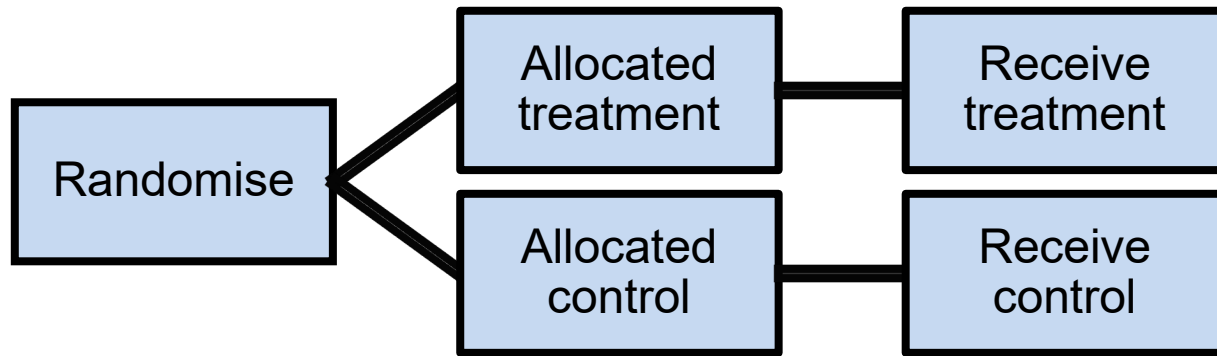


Back on the CACE

Rob Herbert

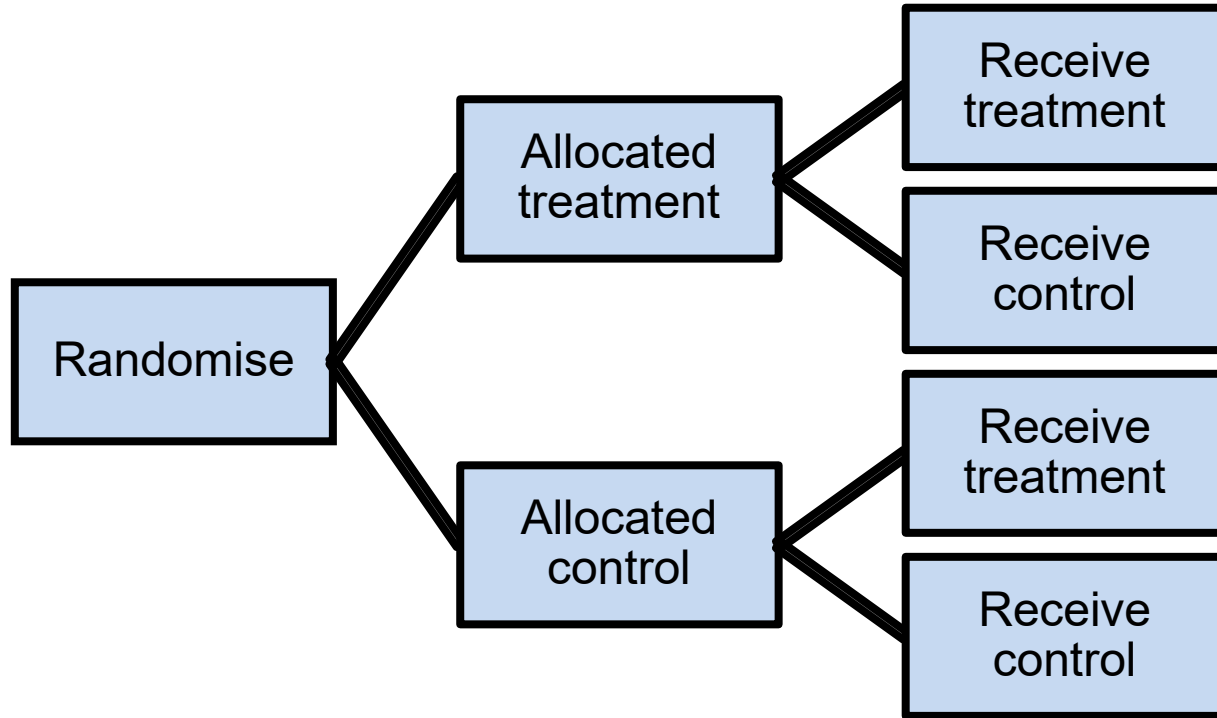
# Statement of the problem



In practice it usually doesn't work out quite as planned.

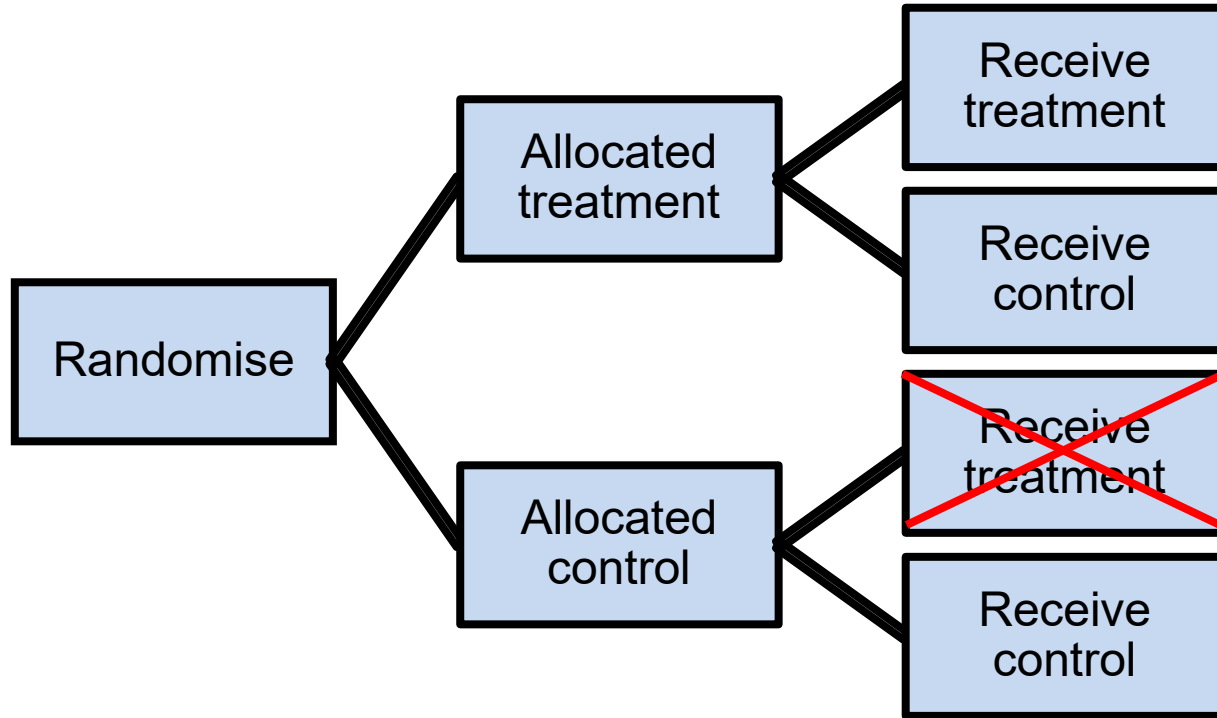
In real trials we usually get something that looks more like this ...

# Statement of the problem



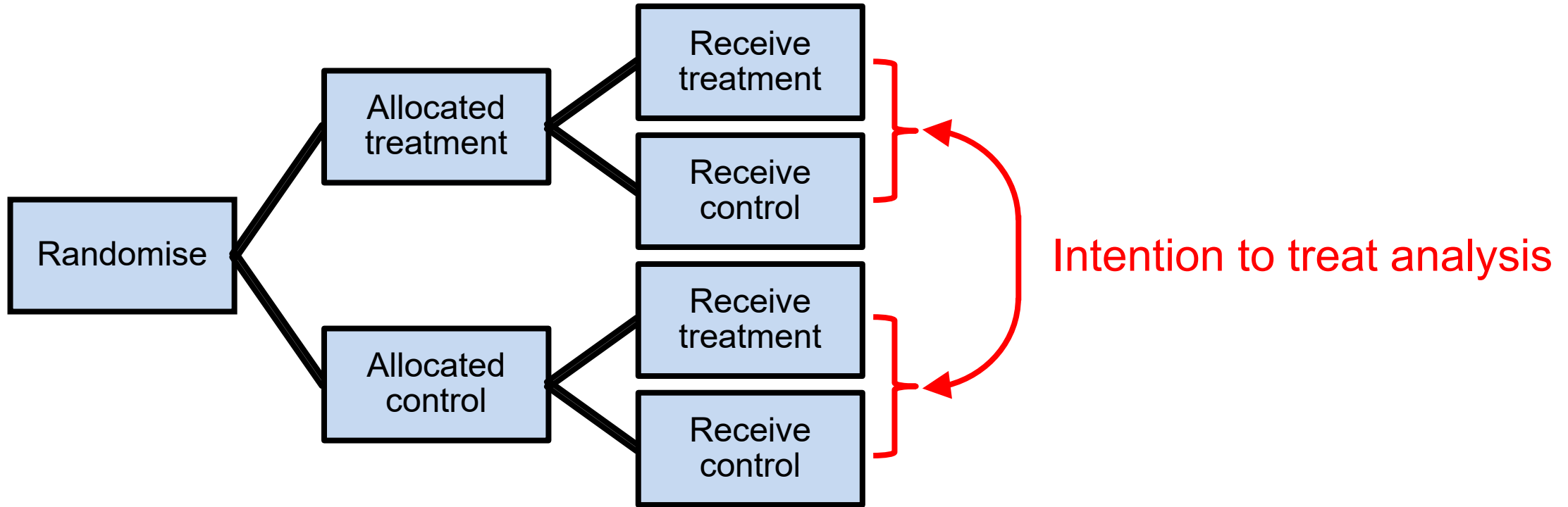
Here we have assumed, as an approximation, that there are only two possibilities: each participant receives either treatment or control. Adherence to allocation is *unidimensional* and *binary*.

# Statement of the problem



In many trials it is not possible for participants in the control group to access the treatment. This makes things a bit simpler.

# Statement of the problem



The standard approach to the analysis of clinical trials, called “analysis by intention to treat”, ignores non-compliance.

## Intention to treat analyses (ITT)

- The primary analysis of randomised trials should almost always be an intention to treat analysis.
- This is because, unlike frequently used alternatives, the intention to treat approach preserves randomisation.

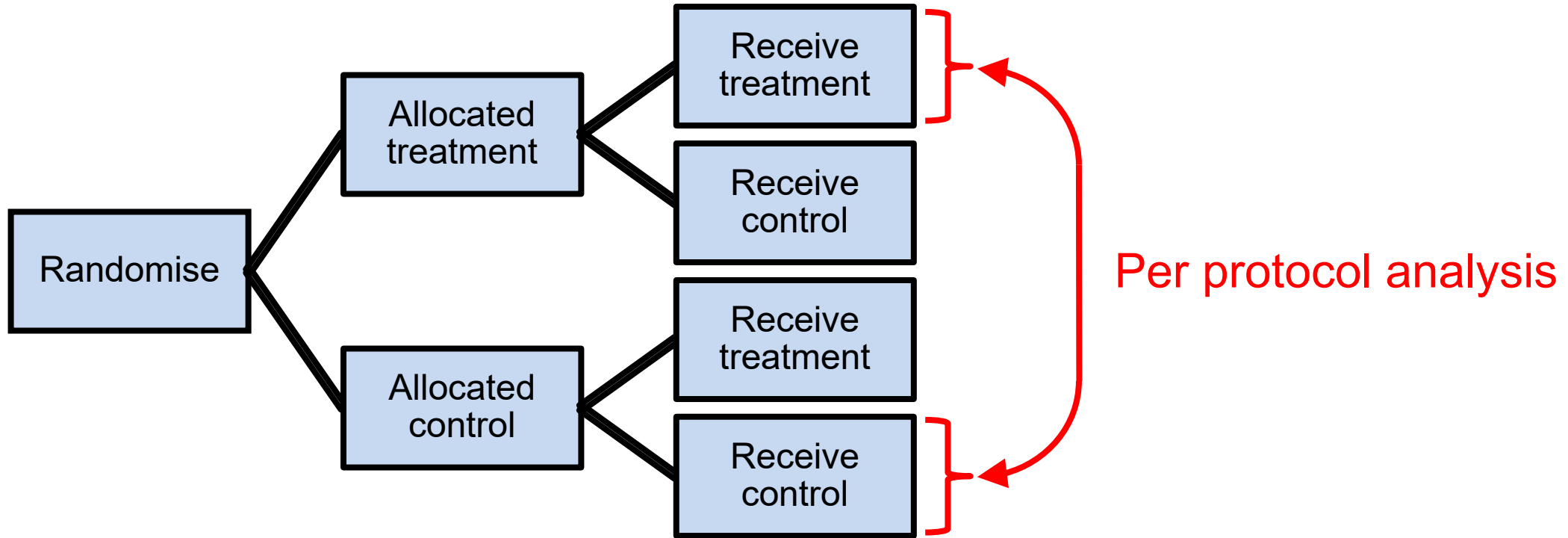
In the presence of non-compliance, intention to treat analyses:

- provide valid estimates of the causal effect of *intending to treat*.
- do not provide an estimate of the causal effect of *treatment*.

## Statement of the problem

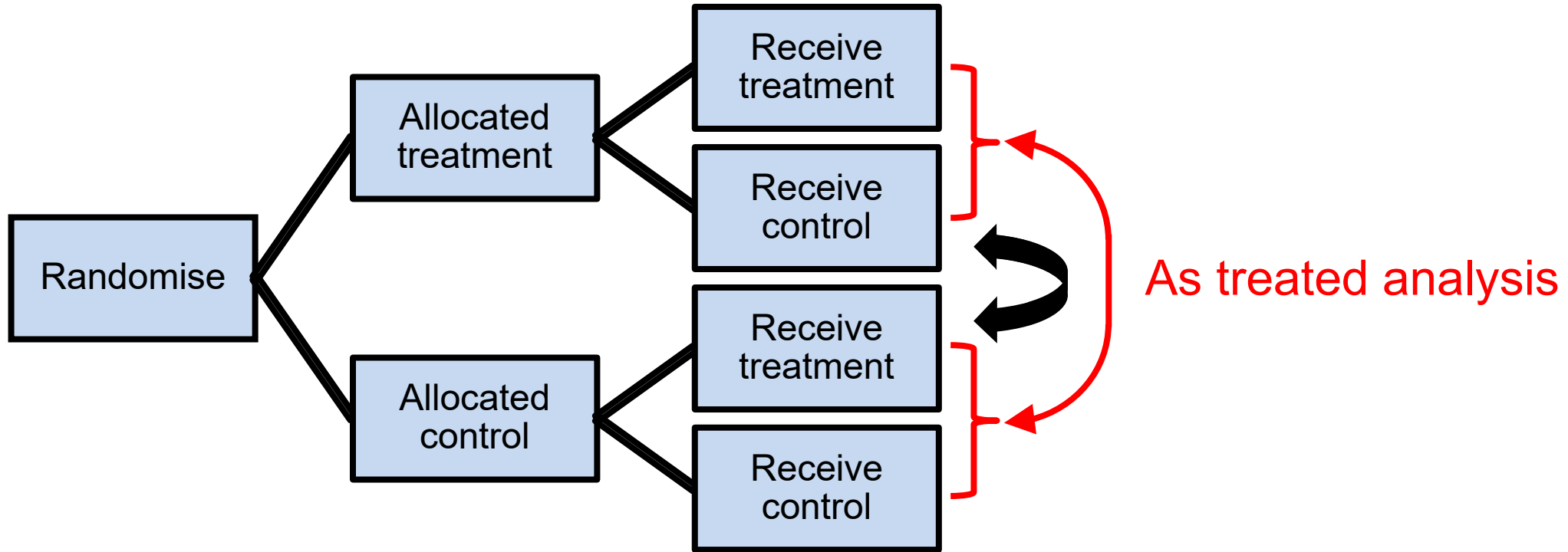
- Pragmatic trialists are happy to estimate the intention to treat effect but explanatory researchers think it is a rip-off.
- Explanatory trialists want to know the effect of treatment, not the effect of intending to treat.
- Conventionally, when explanatory trialists have wanted to estimate the effects of treatment, they have used “per protocol” and “as treated” approaches to analysis. These approaches are not recommended.

# How not to analyse your clinical trial ...





# How not to analyse your clinical trial ...



## Doing it better

- In general, the per protocol and as treated approaches do not generate valid causal inferences.
- There are alternatives which, under assumptions that may often be plausible, lead to valid causal inferences.
- Don't conduct per protocol or as treated analyses.

## Estimating effects of *treatment*

- The *effect* of treatment in an individual is the difference in two *potential* outcomes – the outcomes that would be observed if the person was simultaneously treated and not treated.
- If we wanted to estimate effects of treatment, we could estimate:
  - the average effect of treatment in people who comply with allocation (the complier average causal effect, or CACE), *or*
  - the average effect of treatment in the whole population if everyone complied with allocation (the average treatment effect, or ATE), *or*
  - other estimands (e.g., ATET).
- The CACE and ATE are quite different constructs.
- This presentation is concerned with estimating the CACE ...

## Who are *Compliers*?

We should define Compliers, and other sorts of people, on the basis of their adherence to their allocation *and what their adherence would have been if they had received the alternate allocation.*

If allocated intervention ...	If allocated control ...	Name
receive intervention	receive control	(Baseline) Complier

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receive intervention	receive intervention	Always Taker

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If allocated intervention ...	If allocated control ...	Name
receive intervention	receive control	(Baseline) Complier
receive intervention	receive intervention	Always Taker
receive control	receive control	Never Taker

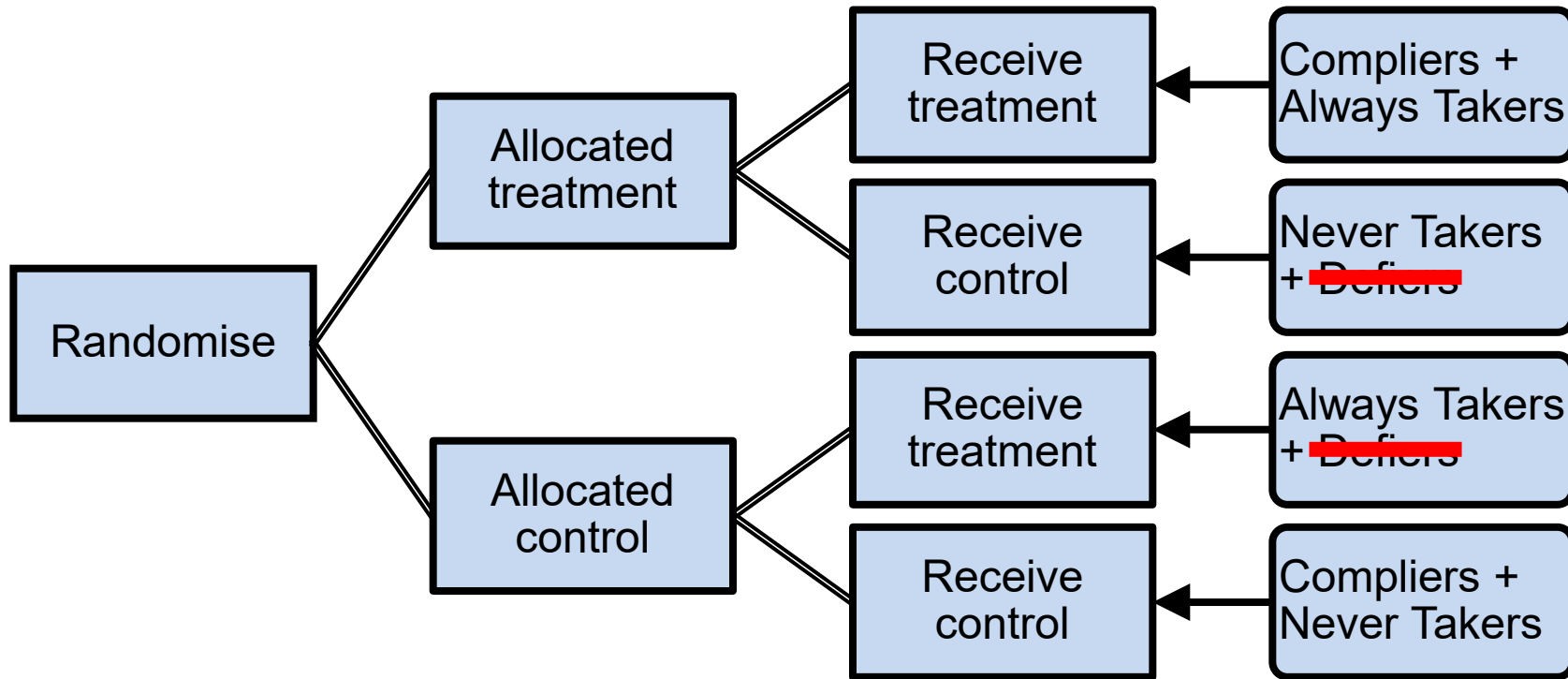
## Who are *Compliers*?

We should define Compliers, and other sorts of people, on the basis of their adherence to their allocation *and what their adherence would have been if they had received the alternate allocation.*

If allocated intervention ...	If allocated control ...	Name
receive intervention	receive control	(Baseline) Complier
receive intervention	receive intervention	Always Taker
receive control	receive control	Never Taker
receive control	receive intervention	Defier

In randomised trials, these four strata are equally represented in intervention and control groups.

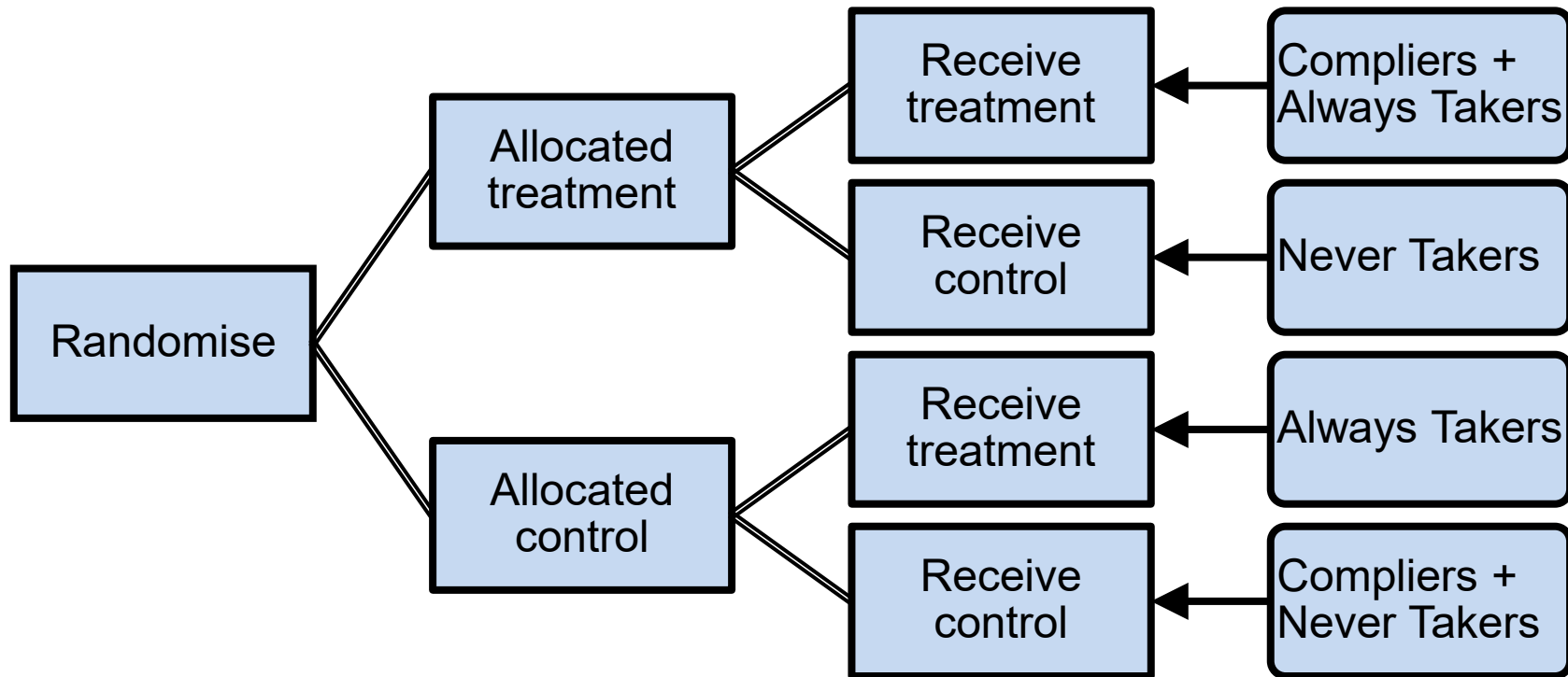
# Who are *Compliers*?



It is often reasonable to assume that there are no Defiers.

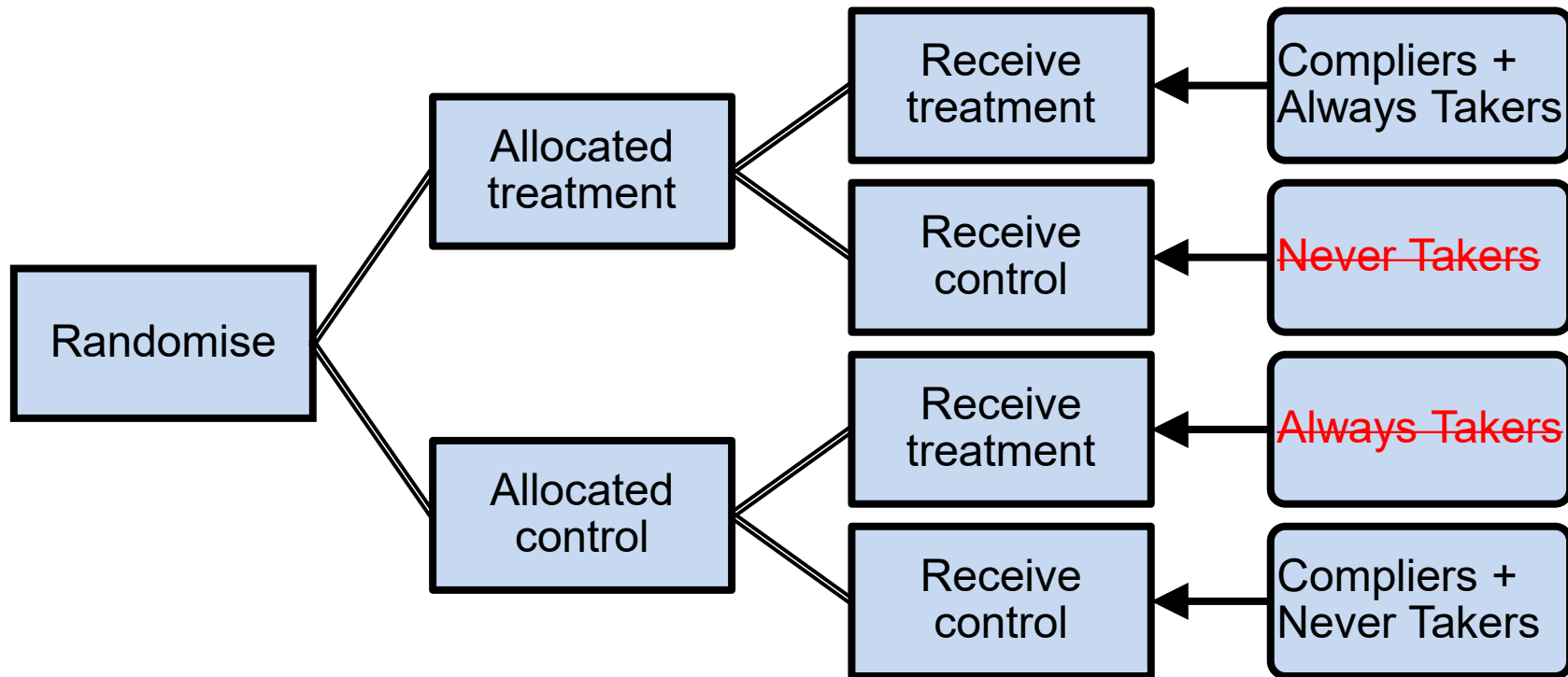


# Who are *Compliers*?



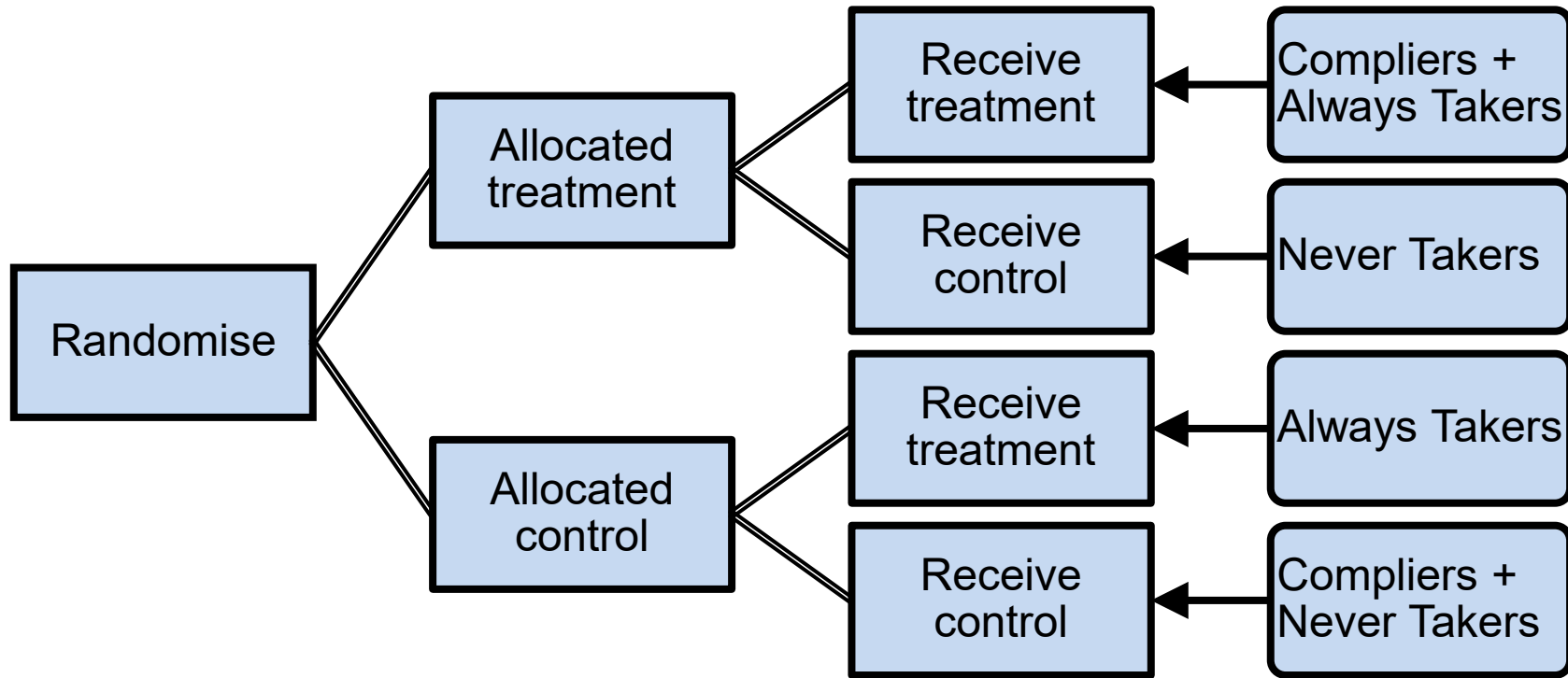
Intention to treat analyses compare comparable groups and estimate effects in well defined populations.

# Who are *Compliers*?



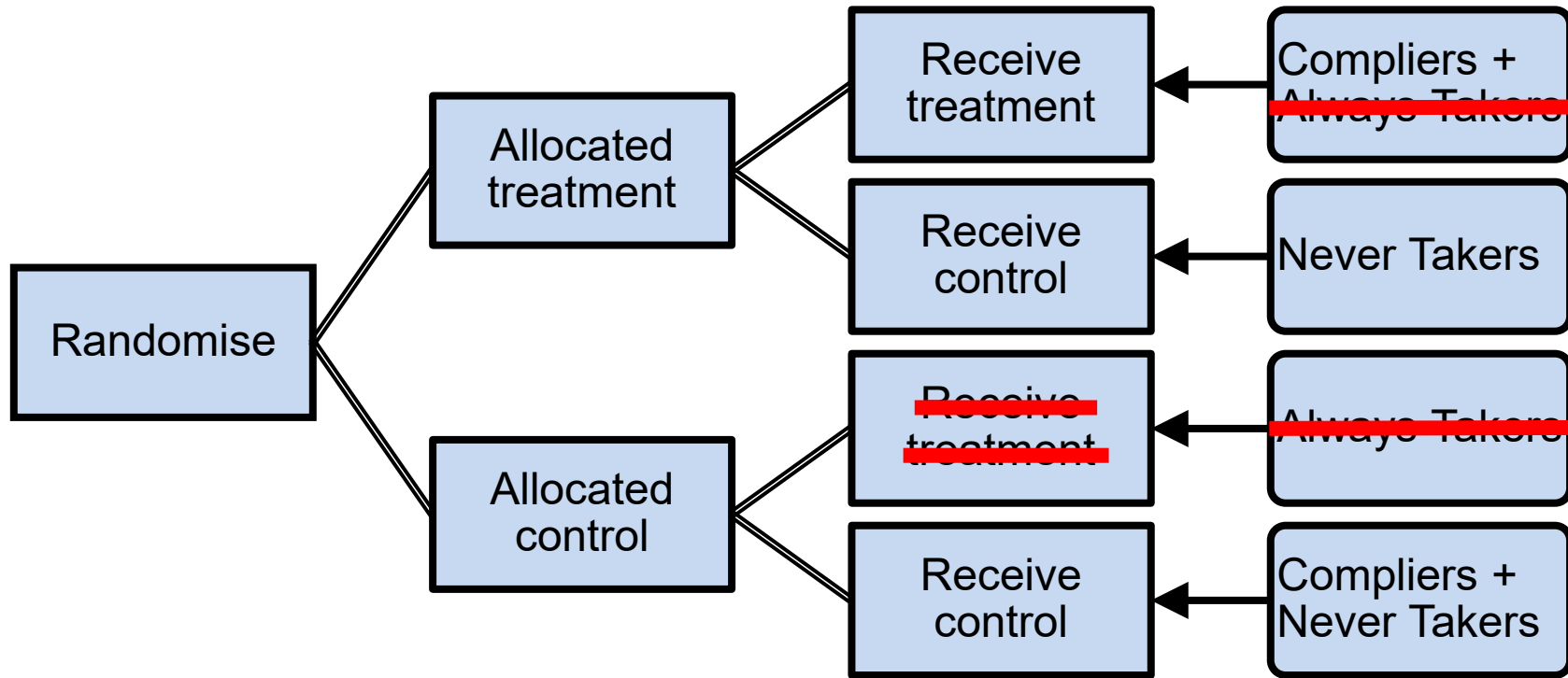
Per protocol and as treated analyses are dodgy because they compare **Compliers + Always Takers** with **Compliers + Never Takers**.

# Who are *Compliers*?



We can identify Never Takers allocated to treatment, and Always Takers allocated to control, but we can't identify Compliers.

# Who are *Compliers*?



If only those allocated treatment can get treatment there are no Always Takers, so we can identify Compliers in the treated group.

## Estimating the CACE with principal stratification

If we assume:

1. participant's *outcomes are independent*,
2. participants were *randomly* allocated to treatment or control,
3. there are *no defiers*, and
4. allocation only affects outcomes *through its effect on treatment*, ...

Then:  $CACE = ITT / P_{diff}$

where  $P_{diff}$  is the difference in the proportions of participants receiving treatment in the treatment and control groups.

The CACE is larger than the ITT effect by an amount that depends on how much more than controls the treatment group was treated.

## Statistical inference

- We can easily calculate the CACE. But it's a little tricky to calculate standard errors, confidence intervals and p values.
- One approach is to bootstrap ITT / Pc.
- Alternatively, we can use instrumental variable regression. In instrumental variable regression, an “instrumental variable” (here, allocation) is used to estimate causal effects of an “endogenous” variable (treatment).
- There are some advantages to instrumental variable regression: it is implemented in many statistical programs, naturally yields confidence intervals and easily accommodates covariates.

## Interpretation of the CACE and alternative estimands

- The CACE is the average effect of treatment in compliers. It tells us nothing about the *effect of compliance*.
- Up to now, we have treated compliance as binary. It is possible to think of compliance as a categorical or continuous and estimate effects of treatment in people with particular levels of compliance.
- If we believe Never Takers and Always Takers could be made to comply, we might consider estimating the average effect of treatment in the whole population if everyone complied with allocation. This is the average treatment effect, or ATE.

## Summary

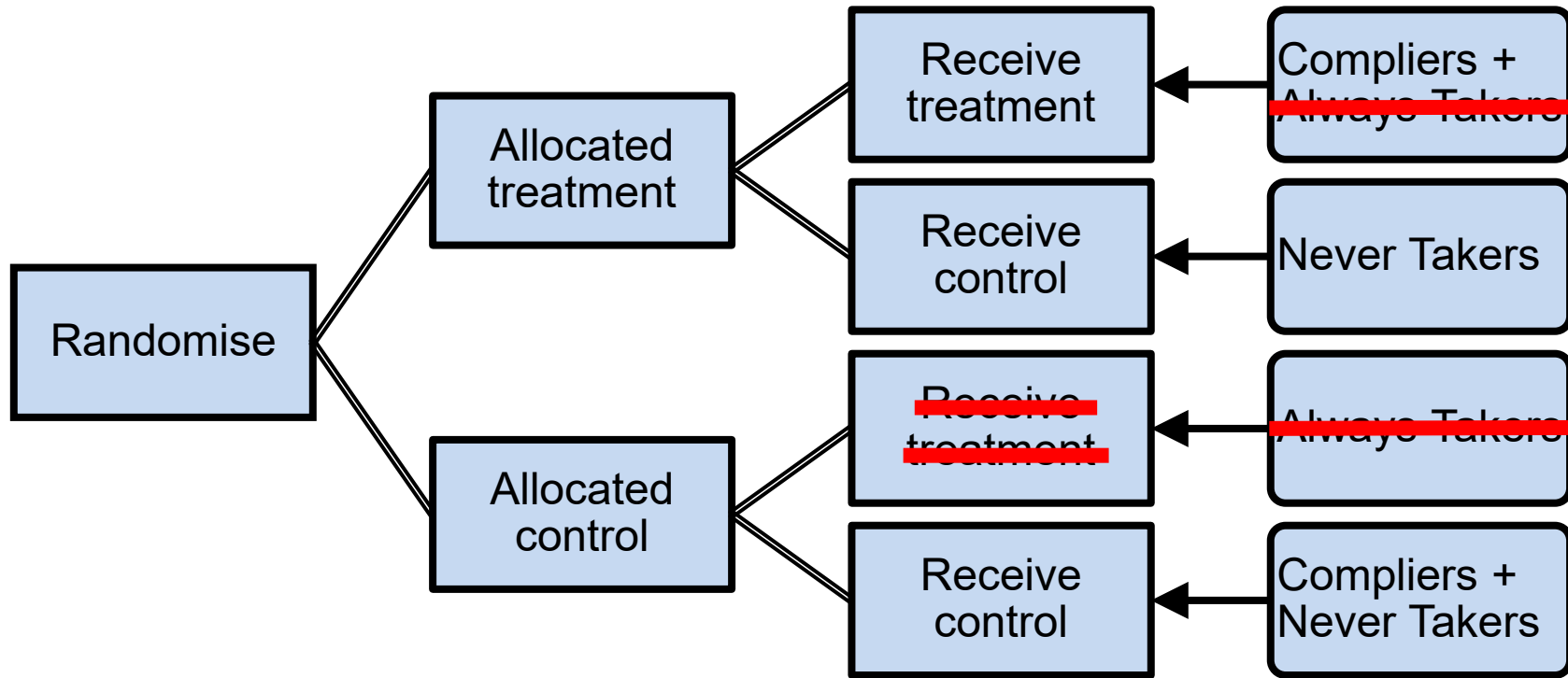
In the presence of non-compliance,

- intention to treat analyses estimate the causal effect of intending to treat, not the causal effect of treatment.
- per protocol and as treated analyses are dodgy. Don't use them.
- when allocation only affects outcome through treatment, we can estimate the CACE with principal stratification or instrumental variable regression. The latter may be more convenient.
- the CACE is the average effect of treatment in compliers. It tells us nothing about the effects of manipulating compliance.
- other estimands (e.g., the ATE) may also be of interest.

Further reading: *Stuart EA (2008) Prevention Science 9: 288-298.*



# Who are *Compliers*?



If only those allocated treatment can get treatment there are no Always Takers, so we can identify Compliers in the treated group.