# MrOS Visit 4
# Medical Alerts and Adverse Events

## 1. Medical Alerts and Adverse Events

### 1.1 Background and Rationale

Certain findings made at the time of the clinic visit may require medical intervention. Although measurements performed as part of the MrOS Study are not considered diagnostic studies, the MrOS investigators have an obligation to intervene when medically necessary. The system that has been established is based on the urgency of the finding – either IMMEDIATE (requiring action prior to participant leaving clinic), or URGENT (requiring review by study physician by the next business day, with follow-up taken no more than 10 days after observation, or sooner if deemed medically necessary).

### 1.2 Designation of a local study physician

Each clinical center has designated a study physician who will be available to be alerted to potential adverse events or clinically-relevant findings, and recommend follow-up action. The study physician does not need to be present at the clinic visit, but should be available via phone, email and/or fax for intervention or follow-up.

### 1.3 Measurements with Alerts

At the fourth clinic visit, the following measures have alert values that require follow-up:

- Blood Pressure
- Pulse
- DXA

More detail regarding these alerts are outlined in the measurement protocols.

Please note that while other measures that will be obtained at MrOS Visit 4 do not have specific alert values that require follow-up, it is possible that other situations will arise during the clinic visit that warrant follow-up. Please see below for more information.

### 1.4 Immediate Referrals

Immediate referrals are potential emergencies which may require immediate notification of the participant and (if so requested by the participant) his primary physician or other available health care provider. Because the technicians performing the physical measurements are neither trained nor licensed to perform clinical diagnostic assessments, all findings requiring immediate referral will be referred by the technician to a physician-investigator of the MrOS Study. The physician, based on information obtained from the technician and/or the participant, will determine whether immediate referral is indicated. Participants receiving immediate referrals are those who would be advised to go directly from home to their physician and/or to a hospital. With participant's

consent (obtained verbally at the time of the alert), the study physician would contact the participant's referring physician directly.

Notification of the participant should be performed by the MrOS Study physician or Study investigator and should occur prior to the participant leaving the clinic.

Findings requiring **immediate** referral at the time of the clinic visit are as follows:

- **Blood pressure** (awake, seated) (on EITHER the first or second reading):

  Systolic blood pressure ≥ 210 mm Hg
  OR
  Diastolic blood pressure ≥ 120 mm Hg

- **Pulse** (awake, seated) (on EITHER the first or second reading):

  Heart Rate > 140 OR < 40 beats/minute

- **Excessive Bone Loss and Osteoporosis from DXA**:

  There are no immediate referrals for excessive bone loss or osteoporosis.

Sites should note all immediate medical alerts and action take on the appropriate Medical Alerts TELEform. The Coordinating Center will report the number of immediate medical alerts biannually to the NIA, NIAMS and OSMB.

## 1.5 Urgent referrals

Urgent referrals are related to abnormalities detected at the time of the clinic visit which require medical attention but generally not on an emergency basis. In most cases, notification of the participant should be sent by mail within 10 days. However, certain urgent referrals may require more immediate attention at the discretion (and responsibility) of the study physician. Therefore, all urgent referrals should be reviewed by the study physician no later than the next business day following the observation of the alert condition. If the study physician judges the condition to require more immediate attention, the study physician has the responsibility of contacting the participant directly by phone to seek consent to notify the participant's referring physician about the condition. If the participant refuses, then the study physician should minimally refer the participant to the ER and / or provide a listing of specialists (e.g. cardiologists or sleep specialists) the participant could contact for immediate medical care.

Finding requiring **urgent** referral are as follows:

- **Blood pressure** (awake, seated) (on EITHER the first or second reading):

  Systolic blood pressure ≥ 180
  OR
  Diastolic blood pressure ≥ 110

- **Pulse** (awake, seated) (on EITHER the first or second reading):

Heart Rate ≥ 120

- **Excessive Bone Loss or Osteoporosis from DXA**:

  -2.5 cutpoint for T-score (total hip or femoral neck) based on female reference data base

  ≥ 16% between baseline and Visit 4 OR ≥ 10% between Visit 3 and Visit 4 (total hip)

  The excessive bone loss and osteoporosis alerts from DXA will be confirmed by the Coordinating Center on a monthly basis. Follow-up with participants about these alerts should take place within 10 business days of clinic notification of an alert.

Sites should note all urgent medical alerts and action take on the appropriate Medical Alerts TELEform. The Coordinating Center will report the number of urgent medical alerts biannually to the NIA, NIAMS and OSMB.

## 1.6 Adverse Events

Although it is not expected, it is possible that adverse events could take place that would warrant follow-up. Such events will be classified as two types of adverse events: adverse events (AEs) and serious adverse events (SAEs). An AE will be defined as any undesirable experience ***associated with the direct participation in the MrOS Study***. A SAE will be defined as any experience that is life-threatening or results in overnight hospitalization or death ***associated with direct participation in the MrOS Study***.

If at any time during the clinic visit the study staff recognizes an immediate, medically significant situation (e.g. a fall, chest pain) the study physician will be notified and appropriate steps will be taken for evaluation and intervention. If a medical emergency that needs immediate attention occurs, clinic staff should alert 911/medical providers. In addition, if an adverse event occurs (e.g. a pulled muscle from getting on or off the DXA table or a mild dermatitis from wearing an activity monitor) sites should follow-up with the local study physician to determine appropriate follow-up action. When appropriate, clinic staff or the study physician can follow-up with the participant's primary clinician (with the participant's consent) to determine appropriate follow-up actions. Please note that it is possible that a medical alert as described above could meet the definition of an AE or SAE. If such event occurs, it should be treated as and tracked as an AE or SAE as appropriate.

If any AEs or SAEs were noted during the participant's visit, please complete the 'Adverse Alerts' TELEform and document any action taken. Each adverse event observed should be reported with its own Adverse Event TELEform. Please use supplemental form ID #1 for the first event, #2 for the second event, and so on.

On the Adverse Events TELEform, sites should report the event type. There are several pre-defined possible events. If the reported event falls within one of these categories, mark the appropriate option. There are several soft tissue effects that may be observed. Please classify as

skin irritation (i.e. rashes, redness), bruising or other minor soft tissue effects (i.e. swelling). If the event is not captured by the pre-defined categories please mark the 'Other' option and spell out the event type in the boxes provided.

Sites should also record the date the site was notified of the adverse event as well as the date of event onset (these may be the same day). Sites should also define if the event is definitely related, possibly related or not related to participation in the study using the following definitions:

> **Not related**: The adverse event is clearly not related to the investigational agent/procedure. - i.e. Another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study; and/or a causal relationship is considered biologically implausible.
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> **Possibly related**: An event that follows a reasonable temporal sequence from the study procedures, follows a known or expected response pattern to the study, but that could readily have been produced by a number of other factors.
>
> **Definitely Related**: The adverse event is clearly related to study – i.e. an event that follows a reasonable temporal sequence from the study, follows a known or expected response pattern to the study, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the patient's clinical state.

Severity of the event should also be noted using the following definitions:

> **Severe:** an experience that requires therapeutic intervention. The experience interrupts usual daily activities. Note that if overnight hospitalization is required for treatment it becomes a serious adverse event.
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> **Moderate:** an experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities.
>
> **Mild:** an experience that is usually transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities.

Sites should also note if the event was expected or not expected using the following definitions:

> **Unexpected**: Any adverse experience, the nature, severity or frequency of which is not consistent with the potential risks of participation in the study as defined by study investigators. Unexpected can also refer to an experience that has not been previously observed. This includes events that are more serious than expected or occur more frequently than expected.
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> **Expected**: Those experiences that have been identified in nature, severity, or frequency by the study investigators as a potential risk of participation in the study. These risks are usually outlined in the current consent form.

If sites are not sure of the classification of a given event, they should follow-up with the local physician for help classifying the event given the definitions above.

Sites should also follow-up with their local IRBs as necessary.

All AEs (serious and non-serious) should be reported to the Coordinating Center within 10 business days of notification of the event.

If an AE has not been resolved within 10 days of notification, submit the form, leaving the "Date of Resolution" blank, and follow-up with the participant in one month (from the date of clinic notification). If after one month, the AE has status has changed, edit the form (for example, change to "resolved" and enter a "Date of resolution"). If after one month, the AE is still not resolved, contact the participant again in three months after the clinic's initial notification. If after three months, the AE status has changed, edit and update the form. If the AE status has not changed, no further follow-up with the participant is needed. It is not necessary to continue follow-up if the AE is still unresolved after three months.

All SAEs should be reported to the Coordinating Center as soon as possible after the local study physician becoming aware of such event.

The Coordinating Center will report all AEs to the NIA, NIAMS and OSMB biannually. The Coordinating Center will report all SAEs to the NIA, NIAMS and OSMB within 48 hours of notification of such event.