SECTION 5
OUTCOME CLASSIFICATIONS:
CARDIOVASCULAR OUTCOMES

INTRODUCTION

Specific cardiovascular diseases (CVDs) are primary or subsidiary outcomes for the WHI Clinical Trial (CT) and Observational Study (OS). The diagnosis of cardiovascular events is derived from a constellation of signs, symptoms, and objective evidence such as imaging studies. These constellations for diagnosis may be different for different patients. Thus, the systematic assignment of Women's Health Initiative (WHI) cardiovascular outcomes diagnoses will be a challenge to the local and central Physician Adjudicators.

This section describes the WHI-defined diagnostic criteria for the WHI cardiovascular outcomes and outlines the necessary documentation to arrive at consistent diagnoses. Note that thromboembolic outcomes (i.e., deep vein thrombosis and pulmonary embolus) are described in detail in *Section 8 - Other Outcomes*.

If the incidence of confirmed CHD or other cardiovascular events is approximately 7.5/1,000 per year in WHI participants (an over-estimate that doesn't reflect monthly recruitment goals), there will be approximately 1200 events per year in the CT and OS, or about 30 per Clinical Center (CC) (2-3 per month). Since all positive and a percentage of negative events (those **reported** as outcomes by participants) will be reviewed, the total number of events will be somewhat more, perhaps as many as 50% greater than the stated incidence.

5.1 Cardiovascular Outcomes

The processing of CVD outcomes follows the established WHI procedures for ascertainment and adjudication of outcomes as outlined in *Figure 1.1 - Local Ascertainment and Adjudication*. Refer to *Section 2 - Outcomes Ascertainment* and *Section 3 - Physician Adjudication* for more details on this multi-step, multi-component process.

5.1.1 Diagnostic Categories

The following cardiovascular diagnoses will be monitored during the WHI (note that thromboembolic diagnoses are discussed in *Section 8 - Other Outcomes*):

- Myocardial infarction (MI) (acute or silent, fatal and nonfatal).
- Sudden unexplained death (within 1 hour of onset of symptoms and in the absence of potentially lethal non-coronary disease process).
- Rapid unexplained death (within 1 to 24 hours of onset of symptoms).
- Other cardiovascular death.
- Congestive heart failure (fatal and nonfatal) requiring hospitalization.
- Angina pectoris requiring hospitalization.
- Coronary artery bypass surgery (CABG).
- Other coronary arterial surgery or procedure, including angioplasty (PTCA), coronary stent placement or atherectomy (hospitalized or outpatient).
- Stroke requiring hospitalization (fatal and nonfatal, hemorrhagic ischemic, or unknown).
- Transient ischemic attack (TIA) requiring hospitalization.
- Carotid artery disease requiring hospitalization.
- Peripheral arterial disease requiring hospitalization.
- Other cardiovascular event associated with hospitalization.

5.1.2 Identification of Potential Outcomes

Clinical Events

All WHI participants (CT and OS) will be asked to self-report any hospitalized CVD event and non-hospitalized PTCA, coronary stent or coronary atherectomy. Clinical Trial participants complete a *Form 33 - Medical History Update* at each semi-annual contact; OS participants complete this form annually. Based on information reported on *Form 33,* if a possible WHI outcomes is reported, *Form 33D – Medical History Update (Detail)* is completed. Currently, nonhospitalized CVD events, **excluding** outpatient revascularization procedures, remain as self-reported outcomes, but their incidence will be monitored over time to determine if such self-report should trigger an outcomes investigation.

Sub-Clinical Events

Silent MI, as diagnosed by WHI electrocardiogram (ECG) studies, is a WHI outcome for the CT. A standard 12-lead electrocardiogram (ECG) will be done at baseline and every three years in the CT. The reading of these ECGs for WHI outcomes will be done by Epicare, the ECG Reading Center (subcontractor to the CCC). Observational Study participants will not have study electrocardiograms.

5.1.3 Ascertainment of Cardiovascular Disease Outcomes

Cardiovascular disease events that are potential WHI outcomes will be reviewed by the local Physician Adjudicator. These events will include hospitalizations or deaths for any manifestations suggestive of any of the diagnoses listed in *Section 5.1.1- Diagnostic Categories*.

Ascertainment is the process of identification, investigation and documentation for potential WHI outcomes. Each specific outcome diagnosis is associated with a specific document set that will be needed to establish a WHI diagnosis. After the self-reported event is entered into WHILMA, the CC will request documents from the admitting hospital to support the diagnosis. The required document set has been chosen to allow the WHI Physician Adjudicator to make the most accurate diagnosis of the morbid event or cause of death. See *Section 2 - Outcomes Ascertainment* and *Table 2.1 - Documentation Requirements for WHI Outcomes* for more details on outcomes ascertainment and required documentation. Briefly, specific documents required include:

Non-Fatal Events

- All **hospitalized** cardiovascular events: discharge summary, hospital face sheet with ICD-9-CM codes, and/or physician attestation sheet with ICD-9-CM codes.
- In addition to these three documents, other documents that must be requested (if available) for specified events are:
  - Myocardial infarction, hospitalized angina pectoris, hospitalized congestive heart failure (CHF) or coronary revascularization: All ECGs from that hospitalization; cardiac enzyme and troponin data; and reports of any cardiac procedures (if done) including coronary angiograms, exercise stress testing, nuclear cardiac imaging, echocardiogram, angioplasty, and any cardiovascular surgical procedures.
  - Stroke or TIA: Report of computerized tomography (CT) scan, magnetic resonance imaging (MRI) scan, lumbar puncture (LP), carotid studies (Doppler angiography), echocardiogram.
  - Peripheral arterial disease: Report of exercise stress testing, diagnostic imaging with angiogram or ultrasound, ankle-arm blood pressure product, Doppler studies, or vascular surgical procedures.
  - Carotid artery disease: Report of carotid studies (doppler, angiography)
  - Coronary revascularization: All ECGs; cardiac enzyme and troponin data; report of cardiac procedures or surgeries (including coronary angiogram, CABG, coronary angioplasty, stent placement and atherectomy).

Fatal Events

A death certificate is required for all deaths. In addition to the death certificate, other documents include; autopsy report, hospital discharge summary/death summary, and if a death occurs out of hospital, a coroner's report or medical examiner report should be included.

- In-hospital death: Hospital discharge summary/death summary and autopsy report (if available).
- Out of hospital death: Coroner's report or medical examiner's report and autopsy report (if available).

5.1.4 Local Adjudication of Cardiovascular Outcomes

The CC Outcomes Coordinator will prepare an adjudication case packet, which will contain the WHILMA *Members Outcomes Status Report (WHIP 1215)* and *Investigation Documentation Summary (IDS; WHIP 0988),* the hospital face sheet and physician attestation sheet (if available), the discharge summary, the supporting documents specific to the suspected cardiovascular outcome, and a blank *Form 121 - Report of Cardiovascular Outcome*. There may be more than one suspected cardiovascular outcome in the case packet. If there are multiple CVD outcomes in one hospitalization, they will all be entered onto one *Form 121 - Report of Cardiovascular Outcome*. There may also be CVD outcomes in case packets created for a

hospitalization in which the participant did not self-report a CVD outcome. Thus, you will want to keep a supply of *Form 121*s on hand. Additionally, for each hospitalization, *Form 125 – Summary of Hospitalization Diagnosis is completed*. All ICD-9-CM diagnostic and procedure codes are collected on this form.

5.1.5 Submission of the Final Documentation Packet to the CCC (For Centrally Adjudicated Outcomes)

Cases are chosen for central adjudication either by the WHI outcomes database or by a local adjudicator's request for clarification of an unclear case, see *Section 2.4.2.1 – Closure Codes*, Closure Code 8. In either instance, the CCC will request the case and CCs should not forward a case until the request is received. Centrally adjudicated outcomes may include any hospitalized MI, angina, CHF and non/hospitalized coronary revascularization or coronary death. For those outcomes requiring central adjudication, a copy of the completed *Form 121 - Report of Cardiovascular Outcome, Form 125 - Summary of Hospitalization Diagnosis* (for hospitalized event) and the entire adjudication case will be sent to the CCC by the CC Outcomes Coordinator.

5.1.6 Final Central Adjudication by the CVD Central Adjudication Working Group

The CVD Central Adjudication Working Group will centrally review selected cardiovascular outcomes at regular intervals. The case packet, with the centrally adjudicated diagnoses, will be forwarded to the CCC for data entry.

At the present time, only the **first** myocardial infarction and the first stroke occurring after enrollment in the study will be centrally adjudicated. However, all first and recurrent hospitalizations for CHF, angina, and coronary revascularization will be adjudicated until a **first** MI is confirmed. All first and recurrent TIA and carotid artery disease hospitalizations will be adjudicated until a first stroke is confirmed. Subsequent outcomes of MI (after the first MI is confirmed) or stroke (after the first stroke is confirmed) will be treated only as hospitalizations and adjudicated as such locally. However, a first MI **and** a second MI (one occurring during or as a result of a procedure during the same hospital stay) will be **documented** on *Form 121 - Report of Cardiovascular Outcome*. A second myocardial infarction occurring during WHI follow-up will not require the extensive documentation that is required for the first occurrence of this outcome (although documentation that a hospitalization has occurred would still be required). Note that if the participant had an MI before WHI randomization or enrollment, her **first** MI for WHI outcomes purposes would still occur after randomization or enrollment.

5.1.6.1 Makeup of the Cardiovascular Central Adjudication Working Group

The CVD Central Adjudication Working Group will consist of selected members of the Morbidity and Mortality (M&M) Committee, CC Physician Adjudicators, CCC Physicians, and Project Office Physicians with expertise in cardiovascular diagnosis (e.g., cardiologists and cardiovascular epidemiologists). Members will be appointed by the chair of the M&M Committee as a core group of central adjudicators with expertise and a historical perspective on adjudication standards in WHI. The chair of the M&M Committee will also select a chair for the CVD Central Adjudication Working Group.

5.2 Criteria for Coronary Heart Disease

For WHI purposes, coronary heart disease (CHD) includes MI, coronary death, hospitalized CHF, hospitalized angina pectoris, and coronary revascularization. The possible diagnoses of CHD will be based on the following:

1. A reported hospitalization with appropriate documentation for CHD.
2. A report of a death possibly due to heart disease with appropriate documentation.
3. For CT participants only: Changes in ECGs at the clinic visits at baseline and/or years 3, 6, and 9 and at close-out. These will be read centrally by Epicare, the ECG Reading Center (subcontractor to the CCC). Coronary heart disease diagnosed by this mechanism will **not** be entered onto *Form 121 - Report of Cardiovascular Outcome* and will **not** be adjudicated by local or central Physician Adjudicators.

5.2.1 Myocardial Infarction

Myocardial infarction is defined as the death of part of the myocardium due to an occlusion of a coronary artery from any cause, including spasm, embolus, thrombus, or the rupture of a plaque. The WHI algorithm for classifying MI includes elements of the medical history, results of cardiac enzyme/troponin determination, and ECG readings. The WHI definition of MI includes events that occurred during surgery and MIs aborted by thrombolytic therapy or procedures.

The differentiation of **definite** vs. **probable** MI vs. aborted will be made by the WHILMA database based on data entered from *Form 121 - Report of Cardiovascular Outcome*, following the diagnostic criteria set out in the following sections.

Table 5-1
Definition of Criteria for Diagnosis of Myocardial Infarction

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

* See *Table 5.2 – Cardiac Enzymes* for definitions.

5.2.1.1 Aborted Myocardial Infarction

A diagnosis of aborted MI must meet all of the following criteria:

- Symptoms and ECG evidence for acute MI at presentation.
- Intervention (e.g., thrombolytic therapy procedure) is followed by resolution of ECG changes.
- All cardiac enzymes are within normal limits.

Physician Adjudicators will document whether or not acute intervention (e.g., thrombolysis or revascularization) is used to abort MI.

5.2.1.2 Definition of Criteria for Diagnosis of Myocardial Infarction

Cardiac Pain

Cardiac pain is defined as:

- Chest, jaw throat or arm pain, discomfort, or tightness of at least 15 minutes duration probably due to myocardial ischemia.
- **And** an absence of a definite non-cardiac cause of chest pain.

Electrocardiographic Criteria

Clinical Centers should request all ECGs for each CVD hospitalization, and adjudicators should read all ECGs in a case packet.

Recommended Readings for ECG Interpretation

Crow, R.S., Prineas, R.J., Jacobs, D.R., et al. (1989). A new epidemiologic classification system for Interim Myocardial Infarction for Serial Electrocardiographic Changes. *American Journal of Cardiology*, 64:454-461.

Dubin, D. (1996). *Rapid interpretation of EKG's*, 5th edition. Tampa, Florida; Cover Publishing Co.

Goldschlager, N., and Goldman, M.J. (1989). *Principles of Clinical Electrocardiography*, 3rd edition. Norwalk, CT; Appleton Lange.

Cardiac Enzyme Criteria

Pertinent enzyme results (as defined below) include those recorded in the hospital chart for days 1 through 4 after hospital admission, or days 1 through 4 after an in-hospital CHD event. Information on any non-ischemic causes for elevated enzymes will be obtained from the hospital discharge summary.

Abnormal Cardiac Enzymes

Cardiac enzymes may be defined as abnormal if they meet one of the three following criteria:

1. Creatine Kinase Heart Fraction (CK-MB)

   CK-MB is listed as elevated in the lab report in one of the following ways (note the total CK may be elevated for other reasons and there may be non-ischemic causes for the elevated CK-MB such as cardiac surgery, cardiac defibrillation, severe muscle trauma, rhabdomyolysis):

   - CK-MB (expressed as a percent, index, or unit) is $\geq$ twice the upper limit of normal for that hospital lab (if upper limit is given in the lab report).
   - **Or** CK-MB listed as "present" (if that lab uses the criterion of "present" or "absent" without reporting a numeric value).

2. Lactate Dehydrogenase (LDH)

   - $LDH_1 \geq LDH_2$ and there is no evidence of other disease associated with elevated LDH (e.g., hemolytic disease, Pneumocystis carinii, etc.).
   - $LDH_1 \geq$ twice the upper limit of normal in the absence of LDH_2.

3. Troponin (C, I, or T)

   - Troponin is $\geq$ twice the upper limit of normal for that hospital laboratory.

4. Total CK and total LDH are both at least twice the upper limit of normal (not necessarily on the same day) and there is no known non-ischemic cause (cardiac surgery, cardiac defibrillation, severe muscle trauma, rhabdomyolysis) for the elevated CK and no evidence of hemolytic disease.

Equivocal Cardiac Enzymes

Cardiac enzymes will be classified as equivocal if they do not meet criteria for abnormal enzymes and meet one of the following criteria:

- CK-MB (expressed as a percent, index, or unit) is greater than the upper limit of normal but less than 2X the upper limit of normal or is "weakly present."
- LDH is greater than the upper limit of normal but less than 2X the upper limit of normal.
- Tropinin (C, I, or T) is greater than the upper limit of normal but less than 2X the upper limit of normal for that hospital lab.
- Either total CK or total LDH, but not both, are at least twice the upper limit of normal.
- Both total CK and total LDH are between the upper limit of normal and twice the upper limit of normal (not necessarily on the same day.)

A summary of the enzyme diagnostic criteria is given in *Table 5.2 - Algorithm for Enzyme Diagnostic Criteria* and can be used to evaluate cardiac enzyme criteria in *Table 5.1 – Definition of Criteria for Diagnosis of Myocardial Infarction*.

Table 5-2 (revised 6/25/02)
Algorithm for Enzyme Diagnostic Criteria

Enzyme	Abnormal	Equivocal	Normal
Creatine kinase MB fraction (CK-MB)	≥ 2x ULN (as %, index, or units); **or** "present" without quantification	1-2x ULN (as %, index, or units); **or** "weakly present"	WNL
LDH_1 and/or LDH_2	$LDH_1 \geq LDH_2$; **or** $LDH_1 \geq$ 2x ULN *	$LDH_1 >$ 1-2x ULN	$LDH_1 < LDH_2$; **or** LDH_1 is WNL
Troponin (C, I, or T)	Troponin ≥ 2x ULN	Troponin 1-2x ULN	Troponin is WNL
Total creatine kinase (CK) **and** total lactic dehydrogenase (LDH)	Total CK **and** total LDH ≥ 2x ULN	Total CK **or** total LDH ≥ 2x ULN but not both; or total CK **and** total LDH 1-2x ULN	Total CK **or** total LDH is WNL

ULN = upper limit of normal
WNL = within normal limits
* in the absence of LDH_2

Other Cardiac-Specific Lab Criteria

New cardiac-specific laboratory tests continue to be identified, studied, and adopted clinically. Tropinin level is one such indicator that will be recorded in WHI. Other lab studies will be documented generally and when appropriate, recorded, specifically in WHI.

5.2.2 Coronary Death

Coronary death is defined as death consistent with coronary heart disease (CHD) as underlying cause **plus** any one of the following:

- Pre-terminal hospitalization with myocardial infarction within 28 days of death.

- Previous angina or myocardial infarction and no known potentially-lethal non-coronary disease process.
- **Or** death resulting from a procedure related to coronary artery disease such as coronary bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA).

Note: Deaths due to a non-coronary underlying cause in which the terminal event was an MI shall be ascribed to the underlying cause-not to CHD.

Coronary death will be subclassified as:

- Definite fatal MI: no known non-atherosclerotic cause **and** definite MI within 4 weeks of 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.)
- **Or** possible fatal CHD: no known non-atherosclerotic cause **and** death certificate consistent with CHD as underlying cause.

In patients without a known potentially lethal non-coronary disease process, coronary death will also be classified as rapid or non-rapid, based on whether death did or did not occur within 24 hours after the onset of symptoms (or the time at which the patient was last seen without symptoms).

5.2.2.1 Fatal Myocardial Infarction

A diagnosis of fatal MI must meet either the first **and** second criteria or the third criterion alone:

a) No known non-atherosclerotic process or event

b) **And** MI within 4 weeks prior to death (use criteria in *Section 5.2.1 - Myocardial Infarction*).

c) **Or** Autopsy evidence of **acute** MI.

5.2.2.2 Sudden Unexplained Death

Sudden unexplained death requires the presence of both characteristics listed below:

- Death witnessed as occurring within **one hour** after the onset of severe cardiac symptoms or within **one hour** after the participant was last seen without symptoms **or** during sleep.
- **And** no documentation of acute MI during the four weeks prior to death.

5.2.2.3 Rapid Unexplained Death

Rapid and unexplained death requires the presence of both characteristics listed below:

- Death witnessed as occurring between **one and twenty-four hours** after the onset of severe cardiac symptoms or between **one and twenty-four hours** after the participant was last seen without symptoms.
- **And** no documentation of acute MI during the four weeks prior to death.

5.2.2.4 Other Cardiovascular Death

A diagnosis of other cardiovascular death requires:

- Presumed MI or other presumed CHD cause (e.g., CHD-related procedure) that did not meet criteria for MI diagnosis by WHI criteria (see *Section 5.2.2.1 - Fatal Myocardial Infarction*); death certificate consistent with MI or other CHD cause without other underlying or immediate cause.

Or

- Presumed sudden or rapid unexplained death that did not meet criteria for a definite diagnosis (see *Section 5.2.2.2 - Sudden Unexplained Death* and *Section 5.2.2.3 - Rapid Unexplained Death*. This requires either characteristic a, c, and d **or** b, c, and d below:

  a) Previous history of MI (before enrollment in WHI) or by WHI record.

  b) **Or** autopsy reporting severe atherosclerotic coronary artery disease without acute MI.

  c) No known non-atherosclerotic process (acute or chronic) or other event that could have explained such a sudden death according to a relative, a physician, or hospital records.

  d) **And** no documentation of definite acute MI during the four weeks prior to death.

5.2.3 Congestive Heart Failure

Congestive heart failure is defined as a constellation of symptoms (such as shortness of breath, fatigue, orthopnea, and paroxysmal nocturnal dyspnea) and physical signs (such as edema, rales, tachycardia, a gallop rhythm, and a displaced point of maximum intensity [PMI]) that occur in a participant whose cardiac output cannot match metabolic needs despite adequate filling pressures.

Only a hospitalization involving new or worsening CHF will be a WHI outcome. Thus, diagnosis and treatment of CHF by a physician or other provider in the office or clinic setting or emergency room without hospital admission will not be considered a WHI outcome. The diagnosis of CHF requires the following documentation:

- Final diagnosis of CHF by a physician and receiving medical treatment (diuretic, digitalis, vasodilator, or angiotension-converting enzyme inhibitor) for symptom relief. See *Appendix E – Medications Used for Cardiovascular Disease* for a list of generic and trade names for these medications.

Data on additional evidence for the diagnosis of CHF, collected as part of the current episode of care, are also recorded. Thus, CHF on clinical grounds can be differentiated from CHF documented by imaging studies.

- Dilated ventricle or wall-motion abnormality by echocardiography, radionuclide ventriculogram, contrast ventriculography or multigated acquisition (MUGA) scan.
- **Or** Pulmonary edema/congestion by chest X-ray.

Note: Differential diagnoses of the symptoms associated with CHF include chronic obstructive pulmonary disease (COPD), pneumonia, or other lung disease.

5.2.4 Angina Pectoris

Angina pectoris is defined as symptoms (such as chest pain, chest tightness, or shortness of breath) produced by myocardial ischemia and not resulting in infarction. The symptoms generally last $\leq$ 20 minutes. Based on review of the hospital record, a diagnosis of angina pectoris for WHI purposes will include symptoms consistent with angina, plus any one of the following.

- Physician diagnosis of angina and receiving medical treatment for angina (e.g., nitrate, beta-blocker, or calcium channel blocker) (See *Appendix E – Medications Used for Cardiovascular Disease*).
- CABG, PTCA, or other revascularization procedure.
- $\geq$ 70% obstruction of any coronary artery on angiography.
- Horizontal or down-sloping ST-segment depression $\geq$ 1 mm on exercise or pharmacologic stress test.
- Positive scintigraphic or echocardiographic stress test.
- Resting ECG shows horizontal or down-sloping ST depression $\geq$ 1 mm with pain which is not present on ECG without pain.

5.2.5 Coronary Revascularization

Coronary revascularization includes surgery or other procedures that provide improved coronary blood flow to the myocardium. This would include:

- CABG
- PTCA
  - Coronary stent
  - Balloon
  - Artherectomy

Note that WHI will also be following MIs that occur as a result of such procedures.

5.3 Stroke, TIA, and Carotid Disease

We estimate that there will be about 7/1,000 stroke cases in the CT (about 400 per year or 10 per CC). Each CC may be required to adjudicate up to 60 cases per year.

5.3.1 Stroke (Fatal and Non-Fatal)

Stroke is defined as the rapid onset of a persistent neurologic deficit attributed to an obstruction or rupture of the brain arterial system. The deficit is not known to be secondary to brain trauma, tumor, infection, or other cause. The deficit must last more than 24 hours unless death supervenes **or** there is a demonstrable lesion on CT or MRI compatible with an acute stroke. A stroke is defined as procedure-related if it occurs within 24 hours after any procedure or within 30 days after a cardioversion or invasive cardiovascular procedure. The diagnosis of stroke will be made by the CC Physician Adjudicator based on the hospitalization record demonstrating that a stroke has occurred. WHI strokes will include those occurring during surgery or procedures and those aborted by thrombolytic therapy (streptokinase, TPA, etc.)

The definition of a stroke **excludes**:

- Headache alone and no demonstrated blood by LP, CT, or MRI scan.
- Bell's palsy or labyrinthine disease.
- Metabolic problems (such as diabetic, uremic, or hepatic coma) as a cause of altered consciousness.
- Brain tumor as found or ruled out by hospital course, CT or MRI scan, angiography, biopsy, or autopsy.
- Trauma as ruled out by history, CT or MRI scan, or angiography.
- Infection (encephalitis, abscess) as ruled out by CT or MRI scan, LP, or absence of fever.
- Old stroke by CT or MRI scan. This is usually diagnosed if the location of the infarct is inappropriate to explain the findings or when there is nearby focal ventricular enlargement. Recent infarcts often have edema or show distortion of the brain, are enhanceable, or show progression between CT or MRI scans.
- Seizures with status and post-ictal paralysis (Todd's) ruled out by history or observation **and** history of past seizures. Sometimes when a stroke causes seizure, CT or MRI scan or angiogram can confirm the stroke.
- Venous infarcts and subdural hematomas.
- Hysteria, which can usually be differentiated by inconsistencies on examination and evidence of secondary gain.

Stroke outcomes will be divided into 3 subtypes: hemorrhagic, ischemic, and unknown stroke type.

5.3.1.1 Definition of Criteria for Diagnosis of Stroke

<u>Hemorrhagic Stroke</u>

A diagnosis of hemorrhagic stroke requires one of the following criteria:

- Blood in subarachnoid space or intraparenchymal hemorrhage by CT or MRI scan. (Intraparenchymal blood must be dense and not mottled--mixed hyperdensity and hypodensity.)
- **Or** bloody spinal fluid by LP plus neurologic signs and symptoms consistent with stroke.
- **Or** death from stroke within 24 hours of symptom onset **and** no LP, CT or MRI scan, or autopsy is available. (Death within 24 hours of onset of stroke is nearly always due to hemorrhage.)
- **Or** surgical or autopsy evidence of hemorrhage as the cause of a clinical syndrome consistent with a stroke.

Ischemic Infarction

A diagnosis of stroke due to ischemic infarction requires one of the following criteria:

- Focal neurologic deficit without CT or MRI scan, LP, or evidence of blood.
- **Or** CT or MRI scan with mottled cerebral pattern or showing decreased density in a location compatible with reported symptoms and signs.
- **Or** Surgical or autopsy evidence of ischemic infarction (cerebral thrombosis or cerebral embolism).

Unknown Type Stroke

- Inadequate information to categorize as hemorrhagic or ischemic infarction, but satisfies criteria for stroke.

5.3.1.2 Stroke Terminology and Definitions

Rapid onset: Symptoms arising within minutes to hours and occasionally days. Symptoms that progress for more than 1 week are less likely to be associated with stroke.

Mottling: High density (blood) within a low density infarction.

Bloody Cerebral Spinal Fluid (CSF): A non-traumatic lumbar puncture (LP) positive for subarachnoid hemorrhage with > 100 cells/mm^3. Counts in the last tube are similar to those in the first tube (no clearing) **or** xanthochromia is present when the specimen is spun down.

Focal neurologic deficit: Signs/symptoms localized to one or a few locations.

"Compatible with": Can explain the neurologic deficit.

5.3.2 Transient Ischemic Attack

Transient ischemic attack is defined as the rapid onset of a neurologic deficit attributed to an embolus or an obstruction of the arterial system that is not known to be secondary to brain trauma, tumor, infection, or other cause. The diagnosis of TIA will be made by the CC Physician Adjudicator based on the information from the hospital record submitted and satisfaction of the criteria described below.

A participant has a diagnosis of TIA if she has one or more episodes of a focal neurologic deficit lasting more than 30 seconds and no longer than 24 hours in the absence of head trauma immediately preceding the onset. There must have been rapid evolution of the symptoms to the maximal deficit in less than 5 minutes with complete resolution within 24 hours. There should be no evidence of clonic jerking, conjugate eye deviation, prolonged Jacksonian march, scintillating scotoma, or headache with nausea and vomiting. Conditions to be ruled out include seizures, hypoglycemia, migraine, drug intoxication, tumor, infection, orthostatic hypotension, and generalized cerebral ischemia. Discovery of an infarct by CT or MRI scan in a location compatible with the symptoms, even if the symptoms cleared in less than 24 hours, shall be diagnosed as a **stroke**, not a TIA.

5.3.3 Carotid Artery Disease

A WHI diagnosis of carotid artery disease requires:

- Hospitalization with mention of carotid artery disease as a final diagnosis.
- **And** angiographic evidence of ≥ 50% stenosis of one or both carotid arteries.
- **Or** Surgical or diagnostic procedure (including artherectomy, angioplasty, surgery or angiogram).

5.4 Peripheral Arterial Disease

Peripheral arterial disease is defined for WHI purposes as hospitalization for leg pain produced by ischemia from peripheral arterial disease; or hospitalization with a positive diagnostic test result or surgical intervention for lower extremity arterial occlusion or abdominal aortic aneurysm. The diagnosis of peripheral arterial disease requires:

- Hospitalization for intermittent claudication, ischemic ulcers, gangrene, or surgery for amputation due to arterial insufficiency in the lower extremity.
- **Or** diagnostic imaging (e.g., angiogram) with evidence of obstruction ≥ 50% of the diameter or ≥ 75% of the cross-sectional area of a greater artery of the lower extremity (iliac arteries and below).
- **Or** surgical procedure, such as vascular bypass surgery, angioplasty, or thrombolysis, or amputation for peripheral arterial disease of the iliac arteries or below.
- **Or** diagnostic imaging with evidence of abdominal aortic aneurysm.
- **Or** surgical or vascular procedure to treat abdominal aortic aneurysm.

5.5 Other Cardiovascular Events Associated with Hospitalization

Any other cardiovascular event not fitting the above categories, yet requiring hospitalization, will be classified under this designation. This information will be collected from the hospital face sheet and/or Physician Attestation Sheet and recorded on *Form 125 - Summary of Hospitalization Diagnosis*. *Form 121 - Report of Cardiovascular Outcome* will not be completed for these outcomes. These would include, but not be limited to:

- thoracic aortic aneurysm
- valvular heart disease*
  - aortic valve stenosis
  - aortic valve regurgitation
  - mitral valve stenosis
  - mitral valve regurgitation
  - mitral valve prolapse
- endocarditis*
- Pericarditis*
- Cardiac tamponade*
- Cardiac hypertrophy*
- Cardiomyopathy*
- Upper extremity peripheral vascular disease

* If associated with a first-time WHI report of congestive heart failure, this would be reviewed as a possible WHI outcome.

Section 5
Outcome Classifications:
Cardiovascular Outcomes

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