Causality assessment from clinical trials

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Randomized experiments are considered the mainstay design for causal inference.

Why?

From Clinical Trials to Observational Studies

From:
- A multicenter, international, randomized, double-blind, parallel-group, 52-week clinical safety study to demonstrate that NEW DRUG X reduces the risk of a predefined ADVERSE EVENT Y as compared to STANDARD TREATMENT, in patients with specific DISEASE Z.

To:
- Risk of outcome Y in relation to Drug X.

Key Issues in Clinical Trials

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**Observational**: Longitudinal (versus cross-sectional) studies in which the temporal order of treatment and outcome is clear.

**How to achieve comparability?**
- Matching, restriction, modeling,
- Propensity scores, instrumental variables, structural nested models,
- Quantification of unmeasured confounding...

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**Reference group**: Active therapy or placebo.
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<td>Loss to follow up &amp; Compliance. Intent-to-treat vs. Per protocol analyses</td>
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### From Clinical Trials to Observational Studies

- Why are they so different?
- Are certain clinical trials more like observational studies?
  - Loss to follow up and compliance
- Can observational studies be more like clinical trials?

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### Exposure Definition

- Intention to treat (ITT), as randomized
  - Pseudo-ITT, if incomplete follow up
  - Complete-case ITT, if incomplete follow up
  - Per protocol analysis, if incomplete follow up
- As treated
- Adherence adjusted

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### Intention to treat (ITT)

- Assigned to one group (arm \( R=1 \)) vs. assigned to the other (arm \( R=0 \)) to be treated regardless of the treatment that each subject actually received.
  - If a difference is found, then treatment is declared to have a causal effect on the outcome because these two groups are expected to be exchangeable with respect to all measured and unmeasured characteristics at baseline.
Intention to treat (ITT)

- Full compliance and no loss to follow up
  - Outcome in group R=1, is also the outcome among the treated, $E[Y|R=1] = E[Y|A=1]$
  - Outcome that would have been observed if all subjects in the population had been treated, $E[Y|a=1]$
  - Similarly $E[Y|R=0] - E[Y|A=0] = E[Y|a=0]$
  
  \[ E[Y \mid R = 1] - E[Y \mid R = 0] = E[Y \mid A = 1] - E[Y \mid A = 0] \]

“Pseudo-ITT” analysis

- When there is incomplete follow up (outcome unknown for some subjects) use the last available observation carried forward.
- Assumptions:
  - No selection bias: those with and without complete follow-up are exchangeable, i.e., unconditional sequential randomization of censoring. Strong assumption.
  - Effect of treatment is the same over time of follow up.

“Complete-case” ITT analysis

- ITT analysis restricted to subjects who completed the follow-up.
- Assumption:
  - No selection bias: those with and without complete follow-up are exchangeable, i.e., unconditional sequential randomization of censoring. Strong assumption.

“Per protocol” analysis

- Even if there is complete follow up, subjects might not stay on their assigned treatment.
- A “Per protocol” analysis compares subjects who stayed on treatment.
- Estimates the effect of continuous treatment.
- Assumption:
  - No selection bias: those with and without full compliance are exchangeable.
As treated

- Participants may deviate from the trial's protocol by
  - switching to a treatment other than that assigned to them
  - dropping out of the study completely
- The greater the proportion of subjects who deviate from the trial's protocol, the more questionable the ITT analysis becomes.

As treated

- Classifies subjects according to the treatment that they actually took.

As treated

- Deviations from protocol are not randomly assigned
- Comparison will be confounded if the reasons that moved participants to take treatment were associated with prognostic factors

As treated

- The greater the proportion of subjects who deviate from the trial's protocol, the closer the resemblance between the RCT and an observational study.
- "large simple trial" or naturalistic trial
- Long follow up makes RCT similar to observational studies with time-varying treatment (with baseline randomization)
  - In the presence of time-varying treatments, what effect do we want to estimate? Continuous treatment during the entire follow-up?
  - Like in observational studies, investigators can collect data on patients characteristics potentially associated with censoring and outcomes.
  - Time-varying confounders are affected by previous treatment

Adherence adjusted

- Estimates the effect that would have been observed if all participants had fully adhered to the treatment originally assigned to them.
Adherence adjusted

- Estimating the effect of continuous treatment requires data on:
  - the time-varying treatment and
  - joint predictors of compliance and the outcome
- And adjustment for such predictors.
  - standard adjustment methods (e.g., stratification, regression analysis, matching) may introduce selection bias when estimating the effect of continuous treatment
  - Inverse probability weighting (IPW), g-estimation, and instrumental variable estimation can reduce the bias introduced by nonadherence and loss to follow-up.

Example

HR: 1.24 (95% CI: 1.00, 1.54)


Conclusions

- Define your research question and the effect you want to estimate
- Well-defined interventions also crucial in causality assessment for observational studies
- Deal with loss to follow up and incomplete adherence appropriately

Conclusions

- ITT analyses often underestimate the treatment effect and are therefore nonconservative for both safety trials and noninferiority trials.
- ‘as treated’ and ‘per protocol’ may be affected by selection bias in either direction.
  - The estimates from these analyses can only be interpreted as the effect of treatment if the analysis is appropriately adjusted.

Conclusions

- RCTs with substantial lack of adherence or loss to follow-up should be analyzed using different methods, including an ITT analysis to estimate the effect of assigned treatment, and appropriately adjusted ‘per protocol’ and ‘as treated’ analyses (i.e., via IP weighting or g-estimation) to estimate the effect of received treatment.
- RCT protocols should include plans to measure adherence and other post-randomization variables.