

Noncompliance in randomized trials

Frequently in randomized trials, subjects do not comply with their assigned treatment regimen

Examples:

Health Insurance Plan (HIP) trial of screening for breast cancer (BC)

2 arms:

- control: no screening
- screening: women invited for (up to) 4 annual screens (no screens after breast cancer)

some women in screening arm refused all screens; some failed to come to some follow-up screens

outcomes: BC incidence, BC mortality, total mortality

Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)

study of cholestyramine

drug to lower serum cholesterol, reduce cardiovascular events, mortality

unpleasant; side-effects

placebo-controlled trial

subjects supposed to visit clinics every 2 months,

- obtain medication
- return unused medication from previous visit (assess adherence)

subjects may use none, some, or all of prescribed medication

adherence with placebo also monitored

Randomized trial of effects of vitamin A supplementation on children's survival

Indonesian villages randomized to receive, not receive supplementation

Some subjects in villages assigned to receive supplementation do not take it

What are proper goals in analyzing these data?

Definitions of desired effects, assumptions, estimation methods disputed

Effects of interest:

Comparison of what would happen were everyone to be assigned treatment versus not assigned treatment:

compare values of Y^r

comparison of $E(Y^1)$, $E(Y^0)$

intent to treatment effect/estimand

what is problem with estimand?

Doesn't represent solely true effect of treatment

mixture of "biological" effect of treatment and noncompliance

if everyone has same effect, "true" effect is diluted by noncompliance

How could one define "true" effect of treatment?

Comparison on Y^a for different values of a

e.g., $E(Y^{a=1}) - E(Y^{a=0})$

What does notation Y^a assume implicitly about (direct) effect of randomization?

That there is no direct effect

Formalize this notion:

Consider potential outcome indexed by both r and a : $Y^{r,a}$

$$Y^{r,a} = Y^{r',a} = Y^a$$

randomization has no effect on outcome except through its effect on treatment received

assumption called *exclusion restriction* in econometrics literature

what other common aspect of randomized trials may make this assumption plausible?

Blinding

consider study of cholestyramine or other drug taken to lower cholesterol

subject who believes taking effective treatment for elevated cholesterol may refrain from taking other measures to lower cholesterol (e.g., diet or exercise)

subject who believes has received effective screening for BC may be less vigilant in self-exam

in studies which treatment group encouraged to participate in activity (e.g., quitting smoking, exercise, etc.), encouragement may have effects other than those mediated by desired behavior change

What does comparison $E(Y^{a=1})$ vs. $E(Y^{a=0})$ imply about potential outcomes Y^a in all subjects?

That Y^a for both treatment levels a meaningfully defined and of interest for every subject

Not always true; potential outcome Y^a not always feasible or meaningful or of interest

suppose treatment causes severe, untreatable side effects

not interested in what would happen to subjects who would develop those side effects only if received treatment

formulate model for describing these effects (structural model)

$g\{E(Y^A|A,\cdot)\} - g\{E(Y^0|A,\cdot)\}$ rather than
 $g\{E(Y^a|A,\cdot)\} - g\{E(Y^0|A,\cdot)\}$ or $g\{E(Y^a|\cdot)\} - g\{E(Y^0|\cdot)\}$

how can one estimate effects defined this way?

G-estimation or instrumental variables (for linear models)

note more circumspect interpretation

what are other alternatives sometimes discussed for in randomized trials?

Intent to treat (ITT):

$$g\{E(Y|R=1)\} - g\{E(Y|R=0)\} = g\{E(Y^{R=1})\} - g\{E(Y^{R=0})\}$$

As treated analysis and variants:

$$E(Y|A=1, \cdot) - E(Y|A=0, \cdot) \quad (\text{as treated})$$

$$E(Y|R=1, A=1) - E(Y|R=0, A=0) \quad (\text{per protocol})$$

what is direction of bias of ITT?

Conventional wisdom; biased towards null

Qualify:

Depends on estimand of interest and conditions

If interested in effect of treatment received on subjects who received it
(explanatory analysis), ITT biased towards null (will qualify later)

If interested in marginal effect of treatment (e.g., $E(Y^1) - E(Y^0)$), not necessarily
biased towards null

$$E(Y^1) - E(Y^0) = pr(A=1|R=1)\{E(Y^1|R=1,A=1) - E(Y^0|R=1,A=1)\} \\ + pr(A=0|R=1)\{E(Y^1|R=1,A=0) - E(Y^0|R=1,A=0)\}$$

ITT effect (assuming no direct effect):

$$E(Y^{r=1}) - E(Y^{r=0}) = pr(A=1|R=1)\{E(Y^1|R=1,A=1) - E(Y^0|R=1,A=1)\}$$

If effect of treatment(s) is same for all subjects, is ITT biased towards null?

Placebo-controlled trial

Equivalence trial (two active treatments)

In placebo-controlled trial, yes

In equivalence trial, no

Suppose that

- effect of treatment 1 different from treatment 2
- probability of remaining on treatment different for treatment 2 than 1
- subjects assigned to one treatment cannot get other but can get no treatment

ITT effects compared to no treatment: for treatment 1: $pr(A_1=1|R=1)\Psi_1$
for treatment 2: $pr(A_2=1|R=2)\Psi_2$

ITT effects comparing treatments: $pr(A_2=1|R=2)\Psi_2 - pr(A_1=1|R=1)\Psi_1$

Suppose $\Psi_2 > \Psi_1$; get reversal if

$$pr(A_2=1|R=2)\Psi_2 - pr(A_1=1|R=1)\Psi_1 < 0$$

$$\Psi_2 < \frac{pr(A_1=1|R=1)}{pr(A_2=1|R=2)} \Psi_1$$

what is direction of bias of as treated analysis?

No general statements

Consider bias in estimates/tests under the null hypothesis of no treatment effect:

ITT (in placebo-controlled trial):

ITT (in equivalence trial):

As treated:

G-estimation/IV analysis:

ITT (in placebo-controlled trial): no bias

$$E(Y|R=1) - E(Y|R=0) = E(Y^0|R=1) - E(Y^0|R=0) = E(Y^1) - E(Y^0) = 0 \text{ (Based on randomization, assumption of no effect)}$$

ITT (in equivalence trial): may still be biased if both treatments have effects compared to no treatment (as before)

As treated: may be biased

G-estimation/IV analysis: no bias

$$0 = \sum (R-p)Y^0(\Psi) = \sum (R-p)(Y-A\Psi) = \sum (R-p)Y$$

test of association of Y and R (i.e., ITT test of null)

what is advantage of ITT test of null in randomized trial?

Confident of randomization assumption

as treated: not confident of ignorability

relax assumption of no direct effect of randomization/exclusion restriction

suggest possible analyses to estimate (direct) effect of randomization, effect of treatment received:

standard analysis:

model $E(Y|X,R,A)$

need to measure all confounders of effect of both R and of A (not guaranteed by randomization)

factors affected by R may confound effect of A

will discuss estimation assuming confounders measured in later session

can base analysis on assumed model for treatment effects, initial randomization (i.e., no assumptions about confounding effect of A)

presumed model for joint effects:

$$Y^{R,A} = Y^{0,0} + R\Phi + A\Psi \text{ (Deterministic version of model)}$$

$$Y^{0,0}(\Phi, \Psi) = Y - R\Phi - A\Psi$$

under randomization, $Y^{0,0} \perp R$

how would one estimate $\{\Phi, \Psi\}$?

Test independence (or uncorrelatedness) of $Y^{0,0}(\Phi, \Psi), R$

calculate vector function $g\{Y^{0,0}(\Phi, \Psi), X\}$ with 2 degrees of freedom

add to estimating equation or logistic regression

problems with jointly estimating effects this way:

relies on single randomization for estimating multiple parameters

efficiency can be poor for estimating joint effects, component effects

especially if R and A highly correlated

can derive optimal functions

Alternative approach/different philosophy

Based on principal stratification (Frangakis and Rubin, 2002)

Complier (someone who would do what assigned to), etc.

Define in terms of potential “outcomes”

Complier: $A^1=1, A^0=0$; alternatively, $A^r=r$

3 other possible classes:

Never taker: $A^1=A^0=0$; $A^r=0$

Always taker: $A^1=A^0=1$; $A^r=1$

Defier: $A^1=0, A^0=1$; $A^r=1-r$

Latent classes of subjects, based on potential receipts

What can one tell about cooperators status from observed data?

$R=1, A=1$

complier or always-taker

similarly, combination of observed compliance status, randomization group
partially identifies cooperator status or limits possibilities

for which class are treatment effects of greatest interest?

Compliers (or defiers)

Argument: not interested in possible effect of treatment for subjects who would not take it no matter what or would take it no matter what (always or never-takers)

Alternatively, always or never-takers provide no information about effect of treatment (will elaborate this argument later)

What is possibly wrong with first argument?

Trial interested in inference for future

Cooperator classes for individuals are characteristic of combination of individual attributes and study conditions

Why might subject's cooperator class change/not be fixed?

Trial shows treatment beneficial

Subjects after trial know

- receiving active treatment, not placebo
- treatment shown to be beneficial

improved adherence expected

Alternatively, trial may provide closer monitoring, more encouragement for adherence to assigned therapy

worse adherence expected after trial

Define treatment effects for subjects in classes (2 approaches):

Compare $Y^{r,a}$ for different values of r, a

4 potential outcomes

Alternative: compare Y^r (Y^{r,A^r} in some readings) for different r

2 potential outcomes

ITT effects for different compliance classes

no attempt to disentangle direct/indirect effects of randomization

perhaps not meaningful: only thing under control of investigator is assignment R

experiment only directly investigates effect of assignment

in some cases, not clear how one could see potential outcome $Y^{r,1-A^r}$

how can one learn about treatment effects for latent classes?

Combinations of:

Restrictions on adherence behavior/latent classes

Restrictions on causal effects within classes

Specification of prior or sensitivity parameters

Parametric assumptions (e.g., potential outcomes have Gaussian distribution)

Restrictions on adherence behavior/latent classes:

Monotonicity: $A^1 \geq A^0$ (No defiers)

In studies in which control group has no access to treatment, automatically satisfied

Otherwise, just an assumption; not identified from data, sometimes more, sometimes less plausible

For binary treatment, monotonicity leads to identification of proportion in each class

$$pr(A^1=1, A^0=1) = pr(A^0=1) = pr(A^0=1|R=0) = pr(A=1|R=0) \quad (\text{Always takers})$$

$$pr(A^1=0, A^0=0) = pr(A^1=0) = pr(A^1=0|R=1) = pr(A=0|R=1) \\ = 1 - pr(A=1|R=1) \quad (\text{Never takers})$$

$$pr(A^1=1, A^0=0) = 1 - pr(A^1=1, A^0=1) - pr(A^1=0, A^0=0) \\ = 1 - pr(A=1|R=0) - \{1 - pr(A=1|R=1)\} \\ = pr(A=1|R=1) - pr(A=1|R=0) \quad (\text{Compliers})$$

additionally, always-takers identified among group randomized to control and never-takers identified among group randomized to treatment

Restriction on causal effects:

exclusion restriction or no direct effect of treatment:

$$Y^{r,a} = Y^{r',a} = Y^a \text{ (Version using direct/indirect effects)}$$

or

$$Y^r = Y^{1-r} \text{ if } A^r = A^{1-r} \text{ (Version not allowing effect of } A)$$

Decompose ITT effect overall in terms of latent classes:

$$\begin{aligned}
 E(Y^1) - E(Y^0) &= pr(A^1=1, A^0=1) \{E(Y^1|A^1=1, A^0=1) - E(Y^0|A^1=1, A^0=1)\} \\
 &\quad + pr(A^1=1, A^0=0) \{E(Y^1|A^1=1, A^0=0) - E(Y^0|A^1=1, A^0=0)\} \\
 &\quad + pr(A^1=0, A^0=0) \{E(Y^1|A^1=0, A^0=0) - E(Y^0|A^1=0, A^0=0)\} \\
 &= pr(A^1=1, A^0=0) \{E(Y^1|A^1=1, A^0=0) - E(Y^0|A^1=1, A^0=0)\}
 \end{aligned}$$

but, can estimate

$$E(Y^1) - E(Y^0) = E(Y|R=1) - E(Y|R=0)$$

$$pr(A^1=1, A^0=0) = pr(A=1|R=1) - pr(A=1|R=0)$$

and so estimate effect for compliers as $\frac{E(Y|R=1) - E(Y|R=0)}{pr(A=1|R=1) - pr(A=1|R=0)}$

standard IV estimator; new interpretation of estimand

In a way, more circumspect interpretation of estimator

Under assumptions, effects of treatment for subjects who do not contribute to differences between randomized groups not defined

explanatory interpretation

effect for unidentifiable group is identified

Suppose subjects assigned control have no access to active treatment (common in studies of drugs not on market)

can identify complier class in group randomized to treatment

If relax exclusion restriction or monotonicity/no defiers assumption, no longer have nonparametric identification of treatment effects

Now, require prior specification for proportion in complier classes

Likelihood:

Let C denote complier class

$$pr(X)pr(C|X)pr(R)pr(Y|R,C,X)$$

suppose we look for ITT effects of treatment:

express in terms of potential outcome:

substitute $pr(Y|X,C,R=r)=pr(Y^r|X,C,R=r)=pr(Y^r|X,C)$

where does treatment received A come in?

Deterministic function of R, C

can do Markov Chain Monte Carlo to obtain estimates of model parameters

example of model: $E(Y^r|X,C)=X\beta+r\gamma_C$

different causal effects of randomization γ_C for different compliance classes

if parametrize $\gamma_C=\Phi+(A^1-A^0)\Psi$, recover SNM with Ψ effect of treatment received and Φ effect of randomization

what are additional problems with characterization in terms of 4 compliance classes?

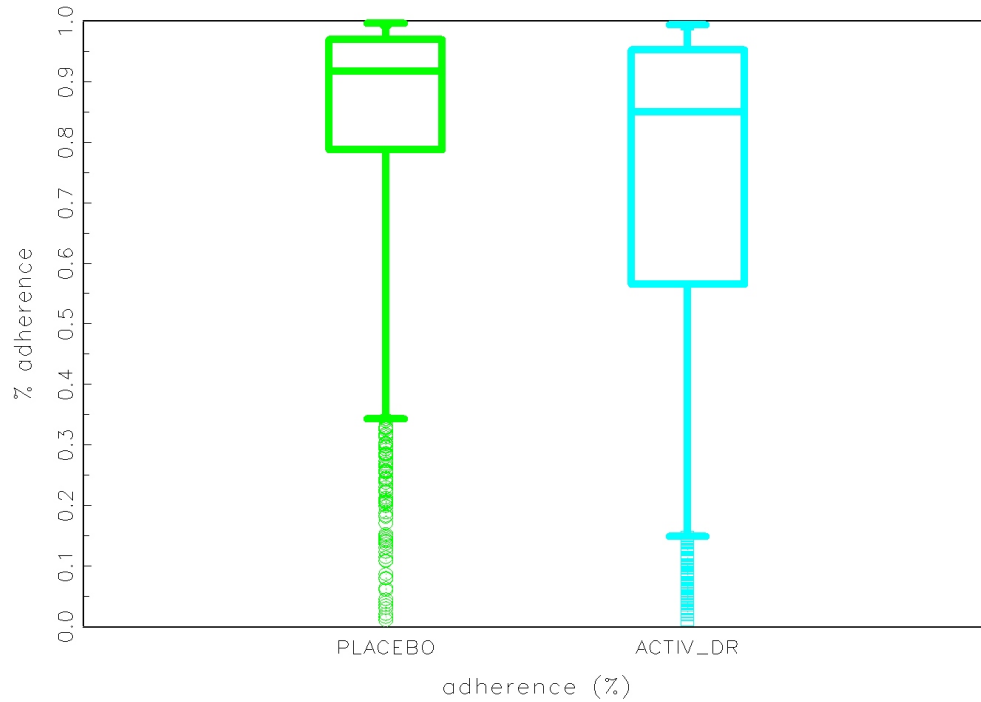
2 steps:

may be many levels of compliance:

consider adherence to drug; typically a subject may take drug over a period of time; partial adherence

example:

LRC-CPPT



treatment adherence worse than placebo adherence

why?

Substantial number of subjects with poor adherence

dichotomizing adherence is substantial simplification

results of various analyses (assume no direct effect):

effect on log cholesterol

analysis type	point estimate	standard error
ITT	-0.057	0.0022
as treated	-0.088	0.0026
G-estimation (simple; continuous treatment)	-0.079	0.0029
G-estimation (complicated; control for covariates)	-0.080	0.0023
G-estimation (simple; dichotomize compliance at 80%)	-0.103	0.0039
G-estimation (simple; dichotomize compliance at 50%)	-0.073	0.0027

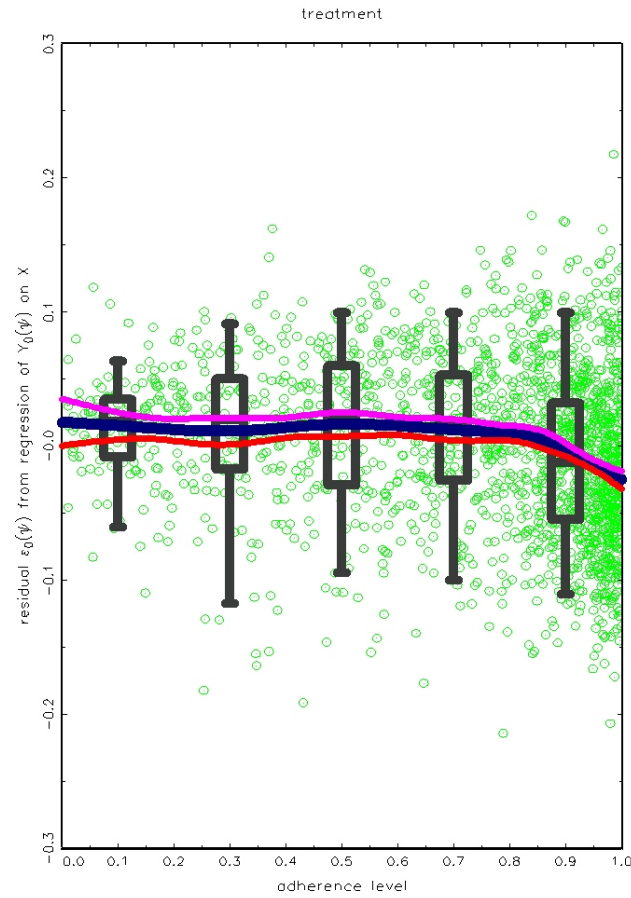
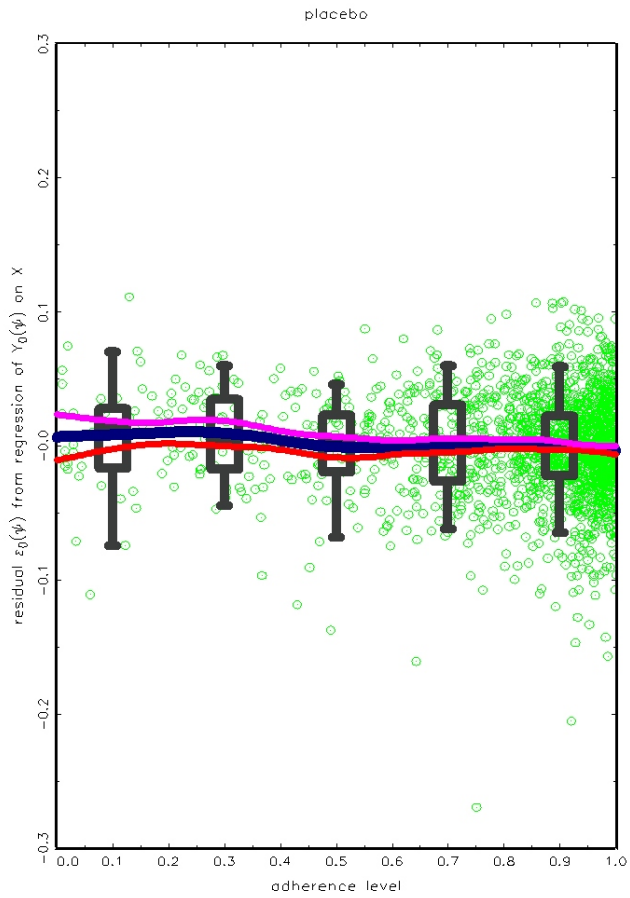
comment

ITT biased towards null

as treated biased away from null

dichotomization can give results in either direction (compared with continuous)

suggests model may not be correctly specified



Plot residual from regression of $Y^0(\Psi)$ on X against adherence

Describe and interpret:

High adherence levels in treatment group associated with lower cholesterol, even after adjusting for measured covariates

i.e., evidence for unmeasured confounding of effect (if causal model correct)

alternatively, model not correct, no unmeasured confounding

(or both)

in study, adherence is, in fact, not a scalar

varies over time

will consider in later unit