Stratification in the two-stage randomized trial design for testing treatment, self-selection, and treatment preference effects

Briana Cameron

Yale School of Public Health

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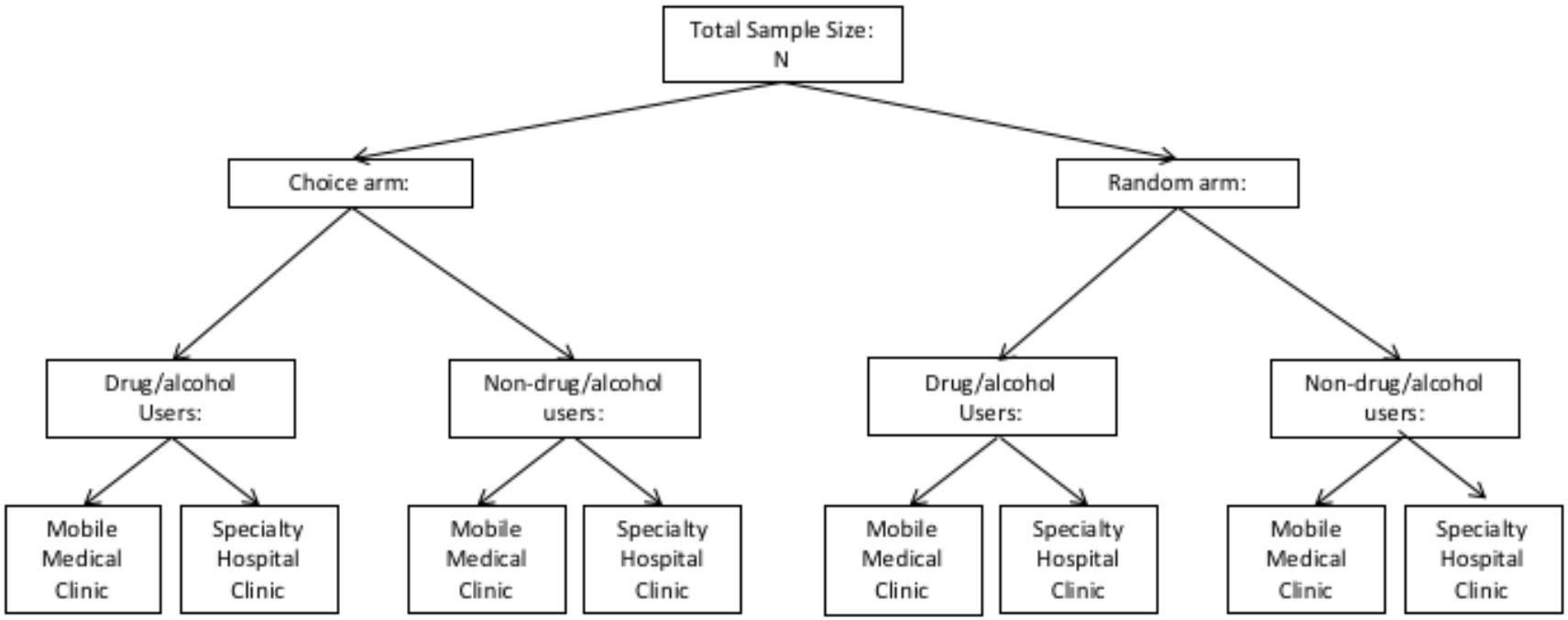
Introduction

- Motivation:
  - Need to understand how a patient's preference for a certain treatment affects his/her outcome response
  - Preference could influence adherence or create an additional psychological response
- Especially important when:
  - No blinding
  - Behavioral intervention

Motivating Example

- Study comparing modes of seeking Hepatitis C (HCV) treatment
- Many providers require patients to have abstained from drug or alcohol use for a minimum of 6 months
  - Less likely to seek the recommended treatment
- Mobile medical clinics attempt to remove many barriers of a traditional healthcare setting
- Drug/alcohol use as the stratification factor
  - Evidence to believe population subgroups have different preference rates for the same treatment options

Stratified Design



Stratified Model

- Stratified model:

$$y_{ijkl} = \mu + \mu_l + \tau_{il} + \nu_{jl} + \pi_{ijl} + \epsilon_{ijkl}$$

μ: overall mean

μ_l: mean response of stratum l

τ_{il}: treatment effect of the assigned treatment i in stratum l

ν_{jl}: selection effect for the preferred treatment j in stratum l

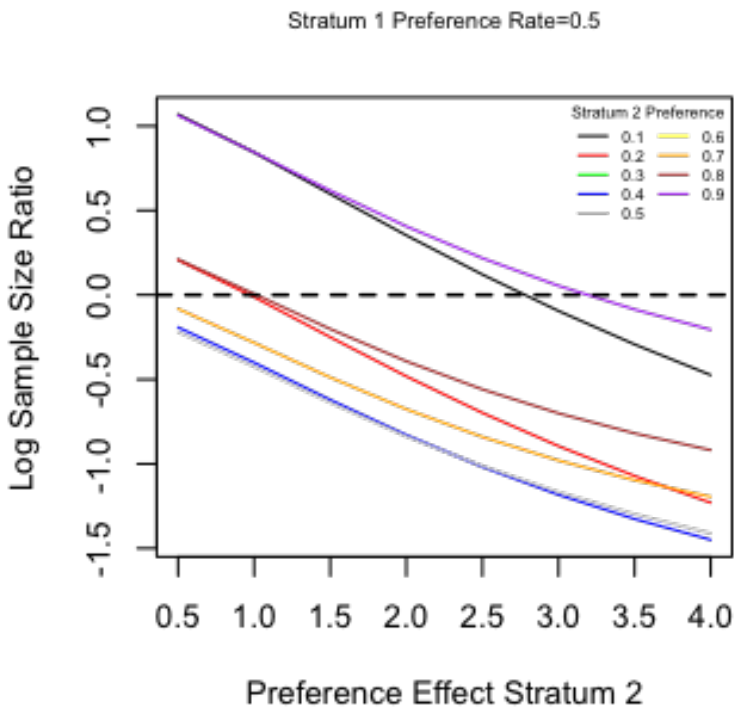
π_{ijl}: preference effect for the assigned treatment i and the preferred treatment j in stratum l

Sample Size for Preference Effect

$$N_\pi = \frac{(Z_\alpha + Z_\beta)^2}{4\theta\Delta\pi^2} \sum_{l=1}^{s} \frac{\xi_l}{\phi_l^2(1-\phi_l)^2} \left[\sigma_l^2 + \phi_l(1-\phi_l)\left[(2\phi_l - 1)\Delta\nu + \Delta\pi\right]^2 + 2\left(\frac{\theta}{1-\theta}\right)\sigma_l^2\left(\phi_l^2(1-\phi_l)^2\right) \right]$$

- Z_α, Z_β: Type I error, power
- θ: proportion assigned to choice arm (usually 0.5)
- $\Delta\pi, \Delta\nu$: preference, selection effect size
- ξ_l: proportion of patients in stratum l
- ϕ_l: preference rate for treatment 1 in stratum l
- σ_l^2: variance of stratum l

Efficiency of Design



- Stratified design is inefficient when preference rate in one arm is extreme
- When preference rates are moderate, stratified design tends to require smaller sample size than unstratified design

Back to Example

- HCV patients who receive preferred treatment have an improved health related qualify of life (HRQoL)
- Drug/alcohol users prefer MMC 70% of time ($\phi_1 = 0.7$), non-drug alcohol prefer 50% ($\phi_2 = 0.5$) of time
  - Assume 30% of population are drug/alcohol users ($\xi_1 = 0.3, \xi_2 = 0.7$)
- Equal allocation between random and choice arm ($\theta = 0.5$)
- Equal variance in each stratum ($\sigma_l^2 = 10$ for all l)

Results

- Can calculate weighted average effects $\Delta\tau = -2$, $\Delta\pi = 7.8$, $\Delta\nu = -4.2$.
- Can calculate sample size required to detect each effect in both stratified and unstratified designs

	80% Power		90% Power	
	Stratified	Unstratified	Stratified	Unstratified
Preference Effect	28	38	38	50
Selection Effect	140	172	186	232
Treatment Effect	156	260	210	346

Conclusion

- The doubly randomized two-stage trial design proposed by Rucker is ideal for addressing the importance of patient preferences in making treatment decisions
- Incorporating stratification into the design allows for a more efficient design, increased power, and decreased variability
- The need to incorporate stratification is clearly seen in the Hepatitis C example discussed previously

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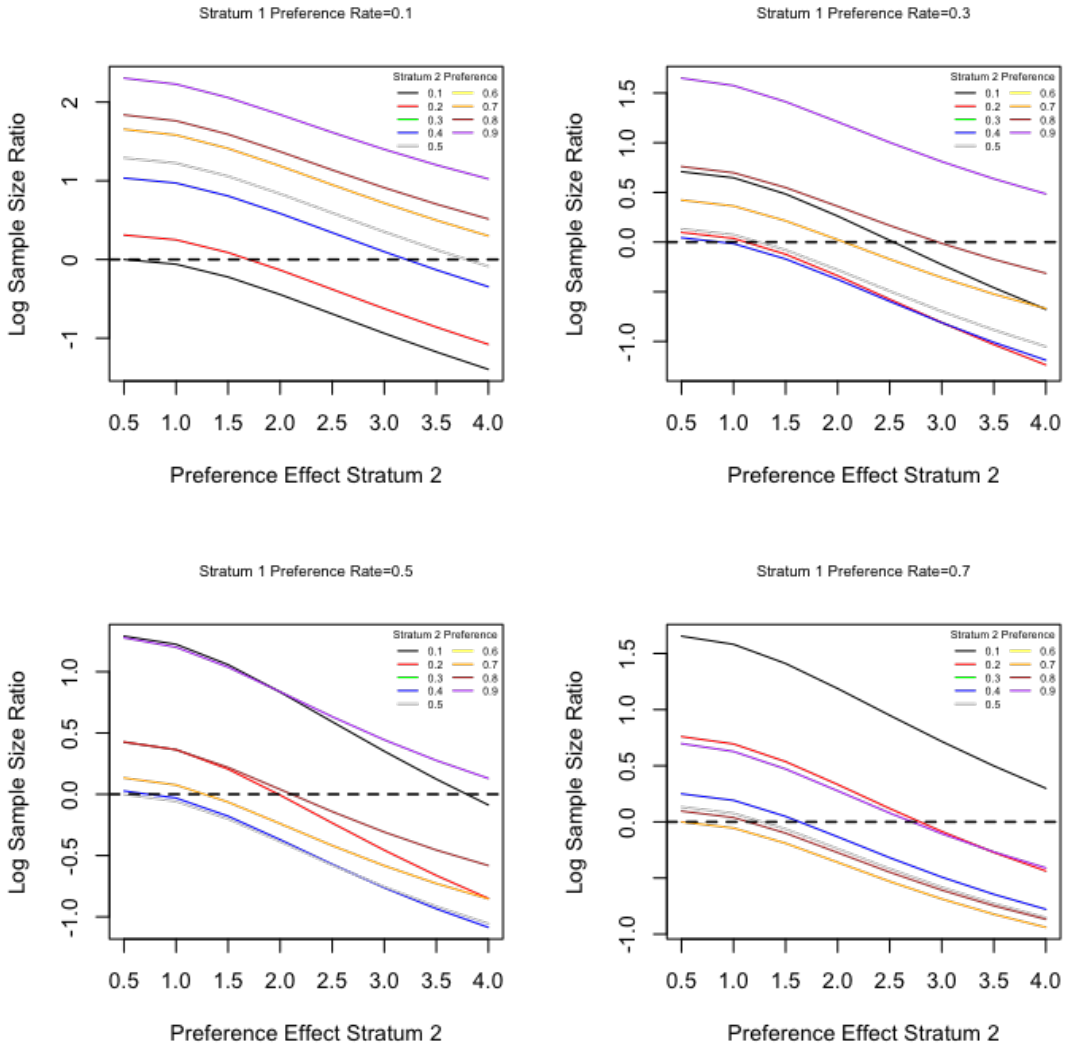
Type I Error Table

Table 1: Empirical Results from 10000 simulations with $\xi_l = 0.5, \mu_l = \tau_l = \nu_l = \pi_l = 0$ for $l = 1, 2$

			Test for preference		Test for selection	
Nominal significance level			0.05	0.01	0.05	0.01
Sample Size	ϕ_1	ϕ_2	Probability of Rejecting Null Hypothesis			
200	0.1	0.1	0.0530	0.0104	0.0534	0.0105
		0.3	0.0512	0.0112	0.0495	0.0104
		0.5	0.0488	0.0118	0.0533	0.0097
		0.7	0.0513	0.0099	0.0522	0.0113
		0.9	0.0472	0.0114	0.0525	0.0124
	0.2	0.2	0.0558	0.0113	0.0525	0.0108
		0.4	0.0531	0.0104	0.0543	0.0116
		0.6	0.0525	0.0101	0.0497	0.0089
		0.8	0.0531	0.0107	0.0523	0.0136
	0.3	0.3	0.0503	0.0098	0.0523	0.0116
		0.5	0.0494	0.0102	0.0480	0.0103
		0.7	0.0521	0.0087	0.0489	0.0102
		0.9	0.0499	0.0082	0.0478	0.0111
	0.4	0.4	0.0498	0.0109	0.0477	0.0086
		0.6	0.0479	0.0088	0.0508	0.0100
		0.8	0.0513	0.0099	0.0501	0.0099
	0.5	0.5	0.0501	0.0093	0.0491	0.0101
		0.7	0.0506	0.0101	0.0524	0.0106
		0.8	0.0500	0.0101	0.0492	0.0118
		0.9	0.0544	0.0118	0.0520	0.0101
	0.6	0.6	0.0502	0.0101	0.0485	0.0105
		0.8	0.0514	0.0107	0.0486	0.0108
	0.7	0.7	0.0486	0.0109	0.0520	0.0100
		0.9	0.0522	0.0096	0.0511	0.0121
	0.8	0.8	0.0544	0.0097	0.0542	0.0089
		0.9	0.0511	0.0123	0.0524	0.0141
	0.9	0.9	0.0527	0.0108	0.0531	0.0105

Efficiency Examples



Example

Table 2a: Mean Mental Component Score and effect sizes for stratum of drug and alcohol users

	No Choice (Random)	Choice		No Choice	
Actual Treatment	**Mean**	**Preferred Specialty**	**Preferred MMC**	**Preferred Specialty**	**Preferred MMC**
Specialty Clinic	45	47	-	47	(45-0.3*47)/0.7=44.1
MMC	47	-	52	(47-0.7*52)/0.3=35.3	52
				Average received preferred treatment=49.5	Average did not receive preferred treatment=39.7
				Preference Effect=49.5-39.7=9.8	
				Average prefer specialty=41.2	Average prefer MMC=48.1
				Selection Effect=41.2-48.1=-6.9	

Table 2b: Mean Mental Component Score and effect sizes for stratum of non-drug and alcohol users

	No Choice (Random)	Choice		No Choice	
Actual Treatment	**Mean**	**Preferred Specialty**	**Preferred MMC**	**Preferred Specialty**	**Preferred MMC**
Specialty Clinic	50	52	-	52	(50-0.5*52)/0.5=48
MMC	52	-	57	(52-0.5*57)/0.5=47	57
				Average received preferred treatment=54.5	Average did not receive preferred treatment=47.5
				Preference Effect=54.5-47.5=7.0	
				Average prefer specialty=49.5	Average prefer MMC=52.5
				Selection Effect=49.5-52.5=-3	

Sample Size Formulas

$$N_\pi = \frac{(Z_\alpha + Z_\beta)^2}{4\theta\Delta\pi^2} \sum_{l=1}^{s} \frac{\xi_l}{\phi_l^2(1-\phi_l)^2} \left[\sigma_l^2 + \phi_l(1-\phi_l)\left[(2\phi_l - 1)\Delta\nu + \Delta\pi\right]^2 + 2\left(\frac{\theta}{1-\theta}\right)\sigma_l^2\left(\phi_l^2(1-\phi_l)^2\right) \right]$$

$$N_\nu = \frac{(Z_\alpha + Z_\beta)^2}{4\theta\Delta\nu^2} \sum_{l=1}^{s} \frac{\xi_l}{\phi_l^2(1-\phi_l)^2} \left[\sigma_l^2 + \phi_l(1-\phi_l)\left[(2\phi_l - 1)\Delta\pi + \Delta\nu\right]^2 + 2\left(\frac{\theta}{1-\theta}\right)\sigma_l^2\left(\phi_l^2(1-\phi_l)^2\right) \right]$$

$$N_\tau = \frac{4(Z_\alpha + Z_\beta)^2}{(1-\theta)\Delta\tau^2} \sum_{l=1}^{s} \xi_l \sigma_l^2$$