Detecting an interaction between treatment and a continuous covariate: a comparison between two approaches

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With larger clinical trials, for example those incorporating measurements of novel genetic markers, there is considerable interest in investigating whether a treatment effect is similar in all patients or whether a subgroup of patients profits more from a treatment than the remainder. Detection of such treatment-covariate interactions is one of the most important current topics in clinical research. For a continuous covariate Z the usual approach to analysis is to categorise Z into groups according to cutpoint(s) and to analyse the interaction in a model with main effects and multiplicative terms. The cutpoint approach raises several well-known and difficult issues for the analyst. Recently Royston & Sauerbrei (2004) [1] extended the multivariable fractional polynomial approach [2], which combines variable selection with determination of functional relationships for continuous predictors, to investigate treatment-covariate interactions. Covariates may be binary, categorical or continuous. Cutpoints are avoided in this approach. To facilitate the interpretation of estimates of a treatment effect derived from different but potentially overlapping subgroups of clinical trial data, defined with respect to a continuous covariate, Bonetti & Gelber (2000) [3] introduced the “subpopulation treatment effect pattern plot” (STEPP) method. We will discuss differences between the fractional polynomial and STEPP approaches and investigate their ability to detect and display treatment/covariate interactions in examples from randomised controlled trials in cancer. For the MFPI approach we also investigate type I errors by means of simulation [4].

References