Pharmacovigilance and Safety Reporting Operational Policy

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1.0 BACKGROUND AND PURPOSE

This Operational Policy sets out how KHP-CTO manages pharmacovigilance and safety reporting for CTIMPs sponsored by a KHP organisation. KHP-CTO uses the web-based SAE Dundee pharmacovigilance system to report and manage safety events. Refer to the SAE Dundee User Manual listed in Section 4.0 for instructions on accessing and using the system.

2.0 SCOPE

This Operational Policy applies to all Clinical Trials sponsored by a KHP organisation.

The following safety event classifications are in scope:

- Adverse Events (AEs)
- Adverse Reactions (ARs)
- Serious Adverse Events (SAEs)
- Serious Adverse Reactions (SARs)
- Suspected Unexpected Serious Adverse Reactions (SUSARs)
- Important Medical Event (IME)

Each safety event is defined in Section 8.0 (Glossary).

Safety event classifications are not mutually exclusive. For example, an AE may also be classified as an SAE, SAR and SUSAR.

This Operational Policy applies to the following Clinical Trial staff:

- Chief Investigators (CIs), Sponsor Teams.
- Principal Investigators (PIs).
- Trial Location Teams Medical Assessors (with no other role in the Clinical Trial).
- KHP-CTO staff, including the:
- Non-Commercial Trials Manager (NCTM).
- Clinical Research Associates (CRAs).
- Clinical Trial Administrator (CTA).

This policy is not an exhaustive list of the safety policies and procedures that Clinical Trial staff must follow. Staff may also need to follow requirements set by:

- The Trial Locations (including the sole Sponsor/NHS Co-Sponsor R&D Dept.).
- The Funder.
- The IMP manufacturer.
- The NIMP manufacturer if applicable.

The CI is responsible for identifying applicable safety-related policies and procedures operated outside KHP-CTO and ensuring that they are followed.

3.0 PROCEDURES

3.1 General roles and responsibilities

3.1.1 Role terminology

The **Chief Investigator (CI)** and **Principal Investigator (PI)** are formally appointed trial roles. The **Sponsor-level Medical Assessor** and **Trial Location-level Medical Assessor** are delegated safety functions requiring medical judgement.

The CI or PI may undertake the relevant Medical Assessor function where they are appropriately qualified and formally delegated. Alternatively, the function may be delegated to another appropriately qualified, GMC-registered medical practitioner.

Delegation of a Medical Assessor function does not appoint the individual as the CI or PI and does not transfer the CI's or PI's overall responsibilities.

SAE Dundee uses system roles to provide access to the relevant assessment functions:

- the **SAE Dundee CI role** enables Sponsor-level medical assessment;
- the **SAE Dundee PI role** enables Trial Location-level medical assessment; and
- the **SAE Dundee Basic User role** enables the creation and completion of safety reports.

Assignment of an SAE Dundee CI or PI role is a system-access designation only. It does not necessarily mean that the individual is the formally appointed CI or PI.

3.1.2 Chief Investigator (CI)

The CI has overall responsibility for the conduct of the Clinical Trial in accordance with the approved protocol, applicable legislation, and GCP.

The CI is responsible for:

- Establishing the Data Monitoring and Ethics Committee (DMEC), including proposing suitable independent members and ensuring the committee is ready to provide oversight in accordance with the DMEC Charter.
- Ensuring that any Serious Adverse Events (SAEs), that are **excluded** from routine SAE reporting, are:
    - Clearly justified.
    - Explicitly described in the protocol.
    - Subject to an alternative reporting mechanism to the Sponsor where necessary.
- Ensuring that the Reference Safety Information (RSI) is clearly indicated in the cover letter of the trial application and that updates to the RSI are implemented and communicated in accordance with Sponsor procedures and regulatory requirements

- Reviewing emerging safety information and, where necessary, recommending Modifications, risk controls, or suspension/termination of the Clinical Trial in response to safety concerns
- Engaging with the Sponsor and DMEC on safety issues, trends, and recommendations

3.1.3 Principal Investigator (PI)

For single-centre trials, the CI and PI may be the same individual.

The PI is responsible for the conduct of the Clinical Trial at the Trial Location, including ensuring that:

- the Trial Location complies with applicable safety-reporting requirements;
- sufficient appropriately qualified and trained staff are available;
- safety-related duties are formally delegated and documented;
- delegated staff are appropriately resourced and supervised.

The PI role in SAE Dundee should be assigned to more than one delegated medically qualified investigator to ensure timely medical review and causality assessment of all individual safety reports.

3.1.4 Medical Assessors

A Medical Assessor is an appropriately qualified GMC-registered medical practitioner who provides clinical judgement on individual safety reports arising during a Clinical Trial.

A Medical Assessor may also hold another trial role (for example CI, PI, Sponsor Team member or Trial Location Team member), or their sole involvement may be as the assessor.

3.1.4.1 Sponsor-level Medical Assessor (typically the CI) responsibilities:

- Assessing the expectedness of SARs against the Reference Safety Information (RSI) and classifying them as SUSARs where appropriate.
- Providing timely medical judgement to support regulatory reporting, risk assessment, and escalation decisions.
- Documenting assessments in accordance with Sponsor pharmacovigilance procedures.

3.1.4.2 Trial Location-level Medical Assessor (typically the PI) responsibilities

The Trial Location-level Medical Assessor undertakes the medical assessment of relevant safety information arising at a Trial Location.

- Assessing AEs for **seriousness** and classifying them as SAEs where appropriate.
- Assessing causality in relation to the Investigational Medicinal Product and classifying events as Adverse Reactions or Serious Adverse Reactions where appropriate.
- Reassessing causality, where new information including a change in diagnosis, may affect the previous assessment.

- Assessing AEs for IME status according to the **IME definition in the protocol** and medical judgement.
- Providing relevant clinical context and follow-up information to support Sponsor safety review.

3.1.5 Trial Location Staff responsibilities:

- Identifying events and assessing whether they meet the definition of an SAE or criteria for an IME.
- Identifying pregnancies in trial participants or their partners.
- Creating SAE/IME/pregnancy reports in SAE Dundee and submitting them for review and sign off.

Trial Location Level Staff who require access to create safety reports will be given SAE Dundee Basic User access to allow them to perform these responsibilities.

3.1.6 Non-Commercial Trials Manager (NCTM) responsibilities

On behalf of the Sponsor, the Non-Commercial Trials Manager (NCTM) has overall responsibility for operational oversight of pharmacovigilance and safety reporting.

The Non-Commercial Trials Manager is responsible for:

- Ensuring that safety reports are submitted to the MHRA in accordance with applicable legislation and regulatory timelines.
- Ensuring that events assessed as SUSARs are reported in accordance with statutory requirements and SOPs.
- Overseeing the preparation and submission of periodic safety reports (e.g. DSURs).
- Ensuring that, for double-blind trials, procedures are in place to prevent the CI and the trial team from having access to information that could result in unblinding, in line with ICH GCP E6 (R3).
- Where unblinding is required, maintaining unblinded safety records.
- Ensuring timely MedDRA coding of all SAEs.
- Coordinating responses to MHRA or REC safety queries, inspections, and follow-up actions.

3.1.7 Clinical Research Associate (CRA) responsibilities

- Reviewing safety reports in SAE Dundee on behalf of KHP-CTO.
- Raising and resolving queries with Trial Location Teams.
- Completing Sponsor review of safety reports.
- Reviewing follow-up reports and responses to queries.
- Coordinating pharmacovigilance activities, supported by the Clinical Trial Administrator (CTA) where appropriate.

3.1.8 Responsibilities of Data Monitoring and Ethics Committee (DMEC) Members

Prior to the DMEC commencing its activities, proposed DMEC members must:

- Provide a current Curriculum Vitae (CV) for filing in the Trial Master File (TMF)

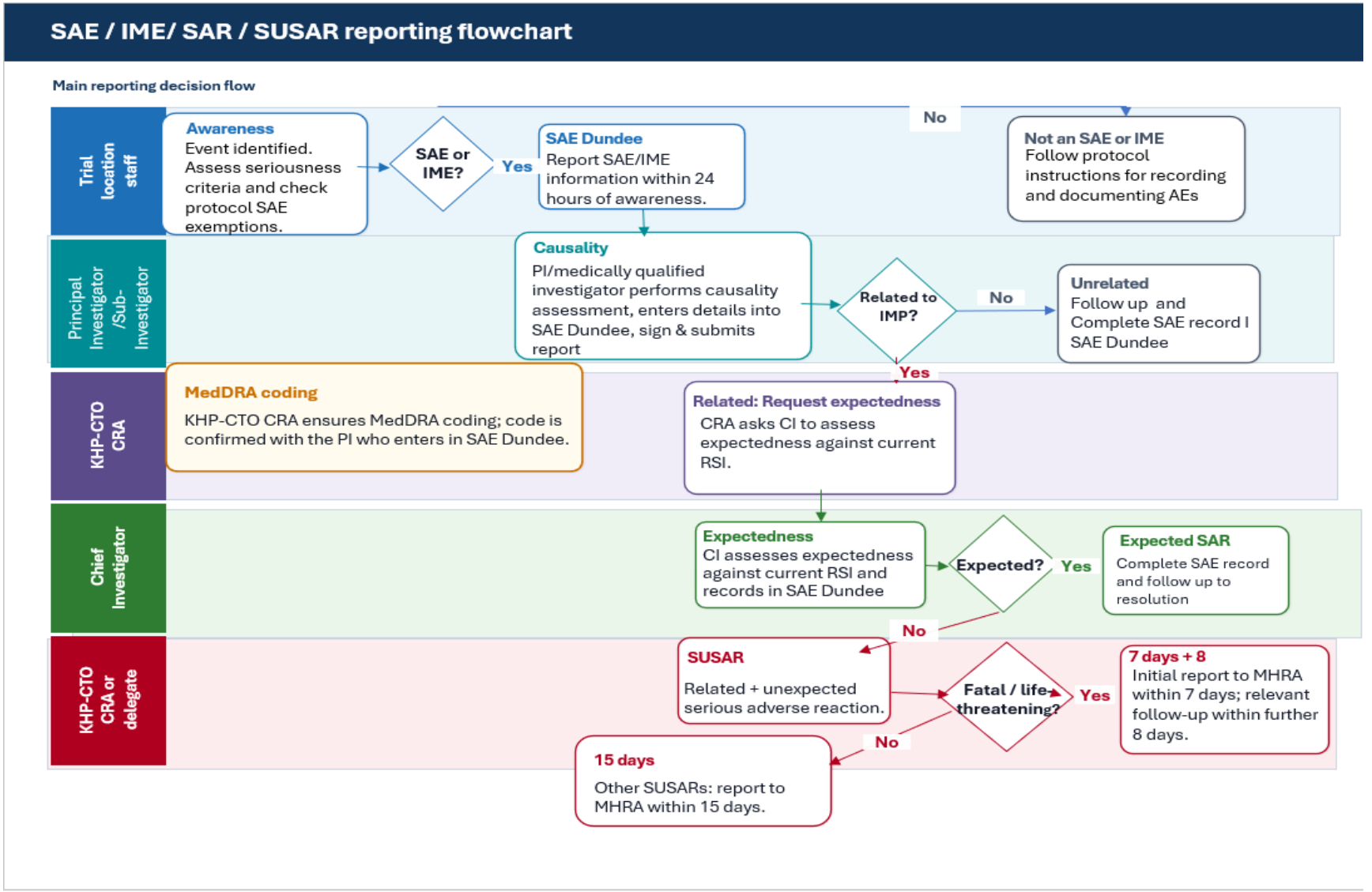
- Complete and sign conflict of interest declarations
- Review and formally agree to the DMEC Charter and any other agreements defining the committee's remit, responsibilities, independence, and operating procedures

Completion of these steps enables the DMEC to be formally constituted and ready to undertake its independent oversight role for the Clinical Trial.

3.1.9 Responsibilities of Sole Sponsor/NHS Co-Sponsor R&D Department

Confirm the appointment of the Sponsor-level Medical Assessor.

3.2 Overview of SAE/IME reporting process:



3.3 Adverse event process

Task	Responsibility	Activity
3.3.1	CRA	Ensure that protocol-defined AE reporting requirements are clearly communicated to the Trial Location Team during the Site Initiation Visit (SIV), including documentation, reporting pathways, and timelines and provide trial locations with this KHP-CTO PV Policy. Follow **KHP CTO SOP 13.0: Study Set-Up and Initiation of an Investigator Site**
3.3.2	PI	The PI must ensure that Clinical Trial-specific requirements for AE recording and reporting are followed (including whether and how non-serious AEs are reported to the Sponsor, and applicable timelines).
3.3.3	PI or delegate	Any untoward medical occurrence in a participant administered an IMP must be identified and recorded as an AE, irrespective of causal relationship. All AEs that are required to be recorded or reported under the protocol must be accurately documented in source records and made available for verification. Source records relating to AEs must be complete, contemporaneous, and accessible for monitoring.
3.3.4	PI	Assess the AE for **seriousness** and classify it as an SAE where appropriate • If the AE is an SAE, report it to the Sponsor via the KHP-CTO SAE Dundee system (See Section 3.4). Assess the AE for IME status according to the **IME definition in the protocol**, and/or **the assessor's medical judgement** • If the AE is an IME, report it to the Sponsor via the KHP-CTO SAE Dundee system. (See Section 3.5) Assess the AE for IMP **causality**
3.3.5	PI or delegate	Where the AE is not an SAE, ensure that all recorded AE data is consistent, complete, and in compliance with protocol requirements.
3.3.6	CRA	Review source Records and reported AE data to verify consistency, completeness, and compliance with protocol requirements in accordance with the Monitoring Plan, review Record activities per **KHP CTO SOP 3.0: Clinical Trial Monitoring.**

3.4 Reporting serious adverse events to KHP-CTO

Task	Responsibility	Activity
3.4.1	Trial Location-level staff or PI	Report all events that meet the definition of an SAE to the Sponsor via the KHP-CTO SAE Dundee system within 24 hours of the trial location team becoming aware of the event. Complete as much information regarding the SAE as available. Do not delay submitting the report to wait for further information. Complete all mandatory fields required to submit the report in SAE Dundee. Where the report is completed by a Basic User, select 'Submit for Sign Off' to send the report to the PI.
3.4.2	PI	Where the PI has created the SAE report or receives an SAE report for sign-off from a Basic User, complete the PI assessment in SAE Dundee to perform a causality assessment to confirm whether the event(s) were related to the IMP(s) and record this in the SAE Dundee system (refer to Section 3.6). Include the verbatim term for the event and where possible the relevant MedDRA preferred term, KHP-CTO will review and confirm the appropriate MedDRA coding where necessary. Confirm all other details in the report are accurate. Submit the report in SAE Dundee via the 'submit for review' button. **Submission electronically signs the report and confirms that the report has been reviewed and confirmed accurate.**
3.4.3	Trial Location-level staff or PI	Review queries received in SAE Dundee as comments or via email and respond by creating a follow up report in SAE Dundee (see section 3.8) or replying to the comment where no change is required.
3.4.4	Trial Location-level staff or PI	Follow-up SAEs until one of the following outcomes is reached: • Resolved • Resolved with sequelae • Participant death or until the participant's status is unlikely to change.

3.5 Reporting Important Medical Events (IMEs) to KHP-CTO

Medical events that may jeopardise a participant or require intervention to prevent a serious outcome are **Important Medical Events (IMEs)** and must be considered serious. See the definition in Section 8.0 (Glossary).

The protocol may identify other events requiring expedited reporting, such as adverse events of special interest. Follow the reporting instructions specified in the protocol.

Task	Responsibility	Activity
3.5.1	Trial Location-level staff or PI	Report all events that meet the definition of an IME to the Sponsor via the KHP-CTO SAE Dundee system within 24 hours of the trial location team becoming aware of the event. Create an 'IME' report and complete as much information as available. Do not delay reporting to wait for further information. Complete all mandatory fields required to submit the report in SAE Dundee. Where the report is completed by a Basic User, select 'Submit for Sign Off' to send the report to the PI.
3.5.2	PI	Where the PI has created the IME report or receives an IME report for sign-off email notification from SAE Dundee, complete the PI assessment in SAE Dundee. Perform a causality assessment to confirm whether the event(s) were related to the IMP(s) and record this in the SAE Dundee system (refer to Section 3.6). Include the verbatim term for the event and where possible include the relevant MedDRA preferred term, KHP-CTO will review and advise on the appropriate MedDRA coding options where necessary Confirm all other details in the report are accurate (if these were completed by another member of the trial location team). Submit the report in SAE Dundee via the 'Submit for Review' button. Submission electronically signs the report and confirms that the report has been reviewed and confirmed accurate.
3.5.3	Trial Location-level staff or PI	Review queries received in SAE Dundee as comments or via email and address by creating a follow up report in SAE Dundee (see section 3.8) or replying to the comment where no change is required.
3.5.4	Trial Location-level staff or PI	Follow-up IMEs until one of the following outcomes is reached: • Resolved • Resolved with sequelae • Participant death Or until the participants status is unlikely to change.

3.6 Assessing the relatedness of AEs and SAEs to the IMP

The PI must assess whether each event is related to the IMP. The assessment must be based on clinical judgement using all available information, including the IB or SmPC, protocol, underlying diseases and concomitant therapies.

Definition	**Category**	**Regulatory reporting**
There is no evidence of any causal relationship	Unrelated	Not related
There is little evidence to suggest there is a causal relationship (e.g. the AE/SAE did not occur within a reasonable time after the administration of the IMP); or There is another reasonable explanation for the AE/SAE (e.g. the participant's clinical condition, other concomitant treatment).	Unlikely	Not related
There is some evidence to suggest a causal relationship (e.g. because the AE/SAE occurs within a reasonable time after administration of IMP); or The influence of other factors may have contributed to the AE/SAE (e.g. the participant's clinical condition, other concomitant treatments).	Possible	Related
There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Likely/ probable	Related
There is clear evidence to suggest a causal relationship and other factors can be ruled out	Definite / definitely	Related

3.7 KHP-CTO and CI review of initial SAE and IME reports

Task	Responsibility	Activity
3.7.1	CRA or Delegate	Review email notifications from SAE Dundee, or system reports to confirm when a valid report has been entered. The minimum information to consider it a valid report is: - Trial name - Participant ID - Reporter's name - SAE details (event term & seriousness criteria) - IMP

		- (*Causality assessment*) this is assumed to be 'related' where not entered The regulatory reporting timeline starts on the Clock Start Date (CSD), also known as Day 0. Day 0 is the date the minimum information above is entered into SAE Dundee. In the event of system failure, it is the date the information is received by email. Information received outside business hours (9am–5pm), at weekends or on Bank Holidays has a Day 0 of the next working day. Contact trial locations where the minimum information has been entered but the report has not been submitted, or the causality has not been completed and request submission and completion of the causality assessment.
3.7.2	CRA	Review SAE/IME details and complete SAE checklist (the relevant document listed in Section 4) within two business days. Retain SAE checklist in the TMF and Sponsor File (SF). Raise queries either via email or via the SAE Dundee system, include a deadline for response which allows regulatory reporting timelines to be met. Send an email with instructions on how to access and respond to queries in the system for queries raised within SAE Dundee.
3.7.3	CRA	**MedDRA Coding:** Review MedDRA coding for the reported event, including the following: • System Organ Class (SOC) • Preferred Term (PT) • Version • Lower-Level Term (LLT) Provide the MedDRA information via email to the PI using the template email, where the MedDRA coding has not been entered into SAE Dundee or the coding needs to be confirmed with them. Ask them to confirm they agree by return email and by entering the details into SAE Dundee. Retain evidence of notification (e.g. email correspondence) in the TMF/SF.
3.7.4	CRA	When an SAE/IME is a SAR, ensure the CI has received the email from SAE Dundee requesting an expectedness assessment. Ensure the version and date of the RSI to be used for the

		expectedness assessment is correctly recorded in SAE Dundee or advised to the CI To expedite reporting, it may be necessary to send a separate email request to the CI to confirm expectedness assessment. The assessment should be entered into SAE Dundee as soon as possible. Where this is not feasible, onward reporting as detailed in Section 3.10 should proceed, based on information received via email and details added into SAE Dundee as soon as possible. Retain evidence of notification (e.g. email correspondence) in the TMF/SF.
3.7.5	CI	Assess the SAR (this includes IMEs assessed as related to IMP) against the applicable RSI to determine whether it is expected or unexpected by referring to the Reference Safety Information (RSI) and record and save in SAE Dundee. - Expected* - the event is listed as an expected adverse event in the RSI and would therefore not need reporting as a SUSAR - Unexpected – the event is not listed as an expected adverse event in the RSI and would need reporting as a SUSAR *Consider the event unexpected, if a reported event is listed in the RSI but is: - More severe. - More specific. - Life-threatening *(unless the RSI specifically lists an expected life-threatening SAR).* - Fatal *(unless the RSI specifically lists an expected fatal SAR).*
3.7.6	CI	Review SAE/IME report and determine if there are any safety concerns or queries for the trial location team.
3.7.7	CRA or delegate	Request that the trial location team resolves queries either via email or via the SAE Dundee system from the CI.
3.7.8	CRA or delegate	Make reasonable efforts to obtain any outstanding causality or expectedness assessments to support SUSAR reporting within required timelines (see Section 3.10) Document all attempts to obtain outstanding assessments in the TMF/SF.
3.7.9	CRA or delegate	When an event has been assessed as related and unexpected or where this information is not received within the regulatory reporting deadline follow process for regulatory reporting (see section 3.10).
3.7.10	CRA or delegate	Ensure the report is categorised as 'Reviewed – No Queries' in SAE Dundee when there are no outstanding queries.

3.7.11	CRA	At End of Trial (EoT), and at interim points where required by the Statistical Analysis Plan (SAP), generate a listing from SAE Dundee of all reported SAEs for: • Reconciliation with the main Clinical Trial database • Provision to the statistician for analysis and reporting Retain the SAE listings in the TMF/SF.

3.8 Providing follow-up information for SAEs and IMEs to KHP-CTO

Task	Responsibility	Activity
3.8.1	Trial Location-level staff	Report • new findings • change of condition • other follow-up information to the Sponsor via the KHP-CTO SAE Dundee system within 24 hours of receiving the information by creating a follow-up report in SAE Dundee. Submit follow-up report via 'submit for sign-off' within the system (where details have been entered by trial location-level staff who are not assigned the PI role in the system).
3.8.2	PI	Review follow-up report to confirm that the information is accurate, where the diagnosis has been changed, review the MedDRA and causality assessment to ensure they remain appropriate for the updated diagnosis. The KHP-CTO CRA will advise on MedDRA coding. Confirm all other details in the report are accurate (if these were completed by another member of the trial location team). Submit the report via 'submit for review' in SAE Dundee. Note submitting a report electronically signs the report, so by submitting this is confirmation that the report has been reviewed and confirmed accurate.

3.9 KHP-CTO and CI review of follow-up SAE and IME information

Task	Responsibility	Activity
3.9.1	CRA or delegate	Review SAE / IME report updates within two business days of the update to confirm whether there is new significant information or changed information e.g. - Diagnosis / event term - Change to seriousness criteria

Task	Responsibility	Activity
		- Onset date (i.e. date the event became serious) - The event description - Addition of new events - Causality - Outcome of the event
3.9.2	CRA or delegate	Ensure each new significant update is reviewed by the CI and ask them to confirm if there is any impact on the expectedness assessment or if there are any safety concerns or queries for the trial location team.
3.9.3	CI	Upon receipt of the email from SAE Dundee or the KHP-CTO CRA, review the follow-up SAE/IME report. Assess whether the follow-up information has any impact on the expectedness assessment, by referring to the Reference Safety Information (RSI) and record in SAE Dundee.
3.9.4	CI	Review the follow-up report and determine if there are any safety concerns or queries for the trial location team.
3.9.5	CRA or delegate	Assess impact of updated information on SUSAR reporting and submit updated reports in accordance with Section 3.10.

3.10 Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting

Calculate regulatory reporting timelines from the clock start date (CSD):

Term	**Reporting timeline from CSD**
Fatal or life-threatening SUSARs	Initial report within 7 calendar days. Followed by any additional relevant information within a further 8 calendar days
Non-life-threatening or non-fatal SUSARs	Within 15 calendar days

Task	Responsibility	Activity
3.10.1	CRA	For SUSARs that are fatal or life-threatening, submit the initial report to the MHRA via ICSR submissions within 7 calendar days of the CSD Retain evidence of submission in the TMF/SF. Collate the required information and submit the follow-up report to the MHRA within a further 8 calendar days

Task	Responsibility	Activity
		If a follow-up SAE report is received before the initial report is submitted, the reports can be combined, whilst still ensuring the 7-day reporting timeframe for the initial report is met. Retain evidence of submission in the TMF/SF.
3.10.2	CRA	For SUSARs that are not fatal or life-threatening, submit the initial report to the MHRA via ICSR submissions within 15 calendar days of the CSD. If a follow-up SAE report is received before the initial report is submitted, the reports can be combined, whilst still ensuring the 15-day reporting timeframe for the initial report is met. Retain evidence of submission in the TMF/SF.
3.10.3	CRA	For open-label trials, if the CI is not the Sponsor-level Medical Assessor, forward the CI the SUSAR report Retain confirmation correspondence in the TMF/SF.
3.10.4	CRA	Submit a follow-up SUSAR reports to the MHRA within 15 calendar days of receiving any significant new information about a previously reported SUSAR. Significant new information includes changes to outcome, seriousness, causality, expectedness, diagnosis, or other clinically important information see also Section 3.8 If a SUSAR initially reported as non-fatal or non-life-threatening is subsequently found to be **fatal or life-threatening**, submit a follow-up report **as soon as possible and no later than 7 calendar days** after becoming aware of the new status.

3.11 Blinded SUSARs in double-blind, placebo-controlled trials

Task	Responsibility	Activity
3.11.1	CRA	For all SARs request expectedness assessments per section 3.7.4, advising the CI to assess according to the RSI for the IMP. If the event is considered unexpected notify one of the SCRAs. If the event is expected it is not a SUSAR and no unblinding or onward reporting is required.
3.11.2	SCRA	Unblind according to the unblinding process for the trial

		- Participant on active IMP – report SUSAR to the MHRA - Participant on placebo – not a SUSAR but may require reporting if related to impurity or excipient.
3.11.3	SCRA	Maintain the blind, do not provide the unblinding information or SUSAR report to the trial location team, CRA, CI or their team. Retain documentation in a restricted access folder of the SF, with access limited to authorised unblinded staff. A blinded DSUR should be created for CI review refer to **KHP-CTO SOP 17: Development Safety Update Reports**

3.12 Reporting pregnancies to KHP-CTO

Task	Responsibility	Activity
3.12.1	PI or delegate	Complete a pregnancy report within the KHP-CTO SAE Dundee system within 24 hours of trial location team awareness of any confirmed pregnancy involving: • A pregnant participant; or • The pregnant partner of a trial participant (where exposure is relevant) Complete the initial information on the pregnancy and 'submit for review' in SAE Dundee. Note submitting a report electronically signs the report, so by submitting this is confirmation that the report has been reviewed and confirmed accurate.
3.12.2	PI or delegate	Request consent for pregnancy monitoring from the pregnant participant or pregnant partner of the trial participant.
3.12.3	PI or delegate	If the pregnant participant or pregnant partner provides consent for pregnancy monitoring, update SAE Dundee with the details of the pregnancy outcome within 24 hours of trial location team awareness of the updated information. Submit pregnancy report for review in the SAE Dundee system. Note submission for review is confirmation that the report has been reviewed and confirmed accurate.
3.12.4	PI or delegate	If the pregnant participant or pregnant partner does not consent to pregnancy monitoring, do not collect further information beyond the initial notification unless there is an SAE (see section 3.4).
3.12.5	PI or delegate	Report an SAE in SAE Dundee within 24 hours of trial location team awareness where the outcome of the pregnancy meets any of the following criteria: - congenital abnormality or birth defect

Task	Responsibility	Activity
		- stillbirth - foetal death / miscarriage - other medically significant pregnancy outcome Follow steps in Section 3.4 to complete and submit the SAE report.

3.13 KHP-CTO and CI review of pregnancy reports

Task	Responsibility	Activity
3.13.1	CRA or delegate	Review pregnancy report and raise queries either via email or via the SAE Dundee system, include a deadline for response. Send an email with instructions of how to access and respond to queries in the system for queries raised within SAE Dundee.
3.13.2	CRA or delegate	Follow-up with the trial location team around the time of the expected birth and request that the outcome of the pregnancy is recorded in SAE Dundee (where the pregnant participant or pregnant partner have consented to this).
3.13.3	CRA or delegate	Ensure that no pregnancy outcome information is entered into SAE Dundee for pregnant participant /pregnant partners that have not consented to this.
3.13.4	CRA or delegate	Where the pregnancy outcome meets a seriousness criterion ensure that the trial location team report an SAE in SAE Dundee.
3.13.5	CRA or delegate	Forward all pregnancy reports to the Chief Investigator.

3.14 SAE Dundee system failure

If SAE Dundee is unavailable for more than one business day, follow the contingency process below.

Task	Responsibility	Activity
3.14.1	Trial location staff / PI	Report initial SAEs and IMEs to KHP-CTO within 24 hours of trial location team awareness by sending the following information in an email to ***jcto.pharmacovigilance@kcl.ac.uk:*** ○ Trial name ○ Site name ○ Participant ID ○ Reporter's name ○ SAE details (event term, severity, seriousness criteria)

Task	Responsibility	Activity
		○ Randomised arm **(if applicable)** ○ IMP(s) ○ Assessment of causal relationship to each IMP (for SAEs and IMEs)
3.14.2	Trial location staff / PI	Report initial pregnancy reports within 24 hours of trial location team awareness to KHP CTO by sending the following information in an email to jcto.pharmacovigilance@kcl.ac.uk.
3.14.3	Trial location staff / PI	Report follow-up information or significant updates on any SAE, IME or pregnancy within 24 hours of awareness to KHP CTO in an email to jcto.pharmacovigilance@kcl.ac.uk. Significant updates include changes to outcome, seriousness, causality, expectedness, diagnosis, or other clinically important information see also Section 3.8..
3.14.4	Trial location staff / PI	Promptly submit the relevant report in SAE Dundee, once notified by KHP-CTO that the system is operational.
3.14.5	CRA or delegate	Review reports received to the jcto.pharmacovigilance mailbox and handle in accordance with relevant process: - SAE/IME Section 3.4 & 3.5 - SUSAR Section 3.10 - Pregnancies Section 3.12

3.15 Safety reporting for Non-IMPs (NIMPs)

Refer to the trial protocol to confirm the NIMPs being used in the trial and their authorisation status.

Reporting requirements:

In case of a suspected interaction of a NIMP with the IMP, events will be reported in accordance with section 3.10.

Authorised NIMPs:
Trial location teams are encouraged to report suspected adverse reactions to the MHRA via the **Yellow Card** scheme.

Unauthorised NIMPs:
Safety reporting will be performed in accordance with the process described in section 3.4 SAE reporting, section 3.5 IMEs and section 3.10 SUSARs**.** SARs should all be considered SUSARS and reported accordingly.

4.0 RELATED TEMPLATES

SAE Dundee User Manual

5.0 RELATED SOPs

- KHP-CTO SOP 3.0: Clinical Trial Monitoring
- KHP-CTO SOP 7.0: Obtaining Informed Consent for Clinical Trials
- KHP CTO SOP 13.0: Study Set-Up and Initiation of an Investigator Site
- KHP CTO SOP 17.0: Development Safety Update Reports (DSURs)

6.0 REFERENCES

1. The Medicines for Human Use (Clinical Trials) Regulations 2004 https://www.legislation.gov.uk/uksi/2004/1031/contents/made

2. The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 https://www.legislation.gov.uk/uksi/2025/538/contents/made

3. ICH Topic (E6) guideline for Good Clinical Practice https://www.ema.europa.eu/en/ich-e6-good-clinical-practice-scientific-guideline

4. MHRA CT Hub: Clinical trials for medicines: collection, verification and reporting of safety events - GOV.UK

5. MHRA Decision Tree to Determine Unblinding Following a SAR https://assets.publishing.service.gov.uk/media/68dac869ef1c2f72bc1e4bc1/Fig3._Unblinding_after_SARs.pdf

6. Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) Guidance for NIHR portfolio trials: Research Governance Guidelines | NIHR

7.0 CHANGE HISTORY

CHANGE HISTORY			
Date	Version Number	Change details	Approved by
01/02/2008	1.0	Original version	Jackie Powell
12/02/2009	2.0	Addition of Pregnancy Safety Reporting	Jackie Powell
31/08/2010	3.0	Updated with respect to change in MHRA policy re 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
11/11/2013	6.0	Minor clarifications to reporting procedure	Jackie Powell
08/12/2016	7.0	Updates of Glossary. Updates to MHRA contact information for Urgent Safety Measures. Clarification that follow-up safety data may be collected from Unblinded participants.	Jackie Pullen
16/04/2018	8.0	Update to clarify reporting process for eSUSARs. Update so Important Medical Event correlates to "Other Medically Important Condition" for eSUSAR reporting. Update to ensure use of MedDRA terminology when coding eSUSAR events. Inclusion of MedDRA in the glossary.	Jackie Pullen
26/09/2018	8.1	Minor amendment to include Clinical Trials managed by the KHP-CTO.	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 of expectedness assessments and responsibilities, MedDRA coding, RSI information, SUSAR processing for Blinded Trials, causality gradings and management, pregnancy of partners of Clinical Trial participants. Removed statement regarding Sponsor withdrawing Unblinded participants.	Ann-Marie Murtagh
02/01/2026	10.0	• Operational Policy template updated • Updated to align with The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and ICH GCP E6 (R3) • Addition of Medical Assessor duties where the CI or PI is not a GMC licensed doctor • Addition of reference to reconciling reported SAEs with main Clinical Trial database	Ann-Marie Murtagh
27/08/2026	11.0	• Updated to incorporate the processes involved with the web-based PV reporting system 'SAE Dundee'	Ann-Marie Murtagh

		• Clarify that IMEs follow the same reporting route as SAEs • Clarify that the CRA and trial team should also remain blinded in the event of unblinding for SUSAR reporting • Include safety reporting for NIMPs	

8.0 GLOSSARY

Adverse Event (AE) - Any untoward medical occurrence in a participant who has been administered an IMP, which does not necessarily have a causal relationship with that IMP.

Adverse Reaction (AR) - An Adverse Event that is suspected to be causally related to the administration of an IMP, regardless of dose, and includes reactions resulting from authorised use, off-label use, misuse, medication error, overdose, or interactions where applicable.

Blinded Trial - A Clinical Trial in which treatment allocation is concealed from one or more parties involved in the Clinical Trial (e.g. participant, investigator, Sponsor staff), in accordance with the protocol and randomisation procedures.

Blinding - A procedure used in a Clinical Trial to withhold information about treatment allocation from one or more parties (e.g. participants, investigators, Sponsor staff) in order to minimise bias in Clinical Trial conduct, assessment, and reporting. 'Blind' and 'Blinded' to be construed accordingly.

Chief Investigator (CI) – The overall lead researcher for a Clinical Trial (Outside the UK the term 'Coordinating Investigator', 'Principal Investigator' or 'Investigator' may be used for the overall lead researcher for a Clinical Trial). Chief Investigators are responsible for the overall conduct of a Clinical Trial.

Clinical Research Associate (CRA) – A staff member employed by the KHP-CTO who conducts monitoring activities for a Clinical Trial, including but not limited to the initiation phase, routine phase, and close down phase.

Clinical Trial of an Investigational Medicinal Product (CTIMP) - Any investigation in human participants (other than a non-interventional trial) intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products and/or to identify any adverse reactions to one or more such products and to study absorption, distribution, metabolism and excretion of one or more such products with the object of ascertaining the safety and/or efficacy of those products. Includes clinical trials of ATMPs.

Clinical Trials Administrator - A staff member employed by the KHP-CTO who conducts administrative activities for a Clinical Trial.

Code Break – The controlled process by which the treatment allocation for an individual participant is Unblinded, typically in the event of a medical emergency, where the identity of the Clinical Trial treatment has been withheld as part of the Clinical Trial's Blinding procedures.

Data Monitoring and Ethics Committee (DMEC) – An independent committee, convened prior to the commencement of a Clinical Trial, that periodically reviews accumulating safety and Clinical Trial data at predefined intervals, or when specified Clinical Trial milestones are met. The DMEC provides independent advice to the CI and Sponsor on whether the Clinical Trial should continue, be modified, or be terminated, taking into account participant safety, ethical considerations, and the overall risk–benefit balance**.**

Development Safety Update Report (DSUR) - A common standard for periodic reporting on drugs under development (including marketed drugs that are under further study).

double-blind trial - A Clinical Trial design in which both the participants, and the investigators responsible for their care and assessment, are unaware of the treatment allocation for the duration of the Clinical Trial.

End of Trial (EoT) – The end of the trial as defined in the protocol. The end of the trial is typically expressed as a condition-based event, not a predetermined date.

Good Clinical Practice (GCP) - An international ethical and scientific quality standard for designing, conducting, recording, and reporting Clinical Trials that involve human participants. It ensures the safety, well-being, and rights of participants are protected while maintaining the credibility and accuracy of trial data. GCP is crucial for safeguarding participants and ensuring Clinical Trials produce reliable, scientifically valid results.

ICH GCP E6 (R3) – The International Council for Harmonisation – Good Clinical Practice, Guideline E6 (Revision 3). This is an internationally recognised ethical and scientific quality standard for the design, conduct, oversight, recording, and reporting of Clinical Trials.

Important Medical Event (IME) - An Adverse Event or Adverse Reaction that may not immediately result in death, be life-threatening, or require hospitalisation, but which, in the judgement of a medically qualified individual, may jeopardise the participant or require medical or surgical intervention to prevent one of those serious outcomes.

Investigator's Brochure (IB) - A Sponsor-prepared reference document that compiles the clinical and non-clinical data on an IMP that are relevant to its use in a Clinical Trial. It's intended to provide Clinical Trial staff with sufficient information to understand the rationale for the Clinical Trial, the known and potential risks and benefits of the IMP, including Adverse Reactions, and the appropriate management of participants. Where the IMP has a Marketing Authorisation, an SmPC will be available and it will supersede the IB as the RSI.

Investigational Medicinal Product (IMP) – A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a Clinical Trial. This includes products with marketing authorisation when used in a way different from the approved form, for an unapproved indication, or to gain further information about an approved use.

King's Health Partners (KHP) - King's College London, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, and South London and Maudsley NHS Foundation Trust.

King's Health Partners Clinical Trials Office (KHP-CTO) – The department established by King's College London, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, and South London and Maudsley NHS Foundation Trust to 1) undertake the set up and financial Management of commercial research hosted by one or more of the KHP Partners, and 2) undertake the regulatory submissions and oversight, as

well as monitoring activity for non-commercial research studies sponsored by one of the KHP Partners.

Marketing Authorisation – A regulatory approval granted by the competent authority that permits a medicinal product to be placed on the market, confirming that its quality, safety, and efficacy have been adequately demonstrated.

Medical Assessor - A medically qualified individual responsible for providing clinical judgement on individual safety reports arising during a Clinical Trial. The assessor may be involved in the Clinical Trial in another role (i.e. as a CI, PI, Sponsor Team member or Trial Location Team member), or their sole involvement may be as the assessor. At Trial Location-level, assessment of safety events involves initial clinical evaluation and causality assessment for participants at the Trial Location. At Sponsor-level, assessment involves reviewing serious safety events across all Trial Locations, confirming seriousness, causality, and expectedness, and supporting regulatory determinations such as SAR and SUSAR reporting.

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.

Medicines & Healthcare products Regulatory Agency (MHRA) – The UK government agency responsible for regulating medicines, medical devices, and Clinical Trials. In the context of Clinical Trials, the MHRA i) acts as the licensing authority for Clinical Trials, ii) reviews the scientific, quality, and safety aspects of a Clinical Trial application, iii) issues CTAs, iv) oversees GCP and GMP inspections, v) monitors pharmacovigilance and safety reporting, and vi) enforces compliance with UK medicines legislation.

Modification - Any change to a Clinical Trial after initial approval that affects the information or conditions on which the Clinical Trial was authorised. Includes minor modifications, Modifications of an Important Detail (MOIDs), Route A and Route B substantial modifications.

Monitoring Plan - A Sponsor-approved document that sets out how Clinical Trial monitoring will be conducted, managed, and documented, using a risk-based approach to ensure participant safety, data integrity, and compliance with the approved protocol and applicable regulations.

Non-Commercial Trials Manager (NCTM) – The most senior member of the KHP-CTO Non-Commercial Team.

Open-Label Trial - a Clinical Trial that is not designed to be Blinded, meaning that the participant, investigator, and trial staff are aware of the treatment being administered.

Operational Policy - A formal governance document that sets out the principles, roles, responsibilities, and high-level requirements for how an aspect of Clinical Trial oversight is managed by the KHP-CTO, ensuring compliance with applicable legislation, regulatory guidance, and GCP.

Principal Investigator (PI) – The individual at a Trial Location who has primary responsibility for the conduct of the Clinical Trial at that Trial Location.

Reference Safety Information (RSI) – The authoritative document used to determine the expectedness of SARs occurring during a Clinical Trial. It defines which SARs are considered expected for the IMP, based on the safety information available at the time, and is used by the Sponsor to assess whether a SAR qualifies as a SUSAR. If the IMP has a Marketing Authorisation, the SmPC will be used as the RSI. If the IMP does not have a Marketing Authorisation, the IB will be used as the RSI.

Regulations – The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended).

Research & Development Department (R&D Dept.) – The NHS department at a Trial Location that's responsible for research and development at that Trial Location.

Research Ethics Committee (REC) – A national independent body 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 Clinical Trial, and to provide public assurance of that protection by, among other things, expressing an opinion on the Clinical Trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform Clinical Trial participants and obtain their informed consent.

Serious Adverse Event (SAE) - An Adverse Event that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR) - An Adverse Reaction that is both serious and suspected to be causally related to an IMP. In other words, it is an untoward and unintended response to the IMP that results in death, is life-threatening, requires or prolongs hospitalisation, results in persistent or significant disability or incapacity, involves a congenital anomaly or birth defect, or is otherwise judged to be a medically important event.

Site Initiation Visit (SIV) - A formal visit conducted by the Sponsor or their representative before a Trial Location begins participant recruitment, to confirm that the Trial Location is fully prepared to conduct the Clinical Trial in accordance with the approved protocol, regulatory requirements, and GCP.

Source Records - The original documents, data, and records in which information about a participant is first recorded.

Sponsor Team – The team selected by the CI to undertake the sponsorship functions of the Clinical Trial.

Standard Operating Procedures (SOPs) - Detailed, written instructions to achieve uniformity of the performance of a specific function. SOPs are the basis upon which Quality Systems and Processes are conducted and monitored against**.**

Statistical Analysis Plan (SAP) - A detailed, pre-specified document that describes the planned statistical methods and analyses to be applied to a Clinical Trial's data.

Summary of Product Characteristics (SmPC) - A regulatory document approved by the MHRA that provides authoritative information for healthcare professionals on the safe and effective use of a medicinal product. It includes details on the product's composition, indications, dosing, contraindications, warnings and precautions, interactions,

pharmacological properties, and known Adverse Reactions, and forms part of the product's Marketing Authorisation. Where a medicinal product does not have a Marketing Authorisation (i.e. an unlicensed IMP), an SmPC will not be available, and the equivalent safety information is provided through the IB, which serves as the RSI for pharmacovigilance and safety reporting.

Suspected Unexpected Serious Adverse Reaction (SUSAR) - A Serious Adverse Reaction to an IMP that is unexpected, meaning that the nature or severity of the reaction is not consistent with the applicable product information according to the RSI.

Trial Location - Means a hospital, health centre, surgery or other establishment, or facility or premises at or from which a Clinical Trial, or any part of such a Clinical Trial, is conducted.

Trial Location Team - The team selected by the PI to undertake the Trial Location functions of the Clinical Trial.

Trial Master File (TMF) - A standard filing system which contains all essential documents which individually and collectively permits the evaluation of the conduct of a Clinical Trial and the quality of the data produced. The filing system can be in the form of a single project file or a number of files/filing cabinets, depending on what is deemed most appropriate for a particular Clinical Trial given its size and complexity. The regulatory documents and approvals within the TMF will be maintained alongside Case Report Forms and Source Records.

Unblinding - A procedure used in a Clinical Trial in which treatment allocation is revealed for an individual participant or, in rare cases, for the Clinical Trial as a whole. Unblinding may occur in accordance with the protocol (e.g. at EoT), or prematurely, where necessary to protect participant safety or to meet regulatory reporting requirements. 'Unblind' and 'Unblinded' to be construed accordingly.