King's Health Partners Clinical Trials Office
Pharmacovigilance & Safety Reporting Policy

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Relevant regulations/legislation/guidelines	Statutory Instrument 2004 no 1031 Statutory Instrument 2006 no 1928 CTFG Q&A on RSI Nov 2017

Change History			
Date	Version Number	Change details	Approved by
01/02/2008	1.0		Jackie Powell
12/02/2009	2.0	Addition of Pregnancy Safety Reporting.	Jackie Powell
31/08/2010	3.0	Change in MHRA policy to eSUSAR reporting, clarification of unblinding & downgrading of PI reports by CI. Transfer to King's Health Partner Livery.	Jackie Powell
14/09/2011	4.0	Amendment of ASR to DSUR as per ICH E2 guidance.	Jackie Powell

19/10/2012	5.0	Change of branding to KHP-CTO and update to include reporting of “Important Medical Events”	Jackie Powell
11/11/13	6.0	Minor clarifications to reporting procedure	Jackie Powell
08/12/16	7.0	Update of Glossary and scheduled review. Update of MHRA contact information for Urgent Safety Measures. Clarification that follow up safety data may be collected from un-blinded participants.	Jackie Pullen
16/04/18	8.0	Update of text to clarify reporting process for eSUSARs, Important Medical Event correlates to “Other Medically Important Condition” for eSUSAR reporting and the use of MedDRA terminology should be used to code eSUSAR events. Inclusion of MedDRA in the glossary.	Jackie Pullen
26/09/2018	8.1	Minor amendment to include trials managed by KHP-CTO are covered by this SOP.	Jackie Pullen
30/11/2021	8.2	Minor amendment to update reporting procedures.	Jackie Pullen
22/09/2023	8.3	Update to align with current MHRA SUSAR reporting requirements	Kirsty Hough
29/01/2024	9.0	Updated as part of MHRA Inspection findings. Updated to include details on expectedness assessments and responsibilities, MedDRA coding, RSI information, SUSAR processing for blinded trials, Causality gradings and management, Pregnancy of partners of trial participants. Removed statement regarding sponsor withdrawing unblinded participants.	Ann-Marie Murtagh
05/12/2024	9.1	Update to pregnancy reporting requirements	Ann-Marie Murtagh

1.0 GLOSSARY

Adverse Drug Reaction (ADR) - Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Adverse Event (AE) - Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Chief Investigator (CI) - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Trial - Any investigation in human subjects, other than a non-interventional trial, intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal product and/or to identify any adverse reactions to one or more such products and/or to study absorption, distribution, metabolism and excretion of one or more such products with the object of ascertaining the safety and/or efficacy.

Data Lock Point – Day prior to the DIBD. The Sponsor can designate this as the last day of the month prior to the month of the DIBD.

Development International Birth Date (DIBD) – Date of the first authorisation to conduct a clinical trial of a specific investigational medicinal product in any country worldwide.

Development Safety Update Report (DSUR) - A common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. In the EU it replaces the annual safety report.

King's Health Partners - King's Health Partners Academic Health Sciences Centre is a pioneering collaboration between one of the King's College London (University) and three of London's most successful NHS Foundation Trusts – Guy's & St Thomas', King's College Hospital and the South London & Maudsley.

King's Health Partners Clinical Trials Office (KHP-CTO) - Established in 2006 by King's College London, Guy's & St Thomas' NHS Foundation Trust, South London and Maudsley NHS Foundation Trust and King's College Hospital Foundation Trust to provide a streamlined approach for all aspects of trial administration.

Important Medical Event (IME) – Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. For the purposes of eSUSAR reports, IME correlates to the ICH Topic E2B criteria "other medically important condition".

Medicines & Healthcare products Regulatory Agency (MHRA) - UK Competent Authority responsible for regulation of clinical trials.

Medical Dictionary for Regulatory Activities (MedDRA) - A clinically validated international medical terminology dictionary (and thesaurus) used by regulatory authorities for the purposes of adverse event classification.

Principal Investigator (PI) - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has responsibility for the conduct of the trial at a host site.

Quality Policy - Policy signed by the Medical Directors of the Partner Organisations and the Vice Principal of the Health Schools of King's College London. The Quality Policy binds all relevant clinical research activity conducted or managed by the Partner Organisations to the KHP-CTO Clinical Trial SOPs.

Reference Safety Information (RSI) - Defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to subjects participating in a clinical trial.

Research Ethics Committee (REC) – An independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.

Serious Adverse Event or Reaction (SAE/SAR) - A serious adverse event is defined as an adverse experience that results in any of the following outcomes:

- death
- a life-threatening adverse experience (any adverse experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death)
- inpatient hospitalisation or prolongation of existing hospitalisation
- a persistent or significant disability/incapacity (a substantial disruption of a person's ability to conduct normal life functions)
- a congenital anomaly/birth defect.

Sponsor - The organisation who takes responsibility for the initiation, management and financing (or arranging the financing) in relation to a clinical trial. The Sponsor organisation has responsibility for carrying out the Sponsor functions of that trial (as defined in the Regulations).

Suspected Unexpected Serious Adverse Reaction (SUSAR) – A Suspected Unexpected Serious Adverse Reaction is a serious adverse drug reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:

- in the case of a product with a marketing authorisation, in the summary of product characteristics for that product.
- in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

The Regulations - Statutory Instrument 2004/1031 – the Medicines for Human Use (Clinical Trials) Regulations 2004 which transposed the European Union Directive 2001/20/EC for Clinical Trials into UK law effective from the 1st May 2004 and any amendments that may arise.

Unexpected Adverse Drug Reaction - An adverse drug reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out:

- in the case of a product with a marketing authorisation, in the summary of product characteristics for that product,
- in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

2.0 BACKGROUND AND PURPOSE

The Medicines for Human Use (Clinical Trials) Regulations 2004 set out specific requirements for the management of serious adverse events (SAE). Of particular importance is the assessment of any event for *causality* and *expectedness*.

AEs that are not considered serious should be included on the relevant case report forms (CRFs) as defined in the trial Protocol. This data will be included in the final trial report.

SAEs can be classified into different categories:

- Serious Adverse Event/Reaction (SAE/SAR)
- Suspected Unexpected Serious Adverse Reaction (SUSAR)

Each type of SAE is subject to different reporting requirements. It is vital that this Policy is followed as failure to report incidents, or deal with incidents adequately, can have the potential to jeopardise the safety and well-being of trial subjects. This 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).

There are a number of responsibilities when managing serious adverse events. Below is a list of responsibilities for both the Investigator and the Sponsor.

3.0 SCOPE

All clinical trials involving Investigational Medicinal Products (IMP); as defined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended from time to time), sponsored or co-sponsored by one or more of King's Health Partners or clinical trials where the sponsor responsibilities are managed by the KHP-CTO.

4.0 RESPONSIBILITIES

The **Chief Investigator** has overall responsibility for the conduct of the study. The CI is delegated by the sponsor to be the pharmacovigilance medical assessor. The KHP-CTO will report to the Medicines and Healthcare products Regulatory Agency (MHRA) according to the timelines defined in Statutory Instrument 2004/1031 as amended from time to time.

A Data Monitoring Committee (DMC) may be convened, prior to commencement of the trial, in order to review safety data regularly throughout the trial and when necessary, recommend to the Chief Investigator and Sponsor whether to continue, modify or terminate the trial. This review procedure will be defined in the protocol. The trial protocol will state if a DMC is to be convened, when they should meet and what they will review.

The **Principal Investigator** has responsibility for the research at each trial site (multi-centre trial). There should be one PI for each research site. In the case of a single-site study, the CI and the PI will normally be the same person, where the CI acts as the PI, they must also adhere to the responsibilities of the PI as well as that of the CI. NB In double-blind trials a process is in place to ensure that the CI does not unblind themselves (from their PI perspective), see section 6.2.

The PI is responsible for informing the KHP-CTO, CI, and the organising research team, of all serious adverse events that occur at their site following the guidelines below. The PI is responsible for reporting SUSARs to their local R&D department.

The **Sponsor** is responsible for ensuring that all relevant information about a **SUSAR** which occurs during the course of a clinical trial in the United Kingdom and is **fatal or life-threatening** is reported as soon as possible to the MHRA, the competent authorities of any EEA State, other than the United Kingdom, in which the trial is being conducted, and the relevant Ethics Committee. This needs to be done **not later than seven days** after the Sponsor was first aware of the reaction. Any additional relevant information should be reported **within eight days** of the initial report.

The Sponsor shall ensure that a **SUSAR** which is **not fatal or life-threatening** is reported as soon as possible, and in any event, **not later than fifteen days** after the Sponsor is first aware of the reaction.

The Sponsor must also ensure that, in relation to each clinical trial in the United Kingdom for which they are the Sponsor, the investigators responsible for the conduct of a trial are informed of any SUSAR which occurs in relation to an investigational medicinal product (IMP) used in that trial, whether that reaction occurs during the course of that trial or another trial for which the Sponsor is responsible.

The **KHP-CTO** will act on behalf of the Sponsor ensuring that the Sponsor’s reporting responsibilities are met.

5.0 REFERENCE SAFETY INFORMATION (RSI)

During trial set-up the Reference Safety Information (RSI) is to be determined by the CI and approved by the Competent Authority (MHRA for UK); this could be presented either as information in the Protocol, in the Investigator's Brochure or in the Summary of Product Characteristics (SmPC). The Reference Safety Information will be defined in the Trial Protocol.

RSI should only contain serious adverse reactions that have occurred more than once and should be presented coded to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT) (as per CTFG guidance).

If the IMP(s) is a licensed product, the RSI will usually be section 4.8 of the SmPC. An IB can also be used for licenced products if the IMP(s) is being used outside its marketing application and the SmPC information is not suitable for the new indication or if one RSI is to be used across a global trial.

Unlicensed products should have a clearly defined RSI section in their IB (refer to KHP-CTO/CT/SOP10.0 Creation & Maintenance of Investigator Brochure).

Note: It is possible to list common expected side effects of an IMP clearly in the protocol. With prior agreement from the Sponsor, Regulatory Authority and the REC, these SARs can be excluded from the normal reporting process and timelines, although they still need to be recorded. It is also possible to list SAEs which do not need to be recorded and reported (those known to be common in an underlying disease i.e. death due to disease progression in cancer).

6.0 PROCEDURE

The PI will report all SAEs, SARs, SUSARs and IMEs (equivalent to ICH Topic E2B "Other Medically Important Condition"), including pregnancies, immediately (but no later than 24 hrs of the trial staff become aware of the event), to the CI and Sponsor. All serious adverse events will be reported using the SAE Report form (see related documents) unless the protocol states otherwise. The CI and PI will supply any supplementary information as requested by the MHRA, REC or KHP-CTO . Event and reaction terms should be coded using the MedDRA Lowest Level Term (LLT) and Preferred Term (PT) most closely corresponding to the reaction/event. If the SAE is not reported with a MedDRA event term, the CRA will code the event using a MedDRA term and inform the site of the coding. Clarification and confirmation should be sought from the Investigator (via responsible CRA) where a term is ambiguous or unclear and good clinical judgment to complete this item with the best MedDRA approximation. If the CI disagrees with this coding, then they must provide an alternative MedDRA term.

The PI will assess the seriousness of each event and the causality between the IMP and/or concomitant therapy and the adverse event.

Any events that are deemed possibly related, likely related or definitely related or any that causality is blank for, are deemed a SAR.

Relationship	Description
Unrelated	There is no evidence of any causal relationship.
Unlikely	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).
Possibly*	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).
Likely*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely*	There is clear evidence to suggest a causal relationship.
No assessment*	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

*If the AE is serious and unexpected, the possible, likely and definitely related should be notified to the MHRA, the relevant REC and the Sponsor as SUSARs. Not assessable or blank assessments will be treated as possibly related by the KHP-CTO.

The CI is responsible for assessing the expectedness of any SARs. The expectedness should be assessed, using the Preferred Term, against the trial specific RSI version in place at the time of the onset of the event, that has been approved by MHRA; this could be either information in the Protocol, in the Investigator's Brochure or in the Summary of Product Characteristics (see section 5.0). The CI Supplementary SAE Form will document the RSI (including version) to be used for expectedness. Fatal or life-threatening events are only deemed expected if the RSI explicitly states they are expected at this severity.

If the causality or expectedness information is not known at the time of reporting, a conservative approach will be taken, and the event will be considered possibly related and unexpected and processed as a SUSAR by the KHP-CTO.
As per the trial protocol, events may also be reviewed by the DMC. The CI is responsible for forwarding applicable reports to the DMC.

Treatment codes must be un-blinded for specific participants, prior to submitting SUSAR reports to the MHRA and REC. Where there is a difference of opinion between CI and PI regarding SAE/SUSAR the PI decision **will not** be downgraded by the CI.

The CI or PI will report all SAEs, SARs SUSARs and IMEs to the KHP-CTO as soon as s/he is aware of and has assessed the event.

6.1 Investigator Reporting to the KHP-CTO

All SAEs, SARs & SUSARs, including any follow up information, must be reported using the SAE Report form which is located on the KHP-CTO website. This form will be completed and e-mailed to the KHP-CTO using the address quoted on the form.

The KHP-CTO will acknowledge receipt of the SAE Report using the KHP-CTO SAE Receipt Email. If the reporter has not received receipt within 24hrs of sending the report (during office hours), the SAE Report Form should be re-sent to the KHP-CTO by email.

The documentation received from site will be reviewed by a member of the KHP-CTO Quality Team for completeness and the SAE Checklist will be completed (and retained by the KHP-CTO).

Additional information, as it becomes available, will also be reported on the SAE report form and returned to the KHP-CTO by email as above.

The SAE Report Form will be filed in the Trial Master File, the patient's hospital notes, the case record form, the Investigator Site File (if applicable) and the Sponsor file.

A record of the SAE will be made in the KHP-CTO Pharmacovigilance database by the person accepting and receipting the initial SAE report.

6.2 SUSARs in Blinded Trials

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of local trial staff involved in the day-to-day running of the trial, data analysis and the interpretation of the study results. Details of the un-blinding process are to be included in the study protocol.

The Investigator blind should therefore be maintained unless it is considered necessary to be broken in the interest of subject safety.

For blinded CTIMPs, SUSARs must be unblinded prior to reporting to the MHRA, REC and pharmaceutical company (if required by the contract). The CRA or delegate not directly involved in the patient management, data analysis or interpretation of results could perform unblinding. Upon receipt of a SUSAR from a site, the CRA/delegate will verify if a potential SUSAR is reportable. The CRA/delegate will unblind a participant's allocation following the trial specific process. If, after unblinding, it is evident that the participant received the IMP (including comparators), the CRA/delegate will follow the procedures described in section 6.3. If, after unblinding, it is evident that the participant received a placebo the event would not require expedited reporting via the SUSAR website, unless in the opinion of the PI the event was related to placebo (e.g. an allergic reaction to an excipient).

To reduce the potential for bias occurring following a SUSAR, each trial must clearly document their procedures and the location of the unblinding information to ensure that all relevant trial personnel remain blinded.

6.3 KHP-CTO Reporting to the MHRA – SUSAR Reporting

A fatal or life-threatening **SUSAR** is reported as soon as possible to the MHRA, the competent authorities of any EEA State, other than the United Kingdom, in which the trial is being conducted, and the relevant Ethics Committee **not later than seven days** after the Sponsor was first aware of the reaction. Any additional relevant information should be reported **within eight days** of the initial report.

A **SUSAR** which is **not fatal or life-threatening** is reported as soon as possible and, in any event, **not later than fifteen days** after the Sponsor is first aware of the reaction.

All SUSARs will be reported to the MHRA within the above timelines, via the ICSR Submissions portal which is found on the MHRA submissions portal website https://icsrsubmissions.mhra.gov.uk/login.

The User Reference Guide – Individual Case Safety Reports (ICSRs) Submissions, is a step-by-step guide on using ICSR Submissions platform to submit clinical trial ICSRs (SUSARs). It provides guidance on how to use the different functions of ICSR Submissions to manage and report SUSARs. The user guide however, is only accessible by reporters via the portal from the Resources tile within the account dashboard.

The following should be noted with respect to entering seriousness criteria and reaction details:

- Seriousness criteria should always be entered. Where a SUSAR has been classed as an IME on the KHP-CTO SAE Report, the eSUSAR E2B criteria **"**Other Medically Important Condition" should be selected.

6.4 Pregnancy Safety Reporting

Depending on the safety profile of the IMP, it may be important to monitor pregnancies in female trial participants receiving an IMP, and occasionally partners of male trial participants. The trial protocol will stipulate the requirements for pregnancy reporting and any actions to be taken. Any pregnancy that requires reporting, whilst not an adverse event, requires monitoring and follow up to term. Please note: Pregnancy ONLY becomes an SAE/SAR/SUSAR if the mother or the foetus suffers any complication of pregnancy or childbirth or any abnormality which fulfils any serious criteria. Reportable pregnancies and outcomes will be included in signal detection and annual safety reports.

If a pregnancy requires reporting, the CI or PI will report this via the SAE report form to the KHP-CTO in the manner described above. If the mother is not the trial participant, consent must be obtained to closely monitor the pregnancy. Each pregnancy will be followed up until outcome of the pregnancy is known. The CI or PI will liaise with the relevant Obstetrician throughout the pregnancy.

A database record of all reportable pregnancies will be held by the KHP-CTO, this will include follow up to term and, where appropriate, long-term follow up of the baby may be required.

6.5 Important Medical Events

Important Medical Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious and reported using the SAE report form.

6.6 Urgent Safety Measures

The Regulations allow the sponsor and investigator to take appropriate urgent safety measures to protect clinical trial subjects from any immediate hazard to their health and safety; these measures should be taken immediately but the Sponsor must notify the MHRA and the REC in writing, of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment. The **CI** must inform the KHP-CTO **as soon as possible after the implementation of the urgent safety measures**. The CI or Sponsor must phone the MHRA's Clinical Trial Unit on 020 3080 6456 to discuss the issue with a safety scientist, ideally within 24 hours.

The MHRA will inform you how to submit the substantial amendment to them within 3 days when you speak to them, but it will usually be by email.

The decision to undertake appropriate safety measures may be taken by:

- The CI and/or PI
- The KHP-CTO – on behalf of the Sponsor and in consultation with the CI or DMC.

6.7 Ongoing safety evaluation of any IMP(s).

The KHP-CTO will ensure that the CI promptly notifies all other Investigators, REC(s) and MHRA of any findings that may affect the health of subjects. The KHP-CTO will ensure that all Investigators using the same IMP in different trials are notified if new safety information comes to light.

A concise safety analysis and risk-benefit evaluation describing all new findings related to the safety of the IMP treatments with respect to their impact for the subjects will be considered by the PI, CI and DMC (if applicable).

7.0 Development Safety Update Reports

The KHP-CTO will ensure that a DSUR is sent to the MHRA and REC annually (refer to KHP-CTO/CT/SOP17.0 Preparation and Submission of Development Safety Update Reports (DSURs)).

The DSUR will be submitted to the MHRA (and any other member state Competent Authority where the trial is being conducted) and approving REC no later than 60 calendar days after the DSUR data lock point.

A copy of the report will be filed in the TMF and Sponsor File.

8.0 Clinical Governance/Risk Management

Any SAE that falls within the criteria defined in the Sponsor's Clinical Incident or Risk Management Policy will be additionally reported to the Clinical Governance/Risk Management Team as detailed in the local policy.

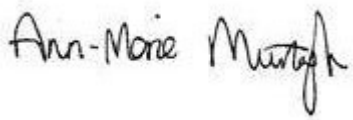
9.0 RELATED DOCUMENTS

9.1 Serious Adverse Event Report Form

9.2 Chief Investigator Supplementary SAE Form
9.3 KHP-CTP/CT/SOP10.0 Creation and Maintenance of Investigator Brochure

9.4 KHP-CTO/CT/SOP17.0 Preparation and Submission of Development Safety Update Reports (DSURs).

APPROVAL and SIGNATURE



05/12/2024

Ann-Marie Murtagh
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Date