BLINDED EVALUATIONS OF EFFECT SIZES IN CLINICAL TRIALS: COMPARISONS BETWEEN BAYESIAN AND EM ANALYSES

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BASS XX

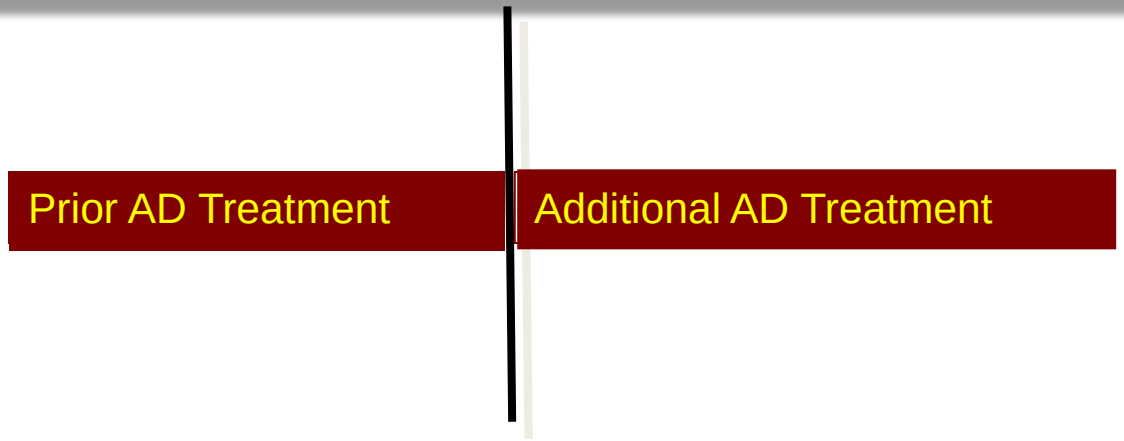
Outline

- Introduction
  - Background
  - Literature Review
  - Objective
- Methods
  - EM Algorithm
  - Bayesian Approaches
  - Model Selection
- Simulations
  - Set-up
  - Results
- Application
- Discussions and Conclusions
- Questions

Background

- Clinical trials can have a major impact on public health
- Required information for designing a clinical trial is not fully available
- Ongoing monitoring of accumulating data is necessary
- Interim analyses are common
  - Usually costly
  - Requires unblinding treatment assignments
  - Statistical implications
- We will investigate the use of the accumulated data for purposes of modifying aspects of the study design IN BLINDED SETTING

Background, Motivating Question, MDD Trial[1]



1. Mahmoud A.R., Pandina J.G., Turkoz I., Kosik-Gonzalez C., Canuso M.C, Kujawa J.M., and Gharabawi G.M. Risperidone for treatment-refractory major depressive disorder. Annals of Internal Medicine, 2007; 147: 593-602.

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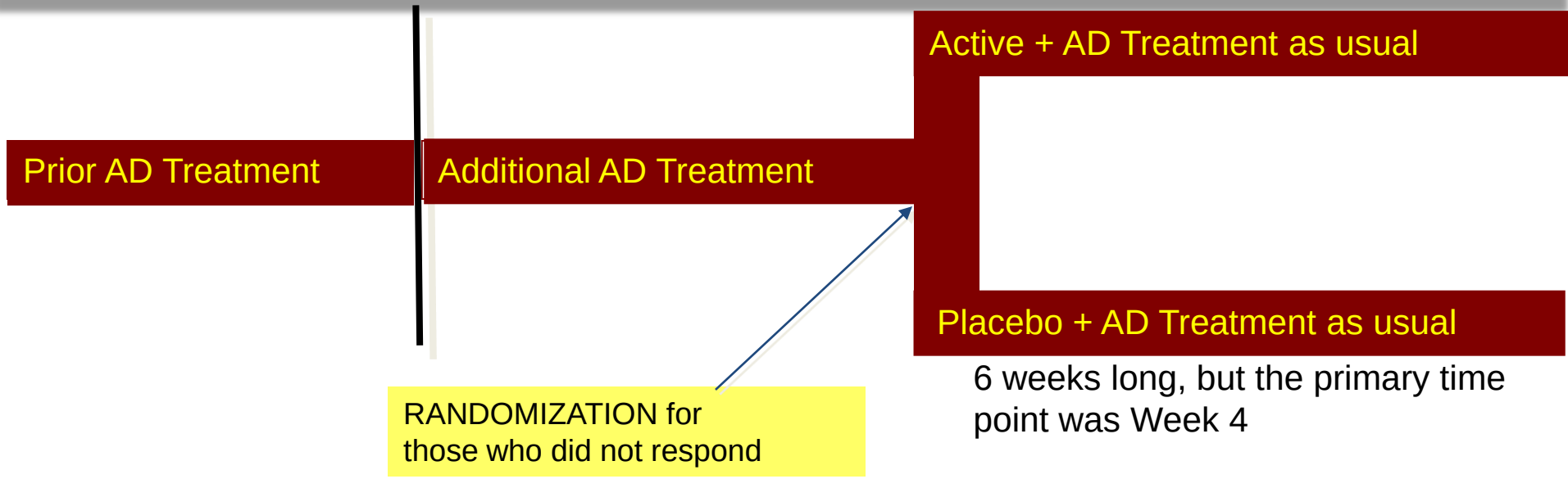

6 weeks long, but the primary time point was Week 4

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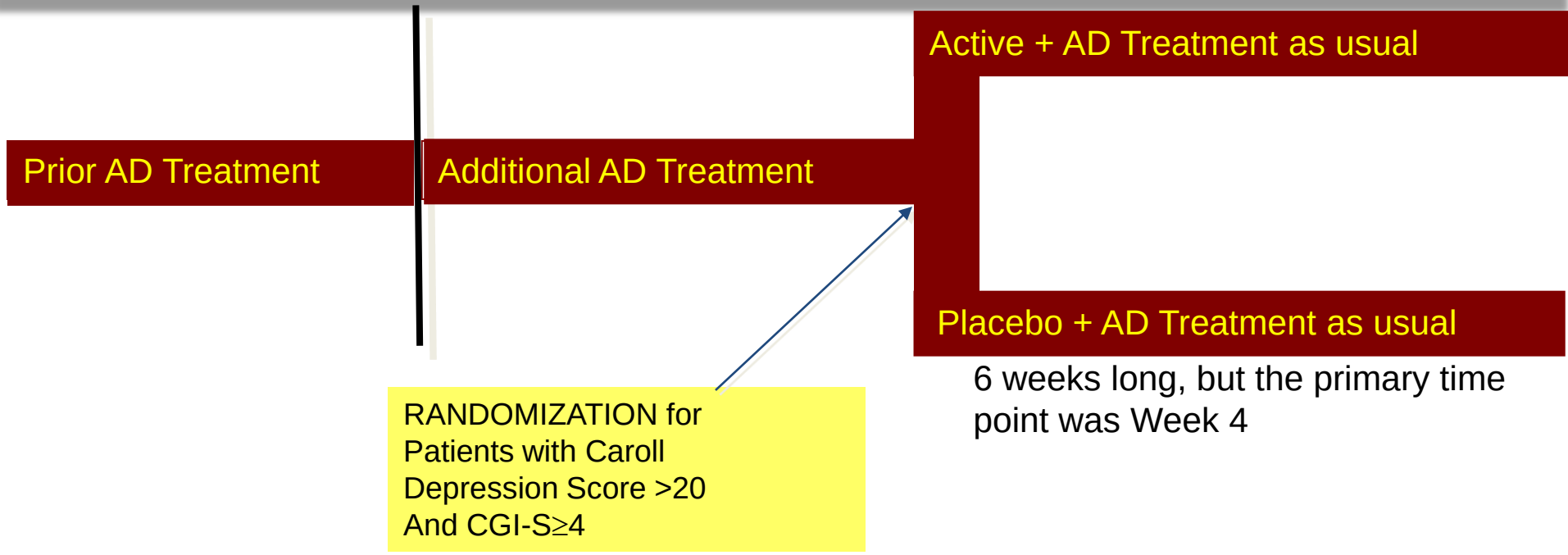


Outcome Parameters

Clinician Rated	Patient Reported
•**HRSD-17 (primary efficacy scale)** •CGI-S	•**Most Troubling Symptoms (MTS) or PaRTS-D** •Patient Global Impression of Severity PGIS

1. Mahmoud A.R., Pandina J.G., Turkoz I., Kosik-Gonzalez C., Canuso M.C, Kujawa J.M., and Gharabawi G.M. Risperidone for treatment-refractory major depressive disorder. Annals of Internal Medicine, 2007; 147: 593-602.

Background, Motivating Question, MDD Trial

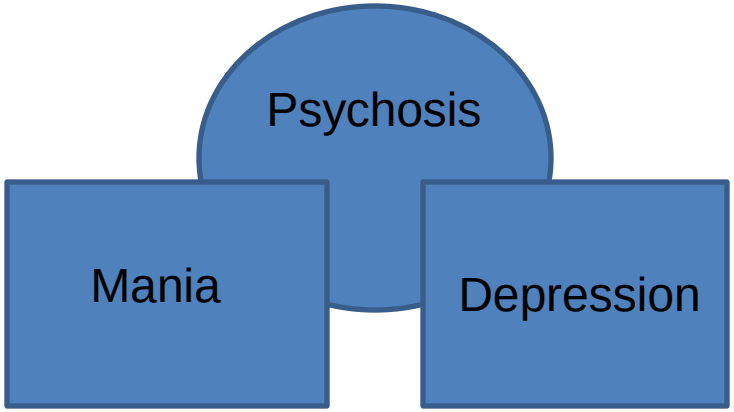
Primary Time Point?

Week 4 or Week 6?

Primary Endpoint?

HRSD-17 or PaRTS-D

Background, Motivating Question, Schizoaffective Trial



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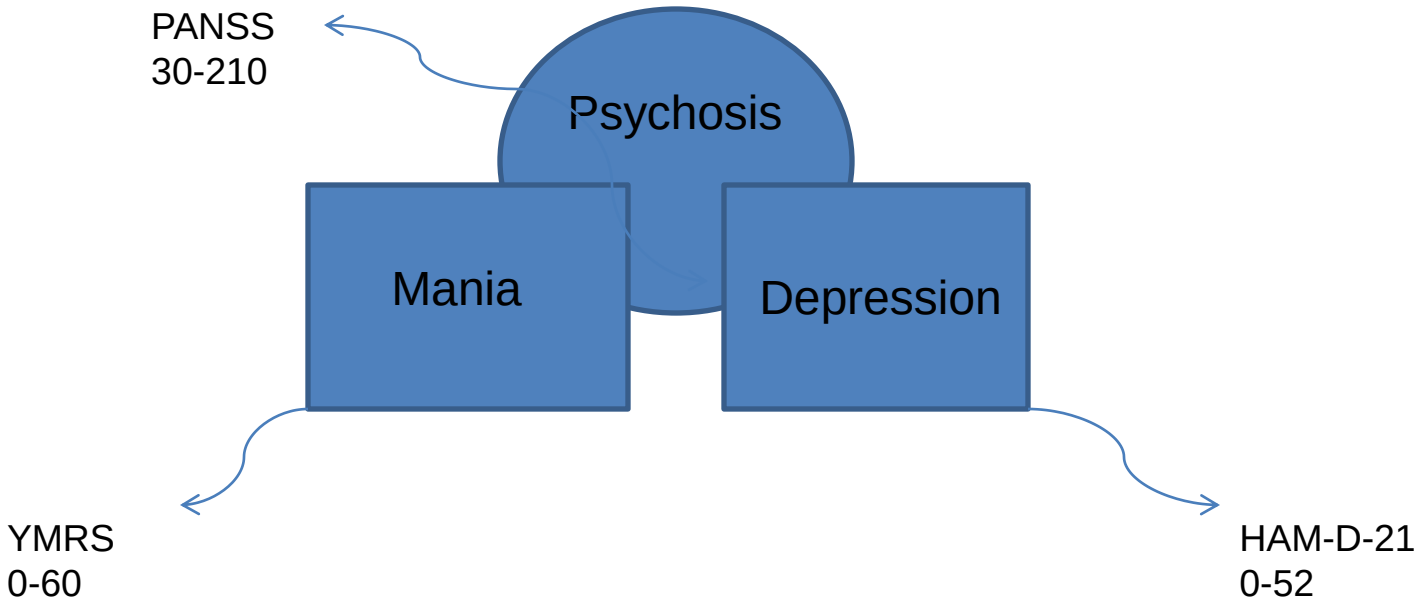

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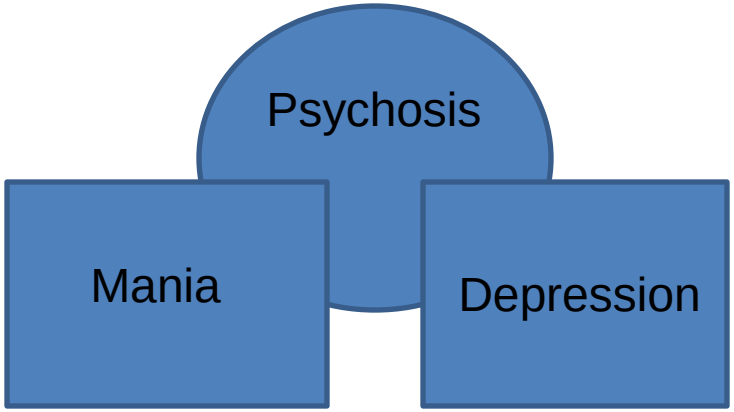
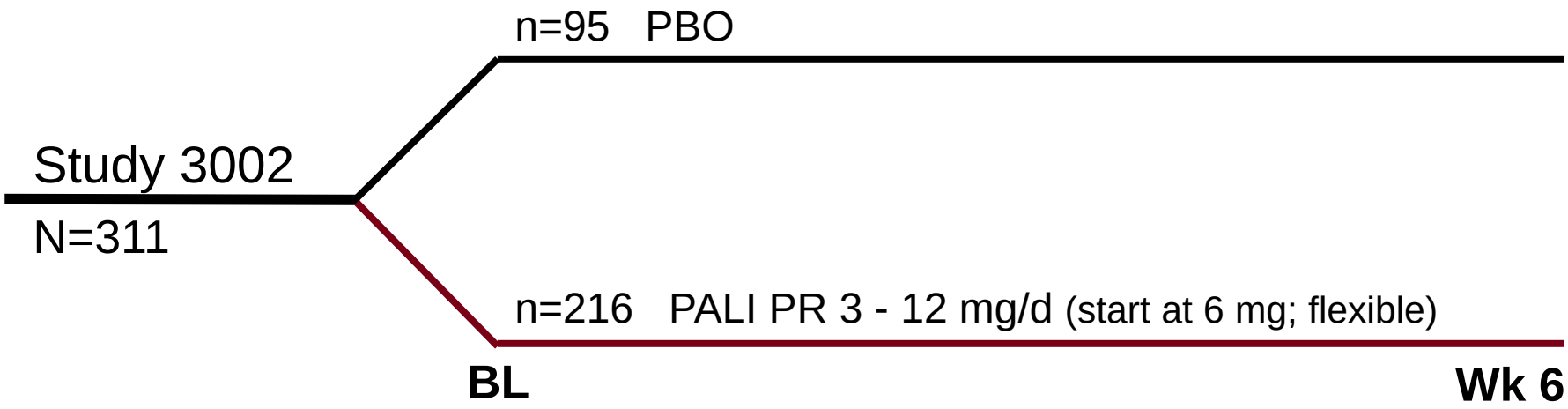
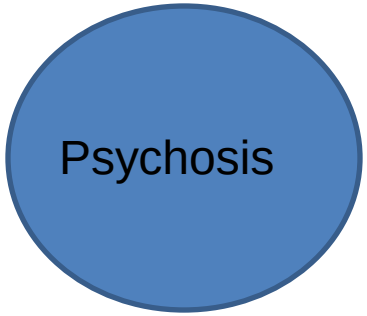




1. Canuso CM, Lindenmayer JP, Kosik-Gonzalez C, Turkoz I, Carothers J, Bossie CA, Schooler NR. A randomized, double-blind, placebo-controlled study of 2 dose ranges of paliperidone extended-release in the treatment of subjects with schizoaffective disorder. J Clin Psychiatry. 2010 May;71(5):587-98.

Background, Motivating Question, Schizoaffective Trial

PRIMARY ENDPOINT



Changes in PANSS
Total Score at Week 6

SECONDARY ENDPOINTS

HAM-D-21

YMRS

Background, Motivating Question, Schizoaffective Trial

PRIMARY ENDPOINT

Psychosis

Changes in PANSS Total Score at Week 6

SECONDARY ENDPOINTS

Depression

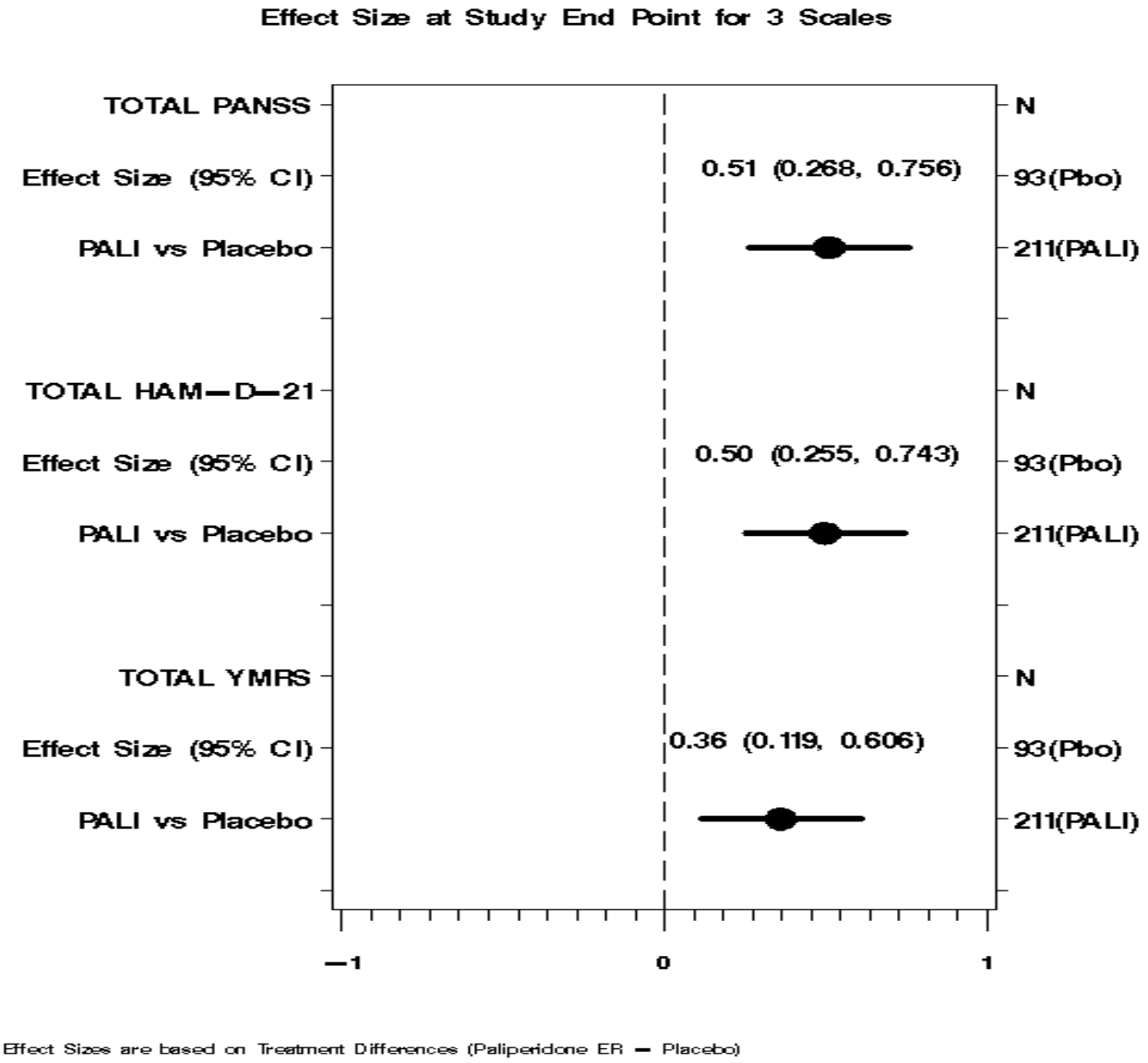
HAM-D-21

FOR REGISTRATION PURPOSES

Mania

YMRS

Background, Motivating Question, Schizoaffective Trial



Background, Motivating Question, ADHD Trial [1]

TABLE 2. EFFICACY OUTCOMES FOR ACADEMIC AND BEHAVIORAL MEASURES IN PRESPECIFIED RANK ORDER DURING DOUBLE-BLIND LABORATORY SCHOOL STUDY DAYS: EFFICACY ENDPOINTS THAT FULFILLED THE GATEKEEPER CRITERIA TO MAINTAIN OVERALL TYPE I ERROR AT 0.05

	Least-squares mean (standard error)				
Efficacy measures	*Placebo*	*OROS MPH*	*Difference*	p *value*	*Cohen's effect size*[a]
Primary efficacy endpoints[b]					
PERMP-attempted	74.9 (2.41)	103.5 (2.41)	28.6	<0.0001	1.4
PERMP-correct	69.0 (2.32)	97.3 (2.32)	28.3	<0.0001	1.5
Secondary efficacy endpoints[c]					
SKAMP-deportment	9.0 (0.57)	3.1 (0.57)	5.9	<0.0001	1.2
SKAMP-composite	20.8 (0.88)	9.8 (0.88)	11.0	<0.0001	1.5
SKAMP-attention	11.8 (0.56)	6.7 (0.56)	5.1	<0.0001	1.1
TOVA ADHD score	−4.62 (0.451)	−1.46 (0.446)	−3.16	<0.0001	0.93
TOVA reaction time	73.67 (2.604)	89.70 (2.586)	16.03	<0.0001	0.74
TOVA reaction time variability	62.69 (4.095)	85.14 (4.076)	−22.45	<0.0001	0.66
Finger windows backward	11.24 (0.463)	12.17 (0.463)	−0.93	0.018	0.24
Finger windows forward	12.93 (0.454)	14.25 (0.454)	−1.32	0.0057	0.35

[a]Based on least-squares mean difference.

[b]Primary efficacy endpoints analyzed using the Hochberg's step-up multiple-comparison procedure in order to maintain the overall type I error at a 0.05 significance level. PERMP results are based on testing 4 hours post dose.

[c]Secondary endpoints analyzed and tested at the 5% significance level using the fixed-sequence gatekeeper approach. SKAMP results are based on testing 4 hours post dose.

PERMP = Permanent Product Measure of Performance; SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham; TOVA = Test of Variables of Attention.

1. Wigal SB, Wigal T, Schuck S, Brams M, Williamson D, Armstrong RB, and Starr HL. Academic, Behavioral, and Cognitive Effects of OROS® Methylphenidate on Older Children with Attention-Deficit/Hyperactivity Disorder . J Child Adolesc Psychopharmacol. 2011 April; 21(2): 121–131.

Background, Motivating Question, ADHD Trial [1]

TABLE 3. EFFICACY OUTCOMES FOR ACADEMIC AND BEHAVIORAL MEASURES IN PRESPECIFIED RANK ORDER DURING DOUBLE-BLIND LABORATORY SCHOOL STUDY DAYS: EFFICACY ENDPOINTS THAT DID NOT FULFILL GATEKEEPER CRITERIA TO MAINTAIN OVERALL TYPE I ERROR AT 0.05

Efficacy measures	*Least-squares mean (standard error)*		*Difference*	p *value*	*Cohen's effect size*[a]
	Placebo	*OROS MPH*			
TOVA Commissions subtest	86.31 (4.084)	92.61 (4.011)	−6.30	0.1091	0.19
Digit Span backward	5.10 (0.243)	5.35 (0.243)	0.25	0.2653	0.12
Gray Silent Reading Test	85.49 (2.522)	91.98 (2.521)	−6.49	0.0038	0.31
Test of Handwriting Skills, Revised	93.56 (2.541)	98.31 (2.541)	−4.75	0.0001	0.22
Dynamic Indicators of Basic Early Literacy Skills ORF	106.15 (4.179)	111.91 (4.179)	−5.76	0.0092	0.16
Digit Span forward (subtest of WISC)	9.24 (0.213)	9.25 (0.213)	−0.02	0.9195	0.01
TOVA Omissions subtest	24.58 (13.08)	64.13 (12.896)	−39.55	0.0002	0.37
Homework tasks					
Grammar task	0.24 (0.023)	0.33 (0.023)	−0.08	0.0002	0.45
Short story with questions for comprehension	0.61 (0.031)	0.63 (0.031)	−0.02	0.4625	0.08
Identify root word	0.74 (0.037)	0.76 (0.3054)	−0.02	0.6262	0.06
Alphabetize list of words	0.67 (0.042)	0.67 (0.041)	0.00	0.9980	0.00
Identify multiple meanings for words	0.69 (0.036)	0.80 (0.035)	−0.10	0.0151	0.35
Complete sentences using words from list provided	0.65 (0.037)	0.74 (0.037)	−0.09	0.0043	0.030
Word search	0.94 (0.019)	0.98 (.019)	−0.04	0.0371	0.28
Decode a mystery sentence	0.96 (0.016)	0.99 (0.015)	−0.03	0.0965	0.27

[a]Based on least-squares mean difference.
ORF = Oral Reading Fluency; WISC = Wechsler Intelligence Scale for Children.

1. Wigal SB, Wigal T, Schuck S, Brams M, Williamson D, Armstrong RB, and Starr HL. Academic, Behavioral, and Cognitive Effects of OROS® Methylphenidate on Older Children with Attention-Deficit/Hyperactivity Disorder . J Child Adolesc Psychopharmacol. 2011 April; 21(2): 121–131.

Background

It is important to evaluate secondary endpoints to differentiate your drug from other drugs in market place.

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Another symptom,

Functionality,

Medication Satisfaction,

Certain Adverse Reactions,

Cognition,

Etc.

Background

It is important to evaluate secondary endpoints to differentiate your drug from other drugs in market place

Another symptom,

Functionality,

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Etc.

Failure to consider important outcomes can limit the conclusions of clinical trials.

Background

- Examination of appropriate statistical methods to test secondary endpoints requires careful consideration
- Fixed sequence gate-keeping procedures [1,2,3,4] are widely used because of their ease of application and interpretation in many circumstances
- These gate-keeping procedures often require prospective ordering of null hypotheses for secondary endpoints
- ***Can we use information that is available to order the null hypotheses based on interim effect sizes without breaking the blind?

1. Demitrienko A., Tamhane A., Bretz F. Multiple testing problems in pharmaceutical statistics 2010; Chapman&Hall/CRC Biostatistics Series
2. Westfall P.H., Krishen, A., Optimally weighted, fixed sequence and gatekeeper multiple testing procedure. J of Statistical Planining and Inference. 99 (2001) 25-40
3. Weins, B., Dmitrienko, A. (2005). The fallback procedure for evaluating a single family of hypotheses. Journal of Biopharmaceutical Statistics 15, 929–942.
4. Bretz F., Maurer W., Brannath W., Posch M., A graphical approach to sequentially rejective multiple test procedures, Stat in Med, 2009; 28:586–604.

Literature Review

- EM algorithm to estimate the within group variance for sample size re-estimation without unblinding at interim stages has been suggested [1,2,3]
- Enrollment order of subjects and the randomization block sizes to estimate the within group variance have also been used [4]
- Risk of unblinding the treatment effect from blinded inferences based on knowledge of the randomization block size for continuous and binary outcomes [5]
- The recent draft FDA guidance on adaptive designs [6] discusses possible study design modifications such as selection and/or order of secondary endpoints in addition to sample size re-estimation
- Blinded treatment effects for survival endpoints[7] were also examined

1.Gould AL, Shih WJ. Sample size re-estimation without unblinding for normally distributed outcomes with unknown variance. Communications in Statistics Theory and Methods 1992; 21: 2833–2853.
2. Shih WJ. Sample size reestimation in clinical trials. In Biopharmaceutical sequential statistical applications, Peace K (ed.). Marcel Dekker: New York, 1992; 285–301.
3. Shih WJ. Sample size reestimation for triple blind clinical trials. Drug Information Journal 1993; 27: 761–764.
4. Xing B, Ganju J. A method to estimate the variance of an endpoint from an on-going blinded trial. Statistics in Medicine 2005; 24: 1807-1814.
5. Miller F., Friede T, Kieser T. Blinded assessment of treatment effects utilizing information about randomization block length. Statistics in Medicine 2009; 28: 1690-1706.
6. Guidance for industry: Adaptive design clinical trials for drugs and biologics.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm201790.pdf
7. Xie J, Quan H, Zhang J. Blinded assessment of treatment effects for survival endpoint in an ongoing trial. *Pharmaceutical Statistics* 2012.

Objective

- Instead of formal interim analyses on unblinded data, use the information from blinded data
- Assess the feasibility of estimating magnitude of treatment effect on various secondary endpoints in ongoing trial
- Primary objective is to compare posterior ordering of the signal-to-noise ratios (effect sizes), $d = \delta / \sigma$, using available data points

Model

$$y_{ijk} = \mu_{0k} - \delta_k z_{ik} + \varepsilon_{ik}, \quad \varepsilon_{ijk} \sim N(0,\ \sigma_k^2) \ \ i.i.d.$$

Y_{ijk} $(i = 1,\ldots,n_j,\ j = 0,1,\ k = 1,2,\ldots,K)$, is the response variable for the k^{th} endpoint from j^{th} treatment group on subject i

$$Y_{i0k} \sim N(\mu_{0k}, \sigma_k^2)$$
$$Y_{i1k} \sim N(\mu_{1k}, \sigma_k^2)$$

μ_{0k} the mean placebo response
δ_k magnitude of the treatment effect
z_{ik} latent binary treatment assignment

We assume that lower y scores are better and the average effect of the treatment is δ_k,

$$Y_{1k} \sim N(\mu_{0k} - \delta_k, \sigma_k^2)$$

Model

For a two component univariate normal mixture model, it is appropriate to specify the complete likelihood function for a given response in the form:

$$p(y,z|\boldsymbol{\theta}) = \lambda\, p(y_1|\boldsymbol{\theta_1}) + (1-\lambda)\, p(y_0|\boldsymbol{\theta_0}); \quad \lambda = \mathrm{p}(z=1)$$

where, $\boldsymbol{\theta}_0 = (\mu_0, \sigma^2)$; $\boldsymbol{\theta}_1 = (\mu_1 = \mu_0 - \delta, \sigma^2)$; λ is randomization weight.

The signal-to-noise ratio for endpoint k, $d_k = \delta_k / \sigma_k$, $(k = 1,...,K)$

***Our objective is to compare the EM and Bayesian algorithm induced posterior ordering of the signal-to-noise ratios of endpoints, $P(d_1 > d_2 > ... > d_k | y)$

EM Algorithm

$$p(y,z|\boldsymbol{\theta}) = \lambda\, p(y_1|\boldsymbol{\theta_1}) + (1-\lambda)\, p(y_0|\boldsymbol{\theta_0}); \qquad \lambda = p(z=1)$$

MMLEs are the most common way to estimate parameters of interest; however, MMLEs often do not have closed form solutions. EM seeks the MMLE by iteratively applying Expectation and Maximizing steps.

E-Step, $E\{\log p(y,z|\boldsymbol{\theta})\,|\,y,\hat{\boldsymbol{\theta}}^{(t)}\}$

M-Step, the conditional expectation is maximized with respect to $\boldsymbol{\theta}$. This yields the new estimates for $\hat{\boldsymbol{\theta}}^{(t+1)}$ and a distribution for $z^{(t+1)}$.

EM Algorithm

Conditional expectation of latent treatment assignment at iteration $(t+1)$ is:

$$P(z_i^{(t+1)}=1 \mid y, \hat{\boldsymbol{\theta}}^{(t)}) = \frac{\lambda N(y \mid \hat{\mu}_0^{(t)} - \hat{\delta}^{(t)}, \hat{\sigma}^{2(t)})}{\lambda N(y \mid \hat{\mu}_0^{(t)} - \hat{\delta}^{(t)}, \hat{\sigma}^{2(t)}) + (1-\lambda) N(y \mid \hat{\mu}_0^{(t)}, \hat{\sigma}^{2(t)})}.$$

In the M-step, the mean parameters $\hat{\mu}_0$, $\hat{\delta}$, and variance parameter $\hat{\sigma}^2$ at iteration are $(t+1)$:

$$\hat{\mu}_0^{(t+1)} = \frac{\sum_{i=1}^{n} P(z_i^{(t+1)}=0 \mid y, \hat{\boldsymbol{\theta}}^{(t)}) y_i}{\sum_{i=1}^{n} P(z_i^{(t+1)}=0 \mid y, \hat{\boldsymbol{\theta}}^{(t)})}, \quad \hat{\delta}^{(t+1)} = \frac{\sum_{i=1}^{n} P(z_i^{(t+1)}=1 \mid y, \hat{\boldsymbol{\theta}}^{(t)})(y_i - \hat{\mu}_0^{(t+1)})}{\sum_{i=1}^{n} P(z_i^{(t+1)}=1 \mid y, \hat{\boldsymbol{\theta}}^{(t)})},$$

$$\hat{\sigma}^{2(t+1)} = \frac{\sum_{i=1}^{n} P(z_i^{(t+1)}=1 \mid y, \hat{\boldsymbol{\theta}}^{(t)})(y_i - \hat{\mu}_1^{(t+1)})^2 + P(z_i^{(t+1)}=0 \mid y, \hat{\boldsymbol{\theta}}^{(t)})(y_i - \hat{\mu}_0^{(t+1)})^2}{n}$$

Bayesian Approach

The likelihood function of the mixture distribution and the prior distributions of $\boldsymbol{\theta}$ and z are combined to obtain the joint posterior distribution, which is assumed to contain all the information about the unknown parameters. Using the Bayes theorem, the posterior distribution satisfies:

$$p(z,\boldsymbol{\theta}\,|\,y) \propto p(y\,|\,z,\boldsymbol{\theta})\,p(z\,|\,\boldsymbol{\theta})\,p(\boldsymbol{\theta})$$

where,

$p(y\,|\,z,\boldsymbol{\theta})$ is the likelihood

$p(z\,|\,\boldsymbol{\theta})$ is the prior probability of latent treatment assignment

$p(\boldsymbol{\theta})$ is the prior distribution of $\boldsymbol{\theta}$

Bayesian Approach

$$p(z,\boldsymbol{\theta}\,|\,y) \propto p(y\,|\,z,\boldsymbol{\theta})\,p(z\,|\,\boldsymbol{\theta})\,p(\boldsymbol{\theta})$$

The conditional distribution of the treatment allocation is proportional:

$p(z\,|\,y,\boldsymbol{\theta}) \propto p(y\,|\,z,\boldsymbol{\theta})$ this reduces to latent treatment allocation probability in EM.

Prior Distributions:

$\mu_j \sim N(\zeta,\psi)$, in order to reduce sensitvity

For simplicity purposes, we have

$\mu_0 \sim N(\bar{y}_0, s_0^2)$,

$\mu_1 = \mu_0 - \delta \sim N(\bar{y}_1, s_1^2)$,

$\sigma^{-2} \sim Gamma(\alpha,\beta)$

Bayesian Approach

Regardless of the structure of the prior distribution, the posterior distribution does not have a simple closed form. In order to make inferences about the unknown parameters, MCMC methodologies are employed to generate samples from the posterior distribution. The joint posterior probability distribution of these parameters satisfies:

$$p(z,\mu_0,\delta,\sigma^2 \mid y) \propto p(y \mid z,\mu_0,\delta,\sigma^2)\,p(z)\,p(\mu_0,\delta,\sigma^2)$$

$$\propto \left(\frac{1}{\sigma^2}\right)^{2n} \exp\left(-\frac{1}{2\sigma^2}\sum_{z_i=1}(y_i-\mu_0+\delta)^2\right)\exp\left(-\frac{1}{2\sigma^2}\sum_{z_i=0}(y_i-\mu_0)^2\right)$$

$$\times\exp\left(-\frac{(\mu_0-\delta-\bar{y}_1)^2}{2s_1^2}\right)\exp\left(-\frac{(\mu_0-\bar{y}_0)^2}{2s_0^2}\right)\left(\frac{1}{\sigma^2}\right)^{\alpha-1}\exp(-\beta\sigma^2)$$

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Likelihood for treatment

Bayesian Approach

Regardless of the structure of the prior distribution, the posterior distribution does not have a simple closed form. In order to make inferences about the unknown parameters, MCMC methodologies are employed to generate samples from the posterior distribution. The joint posterior probability distribution of these parameters satisfies:

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Likelihood for placebo arm

Bayesian Approach

Regardless of the structure of the prior distribution, the posterior distribution does not have a simple closed form. In order to make inferences about the unknown parameters, MCMC methodologies are employed to generate samples from the posterior distribution. The joint posterior probability distribution of these parameters satisfies:

$$p(z,\mu_0,\delta,\sigma^2 \mid y) \propto p(y \mid z,\mu_0,\delta,\sigma^2)\,p(z)\,p(\mu_0,\delta,\sigma^2)$$

$$\propto \left(\frac{1}{\sigma^2}\right)^{2n} \exp\left(-\frac{1}{2\sigma^2}\sum_{z_i=1}(y_i-\mu_0+\delta)^2\right)\exp\left(-\frac{1}{2\sigma^2}\sum_{z_i=0}(y_i-\mu_0)^2\right)$$

$$\times\exp\left(-\frac{(\mu_0-\delta-\bar{y}_1)^2}{2s_1^2}\right)\exp\left(-\frac{(\mu_0-\bar{y}_0)^2}{2s_0^2}\right)\left(\frac{1}{\sigma^2}\right)^{\alpha-1}\exp(-\beta\sigma^2)$$

Prior for treatment arm

Bayesian Approach

Regardless of the structure of the prior distribution, the posterior distribution does not have a simple closed form. In order to make inferences about the unknown parameters, MCMC methodologies are employed to generate samples from the posterior distribution. The joint posterior probability distribution of these parameters satisfies:

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$$\propto \left(\frac{1}{\sigma^2}\right)^{2n} \exp\left(-\frac{1}{2\sigma^2}\sum_{z_i=1}(y_i-\mu_0+\delta)^2\right)\exp\left(-\frac{1}{2\sigma^2}\sum_{z_i=0}(y_i-\mu_0)^2\right)$$

$$\times \exp\left(-\frac{(\mu_0-\delta-\bar{y}_1)^2}{2s_1^2}\right)\exp\left(-\frac{(\mu_0-\bar{y}_0)^2}{2s_0^2}\right)\left(\frac{1}{\sigma^2}\right)^{\alpha-1}\exp(-\beta\sigma^2)$$

Prior for Placebo arm

Bayesian Approach

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$$\times\exp\left(-\frac{(\mu_0-\delta-\bar{y}_1)^2}{2s_1^2}\right)\exp\left(-\frac{(\mu_0-\bar{y}_0)^2}{2s_0^2}\right)\left(\frac{1}{\sigma^2}\right)^{\alpha-1}\exp(-\beta\sigma^2)$$

Prior for Sigma

In computations, α=3 and small scale hyperparameter $\beta(=0.01)$ are assumed.

Bayesian Approach

The posterior conditional distributions of parameters of interest in equation are given by :

$$\mu_0 \sim N\left(\frac{\left(\sum_{i=1}\frac{y_i + z_i\delta}{\sigma^2}\right) + \frac{\bar{y}_0}{s_0^2} + \frac{\bar{y}_1 + \delta}{s_1^2}}{\frac{n}{\sigma^2} + \frac{1}{s_0^2} + \frac{1}{s_1^2}}, \frac{1}{\frac{n}{\sigma^2} + \frac{1}{s_0^2} + \frac{1}{s_1^2}}\right),$$

$$\delta \sim N\left(\frac{\frac{-\sum_{i=1}(y_i - \mu_0)z_i}{\sigma^2} + \frac{\mu_0 - \bar{y}_1}{s_1^2}}{\frac{\sum_{i=1} z_i}{\sigma^2} + \frac{1}{s_1^2}}, \frac{1}{\frac{\sum_{i=1} z_i}{\sigma^2} + \frac{1}{s_1^2}}\right),$$

$$\sigma^2 \sim \frac{\sum_{i=1}(y_i - \mu_0 + z_i\delta)^2 + \beta}{\chi^2_{n+3}}$$

Bayesian Approach with Covariate

We assume a trial with stratified randomization. The sample is divided into subsamples on the basis of stratifaction factor (covariate: additional medication usage, *yes* and *no* groups).

Let g_i denote the known strata membership of the subject i. $g_i = 1$ if observation belongs to the *yes* strata and 0 if it does not. The joint posterior distribution then takes the form:

$$p(z, \mu_0, \delta_{yes}, \delta_{no}, \sigma^2 \mid y) \propto \left(\frac{1}{\sigma^2}\right)^{2n} \exp\left(-\frac{1}{2\sigma^2} \sum_{z_i=1} \sum_{g_i=0,1} (y_i - \mu_0 + \delta_{g_i})^2\right)$$

$$\times \exp\left(-\frac{1}{2\sigma^2} \sum_{z_i=0} (y_i - \mu_0)^2\right) \exp\left(-\sum_{g_i=0,1} \frac{(\mu_0 - \delta_{g_i} - \bar{y}_{1g_i})^2}{2s_1^2}\right) \exp\left(-\frac{(\mu_0 - \bar{y}_0)^2}{2s_0^2}\right)$$

$$\times \left(\frac{1}{\sigma^2}\right)^{\alpha-1} \exp(-\beta\sigma^2)$$

Bayesian Approach with Covariate

We assume a trial with stratified randomization. The sample is divided into subsamples on the basis of stratifaction factor (covariate: additional medication usage, *yes* and *no* groups).

Let g_i denote the known strata membership of the subject i. $g_i = 1$ if observation belongs to the *yes* strata and 0 if it does not. The joint posterior distribution then takes the form:

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$$\times \exp\left(-\frac{1}{2\sigma^2} \sum_{z_i=0} (y_i - \mu_0)^2\right) \exp\left(-\sum_{g_i=0,1} \frac{(\mu_0 - \delta_{g_i} - \bar{y}_{1g_i})^2}{2s_1^2}\right) \exp\left(-\frac{(\mu_0 - \bar{y}_0)^2}{2s_0^2}\right)$$

$$\times \left(\frac{1}{\sigma^2}\right)^{\alpha-1} \exp(-\beta\sigma^2)$$

Bayesian Approach with Covariate

Conditional posterior probability treatment assignment at each iteration is given by:

$$P(z_i = 1) = \begin{cases} \dfrac{\exp\left(-\dfrac{1}{2\sigma^2}\sum(y_i - \mu_0 + \delta_{yes})^2\right)}{\exp\left(-\dfrac{1}{2\sigma^2}\sum(y_i - \mu_0 + \delta_{yes})^2\right) + \exp\left(-\dfrac{1}{2\sigma^2}\sum(y_i - \mu_0)^2\right)}, & \text{Yes strata} \\ \dfrac{\exp\left(-\dfrac{1}{2\sigma^2}\sum(y_i - \mu_0 + \delta_{no})^2\right)}{\exp\left(-\dfrac{1}{2\sigma^2}\sum(y_i - \mu_0 + \delta_{no})^2\right) + \exp\left(-\dfrac{1}{2\sigma^2}\sum(y_i - \mu_0)^2\right)}, & \text{No strata} \end{cases}$$

Bayesian Approach with Covariate

The posterior distribution for parameters of interest are computed to be:

$$\mu_0 \sim N\left(\frac{\left(\sum_{i=1}\frac{y_i + z_i(\delta_{yes}+\delta_{no})}{\sigma^2}\right) + \frac{\bar{y}_0}{s_0^2} + \frac{(\bar{y}_{1,yes}+\delta_{yes})+(\bar{y}_{1,no}+\delta_{no})}{s_1^2}}{\frac{n}{\sigma^2}+\frac{1}{s_0^2}+\frac{2}{s_1^2}}, \frac{1}{\frac{n}{\sigma^2}+\frac{1}{s_0^2}+\frac{2}{s_1^2}}\right),$$

$$\delta_{yes} \sim N\left(\frac{-\sum_{i=1,g=1}(y_i-\mu_0)z_i}{\frac{\sigma^2}{\sum_{i=1,g=1} z_i} + \frac{\mu_0-\bar{y}_{1,yes}}{s_1^2}}, \frac{1}{\frac{\sum_{i=1,g=1} z_i}{\sigma^2}+\frac{1}{s_1^2}}\right), \quad \delta_{no} \sim N\left(\frac{-\sum_{i=1,g=2}(y_i-\mu_0)z_i}{\frac{\sigma^2}{\sum_{i=1,g=2} z_i} + \frac{\mu_0-\bar{y}_{1,no}}{s_1^2}}, \frac{1}{\frac{\sum_{i=1,g=2} z_i}{\sigma^2}+\frac{1}{s_1^2}}\right),$$

$$\sigma^2 \sim \frac{\sum_{i=1,g=1}(y_i-\mu_0+z_i\delta_{yes})^2 + \sum_{i=1,g=2}(y_i-\mu_0+z_i\delta_{no})^2 + \beta}{\chi^2_{n+3}}.$$

Bayesian Approach with Covariate and a Power Prior

Denote the historical data by D_0 and current data by D

$\alpha_0 \in [0,1]$ to control the influence of the historical data on the current study [1,2,3]

$\alpha_0 \to 1$ approaches full barrowing from D_0

$\alpha_0 \to 0$ approaches no barrowing from D_0

The basic idea is to use the power α_0 parameter to control the influence of the historical data on the current study

Let assume

$L(D_0 \mid \theta)$ is the past data likelihood

$L(D \mid \theta)$ is the current data likelihood

$p(\theta \mid D_0, \alpha_0) \propto L(D_0 \mid \theta)^{\alpha_0} \, p(\theta) \, p(\alpha_0)$ is the posterior given past likelihood,

Then, the full likelihood is proportional to $p(\theta \mid D_0, \alpha_0) L(D \mid \theta)$

1. Ibrahim J, Chen MH. Power prior distributions for regression models. *Statistical Science* 2000; 15:46-60.
2. Duan Y, Ye K, Smith EP. Evaluating water quality using power priors to incorporate historical information. *Environmetrics* 2006; 17: 95-106.
3. Hobbs BP, Carlin BP, Mandrekar S, and Sargent DJ. Hierarchical commensurate and power prior models for adaptive incorporation of historical information in clinical trials. *Biometrics*, 2011; 67:1047-1056.

Bayesian Approach with Covariate and a Power Prior

The joint posterior distribution can be extended to include the prior for α_0

Think of $\alpha_0 n_0$ as the historical effective sample size.

The result takes the form :

$$p(z,\mu_0,\delta_y,\delta_n,\sigma^2,\alpha_0 \mid y) \propto \left(\frac{1}{\sigma^2}\right)^{2n} \exp\left(-\frac{1}{2\sigma^2}\sum_{z_i=1}\sum_{g}(y_i-\mu_0+\delta_g)^2\right)$$

$$\times\exp\left(-\frac{1}{2\sigma^2}\sum_{z_i=0}(y_i-\mu_0)^2\right)\left(\frac{\sqrt{n_{1p,yes}\alpha_0}}{s_1}\right)\exp\left(-\frac{(\mu_0-\delta_{yes}-\bar{y}_{1,yes})^2 n_{1p,yes}\alpha_0}{2s_1^2}\right)$$

$$\times\left(\frac{\sqrt{n_{1p,no}\alpha_0}}{s_1}\right)\exp\left(-\frac{(\mu_0-\delta_{no}-\bar{y}_{1,no})^2 n_{1p,no}\alpha_0}{2s_1^2}\right)$$

$$\times\left(\frac{\sqrt{n_{0p}\alpha_0}}{s_0}\right)\exp\left(-\frac{(\mu_0-\bar{y}_0)^2 n_{0p}\alpha_0}{2s_0^2}\right)\left(\frac{1}{\sigma^2}\right)^{\alpha-1}\exp(-\beta\sigma^2)$$

$$\times\alpha_0^{a-1}(1-\alpha_0)^{b-1}$$

Prior for Power Parameter

Bayesian Approach with Covariate and a Power Prior

The posterior distribution of parameters of interest is computed to be:

$$\alpha_0 \propto \alpha_0^{a+\frac{1}{2}}(1-\alpha_0)^{b-1}\exp\left(-\frac{\alpha_0}{2}\left[\left(\frac{(\mu_0-\bar{y}_0)^2 n_{op}}{s_0^2}\right)+\left(\frac{(\mu_0-\delta_{yes}-\bar{y}_{1,yes})^2 n_{1p,yes}}{s_1^2}\right)\right]\right)$$

$$\times\exp\left(-\frac{\alpha_0}{2}\left[\frac{(\mu_0-\delta_{no}-\bar{y}_{1,no})^2 n_{1p,no}}{s_1^2}\right]\right)$$

$$\mu_0 \sim N\left(\frac{\sum_{i=1}\frac{y_i+z_i(\delta_{yes}+\delta_{no})}{\sigma^2}+\frac{\bar{y}_0 n_{0p}\alpha_0}{s_0^2}+\frac{(\bar{y}_{1,yes}+\delta_{yes})n_{1p,yes}\alpha_0+(\bar{y}_{1,no}+\delta_{no})n_{1p,no}\alpha_0}{s_1^2}}{\frac{n}{\sigma^2}+\frac{n_{0p}\alpha_0}{s_0^2}+\frac{n_{1p}\alpha_0}{s_1^2}},\frac{1}{\frac{n}{\sigma^2}+\frac{n_{0p}\alpha_0}{s_0^2}+\frac{n_{1p}\alpha_0}{s_1^2}}\right)$$

Bayesian Approach with Covariate and a Power Prior

The posterior distribution of parameters of interest is computed to be:

$$\delta_{yes} \sim N\left(\frac{-\sum_{i=1,g=1} (y_i - \mu_0) z_i}{\frac{\sigma^2}{\sum_{i=1,g=1} z_i} + \frac{(\mu_0 - \bar{y}_{1,yes}) n_{1p,yes} \alpha_0}{s_1^2}}, \frac{1}{\frac{\sum_{i=1,g=1} z_i}{\sigma^2} + \frac{n_{1p,yes} \alpha_0}{s_1^2}} \right),$$

$$\delta_{no} \sim N\left(\frac{-\sum_{i=1,g=2} (y_i - \mu_0) z_i}{\frac{\sigma^2}{\sum_{i=1,g=2} z_i} + \frac{(\mu_0 - \bar{y}_{1,no}) n_{1p,no} \alpha_0}{s_1^2}}, \frac{1}{\frac{\sum_{i=1,g=2} z_i}{\sigma^2} + \frac{n_{1p,no} \alpha_0}{s_1^2}} \right),$$

$$\sigma^2 \sim \frac{\sum_{i=1,g=1} (y_i - \mu_0 + z_i \delta_{yes})^2 + \sum_{i=1,g=2} (y_i - \mu_0 + z_i \delta_{no})^2 + \beta}{\chi^2_{n+3}}.$$

Model Selection

By contrast with frequentist analogues, Bayesian model comparison distinguishes which likelihood and prior combinations better fit the data. These measures of performance can be used to choose a single "best" model or improve estimation via model averaging.

The deviance information criterion (DIC)[1] provides a natural measure of performance in this setting.

Models with smaller DIC should be preferred to models with larger DIC.

$$
\begin{aligned}
DIC &= p_d + \bar{D}, \\
&= 2\bar{D} - D(\bar{\boldsymbol{\theta}}), \qquad \text{since} \quad p_d = \bar{D} - D(\bar{\boldsymbol{\theta}}) \\
&= 2D(\mu_0, \delta) - D(\hat{\mu}_0, \hat{\delta}) \\
&= 2\,Expectation\ over\ (\mu_0, \delta) - Expectation\ over\ (\hat{\mu}_0, \hat{\delta})
\end{aligned}
$$

1. D.J. Spiegelhalter, N.G. Best, B.P. Carlin, A. Linde. Bayesian measures of model complexity and fit (with discussion). Journal of the Royal Statistics Society, Series B (Statistical Methodology)2002; 64: 583–639.

Model Selection

$$DIC = 2D(\mu_0, \delta) - D(\hat{\mu}_0, \hat{\delta})$$

$D(\mu_0, \delta) = E_{\mu_0, \delta}\left[\sum_{i=1} \frac{(y_i - \mu_0 + z_i\delta)^2}{\hat{\sigma}^2}\right]$, this is a posterior expectation over (μ_0, δ), average after all the iterations

$\hat{\sigma}^2$ = averaged after all the iterations

μ_0 = updates at each iteration

δ = updates at each iteration

z_i = *latent* treatment assignment at each iteration

$D(\hat{\mu}_0, \hat{\delta}) = E_{z_i}\left[\sum_{i=1} \frac{(y_i - \hat{\mu}_0 + z_i\hat{\delta})^2}{\hat{\sigma}^2}\right]$, this is a posterior expectation over z_i, it is using averaged parameters

$\hat{\sigma}^2$ = averaged after all the iterations

$\hat{\mu}_0$ = averaged after all the iterations

$\hat{\delta}$ = averaged after all the iterations

z_i = *latent* treatment assignment at each iteration

MCMC Gibbs Sampling

An important feature of the Gibbs sampler is that each simulated posterior parameter value is always accepted

The main drawback of the Gibbs sampler in this setting is the lack of mixing

We employed a Metropolis-Hastings algorithm with an acceptance-rejection sampling

This involved subsampling 10% of the treatment and placebo group observations and proposing a label switch

1) Draw random candidate samples fromfor switching treatment

2) Generate u from the Uniform (0,1) distribution

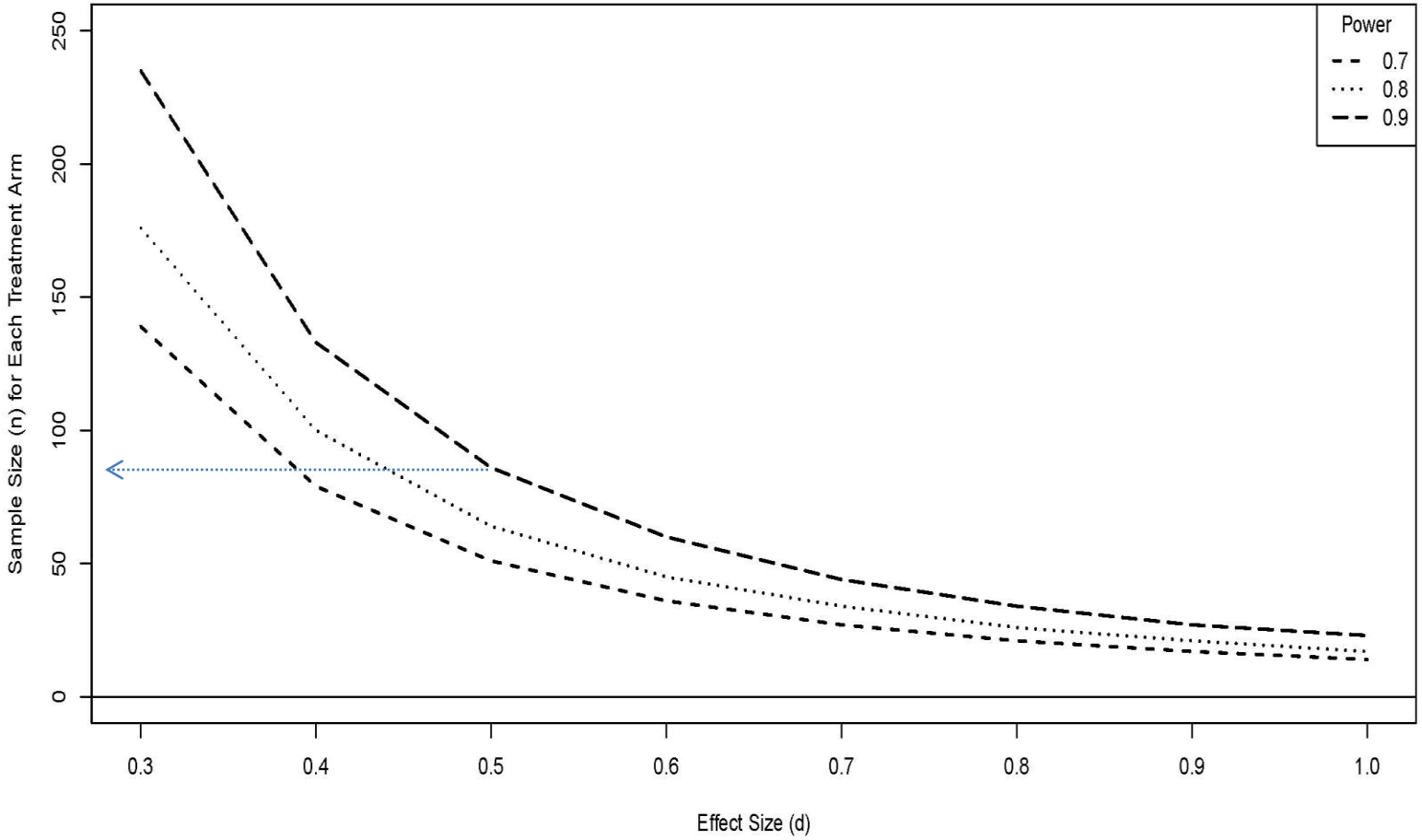
3) If, $u \leq \frac{\prod (1-(p(z_i=1))_i}{\prod p(z_i=1)_i}$ make label change; otherwise return to step 1.

Simulation Set-Up

Scenario	d_1		d_2		d_3	N
1	0.5	=	0.5	=	0.5	170
2	0.8	>	0.5	>	0.3	170
3	1.0	>	0.5	>	~0	170
4	1.0	>	0.5	>	~0	72
5	1.0	>	0.5	>	~0	468

Simulation Set-Up

Sample Size and Power Computations using a Two-Sample t-test with Two-Sided Type I Error=0.05



Simulation Set-Up

2 treatment arms with a 1:1 treatment allocation ratio,

$k = 3$ uncorrelated endpoints, y_1, y_2, and y_3,

No missing data,

For each case 20 data sets are generated, l $(l = 1, ..., 20)$,

Different prior for each of the endpoints.

Scenario	d_1		d_2		d_3	N
1	0.5	=	0.5	=	0.5	170
2	0.8	>	0.5	>	0.3	170
3	1.0	>	0.5	>	0	170
4	1.0	>	0.5	>	0	72
5	1.0	>	0.5	>	0	468

Generate Input Data Sets:

$$\mu_0(k,l) \sim N(\bar{Y}_{0k}, s^2_{0k}),$$

$$\mu_1(k,l) = \mu_0(k,l) - \delta(k,l) \sim N(\bar{Y}_{1k}, s^2_{1k}),$$

$$\sigma^2 \sim IG(\varepsilon_k, b_k),\ k = 1,2,3,\ \ l = 1, ..., 20.$$

Without loss of generality, we assumed that

$$\bar{Y}_{0k} = 10,\ \ s^2_{0k} = s^2_{1k} = 10$$

Simulation Set-Up

◦ Each true input clinical trial data set is based on $\mu_0 \sim N(10, 10^2)$ and μ_1 with normal distribution with variance 10^2 and corresponding mean value to generate effect sizes for a given scenario.

◦ Initial values of $(\mu_0,\ \delta,\ \sigma^2)$ for simulations are based on the true input data set parameters and the initial power parameter α_0 estimate is given as 0.25 and 0.5.

◦ Posterior inferences are based on 1000 iterations.

◦ The first 200 iterations are considered to be the burn – in period for both EM and Bayesian algorithms.

◦ Every 4^{th} point after the burn – in period is stored for the Bayesian simulations to reduce correlations to emulate thinning process.

◦ Eight hundred simulation results in EM and 200 results in Bayesian methods are summarized.

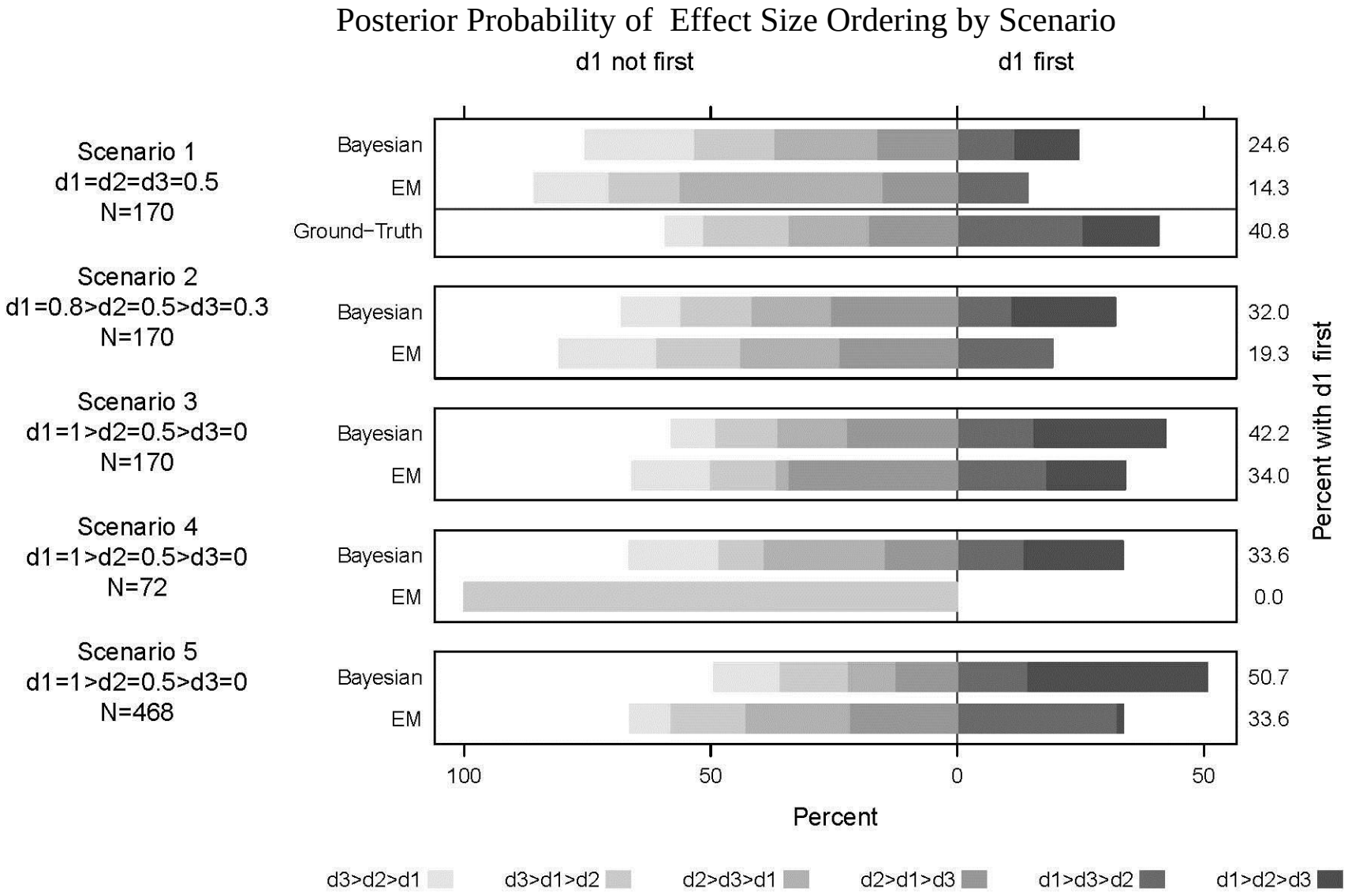
- Posterior parameter estimates are summuarized.
- Empirical probability of each triplet combination of effect size ordering is examined.

◦ In each case for a given data set, the last 20 simulation results are kept for effect size orderings.

◦ For each of the study data sets, a total of $20 \times 20 \times 20 = 8000$ possible triplet combinations of orderings are available.

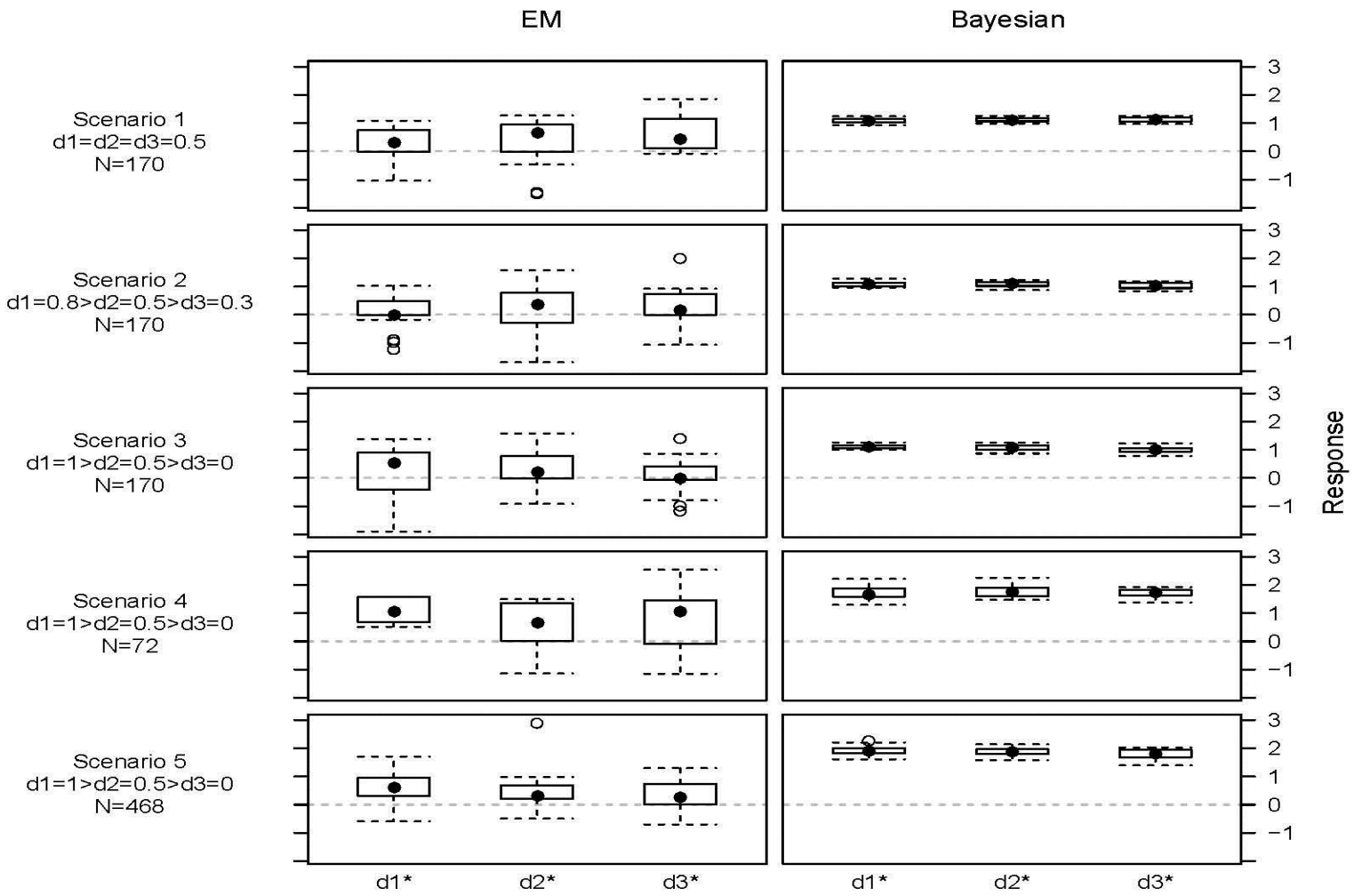
◦ For 20 different study data sets, a total of $160,000$ possible orderings are available.

Simulation Results



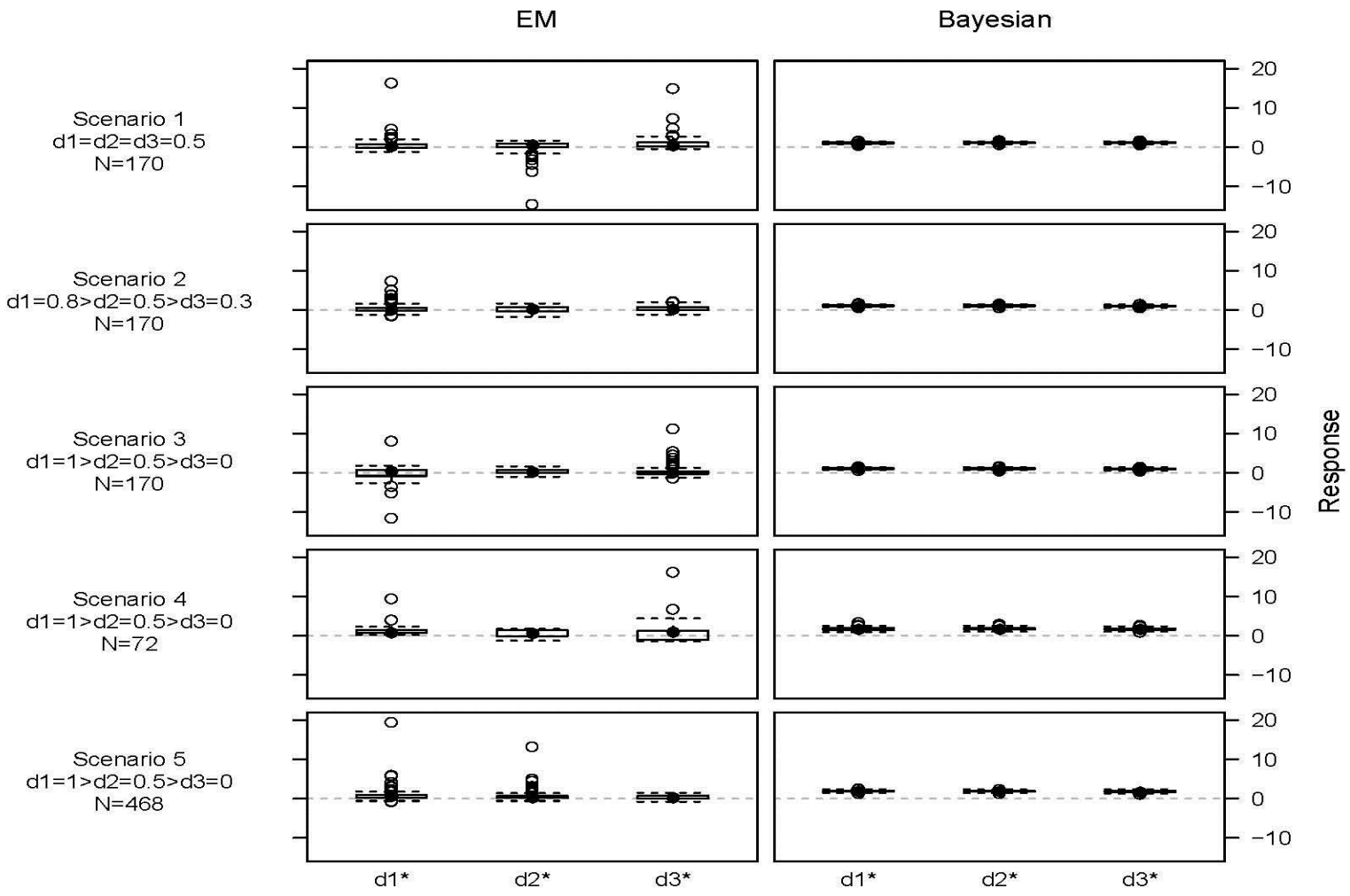
Simulation Results

Posterior Distribution of Effect Sizes by Scenario, Averaged Over 20 Data Sets



Simulation Results

Posterior Distribution of Effect Sizes by Scenario

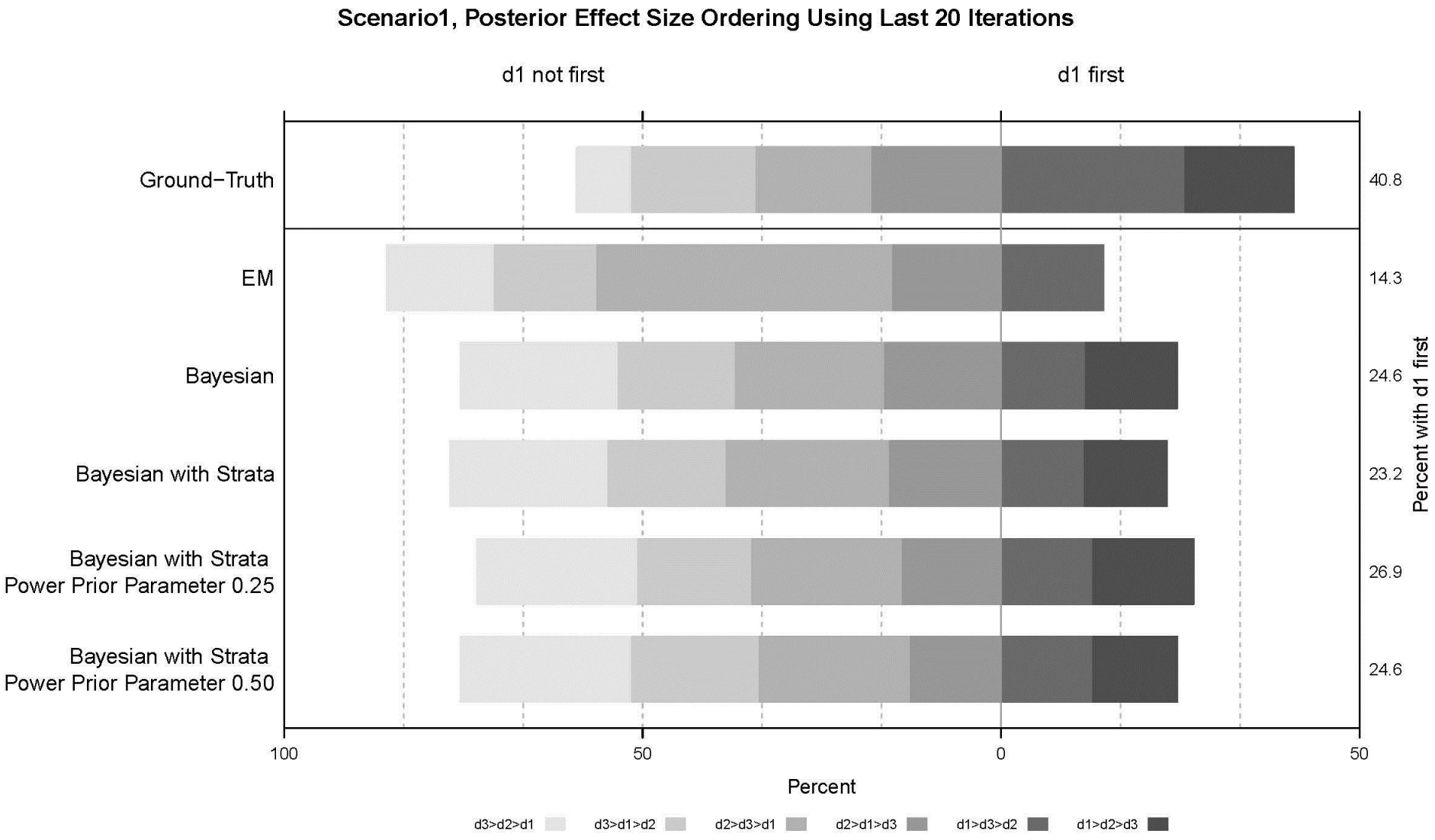


Simulation Results, Scenario 1

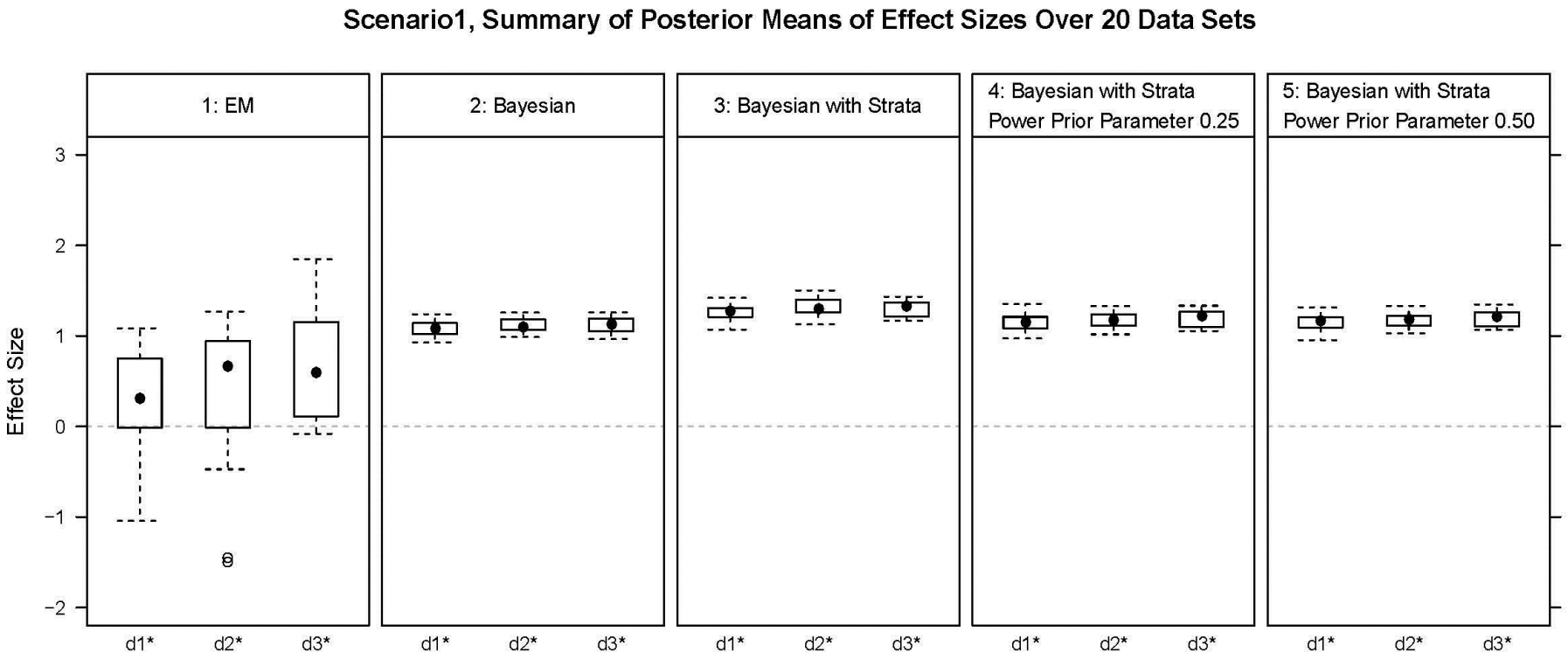
Scenario 1, $d_1 = d_2 = d_3 = 0.5$; N=170, Input Data Set Parameter Characteristics

Parameter	Variable	Statistics			
		N	Mean (SD)	Median	95% CI
Placebo Mean	y1	20	10.2 (0.95)	10.2	8.54; 12.32
	y2	20	10.1 (0.91)	9.9	8.68; 11.89
	y3	20	10.1 (0.91)	10.1	8.27; 12.04
Sigma (STD)	y1	20	10.2 (0.64)	10.2	9.15; 11.13
	y2	20	10.0 (0.53)	10.0	9.09; 10.94
	y3	20	10.0 (0.47)	10.0	9.30; 11.02
Delta	y1	20	5.1 (0.29)	5.0	4.63; 5.52
	y2	20	5.0 (0.27)	5.0	4.42; 5.49
	y3	20	5.0 (0.27)	5.0	4.51; 5.52
Effect Size, d	y1	20	0.50 (0.01)	0.50	0.48; 0.52
	y2	20	0.50 (0.01)	0.50	0.48; 0.52
	y3	20	0.50 (0.01)	0.50	0.48; 0.52

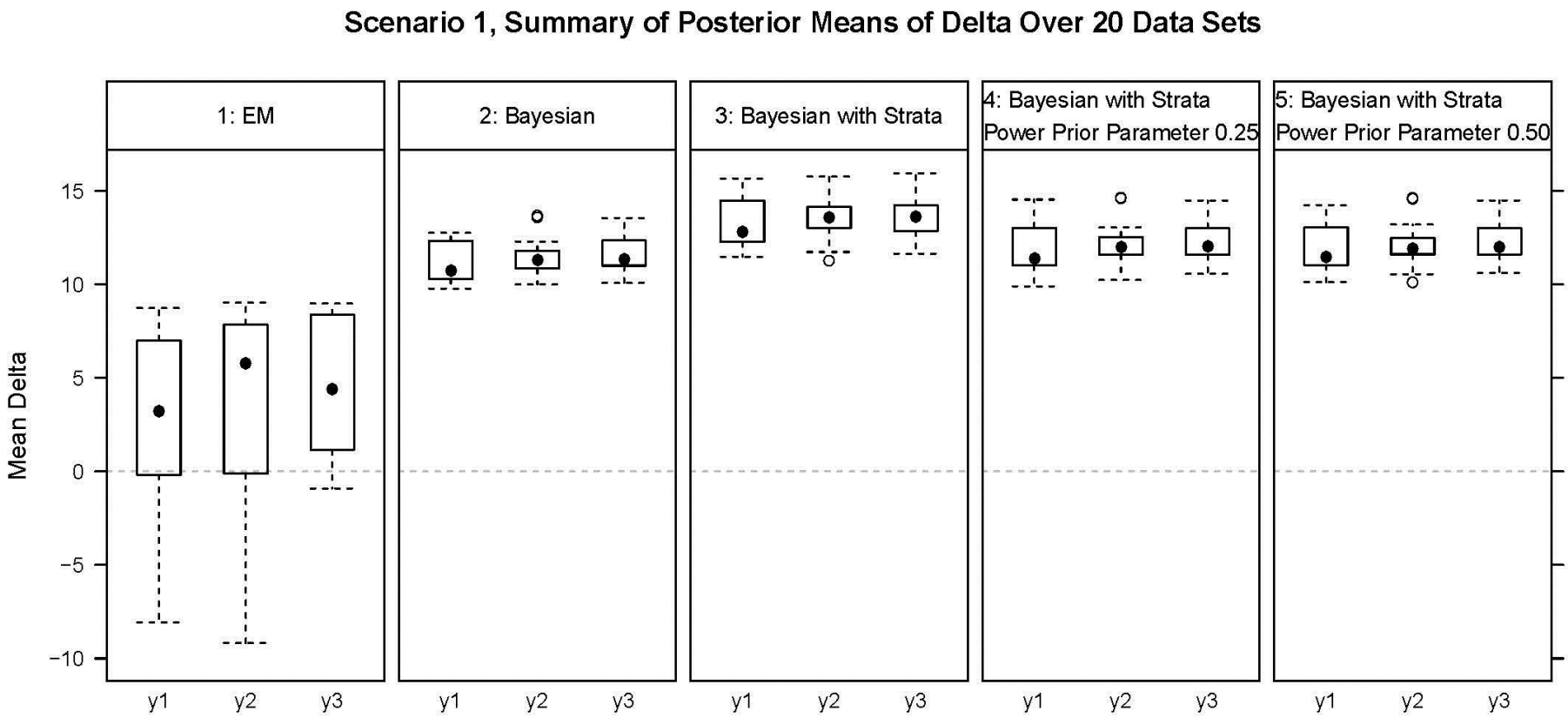
Simulation Results, Scenario 1



Simulation Results, Scenario 1



Simulation Results, Scenario 1



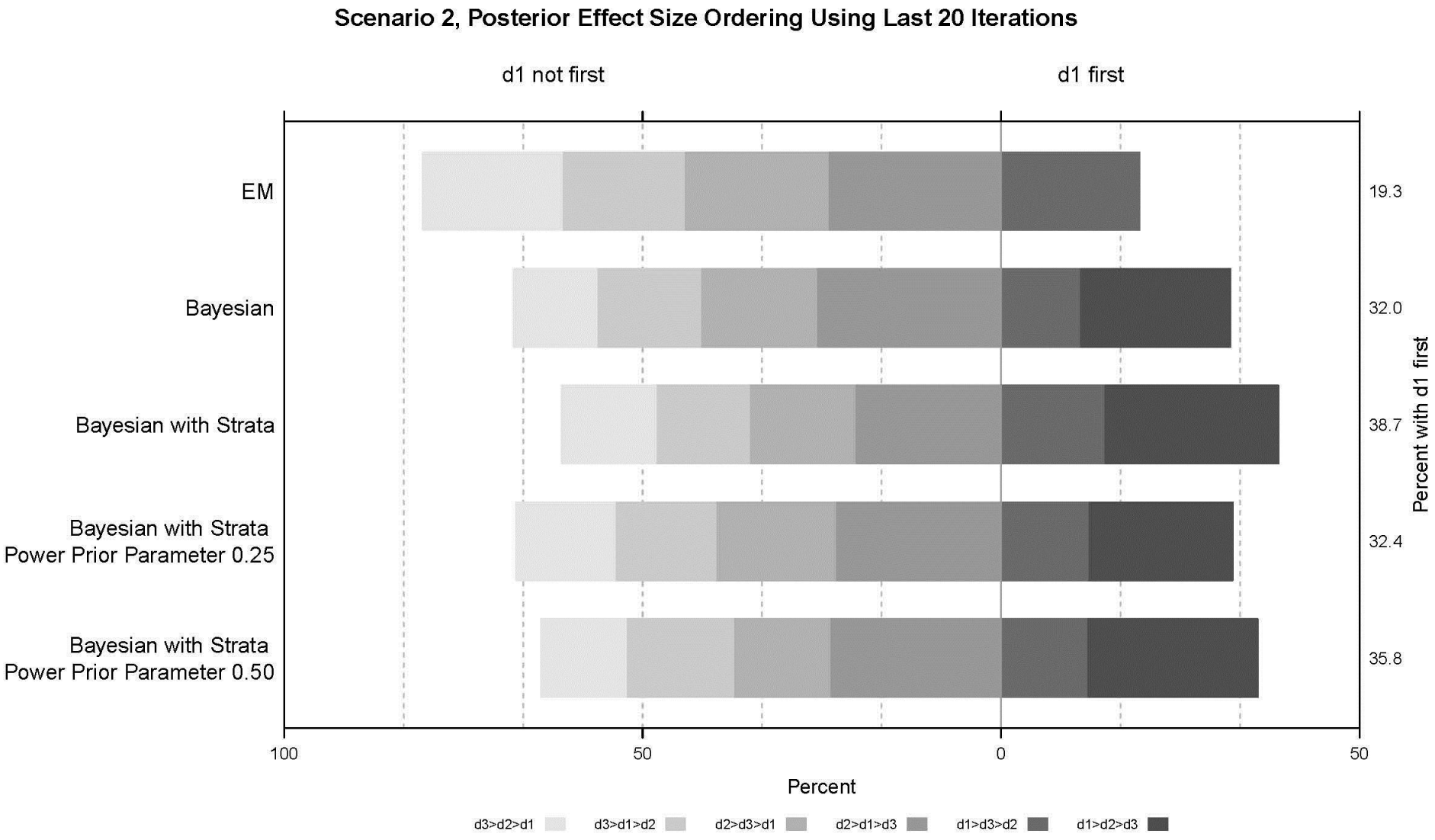
Simulation Results, Scenario 1

Scenario 1, Summary of Posterior Means of Parameters Over 20 Data Sets

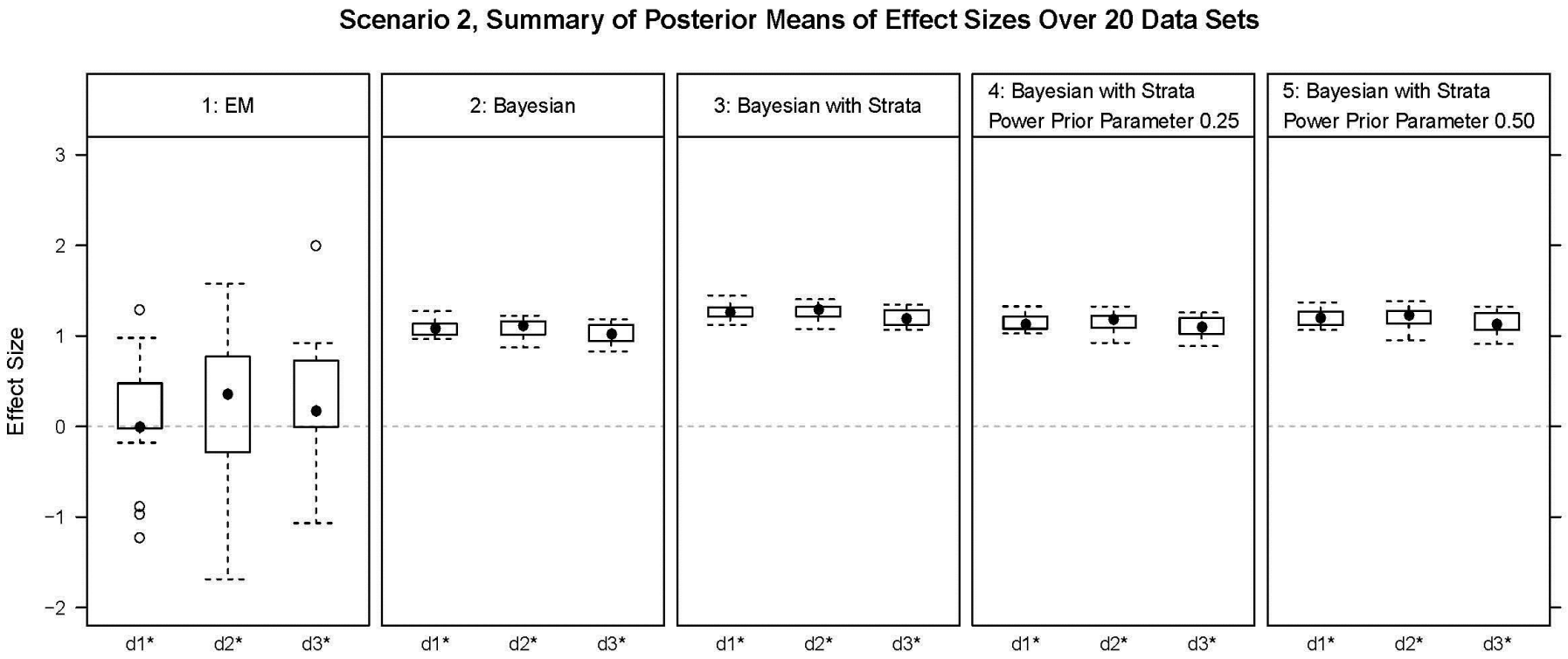
Analysis Type / Parameter	Variable	Statistics			
		N	Mean (SD)	Median	95% CI
EM					
Sigma	y1	15	9.00 (2.055)	10.07	2.9 ; 10.8
	y2	18	8.49 (1.518)	8.87	6.1 ; 11.2
	y3	15	8.88 (2.016)	9.77	4.6 ; 11.2
Delta	y1	15	2.63 (4.996)	3.26	-8.1 ; 8.7
	y2	18	3.07 (5.893)	5.81	-9.2 ; 9.0
	y3	15	4.42 (3.651)	4.42	-0.9 ; 9.0
Effect Size d*	y1	15	81.45 (314.5)	0.31	-1.0 ; 1218.2
	y2	18	0.35 (0.836)	0.67	-1.5 ; 1.3
	y3	15	0.69 (0.618)	0.60	-0.1 ; 1.8
Bayesian					
Sigma	y1	20	10.44 (0.665)	10.47	9.4 ; 11.5
	y2	20	10.28 (0.490)	10.30	9.4 ; 11.2
	y3	20	10.31 (0.518)	10.27	9.6 ; 11.4
Delta	y1	20	11.19 (1.051)	10.75	9.8 ; 12.8
	y2	20	11.43 (0.984)	11.32	10.0 ; 13.7
	y3	20	11.53 (0.953)	11.36	10.1 ; 13.6
Effect Size d*	y1	20	1.08 (0.086)	1.08	0.9 ; 1.2
	y2	20	1.12 (0.078)	1.10	1.0 ; 1.3
	y3	20	1.12 (0.084)	1.13	1.0 ; 1.3

CI= Credible Interval; Sigma= Pooled variance; Delta= Difference between treatment arms.

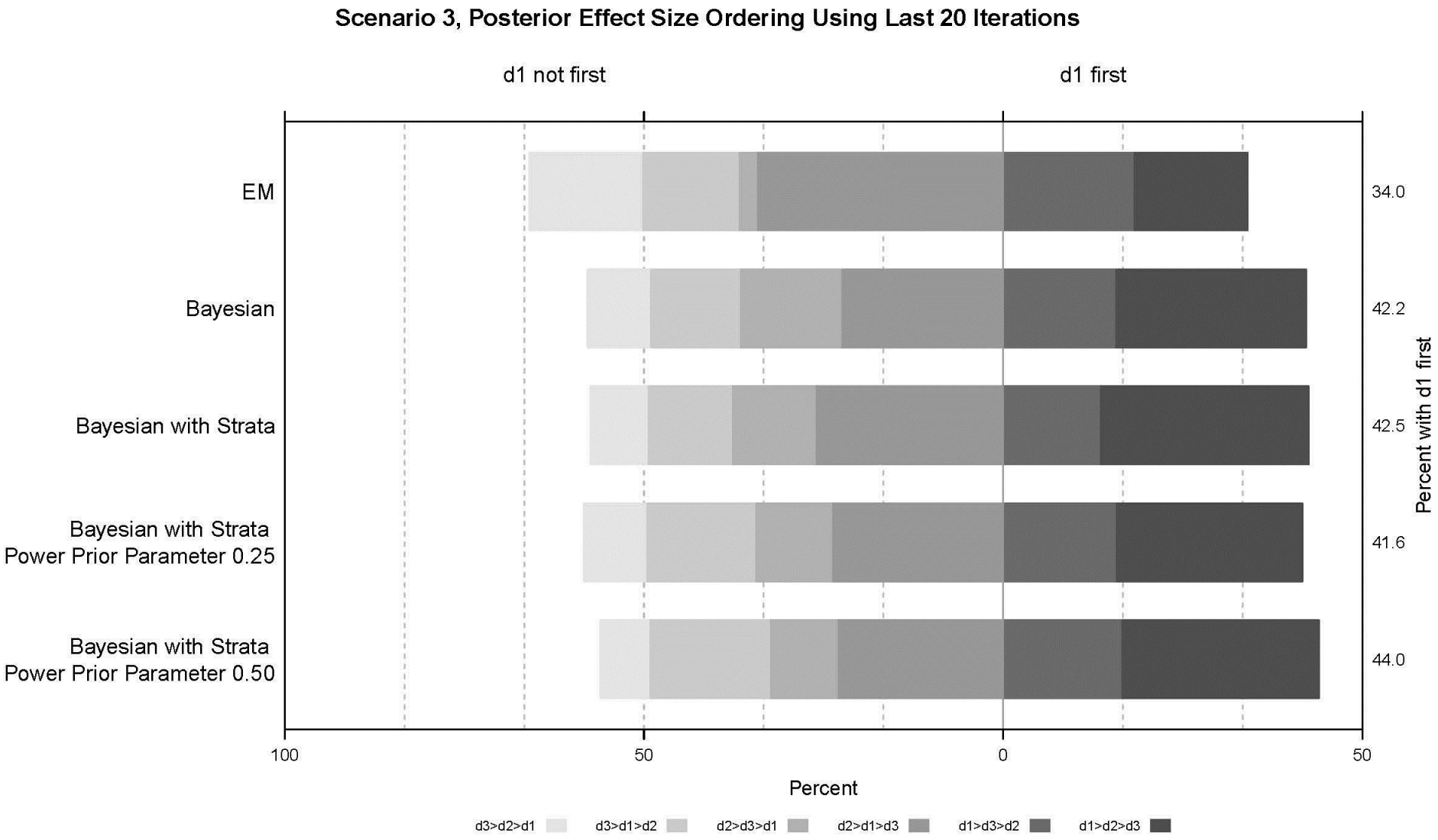
Simulation Results, Scenario 2



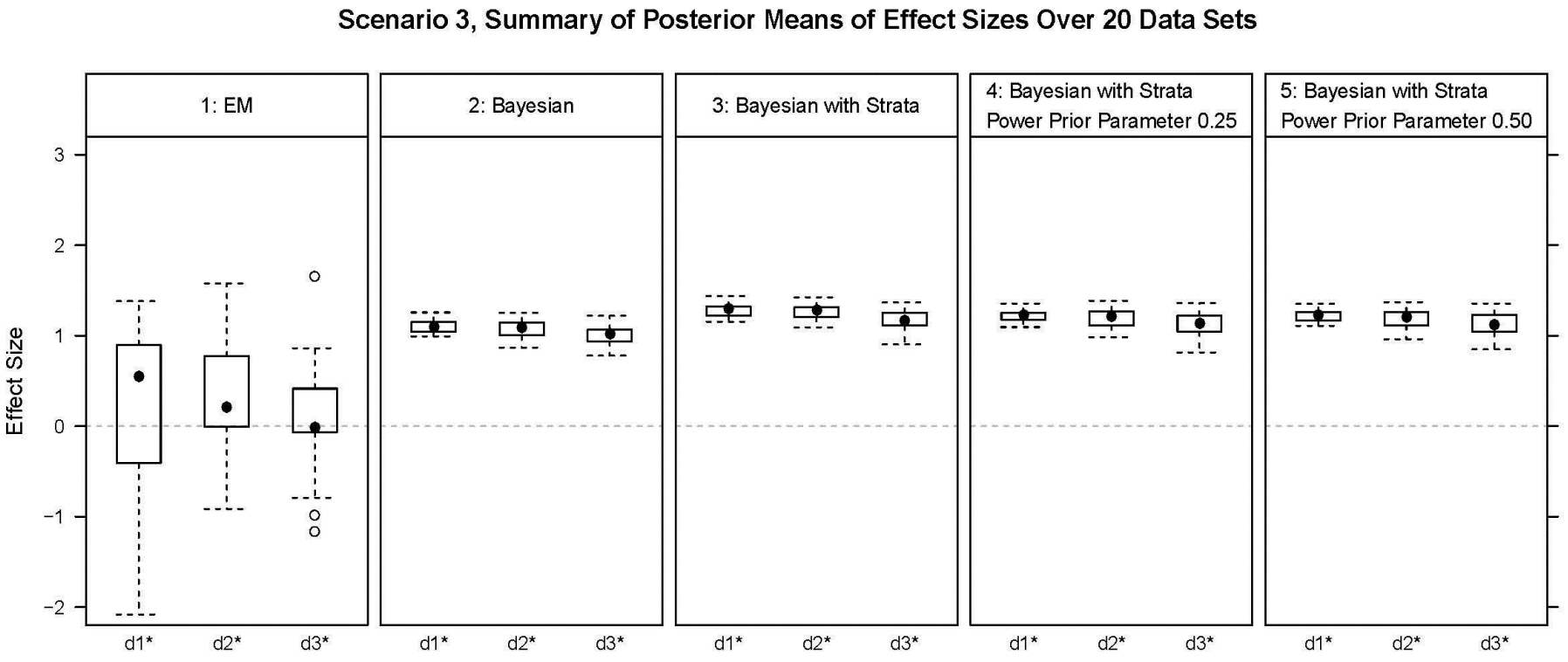
Simulation Results, Scenario 2



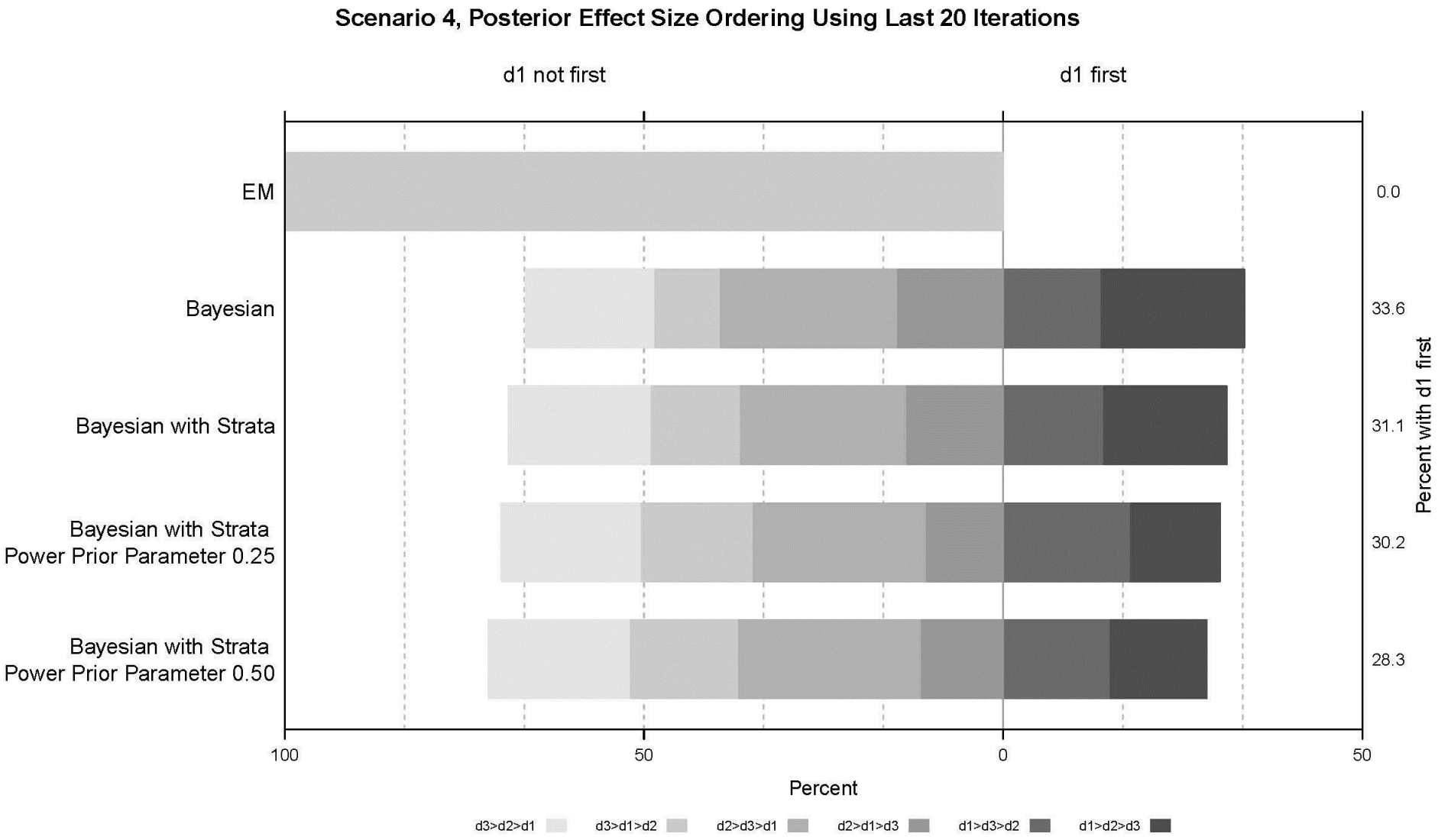
Simulation Results, Scenario 3



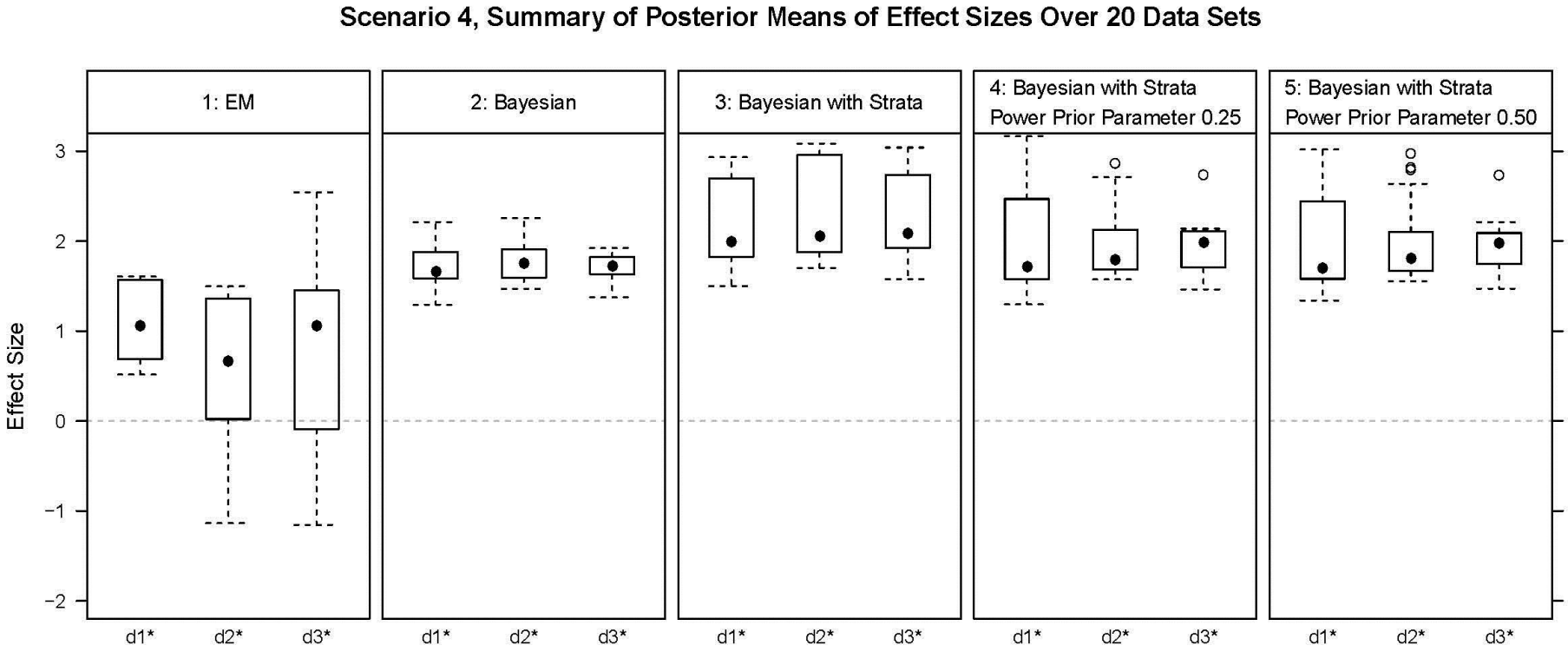
Simulation Results, Scenario 3



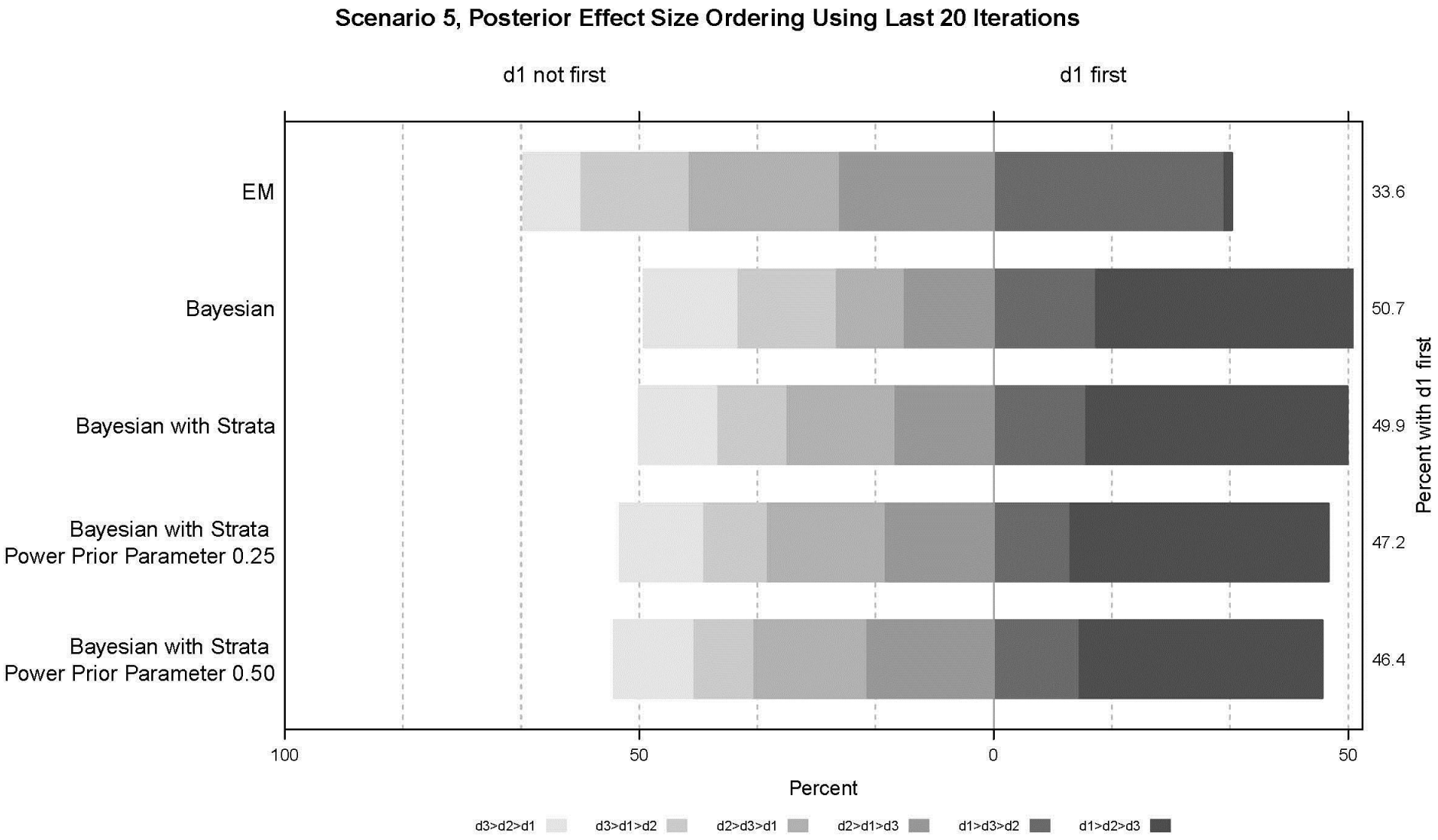
Simulation Results, Scenario 4



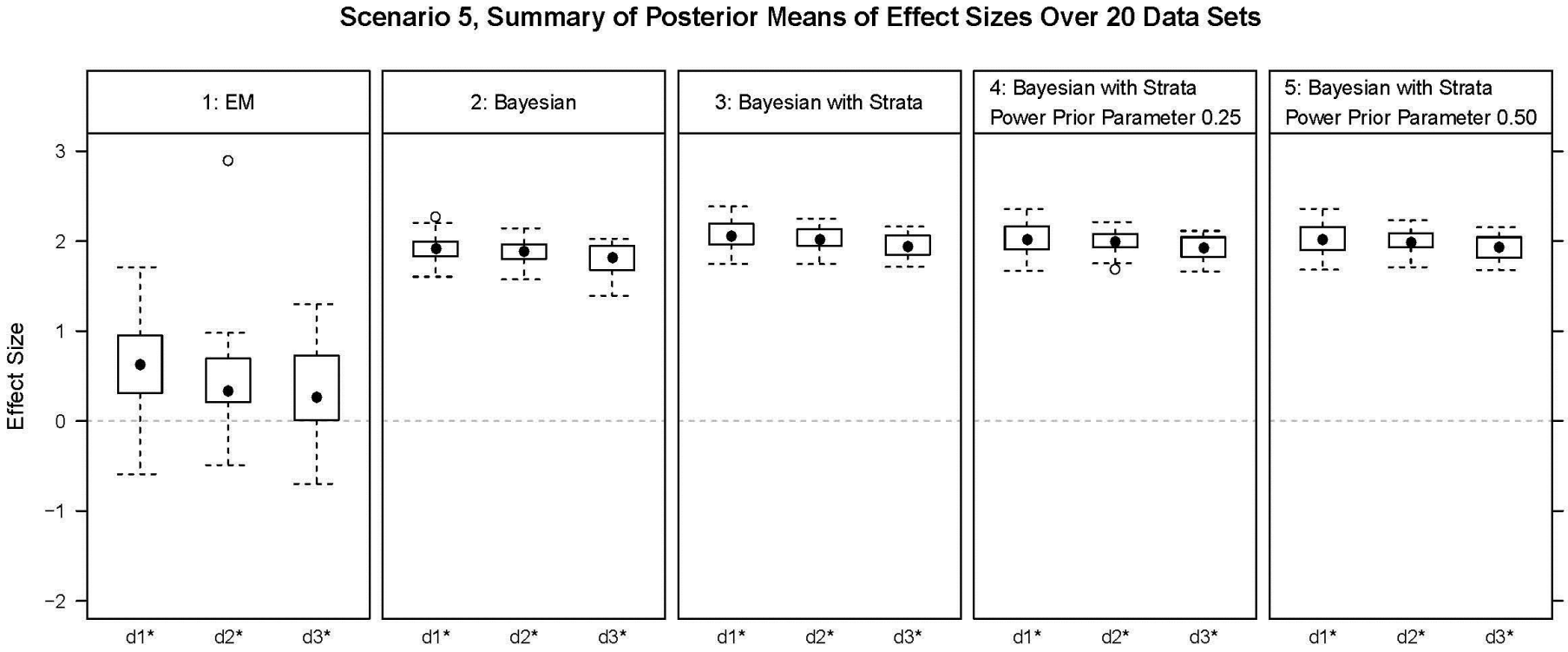
Simulation Results, Scenario 4



Simulation Results, Scenario 5



Simulation Results, Scenario 5



MDD Trial

Primary Time Point?

Week 4 or Week 6?

Primary Endpoint?

HRSD-17 or PaRTS-D

MDD Trial Results

MDD Study Results at Week 4 and Week 6 for HRSD-17 and PaRTS-D Scales Using ANCOVA Models

Parameter	Risperidone	Placebo
Hamilton Rating Scale for Depression (HRSD-17)		
Week 4 LOCF		
N	132	126
LS-Mean Change from Baseline (SE)	-8.8 (0.63)	-7.1 (0.6)
Difference on LS-Means (RIS vs. PBO) (95% CI)		-1.7 (-3.27,-0.20)
Effect Size (95% CI)		-0.3 (-0.53,-0.03)
Week 6 LOCF		
LS-Mean Change from Baseline (SE)	-10.5 (0.68)	-8.1 (0.68)
Difference on LS-Means (RIS vs. PBO) (95% CI)		-2.5 (-4.16,-0.81)
Effect Size (95% CI)		-0.4 (-0.61,-0.12)
Patient-Rated Troubling Symptoms for Depression (PaRTS-D)		
Week 4 LOCF		
N	126	120
LS-Mean Change from Baseline (SE)	-9.1 (0.88)	-7.0 (0.89)
Difference on LS-Means (RIS vs. PBO) (95% CI)		-2.1 (-4.21,0.04)
Effect Size (95% CI)		-0.3 (-0.51,0.00)
Week 6 LOCF		
LS-Mean Change from Baseline (SE)	-11.6 (0.84)	-8.1 (0.84)
Difference on LS-Means (RIS vs. PBO) (95% CI)		-3.5 (-5.57,-1.44)
Effect Size (95% CI)		-0.4 (-0.68,-0.18)

MDD Trial Results

MDD Study Results at Week 4 and Week 6 for HRSD-17 and PaRTS-D Scales Using ANCOVA Models

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MDD Study Simulations

- Decision Rule 1:

Calculate the posterior probability that the HRSD−17 effect size at Week 4 is larger than that of Week 6

$$P(d^*(H_{Wk4}) > d^*(H_{Wk6}) \mid \mathbf{Y})$$

- Decision Rule 2:

Calculate 95% Credible Intervals for Week 4 and Week 6 effect sizes

$$\underline{d}(H_{Wk4}) < d^*(H_{Wk4}) < \bar{d}(H_{Wk4})$$

$$\underline{d}(H_{Wk6}) < d^*(H_{Wk6}) < \bar{d}(H_{Wk6})$$

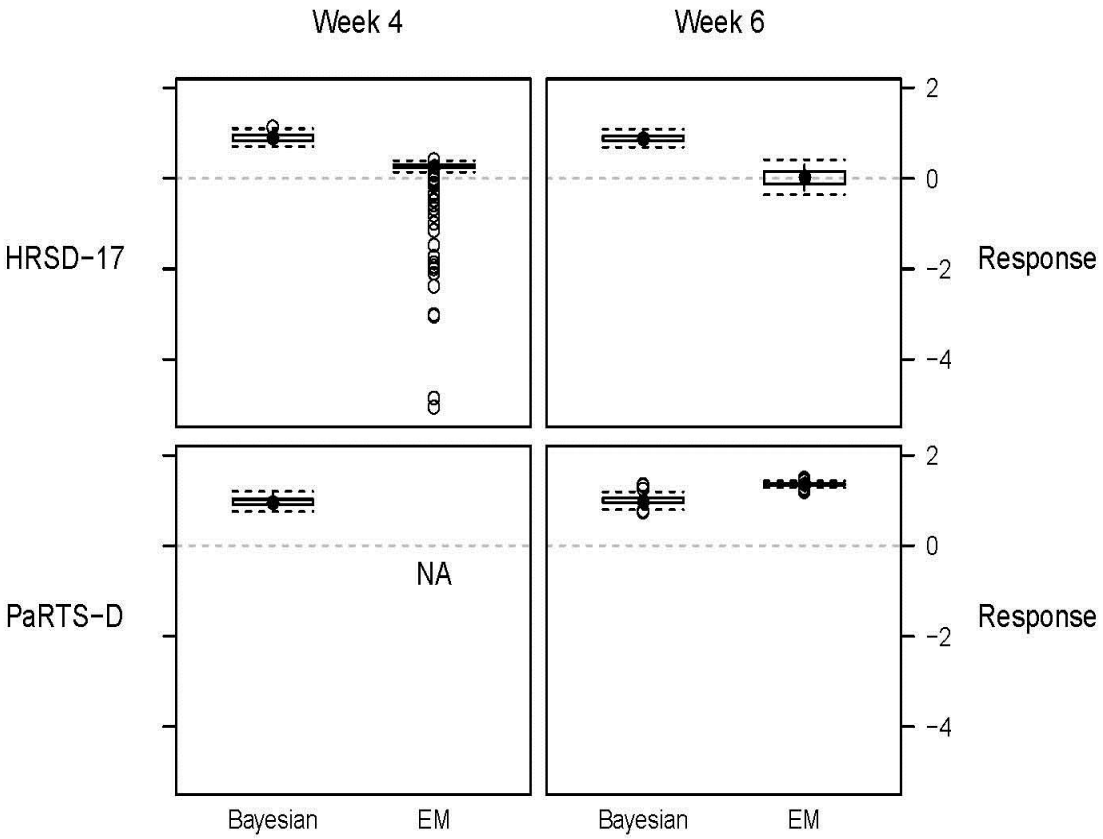
Priors for HRSD−17 placebo and treatment means at Week 4 (H_{Wk4}) were assumed to be:

$$\mu_{04}(H_{Wk4}) \sim N(\bar{Y}_0 = 15, s_0^2 = 7^2),$$

$$\mu_{14}(H_{Wk4}) \sim N(\bar{Y}_1 = 12, s_1^2 = 7^2)$$

MDD Study Simulations

Summary of Effect Sizes for HRSD-17 and PaRTS-D
At Week 4, EM Results were Not Available



Posterior Ordering of Effect Sizes for HRSD-17		
	Week 4	Week 6
EM	0.0%	100.0%
Bayesian	47.7%	52.3%

MDD Study Simulations

DIC Scores on HRSD-17 and PaRTS-D

Model	Week 4	Week 6
Hamilton Rating Scale for Depression (HRSD-17)		
EM	1.06720	1.06866
Bayesian	1.01029	1.00089
Bayesian with Strata	0.98608	1.00091
Bayesian with Strata and Power Prior 0.25	1.01086	1.00520
Bayesian with Strata and Power Prior 0.5	1.00649	1.00453
Patient-Rated Troubling Symptoms for Depression (PaRTS-D)		
EM	N/A	1.27158
Bayesian	1.00352	0.99836

Discussion and Conclusion

- We investigated whether or not the researchers can obtain reliable estimates of effect sizes without knowing treatment assignments.

- Instead of relying on the clinician's subjective evaluations, the suggested methodologies provide numerical assistance.

- We showed how to order secondary null hypotheses while the study is ongoing,
  - without unblinding the treatments,
  - without losing the validity of the testing procedure,
  - and with maintaining the integrity of the trial.

- In our simulations, we used prior distributions whose hyper parameters reflect the true values of the model parameters. In MDD analyses, we used prior distributions whose hyper parameters reflect the original study design elements.

Discussion and Conclusion

- The EM algorithm frequently failed to generate posterior parameter estimates.

- Both the Bayesian and the EM algorithms overestimated treatment differences and standardized effect sizes.

- The Bayesian algorithms performed better than existing EM algorithm counterparts in ordering the standardized effect sizes.

- With the Bayesian algorithm, the posterior probability for identifying the ground-truth ordering increased both as a function of the effect size differences and as a function of the sample size.

- For large sample sizes, the proportion of times the true ordering was selected was high (above 35%) and the variability of standardized effect sizes was low.

- With the EM algorithm, the probability for identifying the ground-truth ordering was low (sometimes near zero) and the variability of standardized effect sizes was high.

Discussion

THANK YOU!

QUESTIONS?