Sensitivity Analysis for the Primary Outcome in a Drug Abuse Intervention Trial

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Outline

- Screening, Motivational Assessment, Referral, and Treatment in Emergency Departments (SMART-ED) study
- Missing data in SMART-ED
- Distribution of the Primary Outcome in SMART-ED
- Primary Outcome Result and Sensitivity Analysis
  *Aim: To study the impact of missing data on the result of the primary outcome of this study*
- Conclusions
Screening, Motivational Assessment, Referral, and Treatment in Emergency Departments (SMART-ED)

- National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) funded Multisite Clinical Trial

- 1285 participants randomized to three treatment arms -
  1. Minimal Screening Only (MSO)
  2. Screening, assessment, and referral to treatment (SAR)
  3. SAR + brief intervention with 2 telephone follow-up booster sessions (BI-B)

- Primary Outcome – Self-reported number of days of primary drug of abuse in past 30 days at 3-month follow-up visit

- Hypotheses – 3 Multiplicity Adjusted 2-sided tests (BI-B vs SAR, BI-B vs MSO and SAR vs MSO) [Bogenschutz (2011)]
Missing Data in SMART-ED

- Missing Data on Primary Outcome

<table>
<thead>
<tr>
<th></th>
<th>BI-B</th>
<th>SAR</th>
<th>MSO</th>
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<tbody>
<tr>
<td></td>
<td>52/427 (12.2%)</td>
<td>45/427 (10.5%)</td>
<td>49/431 (11.4%)</td>
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- Reasons for missing - Died, incarcerated, withdrew consent and eligible but did not return

- Impact of Missing Data on the Primary Outcome

- Graphical Sensitivity Analysis - [Hollis (2002)]
Distribution of Number of drug use days

- Binomial Distribution - Number of drug use days in \( n \) independent days with probability \( p \)

\[ \mu = np \quad \text{and} \quad \sigma^2 = np(1 - p) \]

- For a participant, drug use days are correlated \( \implies \) not independent

- Beta-binomial distribution is the binomial distribution in which the probability of drug use is not fixed but random and follows the beta distribution \( \implies \) correlated drug use days

\[ \mu = n\pi \quad \text{and} \quad \sigma^2 = n\pi(1 - \pi)[1+(n - 1)\rho] \]

- \( \pi \) (probability of drug use) and \( \rho \) (pairwise correlation between the days) are the parameters of the Beta-binomial distribution
Beta-Binomial Distribution \((\rho = 0.66, \text{ varying } \pi)\) [VGAM]
Distribution of Primary Outcome (Observed)

- **BI−B**
- **SAR**
- **MSO**
- **Overall**

The diagrams show the distribution of drug use days across different categories. Each category has a density plot indicating the frequency of drug use days ranging from 0 to 30 days. The plots are color-coded to differentiate between categories.

- **BI−B**
- **SAR**
- **MSO**
- **Overall**

The density plots are normalized to show the proportion of drug use days within the specified range.
Primary Outcome Result & Sensitivity Analysis

- Primary Outcome: No statistically significant treatment effect [Bogenschutz (2014)]

- Could missing data impact this result?

- Sensitivity analysis-assume:
  \( \pi_{BIB} \) - Probability of Drug Use in Missing Ppts in BI-B arm
  \( \pi_{SAR} \) - Probability of Drug Use in Missing Ppts in SAR arm
  \( \pi_{MSO} \) - Probability of Drug Use in Missing Ppts in MSO arm

- For various combinations of these probabilities evaluate the impact of missing data on the result of the primary outcome.
Algorithm for Sensitivity Analysis

1. For the missing participant, simulate number of drug use days using beta-binomial distribution with observed correlation $\rho$ and probability $\pi_{BIB}$ if the ppt is in the BI-B arm; $\pi_{SAR}$ if in the SAR arm; and $\pi_{MSO}$ if in the MSO arm.
Algorithm for Sensitivity Analysis

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2. Analyze the complete data using primary outcome beta-binomial model and calculate the 3 multiplicity adjusted p-values for three comparisons (BI-B vs SAR, BI-B vs MSO and SAR vs MSO).
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2. Analyze the complete data using primary outcome beta-binomial model and calculate the 3 multiplicity adjusted p-values for three comparisons (BI-B vs SAR, BI-B vs MSO and SAR vs MSO).

3. Repeat the steps 1 and 2, 10 times and calculate the average obtaining 3 multiplicity adjusted p-values.

4. For a given comparison, if that average p-value from step 3 is less than 0.05 then that comparison is statistically significant, otherwise not.

5. Repeat for different combinations of $\pi_{BIB}$, $\pi_{SAR}$ and $\pi_{MSO}$ and plot the result.
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Sensitivity Analysis Results - BL-B vs SAR ($\pi_{MSO} = 0.1$)

- **Best Case**
- **Impute Negative**
- **Impute Positive**
- **Worst Case**

- **Significant (p < .05)**
- **Not Significant**
Sensitivity Analysis Results - BI-B vs SAR

Blue Circle - Significant, Red Circle - Not Significant
Sensitivity Analysis Results - BI-B vs MSO

Blue Circle - Significant, Red Circle - Not Significant
Sensitivity Analysis Results - SAR vs MSO

\[ \pi_{BIB} = 0.1 \quad \pi_{BIB} = 0.2 \quad \pi_{BIB} = 0.3 \]

\[ \pi_{BIB} = 0.4 \quad \pi_{BIB} = 0.5 \quad \pi_{BIB} = 0.6 \]

\[ \pi_{BIB} = 0.7 \quad \pi_{BIB} = 0.8 \quad \pi_{BIB} = 0.9 \]

Blue Circle - Significant, Red Circle - Not Significant
Conclusions

- When the assumed probability of drug use in missing participants was the same in the 2 arms, there was never a significant treatment effect between any pair of arms (more plausible scenarios).

- Best and worst case scenarios were usually but not always significant.

- Of the 729 imputation scenarios, only 32.9%, 24.1% and 20.6% were significant for comparing BI-B vs SAR, BI-B vs MSO and SAR vs MSO, respectively.

- These sensitivity analyses performed on the primary outcome provided evidence that the null result in the trial was not drastically impacted by missing data.
Treatment Effect - BI-B vs SAR ($\pi_{MSO} = 0.1$)

