Experimental Study Design

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Oct 2018

Objectives

1. To lean about types of experimental dsign

Quantitative Study Designs

Intervention
True experiment (RCT)

Analytic
Case-control
Cohort

Descriptive
Case studies
Case series
Ecological studies
Cross-sectional surveys

TYPES OF EXPERIMENTAL STUDIES

1. TRUE EXPERIMENTS

   -RANDOMIZED TRIALS

2. QUASI-EXPERIMENTS

Randomized Controlled Trials

- Randomized Clinical Trial (RCT) is gold standard
- RCT minimizes bias
- Can't do RCTs for all important questions (time, funding, ethics)
- Must make choices on what evidence to use for clinical guidelines

Intervention

1. New drugs and new treatment of diseases
2. New medical and health care technology
3. New methods of primary prevention
4. New programs for screening
5. New ways of organizing and delivering health services
6. New community health programs
7. New behavioral intervention program

QUASI-EXPERIMENTS

1-Cross-sectional comparison:

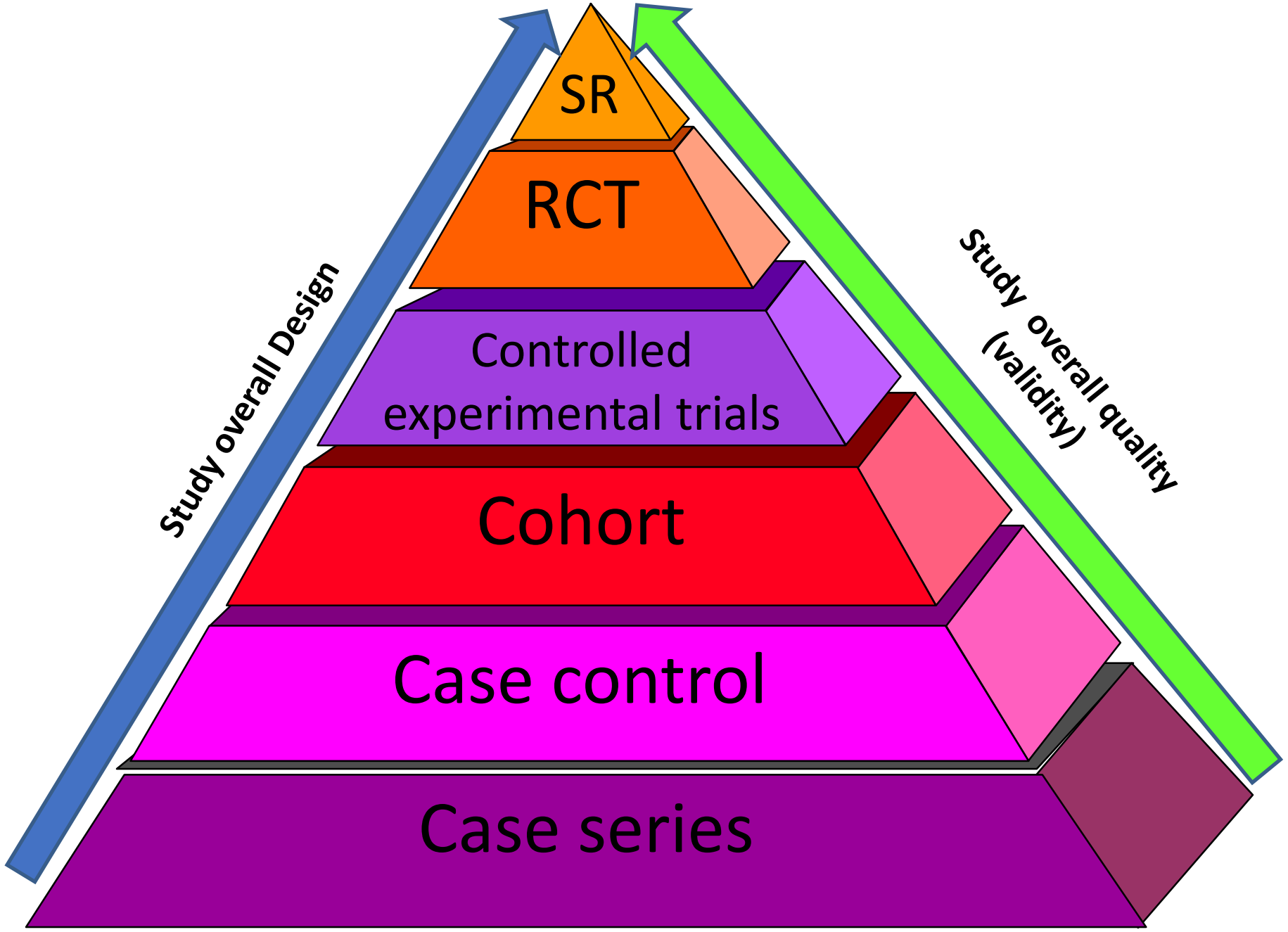
comparable communities or groups

2- Temporal comparison:

before and after the intervention

3- Combinations of the above:

time-series analysis in community trial.


SR
RCT
Controlled experimental trials
Cohort
Case control
Case series
Study overall Design
Study overall quality (validity)

Prospective evaluation

- What is a prospective evaluation?
  - Evaluation designed in advance
- Advantages
  - Collect specific data
  - Collaborative design and evaluation
- Disadvantages?
  - Long term results emerge in the long run
  - Q: What approaches could give us long run results in the short run?

Comparator in experimental study

- Therapy vs. no therapy
- Therapy vs. placebo or sham
- Therapy A vs. Therapy B

RCT Advantages

- Strongest evidence for cause and effect

RCT Disadvantages

1. Costly (time, money)
2. May not be suitable for some research questions
    1. ethical barriers
    2. outcomes rare
3. Generalizability (standardized interventions, follow-up, inclusion/exclusion criteria)

Types of RCT

Randomized Clinical Trial

phase I	the first studies carried out in humans.
phase II	studies carried out in patients, usually to find the best dose of drug and to investigate safety
phase III	pivotal RCTs (usually 2) to establish efficacy. Typically these are the studies on which registration of a new product will be based.
phase IIIb	when a product already has marketing authorization but the indication is being expanded.
phase IV	post registration studies. Usually for marketing purposes, also to gain broader experience with using the new product.

Phase I

Treatment mechanism(s)

Uptake, distribution & elimination

Fibonacci Dose Escalation

- Conservative starting dose (10% of LD_{10})
  - 1, 1, 2, 3, 5, 8, 13, 21, …
  - Groups of 3
  - Continue until 2 of 6 experience toxicity

Mild disease / normal volunteers (n= 20 to 80)

Phase II

- Fixed dose → determine of Tx should be used in a large scale comparative trial
- Feasibility: side effects, toxicity, logistics of administration & cost
- Efficacy: surrogates
- Toxicity, side effects & benefits.
- Randomized SE studies (parallel / x-over)
- Sample size: 50 to 200 patients

Phase III

- Determine efficacy vs. standard therapy
- Compare incidence and severity of side effects vs. standard therapy
  - Single therapy
  - Combined therapies (cancer)
- Often multi-centre
  - Logistics
  - Heterogeneity

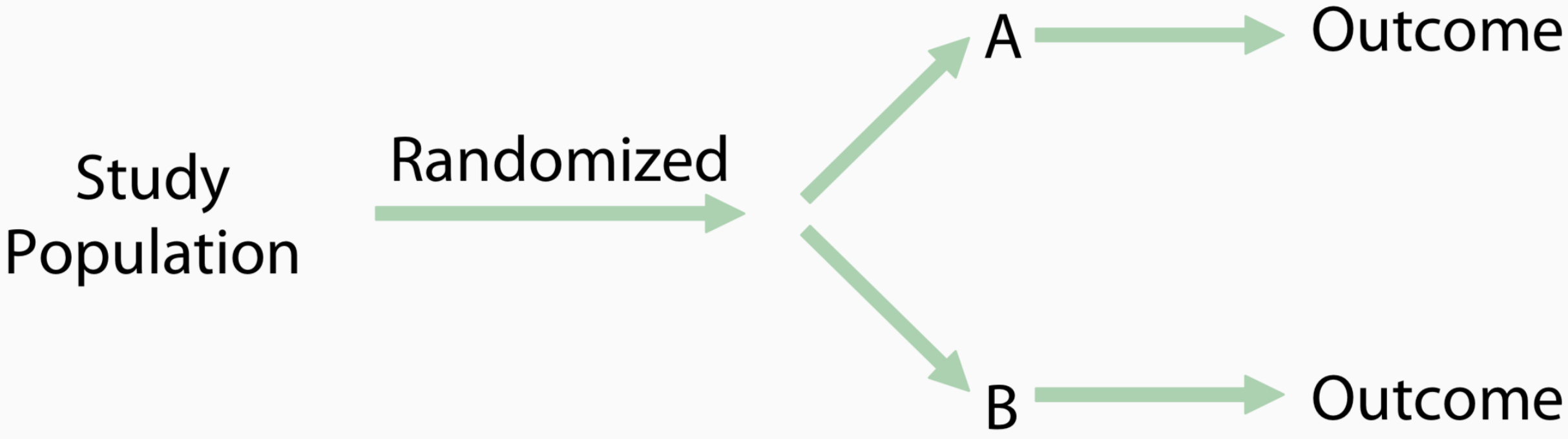
Phase IV

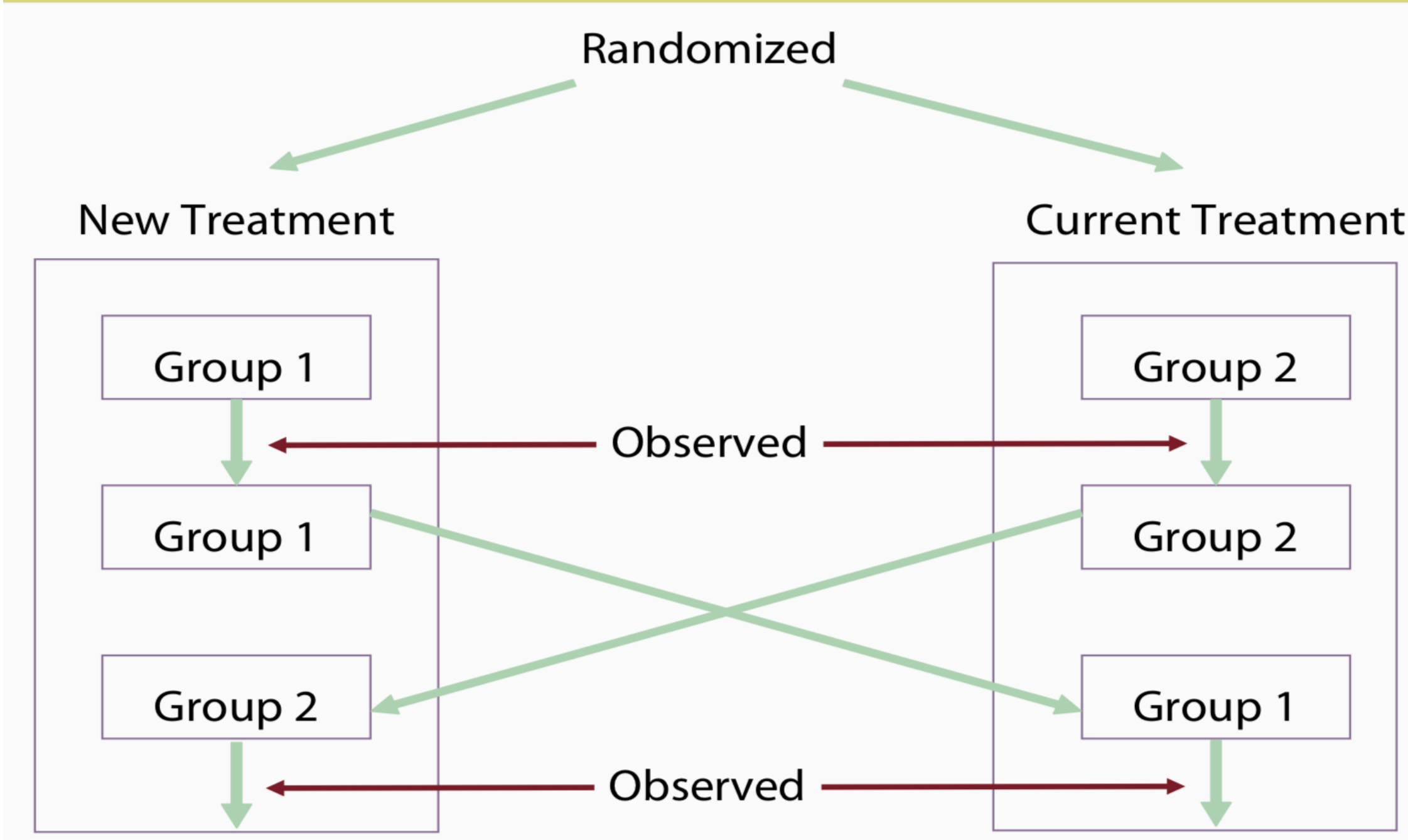
- Longer term data
  - Approval based on small numbers or relatively brief follow-up
- Impact of therapy when applied to large / diverse populations
- Large sample size (rare outcomes)
- Challenge: impact of therapy vs. course of disease or other factors

Designs of RCT

RCT

- Parallel
- Factorial
- Cross-over
- Pragmatic
- Adaptive


Study Population
Randomized
A
Outcome
B
Outcome


Randomized
New Treatment
Current Treatment
Group 1
Group 2
Observed
Group 1
Group 2
Group 2
Group 1
Observed

		Treatment B	
		+	−
Treatment A	+	Both A and B	A only
	−	B only	Neither A nor B

Factorial Design

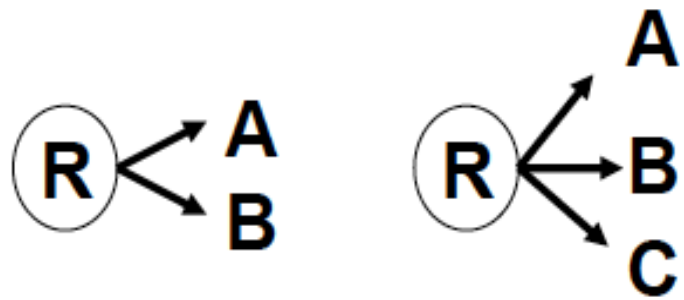
- Advantages
  - Two studies for one
  - Discover interactions

- Disadvantages
  - Test of main effect assumes no interaction
  - Often inadequate power to test for interaction
  - Compliance

- Examples
  - Physicians' Health Study (PHS) *NEJM* 321(3):129-135, 1989.
  - Final report on the aspirin component
  - Canadian Cooperative Stroke Study (1978) *NEJM* p. 53

RCT Designs

Parallel



Crossover

Factorial

	X	Y
A	AX	AY
B	BX	BY

Considerations in Assessing the Validity of a Clinical Trial

1. Randomization
2. Allocation concealment
3. Blinding
4. Loss to follow-up

Randomization

- **Randomization:** is the process by which allocation of subjects to treatment groups is done by chance, without the ability to predict who is in what group
- Primary purpose
  – **Prevent bias in allocating subjects to treatment groups (avoid predictability)**
- Secondary purpose
  – Achieve comparability between the groups (there is no guarantee)

Randomization

- All patients have the same chance of receiving either treatment or control
- Sequence of allocation to treatment or control must be unpredictable
- Helps ensure that the treatment and control groups will have similar characteristics
  - Both known and unknown factors are equalized
- Avoids selection bias
  - Sometimes called “confounding by indication”

Allocation Concealment

- The investigator entering a patient into the study should not know if the patient will be assigned to treatment or control
  - They might try to put the sicker patients into the control group to make the treatment look good
  - They might try to put the sicker patients into the treatment if they believe the treatment is effective

- Can be prevented by using a telephone service or computer for randomization

CONCEALED ALLOCATION

- Concealed allocation is an extension of randomization

- When obtaining informed consent to enroll a patient into a trial, the investigator does not know if the next patient will get new treatment or control

CONCEALED ALLOCATION

- RCT comparing new therapy vs. placebo for abdominal pain in irritable bowel syndrome
- Investigator interviews the next eligible patient, who complains of long-term severe, unrelenting symptoms that have never responded to previous medical therapy
- Next patient to enter trial will get placebo

CONCEALED ALLOCATION

- Investigator thinks that placebo is unlikely to relieve abdominal pain in this patient
  - Investigator may subconsciously try to convince patient not to enroll in the trial
- Consequence: patients with severe abdominal pain will NOT be evenly divided between new therapy and placebo groups

Blinding

- **Masking or blinding** is used to increase the objectivity of the persons dealing with the randomized study (to prevent prejudice)
- Subjects who can be masked/blinded
  – Study participants
  – Caregivers/treaters
  – Data collectors/assessors of outcome – Data analysts
- – Investigators
  Level of masking/blinding
- – Non-blinded (open) – Single
  – Double
  – Triple

Blinding

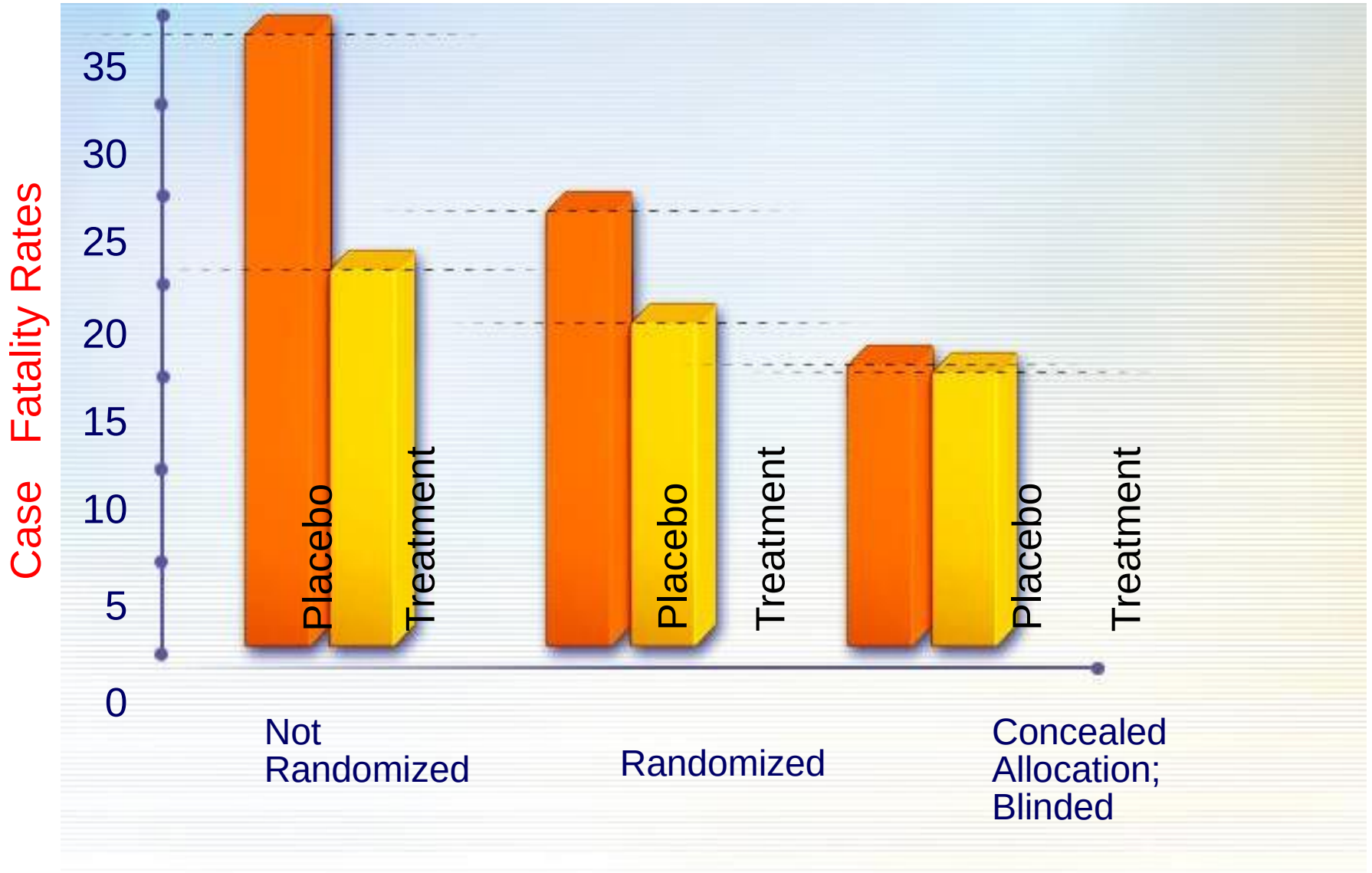
- Single blinded: patient doesn't know which arm any patient is in.
- Double blinded: patient and person administering the intervention don't know.

- Triple blinded: patient, interventionist and data analyst don't know.

Blinding

- Also referred to as “masking”
- Blinding of the investigators prevents ascertainment bias
  - Data collectors
  - Outcome adjudicators
  - Data analysts
- Blinding of patients equalizes the placebo effect
- Blinding of caregivers prevents unequal treatment

TREATMENT EFFECT OVERESTIMATED WITHOUT RANDOMIZATION AND BLINDING



Chalmers, et al. N Engl J Med 1983; 309: 1358

Loss to Follow-Up

- Participants may leave a study for a variety of reasons
  - moving out of town
  - too burdensome to comply with the study protocol
  - experiencing adverse effects from the intervention
  - feeling well or cured by the intervention
  - death

- How to deal with lost participants
  - find out why the were lost
  - assume the worst, and see how it affects results

Compliance

- **Compliance** is the willingness of the participants to carry out the procedures according to the established protocols (adherence)

- **Drop-outs** are the participants who do not adhere to the experimental regimen during follow-up

- **Drop-ins** are the participants who do not adhere to the control regimen during follow-up

Analysis

- Primary: **intention to treat**
  - Analyze according to original allocation
  - Net effect of non-compliance is to reduce the observed differences
- Secondary: actual treatment received – Based on observed data
  - No benefit of randomization

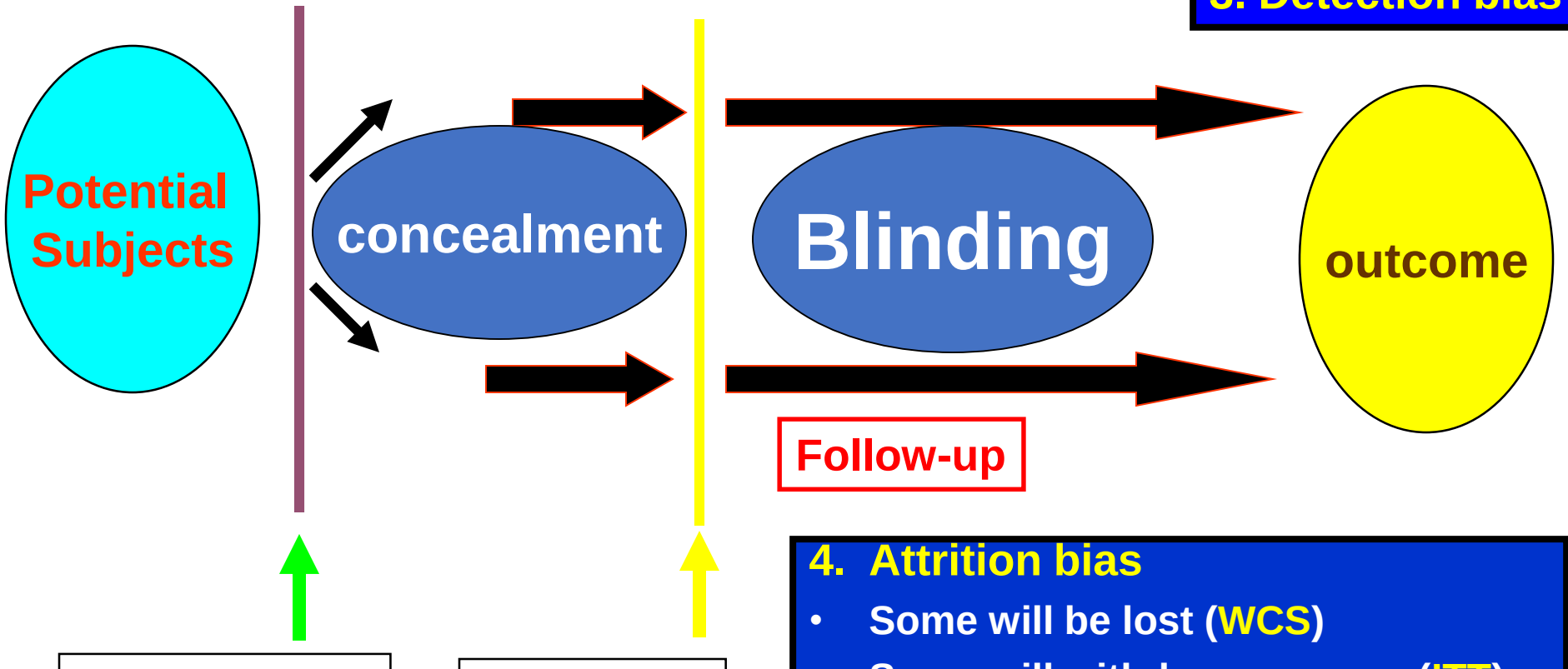
1. Selection bias

- Eligibility criteria
- Randomization
- Concealment

2. Performance bias

- Co-intervention
- Contamination
- Placebo effect

3. Detection bias



4. Attrition bias

- Some will be lost (WCS)
- Some will withdraw or cross (ITT)