Diabetes Prevention Program

Outcomes Study

Outcomes Classification Procedures

Version 4.1

November 2021
Prepared by the DPPOS Outcomes Committee

The George Washington University Biostatistics Center
6110 Executive Boulevard, Suite 750
Rockville, MD 20852

Telephone: (301) 881-9260
Fax: (301) 881-8752

Table of Contents

Preface

Summary of changes from Outcomes Classification Procedures Manual Version 3.0 (April 2013) to Outcomes Classification Procedures Manual Version 4.1 (November 2021):

1. **General Changes (refers to changes made throughout the manual):**

   a. Due to advances in laboratory methodology related to troponin levels, as well as other changes, new criteria for adjudication of MI in clinical trials were established by AHA/ACC and published in 2015 (JACC 2015;66:403-69). These new criteria were adopted by the DPPOS for adjudication of new cases beginning in 2016. EKG readings from hospital records were performed by Epidemiological Cardiology Research Center (EPICARE, Wake Forest University) and used in the adjudication process.

   b. Amend manual regarding mortality events without medical records

   c. General syntax and formatting changes were made as needed throughout all the sections

   d. Updated references

   e. Combine Cardiovascular/Mortality manual with Microvascular and Outside PCP Diagnosis Manuals

2. **Changes in Detail (refers to changes to specific sections) :**

Manual Reference Version 3.0	Manual Reference Version 4.1	Description	Comment
1	1	Introduction	Updated to reflect current DPP methods for MI adjudication and references for previous and new adjudication criteria.
2.1	2.1	Diagnostic Categories	Defined the catagories1,2, 3 & 4
3.1	3.1	Criteria for Diagnosis of Non-Fatal Myocardial Infarction	Changed title from “Definition of Coronary Heart Disease”
3.2		Definition of Myocardial Infarction	Removed to simplify duplicity
	3.1.1	Spontaneous MI (Type 1, Type 2, criteria adopted October 2016, see Table 2)	Adeded and updated new section
3.2.2.31	(a)a)	Abnormal Cardiac Enzymes	Updated diagnostic enzyme criteria for Troponin, CK-MB, and Total CK/total LDH
	3.1.1.3	Identification of an intracoronary thrombus by angiography or autopsy	Added new section
	3.1.2	Post-procedure (PCI) Myocardial infarction (Type 4, criteria adopted October 2016, see Table 2)	Added new section

	3.1.2	Post-procedure (CABG) Myocardial infarction (Type 5, criteria adopted 2016, see Table 2)	Added new section
3.3	3.1.4	Silent Myocardial Infarction (determined by Epicare analysis of ECGs)	Updated
	Table 3.1.	ECG Criteria for Silent MI	Added
3.2.2	3.2.1	Coronary Death	Updated to better clarify clasifications
3.4.2		Fatal Myocardial Infarction	Removed
3.4.3		Other Cardiovascular Death	Removed
3.5.3	3.3.3	Cardiac Arrhythmias	Added prolongation of hospitalization to criteria definition
	3.4	Recurring/Coninuous Cardiovascular Disease Events	New section
4.1	3.5.1	Adjudication Materials	Updated to reflect current electronic adjudication materials
	APPENDIX A	Reference Tables for Diagnosis of Myocardial Infarction – used for adjudications beginning October 1, 2016	Updated to relect new MI criteria. Updated diagnostic enzyme criteria for Troponin, CK-MB, and Total CK/total LDH
	APPENDIX B	Reference Tables for Diagnosis of Myocardial Infarction – used for adjudications prior to October 1, 2016	

DIABETES PREVENTION PROGRAM OUTCOMES STUDY

OUTCOMES CLASSIFICATION MANUAL

Chapter 1

Table of Contents

1. Classification Procedures: Cardiovascular Mortality and Morbidity Events

1.1 Introduction

Cardiovascular disease (CVD) is an important outcome for the Diabetes Prevention Program (DPP) and its Outcomes Study (DPPOS). The diagnosis of cardiovascular events is derived from a constellation of signs, symptoms, and objective evidence such as laboratory results, electrocardiograms (ECGs), and imaging studies. These constellations for diagnosis may differ from patient to patient.

This document describes the diagnostic criteria for clinical cardiovascular outcomes and outlines the necessary documentation to arrive at consistent diagnoses by the DPPOS Outcomes Classification Committee.

From DPP inception in 1996, adjudication of myocardial infarction and other cardiovascular outcomes were based on criteria used in the Women's Health Initiative (Annals of Epidemiol 2003;13:S122-128) and in the randomized clinical trial of the Prevention of Events with ACE Inhibition (PEACE, 1995-2003), sponsored by NHLBI (AJC 1998;82:25H-30H and NEJM 2004;351:2058). Due to advances in laboratory methodology related to troponin levels, as well as other changes, new criteria for adjudication of MI in clinical trials were established by AHA/ACC and published in 2015 (JACC 2015;66:403-69). These new criteria were adopted by the DPPOS for adjudication of new cases beginning in 2016. EKG readings from hospital records were performed by Epidemiological Cardiology Research Center (EPICARE, Wake Forest University) and used in the adjudication process.

1.2 Ascertainment of Cardiovascular Outcomes

1.2.1 Diagnostic Categories

The following cardiovascular diagnoses are monitored:

1. All Fatal Events

- Acute myocardial infarction, fatal
- Fatal stroke
- Sudden death
- Other cardiovascular deaths

2. Non Fatal Cardiovascular

- Non-fatal myocardial infarction
- Congestive heart failure (non-fatal requiring hospitalization)
- Unstable angina pectoris requiring hospitalization (includes acute coronary syndrome [ACS] not meeting criteria for MI)
- Coronary artery disease by angiography only (without revascularization)
- Stroke requiring hospitalization (non-fatal)
- Peripheral arterial disease requiring surgical intervention (revascularization or amputation) or hospitalization
- Cardiac arrhythmia requiring hospitalization

3. Cardiovascualr Procedures

- Coronary artery bypass surgery
- Percutaneous coronary revascularization including: angioplasty, stent placements, laser procedures, atherectomy, balloon dilatation

4.ECG- based Outcomes

- Silent MIs determined by Epicare

1.2.2 Identification of Potential Outcomes

Participants self-report any hospitalized event and outpatient coronary or peripheral revascularization procedures. Program Coordinators complete a Mid-year Visit Inventory Form (F01) at each scheduled mid-year follow-up visit, an Annual Visit Inventory Form (F02) at each scheduled annual follow-up visit, an Interim Visit Inventory Form (F03) at interim visits and follow-up visits when Form F01 and F02 are not completed, and an Non-Clinic Visit Inventory Form (F06) at every scheduled mid-year or annual follow-up visit occurring outside a study clinic. Forms F01, F02, F03, and F06 indicate if the participant had any acute life threatening events, permanent or severe disability, required or prolonged hospitalization, overdose of any medication, pregnancy resulting in congenital abnormality or birth defect, required intervention or treatment to prevent serious adverse event, possible CVD event, renal failure, or kidney transplant. Serious adverse events, deaths, CVD events, and renal events are all reported on the Event Report Form (E08). The E08 Cover Sheet should indicate which type of event(s) is reported. An E08 Supplement: CVD and DEATH Medical Records Checklist should accompany supporting documentation sent to the CoC. Mortality events are reported on the Mortality Event Report Form (E06) in addition to the E08 Form.

Appendix II contains copies of the following Forms:

- E06: Mortality Report Form
- E08: Event Report Form
  - E08 Cover Sheet
  - E08 Supplement: CVD and DEATH Medical Records Checklist

Refer to section 3.5.1 for more information regarding the forms used during adjudication.

1.2.3 Ascertainment of Cardiovascular Disease Outcomes

Ascertainment is the process of identification, investigation and documentation for potential clinical cardiovascular outcomes. Each specific outcome diagnosis is associated with a specific document set that will be needed to establish a clinical cardiovascular outcome diagnosis. The Program Coordinator will request documents from the admitting hospital and secondary sources to support the diagnosis. In the case of sudden death, the death certificate will be requested. The required document set has been chosen to balance accurate adjudication while minimizing workload. Specific documents required for fatal and non-fatal events are outlined in the following two sections.

1.2.3.1 Fatal Events

The entire hospital record should be obtained for the fatal hospitalization, including:

- Death certificate, hospital discharge summary, hospital face sheet with ICD-9-CM or ICD-10-CM codes and, if available, autopsy report. If a death occurs out of the hospital, an EMT report and a coroner's report or medical examiner report and autopsy report should be included. The Principal Investigator, physican or Program Coordinator should prepare a narrative summary of the events prior to the death and other qualifying data.
- In addition, the following documents must also be requested (if available) for a death resulting from a myocardial infarction: first and last ECGs from that hospitalization; cardiac enzyme 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. For all other CVD related deaths, event ECGs should be requested and sent to ECG Central Reading Unit (Epicare).

1.2.3.2 Non-Fatal Events and Procedures

- All hospitalized cardiovascular events: discharge summary, all event ECGs, hospital face sheet with ICD-9-CM or ICD-10-CM codes, and/or physician attestation sheet with ICD-9-CM or ICD-10-CM codes.
- In addition to these documents, other documents that must be requested (if available) for specified events are:

1. Myocardial infarction: 12 lead ECG tracings from hospitalization; cardiac enzyme 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.
2. Revascularization: operative or procedure report.

1.3 Outcomes Definitions

1.3.1 Criteria for Diagnosis of Non-Fatal 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 algorithm for classifying MI includes elements of the medical history, results of cardiac enzyme determination, and ECG readings. The definition of MI includes events that occurred during surgery and MIs aborted by thrombolytic therapy or intervention procedures. During DPP and DPPOS, adjudication of MI was based on criteria used in the Women's Health Initiative (WHI) (Ann Epidemiol 2003;13:S122-128). Due to advances in laboratory methodology related to troponin levels, as well as other changes, new criteria for adjudication of MI in clinical trials were established by AHA/ACC and published in 2015 (JACC 2015;66:403-69). These new criteria were adopted by the DPPOS for adjudication of new cases beginning in July 2016. EKG readings from hospital records were performed by Epidemiological Cardiology Research Center (EPICARE, Wake Forest University) and used in the adjudication process.

The Outcomes Classification Committee will make the differentiation of MI occurring as a consequence of, or during surgery or following PCI, will be differentiated from "spontaneous" MI(s) using the criteria outlined below and summarized in Appendix A, Tables A1-A3.

1.3.1.1 Spontaneous MI (Type 1, Type 2, criteria adopted October 2016, see APPENDIX A Table A1.1)

This category includes a spontaneous clinical syndrome related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection,with resulting intraluminal thrombus, and leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis (type 1) or an ischemic imbalance (type 2). **Requires elevation of cardiac enzymes as described below <u>plus one additional criteria.</u>**

(a) Cardiac Enzyme Criteria

Pertinent enzyme results (as defined below) include those recorded in the hospital chart for days one through four after hospital admission, or days one through four after an in-hospital CHD event. Information on any non-ischemic causes for elevated enzymes will be obtained from the hospital discharge summary. Clinical centers should provide laboratory normal ranges for these cardiac enzymes (troponin and CK-MB).

a) Abnormal Cardiac Enzymes

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

I. Troponin > 99th percentile of the hospital's upper reference limit. In addition, documented rise and/or fall of troponin level is preferred but may not be strictly required in all cases.

II. Creatine Kinase Heart Fraction (CK-MB) > 99th percentile of the hospital's upper reference limit. In addition, documented rise and/or fall of CK-MB level is preferred but may not be strictly required in all cases.

(b) 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.

(c) Electrocardiographic Criteria (ECG code)

Clinical Centers request the 12 lead ECG tracings obtained at every CVD related hospitalization. These "hardcopy" ECGs along with an Event ECG Procedure Log P08 form must be forwarded to the Epicare for analysis. Results of the ECG Reading are forwarded to the Coordinating Center for presentation to the Outcomes Classification Committee. The algorithm for serial analyses of these hospital ECGs are outline below in Table 1

Table 1 Algorithm for Serial Comparison of ECGs used by Epicare

Prior ECG	Current ECG to analyze	Criteria and results
Baseline	Scheduled follow-up ECG	No prior hospitalization ECG and no prior significant serial change (Code Q1-Q7) Coding will be Q0-Q7
Most recent scheduled follow-up ECG	Worst scoring ECG from one hospitalization	Current ECG is the first set of ECGs from hospitalization Coding will be NH1-NH5
Worst scoring ECG from most recent hospitalization	Scheduled follow-up ECG	Scheduled follow-up ECG obtained after hospitalization ECGs Coding will be NH1-NH5
Scheduled follow-up ECG	Scheduled follow-up ECG	Previous finding of Q1-Q7 for participant Coding will be Q0-Q7

(d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

(e) Identification of an intracoronary thrombus by angiography or autopsy

1.3.1.2 Post-procedure (PCI) Myocardial infarction (Type 4, criteria adopted October 2016, see APPENDIX A Table A1.3)

MI associated with and occurring within 48 h of PCI. Requires elevation of cardiac biomarker values to >5 X 99th percentile of the URL in patients with normal baseline values or a rise of cardiac biomarker values >20% if baseline values are elevated and are stable or falling. This classification also requires at least 1 of the following:

(a) Symptoms suggestive of myocardial ischemia (see 3.1.1)

(b) New ischemic changes on ECG or new LBBB (see Appendix ATable A2 and Table xx.

(c) Angiographic loss of patency of a major coronary artery or a side branch or persistent slow flow or noflow or embolization

(d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

1.3.1.3 Post-procedure (CABG) Myocardial infarction (Type 5, criteria adopted 2016, see APPENDIX A Table A1.4)

MI associated with and occurring within 48 h of CABG. Requires elevation of cardiac biomarker values to >10 X 99th percentile of the URL in patients with normal baseline values. This classification also requires at least 1 of the following:

(a) ECG: pathologic Q waves or new LBBB (APPENDIX A: Reference Tables for Diagnosis of Myocardial Infarction – used for adjudications beginning October 1, 2016)

(b) Angiographic new graft or native coronary occlusion

(c) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

1.3.1.4 Silent Myocardial Infarction (determined by Epicare analysis of ECGs)

A silent myocardial infarction is defined as having occurred when changes from the DPP baseline ECG or any previous ECG during DPP or DPPOS show a clear loss of R-wave potential or the appearance of pathologic Q waves in the absence of a known clinical event and without another explanation. The ECGs are compared according to Table 3.2 and 1 and coded as silent MI if it meets any of the 7 criteria outlined in section 5 below. Details are found in the Minnesota Code Manual of Electrocardiographic Findings(1)

1.3.1.4.1 ECG Criteria for Silent MI

Q1. No Q-code in reference ECG followed by a record with a diagnostic Q-code (MC 1-1-1 through 1-2-7) OR an Equivocal Q-code (any MC 1-3-x) in reference ECG followed by record with any code 1-1-x Q-code.

Q2. An Equivocal Q-code (any MC 1-3-x code) and no major ST-segment depression (MC 4-0, 4-4, 4-3) in reference ECG followed by a record with a diagnostic Qcode (MC 1-2-1 – 1-2-7) Plus a major ST-segment depression (MC 4-1-x or 4-2).

Q3. An Equivocal Q-code (any MC 1-3-x) and no major T-wave inversion (MC 5-4, 5-3 or 5-0) in reference ECG followed by a record with a diagnostic Q-code (MC1-2-1 through 1-2-7) Plus a major T-wave inversion (MC 5-1 or 5-2).

Q4. An Equivocal Q-code (any MC 1-3-x) and no ST-elevation in reference ECG followed by a record with a diagnostic Q-code (MC1-2-1 through 1-2-7) Plus an ST-segment elevation (MC 9-2).

Q5. No Q-code and no MC 4-1-x or 4-2 in reference ECG followed by a record with an Equivocal Q- code (any MC 1-3-x) Plus MC 4-1-x or 4-2.

Q6. No Q-code and no MC 5-1 or 5-2 in reference ECG followed by a record with an Equivocal Q-code (any MC 1-3-x) Plus a MC 5-1 or 5-2. Q7. No Q-code and no MC 9-2 in reference ECG followed

1.3.2 Death

Deaths will be categorized as coronary death, other cardiovascular death, or non-cardiovascular death, based on review of available medical records and the death certificate. In the absence of other evidence, the NDI cause of death will be accepted.

1.3.2.1 Coronary Death

Coronary death will be subclassified as:

- *Definite fatal MI:* no known non-atherosclerotic cause and definite MI within twenty-eight days of death; **Or** autopsy evidence of acute MI.
- *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); death resulting from a procedure related to coronary artery disease such as coronary bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA).
- **Or** *possible fatal CHD*: no known non-atherosclerotic cause and death certificate consistent with CHD as underlying cause.

1.3.2.2 Other Cardiovascular Death

A diagnosis of other cardiovascular death is a death from cardiovascular disease not meeting the definition of coronary death; for example, fatal stroke or death resulting from peripheral revascularization procedure, congestive heart failure, cardiomyopathy, pulmonary embolism, ruptured aneurysm, sudden cardiac death or valvular heart disease.

1.3.2.3 Non-coronary or Non-cardiovascular Death

(a) Cancer

(b) Infection

(c) Trauma (e.g., accident, homicide, suicide)

(d) Chronic respiratory disease (e.g., COPD, asthma, interstitial lung disease)

(e) Non-Stroke Neurological Disease (e.g., Alzheimer's, Parkinson's, other degenerative neurological disorder)

(f) Renal Disease

(g) Other

1.3.3 Other Cardiovascular Outcomes

1.3.3.1 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 rales, edema, 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 clinical cardiovascular 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 an outcome. The diagnosis of CHF requires the following documentation:

- Final diagnosis of CHF by a physician, and
- > 24 hr. hospital stay.

1.3.3.2 Unstable Angina Pectoris

Unstable 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 ≤ 20 minutes. A diagnosis of unstable angina pectoris for purposes requires either of the 2 criteria:

- Physician diagnosis of unstable angina, and > 24 hr. hospital stay.
- **Or** Physician diagnosis of acute coronary syndrome (not meeting the definition of MI) and >24 hr. hospital stay

1.3.3.3 Cardiac Arrhythmias

Cardiac arrhythmias are defined as hospitalization for variation from the normal rhythm of the heartbeat including heart block, atrial fibrillation or flutter, paroxysmal supraventricular or ventricular tachycardia or ventricular fibrillation. A determination of cardiac arrhythmia for this purpose requires either of these 2 criteria:

- > 24 hr. hospitalization for physician diagnosis of cardiac arrhythmia OR prolongation of hospitalization due to occurrence of arrhythmia
- **Or** surgical procedure such as permanent pacemaker insertion, implantable defibrillator, cardioversion (including electrical or medical) or ablation therapy.

1.3.3.4 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 dilatation
  - Atherectomy
- Other coronary revascularization (e.g. laser technology)

Note: An attempted revascularization should be captured as a revascularization on the R18 Cardiovascular and Mortality Classification Report Form.

1.3.3.5 Coronary heart disease by angiography only

CAD by angiography is defined as the presence of 50% or greater stenosis of any coronary artery detected by angiography in the absence of clinical events (i.e. 3.1-3.4). This may include either of the 2 criteria:

- Participants with insufficient or inappropriate coronary lesions for revascularization.
- Participants or who refused revascularization.

1.3.3.6 Stroke (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.

The diagnosis of stroke will be made based on the hospitalization record demonstrating that a stroke has occurred. Strokes will include those occurring during revascularization procedures and those aborted by thrombolytic therapy (streptokinase, TPA, etc.)

The definition of stroke excludes old stroke by CT or MRI scans. 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. Stroke outcome requires the following criteria:

- Physician diagnosis of stroke and > 24 hr. hospital stay.

1.3.3.7 Peripheral Arterial Disease

Peripheral arterial disease is defined as atherosclerotic disease of the aorta, carotid artery, iliac artery or arteries below. The diagnosis of peripheral arterial disease requires either of the 2 criteria:

- Revascularization procedure, such as vascular bypass surgery or angioplasty for peripheral arterial disease.

  Or

- Amputation for peripheral arterial disease.

Note: Revascularization procedures for renal artery stenosis are not included in the definition of peripheral arterial disease because of a difference in etiology.

1.3.4 Recurring/Continuous Cardiovascular Disease Events

Repeat hospitalizations for a chronic medical condition (e.g. CHF, arrhythmia) occurring within 4 weeks of the initial hospitalization discharge, are considered recurring events. Recurring events will be reviewed by a member of the Outcomes Committee to determine if the events require adjudication. If the Outcomes Classification reviewer decides a recurring event is a continuation of the initial event and does not meet any new cardiovascular event criteria, the event will be closed without adjudication.

1.3.5 Procedures for the Committee

The purpose of the Outcomes Classification Committee is to establish the guidelines and procedures for the review and classification of study outcomes. The Committee consists of a chairman and other members. Members of the committee will review all deaths and cardiovascular events. Two members (primary and secondary reviewers) will review each cardiovascular and mortality event to ensure that the cases are reviewed properly and thoroughly. Cases will be evenly distributed such that committee members will not review events from his/her clinic. The Chair of the Committee or designee is the final adjudicator of all cases and adjudicates any discrepancies between the other reviewer's cases.

1.3.5.1 Adjudication Materials

Approximately every other month, cardiovascular (CVD) cases and mortality cases are provided to the reviewers for their review. The reviewers have access to MIDAS where CVD and Mortality events can be reviewed online using the Medical Event Monitoring System (MEM). Cardiovascular and Mortality Classification Report Forms (R18), a Summary of CVD events and ECGs, information from Participant Forms, and all available supporting documentation are available in the MEM system. Refer to the MIDAS Medical Event Monitoring Manual for more details about the system.

1.3.5.1.1 Cardiovascular and Mortality Classification (R18) Forms

The Cardiovascular and Mortality Classification Report (R18) is used as documentation of the Outcomes Committee's classification of each event. The reviewer can complete the R18 online directly using the MEM system. The reviewer can also enter any comments, requests and questions on the R18.

1.3.5.1.2 Summary of CVD Events and ECGs

A Summary of CVD Events and ECGs is provided for each case. The Summary displays the ECG results from Epicare Reading Center for all scheduled ECGs preformed at the Clinic and the ECGs for all CVD related events obtained by the clinic. Refer to Attachment 1 for a list of ECG definitions and codes used by Epicare. A list of all reported events and adjudicated events for the participant from are also included in the Summary. If more than one event for a participant is included in the batch sent to the reviewers, the reported event information pertaining to the case is outlined in a black box for differentiation.

1.3.5.1.3 E08 Event Report Form

The E08 Event Report Form is used by the clinics to document the CVD and/or mortality event reported to them. The information in the E08 will be used (along with additional supporting documentation) by the Outcomes Committee to determine the Outcomes Classification.

1.3.5.1.4 E08 Supplement: CVD and DEATH Medical Records Checklist

The E08 Supplement: CVD and Death Medical records checklist can be used by clinics to help ensure that the complete medical records needed to adjudicate an event are sent to the CoC. Among a checklist of the records that should be sent per type of event, recommendations on how to obtain records are provided. Clinics can also use this form to include any additional information that they believe might be helpful in the adjudication of the event.

1.3.5.1.5 E06 Mortality Report

The E06 Mortality Report is used by the clinics to document all participant deaths that occurred. In the case of a mortality event, the E06 should be used with the E08 Event Report Form and supporting documentation to determine the Outcomes Classification.

1.3.5.1.6 Supporting documentation

All medical records and death certificates provided by the clinic are included in MEM for supporting documentation of the event reported on the E08 Event Report Form. If medical records or a death certificate could not be obtained, a memo from the clinic Program Coordinator will be included explaining:

- All known information about the event
- How the clinic obtained the known information
- Steps taken to try to obtain the records
- Reason why medical records or death certificate were not obtained

APPENDIX A: Reference Tables for Diagnosis of Myocardial Infarction – used for adjudications beginning November 1, 2016

Table A1 Definition of Criteria for Diagnosis of Myocardial Infarction

Table A1.1 Algorithm for Type 1 (spontaneous) and Type 2 (ischemic imbalance) MI

Abnormal enzymes (troponin or CK-MB): Detection of at least one cardiac biomarker value >99th%tile of the URL; rise and/or fall of biomarkers should be noted, but may not be required in all cases; plus any ONE of the following:	
1. Symptoms of myocardial ischemia (i.e., chest pain)	MI
2. ECG findings (EPICARE CODE): • New or presumed new significant ST-segment–T wave (ST–T) changes **(NH3 or NH4)** • New LBBB **(NH2)** • Development of pathological Q waves **(NH1)**	MI
3. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality	MI
4. Intracoronary thrombus(applicable only for Type 1)	MI
None of the above	No MI

Table A1.2 Algorithm for Type 3 MI: death, no biomarkers

Death where symptoms suggestive of myocardial ischemia are present, and with (presumed) new ischemic changes or new LBBB on ECG, but where death occurs before cardiac biomarkers can be obtained or could rise or (in rare cases) were not collected.	**Fatal MI**

Table A1.3 Algorithm for Type 4 (PCI related) MI

Abnormal enzymes (troponin or CK-MB): Detection of > 5 x 99th%tile of URL or rise of cardiac biomarkers > 20% from baseline plus any ONE of the following, occurring within 48 hours of PCI	
1. Symptoms **of myocardial ischemia (i.e., chest pain)**	MI
2. ECG findings **(EPICARE CODE):** • New ischemic changes **(NH3 or NH4)** • New LBBB **(NH2)**	MI
3. Angiographic loss of patency, low flow, no flow, or embolization	MI
4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality	MI
None of the above	**No MI**

Table A1.4 Algorithm for Type 5 (CABG related) MI

Abnormal enzymes (troponin or CK-MB): Elevation of cardiac enzymes >10 x 99th%tile of URL plus any ONE of the following, occurring within 48 hours of CABG surgery:	
1. ECG findings **(EPICARE CODE):** • Development of pathologic Q waves **(NH1)** • New LBBB **(NH2)**	MI
2. Angiographic new graft or native coronary occlusion	MI
3. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality	MI
None of the above	**No MI**

Table A2.2 – version 2. Revised ECG Classifications and Minnesota Code Criteria used by Epicare

New Label and description	Concept and permissible value definitions from Hicks 2015	H codes and corresponding Minnesota codes
NH1 **– New pathological Q Waves**	New (or presumed new) a) Q wave in leads V2 to V3 ≥0.02 s or QS complex in leads V2 and V3; b) Q wave≥0.03 s and $0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4 to V6 in any 2 leads of a contiguous lead grouping (I, aVL; V1 to V6; II, III, aVF; V7 to V9); or c) R wave ≥0.04 s in V1 to V2 and R/S ≥1 with a concordant positive T wave in the absence of a conduction defect.	Present H1-H2 (equal Q1-Q7), but require *serial comparison rules* which in MC book Chapter 15 from *page 224-228*
NH2 **– New LBBB**	New (or presumed new) LBBB pattern on ECG.	H2- Evolving Left Bundle Branch Block (equal E-BBB1)
NH3 **- ST-segment depression and/or T wave inversion**	In the absence of LVH and LBBB pattern (or other confounder such as a paced rhythm) on ECG, new (or presumed new) horizontal or downsloping ST-segment depression ≥0.05 mV in 2 contiguous leads and/or T inversion ≥0.1 mV in 2 contiguous leads with prominent R wave or R/S ratio >1	H3 --Major ST-T change (MC-4.1,4.2, MC-5.1, 5.2), and serial change equal ST1,ST2,ST3,ST4,ST6,ST7,ST8)
NH4 **ST-segment elevation only**	In the absence of LVH and LBBB pattern (or other confounder such as a paced rhythm) on ECG, new (or presumed new) ST elevation at the J point in 2 contiguous leads with the following cut points: ≥0.1 mV in all leads other than leads V2 to V3 where the following cut points apply: ≥0.2 mV in men≥40 y of age; ≥0.25 mV in men <40 y of age, or ≥0.15 mV in women;	
NH5**– No significant ECG finding,**		Any other codes
NH6 **–ECG absent or uncodable**		ECG Quality = 5 or Lead reversal Poor quality with 1 or 2 lead only

APPENDIX B: Reference Tables for Diagnosis of Myocardial Infarction – used for adjudications prior to November 1, 2016

Table B1 Definition of Criteria for Diagnosis of Myocardial Infarction

		Cardiac Enzymes*		
ECG Pattern/Symptoms	H Code	Abnormal	Not available	Normal
Cardiac pain present:				
Evolving Q wave and evolving ST-T Abnormalities	**H1** -- Grade 2 Q wave evolution or acute ischemic ST-T evolution	Definite MI	Definite MI	Definite MI
Equivocal Q wave evolution; or Evolving ST-T abnormalities; or new left bundle branch block	**H2** -- Grade 1 Q wave evolution And evolving ST-T; **OR** Acute Ischemic STE evolution; **OR** Incident LBBB	Definite MI	Probable MI	No MI
Q waves or ST-T abnormalities Suggestive of an MI and not classified Above	**H3** -- Grade 1 Q wave evolution; **OR** Evolving ST-T	Definite MI	No MI	No MI
Other ECG	**H4** – Other ECGs, ECG absent or uncodable	Definite MI	No MI	No MI
ECG absent or uncodable	**H5** –ECG absent or uncodable	Definite MI	No MI	No MI
Evidence on imaging of new regional wall motion abnormality or intracoronary thrombus	Any H code	Definite MI	No MI	No MI
Cardiac pain absent:				
Evolving Q wave and evolving ST-T Abnormalities	**H1** -- Grade 2 Q wave evolution or acute ischemic ST-T evolution	Definite MI	Definite MI	Probable MI
Equivocal Q wave evolution; or Evolving ST-T abnormalities; or new left bundle branch block	**H2** -- Grade 1 Q wave evolution And evolving ST-T; **OR** Acute Ischemic STE evolution; **OR** Incident LBBB	Definite MI	No MI	No MI
Q waves or ST-T abnormalities Suggestive of an MI and not classified above	**H3** -- Grade 1 Q wave evolution; **OR** Evolving ST-T	Probable MI	No MI	No MI

Other ECG	**H4** – Other ECGs	No MI	No MI	No MI
ECG absent or uncodable	**H5** –ECG absent or uncodable	No MI	No MI	No MI
Evidence on imaging of new regional wall motion abnormality or intracoronary thrombus	Any H code	Definite MI	No MI	No MI

* See Table B1.1 - Cardiac Enzymes for definitions.

Table B1.1 Algorithm for Enzyme Diagnostic Criteria

Enzyme	Abnormal	Equivocal	Normal
Troponin	≥2x ULN	ULN<Troponin<2x ULN	WNL
CK-MB	≥2x ULN or ≥ 10% of total CK or "present" without quantification	ULN<CK-MB<2x ULN or 5% ≤ of total CK < 10% or "weakly present"	WNL or <5% of total CK
Total CK/total LDH	Total CK **and** total LDH ≥2x ULN	Total CK **or** total LDH (but not both) ≥2x ULN or ULN<total CK **and** total LDH<2x ULN	Total CK WNL or total LDH WNL
LDH_1 and/or LDH_2	$LDH_I \geq LDH_2$ or LDH_I ≥2x ULN	ULN<LDH_I <2x ULN	$LDH_I < LDH_2$ or LDH_I WNL

ULN = upper limit of normal

WNL = within normal limits

DPPOS – The definition for Myocardial Infarction -- 01-28-2010

Table B1.2 ECG Classifications and Minnesota Code Criteria

Current Label and description	Minnesota coding by EPICARE
H1 -- **Grade 2 Q wave evolution or acute ischemic ST-T evolution**	(a) Evolving Diagnostic Q Code (Major Q_code): MC -- 1-1-1 to 1-2-5 plus 1-2-7; (equal Evolving Q1-*page 228*) (b) Evolving Equivocal Q code (Minor Q code) plus Evolving ST-Elevation (equal Evolving Q4, Q7- *page 228*)
H2 -- **Grade 1 Q wave evolution And evolving ST-T;** OR **Acute Ischemic STE evolution;** OR **Incident LBBB**	(a) Evolving Equivocal Q-code (Minor Q_code): MC -- 1-2-8 to 1-3-X plus Evolving ST-Depression / T Wave Inversion (equal Evolving Q2, Q3, Q5, Q6-*page 228*) (b) Evolving ST-Elevation (equal STE-1 [ST5], *page 229*) (c) Evolving Left Bundle Branch Block (equal E-BBB1, *page 230*)
H3 -- **Grade 1 Q wave evolution;** OR **Evolving ST-T**	(a) Evolving ST-Depression / T Wave Inversion (equal from ST-T1 to ST-T7, i.e. ST1,ST2,ST3,ST4,ST6,ST7,ST8 – *page 229*) (b) Evolving Equivocal Q-code (Minor Q_code): MC -- 1-2-8 to 1-3-X (equal Q8, [not show in the document]
H4 – **Other ECGs,**	Any other codes
H5 –**ECG absent or uncodable**	ECG Quality = 5 or Lead reversal

APPENDIX C

Forms used by clinics to report CVD and mortality events:

E06: Mortality Report Form

E08: Event Report Form

E08 Supplement: CVD and DEATH Medical Records Checklist

REFERENCES:

(1) Prineas RJ, Crow RS, Zhang Z. *The Minnesota code manual of electrocardiographic findings.* Springer Science & Business Media; 2009.

DIABETES PREVENTION PROGRAM OUTCOMES STUDY

OUTCOMES CLASSIFICATION MANUAL

Chapter 2

Table of Contents

2. Classification Procedures: Microvascular Events

2.1 Microvascular Outcomes Definition

The composite diabetes-related microangiopathic primary outcome is defined as the presence of one or more of the following at the year 11 visit, or if the participant is deceased or lost to follow-up, the presence at one or more of the following as of his/her last assessment:

a. Nephropathy: micro- or macro-albuminuria (≥30 mg/gram creatinine, confirmed), or renal dysfunction (end-stage renal disease, dialysis or renal transplant) or GFR < 45 ml per min based on serum creatinine, using the CKD-EPI equation or another validated algorithm; the qualifying criteria confirmed)
b. Retinopathy: retinopathy by fundus photography (ETDRS grade of 20 or greater) or adjudicated history of laser or other treatment for retinopathy or
c. Neuropathy: reduction or absence of light touch sensation to monofilament (Semmes-Weinstein 10 gram) in either foot (< 8 of 10 applications detected).

If a participant is taking antihypertensive drugs at the last assessment and does not meet the ACR or eGFR criteria at that time, he or she may be considered to have reached the nephropathy outcome if the nephropathy criteria were met at 2 consecutive past visits. This may substitute for the occurrence of nephropathy. Microvascular outcomes will continue to be assessed and adjudicated as needed during Phase 3.

2.2 Nephropathy

2.2.1 Required Documentation

2.2.1.1 eGFR

The eGFR outcome is reached when:

- eGFR < 45ml/min based on CKD-EPI equation and using study lab data, confirmed by repeat testing.

- If the participant is not available for a visit, then eGFR <45 present at the last 2 consecutive visits

No adjudication required.

2.2.1.2 End Stage Renal Disease

The End Stage Renal Disease (ESRD) outcome requires:

- Medical records document renal transplantation

OR

- Medical records document ongoing hemodialysis or peritoneal dialysis. This does NOT include a single dialysis treatment or treatment during a single hospital stay. Acceptable medical records include hospital records or outpatient dialysis reports that indicate date treatment was initiated.

The Outcomes Committee will adjudicate all renal events documented on the E08 Event Report Form so determine if the ESRD outcome has been reached.

2.2.1.3 Albuminuria

The Albuminuria outcome is reached when:

- UAC >30 mg/g is confirmed by repeat testing.

If a participant is taking antihypertensive drugs at the last assessment and does not meet the ACR criteria at that time, he or she may be considered to have reached the nephropathy outcome if the nephropathy criteria were met at 2 consecutive past visits.

If the participant not available for a visit, then UAC >30 present at the last 2 consecutive visits.

No adjudication required.

2.3 Retinopathy

2.3.1 Ascertainment of Retinopathy Outcomes

The retinopathy outcome will be ascertained by fundus photography (ETDRS grade of 20 or greater) or adjudicated history of laser or other treatment for retinopathy.

2.3.2 Required Documentation

Medical records are needed to document:

- laser treatment for proliferative diabetic retinopathy
- laser treatment for diabetic macular edema
- vitrectomy for diabetic retinopathy
- intravitreal injection for proliferative diabetic retinopathy
- intravitreal injection for diabetic macular edema

Acceptable medical records include hospital records and outpatient surgical reports. Reports of other retinal procedures or retinal surgeries will be reviewed by the Outcomes Committee first to determine if adjudication by the Fundus Photograph Reading Center (FPRC) is necessary. If the Outcomes Committee determines that adjudication is necessary, the CoC will request medical records from the clinic and forward the event to the FPRC. Final adjudication of retinopathy outcomes will be made by the FPRC.

2.4 Neuropathy

2.4.1 Definition of Primary Neuropathy Outcome

The presence of neuropathy will be defined by the reduction or absence of monofilament light touch in either foot (< 8 detected applications of the 10 gram Semmes Weinstein Monofilament) at at the most recent visit. No adjudication required.

2.4.2 Definition of Secondary Neuropathy Outcomes

Secondary Neuropathy Outcomes will be defined by:

- Reduction or absence of light touch sensation to monofilament (Semmes-Weinstein 10 gram) in either foot (< 8 of 10 applications detected)
- Symptom assessment
- Michigan Neuropathy Screening Instrument
- EKG rhythm strip: to measure heart rate variability

The protocol does not provide specific criteria for these outcomes. No adjudication required.

DIABETES PREVENTION PROGRAM OUTCOMES STUDY

OUTCOMES CLASSIFICATION MANUAL

Chapter 3

Table of Contents

3. Classification Procedures: Outside PCP Diabetes Diagnosis

3.1 Diabetes Diagnosis

Participants will not be considered as diabetic in the study until they have been confirmed diabetic through our procedures outlined in the Protocol. The Outcomes Committee will adjudicate cases where participants who have been diagnosed as diabetic by their Primary Care Physician have not been confirmed by procedures in the Protocol.

3.2 Outside PCP Diabetes Diagnosis Adjudication Procedures

All Outside PCP Diabetes Diagnosis events will be adjudicated if the participant has not confirmed within the studyS. Outside PCP Diabetes Diagnosis Adjudication will take place close to the end of each Phase to give participants a chance to confirm with the procedures outlined in the Protocol.

It is expected that diabetes diagnosis (often followed by treatment initiation) outside of the study may be an increasingly common occurrence, as the frequency of testing and follow-up within the study is reduced. The study will accept outside laboratory evidence of diabetes - but in only the following circumstances, all of which will be adjudicated by the Outcomes Committee:

- Labs must be obtained from a recognized, CLIA-certified commercial, hospital or clinic lab. Point of care testing (fingerstick glucose) is NOT acceptable.

- Standard ADA FPG and 2-hr glucose criteria apply. Fasting status needs to be indicated on the lab report and/or confirmed by the participant.

- Outside laboratory evidence of diabetes based on fasting or 2-hr glucose values may apply as a formal "trigger", requiring only a single confirmation test, either in the study clinic or at an outside lab.

- Diabetes diagnosed based on lab values not considered diagnostic in the study (i.e., HbA1c or casual glucose), will require 2 separate visits to obtain both a formal trigger and confirmation using study criteria (FPG and/or 2-hr glucose), either at a study clinic or from an acceptable outside lab.

- Regardless of what prompts the need for confirmatory testing, the participant should have this testing as soon as possible in order to minimize the chance that treatment will be initiated and thus obscure the presence of diabetes.

- Consistent with established study procedures, if a participant was already started on diabetes medication by an outside provider, this medication should be held on the morning of confirmatory glucose testing.