OHDSI Confidence Interval Calibration Evaluation study protocol

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

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# List of abbreviations

CDM Common Data Model

CYCLOPS Cyclic coordinate descent for logistic, Poisson and survival analysis

GI Gastro-Intestinal

NSAID Non-Steroidal Anti-Inflammatory Drug

OHDSI Observational Health Data Sciences and Informatics

OMOP Observational Medical Outcomes Partnership

PS Propensity Scores

SCCS Self-Controlled Case Series

TCA TriCyclic Antidepressants

# Abstract

Observational studies are prone to bias, but unfortunately this bias is often brushed aside with a single comment in the discussion of a paper and is never quantified. In the past we have proposed using negative controls (exposure-outcome pairs where the true relative risk is believed to be one) to produce an empirical bias distribution, and subsequently calibrate p-values. Here we propose to extend this approach to calibrated confidence intervals, which requires the use of positive controls. Since real positive controls are problematic, we will generate artificial positive controls by injection additional (simulated) outcomes on top of negative controls. To demonstrate and evaluate confidence interval calibration, we will reproduce two pairs of observational studies that have produced conflicting results. We will try to demonstrate that our calibration procedure has good internal validity by showing coverage of the confidence interval improves as measured using our negative and positive controls. We will try to show external validity by showing that after calibration our conflicting studies are no longer in disagreement.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Date | Author(s) | Comments |
|  |  |  |  |
| 0.3 | 16 Dec 2016 | Martijn Schuemie | Added requirement that in SCCS replication the 30 days prior to exposure are excluded from analysis. |
| 0.2 | 13 Dec 2016 | Martijn Schuemie | Added sample size information. Generated new set of negative controls for Southworth and Graham replications, this time without concept set optimation. |
| 0.1 | 28 Nov 2016 | Martijn Schuemie | Initial draft |

# Milestones

|  |  |
| --- | --- |
| Milestone | Planned / Estimated Date |
| Start of analysis |  |
| End of analysis |  |
| Posting of results |  |
| Submission of manuscript |  |

# Rationale and Background

Observational studies are prone to bias, but unfortunately this bias is often brushed aside with a single comment in the discussion of a paper and is never quantified. In the past [[1](#_ENREF_1)], we have proposed to measure the magnitude for potential bias in a study design by using a set of negative controls. Negative controls are research hypotheses (typically drug-outcome pairs) where the true effect is believed to be null, in other words where the true relative risk is believed to be equal to one. Observing the effect size estimates that a method produces for these negative controls allowed us to estimate a bias distribution. One use of such a distribution is to compute a calibrated p-value, which takes this bias into account and restored nominal characteristics, for example having only approximately 5% of negative controls have a calibrated p-value < 0.05.

One limitation of this previous approach is that it only considered situations where the null hypothesis of no effect is true. There is no clear information on the behavior of a method when the true relative risk is smaller or greater than one. This would require the use of positive controls, where the null is believed to not be true. Unfortunately, real positive controls for observational research tend to be problematic for three reasons: First, in most research contexts, for example when comparing the effect of two treatments, there often is a paucity of positive controls relevant for that specific context. Second, even if positive controls are available, the magnitude of the effect size may not be known with great accuracy, and often depends on the population in which it is measured. Third, when treatments are widely known to cause a particular outcome, this will shape the behavior of physicians prescribing the treatment, for example by taking actions to mitigate the risk of unwanted outcomes, thereby rendering the positive controls useless as a means for evaluation [[2](#_ENREF_2)]. We therefore use artificial positive controls, created by modifying a negative control through injection of additional, simulated occurrences of the outcome.

Using these positive controls, we can then proceed to estimate a bias distribution that is conditional on the true effect size. With this model we can not only compute calibrated p-values, but also calibrated confidence intervals. The purpose of the research described here is to evaluate the construction of calibrated confidence intervals. Apart from show internal validity, by showing that after calibration the confidence interval has nominal characteristics for our negative and positive controls, we would also like to show external validity; We will reproduce two pairs of conflicting observational studies we found in literature, and our hypothesis is that by calibrating confidence intervals we will be able to resolve the conflicts, which we assume are caused by different biases in the different studies, at least partially. The two pairs of studies we selected are:

1. Dabigatran versus warfarin for GI bleeding, as performed by Southworth et al. [[3](#_ENREF_3)], compared to Graham et al. [[4](#_ENREF_4)] Both studies used a new-user cohort design, but only Graham used propensity scores to adjust for potential confounding. The incidence rate ratio implied by Southworth was 1.6/3.5 = 0.46. The hazard ratio (and 95% confidence interval) reported by Graham was 1.28 (1.14-1.44).
2. SSRIs and upper GI bleeding, both studies performed by Tata et al. [[5](#_ENREF_5)] The first study used a case-control design, the second a self-controlled case series (SCCS) design. The case-control analysis produced an odds ratio (and 95% confidence interval) of 2.38 (2.08-2.72). The SCCS produced an incidence rate ratio (and 95% confidence interval) of 1.71 (1.48-1.98).

# Research Questions and Objectives

## Research Questions

Primary research questions

1. Does calibration of confidence intervals lead to improved coverage of the confidence intervals?
2. Does calibration of confidence intervals reduce heterogeneity between study results?

## Objectives

Primary objective

* Show that confidence interval calibration improves coverage.
* Show that confidence interval calibration reduces heterogeneity between study results.

# Research methods

## Study Design

### Overview

For this study we will replicate the four aforementioned studies as best we can, and perform confidence intervals calibration.

**Southworth replication**

The Southworth study is a new-user cohort design, where new-users of dabigatran are compared to new-users of warfarin for the outcome of GI hemorrhage. Subject are required to have 183 days of continuous observation prior to initiating treatment, a prior diagnose of atrial fibrillation, and are required to have no prior exposure to either dabigatran or warfarin. An incidence rate ratio will be computed without any adjustment for confounders. Time at risk is defined as the time on the drug.

**Graham replication**

The Graham study is also a new-user cohort design, where new-users of dabigtran are compared to new-users of warfarin for the outcome of GI hemorrhage. Subject are required to have 183 days of continuous observation prior to initiating treatment, be at least 65 years old at index date, and are required to have no prior exposure to warfarin or dabigatran (or any other novel anticoagulant). Furthermore, subjects are required to use the treatment for the indication of atrial fibrilation or atrial flutter, which is enforced by requiring a prior diagnose of atrial fibrilation or flutter, and no prior diagnose of other indications. Propensity scores are generated by fitting a model for predicting treatment assignment based on baseline patient characteristics. The propensity scores are used to perform one-on-one matching. A hazard ratio will be computed through a Cox regression on the matched population. Time-at-risk is defined as starting on the day after initiating treatment, and stopping when treatment is stopped, when the outcome occurs, or observation time ends, whichever comes first.

**Tata case-control replication**

Cases of upper GI bleeding are matched to up to six controls on age, gender, and general practice. Only cases and controls age 18 or older are included. Using conditional logistic regression the odds ratio will be estimated for the first upper GI bleed associated with exposure to any SSRI in the 30 days preceding the index date.

**Tata SCCS replication**

A conditional Poisson regression will be used to estimate relative incidence of upper GI bleeding when compared to within-person control periods. Time at risk is defined as the time when exposed to any SSRI. Also included in the model will be age using a spline model, and exposures to NSAIDs and TCAs. Patient time is restricted to time when the patient was at least 18 years old. To account for possible contraindication of antidepressants shortly following a gastrointestinal bleed, the 30 days prior to SSRI exposure were excluded from the analysis.

Two sets of negative control outcomes will be defined. The first set is negative controls that are not believed to be caused by either dabigatran or warfarin. The second set is negative controls that are not believed to be caused by any SSRI. For both sets we will generate positive controls by injecting additional outcomes during exposure to dabigatran and SSRIs, respectively. Outcomes will be injected by drawing from a probability computed through a predictive model for the outcome. The true relative risks will be 1.5, 2, and 4.

For evaluating internal validity, we will compute the coverage of the confidence intervals at the various true effect sizes for all alpha values. To avoid over-optimistic results due to overfitting we will use leave-one cross-validation, where the calibration model is fitted using all but 1 control, and we evaluate the coverage on the left out control.

For evaluating external validity, we will observe the extent to which 95% confidence intervals overlap before and after calibration.

### Study population

**Southworth replication**

The population includes new users of warfarin and dabigatran within the period from 19 October 2010 to 31 December 2011.

**Graham replication**

The population includes new users of warfarin and dabigatran who are 65 years or older at initation of treatment, in the period starting from 19 October 2010 onwards.

**Tata case-control replication**

The population includes cases of upper GI bleeding and matched controls who are 18 years or older at the index date, in the period from 1 January 1990 to 1 November 2003.

**Tata SCCS replication**

The population includes cases of upper GI bleeding, considering all available observation time when the patient was 18 years or older.

### Additional analysis details

The propensity model used in the Graham replication will be fitted using a regularized logistic regression with a LaPlace prior. The regularization hyperparameter will be selected by optimizing the likelihood in a 10-fold cross-validation.

When performing matching on the propensity score, a caliper of 0.25 times the standard deviation of the propensity score distribution will be used.

## Variables

### Exposures

**Dabigatran new users (Southworth replication)**

Initial Event Cohort

People having any of the following:

* a drug era of dabigatran4
  + for the first time in the person's history
  + era start is between 2010-10-19 and 2011-12-31 (inclusive)

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Criteria #1: Has prior atrial fibrillation diagnosis

People having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Atrial fibrillation2 starting between all days Before and 0 days After event index date

Inclusion Criteria #2: Has no prior treatment with comparator drug (warfarin)

People having all of the following criteria:

* exactly 0 occurrences of a drug exposure of warfarin13 starting between all days Before and 0 days Before 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.

2. Atrial fibrillation

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 313217 | Atrial fibrillation | Condition | SNOMED | NO | YES | NO |

4. dabigatran

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40228152 | dabigatran etexilate | Drug | RxNorm | NO | YES | NO |

13. warfarin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 1310149 | Warfarin | Drug | RxNorm | NO | YES | NO |

**Warfarin new users (Southworth replication)**

Initial Event Cohort

People having any of the following: 

* a drug era of warfarin13
  + for the first time in the person's history
  + era start is between 2010-10-19 and 2011-12-31 (inclusive)

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Criteria #1: Has prior atrial fibrillation diagnosis

People having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Atrial fibrillation2 starting between all days Before and 0 days After event index date

Inclusion Criteria #2: Has no prior treatment with comparator drug (dabigatran)

People having all of the following criteria:

* exactly 0 occurrences of a drug exposure of dabigatran4 starting between all days Before and 0 days Before 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.

2. Atrial fibrillation

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 313217 | Atrial fibrillation | Condition | SNOMED | NO | YES | NO |

4. dabigatran

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40228152 | dabigatran etexilate | Drug | RxNorm | NO | YES | NO |

13. warfarin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 1310149 | Warfarin | Drug | RxNorm | NO | YES | NO |

**Dabigatran new users (Graham replication)**

Initial Event Cohort

People having any of the following:

* a drug era of dabigatran4
  + for the first time in the person's history
  + era start is on or after 2010-10-19
  + with age at era start >= 65

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Criteria #1: Has prior atrial fibrillation or atrial flutter diagnosis

People having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Atrial fibrillation2 starting between all days Before and 0 days After event index date
* or at least 1 occurrences of a condition occurrence of Atrial flutter3 starting between all days Before and 0 days After event index date

Inclusion Criteria #2: Has no prior treatment with comparator drug (warfarin)

People having all of the following criteria:

* exactly 0 occurrences of a drug exposure of warfarin13 starting between all days Before and 0 days Before event index date

Inclusion Criteria #3: Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)

People having all of the following criteria:

* exactly 0 occurrences of a drug exposure of rivaroxaban12 starting between all days Before and 0 days After event index date
* and exactly 0 occurrences of a drug exposure of apixaban1 starting between all days Before and 0 days After event index date

Inclusion Criteria #4: Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date

People having all of the following criteria:

exactly 0 occurrences of a visit occurrence of long term care visit10 starting between 0 days Before and 0 days After event index date

and exactly 0 occurrences of a procedure of Hospice observations9 starting between all days Before and 0 days After event index date

and exactly 0 occurrences of an observation of Hospice observations9 starting between all days Before and 0 days After event index date

Inclusion Criteria #5: Not undergoing dialysis or kidney transplant recipient

People having all of the following criteria:

exactly 0 occurrences of a condition occurrence of Hemodialysis, peritoneal dialysis, or kidney transplant7 starting between 183 days Before and 0 days After event index date

and exactly 0 occurrences of a procedure of Hemodialysis, peritoneal dialysis, or kidney transplant7 starting between 183 days Before and 0 days After event index date

and exactly 0 occurrences of an observation of Hemodialysis, peritoneal dialysis, or kidney transplant7 starting between 183 days Before and 0 days After event index date

Inclusion Criteria #6: No mitral valve disease, heart valve repair, or replacement in the prior 6 months

People having all of the following criteria:

exactly 0 occurrences of a condition occurrence of Heart valve disease, repair or replacement6 starting between 183 days Before and 0 days After event index date

and exactly 0 occurrences of a procedure of Heart valve disease, repair or replacement6 starting between 183 days Before and 0 days After event index date

and exactly 0 occurrences of an observation of Heart valve disease, repair or replacement6 starting between 183 days Before and 0 days After event index date

Inclusion Criteria #7: No deep vein thrombosis or pulmonary embolism in the prior 6 months

People having all of the following criteria:

exactly 0 occurrences of a condition occurrence of Deep vein thrombosis5 starting between 183 days Before and 0 days After event index date

and exactly 0 occurrences of a condition occurrence of Pulmonary embolism11 starting between 183 days Before and 0 days After event index date

Inclusion Criteria #8: No joint replacement surgery in the prior 6 months

People having all of the following criteria:

exactly 0 occurrences of a procedure of Hip/knee joint replacement or revision8 starting between 183 days Before and 0 days After event index date

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

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of warfarin13

* allowing 3 days between exposures
* adding 0 days after exposure end

2. Atrial fibrillation

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 313217 | Atrial fibrillation | Condition | SNOMED | NO | YES | NO |

3. Atrial flutter

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 314665 | Atrial flutter | Condition | SNOMED | NO | YES | NO |

4. dabigatran

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40228152 | dabigatran etexilate | Drug | RxNorm | NO | YES | NO |

5. Deep vein thrombosis

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 435887 | Antepartum deep vein thrombosis | Condition | SNOMED | YES | YES | NO |
| 195562 | Hemorrhoids | Condition | SNOMED | YES | YES | NO |
| 4179912 | Intracranial venous thrombosis | 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 |
| 4235812 | Septic thrombophlebitis | Condition | SNOMED | YES | YES | NO |
| 4187790 | Thrombosis of retinal vein | Condition | SNOMED | YES | YES | NO |
| 318775 | Venous embolism | Condition | SNOMED | NO | YES | NO |
| 444247 | Venous thrombosis | Condition | SNOMED | NO | YES | NO |

6. Heart valve disease, repair or replacement

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4060089 | H/O: artificial heart valve | Observation | SNOMED | NO | YES | NO |
| 4195003 | Heart valve stenosis | Condition | SNOMED | NO | YES | NO |
| 44782431 | History of mechanical heart valve replacement | Observation | SNOMED | NO | YES | NO |
| 4013355 | Implantation of heart valve | Procedure | SNOMED | NO | YES | NO |
| 4165384 | Implantation of heart valve prosthesis or synthetic device | Procedure | SNOMED | NO | YES | NO |
| 2617335 | Md inr test revie inter mgmt | Observation | HCPCS | NO | YES | NO |
| 43020459 | Mechanical breakdown of prosthetic heart valve | Condition | SNOMED | NO | YES | NO |
| 312773 | Mechanical complication due to heart valve prosthesis | Condition | SNOMED | NO | YES | NO |
| 4020159 | Mechanical complication of heart valve prosthesis | Condition | SNOMED | NO | YES | NO |
| 44783274 | Mechanical heart valve replacement | Procedure | SNOMED | NO | YES | NO |
| 315273 | Mitral valve stenosis | Condition | SNOMED | NO | YES | NO |
| 4110937 | Non-rheumatic mitral valve stenosis | Condition | SNOMED | NO | YES | NO |
| 2001447 | Open and other replacement of heart valve | Procedure | ICD9Proc | NO | YES | NO |
| 2001448 | Open and other replacement of unspecified heart valve | Procedure | ICD9Proc | NO | YES | NO |
| 4119522 | Prosthetic heart valve sample | Specimen | SNOMED | NO | YES | NO |
| 4145884 | Prosthetic replacement of heart valve | Procedure | SNOMED | NO | YES | NO |
| 2617334 | Provide inr test mater/equip | Observation | HCPCS | NO | YES | NO |
| 4339971 | Reinsertion of heart valve, prosthetic | Procedure | SNOMED | NO | YES | NO |
| 4121484 | Replacement of heart valve poppet, prosthetic | Procedure | SNOMED | NO | YES | NO |
| 4013356 | Resuture of heart valve prosthesis, poppet | Procedure | SNOMED | NO | YES | NO |
| 4181749 | Revision of prosthesis of heart valve | Procedure | SNOMED | NO | YES | NO |
| 4304541 | Rheumatic mitral valve insufficiency AND aortic valve stenosis | Condition | SNOMED | NO | YES | NO |

7. Hemodialysis, peritoneal dialysis, or kidney transplant

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4126124 | Acute disorder of hemodialysis | Condition | SNOMED | NO | YES | NO |
| 4092504 | Adequacy of hemodialysis | Observation | SNOMED | NO | YES | NO |
| 435649 | Complication of hemodialysis | Condition | SNOMED | NO | YES | NO |
| 40480136 | Dependence on hemodialysis | Observation | SNOMED | NO | YES | NO |
| 4181476 | Dependence on hemodialysis due to end stage renal disease | Observation | SNOMED | NO | YES | NO |
| 44786469 | Docrsn for cath maint dia | Observation | HCPCS | NO | YES | NO |
| 4120120 | Hemodialysis | Procedure | SNOMED | NO | YES | NO |
| 2101833 | Hemodialysis plan of care documented (ESRD, P-ESRD) | Observation | CPT4 | NO | YES | NO |
| 4137616 | Hemodialysis-associated amyloidosis | Condition | SNOMED | NO | YES | NO |
| 313232 | Hemodialysis-associated hypotension | Condition | SNOMED | NO | YES | NO |
| 4300099 | Hemodialysis-associated pruritus | Condition | SNOMED | NO | YES | NO |
| 4297919 | Hemodialysis-associated pseudoporphyria | Condition | SNOMED | NO | YES | NO |
| 4297658 | Hemodialysis-associated secondary amyloidosis of skin | Condition | SNOMED | NO | YES | NO |
| 4099603 | Megaloblastic anemia due to hemodialysis | Condition | SNOMED | NO | YES | NO |
| 44782924 | Misplacement of hemodialysis catheter | Condition | SNOMED | NO | YES | NO |
| 44786470 | Patient receiving maintenance hemodialysis for greater than or equal to 90 days with a catheter as the mode of vascular access | Observation | HCPCS | NO | YES | NO |
| 44786471 | Patient receiving maintenance hemodialysis for greater than or equal to 90 days without a catheter as the mode of vascular access | Observation | HCPCS | NO | YES | NO |
| 43533281 | Patient receiving maintenance hemodialysis in an outpatient dialysis facility | Observation | HCPCS | NO | YES | NO |
| 4324124 | Peritoneal dialysis | Procedure | SNOMED | NO | YES | NO |
| 2003564 | Peritoneal dialysis | Procedure | ICD9Proc | NO | YES | NO |
| 4300106 | Skin lesion associated with hemodialysis | Condition | SNOMED | NO | YES | NO |
| 4046829 | Anesthesia for renal transplant, recipient | Procedure | SNOMED | NO | YES | NO |
| 2109584 | Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; ureteral anastomosis, each | Procedure | CPT4 | NO | YES | NO |
| 4021107 | Cadaveric renal transplant | Procedure | SNOMED | NO | YES | NO |
| 4197300 | Donor renal transplantation | Procedure | SNOMED | NO | YES | NO |
| 4324754 | Examination of recipient after kidney transplant | Procedure | SNOMED | NO | YES | NO |
| 4002215 | Kidney implantation | Procedure | SNOMED | NO | YES | NO |
| 4022805 | Live donor renal transplant | Procedure | SNOMED | NO | YES | NO |
| 2003626 | Other kidney transplantation | Procedure | ICD9Proc | NO | YES | NO |
| 40664909 | Patient receiving hemodialysis, peritoneal dialysis or kidney transplantation | Observation | HCPCS | NO | YES | NO |
| 2109586 | Renal allotransplantation, implantation of graft; without recipient nephrectomy | Procedure | CPT4 | NO | YES | NO |
| 2109589 | Renal autotransplantation, reimplantation of kidney | Procedure | CPT4 | NO | YES | NO |
| 4163566 | Renal replacement | Procedure | SNOMED | NO | YES | NO |
| 37521745 | Renal transplant | Procedure | MedDRA | NO | YES | NO |
| 4346636 | Renal transplant arteriogram | Procedure | SNOMED | NO | YES | NO |
| 4346505 | Renal transplant venogram | Procedure | SNOMED | NO | YES | NO |
| 4347789 | Renal transplant venous sampling | Procedure | SNOMED | NO | YES | NO |
| 2721092 | Simultaneous pancreas kidney transplantation | Procedure | HCPCS | NO | YES | NO |
| 4322471 | Transplant of kidney | Procedure | SNOMED | NO | YES | NO |
| 4343000 | Xenograft renal transplant | Procedure | SNOMED | NO | YES | NO |

8. Hip/knee joint replacement or revision

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 2101660 | Anesthesia for open or surgical arthroscopic procedures on knee joint; total knee arthroplasty | Procedure | CPT4 | NO | YES | NO |
| 2101635 | Anesthesia for open procedures involving hip joint; revision of total hip arthroplasty | Procedure | CPT4 | NO | YES | NO |
| 2101634 | Anesthesia for open procedures involving hip joint; total hip arthroplasty | Procedure | CPT4 | NO | YES | NO |
| 2104836 | Arthroplasty, acetabular and proximal femoral prosthetic replacement (total hip arthroplasty), with or without autograft or allograft | Procedure | CPT4 | NO | YES | NO |
| 2103931 | Arthroplasty, elbow; with distal humerus and proximal ulnar prosthetic replacement (eg, total elbow) | Procedure | CPT4 | NO | YES | NO |
| 2105103 | Arthroplasty, knee, condyle and plateau; medial AND lateral compartments with or without patella resurfacing (total knee arthroplasty) | Procedure | CPT4 | NO | YES | NO |
| 2104837 | Conversion of previous hip surgery to total hip arthroplasty, with or without autograft or allograft | Procedure | CPT4 | NO | YES | NO |
| 2104835 | Hemiarthroplasty, hip, partial (eg, femoral stem prosthesis, bipolar arthroplasty) | Procedure | CPT4 | NO | YES | NO |
| 2000075 | Hip bearing surface, ceramic-on-ceramic | Procedure | ICD9Proc | NO | YES | NO |
| 2000076 | Hip bearing surface, ceramic-on-polyethylene | Procedure | ICD9Proc | NO | YES | NO |
| 2000074 | Hip bearing surface, metal-on-metal | Procedure | ICD9Proc | NO | YES | NO |
| 2000073 | Hip bearing surface, metal-on-polyethylene | Procedure | ICD9Proc | NO | YES | NO |
| 4001859 | Hip joint implantation | Procedure | SNOMED | NO | YES | NO |
| 4134857 | Insertion of hip prosthesis | Procedure | SNOMED | NO | YES | NO |
| 4207955 | Insertion of hip prosthesis, total | Procedure | SNOMED | NO | YES | NO |
| 2005902 | Partial hip replacement | Procedure | ICD9Proc | NO | YES | NO |
| 4162099 | Prosthetic arthroplasty of the hip | Procedure | SNOMED | NO | YES | NO |
| 2000085 | Resurfacing hip, partial, acetabulum | Procedure | ICD9Proc | NO | YES | NO |
| 2000084 | Resurfacing hip, partial, femoral head | Procedure | ICD9Proc | NO | YES | NO |
| 2000083 | Resurfacing hip, total, acetabulum and femoral head | Procedure | ICD9Proc | NO | YES | NO |
| 4010119 | Revision of hip replacement | Procedure | SNOMED | NO | YES | NO |
| 2000070 | Revision of hip replacement, acetabular component | Procedure | ICD9Proc | NO | YES | NO |
| 2000072 | Revision of hip replacement, acetabular liner and/or femoral head only | Procedure | ICD9Proc | NO | YES | NO |
| 2000069 | Revision of hip replacement, both acetabular and femoral components | Procedure | ICD9Proc | NO | YES | NO |
| 2000071 | Revision of hip replacement, femoral component | Procedure | ICD9Proc | NO | YES | NO |
| 2000080 | Revision of knee replacement, femoral component | Procedure | ICD9Proc | NO | YES | NO |
| 2000081 | Revision of knee replacement, patellar component | Procedure | ICD9Proc | NO | YES | NO |
| 2000079 | Revision of knee replacement, tibial component | Procedure | ICD9Proc | NO | YES | NO |
| 2000078 | Revision of knee replacement, total (all components) | Procedure | ICD9Proc | NO | YES | NO |
| 45887894 | Revision of total hip arthroplasty | Procedure | CPT4 | NO | YES | NO |
| 2104839 | Revision of total hip arthroplasty; acetabular component only, with or without autograft or allograft | Procedure | CPT4 | NO | YES | NO |
| 2104838 | Revision of total hip arthroplasty; both components, with or without autograft or allograft | Procedure | CPT4 | NO | YES | NO |
| 2104840 | Revision of total hip arthroplasty; femoral component only, with or without allograft | Procedure | CPT4 | NO | YES | NO |
| 4266062 | Revision of total hip replacement | Procedure | SNOMED | NO | YES | NO |
| 2105128 | Revision of total knee arthroplasty, with or without allograft; 1 component | Procedure | CPT4 | NO | YES | NO |
| 2105129 | Revision of total knee arthroplasty, with or without allograft; femoral and entire tibial component | Procedure | CPT4 | NO | YES | NO |
| 2000082 | Revision of total knee replacement, tibial insert (liner) | Procedure | ICD9Proc | NO | YES | NO |
| 2005891 | Total hip replacement | Procedure | ICD9Proc | NO | YES | NO |
| 2005904 | Total knee replacement | Procedure | ICD9Proc | NO | YES | NO |
| 4203771 | Total replacement of hip | Procedure | SNOMED | NO | YES | NO |
| 2005903 | Revision of hip replacement, not otherwise specified | Procedure | ICD9Proc | NO | YES | NO |
| 2104914 | Open treatment of femoral fracture, proximal end, neck, internal fixation or prosthetic replacement | Procedure | CPT4 | YES | YES | NO |

9. Hospice observations

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40483762 | Acute care hospice service | Observation | SNOMED | NO | YES | NO |
| 4123927 | Admission to hospice | Observation | SNOMED | NO | YES | NO |
| 4086294 | Admission to hospice for respite | Observation | SNOMED | NO | YES | NO |
| 4137269 | Discharge from hospice | Observation | SNOMED | NO | YES | NO |
| 4137272 | Discharge from hospice day hospital | Observation | SNOMED | NO | YES | NO |
| 4062333 | Full care by hospice | Observation | SNOMED | NO | YES | NO |
| 40481548 | Home hospice service | Observation | SNOMED | NO | YES | NO |
| 4109386 | Hospice | Observation | SNOMED | NO | YES | NO |
| 4301458 | Hospice care | Observation | SNOMED | NO | YES | NO |
| 4301459 | Hospice care management | Procedure | SNOMED | NO | YES | NO |
| 2720815 | Hospice care provided in inpatient hospice facility | Observation | HCPCS | NO | YES | NO |
| 2720814 | Hospice care provided in inpatient hospital | Observation | HCPCS | NO | YES | NO |
| 2720817 | Hospice care provided in inpatient psychiatric facility | Observation | HCPCS | NO | YES | NO |
| 2720816 | Hospice care provided in long term care facility | Observation | HCPCS | NO | YES | NO |
| 2720812 | Hospice care provided in nursing long term care facility (ltc) or non-skilled nursing facility (nf) | Observation | HCPCS | NO | YES | NO |
| 2720813 | Hospice care provided in skilled nursing facility (snf) | Observation | HCPCS | NO | YES | NO |
| 2617270 | Hospice care supervision | Observation | HCPCS | NO | YES | NO |
| 2721445 | Hospice care, in the home, per diem | Observation | HCPCS | NO | YES | NO |
| 2721700 | Hospice continuous home care; per hour | Observation | HCPCS | NO | YES | NO |
| 2721702 | Hospice general inpatient care; per diem | Observation | HCPCS | NO | YES | NO |
| 40664432 | Hospice home care provided in a hospice facility | Observation | HCPCS | NO | YES | NO |
| 2721701 | Hospice inpatient respite care; per diem | Observation | HCPCS | NO | YES | NO |
| 2721703 | Hospice long term care, room and board only; per diem | Observation | HCPCS | NO | YES | NO |
| 2720811 | Hospice or home health care provided in assisted living facility | Observation | HCPCS | NO | YES | NO |
| 38003372 | Hospice Room & Board-Nursing facility | Revenue Code | Revenue Code | NO | YES | NO |
| 2721699 | Hospice routine home care; per diem | Observation | HCPCS | NO | YES | NO |
| 38003368 | Hospice Service - Continuous Home Care | Revenue Code | Revenue Code | NO | YES | NO |
| 38003366 | Hospice Service - General Classification | Revenue Code | Revenue Code | NO | YES | NO |
| 38003370 | Hospice Service - General Inpatient Care (Non-respite) | Revenue Code | Revenue Code | NO | YES | NO |
| 38003369 | Hospice Service - Impatient Respite Care | Revenue Code | Revenue Code | NO | YES | NO |
| 38003373 | Hospice Service - Other | Revenue Code | Revenue Code | NO | YES | NO |
| 38003371 | Hospice Service - Physician Services | Revenue Code | Revenue Code | NO | YES | NO |
| 38003367 | Hospice Service - Routine Home Care | Revenue Code | Revenue Code | NO | YES | NO |
| 38003131 | Incremental Nursing Charge Rate - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 38003066 | Private (Deluxe) - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 38003036 | Room & Board - Private (Medical or General) - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 38003046 | Room & Board - Semi-private Two Bed (Medical or General) - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 38003076 | Room & Board Ward (Medical or General) - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 4082084 | Routine admission to hospice | Observation | SNOMED | NO | YES | NO |
| 4140947 | Seen in hospice | Observation | SNOMED | NO | YES | NO |
| 38003056 | Semi-Private - Three and Four Beds - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 915618 | Services performed by care coordinator in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915614 | Services performed by chaplain in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915615 | Services performed by dietary counselor in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915616 | Services performed by other counselor in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915619 | Services performed by other qualified therapist in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915620 | Services performed by qualified pharmacist in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915617 | Services performed by volunteer in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 4062044 | Shared care - hospice and GP | Observation | SNOMED | NO | YES | NO |
| 2514512 | Supervision of a hospice patient (patient not present) requiring complex and multidisciplinary care modalities involving regular development and/or revision of care plans by that individual, review of subsequent reports of patient status, review of relate | Procedure | CPT4 | NO | YES | NO |
| 4086777 | Urgent admission to hospice | Observation | SNOMED | NO | YES | NO |

10. long term care visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 42898160 | Long Term Care Visit | Visit | Visit | NO | YES | NO |

11. Pulmonary embolism

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40480461 | Infarction of lung due to iatrogenic pulmonary embolism | Condition | SNOMED | NO | YES | NO |
| 435026 | Obstetric pulmonary embolism | Condition | SNOMED | YES | YES | NO |
| 440417 | Pulmonary embolism | Condition | SNOMED | NO | YES | NO |
| 40479606 | Septic pulmonary embolism | Condition | SNOMED | NO | YES | NO |

12. rivaroxaban

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40241331 | rivaroxaban | Drug | RxNorm | NO | YES | NO |

13. warfarin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 1310149 | Warfarin | Drug | RxNorm | NO | YES | NO |

**Warfarin new users (Graham replication)**

Initial Event Cohort

People having any of the following: 

* a drug era of warfarin13
  + for the first time in the person's history
  + era start is on or after 2010-10-19
  + with age at era start >= 65

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Criteria #1: Has prior atrial fibrillation or atrial flutter diagnosis

People having any of the following criteria:

* at least 1 occurrences of a condition occurrence of Atrial fibrillation2 starting between all days Before and 0 days After event index date
* or at least 1 occurrences of a condition occurrence of Atrial flutter3 starting between all days Before and 0 days After event index date

Inclusion Criteria #2: Has no prior treatment with comparator drug (dabigatran)

People having all of the following criteria:

* exactly 0 occurrences of a drug exposure of dabigatran4 starting between all days Before and 0 days Before event index date

Inclusion Criteria #3: Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)

People having all of the following criteria:

* exactly 0 occurrences of a drug exposure of rivaroxaban12 starting between all days Before and 0 days After event index date
* and exactly 0 occurrences of a drug exposure of apixaban1 starting between all days Before and 0 days After event index date

Inclusion Criteria #4: Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date

People having all of the following criteria:

* exactly 0 occurrences of a visit occurrence of long term care visit10 starting between 0 days Before and 0 days After event index date
* and exactly 0 occurrences of a procedure of Hospice observations9 starting between all days Before and 0 days After event index date
* and exactly 0 occurrences of an observation of Hospice observations9 starting between all days Before and 0 days After event index date

Inclusion Criteria #5: Not undergoing dialysis or kidney transplant recipient

People having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Hemodialysis, peritoneal dialysis, or kidney transplant7 starting between 183 days Before and 0 days After event index date
* and exactly 0 occurrences of a procedure of Hemodialysis, peritoneal dialysis, or kidney transplant7 starting between 183 days Before and 0 days After event index date
* and exactly 0 occurrences of an observation of Hemodialysis, peritoneal dialysis, or kidney transplant7 starting between 183 days Before and 0 days After event index date

Inclusion Criteria #6: No mitral valve disease, heart valve repair, or replacement in the prior 6 months

People having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Heart valve disease, repair or replacement6 starting between 183 days Before and 0 days After event index date
* and exactly 0 occurrences of a procedure of Heart valve disease, repair or replacement6 starting between 183 days Before and 0 days After event index date
* and exactly 0 occurrences of an observation of Heart valve disease, repair or replacement6 starting between 183 days Before and 0 days After event index date

Inclusion Criteria #7: No deep vein thrombosis or pulmonary embolism in the prior 6 months

People having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Deep vein thrombosis5 starting between 183 days Before and 0 days After event index date
* and exactly 0 occurrences of a condition occurrence of Pulmonary embolism11 starting between 183 days Before and 0 days After event index date

Inclusion Criteria #8: No joint replacement surgery in the prior 6 months

People having all of the following criteria:

* exactly 0 occurrences of a procedure of Hip/knee joint replacement or revision8 starting between 183 days Before and 0 days After event index date

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

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of warfarin13

* allowing 3 days between exposures
* adding 0 days after exposure end

2. Atrial fibrillation

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 313217 | Atrial fibrillation | Condition | SNOMED | NO | YES | NO |

3. Atrial flutter

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 314665 | Atrial flutter | Condition | SNOMED | NO | YES | NO |

4. dabigatran

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40228152 | dabigatran etexilate | Drug | RxNorm | NO | YES | NO |

5. Deep vein thrombosis

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 435887 | Antepartum deep vein thrombosis | Condition | SNOMED | YES | YES | NO |
| 195562 | Hemorrhoids | Condition | SNOMED | YES | YES | NO |
| 4179912 | Intracranial venous thrombosis | 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 |
| 4235812 | Septic thrombophlebitis | Condition | SNOMED | YES | YES | NO |
| 4187790 | Thrombosis of retinal vein | Condition | SNOMED | YES | YES | NO |
| 318775 | Venous embolism | Condition | SNOMED | NO | YES | NO |
| 444247 | Venous thrombosis | Condition | SNOMED | NO | YES | NO |

6. Heart valve disease, repair or replacement

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4060089 | H/O: artificial heart valve | Observation | SNOMED | NO | YES | NO |
| 4195003 | Heart valve stenosis | Condition | SNOMED | NO | YES | NO |
| 44782431 | History of mechanical heart valve replacement | Observation | SNOMED | NO | YES | NO |
| 4013355 | Implantation of heart valve | Procedure | SNOMED | NO | YES | NO |
| 4165384 | Implantation of heart valve prosthesis or synthetic device | Procedure | SNOMED | NO | YES | NO |
| 2617335 | Md inr test revie inter mgmt | Observation | HCPCS | NO | YES | NO |
| 43020459 | Mechanical breakdown of prosthetic heart valve | Condition | SNOMED | NO | YES | NO |
| 312773 | Mechanical complication due to heart valve prosthesis | Condition | SNOMED | NO | YES | NO |
| 4020159 | Mechanical complication of heart valve prosthesis | Condition | SNOMED | NO | YES | NO |
| 44783274 | Mechanical heart valve replacement | Procedure | SNOMED | NO | YES | NO |
| 315273 | Mitral valve stenosis | Condition | SNOMED | NO | YES | NO |
| 4110937 | Non-rheumatic mitral valve stenosis | Condition | SNOMED | NO | YES | NO |
| 2001447 | Open and other replacement of heart valve | Procedure | ICD9Proc | NO | YES | NO |
| 2001448 | Open and other replacement of unspecified heart valve | Procedure | ICD9Proc | NO | YES | NO |
| 4119522 | Prosthetic heart valve sample | Specimen | SNOMED | NO | YES | NO |
| 4145884 | Prosthetic replacement of heart valve | Procedure | SNOMED | NO | YES | NO |
| 2617334 | Provide inr test mater/equip | Observation | HCPCS | NO | YES | NO |
| 4339971 | Reinsertion of heart valve, prosthetic | Procedure | SNOMED | NO | YES | NO |
| 4121484 | Replacement of heart valve poppet, prosthetic | Procedure | SNOMED | NO | YES | NO |
| 4013356 | Resuture of heart valve prosthesis, poppet | Procedure | SNOMED | NO | YES | NO |
| 4181749 | Revision of prosthesis of heart valve | Procedure | SNOMED | NO | YES | NO |
| 4304541 | Rheumatic mitral valve insufficiency AND aortic valve stenosis | Condition | SNOMED | NO | YES | NO |

7. Hemodialysis, peritoneal dialysis, or kidney transplant

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4126124 | Acute disorder of hemodialysis | Condition | SNOMED | NO | YES | NO |
| 4092504 | Adequacy of hemodialysis | Observation | SNOMED | NO | YES | NO |
| 435649 | Complication of hemodialysis | Condition | SNOMED | NO | YES | NO |
| 40480136 | Dependence on hemodialysis | Observation | SNOMED | NO | YES | NO |
| 4181476 | Dependence on hemodialysis due to end stage renal disease | Observation | SNOMED | NO | YES | NO |
| 44786469 | Docrsn for cath maint dia | Observation | HCPCS | NO | YES | NO |
| 4120120 | Hemodialysis | Procedure | SNOMED | NO | YES | NO |
| 2101833 | Hemodialysis plan of care documented (ESRD, P-ESRD) | Observation | CPT4 | NO | YES | NO |
| 4137616 | Hemodialysis-associated amyloidosis | Condition | SNOMED | NO | YES | NO |
| 313232 | Hemodialysis-associated hypotension | Condition | SNOMED | NO | YES | NO |
| 4300099 | Hemodialysis-associated pruritus | Condition | SNOMED | NO | YES | NO |
| 4297919 | Hemodialysis-associated pseudoporphyria | Condition | SNOMED | NO | YES | NO |
| 4297658 | Hemodialysis-associated secondary amyloidosis of skin | Condition | SNOMED | NO | YES | NO |
| 4099603 | Megaloblastic anemia due to hemodialysis | Condition | SNOMED | NO | YES | NO |
| 44782924 | Misplacement of hemodialysis catheter | Condition | SNOMED | NO | YES | NO |
| 44786470 | Patient receiving maintenance hemodialysis for greater than or equal to 90 days with a catheter as the mode of vascular access | Observation | HCPCS | NO | YES | NO |
| 44786471 | Patient receiving maintenance hemodialysis for greater than or equal to 90 days without a catheter as the mode of vascular access | Observation | HCPCS | NO | YES | NO |
| 43533281 | Patient receiving maintenance hemodialysis in an outpatient dialysis facility | Observation | HCPCS | NO | YES | NO |
| 4324124 | Peritoneal dialysis | Procedure | SNOMED | NO | YES | NO |
| 2003564 | Peritoneal dialysis | Procedure | ICD9Proc | NO | YES | NO |
| 4300106 | Skin lesion associated with hemodialysis | Condition | SNOMED | NO | YES | NO |
| 4046829 | Anesthesia for renal transplant, recipient | Procedure | SNOMED | NO | YES | NO |
| 2109584 | Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; ureteral anastomosis, each | Procedure | CPT4 | NO | YES | NO |
| 4021107 | Cadaveric renal transplant | Procedure | SNOMED | NO | YES | NO |
| 4197300 | Donor renal transplantation | Procedure | SNOMED | NO | YES | NO |
| 4324754 | Examination of recipient after kidney transplant | Procedure | SNOMED | NO | YES | NO |
| 4002215 | Kidney implantation | Procedure | SNOMED | NO | YES | NO |
| 4022805 | Live donor renal transplant | Procedure | SNOMED | NO | YES | NO |
| 2003626 | Other kidney transplantation | Procedure | ICD9Proc | NO | YES | NO |
| 40664909 | Patient receiving hemodialysis, peritoneal dialysis or kidney transplantation | Observation | HCPCS | NO | YES | NO |
| 2109586 | Renal allotransplantation, implantation of graft; without recipient nephrectomy | Procedure | CPT4 | NO | YES | NO |
| 2109589 | Renal autotransplantation, reimplantation of kidney | Procedure | CPT4 | NO | YES | NO |
| 4163566 | Renal replacement | Procedure | SNOMED | NO | YES | NO |
| 37521745 | Renal transplant | Procedure | MedDRA | NO | YES | NO |
| 4346636 | Renal transplant arteriogram | Procedure | SNOMED | NO | YES | NO |
| 4346505 | Renal transplant venogram | Procedure | SNOMED | NO | YES | NO |
| 4347789 | Renal transplant venous sampling | Procedure | SNOMED | NO | YES | NO |
| 2721092 | Simultaneous pancreas kidney transplantation | Procedure | HCPCS | NO | YES | NO |
| 4322471 | Transplant of kidney | Procedure | SNOMED | NO | YES | NO |
| 4343000 | Xenograft renal transplant | Procedure | SNOMED | NO | YES | NO |

8. Hip/knee joint replacement or revision

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 2101660 | Anesthesia for open or surgical arthroscopic procedures on knee joint; total knee arthroplasty | Procedure | CPT4 | NO | YES | NO |
| 2101635 | Anesthesia for open procedures involving hip joint; revision of total hip arthroplasty | Procedure | CPT4 | NO | YES | NO |
| 2101634 | Anesthesia for open procedures involving hip joint; total hip arthroplasty | Procedure | CPT4 | NO | YES | NO |
| 2104836 | Arthroplasty, acetabular and proximal femoral prosthetic replacement (total hip arthroplasty), with or without autograft or allograft | Procedure | CPT4 | NO | YES | NO |
| 2103931 | Arthroplasty, elbow; with distal humerus and proximal ulnar prosthetic replacement (eg, total elbow) | Procedure | CPT4 | NO | YES | NO |
| 2105103 | Arthroplasty, knee, condyle and plateau; medial AND lateral compartments with or without patella resurfacing (total knee arthroplasty) | Procedure | CPT4 | NO | YES | NO |
| 2104837 | Conversion of previous hip surgery to total hip arthroplasty, with or without autograft or allograft | Procedure | CPT4 | NO | YES | NO |
| 2104835 | Hemiarthroplasty, hip, partial (eg, femoral stem prosthesis, bipolar arthroplasty) | Procedure | CPT4 | NO | YES | NO |
| 2000075 | Hip bearing surface, ceramic-on-ceramic | Procedure | ICD9Proc | NO | YES | NO |
| 2000076 | Hip bearing surface, ceramic-on-polyethylene | Procedure | ICD9Proc | NO | YES | NO |
| 2000074 | Hip bearing surface, metal-on-metal | Procedure | ICD9Proc | NO | YES | NO |
| 2000073 | Hip bearing surface, metal-on-polyethylene | Procedure | ICD9Proc | NO | YES | NO |
| 4001859 | Hip joint implantation | Procedure | SNOMED | NO | YES | NO |
| 4134857 | Insertion of hip prosthesis | Procedure | SNOMED | NO | YES | NO |
| 4207955 | Insertion of hip prosthesis, total | Procedure | SNOMED | NO | YES | NO |
| 2005902 | Partial hip replacement | Procedure | ICD9Proc | NO | YES | NO |
| 4162099 | Prosthetic arthroplasty of the hip | Procedure | SNOMED | NO | YES | NO |
| 2000085 | Resurfacing hip, partial, acetabulum | Procedure | ICD9Proc | NO | YES | NO |
| 2000084 | Resurfacing hip, partial, femoral head | Procedure | ICD9Proc | NO | YES | NO |
| 2000083 | Resurfacing hip, total, acetabulum and femoral head | Procedure | ICD9Proc | NO | YES | NO |
| 4010119 | Revision of hip replacement | Procedure | SNOMED | NO | YES | NO |
| 2000070 | Revision of hip replacement, acetabular component | Procedure | ICD9Proc | NO | YES | NO |
| 2000072 | Revision of hip replacement, acetabular liner and/or femoral head only | Procedure | ICD9Proc | NO | YES | NO |
| 2000069 | Revision of hip replacement, both acetabular and femoral components | Procedure | ICD9Proc | NO | YES | NO |
| 2000071 | Revision of hip replacement, femoral component | Procedure | ICD9Proc | NO | YES | NO |
| 2000080 | Revision of knee replacement, femoral component | Procedure | ICD9Proc | NO | YES | NO |
| 2000081 | Revision of knee replacement, patellar component | Procedure | ICD9Proc | NO | YES | NO |
| 2000079 | Revision of knee replacement, tibial component | Procedure | ICD9Proc | NO | YES | NO |
| 2000078 | Revision of knee replacement, total (all components) | Procedure | ICD9Proc | NO | YES | NO |
| 45887894 | Revision of total hip arthroplasty | Procedure | CPT4 | NO | YES | NO |
| 2104839 | Revision of total hip arthroplasty; acetabular component only, with or without autograft or allograft | Procedure | CPT4 | NO | YES | NO |
| 2104838 | Revision of total hip arthroplasty; both components, with or without autograft or allograft | Procedure | CPT4 | NO | YES | NO |
| 2104840 | Revision of total hip arthroplasty; femoral component only, with or without allograft | Procedure | CPT4 | NO | YES | NO |
| 4266062 | Revision of total hip replacement | Procedure | SNOMED | NO | YES | NO |
| 2105128 | Revision of total knee arthroplasty, with or without allograft; 1 component | Procedure | CPT4 | NO | YES | NO |
| 2105129 | Revision of total knee arthroplasty, with or without allograft; femoral and entire tibial component | Procedure | CPT4 | NO | YES | NO |
| 2000082 | Revision of total knee replacement, tibial insert (liner) | Procedure | ICD9Proc | NO | YES | NO |
| 2005891 | Total hip replacement | Procedure | ICD9Proc | NO | YES | NO |
| 2005904 | Total knee replacement | Procedure | ICD9Proc | NO | YES | NO |
| 4203771 | Total replacement of hip | Procedure | SNOMED | NO | YES | NO |
| 2005903 | Revision of hip replacement, not otherwise specified | Procedure | ICD9Proc | NO | YES | NO |
| 2104914 | Open treatment of femoral fracture, proximal end, neck, internal fixation or prosthetic replacement | Procedure | CPT4 | YES | YES | NO |

9. Hospice observations

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40483762 | Acute care hospice service | Observation | SNOMED | NO | YES | NO |
| 4123927 | Admission to hospice | Observation | SNOMED | NO | YES | NO |
| 4086294 | Admission to hospice for respite | Observation | SNOMED | NO | YES | NO |
| 4137269 | Discharge from hospice | Observation | SNOMED | NO | YES | NO |
| 4137272 | Discharge from hospice day hospital | Observation | SNOMED | NO | YES | NO |
| 4062333 | Full care by hospice | Observation | SNOMED | NO | YES | NO |
| 40481548 | Home hospice service | Observation | SNOMED | NO | YES | NO |
| 4109386 | Hospice | Observation | SNOMED | NO | YES | NO |
| 4301458 | Hospice care | Observation | SNOMED | NO | YES | NO |
| 4301459 | Hospice care management | Procedure | SNOMED | NO | YES | NO |
| 2720815 | Hospice care provided in inpatient hospice facility | Observation | HCPCS | NO | YES | NO |
| 2720814 | Hospice care provided in inpatient hospital | Observation | HCPCS | NO | YES | NO |
| 2720817 | Hospice care provided in inpatient psychiatric facility | Observation | HCPCS | NO | YES | NO |
| 2720816 | Hospice care provided in long term care facility | Observation | HCPCS | NO | YES | NO |
| 2720812 | Hospice care provided in nursing long term care facility (ltc) or non-skilled nursing facility (nf) | Observation | HCPCS | NO | YES | NO |
| 2720813 | Hospice care provided in skilled nursing facility (snf) | Observation | HCPCS | NO | YES | NO |
| 2617270 | Hospice care supervision | Observation | HCPCS | NO | YES | NO |
| 2721445 | Hospice care, in the home, per diem | Observation | HCPCS | NO | YES | NO |
| 2721700 | Hospice continuous home care; per hour | Observation | HCPCS | NO | YES | NO |
| 2721702 | Hospice general inpatient care; per diem | Observation | HCPCS | NO | YES | NO |
| 40664432 | Hospice home care provided in a hospice facility | Observation | HCPCS | NO | YES | NO |
| 2721701 | Hospice inpatient respite care; per diem | Observation | HCPCS | NO | YES | NO |
| 2721703 | Hospice long term care, room and board only; per diem | Observation | HCPCS | NO | YES | NO |
| 2720811 | Hospice or home health care provided in assisted living facility | Observation | HCPCS | NO | YES | NO |
| 38003372 | Hospice Room & Board-Nursing facility | Revenue Code | Revenue Code | NO | YES | NO |
| 2721699 | Hospice routine home care; per diem | Observation | HCPCS | NO | YES | NO |
| 38003368 | Hospice Service - Continuous Home Care | Revenue Code | Revenue Code | NO | YES | NO |
| 38003366 | Hospice Service - General Classification | Revenue Code | Revenue Code | NO | YES | NO |
| 38003370 | Hospice Service - General Inpatient Care (Non-respite) | Revenue Code | Revenue Code | NO | YES | NO |
| 38003369 | Hospice Service - Impatient Respite Care | Revenue Code | Revenue Code | NO | YES | NO |
| 38003373 | Hospice Service - Other | Revenue Code | Revenue Code | NO | YES | NO |
| 38003371 | Hospice Service - Physician Services | Revenue Code | Revenue Code | NO | YES | NO |
| 38003367 | Hospice Service - Routine Home Care | Revenue Code | Revenue Code | NO | YES | NO |
| 38003131 | Incremental Nursing Charge Rate - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 38003066 | Private (Deluxe) - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 38003036 | Room & Board - Private (Medical or General) - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 38003046 | Room & Board - Semi-private Two Bed (Medical or General) - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 38003076 | Room & Board Ward (Medical or General) - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 4082084 | Routine admission to hospice | Observation | SNOMED | NO | YES | NO |
| 4140947 | Seen in hospice | Observation | SNOMED | NO | YES | NO |
| 38003056 | Semi-Private - Three and Four Beds - Hospice | Revenue Code | Revenue Code | NO | YES | NO |
| 915618 | Services performed by care coordinator in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915614 | Services performed by chaplain in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915615 | Services performed by dietary counselor in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915616 | Services performed by other counselor in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915619 | Services performed by other qualified therapist in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915620 | Services performed by qualified pharmacist in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 915617 | Services performed by volunteer in the hospice setting, each 15 minutes | Observation | HCPCS | NO | YES | NO |
| 4062044 | Shared care - hospice and GP | Observation | SNOMED | NO | YES | NO |
| 2514512 | Supervision of a hospice patient (patient not present) requiring complex and multidisciplinary care modalities involving regular development and/or revision of care plans by that individual, review of subsequent reports of patient status, review of relate | Procedure | CPT4 | NO | YES | NO |
| 4086777 | Urgent admission to hospice | Observation | SNOMED | NO | YES | NO |

10. long term care visit

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 42898160 | Long Term Care Visit | Visit | Visit | NO | YES | NO |

11. Pulmonary embolism

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40480461 | Infarction of lung due to iatrogenic pulmonary embolism | Condition | SNOMED | NO | YES | NO |
| 435026 | Obstetric pulmonary embolism | Condition | SNOMED | YES | YES | NO |
| 440417 | Pulmonary embolism | Condition | SNOMED | NO | YES | NO |
| 40479606 | Septic pulmonary embolism | Condition | SNOMED | NO | YES | NO |

12. rivaroxaban

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40241331 | rivaroxaban | Drug | RxNorm | NO | YES | NO |

13. warfarin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 1310149 | Warfarin | Drug | RxNorm | NO | YES | NO |

**SSRI use (Tata replications)**

Initial Event Cohort

People having any of the following: 

* a drug era of SSRIs (replication of Lee et al, J Clin Psychiatry 2016)5
  + era start is between 1988-01-01 and 2003-11-01 (inclusive)
  + with age at era start >= 16

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.**

Date Offset Exit Criteria

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

5. SSRIs

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21604709 | Selective serotonin reuptake inhibitors | Drug | ATC | NO | YES | NO |

**NSAIDS (Tata SCCS replication)**

Initial Event Cohort

People having any of the following: 

* a drug era of NSAIDs3
  + with age at era start >= 16

with continuous observation of at least 0 days prior and 1 days after event index date, and limit initial events to: **all events per person.**

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

Date Offset Exit Criteria

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

3. NSAIDs

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21603933 | ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS | Drug | ATC | NO | YES | NO |

**TCAs** **(Tata SCCS replication)**

Initial Event Cohort

People having any of the following:

* a drug era of Tricyclic Antidepressant4
  + with age at era start >= 16

with continuous observation of at least 0 days prior and 1 days after event index date, and limit initial events to: **all events per person.**

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

Date Offset Exit Criteria

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

4. Tricyclic Antidepressant

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 710062 | Amitriptyline | Drug | RxNorm | NO | YES | NO |
| 713109 | Amoxapine | Drug | RxNorm | NO | YES | NO |
| 798834 | Clomipramine | Drug | RxNorm | NO | YES | NO |
| 716968 | Desipramine | Drug | RxNorm | NO | YES | NO |
| 738156 | Doxepin | Drug | RxNorm | NO | YES | NO |
| 778268 | Imipramine | Drug | RxNorm | NO | YES | NO |
| 794147 | Maprotiline | Drug | RxNorm | NO | YES | NO |
| 721724 | Nortriptyline | Drug | RxNorm | NO | YES | NO |
| 754270 | Protriptyline | Drug | RxNorm | NO | YES | NO |
| 705755 | Trimipramine | Drug | RxNorm | NO | YES | NO |

### Outcomes

**GI bleeding (Southworth and Graham replications)**

Initial Event Cohort

People having any of the following:

* a condition occurrence of Major gastrointestinal (GI) bleeding2
  + 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.**

2. Major gastrointestinal (GI) bleeding

| **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 |

**Upper GI bleeding (Tata replications)**

Initial Event Cohort

People having any of the following:

* a condition era of Upper GI Bleeding (replication Tata APT 2005)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: **earliest event per person.**

1. Upper GI Bleeding (replication Tata APT 2005)

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4280942 | Acute gastrojejunal ulcer with perforation | Condition | SNOMED | YES | YES | NO |
| 4095572 | Appendix hematoma | Condition | SNOMED | YES | YES | NO |
| 28779 | Bleeding esophageal varices | Condition | SNOMED | NO | YES | NO |
| 4119169 | Cecal hematoma | Condition | SNOMED | YES | YES | NO |
| 4095094 | Colonic hematoma | Condition | SNOMED | YES | 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 |
| 192671 | Gastrointestinal hemorrhage | Condition | SNOMED | NO | YES | NO |
| 4106997 | Hematoma of ileum | Condition | SNOMED | YES | YES | NO |
| 46272978 | Hemorrhage of cecum | Condition | SNOMED | YES | YES | NO |
| 46273470 | Hemorrhage of cecum due to diverticulosis | Condition | SNOMED | YES | YES | NO |
| 442190 | Hemorrhage of colon | Condition | SNOMED | YES | YES | NO |
| 46273182 | Hemorrhage of jejunum | Condition | SNOMED | YES | YES | NO |
| 197925 | Hemorrhage of rectum and anus | Condition | SNOMED | YES | YES | NO |
| 4322061 | Hemorrhagic proctitis | Condition | SNOMED | YES | YES | NO |
| 4318829 | Ileal hemorrhage | Condition | SNOMED | YES | YES | NO |
| 4341790 | Large intestine anastomotic hemorrhage | Condition | SNOMED | YES | YES | NO |
| 4338225 | Peptic ulcer with perforation | Condition | SNOMED | NO | YES | NO |
| 4048602 | Perinatal rectal hemorrhage | Condition | SNOMED | YES | YES | NO |
| 4096781 | Rectal hematoma | Condition | SNOMED | YES | YES | NO |
| 4026112 | Rectal hemorrhage | Condition | SNOMED | YES | YES | NO |
| 46269841 | Rectal hemorrhage due to chronic ulcerative pancolitis | Condition | SNOMED | YES | YES | NO |
| 46269847 | Rectal hemorrhage due to chronic ulcerative proctitis | Condition | SNOMED | YES | YES | NO |
| 46269851 | Rectal hemorrhage due to chronic ulcerative rectosigmoiditis | Condition | SNOMED | YES | YES | NO |
| 46269891 | Rectal hemorrhage due to Crohn's disease | Condition | SNOMED | YES | YES | NO |
| 46269877 | Rectal hemorrhage due to Crohn's disease of large intestine | Condition | SNOMED | YES | YES | NO |
| 46269882 | Rectal hemorrhage due to Crohn's disease of small and large intestines | Condition | SNOMED | YES | YES | NO |
| 46269887 | Rectal hemorrhage due to Crohn's disease of small intestine | Condition | SNOMED | YES | YES | NO |
| 46269863 | Rectal hemorrhage due to inflammatory polyps of colon | Condition | SNOMED | YES | YES | NO |
| 46273478 | Rectal hemorrhage due to ulcerative colitis | Condition | SNOMED | YES | YES | NO |

### Potential confounders

The following will be included as potential covariates: (note: most covariates are assessed on or in the 365 days prior to index date)

* Demographics (age in 5-year increments, gender, race, ethnicity, year of index date, month of index date)
* Condition occurrence (one or more variables per diagnose code)
* Condition era (one or more variables per diagnose code)
* Condition group (one or more variables per MedDRA group or SNOMED groups)
* Drug exposure (one or more variables per drug code)
* Drug era (one or more variables per RxNorm ingredient)
* Drug group (one or more variables per ATC group)
* Procedure occurrence (one or more variables per procedure code)
* Observations (one or more variables per observation concept ID)
* Measurements (one or more variables per measurement concept ID, including variables for within / above / below normal range)
* Risk scores (including Charleston, DCSI, CHADS2, CHADS2VASc

For the full details see the OHDSI CohortMethod package (<https://github.com/OHDSI/CohortMethod>).

Variables with less than 100 non-zero values are discarded. All covariates were used in both the propensity model and the outcome model.

### Negative controls

Negative controls were selected using the following criteria:

* No evidence found in literature on clinical trials using the method proposed by Avillach [[6](#_ENREF_6)].
* No evidence found in literature using the method used in SemMedDB [[7](#_ENREF_7)].
* No evidence found in the structured product label (US and EU).
* FAERS Proportional Reporting Ratio (PRR) needed to be less than 2.

Negative controls were rank-ordered by prevalence, and manually reviewed until 50 controls were selected.

**Negative controls for Southworth and Graham replications:**

|  |  |
| --- | --- |
| Atelectasis | Malignant tumor of breast |
| Barrett's esophagus | Multiple sclerosis |
| Blepharitis | Neck pain |
| Bundle branch block | Neurologic disorder associated with MD |
| Cellulitis | Obesity |
| Chronic sinusitis | Osteomyelitis |
| Chronic ulcer of skin | Otitis media |
| Closed fracture | Peripheral vertigo |
| Communication disorder | Plantar fasciitis |
| Crohn's disease | Presbyopia |
| Curvature of spine | Prolapse of female genital organs |
| Diabetic renal disease | Psychotic disorder |
| Diabetic retinopathy | Seborrheic keratosis |
| Dislocation of joint | Simple goiter |
| Dyssomnia | Sleep apnea |
| Dysuria | Superficial mycosis |
| Effusion of joint | Urge incontinence of urine |
| Fracture of femur | Urinary tract infectious disease |
| Fracture of upper limb | Verruca vulgaris |
| Atelectasis | Malignant tumor of breast |
| Barrett's esophagus | Multiple sclerosis |
| Blepharitis | Neck pain |
| Bundle branch block | Neurologic disorder associated with MD |
| Cellulitis | Obesity |
| Chronic sinusitis | Osteomyelitis |

**Negative controls for the Tata replications:**

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

### Positive controls

Positive controls will be generated by starting with the negative controls where the relative risk is assumed to be equal to one, and adding additional outcomes during the time-at-risk until the target relative risk is achieved. For each negative control, three positive controls will be generated, with relative risks of 1.5, 2, and 4. To preserve the (observed) confounding during outcome injection, outcome models will be fitted for all negative control outcomes using the same covariates listed in the section ‘potential confounders’. The predicted probabilities generated by these models will be used to sample the outcomes to inject. For the Southworth and Graham replication a survival model will be used for injection. For the Tata replications a Poisson model will be used.

## Data Sources

**Southworth replication**

Optum ClinFormatics (Optum)

Optum is an administrative health claims database for members of United Healthcare, who enrolled in commercial plans (including ASO, 36.31M), Medicaid (prior to July 2010, 1.25M) and Legacy Medicare Choice (prior to January 2006, 0.36M) with both medical and prescription drug coverage. As of 30November2014, Optum contained 38m patients with patient-level observations from Oct2005 through Dec2013. Source codes used in Optum include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming Optum into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/optum/dashboard>.

**Graham replication**

MDCR is an administrative health claims database for Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans (predominantly fee-for-service plans). Only plans where both the Medicare-paid amounts and the employer-paid amounts were available and evident on the claims were selected for this database.. As of 30November2014, MDCR contained 9m patients with patient-level observations from Jan2000 through Jul2014. Source codes used in MDCR include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming MDCR into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/truven_mdcr/dashboard>.

**Tata replications**

Clinical Practice Research Datalink (CPRD)

CPRD is an anonymized longitudinal electronic health records from primary care practices in UK. Patient management system with many aspects of patient care covered, including diagnoses, prescriptions, signs and symptoms, procedures, labs, lifestyle factors, clinical and administrative/social data. As of 30November2014, CPRD contained 11m patients with patient-level observations from Jan1988 through Nov2013. Source codes used in CPRD include: conditions- Read; drugs: Multilex; procedures: OPCS.

The ETL specification for transforming CPRD into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/cprd/dashboard>.

All databases have been transformed into the OMOP Common Data Model version 5. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>.

## Sample Size and Study Power

For each replication study we computed the number of subjects meeting all study criteria, which in the Graham paper included matching on propensity scores, and in the Tata (case-control) replication included the cases and matched controls. Based on these numbers and the number of observed outcomes for these subjects we computed the minimum detectable relative risk (MDRR) given a target type I error rate (alpha) of 0.05, and a target power of 80%. For the Southworth and Graham replications, MDRR was calculated according to Schoenfeld [[8](#_ENREF_8)]. For the Tata study, MDRR was calculated according to Miettinen [[9](#_ENREF_9)] and Rothman & Boice [[10](#_ENREF_10)].

**Southworth replication**

|  |  |  |  |
| --- | --- | --- | --- |
| Dabigatran users | Warfarin users | Outcomes in exposed | MDRR |
| 6,357 | 21,622 | 1,589 | 1.18 |

**Graham replication**

|  |  |  |  |
| --- | --- | --- | --- |
| Dabigatran users | Warfarin users | Outcomes in exposed | MDRR |
| 19,055 | 50,360 | 764 | 1.25 |

**Tata replication**

|  |  |  |  |
| --- | --- | --- | --- |
| Cases | Controls | Fraction of controls that are exposed | MDRR |
| 31,984 | 190,760 | 0.02 | 1.12 |

## Quality control

The study R code and cohort definitions will undergo peer review.

The EmpiricalCalibration, MethodEvaluation, CohortMethod, SelfControlledCaseSeries, and CaseControl packages used in this study use unit tests for validation.

## Strengths and Limitations of the Research Methods

Strength

* Confidence interval calibration is demonstrated on multiple study designs
* The studies are replications of real published studies, so the results can be considered to be applicable to real life practice
* Both internal and external validity are evaluated

Limitations

* Only two pairs of studies are used, making it hard to generalize
* Using control outcomes limits our ability to detect bias that might be specific to the outcome of interest in the studies

# 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.

# Plans for Disseminating and Communicating Study Results

At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

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