Global Sensitivity Analysis of Randomized Trials with Missing Data

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Missing Data Matters
During almost 30 years of review experience, the issue of missing data in clinical trials has been a major concern because of the potential impact on the inferences that can be drawn when data are missing.....the analysis and interpretation of the study pose a challenge and the conclusions become more tenuous as the extent of missingness increases. Robert Temple and Bob O'Neil (FDA)

Crux: Inference about treatment effects relies on unverifiable assumptions.

Need for Sensitivity Analysis
Sensitivity analyses should be part of the primary reporting of findings from clinical trials. Examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting.

2010 NRC Report
.....it is important to evaluate the robustness of the results to various limitations of the data, assumptions, and analytic approaches to data analysis

ICN Guidance - EU
In all submissions with non-negligible amounts of missing data sensitivity analyses should be presented as support to the main analysis. EMEA 2009 Draft Guidance

Sensitivity Analysis Approaches
Set of possible assumptions is too large to be fully explored. Types of sensitivity analysis:
- Ad-hoc: Specify a few different analytic methods (e.g., LOCF, BOCF, MMRM) and see if the results are consistent.
- Local: Specify a reasonable benchmark assumption and evaluate the robustness within a small neighborhood of this assumption.
- Global (or less local): Specify a reasonable benchmark assumption and evaluate the robustness within a large neighborhood of this assumption. Can see how far one needs to deviate from the benchmark assumption in order for inferences to change. If the assumptions under which the inferences change are judged to be sufficiently far from the benchmark assumption, then greater credibility is lent to the benchmark analysis. If not, the benchmark analysis can be considered to be fragile.
- Operate like “stress testing” in reliability engineering or “tipping point” analysis in business strategy.

Global Sensitivity Analysis
- Randomized study designs where measurements of an outcome are scheduled to be taken at fixed time-points after randomization.
- Focus on impact of missing data pattern.
- Comparison of treatment arms means at the last scheduled visit (in a world with no missing data).

Assumptions
Inference requires two types of assumptions:
- (i) unverifiable assumptions about the distribution of outcomes among those with missing data
- (ii) additional testable assumptions that serve to increase the efficiency of estimation.

Type (i) Assumptions
- strictly individuals with missing outcomes according to the data that we were able to collect on them and the occasions at which the data were collected
- separately for each stratum, hypothetically assign or (or back) between the distribution of the missing outcome(s) with the distribution of the outcome(s) among those with the observed outcome(s) and who share the same recorded data.

Common Benchmark Assumption: Missing at Random (Type (i) Assumption)
- For subjects last seen at visit k with a given recorded history of outcomes through visit k and unobserved history of outcomes at visit k + 1, the distribution of outcomes after visit k + 1 is the same as the distribution of outcomes for subjects who remain on-study after visit k and who share the same recorded history.
- Equivalent to assuming that the conditional distribution of missing data between visits k and k + 1 only depends on the history of recorded outcomes through visit k.

Building a Class of Assumptions Around Missing at Random
- For subjects last seen at visit k with a given recorded history of outcomes through visit k and unobserved history of outcomes at visit k + 1, the distribution of outcomes after visit k + 1 is the same as the distribution of outcomes for subjects who remain on-study after visit k and who share the same recorded history.
- Equivalent to assuming that the conditional distribution of missing data between visits k and k + 1 only depends on the history of recorded outcomes through visit k and the outcome at visit k + 1.
- Equivalent to assuming that the conditional distribution of missing data between visits k and k + 1 only depends on the history of recorded outcomes through visit k, use “exponential tilting” to link the distribution of the missing outcome at visit k + 1 to the distribution of outcomes at the last scheduled visit before a given on-study time at visit k + 1, and share the same recent history through visit k, where there is a parameter (α) that governs “differences” between the distributions being linked.
- For each α, we define α > 0 indicates no differences and yields the missing at random assumption, α < 0) indicates that distribution of the missing outcomes is more heavily weighted toward higher (lower) values than those with observed outcomes.
- Equivalent to assuming that a logistic regression model for the conditional distribution of missing data between visits k and k + 1, where α specifies the difference in the outcome at visit k + 1, above and beyond the recorded history of outcomes through visit k.

Type (ii) Assumptions
- The stratum of people who share the same recorded data will typically be small - need to draw strength across strata by imposing type (ii) “smoothing” assumptions.
- We model the distribution of the observed data and smooth by assuming the conditional distribution of the outcome at visit k given on-study at visit k and the past history of outcomes only depends on the outcomes at visit k + 1, the conditional probability of dropping out between visits k and k + 1 given on-study at visit k and the history of outcomes only depends on the outcomes at visit k and by using non-parametric covariates smoothing techniques.

Estimation and Inference
For given α
- Generalized Newton-Raphson estimator (plug-in plus average of estimated influence functions)
- Confidence intervals via double bootstrap

Case Study: SCA-3004
- Randomized trial designed to evaluate the efficacy/safety of once-monthly, injectable paliperidone palmitate (PP1M) relative to placebo (PBO) in delaying the time to relapse in patients with schizophrenia.
- Open-label phase with a flexible-dose, lead-in period and a fixed-dose, stabilization period.
- Randomized trial designed to evaluate the efficacy/safety of once-monthly, injectable paliperidone palmitate.
- Funding: PCORI

Confidence intervals via double bootstrap

Case Study: SCA-3004
A SAS version is currently under development and will be ready this summer.

Case Study: SCA-3004
- Under missing at random, the estimated means are 69.60 and 74.37 for the PBO and PP1M arms.
- The estimated treatment difference is -4.77 (95% CI: -10.89 to 0.09).
- Relative to the complete-case analysis, the missing at random analysis corrects for bias in a direction and relative magnitude that is anticipated.
- As a consequence, the estimated treatment effect is more favorable to PP1M, although the 95% CI still includes 0.

Conclusion
The methods and software we have developed will help sponsors and regulators more comprehensively assess the robustness of trials with missing data, as per recommendations of the NRC Report and regulatory guidance documents.

Extensions
- Intermittent missing data
- Incorporation of auxiliary covariates

Software
- An R-based software package called SAMON is available at www.missingdatamatters.org.
- A SAS version is currently under development and will be ready this summer.

Funding
- PCORI