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Quantifying the clinical measure of interest in the presence of missing data:

choosing primary and sensitivity analyses in neuroscience clinical trials

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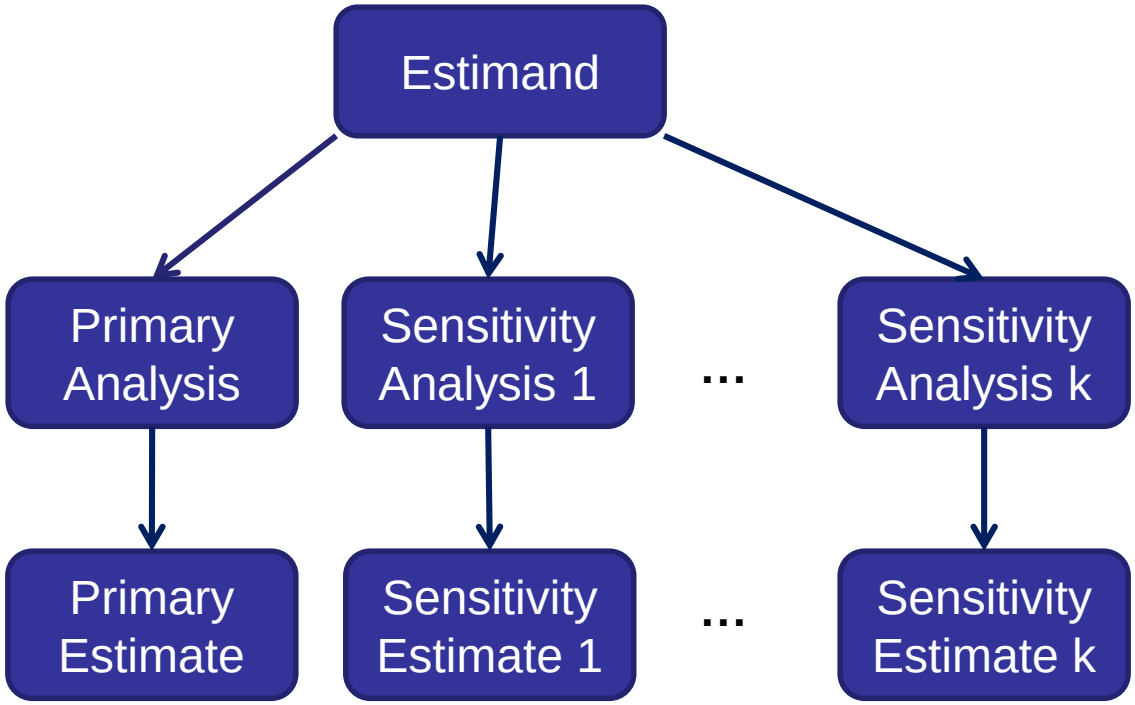
Impact of Missing Data

His wif_ is not working today.

Outline

- Background: Selection of the primary estimand and statistical methods for a clinical trial
- Neuroscience trial simulation example:
  - Assumptions
  - Statistical methods
  - Derived properties
- Role of simulations

Primary and Sensitivity Analyses

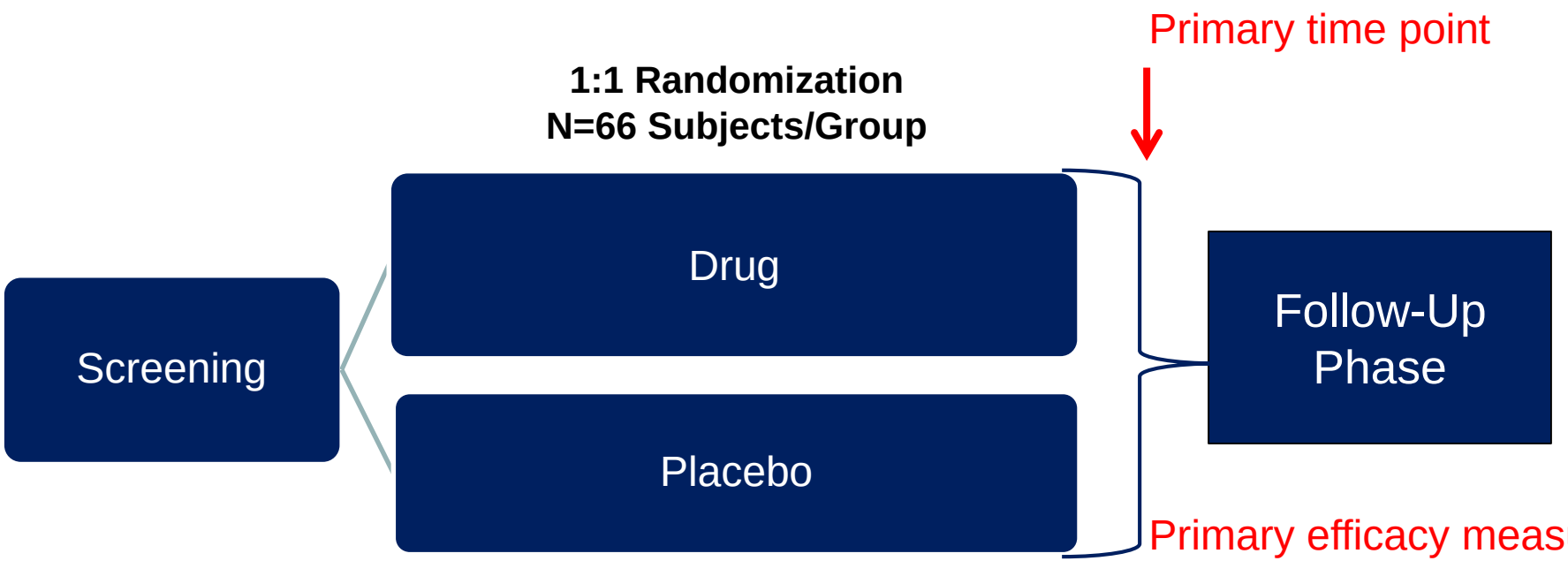


End of Trial

Challenges in Selection of Statistical Methods

- Unique characteristics of each clinical trial:
  - Indication
  - Study population
  - Study design
  - Efficacy response
  - Likelihood of subjects remaining on treatment or in the trial etc.
- Variety of statistical methods
- Regulatory requirements that evolve over time

Simulation Example: Depression Efficacy Trial



Primary efficacy measure: depression scale (MADRS) collected over time in the DB phase

Primary efficacy endpoint: change from baseline to Week 4 in MADRS Total Score

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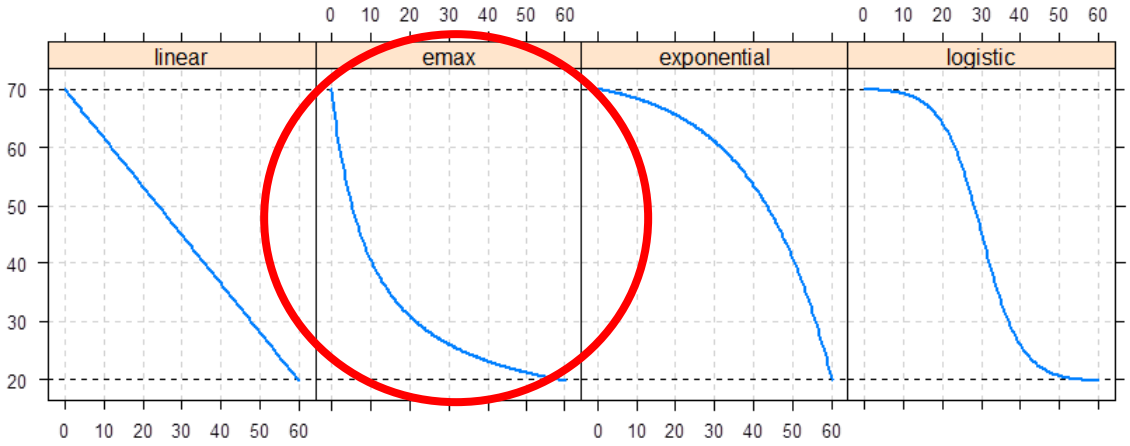
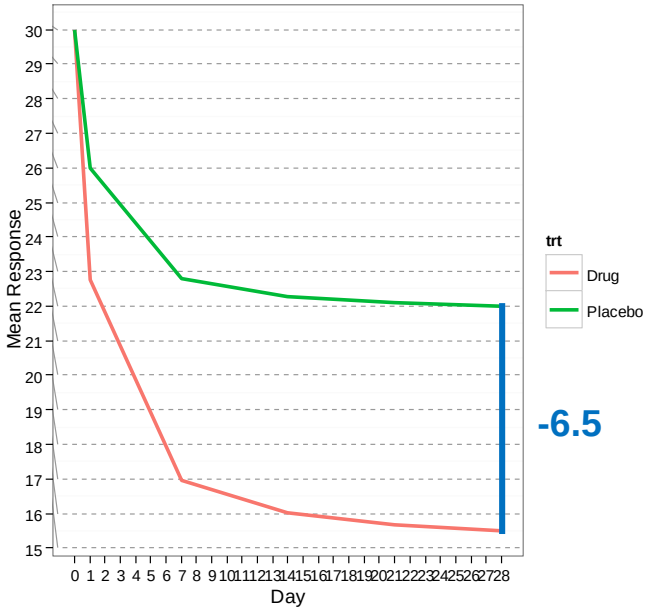
Simulation Evaluation Process

- Simulate full datasets (without any missing data)
- Create over time missing values based on various assumptions (missing data cases)
- Apply considered statistical methods
- Determine operating characteristics of the considered methods:
  - Power (or Type I error rate)
  - Estimated treatment difference and its variability

Simulate Full Datasets
Key Assumption: Over Time Efficacy Response





Simulated Missing Data Cases

Averaged Distribution of Discontinuations for the Evaluated Cases				
Case	**Group**	**Mean Total %DC**	**Mean %DC Other**	**Mean %DC LOE**
1	drug	30.6	25.1	5.4
1	control	26.0	14.7	11.2
2	drug	25.5	20.1	5.4
2	control	26.0	14.7	11.2
3	drug	18.8	15.1	3.7
3	control	22.2	14.6	7.6

DC = Discontinuation
LOE = Lack of Efficacy
Other discontinuation reasons include adverse events, lost to follow-up etc.

Statistical Methods?

MAR vs MNAR

MAR = Missing at Random

After withdrawal subjects would tend to have similar efficacy to subjects who remain in the study after accounting for observed characteristics

MNAR = Missing Not At Random

Assumptions need to be made on the potential "trajectory" or distribution of efficacy after withdrawal, which will be different from the one of subjects remaining in the trial

Multiple Imputation Based Methods

Multiple imputation is a statistical technique for analyzing incomplete datasets.

Application of this technique requires three steps:

DC	c1_oc	c2_oc	c3_oc	c4_oc
OTHER	-1.06215	-5.17018	.	.

c1_oc = observed change at Visit 1, c2_oc = observed change at Visit 2 etc.

Imputation with multiple values

Imputation	c1_mi	c2_mi	c3_mi	c4_mi
1	-1.06215	-5.17018	-3.59436	-6.26150
2	-1.06215	-5.17018	-2.95910	-0.40440
3	-1.06215	-5.17018	-3.93861	-5.58729
4	-1.06215	-5.17018	-5.05197	-4.65008
5	-1.06215	-5.17018	-4.02463	-1.85226
6	-1.06215	-5.17018	-5.29770	-1.28843
7	-1.06215	-5.17018	-3.45573	-3.67338
8	-1.06215	-5.17018	-1.64735	-2.77245
9	-1.06215	-5.17018	-8.62956	-1.87126
10	-1.06215	-5.17018	-6.19145	-4.04486

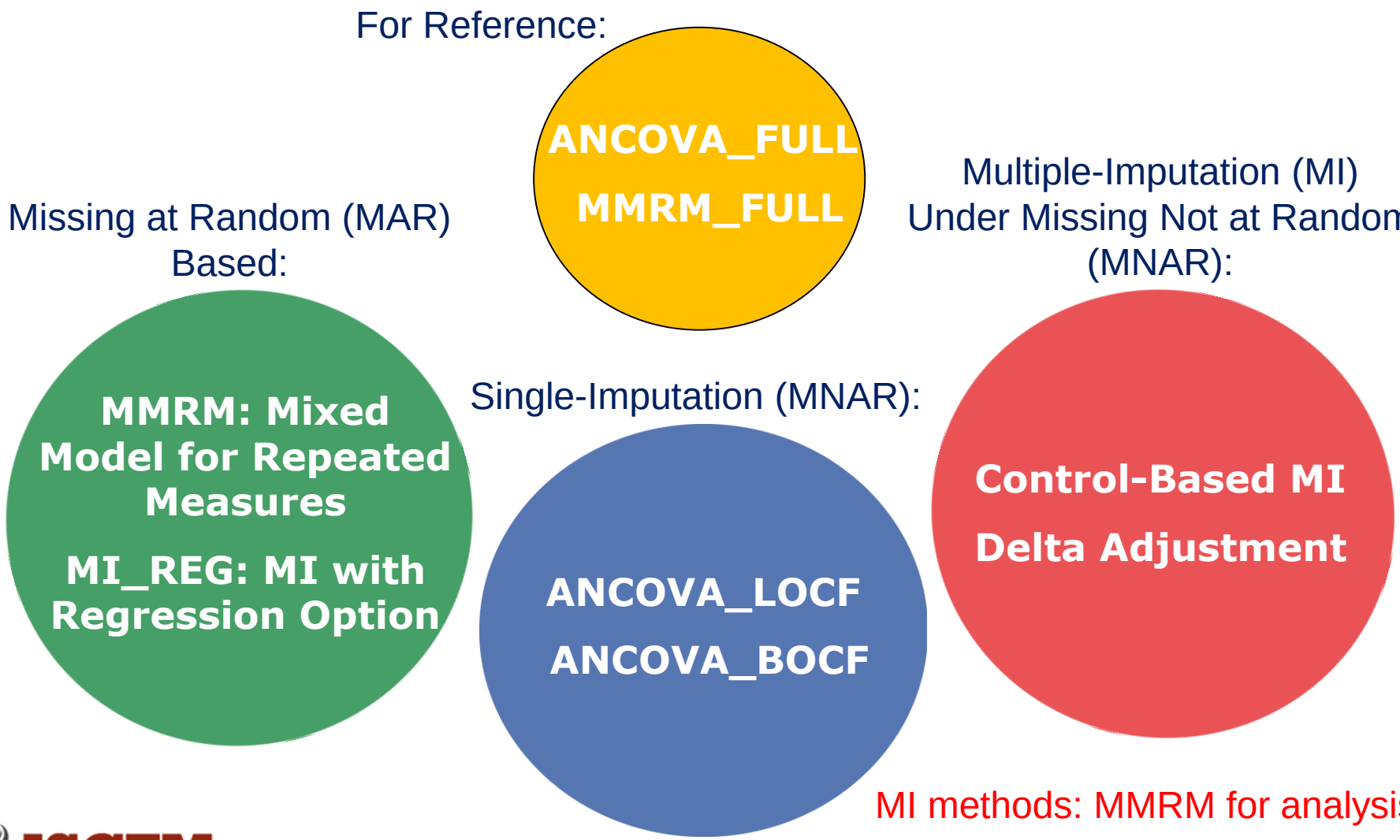
Analysis

Imputation	Diff vs Pbo	StdErr
1	-0.6467	0.2717
2	-0.5798	0.2729
3	-0.4925	0.2800
4	-0.7350	0.2754
5	-0.4891	0.2722
6	-0.7668	0.2758
7	-0.7032	0.2699
8	-0.5977	0.2748
9	-0.6303	0.2709
10	-0.6180	0.2686

Pooling

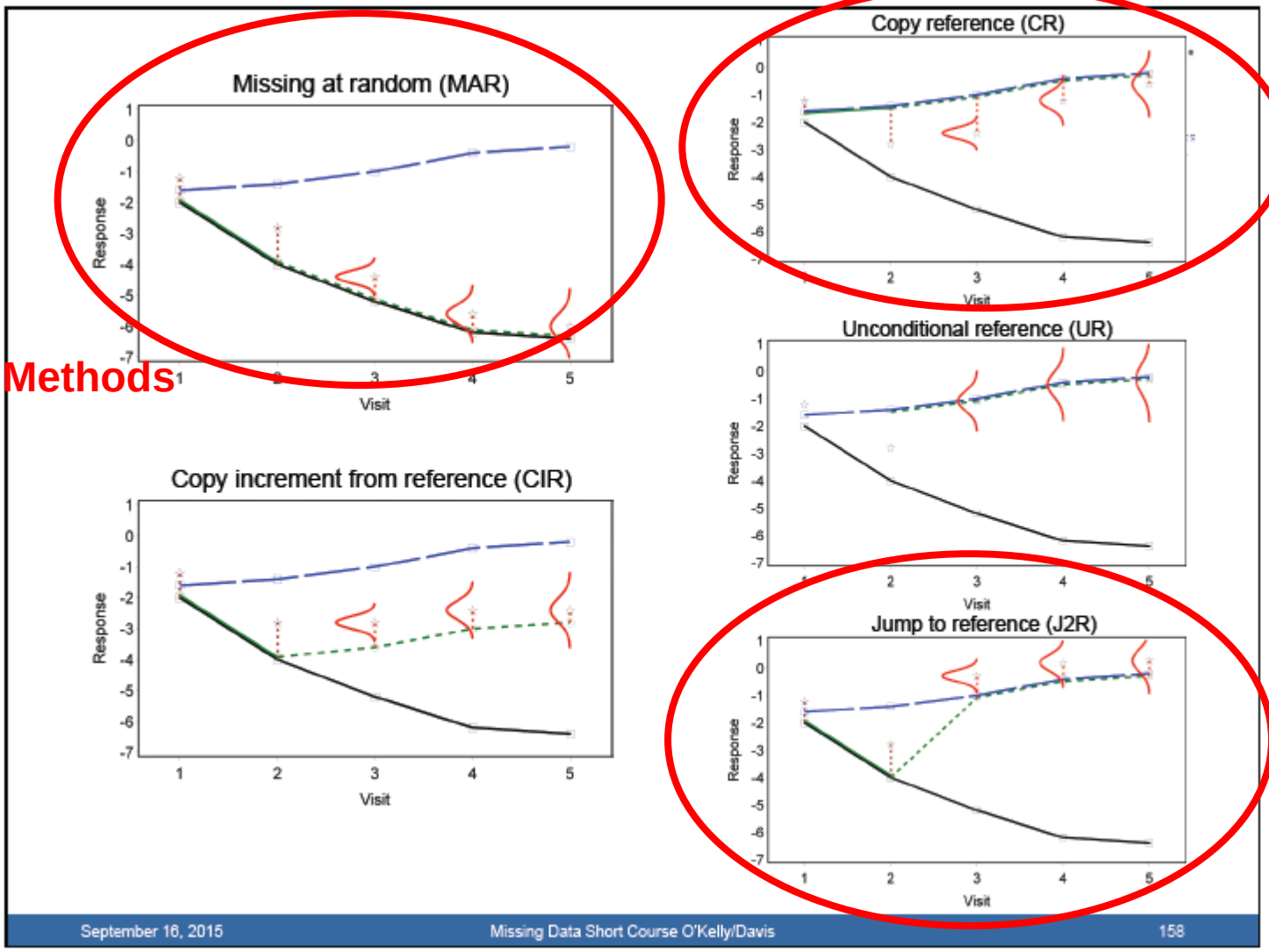
Pooled Diff	Pooled StdErr	Pvalue
-0.625909	0.290099	0.0313

Evaluated Statistical Methods



MI methods: MMRM for analysis

Joint Control-Based MI Methods



MAR Methods

MIJOINT_CR

MIJOINT_J2R

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

Delta Adjustment and Tipping Point Analysis

- Analysis assuming that subjects who discontinue would, on average, have their unobserved efficacy outcome worse by the amount Delta compared to the observed efficacy outcome of subjects who remain in the study.
- Tipping Point Analysis: find the assumption at which conclusions change from favorable to drug (statistically significant) to unfavorable.
- Recommended by the NRC 2010 report* and by FDA**
- Delta adjustment may be applied:
  - only on the experimental groups (of regulatory interest)
  - on all treatment groups
  - for certain reasons of discontinuation.

* National Research Council report on the Prevention and Treatment of Missing Data in Clinical Trials (2010)

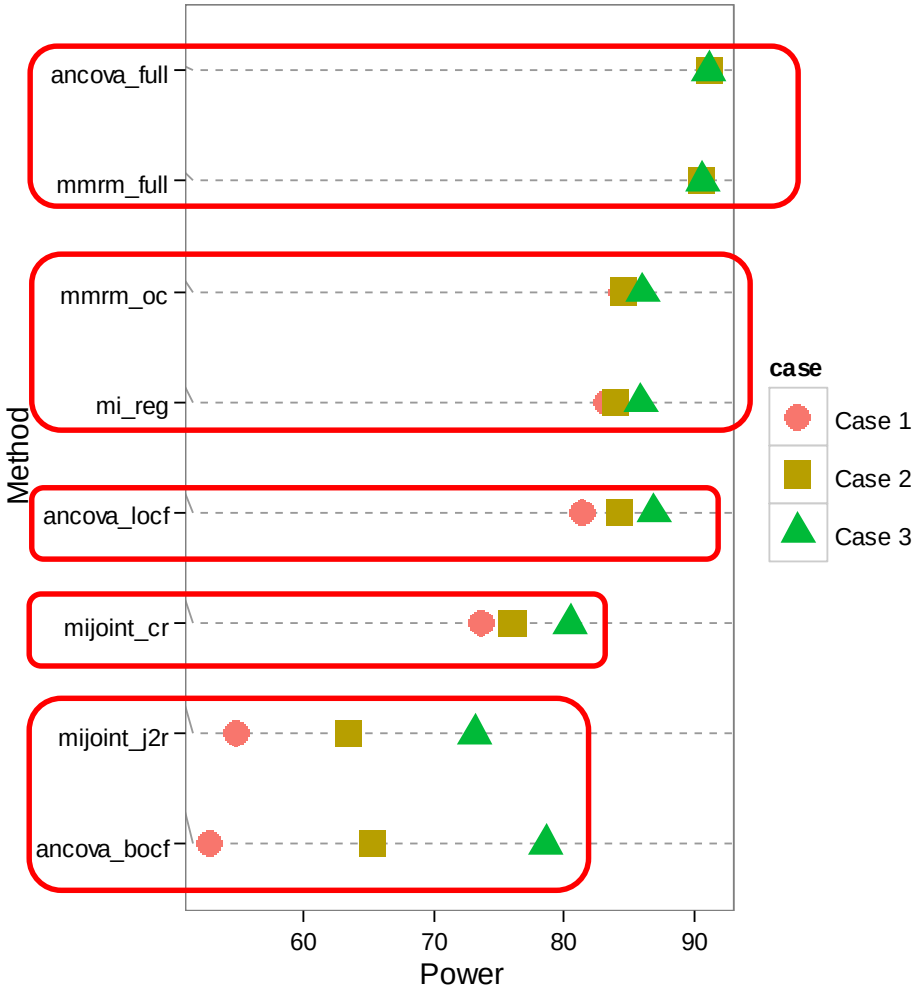
**Thomas Permutt “Sensitivity analysis for missing data in regulatory submissions” Statist. Med. 2015

Delta Adjustment Types

- Types of delta adjustment:
  - sequential (visit-by-visit)
  - marginal (multiple imputations first, then apply delta adjustment)
- In simulation exercise:

  Marginal delta adjustment: MIDELTAMAR
  - first, MAR-based multiple imputation analysis (MI_REG)
  - apply delta mean worsening in active arm only
  - same delta adjustment across visits
  - sequence of delta of increasing severity: 0 to 10 by 1

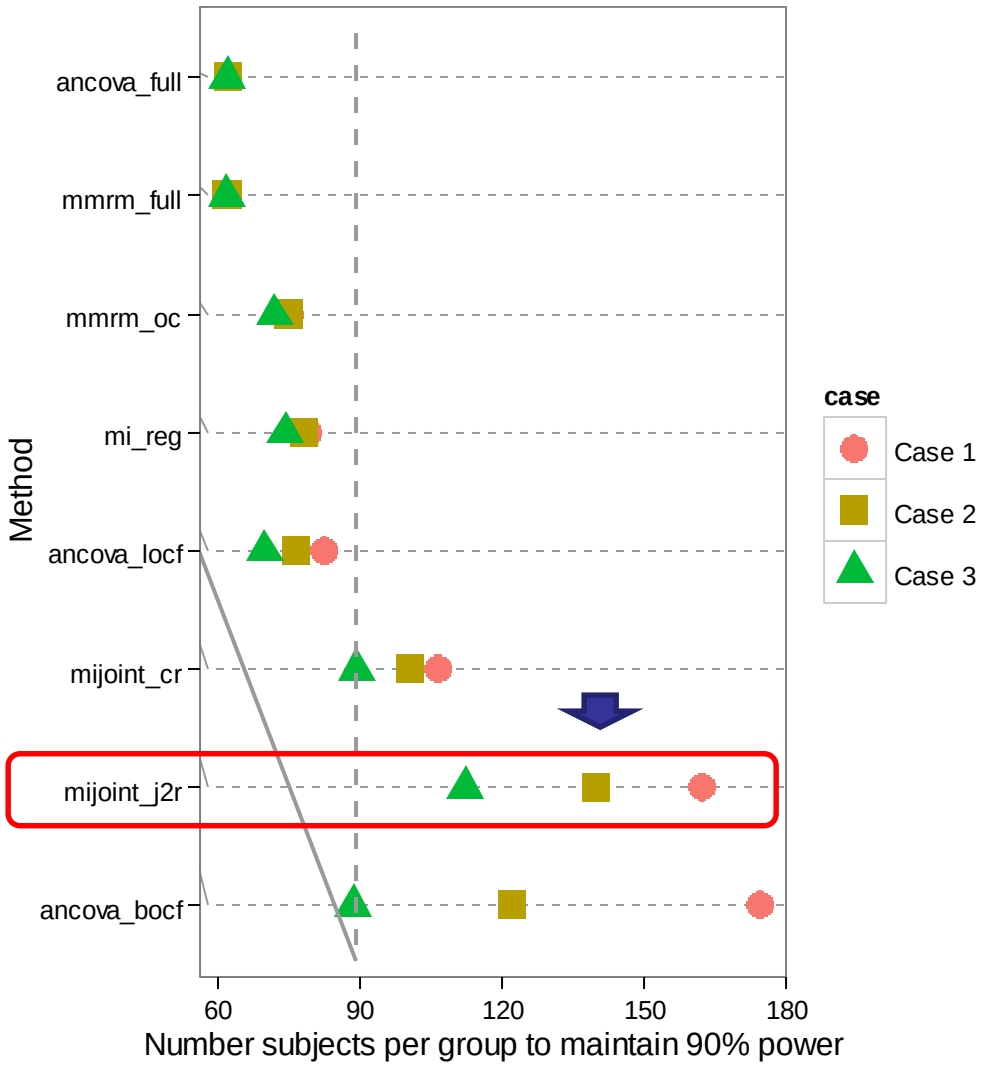
Estimated Power



Case	% DC Control	% DC Active
1	26%	31%
2	26%	26%
3	22%	19%

Assumption:
91% power for the “full dataset”, before missing values applied

Estimated Sample Size to Maintain 90% Power



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Increasing the sample size using expected amount of drop-outs might not be sufficient to maintain power:
Case 2: 26% adjustment to 66 subjects =~ 89 subjects

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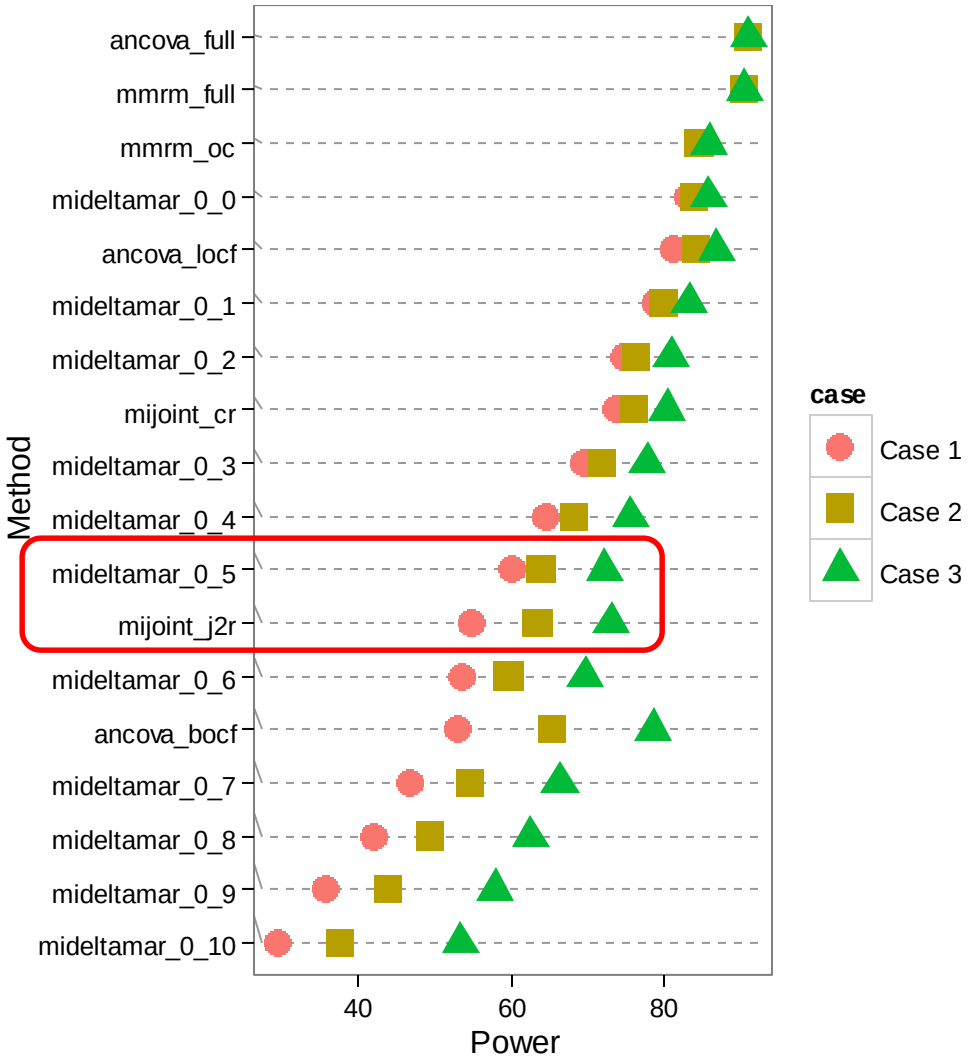
Estimated Power With Increasing Delta Adjustments



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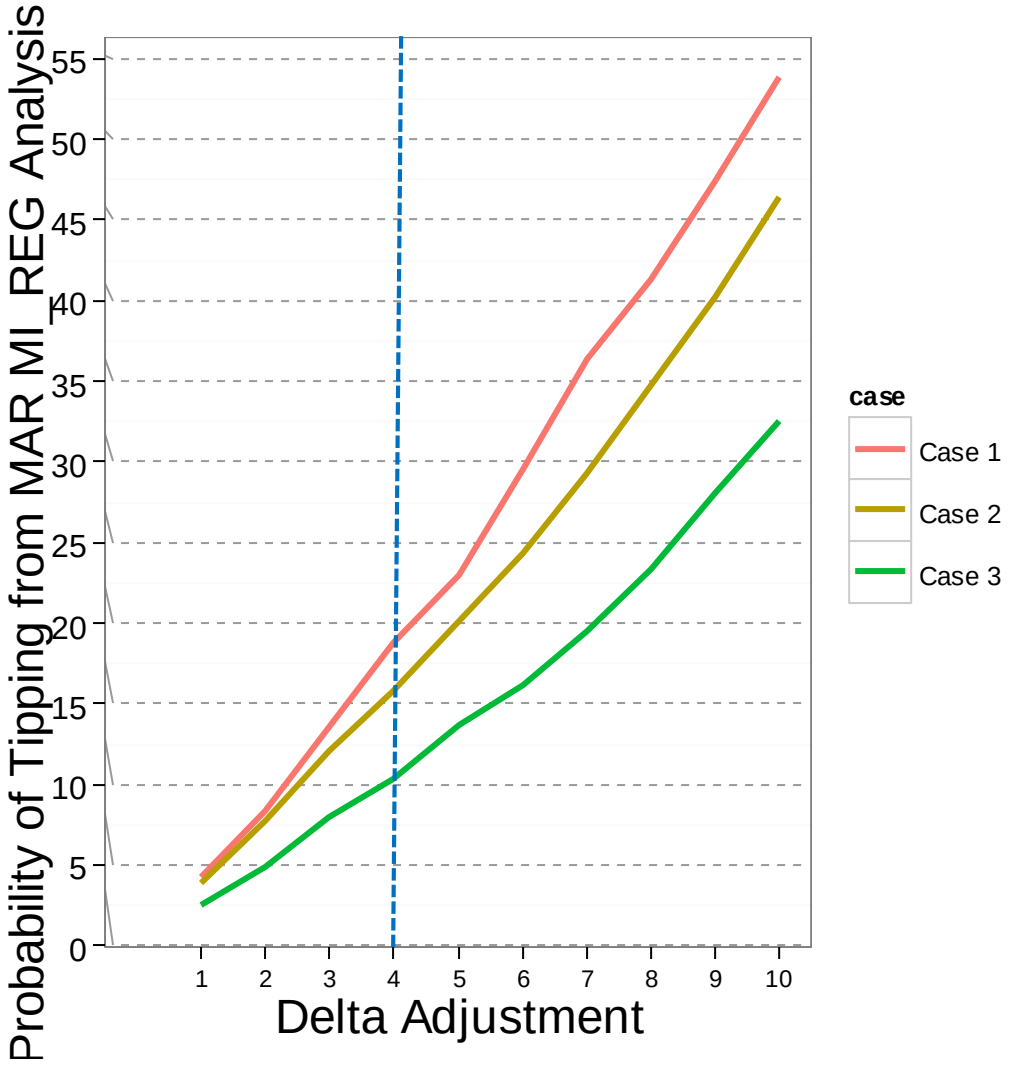
Probability(%) of Tipping From MAR MI Regression



Case	% DC Control	% DC Active
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Tipping point analysis = finding the delta worsening that changes conclusions from favorable to drug (statistically significant) to unfavorable

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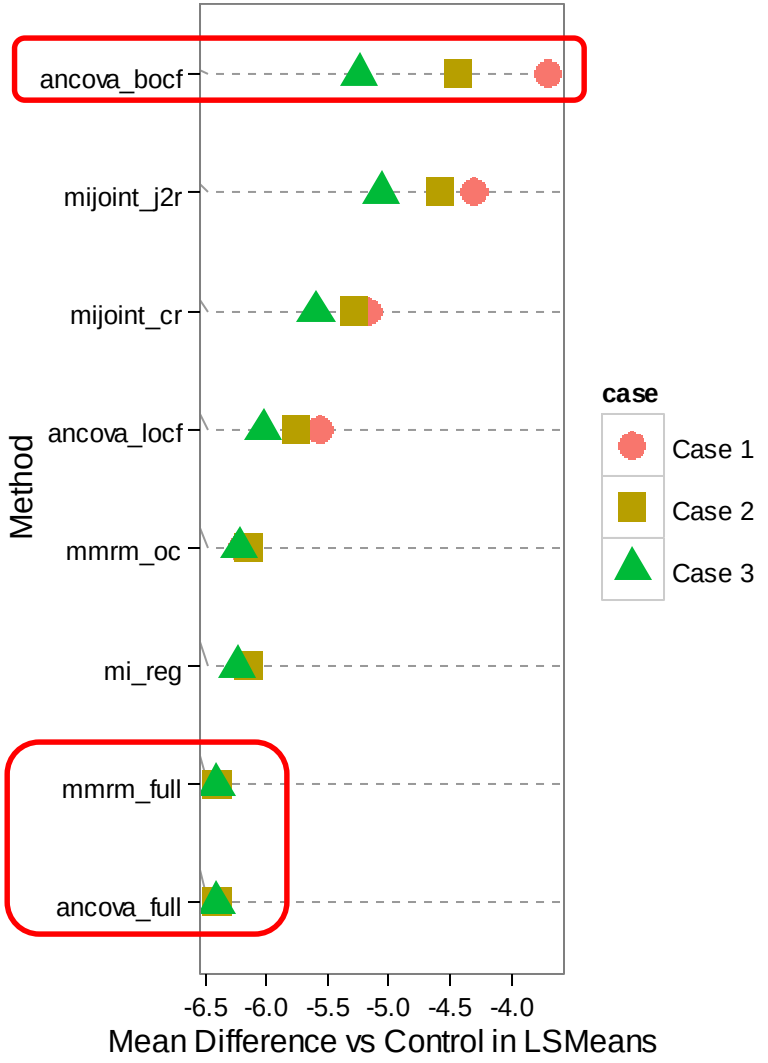
Role of Simulations

- Understand at the study design stage:
  - the impact of amount and reason of missing data
  - the performance of the statistical analysis methods considered for the primary and sensitivity analyses
  - potential sample size adjustments.
- Incorporate clinical feedback
- Communicate with regulatory agencies
- Communicate the impact of missing data and the **importance to reduce the amount of missing data through study design and conduct**

Back-Up

Estimated Mean Treatment Difference and Mean Standard Error



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