Statistical Methods for Causal Inference in Observational and Randomized Studies

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DAY ONE: Review and Recap

National Academy of Sciences FDA Panel Report

The Prevention and Treatment of Missing Data in Clinical Trials
Panel on Handling Missing Data in Clinical Trials
Committee on National Statistics
Division of Behavioral and Social Sciences and Education
NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES
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At the request of FDA, the National Research Council convened the Panel on the Handling of Missing Data in Clinical Trials, under the Committee on National Statistics, to prepare:

"a report with recommendations that would be useful for FDAs development of a guidance for clinical trials on appropriate study designs and follow-up methods to reduce missing data and appropriate statistical methods to address missing data for analysis of results."

Recommendations

Recommendation 11 [Treating Missing Data]

Parametric models in general, and random effects models in particular, should be used with caution, with all their assumptions clearly spelled out and justified. Models relying on parametric assumptions should be accompanied by goodness-of-fit procedures.

Recommendations

Recommendation 12 [Treating Missing Data]

It is important that the primary analysis of the data from a clinical trial should account for the uncertainty attributable to missing data, so that under the stated missing data assumptions the associated significance tests have valid type I error rates and the confidence intervals have the nominal coverage properties.

For inverse probability weighting and maximum likelihood methods, this analysis can be accomplished by appropriate computation of standard errors, using either asymptotic results or the bootstrap.

For imputation, it is necessary to use appropriate rules for multiply imputing missing responses and combining results across imputed datasets because single imputation does not account for all sources of variability.

Recommendations

Recommendation 18 [New Research and Use of Existing Research]

The treatment of missing data in clinical trials, being a crucial issue, should have a higher priority for sponsors of statistical research, such as the National Institutes of Health and the National Science Foundation. There remain several important areas in which progress is particularly needed, namely: (1) methods for sensitivity analysis and principled decision making based on the results from sensitivity analyses, (2) analysis of data where the missingness pattern is nonmonotone, (3) sample size calculations in the presence of missing data, (4) design of clinical trials, in particular plans for follow-up after treatment discontinuation (degree of sampling, how many attempts are made, etc.), and **(5) double robust methods, to more clearly understand their strengths and vulnerabilities in practical settings. The development of software that supports coherent missing data analyses is also a high priority.**