Evaluation of Clinical Endpoints as Potential Surrogates of Clinical Progression of ALS: A Causal Mediation Approach

MGH Biostatistics Seminar Series

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Roadmap

Background

Notation

Methods

Discussion

Background

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disease with no known cure

- Typical age of onset: 40-70 years
- Characterized by gradual loss of motor neurons controlling voluntary muscles
- Eventually causes paralysis and early death

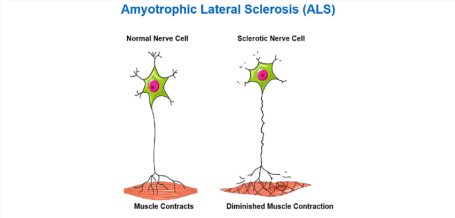

Figure 1: Diagram from Mentis et al. (2021).

Average survival length: 2-5 years

Slow Clinical Development

Key issue: Development of drugs for ALS is slow

- Only 3 FDA-approved treatments, despite > 120 trials being conducted since 2000
  - One (Relyvrio) had approval revoked this year
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Above challenges are further compounded by **budgetary** constraints

- Difficult to detect differences in standard primary outcomes with typical trial durations (24-28 weeks)

Ongoing Work: Surrogate Outcomes of Clinical Progression

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Biogen's VALOR trial for tofersen, a treatment targeted toward ALS associated with mutations in the SOD1 gene, provides some precedent for this growing push

- Granted accelerated approval based on a surrogate analysis of serum neurofilament (NfL), an indicator of neural damage

Tofersen failed to meet its primary endpoint...

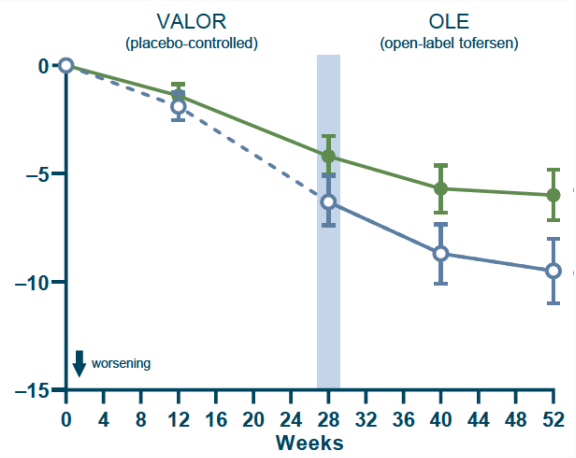

Figure 2: Estimated mean (±SE) change from baseline in ALSFRS-R total score. Green=tofersen at baseline, blue=placebo at baseline. Figure from Miller et al. (2022).

...but ultimately earned accelerated approval based on surrogate analysis of NfL

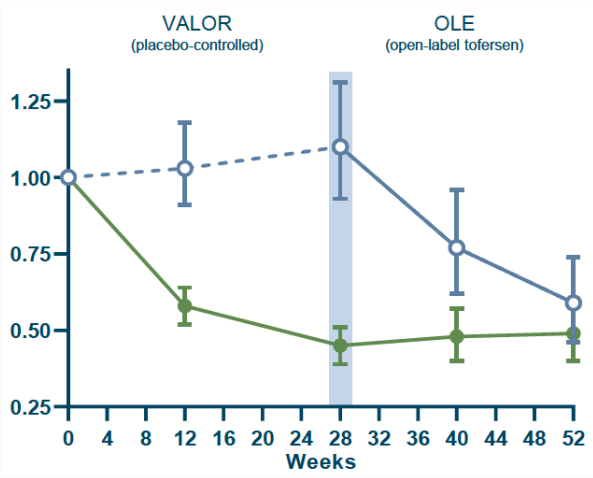

Figure 3: Estimated geometric mean ratio (95% CI) to baseline of NfL. Green=tofersen at baseline, blue=placebo at baseline. Figure from Miller et al. (2022).

Surrogate Outcome Assessment

The statistical assessment of surrogate outcomes is an active research field with a long history

- Big picture goal: find short term outcomes that are predictive of treatment effects on the longer-term primary outcome
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Existing surrogate assessment approaches in ALS research are relatively ad-hoc

- No general sense of existing methods' relative merits

Objectives

1. Propose a unifying framework for assessing the quality of an endpoint for serving as a surrogate for long-term survival, using modern tools from causal mediation analysis
    - **Purpose**: in a model-agnostic manner, provide causal estimands + estimators for ALS researchers aiming to assess candidate surrogate endpoints

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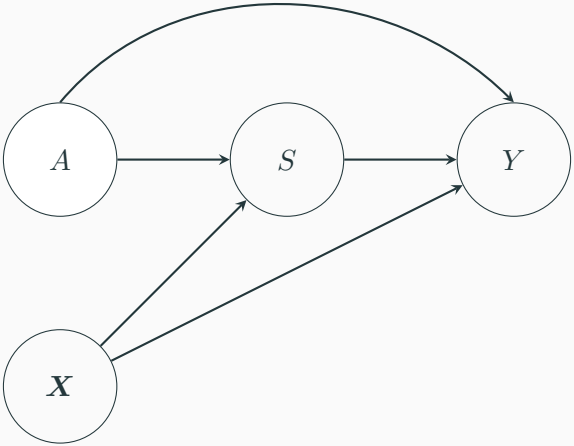
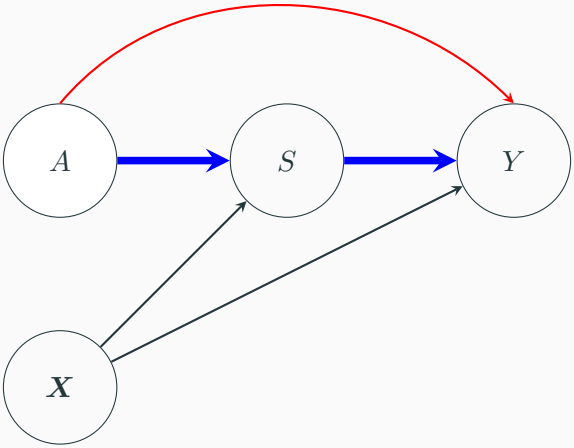
- S_i is a potential surrogate outcome: e.g. serum NfL levels measured 16 weeks post-baseline
- A_i is a binary active treatment indicator: $A_i = 1$ if participant i received active treatment (e.g. tofersen) at baseline
- $\boldsymbol{X}_i$ is a vector of covariates: e.g. age, location of onset, baseline ALSFRS-R, etc



Strong surrogate will have large indirect effects relative to size of direct effects



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Statistical Approach (Baron and Kenny, 1986)

Standard approach to mediation analysis is purely statistical: one postulates linear models for both S and Y:

$$S_i = \alpha_0 + \boldsymbol{X}_i^\top \alpha_{\boldsymbol{X}} + \alpha_A A_i + \epsilon_i, \quad \mathbb{E}[\epsilon] = 0$$

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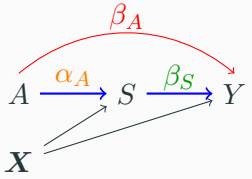
Intuition:



Drawbacks

While the statistical approach is attractive for its parsimony, it suffers from numerous drawbacks:

- Heavily model-dependent
  - No straightforward extension to e.g. nonlinear conditional expectation functions
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In turn, will work extensively with potential outcomes

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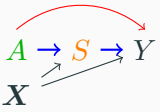
- And Y^0 week 28 ALSFRS-R under placebo ($A = 0$)

The primary estimand in trials is often a contrast of these potential outcomes, e.g. the average treatment effect $\mathbb{E}[Y^1 - Y^0]$

Potential Outcomes in Mediation Analysis



To assess the strength of NfL as a surrogate, we ask *how much of the effect of tofersen on survival/function would remain if we could modify the NfL-dependent pathway?*

This means we need to consider potential outcomes under **joint interventions** which manipulate both treatment assignment and the surrogate

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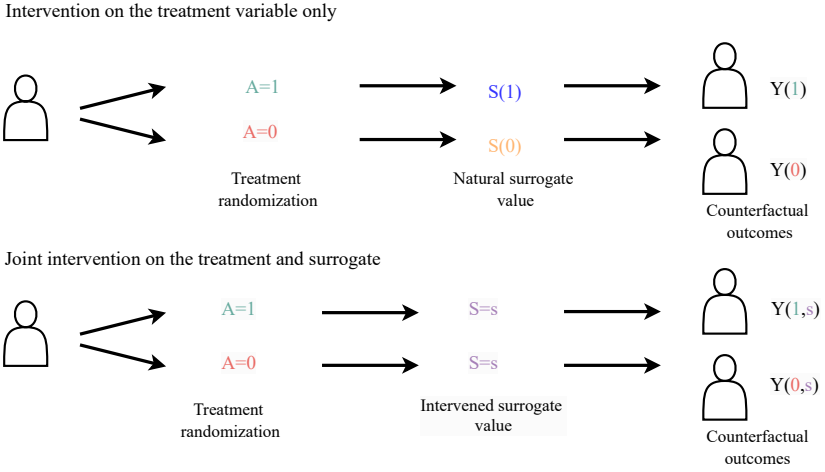
Will consider two frameworks, which will differ in the joint interventions they conceptualize

- Specifically, what values of s are imposed

Joint Interventions



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The ATE can be decomposed into direct and indirect effects

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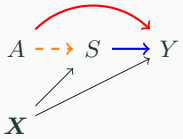

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Quantifying Surrogate Strength

Numerous quantities of interest involving the NIE, including

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This notion of surrogate strength has seen a spike in use in vaccine efficacy trials that aim to find immune markers that act as surrogates for long-term infection risk

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Above, care is required to identify + estimate $\mathbb{E}[Y^{1,S^0}]$

Assumptions

1. Consistency: **(i)** $Y = AY^1 + (1-A)Y^0$, **(ii)** $S = AS^1 + (1-A)S^0$, and **(iii)** $(A, S) = (a, s) \implies Y = Y^{a,s}$
2. Positivity:
   $0 < \mathbb{P}(A = 1|\boldsymbol{X}) < 1$, and
   $f_S(s|A = 1, \boldsymbol{X}) > 0 \iff f_S(s|A = 0, \boldsymbol{X}) > 0$ for all s
3. Unconfoundedness:
   - $S^a \perp\!\!\!\perp A|\boldsymbol{X}$ for $a = 0, 1$
   - $Y^{a,s} \perp\!\!\!\perp A|\boldsymbol{X}$ for all a, s
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For identification of $\mathbb{E}[Y^{1,S^0}]$, we additionally require

4. Cross-world exchangeability: $Y^{1,s} \perp\!\!\!\perp S^0|\boldsymbol{X}$ for all s

Mediation Formula (Zheng and Van Der Laan 2012)

Under these independence assumptions, it can be shown that

$$\mathbb{E}[Y^{1,S^0}] = \mathbb{E}\{\ \mathbb{E}[\quad \mathbb{E}(Y|S, A=1, \boldsymbol{X}) \quad |A=0, \boldsymbol{X}\ ]\ \}$$

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3. Take an average of these predicted values to obtain a final estimate: $\frac{1}{n}\sum_{i=1}^{n} \hat{\mu}_0(\boldsymbol{X}_i)$

Estimation: high-level

Once we've estimated $\mathbb{E}[Y^{1,S^0}]$, estimation of $\frac{\mathsf{NIE}}{\mathsf{ATE}}$ is straightforward:

- Numerous off-the-shelf methods available to estimate $\mathbb{E}[Y^1]$ and $\mathbb{E}[Y^0]$
- Can then form the final estimate as

$$\frac{\widehat{\mathsf{NIE}}}{\widehat{\mathsf{ATE}}} = \frac{\hat{\mathbb{E}}[Y^1] - \hat{\mathbb{E}}[Y^{1,S^0}]}{\hat{\mathbb{E}}[Y^1] - \hat{\mathbb{E}}[Y^0]}$$

Can adopt an estimating equations framework, or base inference on the influence functions of the above estimators

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Stochastic intervention effects

Consider estimands of the form

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Relative to natural effects targeting Y^{1,S^0}, such interventions are more plausible to conceive scientifically

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$$\mathsf{STE}(c) \stackrel{\mathsf{def}}{=} \mathbb{E}[Y^{1,S^1+c}] - \mathbb{E}[Y^{0,S^0}], \quad c \in \mathbb{R}$$

Represents a contrast of potential outcomes under two interventions

- Y^{1,S^1+c}: Provide treatment, and shift the resulting surrogate outcome by c units
- Y^{0,S^0}: Provide placebo, and don't intervene on surrogate (equivalent to Y^0)

Interpretation: If the treatment shifted each individual's surrogate by an additional c units, what would we expect the overall treatment effect to be?

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Framework has been used to assess immune markers for surrogacy in vaccine efficacy trials (Hejazi et al., 2021; Huang et al., 2023; Hejazi et al., 2023)

Estimation

STE(c) consists of two components:

- $\mathbb{E}[Y^{1,S^1+c}]$: Identification requires additional assumptions
- $\mathbb{E}[Y^{0,S^0}] = \mathbb{E}[Y^0]$: Identified by assumptions typically enforced by design in clinical trials

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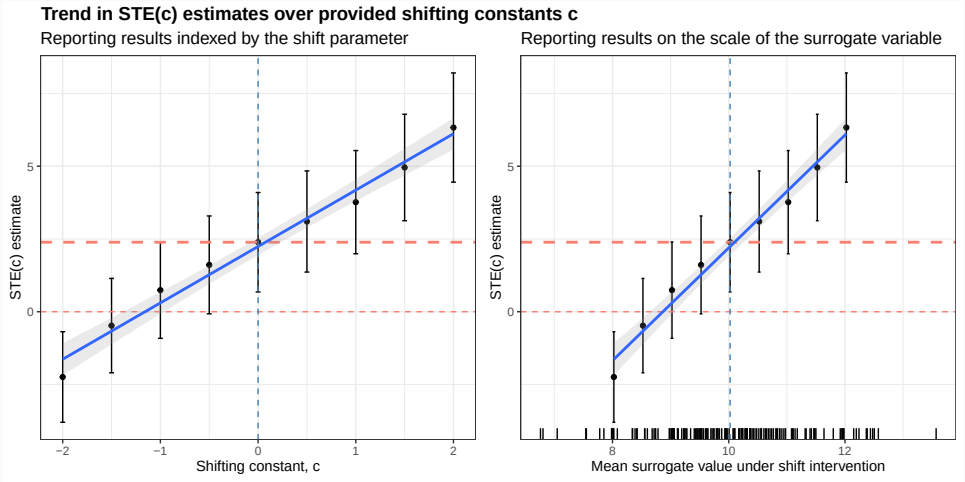
Under a sequential exchangeability assumption $Y(1,s) \perp\!\!\!\perp S | \boldsymbol{X}, A = 1$,

$$\mathbb{E}[Y^{1,S^{1+c}}] = \mathbb{E}[\ \mathbb{E}\{\ \mathbb{E}(Y|A=1, S+c, \boldsymbol{X}) \mid \boldsymbol{X}, A=1\}\ ]$$

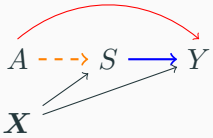
$\implies$ can base estimation + inference on the efficient influence function for the above statistical estimand (Hejazi et al., 2021)

Visualizing STE(c)



Comparing the Two Frameworks

Natural effects framework



Estimand: $\mathbb{E}[Y^{1,S^0} - Y^0]$

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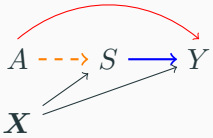

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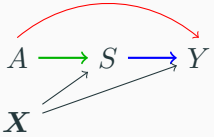

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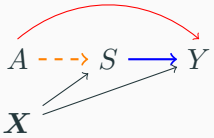

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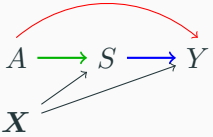

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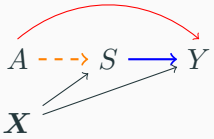

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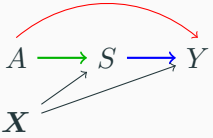

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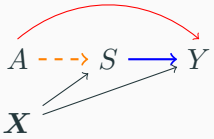
Natural effects: Give participant active treatment, and set their surrogate to the value it would take on under placebo (effectively blocking the effect of A on S)

Comparing the Two Frameworks

Natural effects framework



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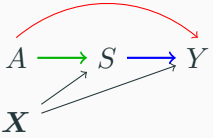

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Stochastic interventions: Give participant active treatment, and shift the resulting surrogate by c total units

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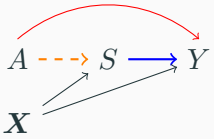

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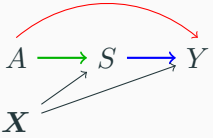

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The stochastic intervention framework requires a less stringent set of conditions to identify relative to the natural effects framework

Roadmap

Short trial durations

ALS trials are often under-powered, typically due to short trial durations

- If ATE ≈ 0 with short trial durations...
- There may be little utility in asking how much of this ATE of ≈ 0 is explained by S?

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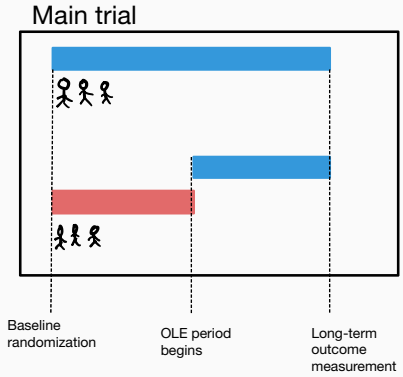
ALS trials commonly incorporate an open-label extension (OLE) period, during which all participants electing to continue in the trial are put on active treatment

- Provides opportunity to observe treatment responses under active treatment over long time horizons, where outcomes may be more responsive to treatments
- Also presents a set of statistical **challenges**

Open-Label Extension + External Controls



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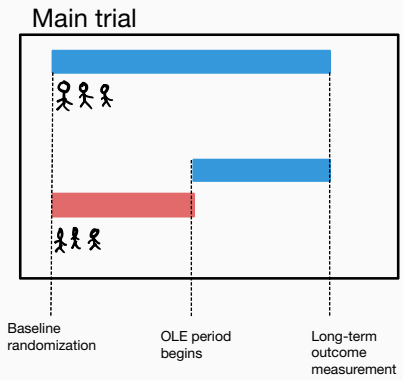
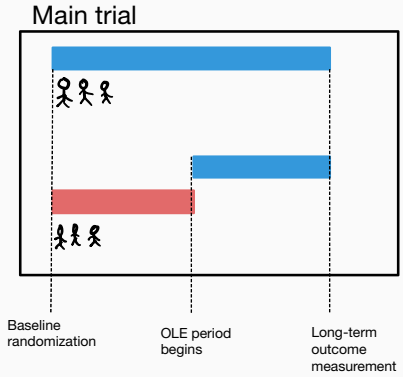


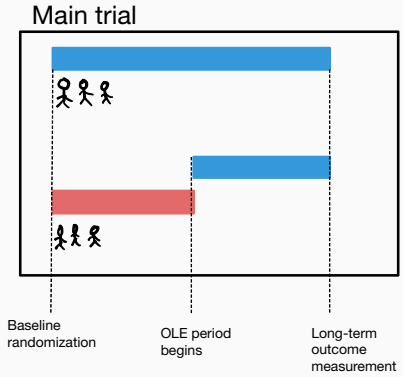
Observe both (i) the primary outcome at the end of the main trial (Y) and (ii) a long-term outcome at the end of the OLE ($\tilde{Y}$)

Open-Label Extension + External Controls



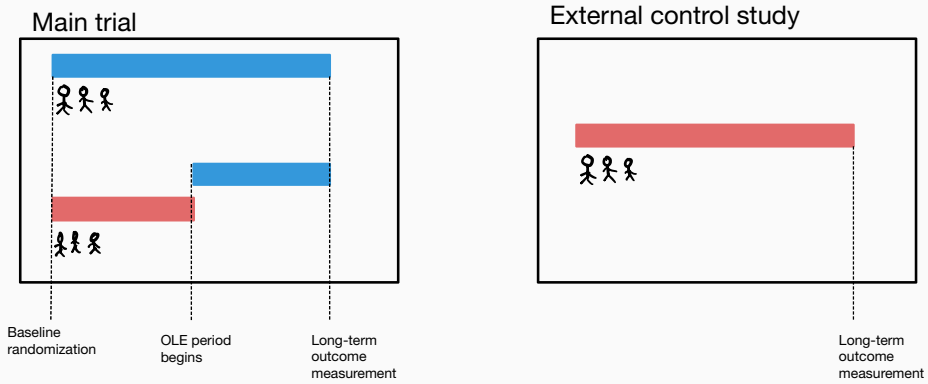
Three possible treatments: **(i)** $A = 1$: active treatment over duration of study, **(ii)** $A = 0$: placebo over duration of study, and **(iii)** $A = -1$: switch from placebo to treatment during the study

Open-Label Extension + External Controls



Challenge: $A = 0$ is never observed within the main trial

Open-Label Extension + External Controls



Workaround: Incorporate long-term data from an external control study

Main Idea

Suppose we observe data from two studies

$$(\tilde{Y}_i, Y_i, A_i, \boldsymbol{X}_i),\ i = 1, \ldots, n_0 \qquad \text{(Main trial)}$$

$$(\tilde{Y}_i, Y_i, A_i = 0, \boldsymbol{X}_i),\ i = 1, \ldots, n_1 \qquad \text{(External controls)}$$

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Implies the pooled data structure

$$(\tilde{Y}_i, Y_i, A_i, \boldsymbol{X}_i, R_i),\ i = 1, \ldots, n_0 + n_1,$$

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Target estimand:

$$\mathsf{STE}_{R=0}(c) := \mathbb{E}[\tilde{Y}^{1,S^1+c} | R = 0] - \mathbb{E}[\tilde{Y}^0 | R = 0]$$

Identification + Estimation: High-level

$\text{STE}_{R=0}(c) := \mathbb{E}[\tilde{Y}^{1,S^1+c}|R=0] - \mathbb{E}[\tilde{Y}^0|R=0]$ can be broken into two pieces

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The above statistical estimand can be estimated with methods proposed in Hejazi et al. (2021) + can be extended to account for informative study drop-out

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The above statistical estimand can be estimated with methods proposed in Hejazi et al. (2021) + can be extended to account for informative study drop-out

Identification is not impacted by the open-label extension design

- Not true for the NIE, since $\mathbb{E}[Y^{1,S^0}|R=0]$ involves a joint intervention that includes S^0, an outcome under placebo

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Does not require measurement of S in the external control study

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Can construct plug-in or doubly-robust estimators using tools from the causal data fusion literature (Zeng et al., 2023)

In ongoing work, we're developing methods which additionally account for informative study dropout and censoring due to death

Roadmap

Background

Notation

Methods

Discussion

Stepping back

1. Since estimation of $\mathbb{E}[Y^1 - Y^0]$ is often under-powered, we seek a surrogate outcome S, aiming to use $\mathbb{E}[S^1 - S^0]$ as an alternative endpoint

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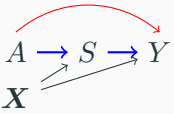

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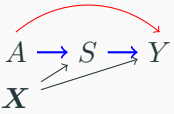

3. Tools from causal mediation analysis provide **clinically interpretable** statistical estimands

Acknowledgments

- Eric Macklin
- Lori Chibnik
- Marie-Abele Bind
- Nima Hejazi
- HEALEY ALS Platform Trial Group
- Peng Sun
- Stephanie Fradette

Thank you!

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Additional information

Extension: doubly-robust estimation (Tchetgen and Shpitser 2012)

As we saw, estimation of $\mathbb{E}[Y^{1,S^0}]$ involved estimating multiple regression functions

- Incorrect specification of any of these models implies the resulting estimator will be biased

We can construct **doubly-robust** estimators of $\mathbb{E}[Y^{1,S^0}]$ that take the form

$$\hat{\mathbb{E}}[Y^{1,S^0}] = \frac{1}{n}\sum_{i=1}^{n} \hat{\mu}_0(\boldsymbol{X}_i) + \widehat{\text{BC}}$$

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where the $\widehat{\text{BC}}$ term can be thought of as a *bias correction* term that partially accounts for the bias arising from model mispecification

- Such estimators can allow for slight mis-specifications of $\mu_0(\boldsymbol{X})$
- Can be crucial in small-sample settings that typically necessitate parsimonious models

Doubly-robust estimation of the NIE

Recall the form of the estimator for $\mathbb{E}[Y^{1,S^0}]$

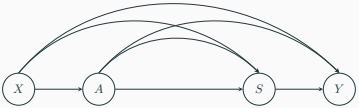
$$\hat{\mathbb{E}}[Y^{1,S^0}] = \frac{1}{n}\sum_{i=1}^{n}\hat{\mu}_0(\boldsymbol{X}_i) + \widehat{\text{BC}}$$

Recalling $m_1(\boldsymbol{X}, S) = \mathbb{E}(Y|\boldsymbol{X}, S, A = 1)$ and letting $g(\boldsymbol{X}) = \mathbb{P}(A = 1|\boldsymbol{X})$, $e(\boldsymbol{X}, S) = \mathbb{P}(A = 1|\boldsymbol{X}, S)$,

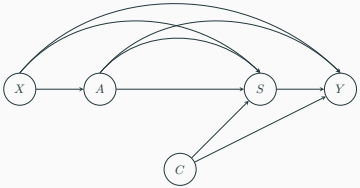
$$\widehat{\text{BC}} = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{A_i \cdot (1 - \hat{e}(\boldsymbol{X}_i, S_i))}{(1 - \hat{g}(\boldsymbol{X}_i)) \cdot \hat{e}(\boldsymbol{X}_i, S_i)}\{Y_i - \hat{m}_1(\boldsymbol{X}_i, S_i)\} + \frac{(1 - A_i)}{1 - \hat{g}(\boldsymbol{X}_i)}\{\hat{m}_1(\boldsymbol{X}_i, S_i) - \hat{\mu}_0(\boldsymbol{X}_i)\}\right)$$

A few possible parameterizations for BC – above avoids need to estimate the conditional density for $S|A, \boldsymbol{X}$

Assumptions

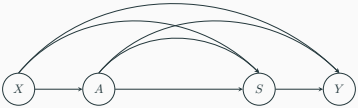


(a) Identifiable

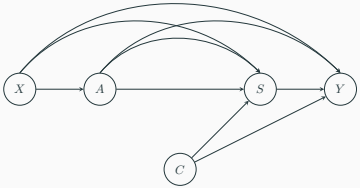


(b) Identifiable

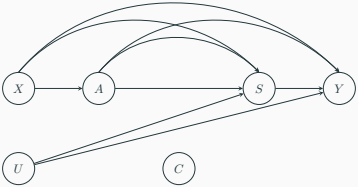
Assumptions



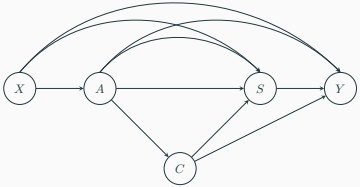
(a) Identifiable



(b) Identifiable



(c) Unidentifiable



(d) Unidentifiable

Estimation Steps

Y	A	S	$\boldsymbol{X}$
33	0	1.3	1.2
15	1	2.1	1.3
20	0	1.2	0.8
38	1	3.5	2.1
27	1	0.6	0.6
8	1	4.2	1.2
11	0	0.9	3.0

Step 1a: Use the trial data to estimate $m_A(\boldsymbol{X}, S) = \mathbb{E}(Y|A, \boldsymbol{X}, S)$ via regression

Estimation Steps

Y	A	S	$\boldsymbol{X}$	$\hat{m}_1(\boldsymbol{X}, S)$
33	0	1.3	1.2	24.3
15	1	2.1	1.3	17.7
20	0	1.2	0.8	21.1
38	1	3.5	2.1	28.0
27	1	0.6	0.6	30.8
8	1	4.2	1.2	14.5
11	0	0.9	3.0	29.7

Step 1b: Use the fitted model to get predictions under treatment:

$$\hat{m}_1(\boldsymbol{X}, S) = \hat{\mathbb{E}}(Y|A = 1, \boldsymbol{X}, S)$$

Estimation Steps

Y	A	S	$\boldsymbol{X}$	$\hat{m}_1(\boldsymbol{X}, S)$	$\hat{\mu}_0(\boldsymbol{X})$
33	0	1.3	1.2	24.3	
15	1	2.1	1.3	17.7	
20	0	1.2	0.8	21.1	
38	1	3.5	2.1	28.0	
27	1	0.6	0.6	30.8	
8	1	4.2	1.2	14.5	
11	0	0.9	3.0	29.7	

Step 2a: Regress $\hat{m}_1(\boldsymbol{X}, S)$ on $\boldsymbol{X}$ among those with $A = 0$. This gives an estimate of

$$\mu_0(\boldsymbol{X}) = \mathbb{E}[m_1(\boldsymbol{X}, S)|\boldsymbol{X}, A = 0]$$

Estimation Steps

Y	A	S	$\boldsymbol{X}$	$\hat{m}_1(\boldsymbol{X}, S)$	$\hat{\mu}_0(\boldsymbol{X})$
33	0	1.3	1.2	24.3	22.1
15	1	2.1	1.3	17.7	19.5
20	0	1.2	0.8	21.1	25.9
38	1	3.5	2.1	28.0	24.9
27	1	0.6	0.6	30.8	32.0
8	1	4.2	1.2	14.5	17.3
11	0	0.9	3.0	29.7	26.2

Step 2b: Use the fitted model to get predictions for all participants

Estimation Steps

Y	A	S	$\boldsymbol{X}$	$\hat{m}_1(\boldsymbol{X}, S)$	$\hat{\mu}_0(\boldsymbol{X})$
33	0	1.3	1.2	24.3	22.1
15	1	2.1	1.3	17.7	19.5
20	0	1.2	0.8	21.1	25.9
38	1	3.5	2.1	28.0	24.9
27	1	0.6	0.6	30.8	32.0
8	1	4.2	1.2	14.5	17.3
11	0	0.9	3.0	29.7	26.2

Step 3: Take the average of the predicted values

$$\hat{\mathbb{E}}[Y^{1,S^0}] = \frac{1}{n}\sum_{i=1}^{n} \hat{\mu}_0(\boldsymbol{X}_i)$$

PRO-ACT Database

The **P**ooled **R**esource **O**pen-Access **A**LS **C**linical **T**rials (PRO-ACT) Database contains data from $\approx 12{,}000$ study participants pooled across previously completed ALS clinical trials

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- Subset of trials with longer trial durations $\implies$ many participants receiving placebo with long-term outcome measurements $\tilde{Y}$

Provides a valuable resource for estimating long-term average outcomes under placebo. $\tilde{Y}(0)$, that are otherwise unobservable

Science Table

A	S^0	S^1	$Y^{0,0}$	$Y^{0,1}$	$Y^{1,s}$
1	S_1^0	S_1^1	$Y_1^{0,0}$	$Y_1^{0,1}$	$Y_1^{1,s}$
1	S_2^0	S_2^1	$Y_2^{0,0}$	$Y_2^{0,1}$	$Y_2^{1,s}$
0	S_3^0	S_3^1	$Y_3^{0,0}$	$Y_3^{0,1}$	$Y_3^{1,s}$
0	S_4^0	S_4^1	$Y_4^{0,0}$	$Y_4^{0,1}$	$Y_4^{1,s}$

Estimation of placebo means with external controls

Recall the identification

$$\mathbb{E}[\tilde{Y}^0|R=0] = \mathbb{E}\{\ \ \mathbb{E}(\tilde{Y}|A=0,\boldsymbol{X},R=1) \mid R=0\}$$

Letting $\mu_0(\boldsymbol{X}) = \mathbb{E}(\tilde{Y}|A=0,\boldsymbol{X},R=1)$, and $\kappa(\boldsymbol{X}) = \mathbb{P}(R=1|\boldsymbol{X})$, a doubly-robust estimator for $\mathbb{E}[\tilde{Y}^0|R=0]$ is

$$\hat{\mathbb{E}}[\tilde{Y}^0|R=0] = \hat{\psi}^{\mathsf{PI}} + \frac{1}{n}\sum_{i=1}^{n}\frac{n}{n_0}\left(\{1-R_i\}\{\hat{\mu}_0 - \hat{\psi}^{\mathsf{PI}}\} + \frac{R_i\cdot(1-\hat{\kappa}(\boldsymbol{X}_i)}{\hat{\kappa}(\boldsymbol{X}_i)}\{\tilde{Y}_i - \hat{\mu}_0(\boldsymbol{X}_i)\}\right),$$

where $\hat{\psi}^{\mathsf{PI}} = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{n}{n_0}\right)R_i\cdot\hat{\mu}_0(\boldsymbol{X}_i)$