Structural models to characterize the clinical benefits of an on-demand drug dosing regimen: model selection and validation.

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In randomized clinical trials, analyses based on the *intention to treat* (ITT) principle are commonly used to establish the efficacy of a new treatment. This approach delivers an unbiased estimate of the average effect of assigning the treatment to a patient. In the presence of variable exposure, resulting from non-adherence to the prescribed therapy, a more relevant question is what the effect of the drug as actually taken is. Henceforth, even in a randomized trial, patients who adhere well to the assigned medication may form a selective subgroup and thus not be comparable to patients who do not adhere well. In order to obtain unbiased estimates of the effect of received dose, we use Structural Mean Models (SMM) (1,2) which express the causal effect of a treatment as a function of the amount of drug actually taken.

In this work, we apply the linear and the loglinear SMM to data on patients suffering from reflux problems and who are prescribed an on-demand proton pump inhibitor (PPI) therapy (i.e. patients take the medication when they feel the need). An electronic medication monitor (MEMS®) was used by all patients in this trial to compile their drug dosing histories. The actual use of the on-demand therapy is driven by the severity of symptoms which varies from periods without symptoms to periods with severe symptoms. The clinical outcome reflects the symptoms severity of a patient by the mean of a score, such that lower scores are suggestive of better health condition. Patients were randomized between active treatment and placebo tablets. Moreover, given the large variability in treatment exposure with the on-demand regimen, it is clinically relevant to estimate the expected treatment benefit for each level of drug exposure. As the clinical outcome is skewly distributed, Bootstrap bias-Correct, Adjusted (BCA) intervals are computed for each parameter and a comparison between the linear and the loglinear SMMs is proposed.

Finally, we investigate the assumptions of the SMM using semiparametric smoothing methods. We check whether the association between treatment-free outcomes and the baseline covariates in the model are the same in both arms. If different associations are detected, this is suggestive for a potential interaction between treatment exposure and the investigated covariate. We model treatment-free outcomes as the sum of a non-linear effect of baseline covariates, the effect of the group and a possible interaction between the group and a non-linear function of baseline covariates. Each non-linear function is modeled using a spline regression (3). The result constitutes a new formal validation tool to verify the hypothesis underlying the estimation of a linear and loglinear SMM.

1. Fisher-Lapp K. and Goetghebeur E. Practical Properties of Some Structural Mean Analyses of the Effect of Compliance in Randomized Trials, *Control Clin Trials* 1999;20:531–546.
2. Vansteelandt S. and Goetghebeur E. Causal inference with generalized structural mean models. *J. R. Statist. Sco. B.* (2003);65:817-835.
3. Ruppert D., Wand M.P., Carroll R.J. Semiparametric regression, Cambridge Series in Statistical and Probabilities Mathematics, Cambridge 2003