Principal Stratification

Frangakis and Rubin (2002)

March 1, 2018

Problem of Adjusting for Post-Treatment Variables

Z = treatment assignment (0 or 1)
S = post-randomization outcome (intermediary)
Y = outcome of interest

Comparisons of $\{Y|S = s, Z = 0\}$ vs. $\{Y|S = s, Z = 1\}$ are biased.

DAG

Examples

- Clinical trials, where S is a measure of compliance.
- Studies with long follow-up, where whether or not the subject drops out is a post-treatment variable.
- Studies where the outcome intended to be recorded can be censored by death.
- Surrogate marker studies.

Example. Clinical Trial in ICU

336 mechanically ventilated patients in intensive care

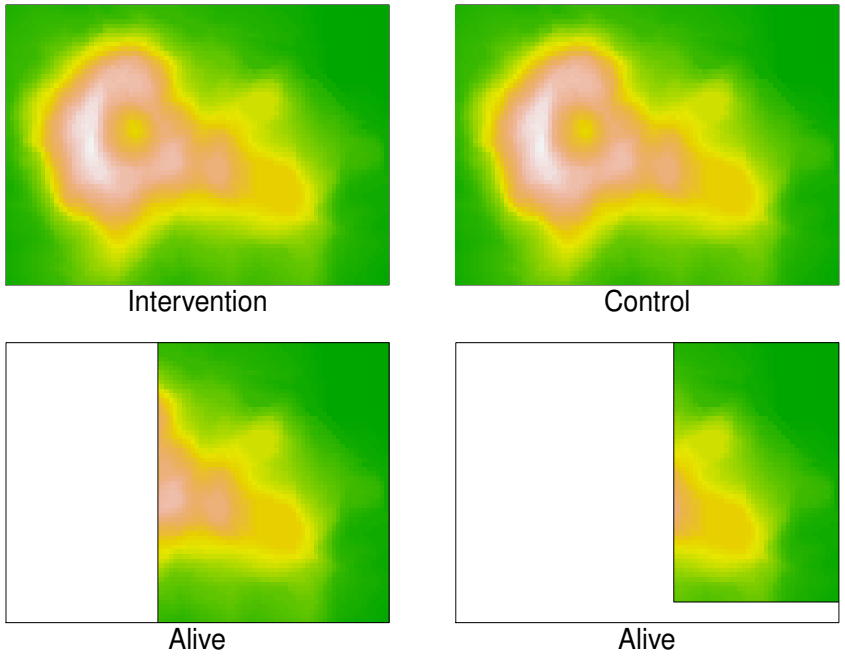
- 168 randomized to intervention (spontaneous awakening through interruption of sedatives)
- 168 randomized to standard of care
- intervention protected against death
    - 58% lived in intervention arm, 39% in control arm; p=0.01.

(Girard TD, et al. (2008). *Lancet*)

Possible Question

What is the impact of the intervention among survivors?

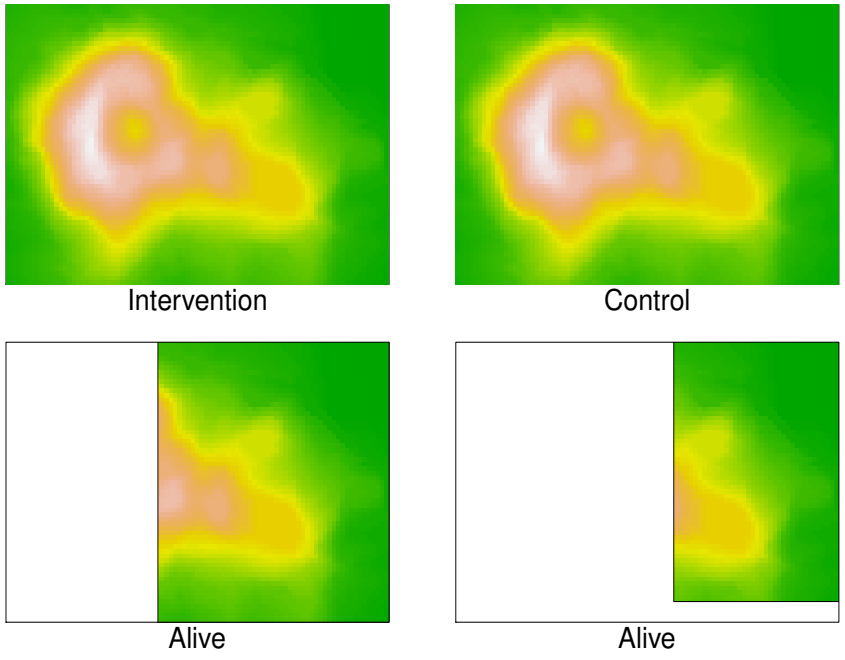
- $E[Y(1)|S(1) = 1] - E[Y(0)|S(0) = 1]$.
- Conditions on post-randomization variable and could lead to bias.



Another Possible Question

What is the impact of intervention on composite endpoint of death and poor cognitive function (Y^*)?

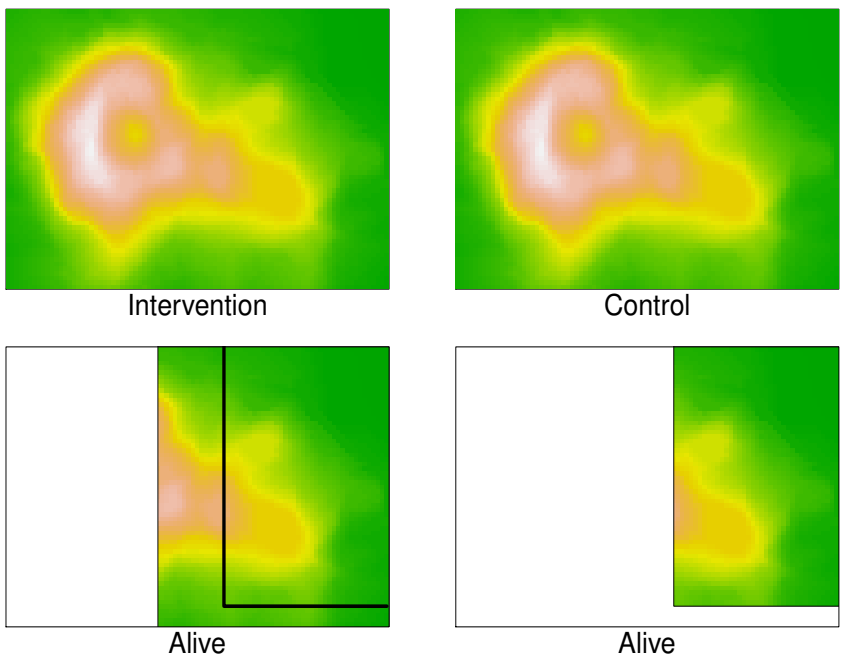
- $E[Y^*(1)] - E[Y^*(0)]$.
- Results dominated by intervention's impact on death.



Another Possible Question

What is the impact of intervention on cognitive function among those who would have survived regardless of treatment assignment?

- $E[Y(1) - Y(0)|S(0) = S(1) = 1]$



Principal Stratification Definition

(a) The basic principal stratification P_0 with respect to posttreatment variable S is the partition of units $i = 1, \cdots, n$ such that, within any set of P_0, all units have the same vector $(S_i(0), S_i(1))$.

(b) A principal stratification P with respect to posttreatment variable S is a partition of the units whose sets are unions of sets in the basic principal stratification P_0.

(c) A principal effect is a comparison of potential outcomes under standard versus new treatment within a principal stratum.

PROPERTY 1: The stratum to which unit i belongs is unaffected by treatment for any principal stratification P.

PROPERTY 2: Any principal effect is a causal effect.

Principal Stratification

Key Publications:

- Robins JM (1986). *Mathematical Modelling*.
  - First mention of the basic idea.
- Angrist JD, Imbens G, and Rubin DB (1996). *JASA*.
  - Idea developed for the compliance literature.
- Frangakis CE and Rubin DB (2002). *Biometrics*.
  - Coined term "Principal Stratification" and popularized idea
  - Lots of citations

Principal Strata

- $S(0) = 0, S(1) = 0$: doomed.
- $S(0) = 0, S(1) = 1$: protected.
- $S(0) = 1, S(1) = 0$: harmed.
- $S(0) = 1, S(1) = 1$: always survivors.

	$Z = 0$	$Z = 1$
$S = 0$	doomed protected (n_0)	doomed harmed (n_1)
$S = 1$	always survivors harmed $(N_0 - n_0)$	always survivors protected $(N_1 - n_1)$
	N_0	N_1

Surrogate Endpoints

Prentice Criterion (1989)

- Distribution of the true endpoint conditional on the surrogate endpoint does not depend on the intervention.
- Called a statistical surrogate by Frangakis and Rubin.

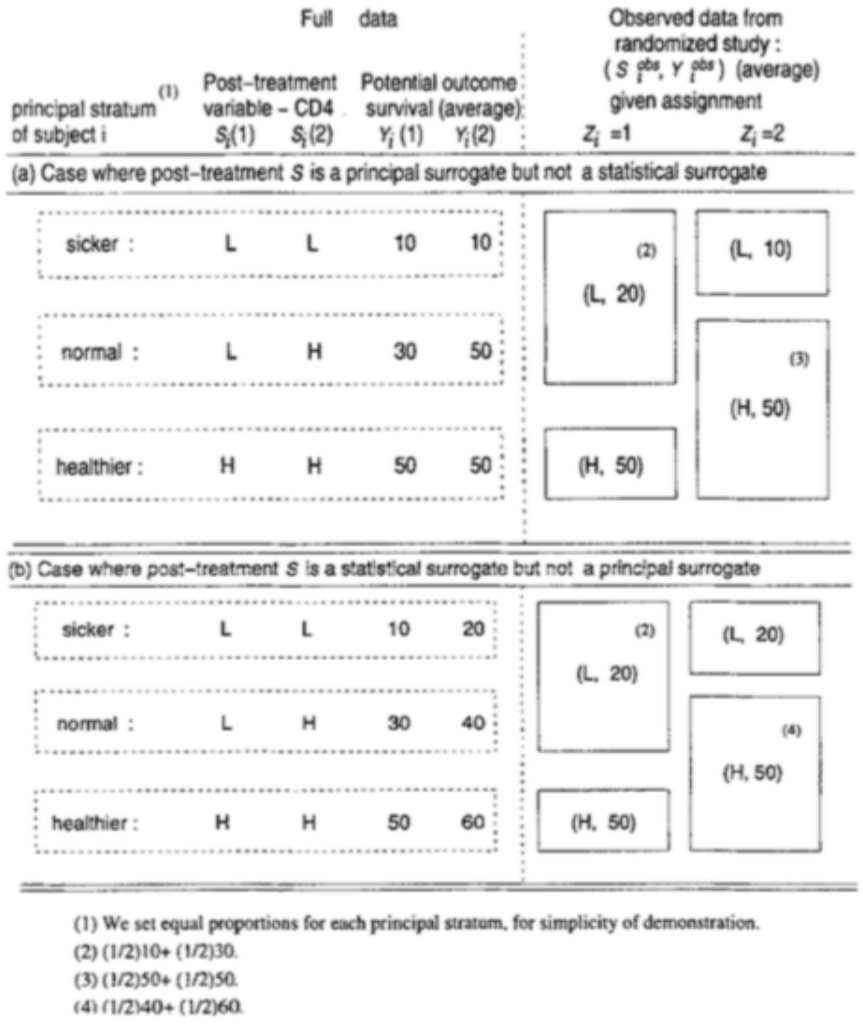
Frangakis and Rubin: In order for S to have an appropriate interpretation as a surrogate it should possess the following two properties:

- Causal Necessity: S is necessary for the effect of treatment on the outcome Y in the sense that an effect of treatment on Y can occur only if an effect of treatment on S has occurred.
- Statistical Generalizability: S^{obs} should well predict Y^{obs} in an application study, where we do not wait for measurements Y^{obs}.

Principal Surrogate

S is a principal surrogate for a comparison of the effect of $z = 1$ versus $z = 0$ on Y if, for all fixed s, that comparison between the ordered sets $\{Y_i(1) : S_i(1) = S_i(0) = s\}$ and $\{Y_i(0) : S_i(1) = S_i(0) = s\}$ results in equality.

Principal Surrogate Differs from Statistical Surrogate



(1) We set equal proportions for each principal stratum, for simplicity of demonstration.
(2) (1/2)10+ (1/2)30.
(3) (1/2)50+ (1/2)50.
(4) (1/2)40+ (1/2)60.

Figure 1. Distinction between statistical and principal surrogates. Dashed boxes represent missing information, solid boxes represent observed information.