

SECTION 1

INTRODUCTION TO WHI OUTCOMES

INTRODUCTION

The Women's Health Initiative (WHI) study outcomes are diverse and complex. The aim of WHI is to assess the effect of particular interventions on a broad range of health and illness conditions in women; therefore several primary, subsidiary, and intermediate outcomes have been identified as important for the study. To ensure that the identified outcomes represent true disease states, detailed outcomes ascertainment procedures and diagnostic criteria for adjudication have been developed by study investigators.

Volume 8 - Outcomes of the WHI Manual of Operations and Procedures includes necessary instructions for Clinical Centers (CCs) to carry out the detailed processing of WHI outcomes, which includes ascertainment (incorporating identification, investigation, and documentation activities) and adjudication (both local and central).

1.1 Outcomes Process

The nature and details of a medical event are often unclear or unknown to a patient, either due to limited explanations offered by health care providers or limited knowledge or interest of the patient. Thus, details of illnesses and medical procedures obtained by self-report may be very inaccurate. The WHI aims to investigate the effects of various interventions and exposures on the occurrence of particular medical conditions and events. For this reason, it is imperative that all self-reported events and procedures related to the WHI primary and secondary outcomes be investigated and documented thoroughly by appropriate WHI staff and adjudicated carefully by WHI investigators (with some exceptions detailed in *Section 2 – Ascertainment and 3-Physician Adjudication*). These objectives will be achieved through a multi-step, multi-component process of ascertainment and adjudication, which has been found in many previous clinical trials and observational studies to provide an accurate portrayal of the health events of study participants. *Figure 1.1 – Local Ascertainment and Adjudication Process* summarizes WHI outcomes processing.

1.1.1 Definitions Used for WHI Outcomes

Definitions specific to WHI Outcomes are included below. Medical terms used in processing WHI outcomes are explained in *Appendix D – Explanation of Terms*. Refer to *Vol. 2 – Procedures, Appendix B – Abbreviations* for other WHI abbreviations.

Adjudication: The assignment of the final decision/diagnosis by a Physician Adjudicator after reviewing the outcome documents contained in an adjudication case packet and recording the details supporting the diagnosis on the outcomes forms. Two types of adjudication are important for WHI outcomes:

- **Local adjudication** refers to a diagnosis assignment by a CC Physician Adjudicator.
- **Central adjudication** refers to a WHI diagnosis assignment by an appropriate central adjudicator, central adjudication committee, or CCC resource.

Adjudication case packet: Materials relevant to a specific outcome case. Includes an *Investigation Documentation Summary* (WHILMA database report - *WHIP 0988*), *Members Outcomes Status Report* (*WHIP 1215*), relevant outcomes forms, and required medical record documents relevant to the type of outcome(s) being adjudicated.

Ascertainment: The initial identification of a possible WHI outcome, investigation of sources of supporting medical records, and documentation for an adjudication case.

Bone Density (BD) CCs: Three CCs (Birmingham, Tucson-Phoenix, and Pittsburgh) where bone densitometry is performed and extensive fracture outcomes in the OS are adjudicated.

Closed outcome case: A WHILMA database function in which further ascertainment and/or adjudication procedures are stopped or concluded, either because a final diagnosis has been assigned or it has been determined that no WHI outcome occurred. A closed outcome is recorded in the database via assignment of a “close date” in the WHILMA Outcomes Management Subsystem.

Documentation: The assembly of required supporting medical records (obtained through investigation of a possible WHI outcome) into an adjudication case packet. Documentation also includes tracking these documents and packets through the WHILMA database and/or manual tracking systems until the adjudication case is closed.

Emergency Room (ER) visit: Visit or admission to a hospital ER. This may or may not lead to an overnight hospitalization. Only certain events (i.e., newly diagnosed fractures, cancers, or thromboembolic events [HRT participants]) occurring or diagnosed solely at an ER visit (without subsequent hospitalization) will be investigated, documented, and adjudicated as possible WHI outcomes. If any ER visit results in an overnight hospital stay, ER documentation should be obtained and included in the adjudication case packet.

Five major cancers: The five primary WHI cancer outcomes sites: breast, colon, rectum, endometrium, and ovary.

Hospitalization: An overnight stay in an acute care hospital, for any reason. There is no minimum length of stay required. Short stays, observation stays, and day surgeries may be referred to in medical records as outpatient visits, but for WHI these stays are considered hospitalizations if they result in overnight stays at an acute-care facility due to a complication or need for close observation. (Note that overnight stays in a rehabilitation facility is **not** considered an overnight hospitalization **unless** that facility is affiliated with an acute care hospital.) Psychiatric admissions are not investigated or adjudicated in WHI. Transfer from one hospital to another, on the same day, are considered one “case” for WHI purposes, but records should be obtained from both

Identification: The routine procedures through which the CC learns of a possible WHI outcome. This may be through participant completion of a semi-annual or annual *Form 33 - Medical History Update* and subsequent *Form 33D - Medical History Update (Detail)* or in the event of a participant’s death through some other interim report to CC staff by the participant’s proxy (family, friend or health care provider). The initial notification of a WHI participant’s death may also come from other sources (e.g., newspaper obituaries, returned mail, National Death Index reports).

Investigation: The process of locating providers (e.g., hospitals, clinics, physicians) information about a possible WHI outcome, requesting medical records that may support its diagnosis, and filing such documents in a participant’s outcomes file.

Outcomes file: A participant’s file of outcomes-related documents. This file may include medical records documents that are not currently required for a pending adjudication case packet, as well as copies of pending and closed adjudication case packets. It is kept separate from the participant’s generic file of WHI forms (33/33D) and notes. This file should be maintained and referenced frequently by the Outcomes Specialist when outcomes are being processed.

Outcomes forms: *Forms 120-131*, which are completed by the Outcomes Specialist, CC Physician Adjudicator, central adjudicator, central adjudication committee, or CCC resource.

Outpatient visits: Any short stay, observation stay, clinic visit, or day surgery that does not involve an overnight stay. Only certain events (i.e., newly diagnosed fractures, cancers, cardiac revascularization procedures, thromboembolic events in HRT participants, or hysterectomy in HRT participants) occurring at an outpatient visit alone without hospitalization will be investigated, documented, and adjudicated as possible WHI outcomes. If any outpatient visit results in an overnight hospital stay, outpatient documentation should be obtained and included in the adjudication case packet.

WHILMA Outcomes Management System: A data collection and tracking subsystem for WHI Outcomes. The tracking part should be used by Outcomes Specialists as an aid to outcomes processing and adjudication. It should not supplant a review of the participant’s outcomes chart and regular communication with the Physician Adjudicator.

1.2 Outcomes Personnel

All WHI personnel are involved in WHI outcomes. This manual emphasizes the roles and responsibilities of two key groups — Outcomes Specialists and Physician Adjudicators. However, a broad-based team effort is critical for ensuring that ascertainment and adjudication procedures result in appropriate and accurate outcomes data for hypothesis-testing.

1.2.1 Ascertainment Personnel

The CC Outcomes Specialist is the key CC person involved in outcomes ascertainment (i.e., identification, investigation, and documentation), but many other WHI staff collaborate in this effort. In many CCs, more than one individual fulfills the different roles of this position. Clinic staff conducting phone contacts and follow-up visits with participants will obtain self-report information about potential WHI outcomes and thereby initiate the ascertainment process with the identification of potential outcomes. Data and support staff are often involved in the investigative and documentation aspects of ascertainment by performing data entry, generating reports, conducting interviews to elaborate self-report data, requesting documents, and preparing and tracking case packets for local and central adjudication. The Outcomes Specialist ensures that this team effort follows the requirements and recommendations for WHI outcomes processing.

To ensure unbiased ascertainment of outcomes, it is **recommended** that CC staff involved in outcomes ascertainment **not** be exposed to information through participant contacts or reports that is effectively or definitively unblinding (i.e., information that, respectively, allows “educated guesses” or provides “proof” of treatment arm.). However, each CC will determine, based on local resources and operations, the extent to which these recommendations can be followed. See *Section 2 - Ascertainment* for more information about the Outcomes Specialist’s and outcomes team roles and responsibilities. See *Vol. 2 - Procedures, Section 4.6.5 - Blinding Considerations and Recommendations* for more detailed information on blinding in WHI.

1.2.2 Adjudication Personnel

1.2.2.1 Local Adjudication

The Physician Adjudicator is the key CC person involved in local outcomes adjudication. The Physician Adjudicator’s work is supported by the Outcomes Specialist and outcomes team in that case packets are received from and returned to these staff for processing. It is **required** that WHI Physician Adjudicators **not** be exposed to information through participant contacts or reports that is effectively or definitively unblinding (i.e., information that, respectively, allows educated guesses or provides “proof” of treatment arm). Thus, Physician Adjudicators should not have contact with participants or participant files (except appropriate adjudication case packets) to ensure unbiased adjudication. WHI Clinic Practitioners and Group Nutritionists, specifically, cannot be involved in adjudication, but both may play key roles in certain aspects of outcomes ascertainment. See *Section 3 - Physician Adjudication* for more information on the local Physician Adjudicator’s roles and responsibilities.

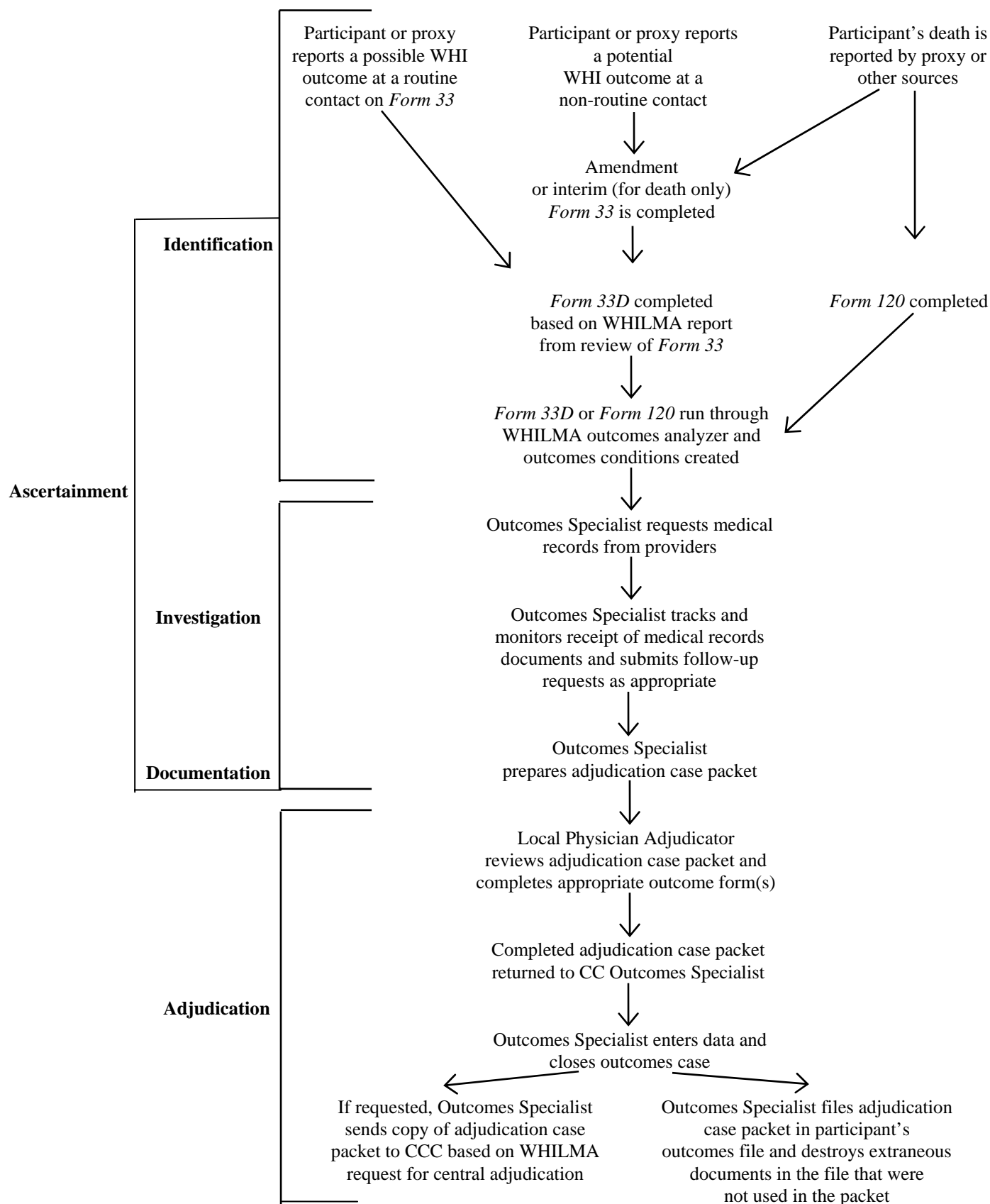
1.2.2.2 Central Adjudication

WHI central adjudicators include designated local adjudicators, other WHI investigators, and appropriate Clinical Coordinating Center (CCC) staff who review selected cases that have been locally adjudicated for quality assurance and more detailed coding:

- Selected cardiovascular outcomes and deaths are centrally adjudicated by the Cardiovascular Central Adjudication Working Group. This committee is made up of CC, CCC, and NIH Program Office cardiologists, internists, and cardiovascular epidemiologists. A CC Outcomes Specialist may be asked to participate in meetings/conference calls as needed.
- Selected cancer outcomes are centrally adjudicated by trained Cancer Surveillance System coders at the CCC.

- Selected fractures outcomes (primarily hip fractures) are centrally adjudicated by investigators at the CCC's Osteoporosis Study Center at the University of California, San Francisco (UCSF).

Figure 1.1
Local Ascertainment and Adjudication Process



1.3 Outcomes Manual

This WHI manual, *Vol. 8 – Outcomes*, contains instructions and resources for CC physicians and staff to follow for each step of an outcome investigation:

- *Section 2 - Outcomes Ascertainment* describes how to process the initial identification of an outcome, investigate and obtain the required documents for each outcome, assemble the documentation into an adjudication case packet, and forward the case packet with appropriate outcomes forms for local and/or central adjudication.
- *Section 3 - Outcomes Adjudication* describes the procedures Physician Adjudicators must follow in reviewing documents related to a possible WHI outcome and assigning a WHI-defined diagnosis.
- *Section 4 - Cancer Outcomes* describes in detail the cancer events to be monitored in WHI, including criteria for adjudication of the five major cancers (breast, colon, rectum, endometrium, and ovary) and other cancers.
- *Section 5 - Cardiovascular Outcomes* describes in detail the cardiovascular events to be monitored in WHI and the criteria for specific diagnoses.
- *Section 6 - Fracture Outcomes* describes fractures to be monitored in WHI, and procedures for classification of fractures. Where appropriate, specific information for fractures occurring at Bone Density CCs is included.
- *Section 7 – Fatal Events* describes WHI outcomes processing and adjudication procedures and guidelines for participant deaths.
- *Section 8 – Other Outcomes* describes WHI outcomes processing and adjudication procedures for thromboembolic disease (i.e., pulmonary embolism and deep vein thrombosis) in HRT participants. Note that other outcomes ascertained by self-report only are identified in *Section 2 – Outcomes Ascertainment*.
- *Appendix A - Outcomes Forms and Instructions*
- *Appendix B - Letters and Forms*
- *Appendix C - Coding Reference*
- *Appendix D - Explanation of Terms*
- *Appendix E - Medications Used For Treatment of Cardiovascular Disease*
- *Appendix F - Sample Outcomes Documents*
- *Appendix G - Sample Medical Chart*

1.4 WHI Manuals

The design and implementation of the WHI (including outcomes), as captured in the study Protocol, policies, procedures, interventions, and data collection instruments, are described fully in the WHI Manuals. The primary function of these manuals is to provide common training and reference materials across all participating WHI organizations as a way of assuring the quality of the study. Each operational unit (e.g., CC, CCC) is responsible for developing its own manual describing the policies and procedures specific to that unit.

The WHI Manuals are contained in several volumes. The allocation of topics to volumes was based on the WHI staff members who would most use the various sections.

Volume 1 - Study Protocol and Policies: This manual contains the Protocol for the Clinical Trial (CT) and Observational Study (OS), the committee structure, the model consent forms, and the policies governing the scientific conduct of the study. As this is a document written for and by WHI Investigators, many procedural aspects of the study that are performed by investigators are included in this manual.

Volume 2 - Procedures: This manual describes all CC procedures and guidelines for operations other than the Dietary Modification Intervention. As the primary CC training and reference source, this manual serves as the standard by which CC operations are assessed. Procedures that are designated as “Required” in the section heading must be followed to adhere to the protocol for consistency and participant safety.

Volume 3 - Forms: All standardized study forms (except outcomes forms) are displayed in this manual in numerical order. Accompanying each form is a detailed set of instructions describing who completes the form, when and how each data item should be coded, and what should happen to the form when completed.

Volume 4 - Dietary Modification Intervention: This manual consists of two parts: the *Group Nutritionist Manual* and the *Participant Manual*. The *Group Nutritionist Manual* describes the procedures for carrying out the intervention sessions for the DM component. The *Participant Manual* contains information pertinent to each intervention session.

Volume 5 - Data System: This is a user’s manual for the WHI computing system. Information is provided on the general hardware and software used as well as the specific WHI database, WHILMA.

Volume 6 - DXA Quality Assurance Manual for Hologic QDR-2000 Bone Densitometer: This is a user’s manual for the WHI Bone Density Clinical Centers. This manual is intended as a supplement to the Hologic User’s Manual.

Volume 7 - Quality Assurance: This manual provides procedures, checklists, and certification forms and other resource materials for CC QA activities.

Volume 8 - Outcomes: This manual provides instructions for CC outcomes staff and physicians to follow for each step of the outcomes process.

Section 1
Introduction to WHI Outcomes

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