The Office of Sponsor and Regulatory Oversight (OSRO) receives and processes Serious Adverse Event (SAE) reports for clinical trials conducted under the Center for Cancer Research (CCR) or OSRO sponsored Investigational New Drug applications (IND) or Investigational Device Exemption (IDE).

The following Frequently Asked Questions (FAQs) address common questions that have been raised around the reporting of SAEs to OSRO.

Questions

1. Do I need to send SAEs to OSRO for all clinical trials conducted in CCR?
2. Where do I need to send the SAE form?
3. Is there anything else that needs to be sent with the SAE form?
4. Do I need to send all the medical records with the SAE form?
5. Do I need to use encrypted e-mail to send the SAE form and other requested documents?
6. What form should I use to report SAE?
7. Where can I find the OSRO SAE form?
8. Who should sign the SAE form?
9. The timeframe for reporting had been changed to reporting within 24 hours of awareness of the event. Why?
10. I am the PI of the protocol; I should be able to determine whether an SAE would require changes in the protocol. Why would that determination be made by OSRO?
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23. Do I need to report hospitalization for elective surgery as an SAE?

24. Mortality is an outcome measure in my protocol. The protocol does not require reporting deaths as SAEs. A participant experienced a severe allergic reaction, minutes after receiving the investigational product and despite all efforts had died. Do I need to report this as SAE?

25. If the hospitalization was less than 24 hours, do I need to report it as a SAE?

26. I have received CIOMS reports from OSRO safety, what are these reports?

27. What are the definitions for the event outcomes of "resolved", "resolved with sequelae", and "resolving?"

28. My PI is not able or available to sign the SAE report form. Can someone else sign? Can I submit it unsigned?

29. Why is the sponsor (OSRO) assessing an event as unexpected if it is listed in the protocol and consent?

30. How does the sponsor determine what is reported to FDA as an expedited report?

31. Do all events that meet CTCAE Grade 4 need to be reported as SAE?

Answers

1. Do I need to send SAEs to OSRO for all clinical trials conducted in CCR?

No. Only send SAEs that happen under clinical trials for which CCR is the IND or IDE sponsor.

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2. Where do I need to send the SAE form?

Follow the instruction listed in your approved protocol. In the future all SAEs will be sent to NCIOSROSafety@mail.nih.gov; however, until your protocol is amended follow the instruction in the approved protocol.

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3. Is there anything else that needs to be sent with the SAE form?

If not provided on the form, attach a list of concomitant medications at the time of the event, provide baseline History and Physical (H&P) and baseline lab results. Provide diagnostic test results (pertinent positive and negative) conducted as part of the SAE evaluation and baseline results for these diagnostic tests, if available. If the event is hospitalization, then provide the discharge summary when it is available.

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4. Do I need to send all the medical records with the SAE form?

No. Please only send the requested information (see Question #3). Please send summary note and consultation notes as they relate to the evaluation of the SAE. The OSRO medical monitor may request additional medical records if necessary.

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5. Do I need to use encrypted e-mail to send the SAE form and other requested documents?

No. The SAE form should not include any Personal Identifiable Information (PII). The supporting documentation needs to be redacted to remove any PII. There is no reason to use encrypted e-mail.

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6. What form should I use to report SAE?

Unless the protocol instructs you otherwise, use the OSRO SAE form.

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7. Where can I find the OSRO SAE form?

The OSRO SAE report form is located on the CCR website, Clinical Research Operations Home Page at the following link https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions.

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8. Who should sign the SAE form?

The SAE form should be signed by the person assessing the event. The qualified person to assess SAE is a licensed physician listed on Form 1572 as the PI or sub-PI. See Question #28 for further information about signing the SAE report form.

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9. The timeframe for reporting had been changed to reporting within 24 hours of awareness of the event. Why?

The regulations require the investigator to report serious adverse events immediately (21CFR312.64). OSRO defines “immediately” as within 24 hours of awareness.

Timely reporting of SAEs is required to ensure the safety of participants (i.e., whether changes in the protocol are necessary or whether the study needs to be halted), and to ensure CCR meets the FDA requirements of timely reporting.

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10. I am the PI of the protocol; I should be able to determine whether an SAE would require changes in the protocol. Why would that determination be made by OSRO?

While the PI is aware of the safety events in his/her protocols, the same intervention or study mechanism of action (i.e., check point inhibitors) is used across other CCR IND hold protocols. As OSRO is the hub for receiving all safety information (SAE events, IBs, SUSARs, etc.) the knowledge will allow for better assessment of the event.

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11. Does anyone look at SAEs sent over the weekend and holidays?

Yes. The safety mail box is monitored over weekends and holidays.

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12. I just got a call from a family member telling me a participant has been hospitalized. Am I now aware of the event? Does the 24 hours clock start now?

The 24 hours clock starts when there is basic information available to assess the event as meeting the protocol defined SAE criteria, to potentially act upon it, and the PI has assessed the event as serious. At a minimum, a diagnosis or constellation of signs and symptoms need to be known before the assessment can be made and the clock starts. However, you may not have enough information to determine potential causality. Based upon the data you have, provide a causality assessment. This assessment may be modified in a follow-up report as more medical data becomes available to you.

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13. Do I need to provide all the information requested on the form?

OSRO expects that all the requested information on the form and the supporting documentation will be sent with the SAE form. OSRO realizes that not all information will be easily accessible after hours or over a weekend or holiday. At a minimum the description of the event including any relevant diagnostic information, a clinical summary of the history of the participant and other information required to assess the case (e.g., key baseline labs, diagnosis, changes in dosing, etc.) should be provided. Remember that while the reporter will know the participant well, the OSRO medical monitor only knows the participant from the information provided. If less than the full information is sent, then the incomplete form should be captured as a protocol non-adherence. Make sure the narrative includes a rationale to support the causality (attribution) determination related to the study interventions that were administered. Please consult the "Instructions for the Serious Adverse Event Form" (FI01-301-S01) for more information.

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14. Do I need to provide an attribution causality assessment on the form?

Yes. Causality assessment for all SAEs needs to be conducted and recorded regardless of relatedness. Causality assessment may change over time as more medical data becomes available.

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15. Can an e-mail notification be sent over the weekend instead of the form?

The protocol requires utilization of the SAE form. OSRO will act upon information received not utilizing the form; however, this is a protocol non-adherence and should be reported as such. OSRO requires all the information that would otherwise be on the form to be present in the alternative mode of communication (see also Question #13).

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16. I am sending copies of the medical record. Do I need to redact them?

Yes. All information sent to OSRO should not include PII. Redact all PII from the medical record and replace them with the protocol number and participant number (PID). Please note: each page must be labeled with Protocol number and PID.

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17. Is there any e-mail format that I need to follow?

Please include the following information in the e-mail subject line:

- Protocol number
- Protocol-specific patient ID number
- Serious adverse event CTCAE term
- Type of report: SAE initial report or follow-up report (with follow-up number)

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18. What notification will I expect to receive from OSRO?

You will receive an email confirmation that OSRO Safety has received the SAE report. Once the assessment has been completed you will either receive queries about the case or a copy of the sponsor assessment.

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19. When do I need to send follow-up SAEs?

Submit follow up reports when new information or relevant updates related to a previous report is available. The new information should raise to the level of potentially changing the causality assessment or provide new information that supports the diagnosis and/or causality assessment. We advise not to submit a follow-up report for diagnostic results that are not relevant in supporting the diagnosis and/or causality assessment. Follow the protocol to determine if abnormal tests should be collected as adverse events.

The following are examples of when a new follow-up report is required:

- When a clinically pertinent diagnostic test and result are available
- When a discharge summary and/or autopsy report is available
- Worsening of the condition
- Change in diagnosis
- A unifying diagnosis instead of signs and symptoms

- Change in causality assessment
- Final outcome (death, event is resolved, resolved with sequela or considered to be on chronically ongoing) is available

If during the diagnostic evaluation a new condition is discovered then you will need to assess whether this is a new event (distinct from the original SAE), or part of the same event. If it is part of the same event, describe it in the follow-up narrative and do not submit the information as a new SAE. If the event is distinct from the original SAE, the new event should be submitted on a new SAE form.

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20. When we submitted the SAE there was no diagnosis available, but only a list of signs and symptoms. Now there is a diagnosis. How this should be handled?

Submit a follow-up SAE report. On the form delete previously reported sign and symptoms, and record only the diagnosis as the event term. In the "Description of the SAE" section, indicate that the signs and symptoms are replaced with a unified diagnosis. The grade of the event and attributions may also be changed based on supporting evidence from further evaluation since the initial report was submitted.

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21. Do the OSRO medical monitors have access to CRIS?

No. The OSRO medical monitors do not have access to CRIS. They receive information from the SAE form and the supporting documentation sent by the study team.

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22. Do I need to report death due to disease progression as an SAE?

You need to follow the protocol as written. If an event is also captured as an end-point, it can be waived from expediated reporting requirements under certain conditions. However, those should be described in the protocol. OSRO can work with the study team to outline appropriate language in the protocol. You must follow the IRB regulations independently from the SAE reporting to OSRO.

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23. Do I need to report hospitalization for elective surgery as an SAE?

You need to follow the protocol as written. If the protocol allows elective hospitalization to be waived from expediated reporting requirements, then you do not need to report the hospitalization as an SAE. However, the diagnosis that led to the hospitalization needs to be assessed to determine whether it is a new event, and whether it meets any other SAE criteria in the protocol.

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24. Mortality is an outcome measure in my protocol. The protocol does not require reporting deaths as SAEs. A participant experienced a severe allergic reaction, minutes after receiving the investigational product and despite all efforts had died. Do I need to report this as SAE?

Yes. Despite mortality being an end-point in the study, events that are suspicious for being caused by the investigational product, need to be reported as an SAE.

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25. If the hospitalization was less than 24 hours, do I need to report it as a SAE?

Yes, hospitalization less than 24 hours needs to be reported if the patient was admitted as an inpatient and discharged. Unless the protocol specifically states planned hospitalizations do not require reporting, any admission for hospitalization (regardless of period of time, including less than 24 hours) requires SAE reporting.

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26. I have received CIOMS reports from OSRO safety, what are these reports?

CIOMS is an acronym for Council for International Organizations of Medical Sciences, the organization that developed this reporting tool. The CIOMS reports are the IND sponsor summary of the SAE based on the SAE report(s), PI assessment and sponsor assessment (OSRO Medical Monitor). The CIOMS is provided to the PIs and to pharmaceutical collaborators as applicable. The study team is not required to take an action. Follow up CIOMS reports are issued when new information is received on SAE follow up reports you send in. The PSO office is copied on the CIOMS reports and will file them in the site regulatory folders.

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27. What are the definitions for the event outcomes of "resolved", "resolved with sequelae", and "resolving?"

27.1. For an event to be considered "resolved":

The event is determined not to an active medical event anymore (improved or recuperated).

For events that required medical intervention, the date of resolution would be the date in which the medical intervention is no longer needed and stopped (e.g., the date antibiotics had stopped, the date a surgical intervention had been performed without post-op complications, the date discharge from the hospital, the date that all conditions stemming from the original event are not active anymore).

27.2. Events "resolved with sequelae":

Sequalae is usually a chronic condition, where the participant recuperated but retained pathological conditions resulting from the prior disease or injury. For example, in diarrhea that leads to dehydration, the dehydration is not a sequalae. However, if that would lead for a kidney failure which is continuing, it would be a sequalae.

The sequalae need to be evaluated to ascertain whether it meets the serious or other reporting criteria by itself. By definition the sequalae is the result of previous adverse event, but if meet serious criteria would need to be reported as a new SAE.

Events that are stemming from the original adverse events but are not chronic (e.g., dehydration following diarrhea, pain following a surgical procedure to address the adverse event) are not considered sequalae but part of the original adverse event. If those events meet the criteria for solicited AE they should be reported as such.

27.3. Events that are "resolving":

Events that require ongoing medical interventions to address the initial event, with event outcome that indicates the event is improving.

The protocol should be specific on how to address repeated hospitalization (hospitalization for the same reason, within 30 days of discharge). They can be considered one event, or different events, as long as it is consistent.

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28. My PI is not able or available to sign the SAE report form. Can someone else sign? Can I submit it unsigned?

It is required that the PI (or someone listed on the 1572 form) provide a signature on the SAE Report form. While OSRO expects all SAE Report forms to be either digitally signed by the PI or wet-signed by the PI, OSRO understands that due to extenuating circumstances and/or technical issues with the documents some PIs may have a problem with signing the SAE Report form digitally or do not have access to a printer and scanner to wet-sign the document. For these atypical situations, OSRO will accept an **unsigned** SAE Report form as long as the two conditions below are met:

- The SAE Report form is sent to NCIOSROSafety@mail.nih.gov directly from the e-mail account of a clinician licensed to diagnose and listed on the 1572; and
- The e-mail containing the SAE Report form includes the following attestation: "Due to <insert reason>, I cannot sign the attached SAE Report form. I confirm that I have approved the content of the attached SAE Report form, for participant [Enter PID] in study [enter Study Number] as correct and complete."

If the PI is not available to sign the Form, then the Form should be signed by the "covering" PI (a clinician licensed to diagnose and listed on the 1572). If no PI is available to sign the report, send the SAE Report immediately and provide the SAE Report with PI signature within 24 hours. Note: once the SAE Report form is signed the report can no longer be modified.

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29. Why is the sponsor (OSRO) assessing an event as unexpected if it is listed in the protocol and consent?

The Sponsor has the regulatory obligation to determine expectedness of the event. The expectedness is based on the Reference Safety Information (RSI) of the Investigator Brochure (IB) which is where the manufacturer lists the expected events (and their severity) for regulatory reporting purposes. As a general rule, life threatening and death events are not listed as part of the RSI (expected events) due to their severity and require expedited reporting to the regulatory agencies.

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30. How does the sponsor determine what is reported to FDA as an expedited report?

According to FDA IND regulations (21 CFR 312.32I(1)(i)), the sponsor is responsible for reporting SUSARs to FDA as well as all participating investigators.

The sponsor must report in an IND safety report any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected. Before submitting an IND safety report, the sponsor needs to ensure that the event meets all three of the definitions for:

- Suspected adverse reaction
- Serious
- Unexpected

FDA's responsibilities for the investigator and the sponsor are listed in Table 1. For additional information, see the FDA Guidance for Industry on Safety Reporting Requirements.

*Table 1. Investigator and Sponsor Reporting Responsibilities**

Term	Investigator Responsibility	Sponsor Responsibility	Final Determination Responsibility
Serious (or life-threatening)	Yes Investigator must report all serious adverse events to the sponsor immediately	Yes	An event is considered serious or life-threatening, based on ***either*** the investigator's or sponsor's opinion.
Unexpected	No No requirement to assess "expectedness"	Yes	The **sponsor** is responsible for determining whether event meets the definition of "unexpected," based on whether the event is listed in the investigator brochure; or if an investigator brochure is not required or available, is not consistent with the risk information described elsewhere in the general investigational plan or elsewhere in the current application.
Suspected Adverse Reaction (causality assessment standard - "reasonable possibility")	Yes Investigator must provide sponsor with an assessment of causality	Yes Sponsor's assessment determines reportability, regardless of investigator's assessment	The **sponsor** is responsible for determining whether there is a reasonable possibility that the drug caused the adverse event, taking into consideration the investigator's assessment.

*Reporting Responsibilities of Investigators are listed under 21 CFR 312.64(b) and of Sponsors are under 21 CFR 312.32(c)(1)(i) for Serious and Unexpected Suspected Adverse Reactions.

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31. Do all events that meet CTCAE Grade 4 need to be reported as SAE?

The CTCAE defines a Grade 4 AE as "life-threatening consequences; urgent intervention indicated." Therefore, there is a rebuttable assumption that a CTCAE Grade 4 event meets the SAE reporting criterion of "Life Threatening" and requires reporting as an SAE.

Some CTCAE terms are graded based on measured values and not a functional definition. In specific cases where an event is graded CTCAE Grade 4 by a measured value, but the event is judged clinically to not be "life threatening" and does not require "urgent intervention" because of the background disease or treatment in a particular participant, then the event does not meet the SAE criterion of "life threatening". In those cases, a note should be provided in the source documents that explains why the event is judged clinically to not meet the "life threatening" criterion.

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