Connecting Instrumental Variable methods for causal inference to the Estimand Framework

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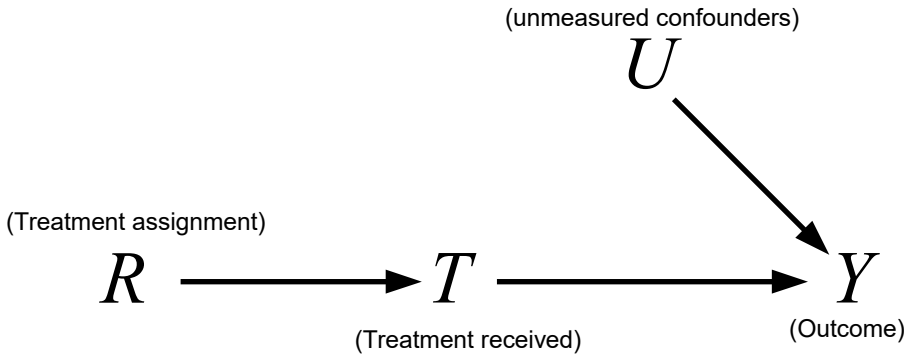
The Estimand Framework

- The ICH E-9 Addendum is forcing trialists to be much more forward thinking and upfront about the issue of **Intercurrent Events**
- An **Intercurrent Event** is

  '*any event occurring between the initial randomization of a patient and the observation of their final outcome which complicates the description and interpretation of the treatment effect*'

- Trialists must have an 'Estimand Strategy'
- So how can IV methods help?
- Focus on trials measuring treatment effect on risk/mean difference scale and a binary intercurrent event

Randomization is the ultimate Instrumental Variable



- IV1: Randomization predicts treatment
- IV2: Randomization is independent of all patient characteristics*
- IV3: Randomization can only influence patient outcome *via* treatment

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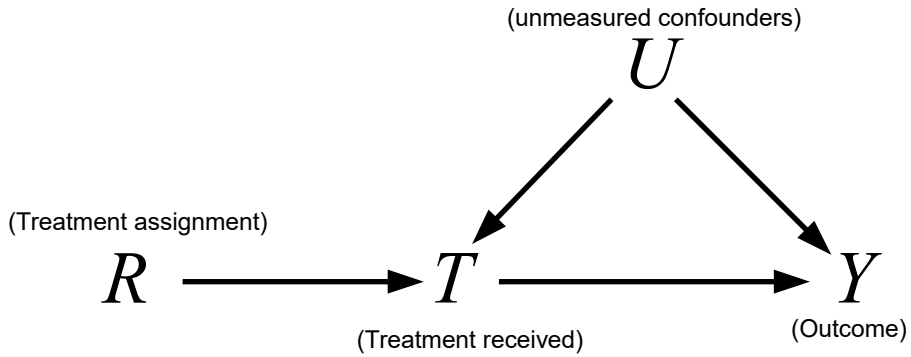


- IV1: Randomization predicts treatment
- IV2: Randomization is independent of all patient characteristics*
- IV3: Randomization can only influence patient outcome *via* treatment

- Randomization still a valid IV even if it does not perfectly predict treatment

- IV methods work without explicit adjustment for confounders
- Treatment here is itself the intercurrent event

Common Estimands expressed using potential outcomes

- **Treatment policy strategy**: *Intercurrent event is deemed to be irrelevant, all patient outcomes are used regardless of whether the intercurrent event occurred or not*

  - $E[Y_i(r = 1)] - E[Y_i(r = 0)]$

- **Principal Stratum strategy:** *Policy estimand in a subgroup for whom the intercurrent event would not occur in one or more treatment groups. e.g*

  - $E(Y_i(r = 1) - Y_i(r = 0) | T_i(r = 1) = 1, T_i(r = 0) = 0)$

- **Hypothetical strategy**: *Estimate the outcome variable for all participants under the hypothetical scenario in which the intercurrent event did not not occur*

  $E[Y_i(t = 1) - Y_i(t = 0)]$

Identification of estimands using IVs

- **Treatment policy**: Requires valid randomization
- **Principal Stratum:** Identified with valid IV + **Monotonicity**

  - No 'Defiers', for whom $T_i(1)=0$ and $T_i(0)=1$
- **Hypothetical**: Identified with a valid IV + **Homogeneity**

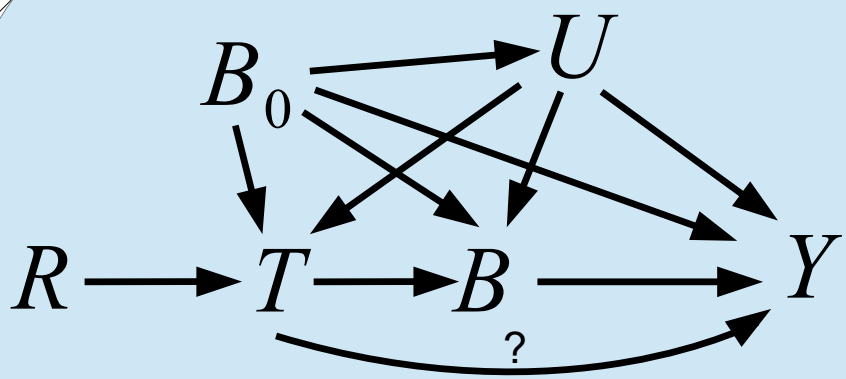
  - Av. effect of *removing* treatment from the **treated** is the same

  - Av. effect of *giving* treatment the **untreated** is the same
- IV-based **estimates** for both **estimands** equal
- True when effect on RD, RR but not OR scale (Clark and Windmeijer, 2010)

Application to a hypothetical 'industry' setting

- Placebo controlled RCT, no access to treatment in control arm
- Some non-adherence in treatment arm: take a **policy** stance w.r.t to this
- Main intercurrent event is 'intermediate response' measured by a relevant binary biomarker B (assumed mechanism of action)
- If a treatment arm patient does not 'respond', we may believe that the drug has failed
- If a control arm patient has a positive biomarker response , we may believe that their future health outcomes have been improved or worsened in line with those who took and responded to treatment
- Naive 'Responder analysis': $E[Y|B = 1] - E[Y|B = 0]$
- No causal interpretation, want to go beyond this

Contemporary trial setting: intercurrent event = biomarker response



- Treatment predicts the likelihood of being a biomarker responder (B=1), as does baseline biomarker value (Bo)
- Randomization a valid IV if it affects outcome Y through B only (exclusion restriction holds)
- Violation if treatment effects Y through alternative mechanism

Compliance Classes	$B(r=1)$	$B(r=0)$	**Proportion**	**Estimated by**
Placebo only Responders	0	1	π_{pr}	0 **(Monotonicity)**
Never Responders	0	0	π_{nr}	$\hat{Pr}(B=0\|R=1)$
Always Responders	1	1	π_{ar}	$\hat{Pr}(B=1\|R=0)$
Treatment only Responders	1	0	π_{tr}	$1-\widehat{\pi_{ar}}-\widehat{\pi_{nr}}$
Treatment arm Responders	1	0/1	$\pi_{tr}+\pi_{ar}$	$\hat{Pr}(B=1\|R=1)$

Policy Estimand: $E[Y_i(r=1)-Y_i(r=0)]$

Hypothetical Estimand: $E[Y_i(b=1)-Y_i(b=0)]$

Principal Stratum Estimand: $E[Y_i(r=1)-Y_i(r=0)|B(1)=1,B(0)=0]$

Principal Stratum Estimand: (Bornkamp & Bermann) $E[Y_i(r=1)-Y_i(r=0)|B(1)=1]$

Simulated trial example: n=10,000, $E(Y)$=50%

- Proportion of biomarker responders in the treatment control group is 77% and 16%
- Responder analysis suggests biomarker responders have a 10% **reduced** risk of Y
- All other estimand estimates suggests treatment or biomarker response **increases** risk of Y (2-4%)

Estimand	Estimate	S.E(model)	S.E(boot)	p-value
Treatment Policy	0.022	0.010	0.010	0.028
Responder	-0.103	0.010	0.010	$< 2 \times 10^{-16}$
TR-ACE & Hypothetical	0.035	0.016	0.016	0.029
PS(BB)	0.025	0.012	0.011	0.028

- Understand results by relaxing **Homogeneity** and **Exclusion Restriction** for Hypothetical estimand

Relaxing the homogengeity assumption

Model allowing for biomarker effect heterogeneity

$$Y_i | B_i, R_i, U_i = \beta_0 + \psi_b B_i R_i + \psi_{ar} B_i (1 - R_i) + U_i$$

Who treatment policy effect applies to under monotonicity

Estimand	Potential outcome contrast	Parameter form
Hypothetical among treatment arm responders	$E[Y_i(B=1) - Y_i(B=0) \mid B(1)=1]$	ψ_b
Hypothetical among control arm responders	$E[Y_i(B=1) - Y_i(B=0) \mid B(0)=1]$	ψ_{ar}

TSLS estimation

$$E[B | R, B_0] = \beta_0 + \beta_1 R + \beta_2 B_0 + \beta_3 R B_0 \quad \textbf{1st stage model}$$

$$\hat{B} = \hat{\beta}_0 + \hat{\beta}_1 R + \hat{\beta}_2 B_0 + \hat{\beta}_3 R B_0 \quad \textbf{Fitted value}$$

$$E[Y | \hat{B}, B_0] = \beta_0 + \psi_b \hat{B} R + \psi_{ar} \hat{B} (1 - R) + \beta_{B_0} B_0 \quad \textbf{2nd stage model}$$

- Requires a baseline covariate B_0 that
  - (i) Differentially predicts biomarker response across treatment arms
  - (ii) Does not modulate treatment effect

Relaxing the Exclusion restriction

- Can use same approach to allow for direct and indirect trt effects under the homogeneity assumption

Model allowing for direct and indirect effects of treatment

$$Y_i | B_i, R_i, U = \beta_0 + \psi B_i + \alpha R_i + U_i$$

Estimand	Potential outcome contrast	Parameter form
Hypothetical estimand allowing for direct effect	$E[Y(r;1) - Y(r;0)]$	ψ
Direct effect	$E[Y(1;b) - Y(0;b)]$	α

TSLS estimation

$$E[B|R, B_0] = \beta_0 + \beta_B B_0 + \beta_R R + \beta_{BR} B_0 R \quad \text{Stage 1 model}$$

$$E[Y|\hat{B}, R] = \beta_{Y0} + \psi \hat{B} + \alpha R + \beta_{B_0} B_0 \quad \text{Stage 2 model}$$

- Essentially causal mediation without the 'sequential ignorability' assumption (Small, 2012)
- *The* true data generating model!

Full results

Estimand	Estimate	S.E(model)	S.E(boot)	p-value
Treatment				
Policy	0.022	0.010	0.010	0.028
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TR-ACE &				
Hypothetical	0.035	0.016	0.016	0.029
PS(BB)	0.025	0.012	0.011	0.028
Hypothetical estimand sensitivity analyses				
Biomarker effect heterogeneity				
ψ_b	-0.034	0.031	0.032	0.286
ψ_{ar}	-0.202	0.097	0.099	0.041
Direct and indirect treatment effects				
ψ	-0.295	0.135	0.139	0.034
α	0.201	0.083	0.086	0.019

- Trt exerts a negative direct effect on Y
- Trt exerts a positive effect through biomarker response
- Can be disentangled with a two-parameter causal model

Discussion

- IV methods have an important role to play within the estimand framework
- Estimands can be identified without invoking 'no unmeasured confounders' assumption

  - see e.g. regression adjustment, propensity scores etc...

- Although most IV frameworks developed by imagining treatment as the intercurrent event (academic legacy), the idea can be extended to any event that sits between randomization and outcome

  - e.g. biomarker response, disease progression

- However, the further the intercurrent event is from initiation of treatment the harder the IV assumptions are to justify

  - Exclusion restriction especially

- This talk is a summary of a tutorial paper soon to be submitted. Watch this space!

Some references

Clarke P, Windmeijer F. Identification of causal effects on binary outcomes using structural mean models. *Biostatistics* 2010. **11**: 756–770

Small D. Mediation analysis without sequential ignorability: using baseline covariates interacted with random assignment as instrumental variables. *Journal of Statistical Research* 2012, **46**: 91–103

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