SENTINEL METHODS PROTOCOL

Development and Evaluation of a Global Propensity Score for Data Mining with Tree-Based Scan Statistics

Prepared by: Shirley V Wang[1], Joshua J Gagne[1], Judith C Maro[2], Efe Eworuke[3], Sushama Kattinakere[1], Martin Kulldorff[1], Elande Baro[4], Rima Izem[4], Michael Nguyen[3], Rita Ouellet-Hellstrom[3], Sandra DeLuccia[2], Ella Pestine[2], Danijela Stojanovic[3]

Author Affiliations: 1. Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; 2. Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; 3. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; 4. Office of Biostatistics, Center for Drug Evaluation and Research, FDA, Silver Spring, MD

Aug 10, 2018
Version 2 Sept 7, 2018
Version 3 Feb 11, 2019
Version 4 May 9, 2019

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.

History of Modifications

Version	Date	Modification	By
V2	Sept 7, 2018	• Responses to comments from Jennifer L Nelson, detailed in Appendix C were incorporated to protocol text. • Maximum follow up for case studies 1 and 2 were changed from 30 days to 183 days • For all examples, patients will be censored if they switch between compared therapies (defined as a dispensation for a drug in the other group during follow up)	Shirley V Wang
V3	Feb 11, 2019	• Revised exclusion and covariate assessment windows for Examples 1-4 to include day 0 • Added exclusions for example 4: liver disease, pancreatitis, pregnancy • Revised Appendix B (added design diagrams for each example) • Added Appendix D detailing follow up analyses for examples 1-4 • Added Appendix E, justification for: ○ allowing tailored covariate assessment window to differ from fixed predefined and empirical covariate assessment windows ○ allowing ascertainment of pregnancy at the time of drug initiation using codes recorded after index date for drug initiation	Shirley V Wang
V4	May 9, 2019	• Changed exclusion criteria for example 4 (allowing other indications for valproic acid and lamotrigine) and added tailored additional covariates related to new indications • Revised to include 2 variants of hdPS estimation strategy to compare – 1) run hdPS as currently implementable in CIDA 2) add hierarchically grouped diagnosis and procedure codes as input dimensions from which covariates can be empirically selected	Shirley V Wang

Sentinel Methods Protocol

Development and Evaluation of a Global Propensity Score for Data Mining with Tree-Based Scan Statistics

Table of Contents

I. INTRODUCTION

TreeScan™ (http://www.treescan.org) is a statistical data mining tool that is compatible with multiple study designs and addresses many methodological challenges[1] with making secondary use of healthcare databases for detection of potential signals related to marketed medical products. It uses a hierarchical outcome tree to group related codes together and applies tree-based scan statistics to adjust for multiple testing when screening across thousands of potential adverse events.[2]

TreeScan has previously been used to screen for adverse events when conducting signal detection in vaccine safety studies that used a self-controlled design.[3-5] Studies of childhood vaccine safety are well suited for self-controlled designs because these are often administered on an age-based schedule[6] rather than in response to a change in clinical condition. In contrast, the clinical context behind decisions of whether, when and for how long to treat patients with specific drugs can make issues of confounding related to timing of exposure more complex than typically found in vaccine studies.[7] While self-controlled designs cannot be confounded by time-invariant characteristics due to the within-person comparisons, they are susceptible to bias from time-varying characteristics (e.g. healthy user bias[8,9], trends in exposure probability in the population[10] or within individual[11,12], decline in overall health status, protopathic bias[13]). Recent work evaluating TreeScan for adverse event screening using drug examples with a self-controlled risk interval design resulted in many alerts for outcomes that were related to underlying changes in health condition that prompted the initiation of therapy (Maro et al, draft in progress). For example, when screening for adverse events after antibiotics, there were numerous alerts for conditions related to the underlying infection that prompted the need for antibiotic.

For drug safety evaluations, a cohort study of new initiators is a powerful design that can better address unmeasured time-varying characteristics associated with initiation of treatment that are also related to outcomes of interest (e.g. confounders) through judicious selection of an appropriate active comparator group.[14,15] While selection of an appropriate comparator in the design phase is crucial, cohort studies often require additional adjustment of measurable confounders and/or their proxies. A common method for adjusting for confounding is via a propensity score (PS). The PS is the predicted probability of exposure (versus comparator) conditional on covariates and is typically estimated via a logistic regression model.[16] When the PS is used to conduct matched, weighted or stratified analyses, the results are adjusted for confounders that are included in the PS model as well as closely related proxies. The covariates selected for inclusion in the PS can be predefined by the investigator or empirically defined via machine learning algorithms.[17-21]

A recent analysis involved simulation to evaluate the performance of tree-based scan statistics with PS matched analysis of new initiator cohorts. These analyses showed promise for TreeScan with PS matching as a method for screening and prioritization of potential adverse events (Wang et al, in press, Epidemiology). In the simulations, the true confounding structure was known to the investigators and the scenarios were limited to under 30 potential confounders for selected outcomes. However, when applying TreeScan for a real drug safety screening using a PS matched active-comparator cohort design, special consideration will be necessary to address confounding. Risk factors, and therefore confounders, will vary by outcome and TreeScan scans across thousands of possible outcomes. Therefore, it would not be feasible to identify potential confounders for every possible adverse event that is screened.

FDA is interested in development of a “global” PS that could be applied generically across different active-comparator cohort studies in varied populations to adjust for many of the major confounders associated with the different outcomes being scanned. A global PS would include a set of pre-defined variables that are risk factors for a variety of outcomes and/or empirically selected variables related to exposure selection. After scanning for potential adverse events using a global PS, outcomes that alert can be further explored and refined in analyses where confounders are carefully selected and tailored to the specific adverse events of interest.

II. SPECIFIC AIMS

This methods project aims to develop and evaluate candidate global propensity scores for application with the propensity score cohort matched design and tree-based scan statistics. The examples used in this project are not part of a regulatory evaluation.

Aim #1: Develop and compare the relative performance of candidate global propensity scores which could be applied generally in cohort studies involving tree-based scan statistics by evaluating 4 case studies for drug safety signal detection, where the selected drugs have well characterized safety profiles.

We will evaluate tree-based scan statistics with crude, age-sex matched and 1:1 global propensity score matched cohorts. The workgroup will identify a set of candidate global propensity scores, then conduct analyses to evaluate performance of 1:1 matched cohorts for each drug safety signal detection case study using a proprietary database licensed by Brigham and Women's Hospital, Truven Health MarketScan® Research Database. Evaluation of performance will focus on a subset of selected outcomes in the hierarchical tree for each example and will include assessment of balance on known risk factors as well as impact of including additional adjustment for known risk factors on alerting (see section VIB for more detail).

Aim #2: Using the *a priori* specified primary global propensity score to adjust for confounding, we will conduct clinical and epidemiologic review of TreeScan alerts.

The workgroup will review alerts from one or more case studies after running TreeScan on a cohort 1:1 matched on the pre-specified primary global propensity score to adjust for confounding. We will review alerts identified at a pre-specified threshold of $p \leq 0.01$ from both clinical and epidemiological perspectives. The interpretation of alerts will include (but not necessarily be limited to) consideration of biologic pathways, confounding by indication, and reverse causality. If there are known signals, the WG will review and interpret the pattern of alerting for these known adverse events. Because the outcome nodes in the hierarchical tree may not reflect the most sensitive or specific algorithms for any particular outcome, this may influence alerting. For example, consider the situation where a drug increases the risk of Type II diabetic ketoacidosis (a very rare outcome), and incident outcomes are defined at level 3 of the Multilevel Clinical Classifications Software (MLCCS) tree hierarchy. At level 3 of the tree, diagnosis codes for diabetic ketoacidosis are part of a node that includes more prevalent general diabetes codes. Thus, when scanning, the effect of the drug on diabetic ketoacidosis may be diluted due to the lack of specificity of the outcome definition. The WG will learn from observing patterns of alerts for known adverse events. After the workgroup considers clinical context and methodological issues to assess whether there may be clear, non-causal explanations for unanticipated alerts, at the FDA's discretion, a separately scoped project may be initiated to distribute relevant Cohort Identification and Descriptive Analyses (CIDA) + Propensity Score Analysis Tool and TreeExtraction software packages to the Sentinel Distributed Database (SDD). [22,23] If similar unknown or unexplained alerts are observed, the workgroup may follow up with clinical review of Patient Episode Profile Retrieval (PEPR)[24], and design of a protocol based safety assessment with confounding control targeted to the outcome of interest.

III. EXPERT ENGAGEMENT

To increase opportunities for input around signal detection and TreeScan methods, the workgroup will invite members of the Methods Core to review and provide input on the project protocols. The workgroup will engage the Methods Core for feedback at three points during the project: Project initiation/protocol review; presentation of interim findings and presentation of project results.

IV. PROPENSITY SCORE MATCHED COHORT DESIGN

The propensity score matched cohort design is currently being used by the FDA Sentinel Program in active surveillance activities.[25-31] In this context, a cohort is generally defined by incident exposure to a new drug and an appropriate comparator drug. The initiators of each drug are then matched based on a propensity score, which is a summary measure capturing the probability of being an initiator of the new drug of interest rather than the comparator drug based on multiple baseline characteristics.

There are many variants on how a cohort may be extracted from longitudinal healthcare claims data (e.g. defining cohort entry, washout period for incidence), choices regarding what goes into the propensity score (e.g. which covariates, defined over what period) as well as variants on how to match patients (e.g. matching caliper, 1:1 versus variable ratio). These design and implementation decisions are captured as options that investigators may alter when using the Sentinel Program's CIDA + Propensity Score analysis tool.[32]

A. CANDIDATE GLOBAL PROPENSITY SCORES

For Aim 1, candidate global PS will include a combination of demographics, comorbidity score, frailty, screening measures, healthcare utilization measures, exposure based high dimensional propensity score (hdPS)[18] and investigator selected risk factors that may influence choice of therapy **(Table 1**).

Table 1. Evaluation of TreeScan with variants of a global propensity score to adjust for confounding

	Predefined global[1]	Empirically selected[2]	Predefined tailored[3]
1	Yes	No	No
2	No	Yes	No
3	Yes	Yes	Yes
4	Yes	Yes	No
5	Yes	No	Yes

[1] Demographics, comorbidity score components, frailty score components, screening, healthcare utilization
[2] Exposure-based high dimensional propensity score selection
[3] Investigator selected confounders tailored to each example

Predefined global covariates can be applied "out of the box" without tailoring for different drug evaluations. While the global predefined covariates may be the same in each application, the coefficients to derive the estimated PS will depend on the covariate relationships with the exposure and comparator. Including covariates selected empirically via the exposure based hdPS algorithm increases computational complexity, while including tailored potential confounders increases staff time and effort. Staff time and effort may be the most difficult to scale up if there are numerous screening activities being launched for active surveillance. The candidate PS models in Table 1 were chosen to allow comparison of models that:

1. use only predefined global covariates to those that use only empirical covariates (model 1 vs 2)
2. models that include predefined global covariates with or without inclusion of covariates tailored to the exposure-comparator under investigation (models 1 vs 5)
3. models that include predefined global covariates and empirically selected covariates with or without inclusion of covariates tailored to the exposure-comparator under investigation (model 3 vs 4)

Algorithms to define independent variables in the global propensity score will be based on previously published papers that evaluated performance of the algorithm whenever available. For example, prior papers have evaluated a claims based combined comorbidity score[33] as well as a claims based frailty index.[34] When published and/or evaluated algorithms are not available, the workgroup will create algorithms based on content validity from selected code descriptions and knowledge of coding for billing purposes. Algorithms for pre-specified covariates included in the candidate global propensity scores (other than exposure based hdPS empirically identified covariates) are provided in **Appendix B**.

We chose to use hdPS rather than other machine learning to select variables such as LASSO[19] or Elastic Net[35] or hybrid approaches[36,37] that combine the two to further reduce the dimensionality of variables included. In the context of variable selection based on potential for bias when evaluating a single outcome, these empirical variable selection approaches have performed similarly in prior evaluations. However, we will be scanning across thousands of potential outcomes. It would not be feasible to apply a machine learning or hybrid approach which selects variables based on association with outcome. Furthermore, it may be helpful in our scanning context to include a slightly broader base of variables to provide proxy adjustment for confounders on a wider range of outcomes.

The hdPS software program creates and selects baseline covariates using diagnosis and procedure codes occurring within a user defined covariate assessment window.[18] The user can provide the data as dimensions representing different aspects of care (e.g. inpatient diagnoses, outpatient diagnoses, procedure codes, drug codes). The algorithm will identify the top n (default 200) most prevalent codes from each dimension and create binary variables for each, as well as a variable measuring frequency of occurrence (once, sporadically, frequently).[38] The exposure based selection option will select k covariates for inclusion (default = 500) based on strength of the association with exposure.

Exposure-based selection is not the default hdPS option.[39] The default selection criterion is based on potential to bias an exposure-outcome relationship, as defined by the Bross formula.[40] The bias based selection option is not appropriate for this signal detection context, because the Bross formula is based on relationships between exposure and covariates with a single outcome. Because we will be screening across thousands of potential outcomes simultaneously rather than focusing on one outcome of interest, we focus on empirically identifying covariates using selection based on relationships with exposure. This may result in inclusion of covariates that are strongly predictive of exposure but not necessarily risk factors for all evaluated outcomes. However, on the whole we expect that there will be little harm to including covariates that are not strong risk factors for a particular outcome relative to the anticipated reduction in confounding for other outcomes.[38,41]

There are many tuning parameters for hdPS. We will implement default settings for hdPS currently available with the Sentinel CIDA routine query tool as well as implement hdPS with additional data dimensions from which empirical covariates can be selected. These data dimensions will include hierarchically grouped diagnosis and procedure codes developed by the Agency for Research and Quality's Multi-Level Clinical Classifications Software (MLCCS) (https://www.hcup-us.ahrq.gov/toolssoftware/ccs/CCSUsersGuide.pdf).[42]

For Aim 2, the pre-specified primary candidate global propensity score to adjust for confounding will include demographic, comorbidity score, frailty, screening and exposure based hdPS selected variables (**#3 from Table 1)**. This PS was selected as primary because it includes all covariates that do not require additional investigator input, making it easier to scale up screening activities. Further investigation of potential alerts could then use PS tailored to refine understanding for specific outcomes of interest.

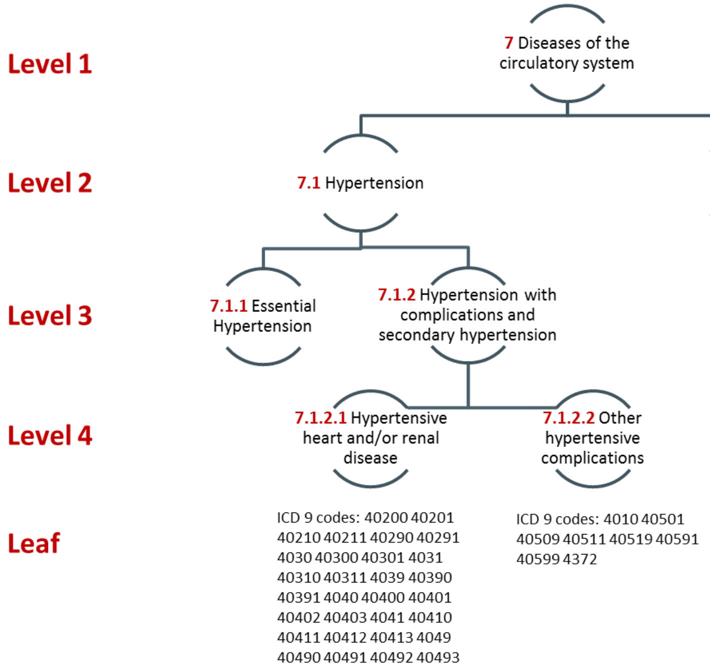
V. TREESCAN

A. HIERARCHICAL TREE (MULTI-LEVEL CLINICAL CLASSIFICATION SOFTWARE)

The tree structure that we will use for TreeScan will be based on the MLCCS International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis tree, which is grouped into 4 hierarchical levels representing increasingly specific clinical concepts. At the top level, there are 18 categories representing different body systems.

The increasing specificity of the hierarchical levels is depicted in **Figure 1**, where at the top level the category specifies only that the person has a disease of the circulatory system. Moving to level 2, one might see that the patient has hypertension. At level 3, essential versus secondary hypertension or hypertension with complications can be differentiated. At level 4, the type of secondary or hypertensive complications are specified. Finally, each node in level 4 of the hierarchy is based on specific ICD-9-CM codes.

Figure 1. Example from Multi-Level Clinical Classification


Level 1
7 Diseases of the circulatory system
Level 2
7.1 Hypertension
...
Level 3
7.1.1 Essential Hypertension
7.1.2 Hypertension with complications and secondary hypertension
Level 4
7.1.2.1 Hypertensive heart and/or renal disease
7.1.2.2 Other hypertensive complications
Leaf
ICD 9 codes: 40200 40201 40210 40211 40290 40291 4030 40300 40301 4031 40310 40311 4039 40390 40391 4040 40400 40401 40402 40403 4041 40410 40411 40412 40413 4049 40490 40491 40492 40493
ICD 9 codes: 4010 40501 40509 40511 40519 40591 40599 4372

Decimal points in ICD-9-CM codes at the leaf level have been removed.

The MLCCS based tree that we will use is a curated tree based on the 2015 version of ICD-9-CM codes. The tree has been independently curated by 2 members of FDA (**Appendix A**). Disagreements were adjudicated after discussion between the curators. Curation of the tree involved removal of conditions that were 1) congenital/hereditary, 2) unlikely to be caused by drugs (e.g. pregnancy, flu, well-visits) as well as 3) conditions with long induction times such as cancer (details on curation in the appendix). The diagnostic codes and their classification into different levels are not based on validated algorithms and could misclassify outcomes. Nevertheless, MLCCS classification of ICD-9-CM codes into clinical concepts can be useful as part of a screening tool for potential adverse events, followed by more rigorous and targeted protocol-based investigations. While an ICD-10-CM version of the MLCCS tree is available, our case studies will be conducted using data prior to widespread use of ICD-10-CM codes in the United States. We may elect to use trees that have been further curated for specific examples.

B. DEFINING INCIDENT OUTCOMES

We will define incident outcomes based on level 3 nodes across the MLCCS tree hierarchy. Incident outcomes will be defined by the first diagnosis from the node that occurs in the emergency department (ED) or inpatient (IP) setting; without any diagnoses in the same MLCCS level 3 node in the prior 183 days in any care settings. Multiple incident outcomes may be contributed by each patient as long as they meet the incidence criteria at MLCCS level 3 nodes.

Each patient will be allowed to enter the cohort only one time, after the first qualifying incident use of either the exposure or comparator of interest. Patients will be censored at death, disenrollment, or maximum days follow up for the example. If one member of a 1:1 propensity score matched set is censored, the other member will also be censored at the same time. Incident outcomes occurring during the patient's follow up after treatment initiation will be included in outcome counts for TreeScan.

C. UNCONDITIONAL BINOMIAL TREE SCAN STATISTIC

We will use the unconditional Bernoulli version of the tree-based scan statistic. This statistic conditions on the number of cases in the node but does not fix the total number of cases across the tree for each exposure group to be the same in the observed and randomly permuted data. The threshold for alerting in both Aims 1 and 2 will be p ≤ 0.01 (1-sided).

The distribution of the test statistic *T* below is unknown. However, a Monte Carlo based p-value can be obtained by generating random datasets under the null hypothesis that every outcome occurs, independently of other outcomes, with the same probability among in the treatment group versus the comparator group.[4]

The log likelihood ratio (LLR) based test statistic *T* can be calculated as:

$$LLR(G) = ln\left(\frac{\left(\frac{c_G}{c_G + n_G}\right)^{c_G}\left(\frac{n_G}{c_G + n_G}\right)^{n_G}}{(p)^{c_G}(1-p)^{n_G}}\right) I\left(\frac{c_G}{c_G + n_G} > p\right)$$

$$T = \max_G LLR(G)$$

Where: T = unconditional Bernoulli tree scan statistic

c_G = cases in the treatment group for a given node G
n_G = cases in the reference group for a given node G
p = probability of being in the treatment group (for 1:1 matched this is 0.5)
G = node of interest

Random datasets can be generated under the null hypothesis by creating replicates of the original data where each node contains the same number of events as observed in the original data, however the events within each node are assigned to exposure based on a binomial draw with the expected proportion based on the null hypothesis. In our 1:1 matched setting, this proportion is 0.5. For these Monte Carlo generated data sets, the outcomes in each node are assigned randomly. If 9,999 random replicates are generated, and ranked according to *T,* then the Monte Carlo based p-value = Rank of the observed data/(9999+1). When the type 1 error alpha for alerting is set to a threshold of 0.01, then only nodes with rank within the top 1% of the real and random replicates will constitute a statistical alert. If the null hypothesis is true, the probability that all p-values are larger than 0.01 is 99%.

Hypothesis tests will be performed at level 3 and all more finely specified nodes at numerically higher levels of the MLCCS, including level 4 and the leaf level (specific ICD-9-CM codes). A LLR will be computed at every node where a hypothesis test is performed.

Some of the major strengths of tree-based scan statistics include:

1. They were developed based on scan statistical theory
2. They use a hierarchical diagnosis tree to simultaneously evaluate outcomes at different levels of granularity (including specific diagnoses and groups of related diagnoses)
3. They use a frequentist method to formally adjust for the multiple testing inherent in evaluation of thousands of potential adverse events that accounts for correlation between tests of related hypotheses (unlike traditional frequentist methods which are too conservative)
4. They can be useful when screening for unanticipated safety signals where there is no informative prior

Some of the major limitations of tree-based scan statistics include:

1. Bias is adjusted by design, not inherent in the scan statistic
2. The hierarchical classification system for outcomes used are generally not based on validated algorithms
3. Adjusting for multiplicity when scanning across outcomes will decrease power compared to evaluating a single pre-specified hypothesis

D. SELECTED OUTCOMES AND ALERTS TO EVALUATE

Realistically, most of the potential outcomes scanned will be unrelated to the evaluated drugs. We will focus on doing a deeper dive for evaluate a subset of outcomes with and without alerts in a variety of examples where we have prior knowledge of where true signals may or may not be present. By focusing on areas where there are known signals or unanticipated alerts, we target high yield areas for learning about the method and its performance. Our case studies are intended to be diverse with respect to study populations as well as types of outcomes with true signals. That said, the performance of global PS in these case studies will not necessarily be generalizable to all contexts.

For Aim 1, we will focus on a subset of up to 5 outcomes with and up to 5 outcomes without alerts for each example. These outcomes will be chosen based on clinical knowledge of the safety profiles for the selected examples and may include outcomes where elevation in risk with exposure relative to the comparator is anticipated, where the risk is expected to be no different for exposure and comparator or where the effect of exposure is unknown (**Figure 2**). These outcomes may be the specific MLCCS nodes that signaled, or a validated algorithm may be used to capture an underlying clinical concept for related nodes. These follow on evaluations will provide insight regarding the relative performance of the candidate global propensity scores.

For Aim 2, all alerts from the pre-specified primary global propensity score will be reviewed by the workgroup.

Figure 2. Sampling specific outcomes to evaluate relative performance of candidate generic propensity scores

	True effect of exposure		
	Known effect	Known null	Unknown ?
Alert	True positive	False positive	True/False positive?
No alert	False negative	True negative	True/False negative?

VI. DRUG SAFETY SIGNAL DETECTION CASE STUDIES

A. DATA

The new initiator cohorts for each example will be created from a commercial insurance claims data licensed and housed by the Brigham and Women's Hospital (BWH), Truven Health MarketScan® Research Database. No use of the SDD is planned for this project. While MarketScan is not part of the

SDD, there is a small, but unknown amount of overlap between Optum (which is a part of the SDD) and MarketScan data.

B. PERFORMANCE METRICS

Performance metrics will include measures of balance on known risk factors for a sample of outcomes in the tree (absolute and standardized differences for individual covariates, average standardized absolute mean difference (ASAMD) across all covariates) and evaluation of how additional adjustment for known risk factors of those outcomes affects alerting. If some candidate global PS tend to have greater imbalance on known risk factors for sampled outcomes, this would suggest that they are missing important dimensions that should be included in a global confounding adjustment score. We will describe what happens to alerts when we do or do not include specific, known risk factors for a selected sample of outcomes in the PS.

In each case study, we have known signals that have previously been identified. As in a real surveillance activity, we may not necessarily have adequate power to find signals of interest at stringent pre-specified alpha levels. However, we will be looking at patterns of alerting in these examples to observe how signal detection using the method could play out in a real scenario. Outcomes that don't alert at the pre-specified threshold may still have relatively low likelihood under the null. The method can play an important part in screening and prioritization even if there is not sufficient power to alert at a pre-specified threshold by painting a clinical picture of the pattern of outcomes that are unlikely to be observed if there was no relationship with exposure.

C. SELECTED EXAMPLES

In consultation with the FDA, the work group chose four case studies to evaluate. We describe these case studies here in brief. Additional details of the specifications for these case studies can be found in **Appendix B**. We deliberately chose older examples with known safety profiles. Given the delays in data refreshes, we have limited years of data available after Oct 2015. Although an ICD10 based tree is available, if we focused only on the ICD-10 era, we would have lower power to detect known signals in our examples. Running hdPS in a mixed ICD9-10 era would require incorporation of forward and backward mapping and is beyond the scope of this project.

We will use Sentinel's routine query tools [22,23] supplemented with *de novo* coding and other software as necessary to extract new initiator cohorts and counts of outcomes across the hierarchical tree. After matching on each candidate global propensity score, the 1:1 matched cohorts will be used as inputs for TreeScan to run scan statistics.

Example 1: New initiators of macrolides versus fluoroquinolones for community acquired pneumonia (a between class comparison)

Macrolides and fluoroquinolones are two classes of antibiotic drugs that are used to treat community acquired pneumonia. There is no clear evidence of a strong benefit or safety risks for one class versus the other. A meta-analysis and review of randomized clinical trials that primarily recruited mild to moderate outpatient cases of community acquired pneumonia reported that macrolides had more gastrointestinal side effects (e.g. diarrhea, nausea, vomiting) and rate of treatment failure (as defined by persistent signs and symptoms of pneumonia requiring treatment modification).[43]

We will identify patients who newly initiate a macrolide or fluoroquinolone after at least 183 days without dispensations of either class. Patients must be enrolled in the database with medical and drug coverage for at least 183 days prior to the initiation date (index date for cohort entry) and have diagnoses for community acquired pneumonia in an outpatient setting as well as codes for chest radiography within 14 days prior to or on the date of initiation (see design diagram in appendix). This algorithm for outpatient community acquired pneumonia is adapted from one developed and validated using Group Health data, which had a positive predictive value of around 71%.[44,45] We will exclude patients who initiate both a macrolide and a fluoroquinolone on the same day, are younger than 18 or over 65 on the date of initiation, or were hospitalized for any reason within 90 days prior to or on the date of initiation of macrolide or fluoroquinolone.

When defining covariates for candidate global propensity scores (see **Table 1** above), we will use diagnosis and procedure codes from claims occurring in the 183 days prior to and including the date of initiation. We will include day 0, the date of initiation from the covariate assessment window to enable capture of diagnoses generated on the date of new initiation for the drug exposure. We will exclude the index date from the follow up window because we cannot distinguish the timing of exposure and health outcomes on the same day . The propensity scores that use investigator specified covariates tailored to the example will include variables such as those listed in **Table 2**.

The study period will include Jan 1, 2003 to Sep 30, 2015. The follow up window when scanning for potential adverse events will begin one day after initiation. The maximum follow up will be 30 days after initiation. Follow up will be censored at Sep 30, 2015 due to transition to ICD-10-CM coding. Patients in matched sets will additionally be censored at death or disenrollment of either member of the set or switching of exposure (defined by dispensation for a drug in the other group). Because there are not *a priori* anticipated safety signals, our evaluation will include selection of up to 5 incident outcome nodes that do and up to 5 nodes that do not alert at the 0.01 threshold. We will select nodes based on our ability to identify known risk factors for those outcomes.

Example 2: New initiators of azithromycin versus clarithromycin for community acquired pneumonia (a within class comparison)

Azithromycin versus clarithromycin are macrolide antibiotics that are used to treat community acquired pneumonia. Prior trials have found them to be similar in terms of both efficacy and safety.[46,47] The specification for this cohort will be identical to that for the between class comparison of macrolides and fluoroquinolone, with the exceptions that initiation will be defined with respect to macrolides as a class and co-prescription or prior use of fluoroquinolones will be included as indication related covariates.

Example 3: New initiators of meloxicam versus celecoxib for osteoarthritis (two nonsteroidal anti-inflammatory drug (NSAID) options)

Meloxicam and celecoxib are two non-steroidal anti-inflammatory drugs that are used to treat osteoarthritis pain. Although potential effect sizes are small, prior research has suggested there could be more gastrointestinal adverse events[48] and fewer vascular and renal events[49,50] with meloxicam versus celecoxib.

We will identify patients who newly initiate meloxicam or celecoxib after at least 183 days without dispensations of any non-steroidal anti-inflammatory drug (see design diagram in appendix). Patients must be enrolled in the database with medical and drug coverage for at least 183 days prior to the initiation date (index date for cohort entry) and have at least one diagnosis for osteoarthritis (ICD-9 715*) in an inpatient or outpatient setting during this time. We will exclude patients who initiate both meloxicam and celecoxib on the same day or are younger than 18 on the date of initiation.

When defining covariates for candidate global propensity scores (**Table 1**), we will use diagnosis and procedure codes from claims occurring in the 183 days prior to and including the date of initiation. In addition to global demographic, comorbidity, frailty, screening and healthcare utilization covariates, we will consider numerous investigator specified covariates for this example such as those listed in **Table 2**.

The study period will include Jan 1, 2003 to Sep 30, 2015. When scanning for potential adverse events, follow up will begin one day after initiation. The maximum follow up will be 183 days after initiation. Follow up will be censored at Sep 30, 2015 due to transition to ICD-10-CM coding. Patients in matched sets will additionally be censored at death or disenrollment for either member of the set, or switching of exposure (defined by dispensation for a drug in the other group). The outcomes that we select for evaluation of balance on known risk factors will include symptomatic upper GI events such as acid/peptic ulcer related, upper GI conditions such as perforations and bleeding, as well as myocardial infarction and cerebrovascular events. Candidate global PS that only includes un-tailored pre-specified covariates will not include the indication related risk factors listed above, but may adjust for them by proxy via correlation with the variables that are included. We will evaluate balance in nodes where alerts are anticipated. Our evaluation will also include selection of up to 5 incident outcome nodes that do and up to 5 nodes that do not alert at the 0.01 threshold. We will select nodes based on our ability to identify known risk factors for those outcomes.

Example 4: New initiators of valproic acid and lamotrigine for epilepsy

Valproic acid and lamotrigine have been used for decades as therapies for treatment of epilepsy.[51-53] There is not a clear consensus regarding superiority in effectiveness for any of the numerous currently available therapies for epilepsy, each of which has different known adverse effects and risk profiles.[54] For example, valproic acid has black box warnings for hepatotoxicity, teratogenicity, and pancreatitis[55] whereas lamotrigine can cause serious rashes (Stevens-Johnson syndrome) within 8 weeks of initiation[53] and serious immune system reactions (hemophagocytic lymphohistiocytosis (HLH))[56].

We will identify patients who newly initiate valproic acid or lamotrigine after at least 183 days without dispensations for either drug. Patients must be enrolled in the database with medical and drug coverage for at least 183 days prior to the initiation date. We will exclude patients who initiate both valproic acid and lamotrigine on the same day, are younger than 2 or older than 65 on the date of initiation, have claims indicative of liver disease, pancreatitis, Stevens-Johnsons syndrome, hemophagocytic lymphohistiocytosis, or pregnancy during the 183 days prior to or on the index date (see design diagram in appendix). We will conduct separate analyses for subgroups of patients aged 2 to 18 years and patients 19-65 years old at the time of initiation.

The study period will include Jan 1, 2003 to Sep 30, 2015. When scanning for potential adverse events, follow up will begin one day after initiation. The maximum follow up will be 183 days after initiation. Follow up will be censored at Sep 30, 2015 due to transition to ICD-10-CM coding. Patients in matched sets will additionally be censored at death or disenrollment for either member of the set, or switching of exposure (defined by dispensation for a drug in the other group). The investigator specified covariates tailored to this example may include risk factors for known adverse events such as those listed in **Table 2**. In addition to evaluation of balance in nodes where alerts are anticipated, our evaluation will include selection of up to 5 incident outcome nodes that do and up to 5 nodes that do not alert at the 0.01 threshold. We will select nodes based on our ability to identify known risk factors for those outcomes.

Table 2. Known adverse events, risk factors and investigator defined covariates for case studies

Example	Known adverse events	Investigator defined measurable risk factors for known adverse events	Other investigator defined covariates
1 Macrolides and fluoroquinolones (between class comparison)	• Diarrhea • Nausea • Vomiting • Treatment failure	n/a	• co-prescription of beta-lactam with macrolide or fluoroquinolone • prior prescription of other antibiotic classes: penicillins, cephalosporins, sulfonamides, tetracyclines, animoglycosides • pregnancy at time of initiation (class B vs class C drug)
2 Azithromycin and clarithromycin (within class comparison)	n/a	n/a	same as above
3 Meloxicam and celecoxib	• Upper GI events (e.g. acid/peptic ulcer, perforations, bleeding) • Myocardial infarction • Cerebrovascular events • Renal failure, acute kidney injury, hyperkalemia	• Anticoagulants • Obesity • Smoking • Angina • Coronary Revascularization • Statins • Hormone Replacement Therapy • Prior Nonselective Nsaid Use • Stroke/Tia • History of Peptic Ulcer Disease or Gi Bleeding • Antiplatelets	• Potential drug interactions: ○ Antidepressants ○ Fluconazole ○ Lithium ○ blood pressure medications ○ cyclosporine ○ methotrexate ○ steroids • Potential contraindications: ○ pregnancy at the time of initiation • Potential other indications: ○ Fibromyalgia ○ rheumatoid arthritis

Example	Known adverse events	Investigator defined measurable risk factors for known adverse events	Other investigator defined covariates
4 Valproic acid and lamotrigine	• hepatotoxicity • teratogenicity (spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly) • pancreatitis • serious rashes (Stevens-Johnson syndrome) • serious immune reactions (hemophagocytic lymphohistiocytosis - HLH)	• HIV infection • Other viral infections (mumps, flu, herpes, Coxsackie, Epstein-Barr, cytomegalovirus, parvovirus B19, pneumocystosis and histoplasmosis) • Bacterial infection • Organ transplant • Autoimmune diseases (e.g. Lupus, type 1 diabetes, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, inflammatory bowel disease, Addison's disease, Grave's disease, Hashimoto's thyroiditis, myasthenia gravis, vasculitis, celiac disease) • Chemotherapy • Cancer • Acute b-lymphoblastic leukemia • Medicines for gout (e.g. Allopurinol) • Sulfa antibiotics (e.g. Bactrim, septra), • Sertraline • "oxicam" anti-inflammatory drugs (e.g. Meloxicam, piroxicam) • Alcohol use disorders • Liver disease • Gallstones • Cystic fibrosis • Kawasaki disease • Reye's syndrome	• Potential other indications: ○ migraine, bipolar disorder

Example	Known adverse events	Investigator defined measurable risk factors for known adverse events	Other investigator defined covariates
		• Hemolytic uremic syndrome (HUS) • Thrombotic thrombocytopenic purpura (TTP) • Hyperparathyroidism • Obstructions in the biliary system • Peptic ulcer • Azathioprine • 6-mercaptopurine (e.g., Imuran®) • Diuretics • Didanosine • Estrogens • Pentamidine • Tetracycline	

VII. REFERENCES

1. Nelson JC, Shortreed SM, Yu O, et al. Integrating database knowledge and epidemiological design to improve the implementation of data mining methods that evaluate vaccine safety in large healthcare databases. Statistical Analysis and Data Mining: The ASA Data Science Journal 2014;7:337-51.

2. Brown JS, Petronis KR, Bate A, et al. Drug Adverse Event Detection in Health Plan Data Using the Gamma Poisson Shrinker and Comparison to the Tree-based Scan Statistic. Pharmaceutics 2013;5:179-200.

3. Yih WK, Maro JC, Nguyen M, et al. Assessment of Quadrivalent Human Papillomavirus Vaccine Safety Using the Self-Controlled Tree-Temporal Scan Statistic Signal-Detection Method in the Sentinel System. American journal of epidemiology 2018;187:1269-76.

4. TreeScan Power (PRISM). US Food and Drug Administration (FDA). (Accessed June 26, 2017, at https://www.sentinelinitiative.org/sentinel/methods/336.)

5. Pilot Of Self-Controlled Tree-Temporal Scan Analysis For Gardasil Vaccine. US Food and Drug Administration (FDA). at https://www.sentinelinitiative.org/sentinel/methods/339.)

6.Medicine) IIo. The childhood immunization schedule and safety: Stakeholders concerns, scientific evidence, and future studies. Washington, DC: The National Academies Press 2013.

7. Taxonomy for monitoring methods within a medical product safety surveillance system: Report of the Mini-Sentinel Taxonomy Project Work Group. 2010. (Accessed August 28, 2018, at https://www.sentinelinitiative.org/sites/default/files/Methods/MiniSentinel_FinalTaxonomyReport.pdf.)

8. Fine PE, Chen RT. Confounding in studies of adverse reactions to vaccines. American journal of epidemiology 1992;136:121-35.

9. Glynn RJ, Knight EL, Levin R, Avorn J. Paradoxical relations of drug treatment with mortality in older persons. Epidemiology 2001;12:682-9.

10. Suissa S. The case-time-control design. Epidemiology 1995;6:248-53.

11. Wang S, Linkletter C, Maclure M, et al. Future cases as present controls to adjust for exposure trend bias in case-only studies. Epidemiology 2011;22:568-74.

12. Wang SV, Gagne JJ, Glynn RJ, Schneeweiss S. Case-crossover Studies of Therapeutics: Design Approaches to Addressing Time-varying Prognosis in Elderly Populations. Epidemiology 2013;24:375-8.

13. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. The American journal of medicine 1980;68:255-8.

14. Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. Pharmacoepidemiol Drug Saf 2010;19:858-68.

15. Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. American Journal of Epidemiology 2003;158:915-20.

16. Brookhart MA, Wyss R, Layton JB, Sturmer T. Propensity score methods for confounding control in nonexperimental research. Circulation Cardiovascular quality and outcomes 2013;6:604-11.

17. Schneeweiss S, Eddings W, Glynn RJ, Patorno E, Rassen J, Franklin JM. Variable Selection for Confounding Adjustment in High-dimensional Covariate Spaces When Analyzing Healthcare Databases. Epidemiology 2017;28:237-48.

18. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512-22.

19. Tibshirani R. The Lasso Method for Variable Selection in the Cox Model. Statistics in Medicine 1997;16.

20. Wyss R, Ellis AR, Brookhart MA, et al. The role of prediction modeling in propensity score estimation: an evaluation of logistic regression, bCART, and the covariate-balancing propensity score. American journal of epidemiology 2014;180:645-55.

21. Ju CC, M; Lendle, SD; Franklin, JM; Wyss, R; Schneeweiss, S; van der Laan, MJ. Propensity score prediction for electronic healthcare databases using Super Learner and High-dimensional Propensity Score Methods. Cornell University Library; 2017.

22. Routine Querying Tools (Modular Programs). 2014. 2016, at http://mini-sentinel.org/data_activities/modular_programs/details.aspx?ID=166.)

23. Gagne JW, SV; Schneeweiss, S. . FDA Mini-Sentinel Prospective Routine Observational Monitoring Program Tool: Cohort Matching. Technical Users' Guide version: 1.0 . January 2014.

24. Cole D, Kulldorff M, Baker M, et al. Infrastructure for Evaluation of Statistical Alerts Arising from Vaccine Safety Data Mining Activities in Mini-Sentinel. 2016 July 22, 2016.

25. Gagne JJ HX, Hennessy S, Leonard CE, Chrischilles EA, Carnahan RM, Wang SV, Fuller C, Iyer A, Katcoff H, Woodworth TS, Archdeacon P, Meyer TE, Schneeweiss S, Toh S. . Successful comparison of US Food and Drug Administration Sentinel analysis tools to traditional pharmacoepidemiologic approaches. . Clinical Pharmacology and Therapeutics

26. Mini-Sentinel Product Assessment: A Protocol for Assessment of Dabigatran Version 3. Food and Drug Administration, Sentinel Program., 2015. at http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_Protocol-for-Assessment-of-Dabigatran.pdf.)

27. Mini-Sentinel Prospective Routine Observational Monitoring Program Tools (PROMPT): Rivaroxaban Surveillance Version 3. Food and Drug Administration, Sentinel Program, 2015. at http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_PROMPT_Rivaroxaban-Surveillance-Plan.pdf.)

28. Toh S, Reichman ME, Houstoun M, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Archives of internal medicine 2012;172:1582-9.

29. Leonard CR, ME; Toh, D; Kulldorff, M; Nelson, JC; Gagne, JJ; Ouellet-Hellstrom, RP; Moeny, DG; Mott, KA; By, K; Wang, SV; Hennessy, S. . Mini-Sentinel Prospective Surveillance Plan: Prospective Routine Observational Monitoring of Mirabegron. .

30. Toh S, Avorn J, D'Agostino RB, Sr., et al. Re-using Mini-Sentinel data following rapid assessments of potential safety signals via modular analytic programs. Pharmacoepidemiol Drug Saf 2013;22:1036-45.

31. Taxonomy for monitoring methods within a medical product safety surveillance system: year two report of the Mini-Sentinel Taxonomy Project Workgroup. 2012. (Accessed June 12, 2017, at

http://www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Taxonomy-Year-2-Report.pdf.)

32. Routine Querying Tools (Modular Programs). 2014. (Accessed June 12, 2017, at http://mini-sentinel.org/data_activities/modular_programs/details.aspx?ID=166.)

33. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol 2011;64:749-59.

34. Kim DH, Schneeweiss S. Measuring frailty using claims data for pharmacoepidemiologic studies of mortality in older adults: evidence and recommendations. Pharmacoepidemiol Drug Saf 2014;23:891-901.

35. Zhou T, Tao D, Wu X. Manifold elastic net: a unified framework for sparse dimension reduction. Data Mining and Knowledge Discovery 2011;22:340-71.

36. Franklin JM, Eddings W, Glynn RJ, Schneeweiss S. Regularized Regression Versus the High-Dimensional Propensity Score for Confounding Adjustment in Secondary Database Analyses. American journal of epidemiology 2015;182:651-9.

37. Karim ME, Pang M, Platt RW. Can We Train Machine Learning Methods to Outperform the High-dimensional Propensity Score Algorithm? Epidemiology 2018;29:191-8.

38. Myers JA, Rassen JA, Gagne JJ, et al. Effects of adjusting for instrumental variables on bias and precision of effect estimates. American journal of epidemiology 2011;174:1213-22.

39. Using the Pharmacoepidemiology Toolbox in SAS. at http://www.drugepi.org/wp-content/uploads/2013/10/Using_the_Pharmacoepi_Toolbox_in_SAS_2.4.15.pdf.)

40. Bross ID. Spurious effects from an extraneous variable. Journal of chronic diseases 1966;19:637-47.

41. Myers JA, Rassen JA, Gagne JJ, et al. Myers et al. Respond to "Understanding Bias Amplification". American Journal of Epidemiology 2011;174:1228-9.

42. Clinical Classification Software (CCS) 2015. Agency for Healthcare Research and Quality, 2016. at https://www.hcup-us.ahrq.gov/toolssoftware/ccs/CCSUsersGuide.pdf.)

43. Skalsky K, Yahav D, Lador A, Eliakim-Raz N, Leibovici L, Paul M. Macrolides vs. quinolones for community-acquired pneumonia: meta-analysis of randomized controlled trials. Clinical Microbiology and Infection 2013;19:370-8.

44. Jackson LA, Neuzil KM, Yu O, et al. Effectiveness of Pneumococcal Polysaccharide Vaccine in Older Adults. New England Journal of Medicine 2003;348:1747-55.

45. Jackson ML, Neuzil KM, Thompson WW, et al. The Burden of Community-Acquired Pneumonia in Seniors: Results of a Population-Based Study. Clinical Infectious Diseases 2004;39:1642-50.

46. Drehobl MA, De Salvo MC, Lewis DE, Breen JD. Single-Dose Azithromycin Microspheres vs Clarithromycin Extended Release for the Treatment of Mild-to-Moderate Community-Acquired Pneumonia in Adults. CHEST 2005;128:2230-7.

47. O'Doherty B, Muller O. Randomized, Multicentre Study of the Efficacy and Tolerance of Azithromycin versus Clarithromycin in the Treatment of Adults with Mild to Moderate Community-Acquired Pneumonia. European Journal of Clinical Microbiology and Infectious Diseases 1998;17:828-33.

48. Layton D, Hughes K, Harris S, Shakir SA. Comparison of the incidence rates of selected gastrointestinal events reported for patients prescribed celecoxib and meloxicam in general practice in England using prescription-event monitoring (PEM) data. Rheumatology 2003;42:1332-41.

49. Asghar W, Jamali F. The effect of COX-2-selective meloxicam on the myocardial, vascular and renal risks: a systematic review. Inflammopharmacology 2015;23:1-16.

50. Layton D, Hughes K, Harris S, Shakir SAW. Comparison of the incidence rates of thromboembolic events reported for patients prescribed celecoxib and meloxicam in general practice in England using Prescription-Event Monitoring (PEM) data. Rheumatology 2003;42:1354-64.

51. Valproic acid and sodium valproate approved for use in epilepsy. FDA drug bulletin 1978;8:14-5.

52. Goldenberg MM. Overview of Drugs Used For Epilepsy and Seizures: Etiology, Diagnosis, and Treatment. Pharmacy and Therapeutics 2010;35:392-415.

53. Highlights of Prescribing Information. (Accessed July 6, 2018, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022251,020764s029,020241s036lbl.pdf.)

54. Karceski SG, P; Dashe, JF. Initial treatment of epilepsy in adults. UpToDate. Jun 2018 ed.

55. Depakote Tablets (divalproex sodium). (Accessed July 6, 2018, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/018723s039lbl.pdf.)

56. Lamictal (lamotrigine): Drug Safety Communication - Serious Immune System Reaction. (Accessed 7/6/2018, at https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm605628.htm.)

VIII. APPENDICES

A. CURATION OF THE MLCCS TREE

Two members of the FDA independently reviewed the MLCCS tree based on 2015 ICD-9-CM codes to remove codes that were unlikely to be caused by drug exposures within a short follow up window. Each reviewer flagged codes that were:

1. of known etiology (e.g. pregnancy, congenital condition),
2. unlikely to be an adverse reaction caused by drugs (e.g. gingival recession, recurrent dislocation of shoulder),
3. not an incident diagnosis (e.g. alcoholism in family, social maladjustment),
4. for conditions with long latency/induction periods (e.g. cancer, osteoporosis)

After adjudication of disagreement, 7,078 of 15,075 (47%) ICD-9-CM diagnostic codes were excluded.

Source:

https://www.sentinelinitiative.org/sentinel/surveillance-tools/software-toolkits/treeextraction-documentation (supporting tree file)

B. DETAILED PROTOCOL SPECIFICATIONS FOR EXAMPLES

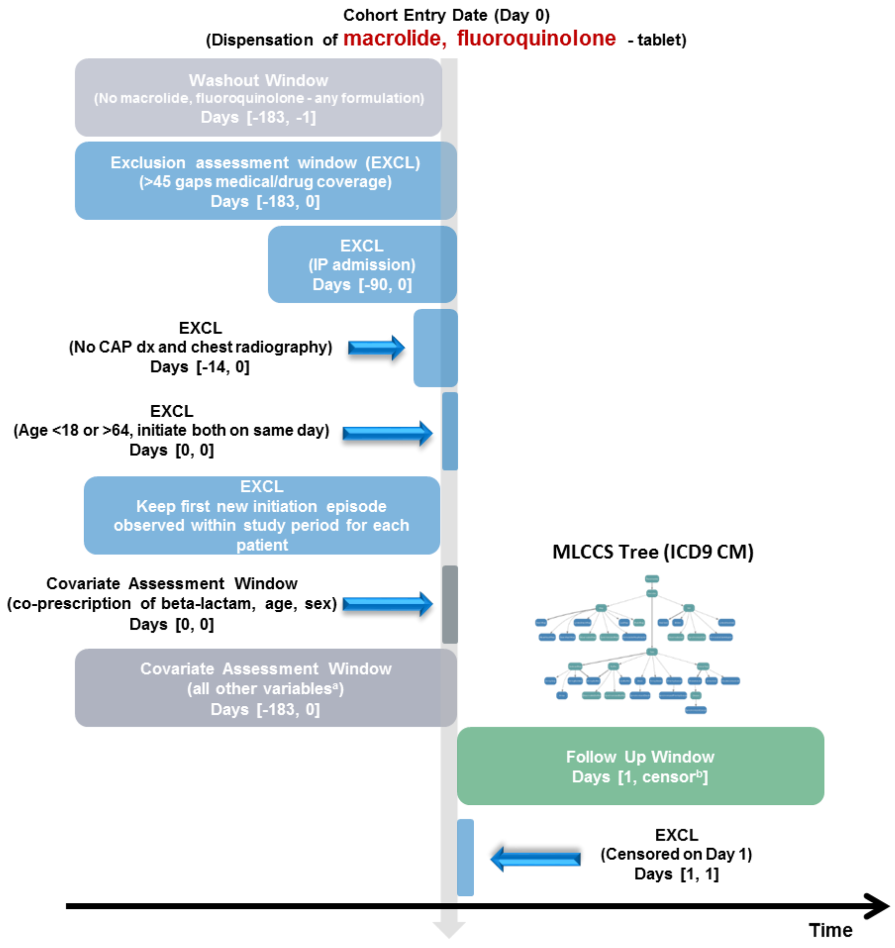
Example 1

[a]All other variables considered in candidate global propensity scores

- Age (continuous)
- Gender
- Metastatic cancer
- Tumor
- Arrhythmia
- Congestive heart failure
- Dementia
- Renal failure
- Weight loss
- Hemiplegia
- Alcohol abuse
- Pulmonary disease
- Coagulopathy
- Complicated diabetes
- Anemia
- Fluid and electrolyte disorder
- Liver disease
- Peripheral vascular disorder
- Psychosis
- Pulmonary circulation disorders
- HIV/AIDS
- Hypertension
- Degenerative disease of central nervous system
- Durable medical equipment
- Vaccine administration
- Screening examinations and disease management training
- Pap smear
- HPV DNA test
- Mammogram
- Fecal occult blood test
- Colonoscopy
- PSA test
- Number of inpatient hospitalizations
- Number of outpatient visits
- Number of emergency department visits
- Number of unique generics
- Prior prescription of penicillins
- Prior prescription of cephalosporins
- Prior prescription of sulfonamides
- Prior prescription of tetracyclines
- Prior prescription of aminoglycosides
- Co-prescription of beta-lactam
- Pregnancy at time of initiation
- Empirically selected

[b]Censoring

- 183 days
- Sep 30, 2015
- Discharged dead
- Disenroll medical or drug (45 day gaps allowed)



Cohort Entry Date (Day 0)
(Dispensation of macrolide, fluoroquinolone - tablet)

Washout Window
(No macrolide, fluoroquinolone - any formulation)
Days [-183, -1]

Exclusion assessment window (EXCL)
(>45 gaps medical/drug coverage)
Days [-183, 0]

EXCL
(IP admission)
Days [-90, 0]

EXCL
(No CAP dx and chest radiography)
Days [-14, 0]

EXCL
(Age <18 or >64, initiate both on same day)
Days [0, 0]

EXCL
Keep first new initiation episode observed within study period for each patient

Covariate Assessment Window
(co-prescription of beta-lactam, age, sex)
Days [0, 0]

Covariate Assessment Window
(all other variables[a])
Days [-183, 0]

MLCCS Tree (ICD9 CM)

Follow Up Window
Days [1, censor[b]]

EXCL
(Censored on Day 1)
Days [1, 1]

Time

Example 2

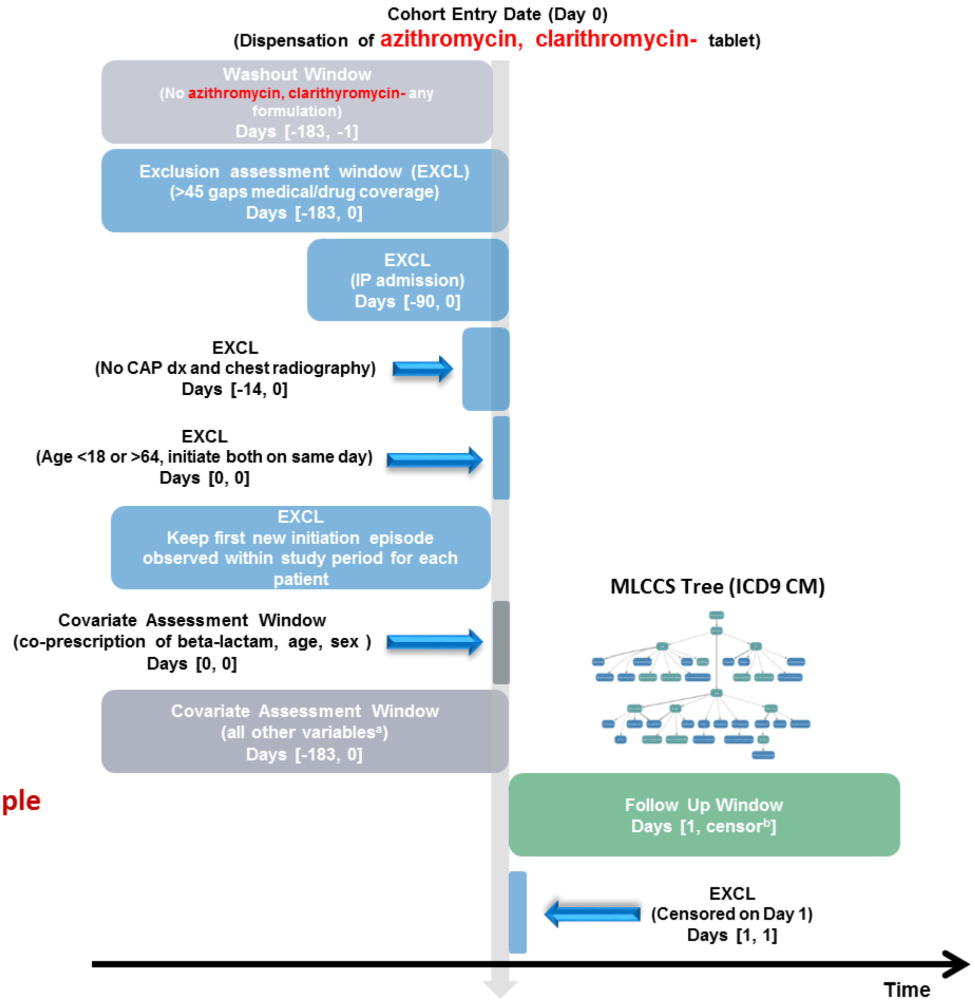
[a]**All other variables considered in candidate global propensity scores**

- Age (continuous)
- Gender
- Metastatic cancer
- Tumor
- Arrhythmia
- Congestive heart failure
- Dementia
- Renal failure
- Weight loss
- Hemiplegia
- Alcohol abuse
- Pulmonary disease
- Coagulopathy
- Complicated diabetes
- Anemia
- Fluid and electrolyte disorder
- Liver disease
- Peripheral vascular disorder
- Psychosis
- Pulmonary circulation disorders
- HIV/AIDS
- Hypertension
- Degenerative disease of central nervous system
- Durable medical equipment
- Vaccine administration
- Screening examinations and disease management training
- Pap smear
- HPV DNA test
- Mammogram
- Fecal occult blood test
- Colonoscopy
- PSA test
- Number of inpatient hospitalizations
- Number of outpatient visits
- Number of emergency department visits
- Number of unique generics
- Prior prescription of penicillins
- Prior prescription of cephalosporins
- Prior prescription of sulfonamides
- Prior prescription of tetracyclines
- Prior prescription of aminoglycosides
- Prior prescription of other macrolides
- Prior prescription of fluoroquinolones
- Co-prescription of beta-lactam
- Pregnancy at time of initiation
- Empirically selected

Tailored to example

[b]**Censoring**

- 183 days
- Sep 30, 2015
- Discharged dead
- Disenroll medical or drug (45 day gaps allowed)



Cohort Entry Date (Day 0)
(Dispensation of azithromycin, clarithromycin- tablet)

Washout Window
(No azithromycin, clarithyromycin- any formulation)
Days [-183, -1]

Exclusion assessment window (EXCL)
(>45 gaps medical/drug coverage)
Days [-183, 0]

EXCL
(IP admission)
Days [-90, 0]

EXCL
(No CAP dx and chest radiography)
Days [-14, 0]

EXCL
(Age <18 or >64, initiate both on same day)
Days [0, 0]

EXCL
Keep first new initiation episode observed within study period for each patient

Covariate Assessment Window
(co-prescription of beta-lactam, age, sex)
Days [0, 0]

MLCCS Tree (ICD9 CM)

Covariate Assessment Window
(all other variables[a])
Days [-183, 0]

Follow Up Window
Days [1, censor[b]]

EXCL
(Censored on Day 1)
Days [1, 1]

Time

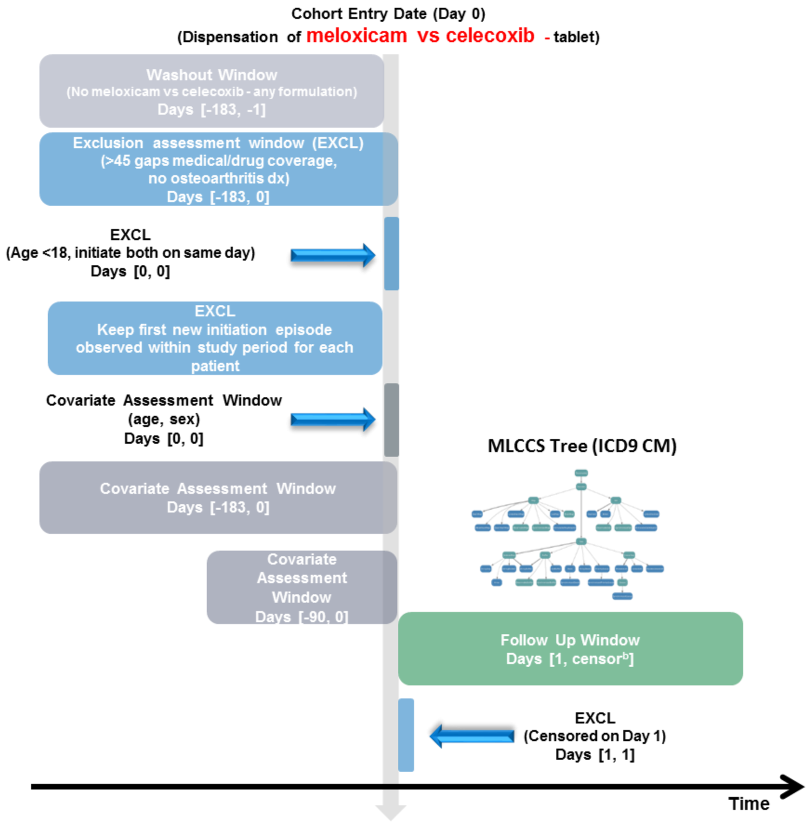
Example 3

Predefined Global Covariates Days:
Empirical Covariates Days:
Tailored Covariates Days:

- Upper GI events
- Lower GI events
- Myocardial infarction
- Cerebrovascular events (stroke, TIA)
- Renal failure, acute kidney injury, hyperkalemia
- Obesity
- Smoking
- Angina
- Coronary Revascularization
- Pregnancy at the time of initiation
- Fibromyalgia
- Rheumatoid arthritis
- Hormone Replacement Therapy
- Statins
- Opioids
- Non-selective NSAIDS
- Selective NSAIDS

Tailored Covariates:

- Anticoagulants
- Antiplatelets
- Antidepressants
- Fluconazole
- Lithium
- Antihypertensives
- Cyclosporine
- Methotrexate
- Steroids
- PPI
- H2B



Cohort Entry Date (Day 0)
(Dispensation of meloxicam vs celecoxib - tablet)

Washout Window
(No meloxicam vs celecoxib - any formulation)
Days [-183, -1]

Exclusion assessment window (EXCL)
(>45 gaps medical/drug coverage,
no osteoarthritis dx)
Days [-183, 0]

EXCL
(Age <18, initiate both on same day)
Days [0, 0]

EXCL
Keep first new initiation episode observed within study period for each patient

Covariate Assessment Window
(age, sex)
Days [0, 0]

MLCCS Tree (ICD9 CM)

Covariate Assessment Window
Days [-183, 0]

Covariate Assessment Window
Days [-90, 0]

Follow Up Window
Days [1, censor[b]]

EXCL
(Censored on Day 1)
Days [1, 1]

[b]**Censoring**

- 183 days
- Sep 30, 2015
- Discharged dead
- Switch
- Disenroll medical or drug (45 day gaps allowed)

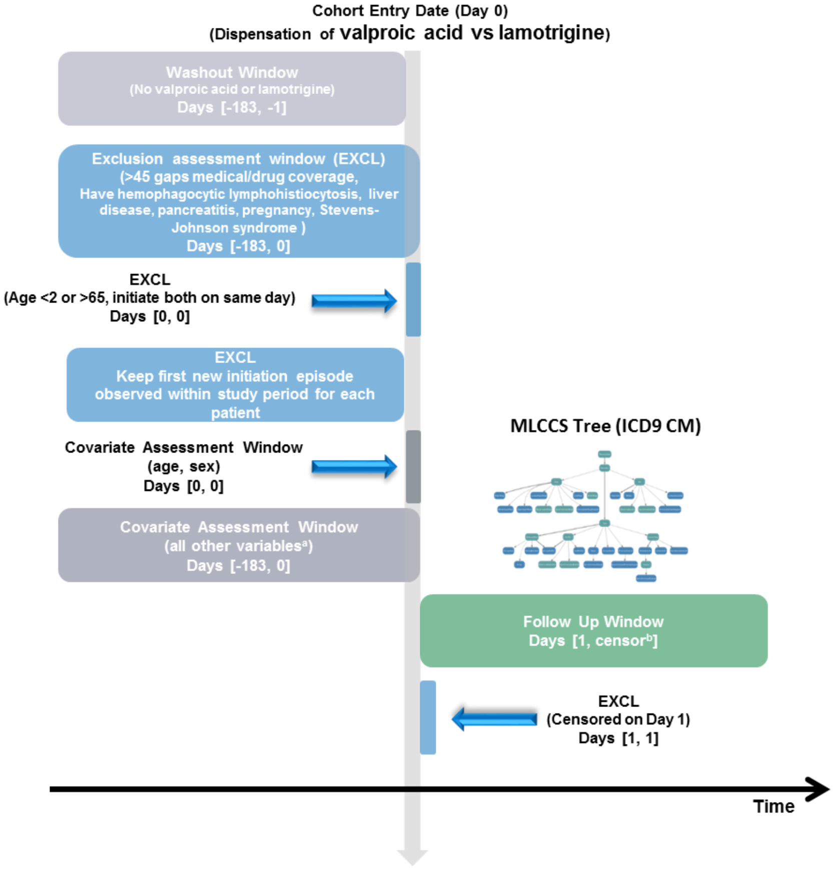
Example 4

[a] Covariates
Predefined Global Covariates
Empirical Covariates
Tailored Covariates:

- HIV infection treatments
- Other viral infections (mumps, flu, herpes, Coxsackie, Epstein-Barr, cytomegalovirus, parvovirus B19, pneumocystosis and histoplasmosis)
- Bacterial infection
- Organ transplant
- Autoimmune diseases
- Chemotherapy
- Cancer
- Acute b-lymphoblastic leukemia
- Medicines for gout (e.g. NSAIDS, corticosteroids, other)
- Sulfa antibiotics (e.g. Bactrim, septra),
- Alcohol use disorders
- Gallstones
- Cystic fibrosis
- Kawasaki disease
- Reye's syndrome
- Hemolytic uremic syndrome (HUS)
- Thrombotic thrombocytopenic purpura (TTP)
- Hyperparathyroidism
- Migraine
- Bipolar disorder
- Epilepsy/Convulsions
- Depression
- Schizophrenia
- Other anticonvulsants
- Antidepressants: SSRI, SNRI, TCA, MOA, Atypical, Other
- Atypical antipsychotics, typical antipsychotics
- Short, long acting BZD
- Stroke
- TBI

[b]Censoring

- 183 days
- Sep 30, 2015
- Discharged dead
- Switch
- Disenroll medical or drug
  (45 day gaps allowed)



Cohort Entry Date (Day 0)
(Dispensation of valproic acid vs lamotrigine)

Washout Window
(No valproic acid or lamotrigine)
Days [-183, -1]

Exclusion assessment window (EXCL)
(>45 gaps medical/drug coverage,
Have hemophagocytic lymphohistiocytosis, liver disease, pancreatitis, pregnancy, Stevens-Johnson syndrome)
Days [-183, 0]

EXCL
(Age <2 or >65, initiate both on same day)
Days [0, 0]

EXCL
Keep first new initiation episode observed within study period for each patient

Covariate Assessment Window
(age, sex)
Days [0, 0]

Covariate Assessment Window
(all other variables[a])
Days [-183, 0]

MLCCS Tree (ICD9 CM)

Follow Up Window
Days [1, censor[b]]

EXCL
(Censored on Day 1)
Days [1, 1]

C. RESPONSES TO PUBLIC COMMENT

Comments on "Development and Evaluation of a Global Propensity Score for Data Mining with Tree-Based Scan Statistics"

1. Given the large number of available empirical approaches for model selection, it could be helpful to provide motivation for why hdps was chosen for this evaluation as opposed to other options. For instance, Karim et al. (Epidemiology 2018 Mar; 29(2): 191-198) recently showed that a machine learning with hdps hybrid often outperforms hdps alone.

   This paper found that machine learning based approaches such as LASSO and ElasticNet in combination with hdPS performed marginally better than hdPS alone in the context of selection based on potential for bias for a single outcome. The machine learning component of the hybrid empirical variable selection methods worked to further reduce the dimensionality of variables identified with hdPS.

   In our context, we are scanning across thousands of potential outcomes. It would not be feasible to apply a hybrid approach which selects variables based on association with outcome. Furthermore, it may be helpful in our scanning context to include a slightly broader base of variables to provide proxy adjustment for confounders on a wider range of outcomes.

   We will include this citation and a brief explanation as above in the background.

2. Similarly, it could be useful to motivate why the TreeScan methodology was selected as opposed to other scan statistics (or, minimally, to provide its major advantages and limitations in this specific setting).

   We will list some of the major strengths and limitations of TreeScan in the protocol. A comparison of different signal detection methods is currently underway in another task order (signalx3).

   Strengths:

   i. Developed based on scan statistical theory
   ii. Use a hierarchical diagnosis tree to simultaneously evaluate outcomes at different levels of granularity (including specific diagnoses and groups of related diagnoses)
   iii. Use a frequentist method to formally adjust for the multiple testing inherent in evaluation of thousands of potential adverse events that accounts for correlation between tests of related hypotheses (unlike traditional frequentist methods which are too conservative)
   iv. Useful when screening for unanticipated safety signals where there is no informative prior

Weaknesses:

v. Bias is adjusted by design, not inherent in the scan statistic

vi. Hierarchical classification system for outcomes are not based on validated algorithms

vii. Adjusting for multiplicity when scanning across outcomes will decrease power compared to evaluating a single pre-specified hypothesis

3. What is the rationale for NOT focusing on data in the ICD-10 era, since future safety studies will this new system and your ICD-9 based results may not (?) be seamlessly generalizable. Minimally, it could be helpful to comment on why an ICD-9 based evaluation is proposed and why you don't have major concerns that your conclusion won't be limited by this feature.

   Although different hierarchical trees may have different properties, the method of TreeScan with PS-matching is not tied to a particular coding system and should be extensible.

   We deliberately chose older examples with known safety profiles. Given the delays in data refreshes, we have limited years of data available after Oct 2015. Although an ICD10 based tree is available, if we focused only on the ICD-10 era, we would have lower power to detect known signals in our examples. Doing hdPS in a mixed ICD9-10 era would require incorporation of mapping and is beyond the scope of this project.

4. It could be helpful to explain why you chose to focus your Aim 1 evaluation on a subset of outcomes (feasibility?) and whether/how this may limit the generalizability of the evaluation of method performance. For instance, why would we expect performance metrics for the selected set of outcomes to carry-over to the other 100's of outcomes one might evaluate? Are there any performance metrics that could be feasibly evaluated for 'all' outcomes to avoid issues of selection and uncertain generalizability?

   The general performance metric of balance on predefined and empirically selected covariates used in the PS will apply to all outcomes. However, the covariates in the PS will not necessarily be relevant or optimal for all outcomes in all drug comparison scenarios. It would be infeasible to identify the best set of covariates for each outcome and evaluate balance on each.

   That is why we will be focusing our deeper dive on balance for known risk factors on a subset of outcomes with and without alerts in a variety of examples where we have prior knowledge of where true signals may or may not be present. These examples are intended to be diverse with respect to study populations as well as types of outcomes with true signals. That said, the performance in these examples will not necessarily be generalizable to all contexts.

   Realistically, most of the potential outcomes scanned will be unrelated to the evaluated drugs. By focusing on areas where there are known signals or unanticipated alerts, we target high yield areas for learning about the method and its performance.

   We will include discussion to that effect in the protocol.

5. How will you ensure that you have identified example scenarios with adequate power to find signals of interest?

   As in a real surveillance activity, we may not necessarily have adequate power to find signals of interest at stringent pre-specified alpha levels. In each of our example scenarios, we have known signals that were previously identified. We will be looking at patterns of alerting in these examples to observe how signal detection using the method could play out in a real scenario. Outcomes that don't alert at the pre-specified threshold may still have relatively low likelihood under the null. The method can play an important part in screening and prioritization even if there is not sufficient power to alert at a pre-specified threshold by painting a clinical picture of the pattern of outcomes that are unlikely to be observed if there was no relationship with exposure.

6. Is there an existing 'standard' data mining method with which you can compare your new global PS-based options? This may help give some evidence about the level of improvement your methods may provide beyond what a more basic approach that a researcher might do typically in practice now.

   There does not appear to be a 'standard' cohort based approach. The signalx3 workgroup will be comparing three signal detection methods that use a self-controlled design, which are more frequently used in pharmacovigilance activities.

7. You might consider referencing an article from our group that motivates the importance of work in this research area. Although this review was more narrowly written in the context of vaccine safety, its conclusions apply to drug safety applications as well.

   This is very relevant. We will cite this review.

   Nelson JC, Shortreed S, Yu O, et al. on behalf of the Vaccine Safety Datalink project. Integrating database knowledge and epidemiological design to improve the implementation of data mining methods to evaluate vaccine safety in large healthcare databases. *Stat Analysis Data Mining* 2014 Oct;7(5):337-351. doi:10.1002/sam.11232

D. FOLLOW UP ANALYSES FOR EXAMPLES 1-3

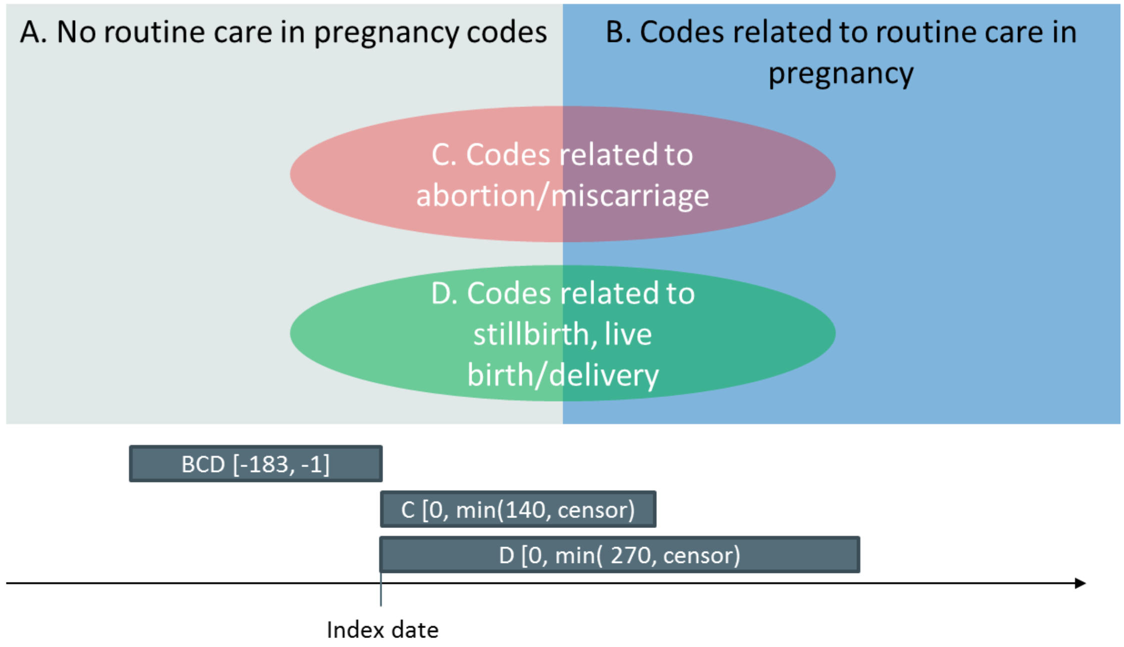
After observing the results for examples 1-3, we decided to initiate post-hoc follow up analyses that would allow us to 1) dig deeper and better understand how baseline pregnancy status affected the results observed after implementing the pre-specified protocol for examples 1 and 2, and 2) evaluate how explicitly balancing on nodes that were highly ranked by LLR would affect subsequent alerting patterns for example 3.

Example 1:

Pregnancy was originally included as a tailored confounder in the pre-specified protocol because we anticipated channeling due to different patterns of antibiotic use in pregnancy. The baseline pregnancy algorithm that we used in the pre-specified analyses may not be ideal. The follow up analyses are exploratory, digging deeper into how we measure pregnancy - how well are we capturing it with different algorithms and how does using different definitions of pregnancy as an exclusion criterion affect results. Screening for outcomes associated with drug exposure in pregnancy will be evaluated in another project. Follow up analyses include first re-analyzing the data after exclusion of pregnant women using different code algorithms and assessment windows, some of which case a broader net to remove patients that were pregnant during the assessment window, second, describing the impact of these different definitions of pregnancy on the study population and results, and third, generating tables to show balance on empirically identified covariates for matched populations that may not have been matched on a PS that included those covariates (additional detail below).

1. Reanalyze after removing pregnant women (ever during the assessment window)
    - Codes indicative of
        - Routine care during pregnancy
        - Live birth/delivery
        - Other end of pregnancy (stillbirth, miscarriage, termination)
    - Compare results with different assessment windows for pregnancy
        - [-183, 1] any codes +
          [0, min(140, censor)] for miscarriage, abortion codes +
          [0, min(270, censor)] for stillbirth or delivery codes

2. Describe frequency of exclusion with different codes and assessment windows


A. No routine care in pregnancy codes
B. Codes related to routine care in pregnancy
C. Codes related to abortion/miscarriage
D. Codes related to stillbirth, live birth/delivery
BCD [-183, -1]
C [0, min(140, censor)
D [0, min(270, censor)
Index date

3. Add tables showing balance on empirically identified covariates when they are versus are not included in the PS

Example 2:

Same follow up analyses as example 1.

Example 3:

The follow up analyses include restriction of data to time prior to a generic version of celecoxib entering the market in case the availability of a generic affected prescribing patterns for patients at different risk of adverse outcomes. Follow up analyses also will involve reanalysis after inclusion of nodes that alerted at the pre-specified threshold or were highly ranked in the propensity score to allow evaluation of scanning results after balancing on those nodes at baseline.

1. Restrict years of study to before May 2014 (before generic celecoxib came on the market)
2. Re-analyze after adding prior history of top nodes from LLR ranking to PS (e.g. stroke, headache, cerebral infarct) and mental health related covariates (e.g. depression, anxiety, antidepressants, anti-anxiety).
3. Add tables showing balance on empirically identified covariates when they are versus are not included in the PS

E. ADDITIONAL JUSTIFICATION FOR DESIGN DECISIONS

Justification for allowing tailored covariate assessment window to differ from fixed predefined and empirical covariate assessment windows:

Predefined covariates and empirically identified covariates can be generically applied to every exposure-comparator evaluation without customization for different exposure-comparator evaluations.

Tailored covariates represent thoughtful consideration of what investigators think is relevant for the exposure-comparator pair and at least one potential adverse event. As such, there are no limitations on which or how tailored covariates are defined. The tailored covariates can be highly customized – including not just different variables but different assessment windows, requirement multiple diagnoses within certain time frames or more complicated algorithms.

Thus, the contrast between PSs that include tailored covariates versus those that do not is between a base case scenario of generically applied covariates using default assessment windows versus the addition of investigator selected covariates defined using whatever covariate definitions the investigators think are the most relevant to the exposure-comparator evaluation. These tailored covariates can and will vary in terms of which variables are included and complexity of definition across different evaluations.

Justification for allowing ascertainment of pregnancy at the time of drug initiation using codes recorded after index date for drug initiation

In pharmacoepidemiology studies, we generally avoid using future information to make decisions about whether patients are eligible for cohort entry, and for good reason. For example, to determine whether patients should enter the cohort at treatment initiation, we generally would not want to require that they have a full year of follow-up after treatment initiation during which they remain alive. If the outcome(s) of interest could sometimes be fatal or were correlated with mortality in other ways, this can create immortal time bias, a form of selection bias. The bias arises when the factor we are conditioning on (mortality, in this example) can be affected by the exposure(s) of interest (or some common cause of exposure and the factor).

In contrast, when using information during follow-up to identify patients who have birth outcomes, the objective is to exclude those that had to have been pregnant prior to the start of follow-up. In this situation, the pregnancies that began prior to treatment initiation could not have been affected by the treatment. There are other (and perhaps rare) situations in which it would also be valid to use future information. For example, imagine that we wanted to conduct an analysis among patients who were 65 years of age or older and we did not know patients' ages at the time of cohort entry, but we did know their ages one year later (or at the time of death for anyone who may have died within that year). In this case, it is safe to use the future information about age to infer patients' ages at the time of cohort entry because the exposure(s) could not have affected patients' age. This is analogous to the pregnancy situation.

There are other reasons to avoiding using future information to define study variables – such as looking into the future to assign exposure status at the start of follow-up, which is classical immortal time bias. However, these are slightly different situations than the pregnancy scenario.