

## I. Dynamic Treatment Regimes in Public Health

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- 9:00-9:05 am Introduction to Session
- 9:05-9:35 am Estimation of Survival Distributions for Treatment Regimes in Two Stage Oncology Trials  
*Marie Davidian*, NC State University
- 9:35-9:40 am Discussion
- 9:40-10:25 am Estimating Mean Response as a Function of Treatment Duration in an Observational Study  
*Anastasios A. (Butch) Tsiatis*, NC State University
- 10:25-10:30 am Discussion
- 10:30-10:45 am *Break*
- 10:45-11:45 am SMART Designs for Developing Dynamic Treatment Regimes  
*Susan A. Murphy*, University of Michigan
- 11:45-noon Discussion

## I. Dynamic Treatment Regimes in Public Health

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### Dynamic treatment regime:

- “Individually-tailored” *sequence* of treatment steps
- The *next step* of treatment is determined according to *subject outcomes and information* up to that point
- Consistent with *clinical practice*

### Issues:

- What are the *options* at each step?
- What *information* should be used to select an option at each step?
- What should be the *timing* of the steps?
- What is the “*best*” sequence of treatment steps?
- From what kinds of *studies* can we learn about all of this?

## I. Dynamic Treatment Regimes in Public Health

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### Objectives of this session:

- Introduce the notion of a *dynamic treatment regime* (or *adaptive treatment strategy*) through two case studies (*Marie*, *Butch*)
- Describe methods for making inference about particular dynamic treatment regimes from *randomized studies* and from *observational data* (*Marie*, *Butch*)
- Describe a general framework for thinking about and *designing* dynamic treatment regimes and in particular for identifying the “*best*” dynamic treatment regime (*Susan*)

## Estimation of Survival Distributions for Treatment Regimes in Two Stage Oncology Trials

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(Joint work with A.A. Tsiatis, J. Lunceford, A. Wahed)

## Outline

1. Dynamic treatment regimes for cancer
2. Randomized oncology trials to compare dynamic regimes
3. Case study: CALGB 8923
4. Analysis
5. Wrinkles
6. Discussion
7. Demonstration using potential outcomes
8. References

## 1. Dynamic treatment regimes for cancer

**A particular dynamic treatment regime:** For a given patient

- **Step 1:** Treat with one or more courses of first-line *induction* chemotherapy  $A$
- **Intermediate outcome:** Observe whether “*response*” occurs
- **Step 2:** If “*response*” occurs, give *maintenance* therapy  $B$  . . .
- . . . else, if “*response*” does not occur (so  $A$  *did not induce* a response), do something else, e.g., try a *second-line* therapy  $B'$
- “*Response*” typically defined as complete or partial remission, tumor shrinkage, etc.

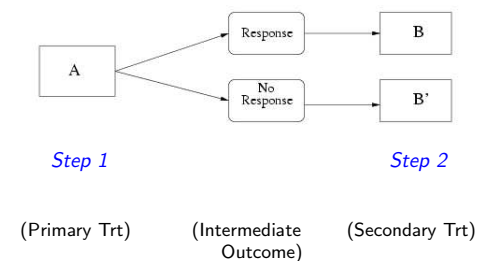
**Primary outcome of interest:** E.g., in cancer, *disease-free survival time*

## 1. Dynamic treatment regimes for cancer

**Goals of cancer therapy:**

- **Induce** remission of disease, usually using powerful chemotherapeutic agents
- **Maintain** remission as long as possible before relapse/recurrence, e.g., by administering additional agents that intensify or augment the effects of the initial induction therapy

**Schematically:** The specific regime “Give first-line induction therapy  $A$  followed by maintenance  $B$  if response else give second-line therapy  $B'$ ”



## 1. Dynamic treatment regimes for cancer

**Options:** There may be *more than one* possible regime

- More than one possible *first-line induction* treatment (*Step 1*), e.g., two options  $A_1$  and  $A_2$
- More than one possible *maintenance* treatment if response occurs (*Step 2*), e.g., two options  $B_1$  and  $B_2$
- More than one possible *second-line induction* treatment if no response occurs (*Step 2*), e.g., two options  $B'_1$  and  $B'_2$

## 2. Randomized trials for dynamic regimes

**Possible ways to compare:**

- An *eight-arm* randomized trial?
- Combine information from a *series* of trials?
- *Something else?*

## 1. Dynamic treatment regimes for cancer

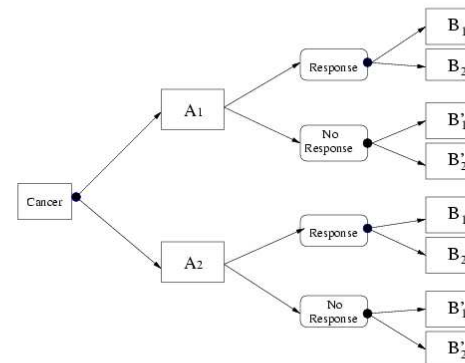
**Eight possible regimes or strategies:**

1.  $A_1$  followed by  $B_1$  if response, else  $B'_1$
2.  $A_1$  followed by  $B_1$  if response, else  $B'_2$
3.  $A_1$  followed by  $B_2$  if response, else  $B'_1$
4.  $A_1$  followed by  $B_2$  if response, else  $B'_2$
5.  $A_2$  followed by  $B_1$  if response, else  $B'_1$
6.  $A_2$  followed by  $B_2$  if response, else  $B'_2$
7.  $A_2$  followed by  $B_1$  if response, else  $B'_1$
8.  $A_2$  followed by  $B_2$  if response, else  $B'_2$

**Question:** How do these eight regimes *compare* on the basis of *disease-free survival time*?

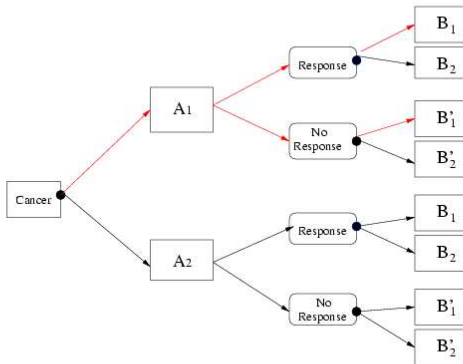
## 2. Randomized trials for dynamic regimes

**“SMART” Trial:** Sequential Multiple Assignment Randomized Trial (Randomization at ●s)



## 2. Randomized trials for dynamic regimes

In red: Regime " $A_1$  followed by  $B_1$  if response else  $B'_1$ "



## 2. Randomized trials for dynamic regimes

**SMART Trials:** Susan will lay out a rationale and framework for this kind of trial for *designing* and *comparing* dynamic treatment regimes!

- As long as the *number of options* at each "decision node" is the same with same probabilities, analysis is *straightforward*
- "Balanced"

**It turns out:** A certain kind of "not quite as SMART" trial is common in oncology ...

- Analysis is a little more fancy ...

## 3. Case study: CALGB 8923

**Cancer and Leukemia Group B (CALGB) Protocol 8923:** A trial with *two* randomizations, conducted in early 1990s

**Background:** *Acute myelogenous leukemia (AML)*

- At the time, *standard induction chemotherapy* (daunorubicin+cytarabine)
- Standard chemotherapy  $\Rightarrow$  *myelosuppression*  $\Rightarrow$  increased risk of death due to *infection* or *bleeding*
- *Add* to standard chemotherapy + *granulocyte-macrophage colony-stimulating factor (GM-CSF)* to reduce risk of these complications (but could possibly *worsen* leukemia...)
- Standard chemotherapy might be followed by "*intensification treatment*" if there is a *response*

## 3. Case study: CALGB 8923

**As before:**

- *Step 1* options:  $A_1$  = Standard chemotherapy,  $A_2$  = Standard chemotherapy + GM-CSF
- *If response*, *Step 2* options:  $B_1, B_2$  = "*intensification*" treatments I and II

### 3. Case study: CALGB 8923

#### Common oncology trial design: "Two stage randomization"

- After enrollment, *randomize* all subjects to *induction* therapies, e.g.,  $A_1$  or  $A_2$  ("stage 1 randomization")
- Observe *intermediate outcome*, e.g., "response"
- *Randomize* responding subjects to *maintenance* therapies, e.g.,  $B_1$  or  $B_2$  ("stage 2 randomization")
- Subjects not responding *follow up* with their physicians (no "stage 2" randomization; *only option*)
- Continue to monitor *all subjects* for the *outcome of interest*, *survival time*
- *Sometimes*: The *nonresponders* are randomized at *stage 2*, *responders* are *not*

### 3. Case study: CALGB 8923

#### CALGB 8923:

- Double-blind, placebo-controlled, two stage randomization trial
- $A_1$  = standard chemotherapy + placebo  $A_2$  = standard chemotherapy + GM-CSF
- 338 elderly (> 60 years old) patients with AML
- "Response" = complete remission
- $B_1, B_2$  = intensification treatments I and II
- Goal: Compare the four regimes on the basis of *disease-free survival*

### 3. Case study: CALGB 8923

#### Four possible regimes:

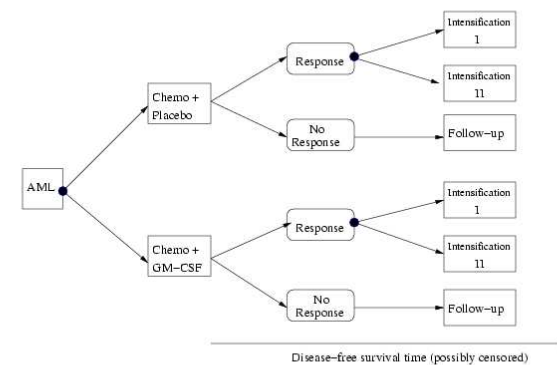
1.  $A_1$  followed by  $B_1$  if response else follow up =  $A_1B_1$
2.  $A_1$  followed by  $B_2$  if response else follow up =  $A_1B_2$
3.  $A_2$  followed by  $B_1$  if response else follow up =  $A_2B_1$
4.  $A_2$  followed by  $B_2$  if response else follow up =  $A_2B_2$

**Question:** How do these four regimes *compare* on the basis of *disease-free survival time*?

- E.g., mean disease-free survival time, proportion surviving without disease after 1 year, etc.
- Which regime to recommend?

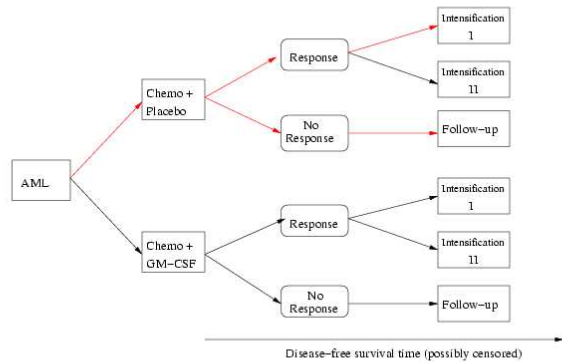
### 3. Case study: CALGB 8923

#### Schematic of CALGB 8923: Randomization at ●s



## 2. Randomized trials for dynamic regimes

Regime  $A_1B_1$ :



## 4. Analysis

**Question of interest:** For each regime  $A_jB_k$ ,  $j = 1, 2$ ,  $k = 1, 2$

- Estimate the *mean disease-free survival time* under regime  $A_jB_k$
- I.e., estimate mean disease-free survival if the *entire AML population were to follow* regime  $A_jB_k$
- “*Following*”  $A_jB_k$  means give  $A_j$  initially followed by  $B_k$  if response else follow up

**How to estimate this quantity from the data in the trial?**

## 4. Analysis

**Standard analysis:**

- Compare *response rates* to  $A_1$  and  $A_2$
- Compare *survival* between  $B_1$  and  $B_2$  among *responders*
- Compare *survival* between  $A_1$  and  $A_2$ , regardless of subsequent response/randomization

**Issues:**

- Does not address *directly* the question of interest
- An induction therapy ( $A$ ) may yield *higher proportion of responders* but also have other effects that render subsequent intensification treatments ( $B$ ) *less effective*
- “*Delayed effects*” (*Susan*)

## 4. Analysis

**Basic idea:** To *estimate the mean* for  $A_jB_k$ , use data from all subjects whose *actual experience* is *consistent with* having followed  $A_jB_k$

- *Assume* that whether response occurs depends only on  $A$
- All subjects receiving  $A_j$  who *respond* and then are randomized to  $B_k$  are *consistent with*  $A_jB_k$
- All subjects receiving  $A_j$  who *do not respond* and hence are not randomized at stage 2 are *also consistent with*  $A_jB_k$
- *Key:* Must *combine* survival times from these subjects in an *appropriate way*...

**An appropriate way:** This is an “*unbalanced*” SMART trial

- $\Rightarrow$  A *weighted average* of survival times
- Consider this *heuristically*...

## 4. Analysis

**Consider  $A_1$  only ( $A_2$  analogous) :** Ideally, suppose everyone were randomized to  $A_1B_1$

- **Nonresponders** to  $A_1 \Rightarrow$  follow up
- **Responders**  $\Rightarrow$  all get  $B_1$
- **Natural estimator:** Sample average of all survival times (*unweighted*)

**In the trial:** Suppose responders are randomized to  $B_1$  or  $B_2$  with probability 1/2

- **Nonresponders** to  $A_1 \Rightarrow$  follow up (same as before)
- **Half of responders** get  $B_1$ , **half** get  $B_2$
- The half who get  $B_2$  have **missing** survival times as far as  $A_1B_1$  is concerned

## 4. Analysis

**In symbols:** Let

$T_i$  = survival time for subject  $i$ ,  $i = 1, \dots, n$ ,

$R_i = 1$  if  $i$  responds to  $A_1$ ,  $R_i = 0$  if not

$Z_i = 1$  for a responder randomized to  $B_1$ ,  $Z_i = 2$  for  $B_2$

$P(Z_i = 1 | R_i = 1) = \pi$  (= 1/2 in previous)

**Estimators:**  $n^{-1} \sum_{i=1}^n Q_i T_i$  or  $\left( \sum_{i=1}^n Q_i \right)^{-1} \sum_{i=1}^n Q_i T_i$ ,

$$Q_i = 1 - R_i + R_i I(Z_i = 1) \pi^{-1}$$

- $Q_i = 0$  if  $i$  is inconsistent with  $A_1B_1$  (i.e., is consistent with  $A_1B_2$ )
- $Q_i = 1$  if  $R_i = 0$
- $Q_i = \pi^{-1}$  if  $R_i = 1$  and  $Z_i = 1$
- To estimate  $S(t) = P(T_i > t)$ , estimate  $F(t) = 1 - S(t)$  by replacing  $T_i$  by  $I(T_i \leq t)$

## 4. Analysis

**Result:** To estimate mean for  $A_1B_1$  from the trial

- The **nonresponders** represent themselves either way  $\Rightarrow$  weight = 1
- Each **responder** represents him/herself and another similar subject who got randomized to  $B_2 \Rightarrow$  weight = 2
- Usual “**inverse probability weighting**” for missing data
- To estimate mean for  $A_1B_2$ , switch the roles

## 5. Wrinkles

**Survival outcome:** Subjects may **die** before having a chance to respond

- **Nonresponders** at the time of death,  $R_i = 0$

**Censoring:** Survival time may be right-censored at time  $C_i$

- **Assume**  $K_1(t) = P(C_i > t | A_1)$
- Consider **restricted survival time**, i.e., survival up to time  $L$  such that  $K_1(L) > 0$
- **Observe**  $V_i = \min(T_i, C_i)$  and  $\Delta_i = I(T_i < C_i)$
- If  $T_i$  is **not censored** for subject  $i$ ,  $V_i = T_i$ ,  $i$  represents  $K_1^{-1}(V_i)$  individuals, including him/herself, who **could have** been uncensored

- **Estimator** becomes

$$n^{-1} \sum_{i=1}^n \frac{\Delta_i Q_i}{K_1(V_i)} V_i$$

## 5. Wrinkles

**Consent of responders:** In CALGB 8923, some subjects who *did respond refused to be randomized* at the second stage

- In CALGB 8923,  $\sim 90\%$  consent rate among responders
- “*Intention to treat*” perspective: Consider instead *offering*  $A_j$  followed by *offering*  $B_k$  if response else follow up
- *Redefine*, e.g., “ $A_1$  followed by  $B_k$  if response *and consent* else follow up” (so make comparisons without regard to differential rates of consent)
- So *redefine*  $\Rightarrow R_i = 1$  if subject  $i$  *both* responds *and consents* to further participation
- ... As opposed to attempt to ask the original *causal* question, with this *noncompliance* as a nuisance ( $\Rightarrow$  *observational study*)

## 6. Discussion

**Remarks:**

- Could equally well *randomize subjects up front* to regimes and use these same estimators
- *Fancier* (in terms of efficiency) estimators are possible
- Methods for *testing* also possible
- If SMART trial is *balanced*, *no need* to do *weighting*

**Looking forward to Susan:**

- Dynamic treatment regimes are what is done in *clinical practice*
- The regimes here are simple and preconceived: *two stages* only, *decision rule* at step 2 based on the single variable “*response*”
- Methods to *design* dynamic treatment regimes are needed

## 7. Demonstration using potential outcomes

**One way to formalize the rationale for weighting:** Again consider  $A_1$  regimes only ( $A_2$  analogous)

- Suppose there are  $n$  subjects randomized to  $A_1$  and that subject  $i$  has *potential outcomes*  $T_{11i}, T_{12i}$
- $T_{1ki}$  = survival time  $i$  *would have* if  $i$  *were to follow* (*or be offered*)  $A_1B_k$ ,  $k = 1, 2$

**Question of interest:** Estimate mean disease-free survival if the *entire AML population were to follow* regime  $A_1B_k$

- Distributions of the  $T_{1k}$  represent survival in the population *if all subjects* followed  $A_1B_k$ ,  $k = 1, 2$
- $\Rightarrow$  Want to estimate  $\mu_{1k} = E(T_{1ki})$

## 7. Demonstration using potential outcomes

**Of course:** Do not observe *both of*  $T_{11i}, T_{12i}$  for each  $i$

**Do observe:**  $(R_i, R_i Z_i, T_i)$ ,  $i = 1, \dots, n$

- $R_i = 1$  if  $i$  *responds*,  $R_i = 0$  if not
- $Z_i = k$  if  $i$  is *randomized at stage 2* to  $B_k$ ,  $k = 1, 2$  (defined only if  $R_i = 1$ )
- $P(Z_i = 1 | R_i = 1) = \pi$  = probability of second stage randomization to  $B_1$  (after first stage randomization to  $A_1$ ) *if response*

**Consider  $k = 1$ :** Want to estimate  $\mu_{11} = E(T_{11i})$ ,  $k = 1, 2$ , based on *observed data*  $(R_i, R_i Z_i, T_i)$ ,  $i = 1, \dots, n$

- The estimators discussed (based on *observed* data) may be shown to be *consistent* for  $\mu_{11}$ , e.g.,  $n^{-1} \sum_{i=1}^n Q_i T_i$

## 7. Demonstration using potential outcomes

**Want to show:**  $E(Q_i T_i) = E(T_{11i})$ ,  $Q_i = 1 - R_i + R_i I(Z_i = 1) \pi^{-1}$

**Assume:** For subjects randomized to  $A_1$

- If  $R_i = 0$ ,  $T_{11i}$  and  $T_{12i}$  are the same; thus

$$T_i = (1 - R_i)T_{11i} + R_i I(Z_i = 1)T_{11i} + R_i I(Z_i = 2)T_{12i}$$

**Using:**  $R_i(1 - R_i) = 0$ ,  $I(Z_i = 1)I(Z_i = 2) = 0$ , etc.

$$\begin{aligned} E(Q_i T_i) &= E[T_{11i}\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1}\}] \\ &= E[T_{11i} E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1} | R_i, T_{11i}\}]\end{aligned}$$

so want to show

$$E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1} | R_i, T_{11i}\} = 1$$

## References

Lunceford JK, Davidian M, Tsiatis AA. (2002) Estimation of survival distributions of treatment policies in two-stage randomization designs in clinical trials. *Biometrics* **58**, 48–57.

Wahed AS, Tsiatis AA. (2004) Optimal estimator for the survival distribution and related quantities for treatment policies in two-stage randomization designs in clinical trials. *Biometrics* **60** 124–133.

Wahed AS, Tsiatis AA. (2006) Semiparametric efficient estimation of survival distribution for treatment policies in two-stage randomization designs in clinical trials with censored data. *Biometrika*, in press.

**These slides available at:**

<http://www.stat.ncsu.edu/~davidian>

## 7. Demonstration using potential outcomes

$$\begin{aligned} &E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1} | R_i, T_{11i}\} \\ &= E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1} | R_i = 0, T_{11i}\}P(R_i = 0 | T_{11i}) \\ &\quad + E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1} | R_i = 1, T_{11i}\}P(R_i = 1 | T_{11i}) \\ &= P(R_i = 0 | T_{11i}) + E\{I(Z_i = 1) | R_i = 1, T_{11i}\}\pi^{-1}P(R_i = 1 | T_{11i}) \\ &= P(R_i = 0 | T_{11i}) + P(R_i = 1 | T_{11i}) = 1 \end{aligned}$$

**Because:** By *randomization*,

$$E\{I(Z_i = 1) | R_i = 1, T_{11i}\} = P(Z = 1 | R = 1, T_{11i}) = P(Z = 1 | R = 1) = \pi$$

$\Rightarrow$  randomization ensures  $i$ 's assignment to  $B_1$  does not depend on  $i$ 's prognosis

**For  $k = 2$ :** Same argument, now  $Q_i = 1 - R_i + R_i I(Z_i = 2)(1 - \pi)^{-1}$ ,