Using Earlier Measures in a Longitudinal Sequence as Potential Surrogate for a Later One

Assam Pryseley Abel Tilahun Ariel Alonso
Geert Molenberghs

Center for Statistics, Hasselt University, Diepenbeek, Belgium

The evaluation of surrogate endpoints in randomized clinical trials has gained momentum over the last decade. Within the so-called meta-analytic framework (Buyse et al. 2000), a variety of endpoint types, including continuous, discrete, time-to event, and longitudinal endpoints, have been studied. The surrogate and true endpoints can, but do not have to be, of the same type. In this paper, we deal with the specific situation where the true endpoint is the last, or at least a later, component of a repeatedly measured sequence, with the candidate surrogate a vector consisting of one or several of the earlier measurements in the same sequence. Incorporating more measurements into the surrogate will increase precision and hence quality of surrogacy, at the expense of the trial's length. We propose an objective-function paradigm to optimize over these two conflicting goals. The specific cases of compound-symmetric and auto-regressive sequences are considered. The proposed methodology is put to the test by means of a simulation study, as well as through the analysis of data from clinical trials in schizophrenia.

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