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.

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# 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

THZ Thiazide or thiazide-like diuretics

# 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 | 26 Jan 2022 | T. Anand, P. Ryan,  M. Schuemie | Initial draft |
|  |  |  |  |

# Milestones

|  |  |
| --- | --- |
| Milestone | Planned / Estimated Date |
| Start of analysis | December 2021 |
| End of analysis | November 2022 |
| Presentation of results | January 2023 |

# 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 the pairwise comparison at the class level of ACE inhibitors and THZ. The treatments in each class are in table 1.

|  |  |  |
| --- | --- | --- |
| 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 |
| 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 |

**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 comparison between the two classes of monotherapy 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 pairwise comparison of monotherapy 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)
* Optum® de-identified Electronic Health Record Dataset (OptumEHR)
* Columbia University Irving Medical Center (CUIMC)

### 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 (OptumDod)

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.

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

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).

### Columbia University Irving Medical Center (CUIMC)

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 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 diagnosis 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.

The end of the exposure cohort is defined as the end of the first exposure, allowing for 30-day gaps between consecutive prescriptions. The end of the exposure cohort may also be defined as the end of monotherapy treatment, meaning exit from the exposure cohort is imposed on the start of a second anti-hypertensive medication.

### Mono therapies

When considering non-combination therapies, no concurrent treatments are allowed. When comparing ACEi to THZ, ACEi users are not allowed to initiate any other treatment at the time of initiating ACEi. Users are removed from the exposure cohort upon starting a second anti-hypertensive medication.

## 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
* Procedure
  + In prior 30d
  + In prior 365d
* Measurement
  + In prior 30d
  + In prior 365d
* 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.

## 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.

# References

1. Schuemie, M.J., et al., *Improving reproducibility by using high-throughput observational studies with empirical calibration.* Philos Trans A Math Phys Eng Sci, 2018. **376**(2128).

2. Goldstein, J.L., et al., *Incidence of outpatient physician claims for upper gastrointestinal symptoms among new users of celecoxib, ibuprofen, and naproxen in an insured population in the United States.* Am J Gastroenterol., 2003. **98**(12): p. 2627-34. doi: 10.1111/j.1572-0241.2003.08722.x.

3. Rao, G., et al., *Identifying, Analyzing, and Visualizing Diagnostic Paths for Patients with Nonspecific Abdominal Pain.* Appl Clin Inform., 2018. **9**(4): p. 905-913. doi: 10.1055/s-0038-1676338. Epub 2018 Dec 19.

4. Saps, M., et al., *Seasonal patterns of abdominal pain consultations among adults and children.* J Pediatr Gastroenterol Nutr., 2013. **56**(3): p. 290-6. doi: 10.1097/MPG.0b013e3182769796.

5. Broder, M.S., et al., *Identification of Potential Markers for Cushing Disease.* Endocr Pract., 2016. **22**(5): p. 567-74. doi: 10.4158/EP15914.OR. Epub 2016 Jan 20.

6. Williams, B.A., *The clinical epidemiology of fatigue in newly diagnosed heart failure.* BMC Cardiovasc Disord., 2017. **17**(1): p. 122. doi: 10.1186/s12872-017-0555-9.

7. Ammann, E.M., et al., *Chart validation of inpatient ICD-9-CM administrative diagnosis codes for acute myocardial infarction (AMI) among intravenous immune globulin (IGIV) users in the Sentinel Distributed Database.* Pharmacoepidemiol Drug Saf., 2018. **27**(4): p. 398-404. doi: 10.1002/pds.4398. Epub 2018 Feb 15.

8. Floyd, J.S., et al., *Validation of methods for assessing cardiovascular disease using electronic health data in a cohort of Veterans with diabetes.* Pharmacoepidemiol Drug Saf., 2016. **25**(4): p. 467-71. doi: 10.1002/pds.3921. Epub 2015 Nov 11.

9. Rubbo, B., et al., *Use of electronic health records to ascertain, validate and phenotype acute myocardial infarction: A systematic review and recommendations.* Int J Cardiol, 2015. **187:705-11.**(doi): p. 10.1016/j.ijcard.2015.03.075. Epub 2015 Mar 5.

10. Singh, S., et al., *Diagnostic Algorithms for Cardiovascular Death in Administrative Claims Databases: A Systematic Review.* Drug Saf, 2018. **23**(10): p. 018-0754.

11. Wahl, P.M., et al., *Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population.* Pharmacoepidemiol Drug Saf., 2010. **19**(6): p. 596-603. doi: 10.1002/pds.1924.

12. Normand, S.L., et al., *Development and validation of a claims based index for adjusting for risk of mortality: the case of acute myocardial infarction.* J Clin Epidemiol., 1995. **48**(2): p. 229-43.

13. Dore, D.D., et al., *Stratum-specific positive predictive values of claims for acute pancreatitis among commercial health insurance plan enrollees with diabetes mellitus.* Pharmacoepidemiol Drug Saf., 2011. **20**(2): p. 209-13. doi: 10.1002/pds.2077. Epub 2010 Dec 23.

14. Dore, D.D., et al., *A pooled analysis of exenatide use and risk of acute pancreatitis.* Curr Med Res Opin., 2013. **29**(12): p. 1577-86. doi: 10.1185/03007995.2013.838550. Epub 2013 Sep 13.

15. Yabe, D., et al., *Use of the Japanese health insurance claims database to assess the risk of acute pancreatitis in patients with diabetes: comparison of DPP-4 inhibitors with other oral antidiabetic drugs.* Diabetes Obes Metab., 2015. **17**(4): p. 430-4. doi: 10.1111/dom.12381. Epub 2014 Sep 17.

16. Chen, H.J., et al., *Epidemiology and outcome of acute pancreatitis in end-stage renal disease dialysis patients: a 10-year national cohort study.* Nephrol Dial Transplant., 2017. **32**(10): p. 1731-1736. doi: 10.1093/ndt/gfw400.

17. Afzal, Z., et al., *Improving sensitivity of machine learning methods for automated case identification from free-text electronic medical records.* BMC Med Inform Decis Mak., 2013. **13:30.**(doi): p. 10.1186/1472-6947-13-30.

18. Lenihan, C.R., et al., *Trends in acute kidney injury, associated use of dialysis, and mortality after cardiac surgery, 1999 to 2008.* Ann Thorac Surg., 2013. **95**(1): p. 20-8. doi: 10.1016/j.athoracsur.2012.05.131. Epub 2012 Dec 25.

19. Winkelmayer, W.C., et al., *Identification of individuals with CKD from Medicare claims data: a validation study.* Am J Kidney Dis., 2005. **46**(2): p. 225-32. doi: 10.1053/j.ajkd.2005.04.029.

20. Grams, M.E., et al., *Performance and limitations of administrative data in the identification of AKI.* Clin J Am Soc Nephrol., 2014. **9**(4): p. 682-9. doi: 10.2215/CJN.07650713. Epub 2014 Jan 23.

21. Arnold, J., et al., *Incidence and impact on outcomes of acute kidney injury after a stroke: a systematic review and meta-analysis.* BMC Nephrol., 2018. **19**(1): p. 283. doi: 10.1186/s12882-018-1085-0.

22. Sutherland, S.M., et al., *AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions.* Clin J Am Soc Nephrol., 2015. **10**(4): p. 554-61. doi: 10.2215/CJN.01900214. Epub 2015 Feb 3.

23. Waikar, S.S., et al., *Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure.* J Am Soc Nephrol., 2006. **17**(6): p. 1688-94. doi: 10.1681/ASN.2006010073. Epub 2006 Apr 26.

24. Rhee, C., et al., *Improving documentation and coding for acute organ dysfunction biases estimates of changing sepsis severity and burden: a retrospective study.* Crit Care., 2015. **19:338.**(doi): p. 10.1186/s13054-015-1048-9.

25. Ooba, N., et al., *Claims-based definition of death in Japanese claims database: validity and implications.* PLoS One., 2013. **8**(5): p. e66116. doi: 10.1371/journal.pone.0066116. Print 2013.

26. Robinson, T.E., et al., *Development and validation of a predictive risk model for all-cause mortality in type 2 diabetes.* Diabetes Res Clin Pract., 2015. **108**(3): p. 482-8. doi: 10.1016/j.diabres.2015.02.015. Epub 2015 Mar 16.

27. Schneider, G., et al., *A systematic review of validated methods for identifying anaphylaxis, including anaphylactic shock and angioneurotic edema, using administrative and claims data.* Pharmacoepidemiol Drug Saf., 2012. **21**(Suppl 1): p. 240-7. doi: 10.1002/pds.2327.

28. Walsh, K.E., et al., *Validation of anaphylaxis in the Food and Drug Administration's Mini-Sentinel.* Pharmacoepidemiol Drug Saf., 2013. **22**(11): p. 1205-13. doi: 10.1002/pds.3505. Epub 2013 Sep 5.

29. Han, C., et al., *A case-control study of anaemia in patients with rheumatoid arthritis treated with disease-modifying antirheumatic drugs in an adult population in the US: prevalence and impact on healthcare utilisation.* J Med Econ, 2008. **11**(2): p. 255-64. doi: 10.3111/13696990802066469.

30. Michalik, D.E., B.W. Taylor, and J.A. Panepinto, *Identification and Validation of a Sickle Cell Disease Cohort Within Electronic Health Records.* Acad Pediatr., 2017. **17**(3): p. 283-287. doi: 10.1016/j.acap.2016.12.005. Epub 2016 Dec 13.

31. Tuck, M.G., et al., *A Comprehensive Index for Predicting Risk of Anemia from Patients' Diagnoses.* Big Data., 2017. **5**(1): p. 42-52. doi: 10.1089/big.2016.0073.

32. Cherepanov, D., et al., *Validation of an ICD-9-based claims algorithm for identifying patients with chronic idiopathic/spontaneous urticaria.* Ann Allergy Asthma Immunol., 2015. **114**(5): p. 393-8. doi: 10.1016/j.anai.2015.02.003. Epub 2015 Mar 12.

33. Bushnell, G.A., et al., *Psychotherapy Claims Surrounding Pharmacotherapy Initiation in Children and Adolescents with Anxiety Disorders.* J Child Adolesc Psychopharmacol, 2018. **19**(10).

34. John, A., et al., *Case-finding for common mental disorders of anxiety and depression in primary care: an external validation of routinely collected data.* BMC Med Inform Decis Mak., 2016. **16:35.**(doi): p. 10.1186/s12911-016-0274-7.

35. Marrie, R.A., et al., *Performance of administrative case definitions for depression and anxiety in inflammatory bowel disease.* J Psychosom Res., 2016. **89:107-13.**(doi): p. 10.1016/j.jpsychores.2016.08.014. Epub 2016 Sep 3.

36. Castro, V.M., et al., *Validation of electronic health record phenotyping of bipolar disorder cases and controls.* Am J Psychiatry., 2015. **172**(4): p. 363-72. doi: 10.1176/appi.ajp.2014.14030423. Epub 2014 Dec 12.

37. Shin, J., M. Gonzales, and M.J. Pletcher, *Risk of emergent bradycardia associated with initiation of immediate- or slow-release metoprolol.* Pharmacotherapy., 2013. **33**(12): p. 1353-61. doi: 10.1002/phar.1319. Epub 2013 Jun 27.

38. Turgeon, R.D., et al., *Ticagrelor and bradycardia: a nested case-control study.* Pharmacoepidemiol Drug Saf., 2015. **24**(12): p. 1281-5. doi: 10.1002/pds.3884. Epub 2015 Oct 7.

39. Hennessy, S., et al., *Validation of diagnostic codes for outpatient-originating sudden cardiac death and ventricular arrhythmia in Medicaid and Medicare claims data.* Pharmacoepidemiol Drug Saf., 2010. **19**(6): p. 555-62. doi: 10.1002/pds.1869.

40. Tamariz, L., T. Harkins, and V. Nair, *A systematic review of validated methods for identifying ventricular arrhythmias using administrative and claims data.* Pharmacoepidemiol Drug Saf., 2012. **21**(Suppl 1): p. 148-53. doi: 10.1002/pds.2340.

41. Gage, B.F., et al., *Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation.* JAMA., 2001. **285**(22): p. 2864-70.

42. Jensen, P.N., et al., *A systematic review of validated methods for identifying atrial fibrillation using administrative data.* Pharmacoepidemiol Drug Saf., 2012. **21**(Suppl 1): p. 141-7. doi: 10.1002/pds.2317.

43. Karnik, S., et al., *Predicting atrial fibrillation and flutter using electronic health records.* Conf Proc IEEE Eng Med Biol Soc, 2012. **2012:5562-5.**(doi): p. 10.1109/EMBC.2012.6347254.

44. Navar-Boggan, A.M., et al., *Accuracy and validation of an automated electronic algorithm to identify patients with atrial fibrillation at risk for stroke.* Am Heart J., 2015. **169**(1): p. 39-44.e2. doi: 10.1016/j.ahj.2014.09.014. Epub 2014 Oct 22.

45. Yahi, A. and N.P. Tatonetti, *A knowledge-based, automated method for phenotyping in the EHR using only clinical pathology reports.* AMIA Jt Summits Transl Sci Proc., 2015. **2015**: p. 64-8. eCollection 2015.

46. Zaher, C., G.A. Goldberg, and P. Kadlubek, *Estimating angina prevalence in a managed care population.* Am J Manag Care., 2004. **10**(11 Suppl): p. S339-46.

47. Chase, H.S., et al., *Under-documentation of chronic kidney disease in the electronic health record in outpatients.* J Am Med Inform Assoc., 2010. **17**(5): p. 588-94. doi: 10.1136/jamia.2009.001396.

48. Fraccaro, P., et al., *An external validation of models to predict the onset of chronic kidney disease using population-based electronic health records from Salford, UK.* BMC Med., 2016. **14:104.**(doi): p. 10.1186/s12916-016-0650-2.

49. Frigaard, M., et al., *Validating laboratory defined chronic kidney disease in the electronic health record for patients in primary care.* BMC Nephrol., 2019. **20**(1): p. 3. doi: 10.1186/s12882-018-1156-2.

50. Holzmann, M.J., et al., *Chronic kidney disease and 10-year risk of cardiovascular death.* Eur J Prev Cardiol., 2016. **23**(11): p. 1187-94. doi: 10.1177/2047487315614491. Epub 2015 Nov 5.

51. Luong, D.T.A., et al., *Extracting Deep Phenotypes for Chronic Kidney Disease Using Electronic Health Records.* EGEMS (Wash DC). 2017. **5**(1): p. 9. doi: 10.5334/egems.226.

52. Muntner, P., et al., *Validation study of medicare claims to identify older US adults with CKD using the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study.* Am J Kidney Dis., 2015. **65**(2): p. 249-58. doi: 10.1053/j.ajkd.2014.07.012. Epub 2014 Sep 19.

53. Nadkarni, G.N., et al., *Development and validation of an electronic phenotyping algorithm for chronic kidney disease.* AMIA Annu Symp Proc., 2014. **2014**: p. 907-16. eCollection 2014.

54. Robertson, L.M., et al., *Is routine hospital episode data sufficient for identifying individuals with chronic kidney disease? A comparison study with laboratory data.* Health Informatics J., 2016. **22**(2): p. 383-96. doi: 10.1177/1460458214562286. Epub 2014 Dec 31.

55. Chen, C.C., et al., *Estimated incidence of pertussis in people aged <50 years in the United States.* Hum Vaccin Immunother., 2016. **12**(10): p. 2536-2545. doi: 10.1080/21645515.2016.1186313. Epub 2016 May 31.

56. Fathima, S., et al., *How well do ICD-9 physician claim diagnostic codes identify confirmed pertussis cases in Alberta, Canada? A Canadian Immunization Research Network (CIRN) Study.* BMC Health Serv Res., 2017. **17**(1): p. 479. doi: 10.1186/s12913-017-2321-1.

57. Lazarus, R., et al., *Using automated medical records for rapid identification of illness syndromes (syndromic surveillance): the example of lower respiratory infection.* BMC Public Health, 2001. **1**: p. 9. Epub 2001 Oct 22.

58. Masterson, J.M., et al., *Elevated Body Mass Index Is Associated with Secondary Hypogonadism Among Men Presenting to a Tertiary Academic Medical Center.* World J Mens Health., 2019. **37**(1): p. 93-98. doi: 10.5534/wjmh.180047. Epub 2018 Oct 10.

59. Ostbye, T., et al., *Identification of dementia: agreement among national survey data, medicare claims, and death certificates.* Health Serv Res., 2008. **43**(1 Pt 1): p. 313-26. doi: 10.1111/j.1475-6773.2007.00748.x.

60. Sibbett, R.A., et al., *Dementia ascertainment using existing data in UK longitudinal and cohort studies: a systematic review of methodology.* BMC Psychiatry., 2017. **17**(1): p. 239. doi: 10.1186/s12888-017-1401-4.

61. Amra, S., et al., *Derivation and validation of the automated search algorithms to identify cognitive impairment and dementia in electronic health records.* J Crit Care., 2017. **37:202-205.**(doi): p. 10.1016/j.jcrc.2016.09.026. Epub 2016 Oct 8.

62. Jaakkimainen, R.L., et al., *Identification of Physician-Diagnosed Alzheimer's Disease and Related Dementias in Population-Based Administrative Data: A Validation Study Using Family Physicians' Electronic Medical Records.* J Alzheimers Dis., 2016. **54**(1): p. 337-49. doi: 10.3233/JAD-160105.

63. Kosteniuk, J.G., et al., *Incidence and prevalence of dementia in linked administrative health data in Saskatchewan, Canada: a retrospective cohort study.* BMC Geriatr., 2015. **15:73.**(doi): p. 10.1186/s12877-015-0075-3.

64. McGuinness, L.A., et al., *The validity of dementia diagnoses in routinely collected electronic health records in the United Kingdom: A systematic review.* Pharmacoepidemiol Drug Saf., 2019. **28**(2): p. 244-255. doi: 10.1002/pds.4669. Epub 2019 Jan 22.

65. Williamson, T., et al., *Validating the 8 CPCSSN case definitions for chronic disease surveillance in a primary care database of electronic health records.* Ann Fam Med., 2014. **12**(4): p. 367-72. doi: 10.1370/afm.1644.

66. Lin, P.J., et al., *An examination of Alzheimer's disease case definitions using Medicare claims and survey data.* Alzheimers Dement., 2010. **6**(4): p. 334-41. doi: 10.1016/j.jalz.2009.09.001.

67. Alaghehbandan, R., et al., *Using administrative databases in the surveillance of depressive disorders--case definitions.* Popul Health Manag., 2012. **15**(6): p. 372-80. doi: 10.1089/pop.2011.0084. Epub 2012 Jul 12.

68. Cepeda, M.S., et al., *Finding treatment-resistant depression in real-world data: How a data-driven approach compares with expert-based heuristics.* Depress Anxiety., 2018. **35**(3): p. 220-228. doi: 10.1002/da.22705. Epub 2017 Dec 15.

69. Davidson, A.J., et al., *Monitoring Depression Rates in an Urban Community: Use of Electronic Health Records.* J Public Health Manag Pract., 2018. **24**(6): p. E6-E14. doi: 10.1097/PHH.0000000000000751.

70. Doktorchik, C., et al., *Validation of a case definition for depression in administrative data against primary chart data as a reference standard.* BMC Psychiatry., 2019. **19**(1): p. 9. doi: 10.1186/s12888-018-1990-6.

71. Buono, J.L., et al., *Economic Burden of Irritable Bowel Syndrome with Diarrhea: Retrospective Analysis of a U.S. Commercially Insured Population.* J Manag Care Spec Pharm., 2017. **23**(4): p. 453-460. doi: 10.18553/jmcp.2016.16138. Epub 2016 Nov 21.

72. Krishnarajah, G., et al., *Public Health Impact of Complete and Incomplete Rotavirus Vaccination among Commercially and Medicaid Insured Children in the United States.* PLoS One., 2016. **11**(1): p. e0145977. doi: 10.1371/journal.pone.0145977. eCollection 2016.

73. Panozzo, C.A., et al., *Direct, indirect, total, and overall effectiveness of the rotavirus vaccines for the prevention of gastroenteritis hospitalizations in privately insured US children, 2007-2010.* Am J Epidemiol., 2014. **179**(7): p. 895-909. doi: 10.1093/aje/kwu001. Epub 2014 Feb 26.

74. Shen, A.K., et al., *Beneficiary characteristics and vaccinations in the end-stage renal disease Medicare beneficiary population, an analysis of claims data 2006-2015.* Vaccine., 2017. **35**(52): p. 7302-7308. doi: 10.1016/j.vaccine.2017.10.105. Epub 2017 Nov 10.

75. Homer, M.L., et al., *Predicting Falls in People Aged 65 Years and Older from Insurance Claims.* Am J Med., 2017. **130**(6): p. 744.e17-744.e23. doi: 10.1016/j.amjmed.2017.01.003. Epub 2017 Jan 20.

76. Kim, D.H., et al., *Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index.* J Gerontol A Biol Sci Med Sci., 2018. **73**(7): p. 980-987. doi: 10.1093/gerona/glx229.

77. McCoy, T.H., Jr., et al., *Validation of a risk stratification tool for fall-related injury in a state-wide cohort.* BMJ Open., 2017. **7**(2): p. e012189. doi: 10.1136/bmjopen-2016-012189.

78. Curtis, J.R., et al., *Validation of ICD-9-CM codes to identify gastrointestinal perforation events in administrative claims data among hospitalized rheumatoid arthritis patients.* Pharmacoepidemiol Drug Saf., 2011. **20**(11): p. 1150-8. doi: 10.1002/pds.2215. Epub 2011 Aug 27.

79. Lanza, L.L., et al., *Peptic ulcer and gastrointestinal hemorrhage associated with nonsteroidal anti-inflammatory drug use in patients younger than 65 years. A large health maintenance organization cohort study.* Arch Intern Med., 1995. **155**(13): p. 1371-7.

80. Lin, K.J., L.A. Garcia Rodriguez, and S. Hernandez-Diaz, *Systematic review of peptic ulcer disease incidence rates: do studies without validation provide reliable estimates?* Pharmacoepidemiol Drug Saf., 2011. **20**(7): p. 718-28. doi: 10.1002/pds.2153. Epub 2011 May 27.

81. Patorno, E., et al., *The Role of Hemoglobin Laboratory Test Results for the Detection of Upper Gastrointestinal Bleeding Outcomes Resulting from the Use of Medications in Observational Studies.* Drug Saf., 2017. **40**(1): p. 91-100. doi: 10.1007/s40264-016-0472-3.

82. Valkhoff, V.E., et al., *Validation study in four health-care databases: upper gastrointestinal bleeding misclassification affects precision but not magnitude of drug-related upper gastrointestinal bleeding risk.* J Clin Epidemiol., 2014. **67**(8): p. 921-31. doi: 10.1016/j.jclinepi.2014.02.020. Epub 2014 May 1.

83. Cadzow, M., T.R. Merriman, and N. Dalbeth, *Performance of gout definitions for genetic epidemiological studies: analysis of UK Biobank.* Arthritis Res Ther., 2017. **19**(1): p. 181. doi: 10.1186/s13075-017-1390-1.

84. Harrold, L.R., et al., *Validity of gout diagnoses in administrative data.* Arthritis Rheum., 2007. **57**(1): p. 103-8. doi: 10.1002/art.22474.

85. MacFarlane, L.A., et al., *Validation of claims-based algorithms for gout flares.* Pharmacoepidemiol Drug Saf., 2016. **25**(7): p. 820-6. doi: 10.1002/pds.4044. Epub 2016 May 27.

86. Malik, A., et al., *Poor validation of medical record ICD-9 diagnoses of gout in a veterans affairs database.* J Rheumatol., 2009. **36**(6): p. 1283-6. doi: 10.3899/jrheum.081195. Epub 2009 May 15.

87. Hurwitz, E.L., et al., *Variations in Patterns of Utilization and Charges for the Care of Headache in North Carolina, 2000-2009: A Statewide Claims' Data Analysis.* J Manipulative Physiol Ther., 2016. **39**(4): p. 229-39. doi: 10.1016/j.jmpt.2016.02.008.

88. Rizzoli, P., E. Loder, and S. Joshi, *Validity of cluster headache diagnoses in an electronic health record data repository.* Headache., 2016. **56**(7): p. 1132-6. doi: 10.1111/head.12850. Epub 2016 Jun 6.

89. Floyd, J.S., et al., *Use of Electronic Health Data to Estimate Heart Failure Events in a Population-Based Cohort with CKD.* Clin J Am Soc Nephrol., 2016. **11**(11): p. 1954-1961. doi: 10.2215/CJN.03900416. Epub 2016 Aug 9.

90. Gini, R., et al., *Automatic identification of type 2 diabetes, hypertension, ischaemic heart disease, heart failure and their levels of severity from Italian General Practitioners' electronic medical records: a validation study.* BMJ Open., 2016. **6**(12): p. e012413. doi: 10.1136/bmjopen-2016-012413.

91. Kaspar, M., et al., *Underestimated prevalence of heart failure in hospital inpatients: a comparison of ICD codes and discharge letter information.* Clin Res Cardiol., 2018. **107**(9): p. 778-787. doi: 10.1007/s00392-018-1245-z. Epub 2018 Apr 17.

92. Li, Q., et al., *Validity of claims-based definitions of left ventricular systolic dysfunction in Medicare patients.* Pharmacoepidemiol Drug Saf., 2011. **20**(7): p. 700-8. doi: 10.1002/pds.2146. Epub 2011 May 14.

93. Patel, Y.R., et al., *Development and validation of a heart failure with preserved ejection fraction cohort using electronic medical records.* BMC Cardiovasc Disord., 2018. **18**(1): p. 128. doi: 10.1186/s12872-018-0866-5.

94. Saczynski, J.S., et al., *A systematic review of validated methods for identifying heart failure using administrative data.* Pharmacoepidemiol Drug Saf., 2012. **21**(Suppl 1): p. 129-40. doi: 10.1002/pds.2313.

95. Schultz, S.E., et al., *Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records.* Chronic Dis Inj Can., 2013. **33**(3): p. 160-6.

96. Feder, S.L., et al., *Validation of the ICD-9 Diagnostic Code for Palliative Care in Patients Hospitalized With Heart Failure Within the Veterans Health Administration.* Am J Hosp Palliat Care., 2018. **35**(7): p. 959-965. doi: 10.1177/1049909117747519. Epub 2017 Dec 18.

97. Rosenman, M., et al., *Database queries for hospitalizations for acute congestive heart failure: flexible methods and validation based on set theory.* J Am Med Inform Assoc., 2014. **21**(2): p. 345-52. doi: 10.1136/amiajnl-2013-001942. Epub 2013 Oct 10.

98. Quach, S., C. Blais, and H. Quan, *Administrative data have high variation in validity for recording heart failure.* Can J Cardiol., 2010. **26**(8): p. 306-12.

99. Andrade, S.E., et al., *A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data.* Pharmacoepidemiol Drug Saf., 2012. **21**(Suppl 1): p. 100-28. doi: 10.1002/pds.2312.

100. Park, T.H. and J.C. Choi, *Validation of Stroke and Thrombolytic Therapy in Korean National Health Insurance Claim Data.* J Clin Neurol., 2016. **12**(1): p. 42-8. doi: 10.3988/jcn.2016.12.1.42. Epub 2015 Sep 11.

101. Gon, Y., et al., *Validation of an algorithm that determines stroke diagnostic code accuracy in a Japanese hospital-based cancer registry using electronic medical records.* BMC Med Inform Decis Mak., 2017. **17**(1): p. 157. doi: 10.1186/s12911-017-0554-x.

102. Sung, S.F., et al., *Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or intracerebral hemorrhage in an administrative claims database.* Int J Cardiol., 2016. **215:277-82.**(doi): p. 10.1016/j.ijcard.2016.04.069. Epub 2016 Apr 14.

103. Tu, K., et al., *Validity of administrative data for identifying patients who have had a stroke or transient ischemic attack using EMRALD as a reference standard.* Can J Cardiol., 2013. **29**(11): p. 1388-94. doi: 10.1016/j.cjca.2013.07.676. Epub 2013 Sep 26.

104. Bui, C.L., et al., *Validation of acute liver injury cases in a population-based cohort study of oral antimicrobial users.* Curr Drug Saf., 2014. **9**(1): p. 23-8.

105. Cheetham, T.C., et al., *An automated causality assessment algorithm to detect drug-induced liver injury in electronic medical record data.* Pharmacoepidemiol Drug Saf., 2014. **23**(6): p. 601-8. doi: 10.1002/pds.3531. Epub 2013 Oct 21.

106. Jinjuvadia, K., W. Kwan, and R.J. Fontana, *Searching for a needle in a haystack: use of ICD-9-CM codes in drug-induced liver injury.* Am J Gastroenterol., 2007. **102**(11): p. 2437-43. doi: 10.1111/j.1572-0241.2007.01456.x. Epub 2007 Jul 27.

107. Lo Re, V., 3rd, et al., *Validity of diagnostic codes and laboratory tests of liver dysfunction to identify acute liver failure events.* Pharmacoepidemiol Drug Saf., 2015. **24**(7): p. 676-83. doi: 10.1002/pds.3774. Epub 2015 Apr 10.

108. Lo Re, V., 3rd, et al., *Validity of diagnostic codes to identify cases of severe acute liver injury in the US Food and Drug Administration's Mini-Sentinel Distributed Database.* Pharmacoepidemiol Drug Saf., 2013. **22**(8): p. 861-72. doi: 10.1002/pds.3470. Epub 2013 Jun 25.

109. Overby, C.L., et al., *A collaborative approach to developing an electronic health record phenotyping algorithm for drug-induced liver injury.* J Am Med Inform Assoc., 2013. **20**(e2): p. e243-52. doi: 10.1136/amiajnl-2013-001930. Epub 2013 Jul 9.

110. Udo, R., et al., *Validity of diagnostic codes and laboratory measurements to identify patients with idiopathic acute liver injury in a hospital database.* Pharmacoepidemiol Drug Saf., 2016. **25**(Suppl 1): p. 21-8. doi: 10.1002/pds.3824. Epub 2015 Jul 5.

111. Wing, K., et al., *Optimising case detection within UK electronic health records: use of multiple linked databases for detecting liver injury.* BMJ Open., 2016. **6**(9): p. e012102. doi: 10.1136/bmjopen-2016-012102.

112. Ryan, P.B., et al., *Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D).* Diabetes Obes Metab., 2018. **20**(11): p. 2585-2597. doi: 10.1111/dom.13424. Epub 2018 Jun 25.

113. Voors, A.A., et al., *Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure.* Eur J Heart Fail., 2017. **19**(5): p. 627-634. doi: 10.1002/ejhf.785. Epub 2017 Mar 1.

114. Saver, B.G., et al., *No pain, but no gain? The disappearance of angina hospitalizations, 1992-1999.* Med Care., 2009. **47**(10): p. 1106-10. doi: 10.1097/MLR.0b013e31819e1f53.

115. Varas-Lorenzo, C., et al., *Positive predictive value of ICD-9 codes 410 and 411 in the identification of cases of acute coronary syndromes in the Saskatchewan Hospital automated database.* Pharmacoepidemiol Drug Saf., 2008. **17**(8): p. 842-52. doi: 10.1002/pds.1619.

116. Abbas, S., et al., *Risk of hyperkalemia and combined use of spironolactone and long-term ACE inhibitor/angiotensin receptor blocker therapy in heart failure using real-life data: a population- and insurance-based cohort.* Pharmacoepidemiol Drug Saf., 2015. **24**(4): p. 406-13. doi: 10.1002/pds.3748. Epub 2015 Feb 12.

117. Betts, K.A., et al., *The prevalence of hyperkalemia in the United States.* Curr Med Res Opin., 2018. **34**(6): p. 971-978. doi: 10.1080/03007995.2018.1433141. Epub 2018 Feb 21.

118. Fitch, K., et al., *The Clinical and Economic Burden of Hyperkalemia on Medicare and Commercial Payers.* Am Health Drug Benefits., 2017. **10**(4): p. 202-210.

119. Krogager, M.L., et al., *Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data.* Eur Heart J., 2017. **38**(2): p. 104-112. doi: 10.1093/eurheartj/ehw129.

120. Koulouridis, I., et al., *Out-of-hospital use of proton pump inhibitors and hypomagnesemia at hospital admission: a nested case-control study.* Am J Kidney Dis., 2013. **62**(4): p. 730-7. doi: 10.1053/j.ajkd.2013.02.373. Epub 2013 May 10.

121. Markovits, N., et al., *The association of proton pump inhibitors and hypomagnesemia in the community setting.* J Clin Pharmacol., 2014. **54**(8): p. 889-95. doi: 10.1002/jcph.316. Epub 2014 May 6.

122. Movig, K.L., et al., *Validity of hospital discharge International Classification of Diseases (ICD) codes for identifying patients with hyponatremia.* J Clin Epidemiol., 2003. **56**(6): p. 530-5.

123. Shea, A.M., et al., *Sensitivity of International Classification of Diseases codes for hyponatremia among commercially insured outpatients in the United States.* BMC Nephrol., 2008. **9:5.**(doi): p. 10.1186/1471-2369-9-5.

124. Chrischilles, E., et al., *Initiation of nonselective alpha1-antagonist therapy and occurrence of hypotension-related adverse events among men with benign prostatic hyperplasia: a retrospective cohort study.* Clin Ther., 2001. **23**(5): p. 727-43.

125. Bekelman, J.E., et al., *Outcomes after intensity-modulated versus conformal radiotherapy in older men with nonmetastatic prostate cancer.* Int J Radiat Oncol Biol Phys., 2011. **81**(4): p. e325-34. doi: 10.1016/j.ijrobp.2011.02.006. Epub 2011 Apr 16.

126. Frederick, L.R., et al., *Undertreatment of erectile dysfunction: claims analysis of 6.2 million patients.* J Sex Med., 2014. **11**(10): p. 2546-53. doi: 10.1111/jsm.12647. Epub 2014 Jul 24.

127. McVary, K., et al., *Identifying patients with benign prostatic hyperplasia through a diagnosis of, or treatment for, erectile dysfunction.* Curr Med Res Opin., 2008. **24**(3): p. 775-84. doi: 10.1185/030079908X260916. Epub 2008 Jan 30.

128. Mulhall, J.P., et al., *Relationship between age and erectile dysfunction diagnosis or treatment using real-world observational data in the USA.* Int J Clin Pract., 2016. **70**(12): p. 1012-1018. doi: 10.1111/ijcp.12908.

129. Yuan, Z., et al., *Risk Prediction for Ischemic Stroke and Transient Ischemic Attack in Patients Without Atrial Fibrillation: A Retrospective Cohort Study.* J Stroke Cerebrovasc Dis., 2017. **26**(8): p. 1721-1731. doi: 10.1016/j.jstrokecerebrovasdis.2017.03.036. Epub 2017 Apr 6.

130. Czwikla, J., K. Jobski, and T. Schink, *The impact of the lookback period and definition of confirmatory events on the identification of incident cancer cases in administrative data.* BMC Med Res Methodol., 2017. **17**(1): p. 122. doi: 10.1186/s12874-017-0407-4.

131. Abraha, I., et al., *Accuracy of administrative databases in detecting primary breast cancer diagnoses: a systematic review.* BMJ Open., 2018. **8**(7): p. e019264. doi: 10.1136/bmjopen-2017-019264.

132. Abraha, I., et al., *Sensitivity and specificity of breast cancer ICD-9-CM codes in three Italian administrative healthcare databases: a diagnostic accuracy study.* BMJ Open., 2018. **8**(7): p. e020627. doi: 10.1136/bmjopen-2017-020627.

133. Baldi, I., et al., *A high positive predictive value algorithm using hospital administrative data identified incident cancer cases.* J Clin Epidemiol., 2008. **61**(4): p. 373-9. doi: 10.1016/j.jclinepi.2007.05.017. Epub 2007 Oct 22.

134. Cea Soriano, L., M. Soriano-Gabarro, and L.A. Garcia Rodriguez, *Validity and completeness of colorectal cancer diagnoses in a primary care database in the United Kingdom.* Pharmacoepidemiol Drug Saf., 2016. **25**(4): p. 385-91. doi: 10.1002/pds.3877. Epub 2015 Oct 5.

135. Chawla, N., et al., *Limited validity of diagnosis codes in Medicare claims for identifying cancer metastases and inferring stage.* Ann Epidemiol, 2014. **2014 Sep;24**(9): p. 666-72.

136. Creighton, N., et al., *Validation of administrative hospital data for identifying incident pancreatic and periampullary cancer cases: a population-based study using linked cancer registry and administrative hospital data in New South Wales, Australia.* BMJ Open., 2016. **6**(7): p. e011161. doi: 10.1136/bmjopen-2016-011161.

137. Dregan, A., et al., *Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study.* Cancer Epidemiol., 2012. **36**(5): p. 425-9. doi: 10.1016/j.canep.2012.05.013. Epub 2012 Jun 21.

138. Goldsbury, D., et al., *Identifying incident colorectal and lung cancer cases in health service utilisation databases in Australia: a validation study.* BMC Med Inform Decis Mak., 2017. **17**(1): p. 23. doi: 10.1186/s12911-017-0417-5.

139. Gupta, S., et al., *Validity of Administrative Data in Identifying Cancer-related Events in Adolescents and Young Adults: A Population-based Study Using the IMPACT Cohort.* Med Care., 2018. **56**(6): p. e32-e38. doi: 10.1097/MLR.0000000000000777.

140. Hassett, M.J., et al., *Validating billing/encounter codes as indicators of lung, colorectal, breast, and prostate cancer recurrence using 2 large contemporary cohorts.* Med Care., 2014. **52**(10): p. e65-73. doi: 10.1097/MLR.0b013e318277eb6f.

141. Kim, S.C., et al., *Validation of claims-based algorithms for identification of high-grade cervical dysplasia and cervical cancer.* Pharmacoepidemiol Drug Saf., 2013. **22**(11): p. 1239-44. doi: 10.1002/pds.3520. Epub 2013 Sep 12.

142. Nordstrom, B.L., et al., *Identification of metastatic cancer in claims data.* Pharmacoepidemiol Drug Saf., 2012. **21**(Suppl 2): p. 21-8. doi: 10.1002/pds.3247.

143. Penberthy, L., et al., *Using hospital discharge files to enhance cancer surveillance.* Am J Epidemiol., 2003. **158**(1): p. 27-34.

144. Stavrou, E., N. Pesa, and S.A. Pearson, *Hospital discharge diagnostic and procedure codes for upper gastro-intestinal cancer: how accurate are they?* BMC Health Serv Res., 2012. **12:331.**(doi): p. 10.1186/1472-6963-12-331.

145. Goldberg, D.S., et al., *Validation of a coding algorithm to identify patients with hepatocellular carcinoma in an administrative database.* Pharmacoepidemiol Drug Saf., 2013. **22**(1): p. 103-7. doi: 10.1002/pds.3367. Epub 2012 Nov 4.

146. Donga, P.Z., et al., *Comparative treatment-related adverse event cost burden in immune thrombocytopenic purpura.* J Med Econ., 2017. **20**(11): p. 1200-1206. doi: 10.1080/13696998.2017.1370425. Epub 2017 Sep 8.

147. Marrett, E., et al., *Health Care Utilization and Costs Associated with Nausea and Vomiting in Patients Receiving Oral Immediate-Release Opioids for Outpatient Acute Pain Management.* Pain Ther., 2016. **5**(2): p. 215-226. doi: 10.1007/s40122-016-0057-y. Epub 2016 Oct 4.

148. Kim, S.Y., et al., *Accuracy of identifying neutropenia diagnoses in outpatient claims data.* Pharmacoepidemiol Drug Saf., 2011. **20**(7): p. 709-13. doi: 10.1002/pds.2157. Epub 2011 May 12.

149. Weycker, D., et al., *Technical evaluation of methods for identifying chemotherapy-induced febrile neutropenia in healthcare claims databases.* BMC Health Serv Res., 2013. **13:60.**(doi): p. 10.1186/1472-6963-13-60.

150. Schneider, G., et al., *A systematic review of validated methods for identifying hypersensitivity reactions other than anaphylaxis (fever, rash, and lymphadenopathy), using administrative and claims data.* Pharmacoepidemiol Drug Saf., 2012. **21**(Suppl 1): p. 248-55. doi: 10.1002/pds.2333.

151. Andrade, S.E., et al., *Health plan administrative databases can efficiently identify serious myopathy and rhabdomyolysis.* J Clin Epidemiol., 2005. **58**(2): p. 171-4. doi: 10.1016/j.jclinepi.2004.10.004.

152. Chan, S.L., et al., *Development and validation of algorithms for the detection of statin myopathy signals from electronic medical records.* Clin Pharmacol Ther., 2017. **101**(5): p. 667-674. doi: 10.1002/cpt.526. Epub 2017 Jan 21.

153. Wahl, P.M., et al., *Validation of claims-based diagnostic codes for idiopathic thrombotic thrombocytopenic purpura in a commercially-insured population.* Thromb Haemost., 2010. **103**(6): p. 1203-9. doi: 10.1160/TH09-08-0595. Epub 2010 Mar 29.

154. Moulis, G., et al., *Validation of immune thrombocytopenia diagnosis code in the French hospital electronic database.* Eur J Intern Med., 2016. **32:e21-2.**(doi): p. 10.1016/j.ejim.2016.02.021. Epub 2016 Mar 21.

155. Khokhar, B., et al., *Systematic review of validated case definitions for diabetes in ICD-9-coded and ICD-10-coded data in adult populations.* BMJ Open., 2016. **6**(8): p. e009952. doi: 10.1136/bmjopen-2015-009952.

156. Leong, A., et al., *Systematic review and meta-analysis of validation studies on a diabetes case definition from health administrative records.* PLoS One., 2013. **8**(10): p. e75256. doi: 10.1371/journal.pone.0075256. eCollection 2013.

157. Chen, G., et al., *Validating ICD coding algorithms for diabetes mellitus from administrative data.* Diabetes Res Clin Pract., 2010. **89**(2): p. 189-95. doi: 10.1016/j.diabres.2010.03.007. Epub 2010 Apr 2.

158. Thorpe, C.T., et al., *Healthcare utilization and expenditures for United States Medicare beneficiaries with systemic vasculitis.* Semin Arthritis Rheum., 2018. **47**(4): p. 507-519. doi: 10.1016/j.semarthrit.2017.08.005. Epub 2017 Aug 10.

159. England, B.R., et al., *Herpes Zoster as a Risk Factor for Incident Giant Cell Arteritis.* Arthritis Rheumatol., 2017. **69**(12): p. 2351-2358. doi: 10.1002/art.40236. Epub 2017 Nov 9.

160. Tamariz, L., T. Harkins, and V. Nair, *A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data.* Pharmacoepidemiol Drug Saf., 2012. **21**(Suppl 1): p. 154-62. doi: 10.1002/pds.2341.

161. Burwen, D.R., et al., *Venous thromboembolism incidence, recurrence, and mortality based on Women's Health Initiative data and Medicare claims.* Thromb Res., 2017. **150:78-85.**(doi): p. 10.1016/j.thromres.2016.11.015. Epub 2016 Nov 15.

162. Coleman, C.I., et al., *External validation of a multivariable claims-based rule for predicting in-hospital mortality and 30-day post-pulmonary embolism complications.* BMC Health Serv Res., 2016. **16**(1): p. 610. doi: 10.1186/s12913-016-1855-y.

163. Ammann, E.M., et al., *Chart validation of inpatient International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) administrative diagnosis codes for venous thromboembolism (VTE) among intravenous immune globulin (IGIV) users in the Sentinel Distributed Database.* Medicine (Baltimore). 2018. **97**(8): p. e9960. doi: 10.1097/MD.0000000000009960.

164. Koo, M., J.C. Chen, and J.H. Hwang, *Risk of Peripheral Artery Occlusive Disease in Patients with Vertigo, Tinnitus, or Sudden Deafness: A Secondary Case-Control Analysis of a Nationwide, Population-Based Health Claims Database.* PLoS One., 2016. **11**(9): p. e0162629. doi: 10.1371/journal.pone.0162629. eCollection 2016.

165. Voss, E.A., et al., *Accuracy of an automated knowledge base for identifying drug adverse reactions.* J Biomed Inform, 2017. **66**: p. 72-81.

166. Winnenburg, R., et al., *Leveraging MEDLINE indexing for pharmacovigilance - Inherent limitations and mitigation strategies.* J Biomed Inform, 2015. **57**: p. 425-35.

167. Duke, J., J. Friedlin, and X. Li, *Consistency in the safety labeling of bioequivalent medications.* Pharmacoepidemiol Drug Saf, 2013. **22**(3): p. 294-301.

168. Evans, S.J., P.C. Waller, and S. Davis, *Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports.* Pharmacoepidemiol Drug Saf, 2001. **10**(6): p. 483-6.

169. Banda, J.M., et al., *A curated and standardized adverse drug event resource to accelerate drug safety research.* Sci Data, 2016. **3**: p. 160026.

170. Schuemie, M.J., et al., *Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data.* Proc Natl Acad Sci U S A, 2018. **115**(11): p. 2571-2577.

171. Schuemie, M.J., et al., *Interpreting observational studies: why empirical calibration is needed to correct p-values.* Stat Med, 2014. **33**(2): p. 209-18.