Statistical Analysis of SMART Studies via Artificial Randomization

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Outline

Dynamic Treatment Regimes

Example (Alcohol Addiction)

Start with a low intensity behavioral modification (low-BMOD) therapy, if he/she does not respond, augment with medication; otherwise continue the same initial treatment

Example (HIV)

Start on a ARV regimen, e.g., containing Efavirenz, switch to second line regimen less than 8 weeks after confirmed virologic failure

Example (Leukemia)

Start with Chemotherapy, if he/she responds to Chemotherapy, start maintenance therapy, otherwise stop treatment

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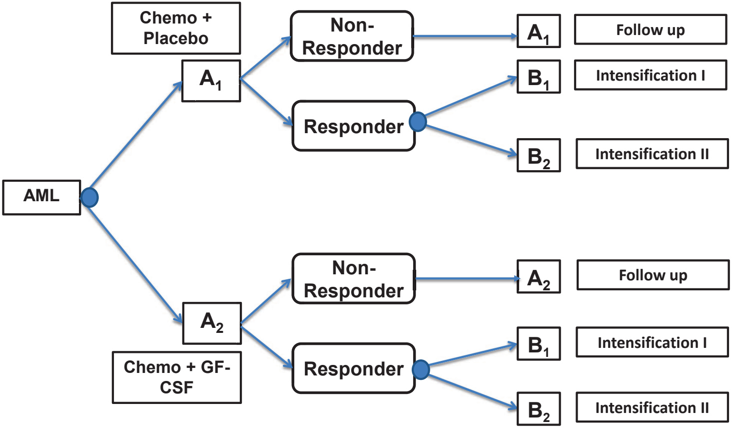
Sequential Multiple Assignment Randomized Trials (SMART)

- 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



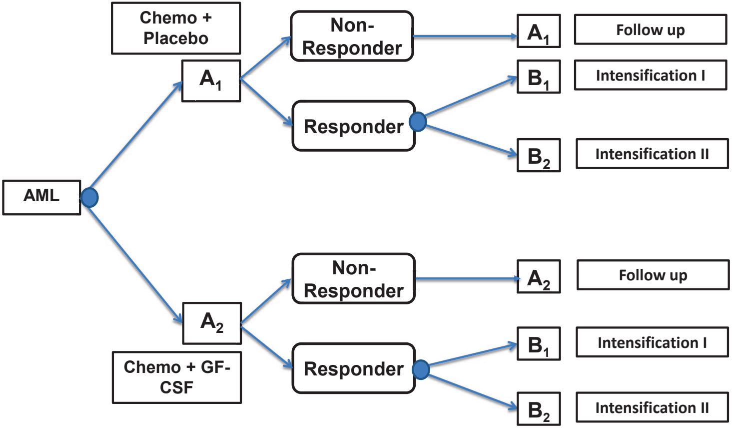
SMART Design: Example

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

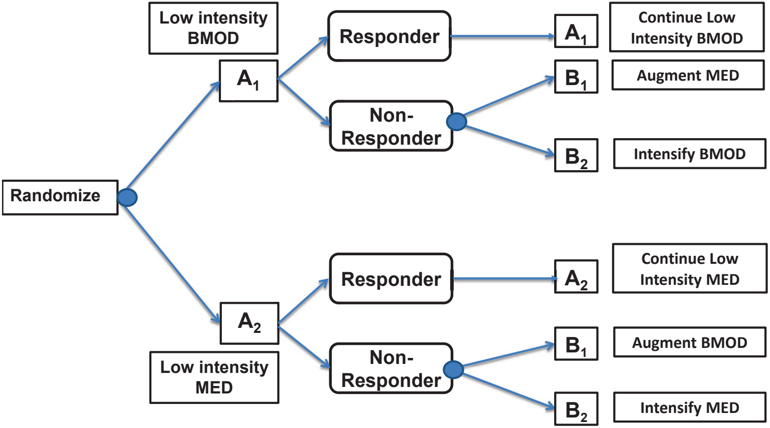
SMART Design: Example

Stone et al. (2001) for CALGB trial



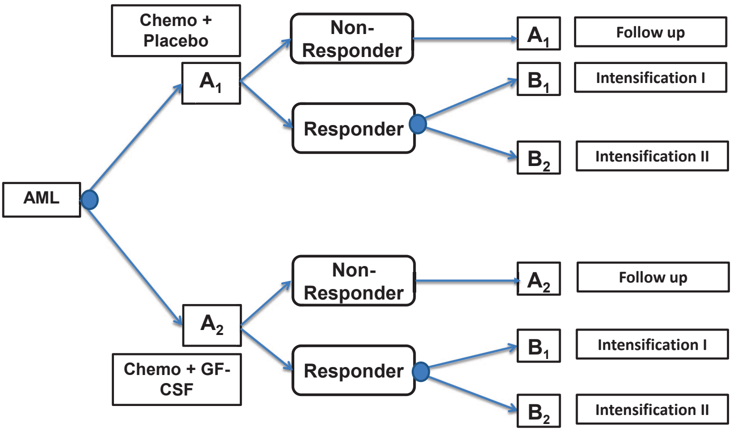
SMART Design: Example

Pelham et al. (2008) for ADHD trial



SMART Design: Example

Stone et al. (2001) for CALGB trial



CALGB Data Analysis

- **Primary scientific aim**: Assess the effects of adding GM-CSF on the probability of success, defined as the patient being alive and in CR.
- Analysis done using logistic regression, Kaplan-Meier plots, and Cox model regression.
- Based on the simplifying assumption that the only relevant treatments were the initial therapies. Second stage therapy was completely ignored.

Dynamic Treatment Regimes

- For CALGB Trial, define:
  A_jB_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_jB_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

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

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

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

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Table: Typical Data Structure for Pelham Trial

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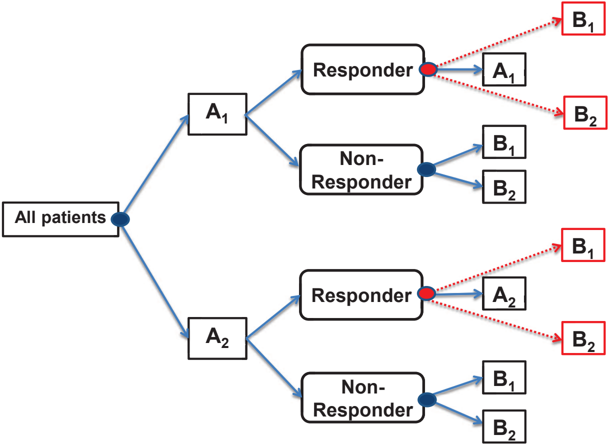
2	1	0	1	-1	-1	1	1	0	0
3	0	1	1	-1	-1	0	0	1	1

Main Idea: Artificial Randomization



Main Idea: Artificial Randomization

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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 Regime Means

- $$Z_{1i}^* = \begin{cases} Z_{1i}, & R_i = 0 \\ \text{Bernoulli}(Q_1), & R_i = 1, \end{cases} \quad (1)$$
  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 $Z_{2i}^* = 1 - Z_{1i}^*$.
- $$\hat{\mu}_{jk}^{AR} = \frac{\sum_{i=1}^{n} X_{ji} Z_{ki}^* Y_i}{\sum_{i=1}^{n} X_{ji} Z_{ki}^*}$$
  is a consistent estimator of $\mu_{jk} = E(Y|A_j B_k)$, mean outcome under $A_j B_k$.

Estimating Regime Means: SMART Estimator

- Simple Multiple Artificial Randomized Tool (SMART) estimator:

  Repeat AR M times and average the estimates to get

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

- Variance:

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

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

Regime Means

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

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

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

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

Regime Means

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

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

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

Regime Means

- Nahum-Shani et al. (2012) cleverly replicated data to estimate the IPTW estimators and the corresponding variance-covariance
- Basically, records that are common between k regimes would be replicated k times and then
- A GEE-type approach can account for the weighting and correlation

Data Replication: Example

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 replication

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

hline

Outline

Simulation Results: n=150

Table: Monte Carlo mean estimates (EST), relative bias (RB, %), Monte Carlo Standard Errors (MCSE), average of the robust standard errors (RSE) and 95% coverage probabilities (CP) when n=150. True regime means: $\mu_{11} = 15$, $\mu_{12} = 20$.

Estimator	Regime	EST	RB	MCSE	RSE	CP
SMART1	A_1B_1	15.01	0.067	1.30	1.25	0.93
	A_1B_2	20.01	0.05	0.97	0.95	0.94
SMART5	A_1B_1	15.01	0.067	1.23	1.36	0.96
	A_1B_2	20.01	0.05	0.94	0.97	0.96
Replication	A_1B_1	15.03	0.20	1.25	1.15	0.92
	A_1B_2	20.02	0.01	0.94	0.91	0.94
NIPW	A_1B_1	15.01	0.067	1.19	1.19	0.92
	A_1B_2	19.99	-0.05	0.93	0.93	0.93

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SMART5	A_1B_1	15.01	0.067	1.23	1.36	0.96
	A_1B_2	20.01	0.05	0.94	0.97	0.96
Replication	A_1B_1	15.03	0.20	1.25	1.15	0.92
	A_1B_2	20.02	0.01	0.94	0.91	0.94
NIPW	A_1B_1	15.01	0.067	1.19	1.19	0.92
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	A_1B_2	20.01	0.05	0.94	0.97	0.96
Replication	A_1B_1	15.03	0.20	1.25	1.15	0.92
	A_1B_2	20.02	0.01	0.94	0.91	0.94
NIPW	A_1B_1	15.01	0.067	1.19	1.19	0.92
	A_1B_2	19.99	-0.05	0.93	0.93	0.93

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	A_1B_2	20.01	0.05	0.97	0.95	0.94
SMART5	A_1B_1	15.01	0.067	1.23	1.36	0.96
	A_1B_2	20.01	0.05	0.94	0.97	0.96
Replication	A_1B_1	15.03	0.20	1.25	1.15	0.92
	A_1B_2	20.02	0.01	0.94	0.91	0.94
NIPW	A_1B_1	15.01	0.067	1.19	1.19	0.92
	A_1B_2	19.99	-0.05	0.93	0.93	0.93

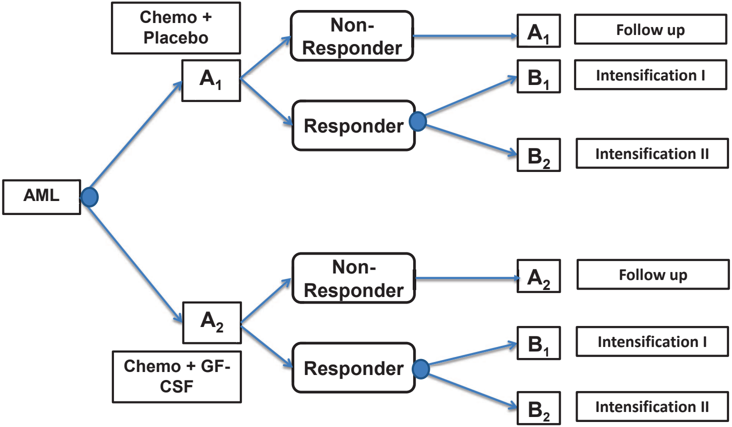
Simulation Results: n=150

Table: Monte Carlo mean estimates (EST), relative bias (RB, %), Monte Carlo Standard Errors (MCSE), average of the robust standard errors (RSE) and 95% coverage probabilities (CP) when n=300. True regime means: $\mu_{11} = 15$, $\mu_{12} = 20$.

Estimator	Regime	EST	RB	MCSE	RSE	CP
SMART1	A_1B_1	14.99	-0.067	0.91	0.88	0.94
	A_1B_2	20.01	0.05	0.67	0.67	0.95
SMART5	A_1B_1	15.02	0.13	0.92	0.88	0.93
	A_1B_1	20.02	0.10	0.68	0.67	0.94
Replication	A_1B_1	15.02	0.13	0.90	0.82	0.92
	A_1B_2	20.00	0.00	0.66	0.65	0.95
NIPW	A_1B_1	15.03	0.20	0.84	0.83	0.93
	A_1B_2	20.01	0.05	0.67	0.66	0.94

Outline

The Design


Chemo + Placebo
A1
Non-Responder
Responder
A1
Follow up
B1
Intensification I
B2
Intensification II
AML
Non-Responder
A2
Follow up
A2
Chemo + GF-CSF
Responder
B1
Intensification I
B2
Intensification II

CALGB Data

Table: Estimated regime means (days) and robust standard errors from the analysis of CALGB 8923 data.

regime	SMART5	Replication
Ch/Cy	468.56	468.49
	(66.14)	(59.47)
$Ch/Cy + Mi$	536.46	539.28
	(78.40)	(73.37)
$Ch + G/Cy$	623.52	620.41
	(81.91)	(73.42)
$Ch + G/Cy + Mi$	627.48	629.36
	(90.75)	(81.23)

Regression with regimes as covariates

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

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

Regression with regimes as covariates

Table: Parameter Estimates for Model of CALGB 8923 data.

Parameter	Estimate	SE	Z	Pr > $\|Z\|$
Intercept	1996.75	487.42	4.097	<0.01
Ch/Cy	25.90	146.64	0.18	0.86
$Ch/Cy + Mi$	-156.38	149.07	-1.05	0.29
$Ch + G/Cy$	71.50	154.77	0.46	0.64
Male	95.74	154.75	0.62	0.54
Age	-20.98	6.87	-3.05	0.002
Ch/Cy*Male	-309.39	230.22	-1.34	0.18
$Ch/Cy + Mi$*Male	281.88	221.34	1.27	0.20
$Ch + G/Cy$*Male	-23.34	224.15	-0.10	0.92

New Dynamic Treatment Regime

$$fA_jB_kmA_{j*}B_{k*}$$

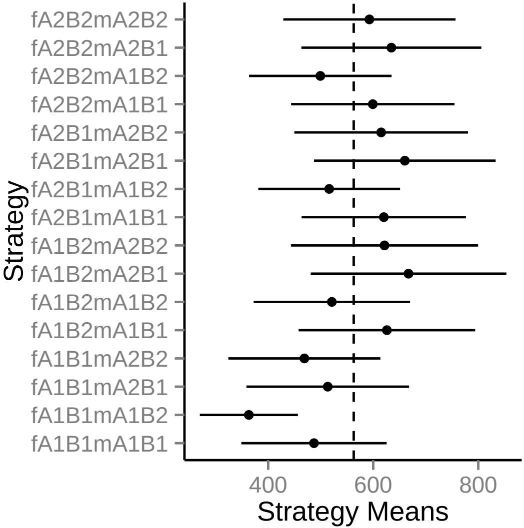
If female, treat with A_j, if she responds to A_j, start maintenance B_k; If male, treat with A_{j*}, if she responds to A_{j*}, start maintenance B_{k*}

For example,

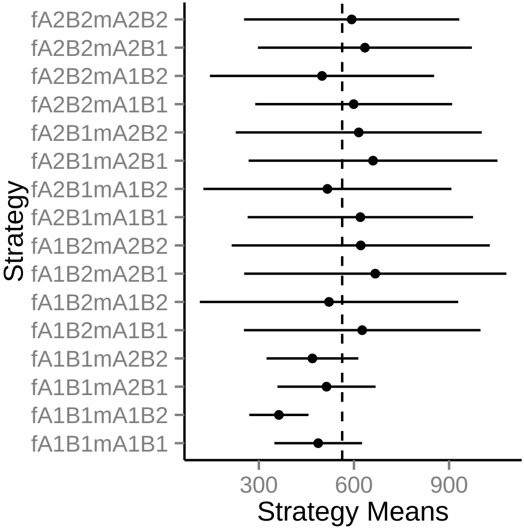
$$fChCymCh(Cy + Mi)$$

If female, treat with Chemo, if she responds to Chemo, start maintenance I; If male, treat with Chemo, if he responds to Chemo, start maintenance II

Forest Plot for SMART1.



Forest Plot for SMART5.



Outline

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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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