Should placebo responders be excluded from RCTs?

Submission ID 3000443

SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Recently, several models predictive of the placebo response in pain RCTs have been published. The most obvious application of these models is the identification and exclusion of placebo responders before randomization in an enriched screening procedure. We investigated the benefit of this approach using real RCT and simulated studies.

Introduction The expected benefit of enriched screening procedures is to decrease the variability of the patients' responses and increase the assay sensitivity. However, the real benefit to assay sensitivity has not been established and there may be an increased cost due to a higher rate of screening failure.

On the other hand, the prediction of the placebo response can be used as a baseline prognostic covariate. Adjusting for this covariate increases the precision of the treatment effect estimation.

Here, we investigate the benefit/cost ratio of both approaches: enrichment screening versus covariate adjustment using real and simulated clinical study data.

Methods A predictive model of placebo response was prospectively applied in an RCT. First, the model calculated the expected placebo response of all patients at baseline using patients' baseline characteristics (demographics, severity of disease, and traits of personality). Then, the enrichment strategy was simulated by removing extreme patients predicted to be strong placebo responders or non-responders by the same algorithm.

This enriched screening strategy was evaluated by the gain in treatment effect precision at various percentages of patients excluded (Table1). These results were compared to a random screening procedure, excluding the same percentage of patients (to simulate a study of the same size without an enriched screening procedure).

Finally, the two screening procedures were also tested while a baseline covariate in the statistical analyses.

Extensive simulations were also performed to further test the benefit of both approaches.

Results The precision of the four procedures (enriched screening or not, with and without covariate adjustment) was compared to the precision of non-adjusted analysis with 0% of patients excluded (Table 1). Without covariate adjustment, the increased exclusion of patients was associated with a decrease in precision. For the random screening procedure, this decrease is proportional to the number of patients excluded. The enriched screening procedure only results in a marginal gain in precision compared to random screening. When removing 30% of the patients, the

precision increases from 0.69 to 0.75 with the enriched screening.

The use of a covariate adjustment is also displayed in Table 1. The covariate adjustment increased the treatment effect precision by +37% for the random screening approach and is superior to the enrichment without adjustment. Combining the enriched screening with the adjustment does not improve further the precision of the treatment effect estimation.

These RCT results were fully consistent with the trial simulations and the mathematical modeling. When the analysis is adjusted for the placebo prediction, the selective screening procedure did not further improve the precision and study power.

Conclusion The application of placebo predictive models allows an estimation of the real impact on the assay sensitivity of strategies such as placebo non-responders population enrichment. Our work demonstrates the limited benefit of excluding placebo responders compared to adjustment of the analyses for the predicted placebo response. Such adjustment can lead to significant gains in precision and power.

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Keywords

Keywords
Placebo
Study design
Enrichment
RCT
Covariate adjustment

Guidelines I have read and understand the Poster Guidelines

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