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

**Version:** 0.1

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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

CI Confidence Interval

ECT Electroconvulsive therapy

MedDRA Medical Dictionary for Regulatory Activities

NDRI Norepinephrine-dopamine reuptake inhibitors

SARI Serotonin antagonist and reuptake inhibitor

SNRI Serotonin–norepinephrine reuptake inhibitor

SSRI Selective serotonin reuptake inhibitor

TCA Tricyclic antidepressant

# Abstract

In this study we will generate population-level estimates at scale for one disease: depression. We perform every possible pairwise comparison between depression 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 antidepressant treatment.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | 17 August 2018 | M.Schuemie | First draft |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

# Milestones

|  |  |
| --- | --- |
| Milestone | Planned / Estimated Date |
| Start of analysis | 1 September 2018 |
| End of analysis | 30 September 2018 |
| Presentation of results | 11 October 2018 |

# Rationale and Background

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

In this study we will generate population-level estimates at scale for one disease: depression. We perform every possible pairwise comparison between depression 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 antidepressant treatment.

# Research Questions and Objectives

## Research Questions

In this study, we are interested in every pairwise comparison between any two treatments in table 1. Treatments will be compared at the treatment level (e.g. comparing bupropion to mirtazapine), but also at the class level (e.g. SSRIs versus SNRIs).

|  |  |  |
| --- | --- | --- |
| **Type** | **Class** | **Treatment** |
| Drug | Norepinephrine-dopamine reuptake inhibitor (NDRI) | Bupropion |
| Drug | Tetracyclic antidepressant | Mirtazapine |
| Procedure | ECT | Electroconvulsive therapy |
| Procedure | Psychotherapy | Psychotherapy |
| Drug | Serotonin antagonist and reuptake inhibitor (SARI) | Trazodone |
| Drug | Serotonin-norepinephrine reuptake inhibitor (SNRI) | Desvenlafaxine |
| Drug | Serotonin-norepinephrine reuptake inhibitor (SNRI) | Duloxetine |
| Drug | Serotonin-norepinephrine reuptake inhibitor (SNRI) | Venlafaxine |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | Citalopram |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | Escitalopram |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | Fluoxetine |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | Paroxetine |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | Sertraline |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | vilazodone |
| Drug | Tricyclic antidepressant (TCA) | Amitriptyline |
| Drug | Tricyclic antidepressant (TCA) | Doxepin |
| Drug | Tricyclic antidepressant (TCA) | Nortriptyline |

**Table 1**. List of depression 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.

|  |  |
| --- | --- |
| Acute liver injury | Hypotension |
| Acute myocardial infarction | Hypothyroidism |
| Alopecia | Insomnia |
| Constipation | Nausea |
| Decreased libido | Open-angle glaucoma |
| Delirium | Seizure |
| Diarrhea | Stroke |
| Fracture | Suicide and suicidal ideation |
| Gastrointestinal hemorrhage | Tinnitus |
| Hyperprolactinemia | Ventricular arrhythmia and sudden cardiac death |
| Hyponatremia | Vertigo |

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

Primary research question

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

We further consider the six following subgroups of interest:

* Renal impairment
* Hepatic impairment
* Pregnant women
* Children (age < 18)
* Elderly (age >=65)
* Gender = female

Secondary research questions

* For each comparison between two depression treatments, for each of the outcomes of interest, how does the hazard ratio change within 6 subgroups of interest?
* What is the incidence rate of each outcome of interest in each exposure group?

## Objectives

Primary objective

* Generate evidence for the comparative effectiveness for each pairwise comparison of depression 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 tareget 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)
* <<add others who agree to participate>>

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

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

### Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)

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

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

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

### Optum ClinFormatics (Optum)

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

## 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 depression)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure to the two treatments in each pairwise comparison before the index date
* A diagnose of major depressive disorder on or preceding the index date
* No diagnosis of bipolar disorder or schizophrenia on or preceding the index date

No diagnose of the outcome of interest preceding the index date

### Subgroups

Interaction effects will be estimates with the following subgroups:

* Renal impairment
* Hepatic impairment
* Pregnant women
* Children (age < 18)
* Elderly (age >=65)
* Gender = female

To do: add definitions of subgroups

## 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 bupropion to mirtazapine), but also at the class level (e.g. SSRIs versus SNRIs).

|  |  |  |
| --- | --- | --- |
| **Type** | **Class** | **Treatment** |
| Drug | Norepinephrine-dopamine reuptake inhibitor (NDRI) | Bupropion |
| Drug | Tetracyclic antidepressant | Mirtazapine |
| Procedure | ECT | Electroconvulsive therapy |
| Procedure | Psychotherapy | Psychotherapy |
| Drug | Serotonin antagonist and reuptake inhibitor (SARI) | Trazodone |
| Drug | Serotonin-norepinephrine reuptake inhibitor (SNRI) | Desvenlafaxine |
| Drug | Serotonin-norepinephrine reuptake inhibitor (SNRI) | Duloxetine |
| Drug | Serotonin-norepinephrine reuptake inhibitor (SNRI) | Venlafaxine |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | Citalopram |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | Escitalopram |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | Fluoxetine |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | Paroxetine |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | Sertraline |
| Drug | Selective serotonin reuptake inhibitor (SSRI) | vilazodone |
| Drug | Tricyclic antidepressant (TCA) | Amitriptyline |
| Drug | Tricyclic antidepressant (TCA) | Doxepin |
| Drug | Tricyclic antidepressant (TCA) | Nortriptyline |

### All drugs

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient

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 or procedure before the index date
* A diagnose of major depressive disorder on or preceding the index date
* No diagnose of bipolar disorder or schizophrenia on or preceding the index date
* No diagnose of the outcome of interest preceding the index date

### Psychotherapy

Initial Event Cohort

People having any of the following:

* a procedure of Psychotherapy2

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Criteria #1: Prior major depressive disorder

People having all of the following criteria:

* at least 1 occurrences of a condition occurrence of Major depressive disorder1 starting between all days Before and 0 days After event index date

Inclusion Criteria #2: No prior bipolar disorder or schizophrenia

People having all of the following criteria:

* at most 0 occurrences of a condition occurrence of Schizophrenia and bipolar disorder3 starting between all days Before and 0 days After event index date

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

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

Appendix 1: Concept Set Definitions

1. Major depressive disorder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4152280 | Major depressive disorder | Condition | SNOMED | NO | YES | NO |

2. Psychotherapy

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4119335 | Analytical psychology | Procedure | SNOMED | NO | NO | NO |
| 4084202 | Anti-criminal psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4079608 | Anti-suicide psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4048385 | Brief group psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4295027 | Brief solution focused psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4299728 | Client-centered psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4164790 | Conjoint psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4208314 | Couple psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4083706 | Crisis intervention | Procedure | SNOMED | NO | NO | NO |
| 4083131 | Daily life psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4121662 | Developmental psychodynamic psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4226276 | Eclectic psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4258834 | Educational psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4148765 | Encounter group therapy | Procedure | SNOMED | NO | NO | NO |
| 2007747 | Exploratory verbal psychotherapy | Procedure | ICD9Proc | NO | NO | NO |
| 4137086 | Expressed emotion family therapy | Procedure | SNOMED | NO | NO | NO |
| 4048387 | Expressive psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4173581 | Extended family therapy | Procedure | SNOMED | NO | NO | NO |
| 46286403 | Family intervention for psychosis | Procedure | SNOMED | NO | NO | NO |
| 2213546 | Family psychotherapy (conjoint psychotherapy) (with patient present) | Procedure | CPT4 | NO | NO | NO |
| 4028920 | Family psychotherapy procedure | Procedure | SNOMED | NO | NO | NO |
| 46286330 | Focal psychodynamic therapy | Procedure | SNOMED | NO | NO | NO |
| 4226275 | Formal psychological therapy | Procedure | SNOMED | NO | NO | NO |
| 45765516 | Functional family therapy | Procedure | SNOMED | NO | NO | NO |
| 4079939 | Functional psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4079500 | General psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4117915 | Generic Jungian-based therapy | Procedure | SNOMED | NO | NO | NO |
| 4100341 | Group analytical psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 44808677 | Group cognitive behavioural therapy | Procedure | SNOMED | NO | NO | NO |
| 4136352 | Group marathon therapy | Procedure | SNOMED | NO | NO | NO |
| 4268909 | Group primal therapy | Procedure | SNOMED | NO | NO | NO |
| 4296166 | Group psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 2213548 | Group psychotherapy (other than of a multiple-family group) | Procedure | CPT4 | NO | NO | NO |
| 2617477 | Group psychotherapy other than of a multiple-family group, in a partial hospitalization setting, approximately 45 to 50 minutes | Observation | HCPCS | NO | NO | NO |
| 4196062 | Group reassurance | Procedure | SNOMED | NO | NO | NO |
| 2213554 | Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (eg, insight oriented, behavior modifying or supportive psychotherapy); 30 minutes | Procedure | CPT4 | NO | NO | NO |
| 2213555 | Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (eg, insight oriented, behavior modifying or supportive psychotherapy); 45 minutes | Procedure | CPT4 | NO | NO | NO |
| 2007730 | Individual psychotherapy | Procedure | ICD9Proc | NO | NO | NO |
| 4088889 | Individual psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4103512 | Interactive group medical psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 2617478 | Interactive group psychotherapy, in a partial hospitalization setting, approximately 45 to 50 minutes | Observation | HCPCS | NO | NO | NO |
| 4221997 | Interactive individual medical psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 40482841 | Interpersonal psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4119334 | Jungian-based therapy | Procedure | SNOMED | NO | NO | NO |
| 4118797 | Long-term exploratory psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4118798 | Long-term psychodynamic psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 44792695 | Marital psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 2213547 | Multiple-family group psychotherapy | Procedure | CPT4 | NO | NO | NO |
| 4118800 | Narrative family psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4242119 | Occupational social therapy | Observation | SNOMED | NO | NO | NO |
| 2007749 | Other individual psychotherapy | Procedure | ICD9Proc | NO | NO | NO |
| 2007750 | Other psychotherapy and counselling | Procedure | ICD9Proc | NO | NO | NO |
| 45887728 | Other Psychotherapy Procedures | Procedure | CPT4 | NO | NO | NO |
| 45763911 | Parent-infant psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 2007746 | Play psychotherapy | Procedure | ICD9Proc | NO | NO | NO |
| 4083133 | Potential suicide care | Procedure | SNOMED | NO | NO | NO |
| 4084195 | Provocative therapy | Procedure | SNOMED | NO | NO | NO |
| 2213544 | Psychoanalysis | Procedure | CPT4 | NO | NO | NO |
| 2007731 | Psychoanalysis | Procedure | ICD9Proc | NO | NO | NO |
| 4114491 | Psychoanalytic and psychodynamic therapy | Procedure | SNOMED | NO | NO | NO |
| 2007763 | Psychodrama | Procedure | ICD9Proc | NO | NO | NO |
| 4202234 | Psychodrama | Procedure | SNOMED | NO | NO | NO |
| 4199042 | Psychodynamic psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4128268 | Psychodynamic-interpersonal psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4118801 | Psychotherapeutic approaches using specific settings | Procedure | SNOMED | NO | NO | NO |
| 4327941 | Psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4083129 | Psychotherapy - behavioral | Procedure | SNOMED | NO | NO | NO |
| 4079938 | Psychotherapy - cognitive | Procedure | SNOMED | NO | NO | NO |
| 45889353 | Psychotherapy for crisis | Procedure | CPT4 | NO | NO | NO |
| 45888237 | Psychotherapy for Crisis Services and Procedures | Procedure | CPT4 | NO | NO | NO |
| 43527991 | Psychotherapy for crisis; each additional 30 minutes (List separately in addition to code for primary service) | Procedure | CPT4 | NO | NO | NO |
| 43527990 | Psychotherapy for crisis; first 60 minutes | Procedure | CPT4 | NO | NO | NO |
| 45887951 | Psychotherapy Services and Procedures | Procedure | CPT4 | NO | NO | NO |
| 2108571 | Psychotherapy services provided (MDD, MDD ADOL) | Observation | CPT4 | NO | NO | NO |
| 43527986 | Psychotherapy, 30 minutes with patient and/or family member | Procedure | CPT4 | NO | NO | NO |
| 43527987 | Psychotherapy, 30 minutes with patient and/or family member when performed with an evaluation and management service (List separately in addition to the code for primary procedure) | Procedure | CPT4 | NO | NO | NO |
| 43527904 | Psychotherapy, 45 minutes with patient and/or family member | Procedure | CPT4 | NO | NO | NO |
| 43527988 | Psychotherapy, 45 minutes with patient and/or family member when performed with an evaluation and management service (List separately in addition to the code for primary procedure) | Procedure | CPT4 | NO | NO | NO |
| 43527905 | Psychotherapy, 60 minutes with patient and/or family member | Procedure | CPT4 | NO | NO | NO |
| 43527989 | Psychotherapy, 60 minutes with patient and/or family member when performed with an evaluation and management service (List separately in addition to the code for primary procedure) | Procedure | CPT4 | NO | NO | NO |
| 4148398 | Psychotherapy/sociotherapy | Procedure | SNOMED | NO | NO | NO |
| 4083130 | Rehabilitation for disabling psychiatric problem | Procedure | SNOMED | NO | NO | NO |
| 44791916 | Relationship psychosexual therapy | Procedure | SNOMED | NO | NO | NO |
| 4265313 | Relationship psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4084201 | Samaritans advisory service | Procedure | SNOMED | NO | NO | NO |
| 4233181 | Sensate focus technique | Procedure | SNOMED | NO | NO | NO |
| 4272803 | Sexual psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4035812 | Sexual psychotherapy, female therapist - female patient | Procedure | SNOMED | NO | NO | NO |
| 4012488 | Sexual psychotherapy, female therapist - male patient | Procedure | SNOMED | NO | NO | NO |
| 4132436 | Sexual psychotherapy, group | Procedure | SNOMED | NO | NO | NO |
| 4143316 | Sexual psychotherapy, group, all female | Procedure | SNOMED | NO | NO | NO |
| 4219683 | Sexual psychotherapy, group, all male | Procedure | SNOMED | NO | NO | NO |
| 4151904 | Sexual psychotherapy, group, male and female | Procedure | SNOMED | NO | NO | NO |
| 4278094 | Sexual psychotherapy, male therapist - female patient | Procedure | SNOMED | NO | NO | NO |
| 4249602 | Sexual psychotherapy, male therapist - male patient | Procedure | SNOMED | NO | NO | NO |
| 4234476 | Sexual surrogate therapy | Procedure | SNOMED | NO | NO | NO |
| 4179241 | Short-term psychodynamic therapy | Procedure | SNOMED | NO | NO | NO |
| 4234402 | Social psychotherapy | Observation | SNOMED | NO | NO | NO |
| 4128406 | Specific task orientated psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4080044 | Stimulative psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4262582 | Structural family psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4263758 | Structural psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4126653 | Supportive expressive psychodynamic psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 2007748 | Supportive verbal psychotherapy | Procedure | ICD9Proc | NO | NO | NO |
| 4311943 | Supportive verbal psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4225728 | Suppressive psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4080048 | Therapeutic psychology | Procedure | SNOMED | NO | NO | NO |
| 44808259 | Therapeutic role play | Procedure | SNOMED | NO | NO | NO |

3. Schizophrenia and bipolar disorder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 436665 | Bipolar disorder | Condition | SNOMED | NO | YES | NO |
| 435783 | Schizophrenia | Condition | SNOMED | NO | YES | NO |

### Electroconvulsive therapy

Initial Event Cohort

People having any of the following:

* a procedure of Electroconvulsive therapy1

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Criteria #1: Prior major depressive disorder

People having all of the following criteria:

* at least 1 occurrences of a condition occurrence of Major depressive disorder2 starting between all days Before and 0 days After event index date

Inclusion Criteria #2: No prior bipolar disorder or schizophrenia

People having all of the following criteria:

* at most 0 occurrences of a condition occurrence of Schizophrenia and bipolar disorderstarting between all days Before and 0 days After event index date

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

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

Appendix 1: Concept Set Definitions

1. Electroconvulsive therapy

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4111663 | Bilateral electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |
| 4030840 | Electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |
| 2108578 | Electroconvulsive therapy (ECT) provided (MDD) | Observation | CPT4 | NO | NO | NO |
| 2213552 | Electroconvulsive therapy (includes necessary monitoring) | Procedure | CPT4 | NO | NO | NO |
| 4020981 | Electronarcosis | Procedure | SNOMED | NO | NO | NO |
| 4210144 | First treatment in a course of electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |
| 4336318 | Multiple electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |
| 4332436 | Multiple monitored electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |
| 2007728 | Other electroshock therapy | Procedure | ICD9Proc | NO | NO | NO |
| 44508134 | Other specified electroconvulsive therapy | Procedure | OPCS4 | NO | NO | NO |
| 2108579 | Patient referral for electroconvulsive therapy (ECT) documented (MDD) | Observation | CPT4 | NO | NO | NO |
| 2007727 | Subconvulsive electroshock therapy | Procedure | ICD9Proc | NO | NO | NO |
| 4004830 | Subconvulsive electroshock therapy | Procedure | SNOMED | NO | NO | NO |
| 4210145 | Subsequent treatment in a course of electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |

2. Major depressive disorder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4152280 | Major depressive disorder | Condition | SNOMED | NO | YES | NO |

3. Schizophrenia and bipolar disorder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 436665 | Bipolar disorder | Condition | SNOMED | NO | YES | NO |
| 435783 | Schizophrenia | Condition | SNOMED | NO | YES | NO |

## Outcomes

### Acute liver injury

Note: This algorithm uses the set of codes identified by Udo et al. [[2](#_ENREF_2)]

Initial Event Cohort

People having any of the following:

* a condition occurrence of acute liver injury1
  + for the first time in the person's history
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

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:

* exactly 0 occurrences of a condition occurrence of acute liver injury exclusion concepts2

starting between 365 days Before and 60 days After event index date

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

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

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

Appendix 1: Concept Set Definitions

1. acute liver injury

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 200763 | Chronic hepatitis | Condition | SNOMED | YES | YES | NO |
| 377604 | Hepatic coma | Condition | SNOMED | NO | YES | NO |
| 196029 | Hepatic coma due to viral hepatitis | Condition | SNOMED | YES | YES | NO |
| 4337543 | Hepatic necrosis | Condition | SNOMED | NO | YES | NO |
| 194087 | Hepatitis due to infection | Condition | SNOMED | YES | YES | NO |
| 196455 | Hepatorenal syndrome | Condition | SNOMED | NO | YES | NO |
| 194990 | Inflammatory disease of liver | Condition | SNOMED | NO | YES | NO |
| 4291005 | Viral hepatitis | Condition | SNOMED | YES | YES | NO |

2. acute liver injury exclusion concepts

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 192956 | Cholecystitis | Condition | SNOMED | NO | YES | NO |
| 200763 | Chronic hepatitis | Condition | SNOMED | NO | YES | NO |
| 4212540 | Chronic liver disease | Condition | SNOMED | NO | YES | NO |
| 197917 | Disorder of biliary tract | Condition | SNOMED | NO | YES | NO |
| 192353 | Disorder of gallbladder | Condition | SNOMED | NO | YES | NO |
| 192963 | Disorder of pancreas | Condition | SNOMED | NO | YES | NO |
| 196456 | Gallstone | Condition | SNOMED | NO | YES | NO |
| 4130518 | Neoplasm of liver | Condition | SNOMED | NO | YES | NO |
| 4291005 | Viral hepatitis | Condition | SNOMED | NO | YES | NO |

### Acute myocardial infarction

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Acute MI1
  + for the first time in the person's history
  + condition type is any of: Inpatient detail - primary, Inpatient header - primary, Primary Condition, Inpatient detail - 1st position, Inpatient header - 1st position
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

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.**

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

Appendix 1: Concept Set Definitions

1. Acute MI

| **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 |

### Alopecia

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Alopecia1
  + 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.**

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

Appendix 1: Concept Set Definitions

1. Alopecia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 133280 | Alopecia | Condition | SNOMED | NO | YES | NO |
| 133959 | Syphilitic alopecia | Condition | SNOMED | YES | YES | NO |

### Constipation

Note: This algorithm requires the occurrence of 2 or more diagnoses, as recommended by Mody et al. [[3](#_ENREF_3)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Constipation1
  + 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.**

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

Appendix 1: Concept Set Definitions

1. Constipation

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 75860 | Constipation | Condition | SNOMED | NO | YES | NO |

### 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.**

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

Appendix 1: Concept Set Definitions

1. Decreased libido

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 436246 | Reduced libido | Condition | SNOMED | NO | YES | NO |

### Delirium

Note: This algorithm relies on diagnosis codes associated with hospitalization. This approach may lead to underreporting, as described by McCoy et al. [[4](#_ENREF_4)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Delirium1
  + for the first time in the person's history
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

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.**

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

Appendix 1: Concept Set Definitions

1. Delirium

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 377830 | Alcohol withdrawal delirium | Condition | SNOMED | YES | YES | NO |
| 373995 | Delirium | Condition | SNOMED | NO | YES | NO |

### Diarrhea

Note: This algorithm follows Broder et al. [[5](#_ENREF_5)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Diarrhea1
  + 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.**

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

Appendix 1: Concept Set Definitions

1. Diarrhea

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 196523 | Diarrhea | Condition | SNOMED | NO | YES | NO |
| 80141 | Functional diarrhea | Condition | SNOMED | NO | YES | NO |

### Fracture

Note: This algorithm follows Lanteigne et al. [[6](#_ENREF_6)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Fracture1
  + 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.**

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

Appendix 1: Concept Set Definitions

1. Fracture

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 435093 | Closed fracture of femur | Condition | SNOMED | NO | YES | NO |
| 441974 | Closed fracture of forearm | Condition | SNOMED | NO | YES | NO |
| 4230399 | Closed fracture of hip | Condition | SNOMED | NO | YES | NO |
| 441422 | Closed fracture of humerus | Condition | SNOMED | NO | YES | NO |
| 439166 | Closed fracture of radius | Condition | SNOMED | NO | YES | NO |
| 4278672 | Fracture of forearm | Condition | SNOMED | NO | YES | NO |
| 442619 | Fracture of humerus | Condition | SNOMED | NO | YES | NO |
| 433856 | Fracture of neck of femur | Condition | SNOMED | NO | YES | NO |
| 4131595 | Fracture of radius | Condition | SNOMED | NO | YES | NO |
| 73571 | Pathological fracture | Condition | SNOMED | NO | YES | NO |

### Gastrointestinal hemhorrage

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Gastrointestinal hemorrhage1
  + for the first time in the person's history
  + condition type is any of: Inpatient detail - primary, Inpatient header - primary, Primary Condition, Inpatient detail - 1st position, Inpatient header - 1st position
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

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.**

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

Appendix 1: Concept Set Definitions

1. Gastrointestinal hemorrhage

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4280942 | Acute gastrojejunal ulcer with perforation | Condition | SNOMED | NO | YES | NO |
| 28779 | Bleeding esophageal varices | Condition | SNOMED | NO | YES | NO |
| 198798 | Dieulafoy's vascular malformation | Condition | SNOMED | NO | YES | NO |
| 4112183 | Esophageal varices with bleeding, associated with another disorder | Condition | SNOMED | NO | YES | NO |
| 194382 | External hemorrhoids | Condition | SNOMED | NO | NO | NO |
| 192671 | Gastrointestinal hemorrhage | Condition | SNOMED | NO | YES | NO |
| 196436 | Internal hemorrhoids | Condition | SNOMED | NO | NO | NO |
| 4338225 | Peptic ulcer with perforation | Condition | SNOMED | NO | YES | NO |
| 194158 | Perinatal gastrointestinal hemorrhage | Condition | SNOMED | YES | YES | NO |

### Hyperprolactinemia

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hyperprolactinemia1
  + 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.**

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

Appendix 1: Concept Set Definitions

1. Hyperprolactinemia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4030186 | Hyperprolactinemia | Condition | SNOMED | NO | YES | NO |

### Hyponatremia

Note: The algorithm here relies on the recording of diagnoses codes, and might not have high sensitivity as remarked by Shea et al.

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hyponatremia1
  + for the first time in the person's history
* a measurement of Serum sodium2
  + for the first time in the person's history
  + with value as number < 136
  + 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: **earliest event per person.**

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

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

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 |

2. Serum sodium

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3032987 | Sodium [Moles/volume] corrected for glucose in Serum or Plasma | Measurement | LOINC | NO | YES | NO |
| 46235784 | Sodium [Moles/volume] in Serum, Plasma or Blood | Measurement | LOINC | NO | YES | NO |
| 3019550 | Sodium serum/plasma | Measurement | LOINC | NO | YES | NO |

### Hypotension

Note: This algorithm follows Wernli et al. [[7](#_ENREF_7)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hypotension1
  + 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.**

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

Appendix 1: Concept Set Definitions

1. Hypotension

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4120275 | Drug-induced hypotension | Condition | SNOMED | NO | YES | NO |
| 317002 | Low blood pressure | Condition | SNOMED | NO | YES | NO |
| 314432 | Maternal hypotension syndrome | Condition | SNOMED | YES | YES | NO |
| 319041 | Orthostatic hypotension | Condition | SNOMED | NO | YES | NO |

### Hypothyroidism

Note: This algorithm requires the occurrences of 2 more diagnose codes, as recommended by Lu et al. [[8](#_ENREF_8)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hypothyroidism1

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 2 occurrences of a condition occurrence of Hypothyroidism1

starting between 0 days Before and 90 days After event index date

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

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

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

Appendix 1: Concept Set Definitions

1. Hypothyroidism

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 140673 | Hypothyroidism | Condition | SNOMED | NO | YES | NO |

### Insomnia

Initial Event Cohort

People having any of the following:

* a condition occurrence of Insomnia1
  + 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.**

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

Appendix 1: Concept Set Definitions

1. Insomnia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 439708 | Disorders of initiating and maintaining sleep | Condition | SNOMED | NO | YES | NO |
| 436962 | Insomnia | Condition | SNOMED | NO | YES | NO |
| 4305303 | Sleep deprivation | Condition | SNOMED | NO | YES | NO |

### Nausea

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Nausea1
  + 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.**

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

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 |

### Open-angle glaucoma

Note: This algorithm follows Stein et al. [[9](#_ENREF_9)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Open-angle glaucoma1
  + for the first time in the person's history

with continuous observation of at least 365 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 Open-angle glaucoma1
  + provider specialty is any of: Ophthalmology, Optometry, Optician

starting between 1 days After and 365 days After event index date

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

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

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

Appendix 1: Concept Set Definitions

1. Open-angle glaucoma

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 432908 | Glaucomatocyclitic crisis | Condition | SNOMED | YES | YES | NO |
| 441561 | Low tension glaucoma | Condition | SNOMED | NO | YES | NO |
| 4216823 | Open angle with borderline findings | Condition | SNOMED | YES | YES | NO |
| 441284 | Open-angle glaucoma | Condition | SNOMED | NO | YES | NO |
| 4072218 | Secondary open-angle glaucoma | Condition | SNOMED | YES | YES | NO |

### Seizure

Note: This algorithm requires either inpatient or emergency room visits as recommended by Wu et al. [[10](#_ENREF_10)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Seizure and seizure disorder1
  + for the first time in the person's history
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

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.**

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

Appendix 1: Concept Set Definitions

1. Seizure and seizure disorder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 380533 | Convulsions in the newborn | Condition | SNOMED | YES | YES | NO |
| 45757050 | Epilepsy in mother complicating pregnancy | Condition | SNOMED | YES | YES | NO |
| 377091 | Seizure | Condition | SNOMED | NO | YES | NO |
| 4029498 | Seizure disorder | Condition | SNOMED | NO | YES | NO |

### Stroke

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Ischemic stroke1
  + for the first time in the person's history
  + visit occurrence is any of: Inpatient Visit

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.**

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

Appendix 1: Concept Set Definitions

1. Ischemic stroke

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 374060 | Acute ill-defined cerebrovascular disease | Condition | SNOMED | NO | YES | NO |
| 4108356 | Cerebral infarction due to embolism of cerebral arteries | Condition | SNOMED | NO | YES | NO |
| 4110192 | Cerebral infarction due to thrombosis of cerebral arteries | Condition | SNOMED | NO | YES | NO |
| 4043731 | Infarction - precerebral | Condition | SNOMED | NO | YES | NO |

### Suicide and suicidal ideation

Note: This algorithm is based on the review by Callagan et al. [[11](#_ENREF_11)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Suicide and suicidal ideation1
  + for the first time in the person's history
* an observation of Suicide and suicidal ideation1
  + 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.**

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

Appendix 1: Concept Set Definitions

1. Suicide and suicidal ideation

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 439235 | Self inflicted injury | Condition | SNOMED | NO | YES | NO |
| 4181216 | Self-administered poisoning | Condition | SNOMED | NO | YES | NO |
| 444362 | Suicidal deliberate poisoning | Condition | SNOMED | NO | YES | NO |
| 4273391 | Suicidal thoughts | Condition | SNOMED | NO | YES | NO |
| 440925 | Suicide | Observation | SNOMED | NO | YES | NO |

### Tinnitus

Note: This algorithm follows Lee et al. [[12](#_ENREF_12)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Tinnitus1
  + 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.**

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

Appendix 1: Concept Set Definitions

1. Tinnitus

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 377575 | Tinnitus | Condition | SNOMED | NO | YES | NO |

### Ventricular arrhythmia and sudden cardiac death

Note: This algorithm follows the definition used by Leonard et al. [[13](#_ENREF_13)]

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Ventricular arrhythmia and sudden cardiac death1
  + for the first time in the person's history
  + condition type is any of: Inpatient detail - primary, Inpatient header - primary, Primary Condition, Carrier claim detail - 1st position, Carrier claim header - 1st position, Inpatient detail - 1st position, Inpatient header - 1st position, Outpatient detail - 1st position, Outpatient header - 1st position
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

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.**

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

Appendix 1: Concept Set Definitions

1. Ventricular arrhythmia and sudden cardiac death

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 321042 | Cardiac arrest | Condition | SNOMED | NO | YES | NO |
| 442289 | Death in less than 24 hours from onset of symptoms | Observation | SNOMED | NO | YES | NO |
| 441139 | Instantaneous death | Observation | SNOMED | NO | YES | NO |
| 4132309 | Sudden death | Observation | SNOMED | NO | YES | NO |
| 4185572 | Ventricular arrhythmia | Condition | SNOMED | NO | YES | NO |
| 437894 | Ventricular fibrillation | Condition | SNOMED | NO | YES | NO |
| 4103295 | Ventricular tachycardia | Condition | SNOMED | NO | YES | NO |

### 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.**

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

Appendix 1: Concept Set Definitions

1. Vertigo

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 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 |

### 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. [[14](#_ENREF_14)]. 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 [[15](#_ENREF_15)], (2) that there is no mention of the drug-condition pair on a US Product Label in the “Adverse Drug Reactions” or “Postmarketing” section [[16](#_ENREF_16)], (3) there are no US spontaneous reports suggesting that the pair is in an adverse event relationship [[17](#_ENREF_17), [18](#_ENREF_18)], (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 x.

|  |  |
| --- | --- |
| Acariasis | Ingrowing nail |
| Amyloidosis | Iridocyclitis |
| Ankylosing spondylitis | Irritable bowel syndrome |
| Aseptic necrosis of bone | Lesion of cervix |
| Astigmatism | Lyme disease |
| Bell's palsy | Malignant neoplasm of endocrine gland |
| Benign epithelial neoplasm of skin | Mononeuropathy |
| Chalazion | Onychomycosis |
| Chondromalacia | Osteochondropathy |
| Crohn's disease | Paraplegia |
| Croup | Polyp of intestine |
| Diabetic oculopathy | Presbyopia |
| Endocarditis | Pulmonary tuberculosis |
| Endometrial hyperplasia | Rectal mass |
| Enthesopathy | Sarcoidosis |
| Epicondylitis | Scar |
| Epstein-Barr virus disease | Seborrheic keratosis |
| Fracture of upper limb | Septic shock |
| Gallstone | Sjogren's syndrome |
| Genital herpes simplex | Tietze's disease |
| Hemangioma | Tonsillitis |
| Hodgkin's disease | Toxic goiter |
| Human papilloma virus infection | Ulcerative colitis |
| Hypoglycemic coma | Viral conjunctivitis |
| Hypopituitarism | Viral hepatitis |
| Impetigo | Visceroptosis |

**Table x**. 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 [[19](#_ENREF_19)]. 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 [[19](#_ENREF_19)].

## Covariates

### Propensity score covariates

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

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

* Demographics
  + Gender
  + Age group (5-year bands)
  + Index year
  + Index month
* Conditions
  + In prior 30d
  + In prior 365d
* Condition aggregation
  + SNOMED
* Drugs
  + In prior 30d
  + In prior 365d
  + Overlapping index date
* Drug aggregation
  + Ingredient
  + ATC Class
* Risk scores
  + Charlson comorbidity index
* Prior number of depression treatments (1,2,3,4, 5 or more)

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, and 3) the end of the observation period that spans the time-at-risk start.

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

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

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

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

### Pooling effect estimates across databases

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

## Analyses to perform

### Comparative analyses

The following comparative analyses will be performed:

* 328 comparisons: 17 \* 16 = 272 comparisons between individual treatments, and 8 \* 7 = 56 comparisons between classes of treatments
* 22 outcomes of interest
* 2 time-at-risk definitions: on-treatment and intent-to-treat
* 2 models: Cox regression using propensity score stratification and Cox regression using propensity score matching
* 4 databases: CCAE, MDCD, MDCR, Optum

The total number of analyses for outcomes of interest is therefore 328 \* 22 \* 2 \* 2 \* 4 = 115,456 analyses.

We will also include 56 negative control outcomes, and 3 \* 56 positive control outcomes, so 224 control outcomes. The total number of control analyses is therefore 328 \* 224 \* 2 \* 2 \* 4 = 1,175,552 analyses.

Additionally, interaction effects will be computed with the 6 subgroups of interest. For efficiency reasons, this will only be computed when using propensity score stratification.

The number of analysis of subgroup interactions is therefore 328 \* 22 \* 2 \* 1 \* 4 \* 6 = 346,368 analyses.

For interaction effects, only negative control outcomes will be added. The total number of control analyses for interaction terms is therefore 328 \* 56 \* 2 \* 1 \* 4 \* 6 = 881,664 analyses.

### Descriptive analyses

The following incidence rate computations will be performed:

* 25 groups of interest: new users of the 17 individual treatments, and new users of the 17 treatment classes
* 22 outcomes of interest
* 2 time-at-risk definitions: on-treatment and intent-to-treat
* 4 databases: CCAE, MDCD, MDCR, Optum

The total number of analyses for outcomes of interest is therefore 25 \* 22 \* 2 \* 4 = 4,400 analyses

## Output

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

## Evidence Evaluation

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

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

Negative control outcomes in the context of this study are outcomes that are not believed to be caused by neither exposure in any comparison and where therefore the true hazard ratio is equal to 1. We will execute the same analysis used for the primary hypotheses to produce hazard ratio estimates for the negative controls. The distribution of effect estimates across all negative controls will be used to fit an empirical null distribution which models the observed residual systematic error. The empirical null distribution will then be applied to the target exposures and outcome of interest to calibrate the p-value [[20](#_ENREF_20)].

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 [[19](#_ENREF_19)].

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

## Cohort Comparability

## Systematic Error Assessment

# 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. 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.

3. Mody, R., et al., *Prevalence and risk of developing comorbid conditions in patients with chronic constipation.* Curr Med Res Opin, 2014. **30**(12): p. 2505-13.

4. McCoy, T.H., Jr., et al., *Underreporting of Delirium in Statewide Claims Data: Implications for Clinical Care and Predictive Modeling.* Psychosomatics, 2016. **57**(5): p. 480-8.

5. Broder, M.S., et al., *Healthcare and economic impact of diarrhea in patients with carcinoid syndrome.* World J Gastroenterol, 2016. **22**(6): p. 2118-25.

6. Lanteigne, A., et al., *Serotonin-norepinephrine reuptake inhibitor and selective serotonin reuptake inhibitor use and risk of fractures: a new-user cohort study among US adults aged 50 years and older.* CNS Drugs, 2015. **29**(3): p. 245-52.

7. Wernli, K.J., et al., *Risks Associated With Anesthesia Services During Colonoscopy.* Gastroenterology, 2016. **150**(4): p. 888-94; quiz e18.

8. Lu, M.C., et al., *Higher Risk of Thyroid Disorders in Young Patients with Type 1 Diabetes: A 12-Year Nationwide, Population-Based, Retrospective Cohort Study.* PLoS One, 2016. **11**(3): p. e0152168.

9. Stein, J.D., T.S. Blachley, and D.C. Musch, *Identification of persons with incident ocular diseases using health care claims databases.* Am J Ophthalmol, 2013. **156**(6): p. 1169-1175 e3.

10. Wu, C.S., et al., *Comparative risk of seizure with use of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders.* J Clin Psychiatry, 2016. **77**(5): p. e573-9.

11. Callahan, S.T., et al., *Identifying suicidal behavior among adolescents using administrative claims data.* Pharmacoepidemiol Drug Saf, 2013. **22**(7): p. 769-75.

12. Lee, C.F., et al., *Increased risk of tinnitus in patients with temporomandibular disorder: a retrospective population-based cohort study.* Eur Arch Otorhinolaryngol, 2016. **273**(1): p. 203-8.

13. Leonard, C.E., et al., *Antidepressants and the risk of sudden cardiac death and ventricular arrhythmia.* Pharmacoepidemiol Drug Saf, 2011. **20**(9): p. 903-13.

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

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

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

17. 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.

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

19. 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.

20. 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.