The Leeds Teaching Hospitals NHS NHS Trust UNIVERSITY OF LEEDS Standard Operating Procedure	Title	**A Researcher's Guide to Pharmacovigilance**				
	Scope	*Describes the process that the researcher follows when reporting SAEs / SUSARs from single-centre CTIMPs being sponsored by the LTHT / UoL*				
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3.0	Clare Skinner *Head of Research Integrity and Governance* Secretariat, University of Leeds	06/10/2020	
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Distribution & Storage:

Distribution to:

All Research Staff conducting or assisting with a CTIMP project sponsored by the University of Leeds (UoL) or The Leeds Teaching Hospitals NHS Trust (LTHT).

Location of Document:

Paper: Joint Quality Assurance Office, Office 5
Research and Innovation Centre, St James's University Hospital

Electronic: http://www.leedsth.nhs.uk/research/information-for-researchers/key-documents

http://lthweb.leedsth.nhs.uk/sites/research-and-development/resources/Sponsored%20CTIMPs%20%28Quality%20Assurance%29

Contents:

Please note: *This SOP should be used and followed in conjunction with other UoL / LTHT SOPs developed for researchers to support study set up and management. These can be found on the LTHT website or by contacting R&I / QA directly.*

For clinical trials where Leeds is not the trial Sponsor, please refer to any Sponsor SOPs for further information.

Section A: Introduction:

1.1 This SOP outlines the pharmacovigilance procedures for LTHT and UoL sponsored Clinical Trials of Investigational Medicinal Products (CTIMPs).

1.2 Pharmacovigilance (PhV) is defined as "*the science of collecting, monitoring, researching, assessing and evaluating information on the adverse effects of medicines with a view to identifying information about potential new hazards and preventing harm to subjects*" (MHRA Good Clinical Practice Guide).

1.3 For investigators this means monitoring the safety of the Investigational Medicinal Product (IMP) and accurately recording and reporting any events to the Sponsor and regulatory authority in the specified timelines.

1.4 This SOP will outline the processes required for:

- Recording and reporting Adverse Events (AEs) / Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs).
- Implementation of Urgent Safety Measures (USMs).
- Annual Safety Reporting (Development Safety Update Reports - DSURs).

Section B: Applicability:

1.1 This SOP is applicable to all members of staff working on CTIMPs sponsored by The Leeds Teaching Hospitals NHS Trust (LTHT) / University of Leeds (UoL).

1.2 Deviations from this SOP must be discussed and agreed with the Sponsor QA Office during protocol development and a written agreement must be in place.

1.3 For CTIMPs managed by a Clinical Trials Research Unit (CTRU) or Clinical Research Organisation (CRO) a clear contractual delegation of pharmacovigilance duties is required. The Sponsor must ensure these procedures are compliant with the clinical trial regulations.

For CTRU trials, some aspects of this SOP may differ. Please consult your Head of Trial Management for further information.

Section C: A Researcher's Guide to Pharmacovigilance:

1.0 Adverse Events (AEs)

An Adverse Event (AE) is any untoward medical occurrence in a patient a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

1.1 Participants must be assessed for AEs at each trial visit as defined in the trial protocol. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease that is concurrent with the use of an Investigational Medicinal Product (IMP).

This is irrespective of whether or not the event is related to the IMP.

1.2 All AEs must be recorded in both the Case Report Form (CRF) and the patient's medical notes. If AEs are being recorded directly in the CRF then a copy must be filed in the patient's medical notes in real time, as different medical specialists / departments may require access to this information.

1.3 The investigator must assess adverse events (as defined in the protocol) for seriousness and causality; the decisions made should be fully documented in both the medical notes and CRF.

1.4 Documentation of AEs and related source data will be checked during routine Sponsor monitoring visits.

Please see '***LTU_QM23 - A Researcher's Guide to Source Documentation***' SOP for further information.

2.0 Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is any adverse event that results in:

- death
- is life-threatening
- requires hospitalisation
- prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect

2.1 All adverse events meeting the seriousness criteria (as outlined above), and therefore assessed as an SAE by the CI/PI or medically qualified delegate must be reported to the Sponsor.

2.2 SAEs must be reported in line with the current REC / MHRA approved protocol, which will include instructions regarding how long SAEs have to be captured and reported for (*e.g. XX days after last dose of IMP*).

2.3 All SAEs must also be fully documented in the CRF and patient's medical notes.

2.4 All SAEs must be assessed for relatedness / causality and expectedness. This assessment must be made by a medically qualified doctor (as authorised on the trial delegation log) using the Reference Safety Information (RSI - approved specifically for trial use at the time of the event).

2.5 All adverse events judged by the investigator / medically qualified delegate as having a reasonable suspected causal relationship with the IMP qualify as Adverse Reactions (*e.g. any event categorised as related or possibly related to the IMP*).

2.6 Reporting Serious Adverse Events (SAEs) to the Sponsor QA Office

2.6.1 Upon identification of an SAE, the investigator or named delegate **must report the SAE via email (leedsth-tr.sponsorqa@nhs.net) to the Sponsor QA Office within 24 hours of awareness.** This must be done using the 'CTT21: SAE Report' form.

Under **no circumstances** should reporting the SAE exceed 24 hours from the time of awareness.

2.6.2 If the SAE is suspected to be related to the trial treatment(s) but is also assessed to be unexpected, in line with your Reference Safety Information, this qualifies as a Suspected Unexpected Serious Adverse Reaction (SUSAR) and additional expedited action is required - please see Section 3.0 for guidance on SUSARs and the required reporting.

2.6.3 A scanned copy of the completed CTT21 SAE report form must be attached to the email and include the following details in the subject field:

- R&I number
- Trial short name
- "SAE - " or "SUSAR Notification"

2.6.4 If initial attempts to obtain all the information needed to fully complete the SAE report have proved unsuccessful, the available information must still be provided to the sponsor within the timeframe specified above (2.6.1).

2.6.5 The research team are then required to provide follow up information to the Sponsor QA Office whenever requested and as soon as possible to ensure a complete audit trail of each event.

2.6.6 If a full response has not been received from the QA Sponsor Office within 3 working days, please contact the team directly to discuss.

2.7 Completing the CTT21 SAE / SUSAR Report Form

2.7.1 Only one SAE / SUSAR can be reported per form**.**

Concurrent events must be reported and followed up accordingly using separate forms.

2.7.2 A unique SAE ID must be assigned using the following standard format:

- R&I trial ID/ Patient ID/ SAE number (patient specific)

(*e.g. the ID 'XY12/3456 / 0001 / 003' would represent Sponsor/R&I trial ID XY12/3456, patient number 0001 with their third SAE.*)

2.7.3 The report form must be legible and completed as fully as possible as onward reporting may be required. The QA Office will be in contact should further information be required.

2.7.4 Where multiple options are listed, tick all that are applicable.

2.7.5 Corrections must be initialled, dated, and clearly legible.

2.7.6 Please use supplementary pages (CTT21A - SAE form Supplemental Page) to provide additional information if required.

2.8 Submitting Follow Up Information

2.8.1 All SAEs **must be followed up to resolution** (unless otherwise stated in the protocol)

2.8.2 On a follow-up report, the individual completing the form must highlight any changes and additional information before sending to the sponsor.

Notification of receipt will be provided by the QA Office within 3 working days. If no response is provided within 3 working days please contact the team directly to discuss.

3.0 Suspected Unexpected Serious Adverse Reactions (SUSARs)

This is a serious adverse reaction where the nature and severity of the event is not defined as expected within the document containing the trial-specific Reference Safety Information.

i.e.

- Summary of Product Characteristics (SPC),
- Investigator Brochure (IB)
- Separate document (approved by the MHRA)

3.1.1 When an SAE is deemed unexpected when assessed against the Reference Safety Information (RSI) the SAE qualifies as a SUSAR and requires expedited reporting.

3.1.2 The RSI is usually a clearly defined section within either an Investigator's Brochure (IB) or Summary of Product Characteristics (SPC) document, as approved for use in the trial by the MHRA.

A specific version of the document containing RSI should be defined in the initial CTA application, or be subsequently updated via a subsequent amendment.

3.1.3 The expectedness assessment can be undertaken by the CI/PI or other medically qualified delegate.

3.1.4 In absence of both the CI and PI, a SUSAR must nevertheless be reported to the Sponsor and the regulator within the legislatively specified timelines.

3.2 Reporting SUSARs:

3.2.1 Upon identification of a SUSAR, the investigator or named delegate **must report the SUSAR via email (leedsth-tr.sponsorga@nhs.net)** to the Sponsor QA Office **immediately and always within 24 hours of awareness**.

This must be done using the CTT21: SAE Report form.

3.2.2 The SUSAR box must be checked on the form to alert the QA Office of the need for urgent review.

3.2.3 It is the investigator's responsibility to provide the Sponsor QA Office with follow-up information as soon as possible, to facilitate accurate onward reporting to the MHRA / REC.

3.2.4 Unless agreed otherwise, the Sponsor QA Office is responsible for reporting the SUSAR to the MHRA and REC.

All SUSARs must be reported to the MHRA and REC in the timelines specified below:

What?	Who?	When?
SUSARs that are fatal or life-threatening	Must be reported to MHRA and REC	**Within 7 days** following date of awareness.
SUSARs that are not fatal or life threatening	Must be reported to MHRA and REC	**No later than 15 days** following date of awareness.
Further follow-up with any additional information relevant to the SUSAR	Must be reported to MHRA and REC	**Within 8 days** of submitting the initial report.

3.3 Handling SUSARs From Blinded Trials

3.3.1 SUSARs should be unblinded prior to reporting to the REC and MHRA.

Unblinding procedures should be found in your current REC / MHRA approved trial protocol (or formal written blinding procedure).

3.3.2 If the CI (or PI for single-centre studies) considers the event as an immediate hazard to the health and safety of trial subjects, an Urgent Safety Measure (USM) may be required.

See Section 4.0 (below) for further guidance.

4.0 Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or Investigator may take in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

4.1 The requirement for an Urgent Safety Measure may potentially be identified upon receipt of a Serious Adverse Event (SAE) or a Suspected Unexpected Serious Adverse Reaction (SUSAR), which then prompts the urgent implementation of a new protocol measure to prevent a future occurrence or recurrence of a safety issue.

4.2 Examples of when an Urgent Safety Measure may be required are as follows:

- Serious adverse reactions with an unexpected outcome (*e.g. death*).
- An increase in the frequency of a serious adverse reaction which is judged to be clinically important.
- A serious adverse event associated with the trial procedures which may be prevented by changing the procedures.
- Lack of efficacy of an investigational medicinal product (IMP) used for the treatment of a life threatening illness.
- A major safety issue identified from other studies (clinical or non-clinical) or from other usage of the IMP.

4.3 Reporting Urgent Safety Measures to the MHRA & REC/HRA

4.3.1 Once an Urgent Safety Measure is identified, the **Chief Investigator** is responsible for notifying the MHRA **within 24 hours**. This is initially by telephone to the MHRA's Clinical Trial Unit on **0203 080 6456**.

This will include a discussion with a safety scientist to outline the reasons for the Urgent Safety Measure.

In <u>parallel</u> you must contact the Sponsor QA Office - see Section 4.4 (*below*)

4.3.2 The CI must then formally notify the MHRA in writing (usually via email) within **3 calendar days** of implementing the measure.

4.3.3 A substantial amendment (covering the changes as a result of the USM) may also be required within approximately two weeks of notification to the MHRA. (**See Section 4.4.5**)

4.3.4 Copies of all UK related safety information supplied to MHRA must also be emailed in parallel to the main Research Ethics Committee, accompanied by a CTIMPs Safety Report form (https://www.hra.nhs.uk/documents/1086/safety-report-form-ctimps.docx). The REC Manager will acknowledge receipt of all safety reports within 30 days by signing and returning a copy of the covering form. Reports sent without the covering form will not be acknowledged.

4.4 Reporting Urgent Safety Measures to the Sponsor QA Office:

4.4.1 The CI or delegate must inform the Sponsor QA Office of the USM immediately by telephone.

4.4.2 A written report must then be submitted by completing Section A of form *CTT07 - LTHT / UoL Notification of Urgent Safety Measure*.

This must be sent to the QA Office via email (leedsth-tr.sponsorqa@nhs.net) within 24 hours of the measure being implemented. This report must be signed and dated.

4.4.3 Upon receipt, the Sponsor QA Office will review the information provided, according to the Sponsor's '*LTU_SOP_03_ Pharmacovigilance for LTHT / UoL Sponsored CTIMPs'* SOP.

Where appropriate, the Sponsor may seek advice from the Joint Governance Committee's clinicians to aid their review.

4.4.4 The Sponsor will respond via e-mail, within 3 calendar days, to confirm that the form has been received and whether any further information is required.

4.4.5 The Chief Investigator together with the Sponsor is responsible for reviewing the Urgent Safety Measure and assessing the best way of implementing the relevant changes to the trial or its protocol.

4.4.6 Prior to submission to the MHRA, any substantial amendment relating to the USM must still be submitted for review by Sponsor QA.

A CTT05 '*LTHT / UoL Sponsor Notification of CTIMP Amendment*' form must also be completed and submitted in accordance with the '*Researchers Guide to Notification of Amendments for UoL / LTHT Sponsored CTIMPs'* SOP.

5.0 Developmental Safety Update Reports (DSURs) / Annual Safety Reports (ASRs)

An annual safety report describing the general progress and any relevant safety data related to the trial that must be submitted to the MHRA, REC, and Sponsor on the anniversary of the Clinical Trial Authorisation being granted.

The annual report should follow the format of a **Developmental Safety Update Report (DSUR) which should be a concise document and focus on the IMP.** A template and guidance for the completion of this report is available from the Sponsor QA Office.

5.1 The CI will receive an e-mail reminder from the Sponsor QA Office to remind them that annual reports are due. The automated reminders are set up upon receipt of the initial Clinical Trial Authorisation (CTA) from the MHRA.

5.2 A DSUR must then be completed by using the DSUR template (CTT55).

Completion guidance is also provided within the CTT55 document and upon request from the Sponsor QA Office.

5.3 The final reported must be signed off by the CI and submitted in parallel to the MHRA, REC and Sponsor (See Sections 5.4 and 5.5).

5.4 Submitting DSURs to the MHRA:

5.4.1 DSURs for non-commercial CTIMPs (*i.e. those sponsored by either LTHT or UoL*) are to be submitted to the MHRA within 60 days of the anniversary of the Clinical Trial Authorisation being first granted.

5.4.2 This is to be done by a member of the research team and a copy must be sent to the Sponsor QA Office in parallel for their records.

5.4.3 The DSUR report must be submitted to the MHRA via the following link to CESP:

http://cesp.hma.eu/home/index

For further guidance and updates on reporting to the MHRA, please use the following link:

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#submit-development-safety-update-reports-dsurs

5.5 Submitting DSURs (*aka Annual Safety Reports*) to the REC:

5.5.1 The DSUR should be submitted to the REC within 60 days of the end of the reporting period.

5.5.2 An Annual Safety Report (ASR) covering form also needs to be provided to the REC. The template form is available via the HRA website:

http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-research-ethics-committee-rec-ctimp-safety-report-form/

5.5.3 The REC should receive the full DSUR including the line listings of SUSARs, however as per NRES guidance, the REC is only expected to review the executive summary.

5.5.4 The REC Manager will acknowledge receipt of all annual safety reports within 30 days by signing and returning a copy of the covering form.

Please note that reports sent without the covering form may not be acknowledged.

Section D: References

MHRA Good Clinical Practice Guide (*September 2012*)

MHRA: *Report an Urgent Safety Issue:*
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#report-an-urgent-safety-issue

NIHR Clinical Trials Toolkit:
http://www.ct-toolkit.ac.uk/routemap/safety-reporting/

Health Research Authority: *Progress and Safety Reporting*
http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/

EC Directive (2001/20/EC):
https://ec.europa.eu/health/human-use/clinical-trials/directive_en#ct6

Section E: Glossary & Acronyms

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report [REC]
CI	Chief Investigator
CTRU	Clinical Trials Research Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
HRA	Health Research Authority
IB	Investigator Brochure
IMP	Investigational Medicinal Product
LTHT	[The] Leeds Teaching Hospitals [NHS] Trust
MHRA	Medicines and Healthcare [Products] Regulatory Agency
PhV	Pharmacovigilance
PI	Principal Investigator
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
UoL	University of Leeds
USM	Urgent Safety Measure

Section F: Version Control:

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1.0	04/12/2015	Clare Skinner, *Faculty Head of R&I Support* Dr. Derek Norfolk, *Associate Director of R&I*	04/12/2015
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