Estimands in a Schizophrenia study

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The Methodological Question Being Addressed

How can estimands be defined in practice? An application of the new draft ICH E9 R1 addendum on estimands to data from a schizophrenia study.

Introduction

The concept of estimands, or "what is to be estimated" has been debated widely, and in August 2017 a new draft addendum R1 to the ICH E9 describing a set of strategies to be used when developing estimands was published for general consultation. Here, the different strategies defined in the addendum will be applied to an example from schizophrenia to illustrate the impact of the various strategies on the results presented.

Methods

In a 6-week, randomized, double-blind, placebo-controlled, short-term study in acute schizophrenia (NCT 01810380), data on the PANSS total score was collected for each visit. In addition, patients withdrawing from treatment early was asked to return for an additional assessment at Week 6, unless the patient had withdrawn consent to participate. The 5 strategies outlined in the ICH E9 R1 addendum on estimands were applied to the data collected, and the resulting analysis performed and interpreted.

Results

In the study, the rate of patients withdrawing from treatment was 90/311 (28.9%). A relatively high number of the patients withdrawn 46/90 (51.1%) returned for a Week 6 visit assessment. When the data was analyzed according to the methods associated with the 5 strategies, large variation was seen. This was both among the interpretation of the endpoint, but also among the degree of efficacy that was suggested by the method applied, varying from a clear statistical significant treatment effect to very limited effect, as the methods imply very different viewpoints on the data.

Conclusions

In this example of symptomatic treatment, with high withdrawal rates, the choice of estimand strategy will have considerable impact on the results. This illustrates that new studies planned under similar circumstances may have to employ a higher sample size, if the ICH E9 R1 strategy of "treatment policy" is required since it will likely reduce the estimated treatment effect considerably, and that although other new options may be available as choice of estimand, they may come with a price with respect to the ease of interpretation of results.

Disclosures