

SECTION 6

OUTCOME CLASSIFICATIONS: FRACTURE OUTCOMES

INTRODUCTION

Hip fractures are a primary outcome of the calcium and Vitamin D (CaD) trial, and a secondary outcome of the hormone replacement and Dietary Modification (DM) trials. All other fractures and total combined fractures are secondary outcomes of all three Clinical Trial (CT) interventions. Hip fractures, all other fractures, and total combined fractures are outcomes in the Observational Study (OS).

6.1 Fracture Definitions for WHI

1. Confirmed hip fractures: Radiographically-confirmed fractures of the proximal femur, including fractures of the femoral neck, intertrochanteric region, and greater trochanter. Hip fractures will be confirmed as follows:
 - a. Written report of hip fracture by a radiologist based on a preoperative radiograph and documenting the presence of a new, acute, or healing fracture of the proximal femur (or one of its regions: the femoral neck or intertrochanteric region). Written reports not by a radiologist must be based on a review of a radiograph, and may be accepted after review and confirmation by the UCSF Bone Density Center radiologist.
 - b. If the radiologist's report confirms a proximal femur fracture **and** the hospital Discharge Summary does not (or is equivocal or missing), then the X-ray report alone confirms a proximal femur fracture.
 - c. Alternatively, a combination of the following:
 - 1) An equivocal written report of a radiograph of the hip (e.g., "possible," "probable," or "suspected" hip fracture).
 - 2) Confirmation of the diagnosis by the UCSF Bone Density Center radiologist, based on the review of preoperative radiographs of the hip, other imaging studies, and clinical findings from the hospital record.
 - d. Alternatively, a combination of the following:
 - 1) A negative or equivocal report of a preoperative radiograph of the hip (e.g., "possible," "probable," or "suspected" hip fracture).
 - 2) A hospital Discharge Summary listing fracture of the proximal femur, femoral neck fracture, intertrochanteric fracture, or hip fracture.
 - 3) A written radiologist's report of either a bone scan, MRI, or CT scan unequivocally stating that a new hip fracture, or healing hip fracture is present.
2. Pathologic Hip Fractures: Those resulting from anatomic compromise due to bone tumors, Paget's disease, bone and joint prosthesis, or surgical manipulation. Confirmation is obtained from the preoperative radiograph and/or the radiologic **and** operative reports.
3. Uncertain Hip Fractures: A hip fracture reported by the participant but found to be uncertain by X-ray report (e.g., "possible," "probable," or "suspected"). Copies of the radiologist's report must be obtained for any nuclear medicine and radiology studies performed (e.g., MRI scans, bone scans) and a copy of the operative report. All uncertain/equivocal hip fracture will be reviewed centrally by the UCSF Bone Density Center.
4. All Other fractures: Defined as radiographically-confirmed new or acute fracture of any bone (**except** ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae or neck). Other fractures will be confirmed as follows:
 - a. Written X-ray report stating that a new, acute, or healing fracture of a bone is present.
 - b. Written report not by a radiologist (but based on a review of the radiograph), including clinic notes, progress notes, ER notes, or operative reports stating that a new, acute, or healing fracture of a bone is present.
 - c. The initial X-ray report is uncertain or equivocal, but a subsequent report based on follow-up X-rays or bone scans clearly is diagnostic of a fracture or healing fracture.

5. Vertebral Fractures usually cannot be diagnosed as new or acute with certainty based on nonserial radiographs alone. Although the criteria listed in 4.a. will be used to confirm the presence of a vertebral fracture, these fractures will be categorized and analyzed separately.
6. Pathologic other fractures are confirmed from the preoperative radiograph and/or are noted in the radiologic **and** operative reports.

6.2 Fracture Ascertainment and Adjudication

Fracture ascertainment in both the CT and OS will be based primarily on self-report of fractures and hospitalization.

6.2.1 Fracture Questions on *Form 33 - Medical History Update* and *Form 33D - Medical History Update (Detail)*

Participants will be asked about any fractures that occurred during the study using *Form 33 - Medical History Update* and, if indicated, *Form 33D - Medical History Update (Detail)*. These forms will be completed at each regularly scheduled follow-up contact which occurs semi-annually in CT participants and annually in OS participants. The general approach is to gather information about fractures directly from the participant.

6.2.2 Ascertainment of Fracture Outcomes by Study Arm

For participants in the CT, self report of a hip fracture and all other fractures require ascertainment and adjudication.

For participants in the OS, self report of all hip fractures requires ascertainment and adjudication. However, ascertainment and adjudication of other fractures is only required for the three Bone Density (BD) sites (Tucson-Phoenix, Birmingham, and Pittsburgh). For all other CCs, other fractures will be collected by self report on *Forms 33/33D*.

6.2.3 Ascertainment of Fractures

Hip (including uncertain hip fractures) and other fractures that will require adjudication for WHI participants include:

- hip (fracture of the proximal femur, including femoral neck, intertrochanteric region, and greater trochanter)
- upper leg* (not hip)
- pelvis*
- knee* (patella or tibial plateau)
- lower leg* (tibia and/or fibula) or ankle (very distal tibia/fibula and/or talus)
- foot* (not toes)
- tailbone* (sacrum and/or coccyx)
- spine or back* (vertebra)
- lower arm or wrist* (radius, ulna, and/or one or more carpal bones)
- hand* (not finger) (one or more metacarpal bone[s]).
- elbow* (lower end of humerus, upper radius and/or ulna)
- upper arm or shoulder* (humerus)
- collarbone*; all clavicular and scapular fractures

*These other fractures are adjudicated in all CT participants, but only in OS participants at the three bone density sites.

If a subsequent fracture results in an overnight hospitalization, the fracture would not be adjudicated (i.e., *Form 123 – Report of Fracture Outcome* would not be completed), but the hospitalization would require completion of *Form 125 – Summary of Hospitalization Diagnoses*.

The following fractures will not be adjudicated in WHI:

- ribs
- chest/sternum
- skull/face, including nose and jaw
- fingers
- toes
- cervical vertebrae or neck

6.2.3.1 Identification of Fractures from Medical Records

Occasionally, fractures not reported by the participant will be identified from medical records obtained to investigate other outcomes. When fractures are identified in this manner, the Physician Adjudicator should return the case and request investigation of the fracture(s). The Outcomes Coordinator should investigate the outcome and obtain the required supporting documentation. Refer to *Appendix C – Coding Reference* for ICD-9-CM fracture codes.

6.2.3.2 Other Sources of Information on Fractures

Fractures can also be reported by proxy respondents, by other informants and by health care professionals when tracing participants with missed follow-up contacts or those who have died. When fractures are reported in this manner, follow the appropriate procedures for outcomes ascertainment (*Section 2*).

6.2.3.3 First vs. Subsequent Fractures

Only the first occurrence of a hip fracture during WHI will be adjudicated. All first-only occurrences of fractures at each anatomical site other than hip will be adjudicated for all CT participants (and OS participants at the Bone Density sites.) For example, a participant with a WHI confirmed left wrist fracture reports a new right wrist fracture. This is considered a subsequent fracture and *Form 123* is not complete. If a participant is hospitalized multiple times for one fracture site, only the **first** occurrence will be adjudicated as fracture. As for any other hospitalizations, subsequent fractures will be treated only as hospitalizations and adjudicated as such locally.

6.2.4 Confirmation of Fractures

Adjudication of fracture reports will be performed without knowledge of the treatment group. The goal is to classify each fracture report as one of the following:

- a) confirmed hip fracture
- b) **Or** confirmed other fracture

Complete *Form 123 – Report of Fracture Outcome* if you can confirm a hip or other fracture, as defined by WHI. Complete Question 1, items 1.1. – 1.5. if reporting a hip fracture (**even if the hip fracture is equivocal**). While more than one fracture can be documented on a single form, *Form 123* is site and side-specific, additional forms may need to be completed for a single event.

6.2.4.1 Central Review of Fracture Confirmation

Fracture confirmation decisions for all hip fractures in the CT and OS will be reviewed centrally. Additionally, a small percentage of other fractures reviewed in the CT (and OS at Bone Density CCs) will be reviewed centrally. All uncertain hip fractures will be reviewed centrally throughout the study.

The UCSF Bone Density Center (subcontractor to the CCC) will be responsible for central adjudication of fractures.

6.2.4.2 Confirmation Criteria

- 1) Confirmed proximal femur (hip) fractures require the following:
 - a) A hospital discharge summary or face sheet listing fracture of the proximal femur, femoral neck, intertrochanteric region or hip.
 - b) A copy of a **radiologist's** report (based on a hip radiograph) that clearly describes the presence of a new, acute, or healing fracture of the proximal femur, femoral neck, or intertrochanteric region. (Fractures of the subtrochanteric region are not included as proximal femur fractures.) The report must meet the following criteria:
 - One or more of the following phrases must appear in the report: “fracture,” “definite fracture,” “break,” “hairline fracture,” or “healing fracture.”
 - **And** the confirmatory report does not contain any of the following phrases: “possible fracture,” “suspicious fracture,” “probable fracture,” “suspected fracture,” or similar language indicating the diagnosis of fracture is “**uncertain**.”
- 2) Additional considerations for confirming proximal femur (hip) fractures include:
 - a) If the radiologist's report confirms a proximal femur fracture (even if the hospital discharge summary does not, is equivocal, or missing), then the X-ray report alone confirms a proximal femur fracture.
 - b) If the radiologist's report from a preoperative hip radiograph is negative or equivocal (“uncertain”) but the hospital discharge summary indicates a proximal femur fracture, then a fracture is confirmed by a written radiologist's report of either a bone scan, MRI, or CT scan that unequivocally describes the presence of a new, acute, or healing fracture of a proximal femur.
 - c) If the preoperative X-ray report indicates a hip fracture, and the X-ray was not evaluated by a radiologist, the fracture may be confirmed after UCSF Bone Density Center review of X-ray reports and other documentation. (UCSF Bone Density Center review required.)
 - d) If the radiologist's report from a preoperative hip radiograph is equivocal (“uncertain”), the fracture may be confirmed by the UCSF Bone Density Center radiologist's review of the preoperative X-ray and other imaging studies, radiology reports, and clinical findings from the hospital record. (UCSF Bone Density Center review required.)
- 3) Considerations when confirming fractures **other than hip** include:
 - a) A copy of a written X-ray report by a physician clearly stating that a new, acute, or healing fracture is present. Reports by a podiatrist are acceptable for foot fractures. Other written reports not by a radiologist (such as clinic notes, progress notes, ER notes, or operative reports) that describe the presence of a new, acute, or healing fracture are acceptable if a radiologist report is not available **and** the other written report is based on a review of radiograph.
 The report must meet the following criteria:
 - One or more of the following phrases must appear in the report: “fracture,” “definite fracture,” “break,” “hairline fracture,” or “healing fracture.”
 - **And** the confirmatory report does not contain any of the following phrases: “possible fracture,” “suspicious fracture,” “probable fracture,” “suspected fracture,” or similar language indicating the diagnosis of fracture is “**uncertain**.”

- b) If the initial X-ray report is equivocal (“uncertain”), the fracture can be confirmed from a subsequent report based on follow-up X-rays or bone scans. Bone scans must be clearly diagnostic of a fracture or healing fracture if used to confirm an “uncertain” fracture (i.e., the report for follow-up studies does not contain any of the following phrases: “possible fracture,” “suspicious fracture,” “probable fracture,” or “suspected fracture”).
 - 4) Fracture site:
 - a) The fracture site for confirmed fractures is based on the information provided in the X-ray report.
 - In instances where fractures extend from one location to another (as defined on *Form 123*) such as intertrochanteric/subtrochanteric fracture, the first location mentioned in the radiology report will be considered the primary fracture site.
 - In instances where the usual documentation (hospital discharge summary, operative report and radiology report), do not agree on the fracture location, final determination will be based on radiology report. In the case of equivocal radiology report, the UCSF Fracture Adjudication Center may review the available films to make a final determination.
 - For the purpose of this study, fractures of the subtrochanteric region will not be considered hip fractures, but will be coded as “shaft of femur including subtrochanteric region and other femur”.
 - b) No fracture site will be coded for undocumented fractures or for confirmed non-fractures.
- 5) Other fractures that cannot be confirmed include the following:
 - a) **Non-fractures**, which require the following:
 - An X-ray report must clearly state that no fracture is seen or that the radiograph is normal (even if reported by the participant or on a discharge summary).
 - **And** none of the available X-ray reports contain any of the following, or similar, phrases: “possible fracture,” “suspicious fracture,” “probable fracture,” or “suspected fracture.”
 - b) **Uncertain** other fractures, which require the following:
 - One or more X-ray reports contains any of the following, or similar, phrases: “possible fracture,” “suspicious fracture,” “probable fracture,” or “suspected fracture.”
 - **And** none of the available X-ray reports or imaging reports (bone scans, MRIs) contain words or phrases indicating a confirmed fracture, such as “fracture,” “definite fracture,” “break,” “hairline fracture,” or “healing fracture.”
 - c) An **undocumented** report of an other fracture, which must satisfy at least one of the following criteria:
 - No medical evaluation was performed or the participant did not see a doctor.
 - Medical treatment was received but no X-ray was taken.
 - An X-ray or other diagnostic study was performed, but no written report of these findings by a physician (or podiatrist for foot fractures) could be obtained.

If any of the above criteria are met, then the Physician Adjudicator checks “no WHI outcome” on the *Investigation Documentation Summary (WHIP 0988)* report.

- 6) Pathologic hip fractures and other fractures will be adjudicated but will be excluded from the primary fracture endpoint. Pathologic fractures result from anatomic compromise related to bone tumors, Paget’s disease, bone and joint prostheses, or surgical manipulation. When present, these conditions are usually evident on the preoperative radiograph, and are noted in the radiologic report and the operative report. For example, a typical radiologic report will note “fracture of proximal femur adjacent to lytic lesions consistent with tumor. Cannot rule out underlying metastatic lesions.” For fractures due to bone tumors,

confirmation is usually available from a pathology report. The radiologic, operative and pathology reports should be read carefully for indications of pathologic fracture. However, these will be rare (< 2% of hip fractures, < 1% of other fractures). Periprosthetic fractures will be the most common type of pathologic hip fracture. Fractures of the proximal femur during or subsequent to hip replacement procedures will be classified as pathologic hip fractures and the location will be "Unspecified Part of the Proximal Femur".

- 7) Vertebral fractures will be classified as in 2) above, except that confirmed fractures must be based on AP or lateral thoracolumbar X-rays. Diagnosis based on chest or plain abdomen (KUB) radiographs will be classified as "uncertain", and thus will **not** be classified as a WHI fracture.

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Outcome Classifications: Fracture Outcomes

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