

FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH

CALL FOR PARTICIPATION: IMPLEMENTING OBSERVATIONAL ANALYSIS METHODS

MAY 28, 2009

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP (OMOP)

Purpose:

The Observational Medical Outcomes Partnership (OMOP) is initiating this call for participation to identify potential resources, tools, and skills to develop and execute analysis code within the OMOP Research Lab. Respondents should have experience in methods implementation and / or development for observational analyses and execution of each code set for each method.

The OMOP Research Lab provides the core IT infrastructure needed to support research conducted using OMOP licensed data. The Research Lab provides OMOP researchers with access to data, statistical analysis tools and a methods library. Data access is provided by standard tools, e.g. SAS, SQL, Oracle Discoverer, and others. The Methods Library provides the capability to import and store methods for use against the OMOP data. Methods will be developed to execute against the OMOP Common Data Model, and will be made publicly available to the broader research community.

Background:

The Observational Medical Outcomes Partnership (<http://omop.fnih.org>) is a public-private partnership designed to help improve the monitoring of drugs for safety. The partnership began in Q4-2008 and is conducting a two-year research initiative to determine the contribution and utility of using existing healthcare databases to identify and evaluate safety issues of drugs already on the market.

OMOP draws on the expertise and resources of the pharmaceutical industry, academic institutions, non-profit organizations, the Food and Drug Administration (FDA), and other federal agencies. It is managed through the Foundation for the National Institutes of Health. In addition to sponsoring specific research efforts, OMOP will create a set of tools—such as data models, experimental protocols, and database evaluation tools—that will be placed in the public domain to encourage research by a broad community of scientific investigators.

All project results will be made public in accordance with the public health mission of the partnership. These will include comprehensive reports on scientific and technical findings, lessons learned, and peer-reviewed articles on the experimental findings by our sponsored investigators.

Invitation to Participate:

Individuals and organizations that have existing programming code for an analysis method, are interested in implementing an existing method, or have an idea for a novel approach for identifying non-specified conditions or monitoring of Health Outcomes of Interest (10 HOIs under study in OMOP: Angioedema, Aplastic Anemia, Acute Liver Injury, Bleeding, GI Ulcer Hospitalization, Hip Fracture, Hospitalization, Myocardial Infarction, Mortality after Myocardial Infarction, and Renal Failure) are invited to submit a proposal for consideration. Please review the attached Specifications

for Observational Analysis Methods document and then provide a description of your method, including an explanation of the following topics, as applicable:

- Comparator selection, including matching approach
- Method for adjustment of confounders
- Output metric (e.g. relative risk vs. risk difference, rate vs. risk)
- Period of exposure
- Inclusion/exclusion criteria (e.g. incident vs. prevalent selection) for exposure and outcome definition
- Adjustment for multiplicity
- How would the method be applied to data accumulating over time

Please include the information listed below in your response. Submit your response by Friday, July 3, 2009. Send your response electronically to Emily Welebob, at ewelebob@fnih.org.

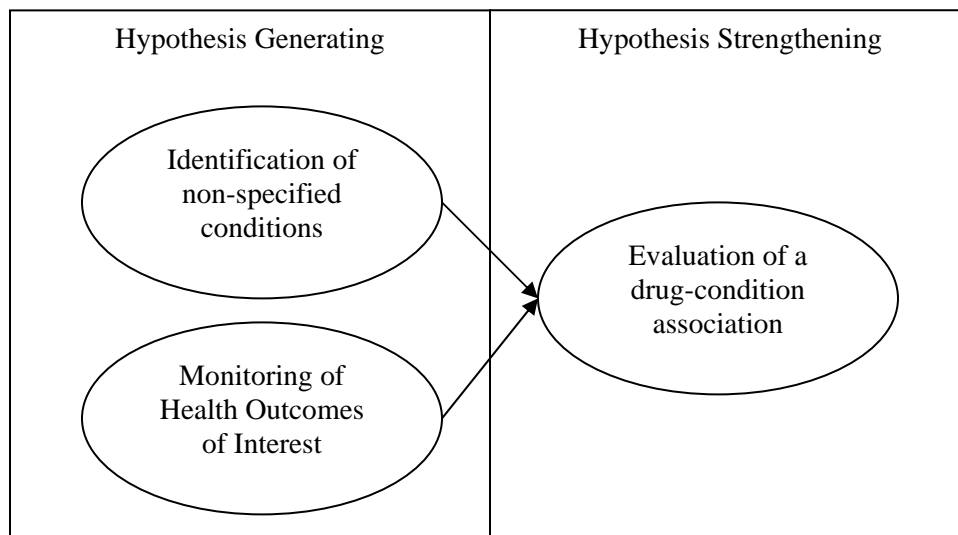
1. Contact information
2. Description of your method according to the above topics
3. Brief proposal for how you envision collaborating with OMOP
4. Cost

Observational Medical Outcomes Partnership: Specifications for Observational Analysis Methods

Patrick Ryan, on behalf of OMOP Research Investigators
Last revised: 8 May 2009

Methods Overview

There are three distinct types of analysis within scope of the Partnership's research. Each analysis type presents different methodological challenges, may require different algorithms and may utilize different data elements within the common data model. The three analysis types are:



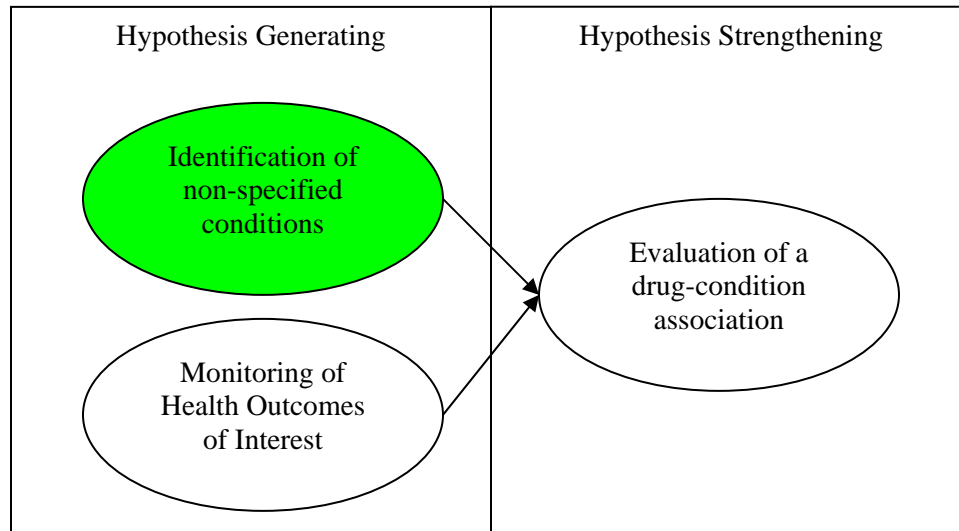
- **Identification of non-specified associations:** This exploratory analysis aims to generate hypotheses from observational data by identifying associations between drugs and conditions for which the relationships were previously unknown. This type of analysis is likely to be considered an initial step of a triaged review process, where many drug-outcome pairs are simultaneously explored to prioritize the drugs and outcomes that warrant further attention. It could be expected that a primary consideration for identification analyses is developing an efficient model to allow high-throughput computing across large sets of potential hypotheses about drug-outcome relationships. Method thresholds can be evaluated on the basis of the tradeoff between observed true positives, false positives, true negatives, and false negatives across the results for a given analysis.

- **Monitoring of Health Outcomes of Interest:** The goal of this surveillance analysis is to monitor the relationship between a series of drugs and specific outcomes of interest. These analyses require an effective definition of the events of interest in the context of the available data (e.g. ‘acute liver injury’ may best be defined by a combination of medical diagnoses, pharmacy records, procedure codes, and/or laboratory results). This is in contrast to the first analysis type, which may concurrently explore many outcomes for a given drug. Where possible, outcomes definitions may be validated within the observational sources to provide broader context for interpreting analysis results.
- **Evaluation of a drug-condition association:** This hypothesis-strengthening analysis is consistent with traditional pharmacoepidemiology practice for comprehensive observational studies. Evaluation studies may require particular data elements specific to the study in question, and will commonly apply multivariate statistics like linear, logistic, or Poisson regression. Evaluations may require specific customization if standard transformations are deemed inappropriate for the particular hypothesis being tested.

For observational analyses, it is important to recognize that the goal is to provide information about associations between drugs and outcomes across a population of interest. The intended objective is not necessarily to conclusively ascertain whether a specific person had a particular outcome due to a particular drug, but instead to infer whether a population of individuals exposed to a product experiences more of the outcome than otherwise expected had they been unexposed. This population-based approach differs from the spontaneous adverse event reporting systems, which considers each data record a specific self-report of a suspected causal association between a drug and an event.

For each type of analysis, the particular method in use may require an analysis dataset in a specific format, such as a single table in which rows represent persons and columns represent indicator variables for the existence of drug exposure or condition occurrence. The OMOP Common Data Model must facilitate the efficient production of analysis datasets. Consideration should be made to determine what data management activities can be pre-processed within the data model as an expedient, and what data manipulations should be reserved for run-time as part of the analysis process. Given that different analysis types may have different specific requirements, it could be anticipated that the Common Data Model may include multiple parallel data tables to facilitate specific tasks. It could also be anticipated that the Terminology Dictionary may include multiple terminologies, to facilitate encoding query result sets with multiple standard codes or terms.

Methods Specification: Identification of non-specified associations



General Issues:

- Each method will be developed as a general procedure to be applied against any drug or outcome.
- Inputs will be defined by sets of codes from the Terminology Dictionary.
- Methods will be tested against 10 drugs of interest:
 - ACE inhibitors
 - Amphotericin B
 - Antibiotics (erythromycin, sulfonamides, tetracyclines)
 - Antiepileptics (carbamazepine, valproic acid, phenytoin)
 - Warfarin
 - Benzodiazepines
 - Alendronate
 - Tricyclic antidepressants
 - Typical antipsychotics
 - Beta blockers
- The outcomes for non-specified conditions will be defined as individual concept codes in the standardized condition terminology.
- Performance requirements
 - Output from analysis will populate a summary analysis table with the following fields:
 - Data source ID
 - Method ID
 - Drug Case ID
 - Outcome Case ID
 - Method Statistic

So, if there are 5 data sources, 10 drug cases, and 1,000 potential outcomes for each drug, each method will produce $5 \times 10 \times 1,000 = 50,000$ records in the result database.

- Procedure must be able to successfully execute one test case (one data source, one drug, all outcomes) in the Research Core environment in less than 3 days to be considered feasible for subsequent testing
- Performance characteristics of the methods will be evaluated at different thresholds, if appropriate. Sensitivity, specificity, positive predictive value and negative predictive value will be estimated by categorizing 'signaled' events as 'true associations' or 'false associations' on the basis of whether the outcome is listed on the product label.

Potential Implementations of Identification Methods

Input: Drug Only

- Output: statistics for all drug-outcome pairs for the given drug
- Execution: Method could be executed sequentially for each drug case of interest
- Examples:
 - Self-controlled cohort design- select all persons on a drug, compare rate of outcome during exposure with rate of outcome for some defined period prior to exposure. Produce rate ratio for each outcome. Potential thresholds could include $RR > 1, 2, 3$.

Input: Outcome Only

- Output: statistics for all drug-outcome pairs for the given outcome
- Execution: Method could be executed sequentially for each outcome
- Examples:
 - Case-control design- Select all persons with an outcome and match controls on some characteristics. Measure differences in drug exposure between the two groups using an odds ratio. Potential thresholds could include $OR > 1, 2, 3$.

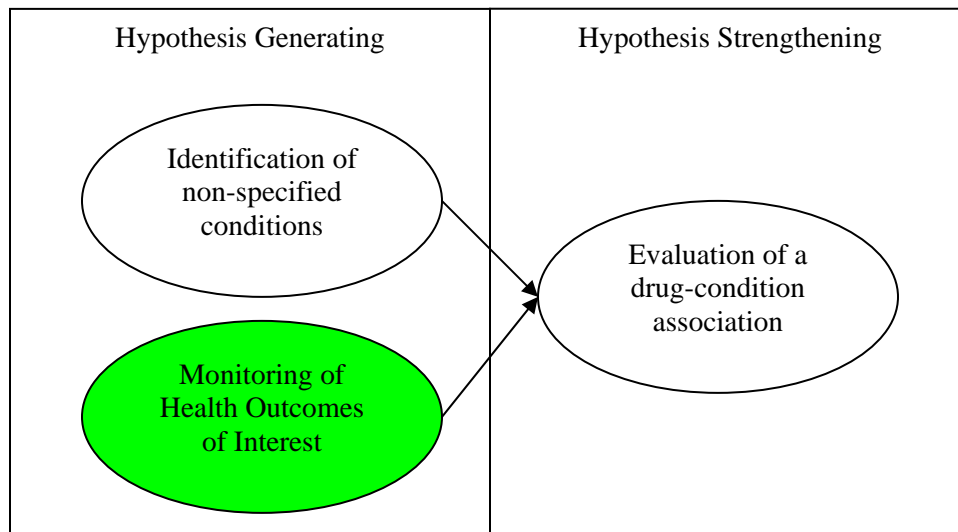
Input: Neither Drug nor Outcome

- Output: statistics for all drug-outcome pairs
- Execution: Method executed once, and the specific drug-outcome pairs of interest are extracted from the resulting dataset
- Examples:
 - Disproportionality analysis- the database is reformatted into drug-condition pairs and proportional reporting ratios (PRR) are calculated for all drug-condition combinations. An example threshold used in spontaneous data mining is $PRR > 2, N > 3, CHISQ > 4$.

Input: Both Drug and Outcome

- Output: statistic for drug-outcome pair
- Execution: Method could be executed sequentially for each drug-outcome pair
- Examples:
 - maxSPRT- Sequential analysis is performed for a specific drug-outcome pair, where 'signal' is identified if the likelihood ratio test exceeds the critical value for the alternative hypothesis (e.g. $LLR > 1.2$)

Methods Specification: Monitoring of Health Outcomes of Interest



General Issues:

- Any method that is feasible for identification of non-specified conditions could be used for monitoring of health outcomes of interest, but methods appropriate for monitoring may not be scalable for identification of non-specified conditions
- Methods will be evaluated on the basis of their performance against the 11 drug-HOI pairs:
 - Angioedema- ACE inhibitors
 - Renal failure- Amphotericin B
 - Acute liver injury- Antibiotics (erythromycin, sulfonamides, tetracyclines)
 - Aplastic anemia- Antiepileptics (carbamazapine, valproic acid, phenytoin)
 - Hemorrhage- Warfarin
 - Hip fracture- Benzodiazepines
 - GI ulcer hospitalizations- Alendronate
 - Myocardial infarction- Tricyclic antidepressants
 - Myocardial infarction- Typical antipsychotics
 - Reduced hospitalizations- ACE inhibitors
 - Lower mortality after MI- Beta blockers
- Each outcome will have a specific definition, pre-defined through a HOI definition process.
- Procedure must be able to successfully execute one test case (one data source, one drug, one outcome) in the Research Core environment in less than 3 days to be considered feasible for subsequent testing

Potential Implementations of Monitoring Methods

Input: Drug Only

- Output: statistics for all drug-outcome pairs for the given drug
- Execution: Method could be executed sequentially for each drug case of interest
- Examples:
 - Self-controlled cohort design- select all persons on a drug, compare rate of outcome during exposure with rate of outcome for some defined period prior to exposure. Produce rate ratio for each outcome. Potential thresholds could include $RR > 1, 2, 3$.

Input: Outcome Only

- Output: statistics for all drug-outcome pairs for the given outcome
- Execution: Method could be executed sequentially for each outcome
- Examples:
 - Case-control design- Select all persons with an outcome and match controls on some characteristics. Measure differences in drug exposure between the two groups using an odds ratio. Potential thresholds could include $OR > 1, 2, 3$.

Input: Neither Drug nor Outcome

- Output: statistics for all drug-outcome pairs
- Execution: Method executed once, and the specific drug-outcome pairs of interest are extracted from the resulting dataset
- Examples:
 - Disproportionality analysis- the database is reformatted into drug-condition pairs and proportional reporting ratios (PRR) are calculated for all drug-condition combinations. An example threshold used in spontaneous data mining is $PRR > 2, N > 3, CHISQ > 4$.

Input: Both Drug and Outcome

- Output: statistic for drug-outcome pair
- Execution: Method could be executed sequentially for each drug-outcome pair
- Examples:
 - maxSPRT- Sequential analysis is performed for a specific drug-outcome pair, where 'signal' is identified if the likelihood ratio test exceeds the critical value for the alternative hypothesis (e.g. $LLR > 1.2$)

Input: Drug, Outcome, and Covariates

- Output: statistic for drug-outcome pair
- Execution: Method could be executed sequentially for each drug-outcome pair
- Examples:
 - Case-control design- covariates specific to the HOI are entered as factors that require balancing prior to analysis to reduce confounding

Existing Methods Identified in the Literature:

Various methods have been proposed for potential application as hypothesis generating tools for observational data. The Review of Observational Analysis Methods details several points to consider in the proposed approaches(1). Below is a brief summary of the existing methods to be considered for implementation.

Epidemiologic Study Designs

Traditional pharmacoepidemiologic studies have been used for hypothesis strengthening, and have been proposed as viable approaches to be systematically implemented as hypothesis-generating tools.

- Cohort
- Case-control(2)
- Case-cohort(3)
- Case-crossover
- Self-controlled case series(4, 5)

Group Sequential Methods

Group sequential methods have been applied in various contexts to identify relationships that emerge over time. In the context of observational data, the methods have been demonstrated as viable solutions for Monitoring Health Outcomes of Interest, and have been proposed to be extended for use in Identification of Non-Specified Conditions.

- Sequential probability ratio test(6-8)
- Maximized sequential probability ratio test(9-12)

Disproportionality Analysis Approaches

An array of studies has explored the application of disproportionality analysis methods to spontaneous data (13-56). Limited work has been published to date that demonstrate the use of these methods on administrative claims or electronic health records databases(57-59). Specific methods include:

- Proportional Reporting Ratio(60)
- Reporting Odds Ratio(61)
- Multi-item Gamma Poisson Shrinker(62)
- Bayesian confidence propagation neural network (63)
- Empirical Bayes (64)
- Mixed-effects Poisson regression model(65)
- Formal Concept Analysis(66)

Other Methods

- CUSUM(7, 67)
- Bayesian updating statistic(68-72)
- MUTARC(73)
- HealthMiner(74)
- PROFILE(75)

In addition, other publications outline analytical considerations that could contribute to a method design, including:

Causal inference modeling methods:

- Propensity score adjustment(76-86)
- Inverse probability weights(87, 88)
- Instrumental variable(88)

Methods for adjusting for multiple testing:

- False discovery rate(89-91)
- Hierarchical modeling(92)

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