RCTs & DESIGN ISSUES

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Randomized Controlled (Compared?) Trials

Some aspects related to design & statistical analysis

- Why control group (comparator arm)?
- Regression to the mean
- Why randomization?
- Why blinding?
- What to adjust for
- Should you test for covariate imbalance after randomization?
- Are some designs better than others?

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Randomized Controlled (Compared?) Trials

Why do you need a comparator arm?

- RCTs are among the best tools available to determine “true” causal effects
- Ideally, both the effect of **treatment** and **non-treatment** should be measured
  - In the same individual
  - At the same time
  - Under the same circumstances
  - ... not easy unless you start cloning people...
- Second best: Obtain a comparator group that is “as similar” to the treatment group as possible.

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Illustration:

1. Select patients at random from a population
2. Administer treatment to reduce blood pressure to everyone
3. Measure blood pressure in everyone after treatment

Not very helpful when nothing to compare to, unless very precise population values are known in advance (i.e. a comparator, albeit not very good)

(... and obviously problematic to treat people who don't necessarily have high blood pressure to begin with, but just for the illustration)

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Illustration:

1. Select patients at random from a population
2. Measure blood pressure
3. Administer treatment to reduce blood pressure to everyone
4. Measure blood pressure in everyone after treatment

This *can* work.... every patient is their own control, and you look at change. Which can be efficient.

However, *anything that changes over time* can destroy this.
Say, first measurement is taken by a doctor at the workplace during stressful work, the second taken at home later by the patients themselves.

How much of the drop in blood pressure is due to the treatment?

This would be solved by a comparator group that was as similar as possible to the treatment group.

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Illustration:

1. Select patients **with high blood pressure** at random from a population
2. Measure blood pressure
3. Administer treatment to reduce blood pressure to everyone
4. Measure blood pressure in everyone after treatment

As before, you look at change.

Sounds great?... but it *does not* work....

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Regression to the mean:

(Happens in soooo many situations)

- Blood pressure fluctuates “randomly” during a day and a week
- Recruitment **specifically picks** those with a by-chance high blood pressure at the moment
- TWO components
  - “True” high blood pressure
  - High random variation at the moment
- Those individuals *will* almost always return to a lower value at next measurement
- Component 2 will typically partly disappear all by itself

Again, having a comparator group under the same conditions as the treatment group can resolve this.

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Without randomization:

$$
\begin{aligned}
\text{Apparent treatment effect} &= \text{True treatment effect} \\
&+ \text{Effect of observed confounders} \\
&+ \text{Effect of unobserved confounders} \\
&+ \text{Random noise}
\end{aligned}
$$

Both *observed* and *unobserved* confounders are *correlated* with treatment and related to outcome.

- Observed confounders can be adjusted for
- Random noise is dealt with using confidence intervals and large sample sizes
- BUT unobserved confounders create systematic bias. Sample size does not help.

With randomization:

$$\begin{aligned} \text{Apparent treatment effect} &= \text{True treatment effect} \\ &+ \textbf{Noise} \text{ from observed confounders} \\ &+ \textbf{Noise} \text{ from unobserved confounders} \\ &+ \text{Random noise} \end{aligned}$$

You *force* treatment to be uncorrelated with covariates.

This moves covariates from systematic effects to "noise" relative to treatment.

- The treatment effect is now unbiased
- The noise is bigger, but can now be dealt with using confidence intervals and large sample sizes
- AND noise from observed confounders can be reduced **by adjusting for them**

(Now isn't that brilliant...!)

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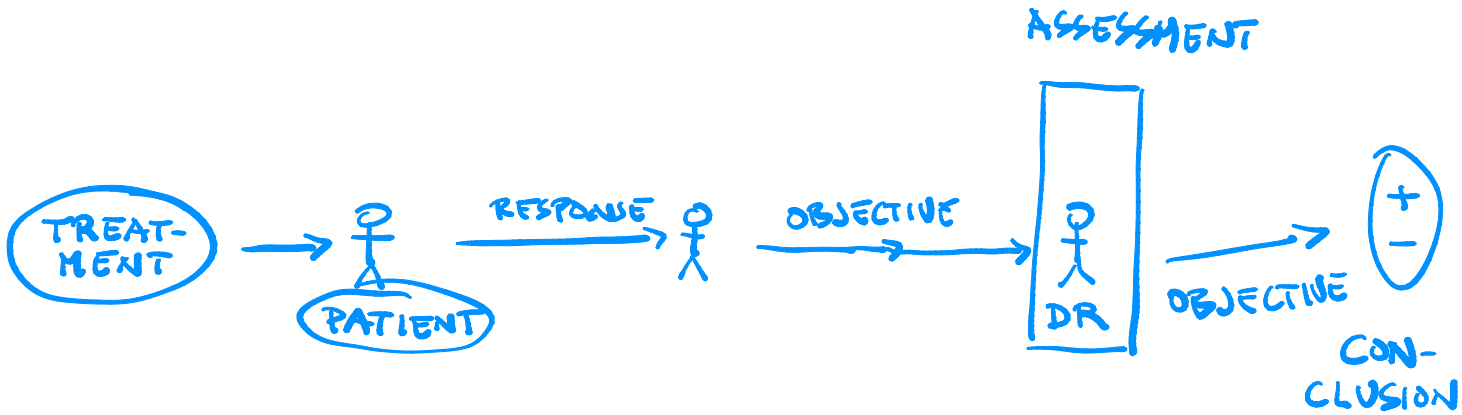
TRIAL, BASIC

A straight causal path from treatment to outcome would be nice...



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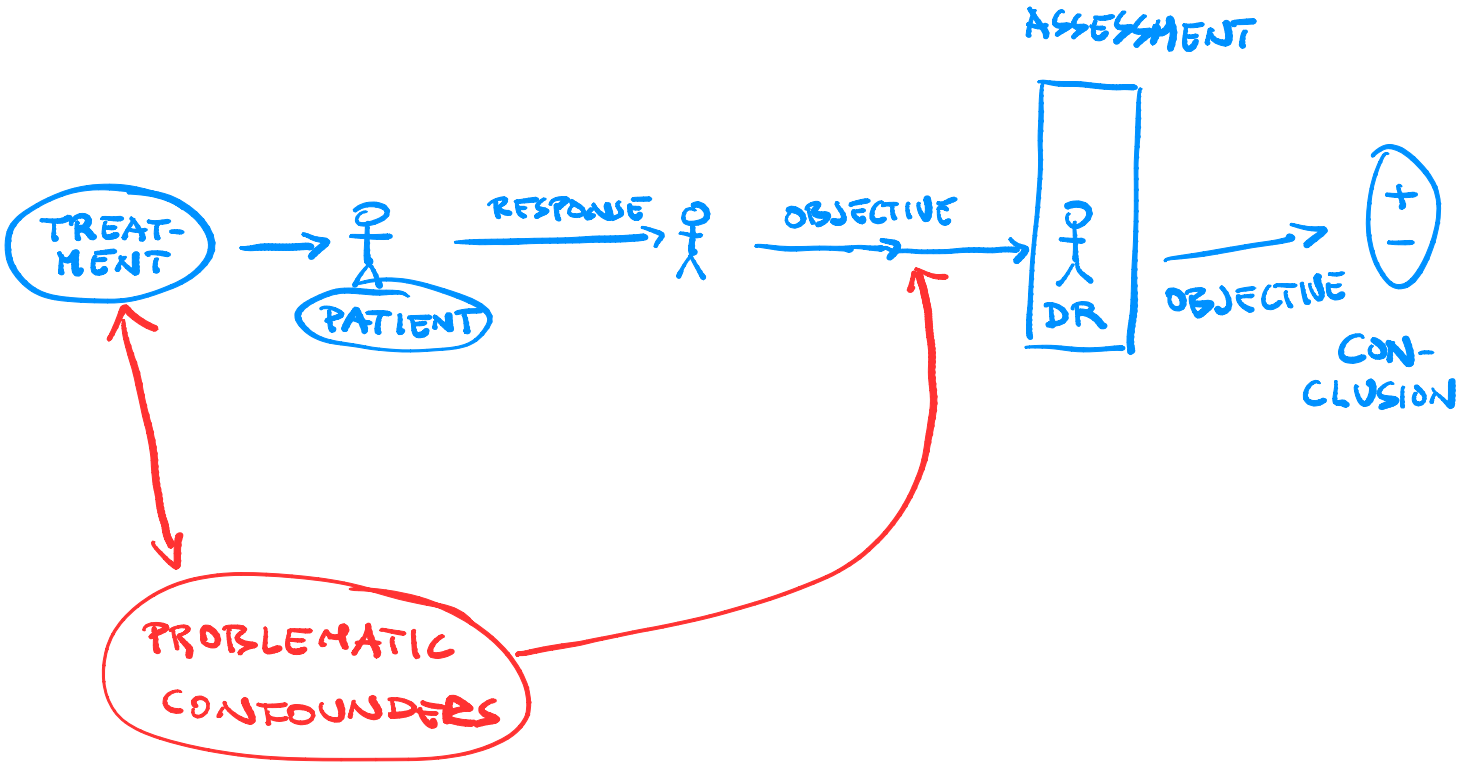
TRIAL, BASIC

... but there will be confounders, *often unseen/unmeasured!!*



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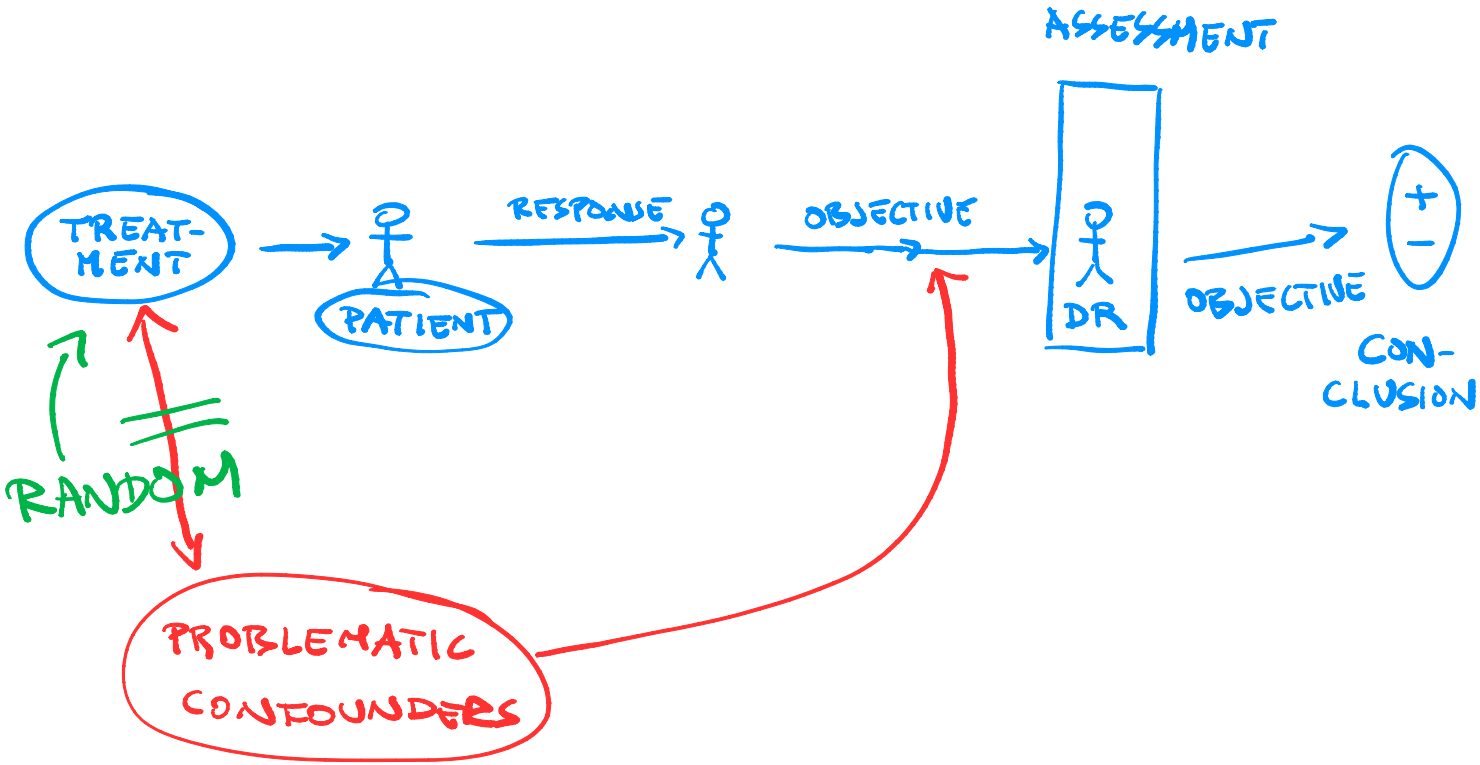
TRIAL, RANDOMIZED

A proper randomization effectively kills confounders, known or unknown!...



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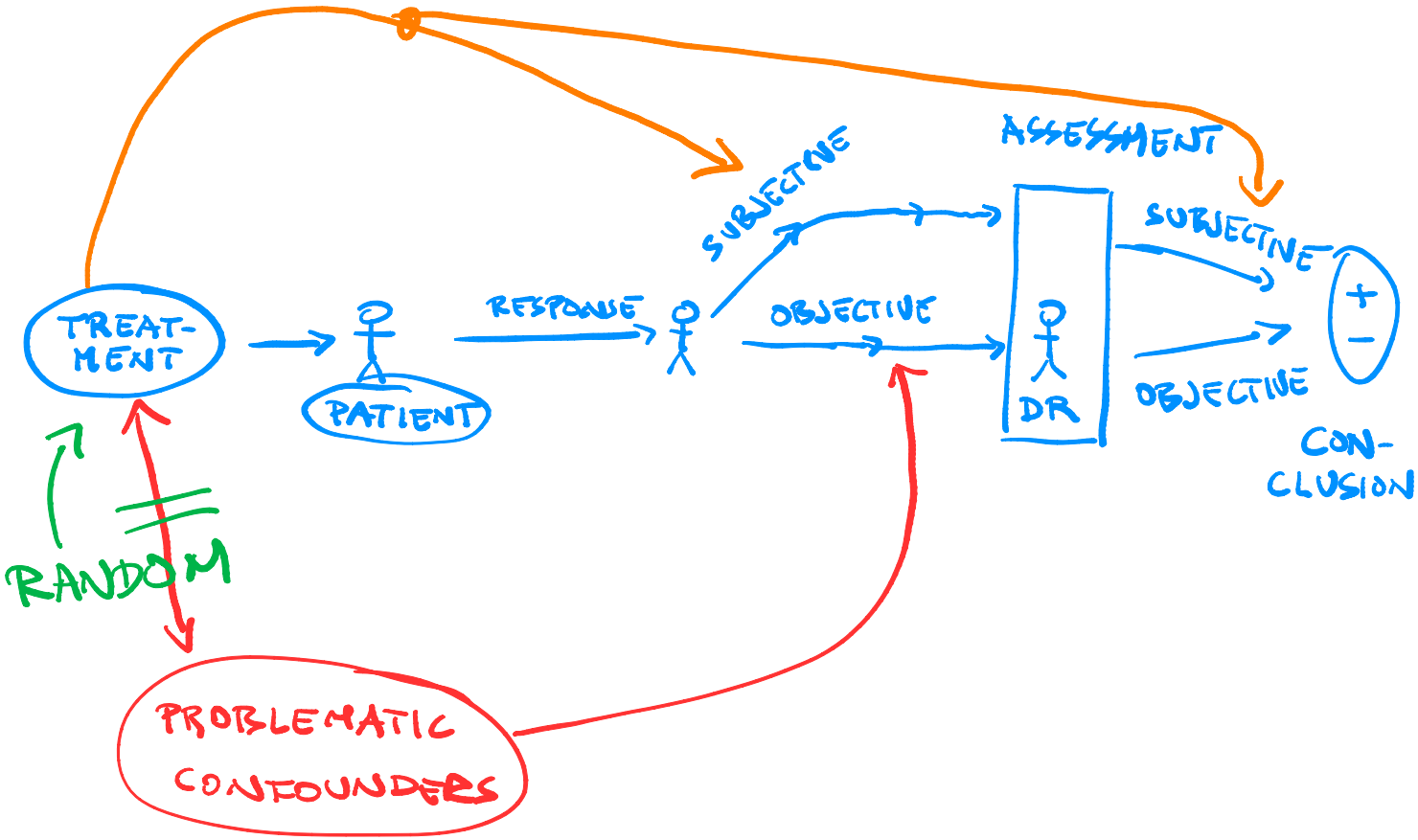
TRIAL, RANDOMIZED

... but knowledge of treatment can influence subjective assessments



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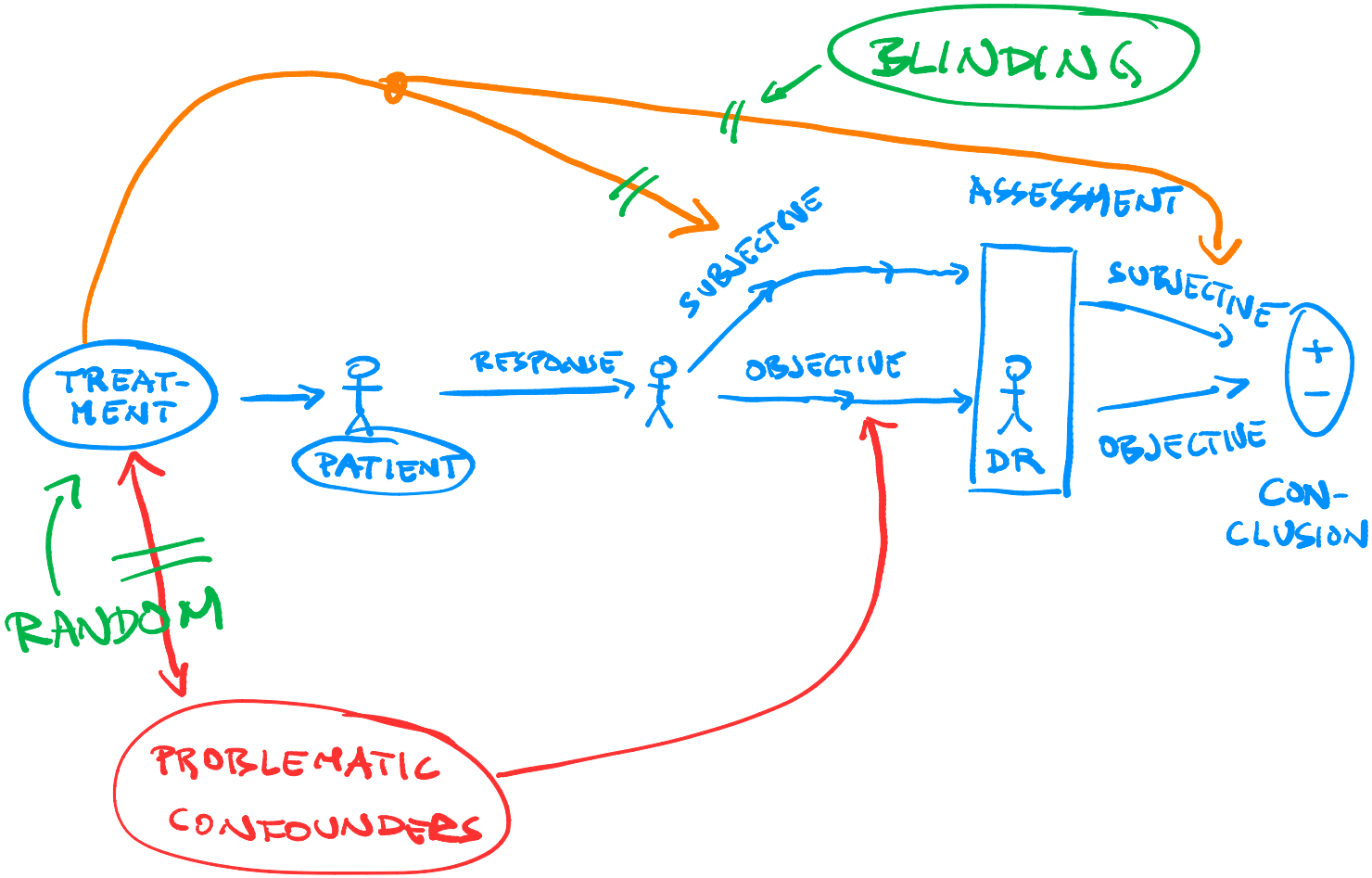
TRIAL, RANDOMIZED AND DOUBLE BLIND

... double blinding can kill those paths... but can be difficult to get perfect



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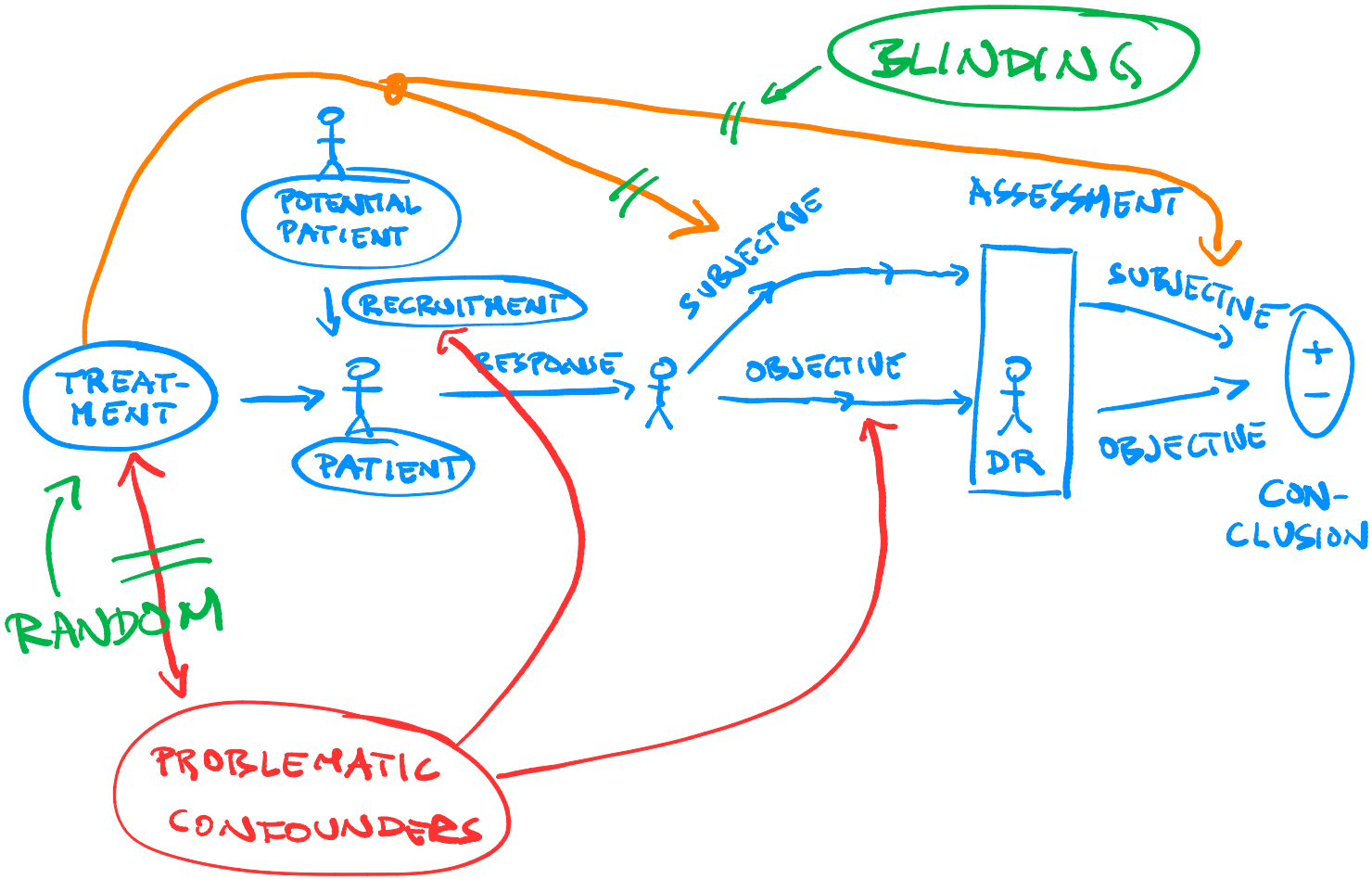
TRIAL, RANDOMIZED AND DOUBLE BLIND

How about biases in the recruitment process?



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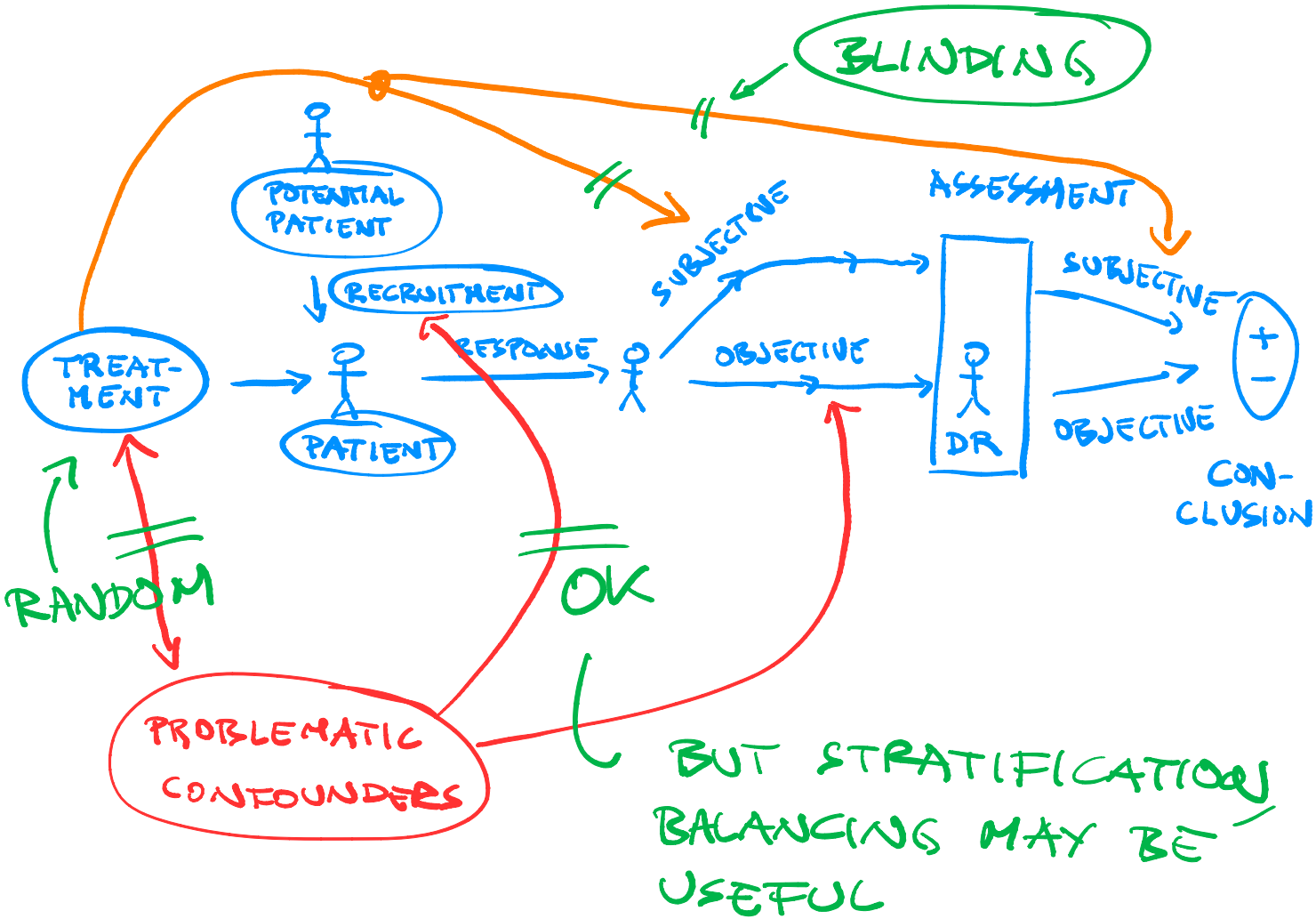
For the most part OK... not correlated with treatment



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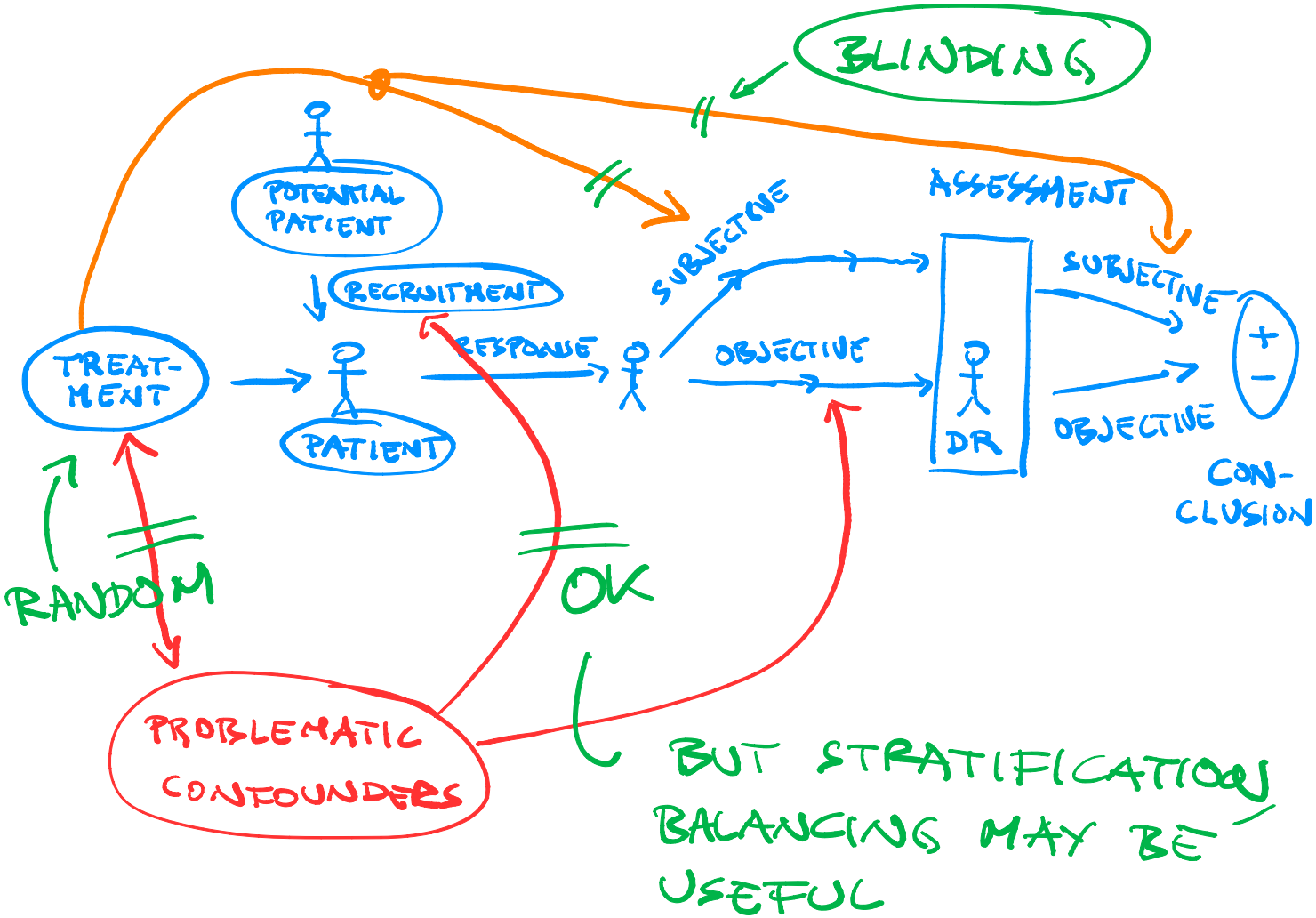
TRIAL, RANDOMIZED AND DOUBLE BLIND

...but balancing/stratification should be considered



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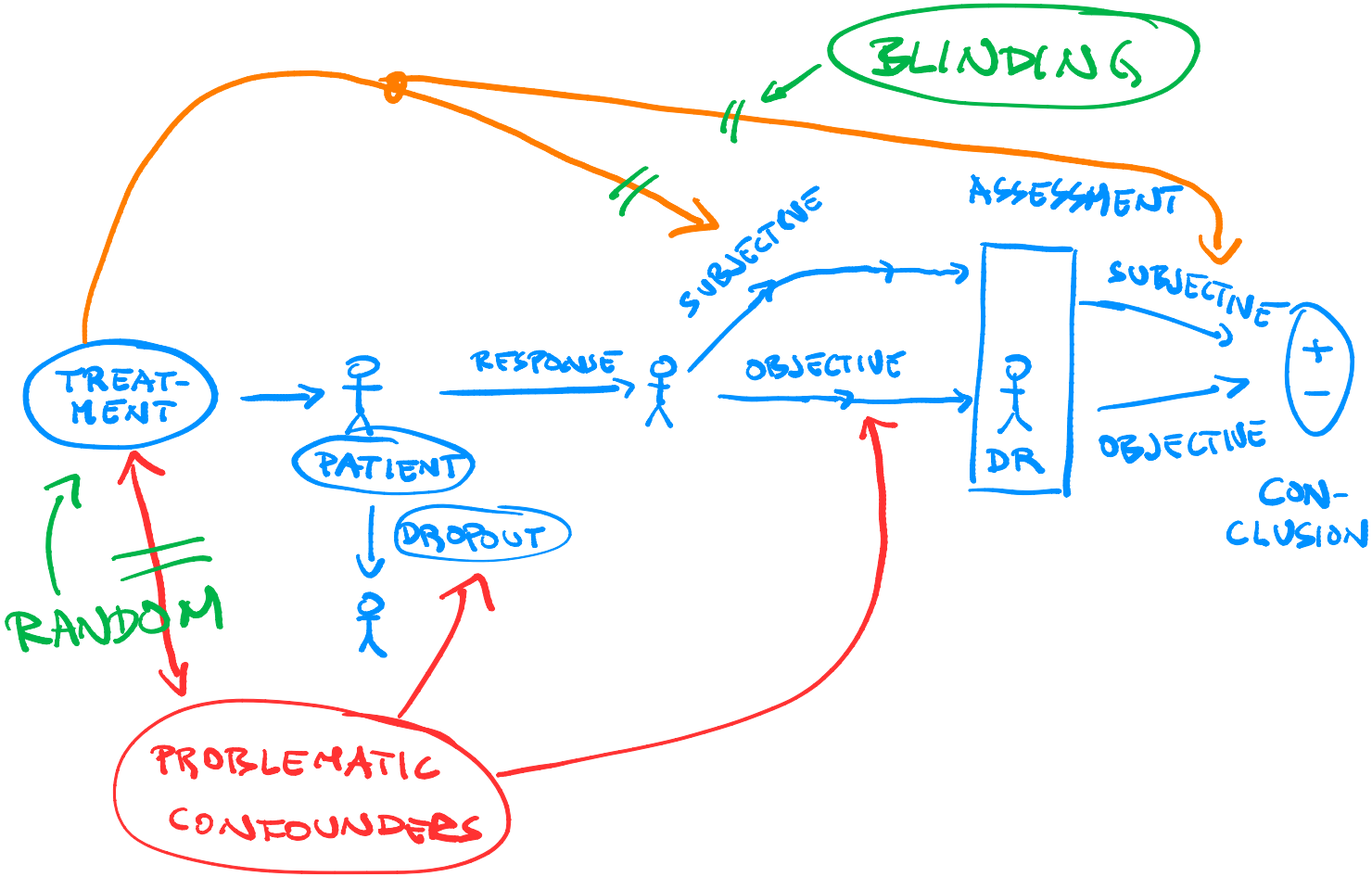
TRIAL, RANDOMIZED AND DOUBLE BLIND

What if there are dropouts, influenced by treatment and confounders?



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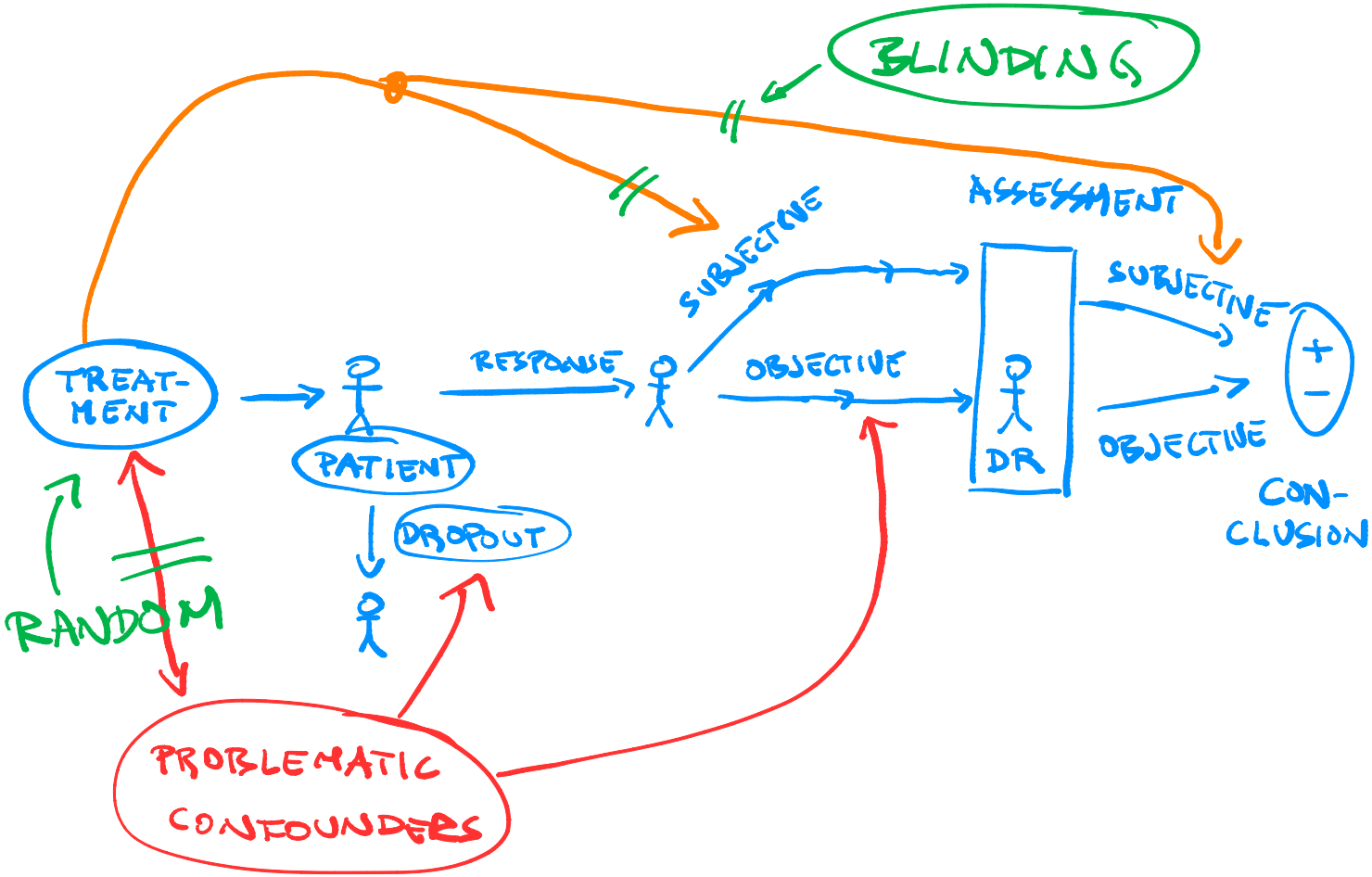
TRIAL, RANDOMIZED AND DOUBLE BLIND

... those pesky confounders can thus re-introduce themselves!



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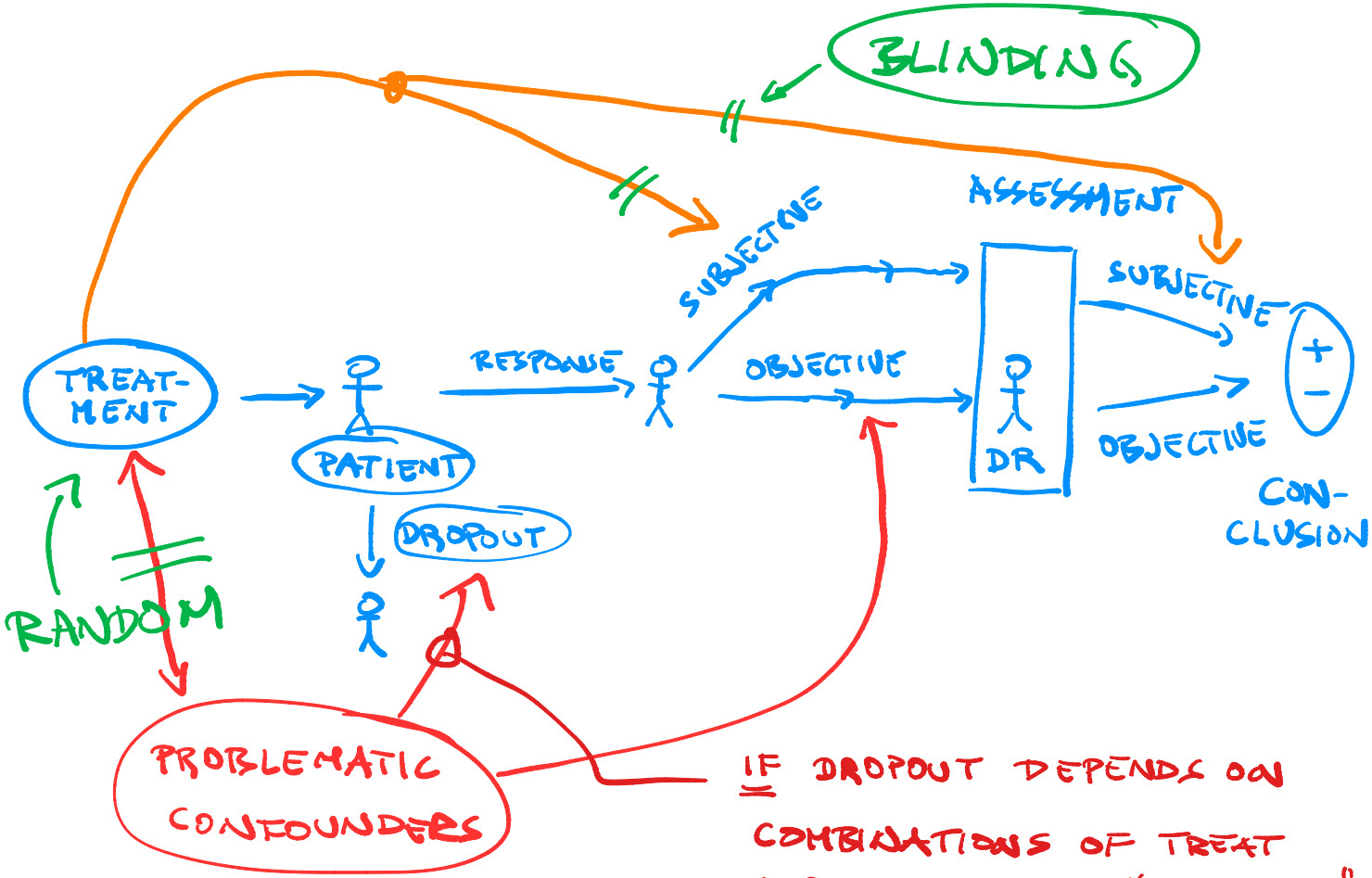
... if confounders **known**, adjustment can help... but, well...



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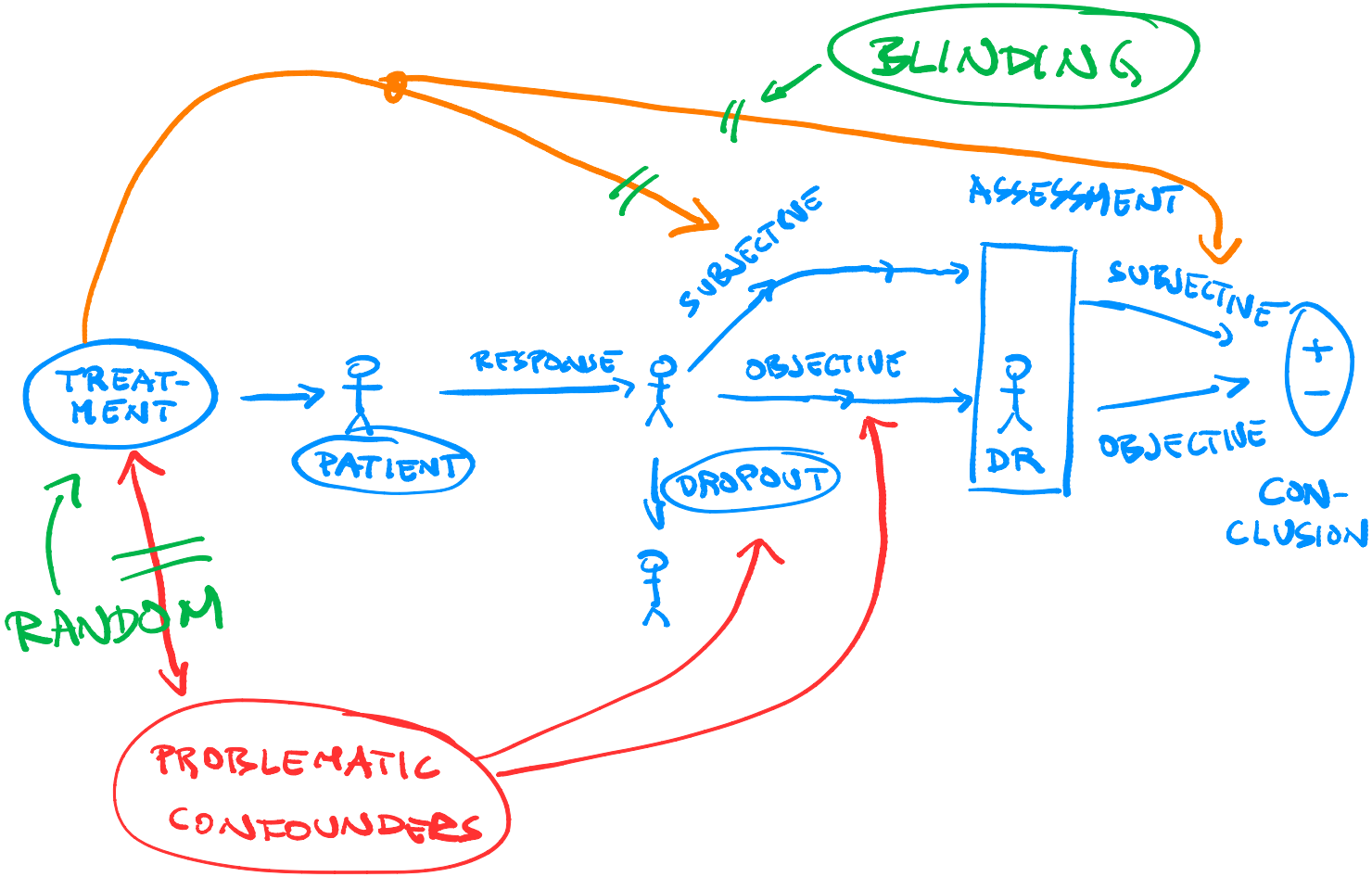
What if dropouts depend on outcome?



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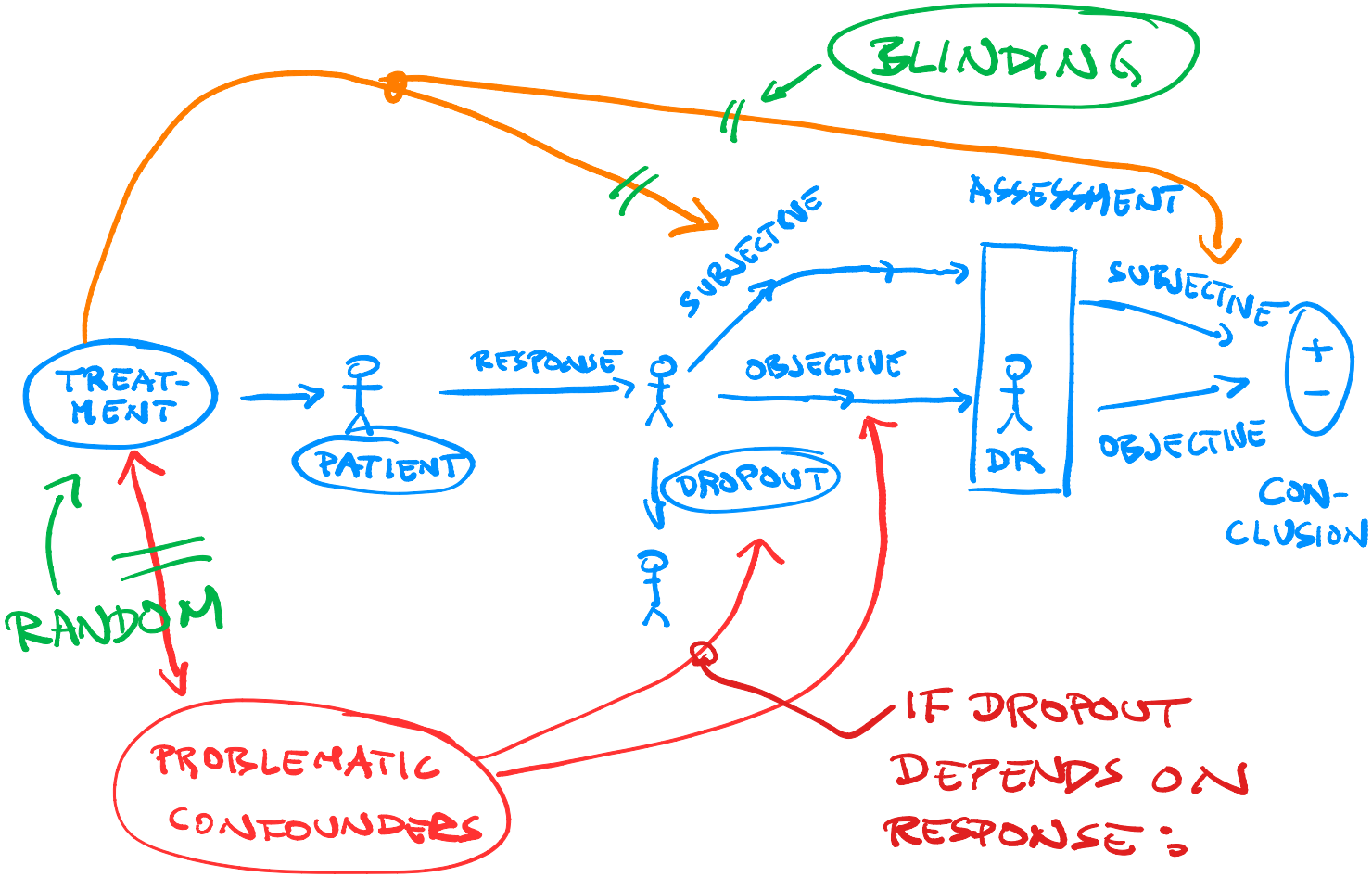
What if dropouts depend on outcome?



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Other topics

Types of randomization

- Simple randomization
- Blocked randomization (possibly varying length)
- Stratified randomization

Other:

- Triple blinding: Do not reveal treatment code until *after* analyses have been performed
- “Intention to treat” vs. “Per protocol”
- Extensive recent development on how to handle dropouts
- Extensive recent development on how to “mimic” RCTs with causal analyses of observational studies

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