Oncology estimand WG session at PSI 2023 conference London

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Session details:

- 11th June – 14th June 2023, London.
- Face-to-face, no hybrid option.
- Title: Estimands – the journey continues or doing now what trial teams need next
- Session chair: **Rui Sammi Tang**

This session will further develop methods and considerations for implementation of the ICH E9 estimands addendum in the broader arena of drug development. The session will report on new results of task forces of the oncology estimand working group.

- **Lynda Grinsted**: For the analysis of a time-to-event (T2E) endpoint in a single-arm (SAT) or randomized clinical trial (RCT) it is generally perceived that interpretation of a given estimate of the survival function, or the comparison between two groups, hinges on some quantification of the amount of follow-up. Typically, a median of some loosely defined quantity is reported. However, whatever median is reported is typically not answering the question(s) trialists actually have in terms of follow-up quantification. This talk will formulate a comprehensive list of relevant scientific questions that trialists have when reporting T2E data and which are often "answered" with reference to some unclearly defined quantifier of follow-up. We illustrate how instead these questions should be answered, and that reference to an unclearly defined "follow-up quantity" is not necessary.
- **Stefan Englert**: Estimand framework related publications thus far have mainly focused on randomized clinical trials. In this presentation we apply it to single arms Phase 1b or Phase 2 trials designed to detect a treatment related efficacy signal, typically measured by objective response rate. Key recommendations regarding the estimand attributes will be made together with detailed strategy recommendations for intercurrent events typically seen in early-stage oncology.
- **Francois Mercier**: The introduction and use of estimand's thinking can bring substantial benefits in early oncology clinical development. In Phase 1a dose-escalation trials, intercurrent events (IE) are common and careful consideration of strategies on how to address them is essential. In this presentation, using examples, we illustrate their use and pitfalls when the intention is to ascertain the maximum tolerated dose.

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- **Hong Tian**: In the era of precision medicine, understanding treatment effect in biomarker defined subgroups in relationship with overall population is essential. For continuous outcomes, Least Square estimates include an interaction term enable an unbiased estimation of treatment effect for the overall population by linearly combining treatment effects of the two subgroups. Such logic is carried to binary and time-to-event outcomes models in most statistical software where model parameters are linearly combined in the log scale and then exponentiated to represent treatment effect in the overall population. Although guaranteeing logical inference in appearance, such calculations do not correspond to the true overall effect which may in fact be illogical for efficacy measures such as odds ratio and hazard ratio, i.e., the overall population effect is outside the range of complementary subgroups effects. To correctly derive efficacy in the overall population, a principle called Subgroup Mixable Estimation (SME) should be followed. We illustrate these common mistakes and demonstrate the application of SME using real trial data.
- **Yufei Wang**: Treatment switching is a particular type of intercurrent event which describes the cases when patients discontinue their randomly assigned treatment and start an alternative treatment in randomized controlled trials (RCTs). It is common in oncology trial to have a sizeable proportion of patients from the placebo arm who switch to the experimental treatment after disease progression. This presents a unique challenge in estimating the treatment effect on overall survival (OS). An overview and walkthrough of the rationale and setup of a recently proposed principal stratification method in addressing treatment switching will be presented. Simulations will be provided to compare with other commonly adopted treatment switching adjustment strategies.
- **Konstantina Skaltsa**: Patient Reported Outcomes (PROs) frequently produce continuous scores that are typically repeatedly collected through a clinical trial. Change from baseline to a predefined timepoint is usually an endpoint of interest and has been encouraged by regulatory assessors (Fiero et al 2020). However, certain events may occur and censor the PROs. In therapeutic areas such as cardiovascular or oncology, death may be the event that renders the PRO data unobservable (up to and at the timepoint of interest). Standard methods used when analyzing continuous change from baseline endpoints, such as the Mixed Model Repeated Measures (MMRM) model, make assumptions about death that may not be plausible and have been challenged by regulators. Specifically, the MMRM approach assumes that post-mortem data can be inferred by prior data from the same patient or similar patients, i.e. employs a hypothetical strategy for the intercurrent event of death. Additionally, if a composite approach is desired, attempting to make any assumptions about post-mortem data can result equally challenging. In this talk, we will discuss what are the potential clinical questions of interest in this setting and how different strategies can be implemented through appropriate estimators.