BROWN
School of Public Health

The Many Tentacles of Estimands: Patient-Reported Outcomes, Real-World Evidence, Health Economics and Outcomes Research, and Beyond

Lightning Introduction to the Potential Outcomes Framework

Roee Gutman, Department of Biostatistics, Brown University

roeegutman.wordpress.com

Virtual ISPOR, May 2021

Polling Question

BROWN
School of Public Health

- Have you heard of the potential outcomes framework?

Goal

BROWN
School of Public Health

- We are interested in learning about the effect of intervention (W) on an outcome (Y)
- Possible clinical outcomes
  - Mortality
  - Progression free survival
- Possible patient reported outcomes (PROs)
  - Time to clinically meaningful improvement in fatigue
  - Patient Quality of Life 3 months after initiation
- Possible system performance outcomes
  - Healthcare expenditures

Intervention

BROWN
School of Public Health

- Causality is tied to an action (or manipulation, treatment, or intervention)
- Example:
  - Ibrutinib combined with bendamustine and rituximab – **add-on therapy**
  - **Placebo**, bendamustine, and rituximab

Potential Outcomes

BROWN
School of Public Health

- **Key question: what *would* have happened, under a different treatment?**
- A potential outcome is the value of the outcome variable for a given value of the treatment
- Y(add-on) = Fatigue improvement at 3 months (Y/N)
- Y(Placebo) = Fatigue improvement at 3 months (Y/N)
- Possibilities:
  - Y(add-on) = N, Y(Placebo) = Y — **Placebo better**
  - Y(add-on) = Y, Y(Placebo) = N — **Add-on better**
  - Y(add-on) = Y(Placebo) = Y
  - Y(add-on) = Y(Placebo) = N

  } **No causal effect**

Causal Effects

BROWN
School of Public Health

- The causal effect is the comparison of the potential outcome under the different treatments
- The mathematical description by which we compare those potential outcomes are called estimands.
- A possible estimand with quantitative potential outcomes is Y(add-on) – Y(placebo)

Units

BROWN
School of Public Health

- These are unit-level causal effect
- Unit: the person, place, or thing upon which the treatment will operate, *at a particular point in time*
- Note: the same person at different points in time = different units
- With quantitative outcomes, the causal effect will probably not be the same for each unit (treatment effect heterogeneity)

Estimation

BROWN
School of Public Health

- For the definition of a causal effect we compare potential outcomes for a single unit
- However, in reality, we can only see ***one*** potential outcome for each unit
- For estimation of a causal effect we need to consider multiple units,
  - Need to compare similar units, some exposed to either of the possible treatments
  - Can be same units at different points in time, or different units at the same point in time

Potential Outcomes with Two Units

BROWN
School of Public Health

- Y_1(add-on, add-on) = Fatigue Y/N
- Y_1(add-on, Placebo) = Fatigue Y/N
- Y_1(Placebo, add-on) = Fatigue Y/N
- Y_1(Placebo, Placebo) = Fatigue Y/N
- Y_2(add-on, add-on) = Fatigue Y/N
- Y_2(add-on, Placebo) = Fatigue Y/N
- Y_2(Placebo, add-on) = Fatigue Y/N
- Y_2(Placebo, Placebo) = Fatigue Y/N
- **Worse problem**

SUTVA

BROWN
School of Public Health

- Often we need to make assumptions, without which we cannot perform further analyses
- A common assumption is the Stable Unit Treatment Value Assumption (SUTVA)

SUTVA (cont.)

BROWN
School of Public Health

- SUTVA has two components:
  - *No interference* (units do not interfere with each other): treatment applied to one unit does not effect the outcome for another unit
  - There is only a single version of each treatment level (potential outcomes must be well defined)
- It cannot be verified from the data, and are based entirely on subject matter knowledge and reasoning
  - Many randomized trials are designed such that SUTVA is plausible

Covariates

BROWN
School of Public Health

- When dealing with multiple units one way to distinguish between units are with covariates.
- A set of variables that are unaffected by the treatment.
- May be related to treatment assignment and/or the outcome
- Usually they are defined by X.

The Observed Data

BROWN
School of Public Health

Patient #	Covariates (X)	Treatment Received (T)	Potential Outcomes		
			Outcomes Treatment 0	Outcomes Treatment 1	Outcomes Treatment 2
1	X_1	0	$Y_1(0)$	?	?
…	…	…	…	?	?
n_1	X_{n_1}	0	$Y_{n_1}(0)$	?	?
n_1+1	X_{n_1+1}	1	?	$Y_{n_1+1}(1)$	?
…	…	…	…	…	?
n_1+n_2	$X_{n_1+n_2}$	1	?	$Y_{n_1+n_2}(1)$	?
n_1+n_2+1	$X_{n_1+n_2+1}$	2	?	?	$Y_{n_1+n_1+1}(2)$
…	…	…	?	…	…
N	X_N	2	?	?	$Y_N(2)$

The Estimands

BROWN
School of Public Health

- Unit level effects
  - $Y_i(s)$ vs. $Y_i(t)$, $\forall s, t \in \{1, \ldots, D\}$
- Population level effects
  - The average difference $\frac{1}{N}\sum_{i=1}^{N}(Y_i(1) - Y_i(0))$
  - The median difference $median(Y_i(1) - Y_i(0))$
  - The odds ratio when the outcome is binary
  - The average effect among women
  - The average effect within temperature classes
  - Odds ratio for men

Estimands - PRO

BROWN
School of Public Health

- PROs may introduce additional complexities that commonly arise from intercurrent events
  - For example, patients are unable to respond
- Possible estimands:
  - While on treatment
    - When the outcome are events $E(Y_i(s)/t_i - Y_i(t)/t_i)$
  - Principal Stratification
    - Estimate the effect only among those that survive under both treatments
  - Hypothetical
    - Estimate the effect assuming plausibpatients outcomes after intercurrent event.

Estimands – PRO (cont.)

BROWN
School of Public Health

- Possible estimands:
  - Composite estimands
    - Assume that either intercurrent event or lack o of improvement in fatigue are bad outcome
  - Intention to Treat
    - In some cases it is possible to observe the PRO even after intercurrent event (e.g. change of drug). A possible estimand is $E(Y_i(s) - Y_i(t))$.