

Einladung zum virtuellen Biometrischen Kolloquium

KASPAR RUFIBACH

F. Hoffmann-La Roche, Switzerland

USE OF MULTISTATE MODELS TO IMPROVE DECISION-MAKING IN CLINICAL TRIALS

9. Dezember 2020, 9:15h

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HOST: Franz König

ABSTRACT:

In this talk, I will illustrate how critical decisions in drug development are typically based on a tiny fraction of the collected data only. As an example, in early development oncology clinical trials, the decision whether to move a molecule to Phase 3 is typically based on response proportions and duration of response in those that respond, while in Phase 3 the primary endpoint will be long-term endpoints such as progression-free (PFS) or overall survival (OS). Effects on response-based short-term endpoints seldom translate in effects on these relevant endpoints. We propose to make decisions not based on intermediate endpoints, but on a prediction of the OS hazard ratio (HR) between data of the new molecule collected in the early phase trial and historical data of the control treatment. This HR prediction is using a multistate model based on the various disease states a patient may go through until death. This yields a gating strategy with improved operating characteristics compared to traditional decision rules in the context of early phase clinical trials.

If time permits, I will further discuss how the joint distribution of PFS and OS as a function of transition probabilities in a multistate model can be derived. No assumptions on copulae or latent event times are needed, and the model is allowed to be non-Markov. From the joint distribution, statistics of interest can then readily be computed. As an example, we provide

closed formulas and statistical inference for Pearson's correlation coefficient between PFS and OS. Our proposal complements existing approaches by providing methods of statistical inference while at the same time working within a much more parsimonious modelling framework.

The main conclusion of this talk is that multistate models are a useful and underutilized tool in the analysis of clinical trial data.

This is joint work with Ulrich Beyer, Jan Beyersmann, Matthias Meller, David Dejardin, and Uli Burger, based on the following two papers:

Ulrich Beyer, David Dejardin, Matthias Meller, Kaspar Rufibach, Hans Ulrich Burger (2019). A multistate model for early decision making in oncology. *Biom. J.*, 62(3), 550-567.

Matthias Meller, Jan Beyersmann, Kaspar Rufibach (2019). Joint modelling of progression-free and overall survival and computation of correlation measures. *Stat. Med.*, 38, 4270-4289.