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NHS Humber Health Partnership

Safety Reporting SOP

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Authorized by		Sign	Date
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R&D Manager	James Illingworth	DocuSigned by: James Illingworth 3DDA0F96873F430...	13/5/2026

This page details the version history and the main changes made for each new version.

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Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 27.10.10	J Pacynko	First SOP approved by R&D Committee on 27.10.10
Version 2, 31.01.11	J Pacynko	Unnecessary wording removed from page 6 line 8.
Version 3, 09.03.11	J Pacynko	Change of SSAR to SAR to be in-line with NIHR GCP training. Contacts with study participants that fall pregnant should be monthly.
Version 4, 12.07.12	J Pacynko	Front cover - SOP available on HEY R&D internet. Internet links updated. Who should use SOP updated. Links and appendices updated. Mention of monthly monitoring under investigator trend analysis.
Version 5, 19.03.13	J Pacynko	Appendix 2 Instructions for processing SAE reports up-dated.
Version 6, 25.11.13	J Pacynko	Checking and up-dating all links Page 6 - Addition of electronic Medicines Compendium link Page 8 - Pregnancy section has been amended to include partners of participants in a clinical trial. Page 8 – Addition of a section on the IMP and reference to the IMP recall SOP Appendix 2 Instructions for processing SAE, SAR & SUSAR report forms, up-dated.
Version 7, 19.10.15	J Pacynko	Main changes are in red font. Checking and up-dating all links. Page 7 - Removal of 5 day timeline for reporting of additional information on serious events to R&D. Pages 5, 8, 13 & 14 - Information regarding reporting of participant safety incidents has been up-dated.
Version 8, 27.10.15	J Pacynko	Renaming of serious event initial and follow-up report forms to SAE initial and follow-up report forms. Sponsor (HEY R&D) together with PI to notify REC of eSUSAR reports. Previously this task was delegated to the PI. Removal of notifying REC of SAE reports of the death of a trial participant where the death is not related to the IMP as assessed by the PI, as these reports are not required by REC. Added that scanned SAE reports to be emailed to R&D Office at research.development@hey.nhs.uk
		Pages 7, 8 and 10 – Information regarding the use of SPCs for assessing expectedness has been updated to reflect the MHRA

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Version 9, 31.01.18	S Moffat J Pacynko	requirements. Page 8 - addition of assessments of adverse events table. Checking and updating hyperlinks. Removal of Appendices.
Version 10, 23.10.18	J Pacynko	3.3 and 4.1.3 - AE reporting starts after consent 4.1.2 – Protocol must list which AEs /SAEs do not need to be recorded/reported. 4.3.7 – Study medical doctor at site (PI or Co-I) to assess severity, seriousness and causality of SAEs. 4.3.10 - R&D Director for single-site and CI for multi-site trials to assess causality and expectedness of SAEs on behalf of the Sponsor. 4.3.12 – Reference Safety Information (RSI) for assessment expectedness is section 4.8 of SmPC or relevant section in the IB. 4.3.15 – RSI must be specified in covering letter of MHRA CTA submission. 4.3.16 – RSI updates must be submitted as a substantial amendment and approved by MHRA prior to implementation. 4.3.19 – CI must not influence or downgrade PIs assessment of causality. 4.3.21 – R&D Director cannot downgrade PIs assessment of causality 4.3.24 – Causality will now by assessed by PI/Co-I as either unrelated to the IMP or possibly related to the IMP. 4.3.33 – Summary of assessments made on SAE forms. 4.3.27 – PI to assess causality again on Follow-up SAE form. 4.8.1 – In multi-site trials, a potential SUSAR will be notified to sites regardless of whether the subject was on placebo or IMP to minimise the risk of unblinding staff. 4.10 – Urgent Safety Measures (USM) added here. USM SOP will be removed. 4.11 – Incident reporting up-dated. 5.4.4 - SUSAR reporting; Day 0 is when the Sponsor received the SAE form. 5.4.6 – SUSAR reporting; PI/CI to unblind in medical emergency. 5.4.7 – If not a medical emergency the R&D or QA manager will unblind for expedited SUSAR reporting. 5.5.1 – For double-blind trials, if an unblinding has occurred, R&D QA staff will need to submit the DSUR to the MHRA, to keep PI/CI blind.
Version 11, 13.03.19	J Pacynko	**4.1.2** Safety section of the protocol needs to specify AEs and SAEs that need to be recorded and reported and those that are expected and may not need to be recorded/reported. **4.2.1** If there is a difference of opinion between the PI and CI/R&D Director as to whether the event is related or not then a SAR or SUSAR (as relevant) will always be reported. **4.7 & 5.5.2** For single-site Type A trials, submitted under the Notification Scheme, the APR will now be used to submit annual safety updates to the MHRA and REC. Multi-site Type A and Type B trials will continue to use the DSUR.
Version 12, 30.12.22	S Moffat	3 yearly review. All links within the SOP checked. 3.4 Clarification that SAR reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events and must be reported as SUSARs. 4.3.8 Updated R&D QA contact details for sending SAEs forms.

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		4.3.12 Addition of "MHRA approved" 4.3.14 Reiteration of the above (3.4). 4.3.15 Addition of fatal and life-threatening SARs should not be considered expected unless specifically stated in the MHRA approved RSI. 4.3.19 Update of table position in document. 4.3.26 Addition of "Signatures can be obtained via Docusign." 4.3.27 Addition of "For multi-centre trials where the CI and Sponsor both sign the SAE reports, the CI should sign first and the Sponsor second." 4.3.28 Addition of "If the SAR is listed in the RSI but is more specific or more severe than described in the RSI then it would be considered unexpected and must be reported as a SUSAR." to the Definitions Table on page 11. 4.3.32 Clarification as SAE report form now includes initial and follow-up sections. 4.3.33 Updated R&D QA contact details for sending SAE follow-up forms. 4.3.35 Addition of use of additional follow-up sections. 4.10.4 Updated instructions for contacting the MHRA to discuss urgent safety measures. 4.7.2 Addition of IRAS Project ID number. 4.10.4 Updating the process of contacting the MHRA in the event of an urgent safety measure. 4.10.8 Rewording to include details of discussion with MHRA medical assessor. 5.3.4 Addition of "MHRA approved". 5.4.10 Updating of SUSAR submission portal web link. 5.4.13 Update to include Combined Review Process for sending SUSAR report to REC. 5.6.1 Amended to state that SAE trend analysis will be performed at Sponsor Oversight Group meetings rather than a 6 monthly review as previously stated.
Version 13, DRAFT		Updated to align with the UK Clinical Trials Regulations 2026 and MHRA/HRA reform package. Adoption of risk proportionate SUSAR reporting model Updated definitions of AE, AR Updated expedited reporting timelines and requirements per updated regulations.. Updated urgent safety measures process per updated regulations. Updated references, hyperlinks. Trust name changed from Hull University Teaching Hospitals NHS Trust (HUTH) to Humber Health Partnership (HHP- Hull University Teaching Hospitals NHS Trust and Northern Lincolnshire and Goole NHS Foundation Trust).

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Please note for definitions of acronyms refer to Appendix 1 of Management of SOPs. Refer to Appendix 2 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.

All the R&D GCP SOPs are available at:
https://www.hey.nhs.uk/research/researchers/gcp-sops-for-hey-sponsored-ctimps/

1 Introduction

1.1 This SOP applies to clinical trials of investigational medicinal products (CTIMPs) sponsored by Humber Health Partnership (HUTH & NLaG).

1.2 The requirements for safety reporting can be found in The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025: Part 6 Amendment to Part 5 (Pharmacovigilance) *https://www.legislation.gov.uk/uksi/2025/538/contents*

1.3 These regulations introduce a risk-proportionate, streamlined safety reporting framework, including revised definitions, reporting timelines, and Sponsor responsibilities and specify the recording and reporting requirements for research related adverse events.

1.4 Compliance with these requirements helps ensure the safety of clinical trial subjects.

1.5 It is a legal requirement for HHP -sponsored trials involving IMPs to comply with the safety reporting procedures specified in this SOP.

1.6 When the MHRA inspect clinical trials, the GCP inspectors focus on the compliance of investigators, sponsor and monitor with these safety requirements.

1.7 Within this SOP, the requirements have been transcribed into investigator and sponsor responsibilities.

2 Purpose and who should use this SOP

2.1 The purpose of this SOP is to describe the responsibilities of investigators and Sponsor when recording and reporting serious and non-serious adverse events to ensure compliance with the UK clinical trials regulations.

2.2 This SOP should be used by:

- All research staff involved with HHP-sponsored CTIMPs – Chief/Principal Investigator, co-investigators, research nurses, clinical trial assistants, trial managers, clinical trial co-ordinators, data managers, administrators etc.
- Clinical trials pharmacy staff – technicians and pharmacists.
- All HHP R&D staff who manage the sponsorship of HHP-sponsored CTIMPs.
- Research staff involved with clinical trials sponsored by an external organisation where the sponsor has no SOP for safety reporting. HHP R&D SOPs are defaulted to in this case.

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3 Acronyms and Definitions

3.1 Adverse event (AE)

Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with any intervention conducted due to the participant participation in the clinical trial, even if not associated to a medicinal product, should also be considered as an AE.

3.2 Adverse reaction (AR)

Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

3.3 Serious adverse event (SAE) or serious adverse reaction (SAR)

Any AE or AR that at any dose of IMP:

(a) results in death
(b) is life-threatening
(c) requires participant hospitalisation or prolongation of existing hospitalisation
(d) results in persistent or significant disability or incapacity
(e) consists of a congenital anomaly or birth defect.
(f) or otherwise medically significant

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Any hospitalisation that was planned prior to consent of the subject will not meet SAE criteria. Any hospitalisation that is planned post consent, will meet the SAE criteria.

3.4 Suspected unexpected serious adverse reaction (SUSAR)

A SUSAR is any AR that is classified as serious (3.3), is suspected to be caused by the IMP and is not consistent with the safety information in section 4.8 of the Summary of Product Characteristics (SmPC) or in the Investigator's Brochure (IB).

Further guidance on safety reporting can be found on the HRA and MHRA website:
'Safety Reporting' – HRA https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/
'Clinical trials for medicines: collection, verification and reporting of safety events' – MHRA MHRA Website.

3.5 Incidents: An SAE, SAR or SUSAR may also require reporting on a HHP Ulysses Incident Report Form. For definitions of participant safety incidents that require reporting refer to the Incident Reporting Policy CP379. For guidance on which research related

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incidents require reporting on Ulysses, refer to section 8.24 of the R&D Operational Policy (CP264) or contact the R&D QA staff for advice.

3.6 Investigational medicinal product: An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference (comparator) in a clinical trial including products:-
- already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form.
- used for an authorised indication.
- used to gain further information about an authorised form.

4 Investigator responsibilities

4.1 Identifying AEs

4.1.1 The Chief/Principal investigator (CI/PI) and Sponsor must determine which AE data will be collected, based on the risk-proportionate approach defined in the protocol.

4.1.2 The safety section of the protocol must define and justify;

- which AEs are expected and therefore do not need to be recorded in the CRF AE log unless they are required as part of the primary or secondary outcomes. These may be AEs that are expected for the participant's medical condition or listed in the Reference Safety Information (in section 4.8 of the SmPC for licensed IMPs).
- which AEs will be recorded.
- which SAEs are expected and therefore not required to be reported on an SAE form within 24 hours to the Sponsor (or delegate). These may be SAEs that are expected for the participant's medical condition or listed in the Reference Safety Information. These SAEs will still need to be recorded on the CRF AE log.
- which SAEs will be recorded and reported within the required timelines.
- Which unfavourable medical events occurring in participants before IMP administration should be considered and reported to the sponsor if required by the protocol.

4.1.3 AEs and SAEs should be recorded from the time the participant signs the consent form to take part in the trial, unless otherwise defined in the protocol.

4.2 Recording all adverse events (non-serious and serious)

4.2.1 Document all adverse events on the AE log at the back of the participant's CRF. The R&D monitor will provide investigators with an electronic AE log template at study set up in case further logs are required.

4.2.2 Record clinically significant lab test values that are different from baseline as AEs unless expected according to the protocol or normal for the participant's condition.

4.2.3 Record relevant details of the adverse event in the participant's medical records. Enter a description of the adverse event, the start and stop date/time and any action taken. Document in the medical records all tests and procedures performed.

4.2.4 Record any follow-up information of the event in the participant's medical records.

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4.2.5 All adverse events should be assessed for **trends in nature and frequency** on an ongoing basis throughout the trial. Reminders to do this are on the CRF AE logs and on the Monitoring Visit Report forms. Any trends should be reported **immediately** to the R&D monitor, QA manager, R&D manager or director and will be escalated to the Sponsor Oversight Group and reported on to the MHRA and Research Ethics Committee (REC).

4.3 Reporting serious adverse events to R&D (SAE/SAR/SUSAR)

4.3.1 The safety section of the protocol will define the 'expected SAEs' that do not require reporting on the SAE form but will require recording on the CRF AE log and in the participant's medical records. All other SAEs will require reporting to R&D QA within 24 hours on an initial SAE form.

4.3.2 **SAE initial report form – timeline, sending and filing**
As soon as possible and **within 24 hours** of becoming aware of a serious adverse event, complete the SAE initial report form. It is important to respect this timeline since the MHRA closely inspect the reporting of SAEs.

4.3.3 The R&D monitor will provide investigators with a study specific SAE report form template at study set up.

4.3.4 Complete the form electronically and as far as possible with the information available at the time.

4.3.5 **SAE initial report – assessment of severity, seriousness and causality**
A study medical doctor (PI or Co-Investigator) must assess the severity, seriousness and causality of the event. Definitions are given in 4.3.25.

4.3.6 The PI/Co-I will need to decide whether the serious event is an SAE or SAR by assessing whether the event is related to the IMP or not (causality).

4.3.7 The PI/Co-I must sign the SAE report form.

4.3.8 Email a scanned copy of the SAE form to the R&D QA team. The email address is R-D.QA@nhs.net . If the person sending the email has not received acknowledgement of receipt from the QA team within 2 days please email the above address asking for confirmation.

4.3.9 File the original signed SAE form in the safety section of the Investigator Site File.

4.3.10 **SAE initial report form – assessment of expectedness and Reference Safety Information**
If the event is a SAR, an assessment needs to be made by the **Sponsor** as to whether the event is expected or not for the IMP. It is important to note, that this is **not** whether the event is expected or not for the subject's medical condition.

4.3.11 If the trial is a single-site trial at HHP only, then the R&D Director (medical professor) will assess expectedness. If the trial is a multi-site trial, then the Chief Investigator will make this assessment. Both the R&D Director and CI must sign that they understand the regulatory requirements and that they will be assessing expectedness on behalf of the Sponsor.

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4.3.12 In order to assess expectedness, the R&D Director/Chief Investigator will need to check if the event is listed in the MHRA approved Reference Safety Information (RSI).

4.3.13 The RSI for IMPs with a marketing authorization (MA) is section 4.8 (Undesirable Effects) of the MHRA approved Summary of Product Characteristics (SmPC) or for IMPs without an MA, the RSI is the MHRA approved relevant section in the Investigator Brochure (IB).

4.3.14 If the SAR is listed in the RSI then it is expected. If the event is not listed in the RSI then it is unexpected and is a SUSAR and subject to expedited reporting to the MHRA and REC (see section 5.4).

4.3.15 However the SAR may be listed in the RSI as a known adverse reaction but if the event is more specific or severe than described in the RSI then it would be considered unexpected and must be reported as a SUSAR.

4.3.16 Fatal and life-threatening SARs should not be considered expected unless specifically stated in the MHRA approved RSI.

4.3.17 The MHRA approved SmPC or IB is the version that was first submitted to the MHRA for clinical trial authorization unless an up-dated version has been approved by the MHRA as a substantial amendment.

4.3.18 The covering letter for submission to the MHRA for clinical trial authorization must include what the Reference Safety Information is for the trial e.g. section 4.8 of the SmPC for the IMP. This is an MHRA requirement. R&D QA has a template covering letter that should be used.

4.3.19 **SAE initial report form – reviews**
The PI must always review the SAE form and sign to confirm the contents of the report are accurate and complete and that the severity, seriousness and causality of the SAE has also been assessed. See table in 4.3.35.

4.3.20 **If the trial is multi-site**, the Chief Investigator must review and sign off all SAE forms on behalf of the Sponsor. The timelines for CI review will usually be **within 7 days for SAEs and SARs and within 24 hours for SUSARs.**

4.3.21 In addition to the PI, the CI will also be required to assess causality and document their assessment on the SAE form. The CI must assess causality after the PI and must confirm that they have not influenced the PI. The PIs assessment of causality must not be downgraded by the CI.

4.3.22 **If the trial is multi-site, and a CTU** is involved and the safety reporting is completed electronically, please follow the relevant agreed SOP in the process of completing the SAE reporting, including the sign off process. Any trial specific SOPs from the CTU should have been received and reviewed prior to the trial commencement.

4.3.23 If the event is a SAR, the CI will be required to check expectedness on behalf of the Sponsor and to document the version of the RSI used on the SAE form and if the event is present in the RSI, the medical term under which the SAR falls.

4.3.24 **If the trial is single-site (HHP only)** the R&D Director will be required to review the SAE form and document their review on the form. The timelines for review will usually be **within 7 days for SAEs and SARs and within 24 hours for SUSARs.**

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4.3.25 As well as the PI, the R&D Director will also be required to assess causality and if the event is a SAR, to check expectedness. The PIs assessment of causality must not be downgraded by the R&D Director.

4.3.26 If there is a difference of opinion between the PI and CI/R&D Director as to whether the event is related or not then a SAR or SUSAR (as relevant) will always be reported.

4.3.27 Both the CI and R&D Director will need to sign that they understand the safety regulations and will be reviewing causality and expectedness on behalf of the Sponsor. Signatures can be obtained via Docusign.

4.3.28 For multi-centre trials where the CI and Sponsor both sign the SAE reports, the CI should sign first and the Sponsor second.

4.3.29 **Definitions**

Severity Assessed by the Co-I and PI or just PI	The assessment of severity of an SAE will be based on the investigator's clinical judgement using the following definitions: **Mild:** An event that is easily tolerated by the trial subject, causing minimal discomfort and not interfering with everyday activities. **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities. **Severe:** An event that prevents normal everyday activities.
Seriousness Assessed by the Co-I and PI or just PI	An event is considered serious if it meets one or more of the following criteria: (a) results in death (b) is life-threatening (c) requires hospitalisation or prolongation of existing hospitalisation (d) results in persistent or significant disability or incapacity (e) consists of a congenital anomaly or birth defect. (f) or otherwise medically significant Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the outcomes listed in the definition above should also be considered serious.
Causality Assessed by the Co-I and PI or just PI	The investigator will make an assessment of whether the SAE is likely to be related to the IMP according to the following definitions: • **Unrelated**: Where an event is not considered to be related to the IMP. • **Possibly related**: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the SAE has a causal relationship to the study drug.
Expectedness Assessed by the CI for multi-site trials or by the R&D Director for single-site trials	In order to assess expectedness, the Chief Investigator/R&D Director will need to check if the SAR is listed in the Reference Safety Information (RSI). The RSI for IMPs with a marketing authorization (MA) is section 4.8 (Undesirable Effects) of the MHRA approved Summary of Product Characteristics (SmPC) or for IMPs without an MA, the RSI is the relevant section in the Investigator Brochure (IB). If the SAR is listed in the RSI then it is expected. If the event is not listed in the RSI then it is unexpected and is a SUSAR and subject to expedited reporting to the MHRA and REC. If the SAR is listed in the RSI but is more specific or more severe than described in the RSI then it would be considered unexpected and must be reported as a SUSAR.

4.3.30 **SAE follow-up report – timelines, sending to R&D and filing**

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As soon as further information becomes available, investigators should complete the Follow-up section of the initial SAE report form. For deaths, provide additional requested information (e.g., terminal reports/autopsy if available) as soon as it becomes available.

4.3.31 The PI is required to assess causality again on the follow-up form. If the PI has a change of opinion on causality after considering the additional follow-up information, the CI/R&D Director will be required to reassess causality and if a SAR, then to assess expectedness.

4.3.32 If the SAE has involved the hospitalisation of a participant, then a follow-up form should be completed on discharge of the participant.

4.3.33 The R&D monitor will provide investigators with an electronic study specific SAE report form in which there are follow-up sections.

4.3.34 Email a scanned copy of the SAE follow-up form to the R&D QA team. The email addresses are leanne.cox@nhs.net and ritakshi.gehlot@nhs.net , please ensure the SAE is sent to both email addresses.
If the person sending the email has not received acknowledgement of receipt from the QA team within 2 days please email the above addresses asking for confirmation.

4.3.35 File the original signed form in the safety section of the Investigator Site File.

4.3.36 Use additional follow-up sections for extra data until the SAE has resolved or a decision has been made for no further follow-up. Send forms to R&D via email or fax as above.

4.3.37 **Assessments done on SAE forms (initial and follow-up)**

Who	Initial form	Follow-up form	Timeline	Comments
PI	● Severity ● Seriousness ● Causality	● Causality reassessed	Initial form must be sent to Sponsor within 24 hours of awareness of SAE. Follow-up form(s) as soon as new information is available.	PI must always, review and sign off the forms.
Co-I	● Severity ● Seriousness ● Causality - related or not to IMP	● Causality reassessed	Initial form must be sent to Sponsor within 24 hours of awareness of SAE. Follow-up form(s) as soon as new information is available.	A medically qualified doctor on the Delegation Log must assess severity, seriousness and causality. This can be the Co-I or PI.
CI Multi-site trial	● Causality If SAR ● Expectedness	If PI has change of opinion, CI will be required to reassess ● Causality If SAR ● Expectedness	SAEs and SARs Within 7 days SUSARs Within 24hrs	PIs assessment must not be influenced or downgraded
R&D Director Single-site trial	● Causality If SAR ● Expectedness	If PI has change of opinion, CI will be required to reassess ● Causality If SAR ● Expectedness	SAEs and SARs Within 7 days SUSARs Within 24hrs	PIs assessment must not be influenced or downgraded

4.4 Breaking the blind in an emergency

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4.4.1 For double-blind trials, on rare occasions, the blind for the study participant may need to be broken for emergency reasons to establish the best course of treatment for the participant. The Chief/Principal Investigator should follow the unblinding procedure for emergencies set-up and tested for the trial. Clinical trials pharmacy's CT016 code break SOP will be followed.

4.5 Pregnancy during trial

4.5.1 If a study participant, or the partner of a study participant, falls pregnant when participating in a clinical trial, the study participant should be withdrawn from the trial unless the Chief/Principal Investigator decides that the risk to the participant is not clinically significant.

4.5.2 The participant, or the partner of the study participant, should be followed up by monthly or two monthly visits/telephone contacts during pregnancy and at birth and at 3 months after the birth of the baby. Whether the visits are every month or two months will depend on clinical judgement and will be agreed with R&D and documented in the TMF.

4.5.3 The visits/telephone contacts need to be documented in the Pregnancy Follow-up Form and signed off by a study medic. The form will be provided by the monitor.

4.5.4 Should there be a congenital anomaly or birth defect, then report as an SAE/SAR/SUSAR as above.

4.6 Safety findings flagged by DMC

4.6.1 Any significant findings and recommendations raised by an independent data monitoring committee or equivalent body established for the trial must be reported to the MHRA and REC.

4.7 Annual safety reporting

4.7.1 Safety updates must be provided annually to the MHRA and REC.

4.7.2 For **all** trials the Development Safety Update Report (DSUR) will be used to report the safety information. The DSUR is available on the HRA website. The R&D monitor will help with the completion and submission of the DSUR. A covering letter will also need to be submitted which includes the IRAS Project ID number and CTA reference number. A list of all the SAEs and SARs will need to be added to section 6 of the DSUR.
The R&D monitor will complete the administrative parts of the DSUR and then send to the CI/PI for completion of the clinical safety information and assessments. The R&D monitor will submit the DSUR to the MHRA and/or REC. If the trial is being managed by a Clinical Trials Unit, the CTU will submit the DSUR.

4.7.3 The MHRA approved SmPCs will need to be reviewed for updates annually at the time the DSUR is completed. This check will be documented in the DSUR.

4.7.4 Signal Management should be performed to determine whether there are new risks associated with an active substance or a medicinal product or whether known risks have changed, and include any related recommendations, decisions, communications and tracking. This is like the pharmacovigilance practices which should be in place for marketing authorisation holders of licensed products but can be adapted accordingly for products still in clinical trials and under development. To undertake signal detection, good

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pharmacovigilance should be built into the systems from the start; protocols and risk assessments should consider the key elements of safety reporting and facilitate the collection and review and reporting of all relevant safety information.

4.7.5 A risk proportionate approach to the presentation of safety data and signal management should be followed. An investigator-led single location phase 4 trial, for example, may require minimal signal management since the safety profiles of the IMPs should be largely already established.

4.7.6 In addition to the processes in place for signal detection, the sponsor should outline any subsequent actions that may be required, highlighting if appropriate mitigation is already in place. Actions may include adding an event as an adverse event of special interest (AESI), additional safety assessments or additional timepoints for assessments already in place, more frequent DSMB oversight, an USM or temporary halt, as well as how the safety concern is communicated to locations and investigators.

4.7.7 If the SmPC or IB has been updated, the CI/PI, Sponsor and Pharma Company (if IB) will risk assess the changes and decide if they have an impact on participant safety. If the decision is that the updated SmPC/IB needs to be used as the new Reference Safety Information (RSI) then this must be submitted to the MHRA as a substantial amendment. The updated SmPC/IB can then be used once approved by the MHRA.

4.7.8 The process and cost for reporting DSURs is given in the R&D GCP SOP 10 Annual Reporting

4.8 Safety notifications

4.8.1 In multi-site trials, the Chief Investigator must inform all sites rapidly of emerging safety issues, such as the occurrence of potential SUSARs. For double-blind trials, a potential SUSAR will be notified to all sites regardless of whether the subject was on placebo or IMP to minimise the risk of unblinding staff. A basic description of the event should be provided, but the sites will remain blind. The Sponsor must be copied into the correspondence to all sites.

4.8.2 If the trial is being managed by a CTU, the responsibility for informing all sites of a potential SUSAR may be delegated to them. Receipts must be obtained from Principal Investigators confirming that they have read the safety notifications.

4.9 Concerns with Investigational Medicinal Product

4.9.1 The investigator team must alert R&D straight away of any concerns regarding the IMP, this may be to do with the expiry of the IMP or the reaction of participants to the IMP or other concerns. R&D will inform pharmacy and with pharmacy and the CI/PI will decide whether it is appropriate to trigger the IMP recall SOP.

4.10 Urgent safety measures

4.10.1 If a major safety issue occurs during a clinical trial, the Chief/Principal Investigator may take appropriate urgent safety measures immediately in order to protect clinical trial subjects against any threat to their health or safety. Please refer to R&D GCP SOP 09 Urgent Safety Measures.

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4.10.2 These urgent safety measures may be taken without prior authorization from the MHRA, REC or Trust (HHP R&D).

4.10.3 The investigator must alert HHP R&D (Sponsor) as soon as possible of the urgent measures taken by contacting the R&D Office via hyp-tr.qa@nhs.net or the Trust Switchboard 875875 (out-of-office hours) and asking for either the R&D Manager (James Illingworth) or R&D Director (Prof Sathyapalan).

4.10.4 The CI/PI or HHP R&D QA should phone the Clinical Trial Unit at the MHRA and discuss the issue with a safety scientist as soon as possible (No later than 3 days after the measures are taken (but ideally within 24 hours). The safety scientist is employed by the MHRA to advise on safety and medical issues. Contact the MHRA CTU via the clinical trials for medicines helpline 020 3080 6456 (Monday - Friday 08:30 -16:30). More information on what will need to be provided to the MHRA can be found specifically in the section ' Urgent safety measures (USMs) https://www.gov.uk/guidance/clinical-trials-for-medicines-collection-verification-reporting-of-safety-events#annual-safety-reporting

4.10.5 HHP R&D should notify pharmacy clinical trials staff as soon as possible.

4.10.6 The CI/PI must notify the MHRA, REC and Trust (HHP R&D) in writing **within 7 days** after the urgent measures have been taken, by emailing the clinical trial helpline at clintrialhelpline@mhra.gov.uk and by submitting a substantial modification. See R&D GCP SOP 08 Modifications.

4.10.7 The process for notifying the MHRA about a potential urgent safety measure can be found on the MHRA website 'Figure 4. Flowchart summarizing the process of notifying the licensing authority about a potential urgent safety measure. https://assets.publishing.service.gov.uk/media/68dac8eec487360cc70c9ed6/Fig4._USMs.pdf

4.10.8 Note that if the decision is made with HHP R&D to halt the study due to the urgent safety measures then this can be added to the substantial modification form and would save submitting another substantial modification for the temporary halt. Halts based on predefined rules do not require submission of a substantial modification to the licensing authority for a temporary halt. However, deviations from the pre-specified dose escalation or other decision-making criteria would warrant the submission of substantial modification.

4.10.9 The substantial modification form and any supporting documents should be sent with a covering letter detailing;

- the urgent measures taken
- the reasons for them
- the details of the discussion with the MHRA medical assessor

4.11 Reporting safety for non-IMPs

4.11.1 In case of a suspected interaction of a non-IMP with the IMP the reporting rules for the IMP apply. Safety reporting (referring to all adverse reactions) with regard to authorised non-IMPs should be made in accordance with post-marketing requirements for that non-IMP, irrespective if they are used in accordance with the terms of the marketing authorisations of these products. It should be noted that investigators and sponsors are encouraged to report suspected adverse reactions to the non-IMP to MHRA (via the Yellow Card Scheme) or to the marketing authorisation holder. Safety of non-authorised non-IMPs (that should be used only

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exceptionally in clinical trials) should be reported in the same way as IMPs. Accordingly, SARs related to non-authorised non-IMPs should all be considered as SUSARs and should be reported to the licensing authority. If any adverse reaction associated with the non-IMP is likely to affect the safety of the trial participants, the sponsor should take any appropriate actions, including an urgent safety measure, as applicable. Sponsors are reminded that where an adverse event occurs that, following a causality assessment, is suspected to be related to a NIMP only, the requirements per regulation 32 of the Clinical Trials Regulations still apply.

4.12 Participant safety incident reporting

4.12.1 If the SAE also comes under the definition of a participant safety incident then report electronically on the Ulysses Incident Reporting form and submit to the Risk Management Department. For definitions of participant safety incidents that require reporting refer to the HHP Incident Reporting Policy CP379. For guidance on which research related incidents require reporting on Ulysses, refer to section 8.24 of the R&D Operational Policy (CP264) or contact the R&D QA staff for advice. For the Ulysses form click on the Report an Incident icon on the HHP Intranet Homepage.

5 Sponsor responsibilities

5.1 Sponsor oversight

5.1.1 The Sponsor is responsible for overseeing the safety of trial participants. Therefore, all aspects of recording, assessing, reviewing, reporting and documenting AEs and SAEs will be checked by HHPR&D QA staff.

5.1.2 For multi-site trials being managed by a CTU who do not use electronic safety reporting, R&D QA staff will be put on copy of all SAE forms sent to the CI for assessment. R&D QA staff will have access when requested to the pharmacovigilance spreadsheet being maintained by the CTU, which will include details of the SAE medical term, causality, expectedness and status (e.g. resolved, ongoing). The spreadsheet will be reviewed monthly by QA staff and quarterly at Sponsor Oversight Group meetings. For multi-site trials managed by a CTU who use electronic safety reporting, R&D QA will have ongoing access to the safety forms usually via a web-based electronic data capture system. If this is a system provided by the CTU, the SOP for this should be reviewed before the trial begins to ensure Sponsor is happy with the CTU's safety procedure. A review will be done quarterly at Sponsor Oversight Group meetings of any reported SAE's.

5.2 At monitoring visits

5.2.1 Check that all AEs have been recorded on CRF AE Logs.

5.2.2 Check that SAEs have been reported within the time limits.

5.2.3 Check all clinically significant laboratory abnormalities have been recorded as AEs.

5.2.4 Check that relevant details about AEs have been entered in the participant's medical records.

5.2.5 Follow up information has been submitted

5.2.6 Expectedness assessments are documented

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5.2.7 Unblinding procedures (if used) are compliant

5.2.8 Safety -related correspondence is filed in the TMF and ISF.

5.2.9 Any safety related findings must be escalated to the QA Manager and SOG.

5.3 Processing SAE initial and follow-up report forms

5.3.1 All SAEs will be processed by either R&D QA staff for single-site trials or by CTU staff for multi-site trials.

5.3.2 QA/CTU staff will process SAE reports **within 24hrs** of receipt of report.

5.3.3 R&D QA staff (monitor or manager) will use Working Instruction 02 for processing SAE report forms.

5.3.4 As part of processing SARs, the QA/CTU staff will check whether the event is present in the MHRA approved RSI.

5.3.5 If the trial is single-site (at HHP only) the R&D Director will be required to review the SAE form and document their review on the form. The R&D Director will also be required to assess causality and check the Reference Safety Information and if the event is a SAR, to assess expectedness. If the trial is a multi-site trial, the Chief Investigator will be required to do the same review, checks and assessments.

5.3.6 If the event is a potential SUSAR, the Working Instruction 03 will be used for eSUSAR reporting.

5.3.7 All SAEs reported to HHP R&D are logged in a CTIMP spreadsheet.

5.4 Reporting SUSARs

5.4.1 R&D QA staff are responsible for reporting SUSARs to the MHRA.

5.4.2 A SUSAR which is fatal or life-threatening must be reported to the MHRA as soon as possible and no later than **7 days** after learning of the event. Any additional information must be reported within **8 days** of sending the first report.

5.4.3 A SUSAR which is not fatal or life-threatening must be reported to the MHRA as soon as possible and no later than **15 days** after learning of the event.

5.4.4 Day 0 for reporting is when the Sponsor receives the SAE form.

5.4.5 Safety recording and reporting in lower risk trials (for example those which the risk is no greater than standard of care, as evaluated in a risk assessment) can be simplified from what is described in this section, applying a risk proportionate approach. Risk adaptations to safety reporting refer to documenting of AEs in source documents, recording of AEs in the case report forms (and hence reporting to the sponsor) and to the requirements of immediate (not later than within 24 hours of obtaining knowledge of the event) reporting (of

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SAEs/SUSARs) by the investigator to the sponsor. Any such adaptation should be clearly stated and justified in the protocol.

5.4.6 Systematic failure to report SUSARs for a trial or a product(s) to the licensing authority in line with applicable regulatory requirements and guidance may be considered a serious breach.

5.4.7 For double-blind trials, the blind will need to be broken before SUSARs are reported to the MHRA.

5.4.8 Emergency unblinding:
In order to quickly establish the study treatment the participant has been receiving. The Chief/Principal Investigator will be responsible for unblinding by following the unblinding procedure for a medical emergency (see section 4.4.1).

5.4.9 Unblinding for expedited reporting:
If it is not a medical emergency, the R&D or QA Manager will be responsible for unblinding by following the unblinding procedure for expedited reporting. In order to maintain the blind, the CI/PI, research team and CTU (if involved) will not be informed of the unblinding result, including the reporting or not to the MHRA.

5.4.10 Unblinding procedures must be set-up, tested and documented prior to issuing Sponsor greenlight

5.4.11 SUSARs reported for subjects receiving placebo will **not** be reported to the MHRA. Unless, in the opinion of the CI/PI or Sponsor the event was related to the placebo (e.g. an allergic reaction to an excipient).

5.4.12 The MHRA require SUSARs to be reported to them electronically via the following website: https://icsrsubmissions.mhra.gov.uk/ . The data should be complete; any missing data should be requested from the site immediately. In the event of a delay in receiving missing data, the report should still be submitted to the MHRA within the timeline. The missing data can then be entered into the Follow-up Form made available after submission of the initial form.

5.4.13 R&D QA staff will need to use Working Instruction 03 for the process of eSUSAR reporting.

5.4.14 Both the PI and Sponsor (R&D Director for single-site or CI for multi-site trials) will need to confirm the causality assessment prior to submission.

5.4.15 SUSARs do not have to be reported to the ethics committee or to the other investigators conducting the trial if multi-site, if it is agreed with the CI and Sponsor. If it is agreed that notification to the other sites is appropriate a letter can be sent to the additional sites.

5.4.16 R&D QA staff will save a copy of all paper SUSAR forms in the paper Trial Master File or Sponsor Study File (SSF) and pdf copies for saving electronically in the eTMF/eSSF.

5.5 Annual Safety Reporting

5.5.1 For double-blind trials, if an unblinding has occurred, R&D QA staff will need to submit the DSUR to the MHRA, to keep the PI/CI blind.

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5.5.2 R&D QA staff will review the MHRA approved SmPCs annually, at the time the DSUR is due (to check for any updates) and this will be documented on the DSUR. This requirement includes IMPs tested in clinical trials approved via automatic authorisation (notifiable trials) or where the DSUR includes a combination of both notified and non-notified trials.

5.5.3 If the SmPC or IB has been updated, the CI/PI, Sponsor and Pharma Company (if IB) will risk assess the changes and decide if they have an impact on participant safety. If the decision is that the updated SmPC/IB needs to be used as the new Reference Safety Information (RSI) then this must be submitted to the MHRA as a substantial amendment. The updated SmPC/IB can then be used once approved by the MHRA.

5.6 Trend analysis

5.6.1 Trend analysis of the SAEs reported to R&D will be performed at the Sponsor Oversight Group meetings unless concerns are raised by the investigator or R&D about the number or type of SAEs in a trial in which case the R&D Director will become involved straight away.

5.6.2 During the trend analysis, the R&D Director will assess the nature and frequency of the SAEs for each trial and any trends will be discussed with the investigator and reported to the MHRA and REC.

6 Implementation

6.1 Implementation of this SOP will conform to the process outlined in R&D SOP 01 Management of SOPs.