A gentle introduction to targeted learning in RCTs: what, why and how?

Tuesday 29th of June 2021, 15:00-18:00 (CET)

There has been a surge in so-called targeted learning methods over recent years. These have been claimed to yield more powerful intention-to-treat analyses of randomised trials, at no `cost', and to deliver more reliable adjustments for confounding bias or selection bias (e.g., due to informative censoring or missing data). Even so, targeted learning remains somewhat of a mystery to many. The aim of this webinar is therefore to provide insight into targeted learning: what deficiencies of routine analyses it aims to remedy, how it succeeds to do that, and when and how it can be used. This introductory webinar is aimed at researchers in the pharmaceutical industry and academia working with clinical trial data; it does not demand prior familiarity with causal inference or targeted learning. The workshop will host a number of experts who will give gentle introductions and perspectives on the theme, and will conclude with a panel discussion involving both experts on targeted learning as well as leading figures from the pharmaceutical industry and regulatory authorities.

Program

15:00-15:05	**Welcome** Kelly Van Lancker, Ghent University
15:05-15:25	**Targeted learning: what, and why you should care** Stijn Vansteelandt, Ghent University and London School of Hygiene & Tropical Medicine
15:25-15:45	**A gentle introduction to marginal and conditional estimands in causal inference** Rhian Daniel, Cardiff University
15:45-16:10	**Improving efficiency in both interim and final analyses** Kelly Van Lancker, Ghent University
16:10-16:25	**Break**
16:25-16:50	**Targeted learning of marginal effects** Alex Luedtke, University of Washington
16:50-17:15	**Principled selection of covariates for targeting conditional effects, with application to the Cox model** Oliver Dukes, Ghent University
17:15-17:25	**Discussion on the utility of targeted learning in RCTs** An Vandebosch, Janssen
17:25-17:55	**Panel discussion moderated by An Vandebosch** Björn Bornkamp, Novartis Laura Balzer, University of Massachusetts-Amherst Susan Gruber, Putnam Data Sciences Frank Pétavy, EMA José Pinheiro, Janssen Hana Lee, FDA
17:55-18:00	**Closing** Stijn Vansteelandt, Ghent University and London School of Hygiene & Tropical Medicine

Registration

Participation in the event will be free, but registration is mandatory via

Link

Questions?

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Abstracts

Targeted learning: what, and why you should care

Stijn Vansteelandt
Ghent University and London School of Hygiene & Tropical Medicine

Statistical modelling lies at the heart of most data analyses in medicine. Yet, the dominant modelling tradition is increasingly being critiqued, for good reasons. Standard models often do not readily convey answers to the primary scientific question, and even when they do, may deliver information that is difficult to communicate to subject-matter experts. Inferring the `true' model from data is often an overly ambitious undertaking; model misspecification may bias the analysis findings. The model building process is moreover difficult to pre-specify, and adds a degree of uncertainty to the analysis results that is difficult to quantify.

The typical response to these concerns is to forego modelling altogether, as commonly seen in the primary intention-to-treat analysis of RCTs. This is itself unsatisfactory. It may lower statistical power and encourage insufficient adjustment for, for instance, informative censoring or drop-out.

In this talk, I will review these concerns. I will then give a conceptual introduction to the targeted learning framework pioneered by Mark van der Laan, which resolves the foregoing tension by targeting the analysis to the primary scientific question at hand in a way that incorporates flexible modelling, but overcomes the aforementioned concerns.

A gentle introduction to marginal and conditional estimands in causal inference

Rhian Daniel
Cardiff University

We briefly introduce the potential outcomes framework, in particular as it relates to RCTs. We see how marginal and conditional estimands can be defined on a number of scales, discussing settings in which each might be preferred over the other. We explain the concept of non-collapsibility and contrast the use of marginal/conditional to describe estimands with the use of unadjusted/adjusted to describe data analyses.

Improving efficiency in both interim and final analyses

Kelly Van Lancker
Ghent University

In randomised experiments, one often has access to pre-treatment covariates that are predictive of the outcome. Parametric models adjusted for these covariates, such as logistic regression, are often used to obtain more precise estimates of treatment effects. However, concerns are routinely raised over the potential for bias when the model is misspecified. In this presentation, we discuss easy to implement, covariate-adjusted estimators for the marginal treatment effect that have the potential to increase the efficiency of interim and final decision-making. Importantly, the estimators that we consider are robust to model misspecification.

Targeted learning of marginal effects

Alex Luedtke
University of Washington

This talk will provide a high-level introduction to the use of data-adaptive methods for the estimation of marginal treatment effects with continuous, binary, and time-to-event endpoints. In non-time-to-event settings, data-adaptive methods tend to be more efficient (lower variance, tighter confidence intervals) than are more traditional methods. In time-to-event settings, these methods tend to rely on more plausible conditions on censoring, and, in some cases, will also be more efficient than traditional methods. Software packages for implementing these estimators will also be introduced.

Principled selection of covariates for targeting conditional effects, with application to the Cox model

Oliver Dukes
Ghent University

We will consider how the principles of targeted learning can be used to infer conditional effects in randomised trials, with a focus on the hazard ratio. In practice, most analyses of time-to-event data invoke the assumption of non-informative censoring. While this assumption usually becomes more plausible as more baseline covariates are being adjusted for, such adjustment also raises concerns. How should we choose which covariates to adjust for, and in what functional form? If variable selection is data-adaptive, how do we account for this in the resulting inferences? I will outline a simple selection strategy designed to produce a valid tests and confidence intervals for a treatment effect parameter indexing a Cox model. I will also describe ongoing research on extending this strategy to settings where the proportional hazards assumption fails.