
**Placebo Multiple Imputation
and
Other Sensitivity Analyses
for
Incomplete Longitudinal Clinical Trial Data**

Craig Mallinckrodt (cmallinc@lilly.com)
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Outline

- Background
- Estimands
- Pattern Mixture Model framework
 - Placebo multiple imputation
- Example

Starting Point

- **Definition and meaning of missing value / data is situation dependent** *Drug Information Journal*. 2009; 43(4): 403-408.
 - **Loss to follow up in depression trial = missing information**
 - **Death from heart attack in a trial to prevent heart attack = incomplete data but no loss of info**
- **Focus here is on MDD, but also applies generally to acute, symptomatic treatments in longitudinal clinical trials**
 - **Pain, psychiatry and neurology, diabetes...**

Missing Data Mechanisms

- **Defined conditional on dependent variable and / or independent variables in the model**
 - **Characteristic of the data AND the model**
 - **Can vary from 1 outcome to another in same dataset**
- **With treatment in the model, differential drop-out by treatment indicates covariate dependence, not mechanism**

Two Ways to Think about MNAR

- **The selection model framework**
 - **If the missing data can be predicted from the observed, missingness is MAR; if not, then missingness is MNAR**
- **The pattern mixture model framework**
 - **If the statistical behavior of the missing data = the behavior of the observed, missingness is MAR, if not, then missingness is MNAR**

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Hypotheses

- ***De-jure* hypothesis**
 - **Efficacy:** **Benefit when taken as directed**
 - **Safety:** **Effect when taken as directed**
- ***De-facto* hypothesis**
 - **Effectiveness:** **Benefit as actually taken**
 - **Safety:** **Effect as actually taken**

Considerations

- **Efficacy – safety/tolerability = Effectiveness**
- **Many combinations of efficacy and safety/tolerability lead to = effectiveness**
- **Need to understand the components to understand the composite**
- **Understanding both efficacy and effectiveness is important**

Five Estimands Noted in **N**ational **R**esearch **C**ouncil Report

- 1) Change in all randomized patients
- 2) Change in patients who tolerate / adhere
- 3) Change if taken as directed
- 4) Change during adherence
- 5) AUC during adherence

• *National Research Council (2010).*

- 6) Change as actually taken

Change In All Randomized Patients

- **Primary analysis is change to planned endpoint**
- **ITT population**
- **Patients allowed to switch/add rescue meds**
- **Data after start of rescue meds / included in the primary analysis**

Rescue Meds and Follow Up Data

- **Rescue meds likely reduce dropout and are often needed ethically**
- **Follow up data with rescue meds in an ITT analysis can mask or exaggerate effect of originally assigned med**
- **Therefore inference is on treatment policy**
- **Early research and initial regulatory reviews typically focus on causal effects of the investigational drug, not on policies for how to use the drug**

Change If Taken As Directed

- **Primary analysis is change to planned endpoint**
- **Inference on all patients - efficacy**
- **Clear assessment of causal effects on safety and efficacy**
- **Estimand is what would be expected if patients stayed on drug, counter to the fact that there will always be some patients who do not adhere**

A 6th Estimand

- **Primary analysis is change to planned endpoint**
- **All Patients**
- **Change as actually taken (effectiveness)**
- **Data after DC of randomized med / start of rescue med collected for secondary analyses**
- **For primary, data after DC of randomized med / start of rescue med imputed based on assumption of no benefit**
- **Inference is on randomized med, not a treatment policy as in the 1st estimand**

Imputing Effectiveness Data

- **BOCF commonly used but often criticized**
- **Single imputation**
- **Improvement scenarios**
 - **No maintained benefit of drug after drop out**
 - **No study effect & no placebo effect**
 - **Most patients improve**
- **Impairment scenarios**
 - **No loss of function after baseline**

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New Methods in the PMM Framework

- PMM framework appealing in that assumptions are transparent and can be debated openly
- “The statistical behavior of drug treated patients after dropout immediately becomes that of placebo patients”
 - This is “placebo multiple imputation”
 - Example: drug for depression / pain with short on target half-life
 - Apply to all or only DC to AE

Placebo MI

- **Effectiveness context**
 - **Assumes no maintained benefit**
 - **Accounts for study effect & placebo effect**
 - **Valid if patients improve or worsen**
 - **Free of confounds in follow up data**
- **Efficacy context**
 - **Worst reasonable case MNAR**
- **Standard software, standard tests**

Placebo MI

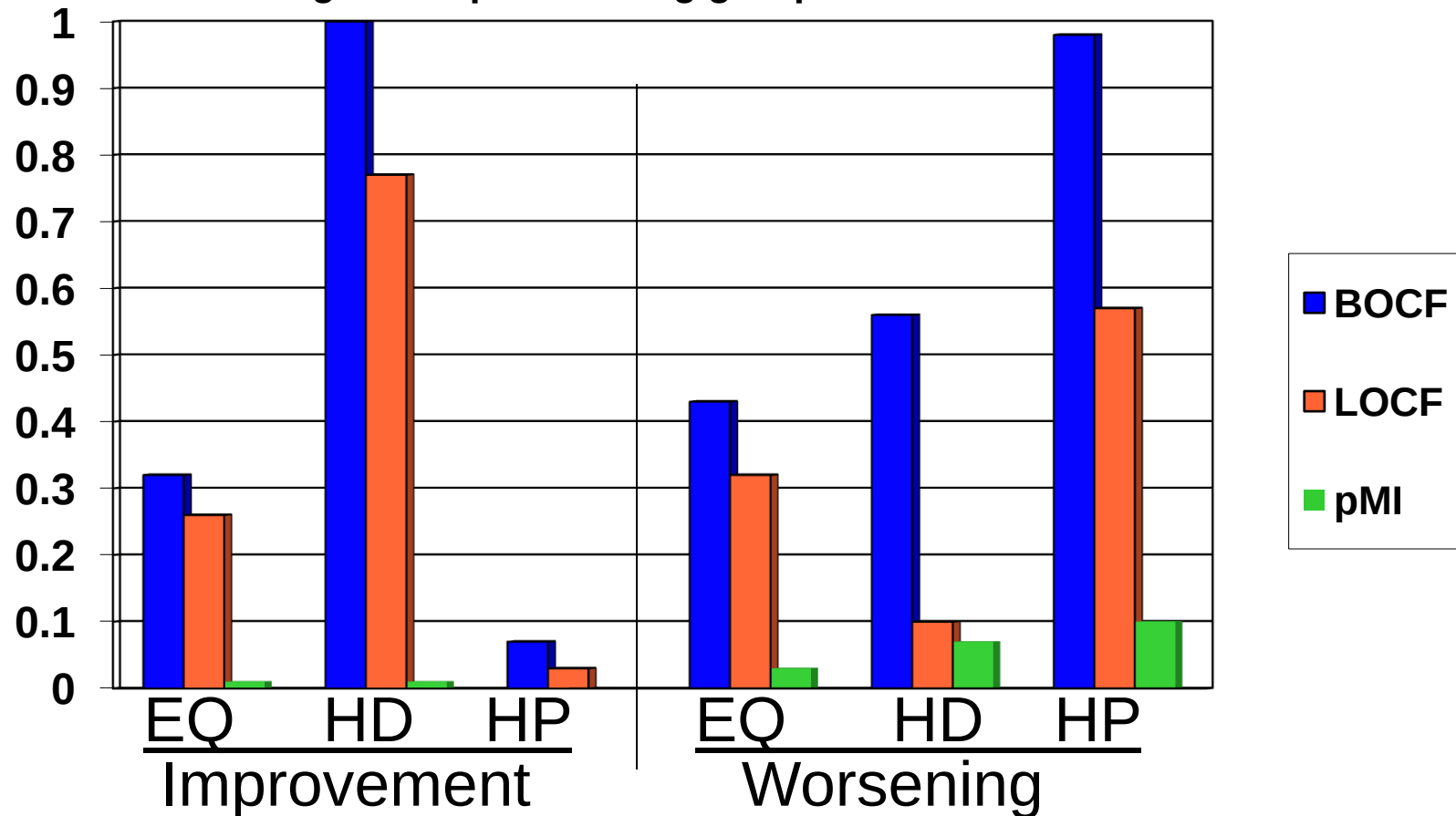
- **Similar to “Standard” MI, except**
 - **Parameters for imputation model obtained from only the placebo (control) group**
 - **Missing data for both placebo and drug group are imputed based on the imputation model derived from placebo data**
 - **After dropout, drug treated patients have values like placebo patients – that is, no benefit from the drug**

Simulation Study

- Compared LOCF, BOCF, pMI
- Simulations in a 2 x 3 x 3 factorial
 - Placebo patients improve or worsen
 - 3 dropout patterns
 - 30/30, 40/20, 20/40
 - 3 levels of effectiveness
 - Mixture distribution
 - Completers $\Delta = 0.5, 0.3$ or 0.0
 - Dropouts $\Delta = 0.0, 0.0$ or 0.0

Relative Bias In Effectiveness Estimates By Time Trend & Dropout Pattern (Drug Is Effective)

EQ is equal dropout in drug and placebo groups
HP = Higher dropout in placebo group
HD = Higher dropout in drug group

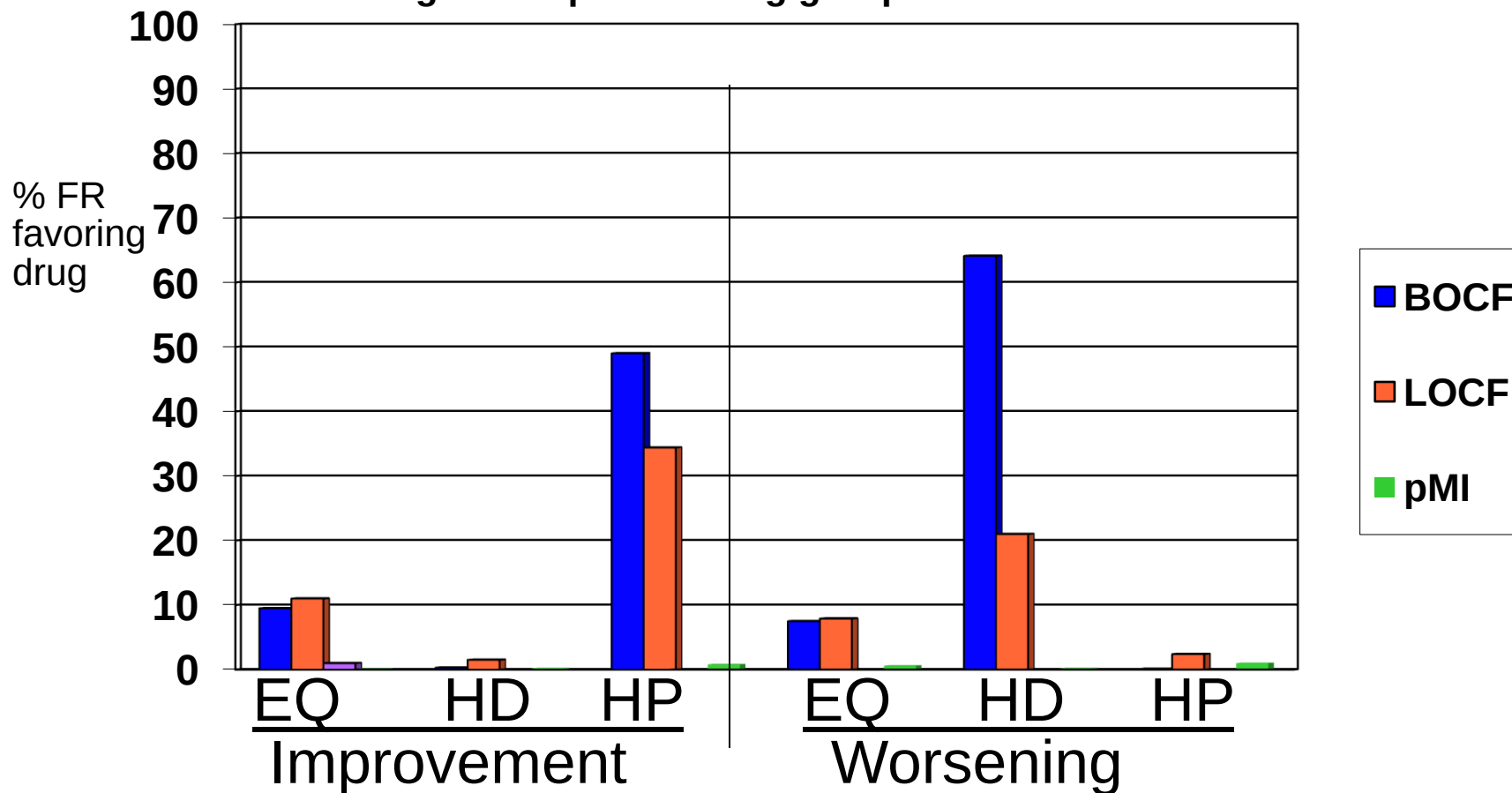


Probability of False Positive Effectiveness Results By Time Trend & Dropout Pattern

EQ is equal dropout in drug and placebo groups

HP = Higher dropout in placebo group

HD = Higher dropout in drug group



New Methods in the PMM Framework

- **“The statistical behavior...**
 - **Gradually transitions to placebo**
 - **Long on-target half-life (antibody)**
 - **Immediately jumps to placebo trajectory**
 - **Drug slope = placebo slope after DC**
 - **Disease modifying Alzheimers drug**
- **Placebo jumps / transitions to SoC**

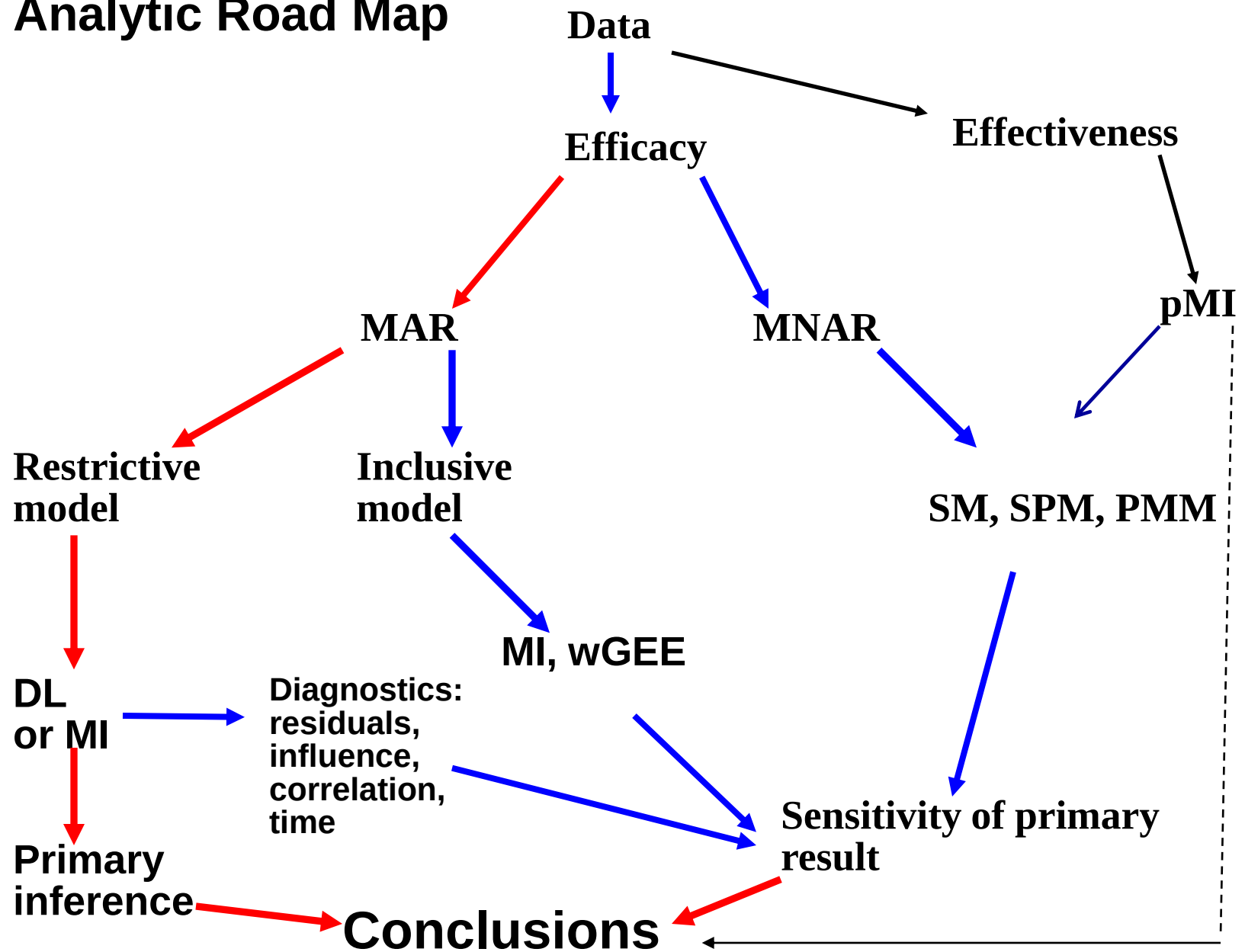
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Example From A Depression Trial

- **Pivotal phase III trial.** *J Psychiatr Res* . 2002; 36: 383-390.
- **259 patients, randomized 1:1 ratio to drug and placebo**
- **Response: Change from baseline in HAMD₁₇**
- **6 post-baseline visits (Weeks 1,2,3,5,7,9)**

Analytic Road Map



Example From A Depression Trial

- **Primary objective: test the difference between drug and placebo in mean change to planned endpoint**
 - *de-jure* (efficacy) hypothesis
 - change when taken as directed
- **Secondary objective:**
 - *de-facto* (effectiveness) hypothesis
 - change as actually taken

Patient Disposition

	Drug	Placebo
Protocol complete	60.9%	64.7%
Adverse event	12.5%	4.3%
Lack of efficacy	5.5%	13.7%

Primary Analysis: Direct Likelihood

```
proc mixed;  
  class subject treatment time site;  
  model Y = baseline treatment time site  
          baseline*time treatment*time ;  
  repeated time / sub = subject type = un;  
  lsmeans treatment*time / cl diff;  
run;
```

Random effects modeled as part of within subject errors.

Full multivariate model: unstructured modeling of time and correlation. More parsimonious approaches possible

Treatment contrast 2.16, $p = .025$

Visitwise Means from Direct Likelihood

Improvement
↓

HAM-D₁₇ Total Score

20

16

12

8

0

1

2

3

4

5

6

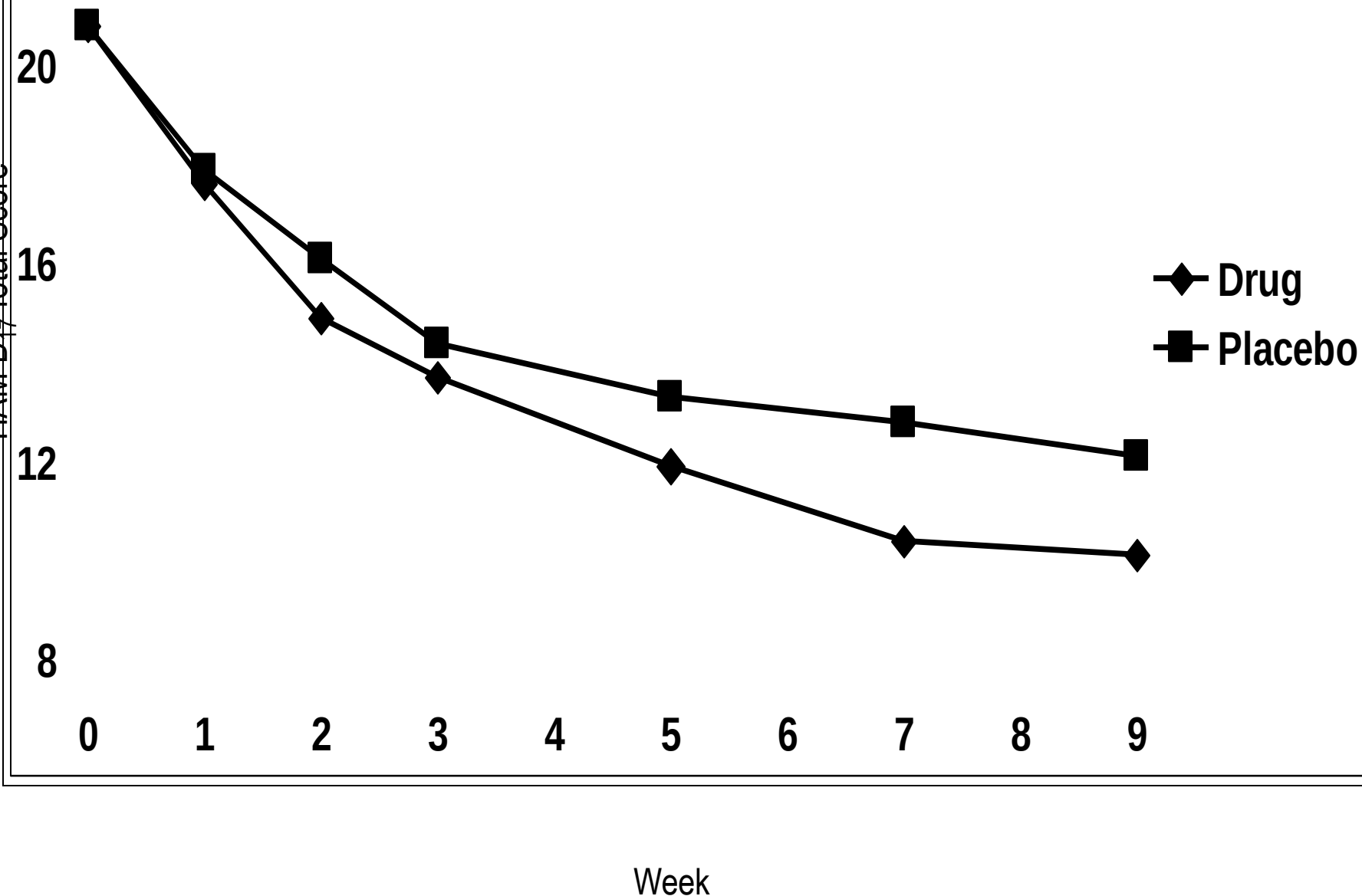
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8

9

◆ Drug
■ Placebo

Week



Selection Model Results

	<u>Estimate</u>	<u>PSI3</u>
MAR (psi3=0)	-2.16	
MNAR	-2.15	-0.22

Tipping point approach. Vary psi3 over wide range and look for change in endpoint contrast

MNAR (psi3)=-0.35	-2.14
MNAR (psi3)=0.10	-2.16

Pattern Mixture Model Results

ID Restriction	Mechanism	Estimate
NFD_CCMV	MNAR	-1.99
NFD_NCMV	MNAR	-2.96

Shared Parameter Model Results

Model	Contrast
Naïve model (MAR)	-2.29
Int + slope linkage	-2.17
Int + slope by trt linkage	-1.91

pMI Results

- **pMI**
 - **Included age, gender, and baseline severity in model in addition to previous changes in HAMD**
 - **Imputed data for all dropouts, not just DC to AE**
 - **Endpoint treatment contrast = -1.54**

Summary of Results

Method	MAR	MNAR	
		Low	High
MI_Inclusive	-2.18		
wGEE_Inclusive	-2.30		
Selection Model	-2.18	-2.14	-2.16
PMM		-1.99	-2.96
SPM	-2.29	-1.91	-2.17
pMI		-1.54	

Discussion

- **Consequences of missing data are situation dependant**
- **In the example data focusing on combination of efficacy (1st) and effectiveness (2nd) was useful**
 - **Objectives could have been switched**
- **Sensitivity analyses for specific assumptions of the primary analysis increased confidence**

Discussion

- **pMI in the example, and more generally the jump and copy to reference procedures, appear to be a useful part of sensitivity analyses**
- **May be considered for primary analyses**
- **More experience would be useful**