Estimating Mean Response as a Function of Treatment Duration in an Observational Study, When Duration may be Informatively Censored

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Outline

1. Motivating Example — ESPRIT Infusion Trial
2. Framework, Methods, Assumptions
3. Main Result
4. Proposed Estimator
5. Analysis of the ESPRIT Data
6. Numerical Studies
7. Closing Remarks
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 policies:**

- 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

Thus, actual infusion is stopped either by physician discretion or a treatment-terminating event occurs.
Research Goal: What should be recommended infusion length? More precisely, what should be recommended infusion length policy?

Definition: Infusion length policy for $t$ units of time
Infuse for $t$ units of time or until a treatment-terminating event occurs, whichever comes first.

To address our goal, we must first be able to estimate the mean outcome (probability of a failure) as a function of treatment duration policy.
Response Summary for Integrilin Patients with No Adverse Events

<table>
<thead>
<tr>
<th>hours</th>
<th>no. of pts</th>
<th>no. of failures</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>61</td>
<td>2</td>
<td>3.3%</td>
</tr>
<tr>
<td>18</td>
<td>479</td>
<td>25</td>
<td>5.2%</td>
</tr>
<tr>
<td>20</td>
<td>194</td>
<td>13</td>
<td>6.7%</td>
</tr>
<tr>
<td>22</td>
<td>85</td>
<td>5</td>
<td>5.9%</td>
</tr>
<tr>
<td>24</td>
<td>111</td>
<td>12</td>
<td>10.8%</td>
</tr>
<tr>
<td></td>
<td>930</td>
<td>57</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

Table 1: Table of Treatment Completion versus Outcome
Response Summary for Integrilin Patients With Adverse Events

<table>
<thead>
<tr>
<th>Status</th>
<th>no. of pts</th>
<th>no. of failures</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Term.</td>
<td>106</td>
<td>20</td>
<td>18.9%</td>
</tr>
<tr>
<td>(&lt; 16 )</td>
<td>89</td>
<td>19</td>
<td>21.3%</td>
</tr>
<tr>
<td>(16-18 )</td>
<td>11</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>(18-20 )</td>
<td>6</td>
<td>1</td>
<td>16.7%</td>
</tr>
<tr>
<td>Completed</td>
<td>930</td>
<td>57</td>
<td>6.1%</td>
</tr>
<tr>
<td></td>
<td>1036</td>
<td>77</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

Table 2: Table of Early Treatment Termination versus Outcome
Ideal experiment: Randomized study

- Randomize patients to different treatment-duration policies
- Know patient treatment assignment
- Patients are, on average, similar across treatment policies
- Compare failure rates among randomized policies
In an observational study, patients are not randomly assigned to policies. 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 policies
- Intended treatment policy is not known for patient whose infusion is terminated because of an adverse event
  - if infusion-terminating occurs at time $C$, then observed infusion history consistent for any policy with $t > C$
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)
- $\tilde{Z}(U) =$ covariate history through time $U$
- For simplicity, we consider a finite number of treatment duration policies by discretizing the duration data; assume $U$ realizes finitely many values $t_1, \ldots, t_k$ when $\Delta = 1$ but may realize values along a continuum of time when $\Delta = 0$

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

- Model the biological process
- Model the treatment decision process
- Make assumptions. Are they feasible?
The Conceptualization of the Biological Process:  
**Potential (Counterfactual) Random Variables**

- \( C \) = time to adverse event if continuously treated
- \( Y^*_t \) = response if treatment terminated at time \( t, t \leq C \).
- \( \bar{Z}(C) \) = covariate history

Imagine that we get to observe \( \{C, Y^*_t, t \leq C, \bar{Z}(C)\} \) for every patient. Then, the response to a treatment duration policy of \( t \) units is

\[
Y^*_{t \wedge C} = Y^*_t 1(C \geq t) + Y^*_C 1(C < t).
\]

- **Goal:** Estimate \( \mu_j = E(Y^*_{t_j \wedge C}), j = 1, \ldots, k \)

- Easy if we had the counterfactual data, but, of course, we don’t
What assumptions will allow us to identify the distribution of $Y_{t \wedge C}$ through the observed data?

**Assumption 1:**

$$Y = \left\{ \sum_{j=1}^{k} Y_{t_j}^* 1(U = t_j, \Delta = 1) \right\} + Y_C^* 1(\Delta = 0)$$

- no interference among patients
- potential outcome for one patient does not affect the treatment for other patients
Modeling the treatment decision process

- Assumption 2 No Unmeasured confounders

\[
P \{ U = t_j, \Delta = 1 | U \geq t_j, \tilde{Z}(t_j), C, Y_x^*, t_j \leq x \leq C \} \\
= P \{ U = t_j, \Delta = 1 | U \geq t_j, \tilde{Z}(t_j) \} = \lambda_j(\tilde{Z}_j),
\]

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

- Assumption 2 implies that the decision 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 data up through time \( t_j \) and not on future prognosis.

- Question: Using the above assumptions, can we construct a consistent estimator for \( \mu_j \)?
Main Result

Under assumptions 1 and 2

\[ E \left[ Y \left\{ \frac{I(U = t_j, \Delta = 1)}{f_j(\tilde{Z}_j)} + \frac{I(U < t_j, \Delta = 0)}{K[U](\tilde{Z}[U])} \right\} \right] = E(Y_{t_j \wedge C}^*) = \mu_j, \]

where

\[ \lambda_j(\tilde{Z}_j) = Pr(U = t_j, \Delta = 1|U \geq t_j, \tilde{Z}_j) \]

\[ f_j(\tilde{Z}_j) = \lambda_j(\tilde{Z}_j) \prod_{m=1}^{j-1} \{1 - \lambda_m(\tilde{Z}_m)\} \]

\[ K_j(\tilde{Z}_j) = \prod_{m=1}^{j} \{1 - \lambda_m(\tilde{Z}_m)\} \]

and \([U] = \max_j \{j : t_j < U\} \).
Heuristic Motivation

- If there were no treatment terminating events; i.e. $\Delta_i = 1$ for all individuals $i = 1, \ldots, n$ in our sample, then $\mu_j$ is

$$E \left[ Y_i \left\{ \frac{I(U_i = t_j)}{f_j(Z_{ij})} \right\} \right]$$

and the estimator

$$\hat{\mu}_j = n^{-1} \sum_{i=1}^{n} Y_i \left\{ \frac{I(U_i = t_j)}{f_j(Z_{ij})} \right\} ,$$

where

$$f_j (\tilde{Z}_j) = \prod_{m=1}^{j-1} \left\{ 1 - \lambda_m (\tilde{Z}_m) \right\} \lambda_j (\tilde{Z}_j)$$
Inverse Weighted Propensity Score

• This is the so-called inverse weighted propensity score estimator proposed by Robins, where $f_j(\bar{Z}_j)$ represents the probability that a randomly selected individual in the population will be assigned to receive treatment duration of $t_j$ units.

• Consequently, any individual $i$ in our sample actually receiving $t_j$ units of treatment duration represents not only themselves but also $1/f_j(\bar{Z}_{ij}) - 1$ similar individuals who receive other treatment durations.
with treatment censoring events

\[
\mu_j = E \left[ Y \left\{ \frac{I(U = t_j, \Delta = 1) + I(U < t_j, \Delta = 0)}{f_j(\tilde{Z}_j)} \frac{f_j(\tilde{Z}_j)}{K[U](\tilde{Z}[U])} \right\} \right]
\]

\[
\hat{\mu}_j = n^{-1} \sum_{i=1}^{n} Y_i \left\{ \frac{I(U_i = t_j, \Delta_i = 1) + I(U_i < t_j, \Delta_i = 0)}{f_j(\tilde{Z}_{ij})} \frac{f_j(\tilde{Z}_{ij})}{K[U_i](\tilde{Z}[U_i])} \right\}
\]

- Heuristically, \( \frac{f_j(\tilde{Z}_{ij})}{K[U_i](\tilde{Z}[U_i])} \) can be viewed as the conditional probability that treatment would be stopped at time \( t_j \) given that treatment duration was greater than \( U_i \).

- This shows how the response of an individual which has treatment censored at time \( U_i \) is “distributed to the right.”
Outline of Proof

Define

\[ T_j = Y \left\{ \frac{I(U = t_j, \Delta = 1)}{f_j(\tilde{Z}_j)} + \frac{I(U < t_j, \Delta = 0)}{K[U](\tilde{Z}[U])} \right\} \]

and the following sequence of \( \sigma \)-algebras for \( j = 1, \ldots, k \),

\[ \mathcal{F}_j = \sigma\{I(U = t_m, \Delta = 1), I(U \leq x, \Delta = 0), \tilde{Z}(x)I(U \geq x), CI(U \geq t_j), Y^*_u I(U \geq t_j), m = 1, \ldots, j - 1, x < t_j \leq u \}. \]

Define \( Y^*_u = Y^*_C \), \( u \geq C \) to keep the above definition well-defined.

The idea is to show

\[ E[E \{ \cdots E \{ E(T_j | \mathcal{F}_j) | \mathcal{F}_{j-1} \} \cdots | \mathcal{F}_1 \}] = \mu_j \]
First, we observe four identities, numbered (A.1)-(A.4) in the paper. One of these identities together with assumption 2 allow us to repeatedly calculate the key conditional expectation

\[
E \{1(U = t_j, \Delta = 1)|\mathcal{F}_j\} = P(U = t_j, \Delta = 1|\mathcal{F}_j) \\
= P(U = t_j, \Delta = 1|U \geq t_j, \tilde{Z}_j)1(U \geq t_j) \\
= \lambda_j(\tilde{Z}_j)1(U \geq t_j),
\]

labeled (A.5).

By assumption 1, $T_j$ may be rewritten as

\[
\frac{Y_{t_j}^* I(U = t_j, \Delta = 1)}{f_j(\tilde{Z}_j)} + \frac{Y_{\hat{C}}^* I(U < t_j, \Delta = 0)}{K[U](\hat{Z}[U])},
\]
Starting with the first piece, using (A.1)-(A.5) and assumption 2,

\[
E \left[ E \left\{ \frac{Y_{t_j}^* 1(U = t_j, \Delta = 1)}{f_j(\bar{Z}_j)} \ \bigg| \mathcal{F}_j \right\} \right] = E \left[ \frac{Y_{t_j}^* P(U = t_j, \Delta = 1|\mathcal{F}_j)}{f_j(\bar{Z}_j)} \right] \\
= E \left[ \frac{Y_{t_j}^* \lambda_j(\bar{Z}_j) 1(U \geq t_j)}{f_j(\bar{Z}_j)} \right] \\
= E \left[ \frac{Y_{t_j}^* 1(U \geq t_j)}{K_{j-1}(Z_{j-1})} \right]
\]

Repeating the recursive conditioning arguments, we eventually show

\[
E \left\{ \frac{Y_{t_j}^* 1(U = t_j, \Delta = 1)}{f_j(\bar{Z}_j)} \right\} = E \left\{ Y_{t_j}^* 1(U \geq t_1, C \geq t_j) \right\} \\
= E \left\{ Y_{t_j}^* 1(C \geq t_j) \right\}
\]
Now the goal is to show the expectation of the second piece of $T_j$ is

$$E \left\{ \frac{Y_C^* 1(U < t_j, \Delta = 0)}{K_U(Z_U)} \right\} = E \{ Y_C^* 1(C < t_j) \}.$$

The manner in which we proceed is to note another identity:

$$\frac{Y_C^* I(U < t_j, \Delta = 0)}{K_U(Z_U)} = Y_C^* \left\{ I(C < t_1) + \sum_{m=2}^{j} \frac{I(U > t_{m-1}, t_{m-1} \leq C < t_m)}{K_{m-1}(Z_{m-1})} \right\}.$$
We consider the expectation of an arbitrary piece in the sum
\[
E \left \{ \frac{Y^*_C I(U > t_{m-1}, t_{m-1} \leq C < t_m)}{K_{m-1}(\bar{Z}_{m-1})} \right \}
\]
and take repeated conditional expectations \( \mathcal{F}_{m-1}, \ldots, \mathcal{F}_1 \). Again using (A.1)-(A.5) and assumption 2, we find
\[
E \left \{ \frac{Y^*_C I(U > t_{m-1}, t_{m-1} \leq C < t_m)}{K_{m-1}(\bar{Z}_{m-1})} \right \} = E \{ Y^*_C \mathbf{1}(t_{m-1} \leq C < t_m) \}.
\]
Therefore,
\[
E \left \{ \frac{Y^*_C \mathbf{1}(U < t_j, \Delta = 0)}{K_U(\bar{Z}_U)} \right \} = E \{ Y^*_C \mathbf{1}(C < t_j) \},
\]
as desired. This allows us to state our conclusion:
\[
E(T_j) = E \left \{ Y^*_{t_j} I(C \geq t_j) + Y^*_C I(C < t_j) \right \} = E(Y^*_{t_j \wedge C}) = \mu_j.
\]
Now, if propensities \( f_j(\tilde{Z}_j) \) and \( K[U](\tilde{Z}[U]) \) were known \textit{a priori}, then a natural estimator for \( \mu_j \) would be the solution to the following estimating equation:

\[
\sum_{i=1}^{n} (Y_i - \hat{\mu}_{jn}) \left[ \frac{I(U_i = t_j, \Delta_i = 1)}{f_j(\tilde{Z}_{ij})} + \frac{I(U_i < t_j, \Delta_i = 0)}{K[U_i](\tilde{Z}[U_i])} \right] = 0,
\]

where \( \tilde{Z}_{ij} \) refers to \( \tilde{Z}_j \) for the \( i \)-th individual. Of course, this may be rewritten as

\[
\hat{\mu}_{jn} = \frac{\sum_{i=1}^{n} Y_i w_{ij}}{\sum_{i=1}^{n} w_{ij}}, \quad w_{ij} = \frac{I(U_i = t_j, \Delta_i = 1)}{f_j(\tilde{Z}_{ij})} + \frac{I(U_i < t_j, \Delta_i = 0)}{K[U_i](\tilde{Z}[U_i])},
\]

a weighted average of the responses.
**Estimating $f_j(\tilde{Z}_j)$ and $K[U](\tilde{Z}[U])$**

We estimate $f_j(\tilde{Z}_j)$ and $K[U](\tilde{Z}[U])$ through the $k$ discrete hazards, $\lambda_j(\tilde{Z}_j), \ j = 1, \ldots, k$, which is modeled as a function of a parameter vector $\gamma$, using the observed data. A convenient and natural choice is the logistic regression model for $\lambda_j(\tilde{Z}_j)$ as a function of $\tilde{Z}_j$

$$
\lambda_j(\tilde{Z}_j) = \frac{\exp(\gamma_{0j} + \gamma_{1j}^t \tilde{Z}_j)}{1 + \exp(\gamma_{0j} + \gamma_{1j}^t \tilde{Z}_j)}.
$$

One may derive the observed data likelihood as

$$
L(\gamma; D_i) = \prod_{i=1}^{n} \prod_{j=1}^{k-1} \left\{ \frac{\lambda_{ij}(\gamma)}{1 - \lambda_{ij}(\gamma)} \right\}^{I(U_i=t_j, \Delta_i=1)} \{1 - \lambda_{ij}(\gamma)\}^{I(U_i\geq t_j)},
$$

where $D_i = \{U_i, \Delta_i, \tilde{Z}(U_i)\}, \ i = 1, \ldots, n$. 

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**Censored Covariates**
Asymptotic Properties

We have cast our estimator as an M-estimator, i.e. $\hat{\mu}_{jn}$ is the first element in the solution vector to the system of equations

$$\sum_{i=1}^{n} \begin{pmatrix} \psi_{\mu_j} (Y_i, D_i, \hat{\mu}_{jn}, \hat{\gamma}_n) \\ \psi_{\gamma}(D_i, \hat{\gamma}_n) \end{pmatrix} = 0,$$

where

$$\psi_{\mu_j} = (Y_i - \mu_j) \left\{ \frac{I(U_i = t_j, \Delta_i = 1)}{f_j(Z_{ij}; \gamma)} + \frac{I(U_i < l_j, \Delta_i = 0)}{K[U_i](Z[U_i]; \gamma)} \right\}$$

$$\psi_{\gamma} = \frac{\partial}{\partial \gamma} \log L(\gamma; D_i).$$

Hence, under suitable regularity conditions, $\hat{\mu}_{jn}$ can be shown to be consistent and asymptotically normal.
Analysis of ESPRIT Infusion Trial

- Implement grouping method and set $t = (16, 18, 20, 22, 24)$
- 106 patients terminated infusion early, 90 before 16 hours
- 934 patients completed infusion, $n = (61, 479, 194, 85, 111)$
- Overall event rate: 0.189 (censored), 0.061 (uncensored)
- Potential Confounders: diabetes, PTCA, angina, heparin, weight, nadir platelet count
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.

<table>
<thead>
<tr>
<th>$t_j$ (hrs)</th>
<th>$T_{1j}$</th>
<th>$T_{2j}$</th>
<th>$\hat{\mu}_j^{(0)}$</th>
<th>$\hat{\mu}_j^{(1)}$</th>
<th>$\hat{\mu}_j^{(2)}$</th>
<th>Placebo $\hat{\mu}_j$</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>.140</td>
<td>.017</td>
<td>.041 (.017)</td>
<td>.042 (.016)</td>
<td>.040 (.012)</td>
<td>.116 (.040)</td>
</tr>
<tr>
<td>18</td>
<td>.047</td>
<td>.046</td>
<td>.066 (.010)</td>
<td>.068 (.010)</td>
<td>.068 (.010)</td>
<td>.083 (.012)</td>
</tr>
<tr>
<td>20</td>
<td>.068</td>
<td>.068</td>
<td>.079 (.017)</td>
<td>.078 (.017)</td>
<td>.078 (.017)</td>
<td>.129 (.022)</td>
</tr>
<tr>
<td>22</td>
<td>.050</td>
<td>.050</td>
<td>.073 (.022)</td>
<td>.072 (.022)</td>
<td>.071 (.022)</td>
<td>.078 (.025)</td>
</tr>
<tr>
<td>24</td>
<td>.115</td>
<td>.115</td>
<td>.117 (.028)</td>
<td>.119 (.035)</td>
<td>.125 (.037)</td>
<td>.141 (.030)</td>
</tr>
</tbody>
</table>
Simulation Studies

SIMULATION 1:

1. Set $t = (15, 20, 25, 30)$.

2. Generate $Z \sim N(0, 1)$

3. Generate a censoring random variable $C \sim Exp(.005 \exp(-2Z))$

4. The treatment duration data were simulated according to the following algorithm:
SIMULATION 1 (continued)

Start with $m = 1$,

1. If $C < t_m$, then define $U = C$ and $\Delta = 0$.

2. For $C \geq t_m$, generate a Bernoulli random variable $Q_m$, the indicator variable for stopping treatment at time $t_m$, with probability $\lambda_m(Z)$ where

   \[
   \text{logit}\{\lambda_m(Z)\} = \alpha_m + \beta Z. 
   \]

3. If $Q_m = 1$, then assign $U = t_m$ and $\Delta = 1$; if $Q_m = 0$ and $m < k$, then increment $m$ to $m + 1$ and goto Step 1.
SIMULATION 1 (continued)

If $U = t_j$ and $\Delta = 1$, then the corresponding response $Y$ was generated as a Bernoulli random variable with probability $\pi$, where

$$\text{logit} (\pi) = \eta_j + \zeta Z,$$

whereas, if $U = C$ and $\Delta = 0$, then the corresponding response $Y$ is generated as a Bernoulli random variable with probability $\pi$, where

$$\text{logit} (\pi) = \min \{a : t_a \geq C\} \eta_a + \zeta Z + \nu.$$

The population parameter of interest $\mu_j$ is difficult to evaluate analytically; thus, we approximated its value by simulation. Using the above algorithm, we forced treatment duration to be stopped at time $t_j$, if not already censored by replacing Step 2 with “$Q_m = 0$ for $m = 1, \ldots, j - 1$ and $Q_j = 1$”, generating the outcome $Y$ 100,000 times, and then taking the sample average.
Table 4: Simulation summary of mean response for 1000 Monte Carlo datasets when treatment-duration data are discrete. $T_{1j}$ is the average $Y$ for $U_i \in I_j$ and $T_{2j}$ is the average $Y$ for $(U_i \in I_j, \Delta_i = 1)$. $\hat{\mu}_{jn}$ is our estimator. ECP is defined as the empirical coverage probability. Estimated standard errors are given in parentheses.

<table>
<thead>
<tr>
<th>$\mu_j$</th>
<th>$\hat{\mu}_{jn}$</th>
<th>$T_{1j}$</th>
<th>$T_{2j}$</th>
<th>ECP $\hat{\mu}_{jn}$</th>
<th>ECP $T_{1j}$</th>
<th>ECP $T_{2j}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.055</td>
<td>0.056(0.010)</td>
<td>0.118</td>
<td>0.045</td>
<td>0.949</td>
<td>0.029</td>
<td>0.808</td>
</tr>
<tr>
<td>0.091</td>
<td>0.091(0.015)</td>
<td>0.099</td>
<td>0.068</td>
<td>0.947</td>
<td>0.927</td>
<td>0.703</td>
</tr>
<tr>
<td>0.100</td>
<td>0.099(0.016)</td>
<td>0.064</td>
<td>0.046</td>
<td>0.949</td>
<td>0.441</td>
<td>0.099</td>
</tr>
<tr>
<td>0.151</td>
<td>0.151(0.027)</td>
<td>0.063</td>
<td>0.052</td>
<td>0.938</td>
<td>0.005</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Discussion

• Through potential outcomes and inverse weighting, we proposed a method to estimate mean response for treatment duration policy at time $t$ 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