The Plan of Enrichment Designs for Dealing with High Placebo Response

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Outline

- Background
  - Enrichment designs for dealing with high placebo response
- Sample size/power optimization
- Numeric Study
  - Utility of sample size/power optimization
  - Implementing interim analysis
- Summary

Background

- In major depressive disorder, Schizophrenia, generalized anxiety disorder, functional bowel disorders, inflammatory bowel diseases …

High placebo response

- interferes with the evaluation of drug efficacy
- compromises new treatment development

Novel Enrichment Designs for Dealing with High Placebo Response

- **Sequential Parallel Design (SPD)**

  Fava et al. (2003)

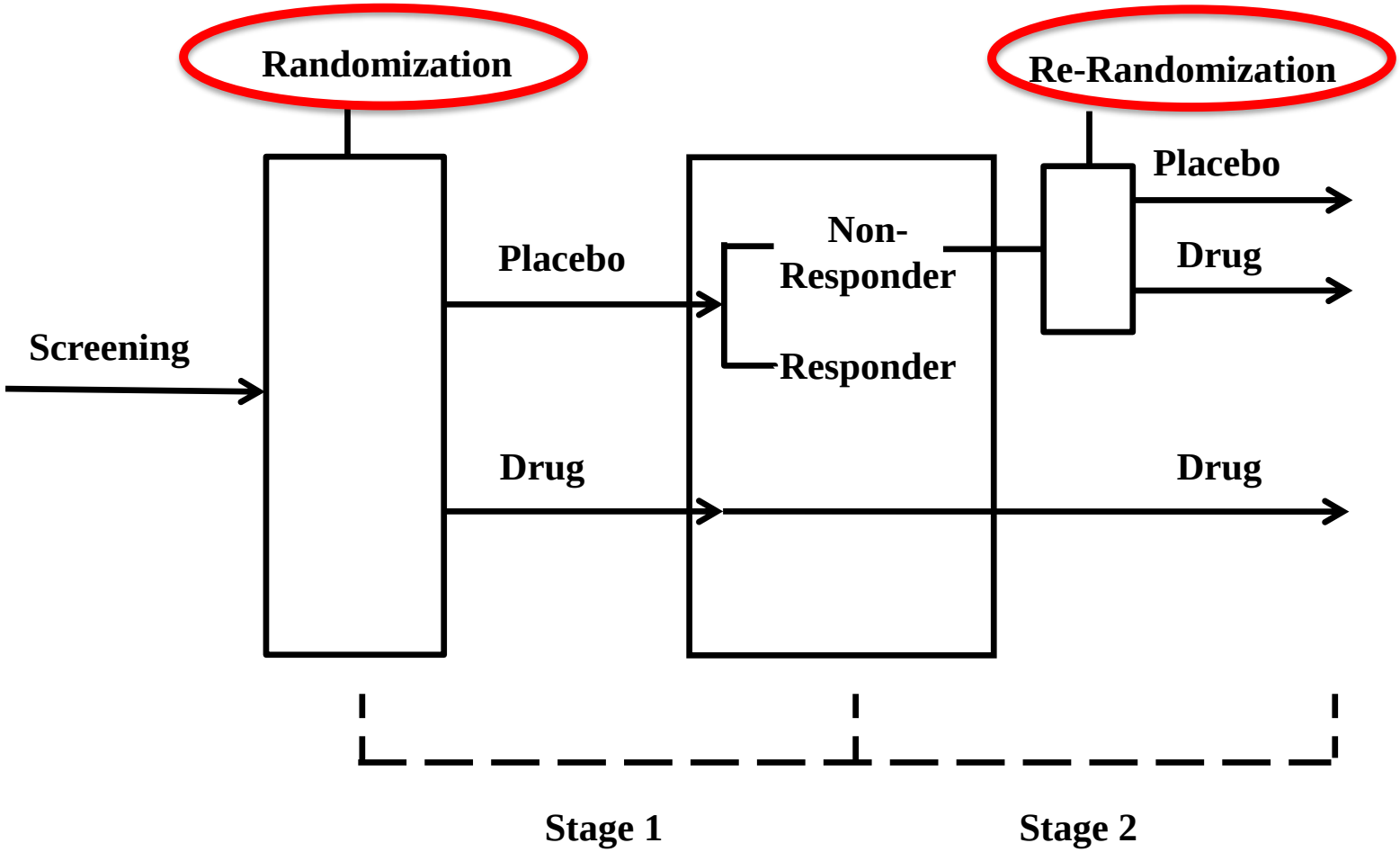
- **Two-way Enriched Design (TED)**

  Ivanova and Tamura (2011)

- **Sequential Enriched Design (SED)**

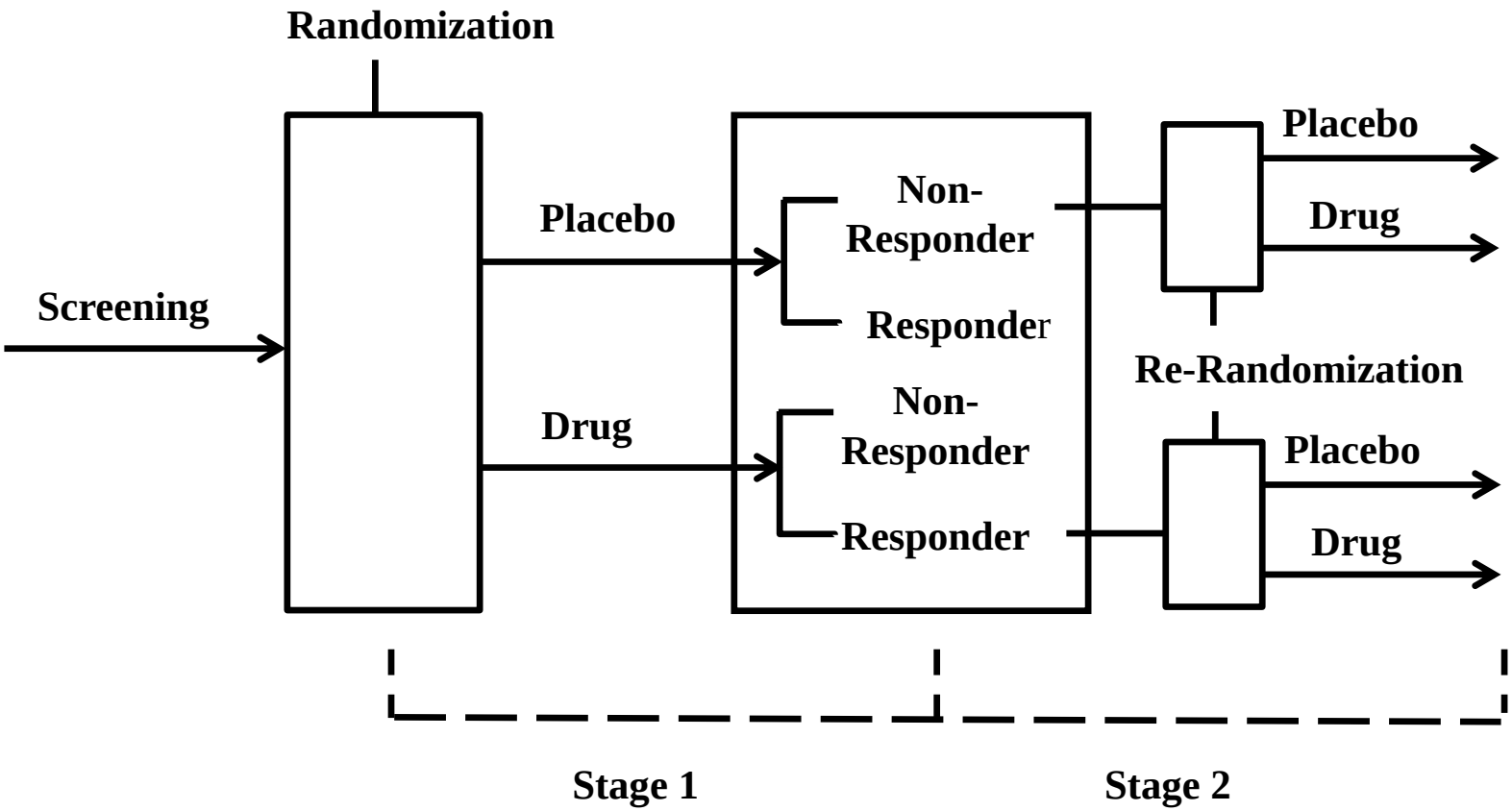
  Chen et al. (2014)

Sequential Parallel Design (SPD) (Fava et al. 2003)

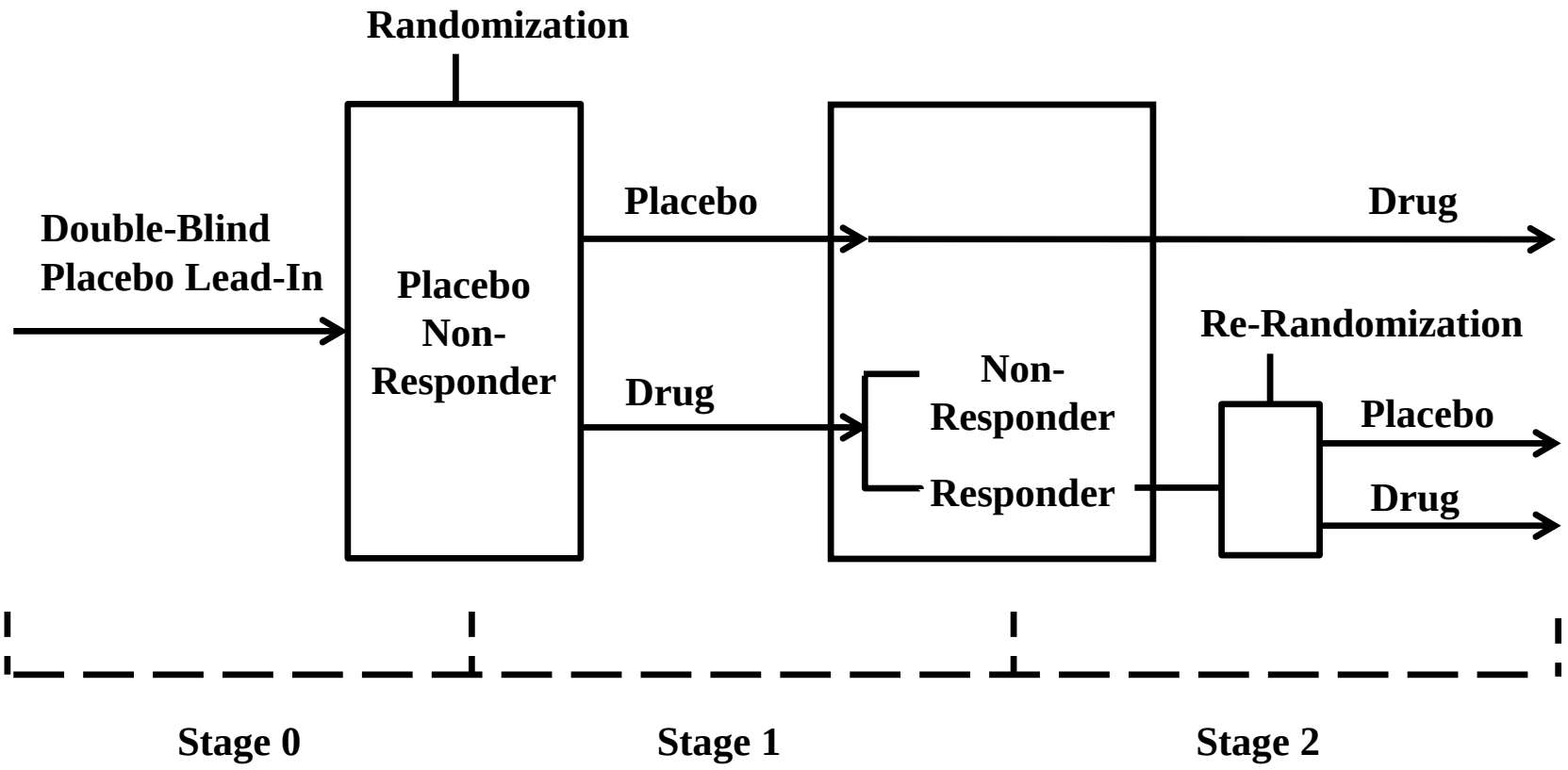


Chen et al., 2011

Two-way Enriched Design (TED) (Ivanova and Tamura, 2011)



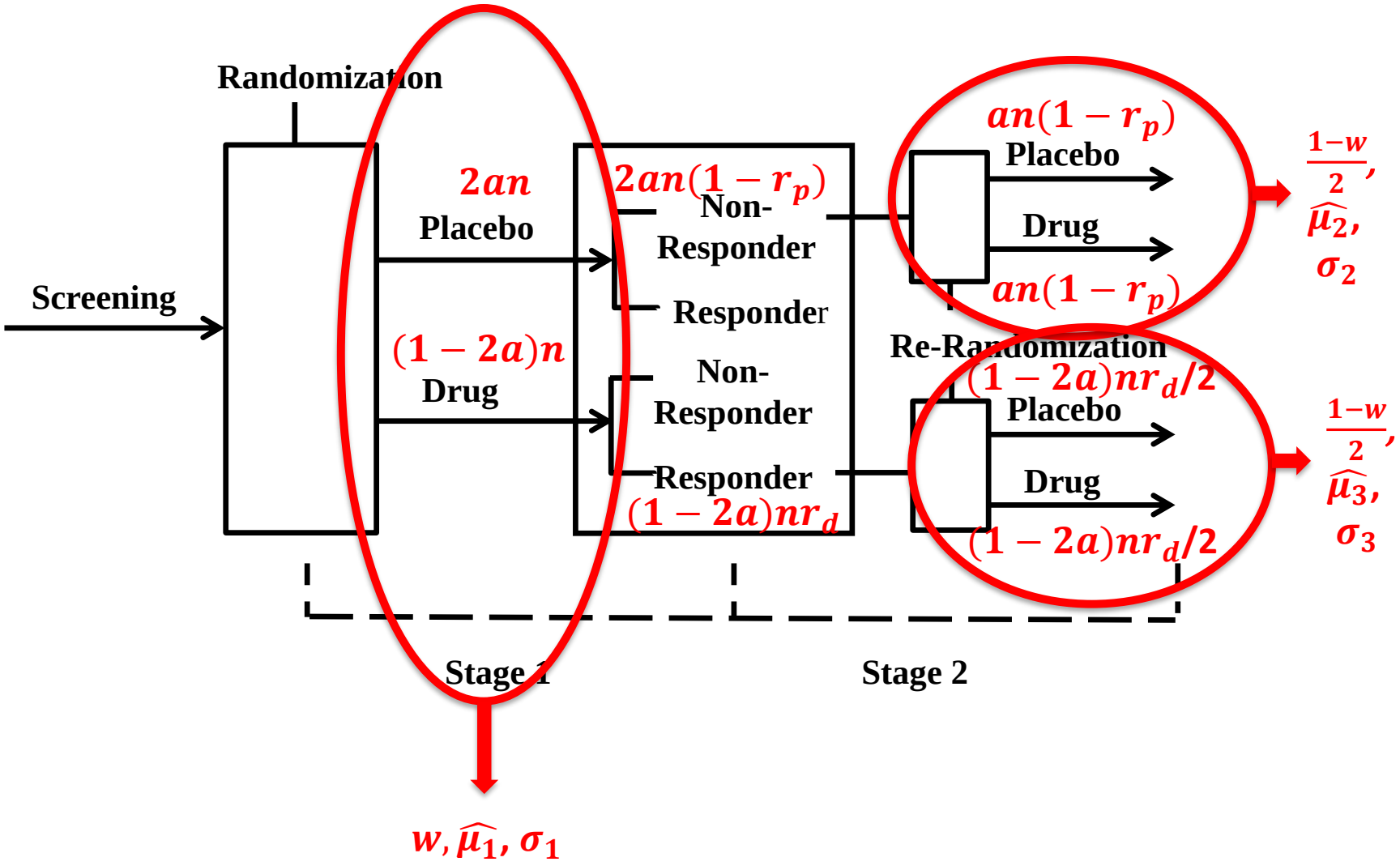
Sequential Enriched Design (SED) (Chen et al, 2014)



Notation

- n is the total sample size at the first randomization
- $a \in (0, 0.5]$ is the allocation ratio (e.g. $2a$ is the proportion of patients who are randomized to the placebo group at stage 1 of each design)
- $w \in (0, 1)$ is the pre-specified weight for stage 1
- $\widehat{\mu_1}$ is the estimated treatment difference of stage 1
- $\widehat{\mu_2}$ and $\widehat{\mu_3}$ are the estimated treatment differences of stage 2
- σ_1 is the intra-patient standard deviation of stage 1
- σ_2 and σ_3 are the intra-patient standard deviations of stage 2
- r_p is the placebo group response rate
- r_d is the drug group response rate

Sample Size Calculation Illustration using the Two-way Enriched Design (TED)



Sample Size Calculation Illustration using the TED (Con't)

- The test statistic is

$$Z_{TED} = \frac{w\hat{\mu}_1 + \left(\frac{1-w}{2}\right)\hat{\mu}_2 + \left(\frac{1-w}{2}\right)\hat{\mu}_3}{\sqrt{w^2\frac{\sigma_1^2}{2an(1-2a)} + \left(\frac{1-w}{2}\right)^2\frac{2\sigma_2^2}{an(1-r_p)} + \left(\frac{1-w}{2}\right)^2\frac{4\sigma_3^2}{n(1-2a)r_d}}}.$$

- The power is

$$1-\beta = \Phi\left(\Phi^{-1}\left(1-\frac{\alpha}{2}\right) - Z_{TED}\right)$$

$f(a, w)$

- The sample size at randomization to achieve 100 $(1-\beta)\%$ power and with significance level α is

$$n = \frac{\left[\Phi^{-1}(1-\beta) + \Phi^{-1}\left(1-\frac{\alpha}{2}\right)\right]^2\left[w^2\frac{\sigma_1^2}{2a(1-2a)} + \left(\frac{1-w}{2}\right)^2\frac{2\sigma_2^2}{a(1-r_p)} + \left(\frac{1-w}{2}\right)^2\frac{4\sigma_3^2}{(1-2a)r_d}\right]}{\left[w\hat{\mu}_1 + \left(\frac{1-w}{2}\right)\hat{\mu}_2 + \left(\frac{1-w}{2}\right)\hat{\mu}_3\right]^2}.$$

- To maximize the power is to minimize the test statistic

Optimal (a, w) pair

Design	Optimal weight w	Optimal allocation ratio a
SPD	$\dfrac{\widehat{\mu_1}}{\widehat{\mu_1} + \widehat{\mu_2}\dfrac{\sigma_1^2(1-r_p)}{4\sigma_2^2(1-2a)}}$	$\dfrac{1}{2 + 2\sqrt{\dfrac{w^2\sigma_1^2(1-r_p)}{w^2\sigma_1^2(1-r_p) + 4\sigma_2^2(1-w)^2}}}$
TED	$\dfrac{\widehat{\mu_1}}{\widehat{\mu_1} + (\widehat{\mu_2} + \widehat{\mu_3})\dfrac{\sigma_1^2(1-r_p)r_d}{2\sigma_2^2(1-2a)r_d + 4\sigma_3^2 a(1-r_p)}}$	$\dfrac{1}{2 + 2\sqrt{\dfrac{w^2\sigma_1^2 + (1-w)^2\dfrac{\sigma_3^2}{r_d}}{w^2\sigma_1^2 + (1-w)^2\dfrac{\sigma_2^2}{1-r_p}}}}$
SED	$\dfrac{\widehat{\mu_{1*}}}{\widehat{\mu_{1*}} + \widehat{\mu_{2*}}\dfrac{\sigma_{1*}^2 r_{d*}}{8\sigma_{2*}^2 a}}$	$\dfrac{1}{2 + 2\sqrt{\dfrac{w^2\sigma_{1*}^2 r_{d*} + 4\sigma_{2*}^2(1-w)^2}{w^2\sigma_{1*}^2 r_{d*}}}}$

In computational application, we can use iterative methods

Optimal w when $\alpha = 0.25$

Design	Optimal weight $\widehat{w}$
SPD	$\dfrac{\widehat{\mu_1}}{\widehat{\mu_1} + \widehat{\mu_2}\dfrac{\sigma_1^2(1-r_p)}{2\sigma_2^2}}$
TED	$\dfrac{\widehat{\mu_1}}{\widehat{\mu_1} + (\widehat{\mu_2} + \widehat{\mu_3})\dfrac{\sigma_1^2(1-r_p)r_d}{\sigma_2^2 r_d + \sigma_3^2(1-r_p)}}$
SED	$\dfrac{\widehat{\mu_{1*}}}{\widehat{\mu_{1*}} + \widehat{\mu_{2*}}\dfrac{\sigma_{1*}^2 r_{d*}}{2\sigma_{2*}^2}}$

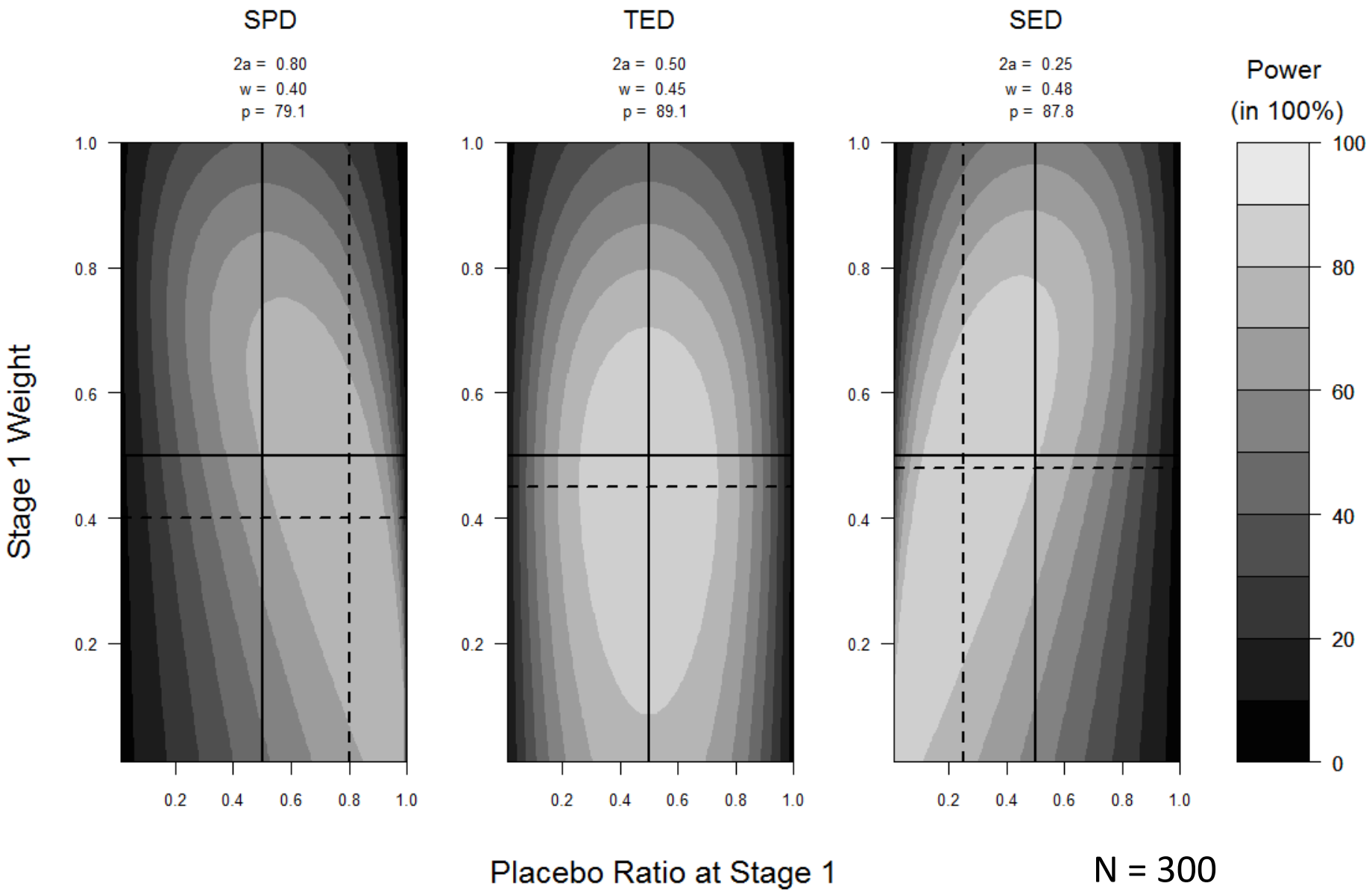
Example: For SPD, $\sigma_1 = \sigma_2$, $\widehat{\mu_2} = 1.5\,\widehat{\mu_1}$, $w = \dfrac{4}{7-3r_p} \in \left(\dfrac{4}{7}, 1\right)$.

Settings for Numerical Illustration

	Stage 1 μ	Stage 2 μ	Placebo Non-response Rate	Drug Response Rate
Setting 1				
SPD	-1	-2	60%	NA
TED	-1	-2	60%	60%
SED	-1.2	-2.2	NA	60%
Setting 2				
SPD	-1.5	-2	60%	NA
TED	-1.5	-2	60%	60%
SED	-1.7	-2.2	NA	60%

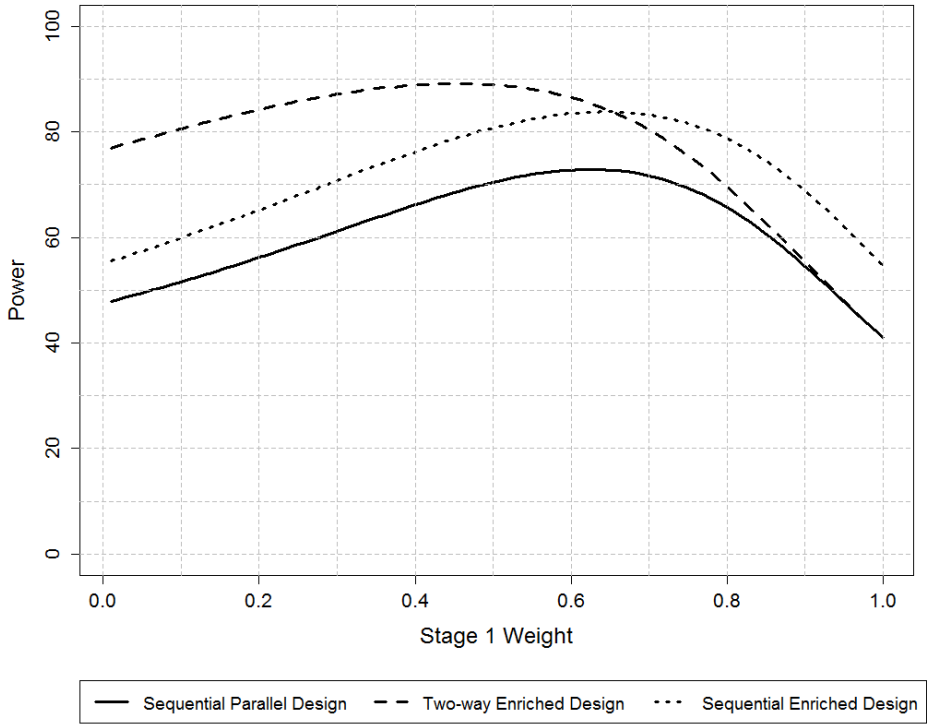
Stage-wise standard deviation = 5

Contour Plots under Setting 1

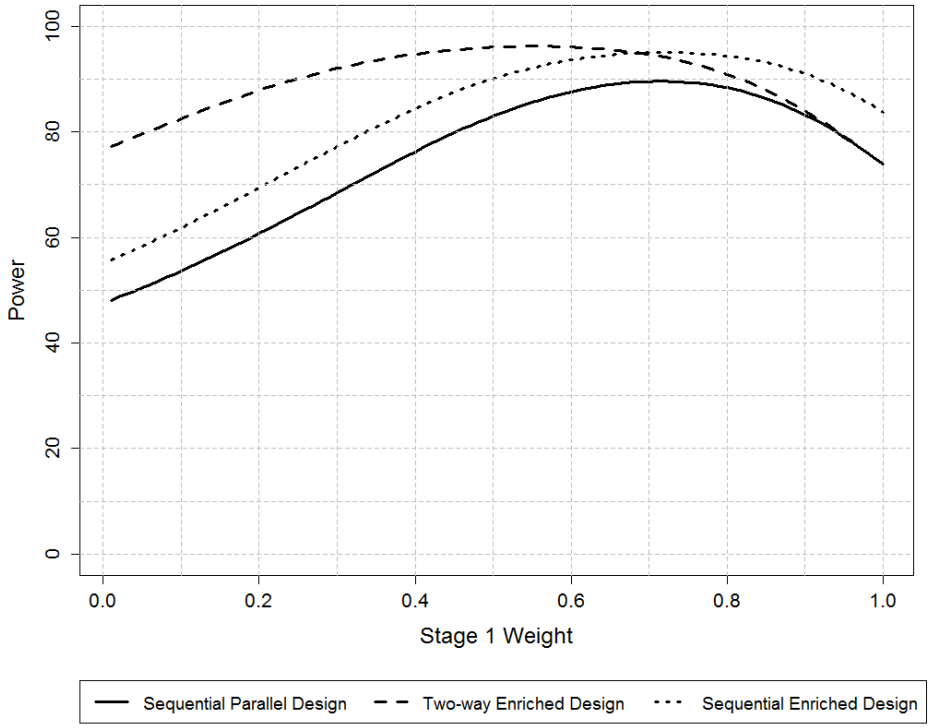


N = 300

Power Plots under Settings 1 and 2, $\alpha = 0.25$

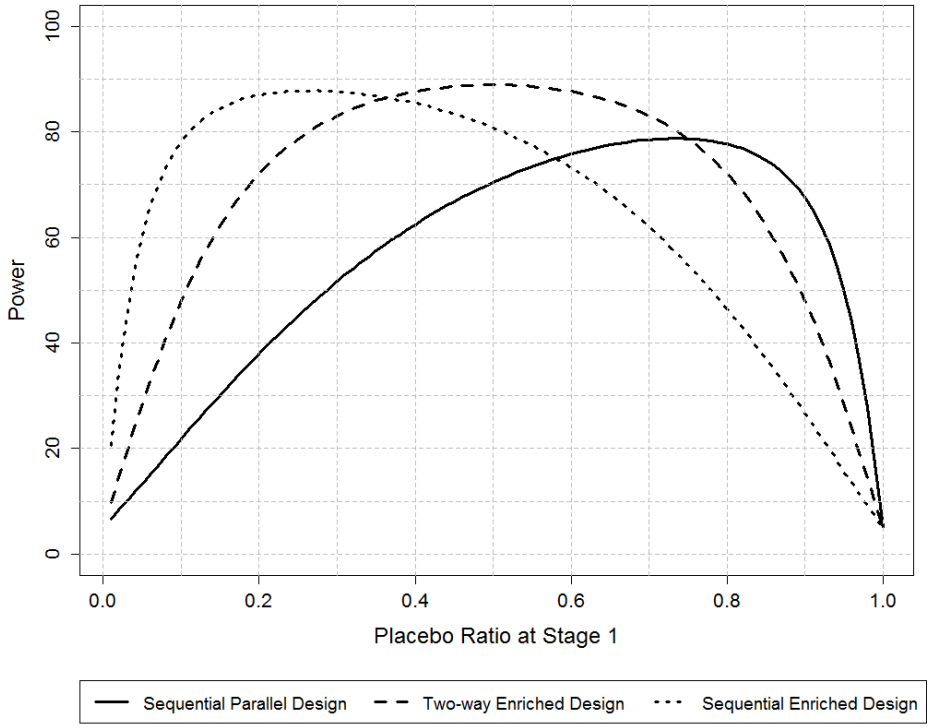


Setting 1

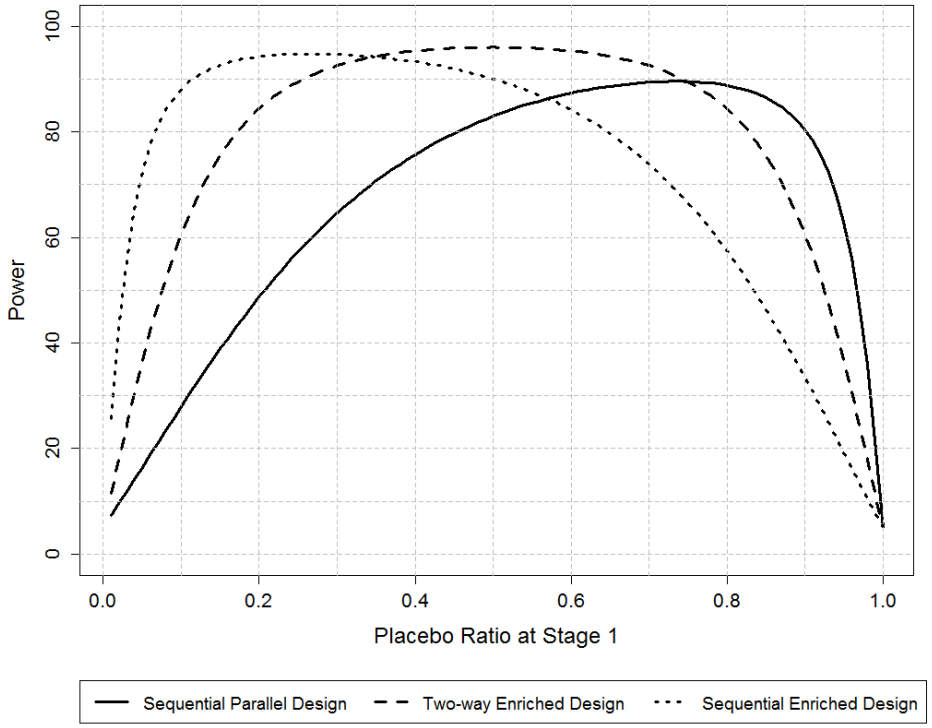


Setting 2

Power Plots under Settings 1 and 2, $w = 0.5$



Setting 1



Setting 2

Sample Size Saved by Optimization

Sample sizes required at the first randomization to achieve 90% power under fixed $(2a, w) = (0.5, 0.5)$ vs. optimal (a, w):

Setting	Design	Fixed (a,w)	Optimal (a,w)			Sample size Reduction due to Optimization (%)
		Sample Size at Randomization	$2a$	w	Sample Size at Randomization	
1	SPD	506	0.80	0.40	411	18.77
	TED	312	0.50	0.45	310	0.64
	SED	394	0.24	0.48	323	18.02
2	SPD	372	0.64	0.65	292	21.51
	TED	229	0.50	0.56	226	1.31
	SED	271	0.38	0.66	233	14.02

Simulation with Interim Analysis: Settings

Drug Response	True Drug Responder	True Drug Non-Responder
True Placebo Responder	- 8	- 7
True Placebo Non-Responder	- 8	- 7

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Placebo Response	True Drug Responder	True Drug Non-Responder
True Placebo Responder	- 7	- 7
True Placebo Non-Responder	- 5	- 5

Treatment Effect	True Drug Responder	True Drug Non-Responder
True Placebo Responder	-1	0
True Placebo Non-Responder	- 3	- 2

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Proportion	True Drug Responder	True Drug Non-Responder
True Placebo Responder	0.1	0.1
True Placebo Non-Responder	0.7	0.1

Overall treatment difference $\mu = -2.4$

Settings (cont.)

- The baseline is normally distributed with mean 25 and standard deviation 3
- The noise standard deviation of change from baseline is 8 for each stage
- 20% is the threshold for responders or non-responders
- Weight w is fixed at 0.7
- 50% information time
- O'Brien-Fleming bound

Selected Simulation Results

Power and Type I error rate are not affected by the implementation of interim analysis

Design	Without Interim		With Interim, OBF, 50% Information Time		
	Planned Sample Size at Randomization	Bias*	Expected Sample Size at Randomization	Bias*	Sample Size Reduction due to Interim (%)
SPD	200	0.58	190.1	0.45	5.0
	400	0.58	348.8	0.41	12.8
TED	200	0.59	185.9	0.45	7.1
	400	0.59	325.2	0.41	18.7
SED	200	0.52	187.9	0.38	6.0
	400	0.51	335.3	0.34	16.2

* Bias = estimated combined treatment effect - target treatment effect (i.e. treatment effect from subpopulation (3)).

Summary

- We provided optimization formulae for (a, w) pair for SPD, TED, and SED.
- Sample size can be saved using optimized (a, w) values.
- To optimize power, more patients need to be assigned to the placebo group for the SPD; more patients need to be assigned to the drug group for the SED.
- The weight for achieving the optimal power depends on the assumed parameter values. It should be pre-specified.
- Implementing interim analysis for an novel enrichment design has benefits.

Reference

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Thank You!