Tools4Patient

TITLE: **CORRECTING FOR THE INDIVIDUAL PATIENT REGRESSION TO THE MEAN EFFECT**

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Abstract

BACKGROUND:
Often, the primary endpoint of RCTs is defined as a change from baseline of a continuous outcome. In such cases, regulators recommend including the outcome's baseline value as a covariate in the statistical analysis. Regression to the mean can explain the benefits of this procedure.

METHODS:
We modeled the regression to the mean effect in this context. We found that the correlation between baseline and endpoint is a function of the outcome's signal to noise ratio (SNR). The SNR is the ratio of the inter-patient and the intra-patient variabilities. We observed that lower is the SNR, higher is the correlation and more efficient is the covariate correction.

To increase this correction, we proposed to combine several baseline measurements in a covariate minimizing the SNR with respect to the primary endpoint. This methodology was tested on placebo patients of two studies in Neuropathic Pain. The continuous outcomes were the weekly mean of the daily average pain score (APS), the brief pain inventory (BPI), and the worst pain score (WPS). The primary endpoint was the change from baseline of the APS.

RESULTS:
As covariate, the baseline value of the APS outcome was able to explain 10.8% of the primary endpoint variance (Adj R-squared with p-value=0.00108). As proposed, we combined the baseline values of the pain outcomes into a single covariate having a low SNR. This new covariate increased the explained variance of the primary endpoint up to 28.5% (Adj R-squared with p-value<5e-08).

CONCLUSION:
The correction for the baseline value of a continuous outcome is a standard procedure recommended by regulatory agencies. Using theoretical analysis of this effect, we improved this procedure and tested it successfully in two pain studies with neuropathic patients.

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