Estimands and Their Estimators – How to Align Them in a Coherent Way?

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Missing Data

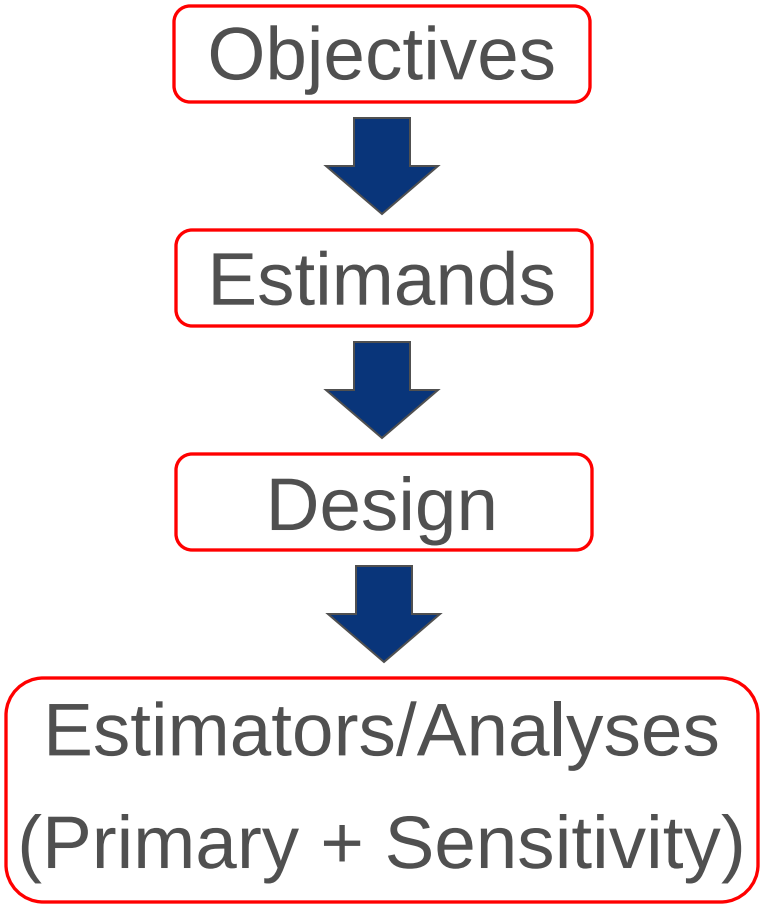
His wif_ is not working today.

Estimands and Estimators?

Outline

- ICH E9(R1) Trial Planning Framework
- Case Study:
  - Intercurrent events
  - Estimands
  - Estimators
  - Simulation investigation
- Summary

ICH E9(R1) - Trial Planning Framework



Estimand

Defined by the following components:

- Population
- Variable
- Intercurrent events and their corresponding strategies
- Summary measure

*Not all intercurrent events need to use the same strategy

ICH E9(R1) Identified Strategies of Addressing Intercurrent Events

- Treatment Policy
- Composite
- Hypothetical
- Principal Stratum
- While on treatment / Prior to the Intercurrent Event

Case Study: Alzheimer Long-Term Prevention Trial

- Objective:

To determine superiority of drug vs placebo in slowing cognitive decline in asymptomatic subjects at risk for developing Alzheimer's dementia.

Potential Intercurrent Events

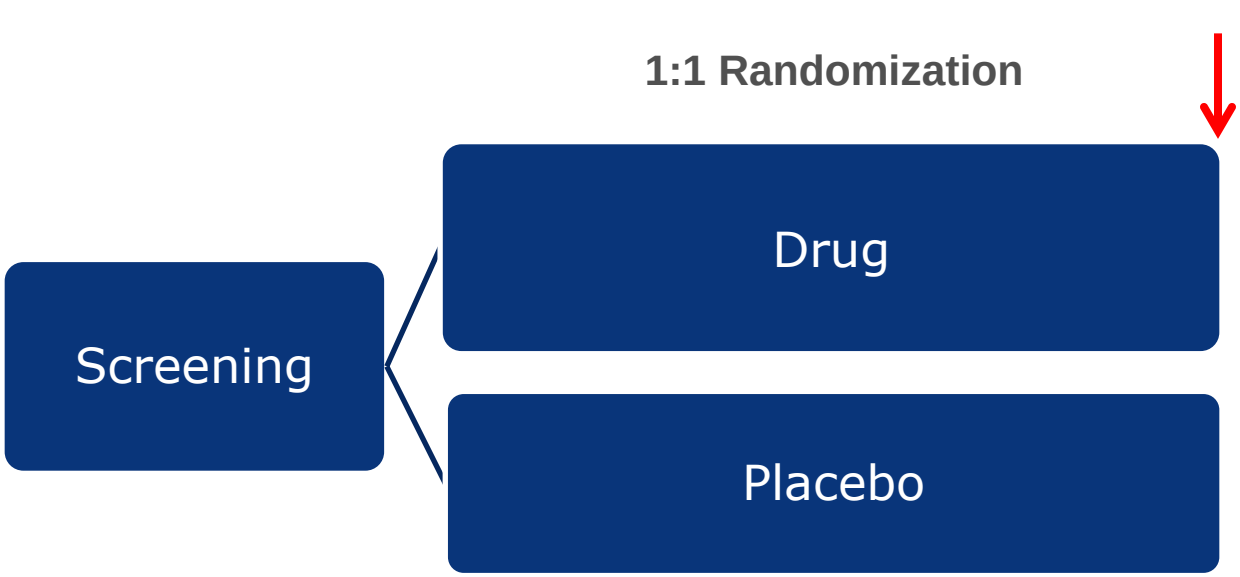
Considered in this example:

- Treatment discontinuation (Trt DC)
- Study discontinuation (Study DC)
- Missed visits and/or cognitive data collection leading to intermediate missing in efficacy measurements (Inter Missing)
- Initiation of Alzheimer disease therapy (Initiation of ADT)

Other potential intercurrent events (not covered):

- Treatment adherence
- Death

Study Design



4.5 years (54 months)
Double Blind (DB) Phase

Primary efficacy measure:
cognitive scale collected over time in the DB phase

Estimand 1: Treatment and Study DC

Population: as defined by the inclusion-exclusion criteria of the study

Variable: change from baseline to Month 54 in the cognitive measure

Intercurrent events and corresponding strategies:

Estimand	Trt DC	Study DC
1	Treatment Policy	Hypothetical*

*Need to specify the hypothetical scenario

Summary measure: mean treatment difference

Treatment Policy Strategy for Trt DC

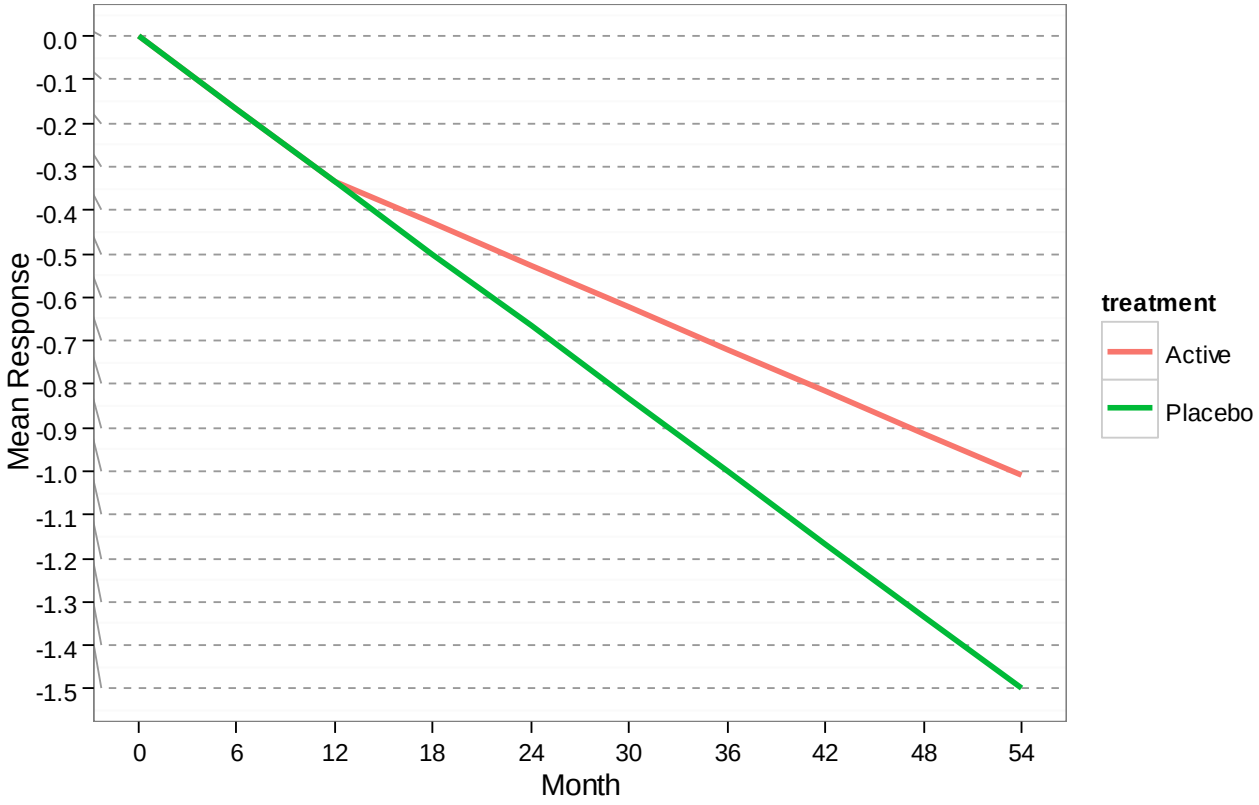
- The variable observed value is of interest regardless of whether the subject has discontinued treatment
  - In general, regardless of whether the intercurrent event has occurred
- Captures the effect attributable to assignment to the treatment group
- Important for many types of studies
- Appropriate estimators?

Hypothetical Scenarios for Study DC

What would have happened if subjects who discontinued the study had instead, after discontinuation:

- H-MAR: similar efficacy as the subjects who did not discontinue the study
  - Treatment completers
  - Subjects who discontinued the treatment but NOT the study
- H-Control: efficacy as determined by the control group
  - E.g. Similar efficacy relative to control as at the time of dropout – disease modifying setting
- H-RD: similar efficacy as the subjects who discontinued the treatment but NOT the study (retrieved dropout subjects)

Mean On-Treatment Change from Baseline



Simulation Scenarios for Treatment Discontinuation

Averaged Distribution of Treatment Discontinuations for the Evaluated Cases					
Case	**Group**	**Mean Total %TrtDC**	**Mean %TrtDC AE**	**Mean %TrtDC Other**	**Mean %TrtDC LOE**
c1a	drug	30.1	15.0	10.0	5.1
	placebo	31.3	15.0	10.0	6.3
c1b	drug	36.1	21.0	10.0	5.1
	placebo	31.3	15.0	10.0	6.3
c1c	drug	42.1	27.0	10.0	5.1
	placebo	31.3	15.0	10.0	6.3

TrtDC = Treatment Discontinuation
AE = Adverse event
Other = Other reasons of TrtDC
LOE = Lack of Efficacy

Study DC and %Retrieved Dropout

- Study DC
  - Could occur at or after Trt DC
  - Leads to missing values for the variable
- % Retrieved Dropout = %subjects, out of all subjects who DC the treatment, who have a retrieved end of study value

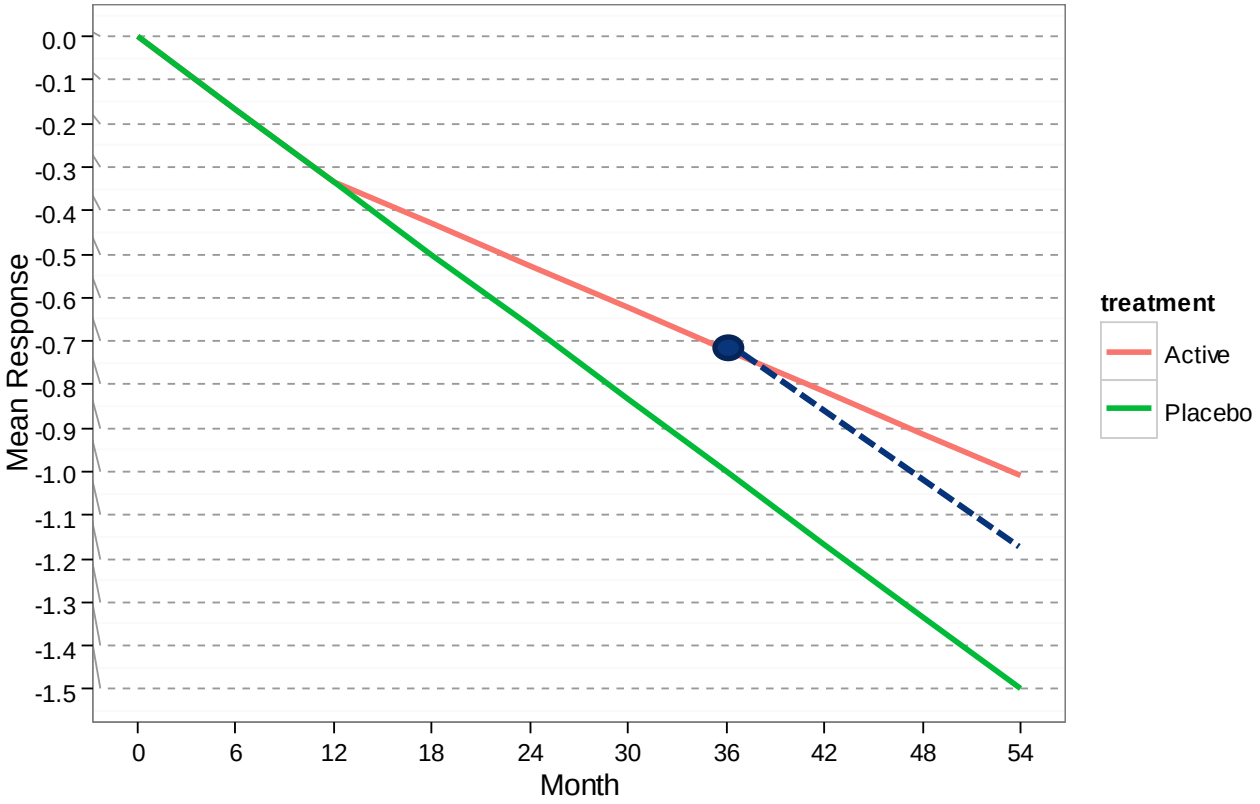
Simulation Scenarios for Study Discontinuation

Mean %Missing at Year 4.5

Case	Group	Mean Total %TrtDC	0%SDC (100% Retrieved)	20%SDC (80% Retrieved)	50%SDC (50% Retrieved)	80%SDC (20% Retrieved)
c1a	drug	30.1	0	6.0	15.1	24.1
	placebo	31.3	0	6.3	15.7	25.0
c1b	drug	36.1	0	7.2	18.1	28.9
	placebo	31.3	0	6.3	15.7	25.0
c1c	drug	42.1	0	8.4	21.1	33.7
	placebo	31.3	0	6.3	15.7	25.0

TrtDC = Treatment Discontinuation
SDC = Study Discontinuation
X% SDC = X% of the subjects who discontinue treatment, who also discontinue the study at some time point

Treatment Retrieved Dropouts: Off-Treatment Response – Scenario 1



Scenario 1: Retain mean treatment difference at treatment discontinuation but continue with placebo slope

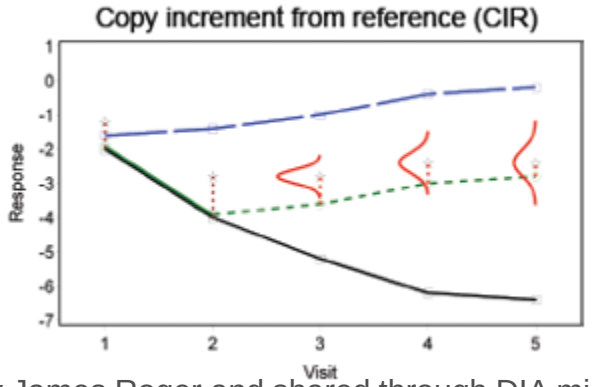
Estimators to be Evaluated

H-MAR:

- MMRM – mixed effect model for repeated measures
- MAR_DC – Standard Multiple Imputation (MI) Regression
  - With indicator of treatment discontinuation in the imputation model

H-Control:

- CIR – Copy Increment from Reference MI



MISTEP SAS macro developed by James Roger and shared through DIA missing data working group site at http://www.missingdata.org.uk; Figure from O'Kelly & Davis short course at the 2015 ASA Biopharmaceutical Workshop

Estimators to be Evaluated (Continued)

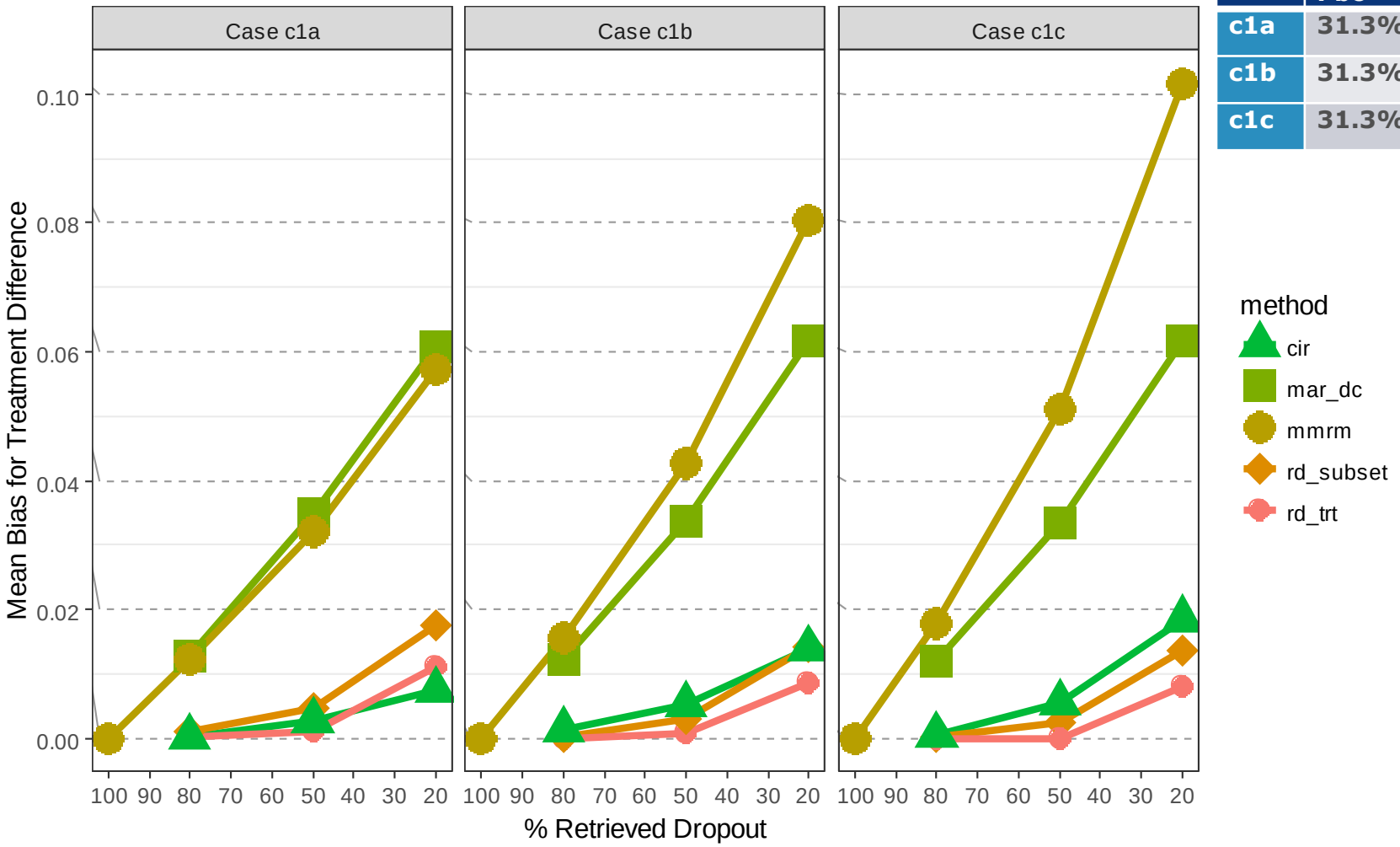
H-RD:

- RD_SUBSET – Standard Multiple Imputation (MI) Regression on the subset of subjects who did not complete treatment
  - PROC MI, MONOTONE REGRESSION
  - Treatment indicator in the imputation model

- RD_TRT – Stepwise MI with different sets of parameters for each pattern: on and off treatment
  - MISTEP SAS macro developed by James Roger and shared through DIA missing data working group site at http://www.missingdata.org.uk

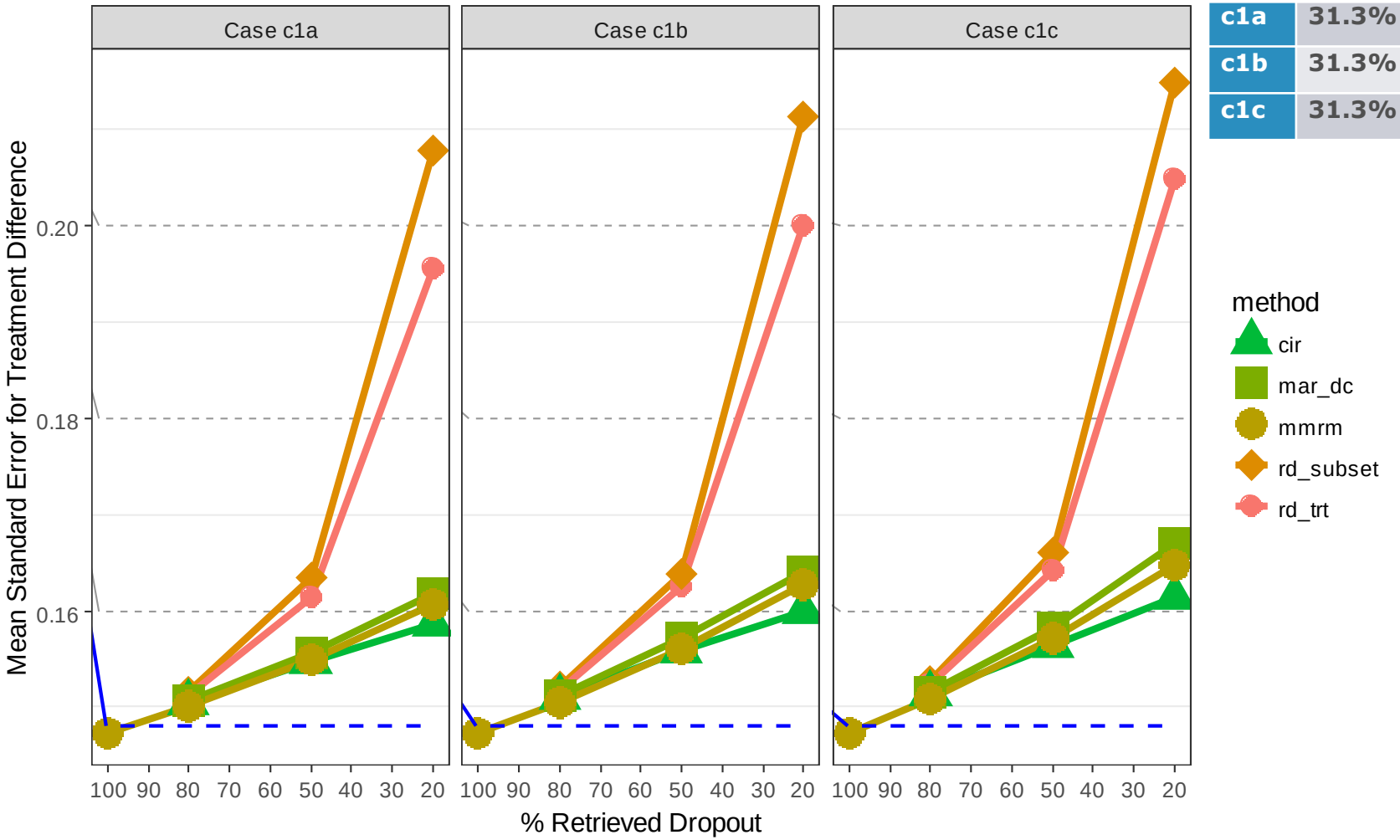
Estimated Mean Bias for Mean Treatment Difference: Scenario 1

Case	%TrtDC Pbo	%TrtDC Drug
c1a	31.3%	30.1%
c1b	31.3%	36.1%
c1c	31.3%	42.1%



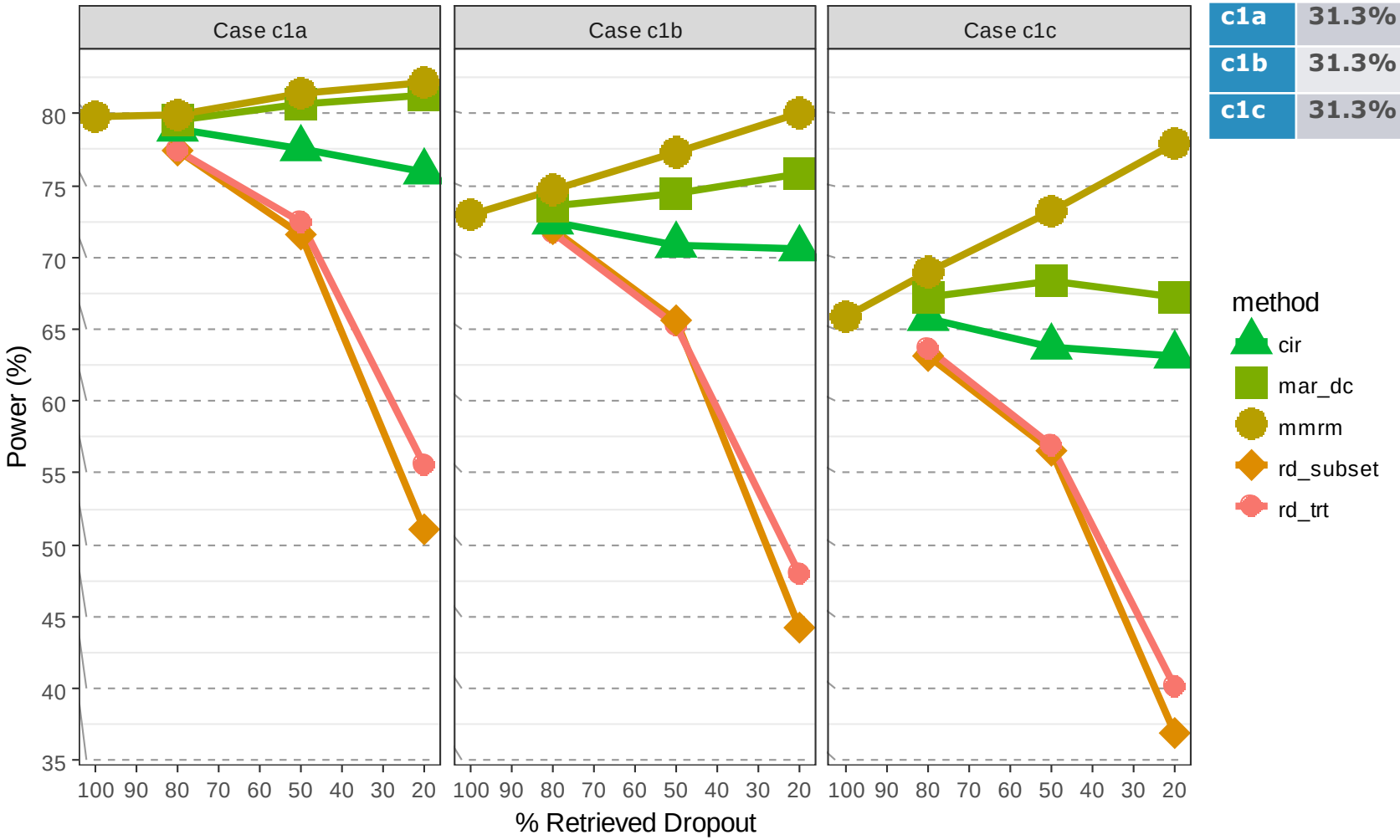
Estimated Mean Standard Error for Mean Treatment Difference: Scenario 1

Case	%TrtDC Pbo	%TrtDC Drug
c1a	31.3%	30.1%
c1b	31.3%	36.1%
c1c	31.3%	42.1%

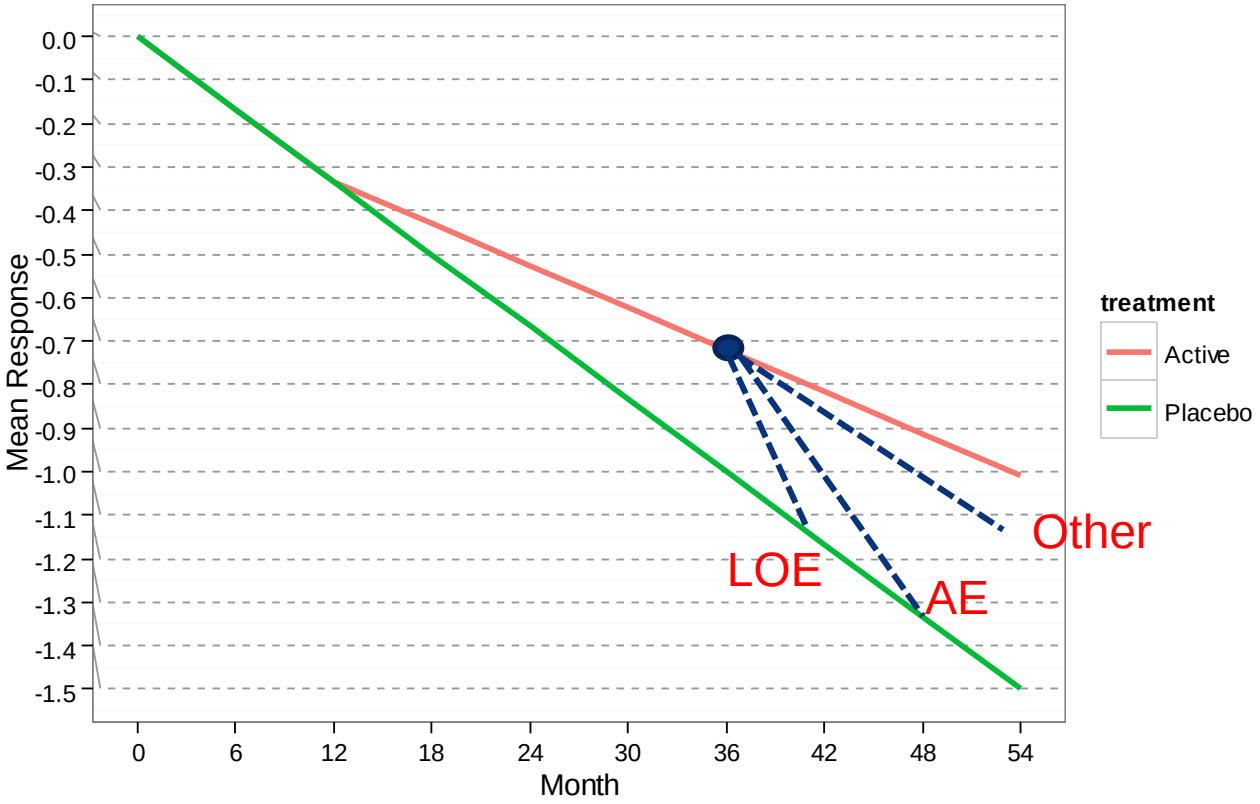


Estimated Power Scenario 1

Case	%TrtDC Pbo	%TrtDC Drug
c1a	31.3%	30.1%
c1b	31.3%	36.1%
c1c	31.3%	42.1%



Treatment Retrieved Dropouts: Off-Treatment Response – Scenario 2



Scenario 2: Different post-treatment response by reason of treatment discontinuation

Estimators to be Evaluated

H-MAR:

- MMRM
- MAR_DC

H-Control (by Reason):

- BY_REASON – MI by reason of discontinuation: CR for AE, J2R for LOE, CIR for Other*

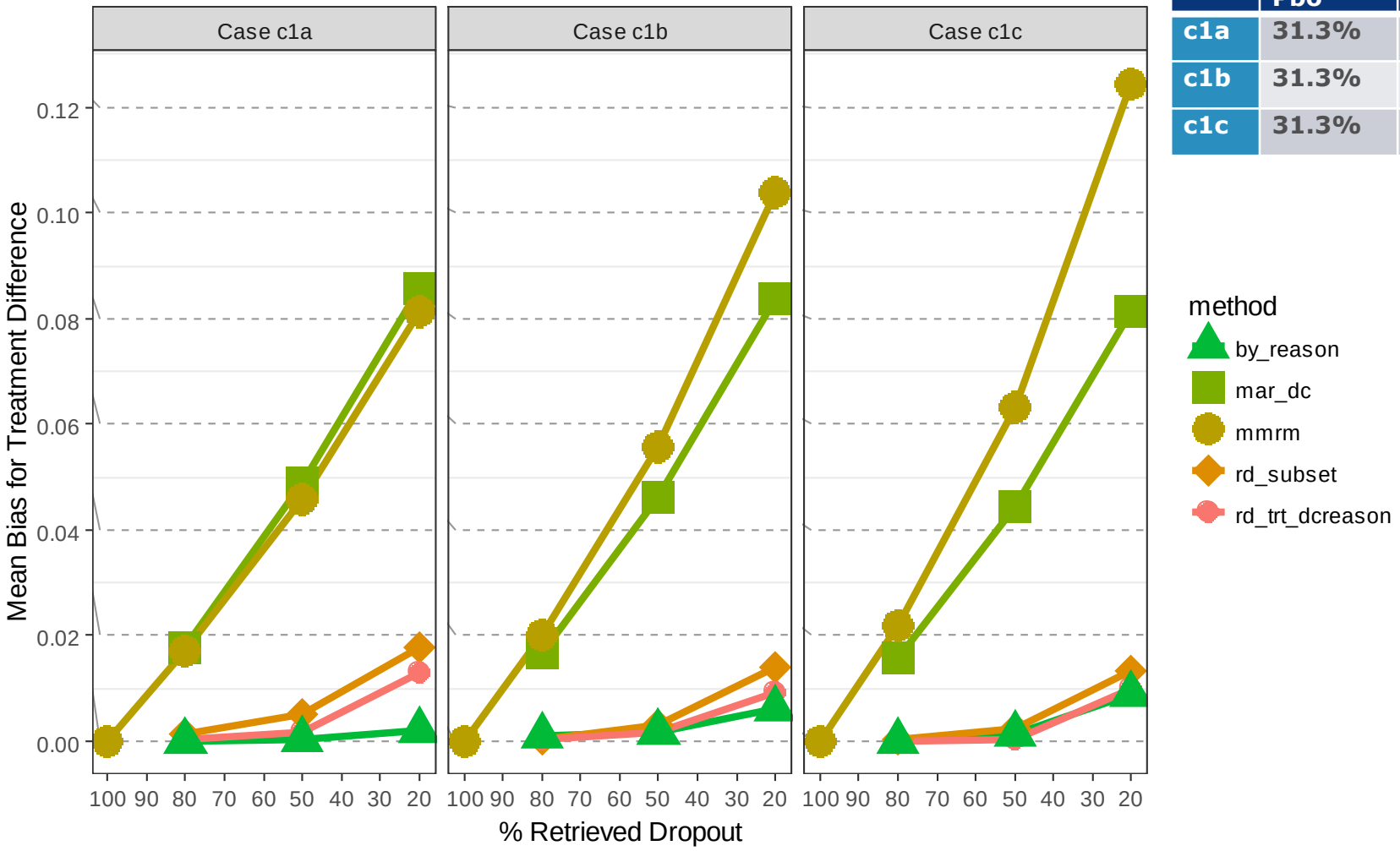
H-RD:

- RD_SUBSET
- RD_TRT_DCREASON: Stepwise MI with different sets of parameters for each pattern: On-treatment, discontinued treatment due to AE, LOE, or Other
  - MISTEP SAS macro developed by James Roger

*CR = Copy Reference; J2R = Jump to Reference; CIR = Copy Increment from Reference

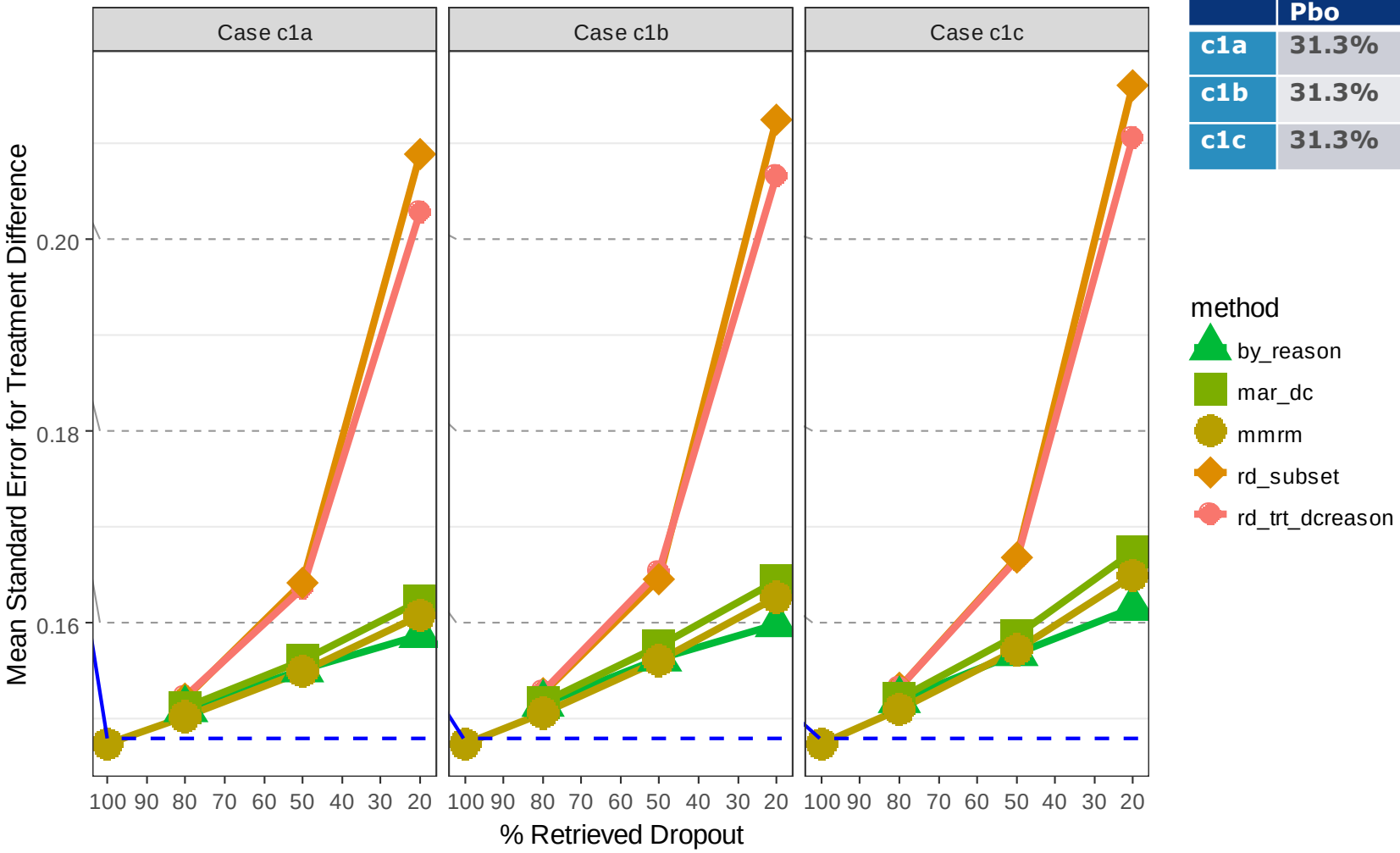
Estimated Mean Bias for Mean Treatment Difference: Scenario 2

Case	%TrtDC Pbo	%TrtDC Drug
c1a	31.3%	30.1%
c1b	31.3%	36.1%
c1c	31.3%	42.1%



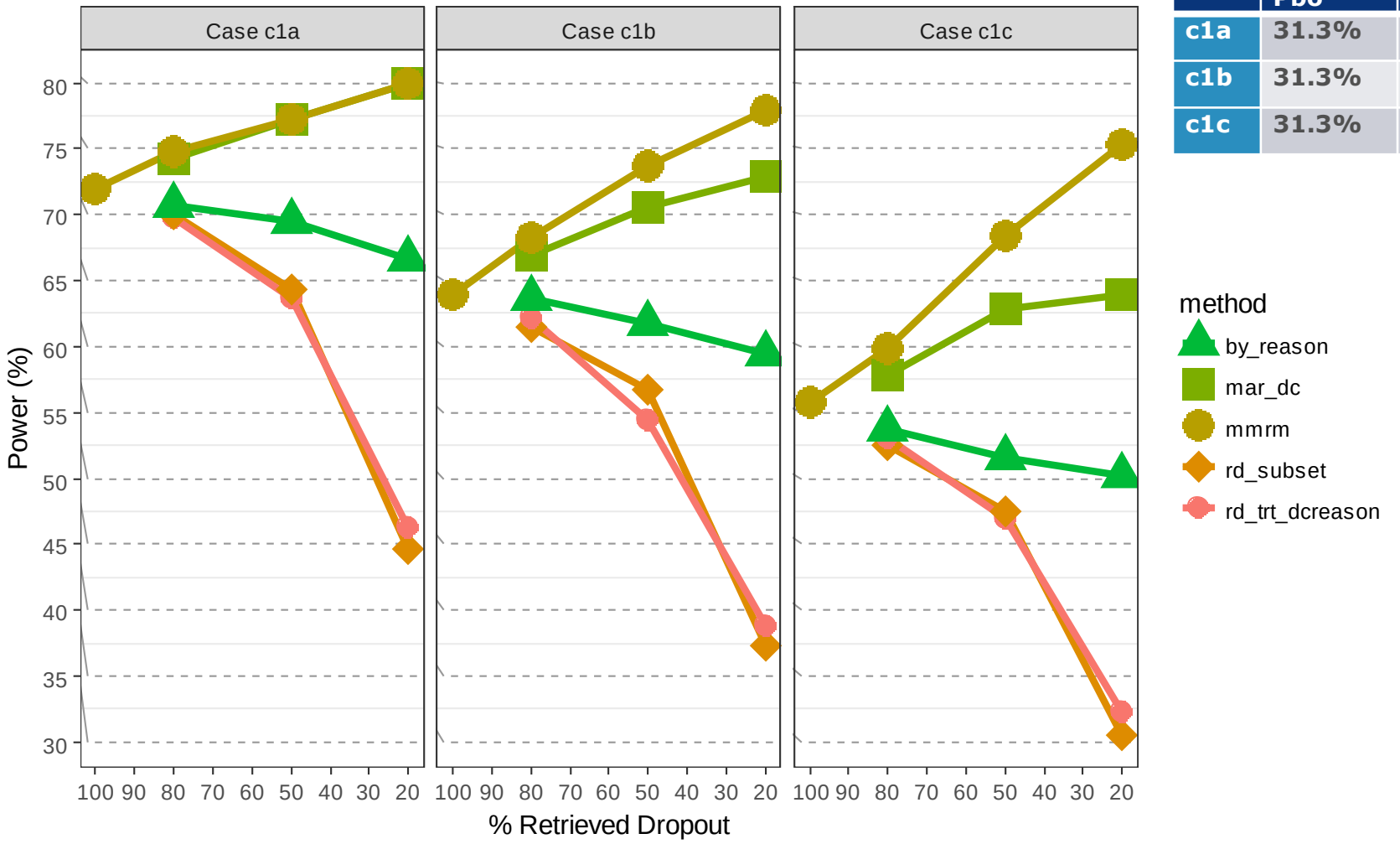
Estimated Mean Standard Error for Mean Treatment Difference: Scenario 2

Case	%TrtDC Pbo	%TrtDC Drug
c1a	31.3%	30.1%
c1b	31.3%	36.1%
c1c	31.3%	42.1%



Estimated Power
Scenario 2

Case	%TrtDC Pbo	%TrtDC Drug
c1a	31.3%	30.1%
c1b	31.3%	36.1%
c1c	31.3%	42.1%



Simulation Investigation Findings

- On and off mean treatment trajectories are expected to be different:
  - MAR models lead to bias
  - Bias could be improved if MMRM replaced by MI that accounts for treatment discontinuation in the imputation model
- Control-based MI or other type of MI could work very well if off-treatment mean trajectory is understood
- Retrieved dropout (RD) MI analyses:
  - Improvement in bias as compared to MAR models but increase in SE for lower %RD
  - When low %RD, the “right” RD model could improve both bias and the variability

Keep subjects in the study!

Estimands – Treatment Policy for Trt DC

Estimand	Trt DC	Study DC	Inter Missing	Main Estimator
1	Treatment Policy	Hypothetical: H-Control	Hypothetical: H-MAR Other Option?	-MAR MI for intermediate missing -control-based MI

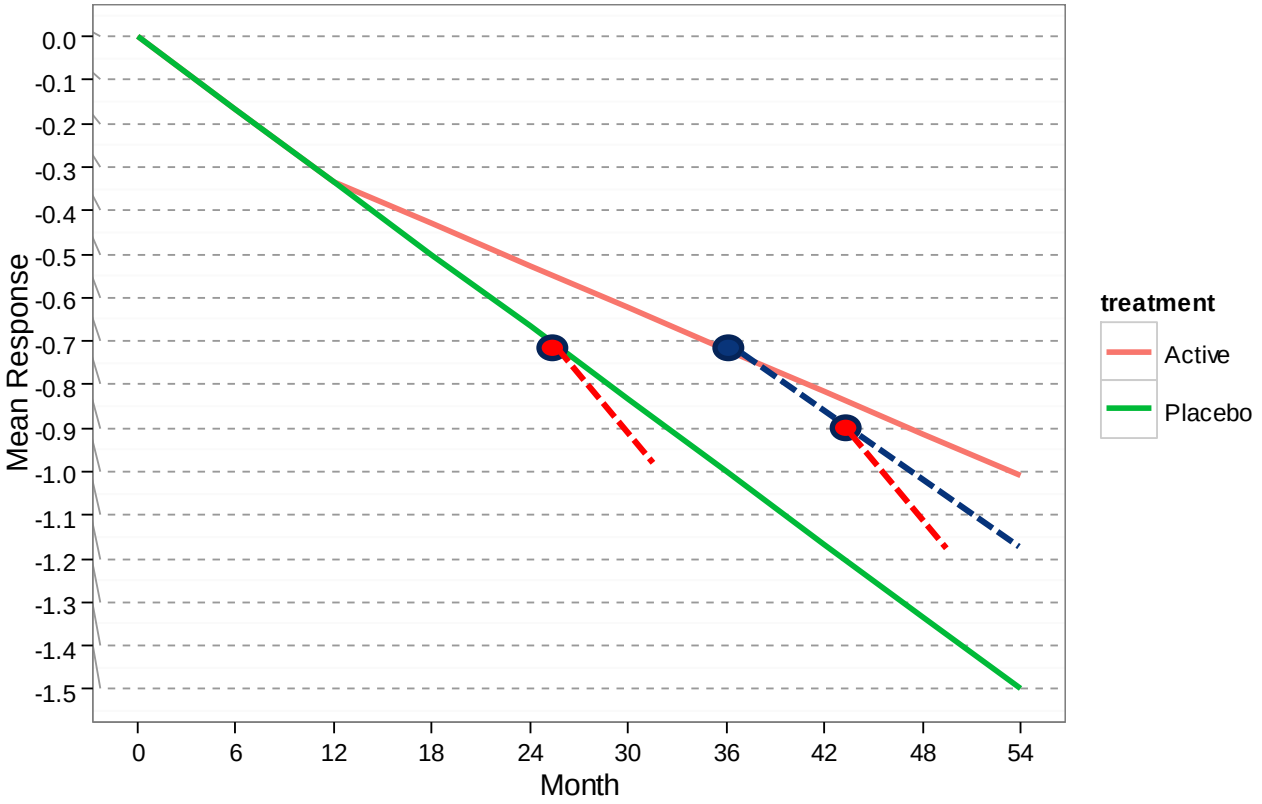
Estimands – Treatment Policy for Trt DC (Cont. 1)

Estimand	Trt DC	Study DC	Inter Missing	Main Estimator
1	Treatment Policy	Hypothetical: H-Control	Hypothetical: H-MAR Other Option?	-MAR MI for intermediate missing -Control-based MI
2		Hypothetical: H-RD		-MAR MI for intermediate missing -MI based on retrieved dropouts (RD_SUBSET, RD_TRT)

Estimands – Treatment Policy for Trt DC (Cont. 2)

Estimand	Trt DC	Study DC	Inter Missing	Initiation of AD therapy (ADT)	Main Estimator
2	Trt Policy	Hypothetical H-RD	Hypothetical H-MAR	NA	-MAR MI for intermediate missing -MI based on retrieved dropouts (RD_TRT)
3				Treatment Policy	-MAR MI for intermediate missing -MI based on retrieved dropouts, with patterns of *On trt *Off trt+no ADT *Off trt + ADT (expanded RD_TRT model)

Hypothetical Example: Initiation of AD Therapy



Estimands – Treatment Policy for Trt DC (Cont. 3)

Estimand	Trt DC	Study DC	Inter Missing	Initiation of AD therapy (ADT)	Main Estimator
2	Trt Policy	Hypothetical H-RD	Hypothetical H-MAR	NA	-MAR MI for intermediate missing -MI based on retrieved dropouts (RD_TRT)
4				Hypothetical -worsening vs subjects who don't initiate ADT	-MAR MI for intermediate missing -MI based on retrieved dropouts (RD_TRT) -Apply a delta worsening adjustment to the imputed values for subjects who initiate ADT

Sensitivity Estimators

- Change/Stress-test the assumptions of main estimator

Examples:

- Estimator for a different hypothetical scenario for study discontinuation
- Delta worsening adjustment (potentially with a tipping point finding)

Summary

- Complex framework of selecting estimands and estimators
  - Multiple intercurrent events that need to be addressed by different strategies
  - Availability of reliable estimators for certain strategies?
- Need for:
  - clear estimand definitions
  - aligned estimators
- Simulation investigation:
  - Estimator selection can have a strong impact on the estimates of the treatment effect
  - Similar operating characteristics for all estimators for high %Retrieved ➡
  - Act to reduce preventable missing