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**CONCEPT SHEET: REGIONAL ANALYSES**

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| **Steering Group approval date:** | *(To be added by UCT data centre)* |
| **Tracking number:** | *(To be added by UCT data centre)* |
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| **Where will statistical analyses be done?** | ISPM, University of Bern |
| **Required variables:** |  |
| **Target journal:** |  |
| **Ethics:** | *Select as appropriate:*  This concept uses only the IeDEA-SA standard dataset and is covered by the core IeDEA-SA ethics approvals.  This concept requires additional collection of health-related data, measurements or tests, or sampling of biological material not included in the IeDEA-SA standard dataset. Additional ethics approval is required.\* (Describe ethical considerations for any additional data collection here, including responsible IRBs.) |
| **Milestones:** | *Circulation of concept sheet: April 1, 2022*  *Ethics approval (for additional data collection): <date>*  *Circulation of mature draft paper: <date>*  *Submission to target journal: <date>* |
| **Abstract:** (about 100 words) | **Background:**  **Aims and objectives:**  **Methods:** |

\* If additional ethics approvals are required, a copy must be sent to the ISPM Program Manager before data collection can begin.

**1. Background**

Posttraumatic stress disorder (PTSD) is a maladaptive reaction to a traumatic event, and it is present in about 7% of the population (1). The current scientific literature shows an association between PTSD and CVD risk factors (2) and cardiovascular disease (CVD). For example, a recent systematic review (3) reported that persons with PTSD had a largely increased risk of subsequent myocardial infection (HR 1.49, 95% CI 1.31-1.69).

Two pathways might explain the increased incidence of CVD in persons with PTSD. PTSD can lead to unhealthy behaviours such as substance use, physical inactivity, sleep disorders and dietary changes that lead to common cardiovascular risk factors (hypertension, diabetes, high cholesterol), which can cause CVD (2). An alternative explanation is that PTSD generates an inflammatory state that can cause CVDs such as myocardial infarction, unstable angina and stroke (2). This hypothesis is supported by studies showing that PTSD is independently associated with an increased risk of coronary heart disease even after adjusting for depression and cardiovascular risk factors, such as high cholesterol, hypertension and high blood pressure (3).

The relationship between PTSD and CVD is bidirectional. Evidence suggests that a cardiovascular event can cause PTSD. For example, Edmonson found a 12% prevalence of PTSD secondary to acute coronary syndromes. PTSD, in turn, doubles the risk for recurrent acute coronary syndromes and mortality. The mechanisms through which CVD causally relates to PTSD are under study (2).

While evidence on the association between PTSD and CVD is emerging, there is little empirical support for causal links between PTSD and CVD. We aim to examine PTSD as a causal risk factor for CVD and quantify the mediating effect of PTSD on CVD through CVD risk factors.

**2. Objectives**

1. To describe the incidence of cardiovascular risk factors and major cardiovascular events in persons with and without PTSD
2. To examine PTSD as a causal risk factor for CVD (total effect)
3. To quantify the mediating effect of PTSD through CVD risk factor or inflammation on CVD (indirect effect via mediators).

**3. Study design**

We will conduct a cohort study of South African adults using routine data from a large South African medical insurance scheme.

**3.1 Eligibility criteria**

Adults aged 18 years or older who had insurance coverage with the medical insurance scheme at any point between January 1, 2011, and July 30, 2020, are eligible for analysis. Persons with unknown sex or age will be excluded.

**3.2 Data sources**

We will use data from a large South African private-sector medical insurance scheme.29 Data include sociodemographic information, reimbursement claims, laboratory results, and information of the vital status of beneficiaries of the medical scheme.

**3.3 Key variables**

* Sociodemographic data: age, sex, ethnicity
* Hospital claims contain the date of admission, date of discharge, International Classification of Diseases, 10th Revision (ICD-10), National Reference Price List (NRPL) codes, and Current Procedural Terminology (CPT) codes.
* Outpatient claims contain ICD-10 diagnoses.
* Pharmacy claims contain information on the active ingredients of drugs coded according to the Anatomical Therapeutic Chemical (ATC) classification system, the drug strengths, the dispensed amount, and the date of dispensing.
* Laboratory data contain the date of specimen collection, the type of laboratory test, the laboratory result, and the unit of measurement.
* Mortality data from the medical scheme records and the National Population Register (NPR): date of death and cause of death (natural/unnatural).
* Administrative data on the start and end of beneficiaries’ medical insurance coverage and the health care plan

**3.4. Assumptions**

The assumptions about the relationship between relevant variables are shown in a directed acyclic graph (DAG) (Figure 1). Ethnicity and associated socioeconomic disparities affect the risk of PTSD (4) and depression (5), and lifestyle factors (e.g. smoking, substance use, alcohol use, diet, and physical activity) (6). Lifestyle factors increase cardiovascular risk factors (e.g. high blood pressure, obesity, high cholesterol, and diabetes) that may cause CVD (7). Ethnicity and socioeconomic disparities are risk factors for HIV (8). HIV is a risk factor for CVD (9). PTSD and depression may lead to lifestyle changes that might lead to cardiovascular risk factors (10). Conversely, after a cardiovascular event, lifestyle might change and thus the cardiovascular risk factors. Depression, PTSD (11), and smoking (12), could also lead to an inflammatory state that increases the risk of CVD. This inflammatory state can also cause PTSD or depression after CVD (13).

**3.5 Measures**

**Outcome:** The primary outcome is a major cardiovascular event (acute coronary syndromes and stroke). Cases of acute coronary syndromes are defined in the presence of any of the ICD-10 codes in primary or secondary position for unstable angina, acute ST-elevation myocardial infarction, acute non-ST-elevation myocardial infarction, or unspecified myocardial infarction; or any of the CPT codes for coronary revascularization procedures are in among hospitalization claims, as explained in the code lists of outcomes and covariates Conditions mimicking stroke will be excluded if any of the listed ICD-10 or ICD-O-3 codes in primary or secondary among hospitalization claims are co-occurring within a window of less or more than 30 days with a stroke diagnosis code is present (table 1).

**Exposures:** The primary exposure is an ICD-10 diagnosis of PTSD (F43.1). The secondary exposure is an ICD-10 diagnosis of a major depressive disorder (F32, F33, F34.1). Exposure variables will be defined as time-varying variables. Persons will be considered “exposed” from the date of their first diagnosis onwards.

**Sociodemographic characteristics**

We will group age into six categories (18-29, 30-39, 40-49, 50-59, 60-69, and ≥70 years). Population groups will be defined as Black African, Indian/Asian, mixed ancestry [“coloured”], white, or unknown, and sex as male and female.

**HIV:** HIV will be defined using lab data for HIV viral load, CD4 count, a positive HIV test, along with a HIV ICD-10 diagnosis (B20 to B24) and use of ART medication

**Cardiovascular risk factors**

**Hypertension:** will be defined using ICD-10 codes for diagnosis in primary or secondary position among hospitalisation claims, or any of the ATC codes for medication claims, or any clinical result of systolic blood pressure >=140mmHg and diastolic blood pressure >=90mmHg (table 2).

**Dyslipidaemia:** will be defined using ICD-10 codes for diagnosis in primary or secondary position among hospitalisation claims, or any of the ATC codes for medication claims, or any laboratory result of HDL<1 mmol/L, LDL >4.1 mmol/L or total cholesterol >6.2 mmol/L (table 2).

**Diabetes mellitus:** any of the ICD-10 codes for diabetes diagnosis, or any of the ATC codes for medications used for diabetes control, or laboratory results of HbA1c >= 6.5% (>=48 mmol/L), fasting blood glucose >= 7 mmol/L or random blood glucose >= 11.1 mmol/L (table 2).

**Overweight and obesity:** any of the ICD-10 codes that range from overweight (E66) to morbid obesity (E66.9).

**Inflammatory markers:** We will include C - reactive protein >= 0.3 mg/L from laboratory test results.

* 1. **Statistical methods**

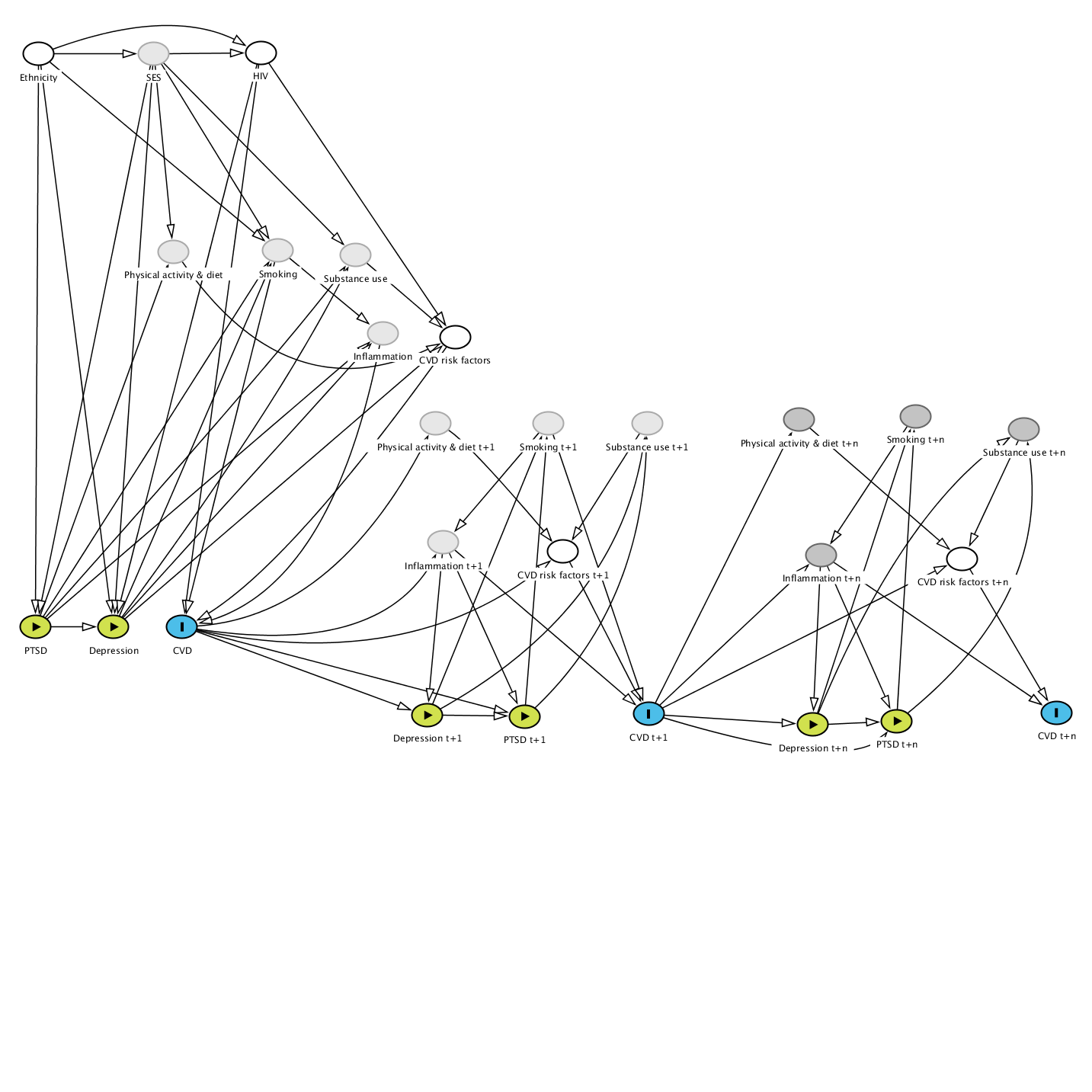
*Descriptive analysis:* We will use descriptive statistics to analyse characteristics of participants with PTSD that belong to both private- and public-sector ART programs. Descriptive analysis will be stratified by sector (public/private) and history of cardiovascular disease treatment utilization (yes/no).

*Objective i:* We will calculate adjusted incidence rate ratios with 95% confidence intervals (CI), comparing the incidence of cardiovascular admissions between public- and private-sector ART programs using Poisson regression.31 Patients will be followed from PTSD diagnosis to their last documented clinic visit. We will model the number of hospital admissions recorded in patients with PTSD using Poisson regression). Models will be adjusted for current age, type of health insurance, gender and ethnicity and will use person-years at risk as an offset.

*Objective ii:* We will use causal inference to quantify the effect of PTSD on cardiovascular disease. The target quantity of interest in this analysis is the average treatment effect. The average treatment effect is defined as the expected outcomes under the counterfactual scenario where everyone was continuously affected by PTSD (always exposed) compared to the expected outcome under the scenario where nobody was affected (never exposed). Adjustment variables will be selected based on a direct acyclic graph (DAG) developed based on an extensive literature review and in consultation with domain experts. The target quantity will be estimated using longitudinal targeted maximum likelihood estimation (LTMLE). LTMLE is a state-of-the-art causal inference method for appropriate handling of time-depend exposures in the presence of time-dependent confounding affected by prior exposure. LTMLE reduces the chances of model miss-specification because it can incorporate flexible machine learning methods while retaining valid statistical inference.Risk of bias due to limitations of our data (e.g. unmeasured confounding) will be critically evaluated.

**3.7 Ethical considerations**

The Human Research Ethics Committee of the University of Cape Town, South Africa, and the Cantonal Ethics Committee Bern, Switzerland, authorised the analysis of the database. Beneficiaries of the medical insurance scheme or their guardians provided consent for their data to be used in research.



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| **Table 1. Code list for major CV event outcomes** | |
| **ICD-10 CODES** | **CPT CODES** |
| **ACUTE CORONARY SYNDROMES** | |
| *Unstable angina* | *Coronary revascularization procedures* |
| I20.0 Unstable angina | 33503 Coronary artery graft |
| *Acute ST-elevation myocardial infarction* | 33504 Coronary artery graft |
| I21.0 Transmural infarct of anterior wall | 33510 Coronary artery bypass graft, vein, single |
| I21.1 Transmural infarct of inferior wall | 33511 Coronary artery bypass graft, vein, two |
| I21.2 Transmural infarct of other sites | 33512 Coronary artery bypass graft, vein, three |
| I21.3 Transmural infarct of unspecified sites | 33513 Coronary artery bypass graft, vein, four |
| I22.0 Subsequent (<4w) infarction of anterior wall | 33514 Coronary artery bypass graft, vein, five |
| I22.1 Subsequent (<4w) infarction of inferior wall | 33516 Coronary artery bypass graft, vein, six or more |
| I22.8 Subsequent (<4w) infarction of other sites | 33517 Coronary artery bypass graft, artery-vein, single |
| I22.9 Subsequent (<4w) infarction of unspecified sites | 33518 Coronary artery bypass graft, artery-vein, two |
| *Acute non-ST-elevation myocardial infarction* | 33519 Coronary artery bypass graft, artery-vein, three |
| I21.4 acute subendocardial myocardial infarction | 33521 Coronary artery bypass graft, artery-vein, four |
| *Unspecified myocardial infarction* | 33522 Coronary artery bypass graft, artery-vein, five |
| I21.9 acute myocardial infarction, unspecified | 33523 Coronary artery bypass graft, artery-vein, six or more |
|  | 33530 Coronary artery, bypass/reoperation |
|  | 33533 Coronary artery bypass graft, arterial, single |
|  | 33534 Coronary artery bypass graft, arterial, two |
|  | 33535 Coronary artery bypass graft, arterial, three |
|  | 33536 Coronary artery bypass graft, arterial, four or more |
|  | 33572 Open coronary endarterectomy |
|  | 92920 Percutaneous transluminal coronary angioplasty, single major coronary artery or branch |
|  | 92921 Percutaneous transluminal coronary angioplasty, each additional branch of major coronary artery |
|  | 92924 Percutaneous transluminal coronary atherectomy, with coronary angioplasty when performed; single major coronary artery or branch |
|  | 92928 Percutaneous transcatheter placement of intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch |
|  | 92929 Percutaneous transcatheter placement of intracoronary stent(s), with coronary angioplasty when performed; each additional branch of a major coronary artery |
|  | 92933 Percutaneous transluminal coronary atherectomy, with intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch |
|  | 92934 Percutaneous transluminal coronary atherectomy, with intracoronary stent, with coronary angioplasty when performed; each additional branch of a major coronary artery |
|  | 92937 Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; single vessel 92938 Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; each additional branch subtended by the bypass graft |
|  | 92941 Percutaneous transluminal revascularization of acute total/subtotal occlusion during acute myocardial infarction, coronary artery or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty, including aspiration thrombectomy when performed, single vessel |
|  | 92943 Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; single vessel |
|  | 92944 Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; each additional coronary artery, coronary artery branch, or bypass graft |
|  | 92973 Percutaneous transluminal coronary thrombectomy |
|  | 92980 Insert intracoronary stent |
|  | 92981 Insert intracoronary stent |
|  | 92982 Coronary artery dilation |
|  | 92984 Coronary artery dilation |
| **STROKE** | |
| *Haemorrhagic stroke* |  |
| I60.0 Subarachnoid haemorrhage from carotid siphon and bifurcation |  |
| I60.1 Subarachnoid haemorrhage from middle cerebral artery |  |
| I60.2 Subarachnoid haemorrhage from anterior communicating artery |  |
| I60.3 Subarachnoid haemorrhage from posterior communicating artery |  |
| I60.4 Subarachnoid haemorrhage from basilar artery |  |
| I60.5 Subarachnoid haemorrhage from vertebral artery |  |
| I60.6 Subarachnoid haemorrhage from other intracranial arteries |  |
| I60.7 Subarachnoid haemorrhage from intracranial artery, unspecified |  |
| I60.8 Other subarachnoid haemorrhage |  |
| I60.9 Subarachnoid haemorrhage, unspecified |  |
| I61.0 Intracerebral haemorrhage in hemisphere, subcortical |  |
| I61.1 Intracerebral haemorrhage in hemisphere, cortical |  |
| I61.2 Intracerebral haemorrhage in hemisphere, unspecified |  |
| I61.3 Intracerebral haemorrhage in brain stem |  |
| I61.4 Intracerebral haemorrhage in cerebellum |  |
| I61.5 Intracerebral haemorrhage, intraventricular |  |
| I61.6 Intracerebral haemorrhage, multiple localized |  |
| I61.8 Other intracerebral haemorrhage |  |
| I61.9 Intracerebral haemorrhage, unspecified |  |
| *Ischaemic stroke* |  |
| I63.0 Cerebral infarction due to thrombosis of precerebral arteries |  |
| I63.1 Cerebral infarction due to embolism of precerebral arteries |  |
| I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries |  |
| I63.3 Cerebral infarction due to thrombosis of cerebral arteries |  |
| I63.4 Cerebral infarction due to embolism of cerebral arteries |  |
| I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries |  |
| I63.8 Other cerebral infarction |  |
| I63.9 Cerebral infarction, unspecified |  |
| H34.1 Central retinal artery occlusion |  |
| *Unspecified stroke* |  |
| I64 Stroke, not specified as haemorrhage or infarction |  |
| **CONDITIONS MIMICKING STROKE** | |
| *Infections of the central nervous system* |  |
| A06.6 Amoebic brain abscess |  |
| A17 Tuberculosis of nervous system |  |
| A52.1 Symptomatic neurosyphilis |  |
| A52.2 Asymptomatic neurosyphilis |  |
| A52.3 Unspecified neurosyphilis |  |
| A54.8 Gonococcal brain abscess |  |
| A81.2 Progressive multifocal leukoencephalopathy |  |
| B00.3 Herpesviral meningitis |  |
| B01.0 Varicella meningitis |  |
| B02.1 Zoster meningitis |  |
| B37.5 Candida meningitis |  |
| B38.4 Coccidioidomycosis meningitis |  |
| B43.1 Phaeomycotic brain abscess |  |
| B45.1 Cerebral cryptococcosis |  |
| B45.9 Cryptococcosis, unspecified |  |
| B58.2 Toxoplasma meningoencephalitis |  |
| B58.9 Toxoplasmosis, unspecified |  |
| B69.0 Cysticercosis of CNS |  |
| B90.0 Sequelae of CNS tuberculosi |  |
| G00 Bacterial meningitis |  |
| G01 Meningitis in bacterial diseases |  |
| G02 Meningitis in other (viral / mycotic) diseases |  |
| G03 Meningitis due to other / unspecified cause |  |
| G04 Encephalitis / myelitis |  |
| G05 Encephalitis / myelitis in other diseases |  |
| G06 Intracranial abscess and granuloma |  |
| G07 Intracranial abscess and granuloma in other diseases |  |
| G09 Sequelae of G00 to G08 |  |
| *Malignancies of the central nervous system* |  |
| C70 Malignant neoplasm of meninges |  |
| C71 Malignant neoplasm of brain |  |
| C72 Malignant neoplasm of rest of CNS / unspecified |  |
| C79.3 Metastases to the brain or meninges |  |
| M9680/3 Malignant lymphoma, large B-cell, diffuse, not otherwise specified |  |
| R90.0 Intracranial space-occupying lesion |  |

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| **Table 2. Code list for CV risk factors** | | | |
| **ICD-10 CODES** | **ATC MEDICATION CLAIMS** | **LABORATORY TESTS** | **CLINICAL RESULTS** |
| **HYPERTENSION** | | | |
| I10 Essential hypertension | C03Axxx Low-ceiling diuretics (thiazides) |  | Systolic blood pressure >= 140mmHg |
| I11.x Hypertensive heart disease | C03Bxxx Low-ceiling diuretics (non-thiazides) |  | Diastolic blood pressure >= 90mmHg |
| I12.x Hypertensive renal disease | C03EAxx Low-ceiling diuretics in combination with potassium-sparing agents |  |  |
| I13.x Hypertensive heart and renal disease | C07Bxxx Beta-blockers combined with thiazides |  |  |
| I15.x Secondary hypertension | C07Cxxx Beta-blockers with "other" diuretics |  |  |
| H35.0 Hypertensive retinopathy | C07Dxxx Beta-blockers with thiazide diuretic with "other" diuretics |  |  |
| I67.4 Hypertensive encephalopathy | C08Gxxx Calcium channel blockers in combination with diuretics |  |  |
|  | C09BAxx ACE-inhibitors with diuretics |  |  |
|  | C09DAxx Angiotensin II receptor-blockers with diuretics |  |  |
|  | C09DX01 Valsartan + amlodipine + hydrochlorothiazide |  |  |
|  | C09DX03 Olmesartan + amlodipine + hydrochlorothiazide |  |  |
|  | C09DX06 Candesartan + amlodipine + hydrochlorothiazide |  |  |
|  | C09XA52 Aliskiren + hydrochlorothiazide |  |  |
|  | C09XA54 Aliskiren + amlodipine + hydrochlorothiazide |  |  |
|  | C10BX13 Rosuvastatin + perindopril + indapamide |  |  |
| **DIABETES MELLITUS** | | | |
| E10.x Type 1 diabetes mellitus | A10xxxx Drugs used in diabetes | HbA1c >= 6.5 % (>= 48mmol/L) |  |
| E11.x Type 2 diabetes mellitus |  | Fasting blood glucose >= 7.0 mmol/L (~126 mg/dL) |  |
| E12.x Malnutrition-related diabetes mellitus |  | Random blood glucose >= 11.1 mmol/L (~200 mg/dL) |  |
| E13.x Other specified diabetes mellitus |  |  |  |
| E14.x Unspecified diabetes mellitus |  |  |  |
| H28.0 Diabetic cataract |  |  |  |
| H36.0 Diabetic retinopathy |  |  |  |
| M14.2 Diabetic arthropathy |  |  |  |
| M14.6 Diabetic neuropathic arthropathy |  |  |  |
| G59.0 Diabetic mononeuropathy |  |  |  |
| G63.2 Diabetic polyneuropathy |  |  |  |
| G99.0 Diabetic autonomic neuropathy |  |  |  |
| **DYSLIPIDEMIA** | | | |
| E78.0 Pure hypercholesterolaemia | C10xxxx Lipid-modifying agents | HDL-cholesterol < 1 mmol/L (~40 mg/dL) |  |
| E78.1 Pure hyperglyceridaemia |  | LDL-cholesterol > 4.1 mmol/L (~160 mg/dL) |  |
| E78.2 Mixed hyperlipidaemia |  | Total cholesterol > 6.2 mmol/L (~240 mg/dL) |  |
| E78.3 Hyperchylomicronaemia |  |  |  |
| E78.4 Other hyperlipidaemia |  |  |  |
| E78.5 Hyperlipidaemia, unspecified |  |  |  |

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