Methodological considerations and treatment of non-randomized controlled trial (RCT) data

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Why RCTs can be useful

1. Participants in treatment groups are **“exchangeable,”** on average. *I.e.,*

   Risks of outcome prior to treatment assignment are distributed evenly across groups.

   No confounding.

Why RCTs can be useful

2. **Treatments** (and non-treatment) are **well-defined** (consistency).

   E.g., In-home music therapy twice per week for 12 weeks with designated therapist and protocol vs. wait list …

   … as opposed to …

   …any music therapy vs. no therapy over 12-week period.

But RCTs are not a panacea for all questions about effective strategies of care

1. Impracticalities of **duration**

2. Can **evaluate only few treatments** at a time. Limited capacity for comparing effectiveness

   E.g., different frequencies of cognitive rehabilitation
   E.g., PWD caregiver social support + cognitive rehabilitation for PWD *vs* one of these *vs* neither.

3. RCT **participants may not reflect population(s)** to which we would like to apply findings.

Potential for non-RCT research to inform care interventions for PWD and their caregivers

Numerous past and ongoing large cohort studies with prospective data collection, representing wide variety in …

- Interventions represented (types, durations, patterns)
- Settings
- Caregiver and PWD characteristics

Harnessing the potential of non-RCT research

1. Design and analyze as if they were RCTs, i.e., "**target trial emulation**"

   Hernán MA, Robins JM. Using big data to emulate a target trial when arandomized trial is not available. *Am J Epidemiol*. 2016 Apr 15;183(8):758-64. frequencies of cognitive rehabilitation

   Match design and analysis choices to fit protocol of RCT you would have conducted

   - Eligibility criteria, treatment strategies, assignment procedures, definition of "time zero" and follow-up period, outcome of interest, causal contract of interest, analysis plan
   - Substitute analytic strategies where protocol impossible to match (e.g., adjustments instead of random assignment)

Harnessing the potential of non-RCT research

2. Use of strategies to address plausible non-causal explanations for findings

- **Confounding** (different risks for outcome prior to "treat
- **Selection bias** (participation and continuation in st
  and risk of outcome; in RCTs, too)
- **Mismeasurement** (of key exposure, outcome, con
- **Reverse causation** (outcome influences exposure)
- **Treatment-confounder feedback bias** (when evaluating patterns of exposure over time, and earlier exposure affects a factor that influences both later exposure and the outcome)

Also use **quantitative bias analysis:** what conditions could "explain away" these findings? Are they plausible?

Harnessing the potential of non-RCT research

3. **How well do results transport** to other settings and populations?
    - Suppose the results of a RCT non-RCT have been determined to be valid *within the study population*.
    - What would the **impact be in a different target population?**
    - The **science of transportability**.
        - Can we identify the transportability of an intervention?
        - Can we satisfy assumptions needed to estimate the effect in another population?
        - What is the impact in another population?

Westreich D, et al. Causal Impact: Epidemiological Approaches for a Public Health of Consequence. *Am J Public Health*. 2016 Jun;106(6):1011-2.
Hernán MA, VanderWeele TJ. Compound treatments and transportability of causal inference. *Epidemiology*. 2011 May;22(3):368-77.

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