Internal and External Validity of Clinical Trials: an Introduction

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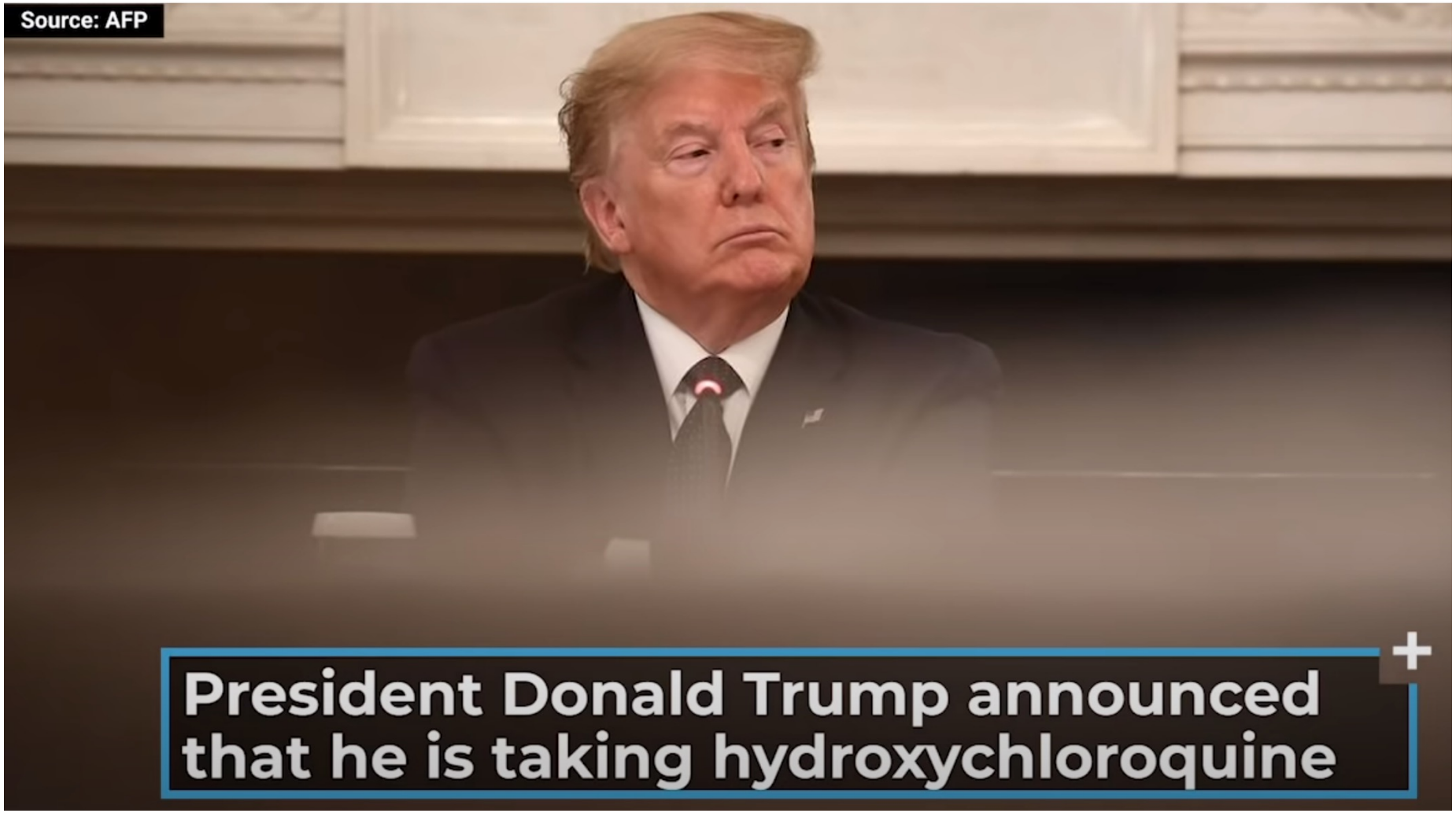
Why is it important to assess trial validity?

"Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial"

"Conclusion: Hydroxychloroquine is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin."

Gautret P, et al., International Journal of Antimicrobial Agents 2020 (Cited by 4903, Journal IF 5.3)

Why is it important to assess trial validity?



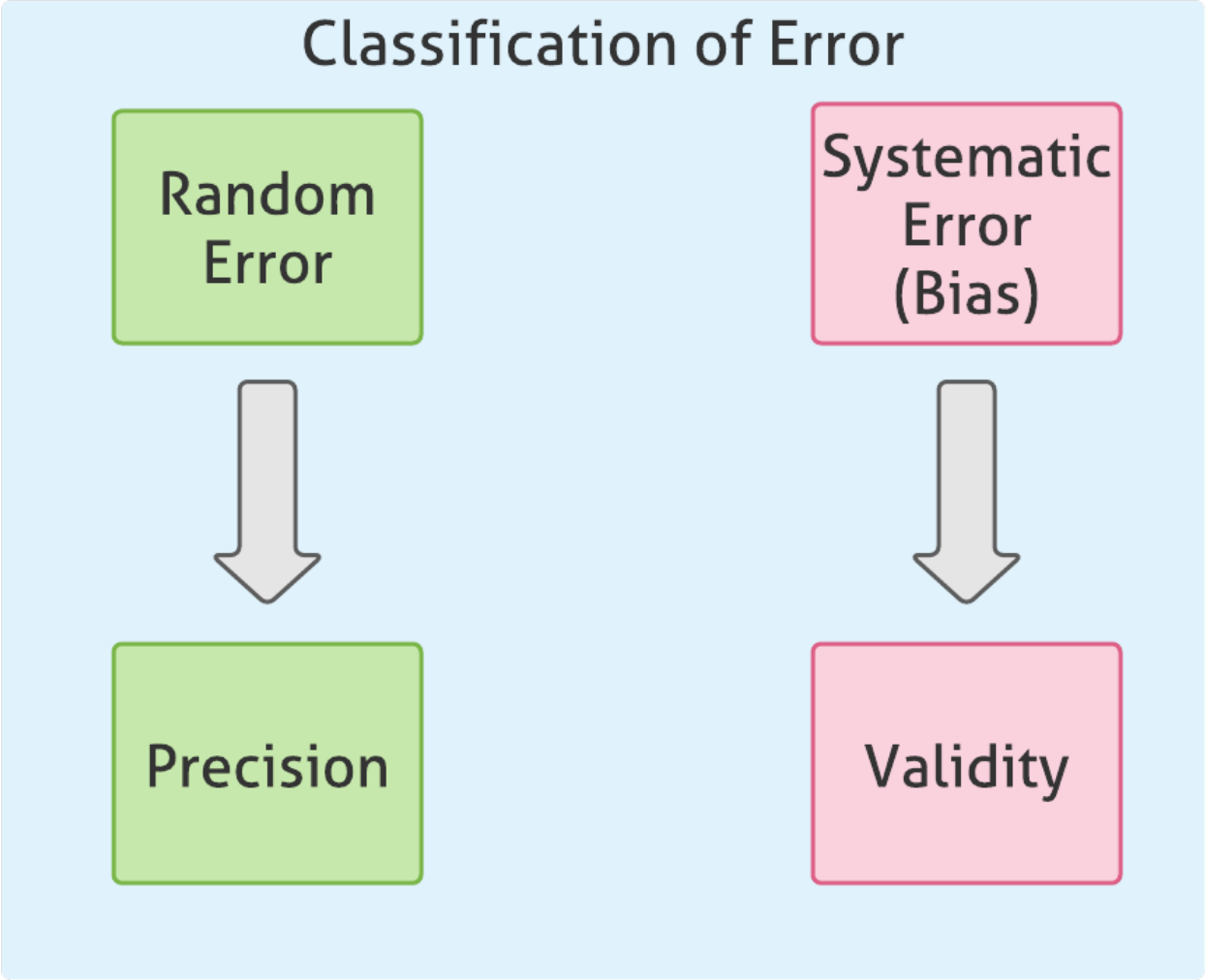
Why is it important to assess trial validity?

Rosendaal lists ten serious problems with the study, then concludes:

> *This is a non-informative manuscript with gross methodological shortcomings. The results do not justify the far-reaching conclusions about the efficacy of hydroxychloroquine in Covid-19, and in the view of this reviewer do not justify any conclusion at all.*

Rochwerg B, et al. A living WHO guideline on drugs for covid-19. BMJ 2020

What is Validity?



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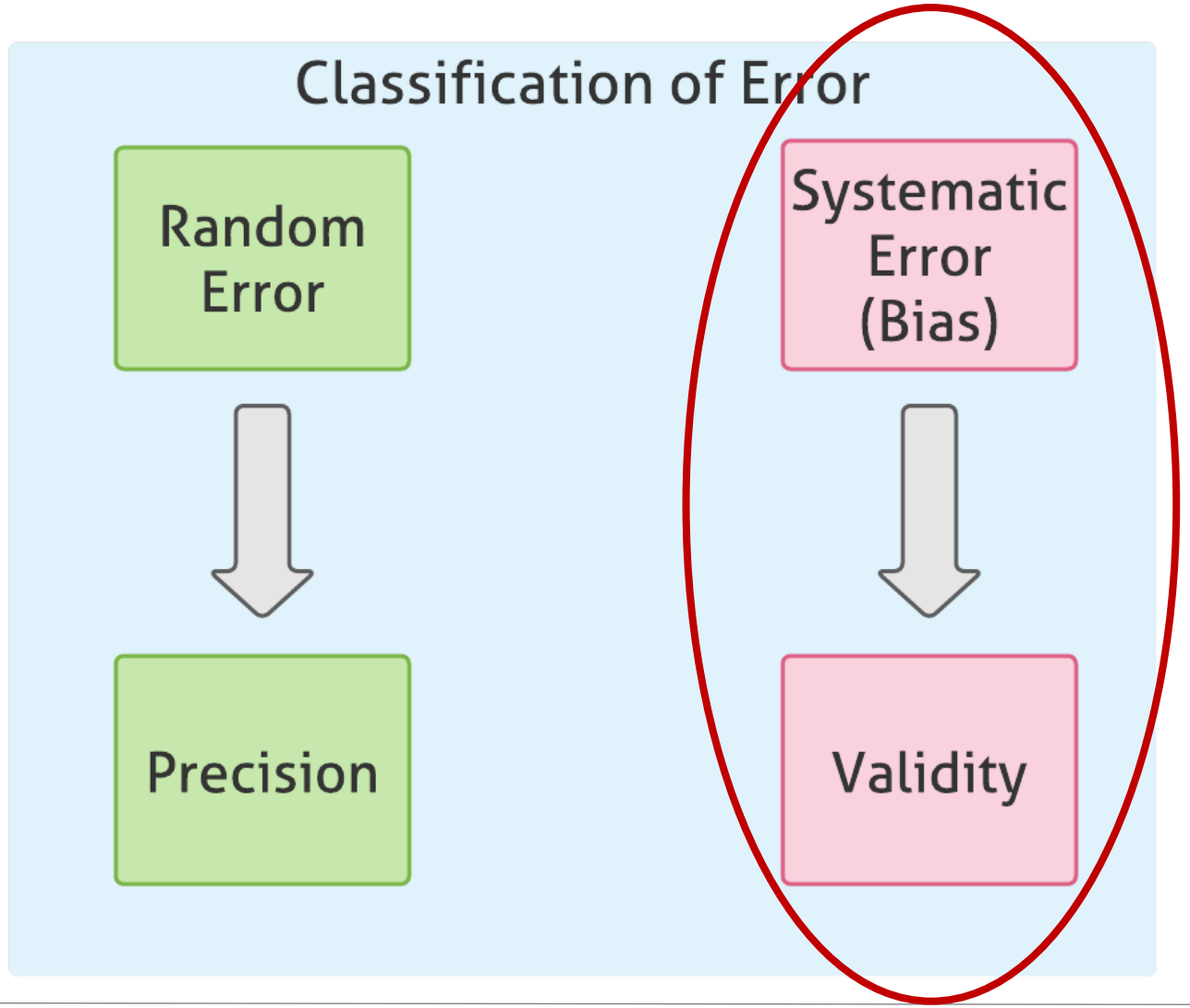

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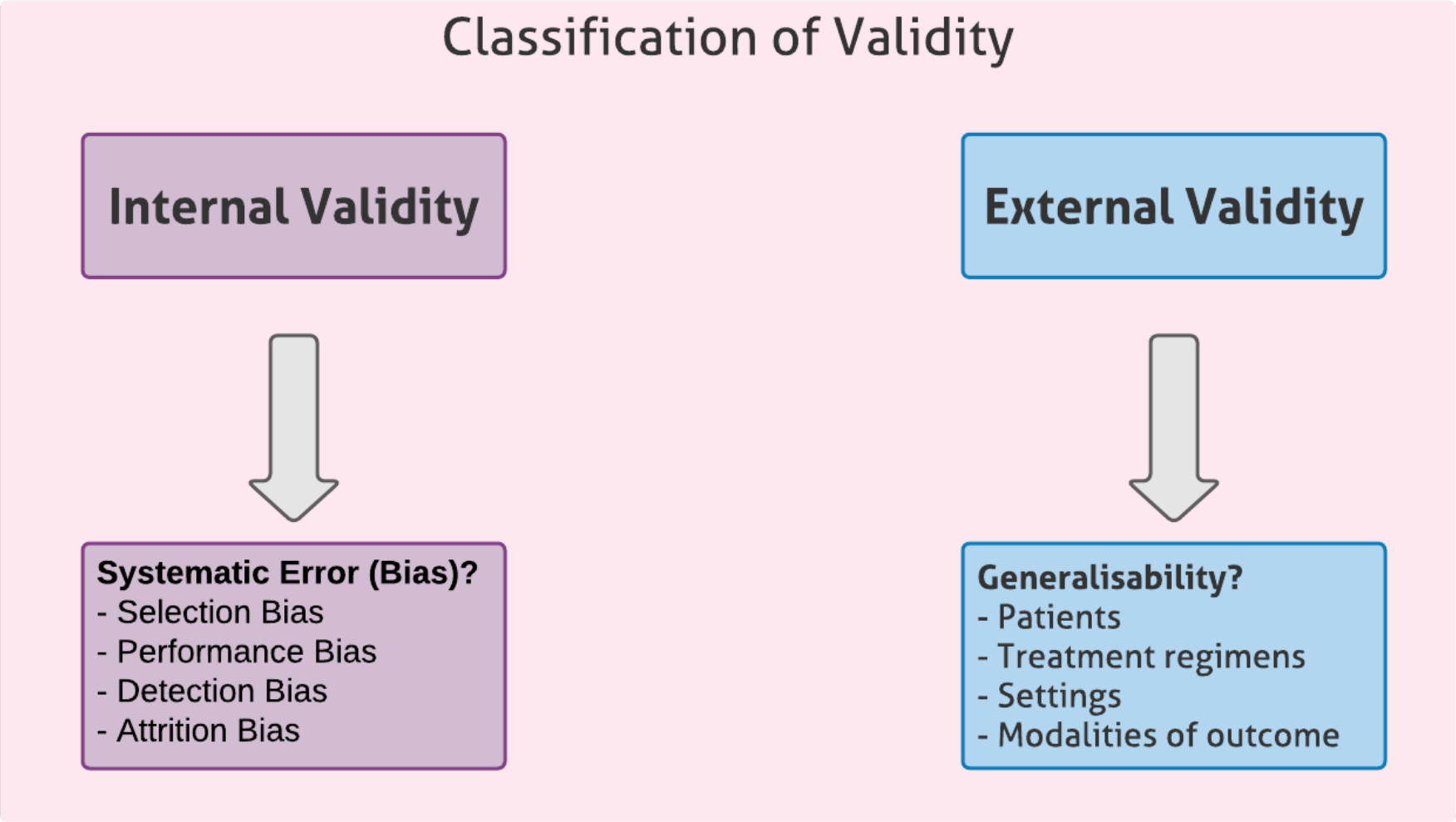

Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. BMJ 2001

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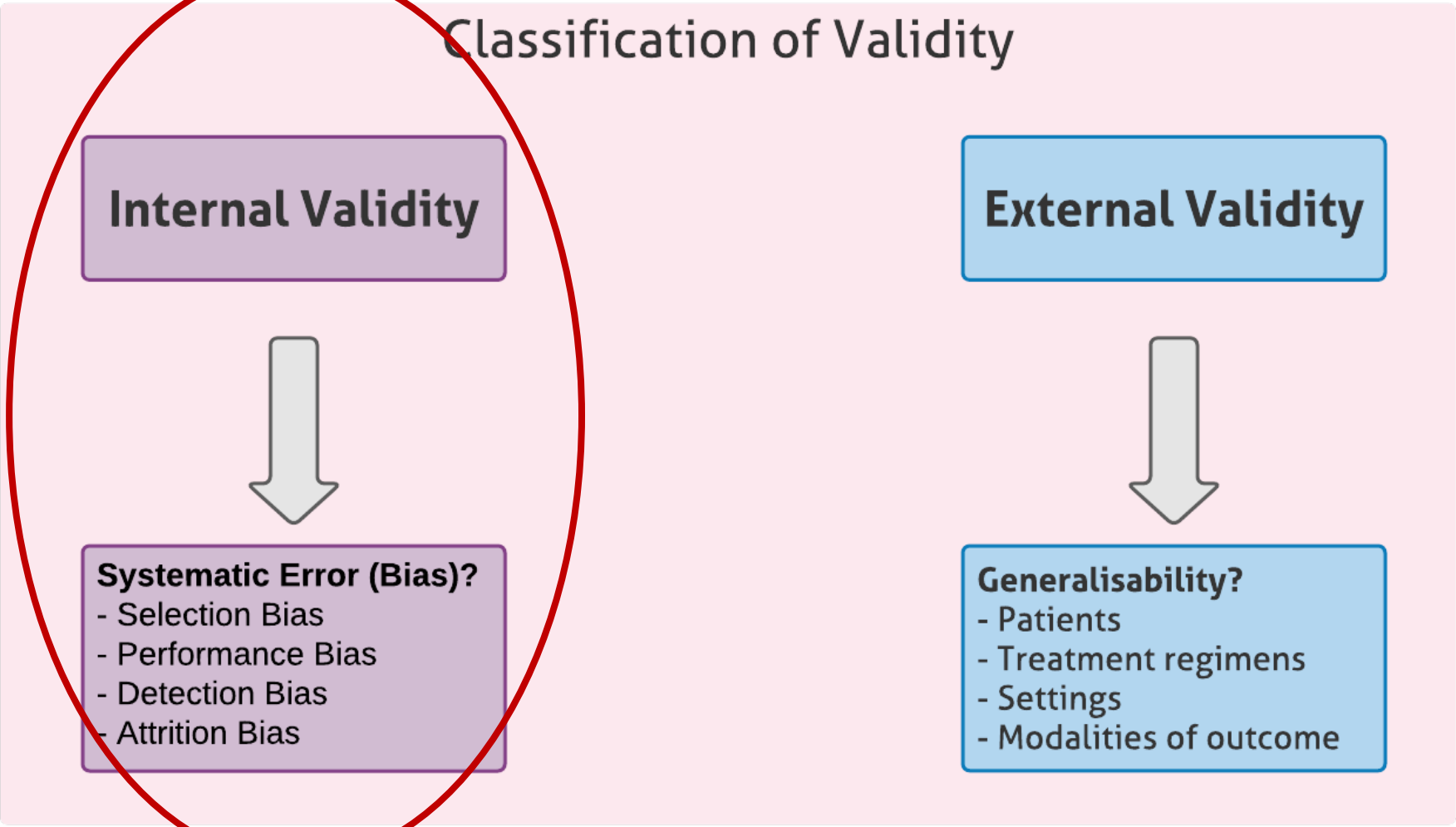

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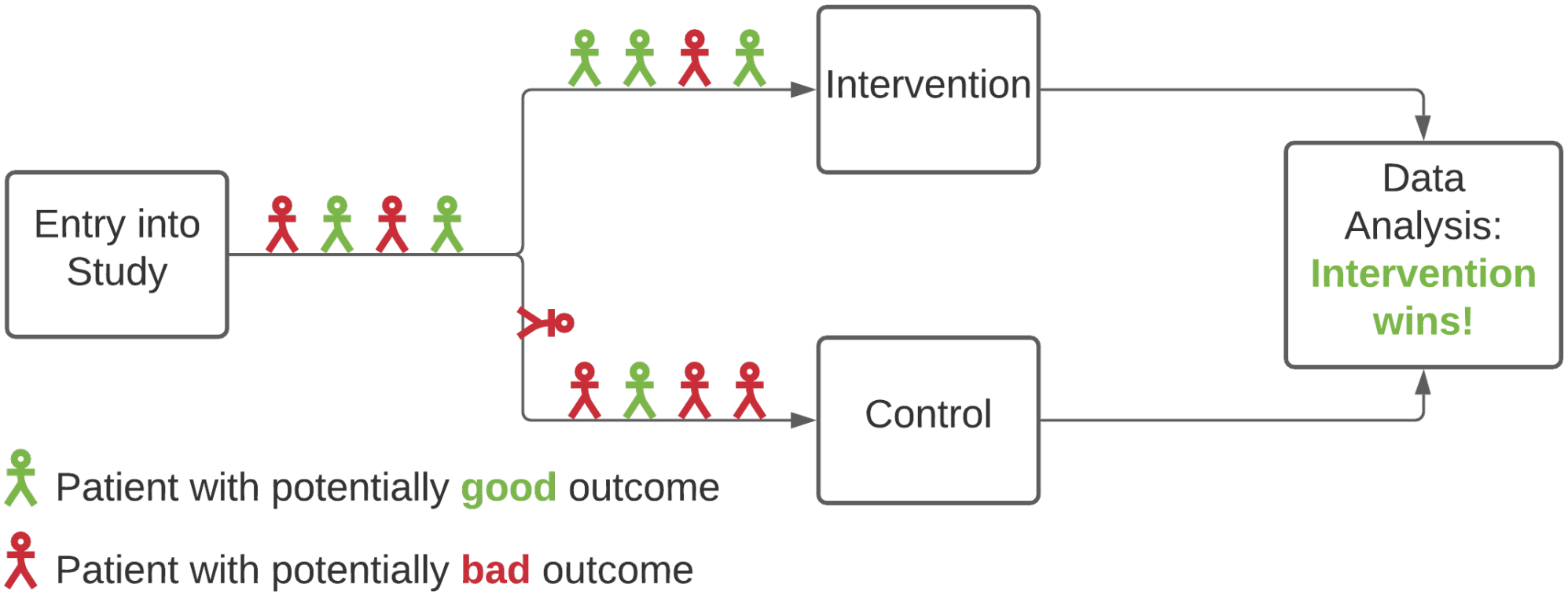
Selection Bias

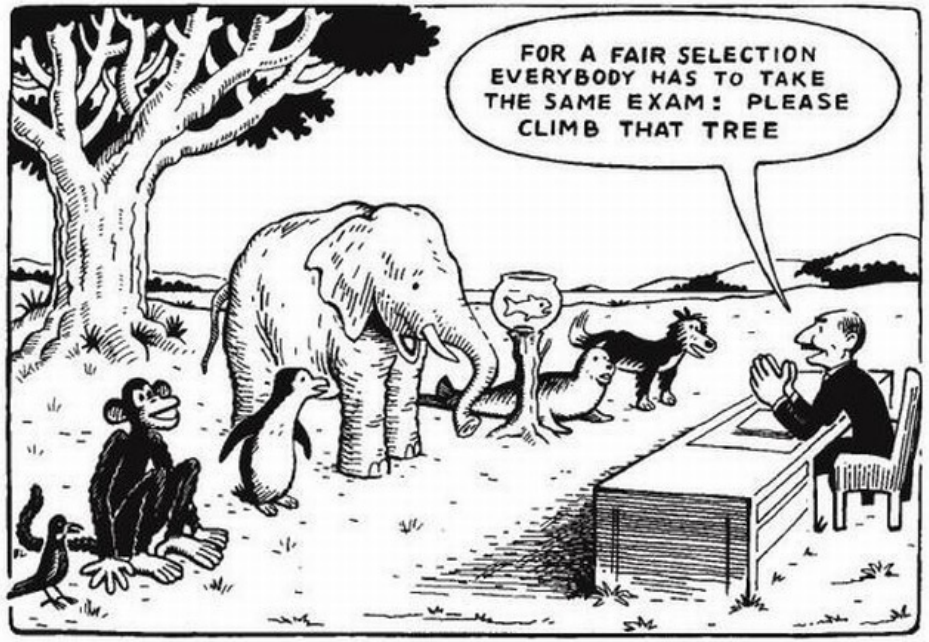
Definition: biased allocation to comparison groups.



Selection Bias

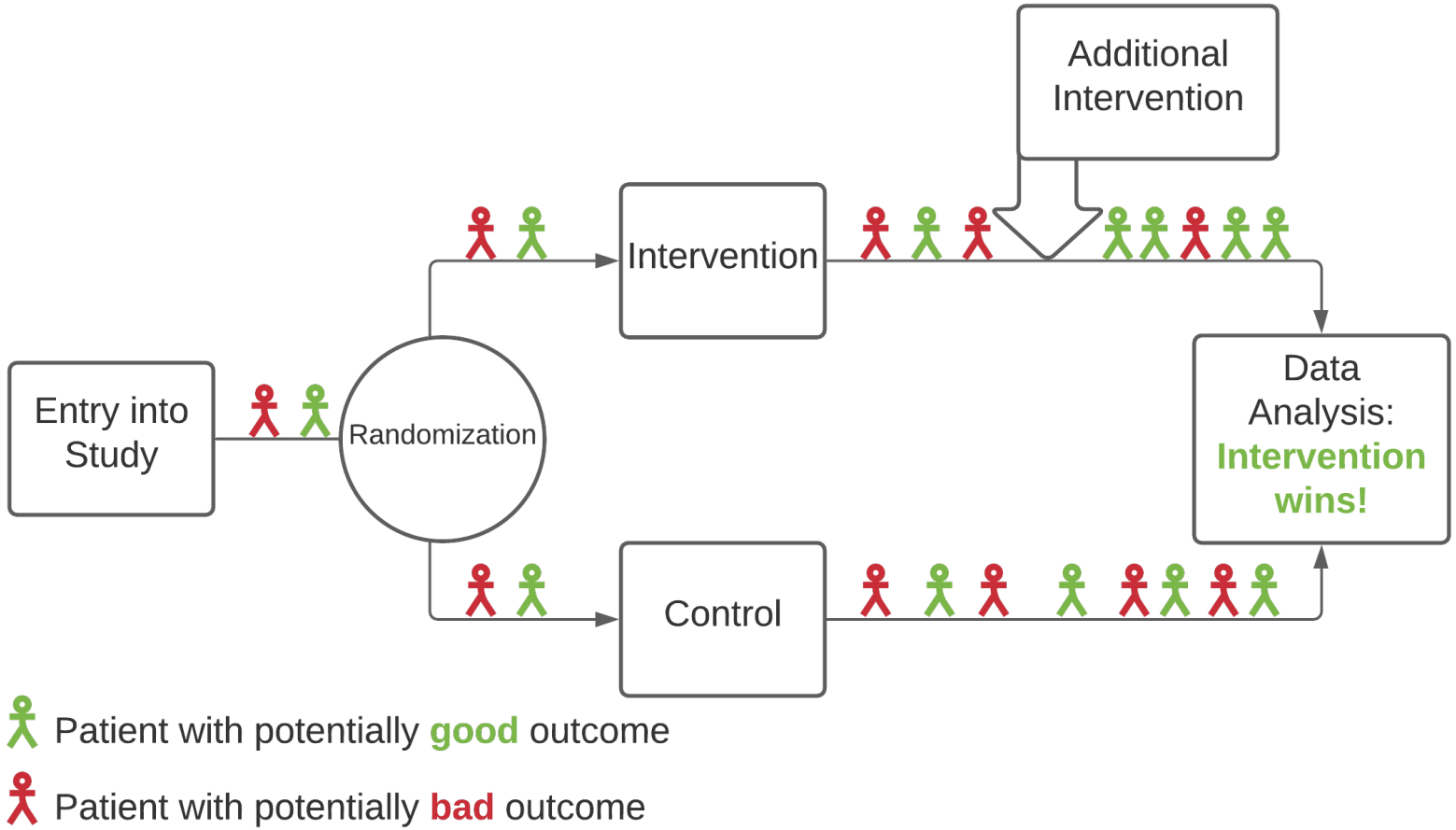
Controlling for selection bias

- Random generation of allocation sequence
- Concealment of allocation sequence



Performance Bias

Definition: additional treatment interventions are provided preferentially to one group.



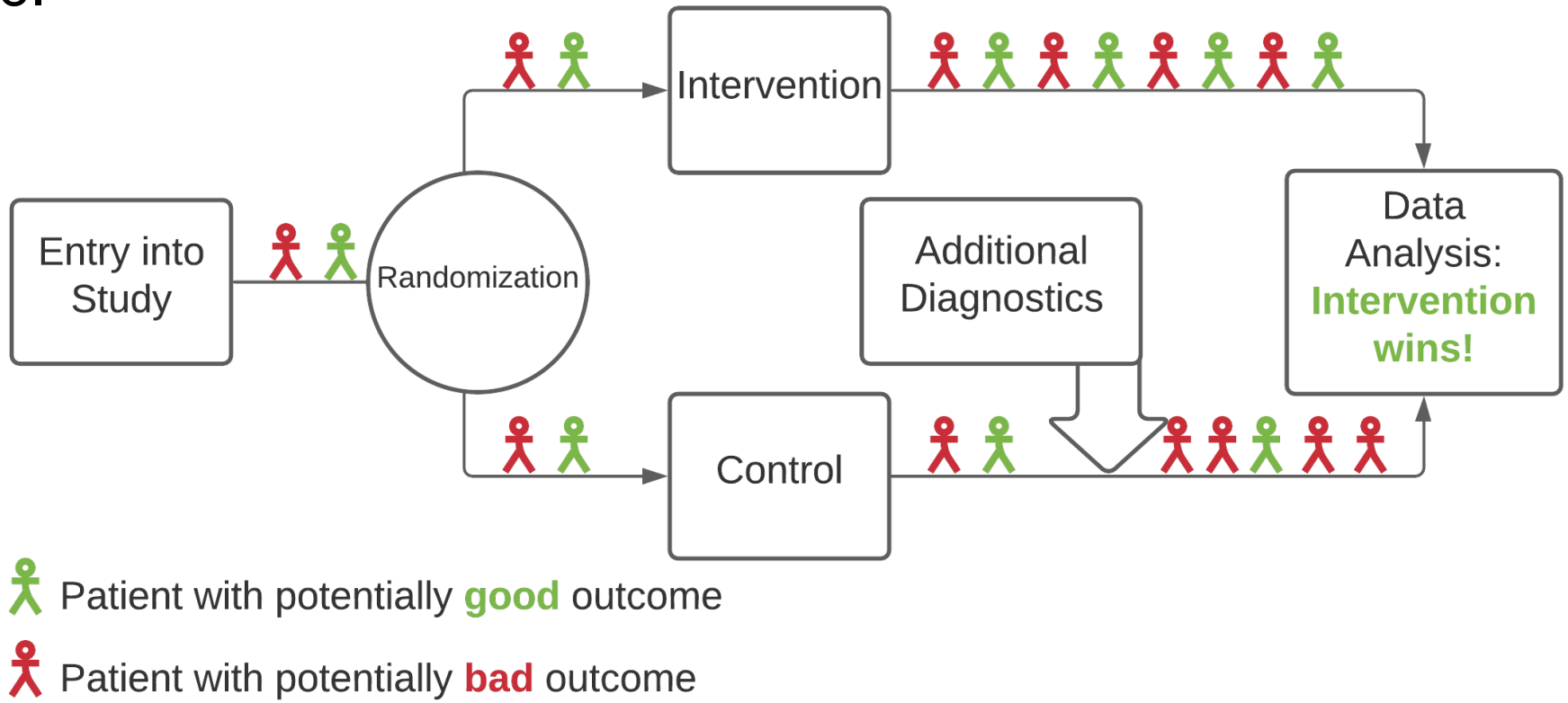
Performance Bias

Controlling for performance bias

- Blinding patients and care providers (including investigators) to group allocation

Detection Bias

Definition: knowledge of patient assignment influences the assessment of outcome.



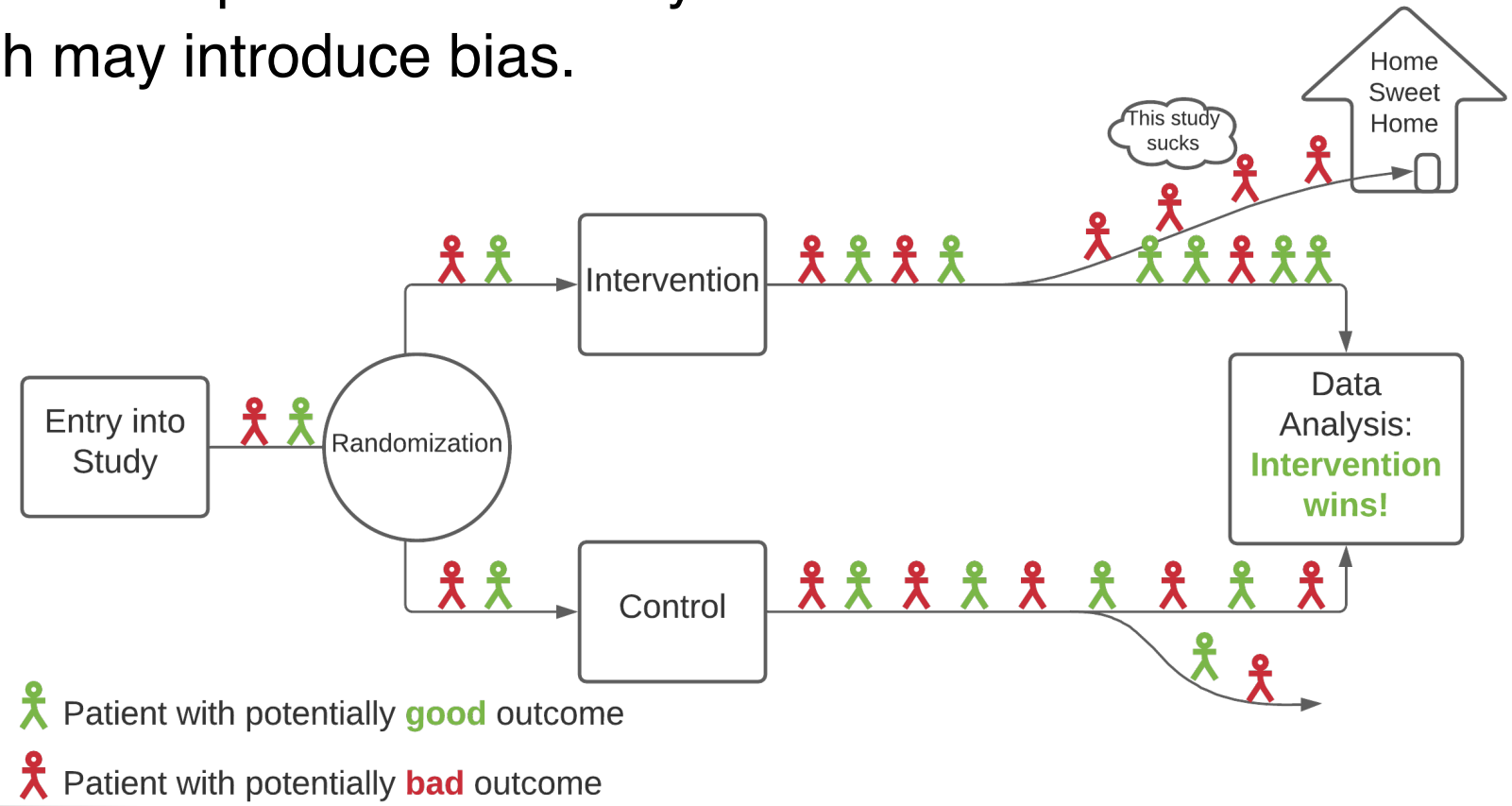
Detection Bias

Controlling for detection bias

- Blinding patients and care providers (including investigators) to group allocation.

Attrition Bias

Definition: deviations from protocol and loss to follow up often lead to the exclusion of patients after they have been allocated to treatment groups, which may introduce bias.

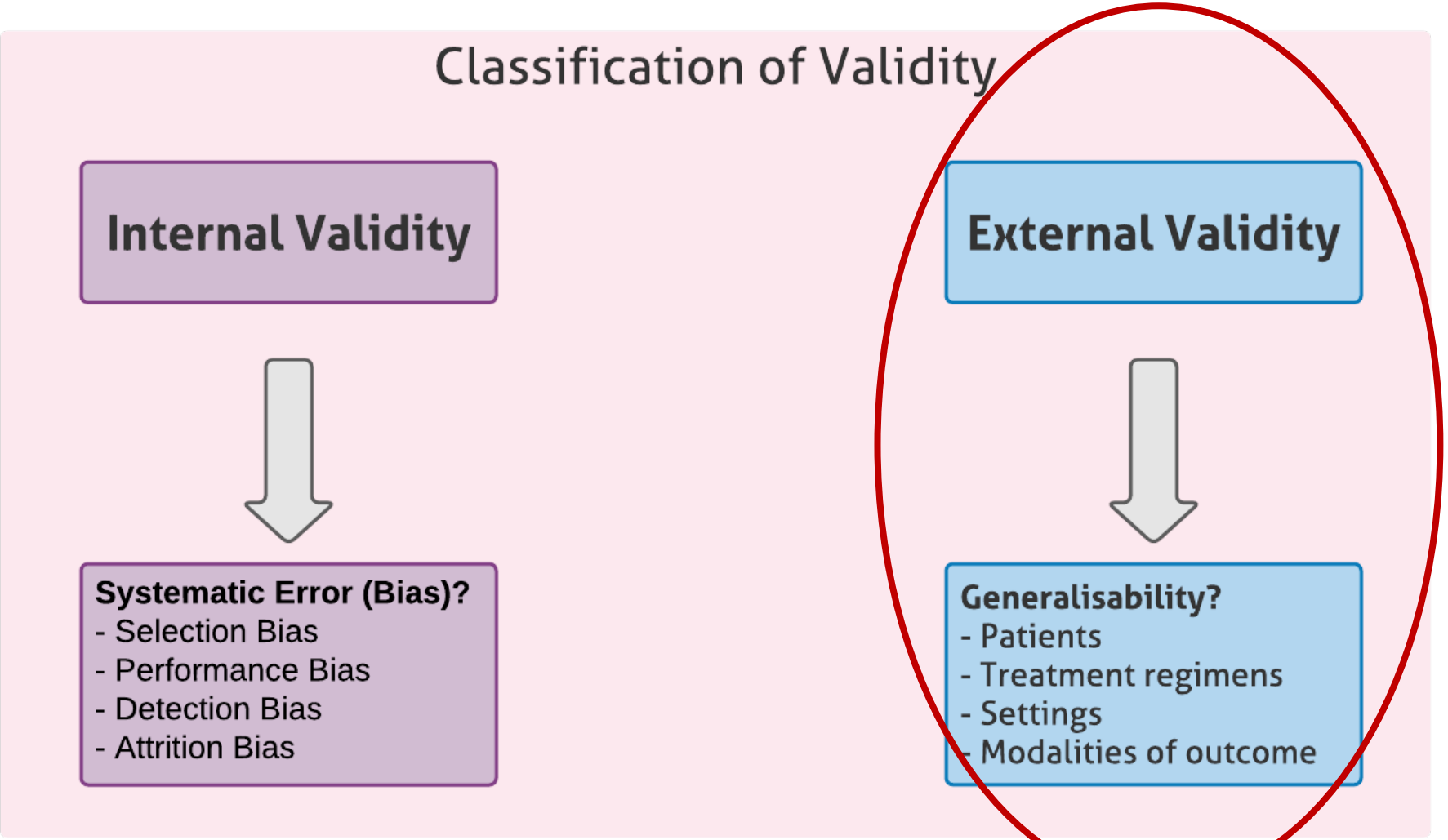


Attrition Bias

Controlling for attrition bias

- All randomized patients should be included in the analysis and kept in their original groups, regardless of their adherence to the study protocol (intention to treat principle).
- With larger loss to follow-up, look for sensitivity analyses

What is Validity?



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External Validity: Patients

- **Age**
- **Sex**
- **Severity of disease and risk factors**
- **Comorbidities**

Do patients selected for the trial match those you intend to treat?

External Validity: Treatment regimens

- **Dosage**
- **Timing and route of administration**
- **Type of treatment within a class of treatments**
- **Concomitant treatments**

Does your patient population match the study population in terms of dosage and treatments?

External Validity: Setting

- **Level of care (primary to tertiary) and experience**
- **Specialization of care provider**

Differences in patient populations depending on level of care and specialization (university hospital vs. general practitioner).

External Validity: Modalities of Outcomes

- **Type or definition of outcomes**
- **Duration of follow-up**

Are the outcomes measured of direct interest for your patient population (surrogate vs. “hard” outcomes)?

Is the duration of follow-up adequate to answer the research question?

Take Home Message

Internal Validity

- Selection Bias: Allocation to comparison groups?
- Performance Bias: Unbalanced co-interventions?
- Detection Bias: Unbalanced assessment of outcomes?
- Attrition Bias: Loss to follow-up?

External Validity

- Generalisability in terms of patients, treatments, setting and outcomes?

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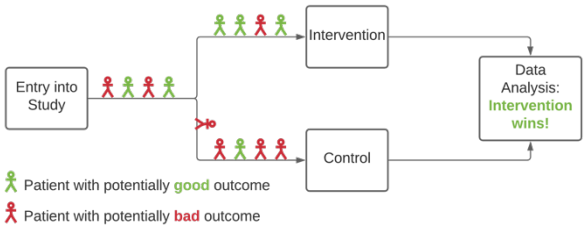
Notes

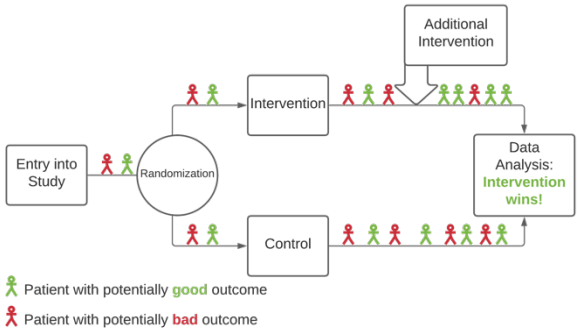
Assessing Systematic Error (Bias) of Clinical Trials

Internal Validity

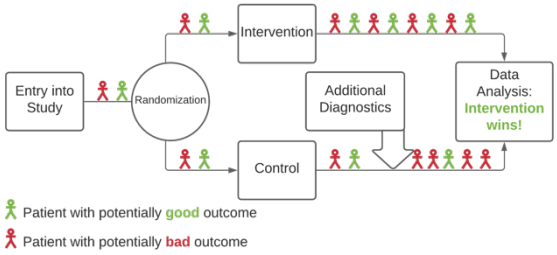
Selection Bias: biased allocation to comparison groups; can be controlled by random allocation of patients and concealment to allocation sequence.



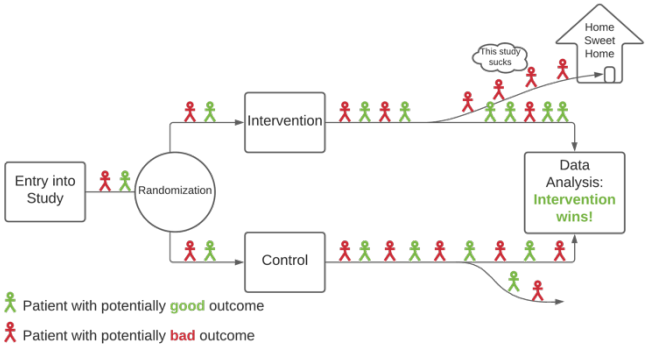
Performance Bias: unbalanced co-interventions; can be controlled by blinding of participants and care providers / investigators to group allocation.



Detection Bias: knowledge about patient assignment leads to unbalanced assessment of outcomes; can also be controlled by blinding of participants and care providers / investigators to group allocation.



Attrition Bias: non-random loss to follow-up can lead to systematic error of results (breaks randomization!); can be somewhat mitigated through “intention-to-treat” analysis.



External Validity

Patients: Do patients selected for the trial match those you intend to treat in terms of age, sex, severity of disease and risk factors, as well as comorbidities?

Treatments: Does your patient population match the study population in terms of dosage and concomitant treatments?

Setting: Differences in patient populations depending on level of care (university hospital vs. general practitioner) and specialization.

Modalities of outcomes: Are the outcomes measured of direct interest for your patient population (surrogate vs. “hard” outcomes)? Is the duration of follow-up adequate to answer the research question?