VALIDATION OF SURROGATE ENDPOINTS IN THE PRESENCE OF MEASUREMENT ERROR

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The paper deals with the situation of a continuous surrogate endpoint and a binary final endpoint. When developing a new drug product that is compared with a marketed product by means of a surrogate endpoint the question of the relative benefit for the individual patient of the change in the surrogate endpoint compared to the total benefit on the final endpoint arises. This benefit might be due to both, the change in the surrogate and additional factors. Freedman et al. defined the proportion explained in order to estimate the proportion of the treatment effect on the final endpoint that is explained by the surrogate. This measure was criticized due to conceptional difficulties and generally low precision of its estimate. Moreover, the presence of measurement error can substantially bias the proportion explained as well as other measures for the validity of a surrogate endpoint. The paper shows that the relative benefit related to the surrogate can considerably be underestimated in the presence of important underlying intra-subject variabilities and compares different measures in situations where no replicated measurements are available. We discuss alternative methods, that incorporate the results of an additional calibrating study on the measurement precision of the surrogate endpoint. The results are illustrated with an example on bone markers as surrogate endpoints and fracture as final endpoint.