Clinical Trials Network

Emmes

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

BI-B	SAR	MSO
52/427(12.2%)	45/427(10.5%)	49/431(11.4%)

- 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

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

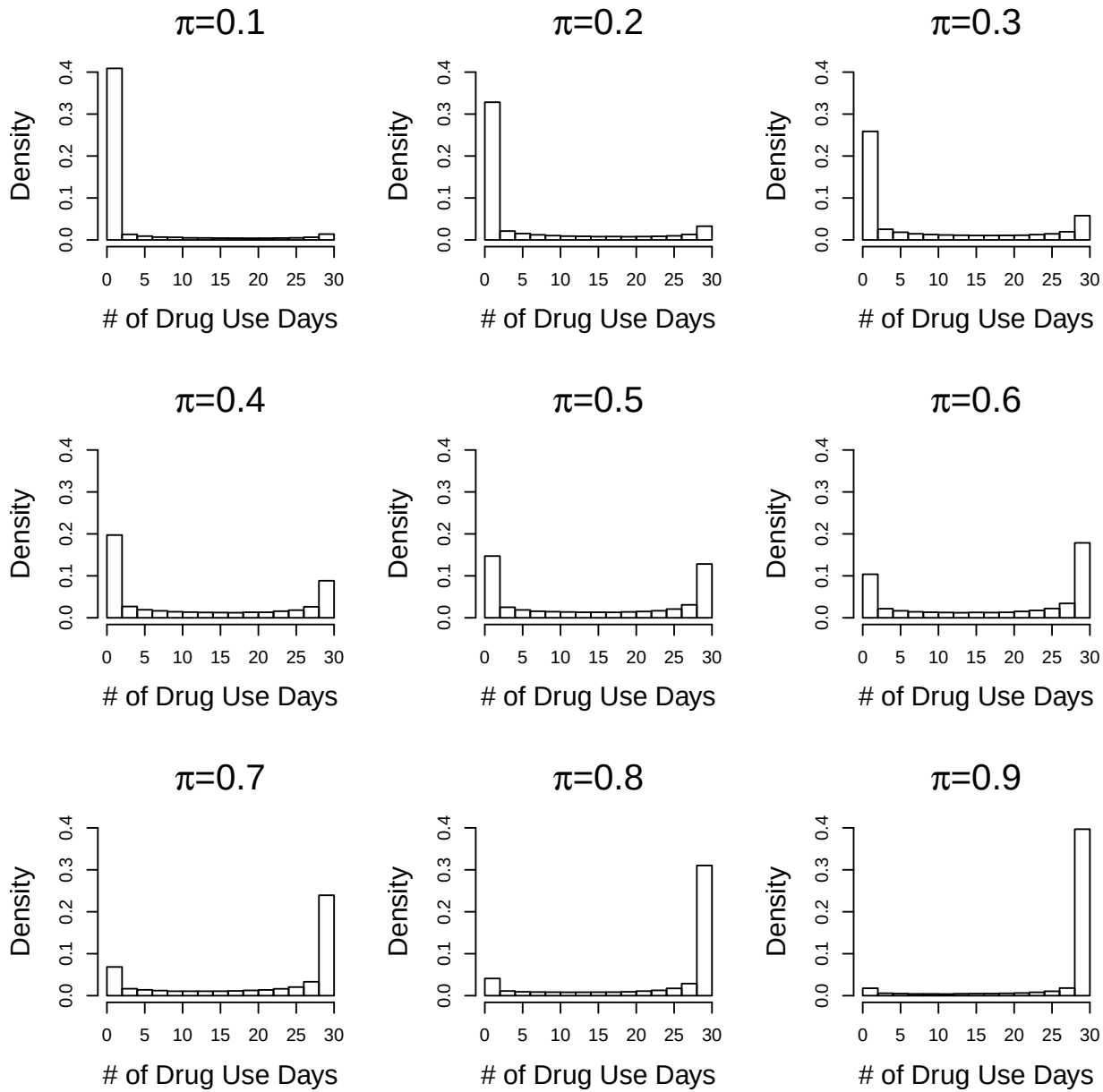
- For a participant, drug use days are correlated $\implies$ not independent

- 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

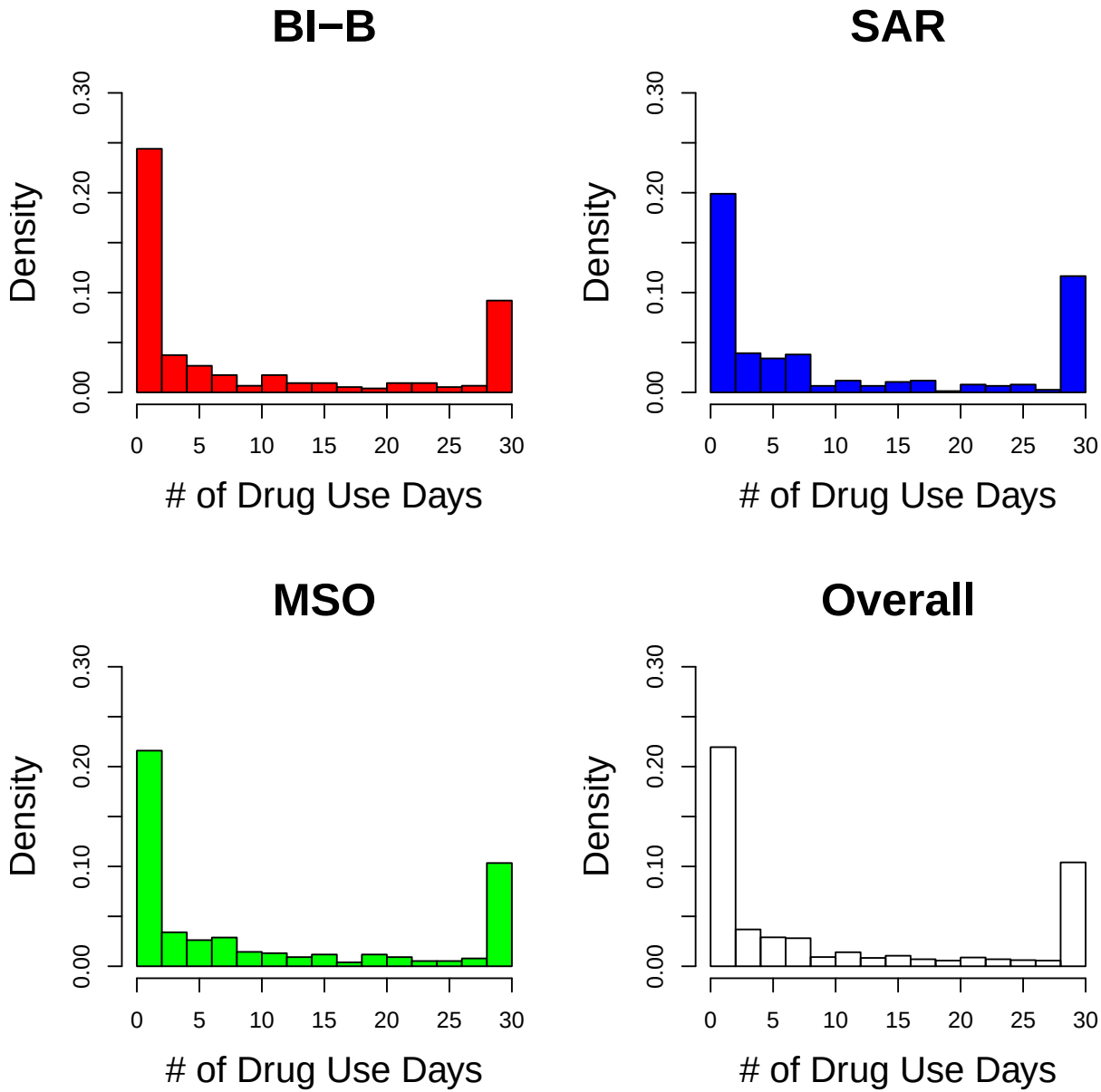
$$\mu = n\pi \quad \text{and} \quad \sigma^2 = n\pi(1-\pi)[1+(n-1)\rho]$$

- π (probability of drug use) and ρ (pairwise correlation between the days) are the parameters of the Beta-binomial distribution

Beta-Binomial Distribution ($\rho = 0.66$, varying π) [VGAM]



Distribution of Primary Outcome (Observed)



Primary Outcome Result & Sensitivity Analysis

- Primary Outcome: No statistically significant treatment effect [Bogenschutz (2014)]
- Could missing data impact this result?
- Sensitivity analysis-assume:

  π_{BIB} - Probability of Drug Use in Missing Ppts in BI-B arm
  π_{SAR} - Probability of Drug Use in Missing Ppts in SAR arm
  π_{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 ρ and probability π_{BIB} if the ppt is in the BI-B arm; π_{SAR} if in the SAR arm; and π_{MSO} if in the MSO arm.

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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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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.

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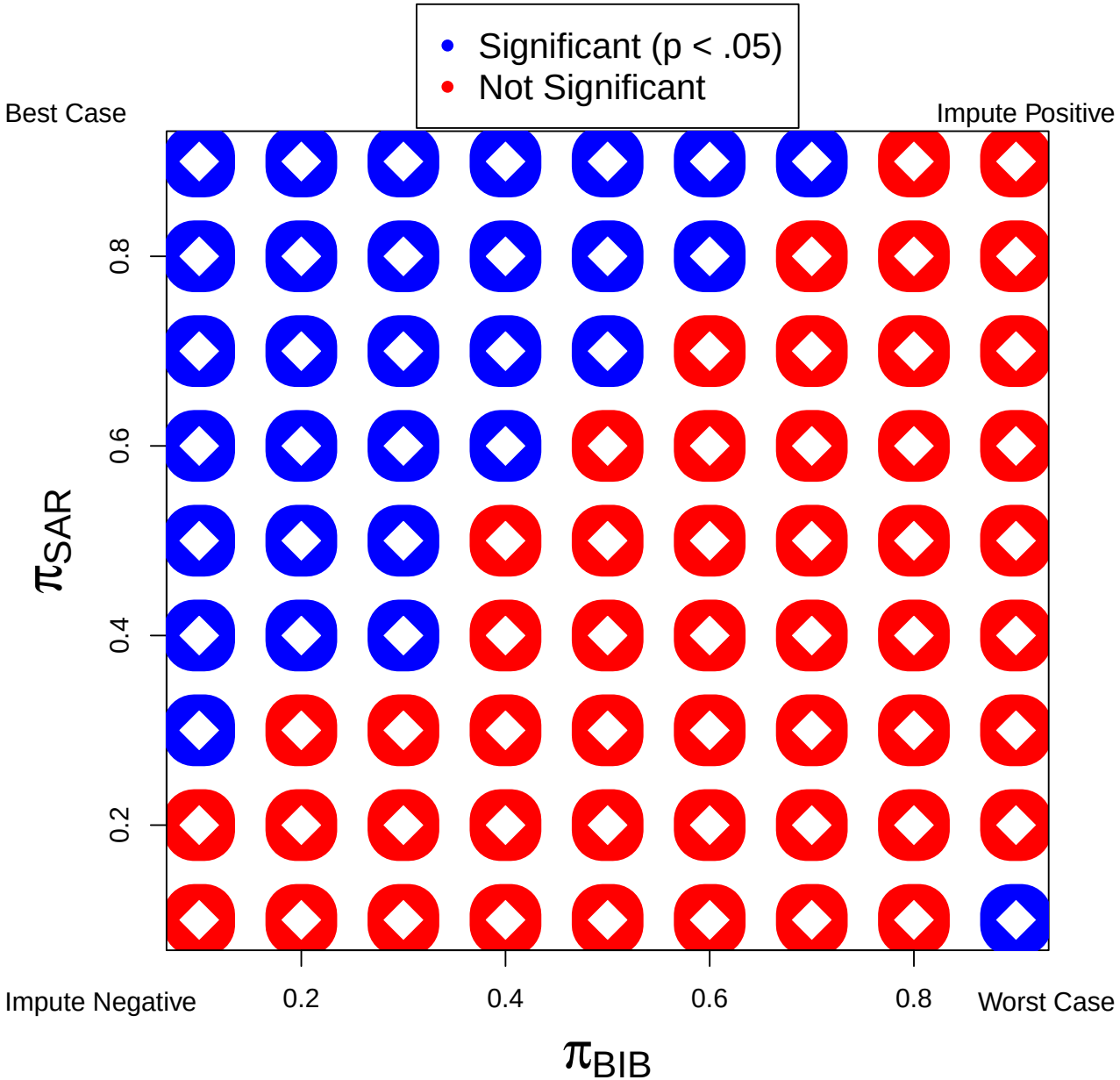
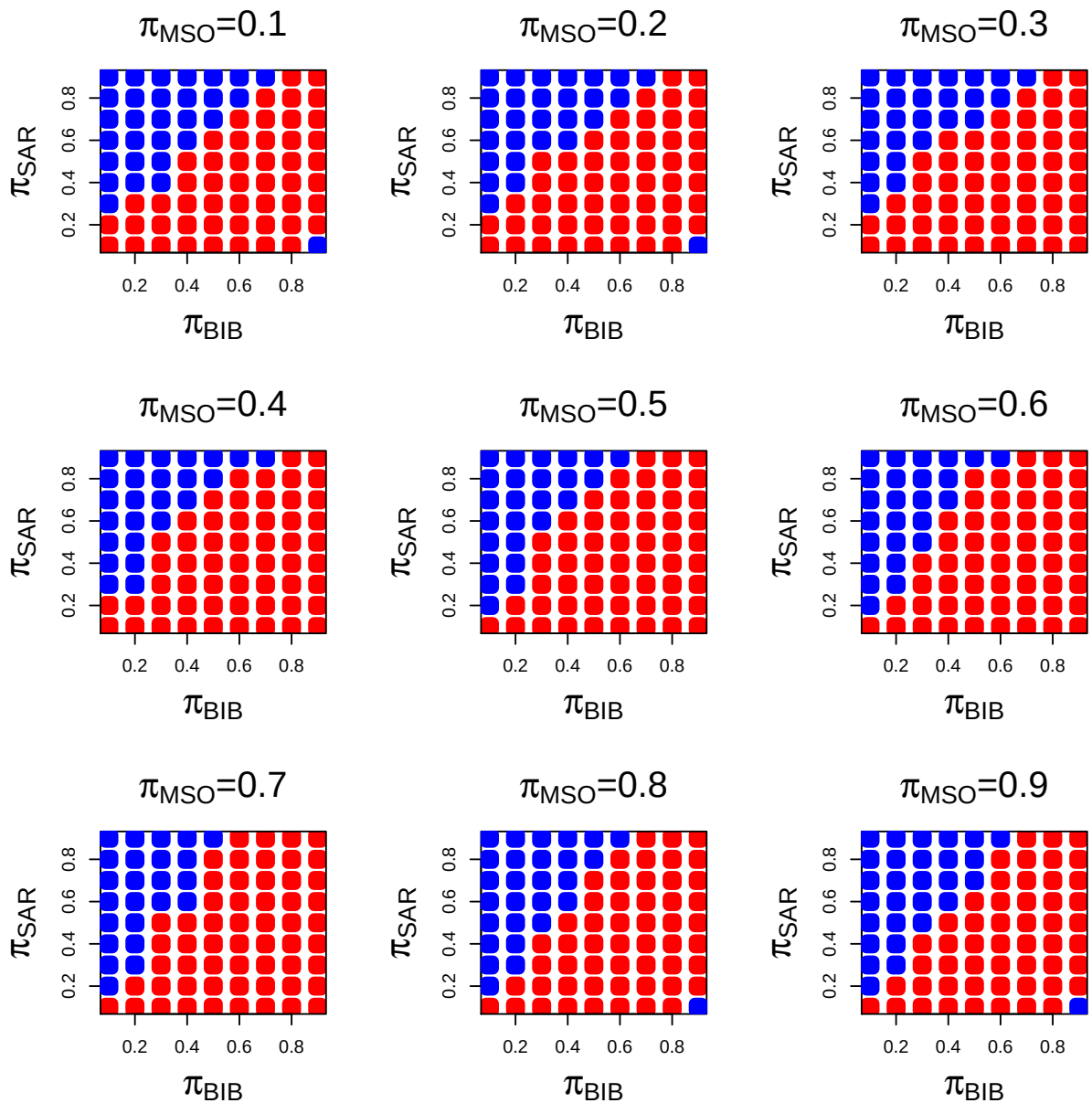
3. Repeat the steps 1 and 2, 10 times and calculate the average obtaining 3 multiplicity adjusted p-values.
4. For a given comparison, if that average p-value from step 3 is less than 0.05 then that comparison is statistically significant, otherwise not.
5. Repeat for different combinations of π_{BIB}, π_{SAR} and π_{MSO} and plot the result.

Sensitivity Analysis Results - BI-B vs SAR ($\pi_{MSO} = 0.1$)

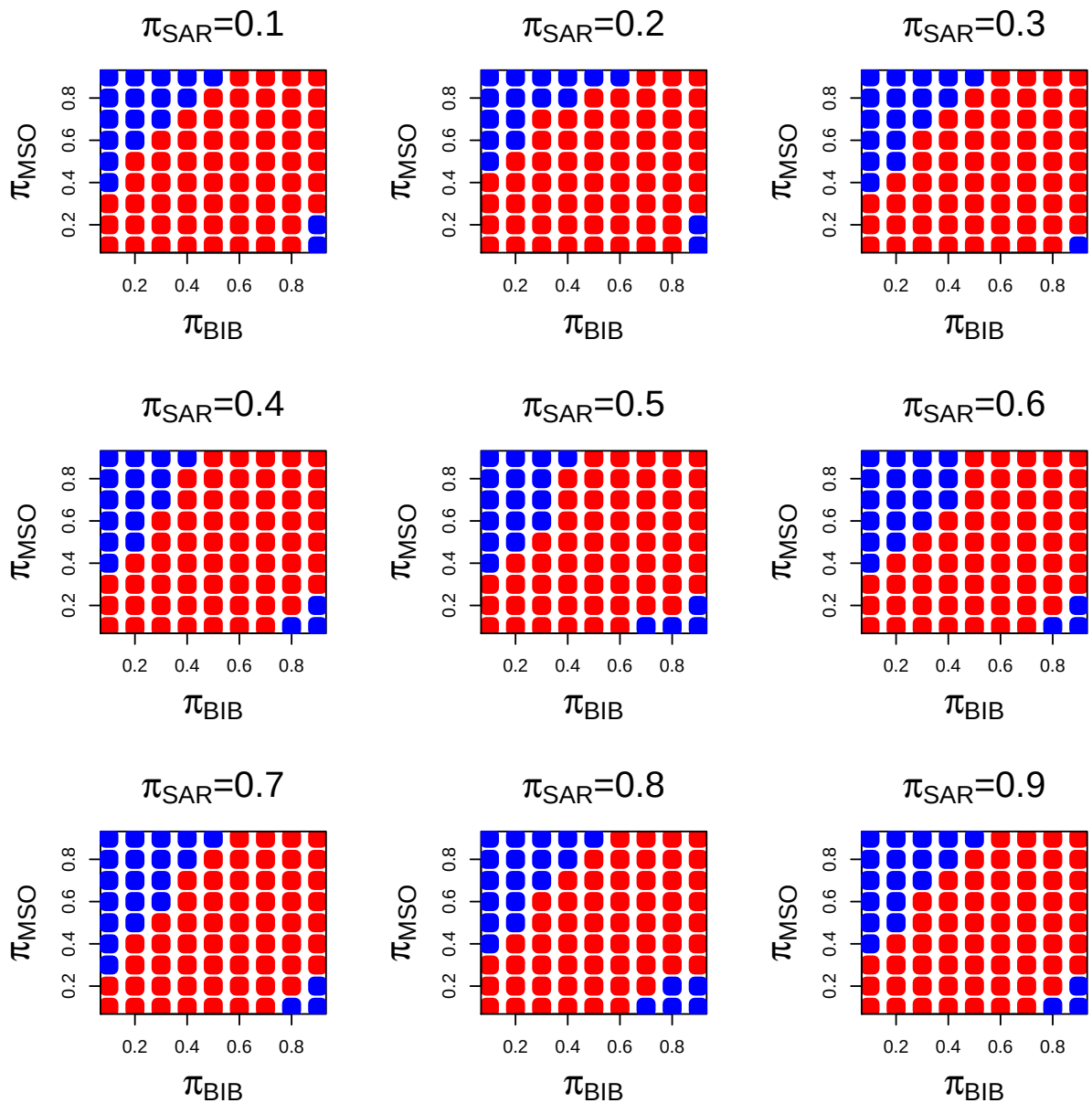


Sensitivity Analysis Results - BI-B vs SAR



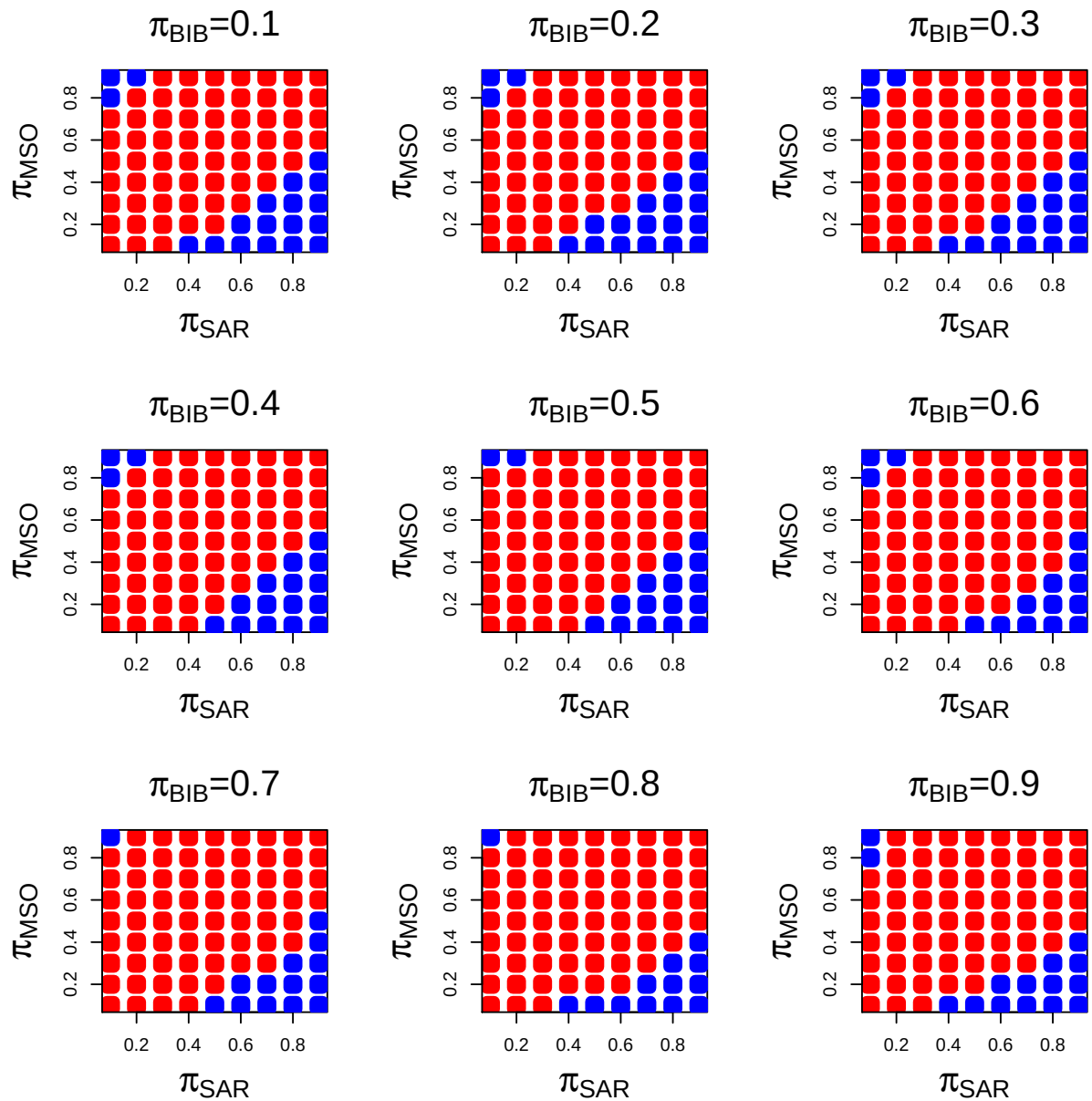
[0] Blue Circle - Significant, Red Circle - Not Significant

Sensitivity Analysis Results - BI-B vs MSO



[0] Blue Circle - Significant, Red Circle - Not Significant

Sensitivity Analysis Results - SAR vs MSO



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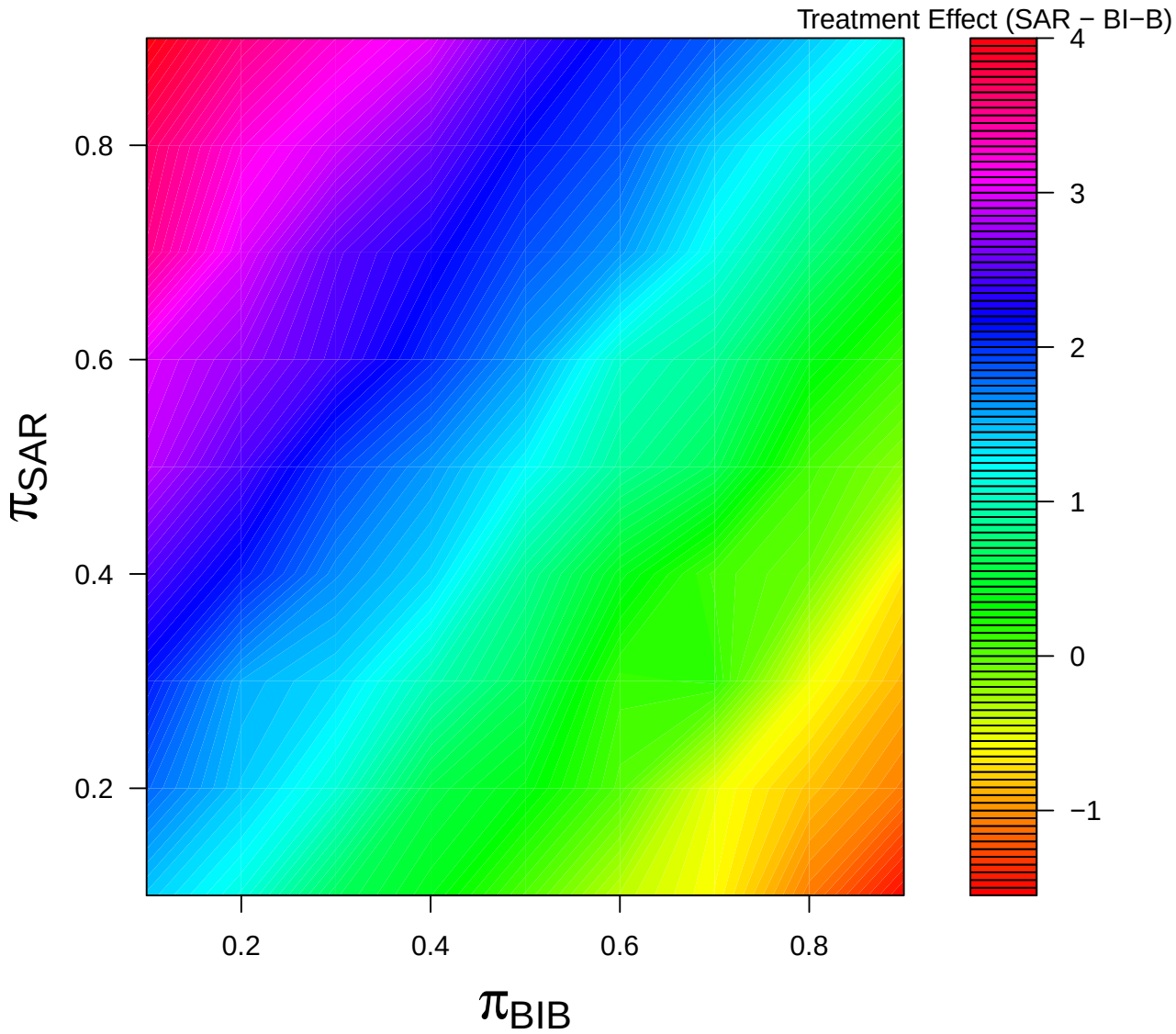
Conclusions

- 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 ($\pi_{MSO} = 0.1$)



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