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
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

\[ Y_{z=0} \] is outcome if assigned control
\[ Y_{z=1} \] 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)

\[
\begin{align*}
Z & \rightarrow A \\
& \rightarrow Y \\
U & \rightarrow Z
\end{align*}
\]

- 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 $A$

$$Z \rightarrow A \rightarrow Y$$

- 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 ($A = 0$)

\[
\begin{array}{ccc}
Z & \rightarrow & A \rightarrow Y \\
\downarrow & & \downarrow \\
U & & \end{array}
\]

- 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

<table>
<thead>
<tr>
<th>Principal stratum</th>
<th>Potential compliance outcomes ( (A^z=1, A^z=0) )</th>
<th>Potential outcome of interest ( (Y^z=1, Y^z=0) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never taker</td>
<td>(0,0)</td>
<td>( (y_1, y_0) )</td>
</tr>
<tr>
<td>Defier</td>
<td>(0,1)</td>
<td>( (y_1, y_0) )</td>
</tr>
<tr>
<td>Complier</td>
<td>(1,0)</td>
<td>( (y_1, y_0) )</td>
</tr>
<tr>
<td>Always Taker</td>
<td>(1,1)</td>
<td>( (y_1, y_0) )</td>
</tr>
</tbody>
</table>
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
