Supplementary Material

Adjudication of cardiovascular events in patients with chronic obstructive pulmonary disease: SUMMIT trial

Supplementary Appendix A

Principles of Operation of the SUMMIT Clinical Endpoint Committee (CEC) Version 003

This document should be used in conjunction with the Charter developed for the SUMMIT CEC (**HZC113782)** protocol and will be updated at subsequent meetings.

Version 001 dated 15Apr2012
Version 002 dated 02Aug2012
Version 003 dated 29Jun2014

Assignment of cause of death

The Clinical Endpoint Committee will designate cause of death by probable cause. Causes of death will be grouped by general categories, e.g. pulmonary, cardiovascular, cancer, or other. If a cause of death cannot be ascertained, the cause of death will be classified as unknown. The general principles and methods used in this classification are listed:

Source documentation will be obtained to help in the assignment of cause of death see Appendix 1 and the form issued in Appendix 4.

The electronic case report form within the electronic Virtual Clinical Adjudication System (PAREXEL Inc, Waltham, MA) is shown in Appendix 2.

If medical records are inadequate and cannot be obtained as affirmatively stated in the documentation, a cause of death will be adjudicated based on the best available evidence of record. When information is incomplete, the adjudication of cause of death may rely on information derived from the participant's relatives or the site physician. The use of this information will inform assignment of cause of death based on consistency of the information as well as the specificity of the information. For example, the attribution of death from a particular type of cancer may be quite specific for the purposes of this study. However, terms such as 'heart attack' may be considered inconclusive with respect to this study in which cardiovascular adverse events are a major outcome.

Medical diagnoses will be based on the principle of Reasonable Degree of Medical Certainty, which can be defined as follows:

- The diagnosis is more likely than not
- The diagnosis is based on the same degree of certainty that would be used in the daily practice of medicine
- A majority of experts in the field would agree with the diagnosis.

The primary cause of death should be attributed to the disorder that causes the patient to present for medical treatment. This should be distinguished from terminal events that are the immediate cause of death.

- For example, if a patient is admitted to the hospital with a COPD exacerbation, from which they do not fully recover, and the patient subsequently develops complications such as pneumonia, respiratory failure, renal failure, sepsis or myocardial infarction, the

primary cause of death will be attributed to COPD. The myocardial infarction will be classified as a cardiovascular event (e.g. myocardial infarction, type 2).

- For example, if a patient undergoes surgery for cancer and dies from complications of the surgery or during the immediate postoperative period, the primary cause of death will be attributed to cancer, even if the cancer was potentially curable by the surgery.

- For example in general, if a patient is admitted to the hospital with pneumonia and develops complications such as respiratory failure, gastrointestinal bleeding, etc. the cause of death will be attributed to pneumonia. If it is unclear if a patient is admitted with a COPD exacerbation or pneumonia, the cause of death will be based on the hospital admission chest radiograph. If pneumonia is present on the admitting chest radiograph, the cause of death will be designated pneumonia. If pneumonia is present only on subsequent chest radiographs, the cause of death will be designated as COPD.

1. Cause of death

Cardiovascular death

Sudden death

Sudden death is a term generally denoting a presumed arrhythmic death when the death is witnessed and another cause cannot be identified. However, it is more likely that the cause is cardiac in nature if the death (not necessarily witnessed) occurred within a reasonable time frame (i.e. <1 hour) of the patient last being seen alive and without evidence of clinical deterioration. If the interval between death and last being observed alive is between 1 and 24 hours and there is no observation of a significantly deteriorating medical condition, then the death is less certain to be of cardiac origin and will be classified as unwitnessed sudden death. If the last observation of the deceased is >24 hours, and there is no other known cause of death, there is less certainty that the cause of death is cardiovascular and will be classified as unknown.

Sub-categories of sudden death are as follows:

Witnessed (observed in usual health within 1 hour of death event)
Unwitnessed (observed in usual health between 1–24 hours of death event)

In cases of out of hospital death, the site coordinator or site physician should interview family or witnesses to ascertain the following information: see Appendix 5 for the actual form.

- When was the person last known to be alive?
- When was the person found to be deceased?
- What were the events surrounding the death?
- Did the deceased have any symptoms or change in health status that preceded the death? Special reference should be made to shortness of breath, fever, infection, chest pain, abdominal pain, fainting, seizures, paralysis and change in mental status.
- Were there recent medical visits or recent changes in medication?
- Was an autopsy performed?

Myocardial infarction

Thygesen 2007

In general, the diagnosis of myocardial infarction will require pathologic evidence, or evidence of medical record including electrocardiographic tracings, blood enzyme measurements, and compatible clinical findings.

Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 × 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 × 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

In circumstances where the source documents such as electrocardiogram tracings or enzyme levels are not available, the committee may base a diagnosis of myocardial infarction on other reliable medical sources, but should not ordinarily accept death certificate or witness statements for this diagnosis.

<u>Stroke</u>

In general, the diagnosis will require compatible clinical findings. With respect to diagnosis of stroke: Although brain imaging is ordinarily required for the diagnosis of stroke, if the clinical syndrome is compelling (e.g. hemiparesis and aphasia) and follows a typical clinical course for stroke, this may be adequate to adjudicate the case as a stroke. Classification of the type of stroke will usually require either supportive imaging or pathological evidence. In some cases, a haemorrhagic stroke may be supported by a compatible clinical syndrome associated with supportive cerebrospinal fluid examination.

Definition of stroke types:

a) ISCHAEMIC: Infarction of brain tissue as a result of either occlusion of a brain artery by any mechanism (e.g. thrombosis, embolism), or decreased perfusion selectively affecting specific brain arterial territories (e.g. borderzone infarction).

b) HAEMORRHAGIC: Damage directly resulting from sudden extravasation of blood into the brain tissue (i.e. intracerebral) or the spaces surrounding the brain (e.g. subarachnoid).
c) INDETERMINATE: Information is insufficient to classify.

When a stroke leads to a chronic disabling condition that results in death, the cause of death will be adjudicated as stroke.

Procedural death

A subject with cardiovascular disease is taken into hospital for an operation related to cardiovascular disease (e.g. percutaneous coronary intervention, coronary artery bypass graft or during insertion of other cardiac device).

Pulmonary death

COPD without pneumonia

For the purpose of adjudication, an episode of pneumonia that occurs >5 days after onset of the terminal illness will be adjudicated as COPD without pneumonia. The intent is to exclude episodes of pneumonia that are secondary complications of a COPD exacerbation, such as ventilator- or healthcare-associated pneumonias.

COPD with pneumonia

For the purpose of this study, pneumonia is generally defined as a clinical syndrome compatible with pneumonia supported by radiographic evidence. It would be uncommon for a person with COPD to have pneumonia without symptoms compatible with a COPD exacerbation; however, it is conceivable that such an event might occur. In that case, the death will be coded as 'Pulmonary – other', with the cause specified as pneumonia.

Pulmonary embolism

For the purpose of adjudication, this diagnosis should be supported by a compatible clinical syndrome supported by imaging or pathological evidence. In the absence of definitive imaging or pathological evidence, this diagnosis should be supported by a high clinical likelihood supported by laboratory and clinical evidence (e.g. evidence of venous thrombosis) as well as a clinical diagnosis of the treating physicians.

Other respiratory deaths

If the death is not related to any of the other respiratory categories although is pulmonary in nature it will be classified as other respiratory death, e.g. pneumothorax, acute upper airway obstruction, pulmonary haemorrhage, or pneumonia in the absence of a COPD exacerbation that are not otherwise specified.

Cancer

All diagnoses of cancer should generally be corroborated by the primary medical record. This should include imaging studies, histologic diagnoses, operative or procedure notes, and records of treatment. If the primary medical record cannot be obtained to confirm the diagnosis, this should be

affirmatively stated in the documentation, and the committee will determine a diagnosis based on their best judgment. Haematological malignancies will be classified as cancer for the purpose of adjudication.

Patients who die with an uncured cancer that would be expected to be fatal will be designated as dying from the cancer. Exceptions to this may include cancers that if left untreated would not be expected to lead to death within 5 years. Examples of such cancers include non-melanoma skin cancers, localised prostate cancer or low-grade haematological malignancies.

For example, a patient with documented gastric cancer who dies of gastrointestinal haemorrhage will be classified to have died from gastric cancer. A patient who dies from neutropenic sepsis while undergoing chemotherapy for lymphoma will be classified as dying from lymphoma.

Sub-categorisation of cancer death will be lung, breast, colorectal or other. Other cancers will be submitted as free text.

Death other specify

If a subject commits suicide (e.g. by shooting themselves in the head, taking an overdose of pills, jumping off a bridge and drowning) the cause of death will be designated as 'Other – suicide', not 'Other (mode of suicide)'.

If a subject has an accident and causes injury to their head that causes death, it should be classified as other and specified as traumatic brain injury (not head trauma, brain trauma, etc.)

Death unknown

In some circumstances, the cause of death cannot be determined based on the evidence available to the committee. This includes deceased who are found deceased after >24 hours have elapsed since they were last observed in their usual state of health and where no other cause of death is apparent. The cause of death may be unknown either, because the medical information is adequate but the cause of death is 'indeterminate'. Such cases should be sub-categorised as indeterminate. In some cases, medical information may exist, but is not available for review. In those cases, the case should be sub-categorised as 'inadequate information'.

Procedure for dealing with multiple serious adverse events for a single death

If a subject has multiple fatal serious adverse events, these will be combined into one death episode in virtual clinical adjudication system and adjudicated as one death event.

2. Determination of COPD relatedness

All cases will have a secondary classification to determine whether the death is related to COPD. The possible choices are NO/UNLIKELY, YES/PROBABLE, UNKNOWN.

1. All cases where primary cause of death is COPD will be classified as YES.

2. In cases where primary cause of death is NOT COPD the classification of COPD relatedness will be based on the sequence of terminal events:

- If the terminal event is documented to be hypercapnic respiratory failure or failure to wean from a ventilator the case will be classified YES.
  - For example, patient dies in hospital on ventilator, but succumbs to fatal pneumonia, arrhythmia, or care is withdrawn.
- If the patient would have been judged to have survived the terminal illness had COPD not been present, the case will be classified YES
  - For example, patient dies from Stage I lung cancer because they have insufficient lung function to undergo surgery.
  - For example, patient has pneumonia or influenza that is fatal.
- If the death occurs at home, where the patient is receiving palliative care for advanced COPD, the case will be classified YES.
  - For example, a patient receiving continuous oxygen, confined to bed and chair, with cor pulmonale, or with advanced malnutrition.
- If the terminal event is NOT respiratory, and would be likely fatal for patients without COPD, the case will be classified NO.
  - For example, death from metastatic cancer, cerebral haemorrhage, severe cardiomyopathy or cardiogenic shock.
- If there is another clear explanation for terminal respiratory failure that would likely have occurred in patients without COPD, then the case will be classified NO.
  - For example respiratory failure secondary to cardiovascular, drug overdose or asphyxia.

3. If the data are inadequate to make a clear YES/PROBABLE or NO/UNLIKELY classification, it will be designated as UNKNOWN, based on the best evidence available. UNKNOWN will be classified as either, indeterminate or inadequate information.

<u>Cardiovascular events</u>

For the purpose of this study, the cardiovascular endpoint comprises myocardial infarction, stroke, transient ischaemic attack, unstable angina and on-treatment cardiovascular death. The cardiovascular electronic case report form page is shown in Appendix 3. The committee will require supportive evidence from the medical records in order to classify an adverse event as a cardiovascular event for this study.

<u>Non-serious possible cardiovascular adverse event only: Investigator declaration, Appendix 6</u>

Non-serious cardiovascular adverse events occasionally are being reported with no source documentation available. This is usually caused by subject self-reporting/diary entry at scheduled study visit, thus there is no evidence for protocol-defined event.

The non-serious possible cardiovascular adverse event only: Investigator Declaration, Appendix 6, was developed to find out if the site investigator believed the reported event could be a study endpoint (unstable angina, myocardial infarction, transient ischaemic attack or stroke) by answering yes or no to question #1. If yes, further documentation is requested of the site. If no, the site investigator will be asked to sign, date and return the form to PAREXEL.

Chest pain

In cases where a Non-Serious adverse event of chest pain or a similar term triggers an event and the clinical study site is unable to obtain medical evidence, the site investigator will be

asked to answer question #2 within 'The non-serious possible cardiovascular adverse event only: Investigator declaration' to assess cardiac cause.

If the site investigator declares that the event is '**non-cardiac**' chest pain, and there is no medical evidence to review, then the event will be administratively determined (deleted in virtual clinical adjudication system) not to be a protocol defined endpoint and will not go to the committee for further review. If there is medical evidence of record for the committee to review such as clinical notes, serious adverse event reports, laboratory findings, or electrocardiographs, then the event will be reviewed by the committee regardless of the investigator's declaration.

Triage process for adverse events

It was agreed by the CEC and GlaxoSmithKline plc. to create a triage process for adverse events only (note: all serious adverse events automatically go to the independent round). This triage process in virtual clinical adjudication would initially be completed by one CEC member only. The electronic case report form in asks 'This is an event which needs further adjudication as it may be transient ischaemic attack, stroke, unstable angina or myocardial infarction' [Yes/No], If 'Yes' it would go to the 'independent' round for full committee review or if 'No' the event is considered complete.

Myocardial infarction

Generally, the definition provided by Thygesen 2007 will be used to determine myocardial infarction.

'The diagnosis of myocardial infarction will require pathologic evidence, or evidence of medical record including electrocardiographic tracings, blood enzyme measurements, and compatible clinical findings'.

Myocardial infarctions will be sub-classified as follows:

- Type 1 – Spontaneous myocardial infarction related to ischaemia due to a primary event such as plaque erosion or rupture fissuring or dissection.
- Type 2 – Myocardial infarction secondary to ischaemia due to imbalance between oxygen demand and supply, e.g. coronary spasm, anaemia or hypotension. This type of event would typically occur in the context of another illness that may or may not be fatal.
- Procedure related – Myocardial infarction associated with percutaneous coronary intervention or in association with a coronary artery bypass graft. This category includes both type 4 and type 5 myocardial infarction according to the Universal definitions.

(Type 3 myocardial infarctions are associated with sudden death and will be coded as a death event under either sudden death or myocardial infarction.)

Unstable angina

Symptoms of myocardial ischaemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity that prompts an unscheduled visit to a healthcare facility. One of the following should also be observed in the absence of evidence of acute myocardial infarction:

1) New or worsening ST or T-wave changes on resting electrocardiograph

a. ST elevation

New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥0.2 mV in men (>0.25 mV in men <40 years) or ≥0.15 mV in women in leads V2–V3 and/or ≥0.1 mV in other leads.

b. ST depression and T-wave changes
New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥0.1 mV in two contiguous leads.

It is recognised that lesser echocardiograph abnormalities may represent an ischaemic response and may be accepted under the category of abnormal echocardiograph findings.

2) Definite evidence of myocardial ischaemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischaemic symptoms/signs

3) Angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischaemic symptoms/signs.

4) Need for coronary revascularisation procedure (percutaneous coronary intervention or coronary artery bypass graft).

<u>Stroke</u>

In general, the diagnosis will require compatible clinical findings. Classification of the type of stroke will usually require either supportive imaging or pathological evidence. In some cases, a haemorrhagic stroke may be supported by a compatible clinical syndrome associated with supportive cerebrospinal fluid examination.

Definition of stroke types:

a) ISCHAEMIC: Infarction of brain tissue as a result of either occlusion of a brain artery by any mechanism (e.g. thrombosis, embolism), or decreased perfusion selectively affecting specific brain arterial territories (e.g. borderzone infarction).
b) HAEMORRHAGIC: Damage directly resulting from sudden extravasation of blood into the brain tissue (i.e. intracerebral) or the spaces surrounding the brain (e.g. subarachnoid).
c) INDETERMINATE: Information is insufficient to classify, but the clinical course is suggestive of a stroke.

<u>Transient ischaemic attack</u>

Temporary focal neurologic deficit is defined as either witnessed by a physician or recorded by a physician as a credible and objectively witnessed event, AND presumably resulting from brain ischaemia, AND lasting less than 24 hours, AND without any evidence of appropriate ischaemic changes in either computed tomography or magnetic resonance imaging if either of these obtained.

<u>None of the above</u>

The event does not meet the definition of an adverse cardiovascular event as listed above.

Related to previous cardiovascular event

If based on the information in the endpoint adjudication package, the CEC determines this is related to a previously adjudicated event then it will be marked as such and not counted as a new event. The previous adverse event reference identifier will be added to the electronic case report form by the CEC.

Appendix 1

Documents provided to the Clinical Endpoint Committee (CEC) for adjudication

Whenever possible, potential endpoints will be sent to the CEC only when all appropriate case report forms and a completed dossier of the information have been obtained. Also, if multiple related or evolving events occur in a single subject, whenever possible, the set of the events will be kept together and sent to the CEC only when all documents for all events are complete. These may include but are not limited to:

- Death certificate
- Discharge summary
- Imaging and procedure notes
- Surgical operation reports
- Hospital records and outpatient records
- Physician notes (i.e. from office or clinic)
- Witness accounts, including non-hospital death where narratives from friends and relatives. A proforma will be developed with questions
- Autopsy reports
- Pathology reports
- Serious adverse event reports
- Echocardiograph reports
- Pertinent radiologic reports (i.e. plain films/magnetic resonance imaging/computed tomography)
- Case report form reports, including con-meds, past history, demography
- Labs including troponins and cardiac enzymes
- Coronary angiogram reports (with no intervention)
- Carotid ultrasound reports
- Angiogram of head and neck procedures coronary artery bypass graft, and percutaneous coronary interventions reports
- Head computed tomography scans and magnetic resonance images
- Other

Appendix 2

Tier	Questions	Responses
1	Classify the primary cause of death	☐ **Cardiovascular** ☐ Sudden Death* ☐ Witnessed less than 1 hour ☐ Un witnessed 1–24 hours ☐ Myocardial Infarction ☐ Stroke ☐ Hemorrhagic ☐ Ischemic ☐ Indeterminate ☐ Procedural death (related to PCI, CABG or during insertion of other cardiac device) ☐ Other, specify _____ ☐ **Pulmonary** ☐ COPD ☐ with pneumonia ☐ without pneumonia ☐ Pulmonary embolism ☐ Other, specify _____ ☐ **Cancer** ☐ Lung ☐ Breast ☐ Colorectal ☐ Other, specify _____ ☐ **Other, specify** ☐ **Unknown, specify (includes sudden death >24hrs)** ☐ inadequate information ☐ indeterminate
2	Was the death COPD related	☐ No or unlikely ☐ Yes or probable ☐ Unknown ☐ inadequate information ☐ indeterminate
Comments (Remark on adjudication rationale):		
* defined as per MERIT -HF trial , Lancet 1999		

Abbreviations: CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure; PCI, percutaneous coronary intervention.

Appendix 3

Tier	Questions	Responses
1	Is this event a	☐ Myocardial Infarction ☐ Type 1 ☐ Type 2 ☐ Procedural related ☐ Unstable Angina ☐ Stroke ☐ Hemorrhagic ☐ Ischemic ☐ Indeterminate ☐ Transient Ischemic Attack ☐ None of the above A. ☐ No evidence for protocol defined CV event B. ☐ Related to previous CV event Adverse Event ID_____ _____
Comments (Remark on adjudication rationale):		

Abbreviation: CV, cardiovascular

Appendix 4

CEC Collection Form

Date			
Centre Number		**Subject Number**	
Clinical Event Term (AE term as entered in DataLabs)			
Event Onset Date			

Please provide the following source documents and make sure the centre/subject study numbers are marked on each document. Remove all patient identifiers. Check one box per line item and provide this form with the source returned:

	Source Document	Enclosed	Requested from facility	Updated in DataLabs	Not Available	Not Applicable
1	Death certificate					
2	Discharge summary					
3	Imaging and procedure notes					
4	Surgical operation reports					
5	Hospital records and outpatient records					
6	Physician notes (from office or clinic)					
7	**Non-hospital death witness account with details from friends and relatives (non-hospital death questionnaire, Appendix 5)					
8	Autopsy reports					
9	Pathology reports					
10	SAE reports (if not already submitted)					
11	ECG reports					
12	Pertinent radiologic reports					
13	CRF reports (please make sure con-meds, past history, demography are updated in DataLabs)					
14	Labs including troponins and cardiac enzymes					
15	Coronary angiogram reports (with no intervention)					
16	Carotid ultrasound reports					
17	Angiogram of head and neck procedures, CABG, PCI reports					
18	Others as requested					

Investigator's Signature: ..... **Date:** .....

- **Please return the completed table, including the Investigator's signature, with all available source documents to PAREXEL**
- **To assist with the CEC review, kindly respond within 2 weeks.**

Abbreviations: AE, adverse event; CABG, coronary artery bypass graft; CEC, Clinical Endpoint Committee; COPD, chronic obstructive pulmonary disease; CRF, case report form; ECG, echocardiograph; PCI, percutaneous coronary intervention; SAE, serious adverse event.

Appendix 5

GSK Protocol HZC113782 SUMMIT –

Non-hospital death witness questionnaire

Date			
Centre Number		**Subject Number**	
Event Onset Date			

**In cases of out of hospital death, the site coordinator or site physician should interview family or witnesses to ascertain the following information:

1	**When was the person last known to be alive?**	
2	**When was the person found to be deceased?**	
3	**What were the events surrounding the death?**	
4	**Did the deceased have any symptoms or change in health status before the death? Special attention should be made to shortness of breath, fever, infection, chest pain, abdominal pain, fainting, seizures, paralysis and change in mental status.**	
5	**Were there recent medical visits or recent changes in medication?**	
6	**Was an autopsy performed?**	

Investigator's Signature: ..... **Date**: .....

- **If applicable, please return the completed questionnaire, including the Investigator's signature, with CEC Collection Form and associated documents to PAREXEL**
- **To assist with the CEC review, kindly respond within 2 weeks.**

Abbreviation: CEC, Clinical Endpoint Committee.

Appendix 6

GSK Protocol HZC113782 SUMMIT

Non-serious possible cardiovascular adverse events only
Investigator declaration

Date			
Centre Number		**Subject Number**	
Clinical Event Term (AE term as entered in DataLabs)			
Event Onset Date			

If no source documents are available due to subject self-reporting for CV events, site investigator will need to complete this form:

****Please complete for chest pain or similar term regardless of your assessment of cause.**

1. Is this event part of a study endpoint (myocardial infarction, unstable angina, transient ischaemic attack or stroke)?
□ YES □NO

If YES, please provide additional evidence (documentation) to support this assessment.
If NO, please sign and date this form and return per instructions below.

2. If this event is CHEST PAIN or a similar term, then complete the following:

Please tick to indicate which one of the following applies:
___ This event is likely cardiac or ischaemic chest pain
____This event is NOT likely cardiac or ischaemic in origin
___ It is indeterminate whether this event is cardiac or ischaemic in origin

Investigator comments:

_____ _____

Investigator's Signature **Date**

- **If applicable, please return the completed questionnaire, including the Investigator's signature, with CEC Collection Form and associated documents to PAREXEL via fax: +1 781 434 5957 or email: GSKSUMMITCEC@PAREXEL.com**
- **To assist with the CEC review, kindly respond within 2 weeks.**

Abbreviations: AE, adverse event; CEC, Clinical Endpoint Committee; CV, cardiovascular.

Supplementary Appendix B

Figure S1.

Number of cardiovascular events triggered by Medical Dictionary for Regulatory Activities preferred term.

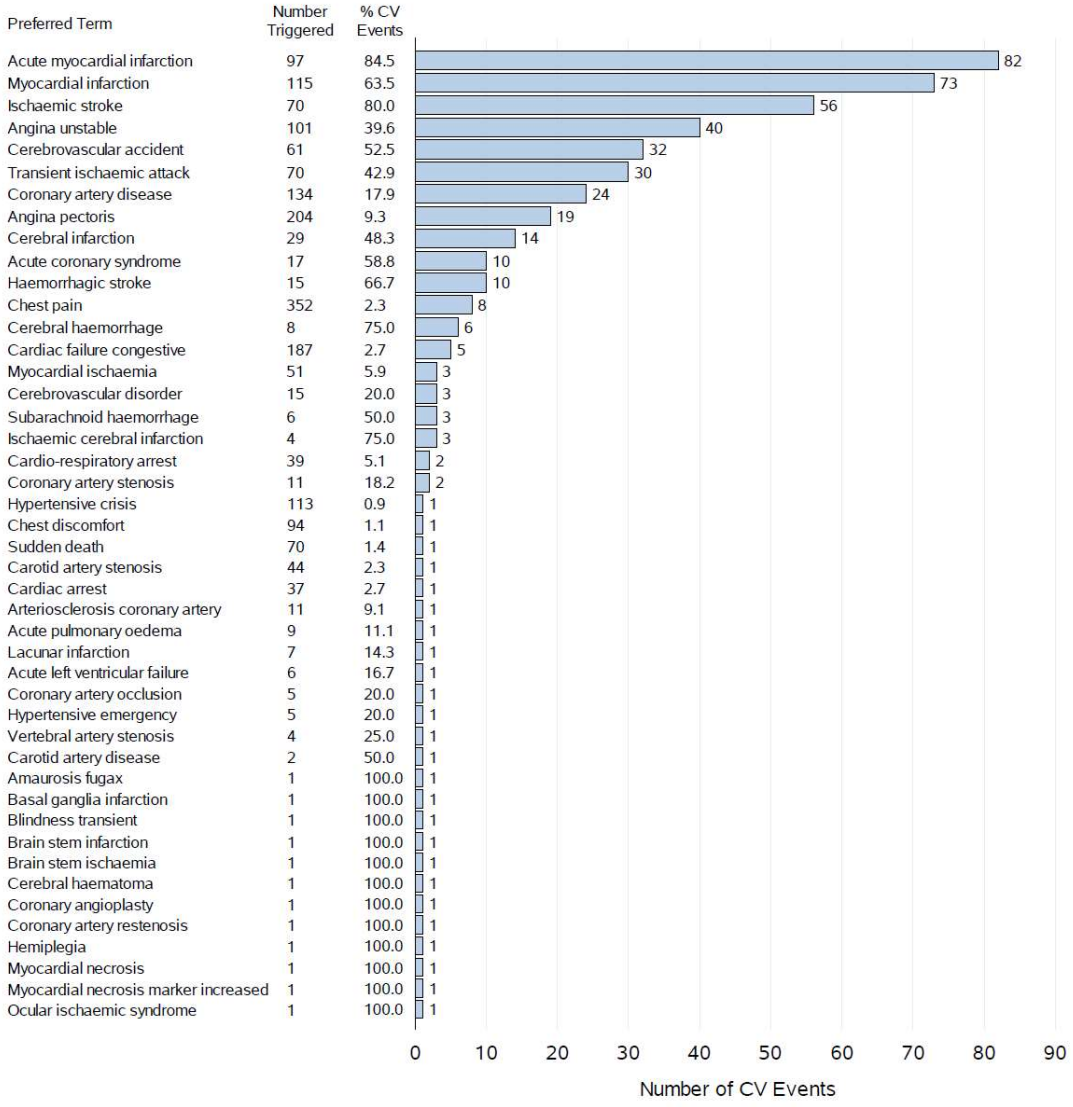

Table S1.

Triggered Medical Dictionary for Regulatory Activities preferred terms that resulted in no cardiovascular events.

Preferred term	Number triggered	Number of cardiovascular events
Cardiac failure	160	0
Syncope	92	0
Peripheral arterial occlusive disease	91	0
Palpitations	74	0
Aortic aneurysm	54	0
Cardiac failure chronic	50	0
Hypoesthesia	50	0
Ventricular extrasystoles	34	0
Peripheral artery stenosis	24	0
Arteriosclerosis	21	0
Cor pulmonale	21	0
Presyncope	21	0
Cardiac failure acute	20	0
Peripheral ischaemia	20	0
Pulmonary congestion	20	0
Intermittent claudication	19	0
Peripheral venous disease	19	0
Pulmonary oedema	19	0
Vascular encephalopathy	18	0
Sudden cardiac death	17	0
Loss of consciousness	16	0
Ventricular tachycardia	16	0
Congestive cardiomyopathy	15	0
Ischaemic cardiomyopathy	14	0
Left ventricular failure	14	0
Cardiopulmonary failure	13	0
Femoral artery occlusion	13	0
Somnolence	13	0
Iliac artery occlusion	12	0
Carotid arteriosclerosis	10	0
Circulatory collapse	9	0
Confusional state	9	0
Left ventricular dysfunction	9	0
Left ventricular hypertrophy	9	0
Carotid artery occlusion	8	0
Cerebral arteriosclerosis	8	0
Lethargy	8	0
Pain in jaw	8	0
Seizure	8	0
Aortic aneurysm rupture	7	0
Ventricular fibrillation	7	0
Vertebrobasilar insufficiency	7	0

Preferred term	Number triggered	Number of cardiovascular events
Cerebral ischaemia	6	0
Diabetic microangiopathy	6	0
Diastolic dysfunction	6	0
Aphonia	5	0
Cardiovascular disorder	5	0
Cerebrovascular insufficiency	5	0
Epilepsy	5	0
Accelerated hypertension	4	0
Arterial occlusive disease	4	0
Blindness	4	0
Bradyarrhythmia	4	0
Brain oedema	4	0
Cardiogenic shock	4	0
Raynaud's phenomenon	4	0
Subclavian artery stenosis	4	0
Tachyarrhythmia	4	0
Aneurysm	3	0
Aortic dissection	3	0
Aphasia	3	0
Arterial stenosis	3	0
Cardiac fibrillation	3	0
Cardiomegaly	3	0
Cardiovascular insufficiency	3	0
Cerebral microangiopathy	3	0
Cyanosis	3	0
Dilatation atrial	3	0
Hypovolemic shock	3	0
Intracranial aneurysm	3	0
Right ventricular failure	3	0
Vascular graft occlusion	3	0
Venous occlusion	3	0
Ventricular arrhythmia	3	0
Ventricular hypokinesia	3	0
Arterial stent insertion	2	0
Atrial thrombosis	2	0
Cardiac discomfort	2	0
Carotid artery aneurysm	2	0
Carotid bruit	2	0
Catheterisation cardiac	2	0
Coma	2	0
Convulsions local	2	0
Coronary artery thrombosis	2	0
Coronary ostial stenosis	2	0
Diabetic vascular disorder	2	0
Dysarthria	2	0
Ejection fraction decreased	2	0
Hemiparesis	2	0
Hyporeflexia	2	0

Preferred term	Number triggered	Number of cardiovascular events
Intraventricular haemorrhage	2	0
Orthopnoea	2	0
Peripheral coldness	2	0
Poor peripheral circulation	2	0
Sensory loss	2	0
Speech disorder	2	0
Troponin increased	2	0
Vasoconstriction	2	0
Amaurosis	1	0
Apraxia	1	0
Arterial bruit	1	0
Arteriogram coronary	1	0
Basilar artery occlusion	1	0
Basilar artery thrombosis	1	0
Blindness unilateral	1	0
Brain natriuretic peptide increased	1	0
Brain stem stroke	1	0
Cardiac aneurysm	1	0
Cardiac death	1	0
Cardiac disorder	1	0
Cardiac function disturbance postoperative	1	0
Cardiac pacemaker evaluation	1	0
Cardiac pacemaker insertion	1	0
Cardiac ventricular thrombosis	1	0
Cardio-respiratory distress	1	0
Cerebral artery stenosis	1	0
Cerebral artery thrombosis	1	0
Complex partial seizures	1	0
Cor pulmonale acute	1	0
Cor pulmonale chronic	1	0
Coronary artery insufficiency	1	0
Coronary vascular graft occlusion	1	0
Diplegia	1	0
Disorientation	1	0
Dry gangrene	1	0
Extremity necrosis	1	0
Eye disorder	1	0
Generalised tonic-clonic seizure	1	0
Haemorrhage intracranial	1	0
Haemorrhagic cerebral infarction	1	0
Hypertensive cardiomyopathy	1	0
Intracranial pressure increased	1	0
Ischaemia	1	0
Motor dysfunction	1	0
Myocardial fibrosis	1	0
Neuritis cranial	1	0
Night blindness	1	0
Paresis	1	0

Preferred term	Number triggered	Number of cardiovascular events
Penetrating atherosclerotic ulcer	1	0
Pericarditis	1	0
Peripheral circulatory failure	1	0
Postictal paralysis	1	0
Pseudoangina	1	0
Pulseless electrical activity	1	0
Right atrial dilatation	1	0
Right atrial hypertrophy	1	0
Ruptured cerebral aneurysm	1	0
Seizure like phenomena	1	0
Shock haemorrhagic	1	0
Troponin I increased	1	0
Ultrasound Doppler abnormal	1	0
Vascular graft thrombosis	1	0
Vascular occlusion	1	0
Vascular pseudoaneurysm	1	0
Vascular stenosis	1	0
Ventricle rupture	1	0
Ventricular failure	1	0
Ventricular hypertrophy	1	0
Visual field defect	1	0

Table S2.

Agreement of individual adjudicators on round 1 with final committee adjudication of primary classification of death (cardiovascular, pulmonary, cancer, other cause or unknown).

	# cases reviewed	# agree with final adjudication	Percent agreement (%)
Adjudicator 1	800	648	81
Adjudicator 2	710	644	91
Adjudicator 3	653	551	84
Adjudicator 4	248	185	75
Adjudicator 5	753	652	87
Adjudicator 6	714	606	85
Total*	3,878	3,286	85

* There were more cases (3,878) than adverse events (3,314) because some adverse events were reviewed by more than one adjudicator in round 1.