NONCOMPLIANCE IN RCTS
A CAUSAL INFERENCE PERSPECTIVE

Introduction

- Based on Hernan and Robins *Causal Inference* (2019; §9, 16) and *NEJM* (2017)
- Potential outcome / counterfactual & graphical perspectives
- Focus on estimands
  - Intention-to-treat effect
  - Per-protocol effect
  - Complier average causal effect

Why focus on estimands?

- Typical RCT approach: pre-specified analysis plan

  Primary analysis will be ITT, compare individuals according to randomization, regardless of compliance ...

  Per-protocol analysis will also be conducted, where individuals who were non-compliant excluded ...

- What effects are these analyses estimating? What are the estimands?

- ICH guidelines (E9 Statistical Principles for Clinical Trials) addendum advocating pre-specifying estimands

  International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Estimands and Sensitivity Analysis in Clinical Trials E9(R1). 2017.

Notation

- Consider randomized trial with possible non-compliance
- Z *assigned* treatment: 0 control, 1 treatment
- A treatment actually *received* (0,1)
- Y outcome of interest

- Consider only treatment at single time point, e.g., surgery,
- If there is perfect compliance then $\Pr[Z = A] = 1$

Potential Outcomes

- Individuals have two potential outcomes

$$Y^{z=0} \text{ is outcome if assigned control}$$

$$Y^{z=1} \text{ is outcome if assigned treatment}$$

- Individual effect of Z on Y

$$Y^{z=1} - Y^{z=0}$$

- Problem: Only one potential outcome observed

$$Y = (1-Z)Y^{z=0} + ZY^{z=1}$$

- Other outcome becomes counterfactual, eg, $Y^{z=1}$ if $Z = 0$

ITT Effect

- Average effect of Z on Y

$$E(Y^{z=1} - Y^{z=0}) = E(Y^{z=1}) - E(Y^{z=0})$$

  (or more generally some contrast in $E(Y^{z=1})$ and $E(Y^{z=0})$)

- In presence of non-compliance *intent to treat* effect
- In randomized trial

$$Z \perp \{Y^{z=0}, Y^{z=1}\}$$

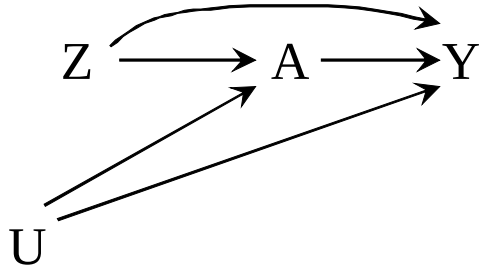
  implying

$$E(Y^{z=1} - Y^{z=0}) = E(Y|Z=1) - E(Y|Z=0)$$

- Progress! Right side identifiable, can draw inference from observable random variables

ITT Effect

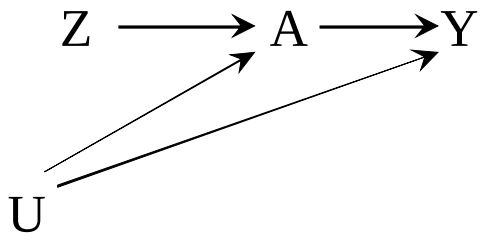
- Directed acyclic graph (DAG)



- No causes of Z because of randomization
- $Z \rightarrow Y$ direct effect, $Z \rightarrow A \rightarrow Y$ indirect (mediated) effect
- $Z \rightarrow Y$ might represent the effect of knowing assigned treatment
- Eg, knowing assigned $Z = 1$ might cause doctor to monitor patient more closely regardless of value of received treatment A
- No confounding, such that the association of Z and Y can be interpreted as the causal effect of Z on Y

ITT Effect

- In a double-blinded placebo-controlled experiment we might not expect $Z \rightarrow Y$ not mediated through A



- The absence of a direct arrow from Z to Y is sometimes described as the *exclusion restriction*
- Again no confounding, such that the association of Z and Y can be interpreted as the causal effect of Z on Y

ITT Effect

- Recap: ITT effect identifiable in randomized study without further assumptions
- Relevant if level of non-compliance/adherence in RCT similar to population of interest
- However, does not measure the effect of treating with A, i.e., the biologic effect of A
- Rather, measures the effect of *assigning* participants to be treated with A, or effect of having the intention to treat with A, which may be of limited utility
- Eg, couple considering use of a certain contraceptive method would want to know effect of contraceptive when used as indicated, which is not the ITT effect from an RCT with non-compliance

Per-protocol effect

- What about the effect $A \rightarrow Y$?
- *Per-protocol effect* : effect of treatment if all individuals had adhered to their assigned treatment as indicated in the protocol of the randomized experiment
- Now denote potential outcomes by $Y^{z,a}$
- An individual now has four potential outcomes
- Eg $Y^{z=0,a=1}$ is potential outcome when an individual is assigned control $z = 0$ but then receives treatment $a = 1$

Per-protocol effect

- Exclusion restriction (ER) assumption

$$Y^{z=0,a} = Y^{z=1,a} \quad \text{for} \quad a = 0, 1$$

  i.e., assignment has no effect on the outcome for fixed value of treatment received

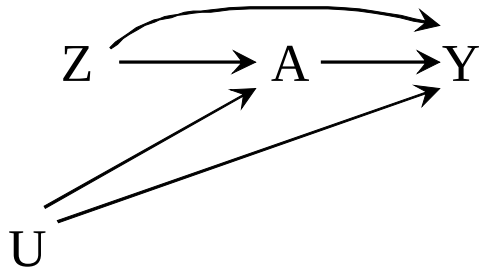
- Let $Y^a = Y^{z=0,a} = Y^{z=1,a}$ and define per-protocol effect

$$E(Y^{a=1}) - E(Y^{a=0})$$

- Because A not randomized, potential for confounding, i.e., per-protocol effect is not identifiable without additional assumptions

Per-protocol effect

- Eg, suppose among those assigned $Z = 0$, the most severely ill seek treatment ($A = 1$) outside of the trial, such that those who receive treatment ($A = 1$) tend to be more ill than those who do not receive treatment ($A = 0$)



- Non-causal association between received treatment A and outcome Y via backdoor path $A \leftarrow U \rightarrow Y$

Per-protocol effect

- Thus, despite randomization, inference about per-protocol effect needs to allow for confounding
- One approach is to employ method that adjusts for confounding, e.g., regression, propensity score methods such as weighting, matching, and so forth
- Generally require assumption no unmeasured confounders assumption, i.e.,

$$A \perp \{Y^{a=1}, Y^{a=0}\} \mid U$$

Per-protocol effect

- Another option: instrumental variable approach, which allows for unmeasured confounding, but relies on effect homogeneity assumption
- Assume for $a = 0, 1$,

$$E[Y^{a=1} - Y^{a=0}|A = a, Z = 1] = E[Y^{a=1} - Y^{a=0}|A = a, Z = 0]$$

  i.e., effect of treatment in treated same regardless of whether $Z = 1$ or $Z = 0$, and likewise for untreated
- Then

$$E[Y^{a=1} - Y^{a=0}] = \frac{E(Y|Z = 1) - E(Y|Z = 0)}{E(A|Z = 1) - E(A|Z = 0)}$$

  which is identifiable
- IV (Wald) estimand: effect of Z on Y divided by effect of Z on A

Complier Average Causal Effect

- Alternative approach is to consider drawing inference about the effect of A on Y among compliers
- Let $A^{z=1}$ denote treatment received if assigned treatment $z = 1$
- Define $A^{z=0}$ analogously
- Consider stratification of individuals according to $(A^{z=1}, A^{z=0})$

Complier Average Causal Effect

Principal stratum	Potential compliance outcomes $(A^{z=1}, A^{z=0})$	Potential outcome of interest $(Y^{z=1}, Y^{z=0})$	
Never taker	(0,0)	(y_1, y_0)	(=?)
Defier	(0,1)	(y_1, y_0)	(dne?)
Complier	(1,0)	(y_1, y_0)	
Always Taker	(1,1)	(y_1, y_0)	(=?)

Complier Average Causal Effect

- Monotonicity assumption: $A^{z=1} \geq A^{z=0}$, i.e., there are no defiers
- Exclusion restriction: $Y^{z=1} = Y^{z=0}$ if $A^{z=1} = A^{z=0}$
- Let $\tilde{A} = (A^{z=1}, A^{z=0})$
- Under monotonicity and exclusion restriction

$$E(Y^{z=1} - Y^{z=0}) = \sum_{a_1=0}^{1} \sum_{a_0=0}^{1} E[Y^{z=1} - Y^{z=0} | \tilde{A} = (a_1, a_0)] \Pr[\tilde{A} = (a_1, a_0)]$$

$$= E[Y^{z=1} - Y^{z=0} | \tilde{A} = (1,0)] \Pr[\tilde{A} = (1,0)]$$

implying

$$E[Y^{z=1} - Y^{z=0} | \tilde{A} = (1,0)] = \frac{E(Y^{z=1} - Y^{z=0})}{\Pr[\tilde{A} = (1,0)]} = \frac{E(Y|Z=1) - E(Y|Z=0)}{E(A|Z=1) - E(A|Z=0)}$$

- I.e., CACE equals IV estimand

Conclusion

- Intention-to-treat effect
  - Effect of treatment *assignment*, identifiable under minimal assumptions
  - Relevant if non-compliance/adherence in the population similar to trial
  - Under certain assumptions, ITT effect may be closer to the null compared to per-protocol effect, thus ITT-based inference "conservative"
  - However, what if outcome Y is a safety endpoint?
  - May lead to incorrect declaration of non-inferiority, or failure to identify effective intervention
  - RCT results may lead to changes in compliance/adherence, rendering ITT effect estimate outdated

Conclusion

- Per-protocol effect
  - Despite randomization, not identifiable without additional assumptions such as no unmeasured confounders or effect homogeneity
  - Unlike ITT effect, PP estimand does not depend on the degree of non-compliance in RCT
  - May be of greater interest to patients/clinicians: what is average effect of treatment when used as indicated?

Conclusion

- Complier average causal effect
  - Effect of treatment in subpopulation/subgroup who would take treatment if and only if assigned treatment
  - CACE identifiable if monotonicity and exclusion restriction hold, which may be reasonable if blinding employed
  - However, cannot identify which individuals are compliers, and treatment effect in compliers may differ from rest of population

- If perfect compliance, all three estimands equivalent

Conclusion

- Here only consider treatment at single time point (e.g., surgery). If instead interested in effect of treatment regimen (e.g., daily antiretroviral therapy), similar considerations apply + additional complexities such as when to censor non-compliant individuals and time-varying confounding
- Hernan, M.A. and Robins, J.M., 2019+. *Causal Inference*. CRC.

  http://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/
- Hernan, M.A. and Robins, J.M., 2017. Per-protocol analyses of pragmatic trials. *N Engl J Med*, 377(14), pp.1391-1398.