CHAPTER 22

ADVERSE EVENTS

Study Documents Referred to in this Chapter

- Adverse Event
- Event Evaluation
- Serious Adverse Event Follow-up
- Health Event Interview
- Event Tracking

CHAPTER 22
ADVERSE EVENTS

22.1 OVERVIEW

The timely and complete reporting of severe and unexpected adverse events is a critical requirement for the protection of human subjects in the LIFE trial. This study tracks the occurrence of all serious adverse events, unexpected adverse events, and any unfavorable medical events that occur at the intervention or assessment site (see definitions below.) Adverse events are captured on all participants who have signed the informed consent form at Screening Visit 1.

Unmasked study personnel at each site will take primary responsibility for reporting adverse events to their site's Medical Safety Officer. 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 adverse events.

Study-wide reporting of adverse events to the Administrative Coordinating Center, the Data Safety Monitoring Board (DSMB), the National Institute on Aging (NIA), and the field center Institutional Review Boards (IRBs) is mediated through the central database system in conjunction with the Data Management and Quality Control Committee guidelines. The Administrative Coordinating Center provides reports of all adverse events that occur at all study sites to the Medical Safety Officer, Study Physician, and other designated personnel at each field center. Each field center takes responsibility for reporting adverse events to their own local IRB.

The LIFE DSMB reviews and approves the LIFE study definitions of adverse events and is involved in regular monitoring of the adverse events reporting system. On a regular and as needed basis, the DSMB will assess adverse events 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: The required qualifications for the MSO are professional training and active licensure as a Registered Nurse or Physician Assistant. The MSO is responsible for reviewing all potential adverse events 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 Adverse Events (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 adverse events 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 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 adverse events are defined. In this document adverse events are defined as unanticipated problems involving risks to study participants and others. For additional clarity and ease of reporting, the LIFE study divides adverse events into several categories of occurrences: Serious Adverse Events, unexpected adverse events, and unfavorable medical events that occur at the intervention or assessment site.

SERIOUS ADVERSE EVENTS

Serious adverse events are defined as follows:

1. Death
2. A life threatening event.
3. An inpatient hospitalization
4. A permanent disability or incapacity.
5. A clinically significant laboratory or clinical test result
6. Any other event that, in opinion of the Field Center principal investigator or study physician, might have resulted in a serious adverse event if medical intervention had not been initiated

UNEXPECTED ADVERSE EVENTS

Unexpected adverse events are defined as medical events that are experienced by study participants that are reported to or witnessed by study staff but that do not commonly occur in the LIFE study population and that are not listed in the informed consent form in the Risks section. The study personnel at the site should consult with their study physician and their Medical Safety Officer in determining whether or not an event is unexpected. 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, any difficulty the site personnel have in determining whether or not an event is unexpected should be addressed to Medical Safety Committee for further clarification.

UNFAVORABLE EVENTS THAT OCCUR AT THE FIELD CENTER INTERVENTION OR ASSESSMENT SITE

An unfavorable medical event that occurs while the participant is at the intervention or assessment field center site is defined as an event that requires that the participant obtain attention from a medical professional. The study personnel at the site should consult with their study physician and their Medical Safety Officer in determining whether or not an event meets the definition of unfavorable. 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, any difficulty the site personnel have in determining whether or not an event meets the definition of unfavorable should be addressed to the Medical Safety Committee for further clarification.

All unfavorable medical events that occur at the field center assessment or intervention site should be recorded on the Adverse Event Form and data entered using the web-based data entry system. The Adverse Event Form should be forwarded immediately to the Medical Safety Officer. These events are reported whether or not they meet the additional criteria for serious or unexpected events. A check box on the Adverse Event Form is provided to identify these events that occur at the assessment or intervention site.

LIFE investigators and staff should understand the difference between a safety procedure that leads to a need to stop testing and/or notify a participant's physician and a reportable adverse event. A reportable adverse event requires the presence of persistent symptoms or abnormal vital signs due to a study activity. For example, if a participant has shortness of breath or heart rate

outside of safety parameters during or after a 400 meter walk, the event is reportable if the symptoms or vital sign abnormality is not improving after two minutes of post exercise rest. If the symptoms or vital sign abnormality are resolving, then the event is not reportable but the participant's provider may still be notified. Similarly, an asymptomatic abnormal finding during screening, such as undiagnosed atrial fibrillation or sinus bradycardia, should be reported to the participant's physician but is not a reportable adverse event.

22.2.3 Adverse Event Reporting System and Timelines

Responsibility for reporting adverse events starts with first on-site contact with a potential participant. Thus on-site events that occur prior to randomization, but after screening starts, are reportable, as are events that occur after randomization. All events are recorded in the LIFE web-based data system by study staff at the site where the participant is enrolled. The Administrative Coordinating Center is responsible for reporting study-defined adverse events 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 adverse events to their respective IRBs according to local requirements in terms of timeline and format.

After the study staff member completes and enters the Adverse Event form into the LIFE database, the information is forwarded to the Medical Safety Officer. The Field Center Medical Safety Officer, Principal Investigator, and Study Physician should thoroughly review the Adverse Event form and any related information to ensure that the event is appropriately classified. The Event Evaluation form is then completed and signed by the Medical Safety Officer and Study Physician, and entered promptly into the study database.

These forms contain the information needed to expedite the reporting of adverse events and should be entered into the database as quickly as possible. Therefore, the LIFE study reporting schedule follows a time frame that reflects the severity of the adverse event. The MSO must complete and enter the Event

Evaluation Form according to the time frames and corresponding events as listed below:

1. **Within 24 hours of the site becoming aware of the adverse event**: For any Serious Adverse Event which results in death or for any unfavorable event that occurs at the intervention or assessment site which results in the need for immediate hospitalization or emergency medical care. As an additional measure to ensure timely notification of these events to the Administrative Coordinating Center, the Field Center Medical Safety Officer is to contact _L.C._ by phone at ___to notify her that a serious adverse event of this type has occurred and that the appropriate forms have been entered into the study database.
2. **Within 48 hours**: For all other Serious Adverse Events
3. **Within 10 working days:** For events that are unexpected but not serious, or for any unfavorable events that occur at the intervention or assessment site but do not result in the need for serious medical attention.

22.3 PARTICIPANT EDUCATION ABOUT ADVERSE EVENTS

Potential adverse events for study related activities and interventions are explained to each participant by trained study personnel during the informed consent process. Each participant is instructed to report the occurrence of an adverse event at scheduled data collection times (scheduled clinical exams or phone interviews) to masked assessors. Participants also have access to unmasked study clinic personnel at other times to report adverse events or concerns about the safety of participating in the LIFE study.

22.4 TEMPORARY INTERRUPTION OR EARLY DISCONTINUATION OF STUDY PROCEDURES

A number of adverse events 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 adverse events 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 adverse events

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 for successful aging or physical activity for reasons that are not serious, the missed visit is recorded only on the appropriate missed visit form. If the reason for the missed visit meets criteria for a serious or unexpected adverse event, an Adverse Event form is completed and forwarded to the Medical Safety Officer.

22.5 MEDICAL PROBLEMS

Medical problems identified during the study should be referred to the participant's health care provider. On center medical problems should be managed as first aid and immediate care only 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 serious adverse events, 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 Data Safety Monitoring Board. 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 is responsible for analyzing interim data and preparing data safety monitoring reports that the committee will review. These reports will include data on all serious adverse events and study outcomes for all study participants. An annual report from the DSMB is sent to the clinical centers to update local Institutional Review Boards.

22.7 ADVERSE EVENT REPORTING FORMS

22.7.1 Instructions for Completion of Adverse Event Form

This form is completed by unmasked study personnel. The only exception is when masked staff witnesses an adverse event at the assessment site during Screening Visit 1 or 2 or at the Follow up Assessment Visits. When providing a description of the event, DO NOT use abbreviations. 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.

1. Record the date of the event.

2. Record who reported the event to the field center staff member

3. Record if the participant was randomized

4. Record where the event occurred:

   a. Assessment site b. Intervention site c. Other

5. Nature of the problem or event:

   Study personnel will use free text narrative to report the details of the event

6. For reporting purposes, the event must to be categorized as one of the listed items a-q if applicable.

7. Report if participation in the study has been

   a. Modified b. Suspended c. Discontinued d. No Change

For tracking purposes, all adverse events are assigned an Event Number sequentially by the data entry system. After the Adverse Event form has been entered into the data entry system, record the Event Number in the boxes provided on the first page of the form.

22.7.2 Instructions for Completion of the Event Evaluation Form

This form is completed by the Safety Officer after notification from the masked or unmasked staff based on the Adverse Event or the Health Events Questionnaire. The Safety Officer may contact the participant or proxy to gather further information. To ensure the appropriate classification of events, the Field Center Principal investigator and/or Field Center Study Physician should thoroughly review the form prior to entering the data from the Event Evaluation form into the web-based data entry system. When providing a description of the event, DO NOT use abbreviations. 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.

Below is a list of questions and definitions found on the LIFE Event Evaluation form.

Record the Event Number from the online Adverse Event form.

Record the date the event occurred.

Record the end date of the event. If the event is ongoing, mark an X in the box provided.

Record the number of events that the participant had for the date recorded.

Record the source of the Adverse Event form

Briefly describe the event or update the description.

Question #1:

Review Criteria for Serious Adverse Event:

Has the participant experienced any of the following events?

A. Death

B. A life-threatening event

C. Inpatient hospitalization

D. Permanent disability or incapacity

E. A clinically significant laboratory or clinical test result

F. Any other event, that in the opinion of the Field Center principal investigator or study physician, that might have resulted in a serious adverse event if medical intervention had not been initiated

If, yes to any of the above questions, notify the Field Center principal investigator and the study physician, and go to the next page to continue with Question 4. If no to any of the above questions, go to Question 2.

Question # 2

Determine if this is an unexpected but not serious adverse event:

Unexpected adverse events are medical events that do not commonly occur in the LIFE study population and that are not listed in the consent form under the Risks section. If yes, go to the next page and continue with Question 4. If no, go to Question 3.

Question #3

Is this an unfavorable event that occurred at the assessment or intervention site?

An unfavorable medical event that occurs while the participant is at the intervention or assessment field center site is defined as an event that requires the participant to obtain attention from a medical professional. If yes, go to the next page and continue with Question 4. If no, stop here and enter form into LIFE database.

Questions #4-11 to be completed by the Study Physician.

Question #4

Report if the participant is in the screening phase or the intervention phase of the study.

Question #5

If determined to be an SAE, an unexpected event, or an unfavorable event, was the event 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

Question #6

Was the event witnessed on-site by the study personnel?

Question # 7

Has the participant experienced other intolerable side effects or symptoms and requested suspension or reduction of study?

Enter yes or no. It may be necessary to query the participant or proxy for the information. For example,

"Have you experience any other symptoms that have led you to request that you decrease or stop exercising?

Record the appropriate answer. If yes, specify what the side effect was and if participation in the study was discontinued. For example, participant reports severe weight bearing pain, and has stopped walking.

Question #8

If the event is determined to be definitely, probably or possibly related to the assessment or intervention procedures, was the adverse event listed in the protocol?

Review protocol for listing of this event.

If not listed, specify event

Question #9

If the event is determined to be definitely, probably or possibly related to the assessment or intervention procedures, was the adverse event listed in the informed consent?

If not listed, specify event

Question # 10

Should a change in the protocol be considered to reduce or eliminate risk to subjects?

If the event is determined to be definitely, probably or possibly related to the intervention, is there a protocol change indicated? If so, please provide a rationale.

Question # 11

Should a change in the informed consent documents be considered to better inform and protect the rights and welfare of study subjects?

If the SAE is determined to be definitely, probably or possibly related to the intervention, is there consent change indicated? If so, please provide a rationale.

Question # 12

Provide the four digit code for the primary organ system involved in the SAE using the attached coding system. 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.

Questions # 13-28

If, after careful review and evaluation of the event by the MSO, the site principal investigator, and the site study physician, it is determined that the event is serious and is definitely, probably, or possibly related to the intervention, the event occurred on the assessment or intervention site or the event was unexpected and definitely, probably or possibly related to the study, complete the Serious Adverse Event Abstract, Questions 13-28. The Serious Adverse Event Abstract is forwarded to all field center sites, the NIA, and the DSMB for review of the event.

The Medical Safety Officer and Study Physician should provide his/her name, signature, and date of review.

22.7.3 Instructions for Completing Adverse Event Follow-up Form

Follow-up action taken for each serious and reportable adverse event is recorded on this form. This form is completed by the Medical Safety Officer and Study Physician. When providing a description of the event, DO NOT use abbreviations.

Record the Event Number from the online Event Evaluation form.

Record the date of the event.

Record the end date of the event. If the event is ongoing, mark an X in the box provided.

22.8 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 do the participants in the Successful Aging Intervention arm, there is a greater opportunity for the Physical Activity participants to report adverse events. In addition, the unmasked staff members may be biased in their reporting of adverse events. Therefore, the LIFE trial makes a distinction between the adverse events reported to or by unmasked study personnel and the health events reported to masked study personnel.

In order to implement this distinction, the LIFE study has developed a parallel reporting system that allows unmasked staff members to report all adverse events as they become aware of them, while also maintaining unbiased staff of masked interviewers and assessors that query the participants on a preset schedule in order to ascertain study outcomes that are also health events (Figures 22.1, 22.2 and 22.3). The Medical Safety Officer reviews data from both reporting systems.

To prevent bias in the outcomes database, the unmasked interventionists and other staff reporting adverse events are not at any time to communicate information regarding these events to masked study assessment personnel responsible for collecting outcome data at scheduled data collection times.

Reporting of Adverse Events by Unmasked Staff (Figure 22.3)

The Adverse Event form is completed by an unmasked staff member (aware of intervention group assignment) as soon as the event is identified. Once completed, the form must be entered in the web-based data entry system within 24 hours. The form is then forwarded to the Medical Safety Officer who completes the Event Evaluation form. The Event Evaluation form is reviewed by the Study Physician and determination is made as to whether or not the adverse event is related to the study procedures. This form is then entered into the LIFE database. This system provides for timely central safety monitoring of all serious, unexpected and unfavorable events occurring at the intervention or assessment site.

Collection of Medical Events by Masked Assessors (Figure 22.2)

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 Health Events form is administered to each participant routinely every three months. Event Tracking forms are completed for hospitalizations, fractures, revascularizations, and deaths. The Health Events form and Event Tracking forms are reviewed by the Medical Safety Officer to detect adverse events that have not already been reported to the IRB. It is the responsibility of the Medical Safety Officer to enter any previously unreported adverse events into the LIFE database. All adverse events reported to the IRB must also be entered in the LIFE database.

Outcomes assessment is a lengthy process requiring thorough collection of corroborating medical records by the local outcomes assessment staff at each center (see Chapter 20). Event Tracking forms are sent to the Medical Records Requestor. The process continues with a masked evaluation of the data and culminates in the careful scrutiny of the materials (assembled into a case adjudication packet by the local outcomes team) by a central adjudicator who makes the final outcomes determination.

Figure 22.1: Overview of Outcomes Collection and Safety Reporting

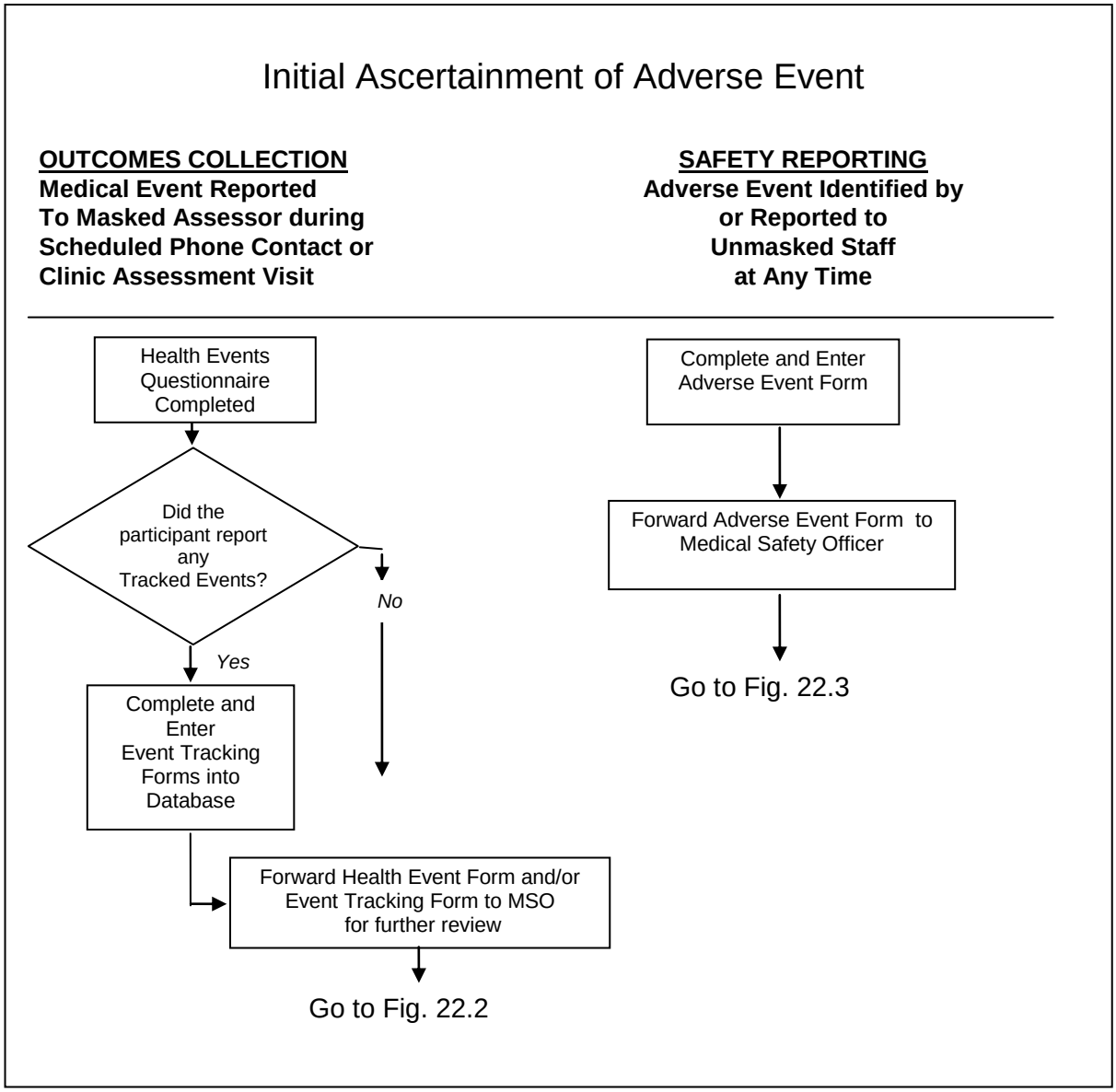


Figure 22.2 Evaluation of Outcome Collection/Safety Reporting Process - Medical Events Identified by Masked Assessors

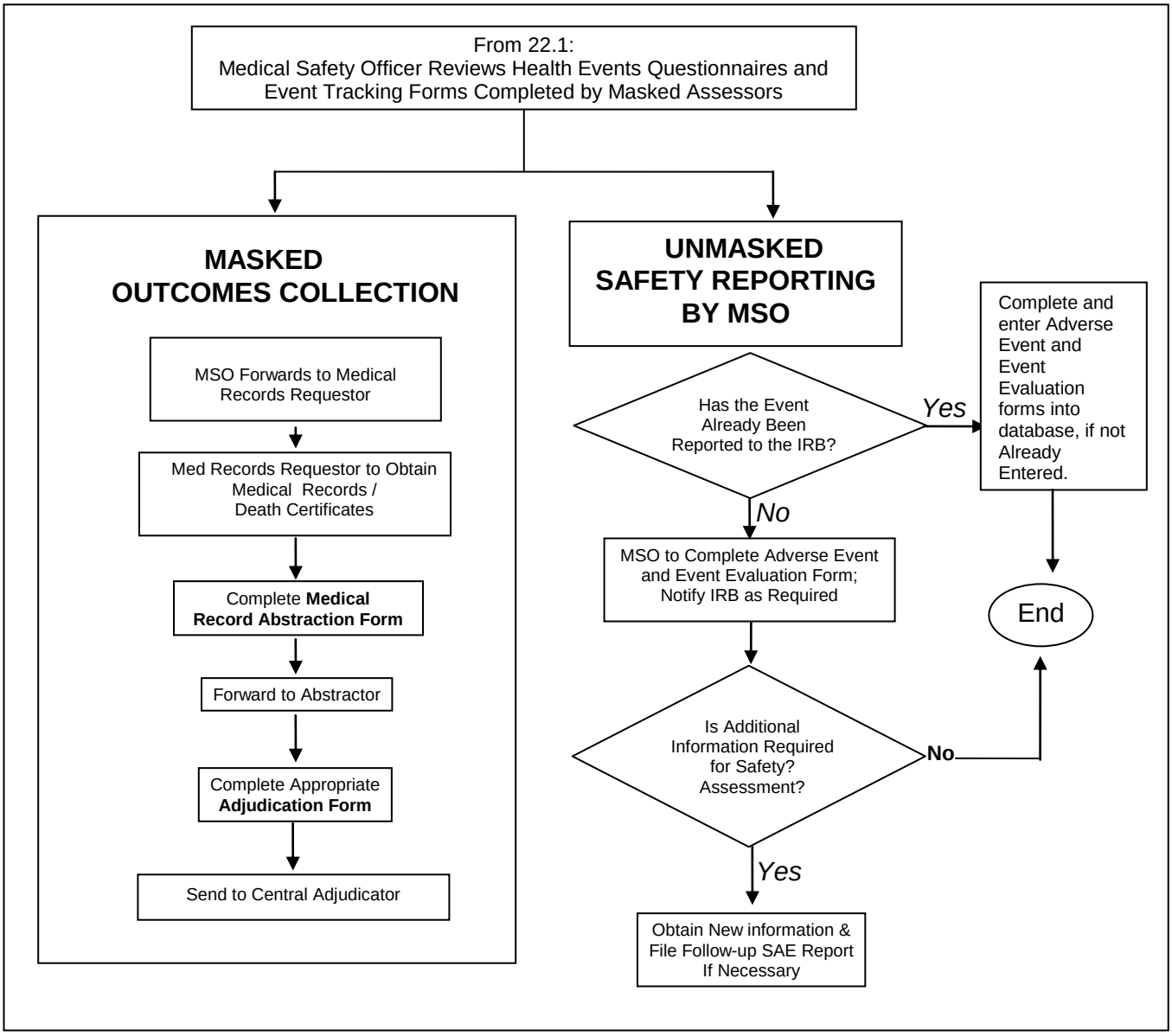
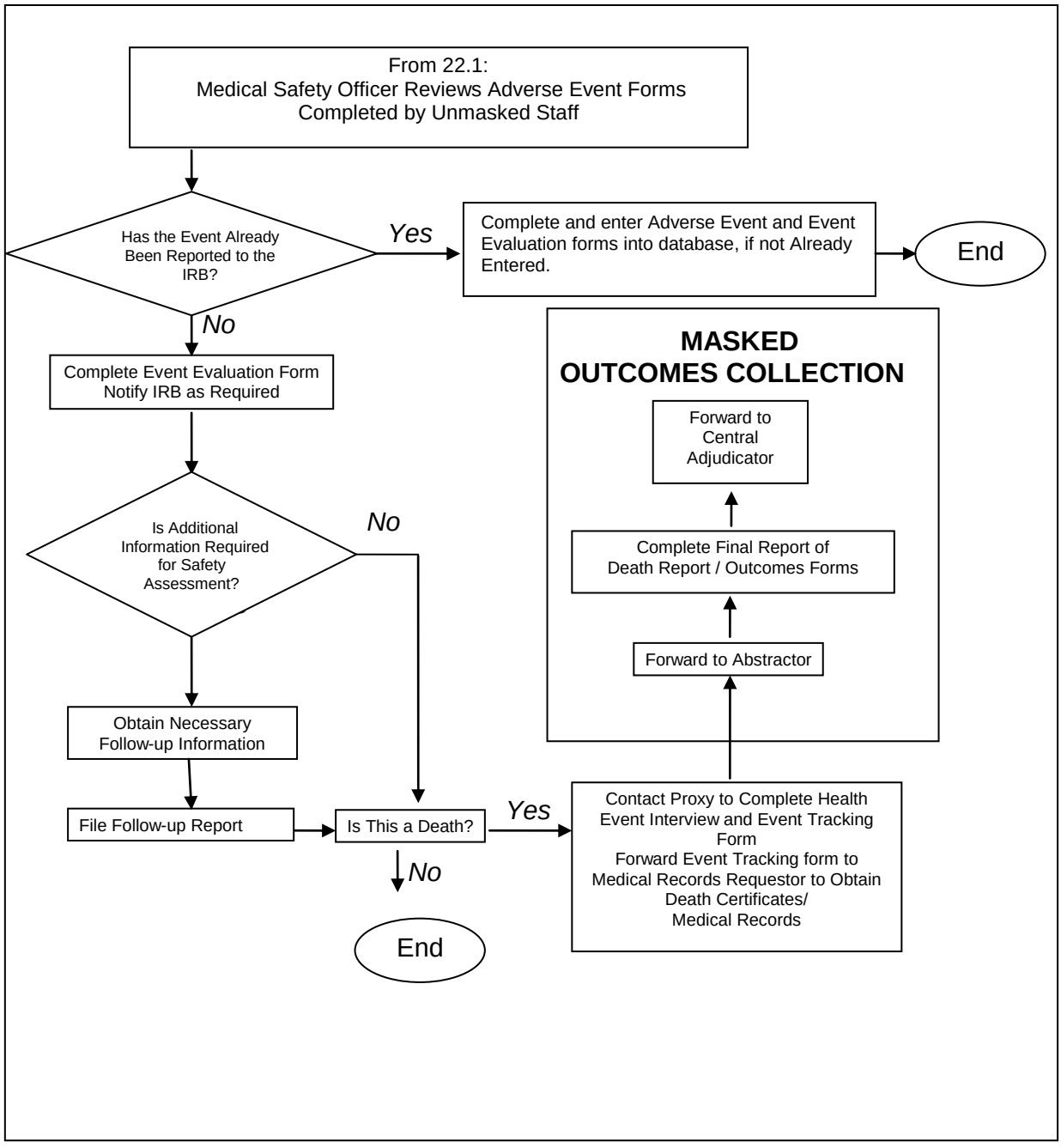


Figure 22.3.
Outcomes Collection/Safety Reporting
Adverse Events Identified by Unmasked Staff



Appendix I

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