ELSEVIER

Outcomes Ascertainment and Adjudication Methods in the Women's Health Initiative

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INTRODUCTION

Establishing, defining, collecting, and classifying outcomes are critical activities in clinical research. The Women's Health Initiative (WHI) has both observational study (OS) and clinical trial (CT) components designed to examine simultaneously the impact of a number of factors on many of the major causes of morbidity and mortality in postmenopausal women. Thus, WHI outcomes cover a wide range of diseases, such as cardiovascular diseases, cancers, fractures, and some age-related illnesses.

Most previous clinical trials in women have examined the effects of a single intervention in a limited pathophysiologic area. As such, effects of the intervention in other areas have often not been carefully monitored. Observational studies have tended to examine a broader range of outcomes but often in less detail and in smaller numbers of individuals than does the WHI OS. In the WHI outcomes process, equal, unbiased, blinded ascertainment across the arms of the clinical trial has been given the highest priority.

The size and complexity of the WHI has offered many challenges to this effort. A concerted attempt has been made to maximize the use of available resources to monitor in detail the many possible outcomes related to the interventions. A complex system was developed to standardize data collection methods across 40 clinical centers following over 160,000 women. This paper describes the definition of WHI outcomes, outlines the process for ascertaining and classifying these health events in all components of WHI, and presents reliability results.

WHI OUTCOMES

Primary and secondary outcomes for the WHI are defined for each study component. The primary outcomes are those associated with the primary clinical trial hypotheses: coronary heart disease for postmenopausal hormone therapy (PHT), breast and colorectal cancer for dietary modification (DM), and hip fracture for calcium and vitamin D supplementation (CaD) (Table 1). Secondary outcomes are defined as those having substantial pre-existing scientific merit, supportive of the primary hypotheses, or of interest for safety monitoring. Data on a variety of other outcomes are being collected from hospitalization records. Additional secondary outcomes include other age-related conditions and quality-of-life measures, whose means of assessment will be described elsewhere.

WHI focuses on disease prevention and risk factors. Statistical analyses will typically involve time-to-event analyses. With this perspective, the emphasis within WHI is on capturing and adjudicating the first event of each type in each woman after enrollment. Subsequent events of the same type generally receive less scrutiny.

Definition of Outcomes and Evidence Required

Cardiovascular diseases. Hospitalized myocardial infarction, definite silent myocardial infarction, and coronary

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TABLE 1. Outcomes for each arm of the WHI Clinical Trial and Observational Study

Outcome	PHT	DM	CaD	OS
Cardiovascular				
Coronary heart disease	1°	2°	x	x
Stroke	2°	2°	x	x
Congestive heart failure	2°	2°	x	x
Angina	2°	2°	x	x
Peripheral vascular disease	2°	2°	x	x
Coronary revascularization	2°	2°	x	x
Venous thromboembolic disease				
Pulmonary embolism	2°	x	x	x
Deep vein thrombosis	2°	x	x	x
Total cardiovascular	2°	2°	x	x
Cancer				
Breast	2°	1°	2°	x
Colorectal	x	1°	2°	x
Endometrial	2°	2°	x	x
Ovarian	2°	2°	x	x
Total cancers	2°	2°	2°	x
Fractures				
Hip	2°	x	1°	x
Other fractures	2°	x	2°	x
Total fractures	2°	x	2°	x
Other				
Diabetes mellitus requiring therapy	x	2°	x	x
Death from any cause	2°	2°	2°	x

"1°" indicates primary outcome; "2°" secondary or safety outcomes; "x" ascertained.

death are combined to form coronary heart disease (CHD), the primary cardiovascular outcome in WHI.

The WHI algorithm for classifying hospitalized myocardial infarction (MI) includes elements of the medical history, electrocardiogram readings, and results of cardiac enzyme/troponin determinations, and is adapted from standardized criteria (1, 2). All available electrocardiograms from a hospitalization are used to evaluate ECG criteria. Cardiac enzyme and/or troponin levels are classified as normal, equivocal (greater than the upper limit of normal but less than twice the upper limit of normal), abnormal (≥ twice the upper limit of normal) or incomplete, based on the normal range at the corresponding hospital. When multiple enzyme determinations are available, the most abnormal results are used in classifying the event. MI events that occur during surgery or are aborted by thrombolytic therapy or procedures are included. Aborted MIs meet all the following criteria: 1) symptoms and ECG evidence for acute MI; 2) therapy is followed by resolution of ECG changes; and 3) all cardiac enzymes are within normal limits. The algorithm defines reported MI events as "definite", "probable", or "not an MI", as indicated in Table 2. Primary analyses of CHD will use both definite and probable MI events as outcomes.

In the clinical trial, CHD also includes silent MI events detected on serial electrocardiograms done at baseline and every 3 years. WHI uses the Novacode (3) algorithm to determine which participants had a silent myocardial infarction. Serial Novacodes 5.1 and 5.2 are classified as "definite silent myocardial infarction" and Novacode 5.3 and 5.4 are classified as "probable silent myocardial infarction." Only definite silent MIs are included in the definition of CHD. Silent myocardial infarction is not ascertained in the observational study.

Coronary death is defined as death consistent with coronary heart disease as the underlying cause, based on review of medical records and death certificate, and is subclassified as:

Definite fatal MI. No known non-atherosclerotic cause and definite MI within 4 weeks prior to death.

Definite fatal CHD. No known non-atherosclerotic cause and one or both of the following: chest pain within 72 hours of death or a history of chronic ischemic heart disease (in the absence of valvular heart disease or non-ischemic cardiomyopathy.)

Possible fatal CHD. No known non-atherosclerotic cause and death certificate consistent with CHD as underlying cause.

TABLE 2. Criteria for the classification of myocardial infarction

	Cardiac Enzymes/Troponin			
ECG Pattern/Symptoms	Abnormal[a]	Equivocal[b]	Incomplete	Normal
Cardiac pain present				
Evolving Q wave and evolving ST-T abnormalities	Definite	Definite	Definite	Definite
Equivocal Q wave evolution; or evolving ST-T abnormalities, or new left bundle branch block	Definite	Definite	Probable	No MI
Q waves or ST-T abnormalities suggestive of an MI and not classified above	Definite	Probable	No MI	No MI
Other ECG, ECG absent or uncodable	Definite	No MI	No MI	No MI
Cardiac Pain absent				
Evolving Q wave and evolving ST-T abnormalities	Definite	Definite	Definite	Probable
Equivocal Q wave evolution; or evolving ST-T abnormalities; or new left bundle branch block	Definite	Probable	No MI	No MI
Q waves or ST-T abnormalities suggestive of an MI and not classified above	Probable	No MI	No MI	No MI
Other ECG, ECG absent or uncodable	No MI	No MI	No MI	No MI

[a]More than twice the upper limit of normal at the corresponding hospital laboratory. When multiple enzyme determinations are available, the most abnormal results are used in classifying the event.
[b]Greater than the upper limit of normal, but less than twice the upper limit of normal at the corresponding hospital laboratory.

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Both hospitalized and out of hospital deaths due to coronary disease are included. It is recognized that when the cause of death is uncertain, the death certificate often lists coronary disease as the cause of death. Therefore, as in other studies, there will be some misclassification of cause of death, including the possibility that fatal pulmonary embolism may be misclassified as coronary death. Coronary disease deaths are subclassified as definite or possible, depending upon the level of evidence.

Table 3 briefly describes the WHI criteria for the secondary cardiovascular outcomes of stroke, congestive heart failure, angina, peripheral vascular disease, coronary revascularization, and the safety outcomes of deep venous thrombosis and pulmonary embolism. For the outcomes of angina, congestive heart failure, stroke, and peripheral vascular disease, only events requiring hospitalization are considered outcome events for WHI. Angina or congestive heart failure managed in the outpatient setting is not included as an outcome since the quality of data and the projected numbers of potential events with records available only in physicians' offices made monitoring these events impractical. It is anticipated that significant changes in clinical practice and in diagnostic technology are likely to occur during the study, however. For example, during the study thus far, the frequency of outpatient angioplasty (PTCA) has been increasing. Since it is important to identify all angioplasty procedures, self-reported outpatient angioplasty is documented as an outcome. Similarly, deep vein thrombosis is increasingly diagnosed and treated in the outpatient setting. While early in WHI this condition was ascertained only if it resulted in a hospitalization, it soon became clear that significant numbers of cases would be missed if outpatient-treated deep vein thrombosis were not included. Since 1999, both outpatient and inpatient cases of deep vein thrombosis are ascertained and adjudicated for participants in the PHT component.

TABLE 3. WHI criteria for angina, congestive heart failure, stroke, peripheral vascular disease, deep venous thrombosis, and pulmonary embolism

WHI outcome	Defining criteria
Stroke	Rapid onset of a persistent neurologic deficit attributed to an obstruction or rupture of the brain arterial system, lasting more than 24 hours and without evidence for other cause.
Congestive heart failure	Symptoms and signs consistent with congestive heart failure, plus: pulmonary edema by chest X-ray; or dilated ventricle or poor ventricular function by imaging studies; or physician diagnosis of congestive heart failure and receiving medical treatment.
Angina pectoris	Symptoms consistent with angina plus: revascularization procedure; *or* ⩾ 70% obstruction of any coronary artery; *or* ST-segment depression ⩾ 1 mm on stress testing or on resting ECG with pain; *or* positive scintigraphic or echocardiographic stress test; *or* angina diagnosed by physician and receiving medical treatment for angina.
Peripheral vascular disease	Disease that is symptomatic and/or requiring intervention, and located in the abdominal aorta, iliac arteries, or lower extremities.
Coronary revascularization	Documented coronary artery bypass graft (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) or coronary stent or artherectomy
Deep venous thrombosis	Physician diagnosis of deep vein thrombosis of the lower extremity and positive findings on a diagnostic test.
Pulmonary embolism	Physician diagnosis of pulmonary embolism and positive findings on a diagnostic test.

Some cardiovascular disease outcomes may be underreported since WHI does not collect all possible outpatient-treated events. The lack of outpatient data will also complicate the task of identifying and classifying such events as angina, especially angina without coronary disease (coronary syndrome X) and congestive heart failure. Changes in treatment patterns, such as more aggressive treatment of women with angina, may also affect the rates of MI or other outcomes. For the clinical trial, there is no reason to expect differential ascertainment by study arm, thus bias is unlikely. For both the clinical trial and observational study, however, power to detect meaningful associations could be affected if a significant proportion of primary cardiovascular outcomes are treated in the outpatient setting in the future or by significant improvements in outcomes resulting from improved treatment. Trends in outpatient treatment will be followed through specific questions about cardiovascular diseases, so that self-reported events can be monitored. WHI collects information about medication use so that new uses of cardiovascular medications can be assessed. Outpatient treatment trends will be followed so that procedures can be adapted to include specific outpatient events if the benefits to the study are determined to outweigh the drawbacks of time and expense to the program.

Cancers. All invasive cancers are documented and coded according to primary site. Five main cancers (breast, colon, rectum, ovary, and endometrium) are coded for anatomic subsite, diagnosis date, extent of disease (stage, tumor size, laterality), tumor morphology (behavior, grade, histology) and estrogen and progesterone receptors (breast cancer only). Incident invasive and in situ (ductal and lobular carcinoma in situ) breast cancers, including second primaries, are ascertained and adjudicated. Incident invasive and in situ colon and rectal cancers are determined. Recurrent cancers are not included, but site-specific cancer deaths are recorded.

Since the diagnosis of some early cancers and cancer precursors is dependent on whether or not screening has

occurred, there is potential for over-reporting of diagnoses in some arms of the study, particularly the unblinded intervention arm of the Dietary Modification component. For this reason and for safety purposes in the Postmenopausal Hormone Therapy component, all clinical trial participants undergo regular screening mammograms as part of study protocol. Screening for colorectal cancer is not done in WHI. At each follow-up contact (semi-annually in the clinical trial, and annually in the observational study), however, information on screening procedures for colorectal cancer is collected, including: fecal occult blood testing, flexible sigmoidoscope, and colonoscopy. This will allow evaluation of rates of colon cancer according to the prevalence of screening.

The diagnosis of a main WHI cancer outcome is made if a pathology report substantiates a malignant primary invasive or in situ cancer of the breast, colon, rectum, endometrium, or invasive, in situ, or borderline (low malignant potential) ovarian cancer. All histologic types and anatomic subsites are included. A pathology report of invasive or in situ cancer also is used to confirm a self-reported diagnosis for other cancers (except non-melanoma skin cancers). Noncancerous colorectal polyps, atypical benign breast disease and other premalignant benign conditions are not adjudicated as WHI outcomes. Self-report of colorectal polyps and breast biopsies are collected for all components of WHI. All cancer related hospitalizations, surgeries, procedures, diagnostics or treatments for each first self-report of a malignant tumor are investigated. Cancer events can be documented with a pathology report from a diagnostic biopsy or from tissue obtained during surgical treatment. For the full coding of the cancer, however, pathology reports from diagnostic aspirations, biopsies, and surgeries, plus the discharge summary, are used. Both inpatient and outpatient cancer diagnoses are included.

Fractures. Fracture outcomes are those related to osteoporosis. Hip fracture is a primary outcome; other fractures (excluding fingers, toes, skull/facial bones, ribs, chest/sternum, and cervical vertebrae) represent a secondary outcome. The diagnosis of all fracture outcomes is based on the radiology report. Radiographs are not routinely obtained. For fractures, both inpatient and outpatient treated events are captured and adjudicated. All fractures are adjudicated in the clinical trial but only hip fractures are adjudicated in the observational study. Self-report of type of trauma is obtained from the participant for possible later exclusion of fractures due to motor vehicle accidents. Repeat occurrences of all fractures during follow-up are not investigated, however only repeat hip fractures are adjudicated.

Deaths. The underlying cause of death is classified on the basis of the death certificate, medical records, and other records such as an autopsy report. Evidence based on recent hospitalization and autopsy records is considered the most reliable for determining cause of death, and every effort is made to acquire such records. The death certificate diagnosis is used when no other records are available.

Outcomes Ascertainment

Potential outcomes are identified primarily through self-report at semi-annual contacts for clinical trial participants and annual contacts for observational study participants. Specific details of illnesses and hospitalizations are obtained as needed via a standardized questionnaire administered by phone or in-person interview, or self-completed form. For primary and secondary outcomes, portions of the medical record (discharge summary and results of relevant diagnostic and laboratory tests) are requested and assembled. These materials are provided to the designated local adjudicator who adjudicates the event. The WHI has set a goal that the ascertainment and adjudication of a WHI diagnosis at the clinical center be completed within 3 months of initial identification of a possible WHI outcome; the majority of WHI Clinical Centers meet this goal.

Following notice of a participant death, an attempt is made to obtain information on any outcomes occurring between the participant's last routine contact and her date of death. To ascertain survival and cause of death for all WHI participants, data linkage with the National Death Index of the National Center for Health Statistics will be performed several times during the study. WHI participants who are lost to follow-up or who are known to be dead will be matched to the National Death Index to search for otherwise unreported deaths and to ascertain causes of death.

Adjudication of Outcomes

Physicians in the Clinical Centers, the Clinical Coordinating Center, and the NIH classify WHI outcomes. In the first stage, the local Clinical Center physician adjudicator reviews the documents and assigns a diagnosis. All locally adjudicated primary and safety endpoint events of each trial component are then centrally reviewed. A fraction of locally adjudicated secondary endpoints are also referred for central adjudication for quality control purposes. The primary results for each clinical trial component will be based on data derived from central adjudication. To minimize potential bias in the ascertainment and classification of outcomes, WHI requires that local and central physician adjudicators not be exposed to any information that could result in potential unblinding, including participant contact or other aspects of the research record.

Local Adjudication

At each clinical center, the local physician adjudicator reviews the medical records and, using standardized criteria,

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determines whether a WHI outcome has occurred and codes specifics of the diagnosis. Documents reviewed for cardiovascular diseases include the discharge summary, electrocardiograms, laboratory values, and diagnostic test reports. Materials collected for all of the cancer outcomes include the pathology report and hospital face sheet. Based on these documents the local adjudicator codes the primary cancer site based on ICD-O-2 codes (5), the date of diagnosis, and tumor behavior (invasive, in situ, borderline). The primary document for fracture adjudication is the radiologist's written report. Additional documentation for hip fracture includes the hospital discharge summary, and for other non-spine fractures includes emergency room, clinic and progress notes when a radiology report is not available. For cause of death, hospitalization records from the time of death and the most recent relevant hospitalization before death, as well as autopsy records and death certificate diagnoses are used. For many out-of-hospital deaths, the only documentation available is likely to be the death certificate. In these cases, the immediate and underlying causes of death are abstracted from the death certificate.

Central Adjudication

The primary and safety outcomes of each trial component, and all deaths in the clinical trial are centrally adjudicated. The purpose of central adjudication is to document and improve the accuracy of diagnoses, to provide continuity of diagnostic decisions in a study that is of longer duration than most clinical trials, and to serve as a source of ongoing training for local physicians. All occurrences of the five main cancers (breast, colon, rectum, endometrium, and ovary) are also reviewed centrally for additional coding.

Cardiovascular diseases. The Cardiovascular Central Adjudication Committee is responsible for review of the following WHI outcomes: MI, angina, congestive heart failure, coronary revascularization, coronary death, and for PHT component participants, pulmonary embolism and deep vein thrombosis. Angina, congestive heart failure, and revascularization are centrally adjudicated primarily to search for unreported MI. Strokes were later included in the list of centrally adjudicated outcomes for the PHT component. Other cardiovascular events that are adjudicated at the local level are not routinely centrally adjudicated, although samples of these events may be reviewed for quality control purposes. The central adjudicators complete coding forms that are identical to those used by the local physician adjudicators.

The Cardiovascular Central Adjudication Committee consists of 10 to 20 physician adjudicators from the clinical centers, the Clinical Coordinating Center, and the NIH. Central adjudicators from clinical centers do not centrally review their own clinic's cases. Early in the study, consensus on diagnostic standards was established in a series of face-to-face adjudication meetings. To reduce time requirements, travel burden, and administrative costs, a system of completing central adjudication by mail was initiated. Initially, two reviewers adjudicated each case and were asked to come to a consensus if they disagreed. If they could not agree, the full committee reviewed the case. The rate of agreement between the two central adjudicators was sufficiently high (94% agreement between the two central adjudicators on MI diagnoses among the first 94 cases of MI) that the system was modified to require only one central adjudication. A second central adjudicator is used to resolve discrepancies between the local and central adjudication. Face-to-face central adjudicator meetings are held as needed to review a sample of cases to ensure consistency of central adjudication and to train new central adjudicators.

Originally, central adjudication was planned to occur on a sampling basis (10% of events) after each local adjudicator had achieved 90% agreement with the central diagnosis on a minimum of 20 cases for a given diagnosis. The implementation of this sampling plan was significantly delayed by the limited number of events per adjudicator and turnover in the local adjudicators. To reduce the central adjudication workload to that originally projected, central adjudication will be required for all key cardiovascular events occurring in PHT participants and a random sample of similar events in the non-PHT participants.

Cancers. For all cases of the five main WHI cancers (breast, colon, rectum, ovary, and endometrium), documentation is sent to the Clinical Coordinating Center for centralized review and coding by trained cancer coders under the supervision of a cancer epidemiologist and physician. These documents include hospital discharge summary, operative reports, history and physical examination, radiology reports, oncology consultation reports, and estrogen and progesterone hormone receptor results for breast cancers. The purpose of the central cancer coding is to finalize each cancer outcome, record detailed characteristics of the cancer such as stage of disease, and review self-reported cases of the primary cancers that were denied by local adjudication.

Primary cancer site, anatomic subsite, diagnosis date, extent of disease (stage, tumor size, laterality), tumor morphology (behavior, grade, histology) and hormone receptor results (breast cancer only) are coded. Central cancer coding uses the SEER coding guidelines (6), which were chosen because they are likely to be relatively stable through the length of the WHI study (in contrast with TNM staging, which may change over time). Initially, a blinded, quality assurance sample was recoded by a different coder to determine inter-coder variability. Unusual or difficult-to-code cases are reviewed with a reference cancer pathologist who performs a similar function for the Seattle-Puget Sound SEER registry.

Fractures. All hip fractures are centrally adjudicated using the same criteria and documentation as used at the local adjudication step. Rarely, the central adjudicator may request the actual radiograph to confirm an equivocal hip fracture.

Deaths. Coding of deaths is difficult and prone to inaccuracies (7), especially when documents are lacking or are of poor quality. For this reason, initially two central adjudicators review all deaths and are required to come to agreement before a case is closed. A random sample of deaths is reviewed annually by the entire Cardiovascular Central Adjudication Committee.

Training

Clinical Center outcomes staff are required to attend initial central training on protocol, procedures, and changes in the health care environment that can impact WHI case documentation. Monthly regional conference calls are used for training and problem-solving. A national workshop provided supplemental training and problem-solving opportunities. Clinical Coordinating Center outcomes staff also conduct on-site training for clinics having problems with outcomes processing.

Local adjudicators complete a formal training process that includes reviewing the study protocol, policies, and procedures, and participation in a training conference call held semi-annually or as needed. Once trained, ongoing communication and feedback to all local adjudicators is maintained through a newsletter. Additional individual training is planned by providing local adjudicators with a review of common problems and difficult cases observed in the study-wide experience. Central adjudicators are trained during Cardiovascular Central Adjudication Committee meetings and through a mentor program, where they are paired with a more senior central adjudicator to review cases together.

RESULTS OF CLASSIFICATION PROCESS

The local adjudication results are shown in Table 4. For major outcomes, the agreement between self-report and local adjudicator diagnosis was good: the local adjudicator verified 91% of self-reported breast cancers and 81% of self-reported hip fractures. In contrast, the local adjudicator verified only 70% of self-reported MIs, although for 16%

TABLE 4. Local adjudication results for self-reported outcomes

				Not confirmed			
		Confirmed		Related outcome confirmed		No outcome found/ No documentation obtained	
	Self-reported N	N	%	N	%	N	%
Cardiovascular							
MI	631	444	70%	104	16%	83	13%
Stroke/TIA[a]	1032	790	77%	49	5%	193	19%
Congestive heart failure	425	293	69%	34	8%	98	23%
Angina[b]	1669	727	44%	216	13%	726	43%
Peripheral vascular disease	170	101	59%	20	12%	49	29%
Coronary revascularization	1260	1103	88%	90	7%	67	5%
DVT (PHT only)	129	83	64%	22	17%	24	19%
PE (PHT only)	58	52	90%	1	2%	5	9%
Carotid artery disease[b]	228	175	77%	33	14%	20	9%
Cancers							
Breast	1608	1471	91%	4	0%	133	8%
Colorectal	393	338	86%	22	6%	33	8%
Endometrial	195	140	72%	31	16%	24	12%
Ovary	150	106	71%	23	15%	21	14%
Other cancer[c]	1699	1183	70%	117	7%	399	23%
Fractures							
Hip	292	236	81%	10	3%	46	16%
Spine[d]	302	156	52%	13	4%	133	44%
Other	3011	2420	80%	22	1%	569	19%

[a]Stroke and TIA have a combined self-report. Only stroke is a WHI outcome.
[b]Angina that is self-reported after a first MI and carotid artery disease that is self-reported after a stroke has been confirmed are not adjudicated and these self-reports are not included in the table.
[c]Excludes non-melanoma skin cancer.
[d]Excludes fractures of the cervical vertebrae.

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TABLE 5. Central adjudication results for locally confirmed outcomes

	Centrally adjudicated		
	Total	Confirmed	
Locally adjudicated outcome	N	N	%
Cardiovascular			
MI	403	351	87%
Angina	911	738	81%
Congestive heart failure	396	313	79%
CABG/PTCA	748	727	97%
Deep vein thrombosis	70	66	94%
Pulmonary embolism	36	34	94%
Cancers			
Breast	332	320	96%
Invasive	258	237	92%
In situ	74	58	78%
Colorectal	101	95	94%
Endometrial	67	63	94%
Ovarian	36	32	89%
Fractures			
Hip	163	157	96%

of self-reported MIs, the physician identified a related cardiovascular outcome such as angina or revascularization.

Local and central adjudication results are in generally good agreement for all outcomes (Table 5). Often, angina and congestive heart failure occur in conjunction with MI. Disagreement on these two events, when there is agreement about the MI, is not considered a serious disagreement. The agreement between local and central adjudication for cause of death is very good for cancer but not as strong for cardiovascular and other causes (Table 6). A relatively high proportion of the disagreement occurs when local adjudicators select "other cardiovascular cause", or "unknown cardiovascular cause", while the central adjudicators identify a specific type of cardiovascular death (data not shown).

TABLE 6. Agreement rates between locally and centrally determined cause of death

	Central adjudication results						
		Cause confirmed		Related cause found		Other cause	
Cause of death as determined by local adjudicator	N	N	%	N	%	N	%
Cardiovascular	305	224	73%	42	14%	39	13%
Cancer	552	521	94%	19	3%	12	2%
Other known cause	181	133	73%	13	7%	35	19%
Unknown cause	30	10	33%			20	67%

DISCUSSION

The identification and classification of outcomes in WHI is complex and challenging for several reasons. First, within WHI there are three trial components as well as an observational study and each has different primary and secondary outcomes. Methods for ascertainment and classification of the various types of outcomes differ. The size and age distribution of the WHI population guarantees a substantial number of outcomes. There are many clinical centers (many with their own satellite clinics) collecting medical information from many local hospitals, clinics, and physicians' offices. Finally, during this era of increased interest in patient privacy, many institutions are setting stringent requirements regarding release of medical information to second parties such as medical researchers. Nevertheless, the WHI program will document a large and diverse number of outcomes in a high-quality and timely manner. The WHI continues to monitor the agreement rates between self-report and adjudicated outcomes. Data from the early experience indicate documentation and adjudication of most major WHI outcomes continue to be necessary to assure the quality of these critical data. The diversity and number of outcomes in WHI will provide a rich data source for many etiologic analyses covering a wide spectrum of diseases and health-related events in women.

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