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Targeted Maximum Likelihood Estimation for Restricted Mean Survival Time in time-to-event data with low event rates: a case study using a previous non-randomised PAS study

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Michael is a statistician at GSK, having joined as a graduate in 2023. He spent 8 months working in Early Development Statistics before moving to the Respiratory Biostatistics Marketed Product Team, where he has been researching the potential impact of causal inference techniques such as Targeted Maximum Likelihood Estimation in both clinical trials and observational studies. Before joining GSK, Michael completed a MSc in Statistics at Imperial College London.

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Alison Donald has been a statistician at GSK since 2006. Her primary focus has been on respiratory research, although she has played a key role in clinical development for a variety of therapies and treatments. Throughout her career at GSK, Alison has worked on numerous projects that have helped develop and evaluate innovative solutions in drug development, showcasing her commitment to scientific excellence and healthcare improvement.

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Tom is a biostatistician at Statistics and Data Science Innovations Hub with an interest in causal inference, machine learning and real-world data analytics.

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Stephen is the head of the Respiratory Biostatistics Marketed Product Team at GSK.

Single topic, multi-speaker session, Workshop or Single presentation submission

A single presentation/poster

Single presentation or poster submission

In non-randomised settings, treatment effect estimates are exposed to bias by confounding: the existence of other variables that have causal effects on both treatment assignment and outcome. Causal inference techniques can be used to account for confounders and estimate causal effects. With time-to-event data there is the additional challenge of different censoring mechanisms in the treatment cohorts.

Targeted Maximum Likelihood Estimation (TMLE) is a semi-parametric estimation approach that chooses a target parameter and optimises the bias-variance trade-off to estimate this quantity alone. Both an outcome model and propensity model are used to generate estimates: TMLE updates predictions from the outcome model using propensity scores to provide estimates that target the quantity of interest. This approach has several advantages: accounting for confounders is a core element to TMLE, and flexible Machine Learning techniques can be leveraged to account for complex, non-linear relationships. It is also doubly-robust: consistent estimates can still be recovered even if one of the initial

models is misspecified. If all models are correctly specified then estimates are asymptotically efficient for the target parameter.

We present an example of using TMLE to estimate the causal difference in Restricted Mean Survival Time (RMST) using time-to-event data from a previous non-randomised study. This accounts both for non-random treatment assignment and censoring mechanism. We discuss why the difference in RMST is targeted, as opposed to a hazard ratio, and discuss its interpretative advantages, especially in the context of low event rates.