Some Proposals in the Analysis of Antibacterial Drug Trials

Margaret Gamalo-Siebers[§] and Ram C. Tiwari[‡]

[§]Office of Analytics and Outreach/CFSAN/FDA

[‡] Office of Biostatistics/CDER/FDA

Clinical Trials Transformation Initiative, Bethesda,19 November 2014

Disclaimer

This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Outline

- Network Meta-analysis
  - Case 1: Placebo Present
  - Case 2: Placebo Not Present
- Bayesian subgroup analysis
  - Flexible Shrinkage estimators
  - Flexible Regression Type Adjustments
  - Application
- Data augmentation
  - Propensity Score Matching schemes
  - Investigations

Network Meta-analysis:
Case 1: Placebo Present

Non-inferiority trial and historical trials with data x, and parameter of interest θ.

Trial	Test	Active-Control	Placebo
Historical Trial 1	θ_{1T}	θ_{1C}	θ_{1P}
	NA	$x_{1,C}$	$x_{1,P}$
Historical Trial 2	θ_{2T}	θ_{2C}	θ_{2P}
	NA	$x_{2,C}$	$x_{2,P}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$
Historical Trial N	θ_{NT}	θ_{NC}	θ_{NP}
	NA	$x_{N,C}$	$x_{N,P}$
Non-inferiority Trial	$\theta_{(N+1)T}$	$\theta_{(N+1)C}$	$\theta_{(N+1)P}$
	$x_{N+1,T}$	$x_{N+1,C}$	NA
NA = Not available			

Network Meta-analysis:
Case 1: Placebo Present

- In non-inferiority, the ultimate goal is to quantify $\theta_T - \theta_P$ which can be decomposed as

$$\theta_T - \theta_P = (\theta_T - \theta_C) + (\theta_C - \theta_P) \tag{1}$$

- Determined via Δ_{CT} and Δ_{CP}
- Model: Say $\eta_{it} = g(\theta_{it})$, $t \in \{T, C, P\}$ and $i = 1, \ldots, I$

$$\eta_{it} = \mu_{iC} + \Delta_{iCt}, \tag{2}$$

where $\Delta_{iCt} = \eta_{it} - \mu_{iC}$ effect of treatment t relative to treatment C in study i.

Network Meta-analysis:
Case 1: Placebo Present

- Simon (1999): Δ_{Ct} is fixed between drug t and C
- Schmidli et al. (2013) based on Lu and Ades (2004), allow for variability between studies, i.e., $\Delta_{iCt} \sim N(\Delta_{Ct}, \sigma^2)$
- $P(\Delta_{CT} > \lambda\Delta_{CP})$ can also be obtained!

Network Meta-analysis:
Case 1: Placebo Present

Predictive Network Meta-analysis

- Sampling Model: $x_{i,t} \sim \text{Bin}(p_{i,t}, n_{i,t}), \quad t \in \{T, C, P\}, i = 1, \ldots, N+1,$ N historical studies plus 1 non-inferiority study
- Model parameters: $\text{logit}(p_{i,t}) = \theta_{i,C} + \Delta_{i,t}$, $\Delta_{i,t} = 0$ if $t = C$
- Priors: $\theta_{i,C} \sim N(\mu_\theta, \tau_\theta^2)$, $\Delta_{i,t} \sim \mathbf{N}(\boldsymbol{\mu}_\Delta, \boldsymbol{\Sigma})$, where $\boldsymbol{\mu}_\Delta = (\delta_{PC}, \delta_{TC})'$, $\boldsymbol{\Sigma} = ((\tau^2, \rho\tau)', (\rho\tau, \tau^2)')$
- Hyperpriors: $\mu_\theta \sim N(0, 100)$, $\tau_\theta^2 \sim N(0, 100)I(0, \infty)$, δ_{PC} II $\delta_{TC} \sim N(0, 100)$, $\tau \sim N(0, 100)I(0, \infty)$
- Parameters of Interest: $p_{N+1,C} = 1/(1 + \exp(-\theta_{N+1,C})$, $p_{N+1,t} = 1/(1 + \eta_{N+1,t})$, where $\eta_{N+1,t} = \exp\{-(\theta_{N+1,C} + \delta_{N+1,tC})\}$, $t \in \{T, P\}$
- Parameters of Interest: $p_C = 1/(1 + \exp(-\theta_C)$, $p_t = 1/(1 + \eta_t)$, where $\eta_t = \exp\{-(\mu_\theta + \delta_{tC})\}$, $t \in \{T, P\}$

Network Meta-analysis:
Case 1: Placebo Present

Data (events/patient) from the ESSENCE non-inferiority trial and 6 historical trials, for active control (C: aspirin + heparin), test (T: aspirin + enoxaparin), and putative placebo (P: aspirin)

Test	Active-control	Placebo	OR (95% CI) vs. Active control
	3/210 (1.4%)	7/189 (3.7%)	2.44 (0.67, 8.80)
	0/37 (0%)	1/32 (3.1%)	3.57 (0.14, 90.8)
	4/105 (3.8%)	9/109 (8.3%)	2.13 (0.67, 6.77)
	42/154 (27.3%)	40/131 (30.5%)	1.17 (0.70, 1.95)
	4/70 (5.7%)	7/73 (9.6%)	1.67 (0.49, 5.63)
Total	55/698 (7.9%)	68/655 (10.4%)	

Network Meta-analysis:
Case 1: Placebo Present

- Fixed margin methods cannot be applied! OR (95% CI) of active control vs. placebo is $0.673(0.449, 1.011)$.
- Synthesis approach may work but λ close to 1 (no preservation)! Solution: show T is superior to P.
- Bayesian putative placebo approach (Simon, 1999). $Pr\{g(\theta_T) - g(\theta_P) < 0\} = 0.994$, where $g(\theta) = \text{logit}(\theta)$

Network Meta-analysis:
Case 1: Placebo Present

	Posterior distribution: median (95% Credible Interval	
Parameter	Historical	Historical and non-inferiority
Between-trial standard deviations for log-OR (vs. C), and log–odds (C)		
τ_θ	0.93 (0.60, 1.45)	0.90 (0.58, 1.40)
τ_δ	0.18 (0.04, 0.53)	0.16 (0.02, 0.54)
OR and probability of superiority in ESSENCE NI trial		
$\exp(\delta_{TP})$		0.50 (0.29, 0.91)
$P(T\ better\ than\ P)$		0.987
$\exp(\delta_{TC})$		0.79 (0.59, 1.02)
$P(T\ better\ than\ C)$		0.965
$\exp(\delta_{CP})$	0.64 (0.38, 1.02)	0.65 (0.35, 1.08)
$P(C\ better\ than\ P)$	0.97	0.947

Network Meta-analysis:
Case 2: Placebo Not Present

Non-inferiority trial and historical trials with data x, and parameter of interest θ.

Trial	Test	Control	Other Controls
Historical Trial 1	θ_{1T}	θ_{1C}	θ_{1C_1}
	NA	$x_{1,C}$	x_{1,C_1}
Historical Trial 2	θ_{2T}	θ_{2C}	θ_{2C_2}
	NA	$x_{2,C}$	x_{2,C_2}
$\vdots$	$\vdots$	$\vdots$	$\vdots$
Historical Trial N	θ_{NT}	θ_{NC}	θ_{NC_K}
	NA	$x_{N,C}$	x_{N,C_k}
Non-inferiority Trial	$\theta_{(N+1)T}$	$\theta_{(N+1)C}$	$\theta_{(N+1)C_1}, \ldots, \theta_{(N+1)C_K}$
	$x_{N+1,T}$	$x_{N+1,C}$	NA

NA = Not available

Network Meta-analysis:
Case 2: Placebo Not Present

- Direct comparison between placebo and active-control are *not* available in the historical data, but the direct comparisons of other treatments with at least one common comparator are available

- Since data for $(\eta_{jC} - \eta_C)$, $j \in \{1, \ldots, K\}$, exists, model $(\eta_T - \eta_C)$ as

$$\eta_{it} = \eta_{iC} + \Delta_{itC}, \quad i = 1, \ldots, S+1 \tag{7}$$

  where $t \in \{C_1, \ldots, C_K, T\}$

- Allows borrowing of information from existing data and at the same time estimates

$$\eta_T - \eta_{jC} = (\eta_T - \eta_C) - (\eta_{jC} - \eta_C) \quad \text{for } j \in \{1, \ldots, K\}! \tag{8}$$

Network Meta-analysis:
Case 2: Placebo Not Present

Predictive Network Meta-analysis with power prior for historical data

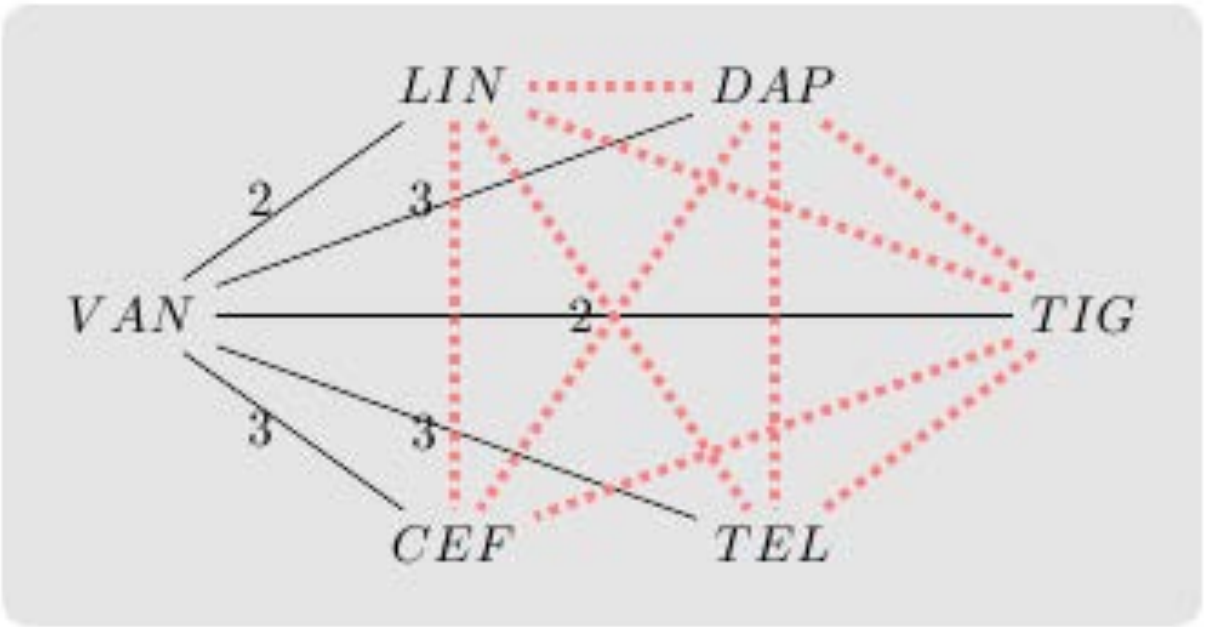
- Sampling Model: $x_{i,t} \sim \text{Bin}(p_{i,t}, n_{i,t}), \quad t \in \{T, C\}, \; i = N+1,$
  $x_{i,t}a_0 \sim \text{Bin}(p_{i,t}, n_{i,t}a_0), \quad t \in \{C, P\}, \; i = 1, \ldots, N,$
- Model parameters: $\text{logit}(p_{i,t}) = \theta_{i,C} + \Delta_{i,t}$, $\Delta_{i,t} = 0$ if $t = C$
- Priors: $\theta_{i,C} \sim N(\mu_\theta, \tau_\theta^2)$, $\Delta_{i,t} \sim \mathbf{DP}(\nu, \boldsymbol{G})$, $\boldsymbol{G} \sim \mathbf{N}(\boldsymbol{\mu}_\Delta, \boldsymbol{\Sigma})$,
- Hyperpriors: $\mu_\theta \sim N(0, 100)$, $\tau_\theta \sim N(0, 100)I(0, \infty)$ $\boldsymbol{\mu}_\Delta \sim \mathbf{N}(\mathbf{0}, \boldsymbol{\Sigma}_\Delta)$,
  $\boldsymbol{\Sigma} = [(\tau^2, \rho\tau)', (\rho\tau, \tau^2)']$, $\tau \sim N(0, \sigma_\tau^2)I(0, \infty)$

Network Meta-analysis:
Case 2: Placebo Not Present

Antibiotic comparison	MITT population, clinical failure at test of cure		
	#. of trials	Proportion of failure	
		Comparator	Vancomycin
LIN vs. VAN	2	144/583 (24.7%)	171/573 (29.8%)
		35/99 (35.4%)	33/87 (37.9%)
DAP vs. VAN	3	12/48 (25.0%)	6/48 (12.5%)
		99/264 (37.5%)	104/266 (39.1%)
		53/270 (19.6%)	57/292 (19.5%)
TIG vs. VAN	2	41/253 (16.2%)	34/250 (13.6%)
		65/268 (24.3%)	59/255 (23.1%)
TEL vs. VAN	3	117/426 (27.5%)	122/429 (28.4%)
		124/472 (26.3%)	129/489 (26.4%)
		18/100 (18.0%)	14/95 (14.7%)
CEF vs. VAN	3	47/351 (13.4%)	50/347 (14.4%)
		51/342 (14.9%)	49/338 (14.5%)
		8/67 (11.9%)	6/32 (18.8%)

Network Meta-analysis:
Case 2: Placebo Not Present

Existing cSSSTI Trial Network



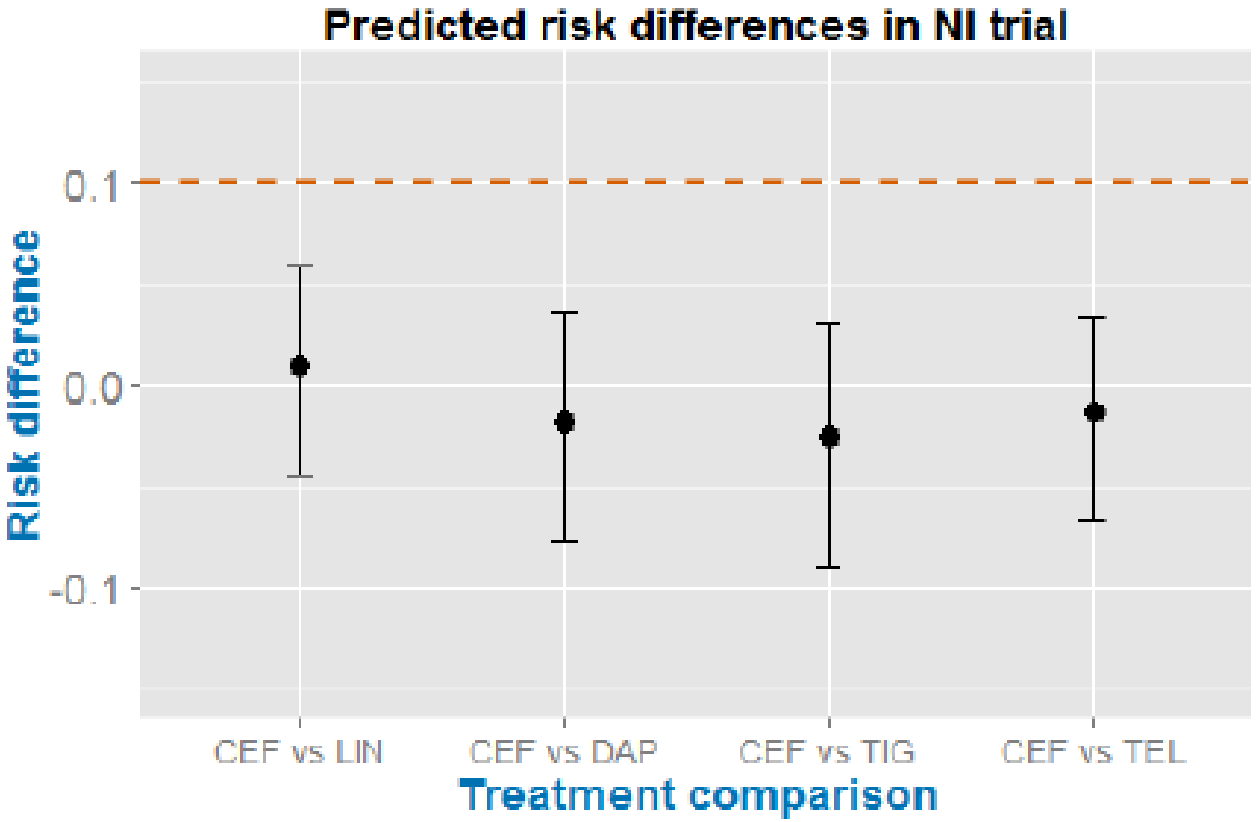
Network Meta-analysis:
Case 2: Placebo Not Present

- All the upper bounds of the credible intervals about the difference in clinical failure rate are less than 0.10.
- Even for NI-3, whose sample size is much smaller than NI-1 and NI-2, non-inferiority is demonstrated by borrowing the strengths from historical data.
- Usual confidence interval with continuity correction for the two-sample proportion difference is $(-0.25, 0.11)$!

	Parameters of interest for the NI trial					
	NI-1		NI-2		NI-3	
	θ	$\theta_t - \theta_{\text{VAN}}$	θ	$\theta_t - \theta_{\text{VAN}}$	θ	$\theta_t - \theta_{\text{VAN}}$
VAN	0.15 (0.12, 0.19)	–	0.15 (0.12, 0.19)	–	0.21 (0.11, 0.32)	–
LIN	0.13 (0.09, 0.19)	-0.02 (-0.06, 0.03)	0.13 (0.09, 0.19)	-0.02 (-0.06, 0.03)	0.18 (0.09, 0.30)	-0.02 (-0.08, 0.03)
DAP	0.16 (0.10, 0.22)	0.01 (-0.03, 0.06)	0.16 (0.10, 0.22)	0.01 (-0.04, 0.06)	0.22 (0.11, 0.35)	0.00 (-0.05, 0.08)
TIG	0.16 (0.11, 0.23)	0.01 (-0.03, 0.06)	0.16 (0.10, 0.23)	0.01 (-0.04, 0.07)	0.23 (0.11, 0.38)	0.02 (-0.05, 0.11)
TEL	0.15 (0.10, 0.21)	0.00 (-0.03, 0.04)	0.15 (0.10, 0.21)	0.00 (-0.04, 0.05)	0.21 (0.10, 0.33)	0.00 (-0.05, 0.05)
CEF	0.14 (0.10, 0.17)	-0.02 (-0.07, 0.04)	0.15 (0.11, 0.19)	-0.00 (-0.06, 0.05)	0.12 (0.06, 0.21)	-0.09 (-0.22, 0.06)

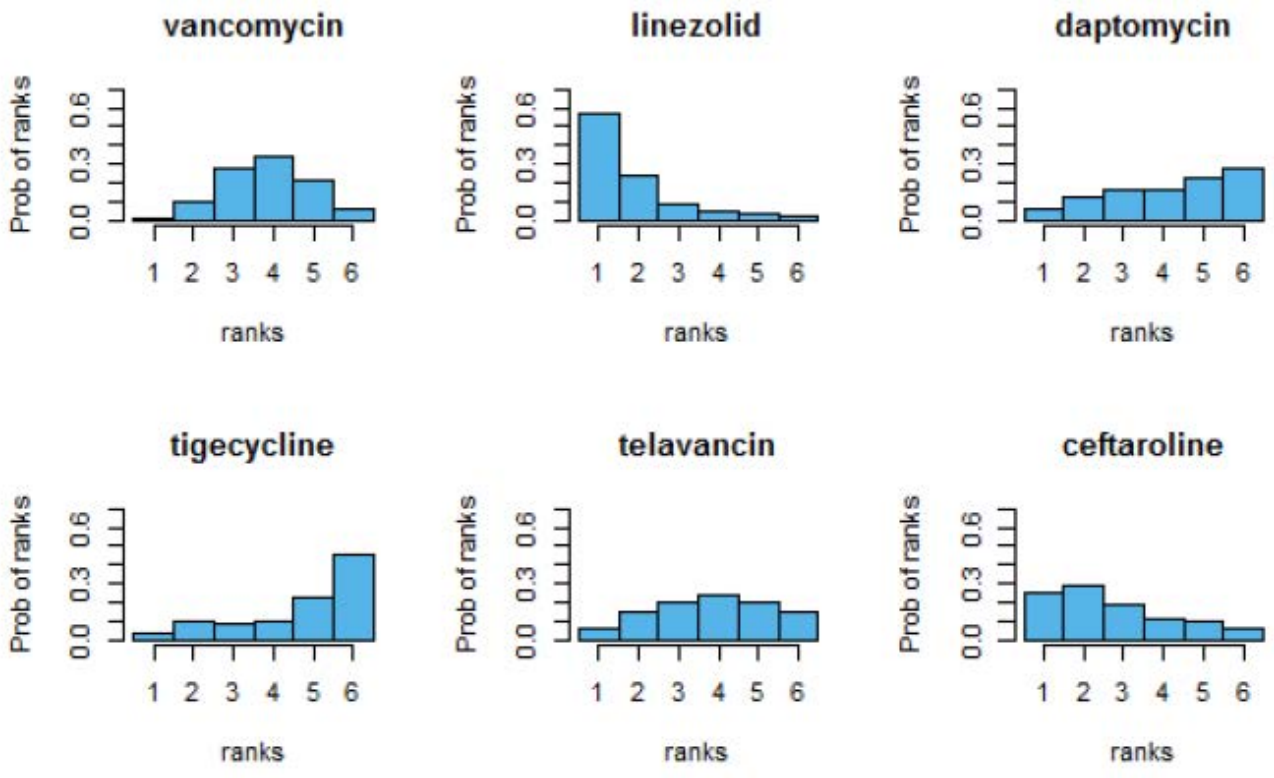
Table 9: Posterior estimates from the network meta-analysis for the cSSTI data, using 200,000 MCMC iterations after discarding 5000 burn-in.

Network Meta-analysis:
Case 2: Placebo Not Present



Network Meta-analysis:
Case 2: Placebo Not Present

Rankogram



Bayesian Subgroup Analysis

- Streamlined or 'Tier C' approach: small trial including infections from different body sites with common infecting MDR pathogen
- Bayesian hierarchical modeling allows for borrowing of information from one subgroup to another
- Effect Modification: waters down the effect of promising subpopulation while attenuates in subpopulation where it is less effective -- not unique to Bayesian models
- Assumes it is acceptable to exchange treatment responses in different treatment groups/infections (Exchangeability)

Bayesian Subgroup Analysis

- Let y_{ji_j} be the treatment response for subject i_j, $i_j = 1, \ldots, n_j$ in subgroup j, $j = 1, \ldots, J$. For $y_{ji_j}|\theta_j \sim \text{Ber}(p_j)$,

$$\text{logit}(p_{ji_j}) = \theta_j, \quad \theta_j|\eta \sim G(\eta), \quad \eta \sim P \tag{3}$$

- What are appropriate models for θ_j? And, what is the choice of G, if there is such a distribution?

- de Finetti Theorem: there is a distribution G such that

$$\theta_1, \ldots, \theta_J \sim G(\eta), \tag{4}$$

i.e., $\theta_1, \ldots, \theta_J$ are iid given $G(\eta)$, $\eta \sim P$.

Bayesian Subgroup Analysis:
Flexible Shrinkage Estimators

- Model 1: Simple shrinkage, partially exchangeable

$$\text{logit}(p_{ji_j}) = \theta_{ji_j}, \quad i = 1, \ldots, n_j, \quad j = 1, \ldots, J$$

$$\theta_{ji_j} = \alpha_{ji_j} + \psi_j \sim G, \quad \text{where} \quad G:$$

$$\alpha_{ji_j}|H \sim H, \quad H|\rho, H_0 \sim \text{DP}(\rho, H_0), H_0 \sim \text{N}(0, \tau^2), \rho \sim \Gamma(2, 1)$$

$$\psi_j \sim \text{N}(0, \omega_{\psi_j}^2), \omega_{\psi_j} \sim \text{N}(0, 1)I(0, \infty)$$

- DP prior on α_{ji_j} induces a product partition model (Hartigan, 1990) on the distribution of ρ

Bayesian Testing:
Example 2

Antibiotic comparison	MITT population, clinical failure at test of cure		
	#. of trials	Proportion of failure	
		Comparator	Vancomycin
LIN vs. VAN	2	144/583 (24.7%)	171/573 (29.8%)
		35/99 (35.4%)	33/87 (37.9%)
DAP vs. VAN	3	12/48 (25.0%)	6/48 (12.5%)
		99/264 (37.5%)	104/266 (39.1%)
		53/270 (19.6%)	57/292 (19.5%)
TIG vs. VAN	2	41/253 (16.2%)	34/250 (13.6%)
		65/268 (24.3%)	59/255 (23.1%)
TEL vs. VAN	3	117/426 (27.5%)	122/429 (28.4%)
		124/472 (26.3%)	129/489 (26.4%)
		18/100 (18.0%)	14/95 (14.7%)
CEF vs. VAN	3	47/351 (13.4%)	50/347 (14.4%)
		51/342 (14.9%)	49/338 (14.5%)
		8/67 (11.9%)	6/32 (18.8%)

Bayesian Subgroup Analysis:
Flexible Shrinkage Estimators

- True mean for α_{ji_j} is $\mu_\alpha = \sum_k^L p_i \mu_{\alpha_k}$ where μ_{α_k} is the mean of cluster k since the finite representation of H (Sethuraman and Tiwari, 1982) is

$$H = \sum_{k=1}^{L} \pi_k \delta_{\alpha_k}; \quad \pi_L = 1 - \pi_1 - \ldots - \pi_{L-1} \tag{5}$$

- The J subgroups are assumed *a priori* normally distributed with common mean and variance. Although the DP prior for α_{ji_j} allows clustering *a posteriori*, it is still *a priori* exchangeable with respect to experimental units

- Model maybe too parsimonious!

Bayesian Subgroup Analysis:
Flexible Shrinkage Estimators

- Model 2A: Shrinkage with regression, partially exchangeable

$$\text{logit}(p_{ji_j}) = \theta_{ji_j}, \quad i = 1, \ldots, n_j, \quad j = 1, \ldots, J$$

$$\theta_{ji_j} = \alpha_{ji_j} + x_{ji_j}\beta_j + \psi_j \sim G, \quad \text{where} \quad G:$$

$$\alpha_{ji_j}|H \sim H, \quad H|\rho, H_0 \sim \text{DP}(\rho, H_0), H_0 \sim \text{N}(0, \tau^2), \rho \sim \Gamma(2,1)$$

$$\beta_j \sim \text{N}(0, \omega_{\beta_j}^2), \omega_{\beta_j} \sim \text{N}(0,1)I(0,\infty)$$

$$\psi_j \sim \text{N}(0, \omega_{\psi_j}^2), \omega_{\psi_j} \sim \text{N}(0,1)I(0,\infty)$$

Bayesian Subgroup Analysis:
Flexible Regression-type Estimators

- Subgroups $j = 1 \ldots, J$ formed from partitions of covariates x_{is} and T_{is}, where $s = 1, \ldots, S$ studies and T_{is} are study-specific treatment indicators.

- Model 3: Regression-type (Dixon-Simon, 1991), partially exchangeable

$$\text{logit}(p_{is}) = \theta_{is}, \quad i = 1, \ldots, N, \quad s = 1, \ldots, S$$

$$\theta_{is} = \alpha_{is} + x_{is}\beta_{1s} + T_{is}\beta_{2s} \sim G, \quad \text{where} \quad G:$$

$$\alpha_{is}|H \sim H, \quad H|\rho, H_0 \sim \text{DP}(\rho, H_0), H_0 \sim \text{N}(0, \tau^2), \rho \sim \Gamma(2, 1)$$

$$\beta_{1s} \sim \text{N}(0, \omega^2_{\beta_{1s}}), \omega_{\beta_{1s}} \sim \text{N}(0, 1)I(0, \infty)$$

$$\beta_{2s} \sim \text{N}(0, \omega^2_{\beta_{2s}}), \omega_{\beta_{2s}} \sim \text{N}(0, 1)I(0, \infty)$$

Bayesian Subgroup Analysis:

Flexible Regression-Type Adjustments

- Model 4: Regression-type (treatment interaction), partially exchangeable

$$\text{logit}(p_{is}) = \theta_{is}, \quad i = 1, \ldots, N, \quad s = 1, \ldots, S$$

$$\theta_{is} = \alpha_{is} + x_{is}\beta_{1s} + T_{is}(\beta_{2s} + x_{is}\beta_{3s}) \quad \text{where} \quad G:$$

$$\alpha_{is}|H \sim H, \quad H|\rho, H_0 \sim \text{DP}(\rho, H_0), H_0 \sim \text{N}(0, \tau^2), \rho \sim \Gamma(2, 1)$$

$$\beta_{1s} \sim \text{N}(0, \omega^2_{\beta_{1s}}), \omega_{\beta_{1s}} \sim \text{N}(0, 1)I(0, \infty)$$

$$\beta_{2s} \sim \text{N}(0, \omega^2_{\beta_{2s}}), \omega_{\beta_{2s}} \sim \text{N}(0, 1)I(0, \infty)$$

$$\beta_{3s} \sim \text{N}(0, \omega^2_{\beta_{3s}}), \omega_{\beta_{3s}} \sim \text{N}(0, 1)I(0, \infty)$$

- When $\beta_{0j} = 0$, the model reduces to an exchangeable 1st-order interactions: Dixon-Simon (1991)

Bayesian Subgroup Analysis:
Non-exchangeable Shrinkage Estimators

- Clusters S_k, $k = 1, \ldots, K$ partitions the ψ_{ji_j}, $i = 1, \ldots, n_j$, $j = 1, \ldots, J$ so that $\psi_{ji_j}|H_k$, H_k is DP with base distribution $H_0 \sim \mathrm{N}(0, \tau^2)$ and cohesion/concentration coefficient $c(S_k) = \rho f(|S_k|, J)$, when $\psi_{ji_j} \in S_k$

- See Leon-Novello et al. (2012) for similar formulation through non-exchangeable product partition models

Bayesian Subgroup Analysis:
Non-exchangeable Shrinkage Estimators

- Model 2B: Shrinkage with regression, non-exchangeable

$$\text{logit}(p_{ji_j}) = \theta_{ji_j}, \quad i = 1, \ldots, n_j, \quad j = 1, \ldots, J$$

$$\theta_{ji_j} = x_{ji_j}\beta_j + \psi_{ji_j} \sim G, \quad \text{where} \quad G:$$

$$\psi_{ji_j}|H_k \sim H_k, \quad H_k|\rho, H_0 \sim \text{DP}(\rho, H_0), H_0 \sim \text{N}(0, \tau^2), \rho \sim \Gamma(2, 1)$$

$$\beta_j \sim \text{N}(0, \omega_{\beta_j}^2), \omega_{\beta_j} \sim \text{N}(0, 1)I(0, \infty)$$

Bayesian Subgroup Analysis:
Exchangeable Non-exchangeable Shrinkage Estimators

- Model 2C: Shrinkage with regression, exchangeable-non-exchangeable (EXNEX)

$$\text{logit}(p_{ji_j}) = \theta_{ji_j}, \quad i = 1, \ldots, n_j, \quad j = 1, \ldots, J$$

$$\theta_{ji_j} = x_{ji_j}\beta_j + \psi_{ji_j} \sim G, \quad \text{where} \quad G :$$

$$\beta_j \sim \text{N}(0, \omega_{\beta_j}^2), \omega_{\beta_j} \sim \text{N}(0,1)I(0,\infty), \quad \text{and}$$

- For each subgroup j, ψ_{ji_j} takes on values from a mixture of k distributions H. H is composed of H_k with probability p_k [say, $H_k = \text{N}(0, \tau_k^2)$] and so on; and $H_K = \text{N}(\mu, \tau^2)$ with probability $1 - \sum_k p_k$

Bayesian Subgroup Analysis:
Exchangeable Non-exchangeable Shrinkage Estimators

- The probabilities p_k can be set or data driven using a degenerate Dirichlet distribution prior on $\{p_1, \ldots, p_{k-1}\}$
- There will be subgroups j, j' with the same distribution H_k (exchangeable) or different distributions (non-exchangeable).

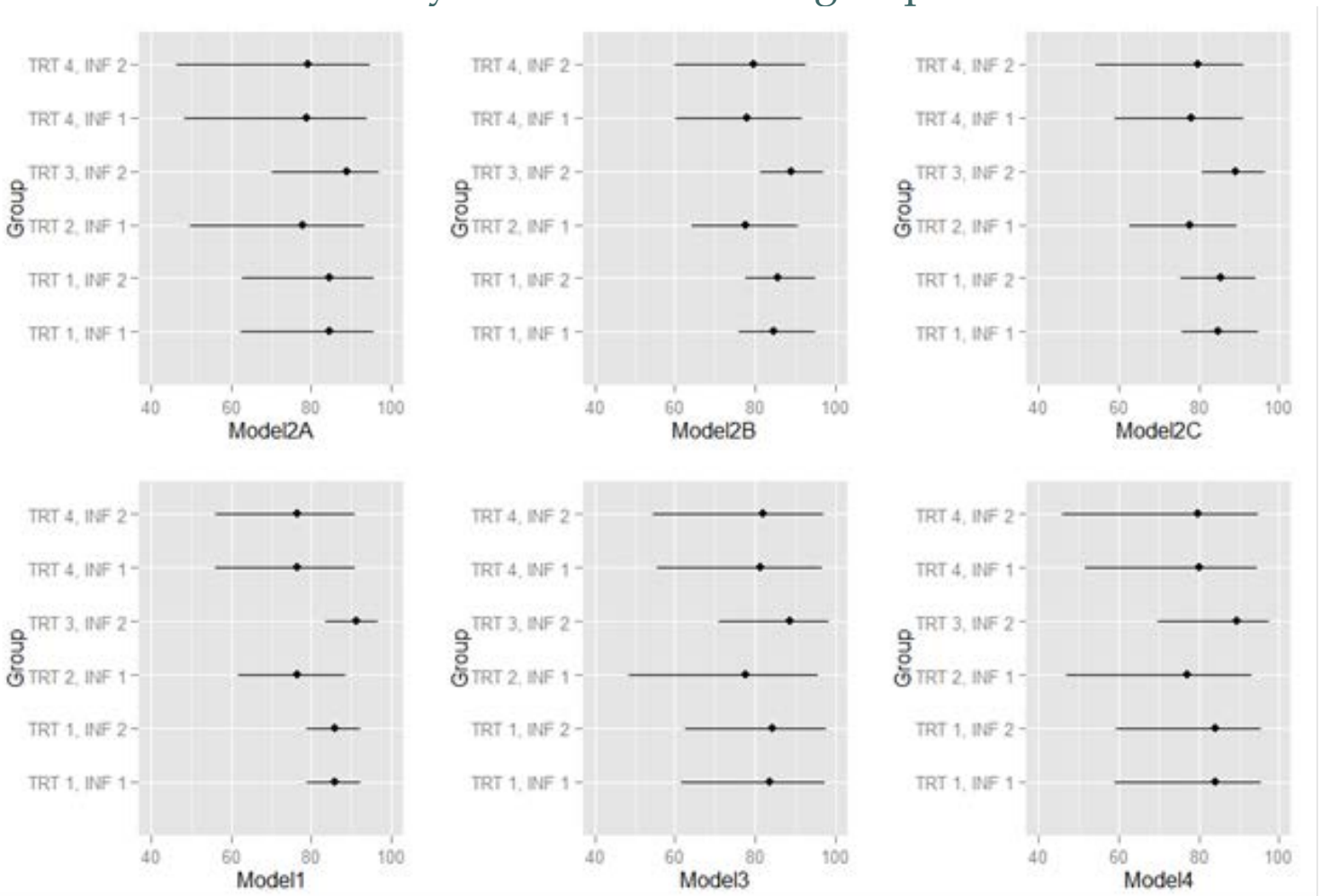
Bayesian Subgroup Analysis:
Application

	Partially Exchangeable				Non-exchangeable	EXNEX
Odds Ratio	**Model 1**	**Model 2A**	**Model 3**	**Model 4***	**Model 2B**	**Model 2C**
OR(TRT1,TRT2)	1.87 (0.78, 4.62)	1.52 (0.72, 3.77)	1.50 (0.72, 3.76)	1.54 (0.74, 3.83	1.59 (0.61, 5.29)	1.68 (0.68, 4.93)
OR(TRT1,TRT3)	0.59 (0.24, 1.35)	0.69 (0.28, 1.43)	0.69 (0.28, 1.46)	0.63 (0.25, 1.45)	0.73 (0.23, 1.97)	0.66 (0.24, 1.62)
OR(TRT1,TRT4)	1.88 (0.60, 5.73)	1.42 (0.61, 4.00)	1.14 (0.65, 2.76)	1.22 (0.69, 3.14)	1.57 (0.55, 5.92)	1.62 (0.57, 7.10)

* Odds ratio is computed at a certain level of covariate

Bayesian Subgroup Analysis:
Application

Predictive Probability of Success Per Subgroup and Model



Bayesian Subgroup Analysis:
Application

- Model fit assessed through logarithm of the pseudo-marginal likelihood (LPML)

$$\text{LPML} = \sum_{j=1}^{J}\sum_{i=1}^{n_j} \log p(y_{ji_j}|y_{-ji_j}) = \sum_{j=1}^{J}\sum_{i=1}^{n_j} \log \text{CPO}_{ji_j}$$

$$\text{CPO}_{ji_j} = p(y_{ji_j}|y_{-ji_j}) = E_{\boldsymbol{\theta}}[p(y_{ji_j}|\boldsymbol{\theta})|y_{-ji_j})]$$

Partially Exchangeable				Non-exchangeable	EXNEX
Model 1	**Model 2A**	**Model 3**	**Model 4**	**Model 2B**	**Model 2C**
-435.4	-425.9	-424.5	-422.5	-421.3	-425.5

Data Augmentation

- A clinical trial design that relies on a historical or external control may be acceptable to evaluate efficacy in a patient population with an unmet need.

- Caveats:
  - control patients should be as similar as possible to the population expected to receive the investigational drug in the trial
  - currency of the historical control group also should be considered

- Consider the possibility of randomizing at least a small number of patients to the active control in the trial (e.g., through disproportionate randomization of 3:1, 4:1, among others)

Data Augmentation:
Data Structure

- Two similar trials $T_1(n_E, n_C)$ and $T_2(n_E, n_C)$ each have n_E assigned to receive treatment E and n_C patients assigned to receive treatment C, $n_E = n_C = 300$, $N = n_E + n_C$.

- Consider T_1 as main trial and reduce the number of patients in the control group so that randomization mimics $r : 1$, $r > 1$. Say, if $r = 2$, then randomly discard 150 patients in T_1 control group. Denote the reduced trial by $T_1^*(n_E, \frac{n_C}{r})$, which has $N^* = n_E + \frac{n_C}{r}$ patients.

- Let $R(n_E, \tilde{n}_C)$ be the reservoir, which has $\tilde{n}_C = n_C + \frac{n_C}{r}$ control records from T_2 and the discarded control records from T_1, and n_E patient records from T_2, $\tilde{N} = n_E + \tilde{n}_C$.

Data Augmentation:
Propensity Score Matching

- Let x_{E_i} be the treatment response of subject i in the experimental group, $i = 1, \ldots, n_E$ and x_{C_j} be the treatment response of subject j in the control group, $j = 1, \ldots, n_C$

- Let $W_E = 1$ indicate that the treatment status is E and let e_i and $\tilde{e}_i$ be the estimated propensity scores of T_1^* and R given measured covariates $\mathbf{Z}$, i.e.,

$$e_i = P(W_E = 1|\mathbf{Z}_i) = \frac{exp(\boldsymbol{\beta}\mathbf{Z}_i)}{1 + exp(\boldsymbol{\beta}\mathbf{Z}_i)}, \quad i = 1, \ldots, N^*, \tag{6}$$

and

$$\tilde{e}_i = P(W_E = 1|\mathbf{Z}_i) = \frac{exp(\boldsymbol{\beta}\mathbf{Z}_i)}{1 + exp(\boldsymbol{\beta}\mathbf{Z}_i)}, \quad i = 1, \ldots, \tilde{N}. \tag{7}$$

Data Augmentation:
Propensity Score Matching

- GOAL: use the propensity score estimates $\tilde{e}_i$ to match the scores e_i and bring in subjects with matched scores from the records of active-control treated patients in R to augment the control group in T_1^*.
- To augment $T_1^*(n_E, \frac{n_c}{r})$, need at most $\tilde{n}_C = \frac{n_C}{r}$ subjects from R to mimic a $1:1$ randomization. Since T_1^* has $n_E = r\tilde{n}_C$, i.e., $n_E > \tilde{n}_C$, how does matching happen?
- How much to augment/borrow? $\tilde{n}_C = ?$
- Unweighted or weighted treatment responses?

Data Augmentation:
Matching Scheme 1

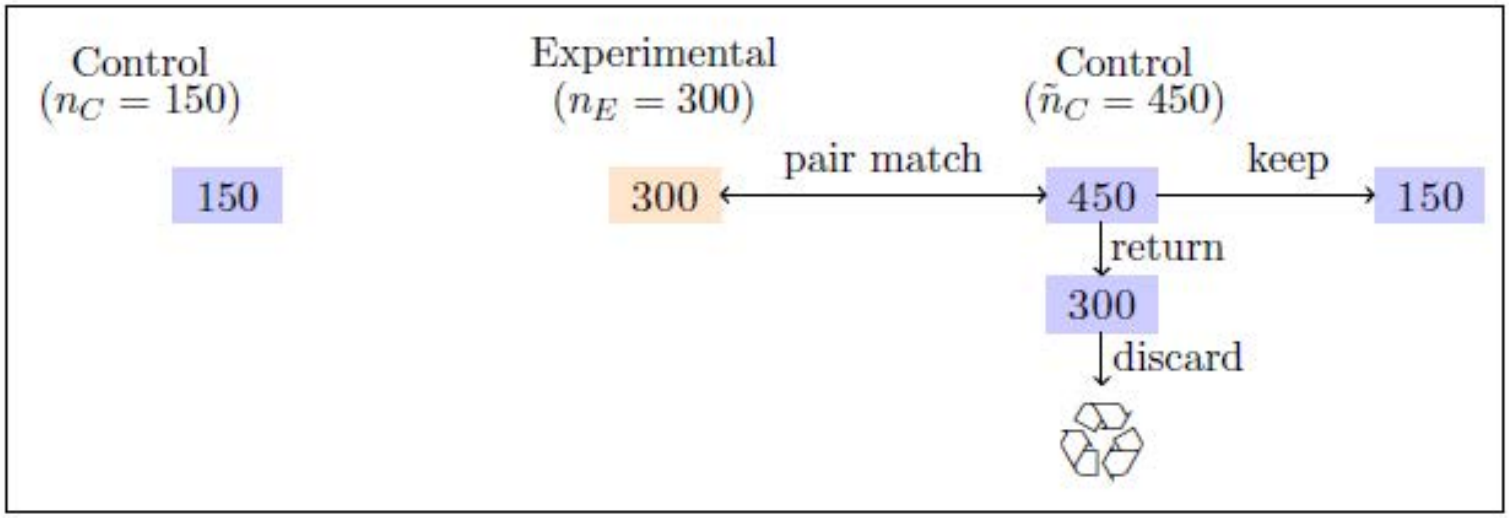
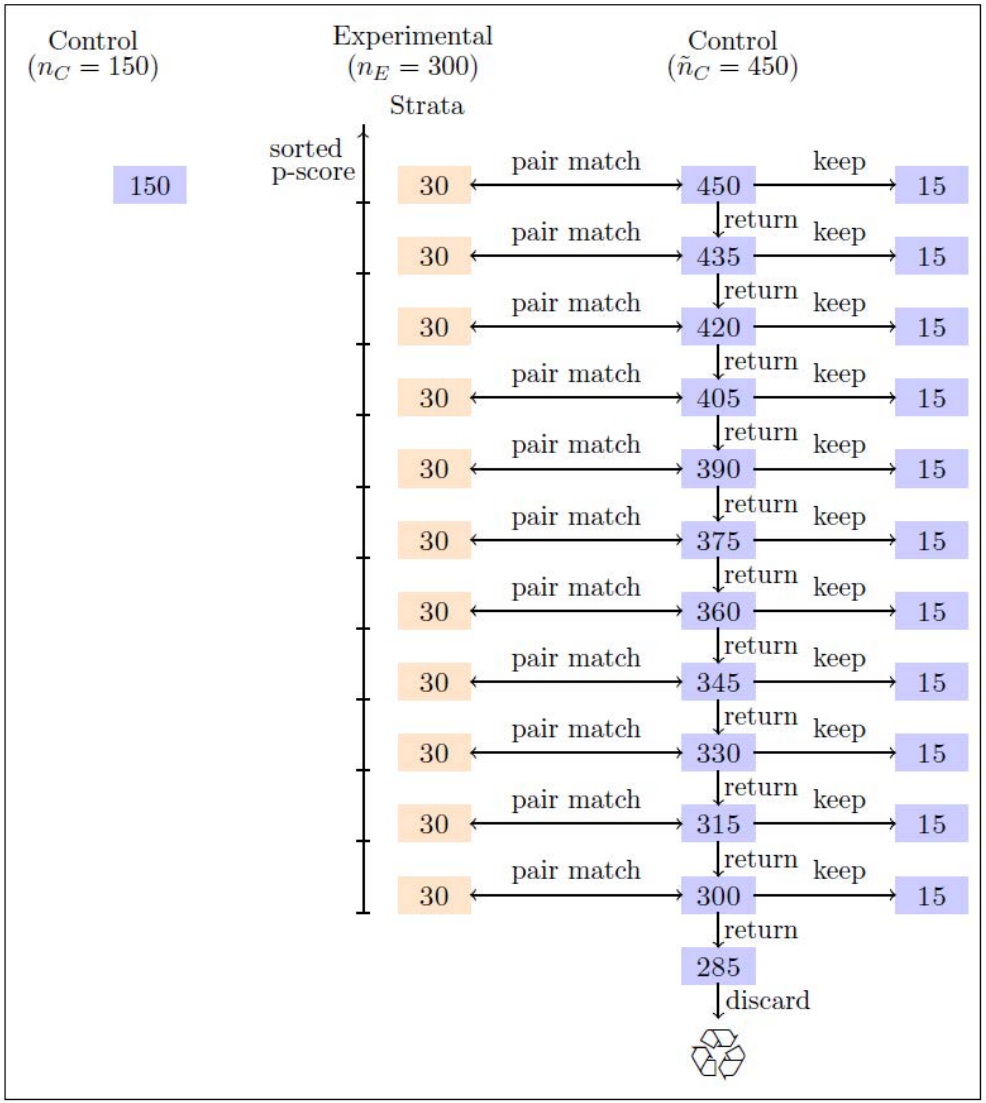
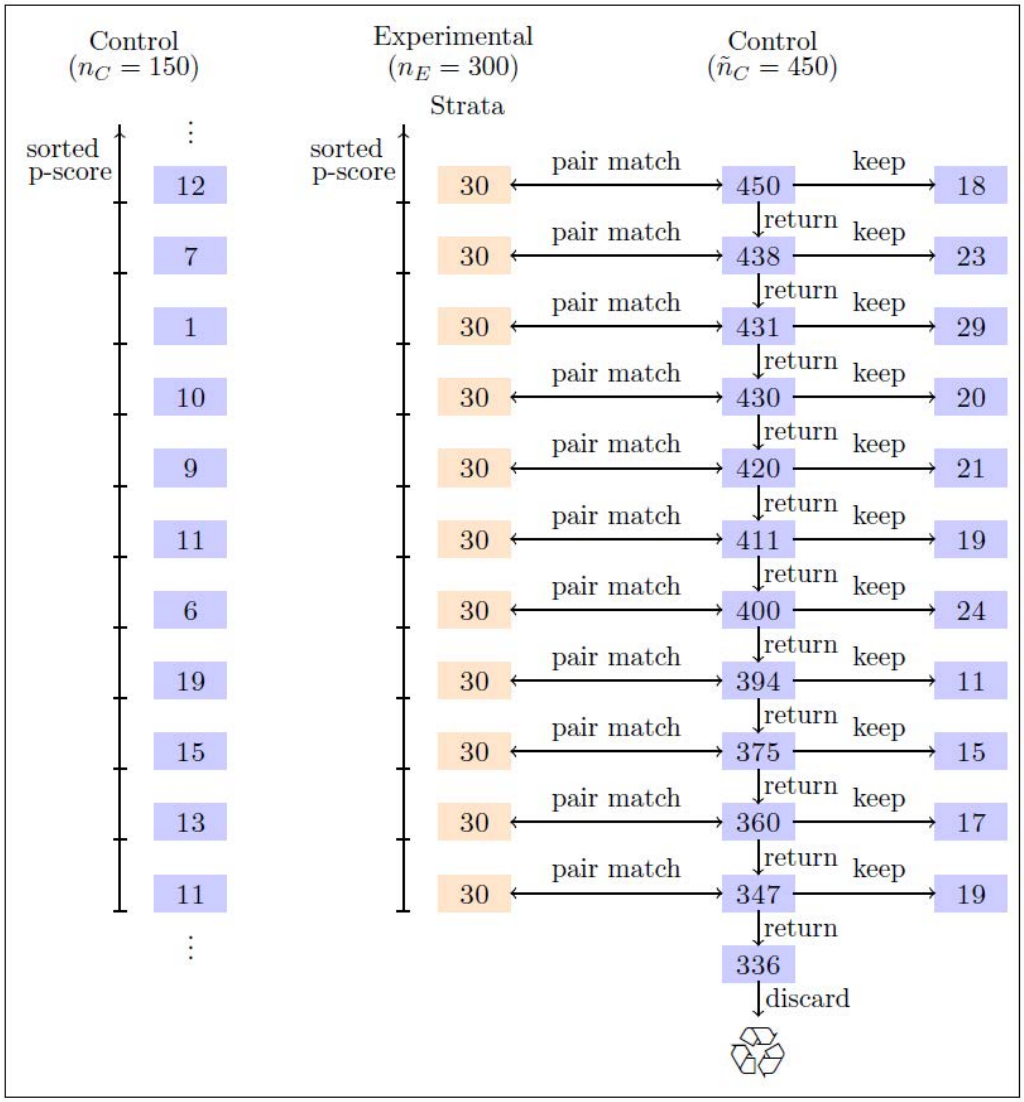


Figure 1: Example of matching scheme 1.

Data Augmentation:
Matching Scheme 2

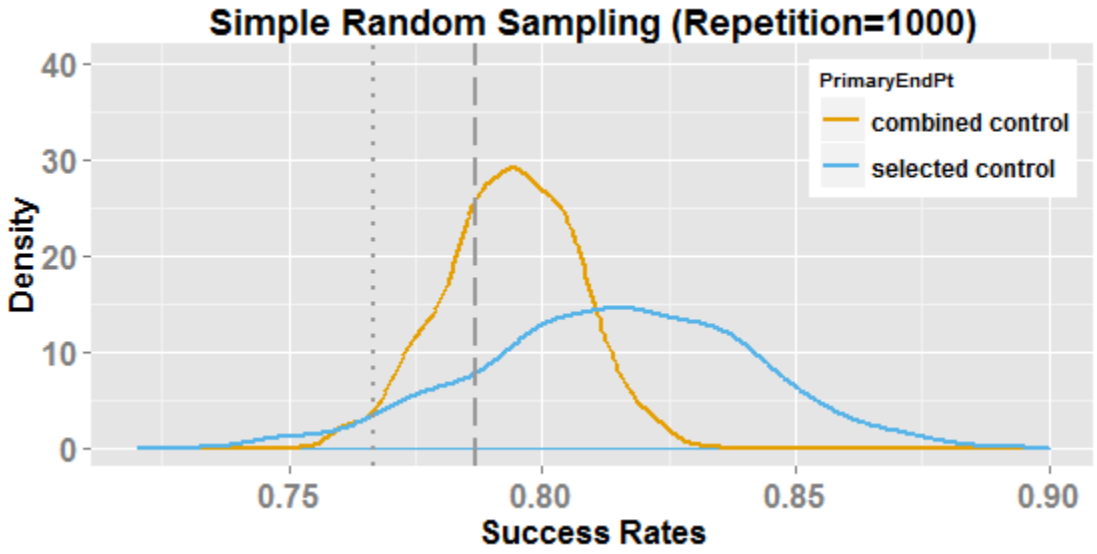


Data Augmentation:
Matching Scheme 3



Data Augmentation:
Investigations

Success rates at primary endpoint of the combined $\frac{n_c}{r} + \tilde{n}_C$ patients treated with active-control from T_1^* and R vs. that of randomly selected (unmatched) $\tilde{n}_C = 150$ records of active-control treated patients from R. Dashed line: mean success rates of experimental drug in T_1^*; dotted line: mean success rates of $n_C = 300$ controls from T_1.



Data Augmentation:
Investigations

- Weight each observation by

$$w_i = \frac{W_i}{\hat{e}(\mathbf{Z}_i)} + \frac{1 - W_i}{1 - \hat{e}(\mathbf{Z}_i)} \tag{8}$$

where $\hat{e}(\mathbf{Z}_i)$ is the estimated propensity score for observation i given covariates $\mathbf{Z}_i$.

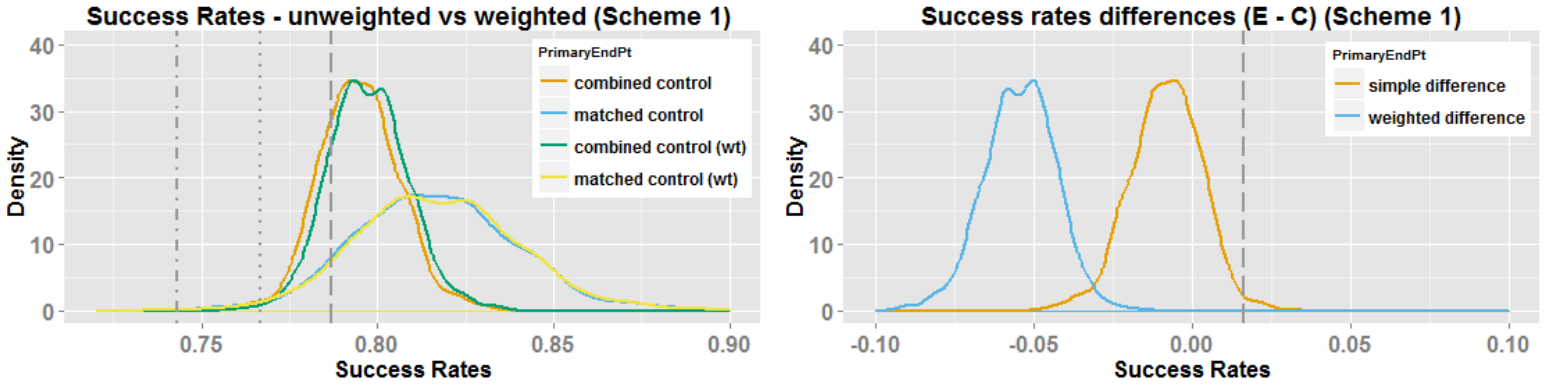
- Average treatment effect (ATE), $\hat{\delta}$, for N^* observations is calculated as

$$\hat{\delta} = \frac{\sum_i^{N^*} x_i \times w_i}{\sum_i^{N^*} w_i}, \tag{9}$$

where x_i is the treatment response for patient i at certain endpoint.

Data Augmentation:
Investigations

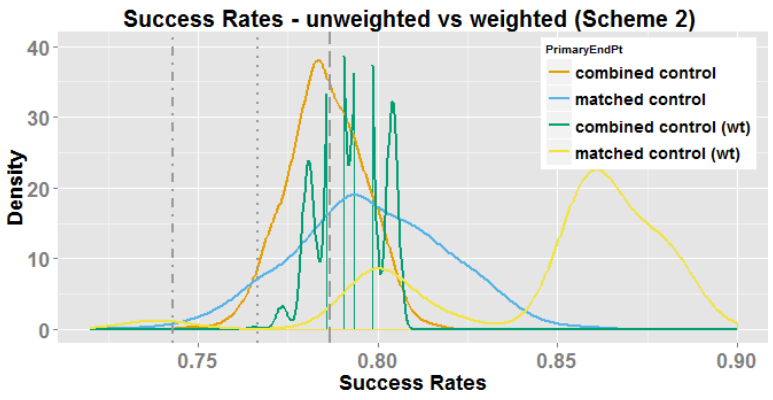
Weighted responses vs. unweighted responses at primary endpoint for combined controls ($\frac{n_c}{r} + \tilde{n}_C$ patients) and matched controls ($\tilde{n}_C$ patients) using Scheme 1. Dashed line: mean success rates of experimental drug in T_1^*; dotted line: mean success rates of $n_C = 300$ controls from T_1; dotdashed line: weighted success rates of experimental drug in Phase T_1^*.

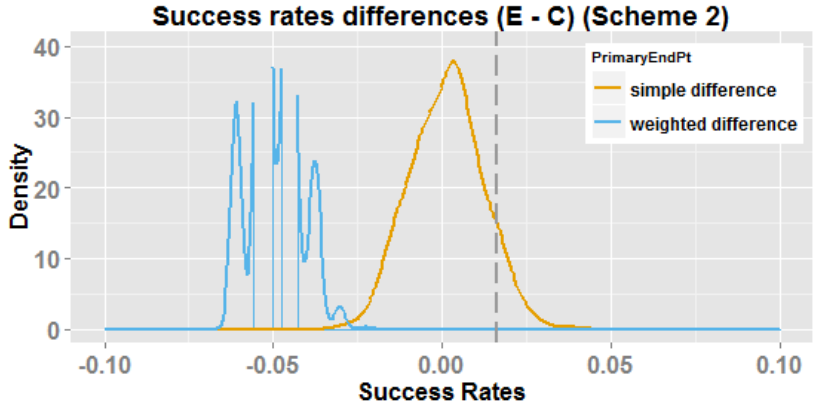


Unweighted: T-C = -0.0082 (-0.0767, 0.0602)
Weighted: T-C = -0.0543 (-0.1248, 0.0162)

Data Augmentation:
Investigations

Weighted responses vs. unweighted responses at primary endpoint for combined controls ($\frac{n_c}{r} + \tilde{n}_C$ patients) and matched controls ($\tilde{n}_C$ patients) using Scheme 2. Dashed line: mean success rates of experimental drug in T_1^*; dotted line: mean success rates of $n_C = 300$ controls from T_1; dotdashed line: weighted success rates of experimental drug in Phase T_1^*.

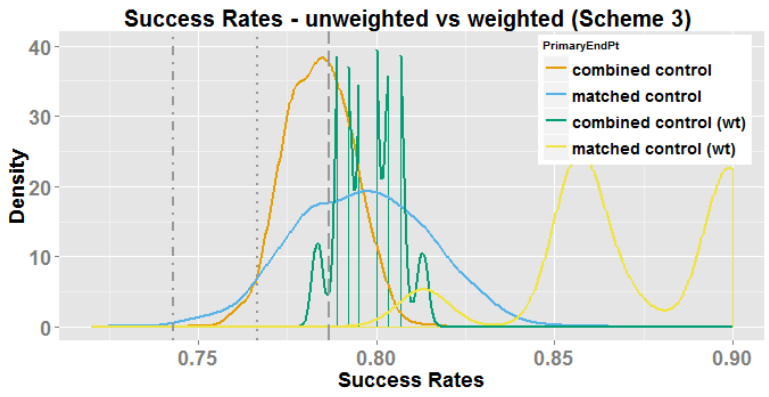


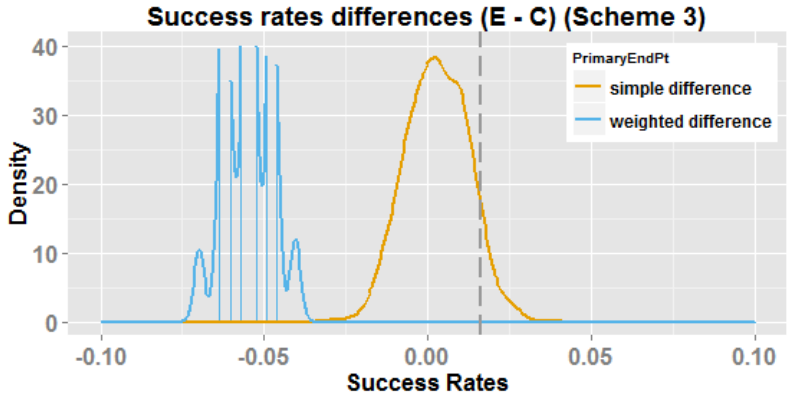


Unweighted: E-C = 0.0013 (-0.0656, 0.0683)
Weighted : E-C =-0.0495 (-0.1203, 0.0213)

Data Augmentation:
Investigations

Weighted responses vs. unweighted responses at primary endpoint for combined controls ($\frac{n_c}{r} + \tilde{n}_C$ patients) and matched controls ($\tilde{n}_C$ patients) using Scheme 3. Dashed line: mean success rates of experimental drug in T_1^*; dotted line: mean success rates of $n_C = 300$ controls from T_1; dotdashed line: weighted success rates of experimental drug in Phase T_1^*.

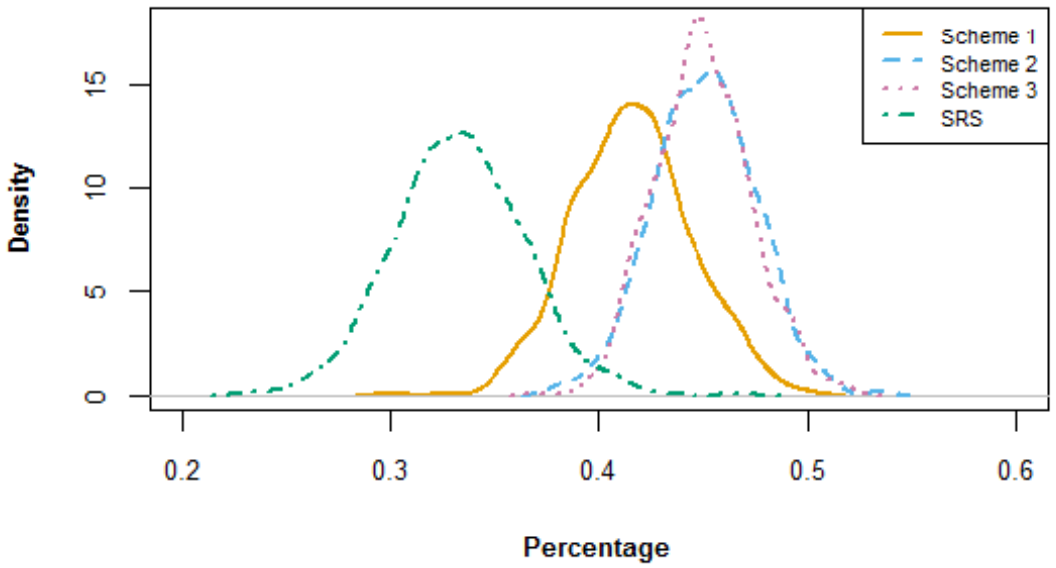




Unweighted E-C = 0.0029 (-0.0657, 0.0714)
Weighted E–C = -0.0548 (-0.1253, 0.0157)

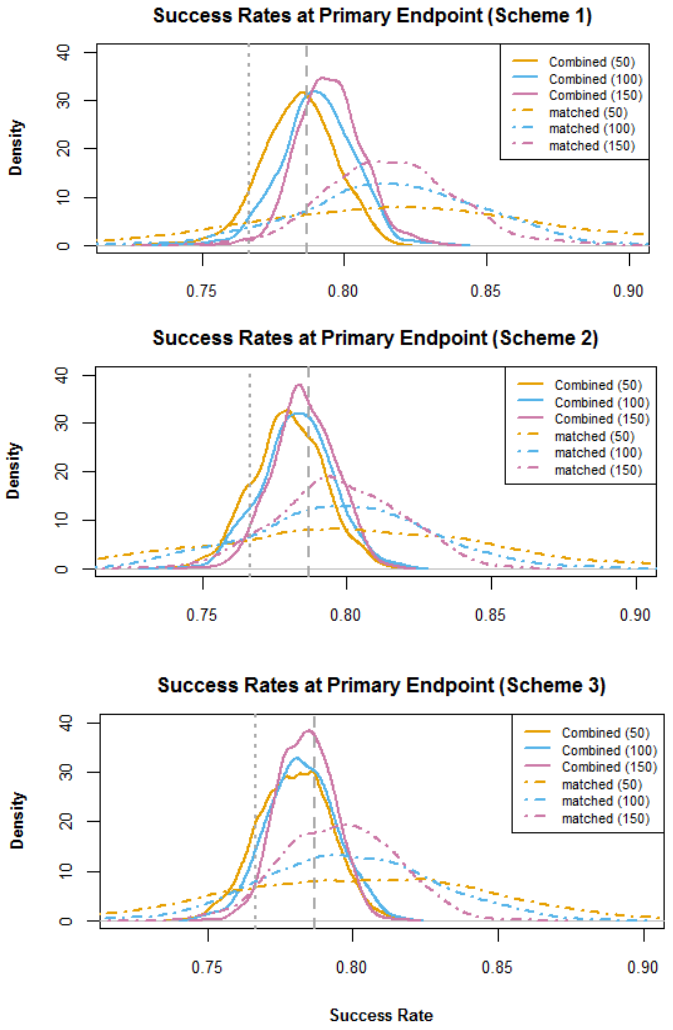
Data Augmentation:
Investigations

Percentages of matched controls from T_1 for each scheme.



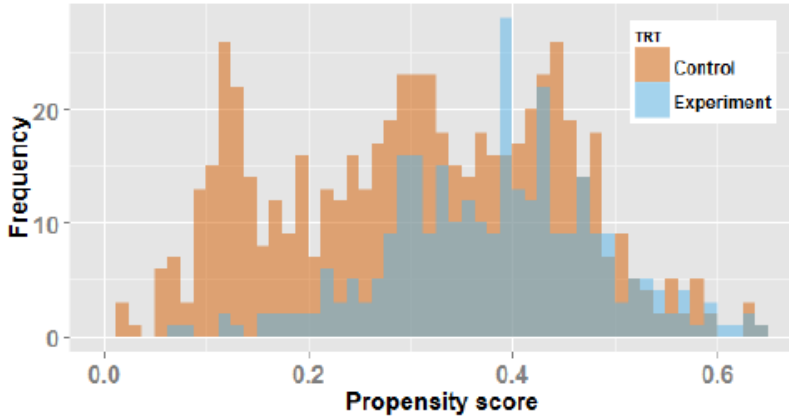
Data Augmentation:
Investigations

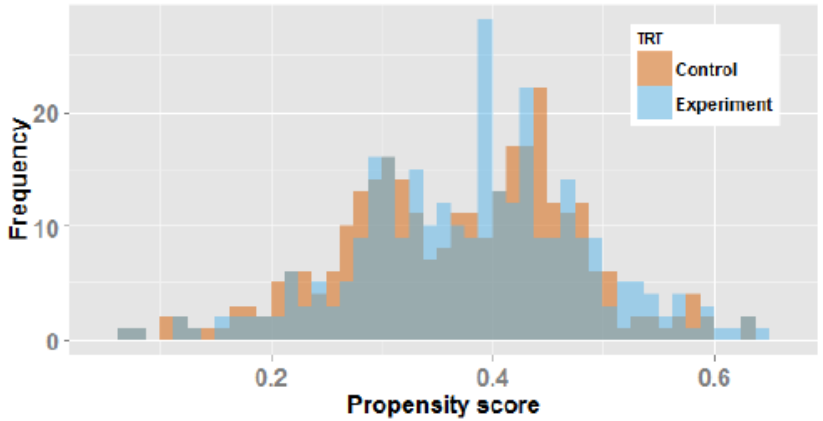
Success rates of combined ($\frac{n_c}{r} + \tilde{n}_C$ patients treated with active-control from T_1^* and R) controls at primary and secondary endpoints. Choose 50/100/150 active control records using scheme 1, 2, and 3. Dashed line: mean success rates of experimental drug in Phase III; dotted line: mean success rates of 300 controls from T_1.

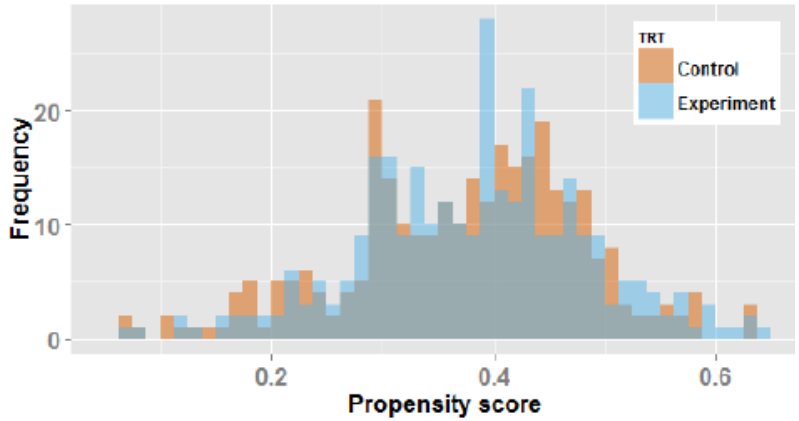


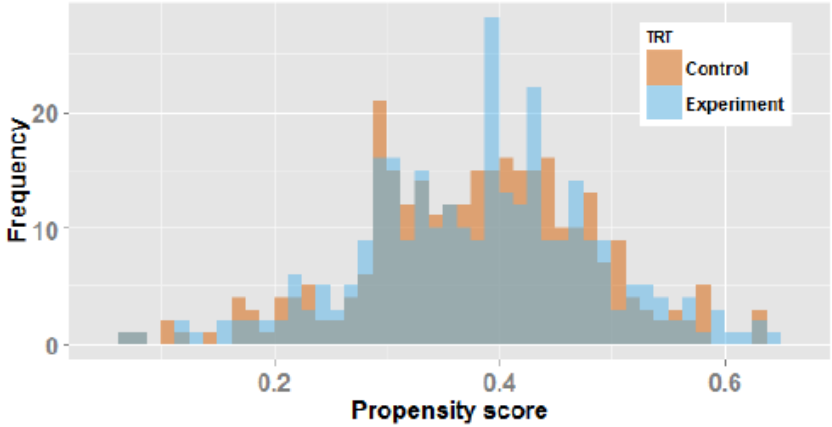
Data Augmentation:
Investigations

Overlaid histograms of estimated propensity scores comparing Experimental group ($n_E = 300$) and Control group ($\tilde{n}_C = 300$) after propensity score matching using different schemes.



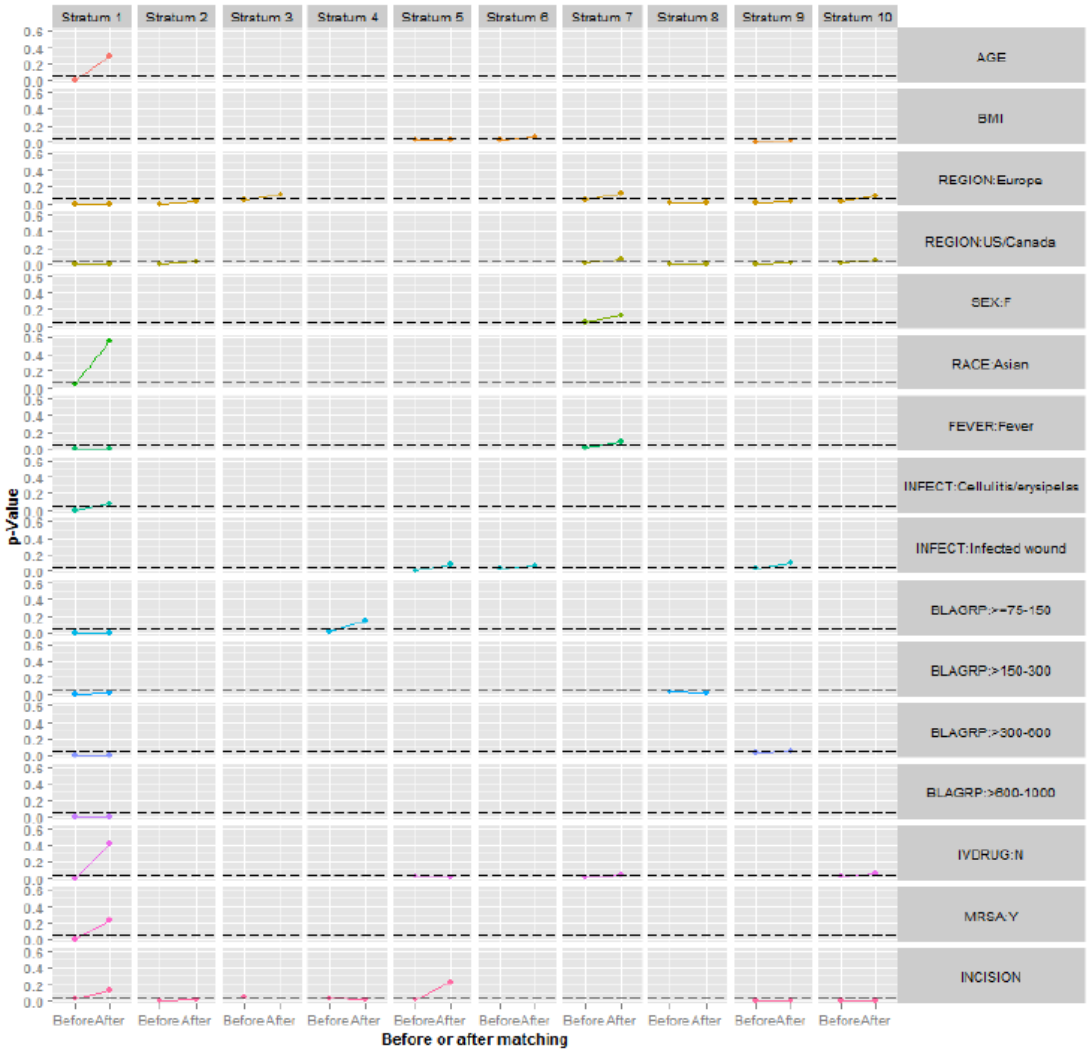






Data Augmentation:
Investigations

Change of p-values for selected covariates of each stratum from before to after matching using Scheme 2. These covariates have p-value p < 0.05 before matching. The dashed lines represent the significance level 0.05 for conducing two sample test for means or proportions.



Data Augmentation:
Investigations

	Covariate	Experimental	Control	SMD	p-value	Stratum
3	REGION:US/Canada	82.00	35.00	107.00	0.00	1
4	REGION:Europe	15.00	50.00	-80.00	0.00	1
9	FEVER:Fever	18.00	40.00	-51.00	0.00	1
13	BLAGRP:>=75-150	33.00	10.00	58.00	0.01	1
14	BLAGRP:>150-300	39.00	15.00	56.00	0.01	1
15	BLAGRP:>300-600	13.00	42.00	-70.00	0.00	1
16	BLAGRP:>600-1000	5.00	30.00	-68.00	0.00	1
25	REGION:US/Canada	82.00	63.00	42.00	0.03	2
26	REGION:Europe	15.00	33.00	-43.00	0.02	2
32	INFECT:Cellulitis/erysipelas	39.00	60.00	-44.00	0.04	2
44	INCISION	0.45	0.67	-0.45	0.02	2
88	INCISION	0.45	0.71	-0.54	0.01	4
90	BMI	27.90	29.99	-0.42	0.03	5
105	IVDRUG:N	65.00	37.00	58.00	0.00	5
149	IVDRUG:N	65.00	43.00	44.00	0.04	7
157	REGION:US/Canada	82.00	100.00	-67.00	0.01	8
158	REGION:Europe	15.00	0.00	60.00	0.01	8
168	BLAGRP:>150-300	39.00	63.00	-50.00	0.01	8
178	BMI	27.90	25.39	0.46	0.02	9
179	REGION:US/Canada	82.00	100.00	-67.00	0.01	9
180	REGION:Europe	15.00	0.00	60.00	0.03	9
198	INCISION	0.45	0.21	0.51	0.00	9
201	REGION:US/Canada	82.00	100.00	-67.00	0.05	10
220	INCISION	0.45	0.09	0.88	0.00	10

Unbalanced covariates for certain strata after matching using Scheme 2

Acknowledgement

Junjing (Jane) Lin, UC-Santa Barbara

References

- Dixon D., Simon R. (1991). *Bayesian Subset Analysis*. Biometrics 47: 871-881
- Ibrahim J., Chen M.. (2000). P*ower prior distributions for regression models.* Statistical Science **15**:46–60.
- Hartigan, J. (1990). *Partition Models*. Communications in Statistics, Theory and Methods, 19: 2745-2756
- Hobbs BP, Carlin BP, Mandrekar SJ, Sargent DJ. (2011) *Hierarchical commensurate and power prior models for adaptive incorporation of historical infomation in clinical trials.* Biometrics **67**:1047-56.
- Leon-Novelo, LG, et al. (2012). *Borrowing strength with nonexchangeable priors over subpopulations*. Biometrics 68: 550-558
- Lu, G. and Ades, A. E. (2004). *Combination of direct and indirect evidence in mixed treatment comparisons*. Statistics in Medicine **23**: 3105-3124.
- Schmidli H, Wandel S, Neuenschwander B (2012) *The network meta-analytic-predictive approach to non-inferiority trials.* Statistical Methods in Medical Research, DOI: 10.1177/0962280211432512

References

- Sethuraman, J. and Tiwari, R. C. (1982) Convergence of Dirichlet measures and the interpretation of their parameter, *Statistical Decision Theory and Related Topics III* 2 305-315.
- Simon R. (1999) *Bayesian design and analysis of active control clinical trials.* Biometrics; **55**: 484-487.