

## **Structural Mean Models for estimating treatment effects in randomized trials with two active arms**

Krista Fischer<sup>1</sup>, Ian White<sup>1</sup>, Els Goetghebeur<sup>2</sup> and Bernard Vrijens<sup>3</sup>

<sup>1</sup> MRC Biostatistics Unit, Cambridge, UK

<sup>2</sup> Department of Applied Mathematics and Informatics, University of Ghent, Belgium

<sup>3</sup> AARDEX Statistical Research Centre, Belgium

Randomized clinical trials comparing two active treatments are common in situations where there is an existing agent with proven efficacy. In this setting, patients failing to take their allocated treatment (non-compliance) could bias results towards or away from the null, compared with results given perfect compliance. Allowing for non-compliance is difficult, because in general we need to estimate the effects of both active treatments from just one randomisation. A common mistake is to use per-protocol analysis – since compliance is a post-randomization characteristic, this can lead to serious biases in the effect estimation.

When relevant compliance summaries have been recorded, a Structural Mean Modeling (SMM) approach allows to parametrize the effects of compliance and to derive estimability conditions. We use baseline covariates that predict compliance to construct consistent estimators of the two treatment effects. However, identification of the two distinct parameters is not possible when the expected compliance levels for the two treatments (given baseline covariates) are proportional. If the two expected compliance levels are equal, then the difference between the two treatment effects can be estimated; otherwise, a sensitivity analysis approach will provide boundaries for the parameters of interest.

We present an estimation algorithm for a linear SMM that requires no untestable parametric assumptions on the error distribution or about comparability between subgroups at different compliance levels. The methodology is used to analyze a trial comparing two antidepressants. The properties of the estimators are also investigated by a simulation study.