Manual of Operations (MOOP) for clinical events

MOOP Version 1.8 2023

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Table of contents

Addendum: Changes from version 1.7 September 2021 to version 1.8 June 2023 (The changes are marked with yellow)

MI events:

p. 10, Section: 3.1.2, line 395,396
To clarify the issue of having experienced two myocardial infarctions (MIs) within a period of 31 days, the sentence was added.

3.1.2. MI validation criteria

3) Null/Insufficient data to qualify as an event
No relevant typical or atypical symptoms.
Please note that if the participant had two MI within 31 days, the second MI will be validated as duplicate/null.

Stroke events:

p. 11,12,13, Section: 3.2.1 and 3.2.2, line 420, 457, 506, 507

To be consistent with the stroke event form, the duration of focal or global symptoms for more than 24 hours has been added to the symptoms' description, to exclude reporting of transient ischemic attacks.
Further, to clarify the issue of having experienced two strokes of the same type (ischaemic / haemorrhagic) within a period of 31 days, the sentence was added.

3.2.1. Stroke event form

ii) *Did the participant have any acute onset focal neurological symptoms related to the event for >24 hours?*
iii) *Did the participant have any acute onset global symptoms for >24 hours?*

3.2.2. Validation criteria stroke
3) Null/ Insufficient data to qualify as an event

No relevant acute onset symptoms.

Please note that if the participant had two strokes of the same type (ischaemic / haemorrhagic) within 31 days, the second stroke will be validated as duplicate/null.

ICP events:

p. 14,15, Section: 3.3.1 and 3.3.2, line 536, 537, 558-563

To clarify the definition of primary prophylaxis for a MI or stroke, the sentence was added.
ICP without indication for the procedure will be considered as a diagnostic procedure and validated as null.
To clarify the issue of having experienced two ICPs of the same type within 31 days, the sentence was added.

3.3.1. ICP event forms

iv) Was the procedure conducted as primary prophylaxis for MI or stroke?*

Applies if the procedure was performed before any MI or stroke event, e.g., on the basis of stable coronary disease (angina pectoris) or presence of carotid stenosis.
Please note that performing ICP as a primary prophylaxis for a MI or stroke means that the participant had no previous MI or stroke.

3.3.2. ICP validation criteria

2) Null/Insufficient data to qualify as an event

Uncompleted invasive procedure (uncompleted bypass, angioplasty, carotid endarterectomy, or carotid stenting without unblocking of artery and/or stent).
If no indication for ICP was selected (ICP was not conducted in relation to a MI or stroke, and ICP was not conducted as primary prophylaxis), it will be considered as a diagnostic procedure and validated as null.
Please note that if the participant had two ICPs of the same type within 31 days, the second ICP will be validated as a duplicate.

Bone fractures:

p. 24, 25, Section: 3.7.1., 3.7.2., line 804-807, 830

To clarify that the fractures after low-energy trauma in participants with osteoporosis should be classified as osteoporotic fractures, the sentence was added.
The validation criteria for possible fractures now include the known location of the fracture.

3.7.1. Bone fracture event form

ii)* Is the type of fracture traumatic, osteoporotic/fragility, or pathologic?

Please note that if a participant with osteoporosis had a fracture following a low-energy trauma (fall from a standing height or low height of less than 1 m), the fracture should be classified as osteoporotic due to the underlying presence of weakened bone structure

3.7.2. Validation criteria fracture

2) Possible fracture:

i) *Bone fractures with unknown imaging but with known location and with verified surgical/ conservative treatment*

ii) *Bone fractures with no imaging but with surgical/ conservative treatment (applies only to fractures of the facial bones/nose, scull, ribs, fingers and toes*

APPENDIX - Guide REDCap event forms

p. 27, line 883

To be considered with the End Stage Liver Disease (ESLD) event form, gastric varices were added as a source of bleeding.

ESLD:

- *Hepatic encephalopathy stage III-IV*
- *Bleeding from oesophageal or gastric varices*
- *Hepato-renal syndrome*
- *Liver transplantation*
- *Ascites*

1 Presentation/Introduction

The International Cohort Consortium of Infectious Disease (RESPOND) is a non - interventional, non-randomized, open-label, multi-cohort observational study.

The aim of RESPOND is to build an innovative, flexible and dynamic cohort consortium for the study of infectious diseases, including HIV and people at risk for HIV, as a generic structure for facilitating multi stakeholder involvement. This consortium builds upon the outstanding collaborative work in HIV cohort studies that has taken place in Europe and beyond over the last 20 years and which has provided crucial information contributing to the improvement in the lives of HIV-positive individuals. RESPOND will continue with a rigorous approach to answering questions with robust and reliable scientific methodologies as well as having the flexibility and willingness to answer the most important questions of interest to the infectious diseases research community. RESPOND will be based on an extremely successful and highly experienced existing infrastructure, which will be adapted and expanded – including an inclusive network of clinics and cohorts and utilizing the operational infrastructure used for EuroSIDA, D:A:D (Data collection on Adverse events of anti-HIV Drugs), INSIGHT and other key studies, based at CHIP since 1994.

1.2 Contact information for the RESPOND and EuroSIDA Coordinating Centre (CC) at CHIP

Address:

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2 RESPOND Data Collection

RESPOND data collection is based on electronic submission of enrolment and follow up data, as described in the Standard Operating Procedure (SOP) for electronic data transfer (Link to the SOP).

Clinical events, including myocardial infarctions (MIs)/strokes/invasive cardiovascular procedures (ICPs)/AIDS-and non-AIDS defining cancers (ADC and NADC)/end-stage liver disease (ESLD) /end-stage renal disease (ESRD) and bone fractures are to be reported separately in REDCap on specifically designated event forms (https://chip-crf.info/redcap). Please note that the reporting of AIDS events (other than AIDS defining cancers according to above), are to be collected electronically via enrolment/follow-up forms (please refer to the RESPOND SOP, table 1.4 page 10). All new clinical events, as well as all clinical events occurring up to 12 months before the last clinic visit prior to RESPOND enrolment, should have an event form completed in REDCap.

The principal investigator at each site is responsible for the data collection for RESPOND including completion of the clinical event forms in REDCap. However, the responsibility of completing clinical event forms can be delegated to other study personnel (e.g. study nurses). When clinical event forms are completed, please ensure that data are entered correctly in accordance with instructions in REDCap and the RESPOND SOP and are of the highest possible standard.

2.1 Download of Data from REDCap

It is possible for each site/cohort to download their own submitted clinical event forms to RESPOND from REDCap. If a site/cohort wishes to download, please contact the RESPOND CC for detailed instructions.

2.2 Queries on Submitted Data

Queries will be performed continuously and directly in REDCap the RESPOND CC and may include requests on additional data, clarifications or corrections. If a query arises, notification E-mails will be sent directly from the coordinating office to the user that has submitted the event form. Please answer to queries from the RESPOND CC in a regular manner to secure the highest possible standard of data.

2.3 Optional upload of source documentation

Source documentation can be provided in-kind by centers/site. If source documentation is uploaded, all person identifiable data (names, social security numbers, admission ids etc.) must be anonymised or crossed out to the extent where it is no longer possible to read. If a document is uploaded with visible person identifiable data, the person spotting this must contact CHIP IT and ask for the document to be deleted.

2.4 RESPOND Data Management

Enrolment and follow-up data will be submitted to the RESPOND CC via the RESPOND Electronic Submission Tool (REST). Please see detailed instructions in the REST user guide and in the RESPOND SOP for data transfer, describing data formats and procedures for electronic transfer. Please find the documents on RESPOND study documents.

Validation of clinical event forms in REDCap is performed centrally by a medical doctor at CHIP at regular intervals. Events will be classified either as definite, possible or null/insufficient data according to the validation criteria described in Section 3.
During the spring period of each year, Cross checks with the number of events indicated in RESPOND enrolment/Follow up forms and the number of corresponding event forms actually reported in REDcap will be performed to identify potential missed/pending clinical events, which can then be queried and gathered retrospectively.

3 Guidelines for completion of clinical event forms in REDCap and validation criteria for each clinical event

The clinical event forms in REDCap are intended to be largely self-explanatory. This section includes more detailed description/background of the items requested for each clinical event in addition to the validation criteria applied for each event.
Items marked "*" are *must provide values*, and are required to be able to validate the event and to receive imbursement. However, we kindly request that you provide data on all variables where possible.

The clinical event definitions in RESPOND are mainly based on those developed and used by the D:A:D Study (1) in the period 1999-2016 with updates taking into account recent developments in diagnostic tools. The D:A:D case definitions can be found at Link to the D.A.D MOOP
Fatal cases are classified based on the Coding causes of Death Methodology (CoDe) (2), for which study documents can be found at Link to CoDe documents.

In case of uncertainty of whether an individual fulfils the diagnostic criteria for a clinical event, whether a new event should be reported or any other questions regarding clinical events, please contact the RESPOND CC in Copenhagen for clarification.

3.1 Myocardial infarction (MI)

The definition for an MI event in RESPOND is based on the manual for the WHO MONICA study (3) (coronary event registration data component; Link to the MONICA study), a study concerning coronary/stroke events and the characteristics hereof. A similar definition was used by the D:A:D Study. However, the criteria have been simplified in this manual to better comply with the format of RESPOND data collection, including adjusting the ECG criteria to the guidelines of the European Clinical Society (4) (5). Please note that unstable angina (symptoms + ECG changes but no abnormal elevation of enzymes (troponin I or troponin T or CKMB)) according to current reference intervals) and missed/old MIs (ECG changes but no symptoms and abnormal elevated enzymes (old MI events)) are not collected as MI events in RESPOND. Detailed description of the validation criteria is found at the end of this section.

3.1.1 MI event form

To be completed for participants who have experienced a non-fatal or fatal MI and where other reasons for symptoms are excluded/not probable (e.g., sepsis, hypotension, hypoxia of different causes, substance abuse (e.g., cocaine) etc.). For fatal cases, please also complete a CoDe event form. If more than one MI event has occurred, please complete one event form for each separate event.

i) Event date MI*
Please enter date of admission/medical check due to relevant symptoms.

ii) Did the participant experience symptoms of MI?*
If yes, please indicate all symptoms related to the event:

- **Typical symptoms including chest pain with or without radiation to arm, back or neck:**
  Symptoms are typical when chest pain is present and characterised by oppressive thoracic pain/ angina pectoris (any synonym for pain is acceptable such as “pressure", "discomfort", "ache"), duration of more than 20 minutes, and no definite non-cardiac, or cardiac non-atherosclerotic cause.

- **Atypical symptoms:**
  Including atypical pain, incl. back pain, upper abdominal pain, pain in arms, jaw or neck only, acute heart failure, shock or syncope, dyspnea without chest pain AND the absence of cardiac disease other than ischaemic heart disease AND no definite non-cardiac or cardiac non-atherosclerotic cause. Atypical pain could be pain recorded as of short duration or intermittent with each lasting for less than 20 minutes, or pain at an unusual site as described above. Acute heart failure means that the diagnosis was made clinically or that the participant became severely breathless suddenly. Chronic heart failure or breathlessness getting worse over several days would not qualify as a single atypical symptom unless accompanied by other typical or atypical symptoms.

- **Other:**
  Could include sudden cardiac arrest, arrhythmias (e.g., atrial fibrillation, ventricular tachycardia or heart block)

iii) Was the MI verified by ECG changes? *

If no, please specify whether an ECG was performed at all or merely didn't verify the MI.

If yes, please specify which changes according to the definitions below.

- **ST-elevation:** New elevation in two related leads. V2-3: = 0.25 mV in men < 40 years of age, = 0.20 mV in men > 40 years of age and = 0.15 mV in women. All other leads = 0.1 mV

- **ST-depression:** New depression (horizontal or descending) = 0.05mV in two related leads

- **Inverted T-waves:** Inverted T-waves = 0.1 mV in two related leads

- **Left bundle branch block (LBBB):** New or supposed new appearance of LBBB

- **Unspecific changes:** Changes in ECG other than those above (e.g. arrythmias, heart block)

- **Development of Q-waves**: progression of Q codes from no Q to a diagnostic Q or progression from no Q to an equivocal Q or from equivocal Q to a diagnostic Q accompanied by deterioration of the ST segment or the T- Wave (any of these types of progression must be accompanied by a T wave on >3 records).

iv) Elevation of enzymes (CK-MB or troponins) within 72 hrs after the event?*

- Elevated enzymes are defined as: Troponins (including cardiac specific troponin T and I) > upper limit of detection
- Creatine kinase (CK)-MB >5% of total CK. Please use peak-values of measurements performed within 72 hours of the MI event.

v) Was an invasive coronary procedure (ICP) performed in direct relation to the event (within 72 hrs)?

Please indicate whether the participant had an ICP, including coronary bypass, Angioplasty/stenting, carotid endarterectomy or carotid stenting, performed in relation to the MI event; if so please also complete an ICP event form.

3.1.2 Validation criteria MI

1) Definite acute non-fatal and fatal MI

i) Definitive electrocardiogram (ECG) (ST-elevation, ST-depression, inverted T-waves, left bundle branch block,) together with either relevant symptoms or abnormal elevated enzymes (including troponins above upper detection limit and creatine kinase (CK)-MB more than 5% of the total CK levels).

ii) Relevant symptoms (including typical: chest pain with or without radiation to left or right arm, back or neck, and atypical: including atypical pain (back pain, upper abdominal pain, pain in arms, jaw or neck only), acute heart failure, shock or syncope, dyspnea without chest pain) together with probable ECG changes and abnormal elevated enzymes (including troponins above upper detection limit and creatine kinase (CK)-MB more than 5% of the total CK levels).

iii) Typical symptoms together with abnormal elevated enzymes (both according to above), OR

iv) Fatal cases with naked eye appearance of fresh MI and/or recent coronary occlusion found at necropsy.

2) Possible acute non-fatal and fatal MI

i) Living participants with relevant symptoms whose ECG and enzymes do not place them as MI and in whom there is no conclusive evidence for another diagnosis for the attack. Additional supportive information for the diagnosis could be if an invasive coronary procedure was performed in relation to the attack OR

ii) Invasive cardiac procedure completed together within 72 hours together with either one of the following: 1) definite or probable ECG changes 2) relevant symptoms or abnormal elevated enzymes OR

iii) Fatal cases where there is no conclusive evidence for another cause of death, clinically or at autopsy: with symptoms (typical, atypical or inadequately described) or history of previous chronic heart disease (definitive/possible MI, coronary insufficiency or angina pectoris in the absence of significant valvular disease or cardiomyopathy), or evidence of chronic coronary occlusion or stenosis or old myocardial scarring at necropsy.

3) Null/Insufficient data to qualify as an event

No relevant typical or atypical symptoms.

Please note that if the participant had two myocardial infarctions within 31 days, the second MI will be validated as duplicate/null.

4) Fatal event with insufficient data to qualify as fatal MI

Fatal case with no autopsy, no history of typical or atypical or inadequately described symptoms, no previous history of chronic ischaemic heart disease and no other diagnosis

3.2 Stroke

To be completed for participants who have experienced a stroke (ischemic or haemorrhagic) defined as rapidly developed clinical signs of focal or global disturbance of cerebral function lasting > 24 hours (unless interrupted by surgery or death), with no apparent cause other than a cardiovascular origin. Secondary stroke caused by trauma should be excluded.
Transient ischemic attacks (implied when symptoms are resolved <24 hours) or stroke-like conditions of non-vascular origin are not included. The differentiation between infarction and haemorrhage should be based on results of cerebral scanning. In case of uncertainty (results not interpretable, or test not performed), please indicate so on the event form.
For fatal cases, please also complete a CoDe event form. If more than one stroke event has occurred, please complete one event form for each separate event.

3.2.1 Stroke event form

i) Event date stroke

Date of admission/medical check due to relevant symptoms, OR date of scan, the earliest available.

ii) Did the participant have any acute onset focal neurological symptoms related to the event for >24 hours?*

If yes, please indicate all relevant focal symptoms related to the event:

Focal symptoms may include acute onset of one or more of the following:

- Acute onset motor impairment (uni-or bilateral paresis or dyscoordination)
- Sensory impairment (uni-or bilateral)
- Aphasia (non-fluentspeech)
- Hemianopia (half-sided impairment of visual fields)
- Diplopia (doublevision)
- Ataxia (lack of voluntary coordination of muscle movements that includes gait abnormality)
- Apraxia (difficulties with performing tasks or movements otherwise managed)

Not acceptable as sole evidence of focal dysfunction (although strokes can present themselves in this way, these signs are not specific and therefore, cannot be accepted as definite evidence for stroke symptoms):

- Dizziness, vertigo

- Localised headache
- Blurred vision of both eyes
- Dysarthria (slurred speech)
- Impaired cognitive function (including confusion)
- Impaired consciousness
- Seizures

3) Did the participant have any acute onset global symptoms for >24 hours?*

If yes, please indicate all relevant global symptoms. Global symptoms apply to participants with subarachnoid haemorrhage or deep coma (coma caused by systemic vascular origin such as cardiac shock, Stokes-Adams syndrome or hypertensive encephalopathy should be excluded):

- Seizures
- Confusion/coma
- Severe acute onset of headache or vertigo

4) Was imaging (CT or MRI) done?*

If yes, please indicate which type of imaging was done and whether this confirmed a stroke event or not. For hemorrhagic events, please specify whether this was a subarachnoid hemorrhage or an intracerebral hemorrhage.

5) Was an invasive coronary procedure (ICP) performed in direct relation to event (within 72 hrs)?

Please indicate whether the participant had an ICP, including coronary bypass, angioplasty/stenting, carotid endarterectomy or carotid stenting, performed in relation to the stroke event; if so, please also complete an ICP event form.

6) Is there any other possible explanation for symptoms and/or imaging results?

Please consider, if possible, whether there could be any non -vascular cause of the event. Secondary stroke caused by trauma should be excluded, and transient

ischemic attacks (implied when symptoms are resolved <24 hours) or stroke-like conditions of non-vascular origin (e. g toxoplasmosis/other CNS infections, space occupying brain lesions) do not count as stroke events in RESPOND.

3.2.2. Validation criteria stroke

1) Definite acute stroke

i) Acute onset focal and/or global symptoms for a duration > 24 hours AND

ii) Imaging (CT or MRI) confirming acute ischaemic changes or haemorrhagic stroke.

2) Possible acute stroke

i) Acute onset focal and/or global symptoms for a duration of > 24 hours without Imaging (CT or MRI) confirming acute ischaemic changes or haemorrhagic stroke.

3) Null/ Insufficient data to qualify as an event

No relevant acute onset symptoms.
Please note that if the participant had two strokes of the same type (ischaemic / haemorrhagic) within 31 days, the second stroke will be validated as duplicate/null.

3.3 Invasive cardiovascular procedures (ICPs)

To be completed for participants undergoing an ICP. In RESPOND, these procedures include coronary bypasses, angioplasties/stenting (coronary procedures), carotid endarterectomy or carotid stenting (extra-coronary procedure). For fatal cases, please also complete a CoDe form.

3.3.1 ICP event forms

If more than one ICP event was performed, please complete one event form for each event**.**

v) Event date ICP*

Date of admission/procedure

vi) Which type of ICP has been conducted?*

Please indicate one of the following: Coronary bypass, angioplasty/stenting, carotid endarterectomy or carotid stenting.

vii) Was the procedure conducted in relation to a MI or stroke?*

Applies if the ICP was conducted as acute treatment of/in direct relation to (within 72 hrs) an acute MI or after an acute MI or stroke. If so please also complete an MI and/or a stroke event form.

viii) Was the procedure conducted as primary prophylaxis for MI or stroke?*

Applies if the procedure was performed before any MI or stroke event, e.g on the basis of stable coronary disease (angina pectoris) or presence of carotid stenosis. Please note that performing ICP as primary prophylaxis for a MI or stroke means that the participant had no previous MI or stroke.

ix) Was the procedure complicated by stroke?

Applies if a stroke event occurred in direct relation to the procedure (within 72 hrs). If so, please also complete a stroke event form.

3.3.2 Validation criteria ICPs

1) **Definite ICP**
   Completed coronary bypass, angioplasty or carotid endarterectomy and carotid stenting performed as prophylaxis or as acute treatment for MI or stroke. For angioplasty; unblocking and/or stenting has to be carried out, an isolated coronary angiography does not qualify as an ICP.

2) **Null/Insufficient data to qualify as an event**

Uncompleted invasive procedure (uncompleted bypass, angioplasty, carotid endarterectomy or carotid stenting without unblocking of artery and/or stent).

If no indication for ICP was selected (ICP was not conducted in relation to a MI or stroke, and ICP was not conducted as primary prophylaxis), it will be considered as a diagnostic procedure and validated as null.

Please note that if the participant had two ICPs of the same type within 31 days, the second ICP will be validated as a duplicate.

3.4 Cancer, both AIDS (ADC) and non-AIDS defining (NADC)

To be completed for all participants diagnosed with AIDS-defining cancer (Kaposi sarcoma, cervical cancer and non-Hodgkin lymphoma) and/or non-AIDS cancer. Pre-cancers, relapses and basal or squamous cell skin cancers are not considered as events in RESPOND and should not be reported. For fatal cases, please also complete CoDe event form.

Please note: If more than one cancer event, please complete one event form for each separate event.

In general, all new cancer events should be reported. If there is a relapse in the same primary location or metastases of cancer from the same primary cancer, a new event form does not need to be completed. However, for both relapses and metastases there can sometimes be doubt whether the primary cancer event was reported previously, or the relapse/metastasis could even be the first appearance of a cancer at one particular site/centre. In these cases, and if in any doubt whether the cancer was previously reported, the event should be reported in REDCap, and it will be classified centrally as either primary cancer, relapse/metastasis and included in analyses accordingly. Alternatively, it is recommended to do an internal check of previously submitted data to RESPOND or to contact the RESPOND CC.

3.4.1 Cancer event forms

i) Event date cancer*

Please enter date of biopsy. If no biopsy date available, then date the event occurrence based on (in prioritised order):

1. Performed imaging (e.g. CT [incl. SPECT, PET-CT], MR, ultrasound)
2. Biochemical assays
3. Cancer treatment and/or confirmed strong clinical suspicion (the latter only applies to Kaposi's sarcoma,malignant melanoma and tissue growth resembling cancer visualized during endoscopy/anoscopy)

ii) Type of cancer*

Please enter the type of primary cancer (only one type).

iii) What was the stage of cancer at time of diagnosis?*

Please indicate whether the cancer was localized or disseminated at the time of diagnosis. Cancer staging systems such as the TNM Classification of Malignant Tumors or imaging results/histology results can be used as guidance.

iv) Was the cancer diagnosed by biopsy, imaging, biochemical assay and/or strong clinical suspicion by visual inspection? *

Please indicate the way of diagnosis, more than one can apply so please indicate all relevant. Please note that strong clinical suspicion by visual inspection only include Kaposi's sarcoma, malignant melanoma and tissue growth resembling cancer visualized during endoscopy/anoscopy.

v) Has the participant undergone or is currently undergoing cancer treatment?

If yes, please indicate only the first cancer therapy given for each event should be indicated, including any of the following: Chemotherapy, radiotherapy, endocrinological therapy, surgery, immune therapy, other anti-neoplastic therapy.

3.4.2 Validation criteria cancer

1) Definite cancer

- Diagnosis of cancer *(excluding pre-cancers, relapse, basal and squamous cell skin cancers)* by biopsy confirming histological diagnosis of cancer.

- Two exceptions to the rule of definite cancer verified by histology are:

- Hepatocellular carcinoma (HCC): Which may also be validated as a definite event based on multiphasic gadolinium based MR or iodine based CT contrast scans. Elevation of alfa-foeto protein provides additional supportive information for the diagnosis.

- Kaposi's sarcoma: Has a very distinctive clinical appearance (making the use of other diagnostics measures including biopsy relatively rare), and is commonly treated solely with antiretroviral therapy. Therefore, validation as a definite event can be made solely on strong clinical suspicion

2) Probable cancer event

Lack of biopsy, but suspicion of cancer due to a combination of at least two of the following:

i) Imaging (e.g. CT [incl. SPECT, PET-CT], MR, ultrasound)

ii) biochemical assays

iii) cancer treatment AND/OR

iv) confirmed strong clinical suspicion by visual inspection (only applies to Kaposi's sarcoma,malignant melanoma and tissue growth resembling cancer visualized during endoscopy/anoscopy) not explained by other known conditions

3) Null/Insufficient data to qualify as an event

No biopsy or strong clinical suspicion according to any of the criteria above.

3.5 End-stage Liver Disease (ESLD)

To be completed for all participants developing clinical symptoms of end-stage liver disease and/or who have undergone a liver transplantation for the first time.
Biopsy results, fibroscan results, ARFI results, any co-infection with hepatitis B or C and any alcohol abuse should be submitted as enrolment/follow-up data according to instructions in the RESPOND SOP and are not part of event forms in REDCap.

Please note that ascites should only be reported if all other relevant clinical causes of ascites than liver cirrhosis (e.g., right ventricular heart failure, ovarian- and pancreatic cancer, peritoneal carcinomatosis, non-hepatic causes of hypoalbuminaemia, pancreatitis and portal vein thrombosis) have been ruled out. The first liver transplantation event should always be reported, irrespective of previously reported ESLD events. For fatal cases, please also complete a CoDe form.

If more than one symptom of ESLD occurred on the same date, please check all symptoms that apply. Recurring events should generally not be reported. However, if there is doubt whether an event has been reported previously (e.g., if there is doubt whether the primary event of ESLD was reported previously or a subsequent ESLD event is the first appearance of an ESLD event at one particular site/centre), a RESPOND event form should be completed the event will then be classified centrally as either a new or a recurring event and included in analyses accordingly. Alternatively, it is recommended to do an internal check of previously submitted data to RESPOND or to contact the RESPOND CC.

3.5.1 ESLD event forms.

i) Event date ESLD*

Please enter date of first time of one of the clinical symptoms or date of liver transplantation, the earliest one available

ii) Has the participant experienced one or more signs of end stage liver disease in relation to the event?*

Signs include:

- Gastric/oesophageal variceal bleeding (verified by endoscopy)
- Hepatic encephalopathy grade III or IV (grade 3: somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation, grade 4: Coma)
- Hepato-renal syndrome
- Ascites (confirmed by imaging or paracentesis) where all other relevant clinical causes of ascites than liver cirrhosis have been ruled out, see above.

- Liver transplantation

3.5.2 Validation criteria ESLD

1) Definite ESLD

i) Clinical symptoms of end-stage liver failure in participants with chronic liver disease, based on the diagnosis documented in a clinical note of either:

ii) Endoscopically verified bleeding from gastric or esophageal varices

OR

iii) Hepatic encephalopathy stage III or IV

OR

iv) Hepatorenal syndrome

OR

v) Ascites (detectable by imaging/paracentesis) where all other relevant clinical causes of ascites than liver cirrhosis have been ruled out, see above.

AND

vi) Pathology report or fibro-scan report documenting advanced liver fibrosis or cirrhosis (Metavir F3 or F4 or fibroscan liver stiffness >= 8 kPa) OR

vii) Liver transplantation

2) Possible ESLD

i) Bleeding from gastric or esophageal varices

OR

ii) Hepatic encephalopathy stage III or IV

OR

iii) Hepatorenal syndrome

OR

iv) Ascites (confirmed by imaging or paracentesis) where all other relevant clinical causes of Ascites than liver cirrhosis have been ruled out, see above.

3) Null/Insufficient data to qualify as an event

No clinical symptoms of ESLD

3.6 End-stage Renal Disease (ESRD)

To be completed for all participants developing ESRD requiring dialysis for >3 months and who have undergone a kidney transplantation for the first time. Please note that the first kidney transplantation should always be reported irrespective of previously reported ESRD. For fatal cases, please also complete CoDe form.

If more than one symptom of ERSD occurred on the same date, please check all symptoms that apply. Recurring events should generally not be reported. However, if there is doubt whether an event has been reported previously (e.g., if there is more than one admission with dialysis for >3 months that has been interrupted in between, and there may be doubt if the primary ESRD event was reported previously or a subsequent ESRD event could even be the first appearance of an ESRD event at one particular site/centre), a REDCap event form should be completed. The event will then be classified centrally as either a new or a recurring event and included in analyses accordingly. Alternatively, it is recommended to do an internal check of previously submitted data to RESPOND or to contact the RESPOND CC.

3.6.1 ESRD event forms

i) Event date ESRD*

Please enter date of start of dialysis or date of renal transplantion, the earliest one available.

iii) Has the participant undergone continuous peritoneal or hemo- dialysis for a duration of more than 3 consecutive months (for chronic renal disease)?*

The dialysis should be continuous at regular intervals, i.e., not finalised and then re-started within the 3 months.

iv) Has the participant undergone kidney transplantation (for chronic kidney disease)?*

v) Please indicate the underlying etiology of the chronic renal failure

Please indicate the category that best applies to characterize the participant's renal disease.

vi) Is the diagnosis of chronic renal impairment based on renal biopsy.

Please indicate whether a kidney biopsy was used to diagnose the underlying renal disease.

3.6.2 Validation criteria ESRD

1) Definite ESRD

i) Hemodialysis or peritoneal dialysis with duration of >3 months OR

ii) Confirmed kidney transplantation

2) Null/Insufficient data to qualify as an event

Hemodialysis less than 3 months and/or no kidney transplant performed

3.7 Bone fractures

For all participants developing a bone fracture. If the fracture is related to a fatal event, please also complete CoDe form. If more than one fracture event, please complete one event form for each event date. If there is one event with multiple fractures on the same date, please indicate the location of each fracture related to that same event.

Please note that bone mass index (BMD) should be reported if possible/available and is collected as part of enrolment /follow up data and not as part of event forms. The number of BMD locations measured with dexa scans could vary between medical centres, but according to general recommendations (6) it should be measured at the spine, the hip and sub regions of the hip, such as femoral neck. Data for available measured regions of each centre are submitted according to RESPOND SOP.

3.7.1 Bone fracture event form

i) Event date bone fracture*

Please enter date of admission/medical check due to trauma/symptoms or surgery, the earliest one available. If one event with multiple fractures on the same date, please report in one event form.

ii) Is the type of fracture traumatic, osteoporotic/fragility or pathologic?*

Please indicate the type of bone fracture, caused by trauma (high-energy), osteoporotic/fragility (low-energy traumas, fractures due to use of prednisolone) or pathologic (due to e.g. bone metastases).
Please note that if a participant with osteoporosis had a fracture following a low-energy trauma (fall from a standing height or low height of less than 1 m), the fracture should be classified as osteoporotic due to the underlying presence of weakened bone structure.

iii) Was the fracture diagnosed by imaging?*

Please indicate whether the fracture was confirmed by either x-ray, CT or MRI

iv) Is the location of fracture known?*

Please indicate the primary location of the fracture. If one event with multiple fractures please indicate all locations.

v) Was the fracture treated?

Please indicate any treatment, incl. surgery or conservative.

3.7.2 Validation criteria fracture

1) Definite fracture

Bone fracture (newly diagnosed: acute or old) with changes confirmed by x-ray, CT or MRI.

2) Possible fracture:

iii) Bone fractures with unknown imaging but with known location and with verified surgical/ conservative treatment

iv) Bone fractures with no imaging but with surgical/ conservative treatment (applies only to fractures of the facial bones/nose, scull, ribs, fingers and toes

3) Null/Insufficient data to qualify as an event

No confirmation of fracture by imaging and no fracture of the facial bones/nose, ribs, scull, finger or toes

3.8 Diabetes mellitus

Diabetes mellitus is collected as part of the follow-up data in RESPOND, and no event form is requested. A diabetes event is classified based on blood glucose levels > 7 mmol/L (126 mg/dL) or HbA1C > 6.5% (48mmol/L) and use of anti-diabetic treatment (7). Having only laboratory values only or report anti-diabetic treatments only qualify as a possible event, whereas both qualify as a definitive event.

3.9 Causes of death

The Coding of Death in HIV-positive persons (the CoDe project) was introduced in 2004 (2), and is a coding system adapted by many observational studies. In 2016 the CoDe was slightly adjusted and simplified and transferred to completion in REDCap. The causes of death are collected routinely during follow-up. For details, we kindly refer to the Code protocol (Link to CoDe documents).

Please ensure that all RESPOND events described on the CoDe form are also reported on a separate case report form.

3.9.1 Event checking chart for fatal cases

i) Event form completed by*

ii) Event form completed date*

iii) Date of death*Brief narrative of the sequence of events leading to death (please include means of diagnosis of illnesses)*

iv) In summary, the causal relation between the conditions leading to death was:

1. Condition that directly caused death (immediate cause)*
2. Due to or as a consequence of
3. Due to or as a consequence of
4. Condition that initiated the train of morbid events (the underlying condition)

Source documentation: E.g., admission letter for admission related to death, discharge letter, autopsy report etc. Please note that SD for Code is only a requirement in EuroSIDA and not in RESPOND.

APPENDIX - Guide REDCap event forms

Clinical event	Report first or any event
Myocardial infarction	Any
Invasive cardiovascular procedure Coronary angioplasty/stenting, coronary bypass surgery, carotic endarterectomy, carotic stenting	Any
Stroke Ischemic or hemorrhagic	Any
ESRD Haemodialysis, peritoneal dialysis, renal transplantation	First of these events + transplantation Please see ESRD event section
ESLD Hepatic encephalopathy stage III-IV Bleeding from oesophageal or gastric varices Hepato-renal syndrome Liver transplantation Ascites	First of these events + transplantation- Please see ESLD event section
Cancer	First diagnosis only for individual cancer types, do not report relapse. Please see cancer event section
Bone fractures	Any

References

1. D:A:D Study MOOP https://www.chip.dk/Portals/0/files/Study%20documents/DAD_MOOP_revised2013.pdf
2. J Kowalska et al: The Coding Causes of Death in HIV (CoDe) Project Initial Results and Evaluation of Methodology, Epidemiology 2011;22: 516–523
3. Tunstall-Pedoe et al: Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents)
4. European Society of Cardiology, guidelines: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Myocardial-Infarction-in-patients-presenting-with-ST-segment-elevation-Ma
5. *European Society of Cardiology, guidelines: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Coronary-Syndromes-ACS-in-patients-presenting-without-persistent-ST-segm*
6. Ensrud et al; 'Osteoporosis' *Ann Intern Med. 2017 (doi:10.7326/AITC201708010)*
7. *EACS Guidelines v11.1, October 2022*