The ICH E9 addendum from an academic causal inference perspective and feedback on talks

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RCTs meeting causal inference: principal stratum strategy and beyond

BBS Webinar
September 7, 2020
Principal Stratification (PS, Frangakis, Rubin, 2002) has its roots in Instrumental Variable (IV) literature but more general.

Angrist, Imbens, Rubin (1996) introduced the notions of Complier (C), Never-Taker (NT), Always-Taker (AT), Defier (D).

The global ITT may be written as the weighted average of the ITT effects across the four subpopulations:

\[
\text{ITT} = \pi_C \text{ITT}_C + \pi_{NT} \text{ITT}_{NT} + \pi_{AT} \text{ITT}_{AT} + \pi_D \text{ITT}_D
\]

ITT ignores treatment actually receipt like the Treatment Policy Strategy.
Bridging the IV-PS Causal Literature with the Addendum

- **ITT$_C$** (or CACE or LATE) is about treatment effect heterogeneity w.r.t. a posttreatment variable, like the **Principal Stratum Strategy**
  - Depending on the subgroup, treatment effects may be have different meaning and can be attributed to different interventions
  - It is like a subgroup analysis, where groups are defined by post-treatment variables
  - This is why is crucial to characterize the subgroups based on the covariates

- **Average Treatment Effect (ATE)**, that is, the effect if everybody, contrary to fact, were forced to take or not take the treatment, is like a **Hypothetical Strategy**, often requiring assumptions of a different type
What can we learn from the PS literature and the talks today

- RCTs with intercurrent events should be designed and analyzed through the lenses of observational studies

- What makes observational studies credible?
  - Plausibility of assumptions
  - Covariates (to assess and describe populations)
  - Sensitivity analysis to deviations from such assumptions

- The plus of having initial randomization on our side!
  - Some assumption hold by design because of randomization (e.g., random assignment = random instrument, monotonicity)
  - Randomization has useful implications for identification and estimation (e.g., PS distribution is the same across treatment arms)
What are the implications for study protocol

- Anticipate intercurrent events so that estimands are defined a priori and possibly incorporated into treatment regimes (different complications imply focus on different subgroups/principal strata).

- Think about plausible assumptions and collect relevant baseline covariates or plan to collect secondary outcomes that may help identification in different ways.

- Identify and collect baseline covariates that you anticipate being associated with PS membership that may help characterize/describe the principal stratum (as with missing data/dropout).

- Do not forget other principal strata! (size and characteristics); include it as a secondary analysis, it may help extrapolate effects to other subgroups or to whole population.

- Plan analysis (Bayesian) and sensitivity analysis.
How can RCTs and causal inference literatures connect

- A lot can be learned from RCTs even with intercurrent events!

- Tools for estimation and sensitivity analysis are possible

- Develop tools that are flexible enough to accommodate several types of intercurrent events and covariates


