CHAPTER 22
ADVERSE EVENTS

Study Documents Referred to in this Chapter

- Adverse Event Form
- Adverse Event Evaluation Form
- Outcomes Event Questionnaire
- Other Health Related Events Questionnaire

CHAPTER 22
ADVERSE EVENTS

22.1 OVERVIEW

The timely and complete reporting of adverse events (AEs), especially those that are serious, unexpected, or that occur while a participant is under the supervision of study related personnel, is a critical requirement for the protection of human subjects in the LIFE trial. While non-serious and expected minor AEs are captured through structured interviews with masked assessors every 6 months, AEs that have potential implications for participant safety require individual event reporting as described in this chapter.

Individually reported AEs will be defined as events that fall into at least one of the following categories:

1) serious adverse events (SAEs),
2) unexpected AEs, and
3) AE that occurs while a participant is under the supervision of study related personnel.

AEs are captured on all participants who have provided verbal consent at telephone screen. Unmasked study personnel at each site will take primary responsibility for reporting adverse events to their site's Medical Safety Officer (MSO). Masked assessors will take responsibility for collecting information on study outcomes at the regular clinic or phone assessment visits that may also be reported as AEs.

Study-wide reporting of AEs to the Administrative Coordinating Center (ACC), the Data Safety Monitoring Board (DSMB), the National Institute on Aging (NIA), and the field centers Institutional Review Boards (IRBs) is mediated through the central database system in conjunction with the Data Management, Analysis, and Quality Control (DMAQC) Committee guidelines. The DMAQC provides reports of all adverse events that occur at all study sites to the MSO, Study Physician, and other unmasked personnel at each field center.

Each field center takes responsibility for reporting AEs to their own local IRB according to local policies. This may include AEs as defined for purposes of the LIFE study as well as reportable events as defined by each field center's local IRB guidelines.

The LIFE DSMB reviews and approves the LIFE study definitions of AEs and is involved in regular monitoring of the AE reporting system. On a regular and as needed basis, the DSMB will assess AEs for the implications for the continuation of the study and/or modification of the consent form.

22.2 DEFINITIONS

22.2.1. Medical Safety Personnel

Each Field Center appoints a Medical Safety Officer (MSO) and a Study Physician.

Medical Safety Officer (MSO): The required qualifications for the MSO are professional training and active licensure as a Registered Nurse, Nurse Practitioner, Physician Assistant, or Physician. The MSO is responsible for reviewing all potential AEs reported from any source at their Center and assuring accurate and timely reports to the local IRB and Administrative Coordinating Center. The MSO works closely with the research staff, including the masked and unmasked staff, and the Medical Safety Committee to evaluate all reported AEs for 1) possible Severe Adverse Events (SAEs), 2) determination of unexpected and unfavorable AEs and 3) the need for medical records. The MSO is expected to discuss all possible SAEs with the Study Physician.

Study Physician: The required qualification for the Study Physician is an active medical license in the same state as the Field Center. The Study Physician is available by telephone for consultation with study personnel at all times that the participants are physically at the field center intervention or assessment sites. The Study Physician is responsible for direct involvement in AEs requiring immediate notification of the IRB and Administrative Coordinating Center (see section 22.1 above), overseeing the work of the MSO and making a final determination of relationship of all SAEs to the intervention or assessment procedures, and the safety of the participant to continue his/her participation. The Study Physician may delegate responsibilities related to immediate notification to a "covering" physician. At certain Field Centers, the MSO and the Study Physician could be the same person.

22.2.2 Adverse Events

For the purposes of the LIFE study, "The NIH Guide: Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multi-center Trials, 1999" is used as the standard by which AEs are defined. In this document AEs are defined as unanticipated problems involving risks to study participants and others. For additional clarity and ease of reporting, the following section describes event categories which are considered "reportable" LIFE study AEs.

Some events are clearly reportable because they meet the definitions provided below. Some are clearly not reportable, because they meet the definitions for non-serious and/or expected adverse events, also defined below. However, non-serious and/or expected adverse events are considered reportable in some cases, as described below. Because our older population has numerous types of health events, some cannot be clearly defined, as reportable or not, in advance. In this case, the event should be discussed with the MSO and/or study physician to determine if it should be reported.

"Reportable" LIFE Adverse Events

Some reportable events may involve more than one of these criteria. When multiple events occur close together in time, such as within a few days, they may be related. Events are considered related if there is considered to be a shared or common underlying pathophysiological cause.

1. SERIOUS ADVERSE EVENT (SAE)

Reportable SAEs are defined as follows:

A. Death
B. Inpatient hospitalization
C. Emergency Room or Urgent Care Visit
D. Fracture
E. Outpatient surgery- Procedures that do not require general anesthesia with intubation are not considered to be reportable.
F. Life threatening illness or accident
G. Permanent disability or incapacity
H. Abnormal laboratory or diagnostic test result requiring immediate medical attention
I. Other serious illness that might have resulted in an SAE without aggressive medical attention
J. Restricted activity that led to an inability to leave the home for at least one week

Restricted activity that led to an inability to leave the home for at least one week

Some events are not considered to present a significant health risk to the participant and are NOT REPORTED BY UNMASKED PERSONNEL; they will be regularly reported by masked personnel at semi-annual follow up assessment visits. These events may be the expected mild effects of the intervention that have been listed in the consent form. In general, they have no long term consequences for change in prognosis or function. However, if these events lead to an inability to leave the home for at least one week (7 consecutive days), they are considered serious and must be reported.

Some examples of common symptoms that are reportable if they restrict activity for at least ONE WEEK are:

- Dizziness
- Muscle or joint aching
- Muscle or joint stiffness
- Fatigue
- Foot pain
- Foot ulcer
- Back pain

- Fainting loss of consciousness
- Shortness of breath or asthma
- Abnormal heart rhythm
- Fall

Some examples of events that are common in older persons and are unlikely to present a health risk include other system symptoms unrelated to physical activity that cause restricted activity for at least ONE WEEK and are **NOT** reportable as individual AE events are:

- sleep disturbance
- appetite disturbance
- tinnitus
- cough
- heartburn
- constipation or diarrhea
- nocturia
- rashes

2. UNEXPECTED ADVERSE EVENT

Unexpected AEs are defined as "medical events that are experienced by study participants that are reported to, or witnessed by, study staff but do not commonly occur in the LIFE study population and are not listed in the informed consent form in the 'Risks' section or in the LIFE study protocol (Section 8.5 Adverse Events)."

Reportable unexpected adverse events should have a potential relationship to study procedures and activities. In other words, if the unexpected adverse event is not potentially related to the study procedures or activities it does not have to be reported.

The study personnel at the Field Center site should consult with their study physician and their MSO in determining whether or not an event is unexpected and reportable. The medical and scientific judgment of the study physician and the Field Center principal investigator should be exercised in deciding whether an occurrence should be reported. In addition, difficulty determining whether or not an event is unexpected and/or attributable to the intervention should be addressed by the Medical Safety Committee, who will determine if the event is to be reported.

3. ADVERSE EVENT THAT OCCURS WHILE UNDER THE SUPERVISION STUDY RELATED PERSONNEL OR GUIDANCE OF THE STUDY

An adverse event that occurs while the participant is under the supervision of study related personnel can occur on site (during an intervention or assessment

visit) and off site (if the study site offers supervision during transportation or during off site activities such as educational programs in the SA arm).

The 400 meter walk test has special safety precautions and reporting requirements. If the participant has symptoms or vital sign abnormalities that lasts for more than two minutes after stopping the exercise it is reportable. If the symptoms or vital sign abnormality are resolving, then the event is not reportable but the participant's provider may still be notified.

An event that occurs during intervention is one that occurs during activities performed by the participant as instructed by the study intervention protocol. Any activities that are performed because the study recommended them as part of the intervention are included. Some of these activities may occur on the physical premises of the study site, such as the exercise or education area. Some study related intervention activities may occur in other locations, such as independent walking bouts in the PA arm at home or group outings in the SA arm.

An AE that occurs under the supervision/guidance of study related personnel is reportable if it results in:

- Any criteria for SAE as defined above
- Requiring active intervention by research staff to reduce potential harm (e.g. intervention to address hypoglycemia),
- Chest pain for more than two minutes after stopping exercise, or
- Dyspnea for more than two minutes after stopping exercise, or
- Vital signs out of range (systolic BP≥ 250 or diastolic ≥ 115, HR $\geq$ 120 or $\leq$ 45) for more than two minutes after stopping exercise.
- A fall during study recommended activity
- A symptom or illness that developed and required medical management or attention.

The study personnel at the site should consult with their study physician and their MSO in determining whether or not an event meets the definition of a reportable event. The medical and scientific judgment of the study physician and the Field Center principal investigator should be exercised in deciding whether an occurrence should be reported. In addition, difficulty determining whether or not an event meets the definition of a reportable event should be addressed by the Medical Safety Committee who will determine if the event is reportable.

22.2.3 Adverse Event Reporting System and Timelines

Responsibility for reporting AEs starts with first verbal consent at telephone screening. Thus adverse events that occur prior to randomization, but after screening starts, are reportable, as are adverse events that occur after randomization. All AEs are recorded in the LIFE web-based data system by study staff at the Field Center where the participant is enrolled.

Non-serious and expected minor AEs are captured through biannual surveys by masked personnel, based on the Other Health Related Events Form, which are then tracked and reported by DMACQ. Since non-serious and expected minor adverse events are captured routinely through the biannual surveys, it is not necessary for unmasked staff to report them. Reportable AEs (SAEs, Unexpected and potentially related AEs, and AEs Under study supervision/guidance) are also captured biannually on the Outcome Event Questionnaire but are also reported by any research team member to become aware of the event, whether they are masked or unmasked. Therefore, reportable AEs are to be submitted at any time by anyone. I

The DMAQC is responsible for reporting study-defined AEs to the DSMB and the NIA by using the information entered in the LIFE web-based data system. Field Centers are responsible for reporting study-defined AEs to their respective IRBs according to local requirements in terms of timeline and format.

The first step in recording the occurrence of a Reportable AE is to complete the Adverse Event Form. A study staff member then enters the Adverse Event form into the LIFE database, and the information is forwarded to the MSO. The Adverse Event Evaluation form is then completed and signed by the MSO and Study Physician, and entered promptly into the study database. The MSO, Principal Investigator, and Study Physician should thoroughly review the events to ensure that they are appropriately classified.

To expedite the reporting of AEs, the Adverse Event Form should be entered into the database as quickly as possible. The LIFE study reporting schedule follows a time frame that reflects the severity of the AE. The AE Form and the Adverse Event Evaluation Form must both be entered according to the time frames and corresponding events as listed below:

1. **Within 24 hours of the site becoming aware of the AE**: Death
2. **Within 10 working days:** All other Reportable Adverse Events

In instances involving death, the initial report of the event must be completed within 24 hours of the site becoming aware of the event, and sites should make every effort to obtain some clinically relevant follow-up information within one month. The main purpose of the one month goal is to be able to begin to assess potential relationship to the trial. Oral information from providers is acceptable. Information from family is welcome but must be tempered by sensitivity to the situation. Preliminary medical records by fax may be helpful since final discharge records may not be available for some weeks.

22.3 PARTICIPANT EDUCATION ABOUT ADVERSE EVENTS

Potential AEs for study related activities and interventions are explained to each participant by trained study personnel during the informed consent process. Participants should be educated about the role of masking and the potential that

some health events will need to be reported more than once to masked and unmasked staff. Each participant is instructed to report the occurrence of an AE at scheduled data collection times (scheduled outcome questionnaires) to masked assessors. Participants also have access to unmasked study clinic personnel at other times to report AEs or concerns about the safety of participating in the LIFE study.

22.4 TEMPORARY INTERRUPTION OR EARLY DISCONTINUATION OF STUDY PROCEDURES

A number of AEs may result in a temporary interruption or early discontinuation of the trial assessments and interventions or components of these assessments and interventions. Please refer to the appropriate MOP chapter(s) for specific instructions on stopping criteria during screening, intervention, and follow-up assessment procedures. All assessors and interventionists are trained to recognize and respond per protocol to these events.

After such AEs occur, a participant may resume the trial intervention when the study practitioner and the primary care provider agree that it is appropriate. For some problems that require temporary cessation of therapy but are mild and not life threatening, the investigator and participant may agree to reintroduce the participant to the study intervention. At any point a participant may be withdrawn from the study intervention for health-related reasons or AEs.

If the participant has a major illness (broken arm, etc.) that does not interfere with the assigned study intervention, the study personnel may need to contact the primary care provider to determine whether it is safe for the participant to continue with the intervention. If the participant has a major illness that interferes with the assigned study intervention or protocol, the study physician determines whether or not it is medically safe to continue the study intervention in consultation with the primary care provider.

If a participant misses an intervention visit, successful aging or physical activity, for reasons that are not serious, the missed visit is recorded only on the group attendance record.

22.5 MEDICAL PROBLEMS

Medical problems identified during the study should be referred to the participant's health care provider. Medical problems that occur at the field center should be managed as first aid and immediate care, as described in Chapter 21.

22.6 DATA SAFETY MONITORING BOARD

An external Data Safety Monitoring Board (DSMB) has been established to periodically review study data for the occurrence of SAEs, safety concerns,

and outcomes of interest. This board is asked to address serious adverse effects and the risk to benefit profile for all study participants. Guidelines for early discontinuation of the study and for recommendations for changes in the study protocol are defined for use by the DSMB. The Board reviews these guidelines and makes recommendations for early discontinuation of any component of the trial based on regular review of all pertinent study data. The Administrative Coordinating Center and DMAQC is responsible for analyzing interim data and preparing data safety monitoring reports that the committee will review. These reports will include data on all SAEs and study outcomes for all study participants. An annual report from the DSMB is sent to the Field Centers to update local IRBs.

22.7 OVERVIEW OF REPORTING SYSTEM FOR ADVERSE EVENTS VS. THE SYSTEMATIC COLLECTION OF OUTCOMES

Since participants randomized to the Physical Activity Intervention arm have more frequent contact with study staff than the participants in the Successful Aging Intervention arm do, there is a greater opportunity for the Physical Activity participants to report AEs. In addition, the unmasked staff members may be biased in their reporting of AEs. Therefore, the LIFE trial makes a distinction between the AEs reported to or by unmasked study personnel and the AEs reported to masked study personnel.

In order to maintain this distinction, the LIFE study has developed a parallel reporting system that allows unmasked staff members to report all AEs as they become aware of them, while also allowing masked staff (interviewers and assessors) to remain unbiased while they query the participants on a preset schedule in order to ascertain study outcomes that are also considered AEs. Outcomes assessment depends on objective, unbiased reporting facilitated by a masked staff member (not aware of intervention group assignment) so that both groups are evaluated equally for the occurrence of primary and secondary outcomes. To accomplish this end, the Outcomes Questionnaire is administered to each participant routinely every six months.

To prevent bias, the unmasked interventionists and other unmasked staff reporting AEs <u>are not</u>, at any time, to communicate information regarding these events to masked study assessment personnel responsible for collecting outcome data at scheduled data collection times.

The following paragraphs delineate the responsibilities and actions related to event reporting for various members of the research team, including masked assessors (as part of outcome assessment or for onsite events), unmasked staff and interventionists, MSOs and Study Physicians.

22.7.1 REPORTING OF ADVERSE EVENTS IDENTIFIED AT THE TIME OF SCHEDULED ASSESSMENTS

REPORTING OF ADVERSE EVENTS CAPTURED ON OUTCOME EVENTS QUESTIONNAIRE FORM BY MASKED PERSONNEL (FIGURE 22.1)

This process provides for timely central safety monitoring of all serious adverse events that are reported to masked interviewers. The main goal of this process is to maintain masking for the individual who has heard of a serious adverse event through outcome events interview during a scheduled follow-up assessment visit or by phone contact. Therefore this individual must complete an Adverse Event Form so that unmasked personnel can follow up and get information about the event.

1. At a scheduled follow-up assessment visit, the scheduled data collection time, a masked study assessment staff member will complete the Outcome Event Questionnaire and the Other Health Related Events Form.

    a. Reportable Adverse Events captured from the Outcome Event Questionnaire Form are noted on the form.

    b. Reportable Events from the Other Health Related Events Form are a Yes response to any sub-question (Did this symptom result in an ability to leave home for at least seven days?) and/or possibly Q11 (if determined to fit the adverse event definition).

2. If a Reportable AE is identified on the Outcome Events Questionnaire or the Other Health Related Events Form, the masked staff will complete an Adverse Event Form for each reportable AE. If more than one adverse event occurred on the same date and they are not considered to have the same underlying pathophysiological cause, each must have a separate Adverse Event Form. (All Outcomes will be tracked with their respective Outcomes Report Form (see Chapter 20).

3. Once completed, the form must be entered in the web-based data entry system within the required time frame as follows.

    a. **Within 24 hours of the site becoming aware of the AE**: Death
    b. **Within 10 working days:** For all other Reportable Adverse Events

4. The Adverse Event Form is then forwarded to the MSO who will have access to all Adverse Event Forms that have been entered and can determine whether an AE has already been reported and complete the Adverse Event Evaluation Form for any event that had not previously been reported.

REPORTING OF ADVERSE EVENTS THAT OCCUR WHILE UNDER SUPERVISION OF STUDY RELATED PERSONNEL

The masked assessor should complete an Adverse Event Form at follow up assessments under the following circumstances:

1) If the masked assessor observes a participant experiencing an adverse event such as those listed in Section 22.2.2. and / or
2) If the masked assessor hears about an adverse event that may be reportable from the participant or significant other that is not included in the Outcome Events Questionnaire or Other Health Related Events form. (If more than one adverse event occurred on the same date, but are not considered to have the same underlying pathophysiological cause, each must have a separate Adverse Event Form.)

    1. Once the Adverse Event Form is completed, it must be entered in the web-based data entry system within the required time frame as follows:
        a. **Within 24 hours of the site becoming aware of the AE**: Death
        b. **Within 10 working days:** For all other Reportable Adverse Events

    2. The Adverse Event Form is then forwarded to the MSO who will have access to all Adverse Event Forms that have been entered and can determine whether an AE has already been reported and complete the Adverse Event Evaluation Form for any event that had not previously been reported.

22.7.2 REPORTING OF ADVERSE EVENTS IN BETWEEN SCHEDULED ASSESSMENT VISITS (FIGURE 22.2)

AEs identified between scheduled assessment visits to either a masked or unmasked study personnel require the same timeliness as if reported at an assessment visit. This would include identification of an AE to a masked staff when on the phone scheduling the next assessment visit or during a reminder call. This would also include identification of an AE to an unmasked staff during an intervention session or at a missed session follow-up call.

REPORTING OF ADVERSE EVENTS BY MASKED OR UNMASKED STAFF

If a potentially reportable AE is detected by masked or unmasked staff in between scheduled assessment visits the staff should follow the steps outlined below. Note that unmasked staff includes interventionists and other site staff who are involved in transportation, scheduling or other project functions that require knowledge of randomization status. Interventionists should especially focus on reportable events during study related intervention activities (section 22.2.2).

Procedures for reporting adverse events by masked or unmasked staff:

1. Complete an Adverse Event Form for each AE identified (All adverse events occurring on the same date but do not have the same

underlying pathophysiological cause must have a separate Adverse Event Form).

2. Once completed, the form must be entered in the web-based data entry system within the required time frame as follows.
   a. **Within 24 hours of the site becoming aware of the AE**: Death
   b. **Within 10 working days:** For all other Reportable Adverse Events
3. The Adverse Event Form is then forwarded to the MSO who will have access to all Adverse Event Forms that have been entered and can determine whether an AE has already been reported and complete the Adverse Event Evaluation Form for any event that had not previously been reported.

22.7.3 ADVERSE EVENT EVALUATION

After the Adverse Event form has been completed and data entered, it is the responsibility of the MSO to complete the Adverse Event Evaluation Form.

1. The MSO will complete an Adverse Event Evaluation Form for each Adverse Event Form. The MSO should gather sufficient information to complete the data gathering/evaluation components of the Form, but is not required to routinely collect medical records.
   a. The MSO may request information by telephone from the participant, significant other, or their health care provider. And the MSO may seek medical records from a physician or care setting if needed.

2. The Adverse Event Evaluation Form is reviewed by the Study Physician who is responsible for making the determination about relatedness to the study (currently Section 3 of the Adverse Event Evaluation Form). If the event is potentially related to the study, the Study Physician must consider whether the event was listed in the protocol and consent and whether modifications to the protocol and consent should be considered.

3. The Adverse Event Evaluation Form is entered into the LIFE web-based data entry system.

4. Local IRB notification is a responsibility of the site and should be performed in accordance with local IRB requirements. (The LIFE DMACQ does NOT provide notices to site IRBs.)

5. The MSO and Study Physician should follow-up on on-going reportable adverse events and update the Adverse Event Evaluation Form until a final status has been determined for the event e.g.(recovered, ended in death, is still present, or status is unknown). Some reportable events may have a status of still present at the conclusion of the LIFE study. The frequency of follow up is determined by rate of change in the problem.
   a. Recovered is an event that has ended.

b. Still Present is an event that is ongoing or where residual effects of the event persists.
c. Unknown should be used when the site is unable to make contact with the participant or proxy.

22.8 Adverse Event Reporting Forms

See section 22.7 for instructions regarding the process for reporting Adverse Events by masked and unmasked study personnel at and in between study assessment visits.

22.8.1 Instructions for Completion of Adverse Event Form

As with all LIFE forms, certain information is standardized. Always remember to affix the participant's ID label and enter the participant's acrostic and the date the form was completed. The date of form completion should coincide with the date of notification.

To complete the Adverse Event Form:

1. Record the date of the event, or events if more than one occurred on the same day. Note: All adverse events occurring on the same date but that do not have the same underlying pathophysiological cause must have a separate Adverse Event Form.
2. Indicate who reported the event to the field center staff member. If other, please specify the source of the report.
3. Indicate whether the participant was randomized or not.
4. Indicate the event description as one or more item listed in A-L.

For tracking purposes, all AEs will be assigned an Event Number by the data entry system which will be recorded on the Adverse Event Evaluation Form.

22.8.2 Instructions for Completion of the Adverse Event Evaluation Form

The Adverse Event Evaluation Form is completed by the MSO and study physician, after receiving the Adverse Event Form from the masked or unmasked study personnel or after completing the Adverse Event Form. One Adverse Event Evaluation Form is completed for all events reported on an Adverse Event Form.

After verifying that the AE was not previously reported, the MSO may contact the participant or proxy to gather further information on an AE and may obtain some medical records if needed to make a determination of relatedness to the study. To ensure the appropriate classification of events, the Field Center Principal Investigator (if unmasked) and/or Field Center Study Physician should thoroughly review the form prior to entering the data from the Adverse Event Evaluation Form into the web-based data entry system.

As with all LIFE forms, certain information is standardized. Always remember to affix the participant's ID label and enter the participant's acrostic and the date the form was completed.

To complete the Adverse Event Evaluation Form:

1. Record the Event Number assigned to the AE by the data entry system. (This is pre-filled on the data entry screen)
2. Record the date the event occurred. (This is pre-filled on the data entry screen)

Q#1 Record the number of events that the participant had for the date recorded.
Q#2 Indicate the source of the Adverse Event form
Q#3 Indicate whether study participation has changed.
Q#4 Indicate where the event occurred.

Section 1
Q# 5 – Review the event and determine whether the participant experienced any of the listed SAEs. If a death, notify the Field Center Principal Investigator and the Field Center Study Physician immediately, and continue.

Q# 6 – Determine if this is an unexpected event:
Unexpected AEs are medical events that do not commonly occur in the LIFE study population, that are not listed in the consent form under the Risks section or in the LIFE study protocol under the Adverse Event section and are potentially related to the study.

Q#7 – Determine if this is an event that occurred under the supervision of study related personnel. This is defined as an SAE or other adverse event that occurred under the supervision or guidance of the study.

The adverse event must receive at least one 'Yes' response in Section to be reportable. If all responses in this Section are 'No', skip to Section 8.

Section 2
Q#8 – Report if the participant is in the screening phase or the intervention phase of the study. If in screening phase complete Q8a.
Q#8a – Indicate whether exclusion criteria was reviewed prior to the SAE.

Q#9 – Determine whether the event was witnessed on-site by the study personnel.

Section 3 – This section is to be completed by the Study Physician
Q#10 – Provide the four digit code for the primary organ system involved in the SAE using the attached coding system (Chapter 22 Appendix 1). The primary system involved should be considered the organ system related to the primary discharge code for a hospitalization or Emergency Room visit. For an event only related to outpatient care, the study physician may use his or her judgment to assign the primary organ system but should emphasize the main symptom, event or medical finding that led to the determination of the event.

Q#10a- Using the NCI Safety Profiler, version 4.0 (found at http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx), determine the adverse event term, category, and MedDRA code for the primary diagnosis of the reportable adverse event. If applicable, the adverse event term, category, and MedDRA code can also be recorded for up to two (2) secondary diagnoses.

Q#11 – If determined to be an SAE, an unexpected event that is potentially related to the study, or an adverse event that occurred while under the supervision of study related personnel, indicate whether the event was definitely, probably, possibly, unknown or unrelated to the assessment or intervention procedures? Definitions of these terms are:
a. Definite - Temporal pattern + Known or expected AE response pattern + Confirmed by stopping the intervention + Reappearance of AE on re-challenge
b. Probable - Temporal pattern + Known or expected AE response pattern + Confirmed by stopping the intervention + Could not be explained by participant's clinical state
c. Possible - Temporal pattern + Known or expected AE response pattern + Could have been produced by a number of other factors
d. Unknown - Relationship for which no evaluation can be made.
e. Not related - AE for which sufficient information exists to indicate that the cause is unrelated to the study intervention

If the event is determined to be definitely, probably or possibly related to the assessment or intervention procedures, continue with Section 4. If not, go to Section 5.

Section 4
Q#12 – Review protocol for listing of this event and determine if adverse event listed in the protocol. If not listed, specify event.

Q#13 – Review informed consent and determine if adverse event is listed in the informed consent. If not listed, specify event.

Q#14 – Indicate whether a change in the protocol should be considered to reduce or eliminate risk to subjects. If not, provide a brief rationale for not considering a protocol change.

Q#15 – Indicate whether a change in the informed consent documents should be considered to better inform and protect the rights and welfare of study subjects. If not, please provide a brief rationale for not considering an informed consent change.

Section 5 – Adverse Events Summary
Information from Section 5 will be compiled with other pertinent information into an Adverse Event report that will be available to all Field Center sites, the NIA, and the DSMB.

Q#16 – Indicate whether the participant received immediate medical treatment for the AE.
Q#17 – List medications that the participant was on at the time of the AE.
Q#18 – List any other medical problems that the participant was having at the time of the AE.
Q#19 – Provide a brief description of the event. When providing a description of the event, DO NOT use abbreviations.
Q#20- If the event is ongoing, complete Section 6 and the remainder of the form as follow- up and final status become available. If the event is has ended, complete Sections 8 & 9.

Section 6 - Signatures

1. For initial reporting of adverse events, the MSO and/or Study Physician who reviewed the Adverse Event Evaluation form should sign and date the form.

22.8.3 Follow-up for SAEs, Unexpected Adverse Events and Adverse Events that Occur While Under the Supervision of Study Related Personnel on the Adverse Event Evaluation Form

Follow-up action taken by the MSO and the Study Physician for each SAE and reportable adverse event is recorded on the Adverse Event Evaluation Form as information becomes available. The frequency of follow up is determined by rate of change in the problem. This information is data entered into the LIFE web-based data system as the follow-up is ongoing and until the event has ended e.g. it has resolved or ended in death.

Section 7- Adverse Events Follow Up

1. Assign each follow-up a sequential number and indicate the date of follow-up.
2. Indicate in the space provided whether the event in ongoing.
3. Indicate whether the participant obtained additional treatment during the follow-up.
4. Provide a description of current follow-up of the event. When providing a description of the event in the NOTES area, DO NOT use abbreviations.

If there are more than 2 follow-ups to an event (and the event is ongoing) use additional copies of page 5 to record the event follow-up.

Once the event is no longer ongoing leave the ‘Ongoing’ box blank and complete Section 8.

Section 8 – Final Status

1. Once a final status for the event has been determined, indicate the status as Recovered, Still Present, Death, or Unknown and enter the Closed

Date. Some reportable events may continue to be ongoing for the duration of the study, and therefore will have a status of Still Present and be closed at the conclusion of the LIFE study.

Recovered: An AE/SAE that is an acute condition can be closed when the condition is stabilized (or is on a predictable path to recovery) and it is expected that participant will return to baseline status (with or without sequelae) and should be labeled in Section 8 as “recovered”.

Death: An AE/SAE that is the death of the participant or an SAE that ended in death (ex. SAE was a hospitalization and participant died before they could be discharged) should be labeled in Section 8 as “death”.

Still Present: An AE/SAE that is a chronic condition can be closed when the condition has reached a stable plateau and should be labeled in Section 8 as “still present”. Note: A new adverse event should be opened when the condition reaches a new step in its progression.

Unknown: An AE/SAE that is opened and the site is unable to locate the participant, unable to locate documentation regarding the condition, or does not meet the criteria above should be labeled in Section 8 as “unknown”.

Section 9 – Signatures (for final reports)

2. Once the status has been recorded in Section 8, the MSO and Study Physician should sign and date the form.

Figure 22.1: Process for Outcomes Collection and Adverse Event Reporting at an Assessment Visit

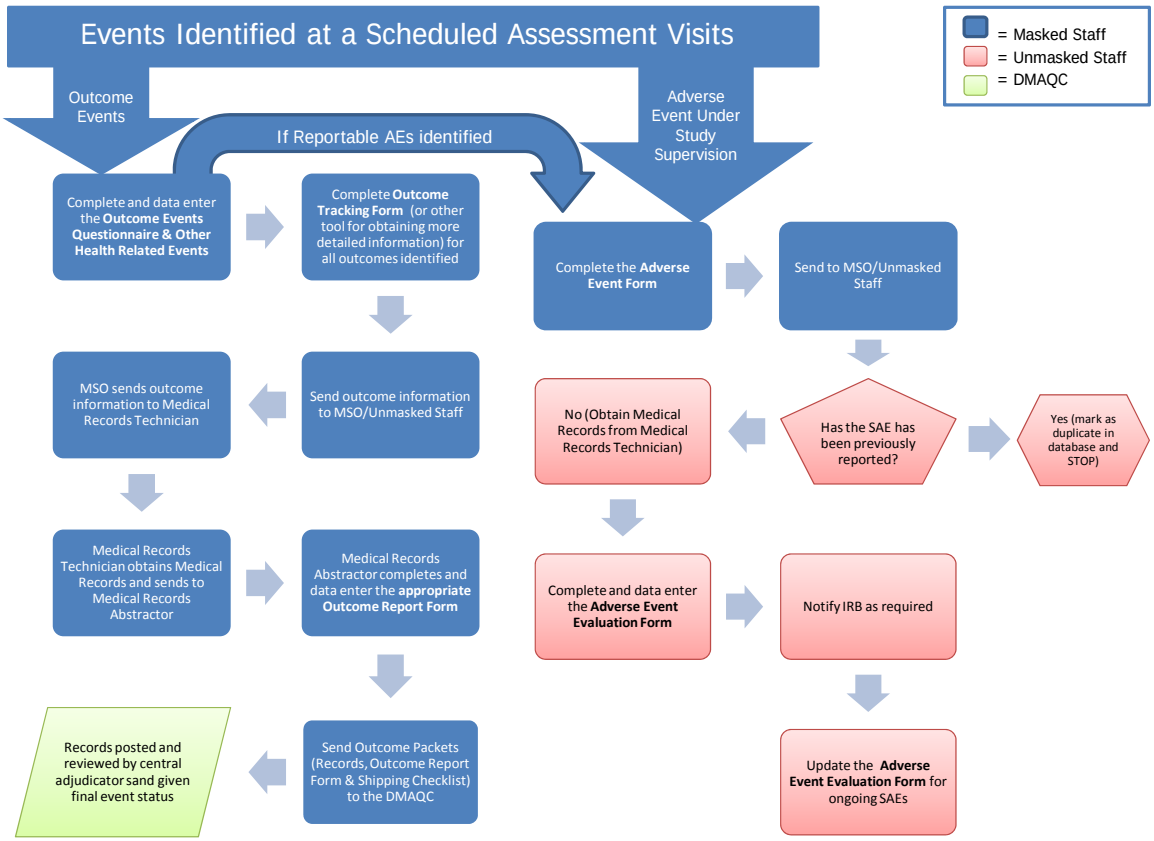
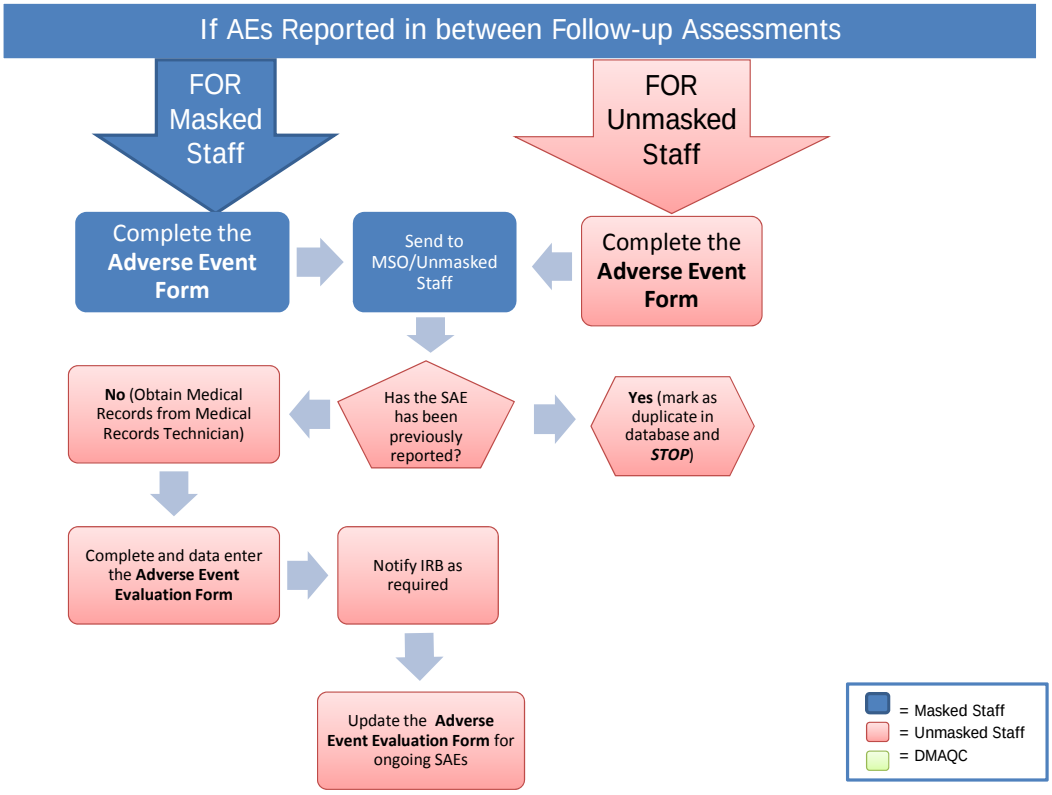


Figure 22.2 Process for Report of Adverse Events in between Assessment Visits (Masked & Unmasked Staff)



Appendix 1 - Primary Organ System Codes

Skin and appendages disorders	0100
Musculo-skeletal system disorders	0200
Collagen disorders	0300
Central & peripheral nervous system disorders	0410
Autonomic nervous system disorders	0420
Vision disorders	0431
Hearing and vestibular disorders	0432
Special senses other, disorders	0433
Psychiatric disorders	0500
Gastro-intestinal system disorders	0600
Liver and biliary system disorders	0700
Metabolic and nutritional disorders	0800
Endocrine disorders	0900
Cardiovascular disorders, general	1010
Myo-, endo-, pericardial & valve disorders	1020
Heart rate and rhythm disorders	1030
Vascular (extracardiac) disorders	1040
Respiratory system disorders	1100
Red blood cell disorders	1210
White cell and RES* disorders	1220
Platelet, bleeding & clotting disorders	1230
Urinary system disorders	1300
Reproductive disorders, male	1410
Reproductive disorders, female	1420
Foetal disorders	1500
Neonatal and infancy disorders	1600
Neoplasms	1700
Body as a whole - general disorders	1810
Application site disorders	1820
Resistance mechanism disorders	1830
Secondary terms - events	2000
Poison specific terms	2100

* RES - Reticuloendothelial system