CRF Instructions

CoDe

Instructions for the completion of the CoDe Cause of Death form

***General*:** Please complete the form by marking the appropriate box with an 'X', by completing a numeric field, or by completing information on day, month and year for date-variables. If information is unknown, mark the appropriate box or write 'NA' (not available). For information on dates, if the day is unknown, write 'NA-mm-year', if the month is unknown, write 'NA-NA-year', if the day, month and year are unknown, write 'NA-NA-NA'. Complete text fields as indicated in the form. Include copies of source documentation where indicated; the source documents should be anonymized (erase patient name) and labelled with Study name and Patient ID on each page.

Heading: ***Study and patient ID.*** Complete the specific study name (cohort or trial) and Patient ID code at the top of each page of the CRF. The patient's date of death should be recorded on the first page only.

Section 1: ***Background demographics.*** Please record most recent measurements of height or weight and the corresponding date. In case there is no information at all on height or weight, please complete the relevant item by 'NA'.

Section 2: ***Data source.*** If several sources of information were available, please include all.
For hospital files and outpatient clinic charts: If the files are **complete** and contains the relevant information describing the events leading to death, the sources should be recorded as **'complete'**. If the files are intact, but does not contain the relevant information the records should be coded as **'incomplete'** (e.g. if the patient was admitted elsewhere with the terminal condition, and a copy of this file from a different hospital is unavailable).

Section 3: ***Risk factors***
Risk factors in the year prior to death: Please note that information is requested for presence of cigarette smoking, excessive alcohol consumption (definition listed below), active illicit drug use and opiate substitution *within the last year*.

If data are not available, or information not provided in the source documents, please indicate 'unknown' (rather than leaving blank).

Definition:
Section 3.1 Cigarette smoking: regular cigarette smoking more than 3 days a week, *or* any mentioning of cigarette smoking in the source documents.
Section 3.2 Excessive alcohol consumption: More than 35 alcohol units per week (or 5 units per day), *or* any mentioning of ongoing excessive alcohol use in the source documents. (one unit of alcohol corresponds to 125ml of wine; 300ml of beer; or 20ml of spirits. This equates to approximately 12g of beer or wine; or 6g of spirits).

Section 4: ***Co-morbidities***
For conditions listed in section 4, presence *at any time point* should be marked with 'Yes'.
If data are not available, or information not provided in the source documents, please indicate 'unknown' (rather than leaving blank). The presence or absence of all listed risk factors should be completed using the definitions provided below.

Definitions:
Section 4.A.1 Hypertension: Systolic blood-pressure $\geq$140 mmHG or diastolic blood pressure $\geq$ 90 mmHg, or any mentioning of arterial hypertension or anti-hypertensive medication in the source documents.

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Section 4.A.2 Diabetes Mellitus:

- Symptoms of diabetes plus random blood glucose concentration ≥ 11.1 mmol/L (200 mg/dL), or
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL), or
- Two-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test, or
- any mention of anti-diabetic therapy in the source documents.

Section 4.A.3 Dyslipidemia: Serum-total cholesterol ≥ 6.2 mmol/L (240 mg/dL), LDL cholesterol ≥ 4.2 mmol/L (160 mg/dL) or HDL cholesterol ≤ 0.9 mmol/L (35 mg/dL), or fasting triglycerides ≥ 2.3 mmol/L (200 mg/dL), or any mentioning of lipid lowering medication.

Section 4.B Prior cardiovascular disease: Prior myocardial infarction (NSTEMI or STEMI), stroke (cerebral infarction or haemorrhage, or subarachnoideal haemorrhage), or invasive cardiovascular procedure (coronary artery stenting or by-pass operation, carotid artery endarterectomy).

Section 4.C History of depression:

Any mentioning in the source documents of depressive episode(s), incl. bipolar (hypomania/ mania plus depression) disorders.

Section 4.D History of psychosis:

Any mentioning in the source documents of psychotic episode(s), incl. schizophrenia, schizoaffective or delusional disorders.

Section 4.E.1 Chronic elevation of liver transaminases: Elevated transaminases (AST (S-GOT) or ALT (S-GPT)) for more than 6 consecutive months.

Section 4.E.2 Chronic hepatitis B: The presence of HBsAg in the serum for at least 6 months.

Section 4.E.3 Chronic hepatitis C*:* Anti-HCV and/or HCV RNA positive (excluding those who have a positive anti-HCV, but are HCV RNA negative).

Section 4.E.4 Hepatitis D*:* Persistent high anti-HDV titer (IgM or IgG), HDV antigen in the liver, and/or HDV RNA in serum or liver.

Section 4.E.6 Clinical signs of liver failure including decompensated liver cirrhosis: Failure of biochemical synthesis (incl. hypo-albuminemia and/or low coagulation factors); ascites,variceal bleeding, hepatorenal syndrome, or hepatic encephalopathy with coma.

Section 4.E.7 Date of most recent liver biopsy (if ever): ***If the day, month, or year is unknown, write 'NA' (not available).***

Stage of liver fibrosis:

0 = no fibrosis, 1 = mild fibrosis, 2 = moderate fibrosis, 3 = severe fibrosis, including bridging fibrosis, 4 = cirrhosis.

Section 5: ***Cause of death.***

- ***Was the death sudden***?: Acute death with no known ongoing terminal illness
- ***Was the death unexpected***?: Not anticipated based on knowledge of the patients physical and psychological health status and risk factors

Examples given:

A. Sudden and unexpected: Patient perceived to be in good health is found dead at home

B. Sudden and expected: Patient with active ongoing illicit intravenous drug use dies from overdose

C. Not sudden and unexpected: Patient with known ongoing severe illness dies unexpectedly from an unrelated illness or from unexpected complications to the patients underlying disease

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Complete the table by recording ***all*** illnesses and conditions (acute and chronic) or injuries that the patient had at the time of death, and indicate the certainty of diagnosis for each illness/condition:

Definite (95-100% certainty)

For the diagnosis to be *definite*, there should be confirmation based on:

- Neoplasms: Histopathology (autopsy or biopsy)
- Infections: Direct microscopy, culture or PCR
- Other: Histopathology (autopsy or biopsy)

Likely (80-95%)

For the diagnosis to be *likely*, there should be confirmation based on:

- Clinical history and supporting evidence by imaging and/or laboratory markers

Possible (50-80%)

For the diagnosis to be *possible*, there should be confirmation based on:

- Clinical history, signs and symptoms

For each illness/condition, please also record the ***date of onset*** (the time of first diagnosis of clinical disease). The illnesses and conditions should be listed chronologically with the most recent and acute conditions in the top, and older and chronic conditions listed in the end. For each illness/condition, please indicate if it was acute or chronic. For chronic conditions with exacerbations, please record information relevant to cause(s) of death in the *brief narrative* section. The dates should be recorded as dd/mm/yy for day, month and year. If the day, month, or year is unknown, write NA (not available).

Brief narrative: Please describe the sequence of events leading to death. Please include details related to the diagnostic confirmation of the causative conditions.

Summary of the narrative:
Please complete the summary by introducing in each line the appropriate *number* (from the above table) for each cause of death (immediate, contributing, underlying).
Please use the following definitions for the categorisation of the causes of death in the summary:

- ***Immediate cause of death:*** The disease(s) or injury directly leading to death.
- ***Contributing cause of death:*** The disease(s) or injury, which contributed to a fatal outcome.
- ***Underlying cause of death:*** The disease or injury, which initiated the train of morbid events leading directly or indirectly to death, or the circumstance of the accident or violence, which produced the fatal injury.

Only one cause should be entered on each line (by entering the appropriate *number* (1-9) from table C in the same section).
The first line (immediate cause of death) must always have an entry. If the condition in the first line resulted from a contributory or underlying condition, put this condition on the next line, and so on, until the full sequence is reported. *Always* enter the underlying cause of death on the lowest used line.
The terminal event (for example, cardiac arrest or respiratory arrest) should not be listed as the underlying cause of death. If a mechanism of death seems most appropriate to you for 'the immediate cause', then you must always list its origin(s) on the line(s) below it (for example, cardiac arrest due to coronary artery atherosclerosis or cardiac arrest due to blunt impact to chest). If an organ system failure such as congestive heart failure, hepatic failure, renal failure, or respiratory failure is listed as a cause of death, always report the aetiology of the organ system failure on the line(s) below (for example, renal failure due to Type I diabetes mellitus).

When indicating neoplasms as a cause of death, include the following: 1) primary site or that the primary site is unknown, 2) benign or malignant, 3) cell type or that the cell type is unknown, 4) grade of neoplasm, and 5) part or lobe of organ affected. (For example, a primary well-differentiated squamous cell carcinoma, lung, left upper lobe.)

Always report the fatal injury (for example, stab wound of chest), the trauma (for example, transection of subclavian vein), and impairment of function (for example, air embolism).

If two or more possible sequences resulted in death, or if two conditions seem to have added together, report this in the narrative.

A listing of the conditions that are AIDS defining (CDC stage C) is included in the Appendix.

Section 6: ***Post-mortem/ Autopsy.***

Please provide a brief summary of the findings from the autopsy report, and describe for each organ system whether pathology was identified and its characteristics. Please also include a copy of the full report. If the autopsy findings differ from the clinical history, please make a note in the *comments* section.

Section 7: ***ART and laboratory values.***

Definitions:

ART: any licensed antiretroviral drug (not necessarily HAART).

Please complete the table with laboratory values of CD4 count and HIV RNA for:

1) the most recent measurement prior to last stopping ART, and
2) the most recent prior to death (if different to the above)
    a. if there was no CD4 count available between the time of stopping ART and death, please write 'NA' (not available)

For Haemoglobin, please record the most recent measurement prior to death. In the field next to the value, please record the units (either mmol/L, g/dL or g/L).

The dates should be recorded as dd/mm/yy for day, month and year. If the day, month, or year is unknown, write NA (not available).

Section 8: ***Adverse effects.***

Adverse effect: An unwanted response to a medicine (side effect; adverse event).

Please indicate if the cause of death was considered to be related to a medical treatment (acute or late onset) or not. If the relation is suspected with 50-80% certainty, indicate it as 'possibly'.

Indicate if the suspected relation was to antiretroviral treatment or other medical treatment, and provide in the *comments* section a brief narrative of the suspected association including the generic name of the medication, type of adverse effect and the date of its onset.

The dates should be recorded as dd/mm/yy for day, month and year. If the day, month, or year is unknown, write NA (not available).

Signature: Please print your name, position, and professional relationship to the patient (whether you were directly involved in the medical care of the patient around the time of death).

Appendix.

AIDS defining illnesses: Modified CDC Category C 1993 Definition

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- CMV disease (other than liver, spleen, or nodes)
- CMV retinitis
- Encephalopathy, HIV-related (including AIDS Dementia Complex)
- Herpes simplex, chronic ulcers (> 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi's sarcoma (mucocutaneous or visceral)
- Lymphoma , Burkitt's (or equivalent term)
- Lymphoma, primary, of the CNS
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- M. tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent bacterial (2 documented episodes within 1 year of each other)
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent (2 documented episodes within 1 year of each other)
- Toxoplasmosis of brain
- Wasting syndrome due to HIV (weight loss (over 10% of baseline) with no other cause, and 30 days or more of either diarrhoea or weakness with fever)

Additions to CDC Definition

- Aspergillosis, invasive
- Bartonellosis
- Chagas disease (American trypanosomiasis) of the CNS
- Herpes zoster, multi-dermatomal (≥10 lesions in a non-contiguous site)
- Leishmaniasis, visceral (kala-azar)
- Lymphoma, non-Hodgkin's, all cell types
- Microsporidiosis (> 1 month's duration)
- Nocardiosis
- Penicillium marneffii, disseminated
- Pneumocystis carinii, extrapulmonary
- Rhodococcus equi diseaseAppendix.

*Please note that Hodgkin's Lymphoma is now classified as a "non-AIDS defining malignancy"