Causality, Non-compliance and Intent-to-treat

10.1 Causality and Counterfactual Random Variables

Throughout the course, we’ve repeatedly said that randomization allows us to make causal statements regarding the effect of treatment on the primary response of interest. In this section, we will be more formal. The actual definition of cause and effect has been hotly debated over the years especially by philosophers. We will take a particular point of view using what are called counterfactual random variables. As usual, we consider a super-population of individuals that we are interested in and assume that the participants in a clinical trial represent a random sample from this population. For concreteness, let us consider a clinical trial which will compare a new treatment (treatment 1) to no treatment or placebo (treatment 0).

We define the counterfactual random variable \( Y^*_1 \) to denote the response (may be a binary or continuous outcome) that a randomly selected individual from our population if, possibly contrary to fact, that individual received treatment 1 (new treatment). Similarly, we define the counterfactual random variable \( Y^*_0 \) to denote the response that a randomly selected individual from our population if, possibly contrary to fact, that individual received treatment 0 (placebo). We imagine the existence of both random variables \((Y^*_0, Y^*_1)\) even though in actuality it would be impossible to observe both responses on any given individual. Thus the term counterfactual or “contrary to fact”. At the individual level, we say that treatment causes the effect \( Y^*_1 - Y^*_0 \). Clearly, if an individual knew their response to both treatment and placebo, then he/she would choose whichever gave the better response. Of course, this is not possible at the individual level but perhaps we can look at this question at the population level. That is, we will consider the population mean causal effect; namely \( \Delta = E(Y^*_1 - Y^*_0) = E(Y^*_1) - E(Y^*_0) \). If \( \Delta \) is positive, then on average the response on treatment 1 will be better than on treatment 0. At the individual level this will not necessarily imply that any specific individual will be guaranteed to benefit, but on average, the population as a whole will benefit.

Knowledge of the average causal effect at the population level, if it can be obtained or estimated, is still useful at the individual level. Say, for example, it has been proved that \( \Delta \) is positive; i.e. that on average treatment 1 is better than treatment 0, then in the absence of any additional a-priori knowledge that would distinguish one individual from the other, the best treatment choice for any
individual in the population is treatment 1. If there are additional pre-treatment characteristics that can distinguish individuals from each other; say, covariates $X$ (e.g. age, gender, race, etc.), then we would be interested in knowing or estimating the conditional expectation $\Delta(x) = E(Y^*_1 - Y^*_0 | X = x)$. If such a relationship were known, then the best choice for an individual whose $X$ characteristics were equal to $x$, without any other additional knowledge of the individual, would be to choose treatment 1 if $\Delta(x) > 0$ and to choose treatment 0 if $\Delta(x) < 0$. The question then becomes whether we can estimate the average causal treatment effect $\Delta$ or the average causal treatment effect conditional on $X = x$, $\Delta(x)$, from a sample of individuals in a clinical trial.

The data that we actually get to observe from a clinical trial can be summarized by $(Y_i, A_i, X_i), i = 1, \ldots, n$, where, for a randomly selected individual $i$ from our population, $A_i = (0, 1)$ denotes the treatment assignment, $Y_i$ denotes the response and $X_i$ denotes any additional characteristics, (prognostic factors) that are collected on the individual prior to treatment assignment (baseline characteristics). We will refer to these as the observable random variables. We distinguish here between the observed response $Y_i$ for the $i$-th individual and the counterfactual responses $Y^*_1, Y^*_0$. We will, however, make the reasonable assumption that

$$Y_i = Y^*_1 I(A_i = 1) + Y^*_0 I(A_i = 0),$$  \hspace{1cm} (10.1)

where $I(\cdot)$ denotes the indicator function of an event; that is, if the event is true this function equals 1, otherwise, it equals 0. In words, assumption (10.1) means that the observed response $Y_i$ equals the counterfactual response $Y^*_1$ if the $i$-th individual were assigned treatment 1; whereas, the observed response would equal the counterfactual response $Y^*_0$ if the $i$-th individual were assigned treatment 0.

Traditional statistical methods and models allow us to make associational relationships regarding the probability distribution of the observable random variables. For example, we can posit regression models that allow us to estimate relationships such as $E(Y_i | A_i, X_i)$. However, these associational relationships are not the causal relationships that we argue are the important parameters of interest. Thus, the question is under what conditions or assumptions can we estimate causal parameters such as $\Delta$ or $\Delta(x)$, from the sample of observable data. This is where randomization plays a key role. Since the assignment of treatment to the patient in a randomized study is made using a random number generator, it is completely independent of
any pre-treatment characteristics of the individual. An individual’s counterfactual responses can be thought of as pre-destined inherent characteristics of that individual and, as such, can be reasonably assumed to be independent of treatment in a randomized clinical trial. That is, how an individual would have responded if given treatment 1 and how he/she would have responded if given treatment 0 would not have an effect on which treatment he/she was randomized to.

Thus, we make the assumption that

\[ A_i \text{ is independent of } (Y_{i1}^*, Y_{0i}^*, X_i). \]  

(10.2)

**Remark:** It is important to note that assumption (10.2) is not the same as saying that \( A_i \) is independent of \( \bar{Y}_i \). Since by assumption (10.1) \( \bar{Y}_i = Y_{i1}^* I(A_i = 1) + Y_{0i}^* I(A_i = 0) \) (i.e. \( \bar{Y}_i \) is a function both of counterfactuals and treatment assignment), \( A_i \) being independent of \( (Y_{i1}^*, Y_{0i}^*) \) will not imply that \( A_i \) is independent of \( \bar{Y}_i \). In fact, if treatment is effective, as one hopes, then we would expect (and want) the distribution of \( \bar{Y}_i \) to depend on \( A_i \).

We will now use assumptions (10.1) and (10.2) to show that the distribution of the counterfactual random variable \( Y_{i1}^* \), i.e. \( P(Y_{i1}^* \leq u) \) is the same as the conditional distribution \( P(Y_i \leq u|A_i = 1) \). This follows because

\[ P(Y_i \leq u|A_i = 1) = P(Y_{i1}^* \leq u|A_i = 1) \]  

(10.3)

\[ = P(Y_{i1}^* \leq u). \]  

(10.4)

Equation (10.3) is a consequence of assumption (10.1) and equation (10.4) is a consequence of assumption (10.2). Similarly, we can show that the distribution of the counterfactual random variable \( Y_{0i}^* \), i.e. \( P(Y_{0i}^* \leq u) \) is the same as the conditional distribution \( P(Y_i \leq u|A_i = 0) \).

Consequently, the average causal treatment effect

\[ \Delta = E(Y_{1}^*) - E(Y_{0}^*) = E(Y|A = 1) - E(Y|A = 0). \]

This is an important relationship as we now have an expression for the causal parameter \( \Delta \) in terms of quantities that are functions of the distribution of the observable random variables. Thus, to estimate \( \Delta \) it suffices to estimate \( E(Y|A = 1) \) and \( E(Y|A = 0) \). But these can be estimated easily using the treatment-specific sample averages. If we let \( n_1 = \sum_{i=1}^{n} I(A_i = 1) \) and \( n_0 = \sum_{i=1}^{n} I(A_i = 0) \), denote the treatment-specific sample sizes, then the treatment specific
sample averages
\[ \bar{Y}_1 = \frac{\sum_{i=1}^{n} Y_i I(A_i = 1)}{n_1}; \quad \bar{Y}_0 = \frac{\sum_{i=1}^{n} Y_i I(A_i = 0)}{n_0}, \]
are unbiased estimators for \( E(Y|A = 1) \) and \( E(Y|A = 0) \) respectively. Thus, an unbiased estimator for the causal treatment effect \( \Delta \) can be derived from a randomized study using
\[ \hat{\Delta} = \bar{Y}_1 - \bar{Y}_0. \]

**Remark:** The above arguments make formal what is intuitively obvious; that is, we can use the difference in the treatment-specific sample averages in a randomized clinical trial to estimate the true population treatment effect.

Similar arguments can also be used to show that in a randomized trial
\[ \Delta(x) = E(Y_1^* - Y_0^*|X = x) = E(Y|A = 1, X = x) - E(Y|A = 0, X = x). \]
Thus, to estimate \( \Delta(x) \), it suffices to estimate the conditional mean of the observable random variables \( E(Y|A, X) \). This can be accomplished, say, by positing a model (either linear or nonlinear with or without interaction terms)
\[ E(Y|A, X) = \mu(A, X, \beta), \]
in terms of unknown parameters \( \beta \). For example, if \( X \) is a single covariate, we might consider a linear model with treatment-covariate interactions such as
\[ \mu(A, X, \beta) = \beta_0 + \beta_1 A + \beta_2 X + \beta_3 AX. \tag{10.5} \]
From a sample of data \((Y_i, A_i, X_i), i = 1, \ldots, n\) we can estimate the parameters \( \beta \) in our model using standard statistical techniques such as least squares or weighted least squares. If we denote the estimator by \( \hat{\beta} \), then the estimate for \( \Delta(x) \) is given by
\[ \hat{\Delta}(x) = \mu(1, x, \hat{\beta}) - \mu(0, x, \hat{\beta}). \]
For example, if we used model (10.5), then
\[ \hat{\Delta}(x) = (\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 x + \hat{\beta}_3 x) - (\hat{\beta}_0 + \hat{\beta}_2 x) = \hat{\beta}_1 + \hat{\beta}_3 x. \]
10.2 Noncompliance and Intent-to-treat analysis

The arguments outlined above assume that patients receive and take the treatment (or control) to which they are randomized. In many clinical trials, if not most, this is rarely the case. There is almost always some form of noncompliance from the intended treatment regimen.

Some reasons for a departure from the ideal treatment schedule are:

- A refusal by the patient to start or continue the assigned treatment, perhaps because of side effects or a belief that the treatment is ineffective
- A failure to comply with detailed instructions, for example, drug dosage, or to attend examinations when requested to do so
- A change of treatment imposed by the physician for clinical reasons, usually occurrence of adverse effects or deterioration of patient’s health
- An administrative error. In its most extreme form this may be the implementation of the wrong treatment.

How should we analyze the data when there is noncompliance? Some strategies that have been proposed and is a source of much debate between clinicians and statisticians include

- **Intent-to-Treat Analysis** (As randomized)
  Everyone is included in the analysis and the comparison of treatments is based on the difference of the average response between the randomized groups ignoring the fact that some patients were non-compliant.

- **As-treated analysis**
  This type of analysis takes on various forms, but the general idea is to compare only those patients who fully complied with their assigned treatment regimen and exclude non compliers from the analysis.
General Dogma of Clinical Trials

The exclusion of patients from the analysis should not allow the potential of bias in the treatment comparisons. Thus, exclusions based on post-randomization considerations, such as noncompliance, are not allowed for the primary analysis.

To illustrate some of the difficulties that can result from noncompliance, we consider some results from a study conducted by the Coronary Drug Project which was published in the New England Journal of Medicine, October, 1980, 303: 1038-1041. This study was a double-blind placebo-controlled clinical trial comparing Clofibrate to Placebo.

Table 10.1: Intent-to-Treat Analysis

<table>
<thead>
<tr>
<th></th>
<th>Clofibrate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year mortality rate</td>
<td>.18</td>
<td>.19</td>
</tr>
<tr>
<td>number of patients</td>
<td>1065</td>
<td>2695</td>
</tr>
</tbody>
</table>

Table 10.2: Clofibrate Patients Only

<table>
<thead>
<tr>
<th>Adherence (%)</th>
<th>5 year mortality rate</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (&lt; 80%)</td>
<td>.25</td>
<td>357</td>
</tr>
<tr>
<td>Good (&gt; 80%)</td>
<td>.15</td>
<td>708</td>
</tr>
</tbody>
</table>

p-value=.001

Table 10.3: Clofibrate and Placebo Patients

<table>
<thead>
<tr>
<th>Adherence (%)</th>
<th>Clofibrate 5 year mortality rate</th>
<th>Number of patients</th>
<th>Placebo 5 year mortality rate</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (&lt; 80%)</td>
<td>.25</td>
<td>357</td>
<td>.28</td>
<td>882</td>
</tr>
<tr>
<td>Good (&gt; 80%)</td>
<td>.15</td>
<td>708</td>
<td>.15</td>
<td>1813</td>
</tr>
</tbody>
</table>
It is clear from this data that patients who comply are prognostically different from those who do not comply. Therefore, analyzing the data according to as-treated may lead to severe biases because we cannot separate out the prognostic effect of noncompliance from the prognostic effect of treatment. An intent-to-treat analysis does not suffer from this type of potentially biased exclusions; nonetheless, we intuitively realize that when some patients do not comply with the intended treatment then an intent-to-treat analysis would diminish the effect of a treatment. Let us look at this issue a bit more carefully with the use of counterfactual modeling.

### 10.3 A Causal Model with Noncompliance

We consider the following simple example for illustrative purposes.

- A randomized study is conducted where patients are randomized with equal probability to active drug (treatment 1) or placebo (control) (treatment 0)
- Response is dichotomous; i.e. a patient either responds or not
- The main goal of the clinical trial is to estimate the difference in the probability of response between active drug and placebo
- Patients may not comply with their assigned treatment
- For simplicity, we assume that everyone either takes their assigned treatment or not (partial compliance is not considered)
- A simple assay can be conducted on patients that were randomized to receive active drug to see if they complied or not
- Patients assigned to placebo do not have access to the study drug
- Compliance cannot be determined for patients randomized to placebo

**Counterfactual and observable random variables**

The problem above can be conceptualized as follows:
Let the counterfactual random variables \((Y_1^*, Y_0^*)\) denote the response (1 if they respond, 0 if they don’t respond) of a randomly selected individual in our population if they received treatment 1 or treatment 0 respectively. Also let \(C\) denote the counterfactual random variable corresponding to whether or not a randomly selected individual in our population would comply or not \(C = (1, 0)\) if offered the new treatment. We refer to this as a counterfactual random variable because we will not know the compliance status if offered new treatment for patients randomized to placebo. Some of the population parameters associated with these counterfactuals are

- A complier (COM) and a noncomplier (NC) refer only to patients complying or not if offered active drug
- \(\theta = P(C = 1)\) denotes the population probability of complying
- \(\pi_{1}^{COM} = P(Y_1^* = 1|C = 1)\) denotes the population probability of response among compliers if given active drug,
- \(\pi_{1}^{NC} = P(Y_1^* = 1|C = 0)\) denotes the population probability of response among noncompliers if given active drug
- \(\pi_{0}^{COM} = P(Y_0^* = 1|C = 1)\) denotes the population probability of response among compliers if given placebo
- \(\pi_{0}^{NC} = P(Y_0^* = 1|C = 0)\) denotes the population probability of response among noncompliers if given placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>COMPLIERS</th>
<th>NONCOMPLIERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\theta)</td>
<td>(\pi_1^{COM})</td>
<td>(\pi_1^{NC})</td>
</tr>
<tr>
<td>(\pi_0^{COM})</td>
<td>(\pi_0^{COM})</td>
<td></td>
</tr>
<tr>
<td>(\Delta^{COM})</td>
<td>(\Delta^{NC})</td>
<td></td>
</tr>
</tbody>
</table>

As we argued previously, it is not reasonable to assume that \((Y_1^*, Y_0^*)\) are independent of \(C\). Thus, we would not expect \(\pi_{1}^{COM} = \pi_{1}^{NC}\) or \(\pi_{0}^{COM} = \pi_{0}^{NC}\).
Using this notation and some simple probability calculations we get that

\[ E(Y^*_1) = P(Y^*_1 = 1) = \pi^{COM}_1 \theta + \pi^{NC}_1 (1 - \theta) = \pi_1 \]

and

\[ E(Y^*_0) = P(Y^*_0 = 1) = \pi^{COM}_0 \theta + \pi^{NC}_0 (1 - \theta) = \pi_0. \]

Therefore, the average causal treatment effect equals

\[ \Delta = E(Y^*_1) - E(Y^*_0) = \pi_1 - \pi_0 = \Delta^{COM} \theta + \Delta^{NC} (1 - \theta). \]

The question is whether we can estimate these counterfactual parameters using the data we get to observe from a randomized clinical trial when there is noncompliance. We denote the observable data as \((Y, A, AC)\), where \(A = (1, 0)\) denotes the treatment that a patient is randomized to. \(C\) will denote the indicator of compliance which is only observed for patients randomized to active treatment. Thus the possible values that \((A, AC)\) can take are

- \((0, 0)\) corresponding to a patient randomized to placebo
- \((1, 1)\) corresponding to a patient randomized to active treatment who complies
- \((1, 0)\) corresponding to a patient randomized to active treatment who does not comply

Finally, the observable random variable \(Y = (0, 1)\) denotes the observed response.

**Remark:** In our scenario, if a patient is randomized to placebo, then that patient will not receive active treatment; whereas, if a patient is randomized to active treatment, then he/she will receive active treatment only if he/she complies; otherwise if the patient doesn’t comply, then he/she will not receive active treatment.

The above considerations lead to the following reasonable assumptions:

\[ Y = Y^*_0 I(A = 0) + Y^*_1 I(A = 1, C = 1) + Y^*_0 I(A = 1, C = 0) \]

and because of randomization

\[ A \text{ is independent of } (Y^*_1, Y^*_0, C). \]
Because of these assumptions, we can equate some of the parameters regarding the distribution of the observable random variables to the parameters of the distribution of the counterfactual random variables.

Namely,

\[ P(C = 1 | A = 1) = P(C = 1) = \theta \]
\[ P(Y = 1 | A = 0) = P(Y^*_0 = 1 | A = 0) = P(Y^*_0 = 1) = \pi_0 \]
\[ P(Y = 1 | A = 1, C = 1) = P(Y^*_1 = 1 | A = 1, C = 1) = P(Y^*_1 = 1 | C = 1) = \pi_{COM}^{1} \]
\[ P(Y = 1 | A = 1, C = 0) = P(Y^*_0 = 1 | A = 1, C = 0) = P(Y^*_0 = 1 | C = 0) = \pi_{NC}^{0} \]

**Note:** All the probabilities above can be estimated using the corresponding sample proportions in a clinical trial.

Interestingly, since we can get estimates of \( \pi_0, \pi_{NC}^{0} \) and \( \theta \), then we can use the relationship that

\[ \pi_0 = \pi_{COM}^{0} \theta + \pi_{NC}^{0} (1 - \theta) \]

to get that

\[ \pi_{COM}^{0} = \frac{\pi_0 - \pi_{NC}^{0} (1 - \theta)}{\theta} \].

In fact, the only counterfactual probability that cannot be estimated is \( \pi_{NC}^{1} \) as it is impossible to deduce the proportion of noncompliers who would have responded if forced to take treatment.

**Intent-to-treat analysis**

In an intent-to-treat analysis, where we compare the response rate among patients randomized to active drug to the response rate among patients randomized to placebo, we are estimating

\[ \Delta_{ITT} = P(Y = 1 | A = 1) - p(Y = 1 | A = 0) \]

Again, by the assumptions made and some probability calculations we get
\[ P(Y = 1|A = 1) = P(Y = 1|A = 1, C = 1)P(C = 1|A = 1) \]
\[ + P(Y = 1|A = 1, C = 0)P(C = 0|A = 1) \]
\[ = P(Y_1^* = 1|A = 1, C = 1)P(C = 1|A = 1) + P(Y_0^* = 1|A = 1, C = 0)P(C = 0|A = 1) \]
\[ = P(Y_1^* = 1|C = 1)P(C = 1) + P(Y_0^* = 1|C = 0)P(C = 0) \]
\[ = \pi_1^\text{COM}\theta + \pi_0^\text{NC}(1 - \theta) \] (10.6)

Also
\[ P(Y = 1|A = 0) = P(Y_0^* = 1|A = 0) = P(Y_0^* = 1) = \pi_0 = \pi_0^\text{COM}\theta + \pi_0^\text{NC}(1 - \theta). \] (10.7)

Subtracting (10.7) from (10.6) we get that
\[ \Delta_{ITT} = P(Y = 1|A = 1) - P(Y = 1|A = 0) = (\pi_1^\text{COM} - \pi_0^\text{COM})\theta, \]
or
\[ \Delta_{ITT} = \Delta^\text{COM}\theta. \] (10.8)

Recall that
\[ \Delta^\text{COM} = P(Y_1^* = 1|C = 1) - P(Y_0^* = 1|C = 1) = E(Y_1^* - Y_0^*|C = 1) \]
is the difference in the mean counterfactual responses between treatment and placebo among patients that would comply with treatment. As such, \( \Delta^\text{COM} \) is a causal parameter and some argue that it is the causal parameter of most interest since the patients that will benefit from a new treatment are those who will comply with the new treatment. Equation (10.8) makes it clear that the intention-to-treat analysis will yield an estimator which diminishes a causal treatment effect. In fact, since we are able to estimate the parameter \( \theta \), the probability of complying if offered the new treatment, then the causal parameter \( \Delta^\text{COM} \) can be identified using parameters from the observable random variables; namely
\[ \Delta^\text{COM} = \frac{P(Y = 1|A = 1) - P(Y = 1|A = 0)}{P(C = 1|A = 1)}. \] (10.9)

Since all the quantities on the right hand side of (10.9) are easily estimated from the data of a clinical trial, this means we can estimate the causal parameter \( \Delta^\text{COM} \).
Remarks

- If the null hypothesis of no treatment effect is true; namely

\[ H_0 : \Delta^{COM} = \Delta^{NC} = \Delta = 0 \]

- The intent to treat analysis, which estimates \( \Delta^{COM} \), gives an unbiased estimator of treatment difference (under \( H_0 \)) and can be used to compute a valid test of the null hypothesis

- If we were interested in estimating the causal parameter \( \Delta^{COM} \), the difference in response rate between treatment and placebo among compliers only, then

  - the intent to treat analysis gives an underestimate of this population causal effect

- Since there are no data available to estimate \( \pi^{NC}_1 \), we are not able to estimate \( \Delta^{NC} \) or \( \Delta \)

As-treated analysis

In one version of an as treated analysis we compare the response rate of patients randomized to receive active drug who comply to all patients randomized to receive placebo. That is, we compute

\[ \Delta_{AT} = \pi^{COM}_1 - \pi_0. \]

Since \( \pi_0 = \pi^{COM}_0 \theta + \pi^{NC}_0 (1 - \theta) \), after some algebra we get that

\[ \Delta_{AT} = \Delta + (\pi^{COM}_1 - \pi^{NC}_1)(1 - \theta), \]

where \( \Delta \) denotes the average causal treatment effect. This makes clear that when there is noncompliance, \( (\theta < 1) \), the as-treated analysis will yield an unbiased estimate of the average causal treatment effect only if \( \pi^{COM}_1 = \pi^{NC}_1 \). As we’ve argued previously, this assumption is not generally true and hence the as-treated analysis can result in biased estimation even under the null hypothesis.

Some Additional Remarks about Intention-to-Treat (ITT) Analyses

- By not allowing any exclusions, we are preserving the integrity of randomization
• With the use of ITT, we are comparing the policy of using treatment A where possible to
the policy of using treatment B (control) where possible

• If the intended treatments are always used, there is of course no problem

• If the treatments are rarely used, then the clinical trial will carry little information about
the true effect of A versus B, but a great deal of information about the difficulties to use
them

• The approach of comparing policies of intentions rather than rigorously standardized regi-
mens may be a more realistic statement of the purpose of the investigation
  – This is the pragmatic approach to a clinical trial
  – As compared to the explanatory approach which looks for a measure of effectiveness
    rather than efficacy.

• The estimate of the causal effect $\Delta^{COM}$ is larger than the intent-to-treat estimator $\Delta^{ITT}$,
but it also has proportionately larger standard deviation. Thus use of this estimator as
a basis for a test of the null hypothesis yields the same significance level as a standard
intent-to-treat analysis