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Title: Comparing Conditional Mean (with Resampling) and Bayesian Imputation under MAR and Reference-Based Strategies in Rare Disease Trials

Imanol Zubizarreta

Denali therapeutics, South San Francisco/Zurich, Switzerland

Abstract

With the aim of handling missing data due to intercurrent events in RCTs under a treatment policy strategy, we evaluated and compared the performance of conditional mean imputation (CMI) with resampling-based inference and Bayesian multiple imputation in small-sample rare disease trials. While Wolbers et al. (2022) evaluated operating characteristics of CMI with resampling in larger trial settings, performance in rare disease context remains unexplored.

We simulated operating characteristics based on longitudinal continuous change from baseline in Vineland-3 ABRS-8 from COMPASS study (NCT05371613) in the rare disease MPSII (n = 42, 2:1 randomization) under a Missing At Random (MAR) mechanism with 15% dropout in the experimental arm. Imputation was performed under both a MAR and reference-based assumption using the copy increments in reference (CIR) strategy. For each, we compared standard Bayesian MI and CMI with bootstrap and jackknife, using the rbmi R package.

Under the null, Bayesian MI was overly conservative (type I error < 4 %), CMI with jackknife achieved nominal control, and CMI with bootstrap showed inflated type I error (> 6 %), consistent with prior findings.

Under the alternative, bootstrap yielded substantial power gains over Bayesian MI (approximately 6-9%) under CIR, while jackknife showed more modest gains than previously reported. Under MAR, all methods produced similar point estimates, but unexpectedly, jackknife showed slightly lower power while bootstrap showed still modest gains. These differences likely reflect finite-sample bias in standard error estimation.

Although CMI with jackknife performs well in large trials, finite-sample bias may alter operating characteristics in small-sample rare disease settings.