OHDSI Celecoxib versus Non-Selective NSAIDs Protocol: Risk of Myocardial Infarction, GI Hemorrhage, Acute Renal Failure, and Angioedema in patients with osteoarthritis.

**Version:** 0.4

**Authors:**

Marc Suchard, MD, PhD, University of California, Los Angeles

Patrick Ryan, PhD, Janssen Research and Development

Martijn Schuemie, PhD, Janssen Research and Development

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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

ATC Anatomic Therapeutic Chemical

CYCLOPS Cyclic coordinate descent for logistic, Poisson and survival analysis

DCSI Diabetes Complications Severity Index

GI Gastro-Intestinal

MedDRA Medical Dictionary for Regulatory Activities

NSAID Non-Steroidal Anti-Inflammatory Drug

nsNSAID Non-Selective Non-Steroidal Anti-Inflammatory Drug

OHDSI Observational Health Data Sciences and Informatics

OMOP Observational Medical Outcomes Partnership

PRR Proportional Reporting Ratio

PS Propensity Scores

# Abstract

This study aims to evaluate the use of the CohortMethod package for comparative effectiveness studies. The CohortMethod package implements a new-user cohort study design, and uses large scale regularized regression with many potential covariates to fit both the propensity score and outcome models. The package directly queries data in the OMOP Common Data Model, and is therefore suited for running in a distributed research network.

Here we would like to provide a proof of principle of the CohortMethod package, and more specifically of our approach to generating and incorporating covariates into the cohort method. In order to this we will focus on the well-documented example of celecoxib vs nsNSAIDs for GI bleed. We would also like to show that studies implemented using the CohortMethod package can be easily deployed in a distributed research network, and across several other outcomes.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Date | Author(s) | Comments |
| 0.4 | 19 October 2015 | Martijn Schuemie  Patrick Ryan | Due to concerns over comparator group not being representative of nsNSAIDs, redefined comparator and regenerated negative control list. |
| 0.3 | 18 October 2015 | Martijn Schuemie  Patrick Ryan | Due to concerns over too few negative controls, the comparator group was restricted to a limited set of drugs, and the list of negative controls was regenerated. |
| 0.2 | 16 October 2015 | Martijn Schuemie | Added negative controls, removed analysis using full outcome model only due to computational complexity. |
| 0.1 | 7 October 2015 | 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 data is often used to estimate causal effects of prescription drugs on health outcomes. One popular study design that is used for this purpose is the cohort method, where we compare the risk of the outcome of interest in two groups (cohorts) of subjects. Typically the two groups represent two treatment options, where one option could be no treatment. In many ways the cohort method mimics a randomized controlled trial, except that the assignment of subjects to one of the two groups is not random. This non-random assignment can easily lead to confounding, when variables associated with the treatment assignment are predictors of the outcome.

Two options are often considered for reducing the risk of confounding. The first option is to fit a propensity score (PS) model, a model that tries to predict treatment assignment based on information available at the start of treatment, and use the PS to make the two groups more similar for example by stratifying the analysis based on PS. The second option is use an elaborate outcome model that tries to predict the outcome not only based on the treatment assignment, but also covariates that are potentially risk factors for the outcome. Traditionally, the covariates included in the PS model and outcome model are hand-picked based on expert assessment of potential for confounding. The CohortMethod package developed in OHDSI (Observational Health Data Science and Informatics) uses a different approach, where very large sets of covariates are created, and regularized regression is used to estimate models.

In the study described here we would like to provide a proof of principle of the CohortMethod package, and more specifically of our approach to generating and incorporating covariates into the cohort method. In order to this we will focus on the well-documented example of celecoxib vs nsNSAIDs for GI bleed. We would also like to show that studies implemented using the CohortMethod package can be easily deployed in a distributed research network, and across several other outcomes.

# Research Questions and Objectives

## Research Questions

Celecoxib is believed to have a lower risk profile for GI hemorrhage than nsNSAIDS. However, this fact is widely known and is expected to lead physicians to prefer prescribing celecoxib to patients who are at higher risk of GI hemorrhage to begin with, causing confounding by indication. We believe CohortMethod is capable of adjusting for this confounding, and detect the fact that celecoxib has a lower risk.

Primary hypothesis

* When comparing the risk of GI hemorrhage between celecoxib and nsNSAIDs using a fully adjusted model, the hazard ratio will be lower than 1

We expect that both adjusting using PS matching and adjusting using covariates in the outcome model will have an effect. We can estimate the amount of residual bias using negative control outcomes (outcomes not believed to be caused by celecoxib nor by nsNAIDs).

Secondary hypotheses 1 and 2:

* PS matching will reduce residual bias compared to no PS matching
* Using both PS matching and a full outcome model will reduce residual bias compared to using only PS matching.

Furthermore, we would like to test whether the CohortMethod package can be deployed in a distributed data network. The study described here will be implemented into an R package, and this package will be distributed to partners willing to execute it.

Secondary hypothesis 3

* The code implementing the study described here can be executed in a distributed network against a range of diverse databases.

## Objectives

Primary objective

* Show that the OHDSI CohortMethod is capable of reproducing known findings

Secondary objectives

* Show effect of various forms of adjusting for confounding
* Show feasibility of running CohortMethod in a distributed data network

# Research methods

## Study Design

### Overview

This study will be a retrospective, observational, new-user cohort study. 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 drugs of interest. By ‘cohort study’ we mean two cohorts, a treatment 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.

The treatment cohort will be new users of celecoxib. The comparator cohort will be new users of non-selective NSAIDs (nsNSAIDs). For both groups we restrict to people with osteoarthritis, one of the main indications for the drugs of interest. The outcomes of interest are Myocardial Infarction, GI Hemorrhage, Acute Renal Failure, and Angioedema Proportional hazard models will be used to assess the hazard ratios between the two exposure cohorts.

Adjustment for baseline confounders will be done in two ways: First, a propensity model will be fitted and used to create propensity scores (PS). These PS will be used to either match or stratify the treatment and comparator cohorts, and the proportional hazards outcome models will be conditioned on the matched sets of strata respectively. Second, covariates will be included in the outcome models.

Negative control outcomes (outcomes not believed to be caused by either celecoxib or nsNSAIDs) will also be included. The hazard ratios computed for these negative controls will be used to evaluate residual bias and compute calibrated p-values for the outcomes of interest [[1](#_ENREF_1)].

### 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 exposure to celecoxib or nsNSAID)

* Exposure to celecoxib or nsNSAID
* At least 183 days of observation time prior to the index date
* No exposure to any NSAID before the index date
* A diagnose of osteoarthritis on or preceding the index date
* No diagnose of the outcome of interest preceding the index date

### Additional analysis details

The propensity model 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.

Variable-ratio propensity score matching will be performed using greedy matching [[2](#_ENREF_2)]. A caliper of 0.25 times the standard deviation of the propensity score distribution will be used.

The outcome model will be fitted using a regularized conditional Cox regression with a LaPlace prior. The regularization hyperparameter will be selected be selected by optimizing the likelihood in a 10-fold cross-validation. No regularization will be applied to the coefficient corresponding to the treatment variable (i.e. those representing the hazard ratio of interest).

### Analysis variations

The following variations of the analysis will be performed:

Primary analysis:

* Using a PS model to match treated and comparator. The outcome model will be condition on the matched sets, and will include all covariates.

Secondary analysis:

* No PS model, a simple outcome model with only the treatment as predictor.
* Using a PS model to match treated and comparator. The outcome model will be condition on the matched sets, but will only contain the treatment as predictor.

## Variables

### Exposures

#### Celecoxib

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient celecoxib

Inclusion rules based on the index date:

* At least 183 days of observation time prior to the index date
* No exposure to any NSAID before the index date
* A diagnose of osteoarthritis on or preceding the index date
* No diagnose of the outcome of interest preceding the index date

#### Non-selective NSAID

Index rule defining the index date:

* First exposure to a drug containing any one of these ingredients: Naproxen, Ibuprofen, Diclofenac

Inclusion rules based on the index date:

* At least 183 days of observation time prior to the index date
* No exposure to any NSAID before the index date
* A diagnose of osteoarthritis on or preceding the index date
* No diagnose of the outcome of interest preceding the index date

### Outcomes

#### Myocardial infarction

Index rule defining the index date:

* Occurrence of a myocardial infarction code (excluding codes referring to an old myocardial infarction) as a primary diagnosis in an inpatient or emergency room setting

Inclusion rules based on the index date:

* Cannot have a myocardial infarction code (excluding codes referring to an old myocardial infarction) in the 90 days preceding the index date.

#### Myocardial infarction and ischemic death

Index rule defining the index date:

* Occurrence of a myocardial infarction code (excluding codes referring to an old myocardial infarction) as a primary diagnosis in an inpatient or emergency room setting, or
* Any occurrence of death

Inclusion rules based on the index date:

Either

* Occurrence of a myocardial infarction code (excluding codes referring to an old myocardial infarction) on the index date as a primary diagnosis in an inpatient or emergency room setting, and
* No myocardial infarction code (excluding codes referring to an old myocardial infarction) in the 30 days preceding the index date

Or

* Any occurrence of death on the index date, and
* A diagnose code indicating angina pectoris, coronary occlusion, preinfarction syndrome, or myocardial infarction (excluding codes referring to an old myocardial infarction) on the index date or on the day before the index date

#### Gastrointestinal hemorrhage

Index rule defining the index date:

* Occurrence of a gastrointestinal hemorrhage code as a primary diagnosis in an inpatient or emergency room setting

Inclusion rules based on the index date:

* Cannot have a gastrointestinal hemorrhage diagnose code in the 30 days preceding the index date.

#### Angioedema

Index rule defining the index date:

* Any occurrence of an angioedema diagnose code

Inclusion rules based on the index date:

* Cannot have an angioedema diagnose code in the 30 days preceding the index date.

#### Acute liver failure

Index rule defining the index date:

* Occurrence of an acute nephropathy code as a primary diagnosis in an inpatient or emergency room setting

Inclusion rules based on the index date:

* Cannot have an acute nephropathy diagnose code in the 30 days preceding the index date.

#### Drug-induced liver injury

Index rule defining the index date:

* Occurrence of a measurement of aminotransferase (aspartate or alanine) with a value at least three times the upper bound of the normal range

Inclusion rules based on the index date:

* Must have a measurement of bilirubin with a value at least twice the upper bound of the normal range in the 30 days before to the 30 days after the index date
* Cannot have a diagnose of viral hepatitis any time before the index date to 30 days after the index date
* Must have a measurement of alkaline phosphatase with a value at least twice the upper bound of the normal range any time before the index date to 30 days after the index date
* Cannot have a diagnose if liver damage any time before the index date

#### Heart failure

Index rule defining the index date:

* Occurrence of a heart failure code as a primary diagnosis in an inpatient or emergency room setting

Inclusion rules based on the index date:

* Cannot have a heart failure code in the 30 days preceding the index date

### 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 [[3](#_ENREF_3)].
* No evidence found in literature using the method used in SemMedDB [[4](#_ENREF_4)].
* No evidence found in the structured product label (US and EU).
* FAERS Proportional Reporting Ratio (PRR) needed to be less than 2.
* Sufficient exposure in a US healthcare database (Over 10,000 occurrence of the diagnoses code in the Truven CCAE database).

Negative controls were defined as any of the following diagnoses associated with an inpatient visit:

|  |  |  |  |
| --- | --- | --- | --- |
| Hb SS disease | Ectropion | Developmental academic disorder | |
| Scoliosis deformity of spine | Purulent otitis media | Rectal mass | |
| Synovial cyst | Otorrhea | Uterine prolapse | |
| Curvature of spine | Abnormal reflex | Diabetic coma with ketoacidosis | |
| Genital herpes simplex | Astigmatism | Diabetes mellitus with hyperosmolar coma | |
| Hydrocele | Benign neoplasm of brain | Malignant tumor of breast | |
| Aseptic necrosis of bone | Retinal dystrophy | Tumor of hypothalamus | |
| Fibrocystic disease of breast | Otitis externa | Malignant tumor of head and neck | |
| Inflammatory disorder of breast | Chalazion | Neoplasm of sigmoid colon | |
| Bone cyst | Secondary malignant neoplastic disease | Neoplasm of pituitary gland | |
| Carcinoma in situ of breast | Deficiency of macronutrients | Fracture of radius | |
| Rectal prolapse | Dysthymia | Neoplasm of rectum | |
| Tinea pedis | Precocious sexual development | Dilatation of aorta | |
| Dental caries | Premature ejaculation | Traumatic brain injury | |
| Viremia | Borderline personality disorder | Disorder of lymphatic vessel | |
| Vesicular eczema of hands and/or feet | Sleep-wake schedule disorder | Pruritus of genital organs | |
| Atrophic condition of skin | Toxic effect of alcohol | Disease due to Papilloma virus | |
| Injury of forearm | Narcolepsy | Disorder of carotid artery | |
| Cachexia | Cervical incompetence | Post-traumatic wound infection | |
| Benign neoplasm of endocrine gland | Respiratory syncytial virus infection | Mastitis |  |
| Skin striae | Intracranial injury | Polyp of large intestine | |
| Ingrowing nail | Failure to thrive | Nodular goiter | |
| Hypoparathyroidism | Hypersomnia | Orchitis |  |
| Verruca vulgaris | Bulimia nervosa | Candidiasis of skin | |
| Molluscum contagiosum infection | Excessive eating - polyphagia | Diabetic retinopathy | |
| Simple goiter | Assault | Murmur |  |
| Paraplegia | Lymphangitis | Tenosynovitis | |
| Urge incontinence of urine | Mental retardation | Infectious enteritis | |
| Nocturnal enuresis | Aphasia | Pulmonic valve stenosis | |
| Premature rupture of membranes | Neoplasm of uncertain behavior of brain and spinal cord | Onychomycosis | |
| Prostatitis | Encopresis | Alcoholism | |
| Hypercortisolism | Torticollis | Viral hepatitis, type A | |
| Polycystic ovaries | Cystic fibrosis | Bladder dysfunction | |
| Vesicoureteric reflux | Human papilloma virus infection | Cutis laxa |  |
| Condyloma acuminatum | Oligomenorrhea | Respiratory failure | |
| Prolapse of female genital organs | Developmental language disorder | Neurogenic dysfunction of the urinary bladder | |
| Congenital uterine anomaly | Vascular dementia | Tracheitis | |
| Pneumothorax | Diabetic oculopathy | Pupillary disorder | |
| Viral pneumonia | Injury of foot | Schizoaffective disorder | |
| Atelectasis | Injury of face | Inguinal hernia | |
| Dissecting aneurysm of artery | Localized infection | Malignant hypertension | |
| Stricture of artery | Tracheobronchitis | Prolapse of intestine | |
| Tachypnea | Hyperandrogenization syndrome | Local infection of wound | |
| Aortic aneurysm | Intracranial aneurysm | Nonreassuring fetal status | |
| Renovascular hypertension | Diabetic neuropathy | Closed fracture | |
| Pulmonary valve disorder | Deformity of foot | Infection of tooth | |
| Presbyopia | Colles' fracture | Testicular mass | |
| Retinopathy of prematurity | Disability | Hypertensive emergency | |
| Cerebral ischemia | Soft tissue injury | Hypertensive crisis | |

### Other variables

Osteoarthritis will be identified using the concept for osteoarthritis and any of its descendants in the OMOP Vocabulary.

## Data Sources

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)
* Clinical Practice Research Datalink (CPRD)
* <<add others who agree to participate>>

Truven MarketScan Commercial Claims and Encounters (CCAE)

CCAE is an administrative health claims database for active employees, early retirees, COBRA continues, and their dependents insured by employer-sponsored plans (individuals in plans or product lines with fee-for-service plans and fully capitated or partially capitated plans). As of 30November2014, CCAE contained 117m patients with patient-level observations from Jan2000 through Jul2014. Source codes used in CCAE 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 CCAE 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_ccae/dashboard>.

Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)

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>.

Truven MarketScan Multi-state Medicaid (MDCD)

MDCD is an administrative health claims database for the pooled healthcare experience of Medicaid enrollees from multiple states. As of 30November2014, MDCD contained 16m patients with patient-level observations from Jan2006 through Dec2012. Source codes used in MDCD 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 MDCD 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_mdcd/dashboard>.

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>.

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>.

*Database X*

*Database X description*

The ETL specification for transforming *Database X* into the OMOP CDM is available at:  *ETL\_specification\_URL*

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available at: *URL to ACHILLES*.

## Sample Size and Study Power

?

## Quality control

We will evaluate the PS by

* Inspection of the fitted PS model for large coefficients (indicative of model-misspecification) and predictors that we cannot explain (post-hoc).
* Inspection of the PS distribution.
* Evaluation of covariate balance after matching using the standardized difference in means between treatment and comparator cohort before and after matching [[5](#_ENREF_5)]. Standardized differences greater than 0.2 will be reported and investigated.

We will investigate the outcome model by

* Inspection of the fitted outcome model for large coefficients and predictors that we cannot explain (post-hoc).

The error distribution estimated using the negative controls will be used to estimate residual bias after adjustments.

The CohortMethod package itself, as well as other OHDSI packages on which CohortMethod depends, use unit tests for validation.

## 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 and full outcome models allow balancing on a large number of baseline potential confounders.
* Use of negative 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.
* Several nsNSAIDs are available over the counter and will not be captured in any of the observational databases. We are therefore likely to misclassify some prevalent users as new users.
* It is unknown whether and to what extends misclassification of any of the outcomes occurs, and whether any such misclassification affects the results. Because we are using outcome controls, we cannot use these to measure bias that is specific to the outcomes of interest.

# 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

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.

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