Module 3: Optimal Confidence Intervals for Adaptive Enrichment Clinical Trial Designs

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July 29, 2016

Example

Population: Subjects with depression.

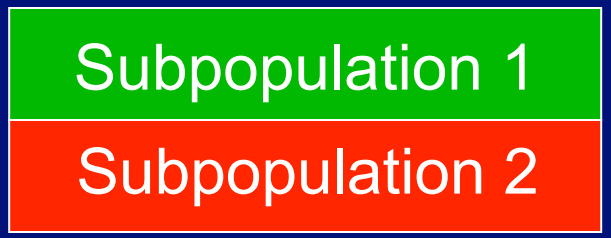
Research Questions: How does a new antidepressant compare to placebo in effect on change in Hamilton Rating Score of Depression (HRSD) after 6 weeks?

Does it differ depending on initial severity of depression?

Prior Data Indicates: Maybe only a treatment benefit for those with severe initial depression. (Kirsch et al, 2008)

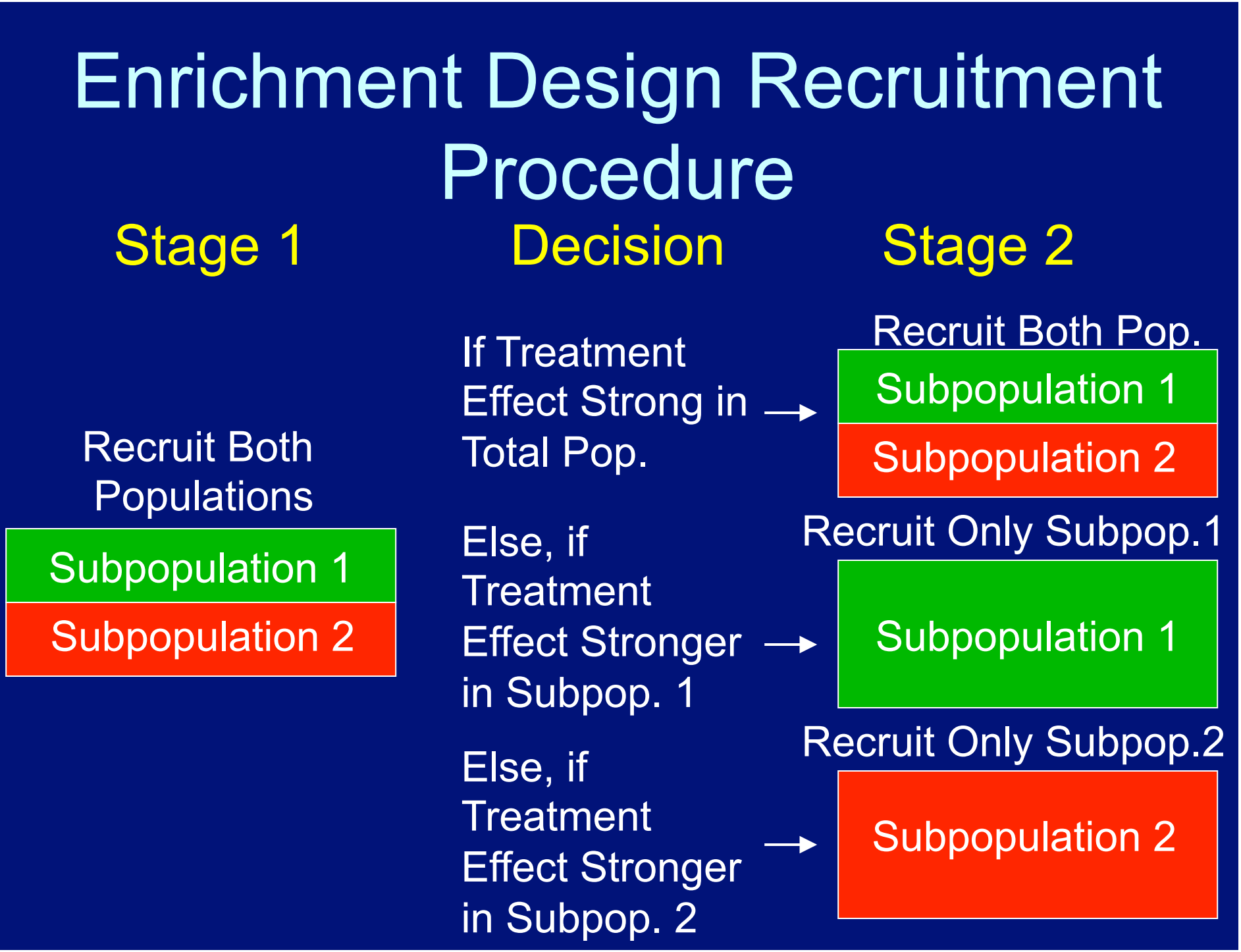
Some Possible Fixed Designs

- Enroll from total population (both those with moderate initial depression and severe initial depression)



- Enroll only from those with severe initial depression

Enrichment Design Recruitment Procedure



Problem Setup

- 2 Subpopulations that partition overall pop.
- Three treatment effects of interest:

  Δ_C: Mean Effect in Total (Mixture) Population

  Δ_1: Mean Effect in Subpopulation 1 (low risk)

  Δ_2: Mean Effect in Subpopulation 2 (high risk)
- Enrichment Design:
  - After Stage 1: if T_C>d, enroll from both subpops.

    Else, enroll only from subpop corresp. to larger of T_1,T_2

    Let S be selected population.
  - At end of trial: Compute Confidence Interval for Δ_S:

$$\hat{\Delta}_S \pm c z_{0.975} \sigma_S / \sqrt{n_S}$$

where c is min. value: CI cov. prob. at least 95%

Problem and Goals

- Problem:

  Analyze Group Sequential Designs that

  Allow Changes to Population Sampled at Interim Points, Based on Earlier Data (Including Outcomes Data) using **Prespecified Rule**

- Goals:

1. Make Inferences about Selected Populations
2. Construct Confidence Intervals for Treatment Effect in Selected Population with Uniformly Correct Coverage Probability

- My Contribution: General Method for Reducing Problem to Optimization Problem that Can Be Easy to Solve with Standard Statistical Software

Some Related Work

Adapt Treatments and/or Population Sampled

Thall, Simon, Ellenberg 1988, Schaid, Wieand, Therneau 1990, Wittes and Brittain 1990, Russek-Cohen and Simon 1997, Follman 1997, Bauer and Köhne 1994, Bauer and Kieser 1999, Sampson and Sill 2005, Bischoff and Miller 2005, Freidlin and Simon 2005, Jennison and Turnbull, 2003, 2006, 2007, Wang, Hung, O'Neill 2007, 2009, Rosenblum and van der Laan 2011

Confidence Intervals for Such Designs:

Jennison & Turnbull 1984, Emerson and Fleming 1990, Proschan & Hunsberger 1995, Lehmacher & Wassmer 1999, Posch et al. 2005, Brannath et al. 2006, and Wu et al. 2010

Uniform, Asymptotic Coverage Probability

- Let S be the population selected.
- The uniform, asymptotic coverage probability for a confidence interval CI, over a class of distributions P', is defined as

$$\liminf_{n \to \infty} [\inf_{P \in \mathrm{P}'} P(\Delta_S(P) \in CI)]$$

- We construct confidence intervals for the mean treatment effect for the selected population that have uniform, asymptotic, coverage probability at least 0.95.

Minimal Expansion Factor c

Let S be selected population.

At end of trial: Compute Confidence Interval for Δ_S:

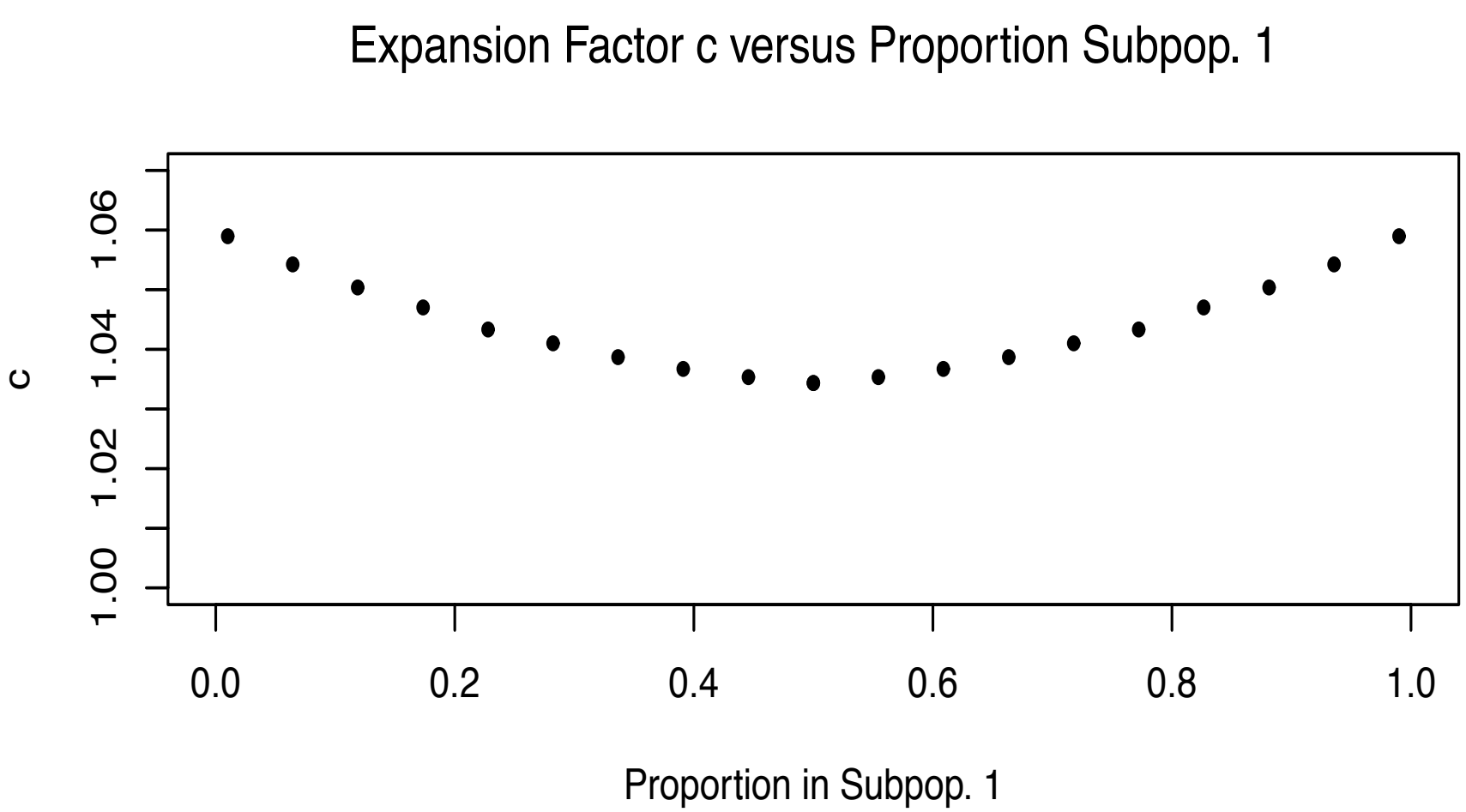
$$\hat{\Delta}_S \pm c z_{0.975} \sigma_S / \sqrt{n_S}$$

where c is min. value: CI cov. prob. at least 95%.

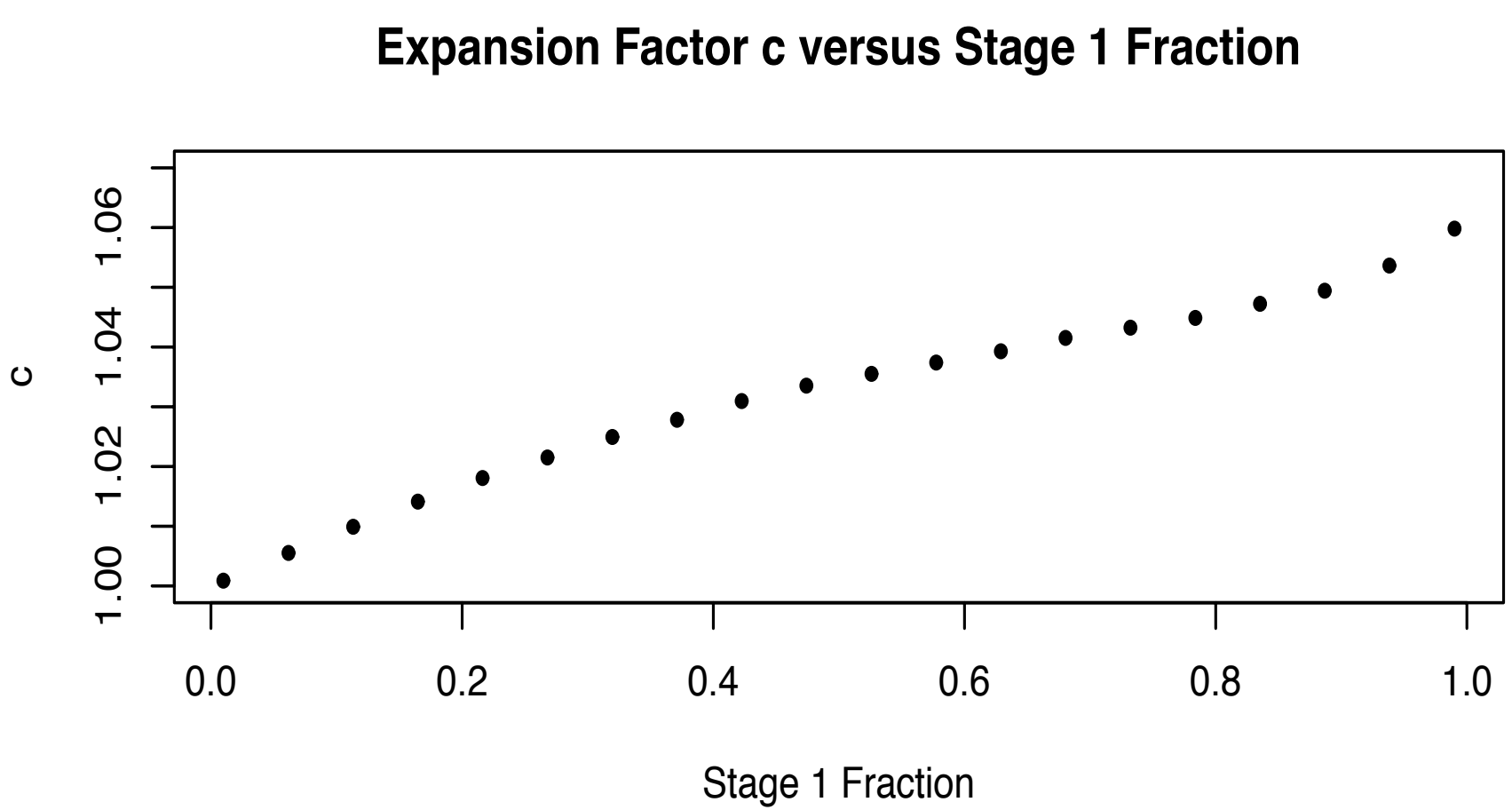
c depends on known population characteristics and features of trial design:

1. proportion in subpop. 1
2. proportion of subjects in stage 1

Expansion Factor c



Expansion Factor c



Worst Case Expansion Factor c

Worst-case expansion factor c is approximately 1.1

As long as neither subpopulation much smaller than other, and first stage sample size at most half total sample size, worst-case expansion factor c is approximately 1.05.

Important Limitation: Results assume outcome measured soon after enrollment.