The **G**lycemia **R**eduction **A**pproaches in **D**iabetes: A Comparative **E**ffectiveness **Study (GRADE Study)**

Outcome Classifications and Adjudication Procedures

Version 1.3

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Maintained by the GRADE Study Coordinating Center
The Biostatistics Center
George Washington University
6110 Executive Boulevard
Rockville, Maryland 20852

Contents

1.0 Introduction

This document describes GRADE-defined criteria for GRADE outcomes and outlines the necessary procedures and documentation required to arrive at consistent classification of outcomes by the GRADE Outcomes Subcommittee. This document was prepared by the Outcomes Subcommittee and maintained by the GRADE Coordinating Center in conjunction with the Outcomes Subcommittee to reflect current definitions and procedures.

The primary outcome for the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study is the time to the observation of an HbA1c value ≥7.0%, subsequently confirmed, while subjects are treated with both metformin (up to 2000 mg per day) and the randomly assigned glucose-lowering medication. This primary metabolic outcome along with the secondary and tertiary metabolic outcomes are outlined in the Metabolic (HbA1c) Outcomes section (Section 3.0) of this manual. Secondary and other composite outcomes include cardiovascular outcomes, adverse effects of drugs such as lactic acidosis, pancreatitis, cancer (except non-melanoma skin cancer), and death.

The classifications of events are derived from a combination of signs and symptoms recorded on case report forms and redacted medical records, and objective evidence such as laboratory results, radiology reports, electrocardiograms (ECGs), etc.

2.0 Description of Adjudication Process

All case reports for study outcome events will be masked (i.e. blinded) to study drug assignment. The Coordinating Center will request documentation from clinical sites and assemble an event case report for review and adjudication. The Coordinating Center will determine when the event information is complete and assign the potential outcome to reviewers for adjudication. All members of the Outcomes Subcommittee will adjudicate events. No reviewer will be assigned his/her own site event for review and adjudication.

2.1 Severe Hypoglycemia

All cases of severe hypoglycemia reported to the study will be reviewed by two reviewers to ensure that they meet the study's definition of this outcome as outlined in Section 10.2.5 of the Manual of Procedures (MOP). A Hypoglycemia Working Group consisting of two study investigators with endocrinology expertise will be appointed by the Outcomes Subcommittee co-chairs to review all reports of severe hypoglycemia. The co-chairs will oversee the performance of this group. They will also serve as alternate or tie-break reviewers as needed. In order to be accepted as a case of severe hypoglycemia, any two reviewers must agree that the event meets the study definition. If a determination cannot be reached, the Hypoglycemia Working Group may seek the guidance of study leadership (e.g. Protocol Oversight Subcommittee, Executive Committee).

2.2 All Other Outcomes

There are five other categories of outcome events for adjudication:

- Cardiovascular disease (CVD)
- Pancreatitis
- Lactic acidosis
- Cancer
- Mortality

Each event will be forwarded to two primary reviewers for review and adjudication. In the case of disagreement, the Coordinating Center will facilitate further review and discussion between the two primary reviewers in an effort to reach agreement. If agreement cannot be reached, the case will undergo a secondary review by one of the Outcomes Subcommittee Co-Chairs. If a determination still cannot be reached, a third-party subject matter expert may be consulted.

2.3 Outcome Definitions

This document, in conjunction with the GRADE Study Protocol, provides definitions to be used for study outcomes. As unforeseen contingencies arise, examples of how these are handled will be circulated to the group. These will be reviewed at meetings of the Outcomes Subcommittee. If the adjudication procedure is found to be unclear or limited, the procedures will be revised or expanded. Since no adjudication process can be completely comprehensive, a record of the handling of unusual outcomes will be maintained as a form of "case law" to establish precedent and ensure consistency when similar situations arise.

2.4 Reporting of Adjudicated SAEs

The Coordinating Center will notify the Study Chair, the Study Intervention Monitor/Co-Chairs of the Protocol Oversight Subcommittee, the appropriate representative at NIH, and the chairperson of the DSMB (as required) when the following are determined to have occurred, if no previous notification has occurred:

- Death
- Lactic acidosis
- Pancreatitis

3.0 Glycemic Outcomes

3.1 Protocol Definitions (see MOP Sections 8.1.2-8.1.4 and charts below)

Primary metabolic outcome: HbA1c ≥7%, confirmed at next quarterly visit if ≤9% or 3-6 weeks if >9%.

Secondary metabolic outcome: HbA1c >7.5%, confirmed at next quarterly visit if ≤9% or 3-6 weeks if >9%.

Tertiary metabolic outcome for all participants except those randomized to glargine: HbA1c >7.5% 3 months after secondary metabolic outcome, confirmed at next quarterly visit if ≤9% or 3-6 weeks if >9%.

All outcomes will be reported per intention-to-treat. Primary and secondary outcomes may be reached simultaneously. The earliest possible time to reach tertiary metabolic outcome is 6 months after achieving the secondary metabolic outcome. At the time the secondary metabolic outcome is reached, the participant is supposed to start glargine. This timing allows 6 months for glargine titration prior to triggering the tertiary metabolic outcome. If the participant refuses to start glargine but HbA1c is persistently elevated, the tertiary metabolic outcome will have been met according to intention-to-treat 6 months after secondary.

Outcome definitions for Reference

Summary of A1C Metabolic Outcomes Triggers and Confirmation

AFTER 3 MONTHS

PRIMARY (MOP Section 8.1.2)

HbA1c Trigger (%)	3-6 weeks Confirmation	Next Quarterly Confirmation	Outcome	Action Taken
7-7.5	N/A	<7	Continue treatment & f/u	None
		7-7.5	Primary	Observe on assigned therapy
		>7.5	Primary, plus trigger for Secondary	Observe on assigned therapy
7.6-9	N/A	<7	Continue treatment & f/u	None
		7-7.5	Primary	Observe on assigned therapy
		>7.5	Primary and Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin
>9	>9		Primary and Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin
	≤9	<7	Continue treatment & f/u	None
		7-7.5	Primary	Observe on assigned therapy
		>7.5	Primary and Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin

SECONDARY (MOP Section 8.1.3)

HbA1c Trigger (%)	3-6 weeks Confirmation	Next Quarterly Confirmation	Outcome	Action Taken
7.6-9	N/A	≤7.5	Continue treatment & f/u	None
		>7.5	Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin
>9	>9		Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin
	≤9	≤7.5	Continue treatment & f/u	None
		>7.5	Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin

TERTIARY** (MOP Section 8.1.4) Note: **For all participants except those randomized to glargine

HbA1c Trigger (%)	3-6 weeks Confirmation	Next Quarterly Confirmation	Outcome	Action Taken
7.6-9	N/A	≤7.5	Continue treatment & f/u	None
		>7.5	Tertiary	Add rapid-acting insulin
>9	>9		Tertiary	Add rapid-acting insulin
	≤9	≤7.5	Continue treatment & f/u	None
		>7.5	Tertiary	Add rapid-acting insulin

4.0 Major Adverse Cardiovascular Events

Cardiovascular outcomes include major adverse cardiovascular events (MACE): fatal and non-fatal myocardial infarctions, fatal and non-fatal strokes, and other cardiovascular deaths. By definition, MACE events are serious adverse events due to resulting hospitalization and/or death. The definition of these events will follow the Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials.

4.1 Outcomes

The GRADE Study Protocol mentions several cardiovascular outcomes that are of interest to the study; however, only the following MACE outcomes will be reviewed and adjudicated:

- Cardiovascular Death
- Myocardial Infarction
- Stroke

4.2 Reporting and Documentation

Events should be reported as a Serious Adverse Event (SAE Form) that should be promptly reported to the local IRB and the Coordinating Center. The following information should be provided to the Coordinating Center as soon as feasible:

1. Summary of the illness
2. Summary of any treatment given
3. The outcome of the event
4. Summary of other associated acute medical disorders, their treatment and outcome
5. Summary of the participant's past medical history
6. Report of all concomitant medications the participant was taking at the time of the initial presentation with the event
7. If the event was fatal, the presumed cause of death. Commonly this information would be present in a hospital discharge summary, but it should be submitted in whichever format it is best available.

The following studies should be reported as appropriate and available from the medical record:

- Troponin T or I with normal ranges; CPK-MB has been largely supplanted by troponin but may be reported with normal range for laboratory if present.

- All ECGs available
- Any imaging studies relevant to event (cardiac catheterization, cardiac echo, brain MRI or CT)
- Procedure and operative reports.

Copies of the medical records, hospital discharge summary and autopsy report (if event was fatal and autopsy performed) will be required for adjudication. If death occurred outside of hospital, copy of death certificate should be obtained, if possible.

4.3 Adjudication

Events to be targeted for review and adjudication include those classified as MACE events and the following hospitalized events:

- Acute coronary syndrome
- Cerebrovascular accident (possibly TIA)
- Sudden death
- Coronary artery bypass graft

5.0 Non-MACE Cardiovascular Events

Non-MACE Cardiac Events include hospitalization for congestive heart failure (CHF), chest pain or unstable angina, arrhythmia, cardiac procedures, and revascularization. Definitions follow the Standardized Definitions for Cardiovascular and Stroke Endpoints in Clinical Trials.

5.1 Outcomes

The GRADE Study Protocol mentions several cardiovascular outcomes that are of interest to the study; however, only the following non-MACE outcomes will be reviewed and adjudicated:

- Unstable angina requiring hospitalization or revascularization
- Transient ischemic attack
- Heart failure requiring hospitalization
- Interventional cardiology procedures (e.g. coronary artery stent placement and percutaneous coronary angioplasty)
- Other vascular interventions (e.g. lower extremity stent, lower extremity angioplasty, carotid endarterectomy, carotid stent, renal artery stent, renal artery angioplasty, and aortic aneurysm repair)
- Stent thrombosis
- Coronary artery bypass graft

5.2 Reporting and Documentation

Events should be reported as a Serious Adverse Event (SAE Form) that should be promptly reported to the local IRB and the Coordinating Center. The following information should be provided to the Coordinating Center as soon as feasible:

1. Summary of the illness
2. Summary of any treatment given
3. The outcome of the event
4. Summary of other associated acute medical disorders, their treatment and outcome
5. Summary of the participant's past medical history
6. Report of all concomitant medications the participant was taking at the time of the initial presentation with the event
7. If the event was fatal, report the presumed cause of death. Commonly this information would be present in a hospital discharge summary, but it should be submitted in whichever format it is best available.

The following studies should be reported as appropriate and available from the medical record for cardiac events:

- Troponin T or I; CPK-MB mass, BNP levels
- All ECGs available
- Any imaging studies relevant to event (chest X-ray, cardiac catheterization, cardiac ultrasound, brain MRI or CT)

Copies of the medical records, hospital discharge summary, and autopsy report (if event was fatal and autopsy performed) will be required for adjudication. If death occurred outside of hospital, copy of death certificate should be obtained.

5.3 Adjudication

Events to be targeted for review and adjudication include those classified as non-MACE events and the following hospitalized events:

- Chest pain
- Dyspnea or shortness of breath
- Leg swelling
- Volume overload
- Transient ischemic attack (TIA)
- Renal artery stenosis
- Hypertensive urgency
- Other ischemic event such as peripheral vascular procedure or mesenteric ischemia

6.0 Lactic Acidosis

Lactic acidosis is a very rare but potentially fatal complication of metformin therapy. The recommendations for management below should be communicated to the medical team caring for the patient.

6.1 Definition

Lactic acidosis is a rare, but serious, metabolic complication due to metformin accumulation. Based on reported experience, the incidence of metformin-associated lactic acidosis (MALA) varies from 1/25,000 to 1/150,000 patient-years with an overall rate (as assessed by the FDA) of about 1/33,000 patient-years. With increasing attention to monitoring and discontinuation of metformin when appropriate, the incidence appears to be much lower than this. Based on the incidence and guidelines for metformin use, we do not anticipate any episodes of MALA in the course of the GRADE Study. However, MALA will be treated as a potentially serious complication and will be considered and reported as a Serious Adverse Event (SAE). Lactic acidosis may also occur in association with a number of other pathophysiologic conditions including diabetes mellitus and renal insufficiency, and whenever there is significant tissue hypoperfusion and/or hypoxia.

Lactic acidosis will be considered to be present if at least 2 of the following characteristics are documented:

1. Elevated blood lactate levels, typically >5 mmol/L (normal level is <1.5 mmol/L) **(REQUIRED)**
2. Metabolic acidosis with decreased blood pH
3. Electrolyte abnormalities with an increased anion gap (>12 regardless of lab normal range, adjusted for albumin)

   Albumin-corrected anion gap = **Anion gap**, mEq/L + [2.5 × (4 – **albumin**, g/dL)]

The participant must be in a hospital with one or more of the abnormalities above. This information should be gathered and sent to the Coordinating Center.

6.2 Reporting and Documentation

Lactic acidosis should be reported as a Serious Adverse Event (SAE Form) that should be promptly reported to the local IRB and the Coordinating Center. The following information should be provided to the Coordinating Center as soon as feasible:

1. Summary of the illness
2. Summary of any treatment given
3. The outcome of the event
4. Summary of other associated acute medical disorders, their treatment and outcome, including report of alcohol intoxication
5. Summary of the participant's past medical history, specifically those conditions which might also predispose to elevations in lactate, such as:
   - History of congestive heart failure with low ejection fraction
   - History of pulmonary disease
   - History of liver disease

6. Report of all concomitant medications the participant was taking at the time of the initial presentation with symptoms of lactic acidosis
7. If the event was fatal, report the presumed cause of death

The following laboratory results should be reported if available from the medical record:

- Blood lactate levels (specify if arterial or venous)
- Arterial blood gas (pH, pO2, pCO2, total CO2, O2 saturation)
- Plasma glucose level
- Serum ketones (β-OH butyrate)
- Electrolytes (Na, Cl, K, CO2, Ca, anion gap)
- Renal function (serum BUN &creatinine/eGFR)
- Hepatic function (ALT/SGOT, AST/SGPT, alkaline phosphatase, bilirubin)
- Alcohol level if present

Copies of the medical records, hospital discharge summary and autopsy report (if event was fatal and autopsy performed) will be required for review and adjudication.

7.0 Pancreatitis

7.1 Definition

Determination that acute pancreatitis is present requires at least two of the following three features:

1. Abdominal pain characteristic of acute pancreatitis
   - Persistent, severe, pain in epigastric area, occasionally in right upper quadrant, or left sided pain, often radiating to the back;
2. Serum amylase and/or lipase >3 times the upper limit of normal in the absence of renal failure or diabetic ketoacidosis at the time of acute pain or significantly elevated in the presence of renal failure or DKA; and
3. Characteristic findings of acute pancreatitis on CT scan, ideally rapid-bolus contrast enhances, within 72 hours;
   - Findings of acute interstitial edematous pancreatitis include focal or diffuse enlargement of the pancreas with heterogeneous enhancement with intravenous contrast; lack of enhancement indicates necrosis
   - Consistent findings on ultrasound or MRI if CT scan not available.

Pancreatitis can further be divided into **mild**, **moderately severe**, and **severe**:

- **Mild:** absence of organ failure and local or systemic complications.
- **Moderately severe:** transient organ failure (resolves within 48 hours) and/or local or systemic complications without persistent organ failure (>48 hours). Local complications include pseudocyst (collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue), necrosis (more than 3 cm or 30% of parenchyma), or abscess (circumscribed collection of pus containing little or no necrosis).
- **Severe:** persistent (>48 hours) organ failure / damage involving one or more organs.

Note: Organ failure is defined as:

- Shock (systolic blood pressure <90 mmHg)
- Pulmonary insufficiency (PaO2 <60 mmHg)
- Renal failure (serum creatinine level >2 mg/dl after rehydration)
- Gastrointestinal bleeding (>500 ml in 24 hours)

Potential precipitants of pancreatitis (report as *present* or *absent*):

- Biliary (Gallstones, microlithiasis, biliary sludge)
- Non-study drugs (list potential drug trigger)
- Hypertriglyceridemia
- Hypercalcemia
- Mechanical obstruction (ampullary stricture, tumor, parasites)
- Alcohol
- Toxins
- Trauma
- ERCP
- Other (describe potential trigger)

7.2 Reporting and Documentation

Pancreatitis should be reported as a Serious Adverse Event (SAE Form) and promptly reported to the local IRB and the Coordinating Center. The following information should be provided to the Coordinating Center as soon as feasible:

1. Summary of the illness
2. Summary of any treatment given
3. The outcome of the event
4. Summary of other associated acute medical disorders, their treatment and outcome, and potential precipitating factors such as alcohol consumption or gall bladder disease
5. Summary of the participant's past medical history
6. Report of all concomitant medications the participant was taking at the time of the initial presentation with the event
7. If the event was fatal, report the presumed cause of death

The following studies should be reported if available; attempts should be made to determine results from medical records:

- CBC with differential
- Amylase and lipase—ideally admission and peak
- Electrolytes (Na, Cl, K, CO2, Ca, anion gap)
- Renal function (serum BUN & creatinine)
- Hepatic function (ALT/SGOT, AST/SGPT, alkaline phosphatase, bilirubin)
- Results of imaging (abdominal CT scan, abdominal ultrasound, ERCP, etc.)
- Potential metabolic contributors: lipids including triglycerides—ideally admission and peak
- Blood alcohol levels if measured

Copies of the medical records, hospital discharge summary and autopsy report (if event was fatal and autopsy performed) will be required for review and adjudication. If death occurred outside of hospital, copy of death certificate should be obtained.

7.3 Adjudication

Events to be targeted for review and adjudication include those classified as pancreatitis and the following:

- Hospitalization for abdominal pain
- Multi-organ failure

8.0 Cancer

8.1 Reporting and Documentation

Cancer other than non-melanoma skin cancer will be reported as a Serious Adverse Event (SAE Form) that should be promptly reported to the local IRB and the Coordinating Center, regardless of hospitalization. The following information should be provided to the Coordinating Center as soon as feasible:

1. Summary of the illness
2. Summary of any treatment given
3. The outcome of the event
4. Summary of other associated acute medical disorders, their treatment and outcome
5. Summary of the participant's past medical history
6. Report of all concomitant medications the participant was taking at the time of the initial presentation with the event
7. If the event was fatal, report the presumed cause of death

The following studies should be reported as appropriate and available from the medical record:

- Specific reports of type of cancer, as available, such as:
    - Oncology inpatient or outpatient note documenting tumor type
    - Pathology reports and staging reports
    - Discharge summaries

8.2 Adjudication

All primary cancers identified during the study will be reviewed and adjudicated for type. Metastases will not be adjudicated. Adjudicators individually review available records and classify type of cancer as specifically as possible based on the available data. Cancer should be classified by organ system and cell subtype. For example: "Lung cancer, small cell," or "pancreatic cancer, adenocarcinoma." If cell subtype is unclear, adjudicators should use https://www.cancer.gov/publications/dictionaries/cancer-terms as a reference.

9.0 Death

9.1 Reporting and Documentation

Events should be reported as a Serious Adverse Event (SAE Form) that should be promptly reported to the local IRB and the Coordinating Center. The following information should be provided to the Coordinating Center as soon as feasible:

1. Summary of the illness
2. Summary of any treatment given
3. The outcome of the event
4. Summary of other associated acute medical disorders, their treatment and outcome
5. Summary of the participant's past medical history
6. Report of all concomitant medications the participant was taking at the time of the initial presentation with the event
7. If the event was fatal, report the presumed cause of death

The following studies should be reported as appropriate and available from the medical record:

- Date of death
- Cause of death
    - Underlying cause
    - Immediate cause
- Sub-classification of causes of death
    - Sudden death
    - Evidence of CVD (history of CVD and absence of other known cause)
    - MACE death, defined as death known to be due to MI or stroke (includes deaths within 30 days of MI or stroke)
    - Hypoglycemia—provide available documentation (witnessed event)
    - Hyperglycemic crisis: diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome
    - Diabetes-related if underlying cause is diabetic nephropathy
    - Cancer death—see Cancer Adjudication form
    - End-stage renal disease
    - Respiratory: specify COPD, other
    - Pneumonia: specify cause if known
    - Infection: specify type if known (sepsis, other)
    - Dementia
    - Chronic liver disease
    - Accident: specify type
    - Suicide
    - Overdose
    - Undetermined
    - Other: specify

9.2 Adjudication

Adjudicators will review all deaths to determine cause, when possible. The *underlying* cause of death will be the primary cause analyzed in GRADE. For example, if the immediate cause is pneumonia but the underlying cause is cancer, cancer will be considered the primary cause for the purposes of outcomes analyses.

By GRADE convention, deaths will be classified as CVD death (immediate cause: Sudden Death; underlying cause: Evidence of CVD) if a participant is known to have CVD and another cause of death cannot be identified. In contrast, MACE death is the appropriate classification if a death is *known* to be due to MACE, for example by autopsy or following witnessed stroke. Death may only be classified as sudden if the participant was seen alive and clinically stable ≤24 hours before being found dead and without any evidence supporting a specific non-cardiovascular cause of death (information about the participant's clinical status preceding death should be provided if available). For participants who were not observed alive within 24 hours of death, undetermined cause of death should be recorded.

If the death involves any of the other adjudicated outcomes (i.e. CVD, cancer, pancreatitis, or lactic acidosis), adjudicators should complete event-specific adjudication forms for all outcomes involved. For example, in the event of a death due to lung cancer, the same reviewers would complete both the Mortality Adjudication Form and the Cancer Adjudication Form.

10.0 References

1. Forsmark, C. E., and Ballie, J., AGA Institute Technical Review on Acute Pancreatitis, Gastroenterology 2007; 132:2022-2044. http://www.gastrojournal.org/article/S0016-5085(07)00591-4/fulltext#sec2

2. Kahn S.E., Haffner S.M., Heise M.A., et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43.

3. Hicks, K. A., Hung, H. J., & Mahaffey, K. W. (2012). Standardized definitions for cardiovascular and stroke end point events in clinical trials. *Draft Definitions for Testing November*, *9*.

4. Hicks, K.A, Tcheng, J.E, Bozkurt, B., Chaitman, B.R, Cutlip, D.E, Farb, A., Fonarow, G.C Jacobs, J.P, Jaff, M.R., Lichtman, J.H., Limacher, M.C., Mahaffey, K.W., Mehran, R., Nissen, S.E., Smith, E.E., Targum, S.L. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). Circulation 2015;132:302-61.

5. Hicks, K.A., Mahaffey, K.W., Mehran R., Nissen, S.E. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation 2018;137;961-972.

11.0 Appendices

11.1 GRADE Documentation of Outcomes Assessments

Outcomes Assessment[1]	Brief Description[2]	GRADE Documentation
METABOLIC		
Treatment failure		
• **Primary**	HbA1c ≥7%, confirmed at 3 months if ≤9% or 3-6 weeks if >9% while prescribed both metformin and the assigned study medication, regardless of adherence, according to intention-to-treat principle.	A1CMET
• **Secondary**	HbA1c >7.5%, confirmed at 3 months if ≤9% or 3-6 weeks if >9%, on assigned medication as described above.	A1CMET
• **Tertiary**	HbA1c >7.5% on metformin and basal insulin.	A1CMET
CARDIOVASCULAR		
MACE • **CV death** • **Myocardial infarction** • **Stroke**	Includes fatal and non-fatal myocardial infarctions, fatal and non-fatal strokes, and other cardiovascular deaths. By definition, MACE events are serious adverse events due to resulting hospitalization and/or death. The definition of these events will follow the Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials.	SAE, QUART/ ANNUAL
Non-MACE cardiovascular events	Includes congestive heart failure (CHF), chest pain or unstable angina, arrhythmia, cardiac procedures, and revascularization. The definition of these events will follow the Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials.	SAE, QUART/ANNUAL
ADVERSE EFFECTS		
Pancreatitis	A diagnosis of acute pancreatitis requires two of three features: 1. Abdominal pain characteristic of acute pancreatitis: persistent, severe, pain in epigastric area, occasionally in right upper quadrant, or left sided pain, often radiating to the back; 2. Serum amylase and/or lipase >3 times the upper limit of normal in the absence of renal failure at the time of acute pain; and/or 3. Characteristic findings of acute pancreatitis on CT scan, ideally rapid-bolus contrast enhances, within 72 hours: Findings of acute interstitial edematous pancreatitis include focal or diffuse enlargement of the pancreas with heterogeneous enhancement with intravenous contrast; lack of enhancement indicates necrosis; consistent findings on ultrasound or MRI if CT scan not available.	SAE, QUART/ANNUAL
SIDE EFFECT PROFILE		
Other (e.g. Lactic Acidosis)	Lactic acidosis is will be considered to be present if the following are documented: 1. Elevated blood lactate levels, typically >5 mmol/L (normal level is <1.5 mmol/L); AND 2. Metabolic acidosis with decreased blood pH; AND/OR 3. Electrolyte abnormalities with an increased anion gap (>12, regardless of lab normal range, adjusted for albumin).	SAE, QUART/ANNUAL
OTHER		
Diagnosis of cancer	Tracking all cancers except non-melanoma skin cancer. Cancer will be classified by organ system and cell sub-type.	SAE, QUART/ANNUAL
All-cause mortality	Mortality will be adjudicated for cause.	SAE

[1] As stated in Protocol v1.6.1

[2] Based on current version of Outcomes Procedures