I. Dynamic Treatment Regimes in Public Health

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

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*)

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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)
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*

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**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 $B'_2$

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 $B_1$ if response, else $B'_2$
7. $A_2$ followed by $B_2$ 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

Possible ways to compare:
- An eight-arm randomized trial?
- Combine information from a series of trials?
- Something else?
2. Randomized trials for dynamic regimes

In red: Regime “A₁ followed by B₁ if response else B₁’”

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 ⇒ myelosuppression ⇒ 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

As before:
- Step 1 options: A₁ = Standard chemotherapy, A₂ = Standard chemotherapy + GM-CSF
- If response, Step 2 options: B₁, B₂ = “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

**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?

**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

**Schematic of CALGB 8923:** Randomization at $s$
2. Randomized trials for dynamic regimes

Regime $A_1B_1$:

- **Symposium on Causal Inference**

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

**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?**

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**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 $A_1$ ⇒ follow up
- Responders ⇒ 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 $A_1$ ⇒ 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

In symbols: Let

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

$R_i = 1$ 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:

$$n^{-1} \sum_{i=1}^{n} Q_i T_i \text{ or } \left( n^{-1} \sum_{i=1}^{n} Q_i \right) \sum_{j=1}^{n} Q_j T_j,$$

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

- $Q_i = 0$ 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 $I(T_i \leq t)$

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

- The nonresponders represent themselves either way ⇒ weight = 1
- Each responder represents him/herself and another similar subject who got randomized to $B_2$ ⇒ 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, ~ 90% consent rate among responders
- “Intention to treat” perspective: Consider instead offering A₁ followed by offering B₂ if response else follow up
- Redefine, e.g., “A₁ followed by B₂ if response and consent else follow up” (so make comparisons without regard to differential rates of consent)
- So redefine ⇒ Rᵢ = 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 (⇒ 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 A₁ regimes only (A₂ analogous)
- Suppose there are n subjects randomized to A₁ and that subject i has potential outcomes T₁₁ᵢ, T₁₂ᵢ
- T₁ⱼᵢ = survival time i would have if i were to follow (or be offered) A₁Bⱼ, j = 1, 2

Question of interest: Estimate mean disease-free survival if the entire AML population were to follow regime A₁Bⱼ
- Distributions of the Tⱼᵢ represent survival in the population if all subjects followed A₁Bⱼ, j = 1, 2
- ⇒ Want to estimate μⱼ = E(Tⱼᵢ)

7. Demonstration using potential outcomes

Of course: Do not observe both of T₁₁ᵢ, T₁₂ᵢ for each i
Do observe: (Rᵢ, RᵢZᵢ, Tᵢ), i = 1, ..., n
- Rᵢ = 1 if i responds, Rᵢ = 0 if not
- Zᵢ = k if i is randomized at stage 2 to Bⱼ, k = 1, 2 (defined only if Rᵢ = 1)
- P(Zᵢ = 1 | Rᵢ = 1) = π = probability of second stage randomization to B₁ (after first stage randomization to A₁) if response

Consider k = 1: Want to estimate μ₁₁ = E(T₁₁ᵢ), k = 1, 2, based on observed data (Rᵢ, RᵢZᵢ, Tᵢ), i = 1, ..., n
- The estimators discussed (based on observed data) may be shown to be consistent for μ₁₁, e.g., n⁻¹ ∑ᵢ=1 Tᵢ.
7. Demonstration using potential outcomes

Want to show: \( E(Q_iT_i) = E(T_{11i}), Q_i = 1 - R_i + R_iI(Z_i = 1)\pi^{-1} \)

Assume: For subjects randomized to \( A_1 \)

- If \( R_i = 0, T_{11i} \) and \( T_{12i} \) are the same; thus \( T_i = (1 - R_i)T_{11i} + R_iI(Z_i = 1)T_{11i} + R_iI(Z_i = 2)T_{12i} \)

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

\[
E(Q_iT_i) = E[T_{11i}((1 - R_i) + R_iI(Z_i = 1)\pi^{-1})]
= E[T_{11i}E[(1 - R_i) + R_iI(Z_i = 1)\pi^{-1}|R_i, T_{11i}]]
\]

so want to show

\[
E((1 - R_i) + R_iI(Z_i = 1)\pi^{-1}|R_i, T_{11i}) = 1
\]

References


These slides available at:

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