The Logic of Causal Inference

Uwe Siebert, MD, MPH, MSc, ScD

(1) Dept. of Public Health, Health Services Research and Health Technology Assessment, UMIT - University for Health Sciences, Medical Informatics and Technology, Hall i.T., Austria

(2) Area HTA, ONCOTYROL - Center for Personalized Cancer Medicine, Innsbruck, Austria

(3) Center for Health Decision Science, Department of Health Policy and Management, Harvard School of Public Health, Boston, MA, USA

(4) Institute for Technology Assessment and Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Acknowledgment

UMIT

oncotyrol
Center for Personalized Cancer Medicine

This work was in part supported by UMIT and the COMET Center ONCOTYROL, which is funded by the Austrian Federal Ministries BMVIT/BMWFJ (via FFG) and the Tiroler Zukunftsstiftung/Standortagentur Tirol (SAT).

2

Estimands

The question is whether to ITT or not to ITT

- Estimand reflects research question
  - Interest in policy effect (intention) or in actual sustained treatment effect of the drug?
  - If interest in sustained drug effect: adjustment for switching needed
  - If interest in policy effect: must compare strategies under assessment (i.e., scenario of no reimbursement of a new drug → no switching possible) → either do not allow for switching or adjust for switching or …
- Estimand has implications on
  - Trial design, data to collect
  - Statistical methods
  - Communication of results (patients, clinicians, payers, etc.)

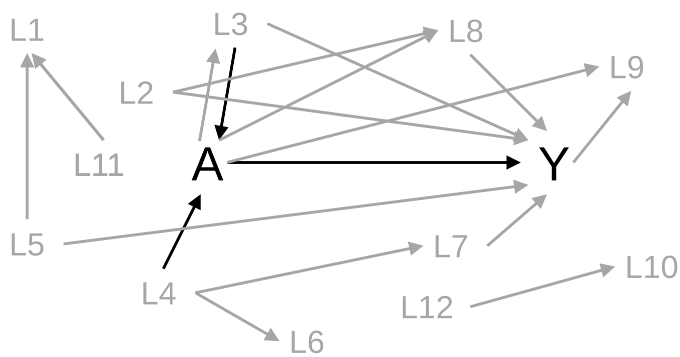
The Goal

Of interest:
the **causal** effect of an intervention on an outcome

$$A \longrightarrow Y$$

Intervention	*Disease*
Treatment	*Symptom*
Strategy	*Death*
Action	*Event*
	Outcome

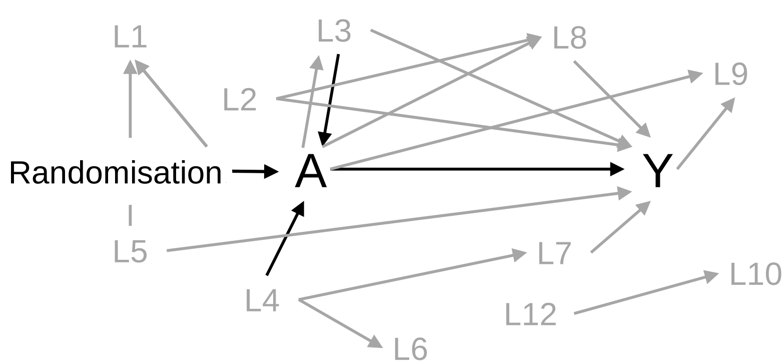
Causal Graph: Observational Study



A: Intervention of interest (Action)
Y: Outcome of interest
L: Other (co)variables

Causal Graph: Observational Study

RCT:



A: Intervention of interest (Action)
Y: Outcome of interest
L: Other (co)variables

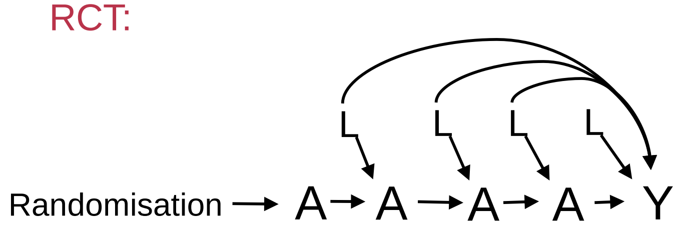
RCT:

Randomisation → A → Y

A: Intervention of interest (Action)
Y: Outcome of interest
L: Other (co)variables

Post-randomisation Confounding

RCT:

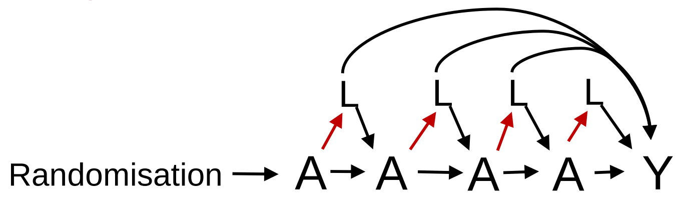


- Confounder L might be
  - Age, cognitive ability, etc.
  - Not influenced by treatment

L = Time-independent confounder

Post-randomisation Confounding

RCT:

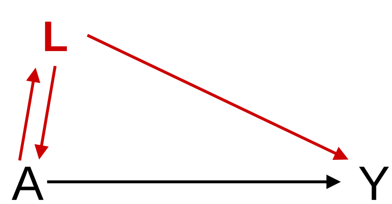


- Confounder L might be
  - Side effects, prognosis, etc.
  - Influenced by treatment

L = Time-dependent confounder

Confounder **AND**
Intermediate step

Time-dependent Confounding



- Confounder **AND**
- Intermediate step

Tx = Treatment

Confounding

Time-independent confounding	Time-dependent confounding
Initial Tumour stage → Tx; Initial Tumour stage → Death; Tx → Death	Severity of Disease (Biomarker) → Tx; Tx → Severity of Disease (Biomarker); Severity of Disease (Biomarker) → Death; Tx → Death
Initial Tumor stage is a common cause of prescribed Tx and Death	Biomarker is a common cause of Tx and Death and is also affected by Tx
⬇	⬇
Traditional stratification or regression analysis **works**	Traditional stratification or regression analysis **fails**

James M. Robins

"Robins cut the Gordian knot by inventing a statistic called the g-estimator that makes analysis of data that are simultaneously confounders and intermediate steps possible. […]
After a long period of seeking converts to his unconventional methods, Professor James Robins is now considered to be one of the leading mathematical statisticians in the world."

Harvard Public Health Review,
Summer 2002:42-43

Causal Methods

- g-formula (nonparametric, parametric)
- g-estimation with structural nested models (SNM)
- Inverse probability weighting (IPW) with marginal structural models (MSM)
- Two-stage estimation

13

Inverse Probability Weighting (IPW) with Marginal Structural Models (MSM)

- MSMs = <u>models</u> for the <u>marginal</u> distribution of <u>counterfactual</u> outcomes (Robins 1998)
- "Structural" = "Causal"

14

Principle of Inverse Probability Weighting

Observed population
Confounded data set

↓ IPW

Pseudo population
Unconfounded data set

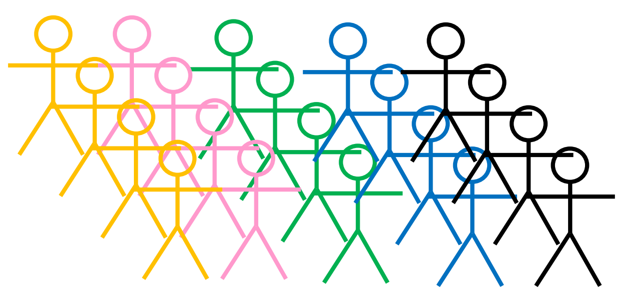
↓

Crude "marginal" analysis

Observational studies: everybody is treated and not treated

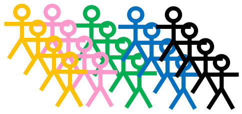
RCTs: nobody "switches away"

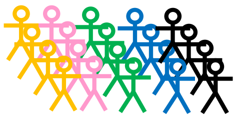
Differential Prognosis Matters!



Good prognosis / mild disease	Intermed. Prognosis / moderate disease	Bad prognosis / severe disease

Inverse Probability of Cencoring Weighting (IPCW)





Differential switching
1. Censoring → selection bias
2. Weighting
3. Crude analysis

*1.3 *2 *2 *4 *4

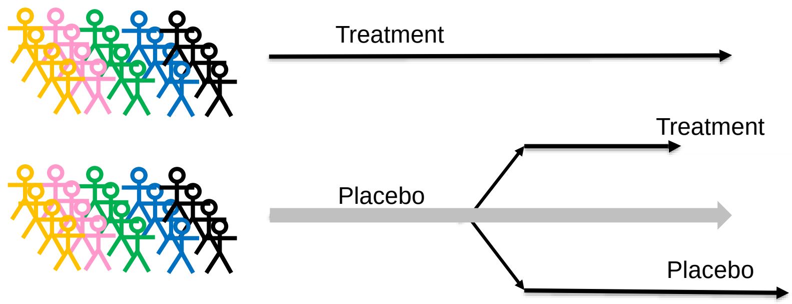
17

g-Estimation with Structural Nested Models

- Uses a structural (= causal) model to "remove" the (unknown) treatment effect from the treated: calculates the counterfactual outcome (e.g., survival time) being untreated (or nonswitcher)
- Used grid search or other methods to estimate effect (i.e., find the correct counterfactual outcome among many possible)
- Often used as structural model:
  rank preserving structural failure time model (RPSFTM)

18

Rank-Preserving Structural Failure Time (RPSFT) Model



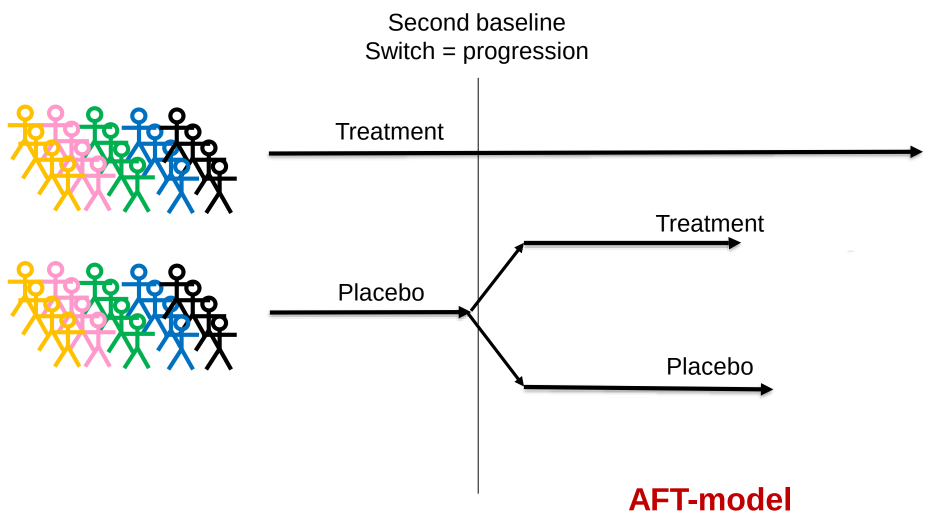
Common survival equation: $T_i = T_{off_i} + k * T_{on_i}$

? g-estimation

Two-Stage Estimation

- Developed for RCTs
- Assume a secondary baseline (e.g., at progression), when patients switch
- Estimate switching effect controlling for time-independent confounders at secondary baseline
- Remove switching effect (= treatment effect) from switchers
- Perform crude analysis

Two-Stage Estimation



21

Key Assumptions of Different Causal Methods

- g-formula
  - No unmeasured confounding
- IPCW
  - No unmeasured confounding (for weight functions)
- RPSFT
  - Common treatment effect (for structural model)
  - Perfect randomization
  - (in observational studies: No unmeasured confounding)
- TSE
  - Switching after progression (secondary baseline)

22