

## 22. SIGNS, SYMPTOMS AND ADVERSE EVENTS

### 22.1 Definition of an Adverse Event

According to ICH Guideline E2a, an adverse event (AE) is, “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.” The CALERIE study has adopted the same adverse event definition. Therefore, an AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the intervention irrespective of whether it is related to the intervention. All expected and unexpected adverse events will be reported in CALERIE. In Phase 1, the most common adverse events reported by study participants included the following:

- headache
- insomnia
- nasopharyngitis
- arthralgia
- dizziness
- fatigue
- constipation
- stress symptoms
- back pain
- sinus congestion
- asthenia
- depressed mood
- pain in extremity
- nausea
- sleep disorders
- diarrhea
- irregular heart rate
- irritability
- anemia
- multiple allergies.

These same adverse events may be reported in Phase 2 or new adverse events may become more prevalent over a longer follow-up period. Symptoms or medically significant laboratory or instrumental abnormalities of a documented **preexisting** disease (such as hay fever or other medical condition) is not considered an adverse event. However, any new symptoms or as well as worsening of existing ones; or those that lead to temporary or permanent withdrawal of the study intervention are all considered adverse events. The following examples are not considered AEs that need to be reported on the AE CRF page for CALERIE, since this information is captured elsewhere and/or transferred to the CALERIE database, so secondary reporting of these events will not be necessary. These include the following:

- An abnormal laboratory value (Esoterix will include these in their electronic files)
- Events already captured on the safety surveillance data forms
- Decreases in BMD

### 22.2 Collecting and Recording of Adverse Events

**All adverse events will be collected from the first baseline visit through the participant’s study completion or early discontinuation.**

A diary will be provided to all study participants for the ease of recording any signs, symptoms or medical events occurring between scheduled visits. The site coordinator is responsible in instructing all participants to record events such as headaches, dizziness,

fatigue, pain, nausea, infections, and menstrual irregularities for women, etc. into their diary and request the participant bring this diary with them back to their scheduled visits for review. The participant will be instructed to record the event starting on the day it happened and indicate in the diary when the event ended.

At each visit the site coordinator will review the diary-reported AEs with the participant and try to obtain as much information as possible on the diary-reported events. This would include probing the participant, asking them when the event started, the intensity and the frequency of the event, if any medication had to be taken for the event, if the event worsened, remained the same, improved or resolved. If the event had resolved, the coordinator should determine with the assistance of the diary and the participant, the end date of the event. Any newly emerging AEs, as well as the status of any prior AEs that have not yet resolved, will be recorded in the case report form.

During scheduled evaluation visits (including phone call visits), the study coordinator will proactively ask whether the participant had any new or unusual symptoms or a medical condition that required a hospital visit since the previous contact. An ER visit may be an indicator of an adverse event occurrence but the ER visit without an overnight stay is not a SAE. The coordinator should ask each participant the following at each scheduled visit: “How are you feeling today? Have you experienced any new problems with your health since our last contact?” Any events reported by the participant should be probed as to the onset of the event, frequency, intensity, if the event required some kind of treatment or increase in food intake above the prescribed level, and whether the event resolved. The discussions should be documented in the visit progress notes at the time of the visit and then transcribed into the CRF.

There has been concern that the CR group may have more reported AEs due to the frequency of their intervention visits. During the interventional counseling sessions, the intervention staff should refrain from proactively seeking the reporting of events during these visits and instead leave this to the evaluation staff instead. All efforts will be made to solicit events and review participants’ diaries in both groups during the same time points. The Control participants will be called monthly by the evaluation staff at the same time frequency as the CR intervention visits (monthly). At the time of the CR intervention visits, if the evaluation staff cannot be available to meet briefly with the participant, they should follow-up instead with a phone call either prior of after the participant’s intervention session. Both groups will be followed at the same frequency so as to provide equal opportunities in reporting events throughout the study.

For each sign, symptom or adverse event, the following information will be recorded in the CRF:

- a brief descriptor of the adverse event
- intensity (mild/ moderate/ severe)
- whether the AE was “serious” or not (as defined in the serious adverse event section)
- frequency (single occurrence/ intermittent/ continuous)
- outcome (resolved/ resolved with sequelae/ improving/still present and unchanging/ death)
- whether any treatment was administered for the AE.

A copy of the completed AE page(s) will be couriered to the Coordinating Center along with appropriate section(s) of the CRF after each study visit. Sites will retain the original copy of the AE page for their reference in the participant's binder. Sites are responsible for reporting to their local IRB in accordance to the site's local practices and IRB requirements in reporting adverse and serious adverse events.

**APPENDIX  
DAILY DIARY**

## CALERIE Daily Diary

In between study visits, subjects will be requested to keep a written log of any symptoms or health problems that may arise between visits and to bring this log to their visits. If you are enrolled in the “calorie restricted” group, your log will be reviewed in person at least monthly and you may be asked questions about any information noted on the log. If you are enrolled in the “control group,” your log will be reviewed monthly over the phone and in person at Months 1, 3, 6, 9, 12, 18, and 24 visits.

There are 2 daily diaries which are gender specific. The logs are labeled accordingly, and the difference is that the log for women has an additional column to capture information on menses.

Subject ID #: ___ - _____	Initials _____	Week: ___/___/___ to ___/___/___	
<p><b>CALERIE Daily Diary – For Women</b></p> <p><i>Please record any adverse events (unfavorable change in your condition) that you experience on a daily basis until your next visit.</i></p>			
Date	Have you experienced any unfavorable changes today <i>(if yes, please describe what the change was, how long did it last, and what you did about it )</i>	Have you taken any medications today? <i>(if yes, medication name &amp; dose)</i>	Menses? <i>(record start, stop and any irregularities)</i>
<p><b>CALERIE Daily Diary – For Men</b></p> <p><i>Please record any adverse events (unfavorable change in your condition) that you experience on a daily basis until your next visit.</i></p>			
Date	Have you experienced any unfavorable changes today <i>(if yes, please describe what the change was, how long did it last, and what you did about it )</i>	Have you taken any medications today? <i>(if yes, medication name and dose)</i>	

### **Completion Instructions** - Each week should be recorded on a separate form

- Header: please record the assigned **Participant ID, Initials**, and the first and last day of the **Week**.
- **Date**: record the date for each day of the week in this column.
- **Unfavorable changes**: please record any symptoms or unfavorable changes in your health (such as headaches, dizziness, fatigue, pain, nausea, infections, insomnia, loss of sexual function, etc).
- **Medications**: please record any medications taken as a result of the symptom/change. When recording the dose, please record the total dose and units (e.g., 250 mg), as indicated on the bottle/box, and the frequency taken (e.g., 2 x day, or once). It is not necessary to record any medications that you take routinely for other conditions.
- **Menses (for women only)**: please record start and stop of your menstrual cycle as well as any irregularities from your typical cycle (such as missed cycle, late start, excessive flow, etc.).
- **Signature & Date**: participant should sign and date each completed form and take it with them to their next study visit for review.

**CALERIE Daily Diary – For Women**

Please record any adverse events (unfavorable change in your condition) that you experience on a daily basis until your next visit.

Date	Have you experienced any unfavorable changes today <i>(if yes, please describe what the change was, how long did it last, and what you did about it )</i>	Have you taken any medications today? <i>(if yes, medication name &amp; dose)</i>	<i>Menses?</i> <i>(record start, stop and any irregularities)</i>
9/18/06	headache - lasted 3 hrs	Tylenol - 650 mg	no
9/19/2006	none		start - on time
9/20/2006	none		ongoing - normal
9/21/2006	nausea - lasted most of the day		ongoing - normal
9/22/2006	nausea - lasted most of the day	Peptobismol, 204 mg	ongoing - normal
9/23/2006	none		stop - shorter than normal
9/24/2006	leg aches - lasted 2 hrs, went away after rest		

Signature: Jane DoeDate: 9/24/06

**CALERIE Daily Diary – For Men**

Please record any adverse events (unfavorable change in your condition) that you experience on a daily basis until your next visit.

Date	Have you experienced any unfavorable changes today <i>(if yes, please describe what the change was, how long did it last, and what you did about it )</i>	Have you taken any medications today? <i>(if yes, medication name and dose)</i>
9/18/06	constipation	Milk of Magnesia,
9/19/2006	constipation	Milk of Magnesia
9/20/2006	none	
9/21/2006	not sleeping well	
9/22/2006	tiredness and not sleeping well	
9/23/2006	tiredness and not sleeping well	
9/24/2006	throbbing headache & stuffy nose	Dayquil- 2 capsules 3 times a day Nyquil- 2 capsules at bedtime

Signature: John Doe

Date: 9/24/06