Investigating Association Between Behavior, Corticosterone, Heart Rate, and Blood Pressure in Rats Using Surrogate Marker Evaluation Methodology

Abel Tilahun[1], John T. Maringwa[1], Helena Geys[2], Ariel Alonso1, Leen Raeymaekers[2], Geert Molenberghs[1], Gerd Van Den Kieboom[2], Pim Drinkenburg[2], Luc Bijnens[2]

[1]Center for Statistics, Hasselt University, Diepenbeek, Belgium
[2] Johnson and Johnson Pharmaceutical Research and Development, a division of Janssen Pharmaceutica, Beerse, Belgium

The drug development process involves identifying a compound and assessing its merit through rigorous pre-clinical and clinical trials. The pre-clinical stage is designed to assess the chemical properties of the new drug, as well as to determine the steps for synthesis and purification. In this stage of drug development, circumstances might dictate the use of alternative endpoints than the originally anticipated clinically relevant endpoint. In this regard, identification and evaluation of surrogate endpoints is of paramount importance. The validation methods enable to quantify degrees of association between the clinically relevant endpoint, also termed the true endpoint, and the alternative, surrogate endpoint. In this paper, we adapt the surrogate marker evaluation methodology of Alonso et al. (2003, 2006), developed for the case of two longitudinal outcomes, to the situation where either a longitudinal surrogate and cross sectional true endpoint or vice versa. The work is motivated by a preclinical experiment conducted to asses association between Corticosterone (CORT), heart rate, and blood pressure in rats, the data from which are then subjected to analysis. It was found that there is a weak relationship between CORT and behavior, and between CORT on the one hand and heart rate and blood pressure on the other hand, but a reasonably high degree of association was registered between heart rate and behavior.

Key Words: fractional polynomial; spline; surrogate endpoint, true endpoint; variance reduction factor.