Acceptability of prognostic score covariate adjustment and Targeted Maximum Likelihood Estimation (TMLE) methods for the primary and key analyses of marginal treatment effects in pivotal clinical trials in absence of prior clinical knowledge about strong predictive factors

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Covariate Adjustment in the Estimation of Marginal Treatment Effects

- Regulatory guidance (EMA, 2015; FDA, 2023) highlighted that analyses of RCT data adjusting for strong prognostic and randomization stratification factors can improve efficiency and precision of treatment effect estimation and/or provide individualized treatment effect estimates depending on the marginal or conditional effect estimation. (See also Brandt, 2023 EFSPI presentation.)
- **Covariate adjustment does not impact the interpretation** of the estimated effect when estimating **marginal treatment effects**. Covariate adjustment is done to gain efficiency and correct for a random (chance) imbalance.

	Which covariates to adjust for?	**Which analysis method to use with adjustment?**
Recommended approach EMA, 2015FDA, 2023	Use existing clinical knowledge to select a **small set** of strong prognostic factors	ANCOVA, G-computation, (A)IPTW, or stratified analysis with **pre-selected covariates** & model-based, robust, or bootstrap variance estimator

- **Sometimes, it is not known a priori which factors are prognostic, or which ones are the strongest**

Prognostic score covariate adjustment Hansen, 2008; EMA, 2022; Siegfried et al., 2023; Liao et al., 2025	Use **historical data** to estimate a prognostic model - summarize prognostic relationships of a **large set** of baseline covariates into a **single "synthetic" prognostic score**, and predict the prognostic score for participants in your study	ANCOVA, G-computation, or (A)IPTW* with the **predicted "synthetic score"** & model-based, robust, or bootstrap variance estimator
Targeted Maximum Likelihood Estimation (TMLE) van der Laan & Rubin, 2006 van der Laan & Rose, 2011	Use **same-study data** for auxiliary modeling of treatment propensity and potential outcomes based on **a (large) set** of covariates and calculate two "clever" covariates to obtain updated, **bias-corrected "targeted" outcome** predictions	Estimate treatment effect as a mean of individual differences of **"targeted" predicted outcomes** & variance estimator based on influence curve methodology

(A)IPTW = (Augmented) Inverse Probability of Treatment Weighting; RCT = Randomized Clinical Trials

*G-computation and (A)IPTW are not part of the EMA (2022) qualification opinion

Some Features of Prognostic Score Covariate Adjustment and TMLE

		Prognostic score	TMLE
Robustness	Coverage and Type 1 error	Preserved	Preserved
	Good empirical performance for efficiency gains	Yes	Yes
	Reduces plug-in estimator bias	No	Yes
	Attains minimum asymptotic variance	No	Yes
	Doubly robust	No	Yes
Modeling	Allows leveraging flexible (machine learning) models for auxiliary modeling	Yes	Yes
Data sources	Requires historical (independent) data for auxiliary modeling	Yes	No
	May take advantage of large historical data sets for auxiliary modeling	Yes	No
	Impact of differences between the historical and current studies	Reduced efficiency	Not applicable
Complexity	Methodology & implementation	Simple	Complex

Note: Coverage and Type 1 error may be affected in very small samples with both approaches, depending on the treatment effect and variance estimators used.

Discussion Topics for the Panel

Both prognostic score covariate adjustment and TMLE enjoy a sound statistical foundation and strong empirical performance. However, both methods appear to be underutilized in the analyses of RCTs.

Discussion topics:

- Could the panel comment on the acceptability of prognostic score covariate adjustment and TMLE methods for the primary and key analyses of pivotal clinical trials aimed at the estimation of marginal treatment effects in the context where prior clinical knowledge does not allow for pre-selection of a small set of strong prognostic covariates?
- What are the pros and cons of these methods from the regulatory perspective?
- If time permits: Given the recent methodological work by Liao et al. (2025), could the panel comment on the acceptability of combining the two approaches for the primary and key analyses of pivotal clinical trials?

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Thank you!