SAFETY

Surveillance After Extremity Tumor Surgery

Study Event Reporting Guidelines

Version 2.0

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Principal Investigator: Michelle Ghert, MD, FRCSC

Center for Evidence-Based Orthopaedics
McMaster University
Methods Center: 711 Concession Street
Lakeview Lodge | Level 3, Room 11
Hamilton, ON L8V 1C3

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Document History

Date (DD-MMM-YY)	Author(s)	Version No.	Description of Amendment(s)
8-JUN-20	Tricia Schneider	1.0	Initial Version
11-JAN-22	Tess Hudson	1.1	Updated references to questions on other CRFs and changed pronouns to gender neutral.
14-FEB-22	Tess Hudson	2.0	Added to FAQ section.

1.0 Introduction

The purpose of this document is to provide guidance on how to properly report study events, including oncologic recurrences, unplanned re-operations and serious adverse events (SAEs), for the **S**urveillance **AF**ter **E**xtremity **T**umor surger**Y** (SAFETY) trial. Clinical site personnel should review this document prior to beginning study enrolment and refer to it when questions arise. If clinical site personnel have questions regarding event reporting, they should contact the Project Manager at the Methods Center via email and / or telephone.

2.0 Documentation of Deaths

The identification and reporting of all deaths (irrespective of cause) is vital to the success of the SAFETY trial. Periodically, clinical site personnel should review their local participant listings to determine if any participants have missed study visits. For participants that have missed study visits and whom clinical site personnel have not been able to contact, clinical site personnel should review their medical records to determine whether the participants have been hospitalized or have died. For participants that have no additional clinical data in their medical records, clinical site personnel should search obituaries to determine whether the participant has died.

Once it has been determined that a participant has died, clinical site personnel, with support from the site investigator, should complete one of a **Local Recurrence Form (Form 12)**, a **Systemic Recurrence Form (Form 13)** or an **Adverse Event Form (Form 16)** depending on the cause of death. Clinical site personnel should also complete an **Early Withdrawal Form (Form 24)**, with the date of death being recorded as the date of the participant's early withdrawal from the study. For guidelines on the completion of these CRFs, please refer to the **Case Report Form Completion Guidelines** in the Study Resource Binder.

The study Central Adjudication Committee will review each reported death to determine if it meets the study event criteria. To facilitate this process, clinical site personnel should submit all clinical notes, operative notes, imaging and photographs. For guidelines on the submission of adjudication materials, please refer to the **Submission of Adjudication Materials Guidelines** in the Study Resource Binder.

3.0 Documentation of Oncologic Events

The identification and reporting of all oncologic events related to a participant's soft-tissue sarcoma (STS) is vital to the success of the SAFETY trial. At each study visit, clinical site personnel should ask a participant if their STS has returned at the initial tumor site (local recurrence) and / or whether it has spread to any other location in the body (systemic recurrence). Clinical site personnel should also verify this information with the participant's medical records.

3.1 Local Recurrence

Not all local recurrences may be managed / treated at the participating clinical site. Therefore, at each study visit, clinical site personnel should ask each participant whether their STS has returned at the initial tumor site. Specifically, clinical site personnel should ask the following questions:

- Has the participant seen another physician or visited an emergency room / urgent care clinic due to problems with the participant's initial tumor site?
- Has the participant undergone any further systemic therapy or radiation?
- Has the participant noticed pain or palpated a lump / bump at the initial tumor site?

If the participant responds 'Yes' to any of the above questions, clinical site personnel should ask for additional details regarding the possible local recurrence (e.g., name of treating physician, hospital / clinic, date of visit, type of treatment, etc.). Clinical site personnel should then reach out to the attending surgeon for additional details if necessary. Please note that permission may be required in order to obtain information pertaining to a participant's care at an outside facility.

Once it has been determined that a participant has a local recurrence, clinical site personnel, with support from the site investigator, should complete a **Local Recurrence Form (Form 12)**. A separate form should be completed for each local recurrence. All local recurrences should be reported irrespective of whether they meet the study event criteria. For guidelines on the completion of this CRF, please refer to the **Case Report Form Completion Guidelines** in the Study Resource Binder.

3.2 Systemic Recurrence

Not all systemic recurrences may be managed / treated at the participating clinical site. Therefore, at each study visit, clinical site personnel should ask each participant whether their STS has returned at the initial tumor site. Specifically, clinical site personnel should ask the following questions:

- Has the participant seen another physician or visited an emergency room / urgent care clinic due to concerns with the spread of their STS?
- Has the participant undergone any further systemic therapy or radiation?
- Has the participant had any chest pain or shortness of breath?

If the participant responds 'Yes' to any of the above questions, clinical site personnel should ask for additional details regarding the possible systemic recurrence (e.g., name of treating physician, hospital / clinic, date of visit, type of treatment, etc.). Clinical site personnel should then reach out to the attending surgeon for additional details if necessary. Please note that permission may be required in order to obtain information pertaining to a participant's care at an outside facility.

Once it has been determined that a participant has a systemic recurrence, clinical site personnel, with support from the site investigator, should complete a **Systemic Recurrence Form (Form 13)**. A separate form should be completed for each systemic recurrence. All systemic recurrences should be reported irrespective of whether they meet the study event criteria. For guidelines on the completion of this CRF, please refer to the **Case Report Form Completion Guidelines** in the Study Resource Binder.

4.0 Documentation of Surgical Interventions

The identification and reporting of all surgical interventions related to a participant's STS or its metastatic spread is vital to the success of the SAFETY trial. At each study visit, clinical site personnel should ask a participant if they have had any re-operations at the initial tumor site or

any surgical interventions anywhere else in the body to treat a metastasis. Clinical site personnel should also verify this information with the participant's medical records.

4.1 Unplanned Re-Operations

Not all re-operations at the initial tumor site may be conducted at the participating clinical site. Therefore, clinical site personnel should ask each participant whether they have had any re-operations at each study visit. Specifically, clinical site personnel should ask the following questions:

- Has the participant undergone any surgery at the initial tumor site (i.e., where the STS was originally located)?
- Are there any further surgeries / operations planned at the initial tumor site?
- Has the participant been to another hospital due to problems with their initial tumor site?

If the participant responds 'Yes' to any of the above questions, clinical site personnel should ask for additional details regarding the possible re-operation (e.g., name of attending surgeon, hospital, date of re-operation, type of re-operation, etc.). Clinical site personnel should then reach out to the attending surgeon for additional details if necessary. Please note that permission may be required in order to obtain information pertaining to a participant's care at an outside facility.

Once it has been determined that a participant has had a re-operation at the initial tumor site, clinical site personnel, with support from the site investigator, should complete an **Unplanned Re-Operation Form (Form 14)**. A separate form should be completed for each re-operation. All re-operations should be reported irrespective of whether they meet the study event criteria. For guidelines on the completion of this CRF, please refer to the **Case Report Form Completion Guidelines** in the Study Resource Binder.

The study Central Adjudication Committee will review each reported re-operation to determine if it meets the study event criteria. To facilitate this process, clinical site personnel should submit all clinical notes, operative notes, imaging and photographs. For guidelines on the submission of adjudication materials, please refer to the **Submission of Adjudication Materials Guidelines** in the Study Resource Binder.

4.2 Other Surgical Interventions

Not all surgical interventions to treat metastasis of the STS may be conducted at the participating clinical site. Therefore, clinical site personnel should ask each participant whether they have had any other surgical interventions (outside of the initial tumor site) at each study visit. Specifically, clinical site personnel should ask the following questions:

- Has the participant undergone any surgery outside of the initial tumor site to treat a metastasis of the participant's STS?
- Are there any further surgeries / operations planned to treat the metastasis of the participant's STS?
- Has the participant been to another hospital due to the spread of their STS?

If the participant responds 'Yes' to any of the above questions, clinical site personnel should ask for additional details regarding the possible surgical intervention (e.g., name of attending surgeon, hospital, date of surgical intervention, type of surgical intervention, etc.). Clinical site personnel should then reach out to the attending surgeon for additional details if necessary. Please note that permission may be required in order to obtain information pertaining to a participant's care at an outside facility.

Once it has been determined that a participant has had a surgical intervention to treat the metastatic spread of a participant's STS, clinical site personnel, with support from the site investigator, should complete an **Other Surgical Intervention Form (Form 15)**. A separate form should be completed for each surgical intervention. All surgical interventions should be reported irrespective of whether they meet the study event criteria. For guidelines on the completion of this CRF, please refer to the **Case Report Form Completion Guidelines** in the Study Resource Binder.

The study Central Adjudication Committee will review each reported surgical intervention to determine if it meets the study event criteria. To facilitate this process, clinical site personnel should submit all clinical notes, operative notes, imaging and photographs. For guidelines on the submission of adjudication materials, please refer to the **Submission of Adjudication Materials Guidelines** in the Study Resource Binder.

5.0 Documentation of Adverse Events

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study, but which does not necessarily have a causal relationship with the study treatment. At minimum, participating clinical sites are required to report all AEs that are listed on the **Adverse Event Form (Form 16)**. Clinical site personnel must report AEs to the Methods Center via the iDataFax study database within five business days of becoming aware of the event. Please complete a separate **Adverse Event Form (Form 16)** for each AE. For guidelines on the completion of these participant questionnaires, please refer to the **Case Report Form Completion Guidelines** in the Study Resource Binder.

5.1 Serious Adverse Events (SAEs)

While serious adverse events (SAEs) are not an outcome of the SAFETY trial, they must be reported for safety monitoring purposes. A SAE is any AE that is any one of the following:

- Fatal;
- Life threatening;
- Requires or prolongs hospitalization;
- Results in persistent or significant disability or incapacity;
- A congenital anomaly or birth defect; or
- An important medical event.

Clinical site personnel must report SAEs to the Methods Center via the iDataFax study database within two business days of becoming aware of the event. Please complete a separate **Adverse Event Form (Form 16)** for each SAE. For guidelines on the completion of these participant

questionnaires, please refer to the **Case Report Form Completion Guidelines** in the Study Resource Binder.

The study Central Adjudication Committee may also review select adverse events to determine if it meets the study event criteria. To facilitate this process, clinical site personnel should submit all clinical notes, operative notes, imaging and photographs for any treatment-related complications or adverse events that result in death. For guidelines on the submission of adjudication materials, please refer to the **Submission of Adjudication Materials Guidelines** in the Study Resource Binder.

6.0 Frequently Asked Questions

This section provides clarification and guidance on the study reporting requirements and procedures. Please contact the Methods Center if you have any questions about the reporting requirements of a particular participant in the trial.

6.1 At which visit should an AE be reported?

Please report all local recurrences, systemic recurrences and reportable AEs at the next visit after they occur. For example, if an AE occurs after the baseline visit for a participant randomized to surveillance visits every six months, the event should be reported at the 6M intervention phase visit.

6.2 How should it be documented if an AE was operatively managed?

If a local recurrence was operatively managed, please select *'Operative Management'* for Q6 on the **Local Recurrence Form (Form 12)**, as well as complete a separate **Unplanned Re-Operation Form (Form 14)** for each re-operation / additional procedure.

If a systemic recurrence was operatively managed, please select *'Operative Management'* for Q6 of the **Systemic Recurrence Form (Form 13)**, as well as complete a separate **Other Surgical Intervention Form (Form 15)** for each surgical intervention performed to treat the systemic recurrence.

For operative procedures performed to treat any other AE, please select *'Operative Management'* for Q2 on the **Adverse Event Form (Form 16)**. No other forms need to be completed.

6.3 What else should be completed if the AE was treated using systemic therapy / radiation?

If a local or systemic recurrence was treated using systemic therapy, the **Systemic Therapy Log (Form 17)** should be updated to add the systemic therapy data (type, name, start and stop dates, reason for administration and therapy completion) for each additional systemic therapy. If a local or systemic recurrence was treated using radiation, the **Radiation Log (Form 18)** should be updated to add the radiation data (mode, dosage, start and stop dates, reason for administration and therapy completion) for each additional radiation therapy.

6.4 How do we determine if an AE is related to the study?

Site investigators should use their clinical judgment when determining whether an AE is related to the SAFETY trial. In general, study events related to disease recurrence (local or systemic) should be considered at least possibly related to the study.

6.5 How do we determine if an AE is unexpected?

Site investigators should use their clinical judgment when determining if an AE is unexpected. Any incident, experience or outcome that meets ALL of the following criteria is defined as unexpected:

- Unexpected in nature, severity or frequency (i.e., not described in study-related documents such as the ethics-committee approved protocol or Informed Consent Form, etc.);
- Related or possibly related to participating in the research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the treatment involved in the research); and
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic or social harm).

6.6 Which forms should be completed if a participant dies?

If a participant dies, one of a **Local Recurrence Form (Form 12)**, a **Systemic Recurrence Form (Form 13)** or an **Adverse Event Form (Form 16)** should be completed depending on the cause of death. Please select either the pathological diagnosis or AE code that most closely fits the cause of death, and select *'Fatal'* as the outcome of the study event (Q9 on the **Local Recurrence Form (Form 12)**, Q9 on the **Systemic Recurrence Form (Form 13)** or Q6 on the **Adverse Event Form (Form 16)**). Please also complete an **Early Withdrawal Form (Form 24)** and select *'Death'* for Q1 as the reason for early withdrawal. Please note that the date of early withdrawal from the study should be the participant's date of death.

6.7 What should be done if an AE is not yet resolved?

If an AE has not yet resolved, select *'Ongoing'* for the outcome of the event (Q9 on the **Local Recurrence Form (Form 12)**, Q9 on the **Systemic Recurrence Form (Form 13)** or Q6 on the **Adverse Event Form (Form 16)**) and leave the date resolved blank. The study database will automatically generate a query as a reminder to update the form once the event has resolved.

6.8 What should be done if an AE never resolves?

If an AE has not resolved by the time of a participant's 60M post-intervention phase visit, select *'Unresolved'* at the time of *'Study Exit'* for the outcome of the event (Q9 on the **Local Recurrence Form (Form 12)**, Q9 on the **Systemic Recurrence Form (Form 13)** or Q6 on the **Adverse Event Form (Form 16)**). If the AE has not resolved by the time of a participant's death, select *'Unresolved'* at the time of *'Death'* for the outcome of the event.

6.9 Are clinic visits while the participant is in hospital considered protocol deviations?

If a participant is hospitalized due to a local recurrence, systemic recurrence, or other adverse event, please complete the applicable form. For any additional visits made by the surgical oncologist, please complete an **Unscheduled Clinic Visit Form (Form 11)** and **Protocol Deviation Form (Form 19).**