

Estimating the Mean Response of Treatment Duration Regimes in an Observational Study

Anastasios A. Tsiatis



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

Outline

- Description of Motivating Example
- Formulating the Statistical Question
- Solution
- Application to Example

The ESPRIT Infusion Trial

Study of the effect of Integrilin therapy on outcome for patients undergoing coronary stent implantation

Study Design and Features:

- Randomized, placebo-controlled trial - 1024 on placebo and 1040 on experimental treatment
- Experimental Integrilin infusion for 18-24 hours
- Outcome: composite endpoint of death, MI, or urgent target revascularization at 30 days

Conclusion: Outcome (failure rate) reduced from 10.5% (on placebo) to 6.8% (on treatment) which was significant ($p=0.0034$).

After the study concluded that Integrilin therapy was effective in reducing the failure rate, attention focused on determining a “recommended” treatment duration.

Treatment duration decision:

- Infusion length ends when attending physician deems it appropriate (physician discretion); generally between 18-24 hours
- Bailout - infusion immediately stopped if patient experiences adverse event
 - severe bleeding
 - abrupt closure
 - no reflow
 - coronary thrombosis
 - failure outcome

Thus, actual infusion is stopped either by physician discretion or the occurrence of a treatment-terminating adverse event.

Research Goal (Dynamic Treatment Regime)

- What should be the recommended infusion length? More precisely, an infusion length recommendation for t hours really means to infuse for t hours or until a treatment-terminating event occurs, whichever comes first.
- Such a recommendation is an example of a dynamic treatment regime because the treatment will vary according to the outcome of the patient.
- We refer to such a dynamic treatment regime as a “Treatment Duration Regime of t Hours”
- To address our goal, we must be able to estimate the mean response (probability of a failure) associated with different treatment duration regimes.

Integrilin Duration for Patients with No Adverse Events

hours	no. of pts
16 (< 17)	61
18 (17-19)	479
20 (19-21)	194
22 (21-23)	85
24 (> 23)	111
	930

Table 1: Table of Treatment Completion versus Outcome

Response Summary for Integrilin Patients With Adverse Events

Status	no. of pts	no. of failures	
Early Term.	106	20	18.9%
(< 17)	89	19	21.3%
(17-19)	11	0	0.0%
(19-21)	6	1	16.7%
Completed	930	51	5.5%
	1036	71	6.8%

Table 2: Table of Early Treatment Termination versus Outcome

Summarizing

- Adverse events occurred early
- Poor outcome associated with adverse events
- Infusion duration was between 16-24 hours

Ideal experiment: Randomized study

- Randomize patients to different treatment-duration regimes
- Know patient treatment assignment
- Patients are, on average, similar across treatment regimes
- Compare failure rates among randomized regimes
(Intent-to-treat analysis)

In an Observational Study

Patients are not randomly assigned to regimes. The study of the duration of Integrilin infusion on outcome is an example of an observational study embedded in a randomized study.

This creates two difficulties:

- No longer reasonable to assume patients are similar across assigned treatment durations
- Unlike the randomized study, the intended treatment duration regime is not known (censored) for a patient whose infusion is terminated because of an adverse event

Observed Data

The data in an observational study can be summarized as

- Y = binary 30-day outcome (failure indicator)
- U = observed infusion length
- $\Delta = 1$ (infusion stopped by physician discretion)
= 0 (infusion stopped by adverse event)
- $\bar{Z}(U)$ = covariate history through time U
- For simplicity, we consider a finite number of treatment duration regimes t_1, \dots, t_k by discretizing the duration data

With such data how do we answer the research question of interest? For that matter what is the research question?

Causal Models

- Conceptualize the problem and define the parameter of interest using potential outcomes (counterfactuals) as defined by Neyman, Rubin, Holland and Robins
- Model the treatment decision (infusion duration) process
- Make assumptions. Are they feasible?

Framework, Methods and Assumptions

The Conceptualization of the Problem using Potential Outcomes (What if Outcomes)

For a randomly selected individual in our population, let

- $\{C, Y^*(C)\}$ = time to adverse event if continuously treated and potential response if treatment continued to that point
- $\{Y^*(t_1), \dots, Y^*(t_k)\}$ = potential responses for treatment regimes t_1, \dots, t_k . Note that $Y^*(t_j) = Y^*(C)$ for $t_j \geq C$
- $\bar{Z}(C)$ = covariate history

Let us denote the all the potential outcomes by

$$V = \{C, Y^*(t_1), \dots, Y^*(t_k), \bar{Z}(C)\}$$

- **Goal:** Estimate $\mu_j = E\{Y^*(t_j)\}, j = 1, \dots, k$
- Easy if we had the potential outcomes, but, of course, we don't
- We only get to observe the responses according to the actual infusion duration each patient received

Assumptions

What assumptions on the treatment decision (infusion duration) process will allow us to identify the distribution of $Y^*(t_j)$ through the observed data?

Observational Study

- **Assumption** No Unmeasured confounders

$$\begin{aligned}\lambda_j(V) &= P\left\{U = t_j, \Delta = 1 \mid U \geq t_j, V\right\} \\ &= P\left\{U = t_j, \Delta = 1 \mid U \geq t_j, \bar{Z}(t_j)\right\} = \lambda_j(\bar{Z}_j),\end{aligned}$$

for $j = 1, \dots, k$, where $\lambda_j(\bar{Z}_j)$ denotes the discrete cause-specific hazard for stopping infusion at t_j with physician discretion.

- **In words**, this assumption implies that the conditional probability to stop or continue treatment at time t_j , given that the patient has continuously received treatment without experiencing an adverse event, only depends on the observed covariate data up through time t_j and not additionally on other potential outcomes.

Question

- Using the above assumptions, can we construct a consistent estimator for μ_j ?

Answer

- A weighted estimator using importance weights defined via the inverse propensity score

Propensity Score

- Let R_{ij} denote the indicator of whether the treatment that patient i receives is consistent with the regime t_j
- That is,

$$\begin{aligned} R_{ij} &= 1 \text{ if } (U_i = t_j, \Delta_i = 1) \text{ or } (U_i < t_j, \Delta_i = 0) \\ &= 0 \text{ otherwise} \end{aligned}$$

- Define the propensity score by $\pi_j(V_i) = P(R_{ij} = 1|V_i)$

Importance Weights

- The importance weight for treatment duration regime t_j is defined by

$$w_{ij} = \frac{R_{ij}}{\pi_j(V_i)}$$

That is, when

- $R_{ij} = 0$ then $w_{ij} = 0$
- $R_{ij} = 1$ then $w_{ij} = 1/\pi_j(V_i)$

- The weighted estimator is then given by

$$\hat{\mu}_j = \frac{\sum_{i=1}^n w_{ij} Y_i}{\sum_{i=1}^n w_{ij}}$$

Motivation

- Suppose everyone in the sample was assigned to regime t_j ; hence $Y_i = Y_i^*(t_j)$, then $\hat{\mu}_j = n^{-1} \sum_{i=1}^n Y_i$
- However, not everyone is assigned treatment consistent with regime t_j
- Therefore, take every one in the sample that is consistent with the regime t_j ; i.e. $\{i : R_{ij} = 1\}$, and weight their response by $1/\pi_j(V_i)$, so that they not only represent their response but also the response of others that didn't receive this treatment regime

Propensity scores

- What is the propensity score $\pi_j(V) = P(R_j = 1|V)$?
- Since V is not observed, can the propensity score be written as a function of the observed data $\{U, \Delta, \bar{Z}(U)\}$?

Propensity scores

- The propensity score $\pi_j(V)$ equals

$$\begin{aligned} \{1 - \lambda_1(V)\} \times \dots \times \{1 - \lambda_{j-1}(V)\} \times \lambda_j(V) & \quad \text{if } C > t_j \\ \{1 - \lambda_1(V)\} \times \dots \times \{1 - \lambda_{[C]}(V)\} & \quad \text{if } C < t_j \end{aligned}$$

- Because of the assumption of **No Unmeasured Confounders**

$$\begin{aligned} \{1 - \lambda_1(\bar{Z}_1)\} \times \dots \times \{1 - \lambda_{j-1}(\bar{Z}_{j-1})\} \times \lambda_j(\bar{Z}_j) & \quad \text{if } C > t_j \\ \{1 - \lambda_1(\bar{Z}_1)\} \times \dots \times \{1 - \lambda_{[C]}(\bar{Z}_{[C]})\} & \quad \text{if } C < t_j \end{aligned}$$

where

$$\lambda_j(V) = Pr(U = t_j, \Delta = 1 | U \geq t_j, V)$$

$$\lambda_j(\bar{Z}_j) = Pr(U = t_j, \Delta = 1 | U \geq t_j, \bar{Z}_j)$$

Weighted estimator

- Define

$$f_j(\bar{Z}_j) = \lambda_j(\bar{Z}_j) \prod_{m=1}^{j-1} \{1 - \lambda_m(\bar{Z}_m)\}$$

$$K_j(\bar{Z}_j) = \prod_{m=1}^j \{1 - \lambda_m(\bar{Z}_m)\}$$

- Consequently,

$$w_{ij} = \frac{R_{ij}}{\pi_j(V_i)} = \frac{I(U_i = t_j, \Delta_i = 1)}{f_j(\bar{Z}_{ij})} + \frac{I(U_i < t_j, \Delta_i = 0)}{K_{[U_i]}(\bar{Z}_{i[U_i]})}$$

- Hence, the weighted estimator is

$$\hat{\mu}_j = \frac{\sum_{i=1}^n w_{ij} Y_i}{\sum_{i=1}^n w_{ij}}$$

Estimating $f_j(\bar{Z}_j)$ and $K_{[U]}(\bar{Z}_{[U]})$

- The discrete hazards $\lambda_j(\bar{Z}_j)$, $j = 1, \dots, k$, needed to compute $f_j(\bar{Z}_j)$ and $K_{[U]}(\bar{Z}_{[U]})$, were estimated using conditional logistic regression models which were then used to estimate the inverse propensity score estimators $\hat{\mu}_j$, $j = 1, \dots, k$.
- Using theory of m-estimation we show that, under suitable regularity conditions, $\hat{\mu}_j$ will be consistent and asymptotically normal with asymptotic variance which can be estimated using a sandwich estimator.

Analysis of ESPRIT Infusion Trial

- The key assumption driving this methodology is that of
No Unmeasured Confounders
- We emphasized this point with the investigators
- General belief was that, other than the adverse events that necessitated termination of treatment, the infusion duration was a matter of physician preference and convenience
- Potential Confounders:
 - Time Independent Covariates: Diabetes, PTCA, Angina, Heparin, Weight,
 - Time Dependent Covariate: Enzyme levels (recorded every six hours)

Table 3: T_{1j} denotes an overall event rate, T_{2j} denotes an uncensored event rate, $\hat{\mu}_j^{(0)}$ is the proposed estimator assuming no confounding is present, $\hat{\mu}_j^{(1)}$ is the proposed estimator assuming confounding is present through baseline factors only, and $\hat{\mu}_j^{(2)}$ is the proposed estimator assuming time-dependent confounding.

t_j (hrs)	T_{1j}	T_{2j}	$\hat{\mu}_j^{(0)}$	$\hat{\mu}_j^{(1)}$	$\hat{\mu}_j^{(2)}$
16	.133	.016	.047(.021)	.040(.016)	.044(.018)
18	.045	.046	.066(.010)	.066(.010)	.070(.011)
20	.065	.062	.079(.017)	.078(.017)	.078(.017)
22	.047	.047	.071(.024)	.071(.024)	.067(.022)
24	.108	.108	.116(.027)	.121(.035)	.109(.032)

Placebo patients

t_j (hrs)	T_{1j}	T_{2j}	$\hat{\mu}_j^{(0)}$	$\hat{\mu}_j^{(1)}$	$\hat{\mu}_j^{(2)}$
16	.187	.097	.106(.036)	.116(.040)	.131(.045)
18	.073	.071	.083(.012)	.083(.012)	.091(.013)
20	.116	.116	.125(.022)	.125(.022)	.126(.022)
22	.070	.070	.081(.026)	.079(.026)	.079(.026)
24	.187	.187	.191(.033)	.170(.031)	.124(.024)

Discussion

- Through potential outcomes and importance weighting, we proposed a method to estimate mean response for treatment duration regime of t hours where only naive and ad hoc methods had been used before
- Estimator is consistent and asymptotically normal under the proposed assumptions
- Simulation studies show that our estimator performs well in realistic sample sizes

References and Future Direction

- For discrete time approximations, results can be found in Johnson and Tsiatis (2004) *Biometrics* 60: 315-323.
- Clinical paper in Rebeiz et al. (2004) *American Journal of Cardiology* 94: 926-929.
- Generalized to estimate duration-response relationships in continuous time
Johnson and Tsiatis (2005) *Biometrika* 92: 605-618.
- Optimal duration regimes, where timing may additionally be influenced by covariate history in a way to obtain best overall average outcome may be considered