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Causal Inference in Randomized Trials with Noncompliance

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1. Introduction

In human clinical trials, ethical considerations for study subjects override the scientific requirements of trial design. Noncompliance with an intervention or study procedure for ethical reasons is thus inevitable in practice (Piantadosi, 1997).

The Coronary Drug Project (CDP) trial (CDP Research Group, 1980) was a typical example of trials with noncompliance. The CDP trial was a large, double-blinded, randomized trial testing the effect of the cholesterol-lowering drug, clofibrate, on mortality. Patients were randomly assigned to the clofibrate or placebo groups and were followed for at least 5 years, documenting clinic visits and examinations. During each 4-month follow-up visit, the physician assessed compliance by counting or estimating the number of capsules returned by the patients. In the protocol, good compliers were defined as patients taking more than 80% of the prescribed treatment. Table 1 summarizes the incidence of death during the 5-year follow-up period, based on the treatment assigned and compliance status. Patients who left the trial before the end of the 5-year follow-up period were excluded.

Group	No. of patients	Deaths	Compliance status	No. of patients	Deaths
Clofibrate	1065	194	More than 80%	708	106
			Less than 80%	357	88
Placebo	2695	523	More than 80%	1813	274
			Less than 80%	882	249
Totals	3760	717			

Table 1. The compliance status and incidence of death during a 5-year follow-up period in the CDP trial.

In the clofibrate group, 708 patients were considered good compliers; 106 died during the follow-up period. There were 357 patients considered poor compliers; 88 died. Comparing the compliance status of the proportion of patients that died yields 106/708 – 88/357 = –9.68%. From this result, clofibrate seems to have been beneficial. However, when we make the same comparison for the placebo group, it yields 274/1813 – 249/882 = –13.12%. Surprisingly, we obtain the result that the placebo was more beneficial than clofibrate. However, nobody would interpret the result as being that the placebo had the effect of decreasing death.

Which subgroups to compare to estimate the treatment effect correctly is an important problem. From the viewpoint of treatment compliance, it is considered best to compare the proportion of deaths for the compliers in each group: 106/708 – 274/1813 = –0.14%. This comparison is called the per-protocol (PP) analysis. The PP analysis generally yields biased estimates of treatment effects, because whether patients comply with the assigned treatment is not randomized and several factors may affect it. This problem can be avoided by intention-to-treat (ITT) analysis, in which patients are analyzed according to the assigned treatment regardless of the treatment actually received (Fisher et al., 1990; Lee et al., 1991): 194/1065 – 523/2695 = –1.19%. The ITT estimate may represent the effect of the treatment intended, but generally does not represent the treatment effect itself (Schwartz & Lellouch, 1967; Sheiner & Rubin, 1995).

Noncompliance data may be obtained from actual clinical trials, as in the CDP trial. To estimate the treatment effect correctly from such data, we should consider the expected outcomes if all patients had received the test treatment and the control, and compare them. The effect yielded from such a comparison is called the average causal effect (ACE) (Robins & Tsiatis, 1991; Robins & Greenland, 1994). Several researchers have discussed methodology to estimate ACE (Pearl, 2000; Manski, 2003; Sato, 2006), but as yet, no standard methodology has been developed. Nevertheless, we can derive bounds on ACE using the deterministic causal model (e.g., Pearl, 1995; Cai et al., 2007; Chiba, 2009b). In this chapter, we discuss how estimates from major analyses, such as ITT and PP, are biased and present bounds on ACE under certain assumptions.

To achieve these objectives, this chapter is organized as follows. In Section 2, notation and definitions are provided. Sections 3 and 4 discuss noncompliance by switching the treatment, which, in contrast to the CDP trial, means that non-compliers in a sub-population assigned to treatment A receive treatment B and those assigned to treatment B receive treatment A. We discuss biases from major analyses such as ITT and PP in Section 3, and discuss the bounds on ACE in Section 4. Section 5 discusses noncompliance by receiving no treatment, as in the CDP trial. As in many publications, the instrumental variable (IV) assumption is used in these sections, but this assumption is relaxed in Section 6. Finally, Section 7 offers some concluding remarks. The derivations of equations and inequalities presented in this chapter are outlined in Section 8.

2. Notation and definitions

In the following sections, R is the randomization indicator, where $R = 2$ for subjects randomized to the test treatment and $R = 1$ for subjects randomized to the control. Similarly, X indicates actual (received) treatment that may not be randomized under protocol violations such as noncompliance, where $X = 2$ for subjects who received the test treatment, $X = 1$ for subjects who received the control, and $X = 0$ for subjects who received no treatment. The observed outcome is Y and $Y_{X=x}$ is the counterfactual value (or equally potential outcome) of Y if treatment X was set to x (Rubin, 1974, 1978, 1990). ACE is defined as $\mathrm{ACE} \equiv \mathrm{E}(Y_{X=2}) - \mathrm{E}(Y_{X=1})$. Note that ITT and PP estimators are represented by $\mathrm{ITT} \equiv \mathrm{E}(Y \mid R = 2) - \mathrm{E}(Y \mid R = 1)$ and $\mathrm{PP} \equiv \mathrm{E}(Y \mid X = 2, R = 2) - \mathrm{E}(Y \mid X = 1, R = 1)$, respectively. Furthermore, we use the notation $E_{xr} = \mathrm{E}(Y \mid X = x, R = r)$ and $p_{x \mid r} = \Pr(X = x \mid R = r)$; then, $\mathrm{PP} \equiv E_{22} - E_{11}$.

We require the consistency assumption that $Y_{X=x} = Y$ for all subjects, so that the value of Y that would have been observed if X had been set to what it in fact was is equal to the value of Y that was in fact observed. Thus, this assumption indicates that $\mathrm{E}(Y_{X=x} \mid X = x) = \mathrm{E}(Y \mid X = x)$ and furthermore $\mathrm{E}(Y_{X=x} \mid X = x, R = r) = \mathrm{E}(Y \mid X = x, R = r)$ $(= E_{xr})$. We assume that $Y_{X=x}$ is

independent from X given R and Z, where Z is a confounder or a set of confounders between X and Y. In Sections 3-5, we also require the instrumental variable (IV) assumption, which states that the potential outcome $Y_{X=x}$ is not affected directly by the treatment assignment R; rather, $Y_{X=x}$ is influenced only by the treatment actually received (Holland, 1986; Angrist et al., 1996). Thus, subjects' potential outcomes are independent of treatment assignment and are constant across the sub-populations of subjects assigned to different treatment arms. The IV assumption is formalized as follows:

ASSUMPTION 1: Instrumental variable (IV)

$$\mathrm{E}(Y_{X=x} \mid R = 2) = \mathrm{E}(Y_{X=x} \mid R = 1).$$

This assumption may hold in successfully blinded randomized trials, because subjects are not aware of their assigned treatments and so the assigned treatments do not affect the potential outcomes. However, this often may not hold in unblinded trials, in which subjects are aware of the assigned treatment and this knowledge may affect the potential outcomes, and needs to be critically evaluated. Assumption 1 is used in Sections 3-5, but is relaxed in Section 6.

3. Biases of estimates

In this section and the next section, we discuss noncompliance by switching the treatment, which means that non-compliers in a sub-population assigned to treatment A receive treatment B and those assigned to treatment B receive treatment A. In this type of noncompliance, all subjects have the value $X = 1$ or 2 (and not $X = 0$) for both $R = 1$ and 2. Thus, $p_{0|r} = 0$ and $p_{1|r} + p_{2|r} = 1$. The derivations of equations in this section are given in Section 8.1.

In this section, we discuss how estimates from major analyses, such as ITT and PP, are biased. To do so, we introduce the following R-specific bias factors due to confounding between X and Y (Brumback et al, 2004; Chiba et al., 2007):

$$a_r \equiv \mathrm{E}(Y_{X=2} \mid X = 2, R = r) - \mathrm{E}(Y_{X=2} \mid X = 1, R = r),$$

$$\beta_r \equiv \mathrm{E}(Y_{X=1} \mid X = 2, R = r) - \mathrm{E}(Y_{X=1} \mid X = 1, R = r),$$

where $r = 1, 2$. a_r and β_r are confounding effects that would arise from R-stratified comparisons of those with $X = 2$ versus those with $X = 1$. When $a_r > 0$ and $\beta_r > 0$, $\mathrm{E}(Y_{X=x} \mid X = 2, R = r) > \mathrm{E}(Y_{X=x} \mid X = 1, R = r)$, which means that the subjects who received the test treatment tend to have larger outcome values than those who received the control, leading to positive confounding. Conversely, when $a_r < 0$ and $\beta_r < 0$, $\mathrm{E}(Y_{X=x} \mid X = 2, R = r) < \mathrm{E}(Y_{X=x} \mid X = 1, R = r)$, which means that the subjects who received the test treatment tend to have smaller outcome values than those who received the control, leading to negative confounding. No confounding occurs between X and Y when $a_r = \beta_r = 0$.

Under Assumption 1, using a_r and β_r, $\mathrm{E}(Y_{X=2})$ and $\mathrm{E}(Y_{X=1})$ are expressed as:

$$\mathrm{E}(Y_{X=2}) = E_{2r} - a_r p_{1|r}, \tag{3.1}$$

$$\mathrm{E}(Y_{X=1}) = E_{1r} + \beta_r p_{2|r}. \tag{3.2}$$

Using these equations, $\mathrm{ITT} \equiv \mathrm{E}(Y \mid R = 2) - \mathrm{E}(Y \mid R = 1)$ can be expressed by a function of $\mathrm{ACE} \equiv \mathrm{E}(Y_{X=2}) - \mathrm{E}(Y_{X=1})$ and bias factors:

$$\text{ITT} = \text{ACE} + \{a_2 - (E_{22} - E_{12})\}p_{1|2} + \{\beta_1 - (E_{21} - E_{11})\}p_{2|1}. \quad (3.3)$$

Thus, the ITT estimator is generally a biased estimator of ACE, and can be unbiased when $a_2 = E_{22} - E_{12}$ and $\beta_1 = E_{21} - E_{11}$, i.e., $\text{E}(Y_{X=2} \mid X = x, R = r) = \text{E}(Y_{X=1} \mid X = x, R = r)$ for $x \neq r$. This equation implies that the ITT estimate can be unbiased when no treatment effect exists for all subjects (under the sharp null hypothesis: $Y_{X=2} = Y_{X=1}$ for all subjects). Furthermore, equation (3.3) shows that, if we know whether the treatment effect is positive or negative, we can know the sign of bias of the ITT estimate.

Likewise, it can be demonstrated that the PP estimator is generally a biased estimator of ACE, because the difference between equation (3.1) with $r = 2$ and equation (3.2) with $r = 1$ derives:

$$\text{PP} = \text{ACE} + a_2 p_{1|2} + \beta_1 p_{2|1}. \quad (3.4)$$

This equation shows that the PP estimate can be unbiased when $a_2 = 0$ and $\beta_1 = 0$, which imply that whether subjects receive the test treatment or control treatment is randomly determined (no confounder exists between X and Y). Furthermore, if we know the common sign of confounding effects (the common signs of a_r and β_r), we can know the sign of the bias of the PP estimate.

In addition to the ITT and PP estimators, the IV estimator has been developed (Cuzick et al., 1997; Greenland, 2000; Hernán & Robins, 2006). The estimate is calculated by the following formula:

$$\text{IV} \equiv \{\text{E}(Y \mid R = 2) - \text{E}(Y \mid R = 1)\}/(p_{2|2} - p_{2|1})$$

for $p_{2|2} \neq p_{2|1}$. Although the IV estimator may yield a less biased estimate of ACE, it is also generally biased. This is because the IV estimator is expressed using bias factors as follows (Chiba, 2010a):

$$\text{IV} = \text{ACE} - w_1(a_1 - \beta_1) + w_2(a_2 - \beta_2), \quad (3.5)$$

where $w_r = p_{1|r}p_{2|r}/(p_{2|2} - p_{2|1})$ and $p_{2|2} \neq p_{2|1}$. Thus, the IV estimate can be unbiased when $a_r = \beta_r$, i.e., $\text{E}(Y_{X=2} - Y_{X=1} \mid X = 2, R = r) = \text{E}(Y_{X=2} - Y_{X=1} \mid X = 1, R = r)$. Similar to the ITT estimate, the IV estimate can also be unbiased when no treatment effect exists for all subjects (under the sharp null hypothesis: $Y_{X=2} = Y_{X=1}$ for all subjects). Additionally, the IV estimate can be unbiased even when $\text{E}(Y_{X=2} - Y_{X=1} \mid X = x, R = 2) = \text{E}(Y_{X=2} - Y_{X=1} \mid X = x, R = 1)$ (Robins, 1989).

Furthermore, as an alternative to the IV estimator, Chiba (2010b) proposed the following estimator of ACE:

$$\text{IV}' \equiv (E_{22}p_{1|1} + E_{12}p_{2|1} - E_{21}p_{1|2} - E_{11}p_{2|2})/(p_{2|2} - p_{2|1}).$$

This estimator is also generally a biased estimator of ACE, and the estimate can be unbiased under $a_1 = a_2$ and $\beta_1 = \beta_2$, which may be reasonable when the influence of confounding between X and Y is equal in both assigned groups.

4. Bounds on average causal effect

In randomized trials with noncompliance by switching the treatment, we cannot generally estimate ACE in an unbiased manner (Section 3). Thus, in this section, we discuss bounds on ACE. We introduce the bounds under some assumptions in Section 4.1, and illustrate them by using data from a classic randomized trial in Section 4.2. The derivations of inequalities in this section are outlined in Section 8.2.

4.1 Assumptions and bounds

In Section 4.1.1, we introduce bounds on ACE under Assumption 1 only. Because the bounds generally have a broad width, we present the bounds with narrower widths by adding some plausible assumptions in Sections 4.1.2 and 4.1.3.

4.1.1 The instrumental variable

When the outcome Y has a finite range $[K_0, K_1]$, the bounds on ACE under Assumption 1 are as follows (Robins, 1989; Manski, 1990):

$$\begin{aligned}\max\begin{Bmatrix}K_0p_{1|1}+E_{21}p_{2|1}\\K_0p_{1|2}+E_{22}p_{2|2}\end{Bmatrix}-\min\begin{Bmatrix}E_{11}p_{1|1}+K_1p_{2|1}\\E_{12}p_{1|2}+K_1p_{2|2}\end{Bmatrix}\\ \le \mathrm{ACE} \le \min\begin{Bmatrix}K_1p_{1|1}+E_{21}p_{2|1}\\K_1p_{1|2}+E_{22}p_{2|2}\end{Bmatrix}-\max\begin{Bmatrix}E_{11}p_{1|1}+K_0p_{2|1}\\E_{12}p_{1|2}+K_0p_{2|2}\end{Bmatrix}.\end{aligned} \tag{4.1}$$

Note that $K_0 = 0$ and $K_1 = 1$ in the case of a binary outcome. Furthermore, using a method of linear programming in the case of a binary outcome, Balke and Pearl (1997) presented the following bounds under Assumption 1 only:

$$\max\begin{Bmatrix}P_{12|2}+P_{01|1}-1\\P_{12|1}+P_{01|2}-1\\P_{12|1}-P_{12|2}-P_{11|2}-P_{02|1}-P_{11|1}\\P_{12|2}-P_{12|1}-P_{11|1}-P_{02|2}-P_{11|2}\\-P_{02|2}-P_{11|2}\\-P_{02|1}-P_{11|1}\\P_{01|2}-P_{02|2}-P_{11|2}-P_{02|1}-P_{21|1}\\P_{01|1}-P_{02|1}-P_{11|1}-P_{02|2}-P_{01|2}\end{Bmatrix} \le \mathrm{ACE} \le \min\begin{Bmatrix}1-P_{02|2}+P_{11|1}\\1-P_{02|1}+P_{11|2}\\P_{02|2}+P_{01|2}+P_{12|1}+P_{01|1}-P_{02|1}\\P_{12|2}+P_{01|2}+P_{02|1}+P_{01|1}-P_{02|2}\\P_{12|2}+P_{01|2}\\P_{12|1}+P_{01|1}\\P_{12|2}+P_{01|2}+P_{02|1}+P_{12|1}-P_{11|1}\\P_{12|1}+P_{01|1}+P_{12|2}+P_{11|2}-P_{11|1}\end{Bmatrix}, \tag{4.2}$$

where $P_{yx|r} = \Pr(Y = y, X = x \mid R = r)$ $(y = 0, 1)$. Inequality (4.2), which is the bounds on ACE having the narrowest width without adding any other assumptions, gives bounds with a narrower width than inequality (4.1) in some situations. However, these bounds generally have broad widths. Thus, in Sections 4.1.2 and 4.1.3, we derive bounds with narrower widths by adding some plausible assumptions.

4.1.2 The monotone treatment response

To derive narrower bounds, Manski (1997) presented the following monotone treatment response (MTR) assumption:

ASSUMPTION 2.1: Monotone treatment response (MTR)
$Y_{X=s} \ge Y_{X=t}$ *for all subjects, where* $s \ge t$.

For $(s, t) = (2, 1)$, the MTR means that a subject takes a larger outcome value if he/she received the test treatment than if he/she received the control. This holds when it is apparent that the test treatment has a positive effect.
Under Assumptions 1 and 2.1, the lower bound on ACE is improved as follows:

$$\mathrm{ACE} \ge \max\{\mathrm{ITT}, -\mathrm{ITT}\}. \tag{4.3}$$

Thus, we can say that ACE is not less than the ITT estimate when the MTR holds. Note that the second and third terms in equation (3.3) are not less than 0 under the MTR, because $E(Y_{X=2} \mid X = x, R = r) \geq E(Y_{X=1} \mid X = x, R = r)$, i.e., $a_2 \geq E_{22} - E_{12}$ and $\beta_1 \geq E_{21} - E_{11}$, hold under the MTR.
Using the reverse sign of the inequality in Assumption 2.1, the following reverse MTR (RMTR) assumption can be applied:

ASSUMPTION 2.2: Reverse monotone treatment response (RMTR)
$Y_{X=s} \leq Y_{X=t}$ *for all subjects, where* $s \geq t$.

In contrast to the MTR, for $(s, t) = (2, 1)$, the RMTR means that a subject takes a smaller outcome value if he/she received the test treatment than if he/she received the control. This holds when it is apparent that the test treatment has a negative effect. Under Assumptions 1 and 2.2, the upper bound on ACE is improved as ACE ≤ min{ITT, –ITT}, implying that ACE is not more than the ITT estimate when the RMTR holds.
Assumptions 2.1 and 2.2 are very strict assumptions, because the inequalities must hold for all subjects. In the case of a binary outcome variable, we can use an alternative assumption that is weaker than Assumptions 2.1 and 2.2, but can derive the same bound as those under these assumptions. This is introduced below after the concept of principal stratification (Frangakis & Rubin, 2002).
Based on principal stratification, four types of potential outcomes are defined as follows: doomed $\{Y_{X=2} = 1, Y_{X=1} = 1\}$, which consists of subjects who always experience the event, regardless of the treatment received; preventive $\{Y_{X=2} = 0, Y_{X=1} = 1\}$, which consists of subjects who do not experience the event when they receive the test treatment but do when they receive the control; causative $\{Y_{X=2} = 1, Y_{X=1} = 0\}$, which consists of subjects who experience the event when they receive the test treatment, but not when they receive the control; and immune $\{Y_{X=2} = 0, Y_{X=1} = 0\}$, which consists of subjects who never experience the event, regardless of the treatment received (Greenland & Robins, 1986). Because X and Y are binary, the potential outcomes could be any of these four types. Note that Assumption 2.1 implies that no preventive subject exists: $\Pr(Y_{X=2} = 0, Y_{A=1} = 1) = 0$, because $Y_{X=2} = 0$ and $Y_{X=1} = 1$ cannot hold simultaneously under $Y_{X=2} \geq Y_{X=1}$. Likewise, Assumption 2.2 implies that no causative subject exists.
We can obtain inequality (4.3) even under the following assumption (Chiba, 2011):

ASSUMPTION 3.1
$$\Pr(Y_{X=2} = 1, Y_{X=1} = 0 \mid X = x, R = r) \geq \Pr(Y_{X=2} = 0, Y_{X=1} = 1 \mid X = x, R = r).$$

This assumption indicates that the number of causative subjects is not less than the number of preventive subjects within all strata with $X = x$ and $R = r$. Thus, Assumption 3.1 is weaker than Assumption 2.1, because Assumption 2.1 requires that no preventive subject exists but this is not the case for Assumption 3.1.
Likewise, the following assumption, 3.2, can derive the same upper bound as that under Assumption 2.2:

ASSUMPTION 3.2
$$\Pr(Y_{X=2} = 1, Y_{X=1} = 0 \mid X = x, R = r) \leq \Pr(Y_{X=2} = 0, Y_{X=1} = 1 \mid X = x, R = r).$$

In contrast to Assumption 3.1, this assumption implies that the number of causative subjects is not more than the number of preventive subjects within all strata with $X = x$ and $R = r$. Again, note that Assumption 2.2 implies that no causative subject exists and thus Assumption 3.2 is a weaker assumption than Assumption 2.2.

4.1.3 The monotone treatment selection

The other assumption to derive narrower bounds is the following monotone treatment selection assumption (Manski & Pepper, 2000; Chiba, 2010c):

ASSUMPTION 4.1: Monotone treatment selection (MTS)
$\mathrm{E}(Y_{X=x} \mid X = s, R = r) \geq \mathrm{E}(Y_{X=x} \mid X = t, R = r)$ *for* $s \geq t$.

For $(s, t) = (2, 1)$, the MTS means that subjects who received the test treatment tend to have larger outcome values than those who received the control within each study treatment-arm subpopulation. For example, when patients with a worse condition prefer to receive the new treatment ($X = 2$), it should be anticipated that the incidence proportion of a bad event ($Y = 1$) such as death will be higher, compared with those who receive the standard treatment ($X = 1$); this indicates that the MTS holds.

Under Assumptions 1 and 4.1, the upper bound on ACE is improved as follows:

$$\mathrm{ACE} \leq \min\{E_{21}, E_{22}\} - \max\{E_{11}, E_{12}\}. \tag{4.4}$$

Specifically, when $\min\{E_{21}, E_{22}\} = E_{22}$ and $\max\{E_{11}, E_{12}\} = E_{11}$, the upper bound is equal to the PP estimator. Thus, ACE is no more than the PP estimate when the MTS holds. Note that this is also verified from equation (3.4) because Assumption 4.1 implies that $a_r \geq 0$ and $\beta_r \geq 0$.

Similar to the RMTR, the following reverse MTS (RMTS) assumption can be applied:

ASSUMPTION 4.2: Reverse monotone treatment selection (RMTS)
$\mathrm{E}(Y_{X=x} \mid X = s, R = r) \leq \mathrm{E}(Y_{X=x} \mid X = t, R = r)$ *for* $s \geq t$.

In contrast to the MTS, for $(s, t) = (2, 1)$, the RMTS means that subjects who received the test treatment tend to have smaller outcome values than those who received the control within each study treatment-arm subpopulation. The lower bound on ACE under the RMTS is $\mathrm{ACE} \geq \max\{E_{21}, E_{22}\} - \min\{E_{11}, E_{12}\}$, implying that ACE is not less than the PP estimate when the RMTS holds.

It is obvious that the combination of Assumptions 2.1 and 4.1 improves both the lower and upper bounds:

$$\max\{\mathrm{ITT}, -\mathrm{ITT}\} \leq \mathrm{ACE} \leq \min\{E_{21}, E_{22}\} - \max\{E_{11}, E_{12}\}.$$

Likewise, under the combination of Assumptions 2.2 and 4.2, bounds on ACE are

$$\max\{E_{21}, E_{22}\} - \min\{E_{11}, E_{12}\} \leq \mathrm{ACE} \leq \min\{\mathrm{ITT}, -\mathrm{ITT}\}. \tag{4.5}$$

These inequalities show that ACE exists between ITT and PP estimates under these combinations of assumptions.

By extending a theory developed in the context of observational studies (VanderWeele, 2008a; Chiba, 2009a), Chiba (2009b) presented another assumption that derives the same upper bound as that under the MTS (Assumption 4.1):

ASSUMPTION 5.1: Monotone confounding (MC)
Both $\mathrm{E}(Y \mid X = 2, R = r, Z = z)$ *and* $\Pr(X = 2 \mid R = r, Z = z)$ *are non-decreasing or non-increasing in z for all r, and the components of Z are independent of each other.*

For an assumption corresponding to the RMTS (Assumption 4.2), Assumption 5.1 is changed as follows:

ASSUMPTION 5.2: Reverse monotone confounding (RMC)
One of $E(Y \mid X = 2, R = r, Z = z)$ *and* $\Pr(X = 2 \mid R = r, Z = z)$ *is non-decreasing and the other is non-increasing in z for all r, and the components of Z are independent of each other.*

Although the MTS and MC (RMTS and RMC) give the same upper (lower) bound on ACE, the relationship between them has not been clear. In Section 8.2, we demonstrate that the MC implies the MTS, but it is unclear whether the converse holds.

4.2 Application

For illustration, the assumptions and bounds presented in this section are applied to data from the Multiple Risk Factor Intervention Trial (MRFIT) (MRFIT Research Group, 1982). The MRFIT was a large field trial to test the effect of a multifactorial intervention program on mortality from coronary heart disease (CHD) in middle-aged men with sufficiently high risk levels attributed to cigarette smoking, high serum cholesterol, and high blood pressure. Intervention consisted of dietary advice on ways to reduce blood cholesterol, smoking cessation counseling, and hypertension medication. All subjects were randomly assigned to the intervention program or the control group.

For this illustration, attention is restricted to the effects of cessation of cigarette smoking. This restriction follows other studies (Mark & Robins, 1993; Matsui, 2005; Chiba, 2010a) and was applied due to the paucity of differences achieved for the other risk factors. Table 2 summarizes the incidence of subject mortality due to CHD during the 7-year follow-up period based on the assigned treatment and the actual subject smoking status 1 year after study entry. R represents the assigned group ($R = 2$ for the test group and $R = 1$ for the control group), X is the actual smoking status 1 year after entry ($X = 2$ for smoking cessation and $X = 1$ for continued smoking), and Y is the incidence of CHD deaths ($Y = 1$ for dead and $Y = 0$ for alive). ITT and PP analyses yielded ITT = 69/3833 – 74/3830 = −0.13% and PP = 11/991 – 70/3456 = −0.92%, respectively. IV and IV′ estimates were −0.82% and −0.72%, respectively.

Group	No. of subjects	CHD deaths	Smoking status at 1 year	No. of subjects	CHD deaths
Test	3833	69	Quit	991	11
			Not quit	2842	58
Control	3830	74	Quit	374	4
			Not quit	3456	70
Totals	7663	143			

Table 2. The status of cigarette smoking and the incidence of mortality due to CHD in the MRFIT during a 7-year follow-up period.

To derive the ACE bounds, it is necessary to discuss whether the assumptions in this section hold. It is clear that cessation of cigarette smoking prevents death from CHD. Thus, Assumption 2.2 (RMTR: $Y_{X=2} \leq Y_{X=1}$ for all subjects) holds (i.e., no causative subject, who died when they quit smoking but lived when they continued smoking, exists). However, it is possible that such subjects do exist, because the stress of quitting smoking might lead to CHD and this stress would have been lower if the subject had continued smoking (i.e., a causative subject existed). Under this observation, Assumption 2.2 does not hold. However, Assumption 3.2 would still hold, because even if a few causative subjects exist, the number would be the smallest in the four principal strata.

In general, health-conscious individuals may tend not to die from CHD and quit smoking compared with individuals who are not health-conscious. Trial subjects would likely have had similar tendencies, and subjects who quit smoking would logically tend not to have died from CHD. Therefore, it is considered that Assumption 4.2 (RMTS: $E(Y_{X=x} \mid X = 2, R = r) \leq E(Y_{X=x} \mid X = 1, R = r)$ for $x = 1, 2$ and $r = 1, 2$) is valid. Although Assumption 1 may not hold because this trial was an unblinded trial (the details are discussed in Section 6), we here use this assumption for illustrative purposes.

The arguments presented above demonstrate that Assumptions 3.2 and 4.2 can be assumed. Thus, from inequality (4.5), the bounds on ACE become $-0.92\% \leq \text{ACE} \leq -0.13\%$. This result indicates that quitting smoking would prevent death from CHD. Note that the bounds under Assumption 1 only become $-11.31\% \leq \text{ACE} \leq 72.60\%$, where inequalities (4.1) and (4.2) yield the same bounds. While the bounds under Assumption 1 only do not give enough information about ACE, adding Assumptions 3.2 and 4.2 greatly improves the bounds.

5. Noncompliance by receiving no treatment

While noncompliance by switching the treatment was discussed in Sections 3 and 4, this section discusses noncompliance by receiving no treatment, which means that non-compliers receive no treatment. In this type of noncompliance, subjects who are allocated to $R = 2$ take the value of $X = 0$ or 2 (and not $X = 1$) and those who are allocated to $R = 1$ take the value of $X = 0$ or 1 (and not $X = 2$). Thus, $p_{0|2} + p_{2|2} = 1$ and $p_{0|1} + p_{1|1} = 1$. The derivations of equations and inequalities in this section are similar to those in Sections 3 and 4, and can be achieved straightforwardly by replacing $x = 1, 2$ in Sections 3 and 4 to $x = 0, 1$ and $x = 0, 2$. Thus, they are omitted.

5.1 Biases of estimates

By following a similar discussion to Section 3, we show that the ITT and PP estimators generally yield biased estimates of ACE. Unfortunately, the IV estimator cannot be defined in this type of noncompliance.

To express the biases of ITT and PP estimators, we introduce the following bias factors instead of a_r and β_r in Section 3:

$$\gamma \equiv E(Y_{X=2} \mid X = 2, R = 2) - E(Y_{X=2} \mid X = 0, R = 2),$$

$$\delta \equiv E(Y_{X=1} \mid X = 1, R = 1) - E(Y_{X=1} \mid X = 0, R = 1).$$

Similar to a_r and β_r, γ and δ are also confounding effects. γ is interpreted as a confounding effect that would arise from comparisons of those with $X = 2$ versus those with $X = 0$ for the test treatment group. When $\gamma > 0$, $E(Y_{X=2} \mid X = 2, R = 2) > E(Y_{X=2} \mid X = 0, R = 2)$, which means that the subjects who received the test treatment tend to take larger outcome values than those who received no treatment. Conversely, when $\gamma < 0$, $E(Y_{X=2} \mid X = 2, R = 2) < E(Y_{X=2} \mid X = 0, R = 2)$, which means that the subjects who received the test treatment tend to take smaller outcome values than those who received no treatment. Whether subjects in the test treatment group actually receive the treatment is randomly determined when $\gamma = 0$. δ is interpreted using a similar process in the control group.

Biases of ITT and PP estimators can be explained in a similar manner to Section 3, using γ and δ. Because $E(Y_{X=2})$ and $E(Y_{X=1})$ are expressed as $E(Y_{X=2}) = E_{22} - \gamma p_{0|2}$ and $E(Y_{X=1}) = E_{11} - \delta p_{0|1}$, the ITT estimator is given by:

$$\text{ITT} = \text{ACE} + \{\gamma - (E_{22} - E_{02})\}p_{0|2} - \{\delta - (E_{11} - E_{01})\}p_{0|1}.$$

Therefore, the ITT estimator is generally a biased estimator of ACE, and can be unbiased when $\gamma = E_{22} - E_{02}$ and $\delta = E_{11} - E_{01}$, i.e., $\text{E}(Y_{X=r} \mid X = 0, R = r) = \text{E}(Y_{X=0} \mid X = 0, R = r)$ for $r = 1, 2$. This equation indicates that the ITT estimate can be unbiased when no effect of the treatments exists against no treatment for all subjects (under the sharp null hypothesis: $Y_{X=x} = Y_{X=0}$ for all subjects, where $x = 1, 2$).
The PP estimator is given by:

$$\text{PP} = \text{ACE} + \gamma p_{0|2} - \delta p_{0|1}.$$

Thus, the PP estimate can be unbiased when $\gamma = 0$ and $\delta = 0$, implying that whether subjects receive the assigned treatment is randomly determined (no confounder exists between X and Y).
In contrast to the case of noncompliance by switching the treatment, it may be difficult to know the signs of biases of ITT and PP estimates.

5.2 Bounds on average causal effect

We extend the bounds concept introduced in Section 4.1 to the case of noncompliance by receiving no treatment.
The bounds under Assumption 1 only are as follows:

$$(E_{22}p_{2|2} + K_0p_{0|2}) - (E_{11}p_{1|1} + K_1p_{0|1}) \le \text{ACE} \le (E_{22}p_{2|2} + K_1p_{0|2}) - (E_{11}p_{1|1} + K_0p_{0|1}), \quad (5.1)$$

where $[K_0, K_1]$ is a finite range of outcome Y. In the case of a binary outcome, this inequality is simplified to:

$$P_{12|2} + P_{01|1} - 1 \le \text{ACE} \le 1 - P_{02|2} - P_{11|1}.$$

As in Section 4.1, the MTR and MTS assumptions and these reverse assumptions can be applied to obtain bounds on ACE with narrower widths. For example, for $(s, t) = (2, 0)$, Assumption 2.1 is $Y_{X=2} \ge Y_{X=0}$, which means that a subject takes a larger outcome value if he/she received the test treatment than if he/she received no treatment. This holds when it is apparent that the test treatment has a positive effect compared with no treatment. The similar interpretation is given for $(s, t) = (1, 0)$ ($Y_{X=1} \ge Y_{X=0}$) in place of the test treatment to the control.
Under Assumptions 1 and 2.1, the lower bound of $\text{E}(Y_{X=x})$ becomes $\text{E}(Y_{X=x}) \ge \text{E}(Y \mid R = x)$ for $x = 1, 2$, which is derived using $t = 0$ in Assumption 2.1. Likewise, $\text{E}(Y_{X=x}) \le \text{E}(Y \mid R = x)$ under Assumptions 1 and 2.2. Although these bounds of $\text{E}(Y_{X=x})$ do not give a bound on ACE in contrast to that in Section 4.1.2, Assumption 2.1 can derive the following bounds by combination with inequality (5.1)[1]:

$$\text{E}(Y \mid R = 2) - (E_{11}p_{1|1} + K_1p_{0|1}) \le \text{ACE} \le (E_{22}p_{2|2} + K_1p_{0|2}) - \text{E}(Y \mid R = 1).$$

Similar to Assumptions 3.1 and 3.2, in the case of a binary outcome variable, we can make weaker assumptions that derive the same bounds as those under Assumptions 2.1 and 2.2, using the principal stratification approach. In the case of noncompliance by receiving no treatment, four types of potential outcomes, based on principal stratification, are re-

[1] If $(s, t) = (2, 1)$ in Assumption 2.1 is used as in Section 4.1, the lower bound on ACE is improved to 0.

defined as follows: doomed $\{Y_{X=x} = 1, Y_{X=0} = 1\}$, which consists of subjects who always experience the event, regardless of whether they receive the assigned treatment; preventive $\{Y_{X=x} = 0, Y_{X=0} = 1\}$, which consists of subjects who do not experience the event when they receive the assigned treatment but do when they receive no treatment; causative $\{Y_{X=x} = 1, Y_{X=0} = 0\}$, which consists of subjects who experience the event when they receive the assigned treatment, but not when they receive no treatment; and immune $\{Y_{X=x} = 0, Y_{X=0} = 0\}$, which consists of subjects who never experience the event, regardless of whether they receive the assigned treatment. In the definition, $x = 2$ for the test treatment group ($R = 2$) and $x = 1$ for the control group ($R = 1$). Similar to Section 4.1.2, Assumption 2.1 implies that no preventive subject exists, and Assumption 2.2 implies that no causative subject exists.

Under this definition of principal strata, alternative assumptions of Assumptions 2.1 and 2.2 are as follows:

ASSUMPTION 3.3

$$\Pr(Y_{X=x} = 1, Y_{X=0} = 0 \mid X = R = x) \geq \Pr(Y_{X=x} = 0, Y_{X=0} = 1 \mid X = R = x) \text{ for } x = 1, 2.$$

ASSUMPTION 3.4

$$\Pr(Y_{X=x} = 1, Y_{X=0} = 0 \mid X = R = x) \leq \Pr(Y_{X=x} = 0, Y_{X=0} = 1 \mid X = R = x) \text{ for } x = 1, 2.$$

Assumption 3.3 implies that the number of causative subjects is not less than the number of preventive subjects, and Assumption 3.4 implies that the number of causative subjects is not more than the number of preventive subjects, within both assigned groups. Thus, these Assumptions are weaker than assumptions 2.1 and 2.2. Nevertheless, they can give the same bounds as those under Assumptions 2.1 and 2.2.

The MTS and RMTS (Assumptions 4.1 and 4.2) can also be applied to the case of noncompliance by receiving no treatment. For example, for $(s, t) = (2, 0)$ and $r = 2$, Assumption 4.1 is $\mathrm{E}(Y_{X=x} \mid X = 2, R = 2) \geq \mathrm{E}(Y_{X=x} \mid X = 0, R = 2)$, which means that subjects who received the assigned test treatment (i.e., compliers) tend to have larger outcome values than those who received no treatment (i.e., non-compliers) for the test treatment group. Under Assumptions 1 and 4.1, the upper bound of $\mathrm{E}(Y_{X=x})$ becomes $\mathrm{E}(Y_{X=x}) \geq E_{xx}$ ($\mathrm{E}(Y_{X=x}) \leq E_{xx}$ under Assumptions 1 and 4.2) for $x = 1, 2$. Thus, the combination with inequality (5.1) derives bounds on ACE of:

$$(E_{22}p_{2|2} + K_0p_{0|2}) - E_{11} \leq \mathrm{ACE} \leq E_{22} - (E_{11}p_{1|1} + K_0p_{0|1}).$$

When both MTR and MTS hold, the bounds on ACE are:

$$\mathrm{E}(Y \mid R = 2) - E_{11} \leq \mathrm{ACE} \leq E_{22} - \mathrm{E}(Y \mid R = 1),$$

because $\mathrm{E}(Y \mid R = x) \leq \mathrm{E}(Y_{X=x}) \leq E_{xx}$ for $x = 1, 2$. When both RMTR and RMTS hold, these signs of inequalities for $\mathrm{E}(Y_{X=x})$ are reversed.

Finally, we note that the MC and RMC (Assumptions 5.1 and 5.2), which derive the same bounds as those under the MTS and RMTS (Assumptions 4.1 and 4.2), are changed as follows for the case of noncompliance by receiving no treatment:

ASSUMPTION 5.3: Monotone confounding (MC)

Both $\mathrm{E}(Y \mid X = R = x, Z = z)$ *and* $\Pr(X = x \mid R = x, Z = z)$ a*re non-decreasing or non-increasing in* z *for* $x = 1, 2$ *and all* r*, and the components of* Z *are independent of each other.*

ASSUMPTION 5.4: Reverse monotone confounding (RMC)
One of $\mathrm{E}(Y \mid X = R = x, Z = z)$ *and* $\Pr(X = x \mid R = x, Z = z)$ *is non-decreasing and the other is non-increasing in z for* $x = 1, 2$ *and all r, and the components of Z are independent of each other.*

In some actual situations, assumptions presented in this section may hold for one of the test treatment and control groups but not for the other. In such cases, the assumptions can be applied only to one group. This example is introduced in the next sub-section.

5.3 Application

We apply the assumptions and bounds presented in Section 5.2 to the CDP trial introduced in Section 1 (Table 1). R represents the assigned group ($R = 2$ for the clofibrate group and $R = 1$ for the placebo group), and X is the compliance status ($X = 2$ for compliers in the clofibrate group, $X = 1$ for compliers in the placebo group, and $X = 0$ for non-compliers). Here, compliers and non-compliers are patients receiving more or less than 80% of the assigned treatment, respectively. Y is the incidence of deaths ($Y = 1$ for dead and $Y = 0$ for alive). Again, we note that ITT and PP analyses yielded ITT = 194/1065 – 523/2695 = –1.19% and PP = 106/708 – 274/1813 = –0.14%, respectively.

As in Section 4.3, it is necessary to discuss whether the assumptions hold. There may be a placebo effect, but it is not thought that the proportion of deaths will increase by receiving the placebo. Thus, Assumptions 2.2 (RMTR) and 3.4 can be assumed for $(s, t) = (1, 0)$ and $x = 1$. However, a preventive effect of clofibrate may not be present (i.e., these assumptions may not be assumed for $(s, t) = (2, 0)$ and $x = 2$) because of side-effects. The World Health Organization (WHO) has reported that in a large randomized trial, there were 25% more deaths in the clofibrate group than in the comparable high serum cholesterol control group (WHO, 1980). Because it is not clear whether the clofibrate has a positive or negative effect, we cannot assume the MTR or RMTR (and Assumption 3.3 or 3.4) for the clofibrate group.

Relating to the patients in this trial, health-oriented subjects might tend not to die and be more likely to comply with the assigned treatment, compared with subjects not concerned about their health. Under this observation, the RMTS (Assumption 4.4) would hold for both assigned groups. However, we note that some researchers may criticize this because some patients might not receive the treatment due to side-effects. In such a case, the RMTS may not hold for the clofibrate group. Nevertheless, we assume the RMTS for both assigned groups for illustrative purposes. Assumption 1 would hold because this trial was a double-blinded trial.

The arguments presented above demonstrate that the RMTR and RMTS can be assumed for the placebo group. Therefore, the bounds of $\mathrm{E}(Y_{X=1})$ are $E_{11} \le \mathrm{E}(Y_{X=1}) \le \mathrm{E}(Y \mid R = 1)$, which yield $15.11\% \le \mathrm{E}(Y_{X=1}) \le 19.41\%$. For the clofibrate group, the RMTS is assumed and then the bounds of $\mathrm{E}(Y_{X=2})$ are $E_{22} \le \mathrm{E}(Y_{X=2}) \le E_{22}p_{2|2} + K_1 p_{0|2}$ for $K_1 = 1$, which yields $14.97\% \le \mathrm{E}(Y_{X=2}) \le 43.47\%$. In conclusion, the bounds on ACE are $-4.43\% \le \mathrm{ACE} \le 28.36\%$. Unfortunately, we cannot conclude whether clofibrate is effective. However, the bounds improve those under Assumption 1 only: $-32.94\% \le \mathrm{ACE} \le 33.31\%$, especially the lower bound.

6. Monotone instrumental variable

Sections 3-5 assumed the IV assumption (Assumption 1). As mentioned in Section 2, however, this assumption often may not hold in unblinded trials, in which subjects are aware of the assigned treatment and this knowledge may affect the potential outcomes. In the MRFIT (Section 4.3), subjects would have been aware of their assigned group because it was an unblinded trial, and thus the intervention itself might have evoked a psychological

response. Furthermore, in addition to smoking cessation counseling, the intervention consisted of dietary advice to reduction blood cholesterol and hypertension medication. These interventions might also have influenced the incidence of CHD independent of smoking status. Thus, in this section, we relax the IV assumption to the following monotone instrumental variable (MIV) assumption (Manski & Pepper, 2000, 2009):

ASSUMPTION 6.1: Monotone instrumental variable (MIV)
$$\mathrm{E}(Y_{X=x} \mid R = 2) \geq \mathrm{E}(Y_{X=x} \mid R = 1).$$

The MIV assumption is only the replacement of equality in the IV assumption with inequality, and means that the values of potential outcomes for subjects assigned to $R = 2$ are overall larger than those assigned to $R = 1$. For example, consider an unblinded trial to compare a new treatment with a standard treatment, where the outcome is a measure such that a larger value is better for the subject's health. In such a trial, subjects may think that the new treatment is more effective than the standard treatment, and this thinking may give rise to better results for subjects assigned to the new treatment than those assigned to the standard treatment; this indicates that the MIV holds.
We can also consider the following reverse MIV (RMIV) assumption:

ASSUMPTION 6.2: Reverse monotone instrumental variable (RMIV)
$$\mathrm{E}(Y_{X=x} \mid R = 2) \leq \mathrm{E}(Y_{X=x} \mid R = 1).$$

We discuss the bounds on ACE under Assumptions 6.1 and 6.2 instead of Assumption 1. Noncompliance by switching the treatment (as in Sections 4) is discussed in Section 6.1, and noncompliance by receiving no treatment (as in Section 5) is discussed in Section 6.2. The derivations of inequalities in this section are outlined in Section 8.3.

6.1 Noncompliance by switching the treatment

The bounds introduced in Section 4 are extended to those under the MIV and RMIV (Assumptions 6.1 and 6.2). Under the MIV and RMIV, the bounds on ACE are:

$$(E_{21}p_{2|1} + K_0p_{1|1}) - (E_{12}p_{1|2} + K_1p_{2|2}) \leq \mathrm{ACE} \leq (E_{22}p_{2|2} + K_1p_{1|2}) - (E_{11}p_{1|1} + K_0p_{2|1}), \quad (6.1)$$

$$(E_{22}p_{2|2} + K_0p_{1|2}) - (E_{11}p_{1|1} + K_1p_{2|1}) \leq \mathrm{ACE} \leq (E_{21}p_{2|1} + K_1p_{1|1}) - (E_{12}p_{1|2} + K_0p_{2|2}). \quad (6.2)$$

These inequalities correspond to inequalities when a or b in $\max\{a, b\}$ and $\min\{a, b\}$ in inequality (4.1) are used. Therefore, the MIV and RMIV assumptions yield bounds on ACE with the same or broader width in comparison with the bounds under the IV assumption.
Even under the MIV (or RMIV) assumption, but not IV assumption, we can derive bounds on ACE with narower widths by applying assumptions in Section 4.2 (Chiba, 2010c). Each combination of the MIV or RMIV and the MTR or RMTR derives the improved lower or upper bounds on ACE in Table 3. Likewise, each combination of the MIV or RMIV and the MTS or RMTS derives the improved lower or upper bounds on ACE in Table 4.

Assumptions	Improved bound on ACE
MIV + MTR	$\mathrm{ACE} \geq \max\{-\mathrm{ITT}, 0\}$
RMIV + MTR	$\mathrm{ACE} \geq \max\{\mathrm{ITT}, 0\}$
MIV + RMTR	$\mathrm{ACE} \leq \min\{\mathrm{ITT}, 0\}$
RMIV + RMTR	$\mathrm{ACE} \leq \min\{-\mathrm{ITT}, 0\}$

Table 3. Improved bound on ACE under the MIV or RMIV and the MTR or RMTR, where $\mathrm{ITT} \equiv \mathrm{E}(Y \mid R = 2) - \mathrm{E}(Y \mid R = 1)$.

Assumptions	Improved bound on ACE
MIV + MTS	ACE ≤ $E_{22} - E_{11}$
RMIV + MTS	ACE ≤ $E_{21} - E_{12}$
MIV + RMTS	ACE ≥ $E_{21} - E_{12}$
RMIV + RMTS	ACE ≥ $E_{22} - E_{11}$

Table 4. Improved bound on ACE under the MIV or RMIV and the MTS or RMTS.

Eight lower or upper bounds in Tables 3 and 4 yield the same or broader bounds as those under the IV assumption. Note that we can use Assumptions 3.1 and 3.2 instead of the MTR and RMTR (Assumptions 2.1 and 2.2), respectively, and Assumptions 5.1 and 5.2 instead of the MTS and RMTS (Assumptions 4.1 and 4.2), respectively. Further combinations of the above bounds can derive further improved bounds; for example, max{−ITT, 0} ≤ ACE ≤ PP under the MIV, MTR and MTS assumptions.

For illustration, we apply the bounds presented here to the MRFIT (Table 2), in which the IV assumption may not hold, as discussed above. Because the intervention consisted of dietary advice and hypertension medication as well as the therapy itself that might have evoked a psychological response, the potential incidence of CHD for subjects assigned to the test group might have been reduced, compared with subjects assigned to the control group. This observation shows that Assumption 6.2 (RMIV: $E(Y_{X=x} | R = 2) \leq E(Y_{X=x} | R = 1)$) is reasonable. Additionally, as discussed in Section 4.3, the RMTR (or Assumption 3.2) and RMTS are reasonable assumptions in this trial. In conclusion, the RMIV, RMTR and RMTS can be assumed, and then bounds on ACE become PP ≤ ACE ≤ min{−ITT, 0}, which yield −0.92% ≤ ACE ≤ 0%. In comparison with the IV (plus RMTR and RMTS) in Section 4.2 (−0.92% ≤ ACE ≤ −0.13%), the lower bound is the same but the upper bound is larger.

6.2 Noncompliance by receiving no treatment

The bounds introduced in Section 5 are extended to those under the MIV and RMIV (Assumptions 6.1 and 6.2). Under these assumptions, the bounds on ACE are:

$$K_0 - K_1 \leq \text{ACE} \leq (E_{22}p_{2|2} + K_1 p_{0|2}) - (E_{11}p_{1|1} + K_0 p_{0|1}), \tag{6.3}$$

$$(E_{22}p_{2|2} + K_0 p_{0|2}) - (E_{11}p_{1|1} + K_1 p_{0|1}) \leq \text{ACE} \leq K_1 - K_0, \tag{6.4}$$

respectively. The upper bound in inequality (6.3) is equal to that in inequality (5.1) and the lower bound in inequality (6.4) is equal to that in inequality (5.1). Unfortunately, the respective lower and upper bounds in inequalities (6.3) and (6.4) do not give any information.

As discussed in the above sub-section, by combining the MTR (or RMTR) and MTS (or RMTS), the bounds on ACE can be improved. Table 5 summarizes the bounds under the MIV or RMIV and the MTR and RMTR, and Table 6 summarizes those under the MIV or RMIV and the MTS and RMTS. The bounds in Tables 5 and 6 include K_0 or K_1, which is the finite range of Y. Specifically, in Table 6, the lower or upper bounds are not improved even when the MTS or RMTS is added. Thus, the bounds may not be greatly improved. However, further combinations of these assumptions can remove K_0 and K_1 from one of the lower and upper bounds. Such bounds are summarized in Table 7.

Assumptions	Bounds on ACE
MIV + MTR	$\mathrm{E}(Y \mid R = 1) - (E_{22}p_{2\mid 2} + K_1 p_{0\mid 2}) \le \mathrm{ACE} \le (E_{22}p_{2\mid 2} + K_1 p_{0\mid 2}) - \mathrm{E}(Y \mid R = 1)$
RMIV + MTR	$\mathrm{E}(Y \mid R = 2) - (E_{11}p_{1\mid 1} + K_1 p_{0\mid 1}) \le \mathrm{ACE} \le K_1 - (E_{02}p_{0\mid 2} + K_0 p_{2\mid 2})$
MIV + RMTR	$K_0 - (E_{02}p_{0\mid 2} + K_1 p_{2\mid 2}) \le \mathrm{ACE} \le \mathrm{E}(Y \mid R = 2) - (E_{11}p_{1\mid 1} + K_0 p_{0\mid 1})$
RMIV + RMTR	$(E_{22}p_{2\mid 2} + K_0 p_{0\mid 2}) - \mathrm{E}(Y \mid R = 1) \le \mathrm{ACE} \le \mathrm{E}(Y \mid R = 1) - (E_{22}p_{2\mid 2} + K_0 p_{0\mid 2})$

Table 5. Bounds on ACE under the MIV or RMIV and the MTR or RMTR[2].

Assumptions	Bounds on ACE
MIV + MTS	$K_0 - K_1 \le \mathrm{ACE} \le E_{22} - (E_{11}p_{1\mid 1} + K_0 p_{0\mid 1})$
RMIV + MTS	$(E_{22}p_{2\mid 2} + K_0 p_{0\mid 2}) - E_{11} \le \mathrm{ACE} \le K_1 - K_0$
MIV + RMTS	$K_0 - K_1 \le \mathrm{ACE} \le (E_{22}p_{2\mid 2} + K_1 p_{0\mid 2}) - E_{11}$
RMIV + RMTS	$E_{22} - (E_{11}p_{1\mid 1} + K_1 p_{0\mid 1}) \le \mathrm{ACE} \le K_1 - K_0$

Table 6. Bounds on ACE under the MIV or RMIV and the MTS or RMTS.

Assumptions	Bounds on ACE
MIV + MTR + MTS	$\mathrm{E}(Y \mid R = 1) - (E_{22}p_{2\mid 2} + K_1 p_{0\mid 2}) \le \mathrm{ACE} \le E_{22} - \mathrm{E}(Y \mid R = 1)$
RMIV + MTR + MTS	$\mathrm{E}(Y \mid R = 2) - E_{11} \le \mathrm{ACE} \le K_1 - (E_{02}p_{0\mid 2} + K_0 p_{2\mid 2})$
MIV + RMTR + RMTS	$K_0 - (E_{02}p_{0\mid 2} + K_1 p_{2\mid 2}) \le \mathrm{ACE} \le \mathrm{E}(Y \mid R = 2) - E_{11}$
RMIV + RMTR + RMTS	$E_{22} - \mathrm{E}(Y \mid R = 1) \le \mathrm{ACE} \le \mathrm{E}(Y \mid R = 1) - (E_{22}p_{2\mid 2} + K_0 p_{0\mid 2})$

Table 7. Bounds on ACE under some combinations of assumptions[3].

For illustration, we apply the bounds presented here to the CDP trial (Table 1). Although the IV (Assumption 1) would hold in this trial because it was a double-blinded trial, we here relax this assumption to the MIV and RMIV (Assumptions 6.1 and 6.2), and yield bounds on ACE under both assumptions. As discussed in Section 5.3, we assume the RMTS for the clofibrate group and the RMTR and RMTS for the placebo group. Then, under the MIV, the bounds of $\mathrm{E}(Y_{X=2})$ and $\mathrm{E}(Y_{X=1})$ are $K_0 \le \mathrm{E}(Y_{X=2}) \le E_{22}p_{2\mid 2} + K_1 p_{0\mid 2}$ and $E_{11} \le \mathrm{E}(Y_{X=1}) \le E_{02}p_{0\mid 2} + K_1 p_{2\mid 2}$, respectively, where $K_0 = 0$ and $K_1 = 1$ because Y is binary. These bounds yield bounds on ACE of $-74.74\% \le \mathrm{ACE} \le 28.36\%$. Likewise, under the RMIV, the bounds on ACE become $-4.43\% \le \mathrm{ACE} \le 90.05\%$, because $E_{22} \le \mathrm{E}(Y_{X=2}) \le K_1$ and $E_{22}p_{2\mid 2} + K_0 p_{0\mid 2} \le \mathrm{E}(Y_{X=1}) \le \mathrm{E}(Y \mid R = 1)$. Unfortunately, these bounds have a very broad width, and thus they do not provide enough information about treatment effects of clofibrate.

7. Conclusion

This chapter has presented bounds on ACE in randomized trials with noncompliance. Although the results presented here are relevant to the causal differences, they can also be readily applied to the causal risk ratio when the outcome is binary.

[2] If $(s, t) = (2, 1)$ in the MTR and RMTR (Assumptions 2.1 and 2.2) is used, the lower bound is 0 under the MTR and the upper bound is 0 under the RMTR.

[3] If $(s, t) = (2, 1)$ in the MTR and RMTR (Assumptions 2.1 and 2.2) is additionally used, a candidate of the lower bound is 0 under the MTR and that of the upper bound is 0 under the RMTR.

It is generally thought that the ITT analysis is likely to yield a downwardly biased estimate of causal effects (Sheiner & Rubin, 1995), whereas the PP analysis is likely to yield an upwardly biased estimate (Lewis & Machine, 1993). Thus, the ACE probably exists between the results of the ITT and PP analyses. As shown in Section 4.1, this is true under IV + MTR + MTS or under IV + RMTR + RMTS for noncompliance by switching the treatment. However, as shown in Sections 5 and 6, we cannot be certain that this is true when noncompliance is due to receiving no treatment and/or the IV assumption does not hold. Thus, investigators should not simply conclude that the ACE exists between the results of the ITT and PP analyses. Unfortunately, no standard method currently exists for estimating the ACE in randomized trials with noncompliance issues. Investigators should consider whether the assumptions presented in this chapter are valid and then yield bounds on ACE using the methodology described herein.

The needs from further methodologies in this field are three-fold. The first is to find weaker assumptions than those given here, which nevertheless can derive the same bounds. The second is to make assumptions that can derive the bounds with a narrower width, which are still reasonable in some situations. The ideal is to make a reasonable assumption that can give a point estimator. The third and final need is to extend the discussions in this chapter to more complex situations: for example, two types of noncompliance in this chapter may occur simultaneously, and more than two arms may be compared (Cheng & Small, 2006).

The other recent interest in causal inference is statistical analysis concerning the role of an intermediate variable between a particular treatment and outcome (Rubin, 2004; Joffe et al., 2007; VanderWeele, 2008b). Investigators are often interested in understanding how the effect of a treatment on an outcome may be mediated through an intermediate variable. For example, in the MRFIT, this implies that investigators are interested in how the effect of a multifactor intervention program on CHD mortality may be mediated through the smoking status 1 year after entry, rather than the effect of the smoking status 1 year after entry on CHD mortality. Such statistical analyses are closely related to issues of inference with a surrogate marker and issues of post-randomization selection bias and truncation-by-death (Zhang & Rubin, 2003; Chiba & VanderWeele, 2011). Further methodological research is needed to answer these issues.

8. Appendix: Derivations of equations and inequalities

This section outlines the derivations of the equations and inequalities presented in Sections 3, 4 and 6, which are outlined in Sections 8.1, 8.2 and 8.3, respectively.

8.1 Derivations of equations in Section 3

Equation (3.1) can be derived as follows:

$$\begin{aligned}
\mathrm{E}(Y_{X=2}) &= \mathrm{E}(Y_{X=2} \mid R=r) \\
&= \sum_{x=1,2} \mathrm{E}(Y_{X=2} \mid X=x, R=r)\Pr(X=x \mid R=r) \\
&= (E_{2r}-\alpha_r)p_{1|r} + E_{2r}p_{2|r} \\
&= E_{2r} - \alpha_r p_{1|r}.
\end{aligned}$$

The first equation holds by Assumption 1, and the third equation is derived by substituting $\mathrm{E}(Y_{X=2} \mid X=1, R=r) = \mathrm{E}(Y_{X=2} \mid X=2, R=r) - a_r$ and applying the consistency assumption: $\mathrm{E}(Y_{X=2} \mid X=2, R=r) = \mathrm{E}(Y \mid X=2, R=r)$ $(= E_{2r})$. A similar calculation derives equation (3.2).

To derive equation (3.3), we consider the difference between $E(Y \mid R = 2)$ and $E(Y_{X=2})$ and between $E(Y \mid R = 1)$ and $E(Y_{X=1})$. The former difference derives:

$$\begin{aligned} E(Y \mid R=2) - E(Y_{X=2}) &= \sum_{x=1,2} E_{x2} p_{x|2} - (E_{22} - \alpha_2 p_{1|2}) \\ &= (E_{12} + \alpha_2) p_{1|2} - E_{22}(1 - p_{2|2}) \\ &= \{\alpha_2 - (E_{22} - E_{22})\} p_{1|2}. \end{aligned}$$

By a similar calculation, the latter difference becomes $E(Y \mid R = 1) - E(Y_{X=1}) = \{\beta_1 - (E_{21} - E_{11})\}p_{2|1}$. The difference between these equations derives equation (3.3).

The derivation of equation (3.5) is as follows. Simple algebra, $p_{2|r} \times$ equation (3.1) plus $p_{1|r} \times$ equation (3.2), yields $p_{2|r}\text{ACE} + E(Y_{X=1}) = E(Y \mid R = r) - (a_r - \beta_r)p_{1|r}p_{2|r}$. The difference between this equation with $r = 2$ and that with $r = 1$ is:

$$(p_{2|2} - p_{2|1})\text{ACE} = E(Y \mid R = 2) - E(Y \mid R = 1) - (a_2 - \beta_2)p_{1|2}p_{2|2} + (a_1 - \beta_1)p_{1|1}p_{2|1}.$$

This equation implies equation (3.5) for $p_{2|2} \neq p_{2|1}$.

8.2 Derivations of inequalities in Section 4

Inequality (4.1) can be derived as presented below. By substituting $K_0 \leq E(Y_{X=x} \mid X = x^*, R = r) \leq K_1$ for $x \neq x^*$ and $E(Y_{X=x} \mid X = x^*, R = r) = E(Y \mid X = x, R = r)$ $(= E_{xr})$ for $x = x^*$ (consistency assumption) into:

$$E(Y_{X=x} \mid R = r) = \sum_{x^*=1,2} E(Y_{X=x} \mid X = x^*, R = r) \Pr(X = x^* \mid R = r), \tag{8.1}$$

we obtain:

$$E_{xr}p_{x|r} + K_0 p_{x^*|r} \leq E(Y_{X=x} \mid R = r) \leq E_{xr}p_{x|r} + K_1 p_{x^*|r} \tag{8.2}$$

for $x \neq x^*$. Because $E(Y_{X=x}) = E(Y_{X=x} \mid R = r)$ by Assumption 1, the bounds of $E(Y_{X=x})$ become:

$$\max\begin{Bmatrix} E_{x1}p_{x|1} + K_0 p_{x^*|1} \\ E_{x2}p_{x|2} K_0 p_{x^*|2} \end{Bmatrix} \leq E(Y_{X=x}) \leq \min\begin{Bmatrix} E_{x1}p_{x|1} + K_1 p_{x^*|1} \\ E_{x2}p_{x|2} + K_1 p_{x^*|2} \end{Bmatrix}$$

for $x \neq x^*$. The difference between the lower and upper bounds of this inequality for $x = 1, 2$ is inequality (4.1).

Inequality (4.3) can be also derived using equation (8.1). Assumption 2.1 implies that $E(Y_{X=2} \mid X = x, R = r) \geq E(Y_{X=1} \mid X = x, R = r)$. Thus, by substituting this inequality with $x = 1$ into equation (8.1), we obtain:

$$\begin{aligned} E(Y_{X=2}) &= E(Y_{X=2} \mid R = r) \\ &\geq \sum_{x=1,2} E(Y_{X=x} \mid X = x, R = r) \Pr(X = x \mid R = r) \\ &= \sum_{x=1,2} E(Y \mid X = x, R = r) \Pr(X = x \mid R = r) \\ &= E(Y \mid R = r), \end{aligned} \tag{8.3}$$

and thus $E(Y_{X=2}) \geq \max\{E(Y \mid R = 1), E(Y \mid R = 2)\}$. Similarly, $E(Y_{X=1}) \leq \min\{E(Y \mid R = 1), E(Y \mid R = 2)\}$ by substituting $E(Y_{X=2} \mid X = 2, R = r) \geq E(Y_{X=1} \mid X = 2, R = r)$ into equation (8.1). The difference between them is inequality (4.3).

In the case of a binary outcome variable, inequality (4.3) can also be derived under Assumption 3.1. By adding $\Pr(Y_{X=2} = 1, Y_{X=1} = 1 \mid X = x, R = r)$ on both sides of the inequality in Assumption 3.1: $\Pr(Y_{X=2} = 1, Y_{X=1} = 0 \mid X = x, R = r) \geq \Pr(Y_{X=2} = 0, Y_{X=1} = 1 \mid X = x, R = r)$, we obtain $\Pr(Y_{X=2} = 1 \mid X = x, R = r) \geq \Pr(Y_{X=1} = 1 \mid X = x, R = r)$. Because this inequality is a binary outcome version of $\mathrm{E}(Y_{X=2} \mid X = x, R = r) \geq \mathrm{E}(Y_{X=1} \mid X = x, R = r)$, inequality (4.3) is derived.
Inequality (4.4) can be derived as follows. Substituting $\mathrm{E}(Y_{X=2} \mid X = 2, R = r) \geq \mathrm{E}(Y_{X=2} \mid X = 1, R = r)$ ($x = 2$ and $(s, t) = (2, 1)$ in Assumption 4.1) into equation (8.1) yields:

$$\begin{aligned} \mathrm{E}(Y_{X=2}) &= \mathrm{E}(Y_{X=2} \mid R = r) \\ &\leq \sum_{x=1,2} \mathrm{E}(Y_{X=2} \mid X = 2, R = r) \Pr(X = x \mid R = r) \\ &= \mathrm{E}(Y \mid X = 2, R = r) (= E_{2r}), \end{aligned} \tag{8.4}$$

and thus $\mathrm{E}(Y_{X=2}) \leq \min\{E_{21}, E_{22}\}$. Similarly, $\mathrm{E}(Y_{X=1}) \geq \max\{E_{11}, E_{12}\}$ by substituting $\mathrm{E}(Y_{X=1} \mid X = 2, R = r) \geq \mathrm{E}(Y_{X=1} \mid X = 1, R = r)$ ($x = 1$ and $(s, t) = (2, 1)$ in Assumption 4.1) into equation (8.1). The difference between them is inequality (4.4).
Inequality (4.4) can also be derived under Assumption 5.1. To prove this, we need the following lemma (Esary et al., 1967):

LEMMA 1

Let f and g be functions with n real-valued arguments such that both f and g are non-decreasing or non-increasing in each of their arguments. If $Z = (Z_1, \ldots, Z_n)$ is a multivariate random variable with n components such that each component is independent of the other components, then $\mathrm{Cov}\{f(Z), g(Z)\} \geq 0$.

Let $f_r(Z) = \mathrm{E}(Y \mid X = 2, R = r, Z = z)$, $g_r(Z) = \Pr(X = 2 \mid R = r, Z = z)$ and $F_{Z \mid R=r}$ denote the cumulative distribution function of Z conditional on $R = r$. Then, by Lemma 1, we obtain:

$$\mathrm{E}_{F_{Z|R=r}}\{f_r(Z)g_r(Z)\} - \mathrm{E}_{F_{Z|R=r}}\{f_r(Z)\}\mathrm{E}_{F_{Z|R=r}}\{g_r(Z)\} = \mathrm{Cov}_{F_{Z|R=r}}\{f_r(Z), g_r(Z)\} \geq 0,$$

if both $f_r(Z)$ and $g_r(Z)$ are non-decreasing or non-increasing in z and the components of Z are independent. Thus, using the assumption that $Y_{X=x}$ is independent from X given R and Z, the following inequality is derived:

$$\begin{aligned} \mathrm{E}(Y_{X=2} \mid X = 1, R = r) &= \sum_z \mathrm{E}(Y_{X=2} \mid X = 1, R = r, Z = z) \Pr(Z = z \mid X = 1, R = r) \\ &= \sum_z \frac{\mathrm{E}(Y \mid X = 2, R = r, Z = z) \Pr(X = 1 \mid R = r, Z = z) \Pr(Z = z \mid R = r)}{\Pr(X = 1 \mid R = r)} \\ &= \mathrm{E}_{F_{Z|R=r}}[f_r(Z)\{1 - g_r(Z)\}] \Big/ \Pr(X = 1 \mid R = r) \\ &\leq \mathrm{E}_{F_{Z|R=r}}\{f_r(Z)\}\mathrm{E}_{F_{Z|R=r}}\{1 - g_r(Z)\} \Big/ \Pr(X = 1 \mid R = r) \\ &= \mathrm{E}_{F_{Z|R=r}}\{f_r(Z)\} \\ &= \mathrm{E}_{F_{Z|R=r}}\{f_r(Z)\}\mathrm{E}_{F_{Z|R=r}}\{g_r(Z)\} \Big/ \Pr(X = 2 \mid R = r) \\ &\leq \mathrm{E}_{F_{Z|R=r}}\{f_r(Z)g_r(Z)\} \Big/ \Pr(X = 2 \mid R = r) \\ &= \sum_z \frac{\mathrm{E}(Y \mid X = 2, R = r, Z = z) \Pr(X = 2 \mid R = r, Z = z) \Pr(Z = z \mid R = r)}{\Pr(X = 2 \mid R = r)} \\ &= \mathrm{E}(Y \mid X = 2, R = r). \end{aligned}$$

The second equation holds because $E(Y_{X=2} \mid X = 1, R = r, Z = z) = E(Y_{X=2} \mid X = 2, R = r, Z = z) = E(Y \mid X = 2, R = r, Z = z)$ by the independency and consistency assumptions. The fourth inequality holds because $1 - g_r(Z)$ is non-increasing when $g_r(Z)$ is non-decreasing. The fifth and sixth equations hold because:

$$\mathrm{E}_{F_{Z|R=r}}\{g_r(Z)\} = \sum_z \Pr(X = 2 \mid R = r, Z = z)\Pr(Z = z \mid R = r) = \Pr(X = 2 \mid R = r).$$

A similar calculation derives $E(Y_{X=1} \mid X = 2, R = r) \geq E(Y \mid X = 1, R = r)$. The inequalities derived here are the same as those in Assumption 4.1. Therefore, inequality (4.4) can be derived under Assumption 5.1.

8.3 Derivations of inequalities in Section 6

$E(Y_{X=x})$ can be expressed as $E(Y_{X=x}) = E(Y_{X=x} \mid R = 1)\Pr(R = 1) + E(Y_{X=x} \mid R = 2)\Pr(R = 2)$. Therefore,

$$E(Y_{X=x} \mid R = 1) \leq E(Y_{X=x}) \leq E(Y_{X=x} \mid R = 2) \tag{8.5}$$

under Assumption 6.1 (MIV: $E(Y_{X=x} \mid R = 1) \geq E(Y_{X=x} \mid R = 0)$). All bounds under the MIV are derived based on inequality (8.5), while those under the IV (Assumption 1) are based on $E(Y_{X=x}) = E(Y_{X=x} \mid R = r)$. This is why inequality (6.1) corresponds to it when a or b in $\max\{a, b\}$ and $\min\{a, b\}$ in inequality (4.1) is used. This is also similar under the RMIV (Assumption 6.2), and then inequality (6.2) and the bounds in Tables 3 and 4 also correspond to those when a or b in $\max\{a, b\}$ and $\min\{a, b\}$ in the bounds presented in Section 4.1 are used. Therefore, the derivations of bounds in Section 6.1 are simple. Inequality (6.1) is derived by the combination of inequalities (8.2) and (8.5).

In Table 3, $ACE \geq \max\{-ITT, 0\}$ under the MIV and MTR is derived as follows. Because $E(Y_{X=2}) \geq E(Y_{X=2} \mid R = 1)$ from inequality (8.5), $E(Y_{X=2}) \geq E(Y \mid R = 1)$ from inequality (8.3) with $r = 1$. Likewise, $E(Y_{X=1}) \leq E(Y \mid R = 2)$ by $E(Y_{X=1}) \leq E(Y_{X=1} \mid R = 2)$ and the MTR (Assumption 2.1). The difference between these inequalities derives $ACE \geq -ITT$. Additionally, the MTR derives $ACE = E(Y_{X=1}) - E(Y_{X=0}) \geq 0$ directly. The other bounds in Table 3 can be derived in a similar way.

In Table 4, $ACE \leq E_{22} - E_{11}$ under the MIV and MTS is derived as follows. Because $E(Y_{X=2}) \leq E(Y_{X=2} \mid R = 2)$ from inequality (8.5), $E(Y_{X=2}) \leq E_{22}$ from inequality (8.4) with $r = 2$. Likewise, $E(Y_{X=1}) \geq E_{11}$ by $E(Y_{X=1}) \geq E(Y_{X=1} \mid R = 1)$ and the MTS (Assumption 4.1). The difference between these inequalities derives $ACE \leq E_{22} - E_{11}$. The other bounds in Table 4 can be derived in a similar way.

The inequalities in Section 6.2 can be derived in straightforward manner as the derivations of those in Section 6.1 by replacing $x = 1, 2$ in Section 6.1 to $x = 0, 1$ and $x = 0, 2$, although they may be somewhat complex.

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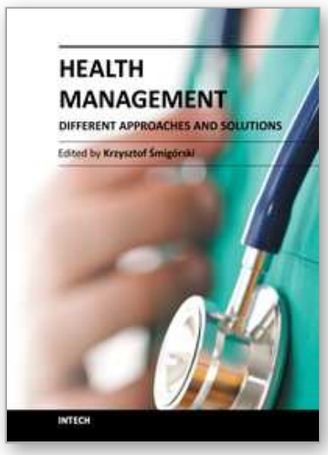

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