Baseline Covariate Adjustment in SMART Studies via Artificial Randomization

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IMPACT

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[1] Joint work with Semhar B. Ogbagaber, PhD

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Outline

Sequential Multiple Assignment Randomized Trials (SMART)

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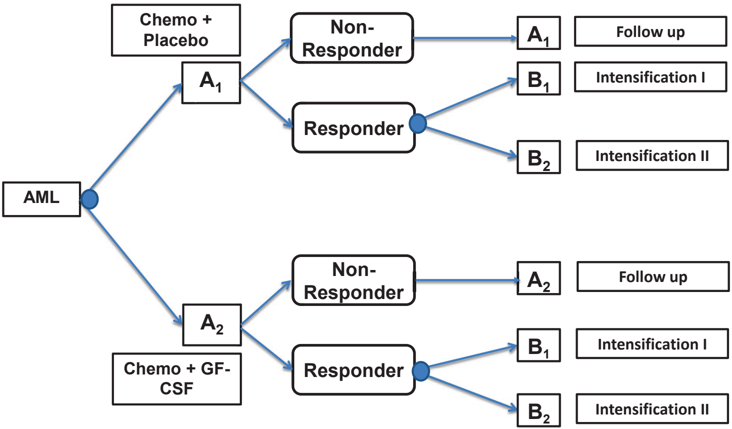
- SMARTs are useful for drawing simultaneous inference about multiple Dynamic Treatment Regimes.
- They aid development of optimal "treatment" or "sequence of treatments" for a particular disease.
- Mimics the process of natural physician-patient relationship of disease management.

SMART Design: Example

Stone et al. (2001) for CALGB trial



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SMART Design: Example

Response (complete remission) is defined as:

- Less than 5% blastic (undifferentiated) blood cells, and none with leukemic phenotype and
- Platelet count $> 10^5/\mu$L and
- WBC count $> 10^3/\mu$L

SMART Design: Example

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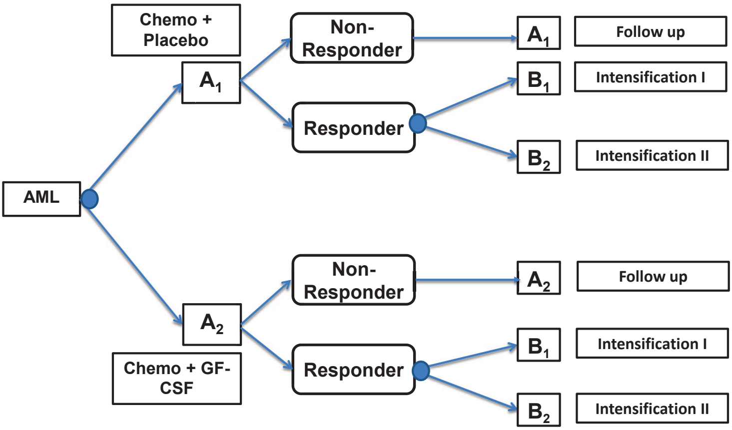
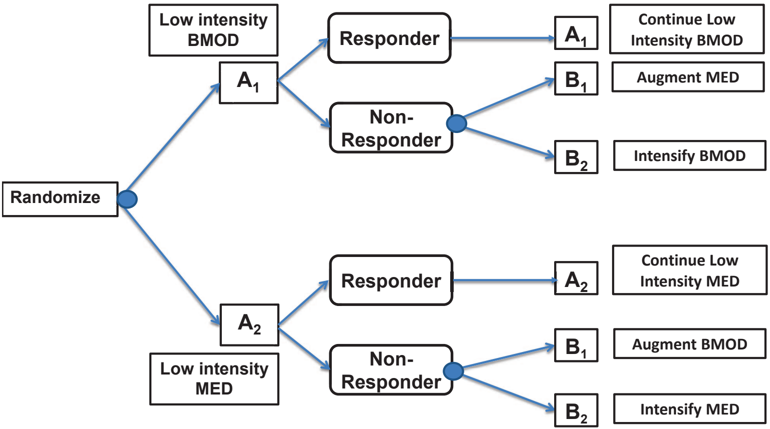


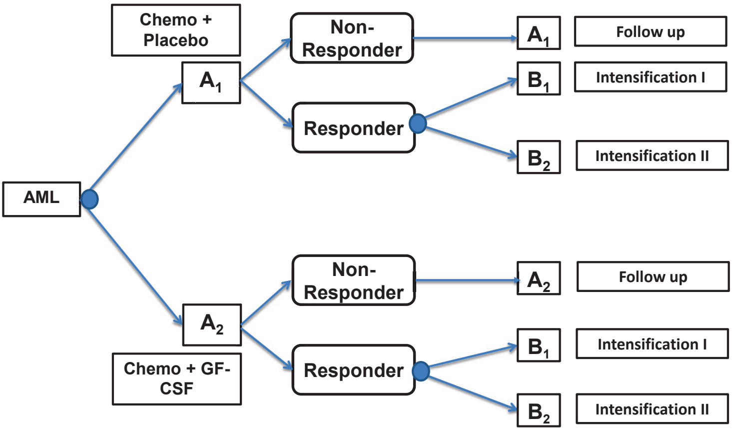
SMART Design: Example

Pelham et al. (2008) for ADHD trial



SMART Design: Example

Stone et al. (2001) for CALGB trial



Outline

Motivation

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- Ignoring maintenance treatment might lead to biased estimation of induction treatment effects → Must consider both induction and maintenance
- Goal: Estimate induction-maintenance treatment combination effects on overall survival → Apply “Dynamic Treatment Regimes” methodology

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Dynamic Treatment Regimes

- For CALGB Trial, define:
  $A_j B_k$ as "Treat with A_j, if he/she responds to A_j, start maintenance B_k, otherwise continue the same initial treatment."

- For Pelham trial, this becomes:
  $A_j B_k$: "Treat with A_j, if he/she does not respond to A_j, switch to B_k; otherwise continue the same initial treatment."

Comparing Dynamic Treatment Regimes

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- Hypothesis testing to compare Dynamic Treatment Regimes are usually based on inverse weighting and g-estimation.
- Regression methods that allow for comparison of treatment strategies that flexibly adjusts for baseline covariates are not as straight-forward
- Goal - facilitate methods to use standard regression approaches to compare the four strategies: $A_1B_1, A_1B_2, A_2B_1, A_2B_2$ adjusting for baseline covariates.

Challenge: Multiple group membership

A_1B_1: "**Treat with** A_1, if he/she does not respond to A_1, switch to B_1; otherwise **continue the same initial treatment**".

A_1B_2: "**Treat with** A_1, if he/she does not respond to A_1, switch to B_2; otherwise **continue the same initial treatment**".

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Table : Typical Data Structure for Pelham Trial

Patient	X_1	X_2	R	Z_1	Z_2	A_1B_1	A_1B_2	A_2B_1	A_2B_2
1	1	0	0	1	0	1	0	0	0
2	1	0	1	-1	-1	1	1	0	0
3	0	1	1	-1	-1	0	0	1	1

Challenge: Multiple group membership

A_1B_1: "**Treat with** A_1, if he/she does not respond to A_1, switch to B_1; otherwise **continue the same initial treatment**".

A_1B_2: "**Treat with** A_1, if he/she does not respond to A_1, switch to B_2; otherwise **continue the same initial treatment**".

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1	1	0	0	1	0	1	0	0	0
2	1	0	1	-1	-1	1	1	0	0
3	0	1	1	-1	-1	0	0	1	1

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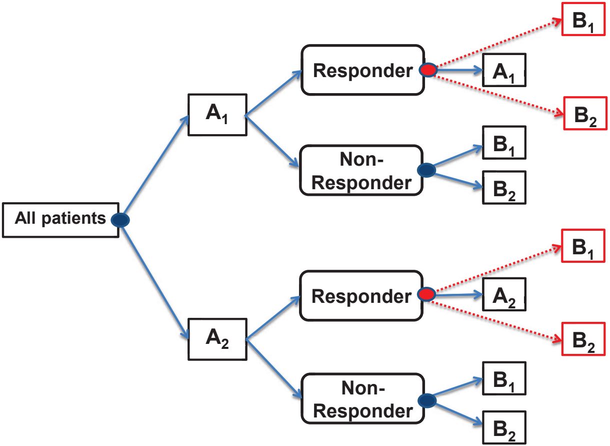
A_1B_1: "**Treat with** A_1, if he/she does not respond to A_1, switch to B_1; otherwise **continue the same initial treatment**".

A_1B_2: "**Treat with** A_1, if he/she does not respond to A_1, switch to B_2; otherwise **continue the same initial treatment**".

Table : Typical Data Structure for Pelham Trial

Patient	X_1	X_2	R	Z_1	Z_2	A_1B_1	A_1B_2	A_2B_1	A_2B_2
1	1	0	0	1	0	1	0	0	0
2	1	0	1	-1	-1	1	1	0	0
3	0	1	1	-1	-1	0	0	1	1

Main Idea: Artificial Randomization



Main Idea: Artificial Randomization

Table : Typical Data Structure for Pelham Trial

Pt	X_1	X_2	R	Z_1	Z_2	A_1B_1	A_1B_2	A_2B_1	A_2B_2
1	1	0	0	1	0	1	0	0	0
2	1	0	1	-1	-1	1	1	0	0
3	0	1	1	-1	-1	0	0	1	1

Table : After Artificial Randomization

Pt	X_1	X_2	R	Z_1	Z_2	Z_1^*	Z_2^*	A_1B_1	A_1B_2	A_2B_1	A_2B_2
1	1	0	0	1	0	1	0	1	0	0	0
2	1	0	1	-1	-1	1	0	1	0	0	0
3	0	1	1	-1	-1	0	1	0	0	0	1

Outline

Estimating Strategy Means

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- $$Z_{1i}^* = \begin{cases} Z_{1i}, & R_i = 0 \\ \text{Bernoulli}(Q_1), & R_i = 1, \end{cases} \quad (1)$$

  where Bernoulli(Q_1), with $Q_1 = Pr(Z_1 = 1) = 1 - Q_2$, indicates a randomly generated value of a Bernoulli random variable with probability Q_1.
- Define $Z_{2i}^* = 1 - Z_{1i}^*$.
- $$\boxed{\hat{\mu}_{jk}^{AR} = \frac{\sum_{i=1}^{n} X_{ji} Z_{ki}^* Y_i}{\sum_{i=1}^{n} X_{ji} Z_{ki}^*}}$$

  is a consistent estimator of $\mu_{jk} = E(Y|A_j B_k)$, mean outcome under $A_j B_k$.

Estimating Strategy Means: SMART Estimator

- Simple Multiple Artificial Randomized Tool (SMART) estimator:

  Repeat AR M times and average the estimates to get

$$\boxed{\hat{\mu}_{jk}^{SMART} = \frac{1}{M}\sum_{m=1}^{M}\hat{\mu}_{jk}^{AR(m)}}$$

- Variance:

$$\hat{\mu}_{jk}^{SMART} = \frac{1}{M}\sum_{m=1}^{M}\widehat{var}(\hat{\mu}_{jk}^{AR(m)}) + \left(\frac{M+1}{M}\right)B$$

$B = \frac{1}{(M-1)}\sum_{m=1}^{M}(\hat{\mu}_{jk}^{AR(m)} - \hat{\mu}_{jk}^{SMART})^2.$

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Estimating Strategy Means: IPW Estimators

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$$\boxed{\hat{\mu}_{jk}^{IPW} = \frac{1}{n}\sum_{i=1}^{n}\frac{X_{ji}}{\kappa_j}\left\{R_i + \frac{(1-R_i)Z_{ki}}{Q_k}\right\}Y_i = \frac{1}{n}\sum_{i=1}^{n}W_{jki}Y_i}$$

where $W_{jki} = \frac{X_{ji}}{\kappa_j}\left\{R_i + \frac{(1-R_i)Z_{ki}}{Q_k}\right\}$.

$$\boxed{\hat{\mu}_{jk}^{IPW1} = \frac{1}{n}\sum_{i=1}^{n}\hat{W}_{jki}Y_i}$$

where $\hat{W}_{jki} = \frac{X_{ji}}{\hat{\kappa}_j}\left\{R_i + \frac{(1-R_i)Z_{ki}}{\hat{Q}_k}\right\}$, $\hat{\kappa}_j = \frac{\sum_{i=1}^{n}X_{ji}}{n}$, $\hat{Q}_k = \frac{\sum_{i=1}^{n}X_{ji}(1-R_i)Z_{ki}}{\sum_{i=1}^{n}X_{ji}(1-R_i)}$.

Estimating Strategy Means: IPW Estimators

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$$\hat{\mu}_{jk}^{NIPW} = \frac{\sum_{i=1}^{n} W_{jki} Y_i}{\sum_{i=1}^{n} W_{jki}}$$

$$\hat{\mu}_{jk}^{NIPW1} = \frac{\sum_{i=1}^{n} \hat{W}_{jki} Y_i}{\sum_{i=1}^{n} \hat{W}_{jki}}$$

Outline

Simulation Results: n=150

Table : Monte Carlo (MC), model-based (MBSE), robust standard error estimates (RSE) and coverage probabilities (CP, 95%) for strategy means. $\mu_{11} = 15$, $\mu_{12} = 20$. SMART1=SM1, SMART5=SM5.

Strategy	Quantities	IPW	NIPW	SM1	SM5	NIPW1	IPW1
A_1B_1	Est	15.00	15.04	15.01	15.01	15.00	15.00
	MBSE	1.85	1.18	1.27	1.39	1.18	1.15
	RSE	1.83	1.16	1.25	1.36	1.10	1.10
	MCSE	1.86	1.19	1.30	1.23	1.12	1.11
	CP	0.93	0.92	0.93	0.96	0.92	0.94
A_1B_2	Est	19.99	19.99	20.01	20.01	19.99	19.98
	MBSE	2.52	0.94	0.96	0.98	0.94	0.94
	RSE	2.47	0.92	0.95	0.97	0.94	0.94
	MCSE	2.61	0.93	0.97	0.94	0.95	0.95
	CP	0.93	0.93	0.94	0.96	0.93	0.93

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	CP	0.93	0.93	0.94	0.96	0.93	0.93

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A_1B_2	Est	19.99	19.99	20.01	20.01	19.99	19.98
	MBSE	2.52	0.94	0.96	0.98	0.94	0.94
	RSE	2.47	0.92	0.95	0.97	0.94	0.94
	MCSE	2.61	0.93	0.97	0.94	0.95	0.95
	CP	0.93	0.93	0.94	0.96	0.93	0.93

Simulation Results: n=300

Table : Monte Carlo (MC), model-based (MBSE), robust standard error estimates (RSE) and coverage probabilities (CP, 95%) for strategy means. $\mu_{11} = 15$, $\mu_{12} = 20$.

Strategy	Quantities	IPW	NIPW	SM1	SM5	NIPW1	IPW1
A_1B_1	Est	15.00	15.03	15.01	15.01	15.00	15.00
	MBSE	1.31	0.83	0.89	0.97	0.83	0.84
	RSE	1.30	0.83	0.88	0.88	0.78	0.78
	MCSE	1.33	0.84	0.91	0.92	0.78	0.78
	CP	0.94	0.93	0.94	0.93	0.92	0.94
A_1B_2	Est	19.99	19.99	20.01	20.02	19.99	19.98
	MBSE	1.78	0.66	0.68	0.69	0.67	0.67
	RSE	1.76	0.66	0.67	0.67	0.66	0.66
	MCSE	1.87	0.67	0.67	0.68	0.67	0.67
	CP	0.93	0.94	0.95	0.95	0.93	0.93

Outline

CALGB Data

Table : Estimated strategy means and robust standard errors from the analysis of CALGB 8923 data.

Strategy	SMART1 (SE)	SMART5 (SE)	IPW (SE)	IPW1 (SE)	NIPW (SE)	NIPW1 (SE)
A_1B_1	487.16	468.56	454.0	478.5	468.5	478.5
	(70.58)	(70.11)	(70.9)	(57.9)	(59.5)	(66.5)
A_1B_2	521.21	536.46	454.0	528.0	468.5	528.0
	(75.97)	(80.74)	(70.9)	(69.0)	(59.5)	(69.0)
A_2B_1	660.16	623.52	623.6	620.4	620.4	620.4
	(88.23)	(90.12)	(91.3)	(71.6)	(73.4)	(71.6)
A_2B_2	592.72	627.48	632.6	629.4	620.4	629.4
	(83.68)	(99.09)	(91.3)	(79.5)	(73.4)	(79.5)

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A_1B_1	487.16	468.56	454.0	478.5	468.5	478.5
	(70.58)	(70.11)	(70.9)	(57.9)	(59.5)	(66.5)
A_1B_2	521.21	536.46	454.0	528.0	468.5	528.0
	(75.97)	(80.74)	(70.9)	(69.0)	(59.5)	(69.0)
A_2B_1	660.16	623.52	623.6	620.4	620.4	620.4
	(88.23)	(90.12)	(91.3)	(71.6)	(73.4)	(71.6)
A_2B_2	592.72	627.48	632.6	629.4	620.4	629.4
	(83.68)	(99.09)	(91.3)	(79.5)	(73.4)	(79.5)

Regression with strategies as covariates

$$Y_i = \beta_0 + \sum_{j,k=1,2} \beta_{jk} S_{jki} + \gamma^T V_i + \sum_{j,k=1,2} \alpha_{jk}^T V_i S_{jki} + \epsilon_i, \tag{2}$$

with $\mathrm{E}(\epsilon_i) = 0$, where parameters β_{jk}, γ and α_{jk} represent vector of coefficients for strategies S_{jk}, covariates V and their interaction $S * V$. S_{jk} is defined as $S_{jk} = 1$ if patient i follows strategy $A_j B_k$, 0, otherwise.

Regression with strategies as covariates

Table : Parameter Estimates for Model of CALGB 8923 data.

Parameter	Estimate	SE	Z	Pr > $\|Z\|$
Intercept	1996.75	487.42	4.097	<0.00
$S_{A_1B_1}$	25.90	146.64	0.18	0.86
$S_{A_1B_2}$	-156.38	149.07	-1.05	0.29
$S_{A_2B_1}$	71.50	154.77	0.46	0.64
Sex	95.74	154.75	0.62	0.54
Age	-20.98	6.87	-3.05	0.002
$S_{A_1B_1}$*Sex	-309.39	230.22	-1.34	0.18
$S_{A_1B_2}$*Sex	281.88	221.34	1.27	0.20
$S_{A_2B_1}$*Sex	-23.34	224.15	-0.10	0.92

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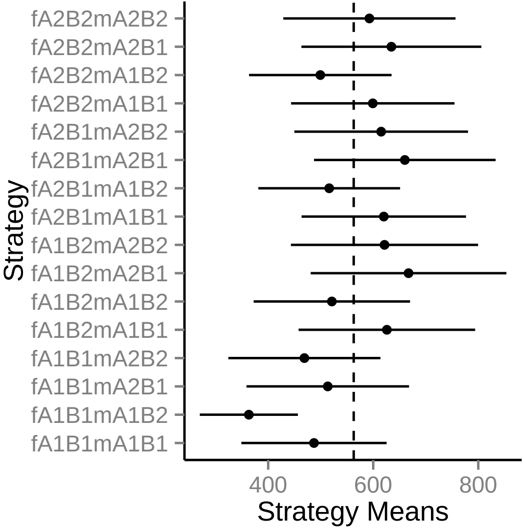
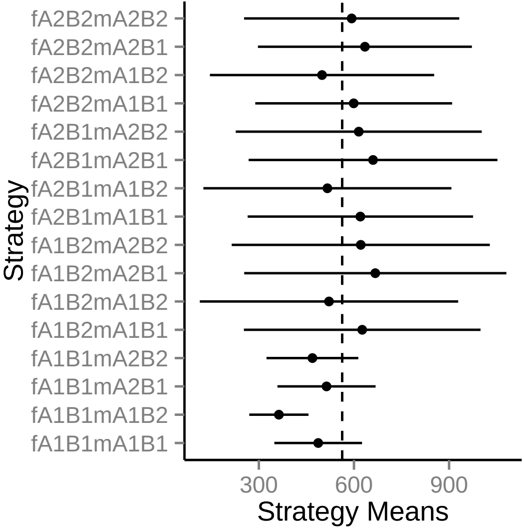
New Dynamic Treatment Regime

- $fA_jB_kmA_{j*}B_{k*}$ as "If female, treat with A_j, if she responds to A_j, start maintenance B_k, otherwise continue A_j; If male, treat with A_{j*}, if she responds to A_{j*}, start maintenance B_{k*}, otherwise continue A_{j*}.""

Forest Plot for SMART1.



Forest Plot for SMART5.



Outline

Summary

- We have proposed an unbiased normalized artificial randomized estimator.
- SMART is easier to implement.
- The procedure can be used in standard regression or ANOVA methods to perform covariate-adjusted comparisons without any modification.
- It could easily be adapted to binary, survival outcomes.

Comments? Suggestions?

THANK YOU!

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Outline

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