CRITICAL APPRAISAL OF MEDICAL LITERATURE

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Contents

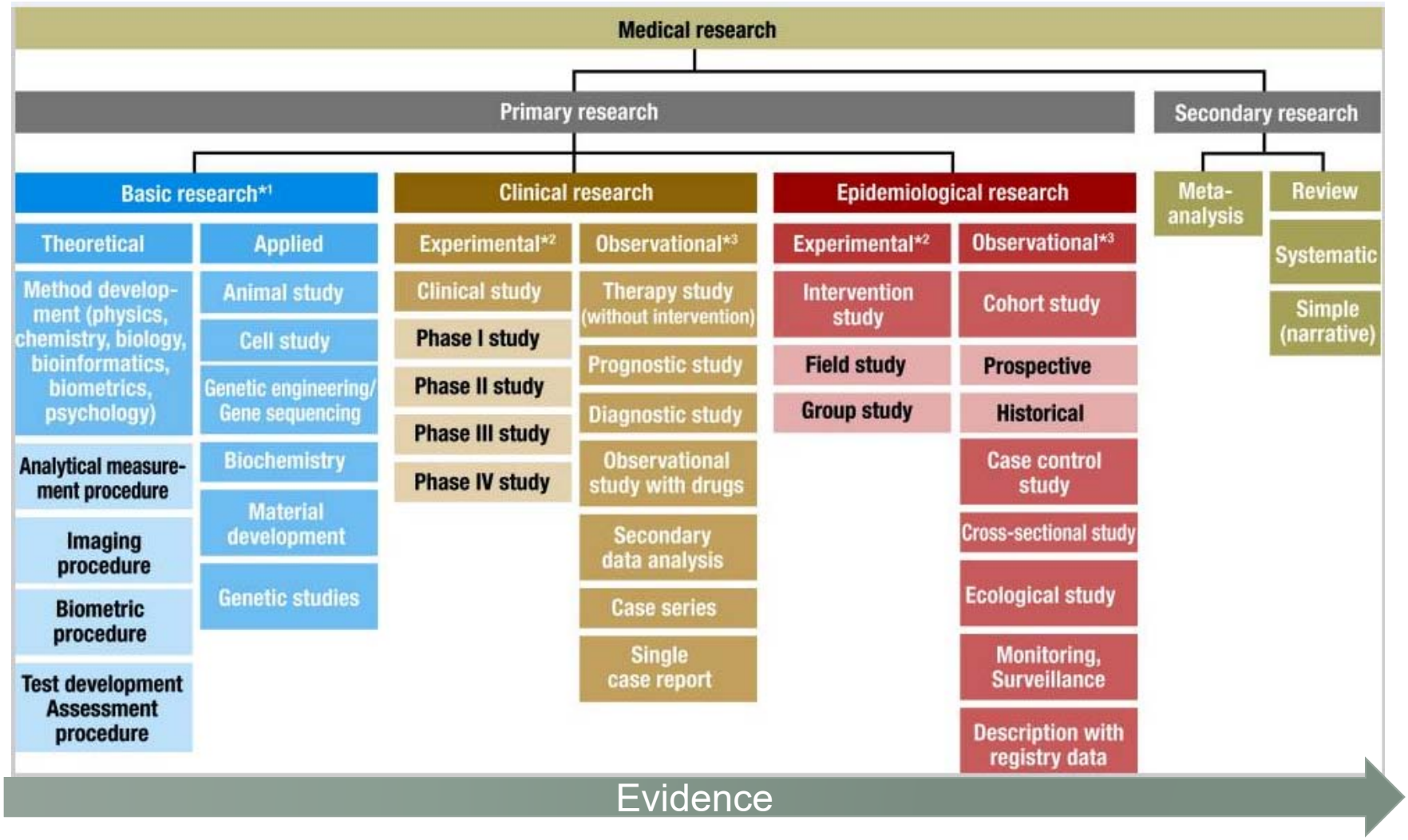
- Study designs
- Asking good questions
- Pitfalls in clinical studies
- How to assess validity (RCT)
- Conclusion

Step-by-step

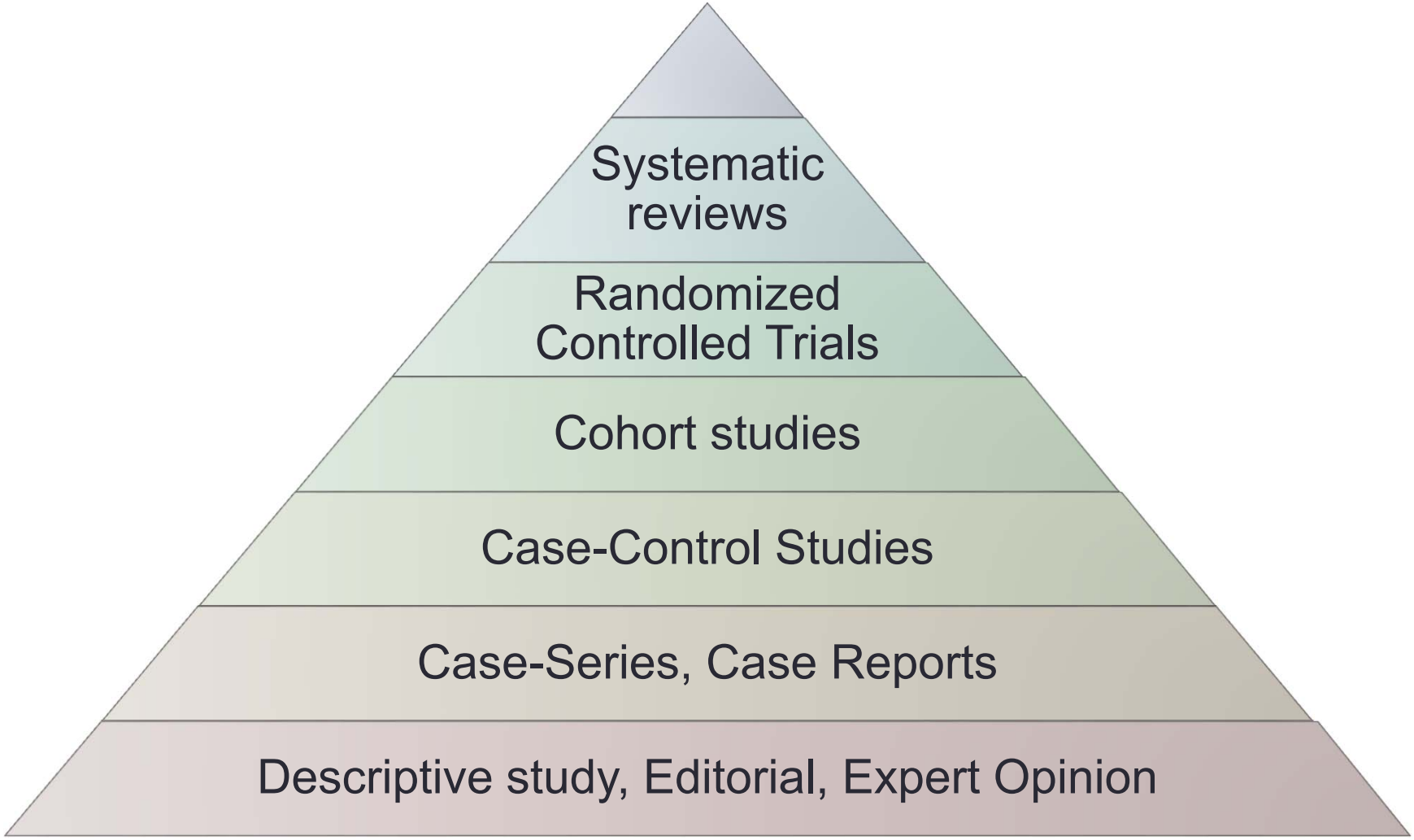
- What is my question I want answered (PICO)
- What study type is best to get that answer (Study type)
- Find the paper (literature search)
- Was the study done properly (Internal validity)
- Does it apply to my patients (External validity)

STUDY DESIGN

Study types


Medical research
Primary research
Secondary research
Basic research*1
Clinical research
Epidemiological research
Meta-analysis
Review
Systematic
Simple (narrative)
Theoretical
Applied
Experimental*2
Observational*3
Experimental*2
Observational*3
Method development (physics, chemistry, biology, bioinformatics, biometrics, psychology)
Animal study
Cell study
Genetic engineering/ Gene sequencing
Biochemistry
Material development
Genetic studies
Clinical study
Phase I study
Phase II study
Phase III study
Phase IV study
Therapy study (without intervention)
Prognostic study
Diagnostic study
Observational study with drugs
Secondary data analysis
Case series
Single case report
Intervention study
Field study
Group study
Cohort study
Prospective
Historical
Case control study
Cross-sectional study
Ecological study
Monitoring, Surveillance
Description with registry data
Analytical measurement procedure
Imaging procedure
Biometric procedure
Test development Assessment procedure
Evidence

Classification of evidence



Classification of evidence

Level I:	Evidence obtained from at least one properly designed randomized controlled trial or meta-analysis.
Level II-1:	Evidence obtained from well-designed controlled trials without randomization.
Level II-2:	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
Level II-3:	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
Level III:	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Cross-sectional study

Cross-sectional study

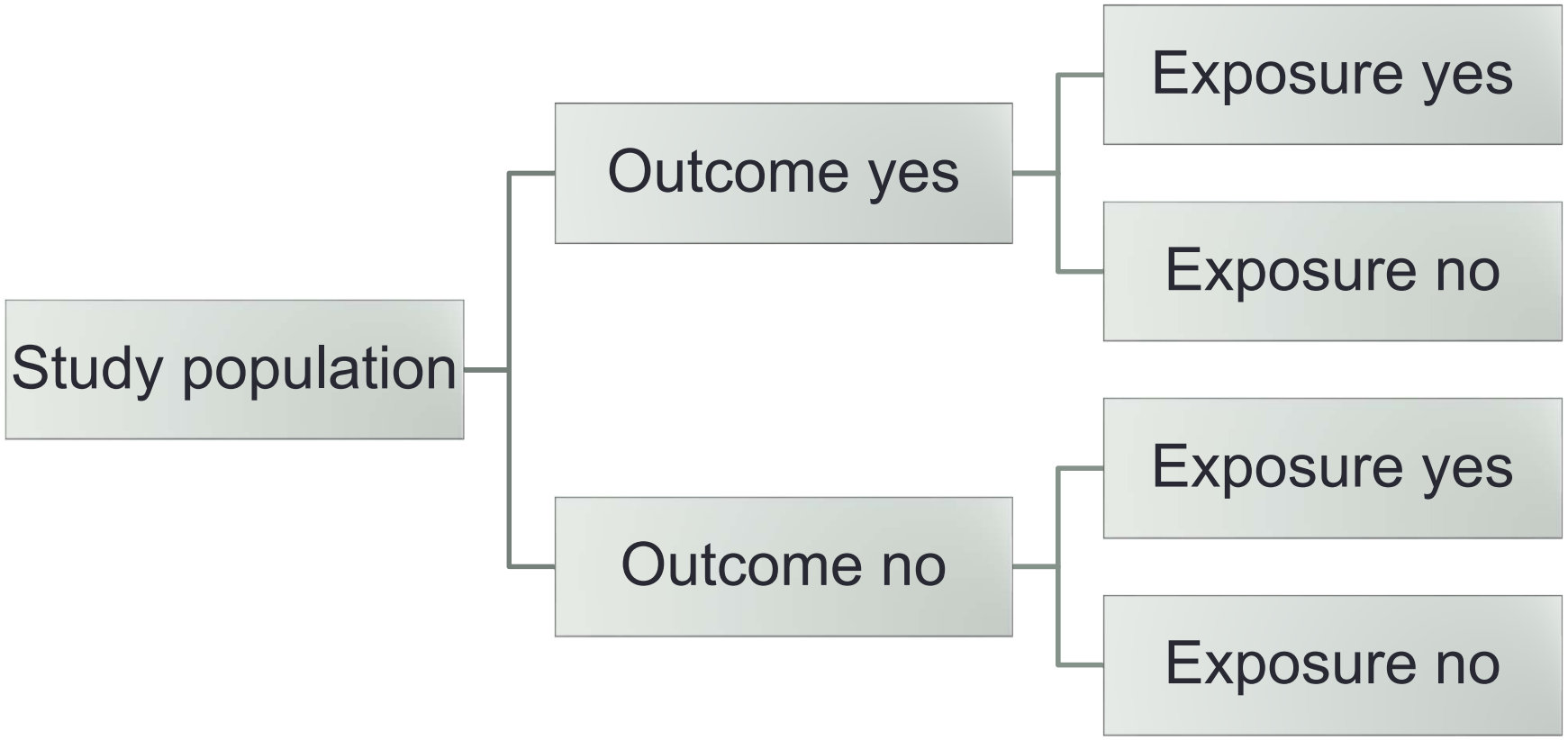
Advantages

- can obtain findings quickly
- can often be undertaken with minimal funding
- multiple outcomes

Disadvantages

- Prevalence only
- No cause and effect association possible
- Confounding

Case-control study



Case-control study

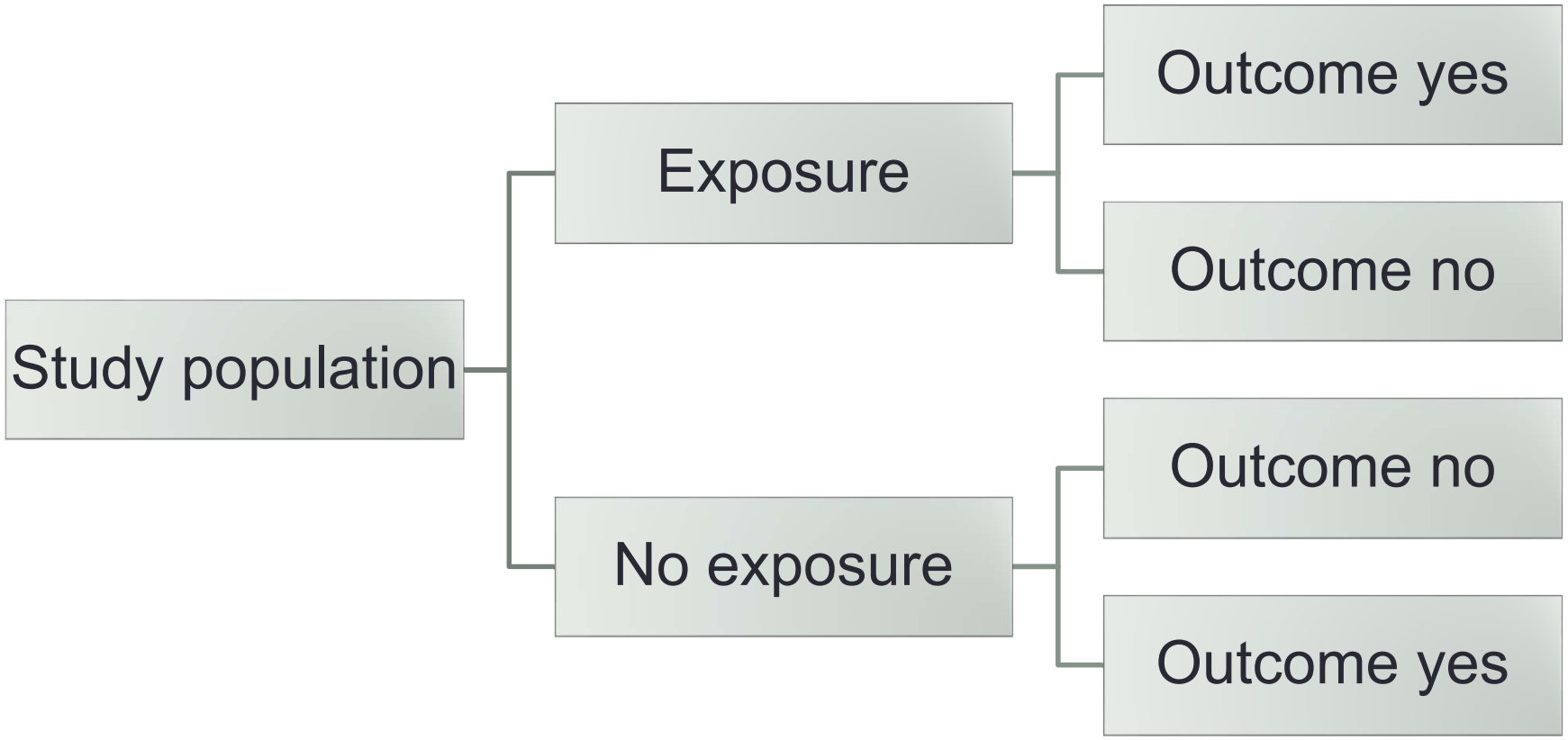
Advantages

- can obtain findings quickly
- can often be undertaken with minimal funding
- efficient for rare diseases
- can study multiple exposures
- generally requires few study subjects

Disadvantages

- subject to bias (sampling bias, observation and recall bias)
- difficult if record keeping is either inadequate or unreliable
- selection of controls can be difficult

Cohort study



Cohort study

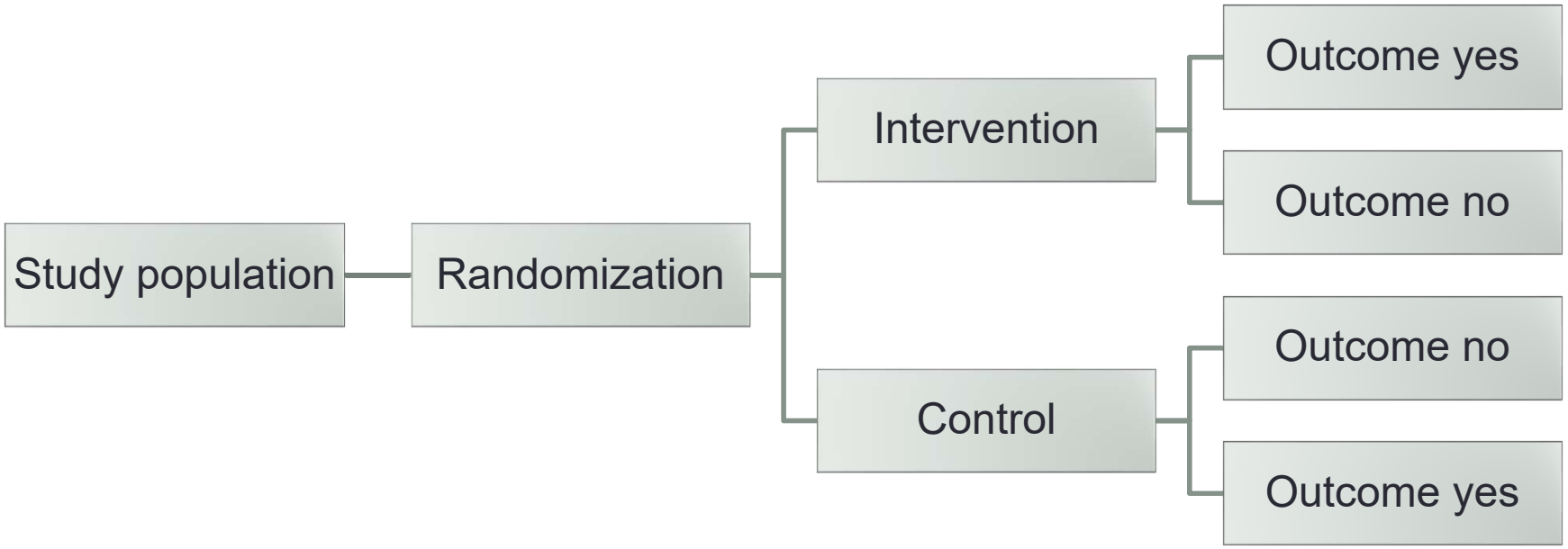
Advantages

- can replace RCTs in unethical settings
- cause-effect relationship is measurable
- examine various outcomes
- effect of each variable on outcome is measurable
- retrospecitve is cheap

Disadvantages

- follow-up might be difficult
- recall bias in retrospecitve setting
- confounding variables

Randomized controlled trial



Randomized controlled trial

Advantages

- “Gold standard”

Disadvantages

- Bias
- Expensive

Study type

- The study type defines the level of evidence
- Each study is subjected to it’s own advantages and weaknesses
- Each clinical question has an optimal study design.

ASKING GOOD QUESTIONS

Clinical questions

The Swiss government needs to provide figures to WHO on the incidence of prostate cancer in Switzerland	Annas mum is worried about Anna using her moblie phone so much – she heard that they are not safe
Mrs. Smiths GP is wondering whether accupuncure might help Mrs. Smiths shoulder pain	Lara has a positive HIV-test but was never exposed to a risk

Medical question

- What are the problems? (Observation)

- How common is it? (Frequency)
- What caused it? (Aetiology)
- Who has the problem? (Diagnosis)
- What will happen? (Prognosis)
- How will the intervention change the outcome? (Intervention)

Question and study design

Question	Possible study design
Intervention/ Outcome	Randomized controlled Trial Cohort study Case-control-study Ecological studiy Pre-Post-study
Aetiology	Randomized controlled Trial Cohort study Case-control-study Ecological study Pre-Post-study
Diagnosis (Test vs. goldstandard)	Cross-sectional study
Diagnosis (Comparison of tests)	Randomized controlled Trial Cohort study Case-control-study
Incidence	Descriptive cross-sectional study Descriptive cohort study
Prognosis/ Frequency	Cohort study

PICO

Poplulation	Who are the relevant patients and what is the problem
Intervention	What is the treatment being considered
Comparator	What is it compared to
Outcome	What are the person-relevant consequences of the exposure

Example

- Mrs. Smiths GP is wondering whether accupuncure might help Mrs. Smiths shoulder pain
- PICO
  - In patients with chronic shoulder pain…
  - … is accupuncture…
  - … compared to placebo…
  - … reducing pain ?

Exercise 1

- PICO:
- *You are referred a patient with recurrent debilitating migraine headaches, who has tried several prophylactic treatments. He comes to clinic with an alternative health magazine containing an article which claims a breakthrough in migraine control using acupuncture, and print-outs from several websites and asks your opinion about whether you acupuncture will lessen his attacks. You are unsure whether acupuncture can be recommended.*

Answer 1

P	In people with migrane..
I	.. does accupuncture..
C	.. compared to regular medication..
O	.. lessen the frequency or severity of attacks?
Study-Type	Intervention

PICO-S

- Patients
- Intervention
- Comparator
- Outcome
- Study type

- Asking the right question will lead you to the right answer. Only good answers are useful in epidemiology.

PITFALLS IN CLINICAL STUDIES

Bias

- Systematic difference between observed result and the truth

Selection Biases

Selection biases occur when the groups to be compared are different. These differences may influence the outcome.

- **Volunteer or referral bias:** Volunteer or referral bias occurs because people who volunteer to participate in a study (or who are referred to it) are often different than non-volunteers/non-referrals. This bias usually, but not always, favors the treatment group, as volunteers tend to be more motivated and concerned about their health.
- **Non-respondent bias**: Non-respondent bias occurs when those who do not respond to a survey differ in important ways from those who respond or participate. This bias can work in either direction.

Measurement Biases

Measurement biases involve systematic error that can occur in collecting relevant data.

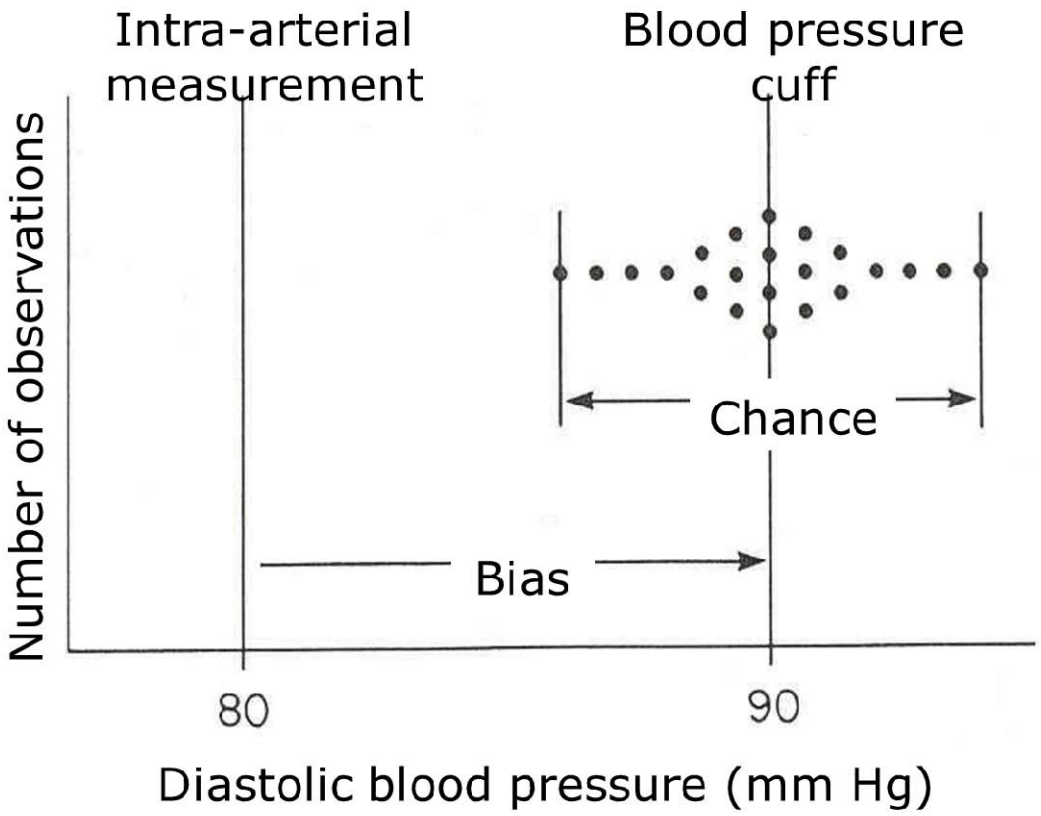
- **Instrument bias**. Instrument bias occurs when calibration errors lead to inaccurate measurements being recorded, e.g., an unbalanced weight scale.
- **Insensitive measure bias.** Insensitive measure bias occurs when the measurement tool(s) used are not sensitive enough to detect what might be important differences in the variable of interest.
- **Expectation bias**. Expectation bias occurs in the absence of masking or blinding, when observers may err in measuring data toward the expected outcome. This bias usually favours the treatment group
- **Recall or memory bias**. Recall or memory bias can be a problem if outcomes being measured require that subjects recall past events. Often a person recalls positive events more than negative ones. Alternatively, certain subjects may be questioned more vigorously than others, thereby improving their recollections.
- **Attention bias**. Attention bias occurs because people who are part of a study are usually aware of their involvement, and as a result of the attention received may give more favourable responses or perform better than people who are unaware of the study's intent.
- **Verification or work-up bias**. Verification or work-up bias is associated mainly with test validation studies. In these cases, if the sample used to assess a measurement tool (e.g., diagnostic test) is restricted only to who have the condition of factor being measured, the sensitivity of the measure can be overestimated.

Intervention (Exposure) Biases

Intervention or exposure biases generally are associated with research that compares groups.

- **Contamination bias**. Contamination bias occurs when members of the 'control' group inadvertently receive the treatment or are exposed to the intervention, thus potentially minimizing the difference in outcomes between the two groups.
- **Co-intervention bias.** Co-intervention bias occurs when some subjects are receiving other (unaccounted for) interventions at the same time as the study treatment.
- **Timing bias(es).** Different issues related to the timing of intervention can bias. If an intervention is provided over a long period of time, maturation alone could be the cause for improvement. If treatment is very short in duration, there may not have been sufficient time for a noticeable effect in the outcomes of interest.
- **Compliance bias.** Compliance bias occurs when differences in subject adherence to the planned treatment regimen or intervention affect the study outcomes..
- **Withdrawal bias.** Withdrawal bias occurs when subjects who leave the study (drop-outs) differ significantly from those that remain.
- **Proficiency bias.** Proficiency bias occurs when the interventions or treatments are not applied equally to subjects. This may be due to skill or training differences among personnel and/or differences in resources or procedures used at different

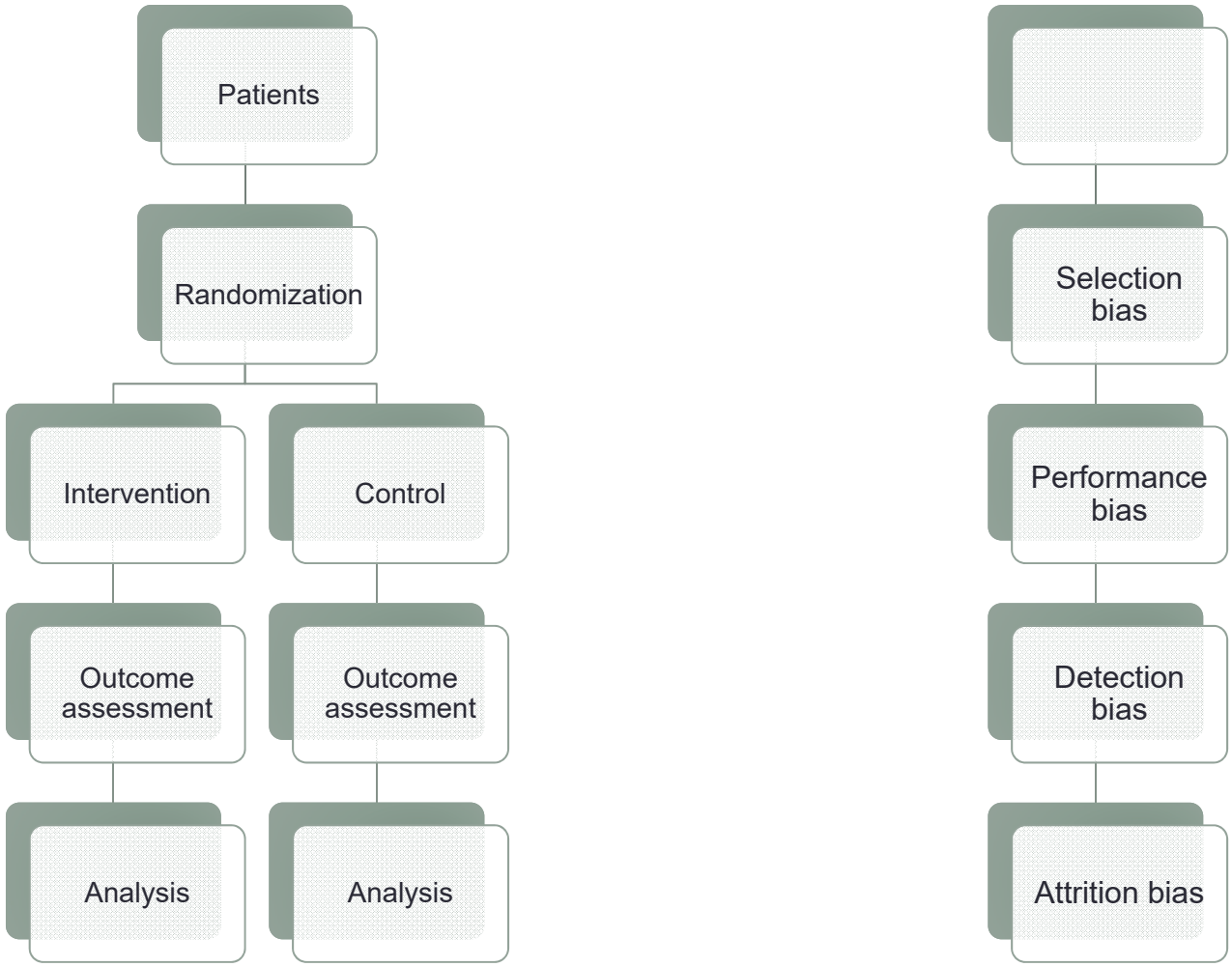
Bias versus chance



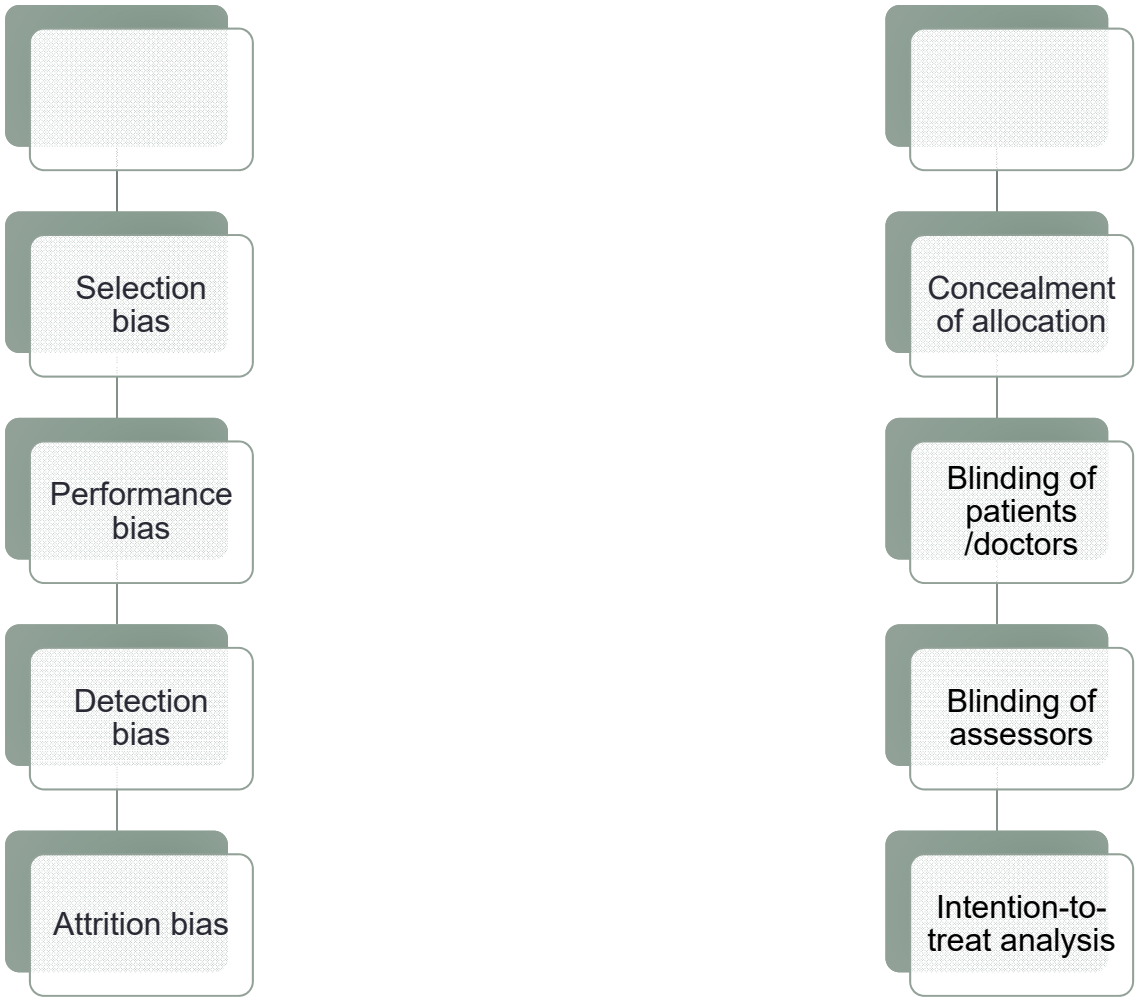
HOW TO ASSESS VALIDITY

Can I use the results for my patients

Bias in RCTs


Patients
Randomization
Intervention
Control
Outcome assessment
Outcome assessment
Analysis
Analysis
Selection bias
Performance bias
Detection bias
Attrition bias

Bias and its remedy

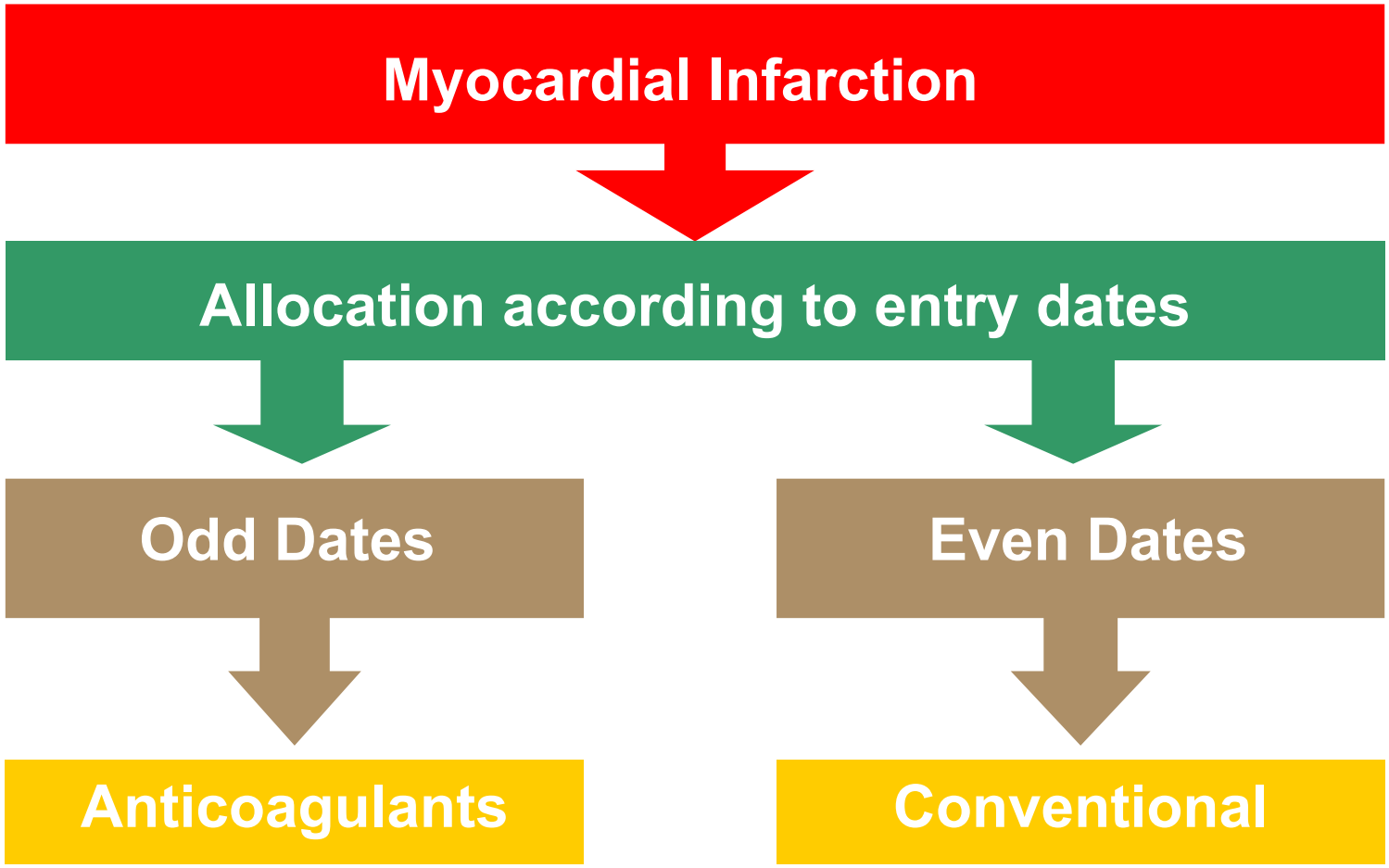


Internal validity

- **Selection bias -** Systematic error in creating intervention groups, such that they differ with respect to prognosis.
- **Performance bias -** Systematic differences in the care provided to the participants in the comparison groups other than the intervention under investigation.
- **Detection bias -** Systematic difference between comparison groups in how outcomes are ascertained, diagnosed or verified
- **Attrition bias -** Systematic differences between comparison groups in withdrawals or exclusions of participants from the results of a study.

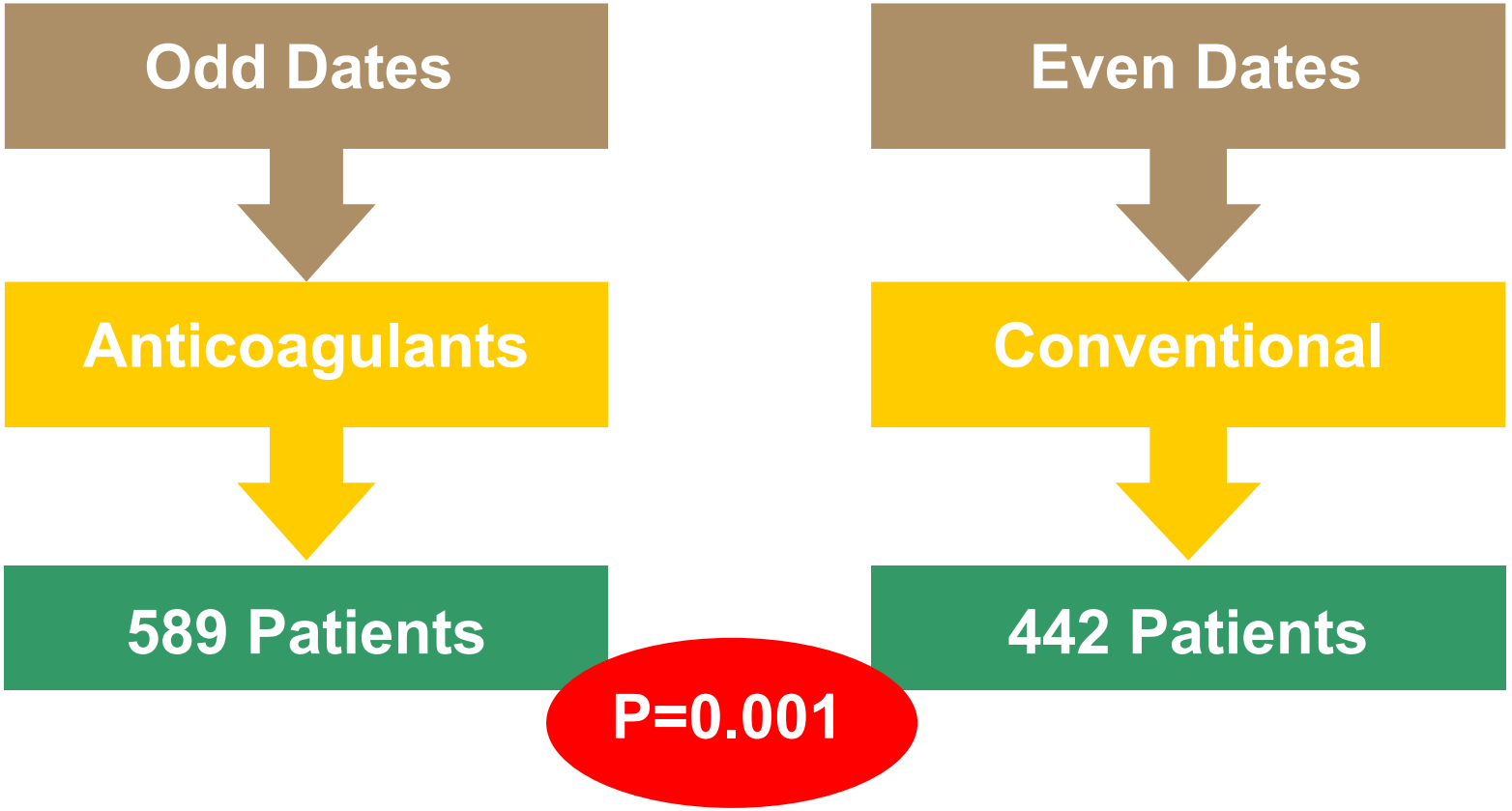
- Careful design, implementation and and analysis lead to good results

Anticoagulation for Myocardial Infarction



Wright et al, Am Heart J 1948

Anticoagulation for Myocardial Infarction



Wright et al, Am Heart J 1948. Pocock, Clinical Trials 1991

Generation of allocation sequence

- Adequate if resulting sequences are unpredictable:
  - coin tossing
  - computer generated random-numbers
  - drawing lots or envelopes
  - shuffling cards
  - table of random-numbers
  - throwing dice
- Inadequate if resulting sequences are predictable:
  - according to case record number
  - according to date of birth
  - according to date of admission
  - alternation

Concealment of allocation

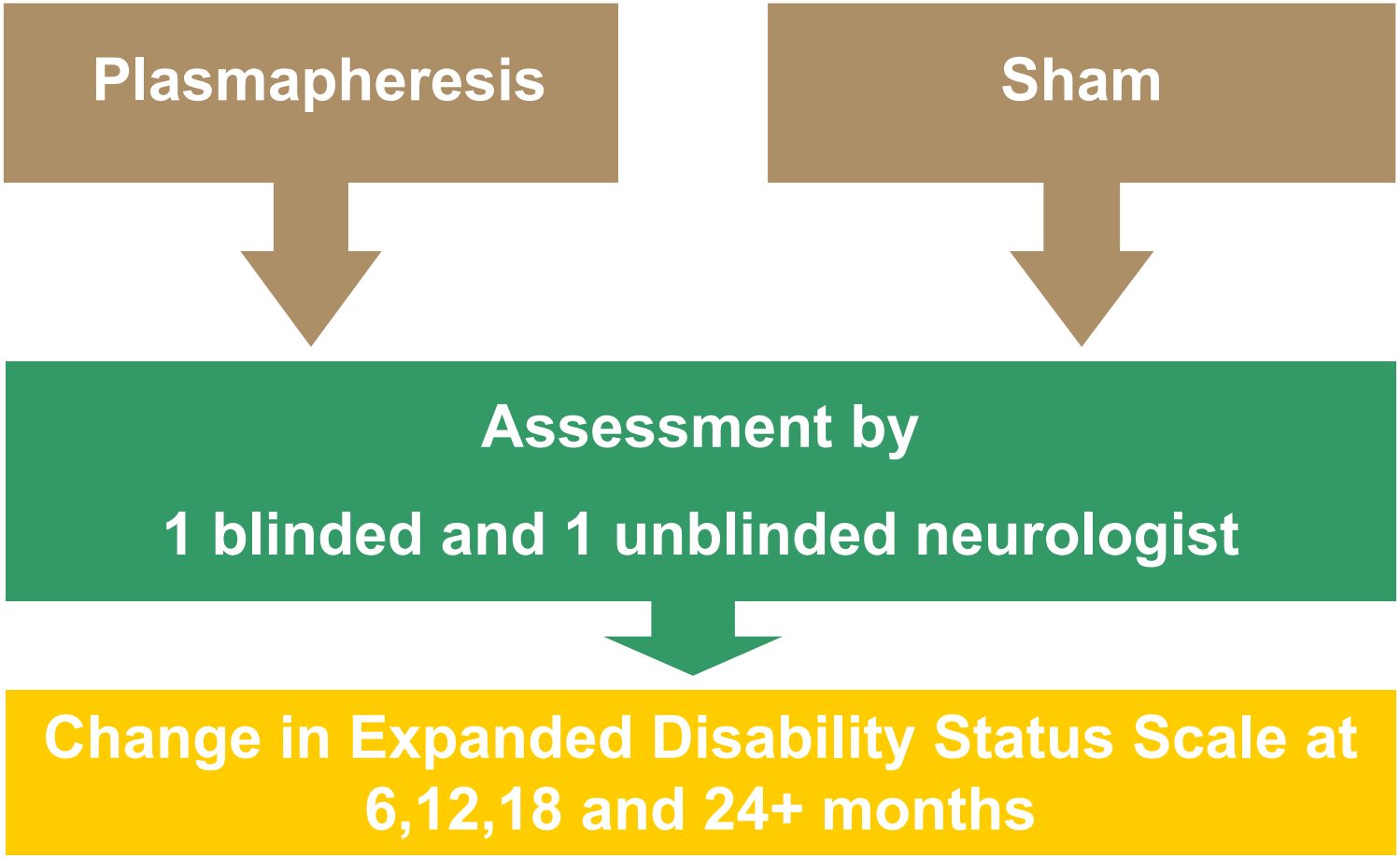
Adequate if patients and enrolling physicians cannot foresee assignment:

- central randomisation
- a priori and independently numbered or coded drug packs
- sequentially numbered, sealed, opaque envelopes

Inadequate if patients or enrolling physicians can foresee assignment:

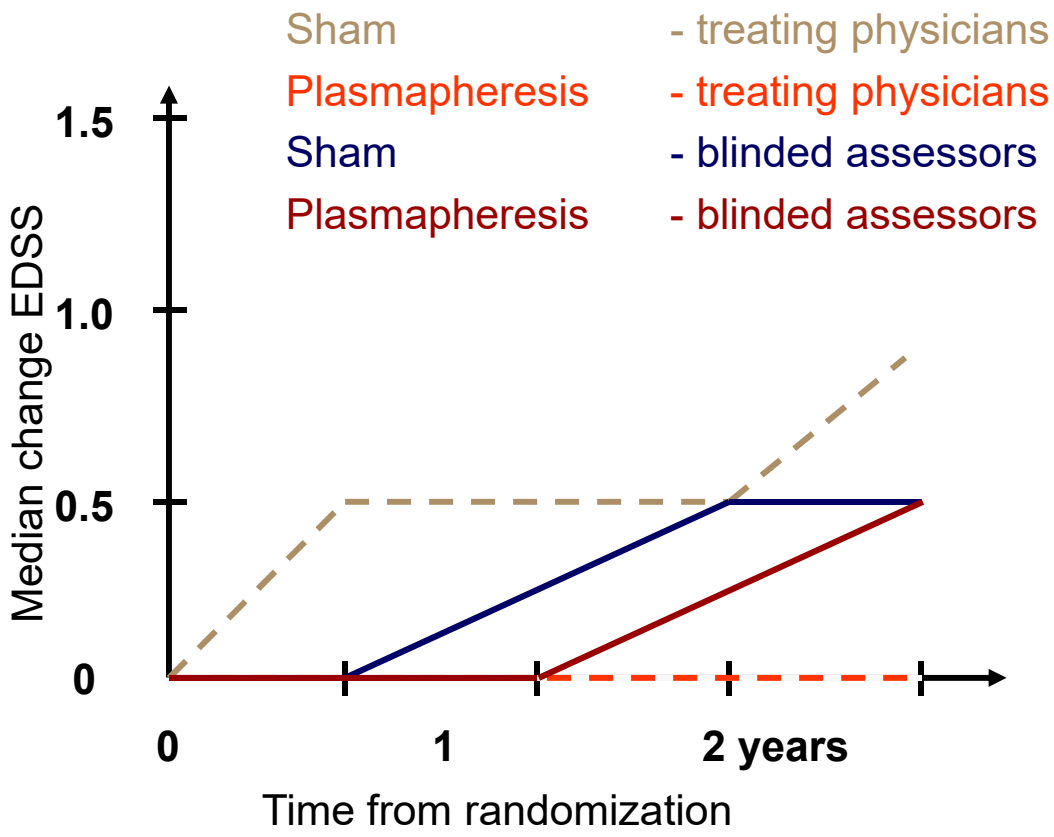
- procedures based on inadequate generation of sequences
- open allocation schedule
- unsealed or non-opaque envelopes

Plasmapheresis for Multiple Sclerosis



Noseworthy et al, Neurology 1994

Plasmapheresis for Multiple Sclerosis



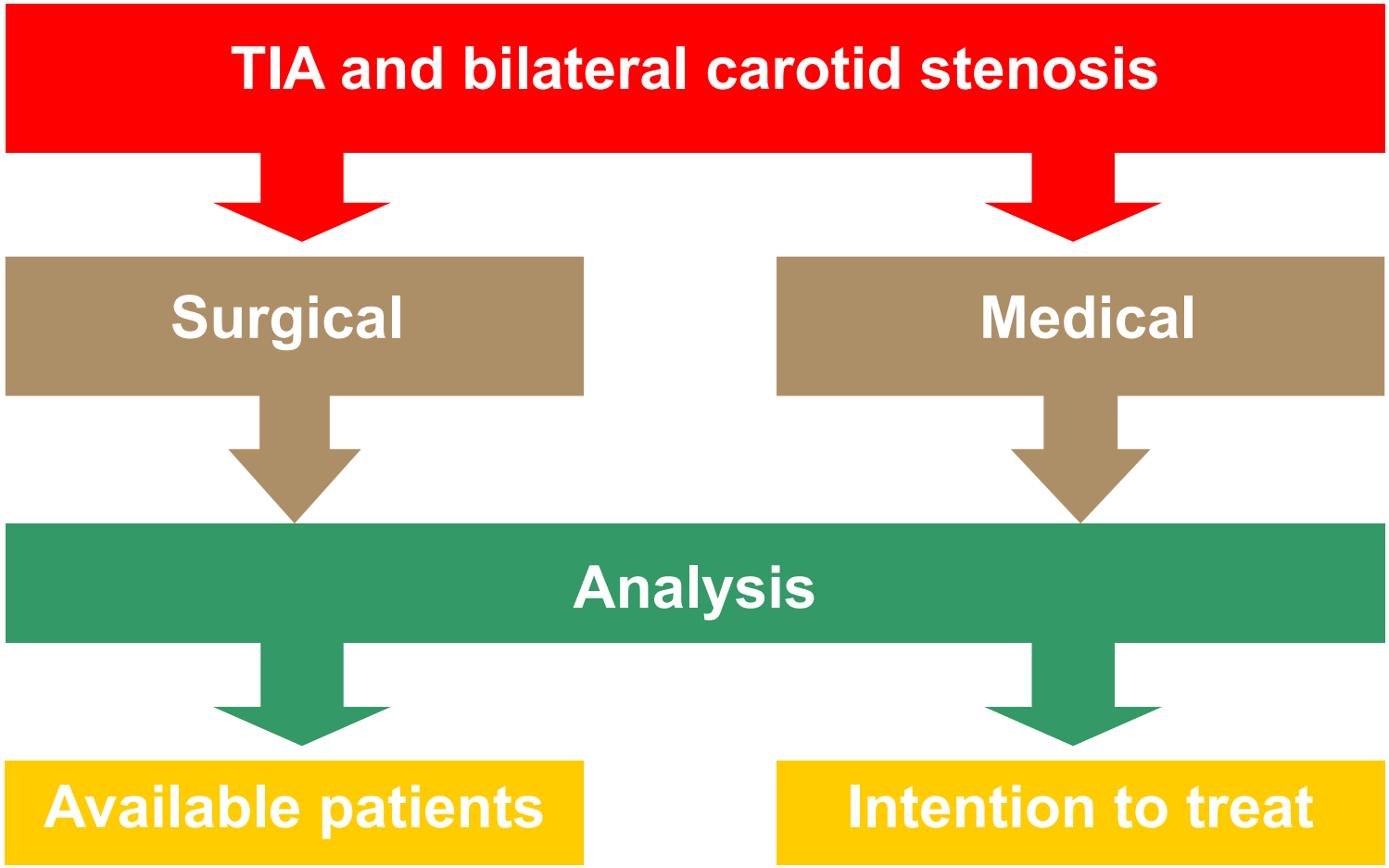
Noseworthy et al, Neurology 1994

Plasmapheresis for Multiple Sclerosis

	Blinded	Unblinded
6 months	0.246	0.047
12 months	0.086	0.004
18 months	0.106	0.072
24 months	0.201	0.031

p values for between tx comparison of proportion of subjects improved, stable, or worse

Surgical Therapy for Bilateral Carotid Stenosis

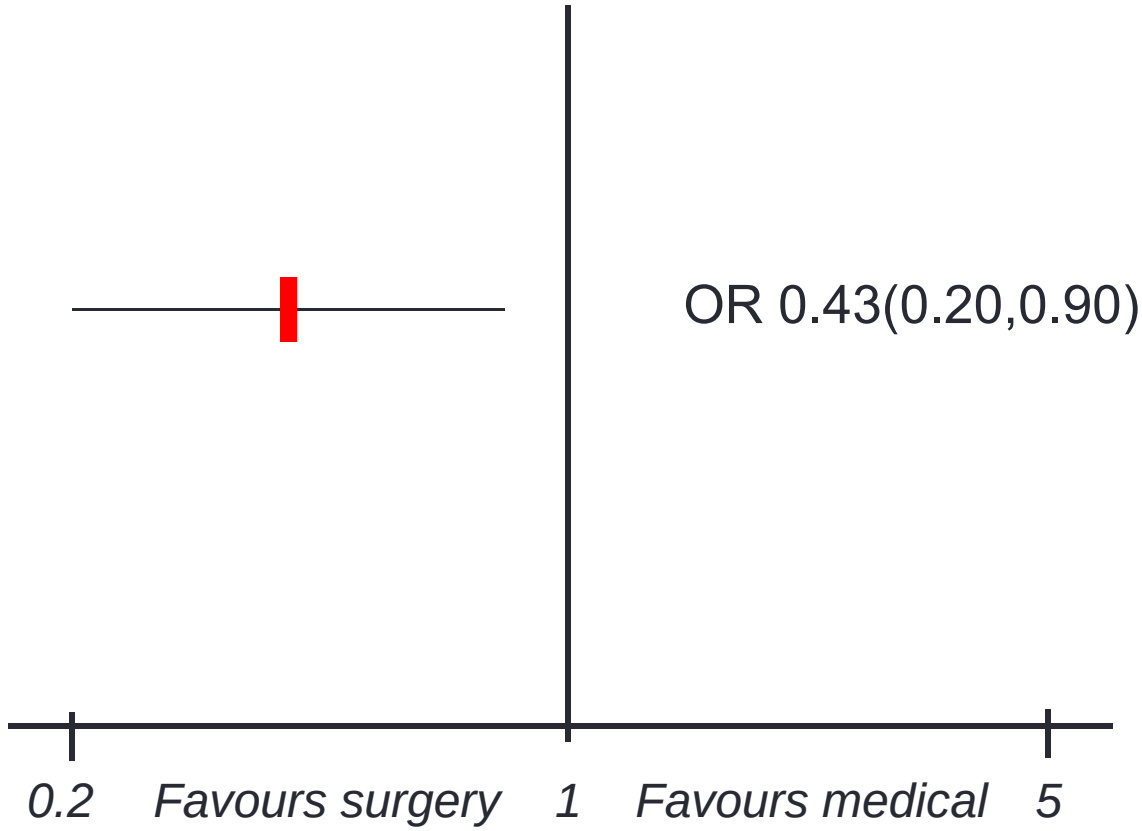


Fields et al, JAMA 1970. Sacket & Gent, N Engl J Med 1979

Surgical Therapy for Bilateral Carotid Stenosis

Patients available for follow-up

(surgical =79, medical =72)



Outcome: Recurrent TIA, stroke or death

Intention-to-treat analysis

- Analysis on the basis of the comparison arm to which participant was randomised
- Not on the basis of
  - Post-randomisation assessment of eligibility
  - Whether treatment was received
  - Whether treatment was completed

CONCLUSION

PICO-SU

- Patients
- Intervention
- Comparator
- Outcome
- Study type

- Form a clinically relevant question

Internal validity (RCT)

- Selection bias
- Performance bias
- Detection bias
- Attrition bias

External validity

Can the results be applied to my patients

- Study patients are comparable to my patients
- Intervention is the same as in the study
- External factors are the same (e.g. race, social status, resources, medical system)
- Same outcome is important in the study as in my patients (e.g. same follow-up time, relevant result)
- Clinically relevant end-points
- Clinically relevant effect size

Stay critical

- Ask for the best evidence
- Question the results
- Use your brain
- Never trust a statistic you did not forge yourself ☺

THANKS ☺

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