Pharmacovigilance: Receipt, Onward Reporting and Follow-Up of Safety Reports

Document No.:	PV001 v10.0
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Issue Date:	03 JUL 2025
Effective Date:	17 JUL 2025

1 Introduction

1.1 The Academic & Clinical Central Office for Research & Development (ACCORD) is a joint office comprising clinical research management staff from NHS Lothian (NHSL) and the University of Edinburgh (UoE).

1.2 The Medicines for Human Use (Clinical Trials) Regulations 2004 and the UK policy framework for health and social care research set out specific requirements for safety reporting. The UoE is responsible for pharmacovigilance (PhV) and safety reporting for studies sponsored by UoE and/or NHSL.

1.3 Unless otherwise defined in a protocol or study-specific work instruction (WI), all Clinical Trials of Investigational Medicinal Products (CTIMPs) sponsored by UoE and/or NHSL will follow the procedure for reporting Serious Adverse Events (SAEs) as described in ACCORD SOP CR005. In addition, where agreed at the Sponsorship review stage, certain non–CTIMP studies sponsored by UoE and/or NHSL will also be subject to safety reporting as described in ACCORD SOP CR006.

2 Purpose

2.1 To document the procedure for handling Pharmacovigilance (PhV) and safety reporting within ACCORD for all studies sponsored by UoE and/or NHSL, where SAEs are to be reported, as described in study specific documentation.

3 Scope

3.1 This SOP applies to the ACCORD Pharmacovigilance Team or designee staff involved in the reporting of SAEs, Serious Adverse Reactions (SARs) and potential/confirmed

Suspected Unexpected Serious Adverse Reactions (SUSARS), for all relevant studies sponsored by UoE and/or NHSL.

4 Responsibilities

4.1 It is the responsibility of the PhV Officer, or designee, to:

- Confirm receipt of safety reports;
- Enter the SAE into the PhV Database;
- Onward report the event as per the study protocol, regulatory, and contractual obligations;
- Request and track follow-up information;
- File the completed SAE in the Trial Master File (TMF), Sponsor File, or study-specific folder held by the PV team in ACCORD.
- Maintain the TARA PhV Database Tracker (for received SAE reports and SAEs reported that require Follow-up) on the ACCORD SharePoint.

4.2 It is the responsibility of the PhV Manager, or designee, (e.g. someone who has not performed the report data-entry into the PhV Database) to perform Quality Control (QC) checks of each safety report and corresponding PhV database entry.

4.3 It is the responsibility of the PhV Manager, or designee, to:

- Break the blind for SUSAR reporting (if applicable);
- Ensure all study sites are informed of a potential SUSAR;
- Ensure all SUSARs are reported to the relevant Research Ethics Committee (REC) and/or Competent Authority (CA) when required.
- Ensure all SUSARs are notified to appropriate parties as per any contractual obligations (e.g. IMP manufacturer).

5 Procedure

5.1 Receipt of SAE/SAR/SUSAR Reports

5.1.1 On receipt of a SAE/SAR/SUSAR report, the PhV Officer, or designee, will review the information provided in the relevant form (CR005-T01 SAE Form CTIMP or CR006-T01 SAE Form non-CTIMP).

5.1.2 A SAE Summary Sheet (PV001-F01) will be completed for each SAE by the PhV Officer, or designee.

5.1.3 A SAE/SAR/SUSAR receipt should be e-mailed to the sender by the PhV Officer, or designee, within 1 working day.

5.1.4 If any of the data is missing, unclear, invalid or otherwise requires follow up, the PhV Officer, or designee, should request the required data or clarifications in writing (e-mail) or by telephone, this include clarification about events that might have been reported in error as per protocol.

5.1.5 The PhV Officer, or designee, will save initial, follow-up, and final electronic copies of the SAE in the appropriate study folder on the ACCORD SharePoint.

5.1.6 SAEs that have been assessed as unrelated (SAE) OR related but expected, (SAR) will be entered into the ACCORD PhV Database by the PhV Officer, or designee, within 5 working days of first receiving the report.

5.1.7 All SAEs received by the PhV Team will be captured in the TARA PhV Database Tracker on SharePoint by the PhV Officer, or designee. The Tracker will be checked by the PhV Manager or designee and completed once QC of the report is performed. QC cannot be performed by the member of the PhV team responsible for SAE data entry.

5.1.8 The PhV Officer, or designee, will ensure that any additional onward reporting requirements (e.g. to Chief Investigator, Trial Manager, manufacturer or other third party) detailed in the protocol and/or agreements and/or working instructions, are met within stipulated timeframes.

5.1.9 For events deemed to be possibly related to the IMP (SAR), the researcher assessing the expectedness of the event must document (on the SAE form) the version of the SPC or IB which contained the Reference Safety Information (RSI) used to make this assessment.

5.1.10 All events related to the IMP (SARs) will be coded to MedDRA for subsequent use in the QC of the expectedness assessment against the RSI (see PV004). The diagnosis will be coded to System Organ Class (SOC) and Preferred Term (PT) level. These codes will be entered onto the SAE Summary Sheet (PV001-F01) in the relevant MedDRA box.

5.1.11 The PhV Officer, or designee, must QC this to ensure that the currently approved version of the SPC or IB has been used for this assessment and that the assessment is consistent with the RSI. The PhV Officer, or designee, will document this QC check on the SAE Summary Sheet (PV001-F01). The PhV Manager, or designee will check this information and document this on the SAE Summary Sheet (PV001-F01).

5.1.12 Fatal and life-threatening SARs should usually be considered unexpected even if previous fatal and life-threatening SARs have occurred.

5.1.13 Fatal SARs can only be considered expected for IMPs with a MA in the EU, when it is clearly stated in the table or list of ARs in section 4.8 of SPC that the IMP can cause these fatal SARs. Thus, the RSI of a product that has not received a MA in the EU should never include fatal SARs.

5.1.14 SAEs that have been assessed as related and unexpected (and therefore are SUSARs) will be handled as described in section 5.2.

5.2 Confirmation and Onward Reporting of SUSARs for Studies Conducted Entirely Within with UK

5.2.1 The following relates to any events which have been deemed to be possibly related to the IMP and unexpected.

5.2.2 The PhV Officer, or designee, will send any queries regarding the potential SUSAR to the PI at the site where the potential SUSAR occurred, for resolution or confirmation. These queries should include a request to the PI to confirm the event is unexpected.

5.2.3 All potential SUSARs are sent to the CI (chief investigator) for review and comment by the PhV Officer, or designee. If no response is received from the CI after 3 working days, the PhV Officer, or designee, will follow-up with the CI to ensure sufficient time to report to the Medicines and Healthcare products Regulatory Agency (MHRA) and REC, if necessary.

5.2.4 If the CI does not agree that the event is a SUSAR, it must still be reported as a SUSAR to the MHRA and the REC (if appropriate), but the CI's comments should be noted in the notification to the MHRA and REC.

5.2.5 For blinded studies, the blind must be broken by the PhV Manager, or designee, before onward reporting of SUSARs to the MHRA/REC as necessary. The unblinding

information must be captured in the unblinding spreadsheet located in the ACCORD Sharepoint Pharmacovigilance folder.

5.2.6 The tab relevant to the study that requires unblinding, in the unblinding Excel tracker spreadsheet will be printed, and the hard (paper) copy will be signed and dated by the PhV Manager or designee, and filed in the unblinded information envelope for that particular SUSAR.

5.2.7 The procedure for breaking the blind must be detailed within the protocol or trial specific Work Instruction (WI).

5.2.8 Potential SUSARs reported for study participants receiving placebo do not need to be reported to the MHRA or REC.

Do not inform the CI or other study staff of the unblinding information (including the reporting or non-reporting to MHRA or REC).

5.2.9 A potential SUSAR report will be notified to all study sites regardless of whether the participant was on placebo or IMP, to minimise the risk of unblinding study staff.

5.2.10 For blinded trials, in order to not unblind the CI or other study staff, the following email example can be used: "The Sponsor has been notified of a potential Suspected Unexpected Serious Adverse Reaction (SUSAR) for [Trial Name]. We have fulfilled our onward reporting obligations for this event if any was needed."

5.2.11 The PhV Officer, or designee, will ensure all sites are informed that a potential SUSAR has been reported for that study. If the study is being co-ordinated by a unit/group/individual, responsibility for informing all sites of a SUSAR may be delegated to them. The Sponsor should be copied into the correspondence to all sites.

5.2.12 The PhV Officer, or designee, will report SUSARs to the MHRA using the ICSR Submissions website (https://icsrsubmissions.mhra.gov.uk/login). 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 for their acknowledgement. Missing data can be followed-up at a later stage and added to the report.

5.2.13 The PhV Officer, or designee, will e-mail the SAE form or the report from the ICSR system (if required) along with the covering REC CTIMP or non-CTIMP Safety Report Form (https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/) to the relevant REC. Any comments from the CI should be added to the covering reporting form, if appropriate.

For CTIMPs submitted via combined review: MHRA will liaise with the REC if deemed appropriate. There is no requirement to email the REC.

5.2.14 The PhV Officer, or designee, will save a paper copy of the SUSAR report to the MHRA and/or REC in the SUSAR folder in the TMF or Sponsor File and electronic file for that study on SharePoint (in the restricted access "SUSAR" folder, accessible only by the PhV Team and QA for any unblinded information), if appropriate. For blinded trials: these should be appropriately labelled to identify that they contain unblinding information, and the paper documents should be filed in the unblinding envelope for the relevant SUSAR. In case an envelope needs to be opened, the date it is opened (and closed), name, job title and signature of the person responsible for the opening / closing of the envelope should be captured on the envelope. A reason for opening should also be added. The envelope must be re-sealed after each opening.

5.2.15 Reporting to MHRA (and REC if applicable): Fatal or life threatening SUSARs will be reported as soon as possible but no later than 7 calendar days after ACCORD is first aware of the reaction. Any additional relevant information will be submitted within 8 days of the initial report. All other SUSARs will be reported within 15 calendar days after ACCORD is first aware of the reaction. .

5.2.16 All SUSARs will be entered into the ACCORD PhV Database, by the PhV Officer, or designee, within 5 working days of first receiving the SUSAR report.

5.2.17 Completed SUSAR reports will be saved on SharePoint by the PhV Officer, or designee, for QC checking by the PhV Manager, or designee. Once the QC of SUSAR reports documents is completed, the PhV Manager or designee will complete the SUSAR QC part on PV001-F01.

5.2.18 The PhV Officer, or designee, will ensure that any additional onward reporting requirements, detailed in the protocol and/or working instructions are met e.g. to a Trial Manager, Company or other third party.

5.2.19 When a SUSAR occurs in a trial, the PhV Officer, or designee, will also ensure that the CI from other trials using the same IMP are also informed that a potential SUSAR was reported for this IMP. The SPC/IB tracker held in the Pharmacovigilance (PhV) folder on the ACCORD SharePoint site will be used to check if other studies use the same IMP. For blind trials, when the participant is taking placebo, CI and trial team from other trials will be contacted and remain blinded..

5.3 SUSAR Reporting Requirements for International Studies

5.3.1 The study protocol or WI will specify the procedures to be followed.

5.3.2 The procedure for reporting relevant events onwards to CAs and RECs will be included in any agreements between international groups performing the study.

5.3.3 If a SUSAR occurs that is UK relevant then this should be reported to the MHRA (see section 5.2). A UK relevant SUSAR is a SUSAR that occurs in any country in a study where there is a UK site, or that occurs in a different study involving the same IMP and also sponsored by UoE and/or NHSL.

5.3.4 In addition to being reported to the MHRA, for SUSARs occurring in sites outwith the UK, these may also be subject to expedited reporting to the relevant CAs in other countries where the study is running. Responsibility for this will be captured in the protocol and study agreements.

5.3.5 SUSARS reported outwith the UK do not require reporting to the UK REC. However, these may need to be reported to the REC in the country from where the SUSAR originated. Responsibility for this will be captured in the protocol and study agreements.

5.3.6 The CIOMS SAR/SUSAR Form (PV001-T01) will be used to report SUSARs to Third countries ie. non-UK, non-EU CAs, where necessary. Responsibility for this will be captured in the protocol and study agreements.

Overview of Reporting SUSARs to CA for UoE/NHSL Sponsored Studies

SUSAR origin	Report to
UK	MHRA
EEA member country	MHRA, EVCTM
Third country	Third country CA (and MHRA if SUSAR is deemed UK-relevant)

5.4 Non-investigational Medicinal Product (NIMP) reporting

5.4.1 Medicinal Products that are not the object of investigations (for example other than the tested product, placebo or active comparator) may be supplied to the participants and used in accordance with the protocol – these do not fall within the definition of an Investigational Medicinal Product (IMP) and are called Non-investigational Medicinal Products (NIMPs).

5.4.2 If the adverse reaction is suspected to be linked to an interaction between a NIMP and an IMP and is serious and unexpected (according to the IMP RSI) this should be reported as a SUSAR following section 5.2.

5.4.3 If a potential SUSAR is reported and it may be linked to either a NIMP or an IMP but cannot be attributed to only one of these, this should be reported as a confirmed SUSAR following section 5.2.

5.4.4 Unless otherwise assessed by the Sponsor, if a SAR is related not to an IMP but to a NIMP (and does not meet the criteria in 5.4.2 and 5.4.3, above), this is not a SUSAR and should not be reported as such. These events should be reported through the Yellow Card scheme (https://yellowcard.mhra.gov.uk/) by the PI, or designee.

5.4.5 Where applicable, the PhV Officer, or designee, will file a copy of the Yellow Card report electronically and in the TMF or sponsor file.

5.5 Follow-Up of SAEs/SARs/SUSARs

5.5.1 The PhV Officer, or designee, will contact the relevant person at the site, requesting a follow-up report be emailed, to include the missing data or resolve inconsistent data. The follow-up reports will be processed in the same way as initial reports as detailed in section 5.1.

5.5.2 On receipt of any subsequent information to the event, the relevant part of the SAE Summary Sheet should be completed (PV001-F001) by the PhV Officer, or designee.

5.5.3 The PhV Officer, or designee, will continue to query missing and inconsistent data until resolution, or database lock, for that study. Initial queries will be followed up approximately one month after the initial report is received and three monthly thereafter (until the SAE form is completed).

5.5.4 Incomplete SAE forms will not be printed, only the final completed SAE form will be printed. The complete paper copies will be filed in the TMF or Sponsor File, as appropriate, by the PhV Officer or designee. The PhV Officer, or designee, will insert a place holder into the TMF or sponsor file to indicate if any SAEs are incomplete. Incomplete SAE forms will be filed on Sharepoint until the completed SAE form is received.

5.5.5 The PhV Officer or designee will complete the Follow-up tab of the TARA PhV Database Tracker on SharePoint to keep track of all the reports that require to be followed-up and when those follow-ups should be sent.

5.6 QC Checking and Filing of SAEs

5.6.1 The PhV Manager, or designee, will QC check all SAEs forms received by ACCORD and the subsequent data entry onto the PhV Database. QC cannot be performed by the member of the PhV team responsible for the SAE data entry.

5.6.2 QC checks will be performed in batches approximately 3-4 weeks apart.

5.6.3 The PhV Manager, or designee, will document any discrepancies on the TARA PhV Database Tracker and on the PhV Database, and send the report back into the Database to the person responsible for data-entry for action.

5.6.4 The PhV Officer, or designee, will address the discrepancies and return the report to the PhV Manager, or designee, for QC.

5.6.5 The PhV Manager, or designee, will document the completion of the QC process on the PhV Database and on the SAE summary sheet (PV001-F01).

5.6.6 Once all QC / follow-up queries have been answered satisfactorily, the SAE report is considered fully completed and the QC of the report in the Database is completed, the PhV Officer, or designee, will file the paper report and sign the SAE summary sheet (PV001-F01). This signature confirms that all the queries have been addressed.

5.6.7 When the QC check is complete and the SAE form is complete, the e-mailed SAE form and signed SAE summary sheet (PV001-F01) will be filed in the TMF or Sponsor File, as appropriate, by the PhV Officer, or designee.

5.6.8 If there is more than one SAE for a participant, then they will be filed in ‘date of onset’ order, from newest to oldest (i.e. the most recent on top)

6 References and Related Documents

- The Medicines for Human Use (Clinical Trials) Regulations, (SI 2004 No. 1031) as amended
- UK policy framework for health and social care research
- PV001-T01 CIOMS Form (SAR/SUSAR Report)
- PV001-W01 TARA Work Instruction
- PV001-F01 SAE Summary Sheet
- CR005 Identifying, Recording and Reporting Adverse Events and Urgent Safety Measures for Clinical Trials of Investigational Medicinal Products.
- CR005-T01 SAE Form CTIMP
- CR006 Identifying, Recording and Reporting Adverse Events and Urgent Safety Measures for Non-Clinical Trials of Investigational Medicinal Products
- CR006-T01 SAE Form non-CTIMP
- Clinical Trial Facilitation Group (CTFG) Q&A Documents – Reference Safety Information November 2017

7 Document History

Version Number	Effective Date	Reason for Change
1.0	20 FEB 2014	New SOP
2.0	02 AUG 2016	PhV spreadsheet has been moved to the ACCORD Sharepoint directory. QC checks of SAEs now the responsibility of the QA team. Periodic review of filed SAEs removed. Minor administrative changes.
3.0	05 AUG 2016	Addition of PV001-F01 SAE Summary Sheet and PV001-F02 SAE QC Form.
4.0	08 JUN 2017	PV001-F01 renamed SAE Initial Summary Sheet. Addition of PV001-F03 SAE Follow-Up Summary Sheet. Minor administrative changes.
5.0	21 MAR 2018	Section 5.1.9. added to capture a RSI check for SARs. Clarification added to section 5.2 and 5.3. on the requirements of onward reporting SUSARs including international studies. Section 5.4 detailing NIMP reporting with reference to the yellow card scheme added. Minor administrative changes throughout.

6.0	25 JUN 2019	Clarification has been added to section 5.1.10 that for SARs expectedness is assessed against the currently approved RSI. Section 5.1.11-13 added following CTFG guidance.
7.0	19 JUN 2020	(i) Instructions have been added relating to MedDRA coding of SARs for the purpose of QC checks against the RSI. (ii) Instructions have been added relating to the documentation and sign-off of unblinding when required for confirmation of SUSARs (iii) Sundry minor clarifications.
8.0	08 JUN 2023	Update to include PhV Manager and PhV Officer responsibilities Removal of fax mentions Update of the SUSAR submission to include ICSR submission website that became mandatory to use in Oct-2022 Update PV001-F01 (now v5.0) and PV001-F03 (now v3.0) to add the new PhV Database name. PV001-W01 (now v3.0) updated with minor administrative changes. PV001-F02 now obsolete Update of the QC process now that TARA is the PhV Database and removed QA responsibilities in the QC process Updates following internal audit Nov2022: precision concerning the unblinded SUSAR process Update of the process for signature of PV001-F01 and update of the document PV001-F01 to reflect those changes and the QC of SUSAR submission Update to incorporate the combined review process for the SUSAR submission.
9.0		Update of Summary Sheet process – creation of "SAE Summary Sheet" that combine "PV001-F01 SAE initial summary sheet" and "PV001-F03 SAE FU summary sheet" – update of PV001-F01 (now v6.0) PV001-F03 is now obsolete

		Update to reflect that only completed SAE forms will be printed. Removal of the mention that MHRA will forward SUSAR to the EMA (EVCTM) as this is not the case anymore.
10.0	17 JUL 2025	Update following internal audit of Nov2024: - addition in 5.1.4 that clarification will be requested from site if the SAE is suspected to have been reported by error as per protocol. - 5.2.15: clarification about the reporting timelines to Health Authorities - PV001-F01 SAE Summary Sheet updated to capture that a check is performed in case of SUSAR to see if other studies are using the same IMP and if yes that CI is made aware of the potential SUSAR. Addition of PV001-W01 on the related documents. Removal of the mention that for EEA country SUSAR have to be submitted to local CA as now the EVCTM submission is the only one required. PV001-T01 and PV001-W01 updated to align with new ACCORD branding

8 Approvals

Sign	Date
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Sweta Rath APPROVED: Sweta Rath, Pharmacovigilance Officer, UoE, ACCORD.	02-Jul-2025
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PV001 Pharmacovigilance Receipt Onward Reporting and Follow-Up of Safety Reports v10.0

Final Audit Report 2025-07-03

Created:	2025-07-02 (British Summer Time)
By:	Roisin Ellis (v1relli8@exseed.ed.ac.uk)
Status:	Signed
Transaction ID:	CBJCHBCAABAAeZ2A4HuHJ2zFI75ftljuqJfH3eP3pxaY

"PV001 Pharmacovigilance Receipt Onward Reporting and Follow-Up of Safety Reports v10.0" History

Document created by Roisin Ellis (v1relli8@exseed.ed.ac.uk)
2025-07-02 - 1:30:34 PM GMT+1- IP address: 62.253.82.242

Document emailed to Camille Bach (Camille.Bach@ed.ac.uk) for signature
2025-07-02 - 1:33:00 PM GMT+1

Document emailed to Sweta Rath (Sweta.Rath@ed.ac.uk) for signature
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Document emailed to Lorn Mackenzie (lorn.mackenzie@nhslothian.scot.nhs.uk) for signature
2025-07-02 - 1:33:00 PM GMT+1

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Document e-signed by Camille Bach (Camille.Bach@ed.ac.uk)
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Email viewed by Sweta Rath (Sweta.Rath@ed.ac.uk)
2025-07-02 - 2:46:32 PM GMT+1- IP address: 104.47.11.254

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Signature Date: 2025-07-02 - 2:46:59 PM GMT+1 - Time Source: server- IP address: 81.147.126.42

Email viewed by Lorn Mackenzie (lorn.mackenzie@nhslothian.scot.nhs.uk)
2025-07-03 - 8:25:17 AM GMT+1- IP address: 52.102.17.117

Document e-signed by Lorn Mackenzie (lorn.mackenzie@nhslothian.scot.nhs.uk)

Signature Date: 2025-07-03 - 8:25:30 AM GMT+1 - Time Source: server- IP address: 77.97.224.249

Agreement completed.

2025-07-03 - 8:25:30 AM GMT+1