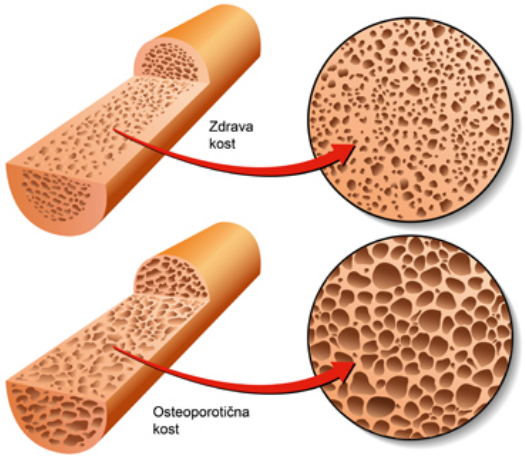
OHDSI Network in Action: The Risk of Angioedema associated with Levetiracetam Use

OHDSI Network Studies

OHDSI Network Studies



Idea

OHDSI Network Studies

Anyone interested in looking at ASA effects on osteoporosis?

Staff

jon_duke < 1m

Hi, I'm an endocrinologist at MUNC and have been looking at this question of whether aspirin causes bone loss and can lead to osteoporosis. The data out there are pretty conflicting. Here's the conclusion for a recent review paper.

> Despite a positive effect on bone mineral density, the limited human epidemiological studies revealed that aspirin could not reduce fracture risk. A study even suggested that the use of aspirin increased fracture risk. As a conclusion, aspirin may increase bone mineral density but its effect on fracture prevention is inconclusive. More data are needed to determine the effects of aspirin and bone health in human.

Is anyone else interested in taking a look at this?

Reply

Discussion

forums.ohdsi.org

Anyone working on opioid crisis related projects?

Researchers

shawndolley May 16

Folks, I am engaging with some stakeholders with funding opportunities for work related to preventing, stopping, understanding the US opioid addiction public health crisis. If anyone here is doing or interested in working in this area, can you let me know at sdolley@cloudera.com or dial 202.460.4660?

Reply

created	last reply	12	390	8	1
May 16	May 25	replies	views	users	link

A

Andrew Andrew Williams May 16

Hi Shawn
I'm interested in finding out more.
Andrew

Reply

F

farbodr Fred R. May 16

I'm interested too. We are in process of setting up OMOP (still a couple of months away). We've done some prelim work using claims data for about 800k members. Would love to get involved in something like this.

FR

Reply

OHDSI Network Studies

Protocol

ohdsi.org/web/wiki

< Title of the research study >

Objective: *<summarize study objective>*

Rationale: *<summarize study rationale>*

Project Lead(s): *<initial proposers, list may grow>*

Coordinating Institution(s): *<your institution>*

Additional Participants: *<usually blank initially, list will grow as individuals are added who are not project leads>*

Full Protocol: *<if available, a link to protocol. not necessary for initial planning>*

Initial Proposal Date:

Launch Date: *<fill out once finalized>*

Study Closure Date: ***<fill out once finalized>***

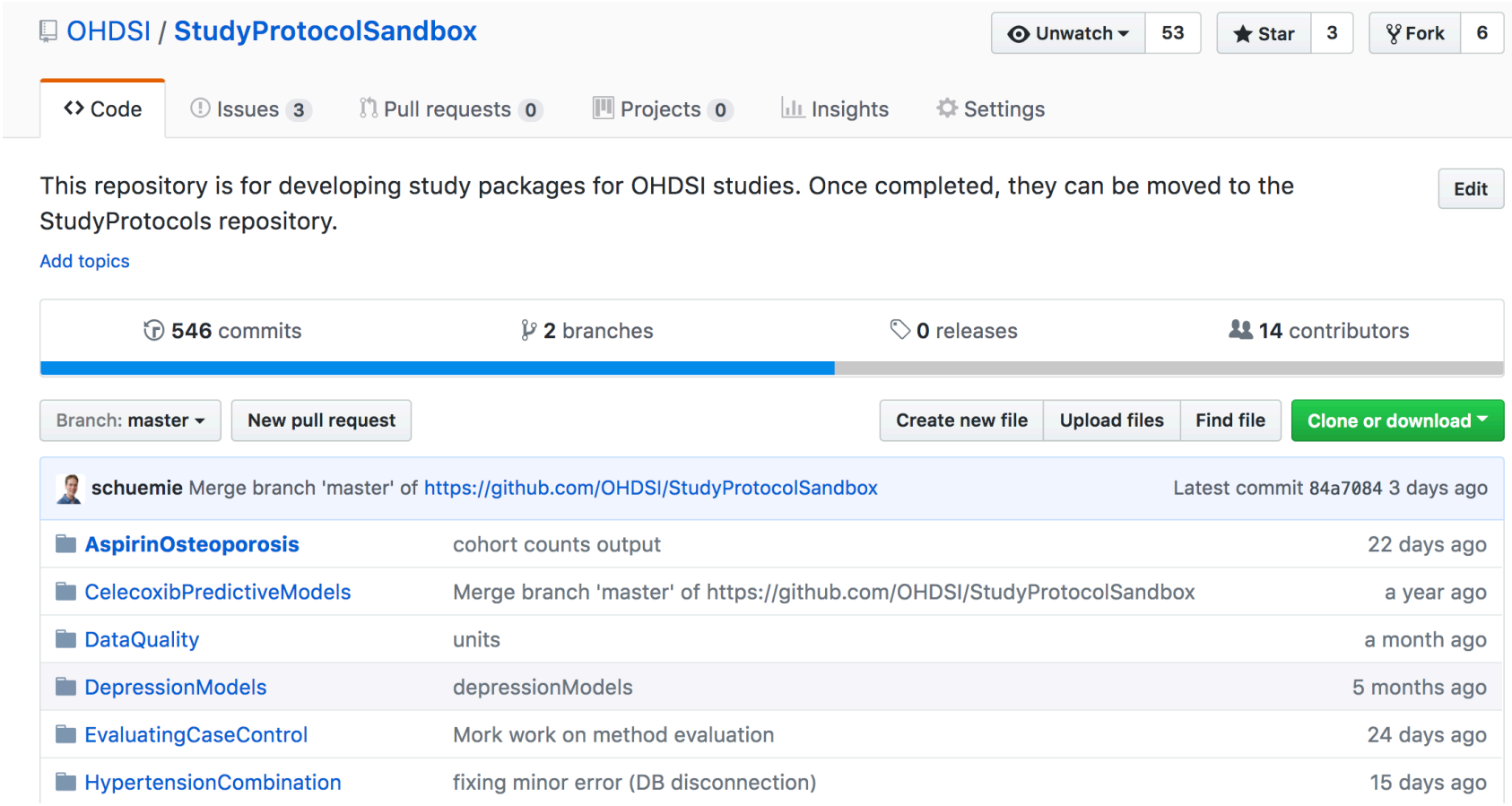
Results Submission: *<method of sumission, eg. Email or SFTP>*

Requirements

CDM: *<V4 or V5 or both>*

Table Accessed: *<e.g., person, drug_exposure, observations>*

OHDSI Network Studies



OHDSI / StudyProtocolSandbox

Unwatch 53 | Star 3 | Fork 6

Code | Issues 3 | Pull requests 0 | Projects 0 | Insights | Settings

This repository is for developing study packages for OHDSI studies. Once completed, they can be moved to the StudyProtocols repository.

Edit

Add topics

546 commits | 2 branches | 0 releases | 14 contributors

Branch: master | New pull request | Create new file | Upload files | Find file | Clone or download

schuemie Merge branch 'master' of https://github.com/OHDSI/StudyProtocolSandbox — Latest commit 84a7084 3 days ago

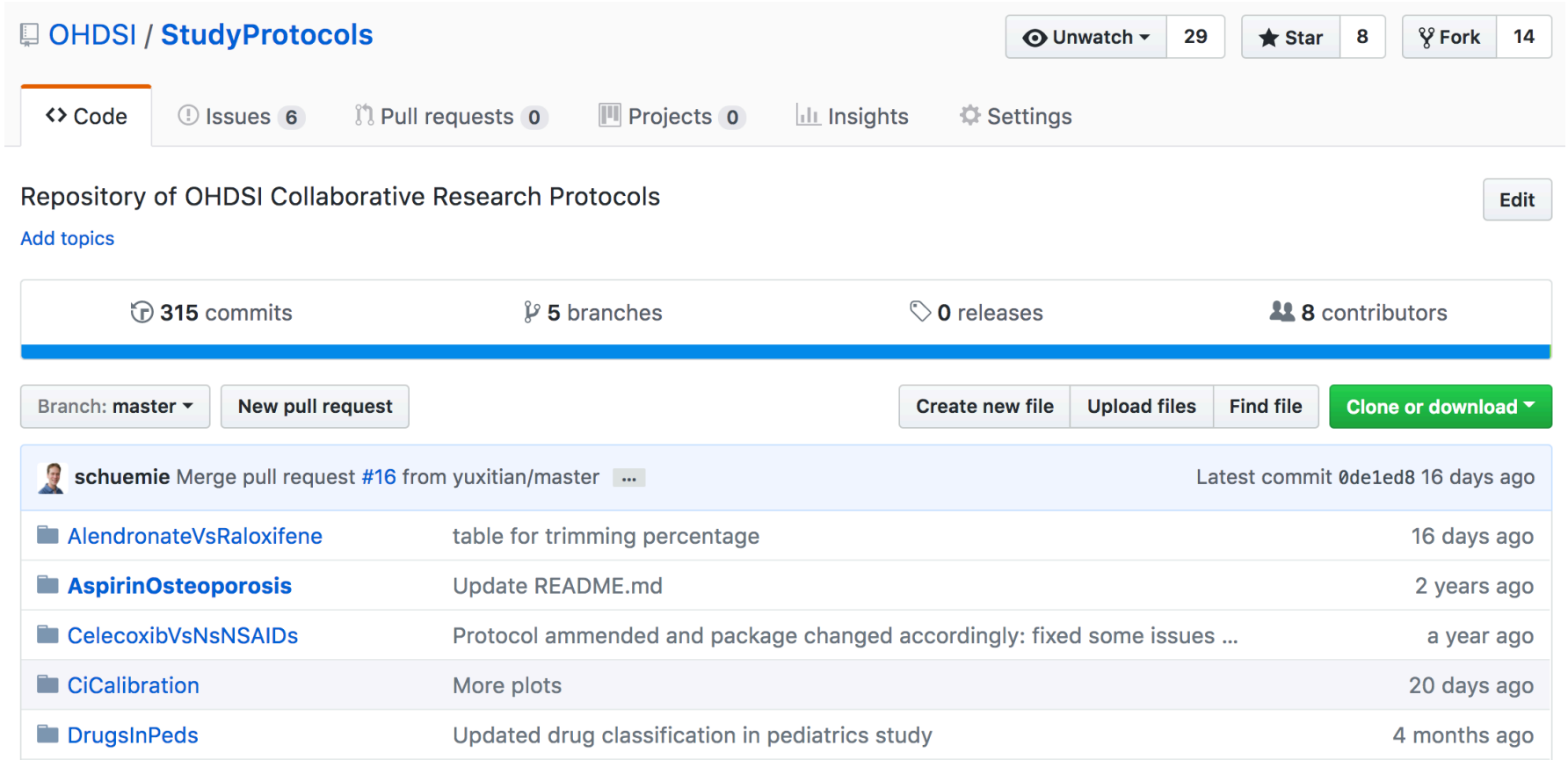
AspirinOsteoporosis	cohort counts output	22 days ago
CelecoxibPredictiveModels	Merge branch 'master' of https://github.com/OHDSI/StudyProtocolSandbox	a year ago
DataQuality	units	a month ago
DepressionModels	depressionModels	5 months ago
EvaluatingCaseControl	Mork work on method evaluation	24 days ago
HypertensionCombination	fixing minor error (DB disconnection)	15 days ago

Preliminary Code

github.com/ohdsi

```
90    if (runAnalyses) {
91      writeLines("Running analyses")
92      cmAnalysisListFile <- system.file("settings",
93                                        "cmAnalysisList.txt",
94                                        package = "AlendronateVsRaloxifene")
95      cmAnalysisList <- CohortMethod::loadCmAnalysisList(cmAnalysisListFile)
96      drugComparatorOutcomesListFile <- system.file("settings",
97                                                    "drugComparatorOutcomesList.txt",
98                                                    package = "AlendronateVsRaloxifene")
99      drugComparatorOutcomesList <- CohortMethod::loadDrugComparatorOutcomesList(drugComparatorOutcomesListFile)
100     CohortMethod::runCmAnalyses(connectionDetails = connectionDetails,
101                                 cdmDatabaseSchema = cdmDatabaseSchema,
102                                 exposureDatabaseSchema = workDatabaseSchema,
103                                 exposureTable = studyCohortTable,
104                                 outcomeDatabaseSchema = workDatabaseSchema,
105                                 outcomeTable = studyCohortTable,
106                                 outputFolder = cmOutputFolder,
107                                 oracleTempSchema = oracleTempSchema,
108                                 cmAnalysisList = cmAnalysisList,
109                                 cdmVersion = 5,
110                                 drugComparatorOutcomesList = drugComparatorOutcomesList,
111                                 getDbCohortMethodDataThreads = 1,
112                                 createStudyPopThreads = min(3, maxCores),
113                                 createPsThreads = 1,
114                                 psCvThreads = min(16, maxCores),
115                                 computeCovarBalThreads = min(3, maxCores),
116                                 trimMatchStratifyThreads = min(10, maxCores),
117                                 fitOutcomeModelThreads = max(1, round(maxCores/4)),
118                                 outcomeCvThreads = min(4, maxCores),
119                                 refitPsForEveryOutcome = FALSE)
```

OHDSI Network Studies



Final Code

OHDSI Network Studies

Branch: master ▾ StudyProtocols / AspirinOsteoporosis / Create new file | Upload files | Find file | History

jreps Update README.md — Latest commit ee718b8 on Oct 19, 2015

- ..
- R
- documents
- inst
- man
- tests
- .Rbuildignore
- .gitignore
- AspirinOsteoporosis.Rproj
- DESCRIPTION
- NAMESPACE
- README.md

README.md

OHDSI Risk of Os

Requirements

- A database in Common Data Model version 5 in one of these platforms: SQL Server, Oracle, PostgreSQL, Amazon RedShift, or Microsoft APS.
- R version 3.2.2 or newer
- On Windows: RTools
- Java
- 100 GB of free disk space

Recommended

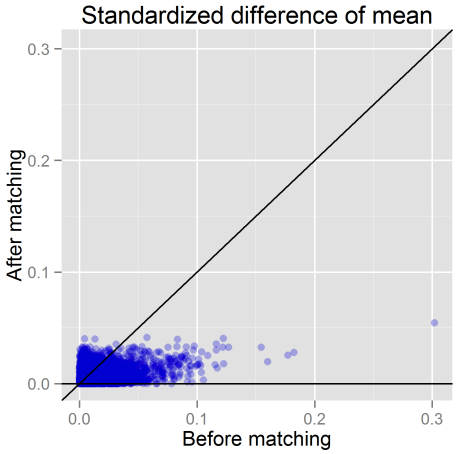
- 8 CPU cores or more
- 32 GB of memory or more

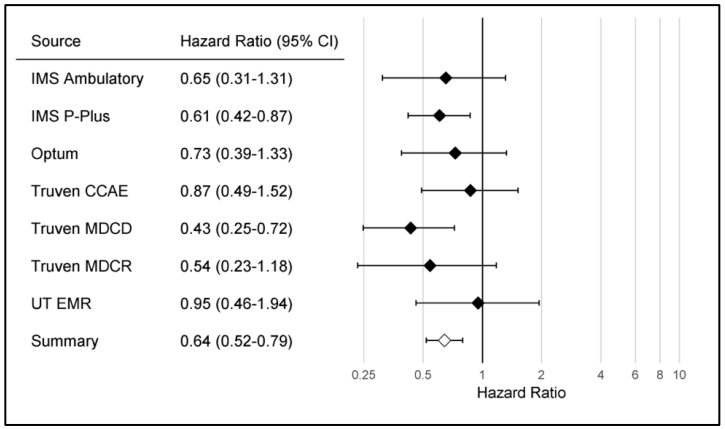
How to run

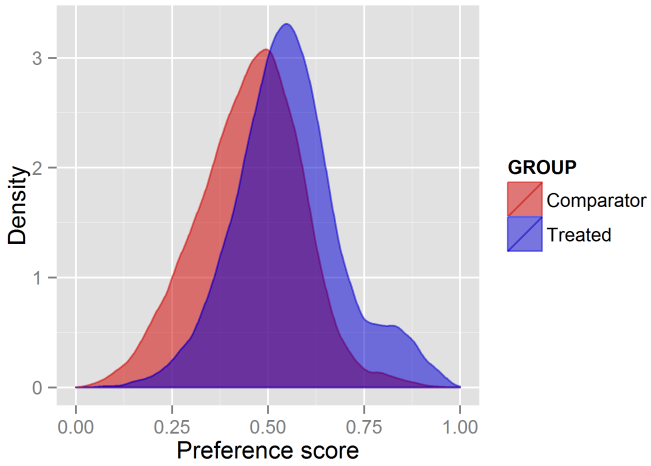
1. Make sure that you have Java installed, and on Windows make sure that RTools is installed. See the OHDSI Wiki for help on setting up your R environment
2. In `R`, use the following code to install the study package and its dependencies:

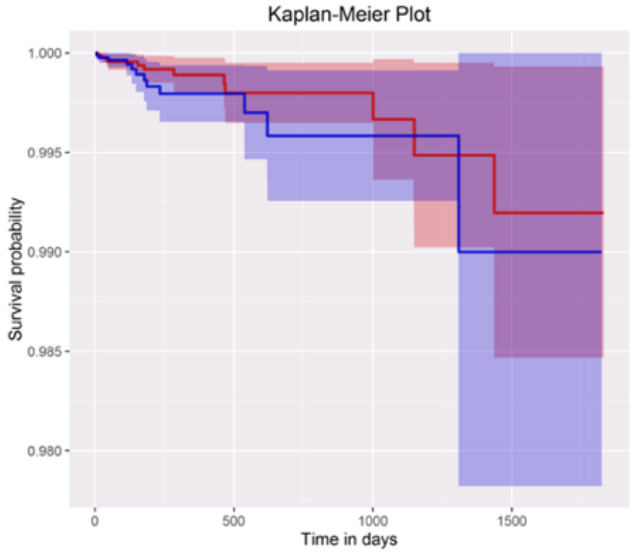
Run at Sites

OHDSI Network Studies









Results

OHDSI Network Studies

Risk of Osteoporosis Associated with Aspirin Use: Findings of the Observational Health Data Sciences and Informatics Research Network

[1]Observational Health Data Sciences and Informatics (OHDSI) Consortium
[2]Georgia Institute of Technology
[3]Janssen Research and Development
[4]University of California Los Angeles
[5]Columbia University
[6]Quintiles-IMS
[7]University of Texas Health Science Center at Houston
[8]Stanford University

Microsoft Office User
Should we change to OHDSI?

Draft Paper!

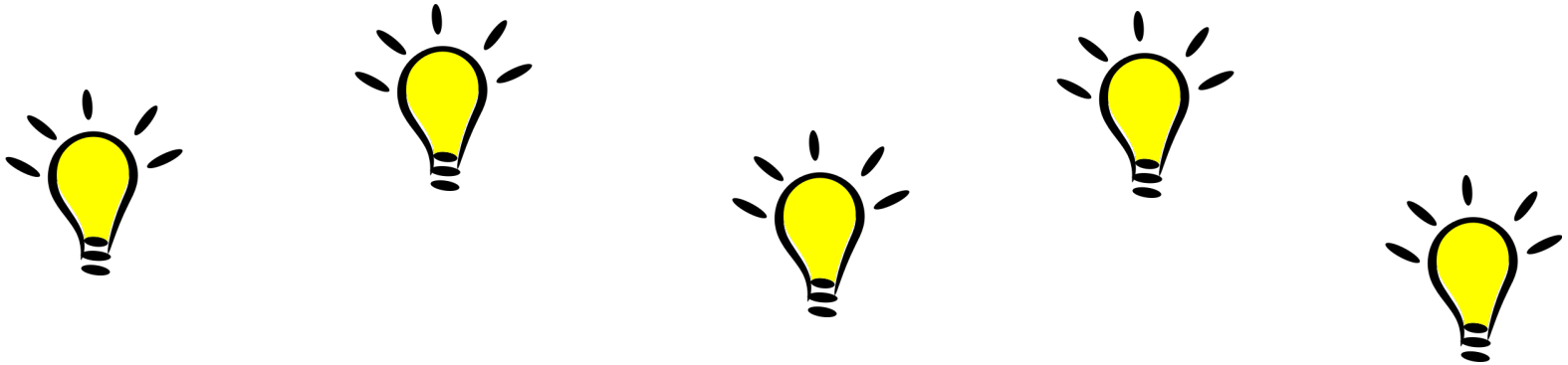
OHDSI Network Studies

ORIGINAL ARTICLE

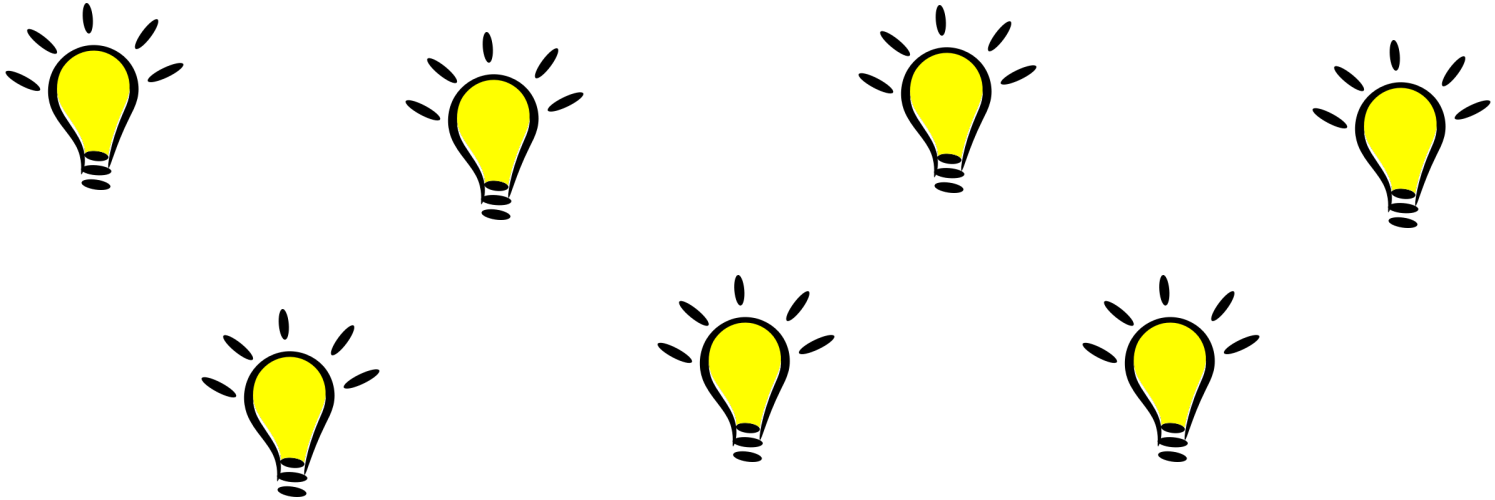
Risk of Osteoporosis with Aspirin Use: Findings of the OHDSI Network

Disseminate!

OHDSI Network Studies



All it takes is an **Idea** to get started.



FDA Highlights a Potential Risk

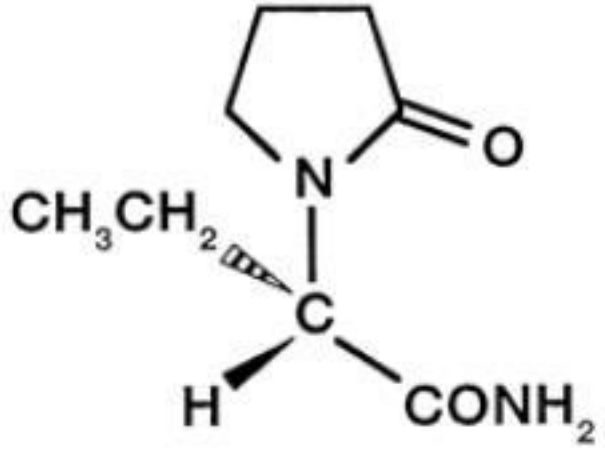
Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS) between October - December 2015

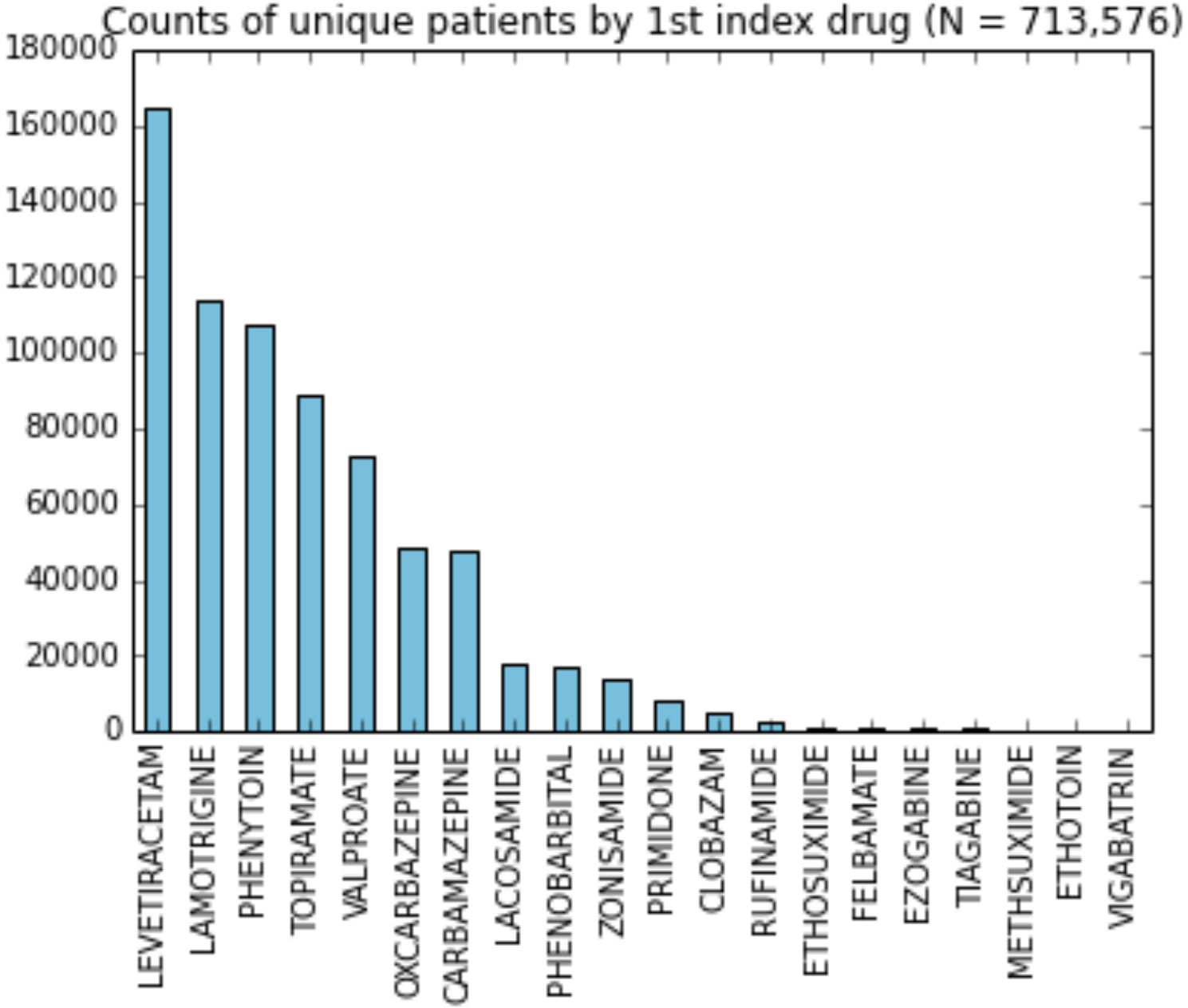
Keppra (levetiracetam) tablet, oral solution, injection	Angioedema	FDA is evaluating the need for regulatory action.

What is Levetiracetam?

Anticonvulsants

Drug	Mechanism of action	Modern approach	Other indications
Carbamazepine	**Na+** channel blocker: binds inactive Na channel, extend inactivation	simple partial, complex partial, secondary generalized (narrow)	bipolar disorder, trigeminal neuralgia
Phenytoin	**Na+** channel blocker: complex actions	simple partial, complex partial, secondary generalized (narrow)	n/a
Lamotrigine	**Na+** channel blocker: selective for excitatory neuron NT like glutamate	all seizure types (broad spectrum)	bipolar disorder; antidepressant effects
Ethosuximide	**Ca2+** channel blocker (α subunit, T type, thalamic)	**absence** seizures (narrow spectrum)	n/a; just first line for absence seizures
Phenobarbital	**GABA** antagonist: augments GABA receptor (Cl channel)	simple partial, complex partial, secondary generalized (narrow)	Tremors (similar to primidone for essential tremor)
Valproate	many: blocks Na, enhance GABA, block Ca	all seizure types (broad spectrum)	Migraine prophylaxis, bipolar disorder
Topiramate	many: blocks Na, enhance GABA, block glutamate (NMDA) receptor	all seizure types (broad spectrum)	Migraine prophylaxis
Gabapentin	unknown or partially known mechanism	simple partial, complex partial, secondary generalized (narrow)	Neuropathic pain, chronic pain
Pregabalin	unknown or partially known mechanism	simple partial, complex partial, secondary generalized (narrow)	Neuropathic pain; fibromyalgia
Levetiracetam	unknown or partially known mechanism	all seizure types (broad spectrum)	n/a




Counts of unique patients by 1st index drug (N = 713,576)
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
LEVETIRACETAM
LAMOTRIGINE
PHENYTOIN
TOPIRAMATE
VALPROATE
OXCARBAZEPINE
CARBAMAZEPINE
LACOSAMIDE
PHENOBARBITAL
ZONISAMIDE
PRIMIDONE
CLOBAZAM
RUFINAMIDE
ETHOSUXIMIDE
FELBAMATE
EZOGABINE
TIAGABINE
METHSUXIMIDE
ETHOTOIN
VIGABATRIN

What is Angioedema?

Why is it hard to study?

- Angioedema is very rare
- Hereditary form incidence 1/50000
- Drug-induced angioedema is more common but still rare as we have seen (reported rates with ACE-inhibitors ranging from 2 to 7/1000 person-years
- Perfect opportunity for a network study!

Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. Hypertension. 2008 Jun 1;51(6):1624-30.

OHDSI Springs into Action!

Protocol Development

- Transparent protocol development

3 Abstract

This study aims to evaluate angioedema risk in seizure disorder patients exposed to Keppra (levetiracetam) compared with those exposed to phenytoin sodium. A potential link between levetiracetam and angioedema has been recently raised by the Food and Drug Administration in their review of spontaneous reporting data. In this study, we will analyze data from a distributed network using the OHDSI CohortMethod package.

4 Amendments and Updates

0.1	18 April 2016	Jon Duke	Initial draft
0.2	30 April 2016	Jon Duke	Added negative controls and updates exclusion criteria
0.3	2 May 2016	Jon Duke	Updated negative controls
0.4	3 May 2016	Jon Duke	Additional edits to negative controls
0.5	17 May 2016	Martijn Schuemie	Updated Methods section

Levetiracetam and Risk of Angioedema in patients with Seizure Disorder

Objective: To assess the risk between exposure to Keppra (levetiracetam) and angioedema.

Rationale: The Food and Drug Administration (FDA) has recently announced that they are evaluating the need for regulatory action regarding a potential association between exposure to the anti-seizure drug Keppra and angioedema. OHDSI seeks to support evidence generation for questions of importance to FDA and other stakeholders seeking to protect and promote the public's health.

Project Lead(s): Jon Duke, Patrick Ryan, Marc Suchard, George Hripcsak, [?Adler], Christian Reich, Yuriy Khoma, Marie-Sophie Schwalm, Yonghui Hu, [Stanford- Juan?], Martijn Schuemie.

Coordinating Institution(s): Regenstrief Institute / Georgia Tech

Participating Institution(s): Regenstrief Institute, Georgia Tech, Janssen Research and Development, Columbia University, University of California Los Angeles, University of Texas Houston, Stanford University, QuintilesIMS.

Full Protocol: Keppra and Angioedema Risk Protocol

Initial Proposal Date: 5/3/2016

Launch Date: 5/18/2016

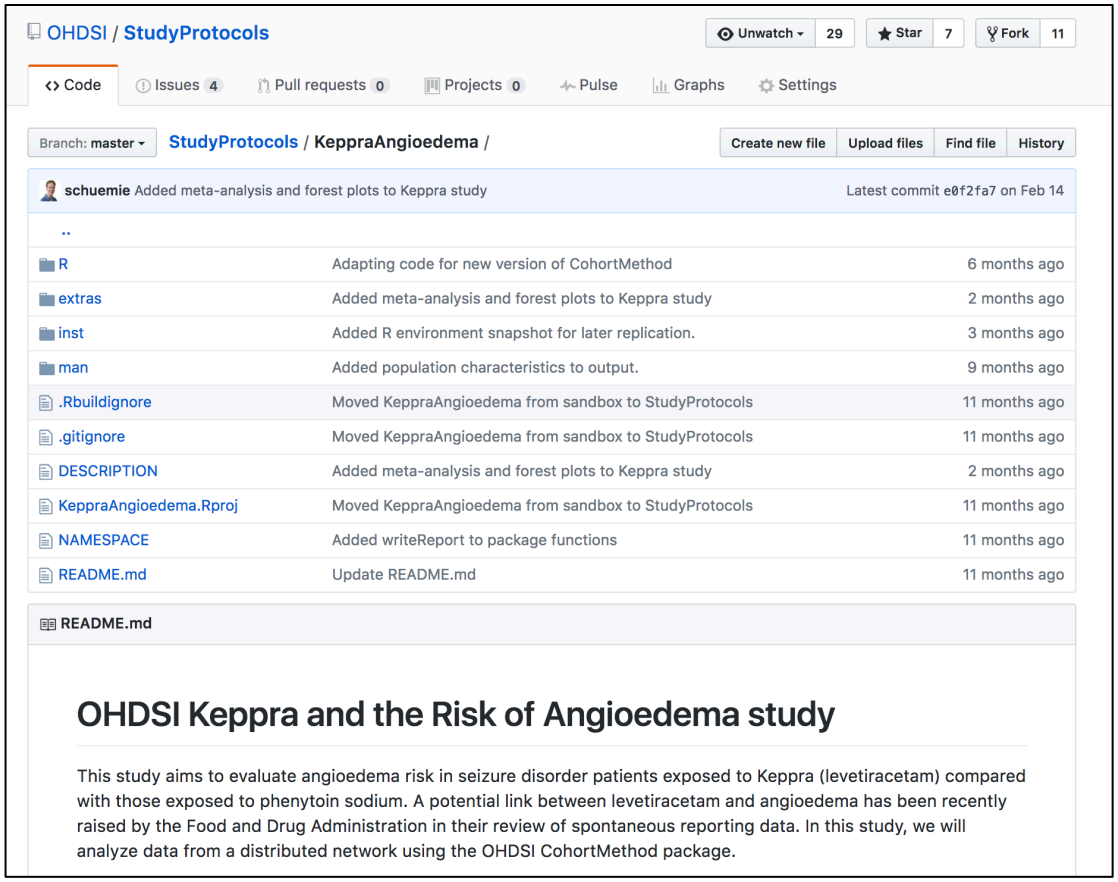
Receive Results for Analysis Date: 7/15/2016

Study Closure Date: 12/1/2016 (**Study closed**)

Results Submission: Via the OHDSI Sharing module embedded in study or via Email.

Code Development

- Leveraged OHDSI CohortMethod R package
- Code tested at 2 sites prior to study start
- All code posted on GitHub



Study Overview

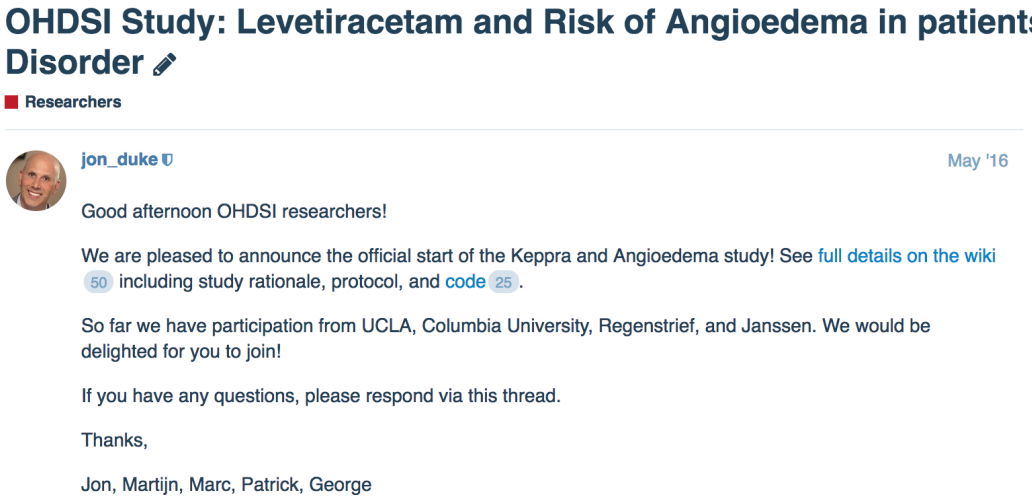
- Retrospective observational new-user cohort study
- Inclusion: Exposure to levetiracetam or phenytoin with prior diagnosis of seizure disorder
  - Phenytoin selected because common first-line anti-seizure treatment, no labeled warning for angioedema after 60 yrs on market, PRR <1 for phenytoin and angioedema in FAERS
- Outcome: diagnosis of angioedema during the time at risk (per protocol and intent-to-treat)
- Exclusion: <6 months continuous observation prior to exposure, previous dx of angioedema

Study Overview

- PS-matched treatment and comparator cohorts using variable ratio matching
- Cox proportional hazard models to assess HRs
- To identify residual bias, calculated HRs for 100 negative controls in order to compute calibrated p-values for angioedema in each dataset
- Performed meta-analysis if low heterogeneity between databases (I^2<.25) and min residual bias
- Set a nominal type 1 error rate of 5% without adjusting for multiple testing

Study Announced

- Once protocol was completed and the code tested, study was announced on forums



OHDSI Study: Levetiracetam and Risk of Angioedema in patients with Seizure Disorder

Researchers

jon_duke May '16

Good afternoon OHDSI researchers!

We are pleased to announce the official start of the Keppra and Angioedema study! See full details on the wiki 50 including study rationale, protocol, and code 25.

So far we have participation from UCLA, Columbia University, Regenstrief, and Janssen. We would be delighted for you to join!

If you have any questions, please respond via this thread.

Thanks,

Jon, Martijn, Marc, Patrick, George

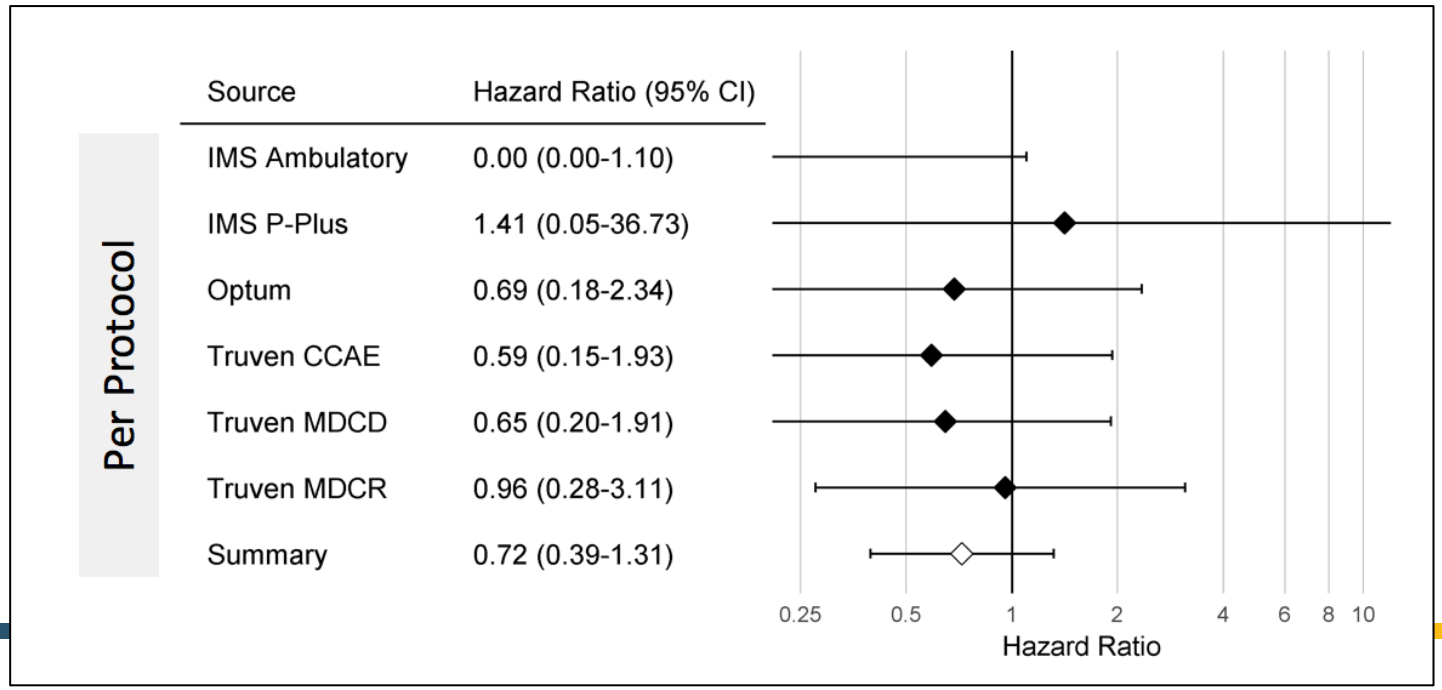
- 50 viewed protocol, 25 viewed the code, and 7 sites ran the code on 10 databases (5 claims / 5 EHR)

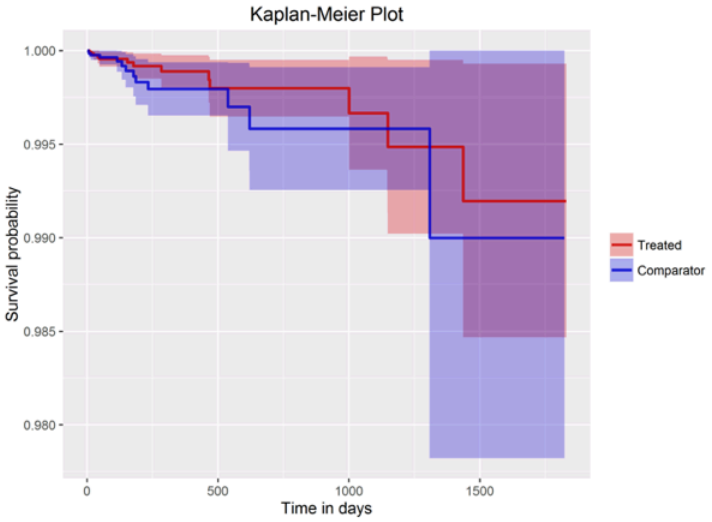
Cohorts

- Per protocol: 59,367 levetiracetam users matched with 74,550 phenytoin users
  - cumulative follow-up of 11,199,152 and 10,597,206 days respectively
- Intent to treat: 75,056 levetiracetam users matched with 95,598 phenytoin users
  - cumulative observation periods of 80,164,173 and 96,182,651 days respectively

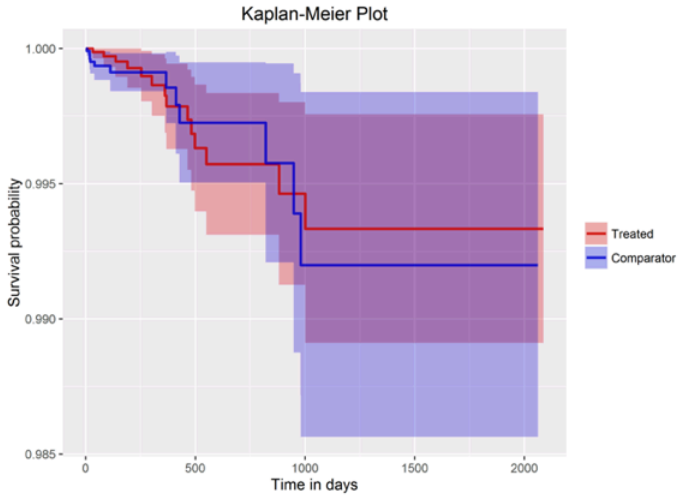
Per Protocol Results

		Levetiracetam			Phenytoin				
	Source	Patients	Days Treated	Events	Patients	Days Treated	Events	Hazard Ratio (CI)	p-value (calibrated)
Per Protocol	IMS P-Plus	6,893	351,090	2	7,745	398,827	2	1.41 (0.05 - 36.73)	0.83 (0.79)
	Optum	10,819	3,150,504	14	14,115	3,030,739	19	0.69 (0.18 - 2.34)	0.57 (0.62)
	Truven_CCAE	13,088	3,549,812	13	16,234	2,962,530	14	0.59 (0.15 - 1.93)	0.41 (0.45)
	Truven_MDCD	8,227	1,883,518	15	9,969	1,666,857	19	0.65 (0.20 - 1.91)	0.45 (0.55)
	Truven_MDCR	4,592	1,400,797	8	6,433	1,564,355	14	0.96 (0.28 - 3.11)	0.94 (0.94)
	IMS Ambulatory	8,762	618,757	1	10,732	730,158	3	0.00 (0.00 - 1.41)	0.23 (0.23)
	Cerner Health Facts (UT)	5,584	54,852	1	7,624	93,543	0	---	---
	Columbia	501	111,307	0	603	68,251	0	---	---
	IMS French_EMR	7	552	0	37	2,463	0	---	---
	Stanford EMR	404	12,313	0	460	13,525	0	---	---

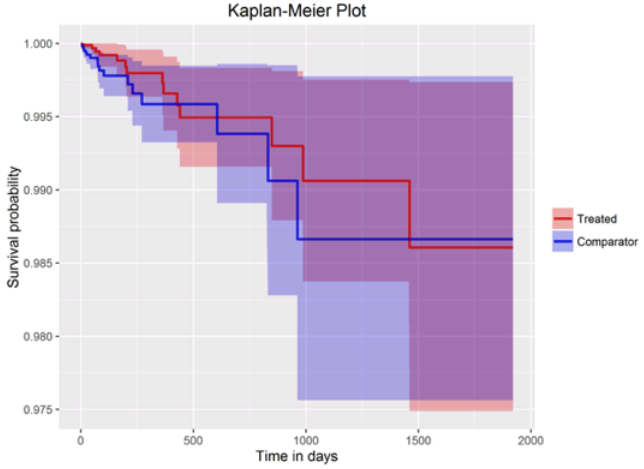




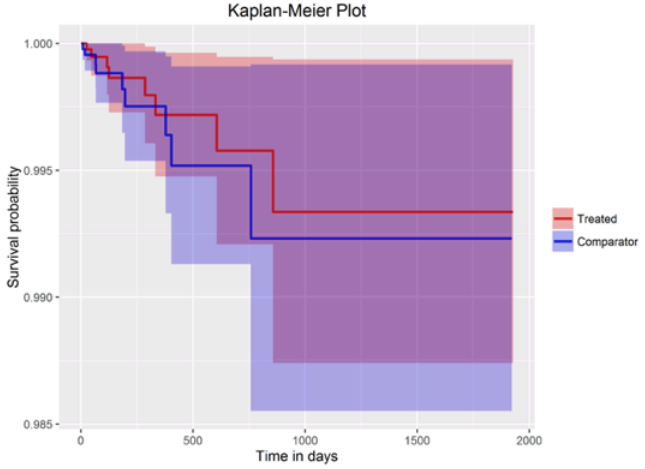
CCAE



OPTUM



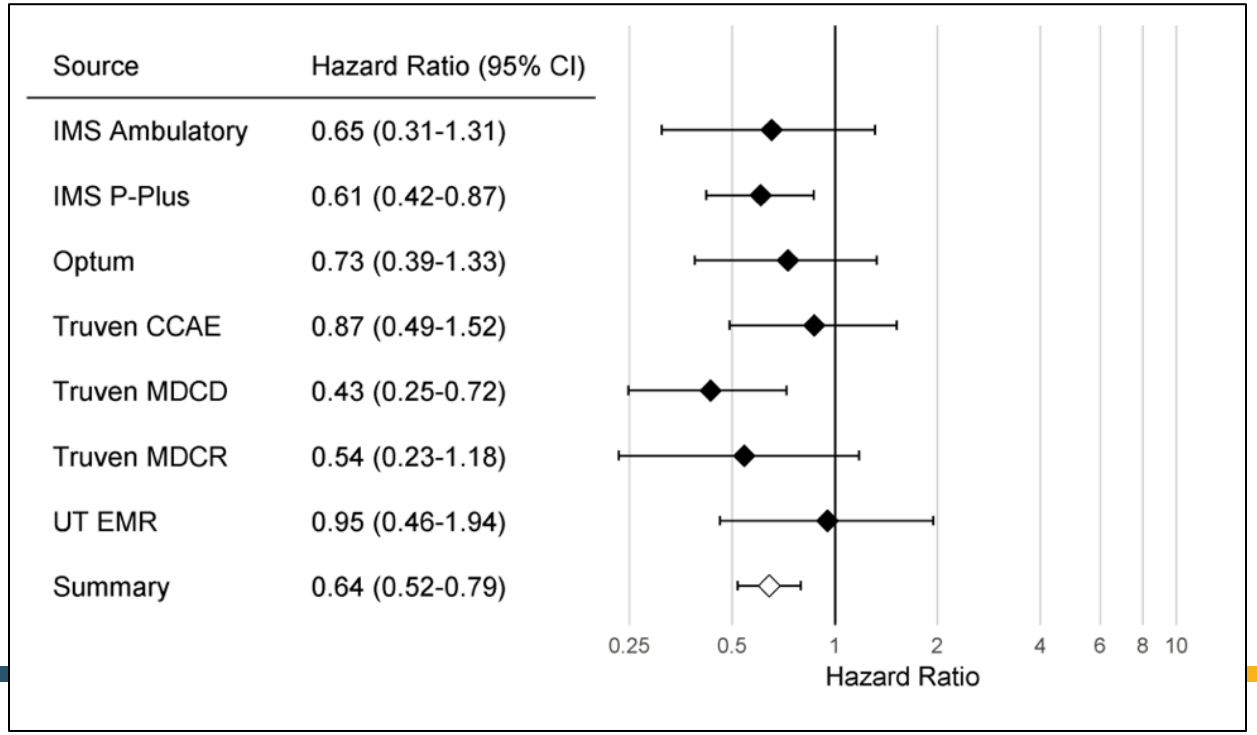
MDCD

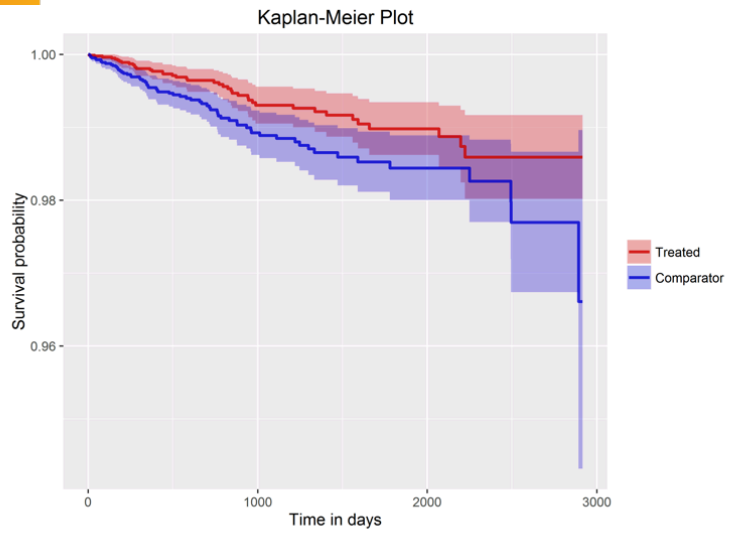


MDCR

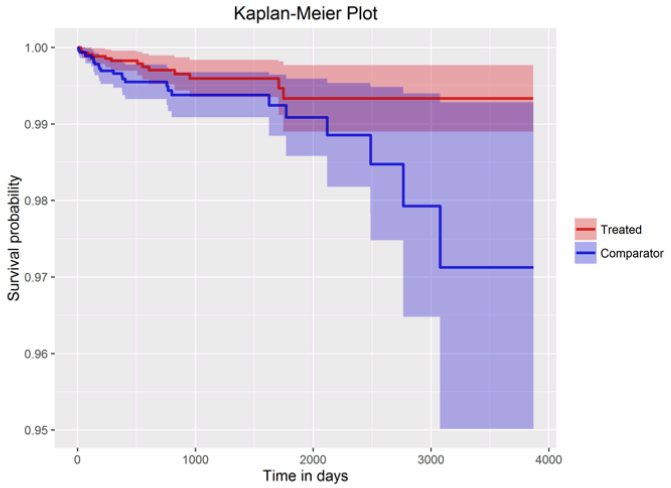
Intent to Treat Results

		Levetiracetam			Phenytoin				
	Source	Patients	Days Treated	Events	Patients	Days Treated	Events	Hazard Ratio (CI)	p-value (calibrated)
Intent-to-Treat	IMS P-Plus	18,213	16,233,093	78	21,631	18,398,218	117	0.61 (0.42 - 0.87)	0.01 (0.008)
	Optum	10,890	9,101,161	31	14,254	10,818,306	65	0.73 (0.39 - 1.33)	0.31 (0.36)
	Truven_CCAE	13,434	11,347,801	41	16,886	13,390,915	61	0.87 (0.49 - 1.52)	0.63 (0.57)
	Truven_MDCD	8,536	7,328,658	41	11,688	9,603,677	96	0.43 (0.25 - 0.72)	0.00 (0.002)
	Truven_MDCR	4,656	4,317,982	15	6,534	5,516,323	37	0.54 (0.23 - 1.18)	0.14 (0.19)
	IMS Ambulatory	8,762	9,978,497	19	10,732	12,739,915	28	0.65 (0.31 - 1.31)	0.25 (0.25)
	Cerner Health Facts (UT)	9,094	5,842,344	22	12,076	8,229,377	29	0.95 (0.46 - 1.94)	0.90 (0.69)
	Columbia	553	523,215	1	686	643,655	1	---	---
	IMS French_EMR	7	5,542	0	37	45,559	0	---	---
	Stanford EMR	404	342,136	0	460	411,371	0	---	---

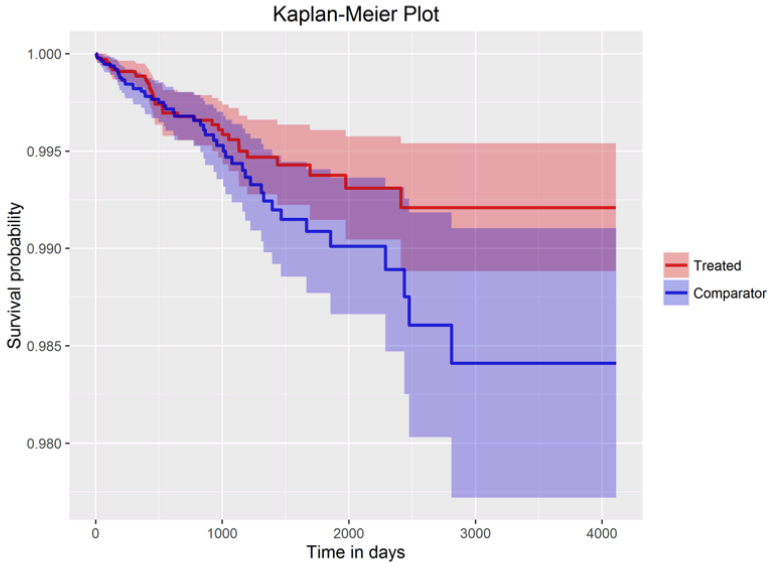




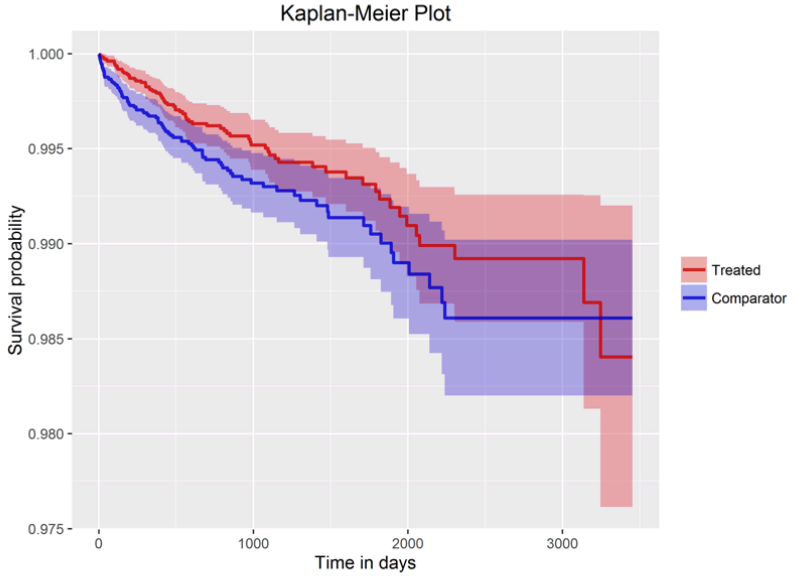
Truven Medicaid



Truven MDCR



Truven CCAE



IMS Pplus

Summary

- No evidence of increased angioedema risk with levetiracetam use compared with phenytoin use
- Results were consistent across datasets including both claims and EHR data
- Further analysis of phenytoin angioedema risk and risk across all anti-epileptic drugs is warranted

Epilepsia®
Official Journal of the International League Against Epilepsy

"Using a large international health care data network, the authors have measured angioedema risk in patients exposed to levetiracetam and compared this to the risk patients exposed to phenytoin. ***The study is focused, appears well designed, and provides new insight that should be of interest to clinicians and regulators.****"*

"Well conducted study with an impressive data material that you were able to combine these databases. ***This is an important contribution to improved pharmacovigilance.****"*

(Impact Factor 4.7)

Epilepsia
Official Journal of the International League Against Epilepsy

Risk of angioedema associated with levetiracetam compared with phenytoin: Findings of the observational health data sciences and informatics research network

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