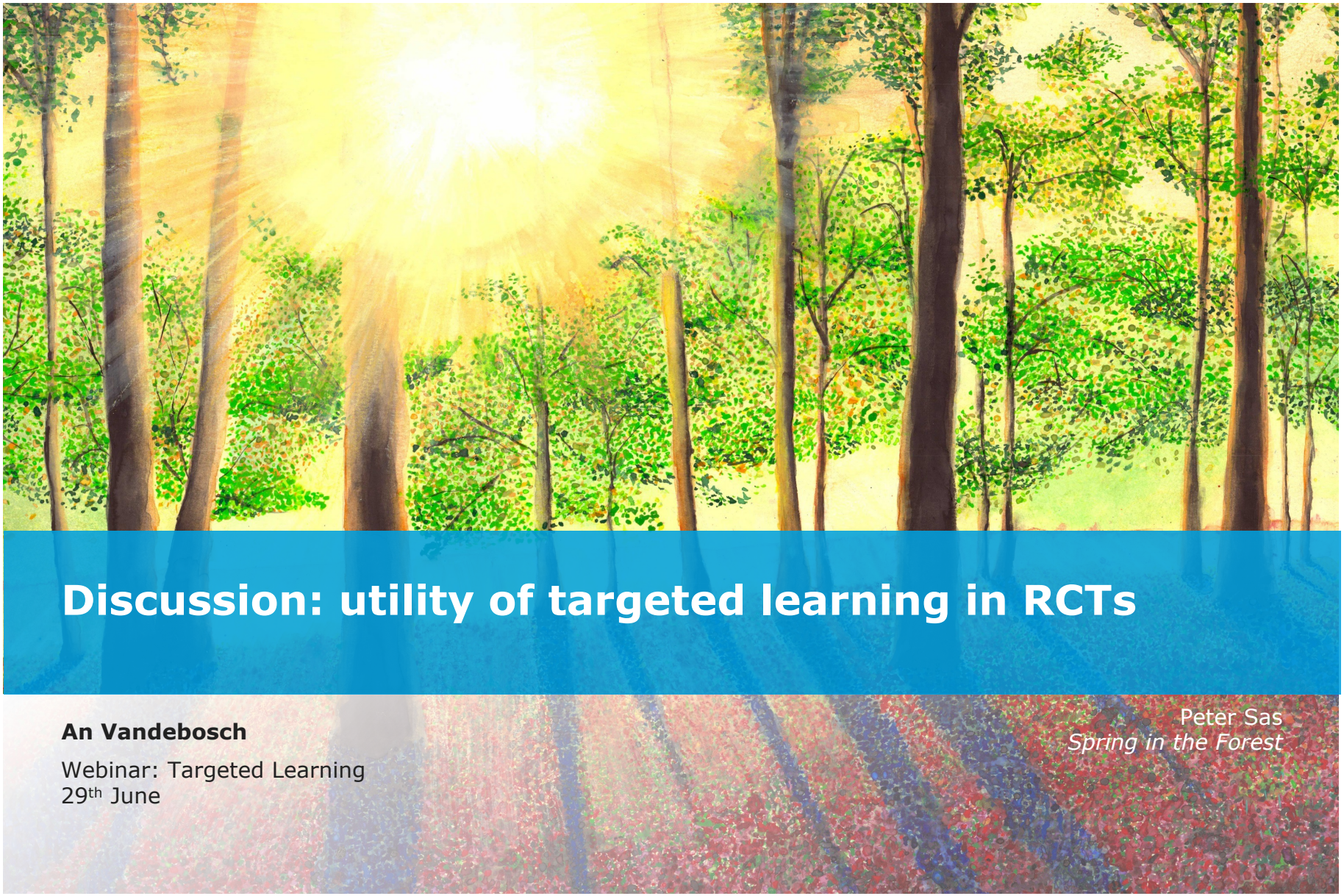

Discussion: utility of targeted learning in RCTs

An Vandebosch

Webinar: Targeted Learning
29th June

Peter Sas
Spring in the Forest

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In a randomized clinical trial…

the evaluation of the treatment effect

For the estimand of interest **requires** an

- Unbiased evaluation of the treatment effect
- Valid inference under the null hypothesis

In addition, we would like to have and often need

- Easy-to-use software, the ability to prespecify, …
- transparancy in assumptions, as few as possible, …

Also,

- (effect estimates for the population under study and/or generalizable to the desired population)

(not the focus of today's discussion)

Learning today targeted…(1)

Adjusted estimators can increase precision for *marginal* estimands

Increased precision through use of baseline covariates:

- Unbiased (robust estimation): combine randomization with an outcome model in each arm to impute the (missing counterfactual) outcome through information captured in baseline covariates
- Efficiency gain may depend on accuracy of model
- Flexible strategies focused on the covariate-outcome model ('Targeted learning') can further increase accuracy (and hence efficiency)

Talks Vansteelandt, Van Lancker, Luedtke

- But there is software (e.g. `tmle` in R), and it often takes just a few lines of code.

Example for non-time-to-event data

```
# Using implementation from tmle package
library(tmle)

# Generate toy data set
set.seed(1)
n = 200 # sample size
W = data.frame(W1=rnorm(n),W2=rnorm(n,1,1/2)) # covariates
A = sample(c(rep(0,n/2),rep(1,n/2))) # treatment
Y = rnorm(n) + A + 0.25*A*W$W1 # outcome

# Estimate average treatment effect E[Y|A=1]-E[Y|A=0]
Q.SL.library = c("SL.glm","SL.gam","SL.glm.interaction")
out = tmle(Y,A,W,gform=A~1,Q.SL.library=Q.SL.library)
# Above, gform specifies model for Pr(A=1|W=w)

# Estimated ATE
out$estimates$ATE$psi
[1] 1.039342

# 95% confidence interval
out$estimates$ATE$CI
[1] 0.7848231 1.2938609
```

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FDA guidance – adjusting for covariates

Inclusion of prognostic baseline factors to improve precision for treatment effect estimates

- Robust estimators to obtain marginal (unconditional) effect estimates for linear and non-linear models

Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biologics
Guidance for Industry[1]

May 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance represents FDA's current thinking on adjusting for covariates in the statistical analysis of randomized clinical trials in drug[2] development programs. This guidance provides recommendations for the use of covariates in the analysis of randomized, parallel group clinical trials that are applicable to both superiority trials and noninferiority trials. The main focus of the guidance is on the use of prognostic baseline factors[3] to improve precision for estimating treatment effects rather than the use of predictive biomarkers to identify groups more likely to benefit from treatment. This guidance does not address use of covariates to control for confounding variables in non-randomized trials or the use of covariate adjustment for analyzing longitudinal repeated measures data.

Learning today targeted…(2)

Survival endpoints are special

- A common treatment parameter in a covariate-adjusted model may differ from the marginal estimand/effect estimate (non-collapsibility)

Unbiased and Valid Inference depends on a correct covariate model for

1. disease risk (which some may argue to look for other data sources)
2. possible (informative) censoring mechanism within the study (could be unique in the study)

Flexible strategies focused on the covariate-outcome model combined with covariate-censoring model ('Targeted learning') can yield valid inference for both marginal effects and conditional effects

Talks Vansteelandt, Luedtke, Daniel, Dukes

Randomized clinical trials…

…are dealing with increased complexity

Inter-current events (loss of randomization):

- robust estimators are frequently employed in observational trials (to control confounding, which randomization handles in RCTs)
- Targeted learning can provide tool to increase accuracy of outcome and/or intervention model

Complex innovative designs

- (Kelly's talk): proposal to combined covariate information and on-treatment responses to increase precision in interim decision-making

Missing data, outliers, …

At the protocol stage…

…when reflecting for the evaluation of the treatment effect

1. Appropriate estimand: marginal or conditional

2. Appropriate study design
   (although not the focus of today)

3. Most powerful analysis method, depending on the assumptions willing to make
   - Robust estimators in general…employ randomization for estimation and inference
   - Targeted learning provide a tool for increased precision in effect evaluation

Additional points to consider for targeted learning:

- Evolving knowledge on baseline risk factors, (lack of) validity/precision in other data sources, wish list of prognostic factors sometimes longer than permuted block randomization can handle easily, informative censoring, …
- A clinical trial has multiple objectives: some with reduced precision

Need for real case studies (protocols) to evaluate!

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Panel discussion

Thank you!

Given the availability of software (e.g., the TMLE package in R and a corresponding macro in SAS), what more is needed to bring these methods across to all trial statisticians?

What are the reservations trial statisticians might have about using these methods?
(Would reservations concern the use of machine learning, or the incorporation of baseline covariates more generally?)

What do you think may be necessary for these methods to be acceptable for the primary analysis of clinical trials?

What evidence (theoretical or empirical) about the performance of these methods is needed, and what concerns need to be resolved, to make these methods acceptable?

To enable pre-specification of these methods, it is important that one can handle unforeseen complexities like missing data, outliers, …

Is it possible to fully automate these methods so that the entire statistical analysis can be pre-specified in the protocol? And if so, how?

Do you have any advice on a minimal or recommended library for the SuperLearner if one wants to use these methods in RCTs? Is it for example good enough to use main effect GLMs with variable selection in RCTs?

Multiple imputation is commonly used to handle missing data, but by being fully parametric, it goes against the spirit of targeted learning. What can be done when there is non-monotone missingness in outcomes or covariates outside the specific setting of RCTs?

There is current interest in the combination of trial data and `real world' evidence in COVID-19 studies, as well as in transporting inferences from a trial to a target population. Do you see these methods also being relevant for these purposes?