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Marginal Estimands and Estimation with Covariate Adjustment for TTE Endpoints

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Sarwar Mozumder
Please provide a brief biography for the Presenting author(s)
Sarwar Mozumder is a Statistician in AstraZeneca's Oncology Biometrics Statistical Innovation group. He mainly works on methods development and application in Oncology late-phase and payer studies. His general research and methodological interests are in estimands for time-to-event data, survival analysis, covariate adjustment for time-to-event endpoints, non-proportional hazards, competing risks, flexible parametric models and the reconstruction of individual-level survival data. He also holds an honorary research fellow position at the University of Leicester.

David Wright
Please provide a brief biography for the Presenting author(s)
Dr Wright became the Head of Statistical Innovation at AstraZeneca in September 2016. David leads a team of expert statistical methodologists who advise colleagues within AstraZeneca on novel trial design and analysis issues. Between 1999 and 2016 David worked for the Medicines and Healthcare products Regulatory Agency (MHRA) (formerly the Medicines Control Agency (MCA)) as a Statistical Assessor. David was Chair of the Biostatistics Working Party at the European Medicines Agency from 2011-2016. He is current chair of the Board of Directors of PSI, one of the Editors-in-Chief of Pharmaceutical Statistics and a member of the EFSPI/EFPIA Estimands Implementation Working group (and has published a number of papers on Estimands).

Rhian Daniel
Please provide a brief biography for the Presenting author(s)
Rhian Daniel is Professor of Statistics at Cardiff University and works on causal inference methods and their application to medical research. Having previously worked on time-dependent confounding, mediation analysis and the application of g-methods to the new estimands framework in RCTs, most of her current research is dedicated to a new framework for regression modelling, called 'regression by composition', and particularly how such flexible statistical models can be guided by first principles causal models, with applications to transportability.

Dominic Magirr
Please provide a brief biography for the Presenting author(s)
Dominic Magirr is a Medical Statistician in the Advanced Methodology and Data Science group at Novartis. With a strong focus on supporting drug development projects, Dominic brings expertise in areas such as multiplicity, survival analysis, covariate adjustment, Bayesian statistics, and missing data handling. He is dedicated to advancing clinical trial

design through the development of innovative methodologies aimed at enhancing efficiency.

Sanne Roels
Please provide a brief biography for the Presenting author(s)
Sanne Roels is an Associate Scientific Director (Biostatistics) at Johnson & Johnson Innovative Medicine.

Tim Morris
Please provide a brief biography for the Presenting author(s)
Tim is a principal research fellow based at the MRC Clinical Trials Unit at UCL. His research focuses on the development, evaluation and understanding of statistical methods. His research interests include simulation studies, handling missing data, estimands, causal inference, sensitivity analysis, covariate adjustment, and IPD meta-analysis. He is an author of the 2024 book ‘Multiple Imputation and its Application

Kelly Van Lancker
Please provide a brief biography for the Presenting author(s)
Kelly is a postdoctoral researcher at Ghent Unversity (Belgium). Kelly's research focuses on more accurate and faster decision-making in randomized clinical trials by making optimal use of the available data.

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

A single topic, mutli-speaker session/workshop

Single topic session or workshop abstracts

Talk 1: Introduction - Current Practice in Regulatory Trials with Case Studies, and the FDA Covariate Adjustment Guidance in Practice (David Wright / Sarwar Mozumder)

Following the recent release of the final FDA guidelines on covariate adjustment and other developments, such as the introduction of digital twins (or synthetic/super covariates), researchers are being encouraged to be more transparent about the estimand of interest to inform the implementation of covariate-adjusted analyses. In this introduction to the session we will set the scene by presenting some case studies of regulatory interactions/feedback that contradict or are misaligned with the recently released FDA guidelines on covariate adjustment. These will be motivated by real interactions. In particular, we will highlight where there may be confusion between the target estimand and estimation method in communication with respect to studies that adjust for further baseline prognostic factors to improve efficiency.

Talk 2: Marginal Hazard Ratios and Covariate Adjustment – A Causal Inference Perspective (Rhian Daniel)

Some issues around covariate-adjusted estimation of conditional and marginal hazard ratios will be introduced from a causal inference perspective. This includes the non-collapsibility of the hazard ratio and other challenges around its causal interpretation (the so-called 'hazard of hazard ratios') as well as the impossibility that the proportional hazards assumption holds both marginally and conditional on covariates. As is increasingly understood, the hazard ratio suffers from an 'in-built selection bias' in the sense that its interpretation is conditional on survival to time t (post-baseline) and in the presence of a non-null treatment effect, those patients who survive to time t are not comparable across treatment arms. Those surviving longer in the treatment arm—assuming a treatment benefit—tend to be frailer compared to those surviving longer in the control arm. The arguments against the reliance

on hazard ratios as a single summary measure are not new and have been extensively discussed in the literature. These points will be presented and summarised in this talk.

Talk 3: Estimation in the context of Covariate Adjustment, Model-free Summary Measures, and Alternatives to the Marginal (Average) Hazard Ratio (Dominic Magirr & Sanne Roels)

We will then discuss estimation methods with and without covariate adjustment and highlight considerations around model-misspecification.

For randomized clinical trials with time-to-event endpoints, proportional hazard models are typically used to estimate treatment effects and log-rank tests are commonly used for hypothesis testing. The summary measure of the primary estimand is frequently a hazard ratio. However, there is growing support for replacing this approach with a model-free summary measure and assumption-lean analysis method—a trend already observed for continuous and binary endpoints. One alternative is to base the analysis on the difference in restricted mean survival time (RMST) at a specific timepoint, a single-number summary measure that can be defined without any restrictive assumptions on the outcome model. In a simple setting without covariates, an assumption-lean analysis can be achieved using nonparametric methods such as Kaplan-Meier estimation. The main advantage of moving to a model-free summary measure and assumption-lean analysis is that the validity and interpretation of conclusions do not depend on the proportional hazards (PH) assumption. The potential disadvantage is that the nonparametric analysis may lose efficiency under PH. There is disagreement in recent literature on this issue, with some studies indicating similar efficiency between the two approaches, while others highlight significant advantages for PH models.

We present asymptotic results and a simulation study to clarify the conflicting results from earlier research. We characterize those scenarios where relative efficiency is close to one, and those where it isn’t. Several illustrative examples are provided.

Several other estimation techniques exist for estimating marginal effects, including G-computation but also targeted learning. While both methods have a favourable marginal interpretation while using covariates, G-computation is only singly robust (i.e., robust to model misspecification of the outcome model), vis-a-vis targeted learning, which is doubly robust (also robust against misspecification of the treatment allocation model). These methods are illustrated while focusing on the summary metric, which is different from the well-known hazard ratio.

Talk 4: Ensuring covariate adjustment methods are fit for use (Tim Morris)

For continuous and binary outcome measures, methods for covariate adjustment are relatively mature in the sense that we can plan to use them with some confidence. This is less true with time-to-event outcomes. We will touch on some practical challenges to be understood to make informed decisions about covariate-adjustment methods.

Discussion Panel: Thoughts from A Regulator’s Perspective – What are the Expectations? (Speaker: TBC – Regulatory.)

To conclude the session, a regulatory statistician representative (TBC) will present the current standpoint of their respective authority on the continued use of hazard ratios in consideration of the talks above. This will be the prelude to the discussion panel. The panel will consist of academic, industry and regulatory statisticians (from those that presented above and additional members from other regulatory bodies). Some of the issues highlighted in the talks, and how we can address these moving forward will be discussed. We will elicit concerns and questions before the conference that will be put forward to the panel. This will help build alignment on what is the most sensible approach, what should we be concerned about in practice, and finally, does it matter, and if not, when does it not?