PCORI Methodology Standards

Standards for Preventing and Handling of Missing Data

JOHNS HOPKINS
SCHOOL of MEDICINE

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

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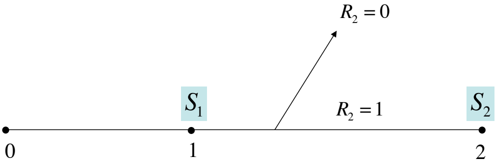
Module listing

- Module 1: Introduction
- Module 2: What are missing data?
- Module 3: Methods to prevent and monitor missing data
- Module 4: Record and report missing data
- Module 5: Describe statistical methods to handle missing data
- **Module 6: Statistical methods to deal with missing data**
- **Module 7: Examine sensitivity of inferences to missing data methods and assumptions**

Hypothetical Study - Two Time Points

- Imagine a study in which eligible individuals are to receive a new drug.
- Individuals are expected to return for two post-enrollment visits (V1-V2) at which the presence (1) or absence (0) of symptoms is recorded.
- The goal is to learn about the probability of having symptoms at V2.
- Assume all individuals show up at V1 and some individuals drop out of the study before V2.
- To start, imagine that we conduct this study in "infinite" population so that there is no sampling variability.

Observed Data



Observed and Unobserved Data

s_1
1
0

Observed and Unobserved Data

s_1
1 p_1
0 $1 - p_1$

Observed and Unobserved Data

S_1	R_2
1 p_1	1
	0
0 $1 - p_1$	1
	0

Observed and Unobserved Data

S_1	R_2
1 p_1	1 $q_2(1)$
	0 $1 - q_2(1)$
0 $1 - p_1$	1 $q_2(0)$
	0 $1 - q_2(0)$

Observed and Unobserved Data

S_1	R_2	S_2
1 p_1	1 $q_2(1)$	1
		0
	0 $1 - q_2(1)$	**1**
		0
0 $1 - p_1$	1 $q_2(0)$	1
		0
	0 $1 - q_2(0)$	**1**
		0

Observed and Unobserved Data

S_1	R_2	S_2
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$
		0 $1 - p_2(1,1)$
	0 $1 - q_2(1)$	**1** $\mathbf{p_2(1,0)}$
		0 $\mathbf{1 - p_2(1,0)}$
0 $1 - p_1$	1 $q_2(0)$	1 $p_2(0,1)$
		0 $1 - p_2(0,1)$
	0 $1 - q_2(0)$	**1** $\mathbf{p_2(0,0)}$
		0 $\mathbf{1 - p_2(0,0)}$

Observed and Unobserved Data

S_1	R_2	S_2	Proportion	
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$	f_{111}	
		0 $1-p_2(1,1)$	f_{110}	
	0 $1-q_2(1)$	**1** $\boldsymbol{p_2(1,0)}$	$\boldsymbol{f_{101}}$	$f_{10?}$
		0 $\boldsymbol{1-p_2(1,0)}$	$\boldsymbol{f_{100}}$	
0 $1-p_1$	1 $q_2(0)$	1 $p_2(0,1)$	f_{011}	
		0 $1-p_2(0,1)$	f_{010}	
	0 $1-q_2(0)$	**1** $\boldsymbol{p_2(0,0)}$	$\boldsymbol{f_{001}}$	$f_{00?}$
		0 $\boldsymbol{1-p_2(0,0)}$	$\boldsymbol{f_{000}}$	

Distribution of Observed Data

- $p_1 = P[S_1 = 1]$
- $q_2(1) = P[R_2 = 1 | S_1 = 1]$
- $q_2(0) = P[R_2 = 1 | S_1 = 0]$
- $p_2(1,1) = P[S_2 = 1 | S_1 = 1, R_2 = 1]$
- $p_2(1,0) = P[S_2 = 1 | S_1 = 0, R_2 = 1]$

- $f_{111} = P[S_1 = 1, R_2 = 1, S_2 = 1] = p_1 q_2(1) p_2(1,1)$
- $f_{110} = P[S_1 = 1, R_2 = 1, S_2 = 0] = p_1 q_2(1)\{1 - p_2(1,1)\}$
- $f_{10?} = P[S_1 = 1, R_2 = 0, S_2 =?] = p_1\{1 - q_2(1)\}$
- $f_{011} = P[S_1 = 0, R_2 = 1, S_2 = 1] = \{1 - p_1\} q_2(1) p_2(1,1)$
- $f_{010} = P[S_1 = 0, R_2 = 1, S_2 = 0] = \{1 - p_1\} q_2(1)\{1 - p_2(1,1)\}$
- $f_{00?} = P[S_1 = 0, R_2 = 0, S_2 =?] = \{1 - p_1\}\{1 - q_2(1)\}$

Distribution of Unobserved Data

- $\mathbf{p_2(1,0)} = P[S_2 = 1 | S_1 = 1, R_2 = 0]$
- $\mathbf{p_2(0,0)} = P[S_2 = 1 | S_1 = 0, R_2 = 0]$

- $\mathbf{f_{101}} = P[S_1 = 1, R_2 = 0, S_2 = 1] = p_1\{1 - q_2(1)\}\mathbf{p_2(1,0)}$
- $\mathbf{f_{100}} = P[S_1 = 1, R_2 = 0, S_2 = 0] = p_1\{1 - q_2(1)\}\{1 - \mathbf{p_2(1,0)}\}$
- $\mathbf{f_{001}} = P[S_1 = 0, R_2 = 0, S_2 = 1] = \{1 - p_1\}\{1 - q_2(1)\}\mathbf{p_2(1,0)}$
- $\mathbf{f_{000}} = P[S_1 = 0, R_2 = 0, S_2 = 0] = \{1 - p_1\}\{1 - q_2(1)\}\{1 - \mathbf{p_2(1,0)}\}$

$P[S_2 = 1]$

S_1	R_2	S_2	Proportion	
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$	f_{111}	
		0 $1 - p_2(1,1)$	f_{110}	
	0 $1 - q_2(1)$	$\mathbf{1}$ $\boldsymbol{p_2(1,0)}$	$\boldsymbol{f_{101}}$	$f_{10?}$
		$\mathbf{0}$ $\boldsymbol{1 - p_2(1,0)}$	$\boldsymbol{f_{100}}$	
0 $1 - p_1$	1 $q_2(0)$	1 $p_2(0,1)$	f_{011}	
		0 $1 - p_2(0,1)$	f_{010}	
	0 $1 - q_2(0)$	$\mathbf{1}$ $\boldsymbol{p_2(0,0)}$	$\boldsymbol{f_{001}}$	$f_{00?}$
		$\mathbf{0}$ $\boldsymbol{1 - p_2(0,0)}$	$\boldsymbol{f_{000}}$	

Fundamental Problem

- Even with infinite data, we cannot learn about the probability of having symptoms at V2.
- We don't know the probability of have symptoms for individuals who have dropped out prior to V2.
- **Need to make assumptions**!
- With assumptions, we can compute $P[S_2 = 1]$

Examples of Assumptions

Worst Case

- If $R_2 = 0$ then $S_2 = 1$

Worst Case

S_1	R_2	S_2	Proportion	
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$	f_{111}	
		0 $1 - p_2(1,1)$	f_{110}	
	0 $1 - q_2(1)$	1 $p_2(1,0) = 1$	$f_{101} = f_{10?}$	$f_{10?}$
		0 $1 - p_2(1,0) = 0$	$f_{100} = 0$	
0 $1 - p_1$	1 $q_2(0)$	1 $p_2(0,1)$	f_{011}	
		0 $1 - p_2(0,1)$	f_{010}	
	0 $1 - q_2(0)$	1 $p_2(0,0) = 1$	$f_{001} = f_{00?}$	$f_{00?}$
		0 $1 - p_2(0,0) = 0$	$f_{000} = 0$	

Examples of Assumptions

Best Case

- If $R_2 = 0$ then $S_2 = 0$

Best Case

S_1	R_2	S_2	Proportion	
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$	f_{111}	
		0 $1 - p_2(1,1)$	f_{110}	
	0 $1 - q_2(1)$	1 $p_2(1,0) = 0$	$f_{101} = 0$	$f_{10?}$
		0 $1 - p_2(1,0) = 1$	$f_{100} = f_{10?}$	
0 $1 - p_1$	1 $q_2(0)$	1 $p_2(0,1)$	f_{011}	
		0 $1 - p_2(0,1)$	f_{010}	
	0 $1 - q_2(0)$	1 $p_2(0,0) = 0$	$f_{001} = 0$	$f_{00?}$
		0 $1 - p_2(0,0) = 1$	$f_{000} = f_{00?}$	

Examples of Assumptions

Maintained Response After Dropout

- If $R_2 = 0$, $S_2 = S_1$

Maintained Response After Dropout

S_1	R_2	S_2	**Proportion**	
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$	f_{111}	
		0 $1 - p_2(1,1)$	f_{110}	
	0 $1 - q_2(1)$	1 $p_2(1,0) = 1$	$f_{101} = f_{10?}$	$f_{10?}$
		0 $1 - p_2(1,0) = 0$	$f_{100} = 0$	
0 $1 - p_1$	1 $q_2(0)$	1 $p_2(0,1)$	f_{011}	
		0 $1 - p_2(0,1)$	f_{010}	
	0 $1 - q_2(0)$	1 $p_2(0,0) = 0$	$f_{001} = 0$	$f_{00?}$
		0 $1 - p_2(0,0) = 1$	$f_{000} = f_{00?}$	

Examples of Assumptions

Missing at Random (MAR)

$$R_2 \text{ independent of } S_2 \text{ given } S_1$$

$$\mathbf{p_2(1,0)} = P[S_2 = 1 | S_1 = 1, R_2 = 0] = P[S_2 = 1 | S_1 = 1, R_2 = 1] = p_2(1,1)$$

$$\mathbf{p_2(0,0)} = P[S_2 = 1 | S_1 = 0, R_2 = 0] = P[S_2 = 1 | S_1 = 0, R_2 = 1] = p_2(0,1)$$

Missing At Random

S_1	R_2	S_2	Proportion	
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$	f_{111}	
		0 $1-p_2(1,1)$	f_{110}	
	0 $1-q_2(1)$	1 $p_2(1,0)=p_2(1,1)$	f_{101}	$f_{10?}$
		0 $1-p_2(1,0)$	f_{100}	
0 $1-p_1$	1 $q_2(0)$	1 $p_2(0,1)$	f_{011}	
		0 $1-p_2(0,1)$	f_{010}	
	0 $1-q_2(0)$	1 $p_2(0,0)=p_2(0,1)$	f_{001}	$f_{00?}$
		0 $1-p_2(0,0)$	f_{000}	

Missing Not at Random (MNAR)

- Missing at Random doesn't hold
- Best/Worst Case and Maintained Response After Drop-out are MNAR assumptions

Missing Not at Random (MNAR)

$$\begin{aligned}&\overbrace{P[S_2 = 1 | S_1 = 1, R_2 = 0]}^{\mathbf{p_2(1,0)}}\\ &\quad \propto \underbrace{P[S_2 = 1 | S_1 = 1, R_2 = 1]}_{p_2(1,1)} \exp(\alpha)\end{aligned}$$

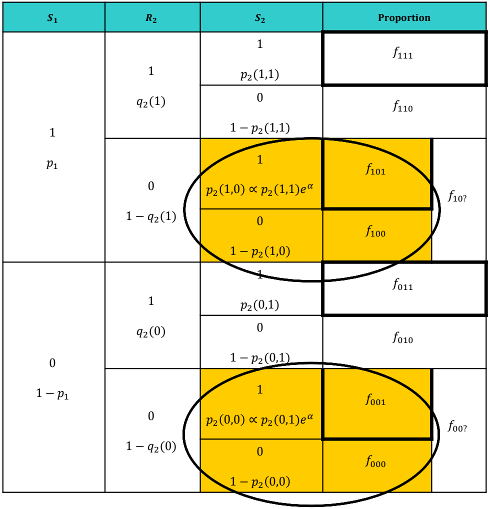
$$\begin{aligned}&\overbrace{P[S_2 = 1 | S_1 = 0, R_2 = 0]}^{\mathbf{p_2(0,0)}}\\ &\quad \propto \underbrace{P[S_2 = 1 | S_1 = 0, R_2 = 1]}_{p_2(0,1)} \exp(\alpha)\end{aligned}$$

- Exponential Tilting
- α is a sensitivity analysis parameter
- $\alpha = 0$ corresponds to MAR

Missing Not at Random (MNAR)

	$p_2(1,1)$	$\mathbf{p_2(1,0)}$
α	$P[S_2 = 1 \mid S_1 = 1, R_2 = 1]$	$P[S_2 = 1 \mid S_1 = 1, R_2 = 0]$
-1	0.2	0.084
-0.5	0.2	0.132
0	0.2	0.200
0.5	0.2	0.292
1	0.2	0.405

Missing Not At Random



S_1	R_2	S_2	Proportion	
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$	f_{111}	
		0 $1-p_2(1,1)$	f_{110}	
	0 $1-q_2(1)$	1 $p_2(1,0) \propto p_2(1,1)e^{\alpha}$	f_{101}	$f_{10?}$
		0 $1-p_2(1,0)$	f_{100}	
0 $1-p_1$	1 $q_2(0)$	1 $p_2(0,1)$	f_{011}	
		0 $1-p_2(0,1)$	f_{010}	
	0 $1-q_2(0)$	1 $p_2(0,0) \propto p_2(0,1)e^{\alpha}$	f_{001}	$f_{00?}$
		0 $1-p_2(0,0)$	f_{000}	

Inference in Finite Samples

- Under the above assumptions, $P[S_2 = 1]$ depends on the distribution of the observed data.
- Estimate $P[S_2 = 1]$ by plugging-in the estimated distribution of the observed data.
- Standard errors and confidence intervals: Re-sampling methods such as jackknife and bootstrap.

Case Study

- Women were enrolled in a randomized trial to evaluate two doses (100 and 150 mg) of the contraceptive DMPA.
- 4 doses (administered via injection) were scheduled to be given at 90 day intervals with the first dose at randomization.
- Women were asked to fill out a daily diary recording bleeding/spotting.
- A women was coded as having "amenorrhea" at an injection visit if she did not have bleeding/spotting for 80 consecutive days since the previous injection.
- The analysis population is restricted to the 1151 women who were randomized and returned their first diary.
- We focus on the analysis of the first two diaries.

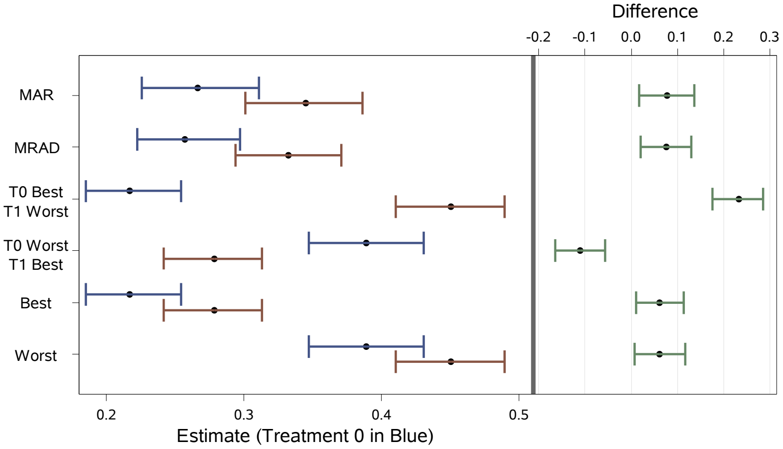
Low Dose (Tx 0)

S_1	R_2	S_2	Proportion	
1 $\frac{107}{576} = 19\%$	1 $\frac{84}{107} = 79\%$	1 $\frac{54}{84} = 64\%$	9.4%	
		0 $\frac{30}{84} = 36\%$	5.2%	
	0 $\frac{23}{107} = 21\%$	$\mathbf{1}$ $\boldsymbol{p_2(1,0)}$	$\boldsymbol{f_{101}}$	4.0%
		$\mathbf{0}$ $\boldsymbol{1 - p_2(1,0)}$	$\boldsymbol{f_{100}}$	
0 $\frac{469}{576} = 81\%$	1 $\frac{393}{469} = 84\%$	1 $\frac{71}{393} = 18\%$	12.3%	
		0 $\frac{322}{393} = 82\%$	55.9%	
	0 $\frac{76}{469} = 16\%$	$\mathbf{1}$ $\boldsymbol{p_2(0,0)}$	$\boldsymbol{f_{001}}$	13.2%
		$\mathbf{0}$ $\boldsymbol{1 - p_2(0,0)}$	$\boldsymbol{f_{000}}$	

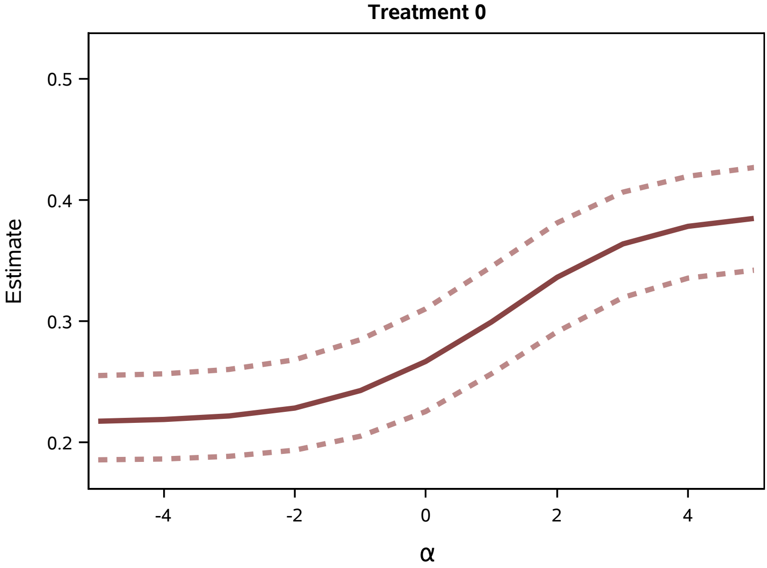
High Dose (Tx 1)

S_1	R_2	S_2	**Proportion**	
1 $\frac{118}{575} = 21\%$	1 $\frac{87}{118} = 74\%$	1 $\frac{56}{87} = 64\%$	9.7%	
		0 $\frac{31}{87} = 36\%$	5.4%	
	0 $\frac{31}{118} = 26\%$	**1** $\boldsymbol{p_2(1,0)}$	$\boldsymbol{f_{101}}$	5.4%
		0 $\boldsymbol{1 - p_2(1,0)}$	$\boldsymbol{f_{100}}$	
0 $\frac{457}{575} = 79\%$	1 $\frac{389}{457} = 85\%$	1 $\frac{104}{389} = 27\%$	18.1%	
		0 $\frac{285}{389} = 73\%$	49.6%	
	0 $\frac{68}{457} = 15\%$	**1** $\boldsymbol{p_2(0,0)}$	$\boldsymbol{f_{001}}$	11.8%
		0 $\boldsymbol{1 - p_2(0,0)}$	$\boldsymbol{f_{000}}$	

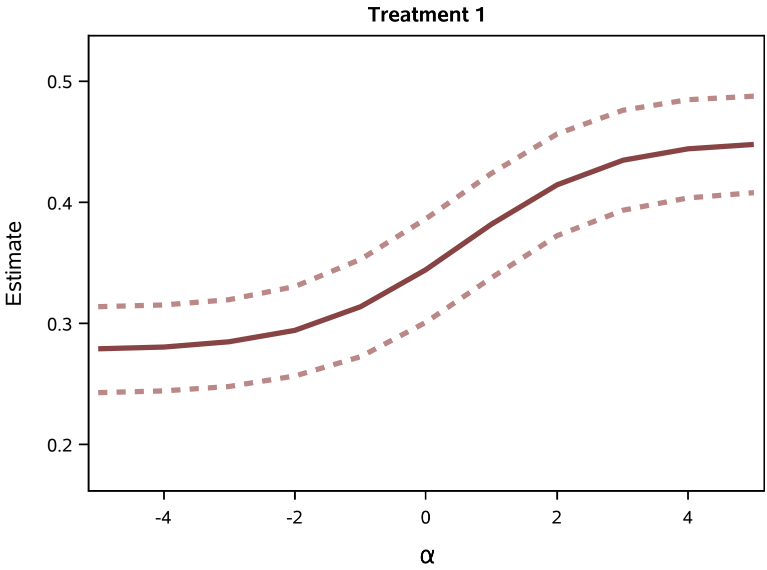
Analysis


Difference
-0.2
-0.1
0.0
0.1
0.2
0.3
MAR
MRAD
T0 Best
T1 Worst
T0 Worst
T1 Best
Best
Worst
0.2
0.3
0.4
0.5
Estimate (Treatment 0 in Blue)

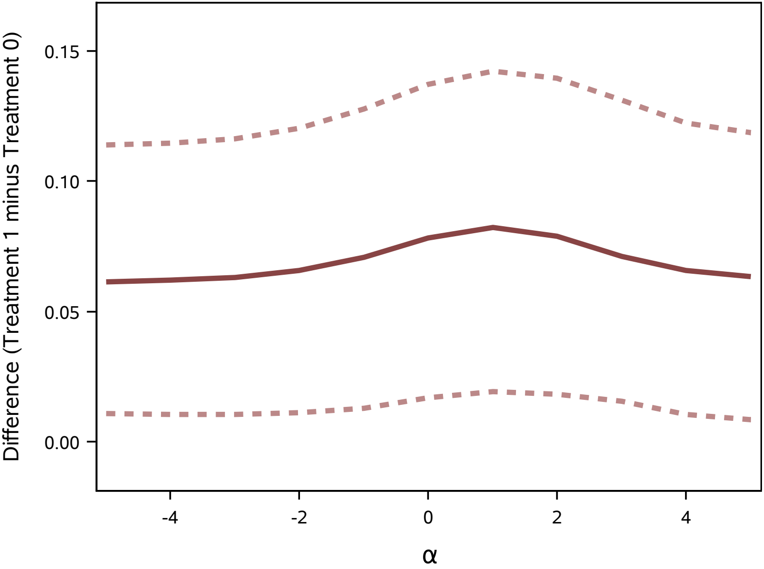
Analysis



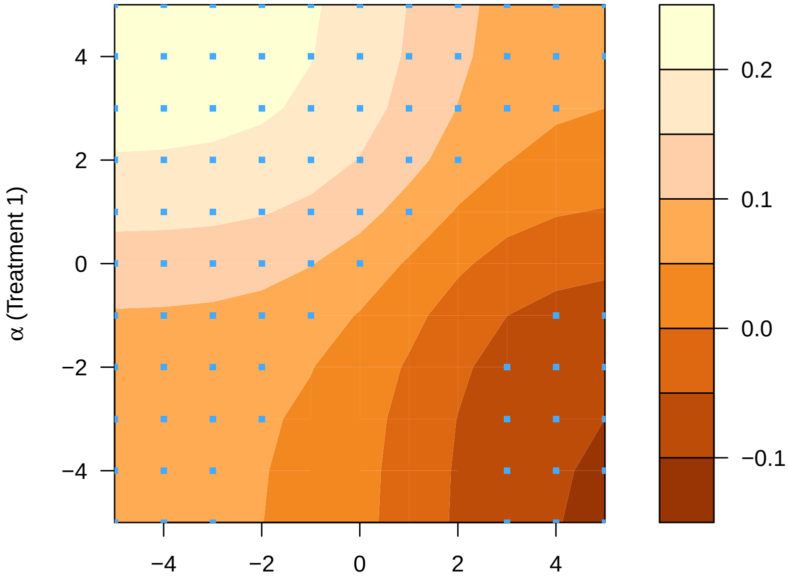
Analysis



Analysis


Difference (Treatment 1 minus Treatment 0)
0.15
0.10
0.05
0.00
-4
-2
0
2
4
α

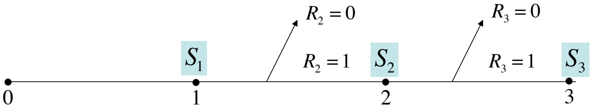
Analysis



Hypothetical Study - Three Time Points

- Imagine a study in which eligible individuals are to receive a new drug to relieve symptoms.
- Individuals are expected to return for three post-enrollment visits (V1-V3) at which the presence (1) or absence (0) of symptoms is recorded.
- The goal is to learn about probability of having symptoms at V3.
- Assume all individuals show up at V1 and some individuals drop out of the study before V3.
- To start, imagine that we conduct this study in "infinite" population so that there is no sampling variability.

Observed Data



Observed and Unobserved Data

S_1	R_2	S_2	R_3	S_3	Proportion	
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$	1 $q_2(1,1,1)$	1 $p_3(1,1,1,1)$	f_{11111}	
				0 $1-p_3(1,1,1,1)$	f_{11110}	
			0 $1-q_2(1,1,1)$	**1** $\boldsymbol{p_3(1,1,1,0)}$	$\boldsymbol{f_{11101}}$	$f_{1110?}$
				0 $\boldsymbol{1-p_3(1,1,1,0)}$	$\boldsymbol{f_{11100}}$	
		0 $1-p_2(1,1)$	1 $q_2(1,1,0)$	1 $p_3(1,1,0,1)$	f_{11011}	
				0 $1-p_3(1,1,0,1)$	f_{11010}	
			0 $1-q_2(1,1,0)$	**1** $\boldsymbol{p_3(1,1,0,0)}$	$\boldsymbol{f_{11001}}$	$f_{1100?}$
				0 $\boldsymbol{1-p_3(1,1,0,0)}$	$\boldsymbol{f_{11000}}$	
	0 $1-q_2(1)$	**1** $\boldsymbol{p_2(1,0)}$	0 $q_2(1,0,1)=1$	**1** $\boldsymbol{p_3(1,0,1,0)}$	$\boldsymbol{f_{10101}}$	$f_{10?0?}$
				0 $\boldsymbol{1-p_3(1,0,1,0)}$	$\boldsymbol{f_{10100}}$	
		0 $\boldsymbol{1-p_2(1,0)}$	0 $q_2(1,0,0)=1$	**1** $\boldsymbol{p_3(1,0,0,0)}$	$\boldsymbol{f_{10001}}$	
				0 $\boldsymbol{1-p_3(1,0,0,0)}$	$\boldsymbol{f_{10000}}$	

Assumptions

- Worst Case
- Best Case
- Maintained Response after Dropout
- Missing at Random

$$R_2 \text{ independent } (S_2, S_3) \text{ given } S_1$$

$$R_3 \text{ independent } S_3 \text{ given } R_2 = 1, S_2, S_1$$

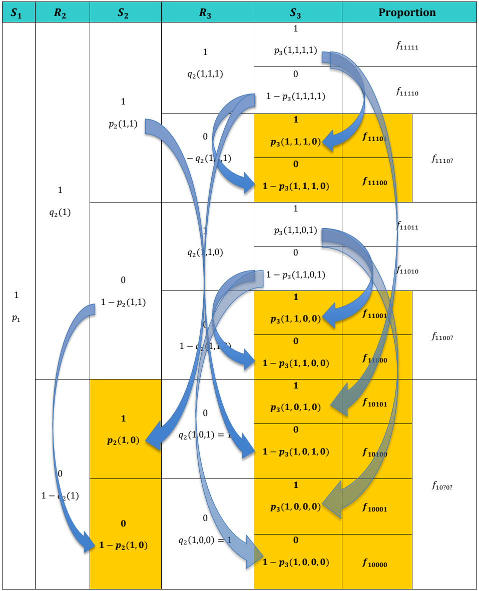
- Missing Not at Random: Exponential Tilting

$$R_2 \text{ independent } S_3 \text{ given } S_2, S_1$$

$$P[S_2 = 1 | R_2 = 0, S_1 = s_1] \propto P[S_2 | R_2 = 1, S_1 = s_1] \exp(\alpha)$$

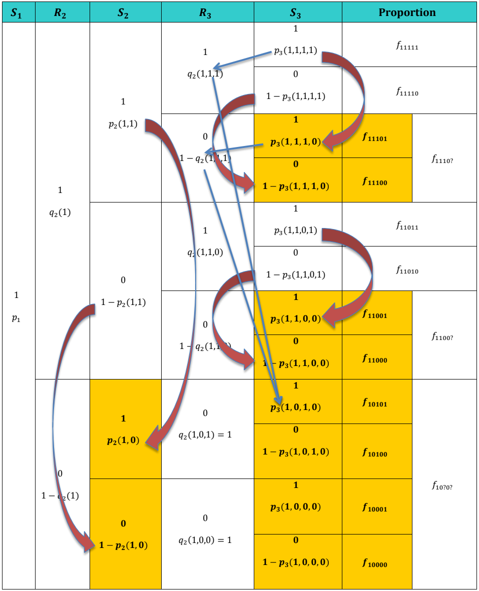
$$P[S_3 = 1 | R_3 = 0, R_2 = 1, S_2 = s_2, S_1 = s_1]$$
$$\propto P[S_3 = 1 | R_3 = 1, S_2 = s_2, S_1 = s_1] \exp(\alpha)$$

Missing at Random



S_1	R_2	S_2	R_3	S_3	Proportion	
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$	1 $q_2(1,1,1)$	1 $p_3(1,1,1,1)$	f_{11111}	
				0 $1-p_3(1,1,1,1)$	f_{11110}	
			0 $1-q_2(1,1,1)$	**1** $\mathbf{p_3(1,1,1,0)}$	$\mathbf{f_{11101}}$	$f_{1110?}$
				0 $\mathbf{1-p_3(1,1,1,0)}$	$\mathbf{f_{11100}}$	
		0 $1-p_2(1,1)$	1 $q_2(1,1,0)$	1 $p_3(1,1,0,1)$	f_{11011}	
				0 $1-p_3(1,1,0,1)$	f_{11010}	
			0 $1-q_2(1,1,0)$	**1** $\mathbf{p_3(1,1,0,0)}$	$\mathbf{f_{11001}}$	$f_{1100?}$
				0 $\mathbf{1-p_3(1,1,0,0)}$	$\mathbf{f_{11000}}$	
	0 $1-q_2(1)$	**1** $\mathbf{p_2(1,0)}$	0 $q_2(1,0,1)=1$	**1** $\mathbf{p_3(1,0,1,0)}$	$\mathbf{f_{10101}}$	$f_{10?0?}$
				0 $\mathbf{1-p_3(1,0,1,0)}$	$\mathbf{f_{10100}}$	
		0 $\mathbf{1-p_2(1,0)}$	0 $q_2(1,0,0)=1$	**1** $\mathbf{p_3(1,0,0,0)}$	$\mathbf{f_{10001}}$	
				0 $\mathbf{1-p_3(1,0,0,0)}$	$\mathbf{f_{10000}}$	

Missing Not at Random

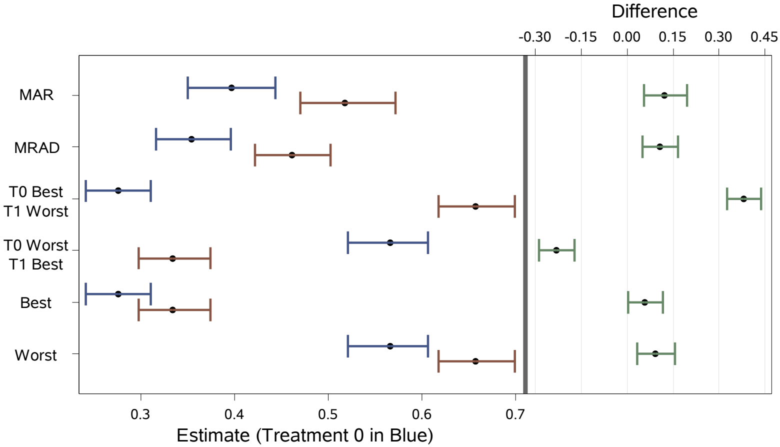


S_1	R_2	S_2	R_3	S_3	Proportion	
1 p_1	1 $q_2(1)$	1 $p_2(1,1)$	1 $q_2(1,1,1)$	1 $p_3(1,1,1,1)$	f_{11111}	
				0 $1-p_3(1,1,1,1)$	f_{11110}	
			0 $1-q_2(1,1,1)$	**1** $\mathbf{p_3(1,1,1,0)}$	$\mathbf{f_{11101}}$	$f_{1110?}$
				0 $\mathbf{1-p_3(1,1,1,0)}$	$\mathbf{f_{11100}}$	
		0 $1-p_2(1,1)$	1 $q_2(1,1,0)$	1 $p_3(1,1,0,1)$	f_{11011}	
				0 $1-p_3(1,1,0,1)$	f_{11010}	
			0 $1-q_2(1,1,0)$	**1** $\mathbf{p_3(1,1,0,0)}$	$\mathbf{f_{11001}}$	$f_{1100?}$
				0 $\mathbf{1-p_3(1,1,0,0)}$	$\mathbf{f_{11000}}$	
	0 $1-q_2(1)$	**1** $\mathbf{p_2(1,0)}$	0 $q_2(1,0,1)=1$	**1** $\mathbf{p_3(1,0,1,0)}$	$\mathbf{f_{10101}}$	$f_{10?0?}$
				0 $\mathbf{1-p_3(1,0,1,0)}$	$\mathbf{f_{10100}}$	
		0 $\mathbf{1-p_2(1,0)}$	0 $q_2(1,0,0)=1$	**1** $\mathbf{p_3(1,0,0,0)}$	$\mathbf{f_{10001}}$	
				0 $\mathbf{1-p_3(1,0,0,0)}$	$\mathbf{f_{10000}}$	

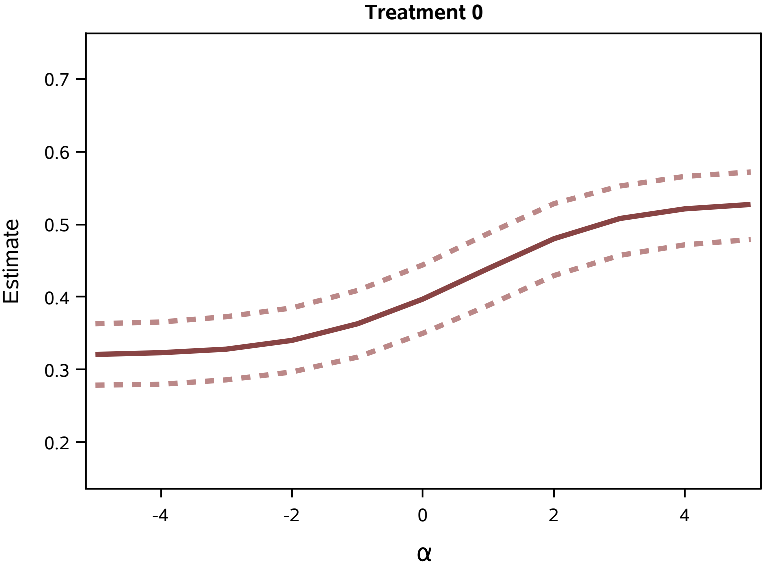
Case Study

- What are the treatment-specific probabilities of symptoms at V3?
- How do these probabilities compare?

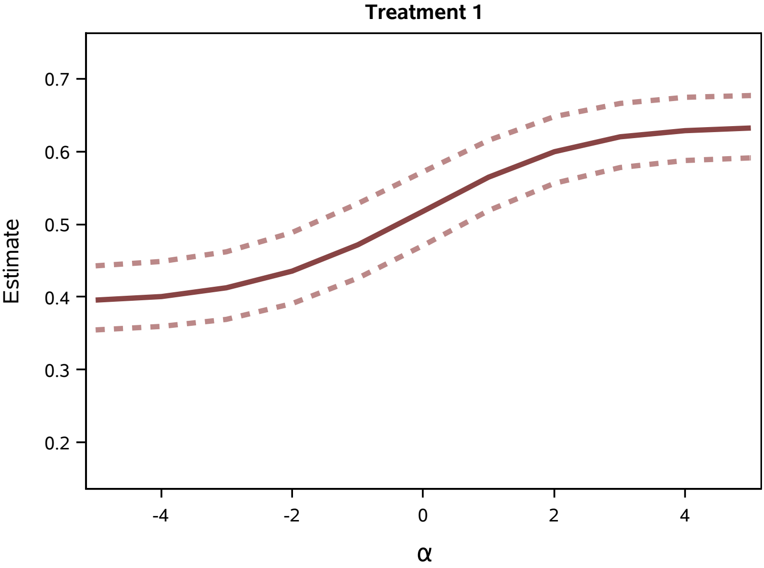
Analysis


Difference
-0.30
-0.15
0.00
0.15
0.30
0.45
MAR
MRAD
T0 Best
T1 Worst
T0 Worst
T1 Best
Best
Worst
0.3
0.4
0.5
0.6
0.7
Estimate (Treatment 0 in Blue)

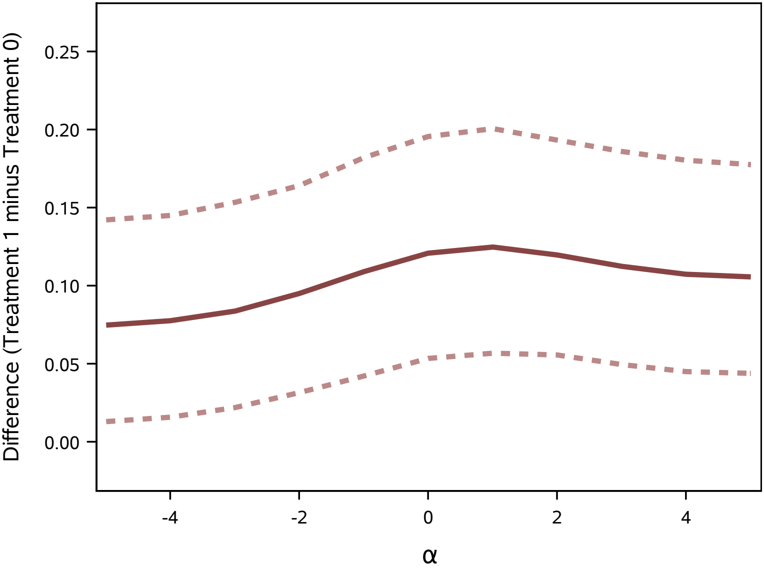
Analysis



Analysis

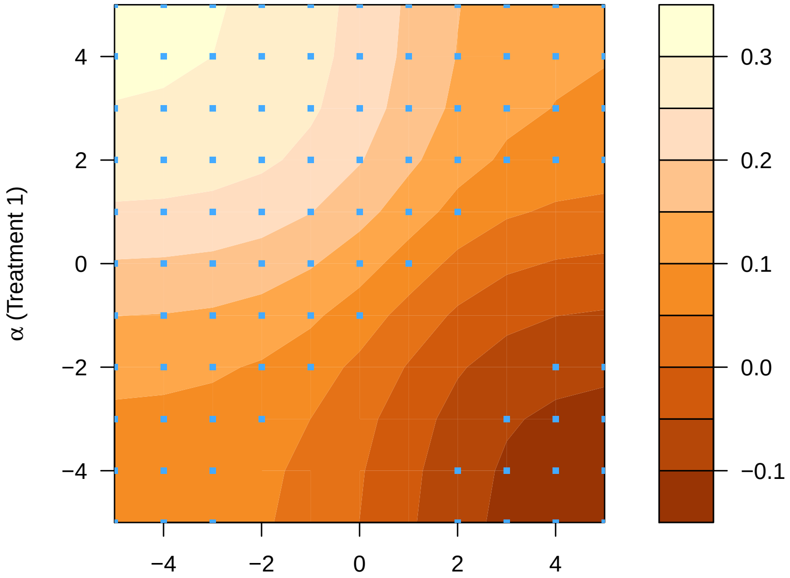


Analysis



Difference (Treatment 1 minus Treatment 0)
0.25
0.20
0.15
0.10
0.05
0.00
-4
-2
0
2
4
α

Analysis



Other Approaches

All require assumptions!!

- Multiple imputation
  - For each individual, draw from the predictive distribution of the missing outcomes given observed outcomes
  - Perform multiple times to generate a series of datasets with complete data
  - Analyze each complete dataset using standard methods
  - Combine results
- Likelihood-based
  - Mixed models
  - Pattern-mixture models
- Estimating equations
  - Inverse-weighted estimators
  - Doubly-robust estimators

Sensitivity Analysis

The set of possible assumptions about the missing data mechanism is very large and cannot be fully explored. There are different approaches to sensitivity analysis:

- Ad-hoc
- Local
- Global

Ad-hoc Sensitivity Analysis

- Analyzing data using a few different analytic methods and evaluate whether the resulting inferences are consistent.
- The problem with this approach is that the assumptions that underlie these methods are very strong and for many of these methods unreasonable.
- More importantly, just because the inferences are consistent does not mean that there are no other reasonable assumptions under which the inference about the treatment effect is different.

Local Sensitivity Analysis

- Specify a reasonable benchmark assumption (e.g., missing at random) and evaluate the robustness of the results within a small neighborhood of this assumption.
- What if there are assumptions outside the local neighborhood which are plausible?

Global Sensitivity Analysis

- Evaluate robustness of results across a much broader range of assumptions that include a reasonable benchmark assumption and a collection of additional assumptions that trend toward best and worst case assumptions.
- Emphasized in Chapter 5 of the NRC report.
- This approach is substantially more informative because it operates like "stress testing" in reliability engineering, where a product is systematically subjected to increasingly exaggerated forces/conditions in order to determine its breaking point.

Global Sensitivity Analysis

- In the missing data setting, global sensitivity analysis allows one to see how far one needs to deviate from the benchmark assumption in order for inferences to change.
- "Tipping point" analysis
- 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.

PCORI Standards

- Properly account for statistical uncertainty
- Single imputation (e.g., last observation carried forward) should not be the primary analytic approach
- Examine sensitivity to assumptions

Properly account for statistical uncertainty

- Statistical inference of intervention effects or measures of association should account for statistical uncertainty attributable to missing data.
- This means that methods used for imputing missing data should have valid type I error rates and that confidence intervals have the nominal coverage properties.
- This standard applies to all study designs for any type of research question.

Single imputation should not be the primary analytic approach

- Single imputation methods like last observation carried forward and baseline observation carried forward generally should not be used as the primary approach for handling missing data in the analysis.
- This standard applies to all study designs for any type of research question.

Examine sensitivity to assumptions

- Examining sensitivity to the assumptions about the missing data mechanism (i.e., sensitivity analysis) should be a mandatory component of the study protocol, analysis, and reporting.
- This standard applies to all study designs for any type of research question.