

A tool for empirically identifying and reviewing candidate comparators for pharmacoepidemiological studies

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Background

The active comparator new user (ACNU) cohort design has emerged as a best practice for the estimation of drug effects from observational data[1]. However, despite its advantages, this design requires the selection and evaluation of comparators for appropriateness, a process which can be challenging. We developed a novel empirical approach to rank candidate comparators in terms of their similarity to a target drug in high-dimensional covariate space[2] and here demonstrate an interactive web application to explore candidate comparators ranked by our method.

Methods

This first step in the similarity calculation pipeline is generating cohorts for comparison. We defined new user cohorts for each RxNorm ingredient and for each Anatomical Therapeutic Chemical (ATC) level 3 class across five administrative claims and two electronic health records databases. We then extracted aggregated pre-treatment covariate data for each cohort using five clinically oriented covariate domains: *demographics* (age and sex), *presentation* (conditions occurring ≤ 30 days before treatment), *medical history* (conditions occurring > 30 days before treatment), *prior medications* (medications begun > 30 days before treatment), and *visit context* (inpatient and emergency visits in the 30 days before treatment). In each database, we formed all pairs of cohorts with $\geq 1,000$ patients and computed a scalar similarity score defined as the average of cosine similarities computed within each covariate domain for each pair. We then developed a web application[3] which allows users to input a target drug or drug class and receive a list of candidate comparators ranked by the overall similarity score. Users wishing to implement this method in their own data can do so using code available on GitHub[4].

Results

In this demonstration, we describe several potential use cases for this tool, exploring its utility for a diverse set of example drugs. We show how users can adapt their queries to focus on specific databases or to require certain hierarchical relationships between target and comparator. Throughout, we show that the tool tends to produce lists of top-ranked comparators that broadly align with subject matter knowledge.

For example, **Figure 1, left** shows a user requesting rankings on RxNorm ingredient-level comparators for the multiple sclerosis treatment ocrelizumab using all available data sources and requiring comparator presence in at least two sources. The returned results (**Figure 1, right**) indicate a similar treatment for multiple sclerosis, natalizumab, as the most similar comparator, with data source-specific information available in a drop-down. By selecting “Explore Comparison”, the user can then inspect the individual components of the overall similarity score (**Figure 2, top**) and compare the distribution of covariates in the target and comparator cohorts interactively (**Figure 2, bottom** and **Figure 3**).

Conclusion

This software demonstration will present a novel utility with which users can obtain empirical comparator recommendations. While the method underlying this tool produces recommendations that broadly align with subject matter knowledge and existing drug hierarchies, the utility of its recommendations may be limited in some cases. For example, recommendations for drugs that are used differently depending on dose, form, or route of administration, or which have multiple unrelated indications, or are used in combination therapies, may be less coherent than for drugs with more uniform characteristics. Nonetheless, this tool serves as a useful aid to investigators and could ultimately enable the automated generation of ACNU-derived evidence, a process that has previously been limited to self-controlled designs.

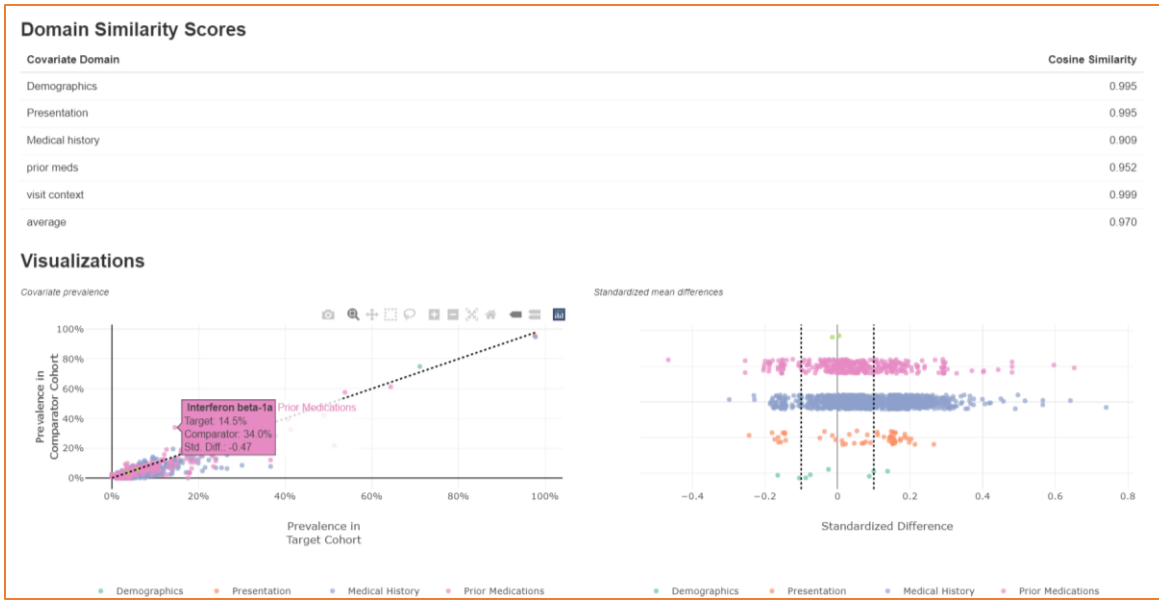


Figure 2: Details of the "Explore Comparison" window, showing the decomposition of the overall similarity score into cosine similarity values in five covariate domains. Figures interactively depict the prevalence of covariates in the target and comparator cohorts, as well as their standardized differences.

Covariate Tables

Demographics Presentation **Medical history** Prior medications Visit context Index date

Medical history
 One covariate per condition observed more than 30 days prior to index
 423 of 1059 covariates (39.9%) have absolute standardized difference less than 0.1

Search

Covariate	RxNorm - ocrelizumab (n = 7,678)	RxNorm - natalizumab (n = 8,737)	Std. Diff.
Fatigue	36.6%	7.8%	0.74
Vitamin D deficiency	51.3%	21.9%	0.64
Anxiety disorder	26.6%	6.4%	0.57
Paresthesia	30.0%	8.6%	0.57
Anesthesia of skin	25.3%	6.9%	0.52
Imaging of brain abnormal	20.9%	4.8%	0.50
Asthenia	24.0%	6.8%	0.49
Displacement of cervical intervertebral disc	17.6%	3.8%	0.46
Gastroesophageal reflux disease without esophagitis	17.1%	3.7%	0.45
Major depression, single episode	21.5%	7.1%	0.42

1-10 of 1059 rows Show 10 Previous 1 2 3 4 5 ... 106 Next

Figure 3: Details of the "Explore Comparison" window show one of the five domain-specific covariate distribution tables. Users are informed of the number of covariates in each domain that are "in balance" (i.e., with absolute standardized difference < 0.1) and can search through the table for relevant features or re-sort the table to identify the most prevalent features in either the target or comparator cohort, or the largest differences between the two.

References/Citations

- 1 Lund JL, Richardson DB, Stürmer T. The Active Comparator, New User Study Design in Pharmacoepidemiology: Historical Foundations and Contemporary Application. *Curr Epidemiol Rep* 2015;**2**:221–8. doi:10.1007/s40471-015-0053-5
- 2 Justin Bohn, James P. Gilbert, Christopher Knoll, *et al.* Large-scale empirical identification of candidate comparators for pharmacoepidemiological studies. *medRxiv* 2023;:2023.02.14.23285755. doi:10.1101/2023.02.14.23285755
- 3 *Comparator Selection Explorer*. <https://data.ohdsi.org/ComparatorSelectionExplorer/> (accessed 6 Jun 2023).
- 4 *ComparatorSelectionExplorer*. Observational Health Data Sciences and Informatics 2022. <https://github.com/OHDSI/ComparatorSelectionExplorer> (accessed 2 Jun 2023).