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A Tipping Point Method to Evaluate Sensitivity to Potential Violations in Missing Data Assumptions

Cesar Torres

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This presentation reflects information from a manuscript that is a product of joint work with:

- Gregory Levin
- Daniel Rubin
- William Koh
- Rebecca Rothwell
- Thomas Permutt

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OVERVIEW

1 Motivation

2 Tipping Point Approach

3 Example

4 Strengths and Limitations

5 Closing Thoughts

1

MOTIVATION

Missing Data Sensitivity Analyses

- Critical to evaluate the sensitivity of conclusions to violations in missing data assumptions
- Sensitivity analyses should:
  - Not consist of a few alternative methods/models assuming same missingness mechanism
  - Not explore only a local or limited space of violations
  - Systematically and comprehensively explore the space of possible assumptions

Tipping Point Analysis

- Independently vary assumptions about missingness mechanism in each arm
- Identify and discuss clinical plausibility of assumptions (the “tipping points”) under which there is no longer evidence of efficacy
- Typically relies on single or multiple imputation of missing outcomes

2

TIPPING POINT APPROACH

Notation

For treatment arm $h \in \{t, c\}$:

- π_h: probability of patient completing study
- μ_h: true mean in completers
- δ_h: difference in true means between dropouts and completers
  - $\mu_h + \delta_h$: true mean in dropouts
- N_h: number of completers
- n_h: sample size

Parameters of Interest

- Mean in treatment arm h is
  $\pi_h\mu_h + (1-\pi_h)(\mu_h + \delta_h) \equiv \mu_h + (1-\pi_h)\delta_h$

- $\theta := [\mu_t + (1-\pi_t)\delta_t] - [\mu_c + (1-\pi_c)\delta_c]$

Assumptions

- Outcomes of completers are i.i.d. under some distribution with mean μ_h and finite variance σ_h^2
  - Normality is not assumed!
- Outcomes of dropouts have common mean $\mu_h + \delta_h$
- Completion probability for each patient equal to $\pi_h \in (0, 1)$
- Completion probabilities are independent of realized outcomes
- Patients are mutually independent
- $\frac{n_t}{n_t + n_c} \xrightarrow{p} r \in (0, 1)$

Proposed Estimator

- For assumed values of δ_t and δ_c,
  $\hat{\theta} := [\hat{\mu}_t + (1 - \hat{\pi}_t)\delta_t] - [\hat{\mu}_c + (1 - \hat{\pi}_c)\delta_c]$

- $Var(\hat{\theta}) \sim_a \frac{s_t^2}{N_t} + \frac{s_c^2}{N_c} + \frac{\delta_t^2 \hat{\pi}_t(1-\hat{\pi}_t)}{n_t} + \frac{\delta_c^2 \hat{\pi}_c(1-\hat{\pi}_c)}{n_c}$

3

EXAMPLE

Xeljanz (tofacitinib)

- Janus kinase inhibitor previously approved for treatment of rheumatoid arthritis
- Evaluated for safety and effectiveness in psoriatic arthritis
- Co-primary endpoints:
  - American College of Rheumatology 20% (ACR20) response at Month 3
  - Change from baseline to Month 3 in Health Assessment Questionnaire-Disability Index (HAQ-DI) score
- More details available in meeting briefing materials for August 3, 2017 Arthritis Advisory Committee Meeting

HAQ-DI

- Patient-reported outcome measure of patient's level of functional ability
- Ranges from 0 to 3, with higher scores being worse

Primary Analysis

- Mixed effects model for repeated measurements (MMRM)
- Carried out in all randomized patients who received at least one dose of randomized treatment
- Can be viewed as having targeted treatment policy estimand

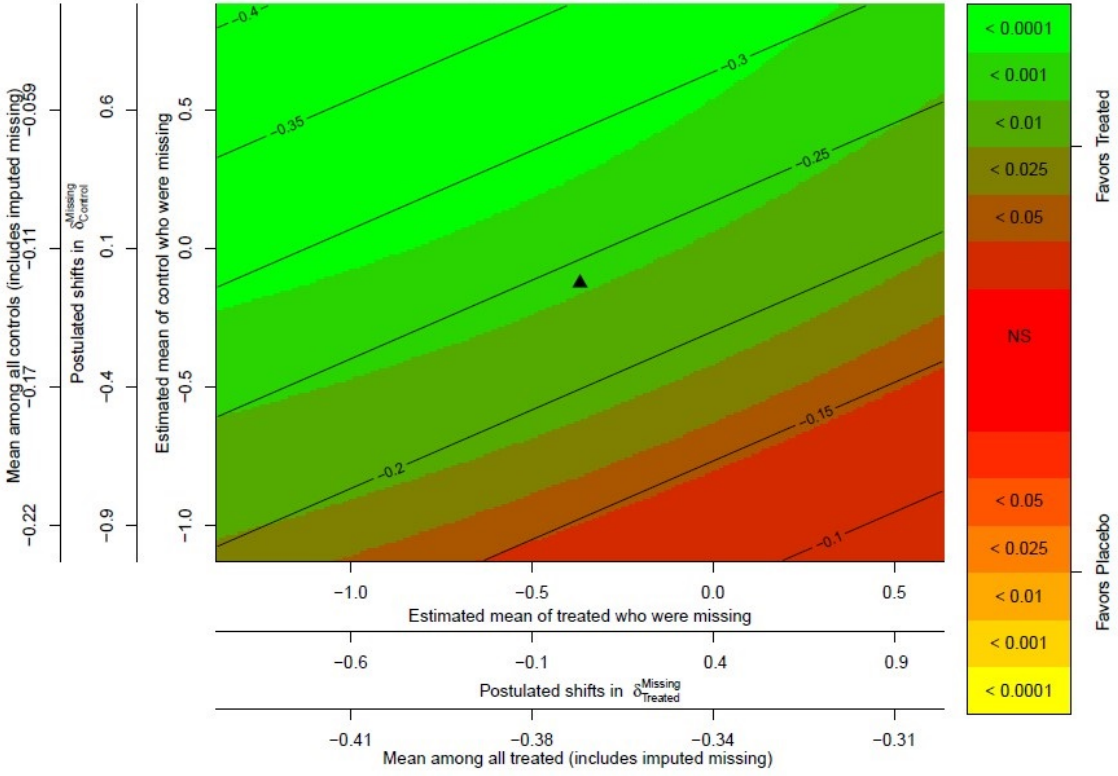
Primary Analysis Results

- Statistically significant: $p < 0.0001$
- Observed difference: -0.25 (95% CI: -0.38 to -0.13)
- 5% of tofacitinib patients and 11% of placebo patients were dropouts
- MMRM assumes that missingness is at random

Applicant's Sensitivity Analysis

- Jump-to-reference multiple imputation
- Can also be viewed as having targeted treatment policy estimand under different missingness mechanism assumption
- Did not comprehensively explore space of plausible, alternative assumptions

FDA Reviewer's Sensitivity Analysis



FDA Reviewer's Sensitivity Analysis

- Proportions of dropouts were low
- Even placebo completers did not observe a mean improvement as large as -0.5
- Points at which results tipped were considered implausible, so evidence of efficacy was convincing despite missing data

4

STRENGTHS AND LIMITATIONS

Data Use Efficiency

- Does not condition on prognostic characteristics, dropout pattern, and outcomes observed prior to dropout
- Tipping point analysis methods that do so may have gains in efficiency

Assumption in Benchmark Setting

- Benchmark setting: $\delta_t = \delta_c = 0$
- Does not assume that missingness depends on both treatment assignment and other variables
  - May not be appropriate for a primary analysis
  - Can differ from assumption made by a primary analysis such as MMRM

Simple to Perform

- No imputation needed
- Calculation of point estimate, test statistic, and CI are all straightforward

Minimal Assumptions

- Normality of outcomes is not assumed
- No particular parametric form is assumed
- Allows for analysis of ordered categorical variables such as HAQ-DI or binary variables such as ACR20

Sensitivity Parameters are Intuitive

- For treatment arm h, δ_h is difference in true means between dropouts and completers
- Ease of interpretation of sensitivity parameters facilitates cross-disciplinary discussion of sensitivity analysis results

5

CLOSING THOUGHTS

Key Takeaways

- Method serves as valuable tool for sensitivity analyses, with limited and transparent assumptions
- Method allows for valid statistical inference without the need for imputation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