Compliance Analysis in Randomized Trials

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Minnesota Treatment Group: Cholestyramine, 200 subjects, 2yr averages

Control group: 201 subjects
Stanford Treatment Group: Cholestyramine, 168 subjects, 2 year averages

Stanford Control Group 180 Subjects
Model (Efron and Feldman, 1991, JASA, p. 9-26)

\[ Y_x(u) = Y_0(u) + \delta(x) + \gamma(x)[Y_0(u) - \bar{Y}_0] + e_x(u) \]

where

\[ Y_x(u) = \text{Response to dose } x \text{ for subject } u \]

\[ Y_0(u) = \text{Placebo response} \]

\[ \delta(x) = E\{Y_x(u) - Y_0(u)\} \]

\[ = \text{true dose-response curve} \]

\[ \gamma(x) = \text{interaction term} \]

\[ \bar{Y}_0 = E\{Y_0(u)\} \]

\[ = \text{average placebo response} \]

\[ E\{e_x(u)\} = 0 \]

\[ \delta(0) = 0, \quad \gamma(0) = 0, \quad e_0(u) = 0 \]

\[ x = 1 \text{ is "full dose"} \]
Linear Regression of $Y_x$ on $Y_0$
Compliance – Response Regressions

- \( z(u) = \) compliance of subject \( u \)
  \((z = 1 \text{ is full compliance})\)

- \( C(z) = E\{y_c(u)|z(u) = z\} \)
  \(= E\{Y_0(u)|z(u) = z\} \)

- \( T(z) = E\{y_T(u)|z(u) = z\} \)
  \(= E\{Y_0 + \delta(x) + \gamma(x)[Y_0 - \bar{Y}_0] + e_x|z\} \)
  \(= C(z) + \delta(z) + \gamma(z)[C(z) - \bar{Y}_0] \)

\[
\begin{align*}
D(z) &= T(z) - C(z) \\
&= \delta(z) + \gamma(z)[C(z) - \bar{Y}_0]
\end{align*}
\]

- Assumes \( E\{e_x(u)|z(u) = z\} = 0. \)
\[ D(z) = T(z) - C(z), \] the difference between the Treatment and Control group regressions
$D(z) = T(z) - C(z)$ for the Stanford Data
QUESTION How well does $D(z)$ approximate $\delta(z)$?

$$\delta(z) = D(z) - \gamma(z)[C(z) - \bar{Y}_0]$$

- $\delta(z) = D(z)$ if $C(z) = \bar{Y}_0$

- If $C(z)$ linear then $C(z_0) = \bar{Y}_0$

- Could define "$z_0$" by $C(z_0) = \bar{Y}_0$
  ($z_0 = .38$ and $.94$ for Minnesota data)

- For Minnesota data $D(1) = 51.9$ and $C(1) - \bar{Y}_0 = -1.4$

so if $|\gamma(1)| \leq 1$ then

$$|\delta(1) - 51.9| \leq 1.4$$
- Want $C(z) = E\{Y_0(u) | z_T(u) = z\}$
  Compliance for Treatment subject

- Can estimate $E\{Y_0(u) | z_C(u) = z\}$
  Compliance for Control subject

- Perfect Blind: $z_T(u) = z_C(u)$
  [sufficient: $z_T(u) = M(z_C(u))$ for monotone $M$]

- Percentile Matching: map $z_c \rightarrow \tilde{z}_c$
  ("Adjusted Compliance") so that

  $$\tilde{z}_C^{(\alpha)} = z_T^{(\alpha)} \text{ for } 0 < \alpha < 1$$
Abdominal Pain and Nausea, Comparing Treatment and Control Groups

tvalues of compliance on eight separate adverse reactions
Minnesota Treatment group:

ab bel cons diar gas hrt naus vom
-3.39 -2.74 -2.92 -2.56 -2.3 -2.42 -4.46 -2.78
- **BAD CASE**: Actual $C(z)$ much steeper than Apparent $C(z)$

- Makes $D(1) = T(1) - C(1)$ look too big

- But then the $y_T$ values for $z_T$ near 0 should be less than $y_C$ values for $z_C$ near 0.
Minnesota data for low compliances
compliance by group for Drug L
placebo controls = 'o'
DRUG L: 0=placebo 1=150 2=300 3=450 4=600

actual dose per day
# patients= (34,25,29,35,24)
THREE-DOSE EXPERIMENT

- Besides Treatment (full dose) and Control (zero dose) have a Fractional Dose group (fraction $f$ of full dose).

- Let $T_1(z) = E\{y_T|z\}$ and $T_f(z) = E\{y_F(z)|z\}$

- Assume $C(z)$ linear, then EF model gives

$$
\delta(z) = \frac{z_0/z - 1/f}{1 - 1/f} T_1(z) + \frac{1 - z_0/z}{1 - 1/f} T_f(z) - \bar{Y}_0
$$

- Can estimate $\delta(z)$ for any value of $z$.

- Interaction $\gamma(x)$ disappears.

- Control group needed only to estimate $\bar{Y}_0$. 
Ideal Choice of Third Dose "f"

**Theorem** Suppose $T_1(z), T_f(z)$, and $C(z)$ are linear, and that

$$z(u) \sim (z_0, \sigma_z^2).$$

Then the choice of $f$ that minimizes the variance of $\hat{\delta}(z)$ is

$$\frac{1}{\hat{f}} = z_0 - \frac{1 - z_0}{1 + 2(1 - z_0)^2/\sigma_z^2}$$

- **Minnesota** $z_0 = .758$ $\hat{\sigma}_z = .266$ gives
  $$\hat{f} = 1.50$$

- Always have $\frac{1}{z_0} \leq \hat{f} \leq \frac{1}{2z_0 - 1}$ for $z_0 > \frac{1}{2}$. 
COMPLIANCE IN 3-ARM BLOOD PRESSURE STUDY

average compliance z0=.75
The data for the first subject:

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[ Drug A]
Thanks to

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