**Retrospective RWE Study Protocol**

**Cover Page**

|  |  |  |
| --- | --- | --- |
| **Short title:** | Comparison of cardinality matching and propensity score matching | |
| **Study Identifier: 46317**  *(Should match identifier from RPD)* | Protocol Version:  Initial | Protocol Date: June 20, 2019 |
| **Research Project Title:** | Comparison of cardinality matching and propensity score matching to adjust for potential confounding: a retrospective study of new users of angiotensin-converting enzyme inhibitor versus thiazide or thiazide-like diuretic monotherapy | |
| **Study Champion** *(one person’s Name)*: | Stephen Fortin | |
| **Study Champion Function** *(select from drop-down list):* | OHDA | |
| **Segment** *(select from drop-down list):* | Janssen | |

**Project Team Information**

|  |  |
| --- | --- |
| **Provide names of the following contributors:** |  |
| **Study Champion:** | **Stephen Fortin** |
| **Primary Programmer/Analyst:** | **Stephen Fortin** |
| **Biostatistician:** | Stephen Fortin & Martijn Schuemie |
| **Other Design Input:** | **Stephen Johnston** |
| **Protocol Classification** *(select from drop-down list):* | Low Risk |

**Note:** Higher-Risk protocol-based studies are those that assess outcomes related to Johnson & Johnson (J&J) branded products (comparative or non-comparative), compare outcomes related to interventions or technologies, and/or are generate evidence for regulatory activities (e.g., seeking a claim or indication

Table of Contents

[1. Protocol Synopsis 3](#_Toc11925978)

[2. List of Abbreviations 4](#_Toc11925982)

[3. Rationale and Background 4](#_Toc11925983)

[4. Research Questions and Objectives 5](#_Toc11925984)

[4.1 Research Question 5](#_Toc11925985)

[4.2 Research Objectives 5](#_Toc11925986)

[4.2.1 Primary objective(s): 5](#_Toc11925987)

[4.2.2 Secondary objective(s): 5](#_Toc11925988)

[5. Research Methods 5](#_Toc11925989)

[5.1 Data Source(s) 5](#_Toc11925990)

[5.2 Study Design 6](#_Toc11925991)

[5.2.1 Inclusion criteria 6](#_Toc11925992)

[5.2.2 Exclusion Criteria 6](#_Toc11925993)

[5.3 Variables 6](#_Toc11925995)

[5.3.1 Primary Independent Variable(s) 6](#_Toc11925996)

[5.3.2 Subgroup/Stratification Variable(s) 6](#_Toc11925997)

[5.3.3 Covariates 7](#_Toc11925998)

[5.3.4 Sample Size and Study Power 8](#_Toc11925999)

[5.4 Data Analysis(es) 9](#_Toc11926000)

[5.4.1 Bivariate Analyses 9](#_Toc11926001)

[5.4.2 Propensity Score Matching 10](#_Toc11926002)

[5.4.3 Adjusted Analyses of Outcomes 10](#_Toc11926003)

[5.4.4 Cardinality Matching Sensitivity Analyses 10](#_Toc11926004)

[5.5 Quality Control 10](#_Toc11926005)

[5.6 Limitations of the Research Methods 11](#_Toc11926006)

[6. Protecting the Confidentiality of the Data Obtained 11](#_Toc11926007)

[7. Management and Reporting of Complaints and Adverse Events 11](#_Toc11926008)

[8. Plans for Disseminating and Communicating Study Results 12](#_Toc11926009)

[9. References 12](#_Toc11926010)

[10. Appendices 13](#_Toc11926011)

[11. Major Amendments 13](#_Toc11926012)

[12. Project Milestones 13](#_Toc11926013)

# Protocol Synopsis

| Title | Comparison of cardinality matching and propensity score matching to adjust for confounding: a retrospective study of new users of angiotensin-converting enzyme inhibitor versus thiazide or thiazide-like diuretic monotherapy |
| --- | --- |
| **Study Objectives** | Primary objective(s): To compare the performance of cardinality matching and propensity score matching at various pre-match sample sizes and parameter settings in terms of the following:   1. Post-match sample size 2. Distributional balance of matching covariates 3. Distributional balance of matching covariate candidates 4. Residual confounding |
| **Data Sources** | IBM® MarketScan® Commercial Claims and Encounters Database standardized to OHDSI’s Observational Medical Outcomes Partnership common data model version 5.3 |
| **Study Design** | Retrospective study using a comparative new user cohort design |
| **Study Population** | The study population will comprise patients with a diagnosis of hypertension who are new users of angiotensin-converting enzyme inhibitor or thiazide or thiazide-like diuretic monotherapy initiated on drug therapy between October 1, 2014 and January 1, 2017, and with no history of treatment with primary antihypertensive medications in the prior 365 days. |
| **Endpoints** | Primary objective(s):  1. Post-match sample size 2. Standardized mean difference (SMD) of matching covariates 3. SMD of covariate candidates (i.e., all observed covariates as defined in §5.5.3) 4. Expected absolute systematic error of the empirical null distribution of negative control outcomes |
| **Data Analyses** | Analyses will be performed across 4 sample groups of varying sample size, including the study population, 10% subsample, 1% subsample, and 0.5% subsample groups. The 10%, 1% and 0.5% subsample groups will include 5, 50 and 100 subsample draws, respectively. Analyses will be performed within each subsample draw independently, and results will be considered jointly within each sample group.  Propensity score and cardinality matching will be performed within each subsample draw, and matching covariates will be identified through a combination of heuristic feature selection and regularized lasso regression. The impact of parameter settings within each matching method will be tested; caliper settings will be tested for propensity score matching, and marginal distributional balance constraints and target estimand specifications will be tested for cardinality matching.  Cox proportional hazards models will be fit in the pre-match and post-match samples for each subsample draw. Markov Chain Monte Carlo will be used to fit the null distribution of joint negative control outcomes across sample groups, and the empirical null distribution will be used to calibrate hazard ratio estimates, 95% confidence intervals and p-values. |

# List of Abbreviations

|  |  |
| --- | --- |
| Abbreviation | Definition |
| ACEI | Angiotensin-converting enzyme inhibitor |
| ATC | Average Treatment Effect on the Controls |
| CCAE | IBM® MarketScan® Commercial Claims and Encounters |
| CCI | Charlson-Romano Comorbidity Index |
| CI | Confidence Interval |
| DCSI | Diabetes Complications Severity Index |
| HR | Hazard Ratio |
| MCMC | Markov Chain Monte Carlo |
| IRB | Institutional Review Board |
| J&J | Johnson & Johnson |

# Rationale and Background

Propensity score matching is the most ubiquitous matching technique for causal inference in observational research. However, propensity score matching is susceptible to substantial bias and large variance in estimates due to limited overlap of covariate distributions between study groups1,2. Furthermore, the number of matching covariates used may be restricted to avoid potential model over-parameterization3. These limitations are especially pronounced in studies including small sample sizes.

A novel matching technique, cardinality matching, uses recent advancements in integer programming to find the largest sample size meeting a set of prespecified balance criterion thereby overcoming the potential limitations of propensity score matching. For instance, investigators may prespecify exact marginal distributional balance or a maximum standardized mean difference of matching covariates between study groups. Cardinality matching also permits for the specification of a target estimand allowing for the estimation of average treatment effects in target populations (e.g., average treatment effect on the controls [ATC])4.

In a recent study, Suchard et al. describe a comprehensive framework to perform large scale analyses in observational research. The authors apply this framework to perform a comprehensive comparative effectiveness and safety study of first-line antihypertensive drug classes, including a comparison of angiotensin converting enzyme inhibitors (ACEI) vs. thiazide or thiazide-like diuretic monotherapy for the safety outcome of angioedema. Potential pitfalls of observational research, such as residual confounding, are addressed by the framework through large-scale propensity adjustment and negative control outcome experiments5.

The purpose of this study is to compare the performance of propensity score and cardinality matching at various sample sizes and parameter settings in the context of a safety study of angioedema among new users of ACEI vs. thiazide or thiazide-like diuretic monotherapy applying the framework setforth by Suchard et al. Performance of propensity score and cardinality matching will be assessed based on post-match sample size, balance of covariate candidates and matching covariates, and residual confounding.

# Research Questions and Objectives

All research questions and objectives will be addressed in the context of a retrospective, observational study comparing the safety outcome of angioedema between new users of ACEI vs. thiazide or thiazide-like diuretic monotherapy diagnosed with hypertension in a real-world setting.

## Research Question

How does cardinality matching perform in controlling for potential confounding as compared to propensity score matching?

## Research Objectives

To assess the performance of cardinality matching and propensity score matching in controlling for potential confounding. To determine the impact of sample size on the performance of cardinality matching and propensity score matching.

### Primary objective(s):

To compare the performance of cardinality matching and propensity score matching at various pre-match sample sizes and parameter settings in terms of the following:

1. Post-match sample size
2. Distributional balance of matching covariates
3. Distributional balance of covariate candidates
4. Residual confounding

# Research Methods

## Data Source(s)

This study will use administrative claim records contained in the IBM® MarketScan® Commercial Claims and Encounters (CCAE) Database, which primarily consists of de-identified, patient-level health data from over 142 million individuals enrolled in employer-sponsored health insurance plans in the United States. The CCAE database includes adjudicated health insurance claims (e.g., inpatient, outpatient, and prescription) and enrollment data from large employers and health plans who provide private insurance coverage. Data was standardized to OHDSI’s Observational Medical Outcomes Partnership common data model version 5.3, which maps international coding systems into standard vocabulary concepts.

## Study Design

This will be a retrospective study using a comparative new user cohort design. Comparisons will be made between new users of ACEI vs. thiazide or thiazide-like diuretic monotherapy diagnosed with hypertension.

### Inclusion criteria

Patients must meet ALL the following criteria to be included in the study:

* Drug exposure to an ACEI, thiazide or thiazide-like diuretic for the first time in a patient’s history between October 1, 2014 and January 1, 2017 (index = date of first drug exposure)
* Continuous observation within the database for a minimum of 365 days prior to index
* Minimum of 1 day at risk of angioedema (e.g., continuous observation within the database for a minimum of 1 day post-index)
* Diagnosis code for hypertensive disorder at or within 365 days prior to index

### Exclusion Criteria

Patients meeting any of the following will be excluded from study:

* Diagnosis code for angioedema at or any time prior to index
* Drug exposure within the past 365 days to any active ingredient within the five drug classes listed in the 2017 AHA/ACC Guidelines as primary agents for the treatment of hypertension, including:
  + ACEIs, thiazide or thiazide-like diuretics, angiotensin receptor blockers, dihydropyridine calcium channel blockers, or non-dihydropyridine calcium channel blockers6
* Drug exposure at or within 7 days post-index to 2 or more active ingredients within the five drug classes listed in the 2017 AHA/ACC Guidelines as primary agents for the treatment of hypertension

## Calculation of Time-at-Risk

Patient time-at-risk will be defined following the intention-to-treat principle; patients will be followed from day 1 post-treatment initiation to the earliest of July 31, 2019 or end of continuous observation within the database.

References:

1. Montori VM, Guyatt GH. Intention-to-treat principle. CMAJ. 2001 (165):1339-1341.

## Sample Groups

The primary analysis will include the following 4 sample groups:

* Study population group
* 10% subsample group
* 1% subsample group
* 0.5% subsample group

The study population group will consist of the entire study population, and the 10%, 1% and 0.5% subsample groups will include a total of 5, 50 and 100 subsample draws, respectively. Each subsample draw will be performed by random sampling without replacement from the study population stratified by study comparison group. Analyses will be performed on each subsample draw independently, and results will be considered jointly within each sample group.

## Variables

All variables will be identified by SNOMED codes, which are standard vocabulary concepts mapped from international coding systems.

### Primary Independent Variable(s)

For all primary and secondary research objectives, the study’s independent variable will be treatment with an ACEI vs. thiazide or thiazide-like diuretic at index.

### Subgroup/Stratification Variable(s)

There will be no subgroup/stratification variables.

### Covariates

Study covariates will be created using the OHDSI Feature Extraction library.

#### Patient Demographics

* Age: patient age at index will be grouped into categories in 5-year increments, e.g.: 0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, and 65-69 years
* Sex: male or female

#### Event Characteristics

* Year of index event: 2014, 2015, 2016
* Month of index event

#### Patient Clinical Characteristics

One covariate will be created for each of the following:

* All observed conditions, drug exposures grouped according to the Anatomical Therapeutic Chemical classification system, procedures, device exposures, measurement values, and observations occurring within the long-term window (i.e., at or within 365 days prior to index) or short-term window (i.e., at or within 30 days prior to index)
* All observed drug exposures grouped according to the Anatomical Therapeutic Chemical classification system within the time-at-risk window

The following characteristics will be measured based on all observed conditions occurring prior to the end of the time-at-risk window:

* Charlson-Romano Comorbidity Index (CCI): the CCI is an aggregate measure of comorbidity created by using select diagnoses associated with chronic disease (e.g., heart disease, cancer). Higher scores are indicative of greater comorbid burden. The CCI includes 19 medical conditions and weights these conditions from +1 to +67.
* Diabetes Complications Severity Index (DCSI): the DCSI is an aggregate measure of diabetes complications severity created based on a 13-point scale scored from automated clinical baseline data (e.g., diagnostic, pharmacy, and laboratory data)8.
* CHADS2 score: the CHADS2 (congestive heart failure, hypertension, age≥75 years, diabetes mellitus, previous stroke/transient ischemic attack (TIA) [double weight]) score is an aggregate measure created by using select diagnoses and patient demographics associated with risk of stroke. Scores range from 0-6 with higher scores indicative of higher risk of stroke9.
* CHA2DS2-VASc score: the CHA2DS2-VASc (vascular disease, age 65–74 years, female sex category) score is an aggregate measure of risk of stroke that supplements the CHADS2 score. Scores range from 0-9 with higher scores indicative of higher risk of stroke10.

#### Outcomes for Primary Objective(s)

1. Post-match sample size
2. Standardized mean difference (SMD) of matching covariates with a minimum of 2 observations
   1. A minimum of 2 observations are necessary for SMD calculations
3. SMD of covariate candidates (i.e., all observed covariates as defined in §5.5.3) with a minimum of 2 observations
4. Expected absolute systematic error of the empirical null distribution of negative control outcomes

### Sample Size and Study Power

All research questions and objectives will be addressed through analyses of new users of ACEI vs. thiazide or thiazide-like diuretic monotherapy, and analyses will be performed independently across all subsamples drawn for each sample group described in §5.4. While it is expected that insufficient negative control outcomes will occur across individual sample draws for the 0.5%, 1% and 10% subsample groups to generate inferences, a sufficient number of negative control outcomes are expected when results from subsample draws are considered jointly within their respective sampling groups.

Power calculations were not performed as primary objective of the study is to compare cardinality matching and propensity score matching rather than the comparison of the risk of angioedema events between new users of ACEI vs. thiazide or thiazide-like diuretic monotherapy among patients with hypertension. That being said, a total of 172,696 patients met the study eligibility criteria. The sample size of each sample group stratified by study comparison group is listed in Table 5.4.4a.

**Table 5.4.4a. Sample size of each sample group stratified by study comparison groups.**

|  |  |  |
| --- | --- | --- |
|  | ACEI | Thiazide or thiazide-like diuretic |
| Study population group | 125,914 | 43,812 |
| 10% subsample group | 12,907 | 4,303 |
| 1% subsample group | 1290 | 430 |
| 0.5% subsample group | 645 | 215 |

## Data Analysis(es)

### Propensity Score Matching

For each study comparison group, a propensity score model will be fit through regularized lasso regression in which the outcome will be a binary indicator for the potential comparator (e.g., variable = 1 if patient is in the ACEI group, variable = 0 if the patient is in the thiazide or thiazide-like diuretics group). Covariate candidates will include all patient demographic, event characteristics and patient clinical characteristics, and heuristic feature selection will be used to limit covariate candidates to those with a frequency >0.1%. The extent of overlap in the distribution of propensity and preference (scaled propensity) scores between study comparison groups will be examined to provide information regarding the pre-match comparability of groups11.

Patients will be matched to one another at a 1:1 ratio using the nearest neighbor technique, without replacement. Propensity score matching will be performed twice, enforcing a separate caliper of 0.10 and 0.20 within each match. SMDs, as defined by Rosenbaum et al (see equation 1), will be used to assess the post-match balance of covariate candidates and matching covariates, defined as covariates with a non-zero regularized lasso regression beta coefficient12. A balanced covariate will be defined by an absolute SMD <0.10. Post-match balance of covariate candidates and matching covariates will be assessed in terms of summary statistics (e.g., range, mean, median, interquartile range, standard deviation) of absolute SMDs and frequency of covariate balance. Analyses will be conducted in R version 3.6.3 using the CohortMethods package.

**Equation 1.** SMD = (x̄treatment - x̄comparator) / sp

\*x̄treatment and x̄comparator refer to the mean of the covariate in the treatment and comparator groups in the post-match sample, respectively, and sp refers to the pooled standard deviation of a covariate in the treatment and comparator groups in the pre-match sample.

### Cardinality Matching

Cardinality matching utilizes recent advancements in mathematical programming (i.e., integer programming) to maximize the size of a matched sample subject to investigators’ constraints for covariate balance among matching covariates. Furthermore, cardinality matching allows for the estimation of average treatment effect in target populations (e.g., average treatment effect on the controls [ATC]) through the specification of target estimands4. Matching covariates identified during propensity score matching as described in §5.6.1 will be used as matching covariates for cardinality matching with one notable exception: due to memory constraints associated with cardinality matching, in the study population group, matching covariates will be identified using regularized lasso regression as described in §5.6.1 using heuristic feature selection to limit covariate candidates to those with a frequency >2.0%.

Patients will be matched to one another at a 1:1 ratio. A total of 7 cardinality matching procedures will be performed with varying covariate balance constraints, including: exact marginal distributional balance; maximum SMD target of 0.01, 0.05 and 0.10; and maximum SMD target of 0.01, 0.05 and 0.10 targeting the ATC estimand. Post-match balance of covariate candidates and matching covariates will be assessed as described in §5.6.1. Analysis wil be conducted using R version 3.6.3, GurobiTM Solver version 9.0.1 and the designmatch library.

### Analyses of Negative Control Outcomes

Negative controls are exposure-outcome pairs for which there is no expected causal relationship, such that unbiased analyses can be expected to generate effect estimates consistent with relative risk = 1. A total of 105 negative control outcomes were identified through a data-rich algorithm, and evaluated for lack of causal relationship through clinical review13. A list of negative control outcomes used in the current study is available in Appendix I.

For each negative control outcome, cox proportional hazards models will be fit where the null hypothesis of no treatment effect is presumed to be true. Cox proportional hazards models will be fit independently across all subsample draws, and results will be considered jointly within sample groups. A total of 163,800 cox proportional hazards models will be attempted to be fit as depicted in Table 5.5.3.a.

**Table 5.5.3.a.** Summary of cox proportional hazards models considered in the analyses of negative control outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sample Group | Study Population | 10% Subsample | 1% Subsample | 0.5% Subsample | Total |
| a. Subsample Draws | 1 | 5 | 50 | 100 | 156 |
| b. Samples per Subsample Draw | 10 | 10 | 10 | 10 | - |
| i. Pre-match | 1 | 1 | 1 | 1 | - |
| ii. Post-Propensity Score Matching | 2 | 2 | 2 | 2 | - |
| iii. Post-Cardinality Matching | 7 | 7 | 7 | 7 | - |
| c. Negative Control Outcomes | 105 | 105 | 105 | 105 | - |
| Total (a \* b \* c) | 1050 | 1050 | 52500 | 52500 | 163800 |

Markov Chain Monte Carlo (MCMC) will be used to fit the null distribution of joint negative control outcomes across sample groups, and the empirical null distribution will be used to calibrate hazard ratio (HR) estimates, 95% confidence intervals (CI) and p-values. Potential residual confounding will be assessed based on the expected absolute systematic error of the empirical null distribution.

## Quality Control

The study will be completed per the quality control guidances adopted by the individual/ champion evidence generation functions.

## Limitations of the Research Methods

* Due to memory constraints, matching covariates identified for cardinality matching were limited to covariate candidates with a frequency >2% during heuristic feature selection. This may have led to a suboptimal selection of matching covariates during regularized lasso regression as compared to propensity score matching, which limited covariate candidates to those with a frequency >0.1% during heuristic feature selection. As such, the current study may underestimate the performance of cardinality matching relative to propensity score matching in large sample sizes.
* The current study compares the performance of propensity score and cardinality matching in sample groups of decreasing sample sizes. The smallest sample group examined in this study contained 860 patients (treatment=645, control=215). Study findings may not be applicable to sample sizes smaller than those used in the current study.

# Protecting the Confidentiality of the Data Obtained

The use of CCAE was reviewed by the New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subjects research.

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. At no time during the study will the Johnson & Johnson MD company receive patient identifying information except when required by law.

# Management and Reporting of Complaints and Adverse Events

In this study, potential product complaints or safety signals may be identified. Thus, any potential combinations of specific product brand and safety outcomes will be reported to the operating company complaint handling unit (CHU) upon completion of the study. For all events that may be deemed product complaints, the data captured in the final study report will constitute all clinical information known regarding these product complaints/adverse events. No follow-up on these potential adverse events or complaints will be conducted. The operating companies CHU is responsible for determining if they are actual product complaints and/or product-related adverse events.

Communication of all potential Product Complaints to the appropriate operating company CHU must be done within 48 hours of completion of the final study report using the Database RRA Potential Complaint Forwarding Form (TV-eFRM-03668).

# Plans for Disseminating and Communicating Study Results

A final report will be created from study results which may be considered for publication in a peer reviewed publication. Any plans for submission of progress reports, final reports, and publications; any arrangements made between marketing authorization holders for the disseminating and communicating study results of Joint Post-Authorization Safety Studies will be made in accordance to the MD Med Device Publication Policy (see attached Appendix III).

# References

1. Crump RK, Hotz VJ, Imbens GW, Mitnik OA. Dealing with limited overlap in estimation of average treatment effects. *Biometrika*. 2009; 96 (1), pp. 187–199.
2. Rothe C. Robust confidence intervals for average treatment effects under limited overlap. *Econometrica*. 2017; 85: 645-660. doi: 10.3982/ECTA13141.
3. Pirracchio R, Resche-Rigon M, Chevret S. Evaluation of the propensity score methods for estimating marginal odds ratios in case of small sample size. *BMC Med Res Methodol.* 2012;12:70. doi:10.1186/1471-2288-12-70.
4. Visconti G, Zubizarreta, JR. Handling limited overlap in observational studies with cardinality matching. *Observational Studies*. 2018; 4, 217-249.
5. Suchard MA, Schuemie MJ, Krumholz HM, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *Lancet*. 2019;394(10211):1816-1826. doi:10.1016/S0140-6736(19)32317-7.
6. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018;138(17):e426‐e483. doi:10.1161/CIR.0000000000000597
7. 1. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives, J Clin Epidemiol, 1993, vol. 46 10(pg. 1075-1079)
8. 2. Young BA, Lin E, Von Korff M, et al. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. *Am J Manag Care*. 2008;14(1):15‐23.
9. 3. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285(22):2864‐2870. doi:10.1001/jama.285.22.2864
10. 4. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263‐272. doi:10.1378/chest.09-1584
11. Walker AM, Patrick AR, Lauer MS, Hornbrook MC, Marin MG, Platt R, Roger VL, Stang P, Schneeweiss S. A tool for assessing the feasibility of comparative effectiveness research. Comparative Effectiveness
12. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *The American Statistician*. 1985; 39(1):33-38. doi:10.1080/00031305
13. Voss AE, Boyce RD, Ryan PB, van der Lei J, Rijbbeek PR, Schuemie MJ. Accuracy of an automated knowledge base for identifying drug adverse reactions. *J Biomed Inform*. 2017; 66: 72-81.

# Appendices

1. Appendix I: Please see attached Excel File “Appendix I – Negative Control Outcomes.xlsx”.

# Major Amendments

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| # | Date | Section of study protocol | Amendment or update | Reason |
| 1 |  |  |  |  |
| 2 |  |  |  |  |
| 3 |  |  |  |  |