Dealing with placebo response - Sequential Parallel Comparison Designs

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BASS XXIII, October, 2016

1. Placebo response
2. Sequential Parallel Comparison Design
3. Review of Methodology
4. Placebo Response Characteristic
5. Example
6. Discussion

Placebo response

- The placebo response - a beneficial effect in a patient following a particular treatment that arises from the patient's expectations concerning the treatment rather than from the treatment itself

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- Biological mechanisms of placebo response are still debated

- The placebo response can:
  - Introduce bias in estimate of the treatment effect
  - Jeopardize the effort of all involved in a clinical trial
  - Deprive patients of potentially efficacious treatment

Problems in randomized clinical trial

- The classical double blinded RCT may be suboptimal
- The placebo response may depend on patient expectation to be assigned active drug - comparator studies

  Rutherford BR. et al. Does study design influence outcome? The effects of placebo control and treatment duration in antidepressant trials. Psychother Psychosom. 78: 172-181, 2009
- The placebo response increases overall response rate - harder to detect difference
- Possibly non-additive nature of placebo response

  Enck P. et al. The placebo response in clinical trials: more questions than answers. Phil Trans R Soc B. 366: 1889-1895, 2011

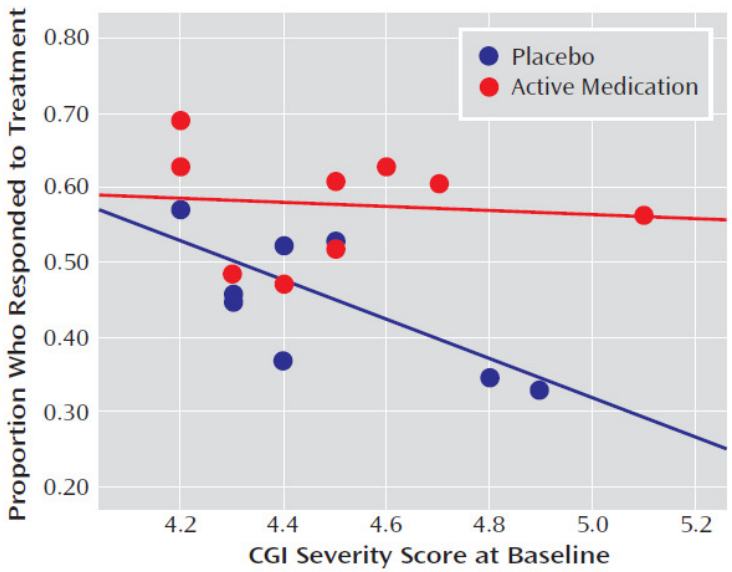
  Bridge JA. et al. Placebo Response in Randomized Controlled Trials of Antidepressants for Pediatric Major Depressive Disorder Am J Psychiatry.166(1): 42-49, 2009

  Kirsch I. et al. Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration PLoS Med. 5(2): e45, 2008

Placebo response in Psychiatry

- The problem of placebo response in clinical trials in psychiatry is well recognized, Trivedi and Rush 1994, Fava *et al.* 2003
- Robust placebo responses lead to
  1. Difficulties in estimation of the true effect size
  2. May prevent effective compounds from entering the market or existing drugs from new applications

FIGURE 2. Proportion of Participants Assigned to Placebo and Antidepressant Medication Who Responded to Treatment, by Initial Severity of Illness[a]



Bridge JA. at al. 2009 Am J Psychiatry. 166(1):42-49

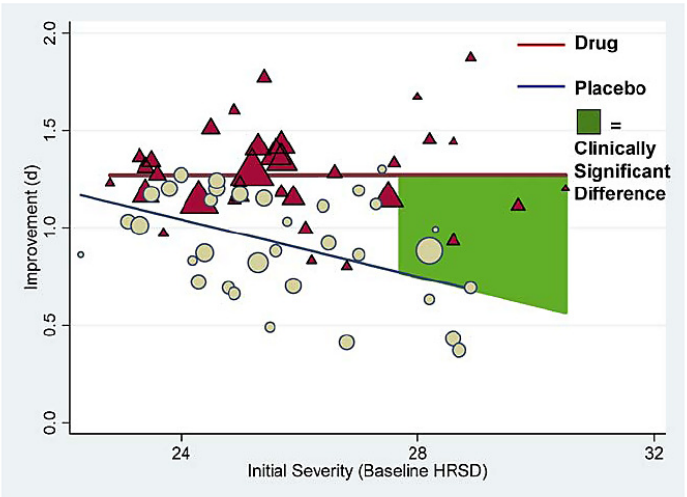


Figure 3. Mean Standardized Improvement as a Function of Initial Severity and Treatment Group, Including Only Trials Whose Samples Had High Initial Severity

Kirsch I. at al. PLoS Med 5(2): e45

Proposed Designs

- 'Placebo lead-in' - fell short of expectation, Trivedi and Rush 1994, Faries *et al.* 2001, Walsh *et al.* 2002.

Table 5. Drug Response Rates in Studies with and without a Placebo Run-In[ab]

	Outpatient		Inpatient	
	Placebo Run-In	No Placebo Run-In	Placebo Run-In	No Placebo Run-In
Tricyclics	53.1% (6.4) [58]	48.9% (5.2) [58]	52.5% (11.6) [11]	59.7% (15.8) [21]
Heterocyclics	58.6% (6.6) [12]	58.6% (10.0) [22]	49.5% (19.8) [8]	51.4% (11.9) [8]
SSRIs	43.6% (5.7) [37]	54.9% (8.2) [6]	58.1% (9.2) [4]	53.6% (12.6) [7]
MAOIs	56.2% (6.4) [6]	57.8% (6.9) [16]	78.6% (14.5) [1]	54.2% (10.2) [14]
Total	52.4% (3.8) [103]	53.9% (4.4) [102]	58.1% (8.2) [24]	54.3% (7.3) [50]

[a] Numbers in parentheses are standard deviations.
[b] Numbers in brackets are number of cells metaanalyzed.
SSRIs = selective serotonin reuptake inhibitors; MAOIs = monamine oxidase inhibitors.

Trivedi MH and Rush AJ. Does a placebo run-in or placebo treatment cells affect the efficacy of antidepressant medication? Neuropsychopharmacol 1994;11:33-43

- Sequential Parallel Comparison Design (SPCD) - Fava *et al.* 2003; addresses some shortcomings
- Two-Way Enriched Design - Ivanova and Tamura 2012 & Sequential Enriched Design - Chen *et al.* 2013; extensions of SPCD

Sequential Parallel Comparison Design

- SPCD consists of two stages (Stage I and Stage II), typically of equal duration (e.g. 6 weeks), *Fava et al.* 2003
- One version randomizes to one of three groups
  1. Active drug in both Stage I and Stage II (DD)
  2. Placebo in Stage I and active drug in Stage II (PD)
  3. Placebo in both Stage I and Stage II (PP)
- Other version ("SPD-ReR") in *Fava et al.* 2003 advocated by Chen *et al.* 2011 randomizes subjects in Stage I to treatment groups; typically more subjects allocated to placebo, e.g. 2:1
- Liu et al. (2012) proposed a doubly randomized delayed start (DRDS) design.
- Two-Way Enriched Design - Ivanova and Tamura 2013 & Sequential Enriched Design - Chen *et al.* 2014; extensions of SPCD

SPD-ReR flowchart

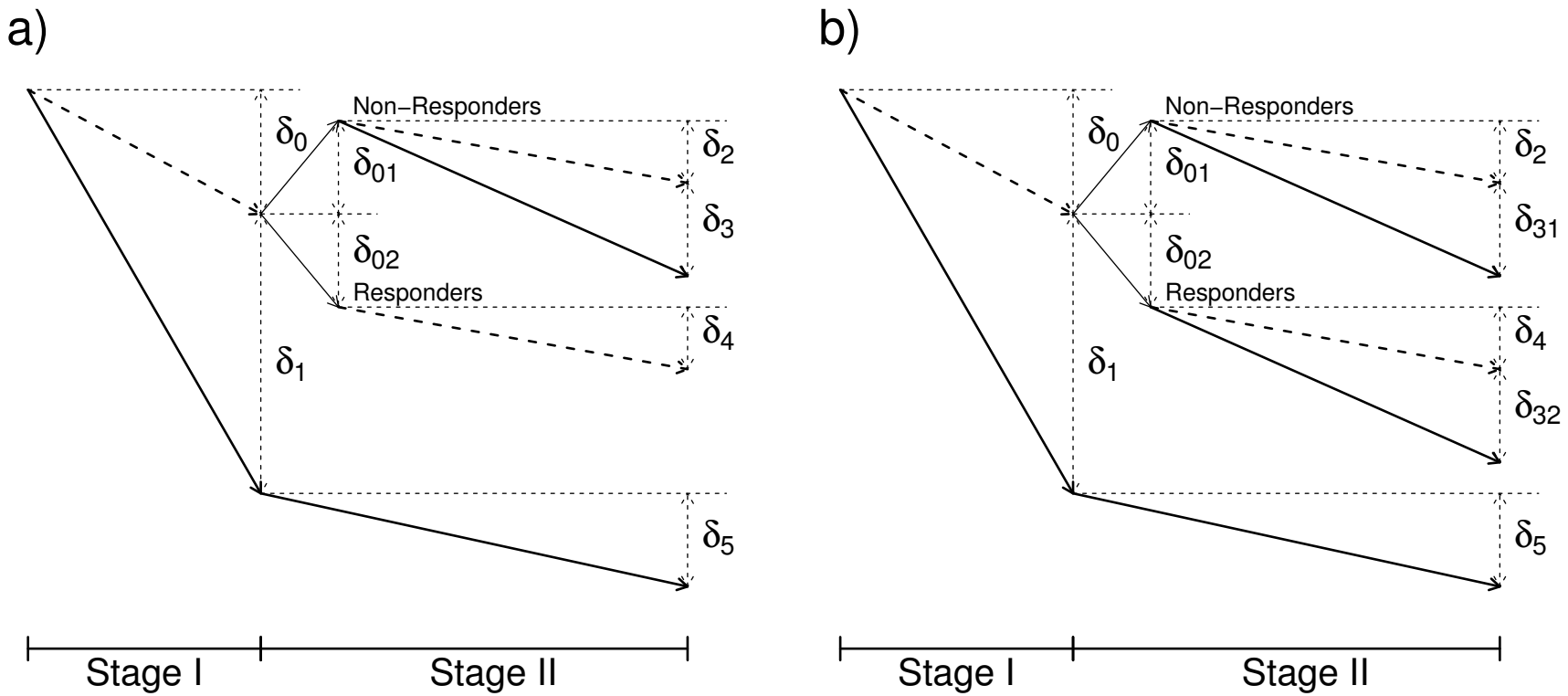


Figure: SPCD Design: N - total number of subjects enrolled in Stage I; n_{NR} and n_R numbers of Stage I placebo non-responders and placebo responders; p_{NR} - placebo non-responder rate; P - placebo; D - drug; P^+ - placebo responders; P^- - placebo non-responders; ρ - intra-subject correlation

SPD-ReR parametrization

- δ_0, δ_{01}, δ_{02}, δ_2 and δ_4 are the characteristics of subjects who receive only placebo, thus the information can be elicited from previous trials
- δ_2 - placebo response among placebo non-responders, δ_4 - placebo response among placebo responders
- δ_0, δ_{01}, and δ_{02} derived from non-response rate (Doros *et al.* 2013)
- δ_5 Stage II drug response for patients on drug in Stage I
- δ_1 and δ_3 treatment effects in Stage I and Stage II; overall treatment effect defined as

$$\delta_w = w\delta_1 + (1 - w)\delta_3$$

- δ_1, δ_3, w, ρ and p_{NR} (mainly) determine the size of the trial

Benefits of SPCD over traditional design (1/2)

Design - High Placebo response

	Drug	Placebo	Difference
Single Stage or SPCD Stage 1	60%	45%	15%
SPCD Stage 2	50%	25%	25%

	Total n		Power		
Power	Single Stage Design	SPCD	Total n	Single Stage Design	SPCD
70%	274	156	250	66%	88%
80%	346	199	300	74%	93%
90%	462	266	350	80%	96%

Benefits of SPCD over traditional design (2/2)

Design - Low Placebo response

	Drug	Placebo	Difference
Single Stage or SPCD Stage 1	25%	10%	15%
SPCD Stage 2	20%	5%	15%

	Total n		Power		
Power	Single Stage Design	SPCD	Total n	Single Stage Design	SPCD
70%	158	95	100	51%	73%
80%	200	121	125	59%	82%
90%	266	161	150	68%	88%

SPCD Methodology - Binary outcomes

- Original SPCD trials focused on binary outcomes
- Methods for binary outcomes include
  1. *Fava M., Evins A., Dorer D., Schoenfeld D.: The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach; Psychotherapy and Psychosomatics 2003; 72:115-127; and Erratum 2004; 73:123.*
  2. *Ivanova A., Qaqish B., Schoenfeld D.: Optimality, sample size and power calculations for the sequential parallel comparison design; Statistics in Medicine 2011; 30: 2793-2803.*
  3. *Ivanova A, Tamura RN. A two-way enriched clinical trial design: combining advantages of placebo lead-in and randomized withdrawal. Statistical Methods in Medical Research 2012*
- Information is lost through dichotomization; using the continuous (or ordinal) outcome more efficient

SPCD Methodology - Continuous

- *Tamura and Huang 2007* - uses Seemingly Unrelated Regression
- *Chen et al. 2011* - uses two ANCOVA models (OLS) to estimate the treatment effect in the stages

Above methods ignore data on placebo responders and Stage I drug subjects, i.e. the contribution $f(y_2|y_1)$ for for these subjects not used in estimation.

- *Doros, Pencina et al. 2013* - propose a repeated measures model that uses all data in assessing the treatment effect
- *Rybin D, Doros G, et al. 2015* Placebo non-response measure in sequential parallel comparison design studies.

Weighting methods for SPCD

- Methods above give *in effect* zero weight to responders and stage I drug subjects
- Participants classified either as responder or not - this might be unrealistic and subject to missclassification
- Weighting methods
  - Construct a continuum (*propensity for placebo response*) based on outcome up to the end of Stage I
  - Subject data are then weighed in the analysis
  - Besides response, other relevant variables can be included in determining the weight

A Common Theme - Placebo Non-response in SPCD

- Definition of placebo nonresponder
  - Eiji: large relative improvement in outcome

$$Y_{\text{Phase End}} / Y_{\text{Phase Start}} > 1 + \tau$$

  - Yihan and Akiko: a subject with a good outcome

$$Y_{\text{Phase End}} > C$$

  - Other work (Doros et al., Fava et al.) a responder meets either of the above
- In all cases placebo response is defined based on Stage I data
- Response - a Yes/No classification treated as a measured quantity with no stochastic component

Placebo non-response in SPCD

- Subjects are classified either as responder or not based on observed data, e.g. Responder if either $Y_1/Y_0 < 0.5$ or $Y_1 < 16$
  1. Uncertainty regarding the criterion
  2. Subject to missclassification
  3. Might not be appropriate

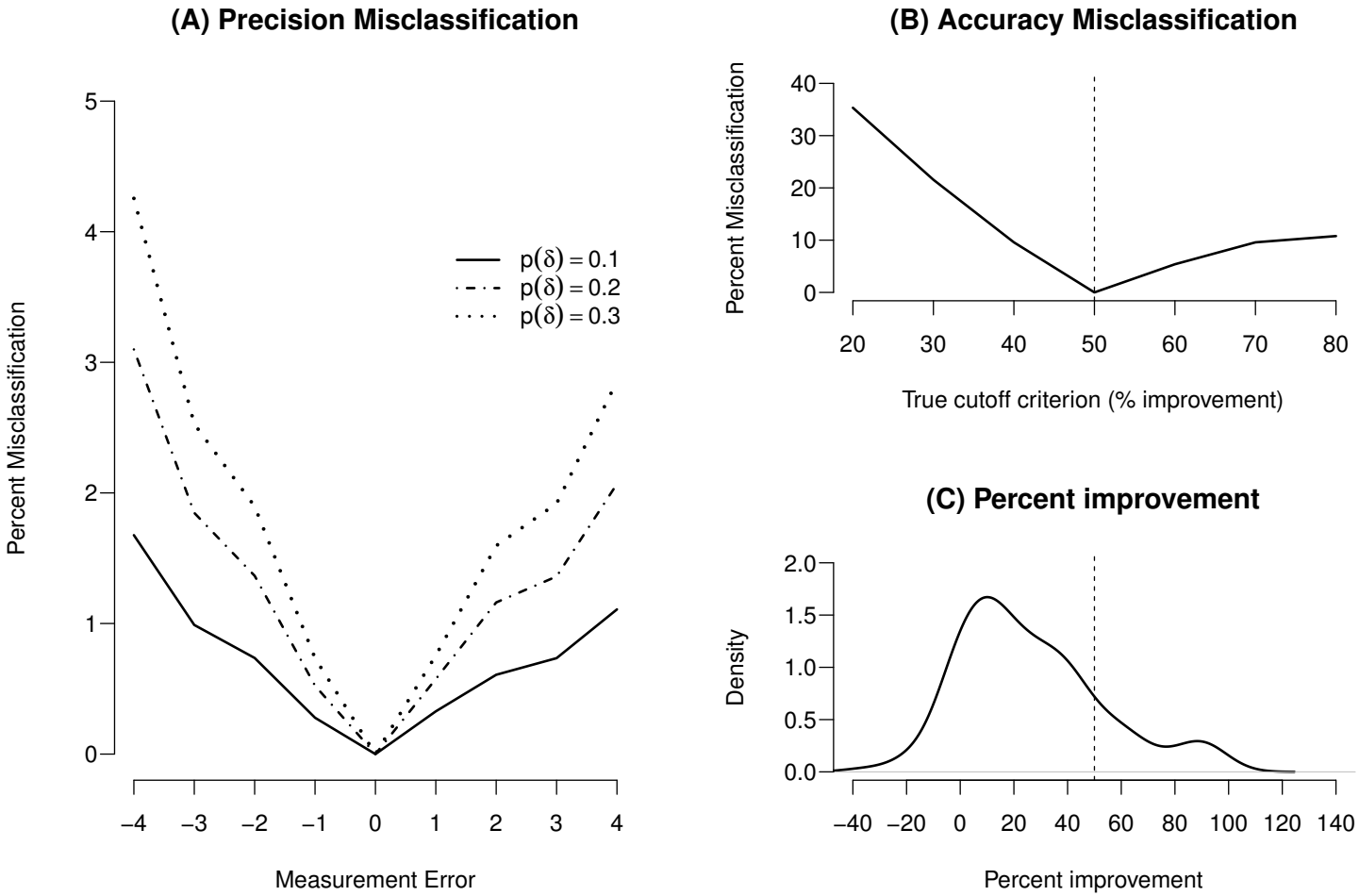
1. {Appropriateness} Should all responders be treated the same? i.e. should subjects with $Y_1/Y_0 \in (0.5 - \varepsilon, 0.5)$ be excluded from evaluation in Stage II?

Sensitivity to criterion

2. {Missclassificatiom} For each subject in DAPT (Fava et al 2019), assuming a measurement error $\delta \in (-2, -1, 0, 1, 2)$ with corresponding probabilities
   - The 'misclassification' rate ranged from 0 to 8%
   - The 'placebo-response' rate ranged from 20.1 to 29.2% (calculated in the study sample at 22.7%)
3. {Criterion} The distribution parameters vary with different criterion applied to define non-response

Criterion	Non-Responders		Responders		Treatment Effect
	Mean	SD	Mean	SD	Non-Responders
50% change	-5.47	5.31	-19.34	6.73	-2.75 (1.01)
48% change	-5.38	5.25	-19.25	6.66	-2.84 (1.01)
46% change	-5.29	5.17	-19.16	6.59	-2.93 (1.00)
44% change	-5.21	5.12	-19.05	6.53	-3.02 (1.00)
42% change	-4.88	4.89	-18.62	6.36	-3.35 (0.98)
40% change	-4.44	4.55	-18.15	6.16	-3.79 (0.96)

Placebo Response uncertainty



Proposed Approaches

1. Treat placebo response as a continuous characteristic (Rybin et al. 2015)
   - Model the response
   - Include it as a weight in the model of outcome
2. Treat placebo response as a dichotomous characteristic (Rybin et al. 2016 (*Under Review*))

Placebo Non-Response Measure in SPCD Studies

Rybin, Doros, Pencina, Fava. 2015 - proposes a Placebo Non-Response Measure in SPCD

- Construct a continuum (*propensity for placebo response*) based on outcome up to the end of Stage I
- Besides outcome, other relevant variables can be included in determining the weight
- Subject data in Stage II are included with approriate weight in the analysis

Contructing weights (1/3)

1. Perform K-means clustering - assume $K = 2$ in two dimensions
2. Collect the center-point coordinates:

$$c_1 = \frac{m_{11}s_{21} + m_{21}s_{11}}{s_{11} + s_{21}}$$

$$c_2 = \frac{m_{12}s_{22} + m_{22}s_{12}}{s_{12} + s_{22}},$$

m_{11}, m_{21}, m_{12}, m_{22}, s_{11}, s_{21}, s_{12}, s_{22}- mean and SD of x- and y - coordinates of clusters

3. Used euclidian distance to define

$$d_i = (-1)^{C_i}\sqrt{(p_{1i} - c_1)^2 + (p_{2i} - c_2)^2}; \quad i = 1 : n_P$$

$C_i \subset \{1, 2\}$ - the cluster; p_{1i} and p_{2i} coordinates for i^{th} subject.

Constructing weights (2/3)

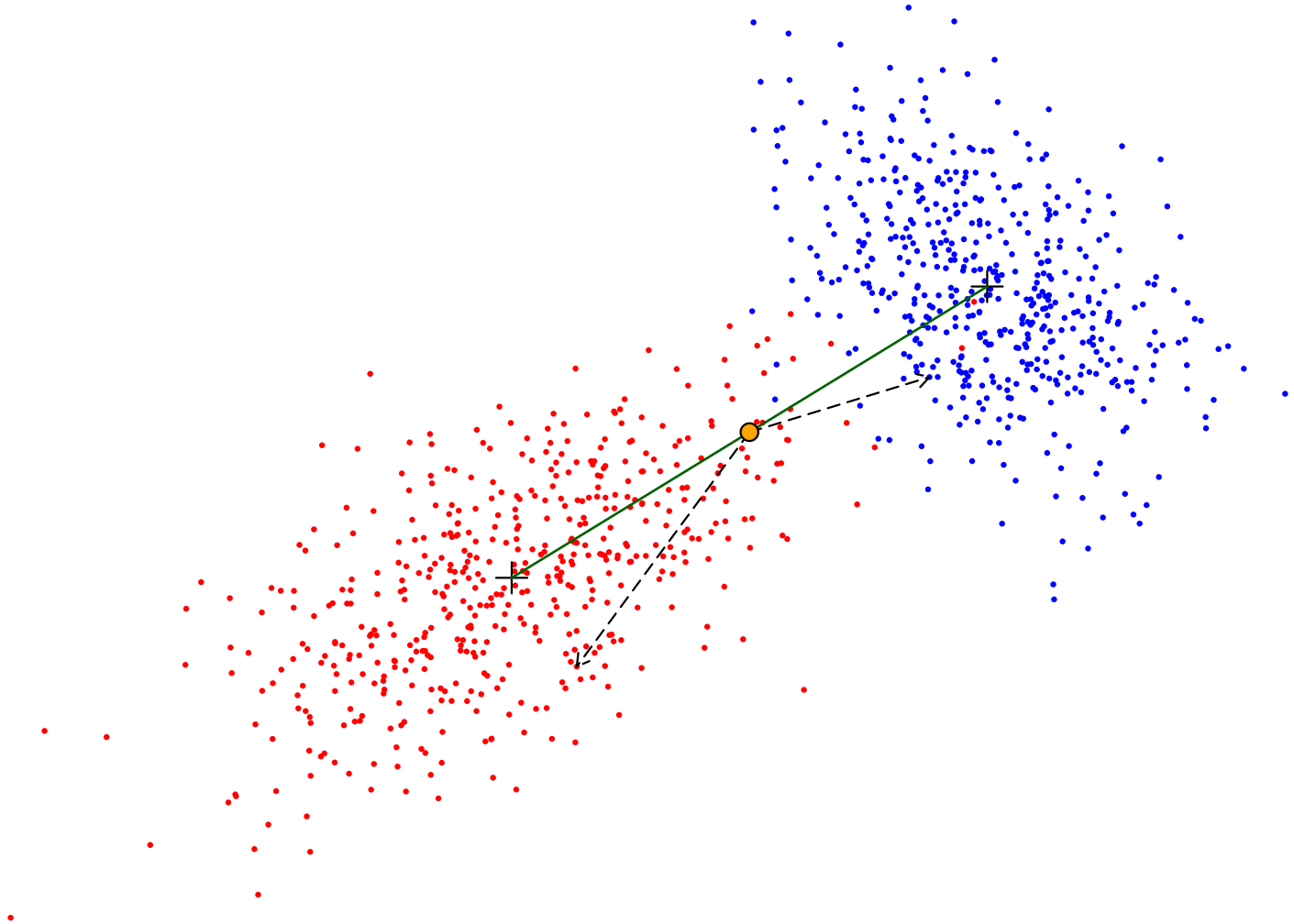


Figure: Constructing Weights based on clustering

Contructing Weights (3/3)

1. Subject specific weights computed as

$$w_{i,k} = \Phi_k(d_i)$$

where Φ_k - CDF with mean 0 and standard deviation $k \times s_T$ (s_T total standard deviation).

2. Weights ranging from 0 to 1 - scores close to 0 interpreted as high placebo response; scores close to 1 interpreted as placebo non-responders
3. Lower k produce weight $w_{.,k}$ function close to a step-function
4. Approach can be generalized to larger number of measured parameters

Statistical Model

1. Stage I outcome

$$Z_{i1} = \alpha_{01} + \alpha_{11} Y_{i1,0} + \delta_1 G_{i1} + \varepsilon_{i1}; \quad i = 1 : N,$$

$Z_{i1} = Y_{i2} - Y_{i1,0}$ - baseline change; $Y_{i1,0}$ -Stage I baseline; G_{i1} Stage I treatment

2. Stage II outcome in Stage I controls

$$Z_{i2} = \alpha_{02} + \alpha_{12} Y_{i2,0} + \delta_3 G_{i2} + \varepsilon_{i2}; \quad i = 1 : n_P,$$

$Z_{i2} = Y_{i3} - Y_{i2,0}$ - Stage II baseline change; $Y_{i2,0}$-Stage II baseline ; G_{i2} Stage II treatment indicator

3. Stage II outcome in Stage I drug

$$Z_{i2} = \alpha_{03} + \alpha_{13} Y_{i2,0} + \varepsilon_{i3}; \quad i = (n_P + 1) : N.$$

N - total number of subjects; n_P - number of Stage I placebo

Convariance structure

Error terms $\{\varepsilon_{i1}\}_i$, $\{\varepsilon_{i2}\}_i$, and $\{\varepsilon_{i3}\}_i$ assumed independent and identically distributed

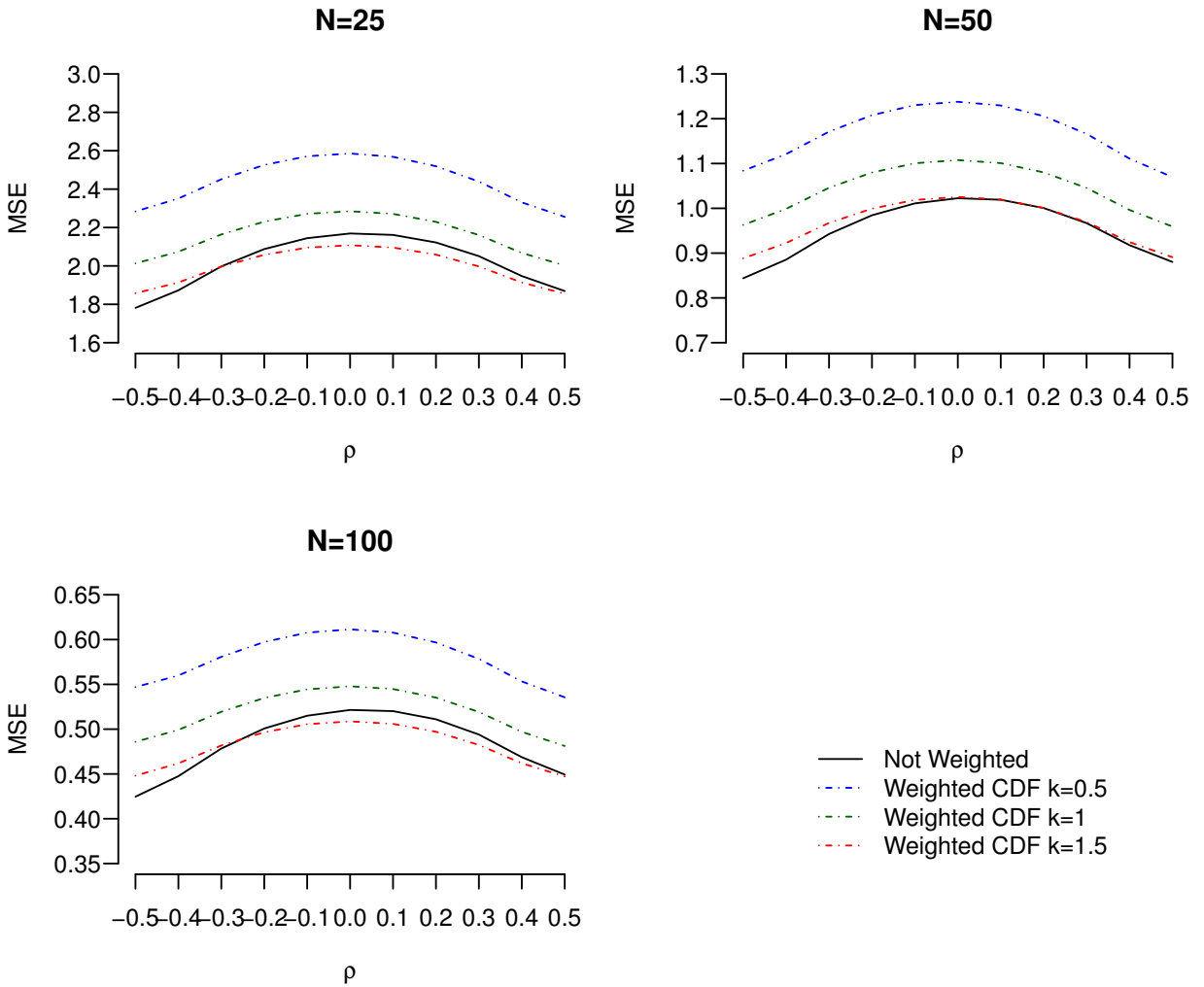
$$(\varepsilon_{i1}, \varepsilon_{i2}, \varepsilon_{i3}) \sim N(0, \Sigma_i)$$

Variance-covariance matrix

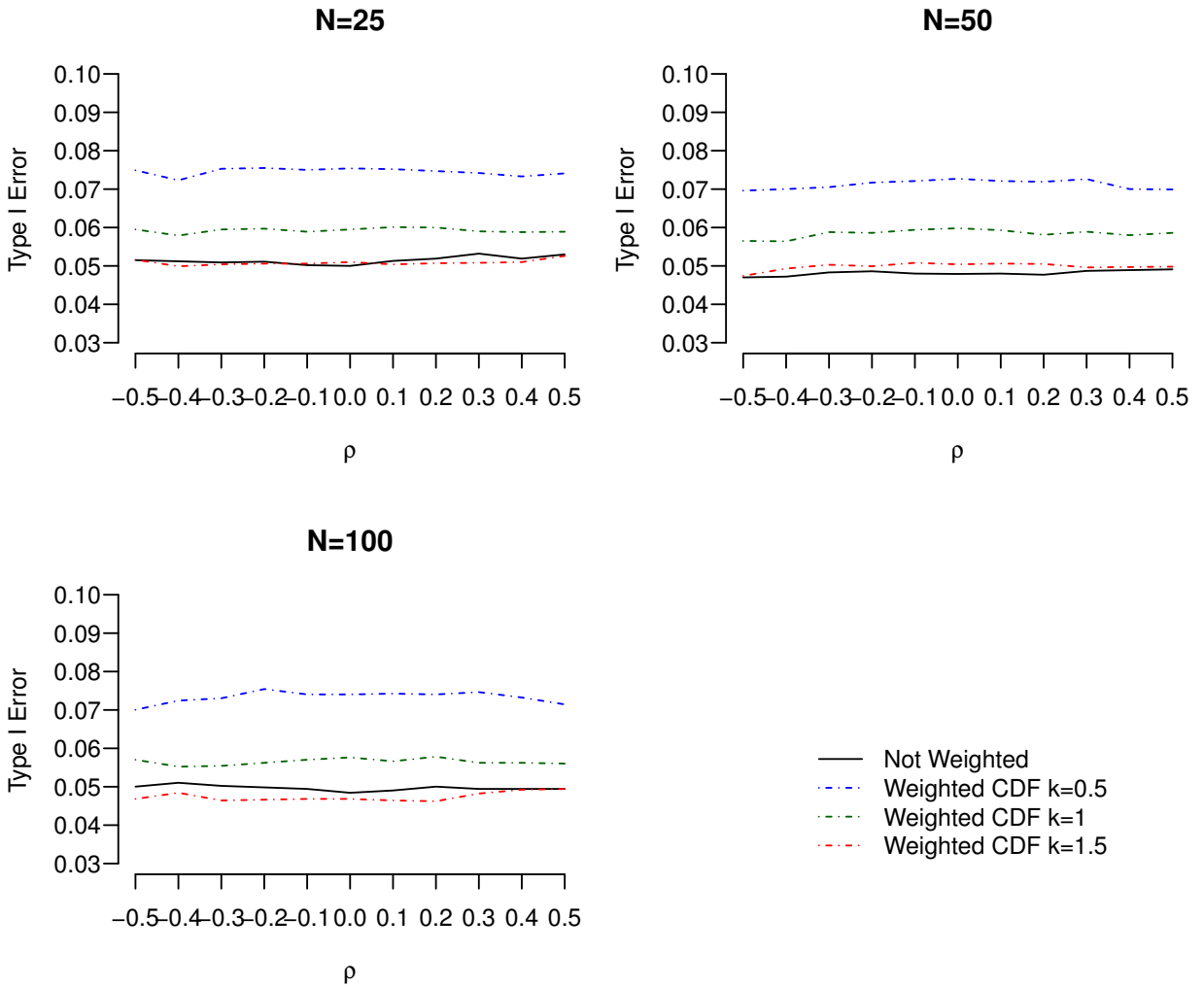
$$\Sigma_i = \mathbf{w_i}^{-1/2} \begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 & 0 \\ \sigma_{21} & 0 & \sigma_2^2 \end{bmatrix} \mathbf{w_i}^{-1/2}$$

$$\mathbf{w_i} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & w_i & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

Simulation Results - MSE



Simulation Results - Type I Error



Simulation Results - Power

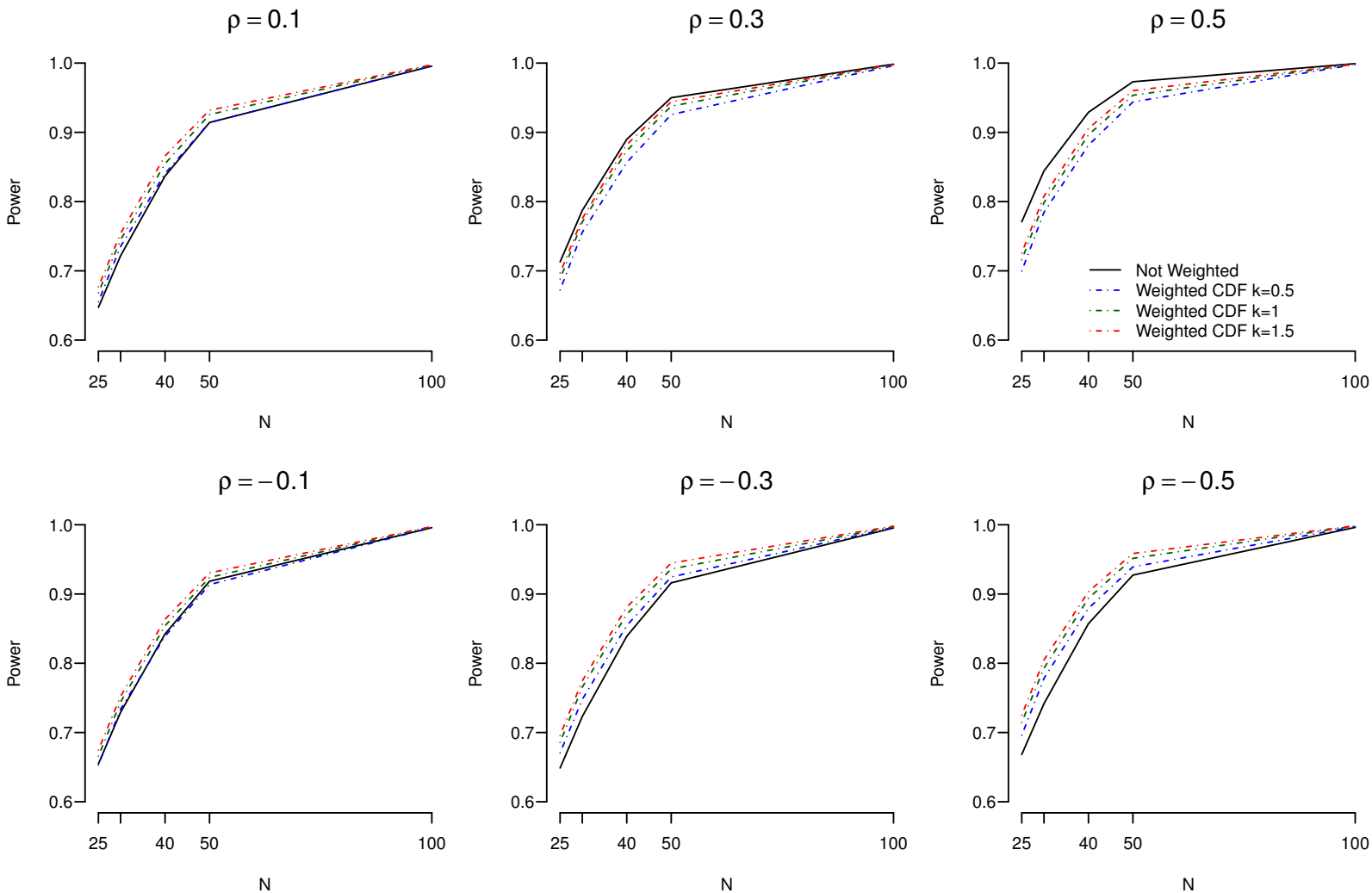


Figure: Power: Effect Size = 0.5SD in both Stages

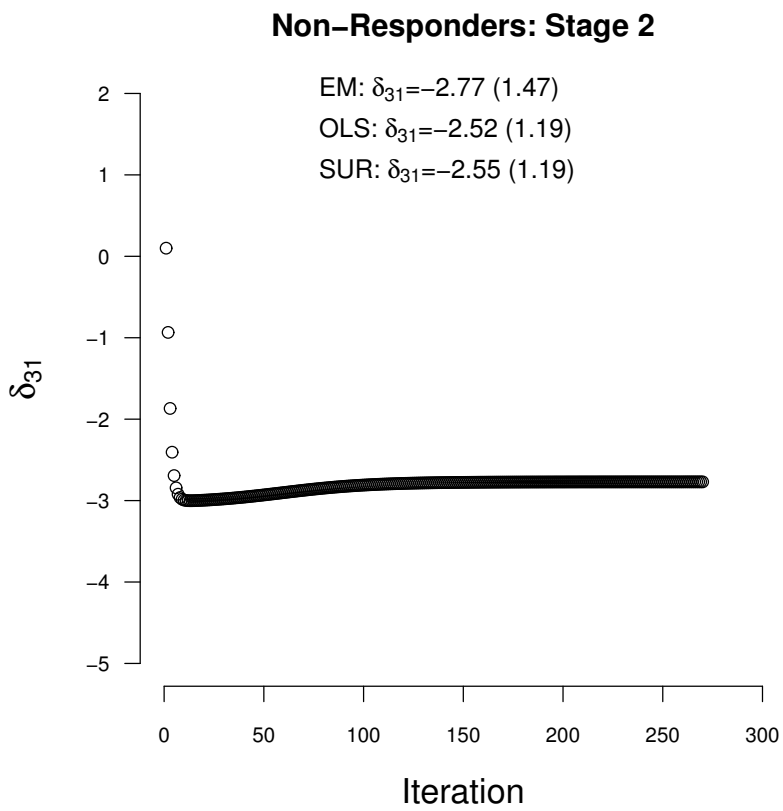
Non-Response as unobserved characteristics

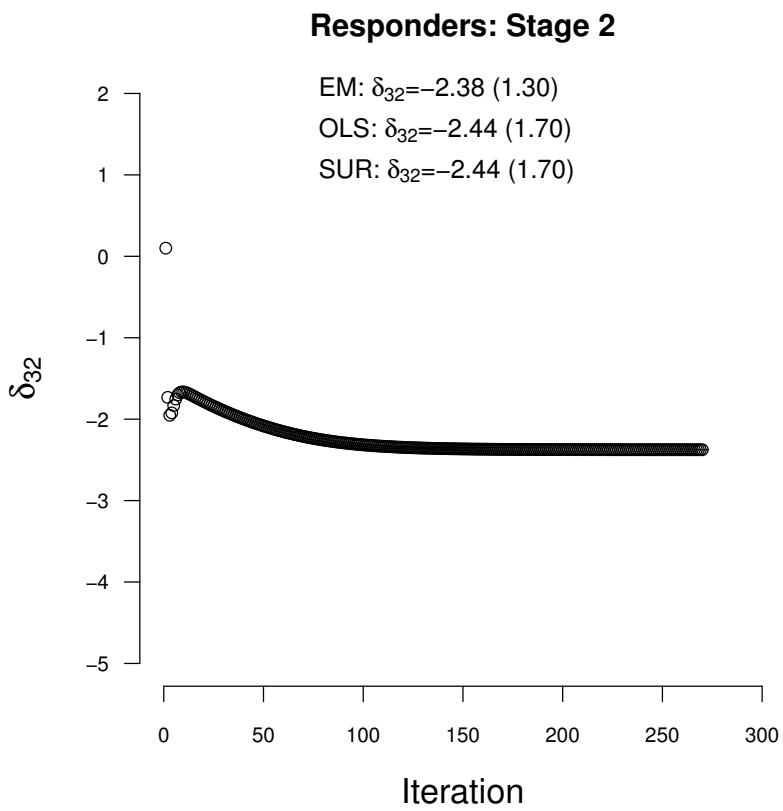
- Suppose we observe three values of a disease severity Y_{01}, Y_{02} and Y_{03} at baseline, end of Stage I and end of Stage II
- The outcome for Stage I is $Z_1 = Y_{02} - Y_{01}$, and the outcome for Stage II is $Z_2 = Y_{03} - Y_{02}$
- Let $g_{1i} \in (0, 1)$ and $g_{2i} \in (0, 1)$ be indicators for Stage I and Stage II group assignment (placebo, drug) for subject i
- Let $R_i \in (0, 1)$ be an indicator of being 'placebo responder' for subject i. The R_i is a latent variable $R_i \sim Bin(1, p_R)$
- Joint distribution for DD and PP/PD

$$p(Z_1, Z_2) = p_{11}(Z_1)p_{21}(Z_2|Z_1)$$

$$p(Z_1, Z_2) = p_R p_{01}(Z_1)p_{201}(Z_2|Z_1) + (1-p_R)p_{02}(Z_1)p_{202}(Z_2|Z_1)$$

Results: ADAPT-A Stage II treatment effect (Stage I based)





ADAPT-A Trial

- A multi-center, double-blind placebo-controlled study of the efficacy of low-dose aripiprazole adjunctive to antidepressant therapy (ADT) in the treatment of major depressive disorder patients with a history of inadequate response to prior ADT (ADAPT-A) Fava *et al.* 2009, Fava *et al.* 2012
- Funded by Bristol-Myers Squibb
- HCRI provided full service

Table: Change in MADRS score in ADAPT-A trial (†)

	Stage I		Stage II	
Measure	Drug ($N = 52$)	Placebo ($N = 162$)	Drug ($N = 58$)	Placebo ($N = 61$)
Mean±SD	-8.46±7.18	-8.26±8.15	-5.84±6.98	-3.30±6.00
Range	(-28.00,4.00)	(-35.00,10.00)	(-27.00,10.00)	(-23.00,11.00)
Median	-8.00	-6.50	-4.00	-3.00

(†) Contrary to the primary ADAPT analysis (Fava *et al.* 2012) no imputation was performed here.

ADAPT-A estimated weights

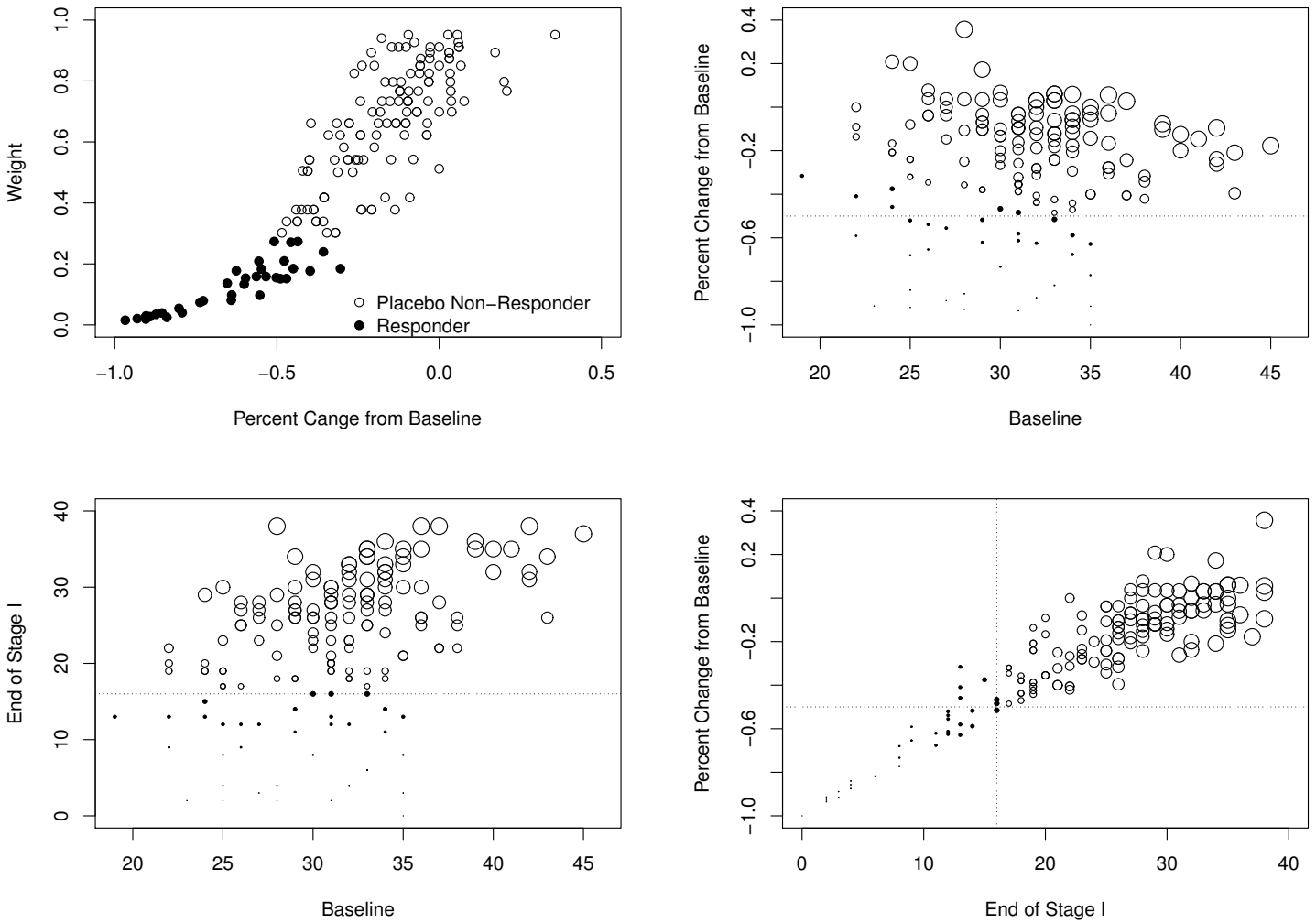


Figure: Weight for placebo subjects as a function of baseline score and change in score from baseline to end of Stage I

ADAPT-A Trial: Results - Continuous Outcome

Table: ADAPT-A estimates of treatment effect based on the proposed methods

Method	Estimate	Standard Error	Statistic	P-Value
Unweighted Method	-0.824	0.991	-0.830	0.407
Weighted Propensity	-0.819	0.985	-0.830	0.407
Weighted CDF k=0.5	-0.846	0.990	-0.850	0.394
Weighted CDF k=1.0	-0.867	0.991	-0.880	0.382
Weighted CDF k=1.5	-0.872	0.991	-0.880	0.380

Discussion

- Unacounted placebo response may prevent effective compounds from entering the market
- SPCD design reduces problem of placebo response
- Several tested methods allow for analyzing SPCD trials
- Two methods for accounting placebo response are proposed
  - Flexible and use all available data
  - More information included in analysis
  - Allows for more variables used in the construction of the responder status
- Models that more faithfuly represent the data generation are needed

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Acknowledgements

Work with

Michael Pencina
Maurizio Fava
Denis Rybin
Baiyun Yao