Targeted Learning in Vaccines and Immune Therapies: *for high precision and the lowest possible bias*

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Table of contents

Targeted Learning for Real-World Data

Observational real-world data (RWD) has the potential to transform clinical research. However, leveraging these data often presents a host of challenges. Learning from these data requires us to address multiple potential sources of bias and specify appropriate mitigation strategies.

The **Targeted Learning** roadmap provides a rigorous framework for synthesizing evidence from randomized controlled trials and RWD. Specifically, Targeted Learning methods allow us to identify a target parameter of interest and use targeted maximum likelihood estimation (tmle) and super learning for unbiased and precise causal inference. These methods also provide the ability to mine multiple databases, observational studies, and past trials to generate the most promising new treatment strategies that maximize patient health outcomes, which can then be formally evaluated through trials.

Enabling the Most Efficient Use of Data Across all Study Designs

Parexel's RWD Analytics team believes the most *unbiased* and *precise* way of estimating vaccine effectiveness from RWD is through the application of Targeted Learning to comprehensive data sets.

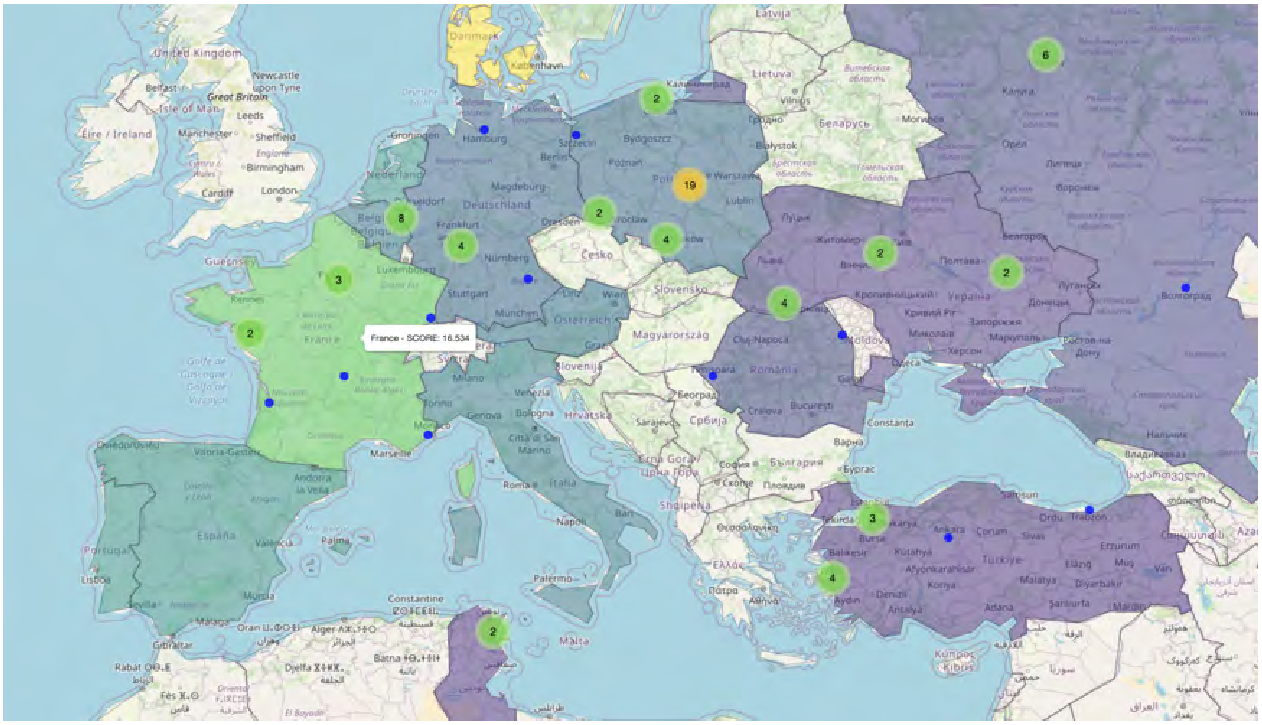
- Targeted Learning is an established method that leverages state-of-the-art machine learning for causal estimation.
- It works by applying *super-learning*, which is the best-weighted combination of input models to derive the best possible prediction of both outcome models and the propensity score. These models are then combined using innovative *targeted maximum likelihood estimation* to remove bias.
- Targeted Learning represents a paradigm shift in high-utility RWD through compiling disparate data, using state-of-the-art feature engineering and prediction engineering, and digesting it into actionable intelligence for decision support.
- Parexel is currently working with **Mark van der Laan**, the inventor of Targeted Learning and a pioneer in modern casual interference, on novel methodologies to complement standard analytical approaches for more predictive outcomes in clinical research.
- Improving causal inference from RWD for evaluating the safety and effectiveness of medical products is an important goal of the **FDA's Sentinel Initiative**. Targeted Learning has been proposed as an alternative and potentially better approach than current casual interference approaches. As part of a continuing push to modernize the regulation of digital health technologies, the FDA is encouraging its adoption and training internal staff on methodology.

How it Works: Predicting Vaccine Effectiveness

Estimating vaccine effectiveness from randomized clinical trials is relatively straightforward, as the difference in outcomes between the treated and untreated groups represents the causal difference we expect (if assumptions from the trial, e.g., identifiability, hold). However, there are almost always stark differences between treatment and control groups in real-world studies that must be carefully addressed, i.e., groups are not *naturally* 'exchangeable' without design or analytic remedies. Methods have been developed and implemented to address these differences and make groups comparable.

Additionally, developments in Targeted Learning have been applied to vaccine effectiveness, specifically, relative vaccine effectiveness – both within relative exposure groups (e.g., immunocompromised) and comparing relative outcomes (e.g., variant outcomes; within a competing-risk framework).

To support feasibility, feature and prediction engineering techniques can be implemented by layering key criteria, such as region-specific disease incidence, hospitalization, and death rates. These can be combined with historical site performance indicators such as patient recruitment and other cycle time and data quality metrics. In addition, we will use different methods for forecasting, layering final results, and incorporating decision support metrics and 'what if' scenarios. Finally, while comprehensive prediction scores will be produced, we will retain individual components and their contributions. This can enable flexible re-prioritizing of risk factors.



Interactive Feasibility Map with country, regional, and site level intellgence

Advisory Oversight

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Andy Wilson, Ph.D., MStat, is the Head of Innovative RWD Analytics within the Scientific Data Organization at Parexel. He is a pharmacoepidemiologist with 20 years of experience in statistics, epidemiology, and public health. In his role, Andy provides consulting services for applied predictive analytics and is currently an Adjunct Assistant Professor at the University of Utah Division of Public Health.

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Mark van der Laan, Ph.D. is the Jiann-Ping Hsu/Karl E. Peace Professor of Biostatistics and Statistics at the University of California, Berkeley, and a consultant to Parexel. He has made contributions to survival analysis, semiparametric statistics, multiple testing, and causal inference. He also developed the targeted maximum likelihood estimation methodology. He is a founding editor of the Journal of Causal Inference.

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We're always available for a conversation

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