Dynamic Treatment Regime, Sequentially Randomized Designs, and Semi-parametric Theory

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Dynamic Treatment Regime

- An algorithm that chooses treatment for patients based on the patient characteristics, previous treatment history and response to previous treatments.
- Examples:

Depression	Sertraline for 8 weeks, if the patient does not respond, treat the patient with Sertraline as well as with cognitive behavioral therapy; if the patient responds, continue Sertraline
HIV	Start on a ARV regimen, e.g., containing Efavirenz, switch to second line regimen less than 8 weeks after confirmed virologic failure
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Dynamic Treatment Regime

Usual goal is

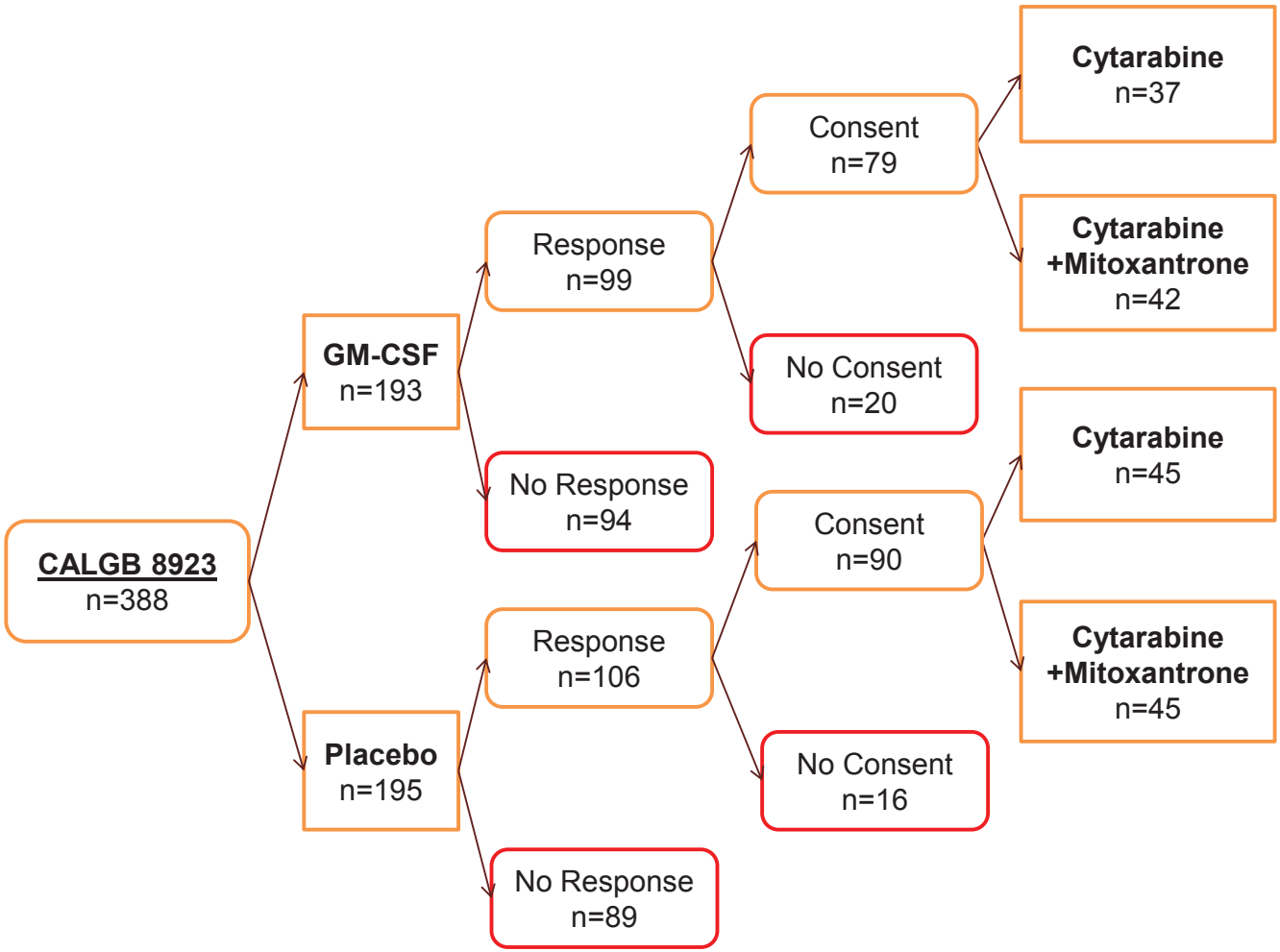
- To develop optimal treatment regime to achive maximum patient benefit.
- To compare a fixed number of treatment regimes arising from a sequence of treatments available at different stages of therapy.

Sequentially Randomized Trials

- Patients are randomized to treatment options sequentially as they become eligible to receive treatments.
  - Useful for comparing treatment regimes with discrete treatment options and intermediate responses
  - Has been emloyed in various reseach settings such as
    - cancer
    - depression
    - drug and alcohol addiction
    - education

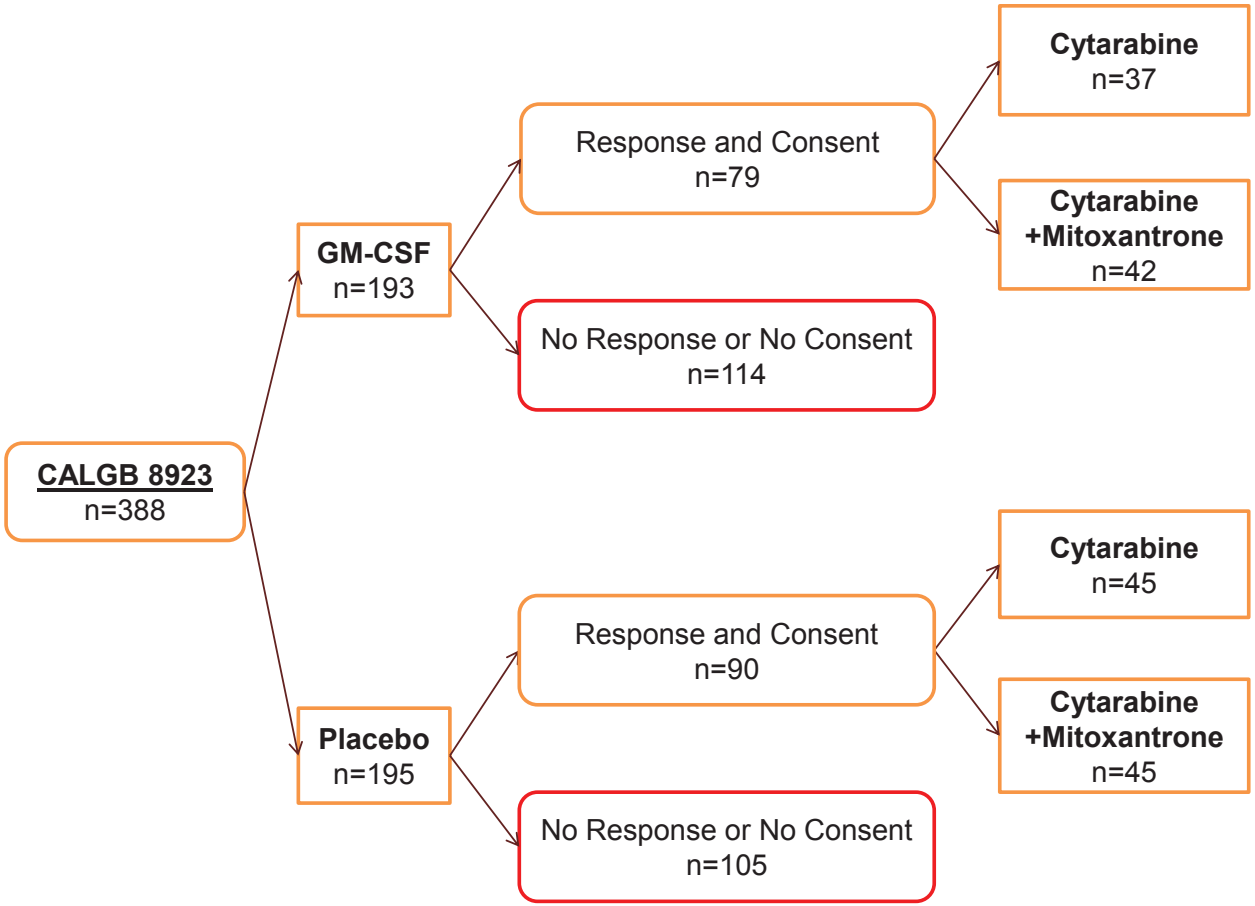
CALGB 8923 Trial

Figure : Patient flow and study design for CALGB 8923 trial



Motivation: CALGB 8923 Trial

Previous analyses[1] treated non-responders and non-consenters alike.



[1] Lunceford et al. (2002), Wahed & Tsiatis (2006), and Lokhnygina & Helterbrand (2007)

Objective

However, the goal of such design is to determine which of the treatment regimes result in longer survival.

Examples of regimes:

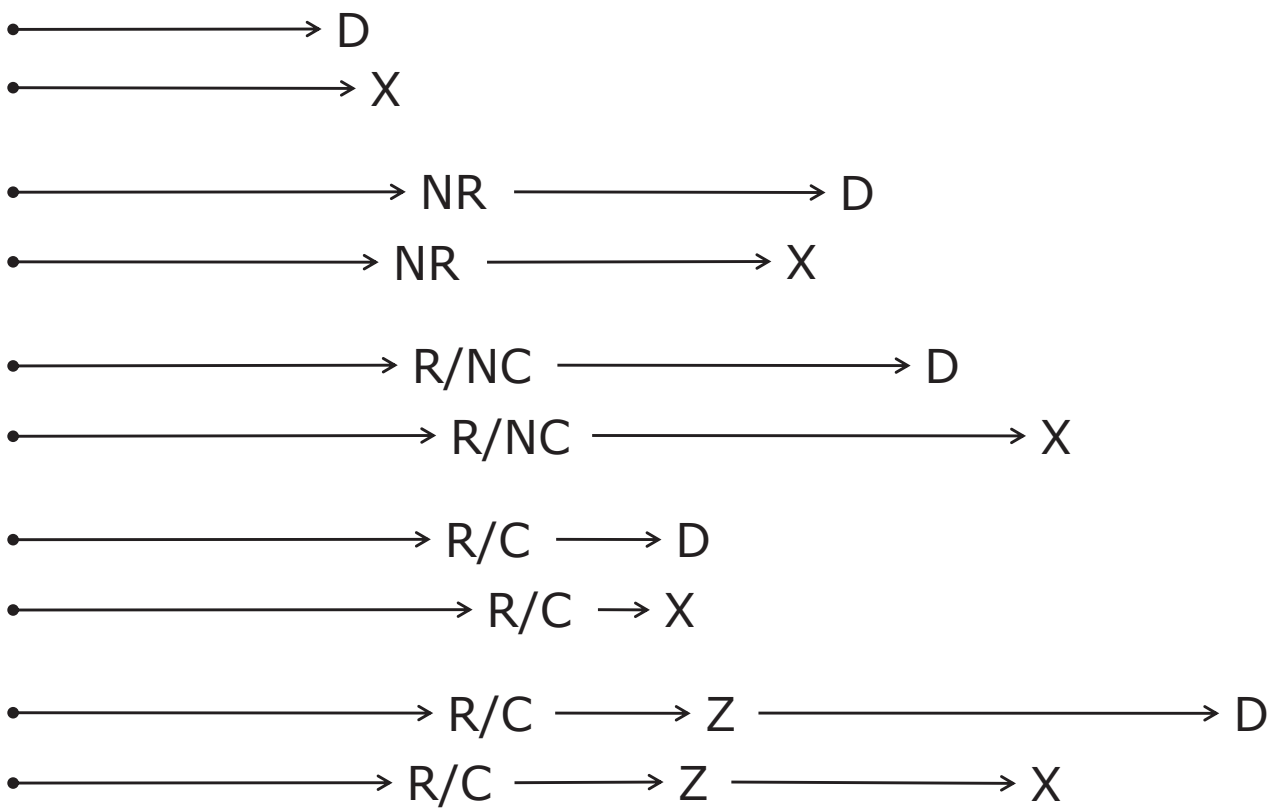
- "Treat with GM-CSF followed by Cytarabine if respond"
- "Treat with GM-CSF followed by Cytarabine+Mitoxantrone if respond"
- "Treat with placebo followed by Cytarabine if respond"
- "Treat with placebo followed by Cytarabine+Mitoxantrone if respond"

In general, let us define regime $A_j B_k$ as "treat with A_j followed by B_k if respond".

Objective

But *combining response and consent together* does not allow us to answer that question.

Evolution of a Paitent's Status in CALGB Trial

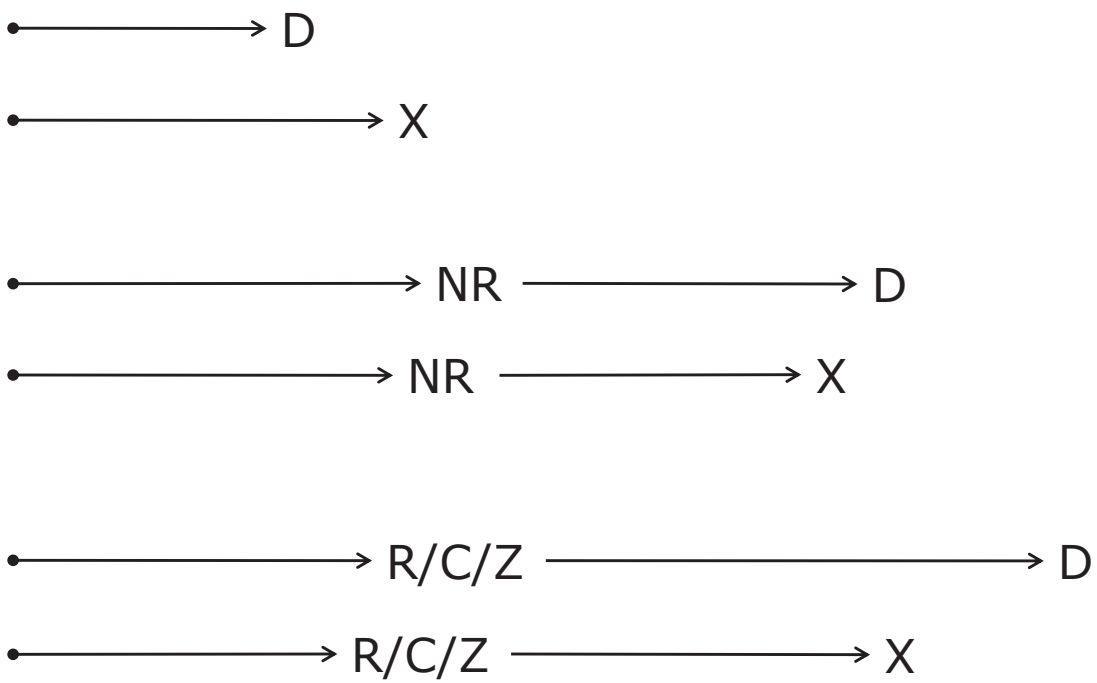


R: responded
C: consented
Z: 2nd randomization

D: dead
X: censored

NC: not consented
NR: not responded

Evolution of a Paitent's Status - dealt in previous analyses



R: responded
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X: censored

NC: not consented
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Goal of this work

- Consistent and efficient estimation of mean survival under a given treatment regime taking into account the actual data structure. Specifically,
  - We will treat non-responders and non-consenters separately.
  - We will take into account the delay from becoming eligible for second stage treatment to the assignment of treatment.

For the rest of the work, assume:

- Two stage 1 treatments $A_j, j = 1, 2$
- Two stage 2 treatments $B_k, k = 1, 2$ for responders

Consider data from patients who received treatment A_1.

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Counterfactual Variables

Each patient i has an associated set of random variables

$$\left\{R_i, (1-R_i)T_i^{NR}, R_i T_i^R, R_i C_i, R_i(1-C_i)T_i^{NC}, R_i C_i T_i^Z, R_i C_i T_{1i}^*, R_i C_i T_{2i}^*\right\}$$

R_i: response status
T_i^{NR}: survival time for a patient who did not respond
T_i^R: time from initial treatment, A_1, to the time a patient responded to A_1
C_i: consent status
T_i^{NC}: survival time for a patient who responded but did not consent to B_k
T_i^Z: time from initial treatment, A_1, to the initiation of second-stage treatment
T_{1i}^*: survival time if patient responded to A_1 and received treatment B_1
T_{2i}^*: survival time if patient responded to A_1 and received treatment B_2

Survival Time Under regime $A_1 B_k$

- In terms of counterfactual variables, the survival time under regime $A_1 B_k$ can be expressed as

$$T_{ki} = (1 - R_i) T_i^{NR} + R_i T_{ki}^*, k = 1, 2$$

- The goal is to draw inference on the distribution of $T_k, k = 1, 2$. For example, we may be interested in

$$\mu_k = E[T_{ki}]$$

Observed Data

The observed data in the presence of right censoring can be charaterized as the collection of i.i.d random vectors

$$\left[R_i, R_i C_i, R_i T_i^R, R_i C_i T_i^Z, R_i C_i Z_{ki}, U_i, \Delta_i, \{G_i^H(u), u \leqslant U_i\}\right],$$
$$i = 1, 2, \ldots, n; k = 1, 2.$$

R_i, C_i, T_i^R, and T_i^Z are defined as before.

Z_{1i}: the B_1 treatment assignment indicator
Z_{2i}: the B_2 treatment assignment indicator
T_i: observed survival time
X_i: censoring time
U_i: $\min(T_i, X_i)$
Δ_i: $I(T_i < X_i)$
$G_i^H(u)$: data history collected on patient i prior to time u

Assumptions

In order to draw conclusion about counterfacters, we need to relate them to the observed data, which is done through some assumptions.

- Consistency, or Stable Unit Treatment Value Assumption (SUTVA)

$$T_i = (1 - R_i)\, T_i^{NR} + R_i(1 - C_i)\, T_i^{NC} + R_i C_i (Z_{1i}\, T_{1i}^{*} + Z_{2i}\, T_{2i}^{*}),$$
$$\text{where } Z_{2i} = 1 - Z_{1i}.$$

- No unmeasured confounding given data history, or Sequential Randomization Assumption (SRA)

$$\pi_k = P\left\{ Z_{ki} = 1 \,\middle|\, R_i = 1, C_i = 1, G_i^H(T_i^Z) \right\} = P\left\{ Z_{ki} = 1 \,|\, R_i = 1, C_i = 1 \right\}$$

IPW Estimator

- Given a treatment regime, $A_1 B_k$, the inverse-probability-weighted (IPW) estimator for mean survival time is

$$\hat{\mu}_k^{IPW} = n^{-1} \sum_{i=1}^{n} \frac{\Delta_i}{K(U_i)} \left\{ 1 - R_i + \frac{R_i C_i Z_{ki}}{\pi_{C_i} \pi_k} \right\} U_i$$

- Note that there are two nuisance parameters, $K(.)$ and π_{C_i}.
- $K(.)$ is estimated by the Kaplan-Meier method.
- π_{C_i}, the consent rate, we considered two estimators:
  - π_{C_i} is calculated as the proportion of responders who consented, e.g. $\hat{\pi}_{C_i} = \sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(U_i)} R_i C_i \Big/ \sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(U_i)} R_i$
  - π_{C_i} is modeled by logistic regression on baseline and the 1^{st} stage covariate, e.g. $logit(\hat{\pi}_{C_i}) = \hat{\alpha} + \hat{\beta} \times T_i^R + \hat{\gamma} \times W_i$, where W_i is the collection of baseline covariates.

Variance of IPW Estimator

- When π_{C_i} is estimated empirically:

$$\hat{var}(\hat{\mu}_k^{IPW}) = \frac{1}{n}\left\{\frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}\left[\left(1 - R_i + \frac{R_i C_i Z_{ki}}{\hat{\pi}_{C_i}\pi_k}\right)U_i - \hat{\mu}_k^{IPW}\right.\right.$$
$$\left. - \left(\frac{R_i C_i}{\hat{\pi}_R} - \pi_{C_i}\right)\hat{E}\left(\frac{R_i C_i Z_{ki}}{\pi_{C_i}^2 \pi_k} T_i\right) + (R_i - \hat{\pi}_R)\hat{E}\left(\frac{R_i C_i}{\pi_R^2}\right)\hat{E}\left(\frac{R_i C_i Z_{ki}}{\pi_{C_i}^2 \pi_k} T_i\right)\right]^2$$
$$\left. + \int_0^L \frac{dN^c(u)}{\hat{K}(u)Y(u)}\hat{E}\left[L_i'(u, \hat{\pi}_{C_i})\right]^2\right\} \quad (1)$$

Variance of IPW Estimator

where

$$\hat{E}\left[L_i'(u,\hat{\pi}_{C_i})\right]^2 = \frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}\left[\left\{1-R_i+\frac{R_iC_iZ_{ki}}{\hat{\pi}_{C_i}\pi_k}\right\}U_i-\hat{G}(u,\hat{\pi}_{C_i})\right.$$
$$+\left\{\frac{R_iC_i}{\hat{\pi}_R}-\hat{G}'(u,\hat{\pi}_R)+\left[R_i-\hat{G}''(u)\right]\hat{E}\left(\frac{R_iC_i}{\pi_R^2}\right)\right\}$$
$$\left.\times I(T_i^R\geq u)\hat{E}\left(\frac{R_iC_iZ_{ki}}{\pi_{C_i}^2\pi_k}T_i\right)\right]^2 I(T_i\geqslant u)$$

$$\hat{G}(u,\hat{\pi}_{C_i}) = \frac{1}{n\hat{S}(u^{-1})}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}\left\{1-R_i+\frac{R_iC_iZ_{ki}}{\hat{\pi}_{C_i}\pi_k}\right\}U_i\times I(U_i\geqslant u)$$

$$\hat{G}'(u,\hat{\pi}_R) = \frac{1}{n\hat{S}(u^{-1})}\sum_{i=1}^{n}\frac{\Delta_i^R}{\hat{K}(T_i^R)}\frac{R_i}{\hat{\pi}_R}C_i\times I(T_i^R\geq u)$$

$$\hat{G}''(u) = \frac{1}{n\hat{S}(u^{-})}\sum_{i=1}^{n}\frac{\Delta_i^R}{\hat{K}(T_i^R)}R_i\times I(T_i^R\geq u)$$

Variance of IPW Estimator

- When π_{C_i} is modeled by logistic regression:

$$\hat{var}(\hat{\mu}_k^{IPW}) = \frac{1}{n}\left[\frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}\left(\left\{1 - R_i + \frac{R_i C_i Z_{ki}}{\hat{\pi}_{C_i}\pi_k}\right\}U_i - \hat{\mu}_k^{IPW}\right.\right.$$
$$- \left\{\frac{\Delta_i^R R_i}{K(T_i^R)}\frac{C_i - \hat{\pi}_{C_i}}{\hat{\pi}_{C_i}(1-\hat{\pi}_{C_i})}\right\}\hat{E}\left(\frac{(\pi_{C_i} - C_i)^2}{\left[\pi_{C_i}(1-\pi_{C_i})\right]^2}\right)^{-1}\hat{E}\left(\frac{R_i C_i Z_{ki}}{\pi_{C_i}^2\pi_k}T_i\right)\Bigg)^2$$
$$\left. + \int_0^L \frac{dN^c(u)}{\hat{K}(u)Y(u)}\hat{E}\left[L_i''(u,\hat{\pi}_{C_i})\right]^2\right] \qquad (2)$$

Variance of IPW Estimator

where

$$\hat{E}\left[L_i''(u,\hat{\pi}_{C_i})\right]^2 = n^{-1}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}\left[\left\{1-R_i+\frac{R_iC_iZ_{ki}}{\hat{\pi}_{C_i}\pi_k}\right\}U_i-\hat{G}(u,\hat{\pi}_{C_i})\right.$$
$$\left.+\hat{G}''(u)\hat{E}\left(\frac{R_iC_i}{\pi_R^2}\right)\hat{E}\left(\frac{R_iC_iZ_{ki}}{\pi_{C_i}^2\pi_k}T_i\right)I(T_i^R\geq u)\right]^2 I(T_i\geqslant u)$$

Semiparametric Efficient Estimator

- The IPW estimator is consistent, but not efficient[1].
- Fails to take into account information from the censored patients as well as patients who fail to receive the treatment B_k due to randomization to other B-treatment or refusal to take B-treatment.

[1] Robins, Rotnitzky, & Zhao (1994)

Semiparametric Efficient Estimator

Semi-parametric efficient estimator[1]:

$$\hat{\mu}_k^{EFF} = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{\Delta_i}{\hat{K}(U_i)}\left(1 - R_i + \frac{R_i C_i Z_{ki}}{\hat{\pi}_{C_i}\pi_k}\right)U_i + \int_0^L \frac{dM_i^c(u)}{K(u)}\hat{\tau}\left(G_i^H(u)\right)\right.$$
$$\left. - \frac{\Delta_i^R R_i(C_i - \hat{\pi}_{C_i})\hat{\nu}_{R_i}}{\hat{K}(U_i^R)\hat{\pi}_{C_i}} - \frac{\Delta_i^C R_i C_i(Z_{ki} - \pi_k)\hat{\nu}_{C_i}}{\hat{K}(U_i^C)\hat{\pi}_{C_i}\pi_k}\right] \quad (3)$$

[1] Robins, Rotnitzky, & Zhao (1994)

Semiparametric Efficient Estimator

$\tau(.)$, ν_{R_i}, and ν_{C_i} are estimated from the data based on suitable regression models.

$$\tau\left(G_i^H(u)\right) = E\left\{ \frac{\Delta_i}{K(U_i)} U_i \middle| G_i^H(u) \right\}$$

$$\nu_{R_i} = E\left\{ T_i | R_i = 1, Z_{ki} = 1, T_i^R, G_i^H(T_i^R) \right\} = \alpha + \beta T_i^R$$

$$\nu_{C_i} = E\left\{ T_i | R_i = 1, C_i = 1, Z_{ki} = 1, T_i^Z, G_i^H(T_i^Z) \right\} = \alpha + \beta_1 T_i^R + \beta_2 (T_i^Z - T_i^R)$$

where $(T_i^Z - T_i^R)$ is the delay of the second randomization

Variance of Semiparametric Efficient Estimator

$$\hat{var}(\hat{\mu}_k^{EFF}) = \frac{1}{n^2}\sum_{i=1}^{n}\left[\frac{\Delta_i}{\hat{K}(U_i)}\left\{1 - R_i + \frac{R_i C_i Z_{ki}}{\hat{\pi}_{C_i}\pi_k}\right\}U_i + \int_0^L \frac{dM_i^c(u)}{K(u)}\hat{\tau}\left(G_i^H(u)\right)\right.$$
$$\left. - \frac{\Delta_i^R R_i(C_i - \hat{\pi}_{C_i})\hat{\nu}_{R_i}}{\hat{K}(U_i^R)\hat{\pi}_{C_i}} - \frac{\Delta_i^C R_i C_i(Z_{ki} - \pi_k)\hat{\nu}_{C_i}}{\hat{K}(U_i^C)\hat{\pi}_{C_i}\pi_k} - \hat{\mu}_k^{EFF}\right]^2 \quad (4)$$

Simulation Scenarios

- Population:
  - $R \sim \text{Bernoulli}(\pi_r)$;
  - $T^R \sim \text{EXP}(\alpha_r)$ truncated at b_r;
  - $T^{NR} \sim \text{EXP}(\alpha_0)$ truncated at b_0;
  - $T^Z \sim T^R + U_r;\ U_r \sim \text{uniform}(0, \theta_r)$;
  - $T_k^* \sim T^Z + (\beta_1 + \beta_2 \times T^Z) U_k;\ U_k \sim \text{uniform}(0, \theta_k),\ k = 1, 2$;
  - $T_k = (1 - R) T^{NR} + R T_k^*,\ k = 1, 2$;
- Data generation:
  - $C \sim \text{Bernoulli}(\pi_C);\ \text{logit}(\pi_C) = \alpha + \beta \times T^R$;
  - $T^{NC} \sim T^R + U^{NC};\ U^{NC} \sim \text{uniform}(0, \theta^{NC})$;
  - $Z_1 \sim \text{Bernoulli}(\pi_1), Z_2 = 1 - Z_1$;
  - $T = \min((1-R)T^{NR} + R(1-C)T^{NC} + RC\{Z_1 T_1^* + Z_2 T_2^*\}, L)$;
  - $X \sim \text{uniform}(0, \xi)$;
  - $U = \min(T, X)$;

Simulation Results

Table : Results of Monte-Carlo simulations for treatment regimes A_1B_1 and A_1B_2 under 50% response rate and 51%, and 25% censoring rate

Simulation=2000, n=500, 50% response								
51% censoring	$A_1B_1(\mu_1 = 386)$				$A_1B_2(\mu_2 = 359)$			
Estimator	$\hat{\mu}_1$	$SE_{MC}(\hat{\mu}_1)$	$SE(\hat{\mu}_1)$	CP%	$\hat{\mu}_2$	$SE_{MC}(\hat{\mu}_2)$	$SE(\hat{\mu}_2)$	CP%
IPW (emp[1])	386.3	29.3	30.1	95.4	360.1	27.4	28.3	95.7
IPW (mod[2])	385.9	29.6	30.2	95	360.7	28.1	28.6	95.4
Efficient (emp[1])	389.2	18.5	19.6	96.4	362.0	18.0	19.2	96.7
Efficient (mod[2])	386.4	19.4	20.8	97	359.9	19.2	20.5	96.9

[1] empirical estimator for π_C

[2] logistic regression estimator for π_C with covariates of T_i^R

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Efficient (mod[2])	386.4	19.4	20.8	97	359.9	19.2	20.5	96.9
25% censoring	$A_1B_1(\mu_1 = 386)$				$A_2B_2(\mu_2 = 359)$			
Estimator	$\hat{\mu}_1$	$SE_{MC}(\hat{\mu}_1)$	$SE(\hat{\mu}_1)$	CP%	$\hat{\mu}_2$	$SE_{MC}(\hat{\mu}_2)$	$SE(\hat{\mu}_2)$	CP%
IPW (emp[1])	386	20.8	21.3	95.5	358.2	18.9	19.8	96.0
IPW (mod[2])	386.7	21.0	21.1	95.3	359.7	19.3	19.6	95.4
Efficient (emp[1])	388.2	12.4	12.8	95.0	361.6	12.1	12.3	94.9
Efficient (mod[2])	386.7	12.7	13.1	95.3	360.2	12.5	12.7	95.1

[1] empirical estimator for π_C

[2] logistic regression estimator for π_C with covariates of T_i^R

Simulation Results

- Both IPW and efficient estimators consistently estimated the mean survival time, but the efficient estimators improved the efficiency significantly, in some cases by as large as 69%.
- The Monte-Carlo and estimated variances increase with the increase in censoring rate.
- Decreasing the sample size from 500 to 250 and increasing the response rate from 50% to 70% (results not shown here) showed similar results.
- When consent rate was estimated empirically, the precision of the estimators was better than when consent rate was estimated using logistic regression.

CALBG 8923 Trial

- Double-blind, placebo-controlled two-stage trial;
- The effects of infusions of granulocyte-macrophage colony-stimulating factor (GM-CSF) after initial chemotherapy in 388 elderly patients with acute myelogenous leukemia (AML);
- Patients were randomized initially to GM-CSF or placebo following standard chemotherapy. Later, patients meeting the criteria for complete remission were offered a second randomization to one of two intensification treatments (Cytarabine or Cytarabine+Mitoxantrone);
- The treatment regimes: *"treat with GM-CSF or placebo followed by Cytarabine or Cytarabine+Mitoxantrone if respond"*

Results of Analysis of CALGB 8923 Trial

Table : Estimated mean survival time (days) and its variance for the CALGB 8923 study

	A_1B_1[3]		A_1B_2[4]		A_2B_1[5]		A_2B_2[6]	
Estimator	$\hat{\mu}$	$SE(\hat{\mu})$	$\hat{\mu}$	$SE(\hat{\mu})$	$\hat{\mu}$	$SE(\hat{\mu})$	$\hat{\mu}$	$SE(\hat{\mu})$
IPW (emp[1])	404.1	59.6	406.3	69.3	363.2	45.7	760.0	192.4
IPW (mod[2])	414.9	66.4	395.6	68.9	358.9	46.8	767.8	195.4
Efficient (emp[1])	452.5	49.1	421.8	62.1	414.0	41.5	717.0	227.5
Efficient (mod[2])	461.1	48.7	417.1	60.1	415.6	41.4	722.2	222.1

[1] empirical estimator for π_C

[2] logistic regression estimator for π_C with covariates of T_i^R, gender, race, age, and white blood cell counts

[3] treatment regime "treat with GM-CSF followed by Cytarabine if respond"

[4] treatment regime "treat with GM-CSF followed by Cytarabine+Mitoxantrone if respond"

[5] treatment regime "treat with placebo followed by Cytarabine if respond"

[6] treatment regime "treat with placebo followed by Cytarabine+Mitoxantrone if respond"

Results of Analysis of CALGB 8923 Trial

- The IPW estimators tend to provide smaller estimates for the mean survival time compared to the efficient estimators.
- Standard errors of efficient estimators are smaller than that of IPW estimators, as expected by theory.
- Based on the estimates, it seems that treatment regime "treat with placebo followed by Cytarabine + Mitoxantrone if respond" provides the largest mean survival time among four regimes. However, considering the large SE for the corresponding estimator, a formal test of hypothesis might not be able to show statistical significance.
- Treatment regime "treat with placebo followed by Cytarabine if respond" provides the shortest mean survival time among four regimes.
- Adding GM-CSF to chemotherapy does not improve regime mean survival time.

Conclusion

- We have presented several approaches to estimate mean survival time and its variance in two-stage randomization designs when some patients did not consent after responding to the initial treatment.
- The efficient (semi-parametric) estimator shows considerable gain in efficiency over IPW estimator. This method allows us to use information from auxiliary covariates.
- We have demonstrated our methods through application of a leukemia clinical trial data set.
- In some cases, it might be of interest to estimate survival probability at certain time point other than mean survival time. In such case, an entirely similar strategy can be followed by replacing T_i by $I(T_i > t)$ for survival probability.

THANK YOU!