OHDSI Large-Scale Evidence Generation and Evaluation in a Network of Databases (LEGEND): Study of the Effects of Treatments for Hypertension

**Version:** 0.3

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The authors declare the following disclosures: Dr. Schuemie and Dr. Ryan are employees of Janssen Research & Development.

# Table of contents

[1 Table of contents 2](#_Toc2087220)

[2 List of abbreviations 4](#_Toc2087221)

[3 Abstract 4](#_Toc2087222)

[4 Amendments and Updates 4](#_Toc2087223)

[5 Milestones 5](#_Toc2087224)

[6 Rationale and Background 5](#_Toc2087225)

[7 Research Questions and Objectives 6](#_Toc2087226)

[7.1 Research Questions 6](#_Toc2087227)

[7.2 Objectives 8](#_Toc2087228)

[8 Research methods 9](#_Toc2087229)

[8.1 Study Design 9](#_Toc2087230)

[8.2 Data Source(s) 9](#_Toc2087231)

[8.2.1 Truven MarketScan Commercial Claims and Encounters (CCAE) 9](#_Toc2087232)

[8.2.2 Truven MarketScan Medicare Supplemental Beneficiaries (MDCR) 9](#_Toc2087233)

[8.2.3 Truven MarketScan Multi-state Medicaid (MDCD) 10](#_Toc2087234)

[8.2.4 Optum ClinFormatics (Optum) 10](#_Toc2087235)

[8.2.5 QuintilesIMS Disease Analyzer (DA) Germany 10](#_Toc2087236)

[8.2.6 Japan Medical Data Center (JMDC) 10](#_Toc2087237)

[8.2.7 Optum® de-identified Electronic Health Record Dataset (PanTher) 11](#_Toc2087238)

[8.2.8 Korea National Health Insurance Service (NHIS) National Sample Cohort (NSC) 11](#_Toc2087239)

[8.2.9 Columbia University Medical Center (CUMC) 11](#_Toc2087240)

[8.3 Study population 11](#_Toc2087241)

[8.4 Exposures 11](#_Toc2087242)

[8.4.1 All drugs 11](#_Toc2087243)

[8.4.2 Mono therapies 12](#_Toc2087244)

[8.4.3 Combination therapies 12](#_Toc2087245)

[8.5 Outcomes 12](#_Toc2087246)

[8.5.1 Abdominal pain 12](#_Toc2087247)

[8.5.2 Abnormal weight gain 13](#_Toc2087248)

[8.5.3 Abnormal weight loss 13](#_Toc2087249)

[8.5.4 Acute myocardial infarction 14](#_Toc2087250)

[8.5.5 Acute pancreatitis 15](#_Toc2087251)

[8.5.6 Acute renal failure 16](#_Toc2087252)

[8.5.7 All-cause mortality 18](#_Toc2087253)

[8.5.8 Anaphylactoid reaction 18](#_Toc2087254)

[8.5.9 Anemia 20](#_Toc2087255)

[8.5.10 Angioedema 21](#_Toc2087256)

[8.5.11 Anxiety 22](#_Toc2087257)

[8.5.12 Bradycardia 26](#_Toc2087258)

[8.5.13 Cardiac arrhythmia 27](#_Toc2087259)

[8.5.14 Cardiovascular disease 30](#_Toc2087260)

[8.5.15 Cardiovascular-related mortality 33](#_Toc2087261)

[8.5.16 Chest pain or angina 36](#_Toc2087262)

[8.5.17 Chronic kidney disease 37](#_Toc2087263)

[8.5.18 Cough 41](#_Toc2087264)

[8.5.19 Decreased libido 41](#_Toc2087265)

[8.5.20 Dementia 42](#_Toc2087266)

[8.5.21 Depression 43](#_Toc2087267)

[8.5.22 Diarrhea 46](#_Toc2087268)

[8.5.23 End stage renal disease 47](#_Toc2087269)

[8.5.24 Fall 49](#_Toc2087270)

[8.5.25 Gastrointestinal bleeding 49](#_Toc2087271)

[8.5.26 Gout 54](#_Toc2087272)

[8.5.27 Headache 55](#_Toc2087273)

[8.5.28 Heart failure 56](#_Toc2087274)

[8.5.29 Hemorrhagic stroke 56](#_Toc2087275)

[8.5.30 Hepatic failure 58](#_Toc2087276)

[8.5.31 Hospitalization with heart failure 59](#_Toc2087277)

[8.5.32 Hospitalization with preinfarction syndrome 60](#_Toc2087278)

[8.5.33 Hyperkalemia 61](#_Toc2087279)

[8.5.34 Hypokalemia 62](#_Toc2087280)

[8.5.35 Hypomagnesemia 63](#_Toc2087281)

[8.5.36 Hyponatremia 64](#_Toc2087282)

[8.5.37 Hypotension 65](#_Toc2087283)

[8.5.38 Impotence 65](#_Toc2087284)

[8.5.39 Ischemic stroke 66](#_Toc2087285)

[8.5.40 Malignant neoplasm 67](#_Toc2087286)

[8.5.41 Measured renal dysfunction 78](#_Toc2087287)

[8.5.42 Nausea 79](#_Toc2087288)

[8.5.43 Neutropenia or agranulocytosis 80](#_Toc2087289)

[8.5.44 Rash 81](#_Toc2087290)

[8.5.45 Rhabdomyolysis 82](#_Toc2087291)

[8.5.46 Stroke 84](#_Toc2087292)

[8.5.47 Sudden cardiac death 86](#_Toc2087293)

[8.5.48 Syncope 87](#_Toc2087294)

[8.5.49 Thrombocytopenia 88](#_Toc2087295)

[8.5.50 Transient ischemic attack 89](#_Toc2087296)

[8.5.51 Type 2 diabetes mellitus 90](#_Toc2087297)

[8.5.52 Vasculitis 94](#_Toc2087298)

[8.5.53 Venous thromboembolic events 97](#_Toc2087299)

[8.5.54 Vertigo 99](#_Toc2087300)

[8.5.55 Vomiting 100](#_Toc2087301)

[8.5.56 Negative control outcomes 102](#_Toc2087302)

[8.5.57 Positive control outcomes 103](#_Toc2087303)

[8.6 Covariates 103](#_Toc2087304)

[8.6.1 Propensity score covariates 103](#_Toc2087305)

[9 Data Analysis Plan 104](#_Toc2087306)

[9.1 Calculation of time-at risk 104](#_Toc2087307)

[9.2 Model Specification 104](#_Toc2087308)

[9.2.1 Pooling effect estimates across databases 105](#_Toc2087309)

[9.3 Analyses to perform 105](#_Toc2087310)

[9.3.1 Comparative analyses 105](#_Toc2087311)

[9.3.2 Descriptive analyses 106](#_Toc2087312)

[9.4 Output 106](#_Toc2087313)

[9.5 Evidence Evaluation 106](#_Toc2087314)

[10 Study Diagnostics 107](#_Toc2087315)

[10.1 Sample Size and Study Power 107](#_Toc2087316)

[10.2 Cohort Comparability 107](#_Toc2087317)

[10.3 Systematic Error Assessment 107](#_Toc2087318)

[11 Strengths and Limitations of the Research Methods 107](#_Toc2087319)

[12 Protection of Human Subjects 108](#_Toc2087320)

[13 Management and Reporting of Adverse Events and Adverse Reactions 108](#_Toc2087321)

[14 Plans for Disseminating and Communicating Study Results 108](#_Toc2087322)

[15 References 108](#_Toc2087323)

# List of abbreviations

ATC Anatomic Therapeutic Chemical

CYCLOPS Cyclic coordinate descent for logistic, Poisson and survival analysis

SNOMED Systematized Nomenclature of Medicine

OHDSI Observational Health Data Sciences and Informatics

OMOP Observational Medical Outcomes Partnership

T Target cohort

C Comparator cohort

O Outcome cohort

PS Propensity Scores

LASSO Least absolute shrinkage and selection operator

LEGEND Large-scale Evidence Generation and Evaluation in a Network of Databases

CI Confidence Interval

ECT Electroconvulsive therapy

MedDRA Medical Dictionary for Regulatory Activities

ACE inhibitors Angiotensin Converting Enzyme inhibitors

ARB Angiotensin receptor blocker

CCB Calcium channel blocker

dCCB Dihydropyridine calcium channel blocker

# Abstract

In this study we will generate population-level estimates at scale for one disease: hypertension. We perform every possible pairwise comparison between hypertension treatments for a large set of outcomes of interest. Most of these outcomes are generic safety outcomes, but some outcomes are related more specifically to the effectiveness of hypertension treatment.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | 11 Sep 2018 | P. Ryan,  M. Schuemie | Initial draft |
| 02. | 24 Jan 2019 | All | * Corrected section 8.4.1 to reflect how exposures were defined in the study package. * Removed outcome “coronary heart disease”. It was a composite of acute MI and sudden cardiac death; however, databases encoded sudden cardiac death so rarely that coronary heart disease almost replicated acute MI outcomes. * Removed outcome “edema”. Performed poorly because of coding change from ICD 9 to 10 * Added outcome “Kidney disease” to protocol. This was already in the analysis code. * Removed subgroup analysis, as this was too computationally expensive to execute in all databases. Also, a hazard rate ratio proved to be hard to interpret. It is recommended that in a next study we report hazard ratios per subgroup as well. * Added description of NHIS and CUMC databases. * Dropped CPRD database |
| 0.3 | 26 Feb 2019 | All | * Removed “Kidney disease”, as it was replaced by chronic kidney disease * Added literature references and short descriptions to all outcome definitions. |
|  |  |  |  |

# Milestones

|  |  |
| --- | --- |
| Milestone | Planned / Estimated Date |
| Start of analysis | 9 September 2018 |
| End of analysis | 30 September 2018 |
| Presentation of results | 11 October 2018 |

# Rationale and Background

The Large-scale Evidence Generation and Evaluation in a Network of Databases (LEGEND) project aims to generate reliable evidence on the effects of medical interventions using observational healthcare data to support clinical decision making. LEGEND follows ten guiding principles (see Supplementary Material); chief among these stand that we generate evidence at large-scale to achieve completeness and facilitate analysis of the overall distribution of effect size estimates across treatments and outcomes. We also generate evidence consistently by applying a systematic approach across all research questions and disseminate evidence regardless on the estimates effects to avoid publication bias. These aims help overcome the questionable reliable of observational research [[1](#_ENREF_1)].

In this study we will generate population-level estimates at scale for one disease: hypertension. We perform every possible pairwise comparison between hypertension treatments for a large set of outcomes of interest. Most of these outcomes are generic safety outcomes, but some outcomes are related more specifically to the effectiveness of hypertension treatment.

# Research Questions and Objectives

## Research Questions

In this study, we are interested in every pairwise comparison between any two treatments in table 1. Treatments will be compared at the treatment level (e.g. comparing lisinopril to amlodipine), but also at the class level (e.g. ACE inhibitors versus Dihydropyridine calcium channel blockers) and the major class level (e.g. ACE inhibitors versus calcium channel blockers). Furthermore, we compare all combination therapies at the various levels of granularity (e.g. comparing hydrochlorothiazide combined with ramipril to amlodipine monotherapy, or ACE inhibitor monotherapy to ACE inhibitors in combination with beta blockers).

Only comparisons where each treatment cohort has more than 2,500 subjects will be performed.

|  |  |  |
| --- | --- | --- |
| Drug | Class | Major class |
| Benazepril | ACE inhibitors | ACE inhibitors |
| Captopril | ACE inhibitors | ACE inhibitors |
| Enalapril | ACE inhibitors | ACE inhibitors |
| Fosinopril | ACE inhibitors | ACE inhibitors |
| Lisinopril | ACE inhibitors | ACE inhibitors |
| Moexipril | ACE inhibitors | ACE inhibitors |
| Perindopril | ACE inhibitors | ACE inhibitors |
| Quinapril | ACE inhibitors | ACE inhibitors |
| Ramipril | ACE inhibitors | ACE inhibitors |
| Trandolapril | ACE inhibitors | ACE inhibitors |
| Doxazosin | Alpha-1 blockers | Alpha-1 blockers |
| Prazosin | Alpha-1 blockers | Alpha-1 blockers |
| Terazosin | Alpha-1 blockers | Alpha-1 blockers |
| Azilsartan | Angiotensin receptor blockers (ARBs) | Angiotensin receptor blockers (ARBs) |
| Candesartan | Angiotensin receptor blockers (ARBs) | Angiotensin receptor blockers (ARBs) |
| Eprosartan | Angiotensin receptor blockers (ARBs) | Angiotensin receptor blockers (ARBs) |
| irbesartan | Angiotensin receptor blockers (ARBs) | Angiotensin receptor blockers (ARBs) |
| Losartan | Angiotensin receptor blockers (ARBs) | Angiotensin receptor blockers (ARBs) |
| Olmesartan | Angiotensin receptor blockers (ARBs) | Angiotensin receptor blockers (ARBs) |
| Telmisartan | Angiotensin receptor blockers (ARBs) | Angiotensin receptor blockers (ARBs) |
| Valsartan | Angiotensin receptor blockers (ARBs) | Angiotensin receptor blockers (ARBs) |
| Atenolol | Beta blockers - cardioselective | Beta blockers |
| Betaxolol | Beta blockers - cardioselective | Beta blockers |
| Bisoprolol | Beta blockers - cardioselective | Beta blockers |
| Metoprolol | Beta blockers - cardioselective | Beta blockers |
| Nebivolol | Beta blockers - cardioselective and vasodilatory | Beta blockers |
| Carvedilol | Beta blockers - combined alpha and beta receptor | Beta blockers |
| Labetalol | Beta blockers - combined alpha and beta receptor | Beta blockers |
| Acebutolol | Beta blockers - intrinsic sympathomimetic activity | Beta blockers |
| Penbutolol | Beta blockers - intrinsic sympathomimetic activity | Beta blockers |
| Pindolol | Beta blockers - intrinsic sympathomimetic activity | Beta blockers |
| Nadolol | Beta blockers - noncardioselective | Beta blockers |
| Propranolol | Beta blockers - noncardioselective | Beta blockers |
| Amlodipine | Dihydropyridine calcium channel blockers (dCCB) | Calcium channel blockers (CCB) |
| Felodipine | Dihydropyridine calcium channel blockers (dCCB) | Calcium channel blockers (CCB) |
| Isradipine | Dihydropyridine calcium channel blockers (dCCB) | Calcium channel blockers (CCB) |
| Nicardipine | Dihydropyridine calcium channel blockers (dCCB) | Calcium channel blockers (CCB) |
| Nifedipine | Dihydropyridine calcium channel blockers (dCCB) | Calcium channel blockers (CCB) |
| Nisoldipine | Dihydropyridine calcium channel blockers (dCCB) | Calcium channel blockers (CCB) |
| Diltiazem | Nodihydropyridine calcium channel blockers (ndCCB) | Calcium channel blockers (CCB) |
| Verapamil | Nodihydropyridine calcium channel blockers (ndCCB) | Calcium channel blockers (CCB) |
| Hydralazine | Direct vasodilators | Direct vasodilators |
| Minoxidil | Direct vasodilators | Direct vasodilators |
| Eplerenone | Aldosterone antagonist diuretics | Diuretics |
| Spironolactone | Aldosterone antagonist diuretics | Diuretics |
| Bumetanide | Loop diuretics | Diuretics |
| Furosemide | Loop diuretics | Diuretics |
| Torsemide | Loop diuretics | Diuretics |
| Amiloride | Potassium sparing diurectics | Diuretics |
| Triamterene | Potassium sparing diurectics | Diuretics |
| Chlorthalidone | Thiazide or thiazide-like diuretics | Diuretics |
| Hydrochlorothiazide | Thiazide or thiazide-like diuretics | Diuretics |
| Indapamide | Thiazide or thiazide-like diuretics | Diuretics |
| Metolazone | Thiazide or thiazide-like diuretics | Diuretics |
| Aliskiren |  |  |
| Clonidine |  |  |
| Guanfacine |  |  |
| Methyldopa |  |  |

**Table 1**. List of hypertension treatments considered in this study

For each comparison of two treatments, we are interested in the comparative effect on each of the outcomes listed in table 2.

|  |  |
| --- | --- |
| Abdominal pain | Hemorrhagic stroke |
| Abnormal weight gain | Hepatic failure |
| Abnormal weight loss | Hospitalization with heart failure |
| Acute myocardial infarction | Hospitalization with preinfarction syndrome |
| Acute pancreatitis | Hyperkalemia |
| Acute renal failure | Hypokalemia |
| All-cause mortality | Hypomagnesemia |
| Anaphylactoid reaction | Hyponatremia |
| Anemia | Hypotension |
| Angioedema | Impotence |
| Anxiety | Ischemic stroke |
| Bradycardia | Malignant neoplasm |
| Cardiac arrhythmia | Measured renal dysfunction |
| Cardiovascular disease | Nausea |
| Cardiovascular-related mortality | Neutropenia or agranulocytosis |
| Chest pain or angina | Rash |
| Chronic kidney disease | Rhabdomyolysis |
| Cough | Stroke |
| Decreased libido | Sudden cardiac death |
| Dementia | Syncope |
| Depression | Thrombocytopenia |
| Diarrhea | Transient ischemic attack |
| End stage renal disease | Type 2 diabetes mellitus |
| Fall | Vasculitis |
| Gastrointestinal bleeding | Venous thromboembolic events |
| Gout | Vertigo |
| Headache | Vomiting |
| Heart failure |  |

**Table 2.** Outcomes of interest considered in this study

Primary research question

* For each comparison between two hypertension treatments, for each of the outcomes of interest, what is the hazard ratio?

Secondary research questions

* What is the incidence rate of each outcome of interest in each exposure group?

## Objectives

Primary objective

* Generate evidence for the comparative effectiveness for each pairwise comparison of hypertension treatments for the outcomes of interest.

Secondary objectives

* Asses the bias inherent in each analysis by including negative and positive control outcomes.

# Research methods

## Study Design

This study will be a set of retrospective, observational, new-user cohort studies. By ‘retrospective’ we mean the study will use data already collected at the start of the study. By ‘observational’ we mean no intervention will take place in the course of this study. By ‘new-user’ we mean we will only analyze the first exposure of a subject to the treatment of interest. By ‘cohort study’ we mean two cohorts, a target and comparator cohort, will be followed from index date (start of first exposure) to some end date, and assessed for the occurrence of the outcomes of interest.

## Data Source(s)

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 4 or OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 4 is available at: <http://omop.org/cdm>. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>. The following databases will be included in this analysis:

* Truven MarketScan Commercial Claims and Encounters (CCAE)
* Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)
* Truven MarketScan Multi-state Medicaid (MDCD)
* Optum ClinFormatics (Optum)
* QuintilesIMS Disease Analyzer (DA) Germany
* Japan Medical Data Center (JMDC)
* Optum® de-identified Electronic Health Record Dataset (PanTher)
* Korea National Health Insurance Service (NHIS) National Sample Cohort (NSC)
* Columbia University Medical Center (CUMC)

### Truven MarketScan Commercial Claims and Encounters (CCAE)

Truven Health MarketScan® Commercial Claims and Encounters Database (CCAE) represent data from individuals enrolled in United States employer-sponsored insurance health plans. The data includes adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy) as well as enrollment data from large employers and health plans who provide private healthcare coverage to employees, their spouses, and dependents. Additionally, it captures laboratory tests for a subset of the covered lives. This administrative claims database includes a variety of fee-for-service, preferred provider organizations, and capitated health plans.

### Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)

Truven Health MarketScan® Medicare Supplemental and Coordination of Benefits Database (MDCR) represents health services of retirees in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. These data include adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy). Additionally, it captures laboratory tests for a subset of the covered lives.

### Truven MarketScan Multi-state Medicaid (MDCD)

Truven Health MarketScan® Multi-State Medicaid Database (MDCD) adjudicated US health insurance claims for Medicaid enrollees from multiple states and includes hospital discharge diagnoses, outpatient diagnoses and procedures, and outpatient pharmacy claims as well as ethnicity and Medicare eligibility. Members maintain their same identifier even if they leave the system for a brief period however the dataset lacks lab data. [For further information link to RWE site for Truven MDCD.

### Optum ClinFormatics (Optum)

Optum Clinformatics Extended DataMart is an adjudicated US administrative health claims database for members of private health insurance, who are fully insured in commercial plans or in administrative services only (ASOs), Legacy Medicare Choice Lives (prior to January 2006), and Medicare Advantage (Medicare Advantage Prescription Drug coverage starting January 2006). The population is primarily representative of commercial claims patients (0-65 years old) with some Medicare (65+ years old) however ages are capped at 90 years. It includes data captured from administrative claims processed from inpatient and outpatient medical services and prescriptions as dispensed, as well as results for outpatient lab tests processed by large national lab vendors who participate in data exchange with Optum. This dataset also provides date of death (month and year only) for members with both medical and pharmacy coverage from the Social Security Death Master File (however after 2011 reporting frequency changed due to changes in reporting requirements) and location information for patients is at the US state level.

### QuintilesIMS Disease Analyzer (DA) Germany

The QuintilesIMS Disease Analyzer (DA) Germany database consists of data collected from physician practices and medical centers for all ages. Mostly primary care physician data however some data from specialty practices (where practices are electronically connected to each other) and some lab data is included. Key attributes include demographics, prescriptions as prescribed at brand level, diagnosis, lab measurements, actions (e.g. referrals, sick notes).

### Japan Medical Data Center (JMDC)

Japan Medical Data Center (JDMC) database consists of data from 60 Society-Managed Health Insurance plans covering workers aged 18 to 65 and their dependents (children younger than 18 years old and elderly people older than 65 years old). JMDC data includes membership status of the insured people and claims data provided by insurers under contract (e.g. patient-level demographic information, inpatient and outpatient data inclusive of diagnosis and procedures, and prescriptions as dispensed claims information). Claims data are derived from monthly claims issued by clinics, hospitals and community pharmacies; for claims only the month and year are provided however prescriptions, procedures, admission, discharge, and start of medical care as associated with a full date. All diagnoses are coded using ICD-10. All prescriptions refer to national Japanese drug codes, which have been linked to ATC. Procedures are encoded using local procedure codes, which the vendor has mapped to ICD-9 procedure codes. The annual health checkups report a standard battery of measurements (e.g. BMI), which are not coded but clearly described.

### Optum® de-identified Electronic Health Record Dataset (PanTher)

Optum© de-identified Electronic Health Record Dataset represents Humedica’s Electronic Health Record data a medical records database. The medical record data includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, procedures, and information derived from clinical Notes using Natural Language Processing (NLP).

### Korea National Health Insurance Service (NHIS) National Sample Cohort (NSC)

Korean 2% sample cohort representing whole population from 2002-2013.

### Columbia University Medical Center (CUMC)

NYP EHR records consisting of over 5 million patients.

## Study population

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the first treatment for hypertension)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure of any hypertension treatment before the index date
* A diagnose of hypertensive disorder on or preceding the index date
* No diagnose of the outcome of interest preceding the index date

## Exposures

In this study, we are interested in every pairwise comparison between any two treatments in table 1. Treatments will be compared at the treatment level (e.g. comparing lisinopril to amlodipine), but also at the class level (e.g. ACE inhibitors versus Dihydropyridine calcium channel blockers) and the major class level (e.g. ACE inhibitors versus calcium channel blockers). Furthermore, we compare all combination therapies at the various levels of granularity (e.g. comparing hydrochlorothiazide combined with ramipril to amlodipine monotherapy, or ACE inhibitor monotherapy to ACE inhibitors in combination with beta blockers).

### All drugs

Index rule defining the index date:

* First exposure to any drug or combination of drugs containing the RxNorm ingredient(s) of interest.

Inclusion rules based on the index date:

* At least 365 days of observation time prior to the index date
* No exposure to the target or comparator ingredient(s) before the index date
* No exposure to any other hypertension treatment on or before the index date
* A diagnose of hypertension on or preceding the index date

Note that no prior exposure to other hypertension treatments prior to or on the index date is allowed. For example, when comparing lisinopril to amlodipine, no prior exposure to furosemide or any other hypertension treatment is allowed.

The end of the exposure cohort is defined as the end of the first exposure, allowing for 30-day gaps between consecutive prescriptions.

### Mono therapies

When considering non-combination therapies, no concurrent treatments are allowed. For example, when comparing lisinopril to amlodipine, lisinopril users are not allowed to initiate any other treatment at the time of initiating lisinopril.

### Combination therapies

Combination therapies are two therapies that are initiated with 7 days of each other. The date of first treatment initiation is used as the index date. No other therapies are allowed to be initiated concurrently.

## Outcomes

### Abdominal pain

Abdominal pain events [[2-4](#_ENREF_2)]

Abdominal pain condition record of any type; successive records with > 90 day gap are considered independent episodes

Initial Event Cohort

People having any of the following:

* a condition occurrence of Abdominal pain1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Abdominal pain

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 200219 | Abdominal pain | Condition | SNOMED | NO | YES | NO |

### Abnormal weight gain

Abnormal weight gain events [[5](#_ENREF_5)]

Abnormal weight gain record of any type; successive records with > 90 day gap are considered independent episodes; note, weight measurements not used

Initial Event Cohort

People having any of the following:

* an observation of Abnormal weight gain1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Abnormal weight gain

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 439141 | Abnormal weight gain | Observation | SNOMED | NO | YES | NO |

### Abnormal weight loss

Abnormal weight loss events [[6](#_ENREF_6)]

Abnormal weight loss record of any type; successive records with > 90 day gap are considered independent episodes; note, weight measurements not used.

Initial Event Cohort

People having any of the following:

* an observation of Abnormal weight loss1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Abnormal weight loss

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 435928 | Abnormal weight loss | Observation | SNOMED | NO | YES | NO |

### Acute myocardial infarction

Acute myocardial infarction events [[7-12](#_ENREF_7)]

Acute myocardial infarction condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Acute myocardial Infarction2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Acute myocardial Infarction

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 314666 | Old myocardial infarction | Condition | SNOMED | YES | YES | NO |

### Acute pancreatitis

Acute pancreatitis events [[13-16](#_ENREF_13)]

Acute pancreatitis condition record during an inpatient or ER visit; successive records with >30 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Acute pancreatitis2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Acute pancreatitis

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 199074 | Acute pancreatitis | Condition | SNOMED | NO | YES | NO |

### Acute renal failure

Acute renal failure events [[17-24](#_ENREF_17)]

A diagnosis of 'acute renal failure' in an inpatient or ER setting; must be at least 30d between inpatient/ER visits to be considered separate episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Acute Renal Failure2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 30 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Acute Renal Failure

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 197320 | Acute renal failure syndrome | Condition | SNOMED | NO | YES | NO |
| 432961 | Acute renal papillary necrosis with renal failure | Condition | SNOMED | NO | YES | NO |
| 444044 | Acute tubular necrosis | Condition | SNOMED | NO | YES | NO |

### All-cause mortality

All-cause mortality [[10](#_ENREF_10), [25](#_ENREF_25), [26](#_ENREF_26)]

Death record of any type

Initial Event Cohort

People having any of the following: 

* a death occurrence from Any Death

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

### Anaphylactoid reaction

Anaphylactoid reaction events [[27](#_ENREF_27), [28](#_ENREF_28)]

Anaphylactoid reaction condition record during an inpatient or ER visit; successive records with >7 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Anaphylactoid reaction2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 7 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Anaphylactoid reaction

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 441202 | Anaphylaxis | Condition | SNOMED | NO | YES | NO |
| 4330225 | Anaphylaxis due to hymenoptera venom | Condition | SNOMED | YES | YES | NO |
| 40479646 | Anaphylaxis due to latex | Condition | SNOMED | YES | YES | NO |
| 4299299 | Anaphylaxis secondary to bite and/or sting | Condition | SNOMED | YES | YES | NO |
| 4084633 | Bee sting-induced anaphylaxis | Condition | SNOMED | YES | YES | NO |
| 434219 | Food anaphylaxis | Condition | SNOMED | YES | YES | NO |
| 4086737 | Insulin-induced anaphylaxis | Condition | SNOMED | YES | YES | NO |
| 4084634 | Wasp sting-induced anaphylaxis | Condition | SNOMED | YES | YES | NO |

3. Angioedema

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 432791 | Angioedema | Condition | SNOMED | NO | YES | NO |

### Anemia

Persons with anemia [[29-31](#_ENREF_29)]

The first condition record of anemia

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Anemia1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Anemia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 439777 | Anemia | Condition | SNOMED | NO | YES | NO |
| 137829 | Aplastic anemia | Condition | SNOMED | NO | YES | NO |
| 437090 | Hemolytic disease of fetus OR newborn due to ABO immunization | Condition | SNOMED | YES | YES | NO |
| 440218 | Hemolytic disease of fetus OR newborn due to isoimmunization | Condition | SNOMED | YES | YES | NO |
| 25518 | Sickle cell trait | Condition | SNOMED | NO | YES | NO |
| 24006 | Sickle cell-hemoglobin C disease | Condition | SNOMED | NO | YES | NO |
| 4301602 | Thrombotic thrombocytopenic purpura | Condition | SNOMED | YES | YES | NO |

### Angioedema

Angioedema events [[27](#_ENREF_27), [32](#_ENREF_32)]

Angioedema condition record during an inpatient or ER visit; successive records with >7 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Angioedema2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Angioedema

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 432791 | Angioedema | Condition | SNOMED | NO | YES | NO |

### Anxiety

Persons with anxiety [[33-36](#_ENREF_33)]

The first condition record of anxiety, which is followed by another anxiety condition record or a drug used to treat anxiety

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Anxiety1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Anxiety1

where event starts between 1 days After and all days After index start date

* or at least 1 occurrences of a drug exposure of Drugs to treat anxiety3

where event starts between 0 days Before and 30 days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Anxiety

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 442077 | Anxiety disorder | Condition | SNOMED | NO | NO | NO |
| 37109206 | Anxiety disorder caused by drug | Condition | SNOMED | NO | YES | NO |
| 4199892 | Anxiety disorder due to a general medical condition | Condition | SNOMED | NO | YES | NO |
| 434613 | Generalized anxiety disorder | Condition | SNOMED | NO | YES | NO |
| 4338031 | Mixed anxiety and depressive disorder | Condition | SNOMED | NO | YES | NO |
| 381537 | Organic anxiety disorder | Condition | SNOMED | NO | YES | NO |
| 436074 | Panic disorder | Condition | SNOMED | NO | YES | NO |
| 4304010 | Phobic disorder | Condition | SNOMED | YES | YES | NO |

2. Depression

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 442306 | Adjustment disorder with depressed mood | Condition | SNOMED | NO | YES | NO |
| 436665 | Bipolar disorder | Condition | SNOMED | YES | YES | NO |
| 440383 | Depressive disorder | Condition | SNOMED | NO | YES | NO |
| 4175329 | Organic mood disorder of depressed type | Condition | SNOMED | NO | YES | NO |

3. Drugs to treat anxiety

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 781039 | Alprazolam | Drug | RxNorm | NO | YES | NO |
| 733301 | Buspirone | Drug | RxNorm | NO | YES | NO |
| 990678 | Chlordiazepoxide | Drug | RxNorm | NO | YES | NO |
| 797617 | Citalopram | Drug | RxNorm | NO | YES | NO |
| 19050832 | clobazam | Drug | RxNorm | NO | YES | NO |
| 798874 | Clonazepam | Drug | RxNorm | NO | YES | NO |
| 790253 | clorazepate | Drug | RxNorm | NO | YES | NO |
| 717607 | Desvenlafaxine | Drug | RxNorm | NO | YES | NO |
| 723013 | Diazepam | Drug | RxNorm | NO | YES | NO |
| 739323 | Droperidol | Drug | RxNorm | NO | YES | NO |
| 715259 | duloxetine | Drug | RxNorm | NO | YES | NO |
| 715939 | Escitalopram | Drug | RxNorm | NO | YES | NO |
| 755695 | Fluoxetine | Drug | RxNorm | NO | YES | NO |
| 751412 | Fluvoxamine | Drug | RxNorm | NO | YES | NO |
| 777221 | Hydroxyzine | Drug | RxNorm | NO | YES | NO |
| 791967 | Lorazepam | Drug | RxNorm | NO | YES | NO |
| 702865 | Meprobamate | Drug | RxNorm | NO | YES | NO |
| 724816 | Oxazepam | Drug | RxNorm | NO | YES | NO |
| 722031 | Paroxetine | Drug | RxNorm | NO | YES | NO |
| 739138 | Sertraline | Drug | RxNorm | NO | YES | NO |
| 743670 | venlafaxine | Drug | RxNorm | NO | YES | NO |

4. Drugs to treat depression

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21604686 | ANTIDEPRESSANTS | Drug | ATC | NO | YES | NO |

### Bradycardia

Persons with bradycardia [[37](#_ENREF_37), [38](#_ENREF_38)]

The first condition record of bradycardia, which is followed by another bradycardia condition record

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Bradycardia1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of Bradycardia1

where event starts between 1 days After and all days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Bradycardia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4169095 | Bradycardia | Condition | SNOMED | NO | YES | NO |
| 316999 | Conduction disorder of the heart | Condition | SNOMED | NO | NO | NO |
| 4171683 | Sinus bradycardia | Condition | SNOMED | NO | YES | NO |
| 317302 | Sinus node dysfunction | Condition | SNOMED | NO | YES | NO |

### Cardiac arrhythmia

Person with cardiac arrhythmia [[39-45](#_ENREF_39)]

The first condition record of cardiac arrhythmia, which is followed by another cardiac arrhythmia condition record, at least two drug records for a drug used to treat arrhythmias, or a procedure to treat arrhythmias

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Cardiac arrhythmia1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Cardiac arrhythmia1

where event starts between 1 days After and all days After index start date

* or at least 2 occurrences of a drug exposure of Drugs used to treat cardiac arrhythmia2

where event starts between 0 days Before and all days After index start date

* or at least 1 occurrences of a procedure of Procedures to treat cardiac arrhythmia3

where event starts between 0 days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Cardiac arrhythmia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 44784217 | Cardiac arrhythmia | Condition | SNOMED | NO | YES | NO |
| 38001137 | Cardiac arrhythmia & conduction disorders w CC | Observation | DRG | NO | YES | NO |
| 38001138 | Cardiac arrhythmia & conduction disorders w/o CC/MCC | Observation | DRG | NO | YES | NO |
| 315078 | Palpitations | Condition | SNOMED | NO | YES | NO |
| 444070 | Tachycardia | Condition | SNOMED | NO | YES | NO |

2. Drugs used to treat cardiac arrhythmia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21600248 | ANTIARRHYTHMICS, CLASS I AND III | Drug | ATC | NO | YES | NO |
| 43013024 | apixaban | Drug | RxNorm | NO | YES | NO |
| 40228152 | dabigatran etexilate | Drug | RxNorm | NO | YES | NO |
| 40241331 | rivaroxaban | Drug | RxNorm | NO | YES | NO |
| 1310149 | Warfarin | Drug | RxNorm | NO | YES | NO |

3. Procedures to treat cardiac arrhythmia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 45890325 | Cardioversion, elective, electrical conversion of arrhythmia | Procedure | CPT4 | NO | YES | NO |
| 45890400 | Operative tissue ablation and reconstruction of atria, extensive (eg, maze procedure) | Procedure | CPT4 | NO | YES | NO |
| 2107068 | Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), extensive (eg, maze procedure), with cardiopulmonary bypass (List separately in addition to code for primary procedure) | Procedure | CPT4 | NO | YES | NO |
| 4051932 | Procedure for arrhythmia | Procedure | SNOMED | NO | YES | NO |

### Cardiovascular disease

Total cardiovascular disease events (ischemic stroke, hemorrhagic stroke, heart failure, acute myocardial infarction or sudden cardiac death) [[7-12](#_ENREF_7), [39](#_ENREF_39)]

A condition record of ischemic stroke, hemorrhagic stroke, heart failure, acute myocardial infarction or sudden cardiac death during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Acute myocardial Infarction2
* a condition occurrence of Sudden cardiac death6
* a condition occurrence of Ischemic stroke5
* a condition occurrence of intracranial bleed Hemorrhagic stroke4
* a condition occurrence of Heart Failure 3

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having all of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Acute myocardial Infarction

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 314666 | Old myocardial infarction | Condition | SNOMED | YES | YES | NO |

3. Heart Failure

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 315295 | Congestive rheumatic heart failure | Condition | SNOMED | YES | YES | NO |
| 316139 | Heart failure | Condition | SNOMED | NO | YES | NO |

4. intracranial bleed Hemorrhagic stroke

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 376713 | Cerebral hemorrhage | Condition | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | Condition | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | Condition | SNOMED | NO | NO | NO |

5. Ischemic stroke

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 372924 | Cerebral artery occlusion | Condition | SNOMED | NO | NO | NO |
| 375557 | Cerebral embolism | Condition | SNOMED | NO | NO | NO |
| 443454 | Cerebral infarction | Condition | SNOMED | NO | YES | NO |
| 441874 | Cerebral thrombosis | Condition | SNOMED | NO | NO | NO |

6. Sudden cardiac death

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4048809 | Brainstem death | Condition | SNOMED | NO | YES | NO |
| 321042 | Cardiac arrest | Condition | SNOMED | NO | YES | NO |
| 442289 | Death in less than 24 hours from onset of symptoms | Observation | SNOMED | NO | YES | NO |
| 4317150 | Sudden cardiac death | Condition | SNOMED | NO | YES | NO |
| 4132309 | Sudden death | Observation | SNOMED | NO | YES | NO |
| 437894 | Ventricular fibrillation | Condition | SNOMED | YES | YES | NO |

### Cardiovascular-related mortality

Cardiovascular-related mortality [[10](#_ENREF_10)]

Death record with at least 1 cardiovascular-related condition record (myocardial infarction, ischemic stroke, intracranial hemorrhage, sudden cardiac death, hospitalization for heart failure) in 30 days prior to death

Initial Event Cohort

People having any of the following: 

* a death occurrence from Any Death

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Acute myocardial Infarction2

where event starts between 30 days Before and 7 days After index start date

* or at least 1 occurrences of a condition occurrence of Ischemic stroke5

where event starts between 30 days Before and 7 days After index start date

* or at least 1 occurrences of a condition occurrence of intracranial bleed Hemorrhagic stroke4

where event starts between all days Before and all days After index start date

* or at least 1 occurrences of a condition occurrence of Sudden cardiac death6

where event starts between 30 days Before and 7 days After index start date

* or at least 1 occurrences of a condition occurrence of Heart Failure 3

Having all of the following criteria:

* + - at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

where event starts between 30 days Before and 7 days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Acute myocardial Infarction

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 314666 | Old myocardial infarction | Condition | SNOMED | YES | YES | NO |

3. Heart Failure

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 315295 | Congestive rheumatic heart failure | Condition | SNOMED | YES | YES | NO |
| 316139 | Heart failure | Condition | SNOMED | NO | YES | NO |

4. intracranial bleed Hemorrhagic stroke

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 376713 | Cerebral hemorrhage | Condition | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | Condition | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | Condition | SNOMED | NO | NO | NO |

5. Ischemic stroke

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 372924 | Cerebral artery occlusion | Condition | SNOMED | NO | NO | NO |
| 375557 | Cerebral embolism | Condition | SNOMED | NO | NO | NO |
| 443454 | Cerebral infarction | Condition | SNOMED | NO | YES | NO |
| 441874 | Cerebral thrombosis | Condition | SNOMED | NO | NO | NO |

6. Sudden cardiac death

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4048809 | Brainstem death | Condition | SNOMED | NO | YES | NO |
| 321042 | Cardiac arrest | Condition | SNOMED | NO | YES | NO |
| 442289 | Death in less than 24 hours from onset of symptoms | Observation | SNOMED | NO | YES | NO |
| 4317150 | Sudden cardiac death | Condition | SNOMED | NO | YES | NO |
| 4132309 | Sudden death | Observation | SNOMED | NO | YES | NO |
| 437894 | Ventricular fibrillation | Condition | SNOMED | YES | YES | NO |

### Chest pain or angina

Persons with chest pain or angina [[46](#_ENREF_46)]

The first condition record of chest pain or angina

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Chest pain or angina1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Chest pain or angina

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 321318 | Angina pectoris | Condition | SNOMED | NO | YES | NO |
| 77670 | Chest pain | Condition | SNOMED | NO | NO | NO |

### Chronic kidney disease

Persons with chronic kidney disease [[19](#_ENREF_19), [47-54](#_ENREF_47)]

The first condition record of chronic kidney disease, which is followed by either another chronic kidney disease condition record or a dialysis procedure or observation

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Chronic kidney disease1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Chronic kidney disease1

where event starts between 1 days After and all days After index start date

* or at least 1 occurrences of a procedure of Dialysis2

where event starts between 0 days Before and all days After index start date

* or at least 1 occurrences of an observation of Dialysis2

where event starts between 0 days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Chronic kidney disease

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 444044 | Acute tubular necrosis | Condition | SNOMED | NO | YES | NO |
| 194385 | Aneurysm of renal artery | Condition | SNOMED | NO | YES | NO |
| 195834 | Atherosclerosis of renal artery | Condition | SNOMED | NO | YES | NO |
| 45769152 | Bartter syndrome | Condition | SNOMED | YES | YES | NO |
| 46271022 | Chronic kidney disease | Condition | SNOMED | NO | YES | NO |
| 193016 | Cystic disease of kidney | Condition | SNOMED | NO | YES | NO |
| 192279 | Diabetic renal disease | Condition | SNOMED | NO | YES | NO |
| 4263367 | Glomerulonephritis | Condition | SNOMED | NO | YES | NO |
| 261071 | Glomerulosclerosis | Condition | SNOMED | NO | YES | NO |
| 195289 | Goodpasture's syndrome | Condition | SNOMED | YES | YES | NO |
| 195737 | Hemorrhagic nephroso-nephritis | Condition | SNOMED | YES | YES | NO |
| 201313 | Hypertensive renal disease | Condition | SNOMED | NO | YES | NO |
| 43530912 | Induced termination of pregnancy complicated by renal failure | Condition | SNOMED | YES | YES | NO |
| 4103224 | Interstitial nephritis | Condition | SNOMED | NO | YES | NO |
| 193253 | Nephritis | Condition | SNOMED | NO | NO | NO |
| 195314 | Nephrotic syndrome | Condition | SNOMED | NO | YES | NO |
| 4066005 | Post-delivery acute renal failure with postnatal problem | Condition | SNOMED | YES | YES | NO |
| 37116834 | Postpartum acute renal failure | Condition | SNOMED | YES | YES | NO |
| 195014 | Renal failure following molar AND/OR ectopic pregnancy | Condition | SNOMED | YES | YES | NO |
| 192359 | Renal failure syndrome | Condition | SNOMED | NO | YES | NO |
| 197930 | Renal hypertension complicating pregnancy, childbirth and the puerperium | Condition | SNOMED | YES | YES | NO |
| 4128219 | Urate nephropathy | Condition | SNOMED | NO | YES | NO |

2. Dialysis

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4090651 | Dialysis finding | Observation | SNOMED | NO | YES | NO |
| 4032243 | Dialysis procedure | Procedure | SNOMED | NO | YES | NO |
| 45889365 | Dialysis Services and Procedures | Procedure | CPT4 | NO | YES | NO |

### Cough

Cough events [[55-57](#_ENREF_55)]

Cough condition record of any type; successive records with > 90 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Cough1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Cough

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 254761 | Cough | Condition | SNOMED | NO | YES | NO |

### Decreased libido

Persons with decreased libido [[58](#_ENREF_58)]

The first condition record of decreased libido

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Decreased libido1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Decreased libido

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4087317 | Lack of libido | Condition | SNOMED | NO | YES | NO |
| 443262 | Lack or loss of sexual desire | Condition | SNOMED | NO | YES | NO |
| 436246 | Reduced libido | Condition | SNOMED | NO | YES | NO |

### Dementia

Persons with dementia [[59-66](#_ENREF_59)]

The first condition record of dementia

Initial Event Cohort

People having any of the following:

* a condition occurrence of Dementia1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Dementia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4182210 | Dementia | Condition | SNOMED | NO | YES | NO |
| 377788 | General paresis - neurosyphilis | Condition | SNOMED | YES | YES | NO |
| 372610 | Postconcussion syndrome | Condition | SNOMED | YES | YES | NO |

### Depression

Persons with depression [[34](#_ENREF_34), [35](#_ENREF_35), [65](#_ENREF_65), [67-70](#_ENREF_67)]

The first condition record of depression, which is followed by another depression condition record, at least two drugs used to treat depression without another indication, or two psychotherapy procedures

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Depression1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Depression1

where event starts between 1 days After and all days After index start date

* or at least 2 occurrences of a drug exposure of Drugs to treat depression2

Having all of the following criteria:

* + exactly 0 occurrences of a condition occurrence of Other indications for drugs used to treat depression3

where event starts between 30 days Before and 7 days After index start date

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a procedure of Procedures for depression4

where event starts between 0 days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Depression

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 442306 | Adjustment disorder with depressed mood | Condition | SNOMED | NO | YES | NO |
| 436665 | Bipolar disorder | Condition | SNOMED | YES | YES | NO |
| 440383 | Depressive disorder | Condition | SNOMED | NO | YES | NO |
| 4175329 | Organic mood disorder of depressed type | Condition | SNOMED | NO | YES | NO |

2. Drugs to treat depression

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21604686 | ANTIDEPRESSANTS | Drug | ATC | NO | YES | NO |

3. Other indications for drugs used to treat depression

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 438407 | Bulimia nervosa | Condition | SNOMED | NO | YES | NO |
| 4311708 | Diabetic peripheral neuropathy | Condition | SNOMED | NO | YES | NO |
| 434613 | Generalized anxiety disorder | Condition | SNOMED | NO | YES | NO |
| 436962 | Insomnia | Condition | SNOMED | NO | YES | NO |
| 440374 | Obsessive-compulsive disorder | Condition | SNOMED | NO | YES | NO |
| 436074 | Panic disorder | Condition | SNOMED | NO | YES | NO |
| 436676 | Posttraumatic stress disorder | Condition | SNOMED | NO | YES | NO |
| 4242733 | Premenstrual dysphoric disorder | Condition | SNOMED | NO | YES | NO |
| 440690 | Social phobia | Condition | SNOMED | NO | YES | NO |

4. Procedures for depression

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4030840 | Electroconvulsive therapy | Procedure | SNOMED | NO | YES | NO |
| 2795842 | Mental Health, Electroconvulsive Therapy | Procedure | ICD10PCS | NO | YES | NO |
| 2795675 | Mental Health, Individual Psychotherapy | Procedure | ICD10PCS | NO | YES | NO |
| 4327941 | Psychotherapy | Procedure | SNOMED | NO | YES | NO |
| 45887951 | Psychotherapy Services and Procedures | Procedure | CPT4 | NO | YES | NO |

### Diarrhea

Diarrhea events [[71-73](#_ENREF_71)]

Diarrhea condition record of any type; successive records with > 30 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of [LEGEND HTN} Diarrhea1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

Appendix 1: Concept Set Definitions

1. [LEGEND HTN} Diarrhea

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 196523 | Diarrhea | Condition | SNOMED | NO | YES | NO |
| 4134607 | Diarrheal disorder | Condition | SNOMED | NO | YES | NO |
| 201773 | Enteritis of small intestine | Condition | SNOMED | NO | NO | NO |
| 80141 | Functional diarrhea | Condition | SNOMED | NO | YES | NO |
| 4207688 | Infectious enteritis | Condition | SNOMED | NO | NO | NO |
| 4324838 | Noninfectious enteritis | Condition | SNOMED | NO | NO | NO |
| 197596 | Toxic gastroenteritis | Condition | SNOMED | NO | YES | NO |
| 196620 | Viral enteritis | Condition | SNOMED | NO | YES | NO |

### End stage renal disease

Persons with end stage renal disease [[16](#_ENREF_16), [52](#_ENREF_52), [74](#_ENREF_74)]

End stage renal disease (ESRD) is defined by at least one diagnosis in any setting, followed by at least one additional diagnosis of a dialysis-related procedure within 90 days

Initial Event Cohort

People having any of the following: 

* a condition occurrence of End stage renal disease2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a condition occurrence of End stage renal disease2

where event starts between 1 days After and 90 days After index start date

* or at least 1 occurrences of a procedure of Dialysis1

where event starts between 0 days After and 90 days After index start date

* or at least 1 occurrences of an observation of Dialysis1

where event starts between 0 days After and 90 days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Dialysis

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4090651 | Dialysis finding | Observation | SNOMED | NO | YES | NO |
| 4032243 | Dialysis procedure | Procedure | SNOMED | NO | YES | NO |
| 45889365 | Dialysis Services and Procedures | Procedure | CPT4 | NO | YES | NO |

2. End stage renal disease

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443611 | Chronic kidney disease stage 5 | Condition | SNOMED | NO | YES | NO |
| 193782 | End stage renal disease | Condition | SNOMED | NO | YES | NO |

### Fall

Fall events [[75-77](#_ENREF_75)]

Fall condition record of any type; successive records with > 180 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* an observation of Falls1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Appendix 1: Concept Set Definitions

1. Falls

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 436583 | Fall | Observation | SNOMED | NO | YES | NO |

### Gastrointestinal bleeding

Gastrointestinal bleeding events [[2](#_ENREF_2), [11](#_ENREF_11), [78-82](#_ENREF_78)]

Gastrointestinal hemorrhage condition record during an inpatient or ER visit; successive records with > 30 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Gastrointestinal hemorrhage GI bleeding2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Gastrointestinal hemorrhage GI bleeding

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4138962 | Acute duodenal ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4195231 | Acute gastric ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4147683 | Acute gastrojejunal ulcer without hemorrhage AND without perforation | Condition | SNOMED | NO | NO | NO |
| 4163865 | Acute peptic ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 195584 | Acute peptic ulcer without hemorrhage AND without perforation but with obstruction | Condition | SNOMED | YES | YES | NO |
| 40482685 | Angiodysplasia of duodenum | Condition | SNOMED | NO | YES | NO |
| 28779 | Bleeding esophageal varices | Condition | SNOMED | NO | YES | NO |
| 4222896 | Chronic duodenal ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4296611 | Chronic gastric ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 200769 | Chronic gastric ulcer without hemorrhage, without perforation AND without obstruction | Condition | SNOMED | YES | YES | NO |
| 4177387 | Chronic gastrojejunal ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 434400 | Chronic gastrojejunal ulcer without hemorrhage AND without perforation but with obstruction | Condition | SNOMED | YES | YES | NO |
| 438795 | Chronic gastrojejunal ulcer without hemorrhage, without perforation AND without obstruction | Condition | SNOMED | YES | YES | NO |
| 4204555 | Chronic peptic ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 24973 | Chronic peptic ulcer without hemorrhage AND without perforation but with obstruction | Condition | SNOMED | YES | YES | NO |
| 23808 | Chronic peptic ulcer without hemorrhage, without perforation AND without obstruction | Condition | SNOMED | YES | YES | NO |
| 2002608 | Control of hemorrhage and suture of ulcer of stomach or duodenum | Procedure | ICD9Proc | NO | YES | NO |
| 198798 | Dieulafoy's vascular malformation | Condition | SNOMED | NO | YES | NO |
| 4198381 | Duodenal ulcer disease | Condition | SNOMED | NO | YES | NO |
| 4209746 | Duodenal ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 4112183 | Esophageal varices with bleeding, associated with another disorder | Condition | SNOMED | NO | YES | NO |
| 2108900 | Esophagogastroduodenoscopy, flexible, transoral; with control of bleeding, any method | Procedure | CPT4 | NO | YES | NO |
| 2108878 | Esophagoscopy, flexible, transoral; with control of bleeding, any method | Procedure | CPT4 | NO | YES | NO |
| 4265600 | Gastric ulcer | Condition | SNOMED | NO | YES | NO |
| 4248429 | Gastric ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 192671 | Gastrointestinal hemorrhage | Condition | SNOMED | NO | YES | NO |
| 4101104 | Gastrojejunal ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |
| 443530 | Hematochezia | Condition | SNOMED | YES | YES | NO |
| 197925 | Hemorrhage of rectum and anus | Condition | SNOMED | YES | YES | NO |
| 4027663 | Peptic ulcer | Condition | SNOMED | NO | YES | NO |
| 4291028 | Peptic ulcer without hemorrhage AND without perforation | Condition | SNOMED | YES | YES | NO |

### Gout

Persons with gout [[83-86](#_ENREF_83)]

The first condition record of gout

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Gout1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Gout

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 440674 | Gout | Condition | SNOMED | NO | YES | NO |
| 4096347 | Gouty arthropathy | Condition | SNOMED | NO | YES | NO |
| 4128219 | Urate nephropathy | Condition | SNOMED | NO | YES | NO |
| 80070 | Uric acid urolithiasis | Condition | SNOMED | NO | YES | NO |

### Headache

Headache events [[87](#_ENREF_87), [88](#_ENREF_88)]

Headache condition record of any type; successive records with > 30 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Headache1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

Appendix 1: Concept Set Definitions

1. Headache

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 378253 | Headache | Condition | SNOMED | NO | YES | NO |
| 375527 | Headache disorder | Condition | SNOMED | NO | YES | NO |

### Heart failure

Persons with heart failure [[8](#_ENREF_8), [89-98](#_ENREF_89)]

The first condition record of heart failure, which is followed by at least 1 heart failure condition record in the following year

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Heart Failure 1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of Heart Failure 1

where event starts between 1 days After and 365 days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Heart Failure

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 315295 | Congestive rheumatic heart failure | Condition | SNOMED | YES | YES | NO |
| 316139 | Heart failure | Condition | SNOMED | NO | YES | NO |

### Hemorrhagic stroke

Hemorrhagic stroke (intracerebral bleeding) events [[99-103](#_ENREF_99)]

Intracranial, cerebral or subarachnoid hemorrhage condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of intracranial bleed Hemorrhagic stroke2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. intracranial bleed Hemorrhagic stroke

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 376713 | Cerebral hemorrhage | Condition | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | Condition | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | Condition | SNOMED | NO | NO | NO |

### Hepatic failure

Persons with hepatic failure [[17](#_ENREF_17), [104-111](#_ENREF_104)]

The first condition record of hepatic failure, necrosis, or coma

Initial Event Cohort

People having any of the following: 

* a condition occurrence of hepatic failure, necrosis or coma1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. hepatic failure, necrosis or coma

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 377604 | Hepatic coma | Condition | SNOMED | NO | NO | NO |
| 4029488 | Hepatic encephalopathy | Condition | SNOMED | NO | NO | NO |
| 4245975 | Hepatic failure | Condition | SNOMED | NO | YES | NO |
| 4337543 | Hepatic necrosis | Condition | SNOMED | NO | YES | NO |

### Hospitalization with heart failure

Hospitalization with heart failure events [[91](#_ENREF_91), [96](#_ENREF_96), [97](#_ENREF_97), [112](#_ENREF_112), [113](#_ENREF_113)]

Inpatient or ER visits with heart failure condition record; all qualifying inpatient visits occurring > 7 days apart are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a visit occurrence of Inpatient or ER visit1

Having all of the following criteria:

* + - at least 1 occurrences of a condition occurrence of Heart Failure 2

where event starts between 0 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's end date plus 0 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 7 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Heart Failure

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 315295 | Congestive rheumatic heart failure | Condition | SNOMED | YES | YES | NO |
| 316139 | Heart failure | Condition | SNOMED | NO | YES | NO |

### Hospitalization with preinfarction syndrome

Hospitalization with preinfarction syndrome events [[46](#_ENREF_46), [114](#_ENREF_114), [115](#_ENREF_115)]

Inpatient or ER visits with preinfarction syndrome condition record; all qualifying inpatient visits occurring > 7 days apart are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a visit occurrence of Inpatient or ER visit1

Having all of the following criteria:

* + - at least 1 occurrences of a condition occurrence of Preinfarction syndrome2

where event starts between 0 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's end date plus 0 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 7 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Preinfarction syndrome

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 315296 | Preinfarction syndrome | Condition | SNOMED | NO | YES | NO |

### Hyperkalemia

Hyperkalemia events [[116-118](#_ENREF_116)]

Condition record for hyperkalemia or potassium measurements > 5.6 mmol/L; successive records with >90 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hyperkalemia1
* a measurement of Potassium measurement2
  + with value as number > 5.6
  + unit is any of: millimole per liter

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Hyperkalemia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 434610 | Hyperkalemia | Condition | SNOMED | NO | YES | NO |

2. Potassium measurement

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40789893 | Potassium | Bld-Ser-Plas | Measurement | LOINC | NO | YES | NO |
| 4245152 | Potassium measurement | Measurement | SNOMED | NO | YES | NO |
| 4276440 | Potassium level - finding | Condition | SNOMED | NO | YES | NO |

### Hypokalemia

Hypokalemia events [[119](#_ENREF_119)]

Hypokalemia condition record of any type; successive records with > 90 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hypokalemia1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Hypokalemia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 45769152 | Bartter syndrome | Condition | SNOMED | YES | YES | NO |
| 437833 | Hypokalemia | Condition | SNOMED | NO | YES | NO |

### Hypomagnesemia

Hypomagnesemia events [[120](#_ENREF_120), [121](#_ENREF_121)]

Hypomagnesemia condition record of any type; successive records with > 90 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hypomagnesemia1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Hypomagnesemia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 438725 | Disorder of magnesium metabolism | Condition | SNOMED | NO | YES | NO |
| 4098604 | Hypomagnesemia | Condition | SNOMED | NO | YES | NO |

### Hyponatremia

Hyponatremia events [[122](#_ENREF_122), [123](#_ENREF_123)]

Hyponatremia condition record of any type; successive records with > 90 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hyponatremia1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Hyponatremia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 435515 | Hypo-osmolality and or hyponatremia | Condition | SNOMED | NO | YES | NO |
| 4232311 | Hyponatremia | Condition | SNOMED | NO | YES | NO |

### Hypotension

Hypotension events [[124](#_ENREF_124)]

Hypotension condition record of any type; successive records with > 90 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hypotension1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Hypotension

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 313232 | Hemodialysis-associated hypotension | Condition | SNOMED | YES | YES | NO |
| 317002 | Low blood pressure | Condition | SNOMED | NO | YES | NO |
| 314432 | Maternal hypotension syndrome | Condition | SNOMED | YES | YES | NO |

### Impotence

Persons with impotence [[125-128](#_ENREF_125)]

The first condition record of impotence

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Impotence1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Impotence

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4250163 | Sexual arousal disorder | Condition | SNOMED | NO | YES | NO |

### Ischemic stroke

Ischemic stroke events [[8](#_ENREF_8), [10](#_ENREF_10), [11](#_ENREF_11), [99](#_ENREF_99), [129](#_ENREF_129)]

Ischemic stroke condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes

Initial Event Cohort

People having any of the following:

* a condition occurrence of Ischemic stroke2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1 where event starts between all days Before and 1 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Ischemic stroke

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 372924 | Cerebral artery occlusion | Condition | SNOMED | NO | NO | NO |
| 375557 | Cerebral embolism | Condition | SNOMED | NO | NO | NO |
| 443454 | Cerebral infarction | Condition | SNOMED | NO | YES | NO |
| 441874 | Cerebral thrombosis | Condition | SNOMED | NO | NO | NO |

### Malignant neoplasm

Persons with a malignant neoplasm other than non-melanoma skin cancer [[130-145](#_ENREF_130)]

First occurrence of malignant neoplasm, followed by at least one additional diagnosis of the same type (melanoma, bladder, brain, breast, colon and rectum, kidney, leukemia, liver, lung, lymphoma, multiple myeloma, ovary, pancreas, prostate, thyroid, uterus, myelodysplastic syndrome)

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Malignant neoplasms excluding non-melanoma skin cancer2
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 2 occurrences of a condition occurrence of Malignant neoplasms of breast5

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of prostate15

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of lung10

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of multiple myeloma12

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of colon and rectum6

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of bladder3

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of lymphoma11

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of ovary13

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of thyroid16

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of kidney7

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of leukemia8

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of brain4

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of pancreas14

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of liver9

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant neoplasms of uterus17

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Malignant melanoma1

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a condition occurrence of Myelodysplastic syndrome18

where event starts between 0 days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Malignant melanoma

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4162276 | Malignant melanoma | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

2. Malignant neoplasms excluding non-melanoma skin cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

3. Malignant neoplasms of bladder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 197508 | Malignant tumor of urinary bladder | Condition | SNOMED | NO | YES | NO |
| 196360 | Primary malignant neoplasm of bladder | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

4. Malignant neoplasms of brain

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 443588 | Malignant neoplasm of brain | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

5. Malignant neoplasms of breast

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112853 | Malignant tumor of breast | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |

6. Malignant neoplasms of colon and rectum

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4180790 | Malignant tumor of colon | Condition | SNOMED | NO | YES | NO |
| 443390 | Malignant tumor of rectum | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

7. Malignant neoplasms of kidney

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 196653 | Malignant tumor of kidney | Condition | SNOMED | NO | YES | NO |
| 198985 | Primary malignant neoplasm of kidney | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

8. Malignant neoplasms of leukemia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 317510 | Leukemia | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

9. Malignant neoplasms of liver

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4246127 | Malignant neoplasm of liver | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

10. Malignant neoplasms of lung

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 443388 | Malignant tumor of lung | Condition | SNOMED | NO | YES | NO |
| 4311499 | Primary malignant neoplasm of respiratory tract | Condition | SNOMED | NO | NO | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

11. Malignant neoplasms of lymphoma

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4082311 | B-cell chronic lymphocytic leukemia | Condition | SNOMED | YES | YES | NO |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 432571 | Malignant lymphoma | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

12. Malignant neoplasms of multiple myeloma

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 437233 | Multiple myeloma | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

13. Malignant neoplasms of ovary

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4181351 | Malignant tumor of ovary | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

14. Malignant neoplasms of pancreas

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4180793 | Malignant tumor of pancreas | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

15. Malignant neoplasms of prostate

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4163261 | Malignant tumor of prostate | Condition | SNOMED | NO | YES | NO |
| 200962 | Primary malignant neoplasm of prostate | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

16. Malignant neoplasms of thyroid

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4181483 | Malignant tumor of parathyroid gland | Condition | SNOMED | NO | YES | NO |
| 4178976 | Malignant tumor of thyroid gland | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

17. Malignant neoplasms of uterus

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 197230 | Malignant neoplasm of uterus | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |

18. Myelodysplastic syndrome

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 138994 | Myelodysplastic syndrome | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |

### Measured renal dysfunction

Persons with measured renal dysfunction [[24](#_ENREF_24)]

The first creatinine measurement with value > 3 mg/dL

Initial Event Cohort

People having any of the following: 

* a measurement of Creatinine measurement1
  + with value as number > 3
  + unit is any of: milligram per deciliter

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Creatinine measurement

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40796376 | Creatinine | Bld-Ser-Plas | Measurement | LOINC | NO | YES | NO |

### Nausea

Nausea events [[2](#_ENREF_2), [146](#_ENREF_146), [147](#_ENREF_147)]

Nausea condition record of any type; successive records with > 30 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Nausea1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

Appendix 1: Concept Set Definitions

1. Nausea

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 30284 | Motion sickness | Condition | SNOMED | YES | YES | NO |
| 31967 | Nausea | Condition | SNOMED | NO | YES | NO |

### Neutropenia or agranulocytosis

Persons with neutropenia or agranulocytosis [[148](#_ENREF_148), [149](#_ENREF_149)]

The first condition record of neutropenia or agranulocytosis

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Neutropenia and agranulocytosis1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Neutropenia and agranulocytosis

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4150156 | Agranulocytopenic disorder | Condition | SNOMED | NO | NO | NO |
| 440689 | Agranulocytosis | Condition | SNOMED | NO | NO | NO |
| 4322386 | Chemotherapy-induced neutropenia | Condition | SNOMED | NO | NO | NO |
| 4174297 | Chloramphenicol-induced neutropenia | Condition | SNOMED | NO | NO | NO |
| 4211401 | Dose-related drug-induced neutropenia | Condition | SNOMED | NO | NO | NO |
| 432289 | Drug-induced neutropenia | Condition | SNOMED | NO | NO | NO |
| 320073 | Neutropenia | Condition | SNOMED | NO | NO | NO |
| 4119158 | Neutropenic disorder | Condition | SNOMED | NO | NO | NO |
| 4190716 | Non dose-related drug-induced neutropenia | Condition | SNOMED | NO | NO | NO |
| 4135712 | Toxic neutropenia | Condition | SNOMED | NO | NO | NO |

### Rash

Rash events [[150](#_ENREF_150)]

Rash condition record of any type; successive records with > 90 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Rash1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Rash

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 140214 | Eruption | Condition | SNOMED | NO | YES | NO |
| 139900 | Urticaria | Condition | SNOMED | NO | YES | NO |

### Rhabdomyolysis

Rhabdomyolysis events [[151](#_ENREF_151), [152](#_ENREF_152)]

Rhabdomyolysis condition record or muscle disorder condition record with creatine measurement 5\*ULN during an inpatient or ER visit; successive records with >90 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Rhabdomyolysis narrow4
* a condition occurrence of Rhabdomyolysis broad2

Having all of the following criteria:

* + - at least 1 occurrences of a measurement of Rhabdomyolysis measurement of creatine kinase3
      * with value as number > 0
      * with high range ratio > 5

where event starts between 7 days Before and 7 days After index start date

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having all of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Rhabdomyolysis broad

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 137967 | Muscle, ligament and fascia disorders | Condition | SNOMED | NO | NO | NO |
| 439142 | Myoglobinuria | Condition | SNOMED | NO | YES | NO |
| 4345578 | Rhabdomyolysis | Condition | SNOMED | NO | YES | NO |

3. Rhabdomyolysis measurement of creatine kinase

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40782593 | Creatine kinase | Measurement | LOINC | NO | YES | NO |
| 4265595 | Creatine kinase measurement | Measurement | SNOMED | NO | YES | NO |

4. Rhabdomyolysis narrow

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 439142 | Myoglobinuria | Condition | SNOMED | NO | YES | NO |
| 4345578 | Rhabdomyolysis | Condition | SNOMED | NO | YES | NO |

### Stroke

Stroke (ischemic or hemorrhagic) events [[8](#_ENREF_8), [10](#_ENREF_10), [11](#_ENREF_11), [41](#_ENREF_41), [99-103](#_ENREF_99), [129](#_ENREF_129)]

Stroke (ischemic or hemorrhagic) condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Stroke (ischemic or hemorrhagic)2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 1 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Stroke (ischemic or hemorrhagic)

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 372924 | Cerebral artery occlusion | Condition | SNOMED | NO | NO | NO |
| 375557 | Cerebral embolism | Condition | SNOMED | NO | NO | NO |
| 376713 | Cerebral hemorrhage | Condition | SNOMED | NO | NO | NO |
| 443454 | Cerebral infarction | Condition | SNOMED | NO | YES | NO |
| 441874 | Cerebral thrombosis | Condition | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | Condition | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | Condition | SNOMED | NO | NO | NO |

### Sudden cardiac death

Sudden cardiac death events [[10](#_ENREF_10), [39](#_ENREF_39)]

Sudden cardiac death condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Sudden cardiac death2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having all of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Sudden cardiac death

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4048809 | Brainstem death | Condition | SNOMED | NO | YES | NO |
| 321042 | Cardiac arrest | Condition | SNOMED | NO | YES | NO |
| 442289 | Death in less than 24 hours from onset of symptoms | Observation | SNOMED | NO | YES | NO |
| 4317150 | Sudden cardiac death | Condition | SNOMED | NO | YES | NO |
| 4132309 | Sudden death | Observation | SNOMED | NO | YES | NO |
| 437894 | Ventricular fibrillation | Condition | SNOMED | YES | YES | NO |

### Syncope

Syncope events [[124](#_ENREF_124)]

Syncope condition record of any type; successive records with > 180 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Syncope1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Appendix 1: Concept Set Definitions

1. Syncope

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 140586 | Heat syncope | Condition | SNOMED | YES | YES | NO |
| 135360 | Syncope | Condition | SNOMED | NO | YES | NO |
| 38001140 | Syncope & collapse | Observation | DRG | NO | NO | NO |

### Thrombocytopenia

Persons with thrombocytopenia [[146](#_ENREF_146), [153](#_ENREF_153), [154](#_ENREF_154)]

The first condition record of thrombocytopenia

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Thrombocytopenia1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Thrombocytopenia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 432870 | Thrombocytopenic disorder | Condition | SNOMED | NO | YES | NO |

### Transient ischemic attack

Transient ischemic attack events [[99](#_ENREF_99), [129](#_ENREF_129)]

Transient ischemic attack condition record during an inpatient or ER visit; successive records with > 30 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Transient ischemic attack (TIA) Transient cerebral Ischemia (TCA)2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Transient ischemic attack (TIA) Transient cerebral Ischemia (TCA)

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 373503 | Transient cerebral ischemia | Condition | SNOMED | NO | YES | NO |

### Type 2 diabetes mellitus

Persons with type 2 diabetes mellitus [[65](#_ENREF_65), [155-157](#_ENREF_155)]

The first condition record of Type 2 Diabetes Mellitus, which is followed by another Type 2 Diabetes Mellitus condition record, at least 2 drugs used to treat Type 2 diabetes, or at least 2 HbA1c measurements with value > 6.5%

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Type 2 Diabetes Mellitus3
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Type 2 Diabetes Mellitus3

where event starts between 1 days After and all days After index start date

* or at least 2 occurrences of a drug exposure of Drugs to treat Type 2 Diabetes Mellitus excluding insulin1

where event starts between 0 days Before and all days After index start date

* or at least 2 occurrences of a measurement of Hemoglobin A1c measurement2
  + with value as number between 6.5 and 30 (inclusive)
  + unit is any of: percent

where event starts between 7 days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Drugs to treat Type 2 Diabetes Mellitus excluding insulin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21600744 | BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS | Drug | ATC | NO | YES | NO |

2. Hemoglobin A1c measurement

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4197971 | HbA1c measurement | Measurement | SNOMED | NO | NO | NO |
| 44786901 | HEDIS 2014 Value Set - HbA1c Tests | Measurement | LOINC | NO | NO | NO |
| 3004410 | Hemoglobin A1c (Glycated) | Measurement | LOINC | NO | NO | NO |
| 3034639 | Hemoglobin A1c [Mass/volume] in Blood | Measurement | LOINC | NO | NO | NO |
| 40758583 | Hemoglobin A1c in Blood | Measurement | LOINC | NO | NO | NO |
| 3007263 | Hemoglobin A1c/Hemoglobin.total in Blood by calculation | Measurement | LOINC | NO | NO | NO |
| 3003309 | Hemoglobin A1c/Hemoglobin.total in Blood by Electrophoresis | Measurement | LOINC | NO | NO | NO |
| 3005673 | Hemoglobin A1c/Hemoglobin.total in Blood by HPLC | Measurement | LOINC | NO | NO | NO |
| 40762352 | Hemoglobin A1c/Hemoglobin.total in Blood by IFCC protocol | Measurement | LOINC | NO | NO | NO |
| 2212392 | Hemoglobin; glycosylated (A1C) | Measurement | CPT4 | NO | NO | NO |

3. Type 2 Diabetes Mellitus

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443735 | Coma associated with diabetes mellitus | Condition | SNOMED | NO | YES | NO |
| 4225656 | Diabetic cataract associated with type 1 diabetes mellitus | Condition | SNOMED | YES | YES | NO |
| 443767 | Diabetic oculopathy | Condition | SNOMED | NO | YES | NO |
| 192279 | Diabetic renal disease | Condition | SNOMED | NO | YES | NO |
| 4227210 | Diabetic retinopathy associated with type 1 diabetes mellitus | Condition | SNOMED | YES | YES | NO |
| 435216 | Disorder due to type 1 diabetes mellitus | Condition | SNOMED | YES | YES | NO |
| 443732 | Disorder due to type 2 diabetes mellitus | Condition | SNOMED | NO | YES | NO |
| 37016355 | Hyperosmolar coma due to secondary diabetes mellitus | Condition | SNOMED | YES | YES | NO |
| 4228112 | Hypoglycemic coma in type 1 diabetes mellitus | Condition | SNOMED | YES | YES | NO |
| 4224254 | Ketoacidotic coma in type 1 diabetes mellitus | Condition | SNOMED | YES | YES | NO |
| 376065 | Neurologic disorder associated with type 2 diabetes mellitus | Condition | SNOMED | NO | YES | NO |
| 443729 | Peripheral circulatory disorder associated with type 2 diabetes mellitus | Condition | SNOMED | NO | YES | NO |
| 200687 | Renal disorder associated with type 1 diabetes mellitus | Condition | SNOMED | YES | YES | NO |
| 201254 | Type 1 diabetes mellitus | Condition | SNOMED | YES | YES | NO |
| 201531 | Type 1 diabetes mellitus with hyperosmolar coma | Condition | SNOMED | YES | YES | NO |
| 4295011 | Type 1 diabetes mellitus with persistent microalbuminuria | Condition | SNOMED | YES | YES | NO |
| 201826 | Type 2 diabetes mellitus | Condition | SNOMED | NO | YES | NO |

### Vasculitis

Persons with vasculitis [[158](#_ENREF_158), [159](#_ENREF_159)]

The first condition record of vasculitis, which is followed by another vasculitis condition record or drug to treat vasculitis

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Vasculitis2
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Vasculitis2

where event starts between 1 days After and all days After index start date

* or at least 1 occurrences of a drug exposure of Drugs to treat vasculitis1

where event starts between 0 days Before and 30 days After index start date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Drugs to treat vasculitis

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 920458 | Betamethasone | Drug | RxNorm | NO | YES | NO |
| 1507705 | Cortisone | Drug | RxNorm | NO | YES | NO |
| 1310317 | Cyclophosphamide | Drug | RxNorm | NO | YES | NO |
| 1518254 | Dexamethasone | Drug | RxNorm | NO | YES | NO |
| 1305058 | Methotrexate | Drug | RxNorm | NO | YES | NO |
| 1506270 | Methylprednisolone | Drug | RxNorm | NO | YES | NO |
| 1550557 | prednisolone | Drug | RxNorm | NO | YES | NO |
| 1551099 | Prednisone | Drug | RxNorm | NO | YES | NO |
| 903963 | Triamcinolone | Drug | RxNorm | NO | YES | NO |

2. Vasculitis

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 314381 | Acute febrile mucocutaneous lymph node syndrome | Condition | SNOMED | NO | YES | NO |
| 4324395 | Aortitis | Condition | SNOMED | NO | YES | NO |
| 436642 | Behcet's syndrome | Condition | SNOMED | NO | YES | NO |
| 4096220 | Cryoglobulinemic vasculitis | Condition | SNOMED | NO | YES | NO |
| 314963 | Giant cell arteritis | Condition | SNOMED | NO | YES | NO |
| 195289 | Goodpasture's syndrome | Condition | SNOMED | NO | YES | NO |
| 313223 | Granulomatosis with polyangiitis | Condition | SNOMED | NO | YES | NO |
| 4101602 | Henoch-Schönlein purpura | Condition | SNOMED | NO | YES | NO |
| 320749 | Polyarteritis nodosa | Condition | SNOMED | NO | YES | NO |
| 44783716 | Primary angiitis of central nervous system | Condition | SNOMED | NO | YES | NO |

### Venous thromboembolic events

Venous thromboembolic (pulmonary embolism and deep vein thrombosis) events [[160-163](#_ENREF_160)]

Venous thromboembolism condition record of any type; successive records with > 180 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Venous thromboembolism (pulmonary embolism and deep vein thrombosis)1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Appendix 1: Concept Set Definitions

1. Venous thromboembolism (pulmonary embolism and deep vein thrombosis)

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 435616 | Amniotic fluid embolism | Condition | SNOMED | YES | YES | NO |
| 435887 | Antepartum deep vein thrombosis | Condition | SNOMED | YES | YES | NO |
| 196715 | Budd-Chiari syndrome | Condition | SNOMED | YES | YES | NO |
| 4062269 | Cerebral venous thrombosis in pregnancy | Condition | SNOMED | YES | YES | NO |
| 442055 | Obstetric air pulmonary embolism | Condition | SNOMED | YES | YES | NO |
| 433832 | Obstetric blood-clot pulmonary embolism | Condition | SNOMED | YES | YES | NO |
| 435026 | Obstetric pulmonary embolism | Condition | SNOMED | YES | YES | NO |
| 440477 | Obstetric pyemic and septic pulmonary embolism | Condition | SNOMED | YES | YES | NO |
| 318137 | Phlebitis and thrombophlebitis of intracranial sinuses | Condition | SNOMED | YES | YES | NO |
| 199837 | Portal vein thrombosis | Condition | SNOMED | YES | YES | NO |
| 438820 | Postpartum deep phlebothrombosis | Condition | SNOMED | YES | YES | NO |
| 440417 | Pulmonary embolism | Condition | SNOMED | NO | YES | NO |
| 254662 | Pulmonary infarction | Condition | SNOMED | NO | YES | NO |
| 4235812 | Septic thrombophlebitis | Condition | SNOMED | YES | YES | NO |
| 195294 | Thrombosed hemorrhoids | Condition | SNOMED | YES | YES | NO |
| 4187790 | Thrombosis of retinal vein | Condition | SNOMED | YES | YES | NO |
| 444247 | Venous thrombosis | Condition | SNOMED | NO | YES | NO |

### Vertigo

Persons with vertigo [[164](#_ENREF_164)]

The first condition record of vertigo

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Vertigo1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. Vertigo

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 437496 | Epidemic vertigo | Condition | SNOMED | NO | YES | NO |
| 78162 | Peripheral vertigo | Condition | SNOMED | NO | YES | NO |
| 439383 | Vertigo | Condition | SNOMED | NO | YES | NO |
| 381035 | Vertigo of central origin | Condition | SNOMED | NO | YES | NO |

### Vomiting

Vomiting events [[2](#_ENREF_2), [146](#_ENREF_146), [147](#_ENREF_147)]

Vomiting condition record of any type; successive records with > 30 day gap are considered independent episodes

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Vomiting1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

Appendix 1: Concept Set Definitions

1. Vomiting

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40480291 | Hyperemesis | Condition | SNOMED | YES | YES | NO |
| 4216862 | Postoperative vomiting | Condition | SNOMED | YES | YES | NO |
| 441408 | Vomiting | Condition | SNOMED | NO | YES | NO |
| 440785 | Vomiting of pregnancy | Condition | SNOMED | YES | YES | NO |

### Negative control outcomes

Negative controls are concepts known to not be associated with the target or comparator cohorts, such that we can assume the true relative risk between the two cohorts is 1. Negative controls are selected using a similar process to that outlined by Voss et al. [[165](#_ENREF_165)]. Person counts of all potential drug-condition pairs are reviewed in observational data; this person count data helps determine which pairs are even probable for use in calibration. Given the list of potential drug-condition pairs, the concepts in the pairs must meet the following requirements to be considered as negative controls: (1) that there is no Medline abstract where the MeSH terms suggest an association between the drug and the condition [[166](#_ENREF_166)], (2) that there is no mention of the drug-condition pair on a US Product Label in the “Adverse Drug Reactions” or “Postmarketing” section [[167](#_ENREF_167)], (3) there are no US spontaneous reports suggesting that the pair is in an adverse event relationship [[168](#_ENREF_168), [169](#_ENREF_169)], (4) that the OMOP Vocabulary does not suggest that the drug is indicated for the condition, (5) that the concepts are usable (i.e. not too broad, not suggestive of an adverse event relationship, not pregnancy related), and (6) the exact concept itself is utilized in patient level data (i.e. concepts that are not usually used within the data are usually indicative a broad concept that has a child that is more specific). The remaining concepts are “optimized”, meaning parent concepts remove children as defined by the OMOP Vocabulary (e.g. if both “Non-Hodgkin’s Lymphoma” and “B-Cell Lymphoma” we selected, child concept “B-Cell Lymphoma would be removed for its parent “Non-Hodgkin’s Lymphoma”). Once potential negative control candidates were selected, manual clinical review to exclude any pairs that may still be in a causal relationship or similar to the study outcome was be performed to select the top concepts by patient exposure. The final list can be found in Table 3.

|  |  |
| --- | --- |
| Abnormal cervical smear | Homocystinuria |
| Abnormal pupil | Human papilloma virus infection |
| Abrasion and/or friction burn of trunk without infection | Ileostomy present |
| Absence of breast | Impacted cerumen |
| Absent kidney | Impingement syndrome of shoulder region |
| Acid reflux | Ingrowing nail |
| Acquired hallux valgus | Injury of knee |
| Acquired keratoderma | Irregular periods |
| Acquired trigger finger | Kwashiorkor |
| Acute conjunctivitis | Late effect of contusion |
| Amputated foot | Late effect of motor vehicle accident |
| Anal and rectal polyp | Leukorrhea |
| Burn of forearm | Macular drusen |
| Calcaneal spur | Melena |
| Cannabis abuse | Nicotine dependence |
| Cervical somatic dysfunction | Noise effects on inner ear |
| Changes in skin texture | Nonspecific tuberculin test reaction |
| Chondromalacia of patella | Non-toxic multinodular goiter |
| Cocaine abuse | Onychomycosis due to dermatophyte |
| Colostomy present | Opioid abuse |
| Complication due to Crohn's disease | Passing flatus |
| Contact dermatitis | Postviral fatigue syndrome |
| Contusion of knee | Presbyopia |
| Crohn's disease | Problem related to lifestyle |
| Derangement of knee | Psychalgia |
| Difficulty sleeping | Ptotic breast |
| Disproportion of reconstructed breast | Regular astigmatism |
| Effects of hunger | Senile hyperkeratosis |
| Endometriosis | Somatic dysfunction of lumbar region |
| Epidermoid cyst | Splinter of face, without major open wound |
| Feces contents abnormal | Sprain of ankle |
| Foreign body in orifice | Strain of rotator cuff capsule |
| Ganglion cyst | Tear film insufficiency |
| Genetic predisposition | Tobacco dependence syndrome |
| Hammer toe | Vaginitis and vulvovaginitis |
| Hereditary thrombophilia | Verruca vulgaris |
| Herpes zoster without complication | Wrist joint pain |
| High risk sexual behavior | Wristdrop |

**Table 3**. Negative control outcomes

For each negative control outcome, a patient enters the negative control outcome cohort at the occurrence of a diagnose code identified by the concepts listed above, or any one of its descendant codes.

### Positive control outcomes

In addition to negative control outcomes, we will also include synthetic positive control outcomes. These are outcomes based on the real negative controls, but where the true effect size is artificially increased to a desired effect size by injection of additional, simulated outcomes [[170](#_ENREF_170)]. To preserve confounding, these additional outcomes are sampled from predicted probabilities generated using a fitted predictive model. For each negative control outcome, three positive control outcomes will be generated with true relative risk is 1.5, 2, and 4. Using both negative and positive controls, we will fit a systematic error model and perform confidence interval calibration [[170](#_ENREF_170)].

## Covariates

### Propensity score covariates

Propensity scores (PS) will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates.

The types of baseline covariates used to fit the propensity score model will be:

* Demographics
  + Gender
  + Age group (5-year bands)
  + Index year
  + Index month
* Conditions
  + In prior 30d
  + In prior 365d
* Condition aggregation
  + SNOMED
* Drugs
  + In prior 30d
  + In prior 365d
  + Overlapping index date
* Drug aggregation
  + Ingredient
  + ATC Class
* Risk scores
  + Charlson comorbidity index

All covariates that occur in fewer than 0.1% of the persons between the target and comparator cohorts combined will be excluded prior to model fitting for computational efficiency.

# Data Analysis Plan

## Calculation of time-at risk

Two time-at-risk periods will be used:

* On-treatment. Starting on the day of treatment initiation, and stopping at treatment end, allowing for a maximum gap of 30 days between prescriptions.
* Intent-to-treat: Starting on the day of treatment initiation and stopping at the end of observation.

## Model Specification

In this study, we compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model.

The time-to-event of outcome among patients in the target and comparator cohorts is determined by calculating the number of days from the start of the time-at-risk window (the cohort start date), until the earliest event among 1) the first occurrence of the outcome, 2) the end of the time-at-risk window as defined in section 9.1 (i.e. ‘on-treatment’ or ‘intent-to-treat’), and 3) the end of the observation period that spans the time-at-risk start.

Patients with the outcome observed prior to target or comparator cohort entry are excluded from consideration.

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates. In this study, the propensity score is estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross, a starting variance of 0.01 and a tolerance of 2e-7. Covariates to be used in the propensity score model are listed in section 8.6.

In one analysis the target cohort and comparator cohorts will be stratified into ten quantiles of the propensity score distribution. A second analysis will use variable ratio matching based on the propensity score, using a caliper of 0.2 on the standardized logit scale. The final outcome model will apply a conditional Cox proportional hazard model, conditioned on the propensity score strata or matched sets.

Incidence rates will be computed for each outcome in each exposure group, in both the on-treatment and intent-to-treat windows.

### Pooling effect estimates across databases

Effects will be pooled across databases using a random-effects meta-analysis. Estimates for negative and positive controls will be pooled before performing empirical calibration on the pooled estimates.

## Analyses to perform

### Comparative analyses

The following comparative analyses will be performed if sufficient data is present (e.g. if at least 2,500 subjects are observed in both target and comparator cohort):

* 11,365,884 comparisons in total between treatments:
  + Drug level: (58 \* 57 =) 3,306 combination therapies + 58 monotherapies \* (3,306 + 58 -1) = 11,313,132 comparisons
  + Drug class level: (15 \* 14 =) 210 combination therapies + 15 monotherapies \* (210 + 15 - 1) = 50,400 comparisons
  + Major drug class level: (7 \* 6 =) 42 combination therapies + 7 monotherapies \* (42 + 7 - 1) = 2,352 comparisons
* 56 outcomes of interest
* 2 time-at-risk definitions: on-treatment and intent-to-treat
* 2 models: Cox regression using propensity score stratification and Cox regression using propensity score matching

The total number of analyses for outcomes of interest is therefore 11,365,884 \* 56 \* 2 \* 2 = 2,545,958,016 analyses per database.

We will also include 76 negative control outcomes, and 3 \* 76 positive control outcomes, so 304 control outcomes. The total number of control analyses is therefore 11,365,884 \* 304 \* 2 \* 2 = 13,820,914,944 analyses.

Additionally, interaction effects will be computed with the 8 subgroups of interest. For efficiency reasons, this will only be computed when using propensity score stratification.

The number of analysis of subgroup interactions is therefore 11,365,884 \* 57 \* 2 \* 1 \* 8 = 10,365,686,208 analyses per database.

For interaction effects, only negative control outcomes will be added. The total number of control analyses for interaction terms is therefore 11,365,884 \* 76 \* 2 \* 1 \* 8 = 13,820,914,944 analyses per database.

### Descriptive analyses

The following incidence rate computations will be performed:

* 3,638 cohorts of interest:
  + Drug level: (58 \* 57 =) 3,306 combination therapies + 58 monotherapies = 3,364 cohorts
  + Drug class level: (15 \* 14 =) 210 combination therapies + 15 monotherapies = 225 cohorts
  + Major drug class level: (7 \* 6 =) 42 combination therapies + 7 monotherapies = 49 cohorts
* 56 outcomes of interest
* 2 time-at-risk definitions: on-treatment and intent-to-treat
* 4 databases: CCAE, MDCD, MDCR, Optum

The total number of analyses for outcomes of interest is therefore 3,306 \* 56 \* 2 \* 4 = 1,481,088 analyses.

## Output

The output will be stored in the LEGEND evidence model, which is described elsewhere.

## Evidence Evaluation

We have executed diagnostics to determine if the analysis can be appropriately conducted. The diagnostics include:

* Propensity score distribution
* Covariate balance before and after propensity score matching
* Estimation for negative and positive controls, to assess residual error
* Negative and positive control exposures and outcomes will be used to evaluate the potential impact of residual systematic error in the study design, and to facilitate empirical calibration of the p-value and confidence interval for the exposures and outcome of interest.

Negative control outcomes in the context of this study are outcomes that are not believed to be caused by neither exposure in any comparison and where therefore the true hazard ratio is equal to 1. We will execute the same analysis used for the primary hypotheses to produce hazard ratio estimates for the negative controls. The distribution of effect estimates across all negative controls will be used to fit an empirical null distribution which models the observed residual systematic error. The empirical null distribution will then be applied to the target exposures and outcome of interest to calibrate the p-value [[171](#_ENREF_171)].

Positive control exposures and outcomes are pairs of exposures and outcomes where the hazard ratio is known to be of some magnitude greater than 1. We will synthesize positive controls by starting with the negative controls defined earlier, and adding additional, simulated outcomes during the time-at-risk until the desired true hazard ratio is achieved. The target hazard ratios are 1.5, 2 and 4. The negative and positive controls together will be used to estimate an empirical systematic error model, which will inform whether systematic error changes as a function of true effect size. The empirical systematic error model will then be applied to the target the target exposures and outcome of interest to calibrate the confidence interval [[170](#_ENREF_170)].

Empirical calibration serves as an important diagnostic tool to evaluate if the residual systematic error is sufficient to cast doubt on the accuracy of the unknown effect estimate. The calibration effect plot and calibration probability plots will be generated for review. We will report the traditional and empirically calibrated p-value and confidence interval for each negative control, as well as the hypothesis of interest.

# Study Diagnostics

## Sample Size and Study Power

This will be reported in the output (see the LEGEND data model).

## Cohort Comparability

This will be reported in the output (see the LEGEND data model).

## Systematic Error Assessment

This will be reported in the output (see the LEGEND data model).

# Strengths and Limitations of the Research Methods

Strength

* Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
* PS matching allow balancing on a large number of baseline potential confounders.
* Use of negative and positive control outcomes allow for evaluating the study design as a whole in terms of residual bias.

Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Management and Reporting of Adverse Events and Adverse Reactions

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse events reports. The study results will be assessed for medically important results.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal. The results will also be presented at the OHDSI 2018 Symposium.

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