Clinical trials with non-adherence & unblinding: a graphical perspective

NIPS 2013: Causality Workshop

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Overview

Even with perfect randomization, clinical trials can be confounded!

Goal:

- Represent graphically:
  - Non-adherence and
  - Unblinding

  within clinical trials
- So as to compare:
  - Intent-to-treat vs.
  - Per Protocol analyses

  in terms of confounding.

Non-adherence in clinical trials

Difference between group outcomes =
Average effect of *being assigned to* treatment A v. B!

Two separate questions:

- Average effect of *prescribing* the treatment (for this population)?
- Average causal effect of *taking* the treatment (in this population)?

Intent to treat v. per protocol analyses

- **Intent-to-treat analysis**: compare everyone assigned to treatment with everyone assigned to placebo
- **Per protocol analysis**: compare people who adhered to treatment with people who adhered to placebo. (More generally: condition on adherence level when comparing groups)

Table: Example: mortality in the Coronary Drug Project ($n = 3{,}892$)

	Clofibrate	Placebo
Adherance $\geq$ 80%	15.0%	15.1%
Adherance $<$ 80%	28.2%	24.6%
Total	20.0%	20.9%

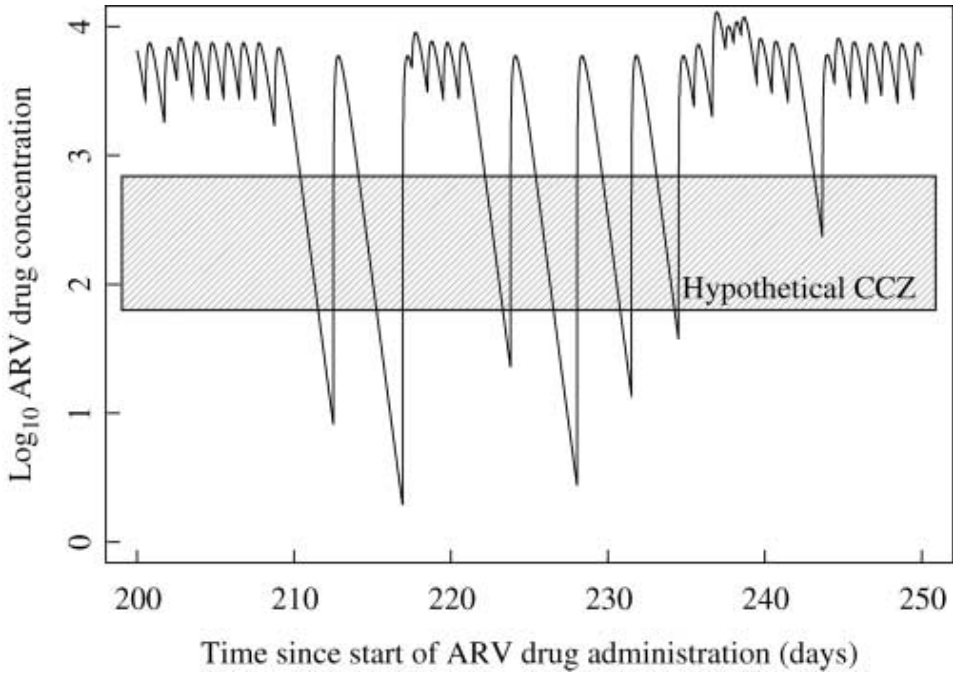
- In the CDP, Intent-to-treat and per protocol produce same result
- Widely cited as an example of why per protocol analyses may be biased (!)

Non-adherence as an opportunity

Third category of questions:

- Average causal effect of:
  - Missing a dose?
  - Taking a shorter course?
  - Making Dose Timing Errors (DTEs)?
  - Taking "drug holidays"?

(compared to perfect adherence)



Example: The "critical concentration zone", in which antiretroviral drugs select for resistant viruses. Dose timing errors mean the patient spends more time in this zone.

Figure from Vrijens, B. & Urquhart, J. (2005) 'Patient adherence to prescribed antimicrobial drug dosing regimens.' *Journal of Antimicrobial Chemotherapy*, 55:616–627.

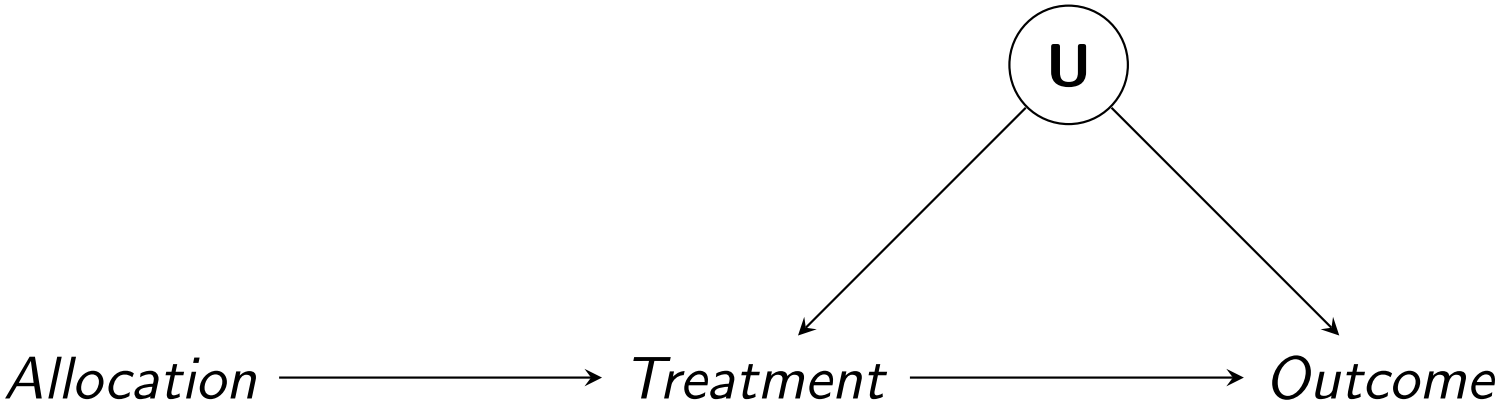
Spokesperson for the FDA cites the CDP

Russell Katz:

> *[...] there is absolutely no assurance that the compliers in the placebo group are the same as the compliers (or noncompliers to noncompliers) on both known and unknown factors that might affect outcome. It is possible, for example, that the reasons for compliance (or noncompliance) are different between treatment groups and that those differences might have an effect on the outcome.*

Katz, R. "Regulatory view: Use of subgroup data for determination of efficacy." In J A Cramer & B Spilker (eds.), *Patient compliance in medical practice and clinical trials*, Raven Press, Ltd., 1991.

Standard causal graph of a clinical trial

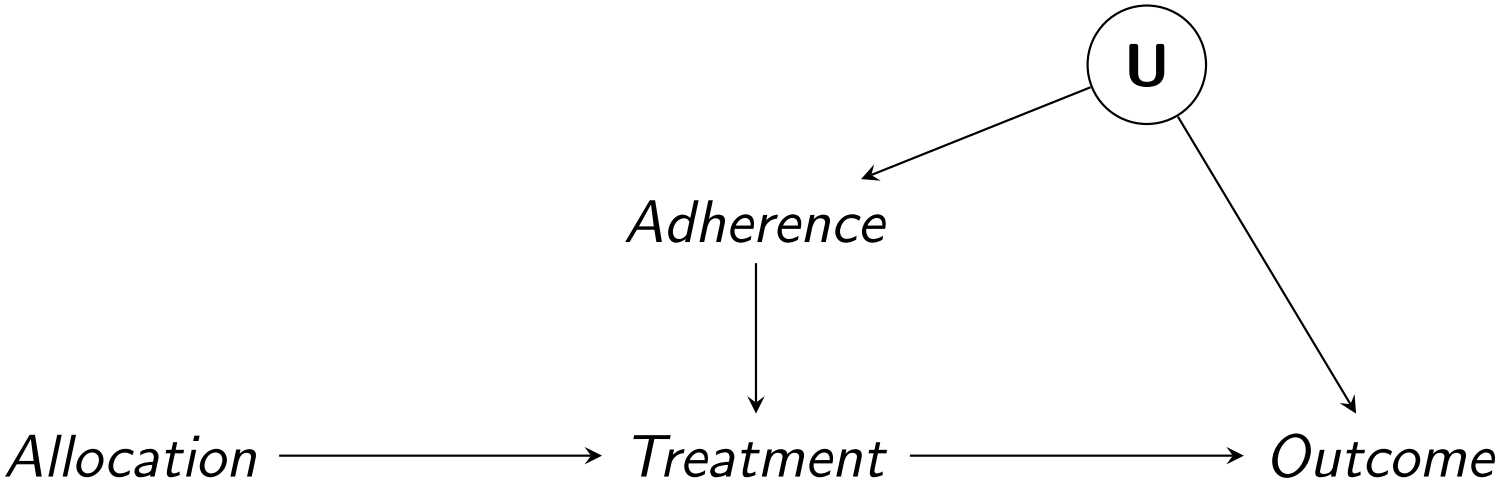


We assume that:

- *Allocation* is exogenous (by randomization)
- *Allocation* affects *Outcome* only through its effect on *Treatment* (thanks to double-blind design)

Note: *Treatment* $\neq$ *Adherence*!
Treatment means "amount of active treatment received"

Representing *Adherence* in the graph



In this model:

- Conditional on *Adherence* (as in a per protocol analysis), our estimate of the effect of *Treatment* on *Outcome* is unconfounded
- However, *Adherence* $\perp\!\!\!\perp$ *Allocation*.
  Katz was worried about the case where *Adherence* $\not\perp\!\!\!\perp$ *Allocation*

*Notice the deterministic edges: *Allocation* and *Adherence* jointly determine *Treatment*

Unblinding

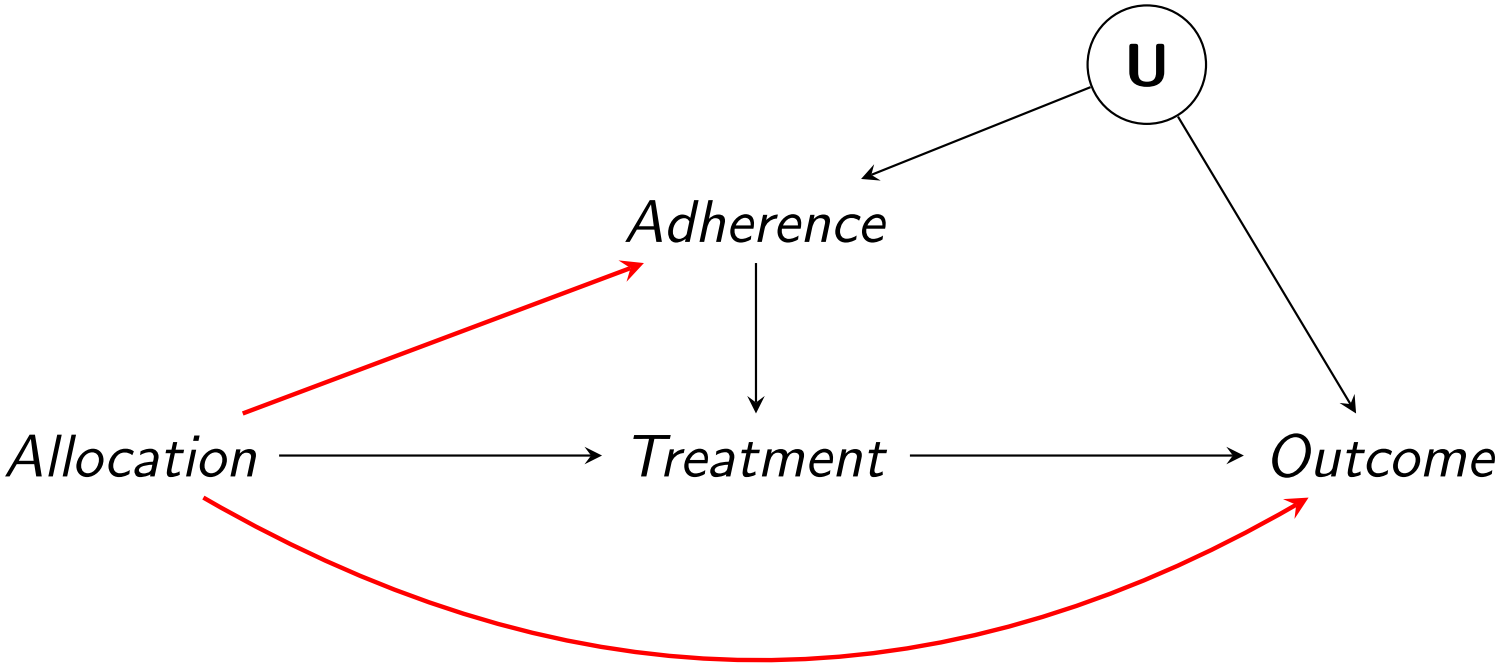
Causes of unblinding:

- (Noticeably) effective treatment – or noticeably ineffective placebo
- Adverse effects

Effects of unblinding:

- Reporting biases:
  - Noseworthy et al. (1994): When assessing MS patients, Unblinded neurologists favored the treatment. Blinded neurologists favored the placebo, if anything.
- Differential treatment:
  - Non-trial medication, dose adjustment, withdrawal from trial, etc.
  - Differential adherence

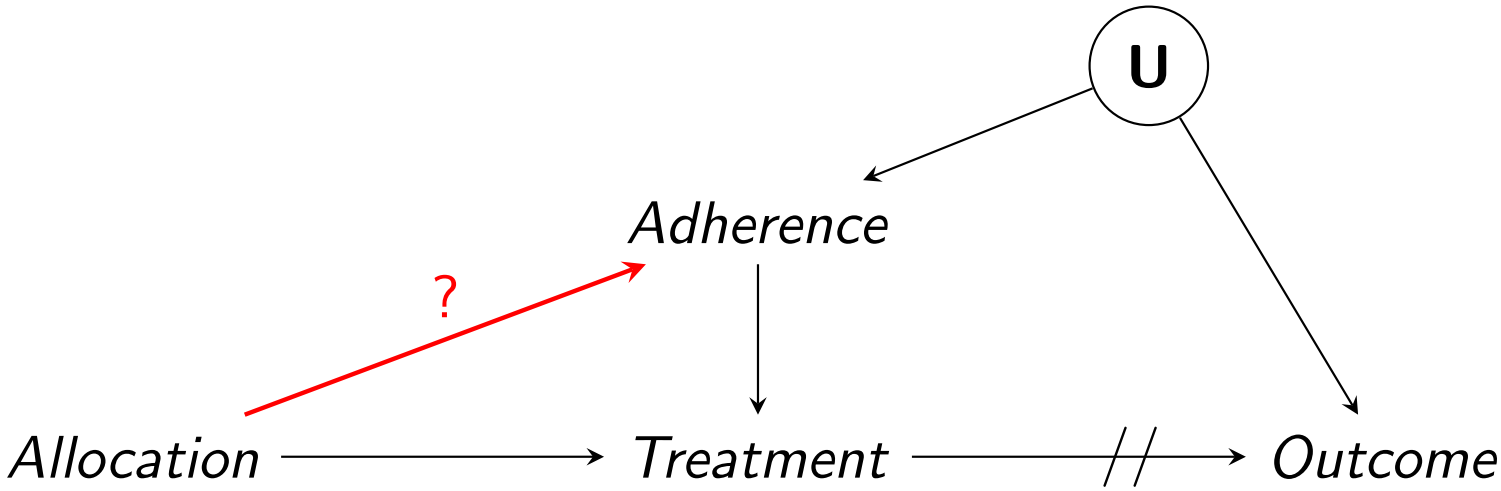
Representing Unblinding



- In theory, unblinding biases the per protocol analysis via: *Allocation* $\rightarrow$ *Adherence* $\leftarrow$ **U** $\rightarrow$ *Outcome*
- & biases both per protocol and ITT via: *Allocation* $\rightarrow$ *Outcome*
- These effects are testable

Did *Allocation* affect *Adherence* in the CDP?

- Clofibrate and placebo adherence distributions were no different ($\chi^2(5) = 5.86$, $p = 0.32$).
- *Allocation* was independent of *Outcome* conditional on *Adherence* ($\chi^2(3) = 1.89, p = 0.60$), despite *Adherence*–*Outcome* association
- Similar distributions of side effects & dropout rates between groups



Problem: The graph still doesn't represent our background knowledge

First problem:

- We assume the trial was *designed* to be double blind.
- This implies that all effects of *Allocation* go through *Treatment*. Acyclicity prohibits any effect on *Adherence*.
- Solution: Time-series representation.

Second problem:

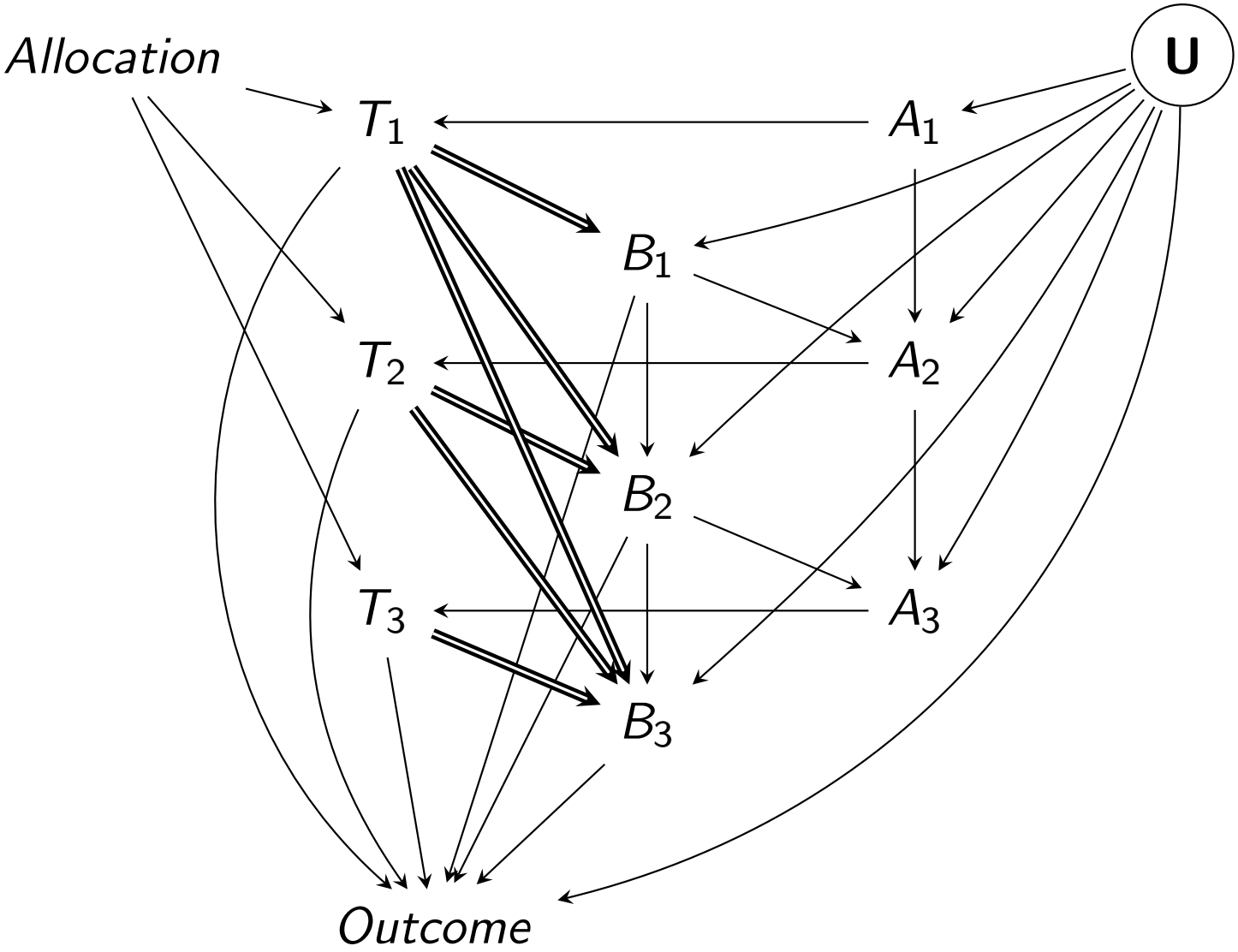
- "Reporting biases" and "differential treatment" no longer distinct from direct physical effects of treatment.
- Solution: Introduce the mediating variable: Patients' & doctors' *Beliefs* about allocation

Causal understanding of unblinding

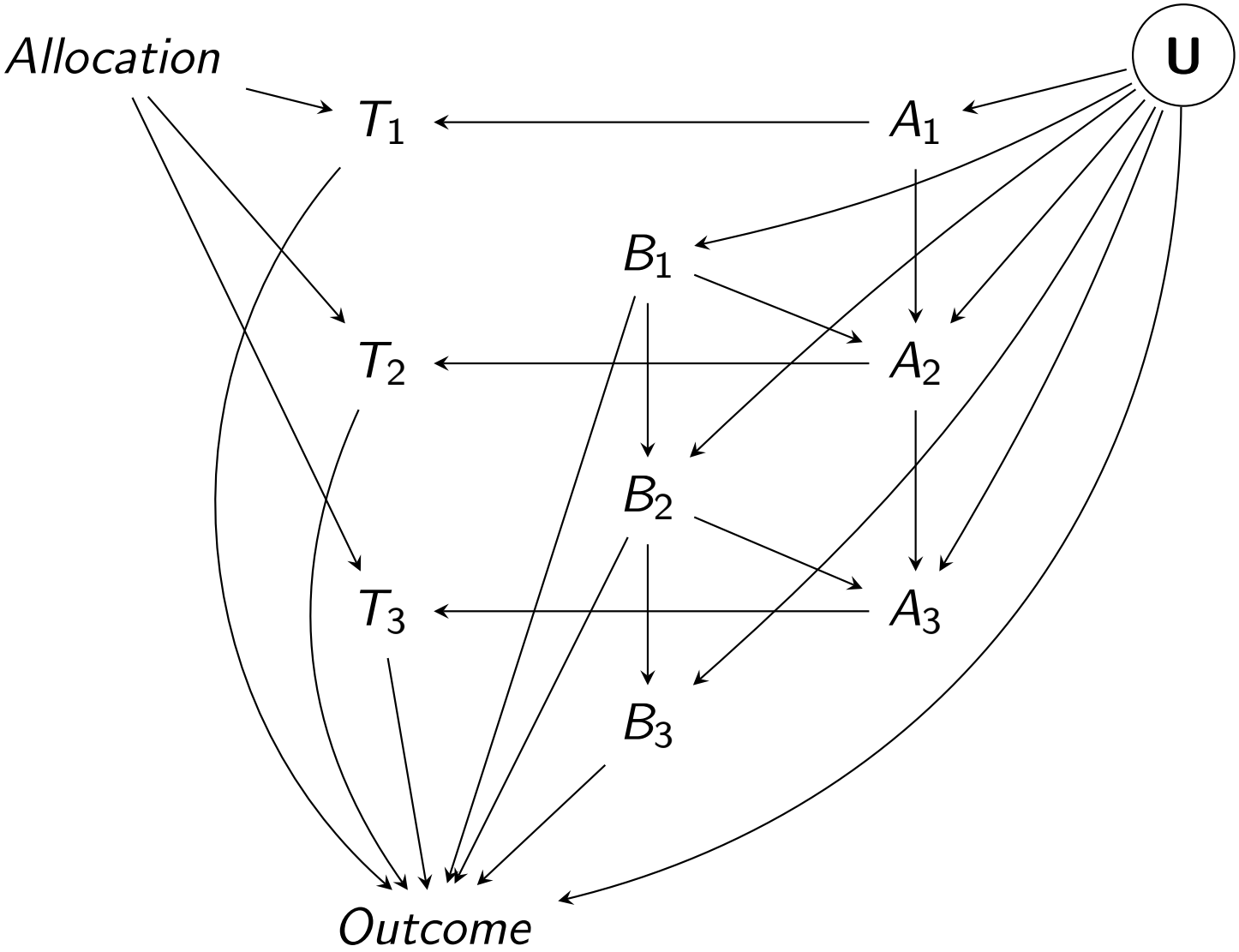
How unblinding is typically measured:
Ask patients and doctors to guess patients' *Allocation*.
If they can guess better than chance, infer unblinding

Def: Unblinded. *A trial is unblinded iff there is a directed path from* $Allocation$ *to patients' or assessors'* $Beliefs$ *about allocation.*

Time series of an unblinded trial



Time series of a blinded trial



Possible approaches if the blind fails

The time series graph, like the static graph, implies that per protocol will be confounded in an unblinded trial. If the blind fails, we can:

1. Expand the causal structure: Measure variables in **U**, or
2. Do an Instrumental Variables analysis

Assuming that reporting bias and differential treatment bias are negligible.

Measuring **U**

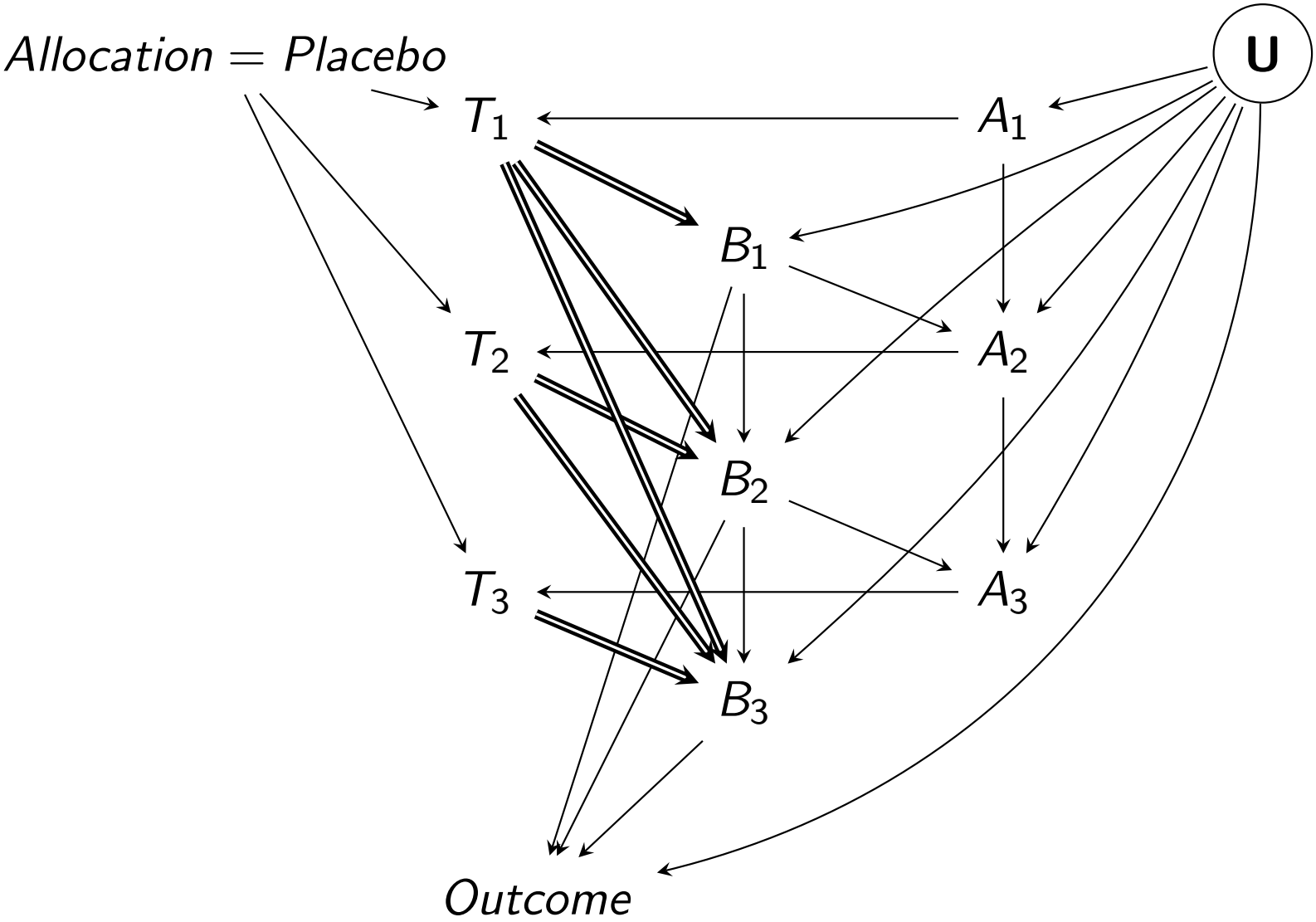
Candidate members of **U**:

- Diet
- Exercise
- Regular Dr's appts.
- Vaccinations
- Depression
- ....
- Adherence to effective non-trial medication

Check for success:

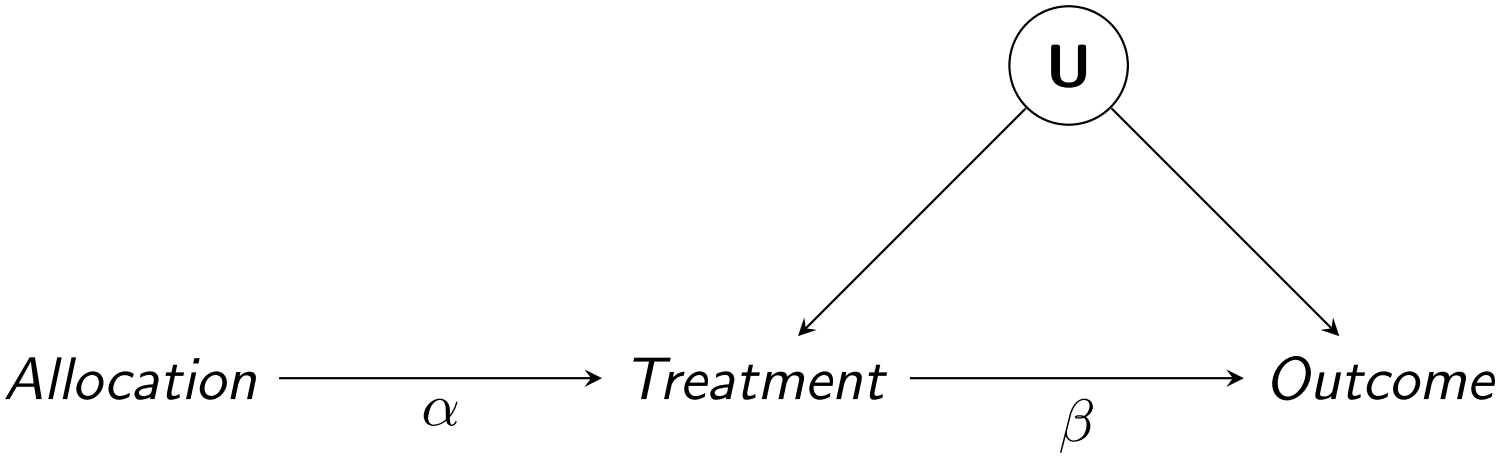
- In placebo group, we assume no edges from *Treatment* to *Outcome*
- Thus, in the placebo group, $Adherence \perp\!\!\!\perp Outcome | Beliefs, \mathbf{U}$

Using the placebo group as a check



Instrumental Variables

Use a combination of graphical and parametric assumptions to estimate the average causal effect (ACE) of treatment on outcome



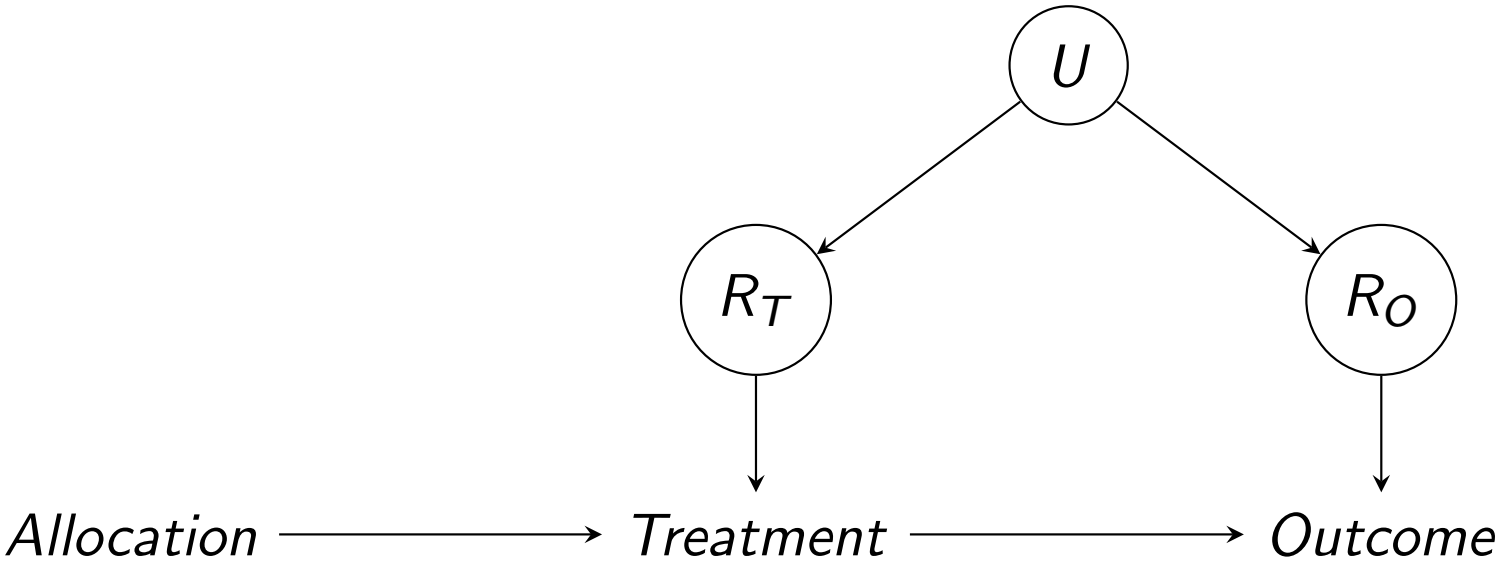
Sufficient parametric assumptions:

- Linearity,
- Log-linearity, or
- Monotonicity

Like ITT, assumes no direct edge from *Allocation* to *Outcome* (i.e. no reporting biases, no differential treatment biases, no bias induced by *Dropout*).

IV: ACE with finite response variables

Alternatively: make *Treatment* and *Outcome* binary, and use finite response variables (Pearl)



Gives bounds rather than point estimation. No linearity required!

However: requires that d-separation relationships remain the same after coarsening into binary variables.

Recommendations for trial design

1. Test the success of the double-blind design
   - Directly: by asking participants and doctors to guess *Allocation*
   - Indirectly: By measuring the association between *Allocation* and *Adherence*; by comparing the distributions of dropouts and adverse effects between groups; etc.
2. Measure *Adherence* accurately – i.e. use electronic monitoring
3. Measure as many candidate members of **U** as possible

Thank you

Cochrane Collaboration cites the CDP

The Cochrane Handbook for authors of systematic reviews:

> **'As-treated' (per-protocol) analyses**
> *[...] A similarly inappropriate approach to analysis of a study is to focus only on participants who complied with the protocol. A striking example is [the CDP]. [...] Those who adhered well to the protocol in the clofibrate group had lower five-year mortality (15.0%) than those who did not (24.6%). However, a similar difference between 'good adherers' and 'poor adherers' was observed in the placebo group (15.1% vs 28.3%). Thus, adherence was a marker of prognosis rather than modifying the effect of clofibrate. These findings show the serious difficulty of evaluating intervention efficacy in subgroups determined by patient responses to the interventions. [...]*