervention, this also needs to be reported to the R&I Management Team via the Datix Incident Reporting system, the process of which is outlined in Appendix B.

The sponsor (or delegate) must also immediately inform all PIs involved in the trial of relevant information about SUSARs that could adversely affect the safety of their trial patients. Any such notifications should be signed and dated by the PI as acknowledgement of the information, the research team informed of these and the documentation filed in the safety reporting section of the site file.

Reporting SUSARs

All SAEs that are SUSARs are subject to expedited reporting to the MHRA and the REC (by the Sponsor) and there are strict timelines set out in the Trials Regulations. Therefore, PIs must report events to the sponsor or delegate immediately so as to satisfy these requirements. These are:

1. A SUSAR which is fatal or life-threatening must be reported as soon as possible and in any event within 7 days after the sponsor (or delegate) became aware of the event. All follow-up information must be reported within 8 days of sending the first report.
2. A SUSAR which is not fatal or life-threatening must be reported as soon as possible and in any event within 15 days after the sponsor (or delegate) became aware of the event.

All SUSARs associated with a comparator product in the clinical trial should be reported, even if this product is approved. Generally treatment codes should be broken before

reporting a SUSAR to the MHRA and the REC, although the blind could potentially be broken by the sponsor / CI and not made known to the PI if there is no danger in this to the patient. For trials in high morbidity and/or high mortality disease, where efficacy end-points could also be SUSARs or when a fatal or other "serious" outcome is the primary endpoint in a trial, the integrity of the trial may be compromised if the blind is broken. Under these and similar circumstances, it may be appropriate to reach agreement with the MHRA in advance concerning serious events that would be treated as disease-related and not subject to systematic unblinding and expedited reporting. This agreed procedure will be outlined in the protocol

Other expedited reporting

Other safety issues qualify for expedited reporting by the sponsor:

- Single case reports of expected SARs with an unexpected outcome.
- An increase in the rate of occurrence of an expected SAR, judged to be clinically important.
- Post-study SUSARs that occur after the patient has completed a trial (the length of time after completion of the trial may be specified in the protocol).
- A new event, related to the conduct of the trial or the development of the investigational medicinal product, that is likely to affect the safety of subjects, e.g. an SAE which could be associated with the trial procedures and which could modify the conduct of the trial or a significant hazard to the subject population such as lack of efficacy of a product used for the treatment of a life-threatening disease.
- A major safety finding from a newly completed animal study.

Sending a report

The Investigators Brochure usually outlines the format for event reporting and this should be followed. Reports of SUSARs will normally be in the CIOMS-1 format (available at www.cioms.ch) that is widely accepted as the standard within the pharmaceutical industry. Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits and must contain the following minimum information:

1. A suspected investigational medicinal product.
2. An identifiable subject (e.g. study subject code number).
3. An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship.

4. An identifiable reporting source.

5. Where applicable, EudraCT number or in case of non EU trials the sponsor's trial protocol code number.

6. A unique case identification, i.e. sponsor's case identification number.

Where there is incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought. The sponsor or delegate should report further relevant information after receipt as follow-up reports.

SUSARs reported at other sites

SUSAR reports will usually be distributed by the Sponsor to all sites participating in the trial. There is usually a requirement for the PI to acknowledge receipt and review of the SUSAR. In order for the wider delivery team to be updated, it is recommended that all SUSARs should be discussed at the next scheduled PI Oversight meeting, or sooner if necessary, in order to identify any relevant information that would impact on patient safety or clinical processes.

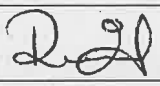
4. OTHER RELATED PROCEDURES, POLICIES, LEGISLATION OR GUIDANCE

International Conference on Harmonisation of Good Clinical Practice 1996
Medicines for Human Use (Clinical Trials) Regulations 2004
Medicines for Human Use (Clinical Trials) Amendment Regulations 2006

Glossary
Adverse Event (AE)
Adverse Reaction (AR)
Case Report Form (CRF)
Chief Investigator (CI)
Electronic Case Report Form (eCRF)
Medicines and Healthcare products Regulatory Agency (MHRA)
Research Ethics Committee (REC)
Principal Investigator (PI)
Serious Adverse Event (SAE)
Serious Adverse Reaction (SAR)
Standard Operating Procedure (SOP)
Suspected Unexpected Serious Adverse Reaction (SUSAR)

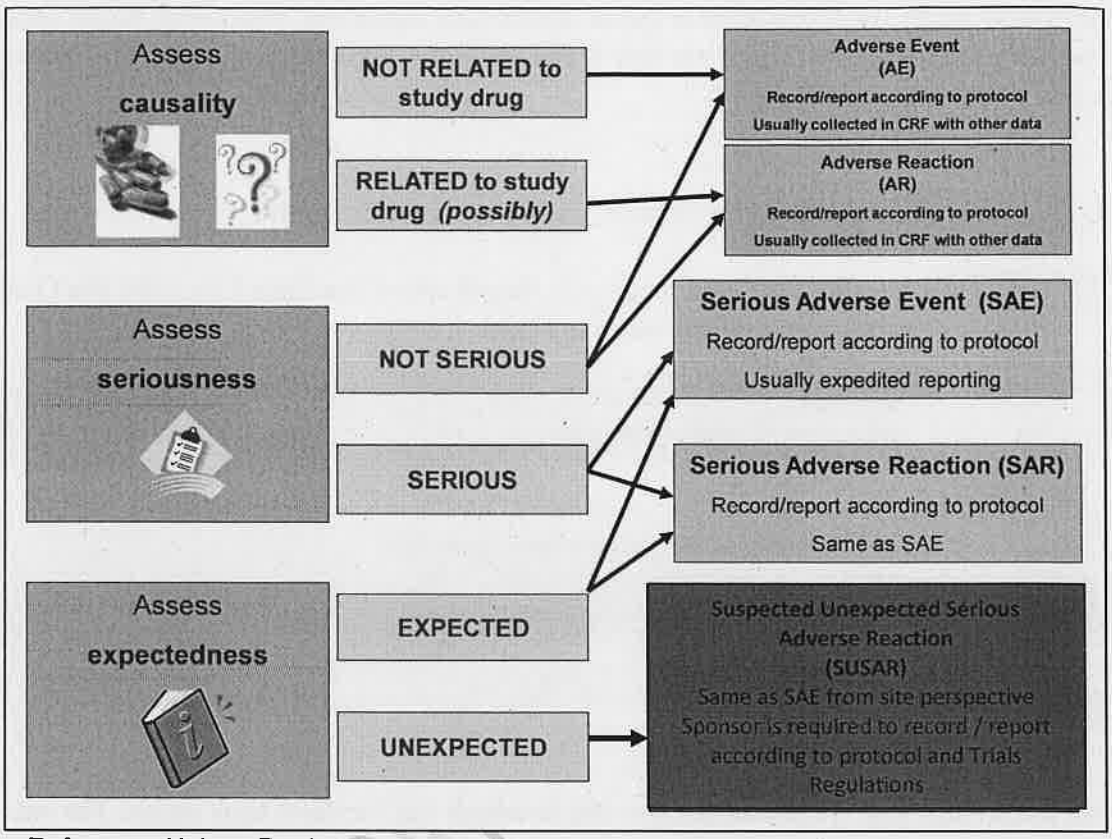
APPENDICES

Appendix A – Determination and reporting of adverse events
Appendix B – Safety Reporting at Lancashire Teaching Hospitals via Datix

Sign Off			
Lead Author:			
Name and Position	Kina Bennett, Research Operations Manager		
Signature		**Date**	11-03-2022
Reviewed and approved by:			
Name and Position	Paul Brown, on behalf of Lancashire Teaching Hospitals NHS Foundation Trust Research & Innovation Committee Chair		
Signature		**Date**	11-03-2022
Authorised for release by:			
Name and Position	Rebecca Wilby, Research Access Project Manager		
Signature		**Date**	11-03-2022

Controlled Copy Authorisation			
Copy Number			
Location			
Authorised signature		**Date**	
Print-out only valid with original authorised signature			

APPENDIX A – DETERMINATION AND REPORTING OF ADVERSE EVENTS



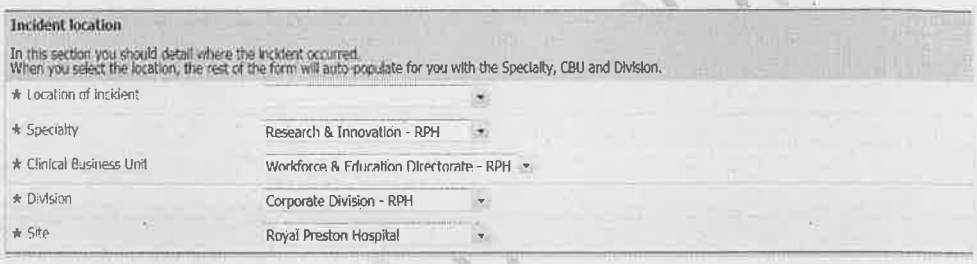
Reference: Helena Prady

APPENDIX B - SAFETY REPORTING AT LANCASHIRE TEACHING HOSPITALS VIA DATIX

If an SAE / SUSAR is found to have been related to the clinical trial / intervention, as well as following study specific protocol guidance for SAE reporting, this needs to be reported to the R&I Management Team via the Datix Incident Reporting system, the process of which is outlined in Appendix B.

Datix is available through the LTH Intranet via the exclamation mark:

On the LTH Home page you should select the Datix icon from the Quick Links menu on the left hand side



In the Datix form you should select the site at which the incident took place. For research we sit within the Corporate Division, and Workforce and Education Directorate. Pick an exact location from the drop down list.

You should then select the 'incident type' and 'incident relating to' options as above which will provide you with a drop down menu to select the type of incident you are reporting.

Complete the rest of the form as per the on screen instructions.

This is a mandatory requirement for all SAEs and SUSARs that have been determined as being related to the study intervention, regardless of whether the Trust is acting as Sponsor for the study. This data contributes to monthly safety reports compiled by the Centre for Health Research and Innovation.

Description of the Incident: Please note, there should be no person identifiable information in the description. You can use initials and give an explanation in the 'Action taken' section.