EBM:
Therapeutic Studies

Pawin Numthavaj, M.D. Ph.D.
Department of Clinical Epidemiology & Biostatistics
Faculty of Medicine Ramathibodi Hospital
Mahidol University
pawin.num@mahidol.ac.th

Scope of lecture

- Therapeutic Studies & Clinical Trials
  - Types of clinical trial design
  - Process of clinical trial
  - Basic calculation from therapeutic studies
  - Critical appraisal of therapeutic studies

Clinical Trials

- **Clinical trials:**
  A systematic study on **pharmaceutical products in human subjects** in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their **efficacy and safety**.

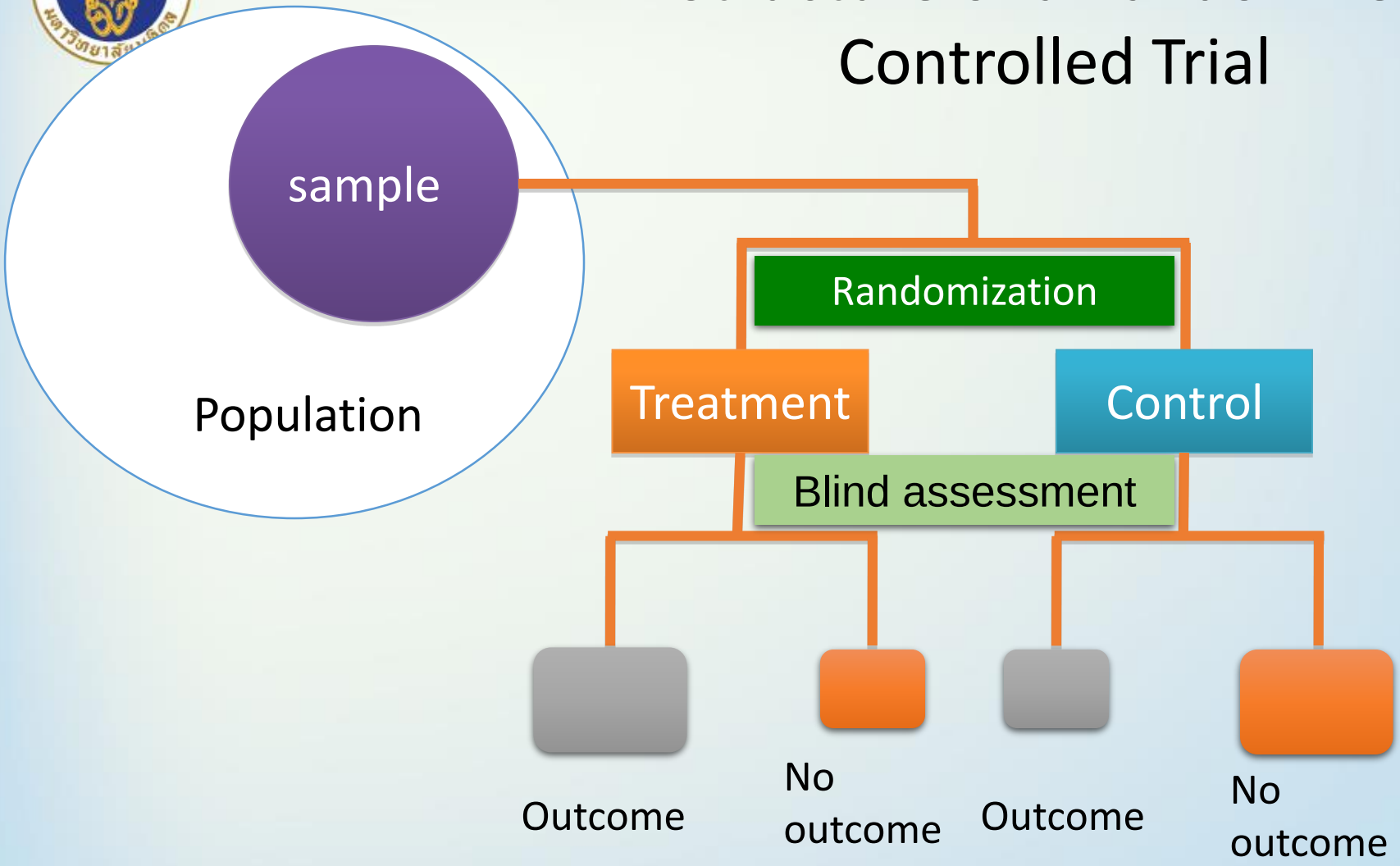
Phases of Clinical Trial

Phase I	Clinical pharmacology / toxicology, dose fining, safety, perfection of technique
Phase II	Initial clinical investigation for treatment effect, pilot study
Phase III	Full-scale evaluation of treatment effect (efficacy)*
Phase IV	Post-market surveillance (effectiveness)

Efficacy vs Effectiveness study

- **Efficacy:** Does receiving treatment work under ideal conditions?
  - Limit only to patients that will cooperate fully with medical advice
- **Effectiveness:** Does offering treatment help under ordinary circumstances?
  - Offering treatment to patients and allowing them to accept or reject it as they might ordinarily do
  - If a treatment is found to be ineffective:
    - Lack of efficacy
    - Lack of patient acceptance

Structure of a Randomized Controlled Trial



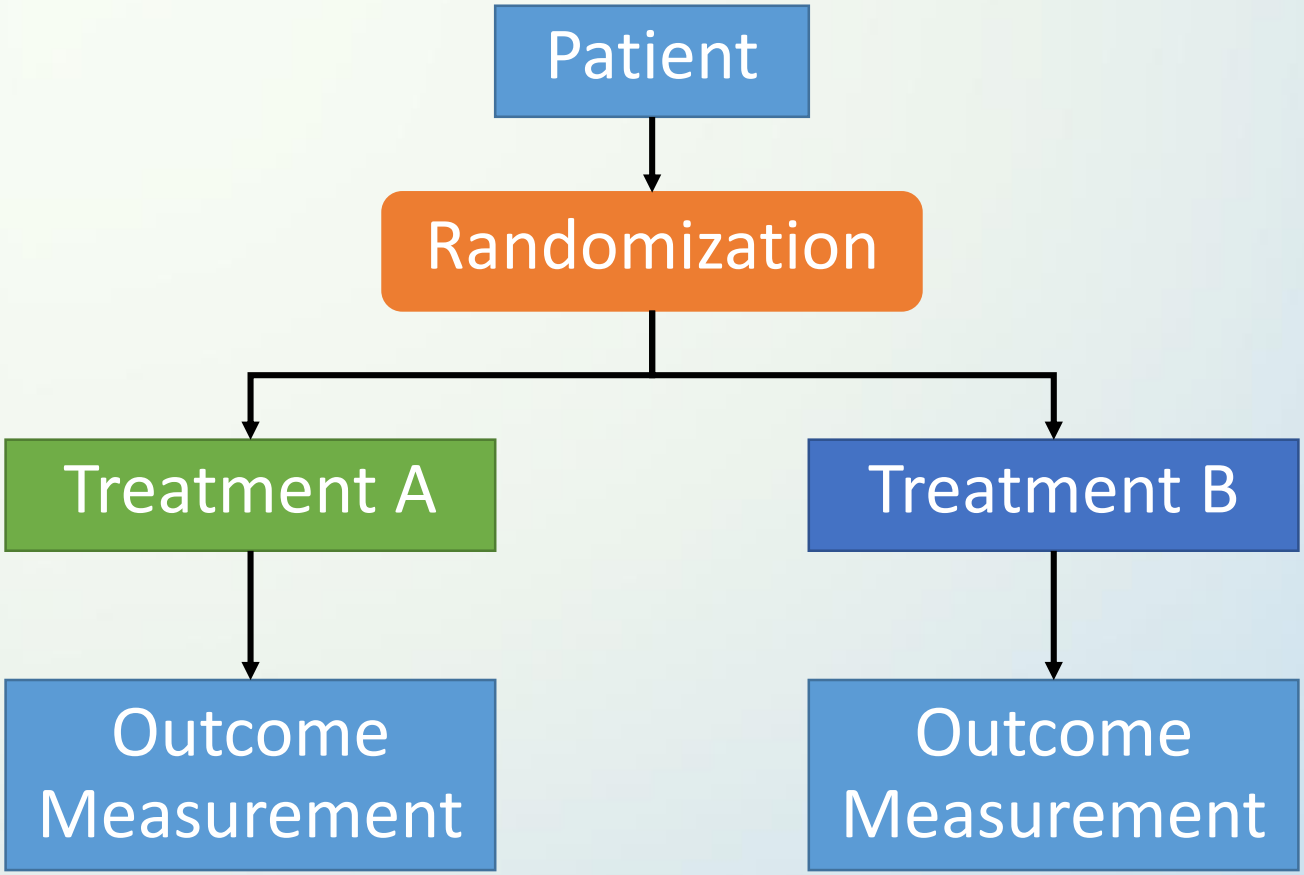
Common Types of Trial Design

1. Parallel
2. Cross-over
3. Group allocation (Clustered)
4. Factorial design

1. Parallel Design

- Treatment & control group
- Each person is randomly assigned to one treatment group

Parallel Design

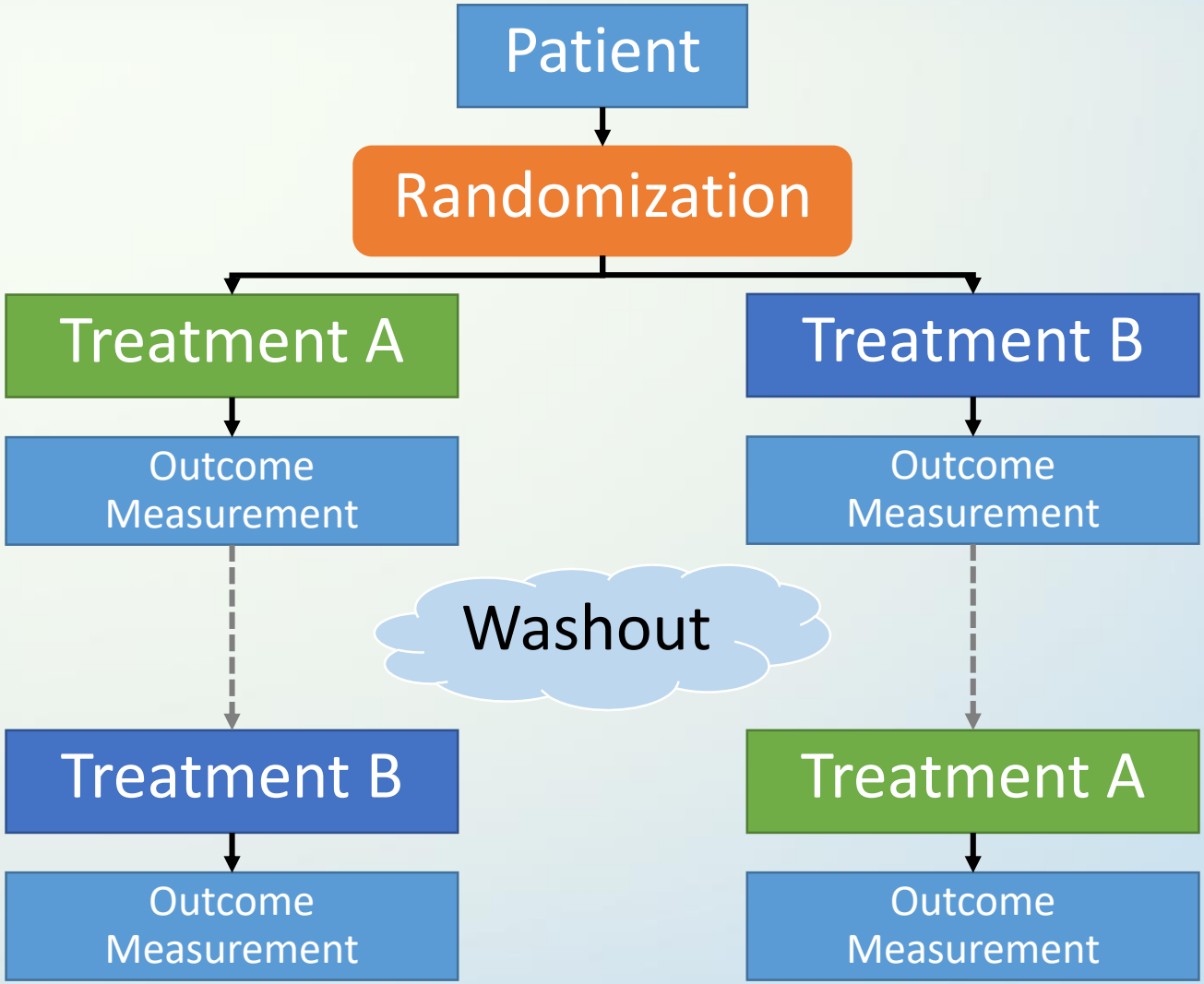


2. Crossover Design

- Randomization of **order** in which treatments are received
- AB or BA

- Patients serves as their own control
- Fewer patients needed
- Use in chronic disease with constant intensity of underlying disease
- Look for short-term treatment effects

Crossover Design



Disadvantages of Crossover Design

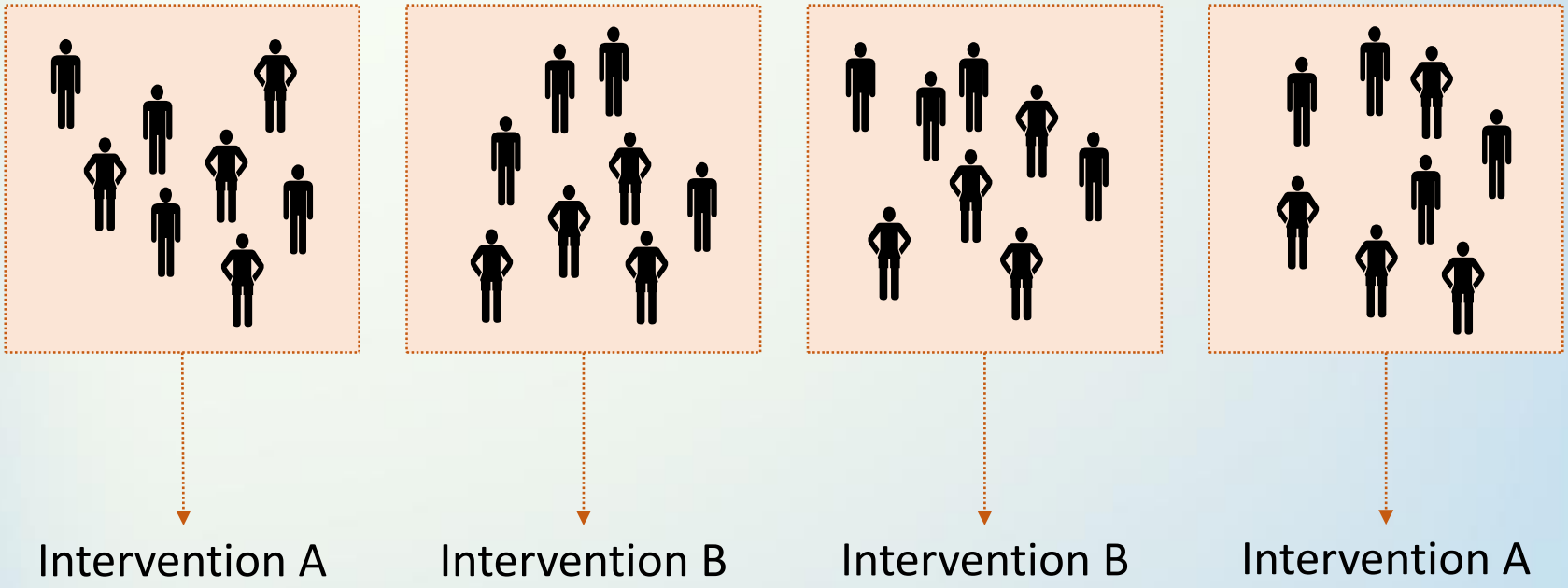
- Treatment cannot have permanent effect
- Potential “carry-over” effect
- Need for “washout” period
- Dropouts are more significant
- Analysis may be more difficult

3. Group Allocation Design

- “Cluster” design
- Unit of randomization = “Group of patients” (Community, hospital, school)

- Use when individual randomization is not feasible ex. contamination

Group Allocation Design



4. Factorial Design

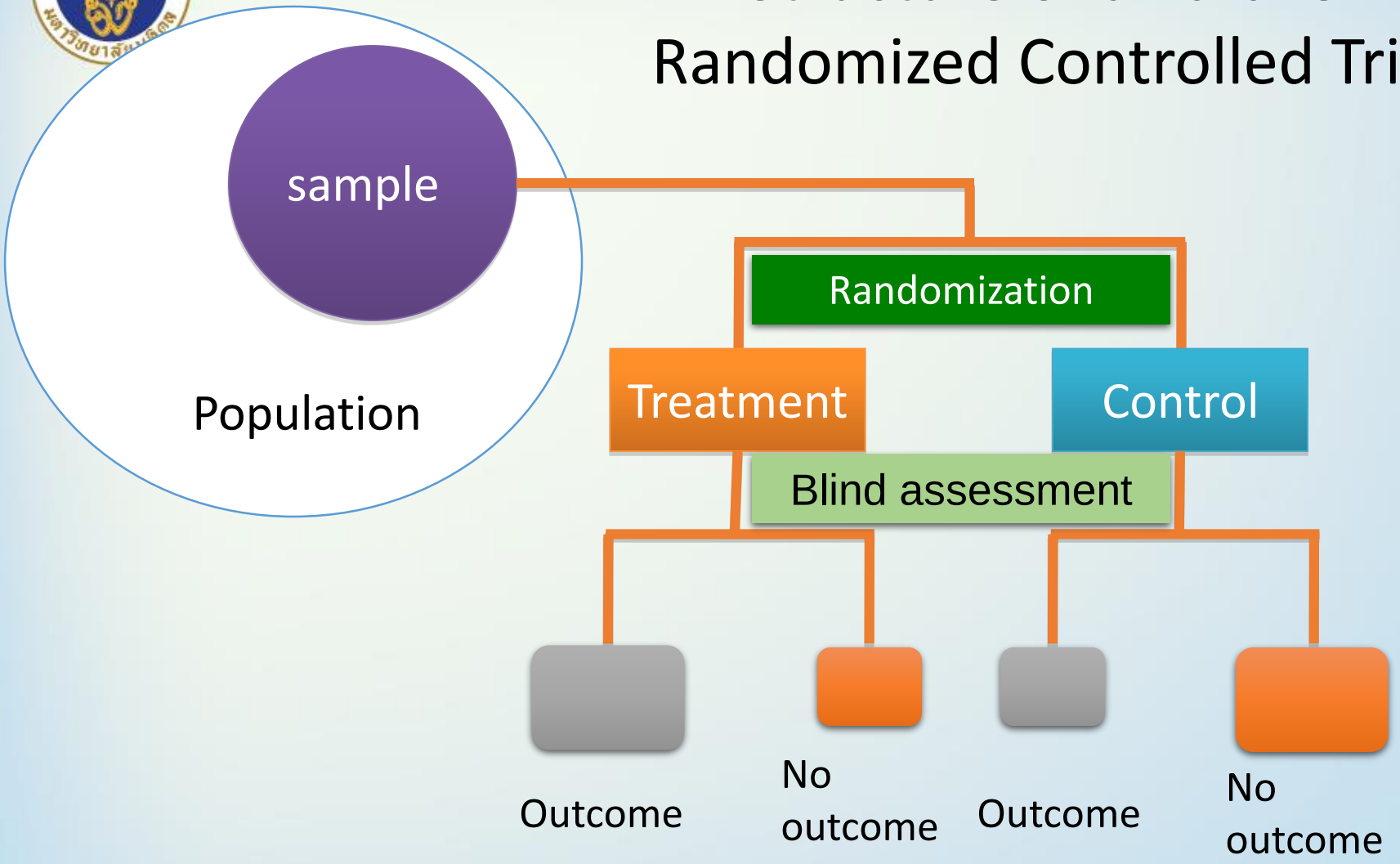
- Test two (or more) interventions simultaneously
  - Economical way
  - Determine treatment interaction
- Assumption: treatments are independent (no interaction)

Example of 2 Treatments Factorial Design (A and B)

	Treatment B +	**Treatment B -**	
Treatment A +	A & B	A, Not B	A, with or without B
Treatment A -	B, Not A	Not A & Not B	Not A, with or without B
	B, With or without A	Not B, With or without A	

Process of Clinical Trial

Structure of a Parallel Randomized Controlled Trial



Randomized Allocation or Randomization

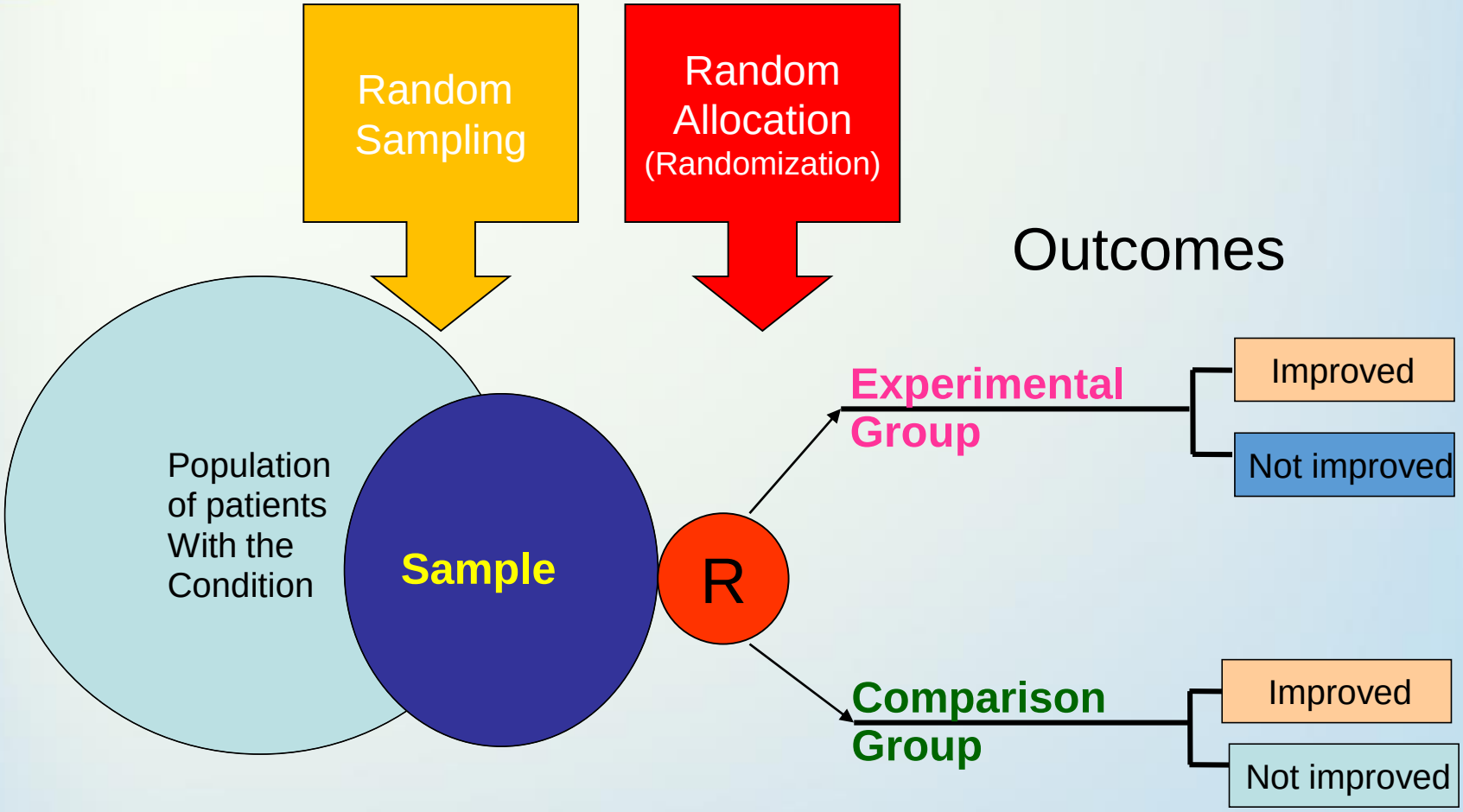
- Allocation of individuals to groups ***by chance.***

- Within the limits of chance variation, randomization *should make the control and the experimental groups similar at the start of the investigation* and ensure that personal judgment and prejudices of the investigator do not influence allocation

Randomization

- All subjects in the sample have same probability of being assigned to the experimental or control group.
- Any underlying factors that may affect the outcome are equivalent for each group.

Randomization



Is this randomization technique proper?

Introduction

Patent ductus arteriosus (PDA) is one of the most common clinical findings and most frequent source of complications in premature infants [1]. The presence of respiratory distress syndrome (RDS) is also associated with increased frequency of significant PDA [2]. The incidence of PDA in very-low-birth weight infants with RDS is about 40% on the 3rd day of life, leading to several undesirable consequences, including haemodynamic, pulmonary, cerebral, renal and gastrointestinal disturbances [3]. The treatment of PDA, particularly when accompanied by RDS, is therefore crucial in preterm infants.

A number of studies carried out in the last decade have demonstrated the effectiveness of intravenous indomethacin and ibuprofen for closure of PDA, and these are now widely used as treatments [1–7]. However, the intravenous form of these drugs is unavailable in the Islamic Republic of Iran, and a comparative study was therefore conducted to evaluate the therapeutic effects of oral administration of indomethacin capsules or ibuprofen suspension on closure of PDA in preterm infants.

Methods

This study was conducted in the neonatal intensive care unit of the Nemazee hospital, Shiraz, Islamic Republic of Iran over a 6-month period in 2001.

All eligible premature infants of less than 37 weeks gestation who were admitted to the hospital during their first 10 days of life with clinical PDA confirmed by Doppler echocardiography were enrolled in the study. They were randomized into ibuprofen or indomethacin groups. As soon as the diagnosis was made for the 1st eligible baby, he/she was enrolled to the ibuprofen group and then the next eligible baby was assigned to the indomethacin group, and so on. The randomized distribution sequence was continued until the statistically recommended sample size was achieved.

The non-eligible infants were those with major congenital malformations, congenital heart defects, persistent pulmonary hypertension, intraventricular haemorrhage, blood urea nitrogen (BUN) concentration > 14 mmol/L, hyperbilirubinaemia in the level of exchange transfusion [3], bleeding tendency, evidence of necrotizing enterocolitis (NEC), platelet count < 50 000 /mm³, oliguria < 1 mL/kg/hr, and serum creatinine concentration > 1.8 mg/dL [8].

For the indomethacin group, the powder content of a 25 mg indomethacin capsule (Hakim Pharmaceutical Company, TI-67-HM-026) was freshly prepared by dissolving in 25 mL distilled water. This was given orally as 0.2 mg/kg for 3 doses at 24-hour intervals [8]. For the ibuprofen group, an ibuprofen oral suspension containing 100 mg in 5 mL (Hakim Pharmaceutical Company, 75-HM-30) was given as an initial dose of 10 mg/kg, followed by 2 further doses of 5 mg/kg at 24-hour intervals [8]. Administration of the 2nd or 3rd doses of each drug was dependent on achievement of ductal closure after the initial doses.

Apart from the regular daily care and clinical examinations, a 2nd and 3rd Doppler echocardiographic evaluation was performed for all neonates shortly after receiving the last doses of the drugs and 1 week later to visualize the state of the ductus and the shunting through it.

The 2 groups were evaluated and compared for sex, gestational age, vital signs and age at starting treatment, ductal closure, serum bilirubin level, renal function, thrombocyte count and evidence of NEC.

The Fisher exact test was used for data analysis.

All eligible premature infants of less than 37 weeks gestation who were admitted to the hospital during their first 10 days of life with clinical PDA confirmed by Doppler echocardiography were enrolled in the study. They were randomized into ibuprofen or indomethacin groups. As soon as the diagnosis was made for the 1st eligible baby, he/she was enrolled to the ibuprofen group and then the next eligible baby was assigned to the indomethacin group, and so on. The randomized distribution sequence was continued until the statistically recommended sample size was achieved.

Pourarian S, Pishva N, Madani A, Rastegari M. Comparison of oral ibuprofen and indomethacin on closure of patent ductus arteriosus in preterm infants. Eastern Mediterranean health journal. 2008;14(2):360-5.

Techniques of randomization

1. Simple (Unrestricted) Randomization
2. Restricted Randomization
   - Block Randomization
   - Stratified Randomization

1. Simple (unrestricted) randomization

- Coin, dice *(not preferred)*
  - May be biased
  - Can not be audit by others
- Table of random numbers
- Computer generated

	1 2 3 4	5 6 7 8	9 10 11 12	13 14 15 16	17 18 19 20	21 22 23 24	25 26 27 28	29 30 31 32
1	8 0 9 4	2 5 2 5	8 2 4 7	1 3 4 7	7 4 3 3	3 6 2 0	1 8 9 7	2 1 3 4
2	3 5 6 3	2 1 9 8	8 2 1 1	9 0 4 5	2 6 1 8	2 7 5 1	2 6 2 7	1 0 9 5
3	1 3 3 0	6 3 3 1	3 7 5 3	9 6 9 3	8 7 3 8	6 8 1 5	1 5 3 8	8 5 4 3
4	3 5 6 5	0 0 1 6	2 2 4 3	6 4 3 2	4 7 9 6	6 0 9 5	5 2 8 3	1 6 2 0
5	7 8 5 0	5 9 2 5	5 5 8 8	7 3 1 1	2 1 9 2	4 5 4 5	3 5 3 0	5 5 8 9
6	4 4 9 0	5 4 1 7	9 7 2 7	6 1 5 3	5 9 0 1	4 8 7 8	9 9 8 0	9 8 7 7
7	6 5 4 5	9 1 0 4	9 3 1 8	8 8 1 9	7 5 3 7	2 7 8 5	9 3 7 3	2 4 4 5
8	3 6 2 6	5 9 9 5	1 2 1 5	9 7 5 3	9 2 2 3	5 6 5 8	2 9 4 4	2 8 9 9
9	4 8 6 5	4 8 2 0	7 5 5 4	0 6 1 2	9 6 8 3	4 2 5 1	9 1 3 8	1 7 0 9
10	6 4 9 8	7 5 1 9	0 4 7 4	7 8 1 8	6 8 3 2	9 6 8 3	9 8 7 2	4 0 9 0
11	6 7 2 2	9 8 6 9	9 3 6 1	7 8 7 5	4 8 8 3	1 3 1 5	9 6 7 9	8 8 3 4
12	9 7 4 8	5 9 3 2	5 1 1 5	2 7 2 1	0 0 3 3	9 3 0 3	9 7 1 3	4 0 1 2
13	5 6 4 1	1 4 1 7	1 4 1 9	7 4 3 4	8 1 6 5	7 3 6 8	1 2 1 8	5 0 3 9
14	7 4 4 4	9 2 0 0	8 8 4 0	5 8 8 2	4 3 9 8	3 9 0 4	9 1 9 9	9 3 3 6
15	8 2 7 9	3 0 1 9	4 6 7 2	3 7 4 3	3 9 7 9	4 6 8 9	9 0 2 1	6 9 9 0
16	0 1 6 1	7 6 1 7	1 0 2 4	2 3 8 7	2 8 9 1	6 6 7 7	1 5 8 5	2 4 8 2
17	7 3 8 8	9 7 5 9	7 5 5 5	6 6 2 4	9 9 7 7	2 0 0 8	5 5 9 6	9 7 4 0
18	7 8 3 0	4 7 1 4	3 6 9 5	2 9 1 9	1 8 0 4	4 0 4 4	1 0 3 4	2 5 9 7
19	9 8 8 7	4 2 1 6	6 5 2 6	4 5 3 5	8 4 3 0	5 2 7 0	9 6 0 5	0 7 6 8
20	1 2 6 1	2 5 1 6	8 5 6 9	2 3 1 0	3 9 3 9	8 7 0 3	9 8 4 1	0 3 5 3
21	3 9 4 7	4 9 3 7	7 6 3 4	2 5 4 3	6 2 3 9	7 4 5 5	2 0 5 5	7 7 9 5
22	4 5 5 0	8 1 0 3	1 2 5 0	2 3 0 4	1 1 3 8	9 7 8 8	9 1 4 4	4 5 2 6
23	1 3 4 4	9 8 9 7	2 3 8 3	6 9 7 6	6 2 5 1	4 2 0 1	2 0 3 8	6 5 5 2
24	8 9 7 6	5 8 2 3	8 4 8 7	0 4 5 0	3 1 0 6	9 1 6 6	2 7 1 7	7 6 0 1
25	7 7 1 0	9 9 4 3	6 9 7 8	8 2 7 3	9 7 1 4	9 7 0 0	1 5 6 6	2 8 8 9
26	6 9 5 9	6 0 0 8	8 4 4 2	2 2 8 2	1 5 2 4	2 5 1 7	5 8 1 8	0 0 8 1
27	7 9 4 1	2 3 1 2	2 4 3 1	6 7 0 2	9 9 8 4	3 4 6 9	3 0 8 5	4 7 6 2
28	2 2 8 4	0 8 9 6	9 1 0 7	5 5 4 2	7 3 1 9	3 7 8 2	1 0 6 8	9 5 7 4
29	9 5 9 4	7 4 1 6	9 3 6 5	6 0 4 5	1 1 8 3	5 9 1 6	9 5 9 9	1 1 4 3
30	4 6 1 3	8 5 4 9	6 3 6 9	3 2 0 8	5 1 0 9	9 6 8 0	1 1 6 8	6 1 3 3

Ex: Randomized 20 subjects for either treatment “A” or “B”

Patient No.	1	2	3	4	5	6	7	8	9	10
Treatment	A	A	A	B	A	B	A	A	A	A

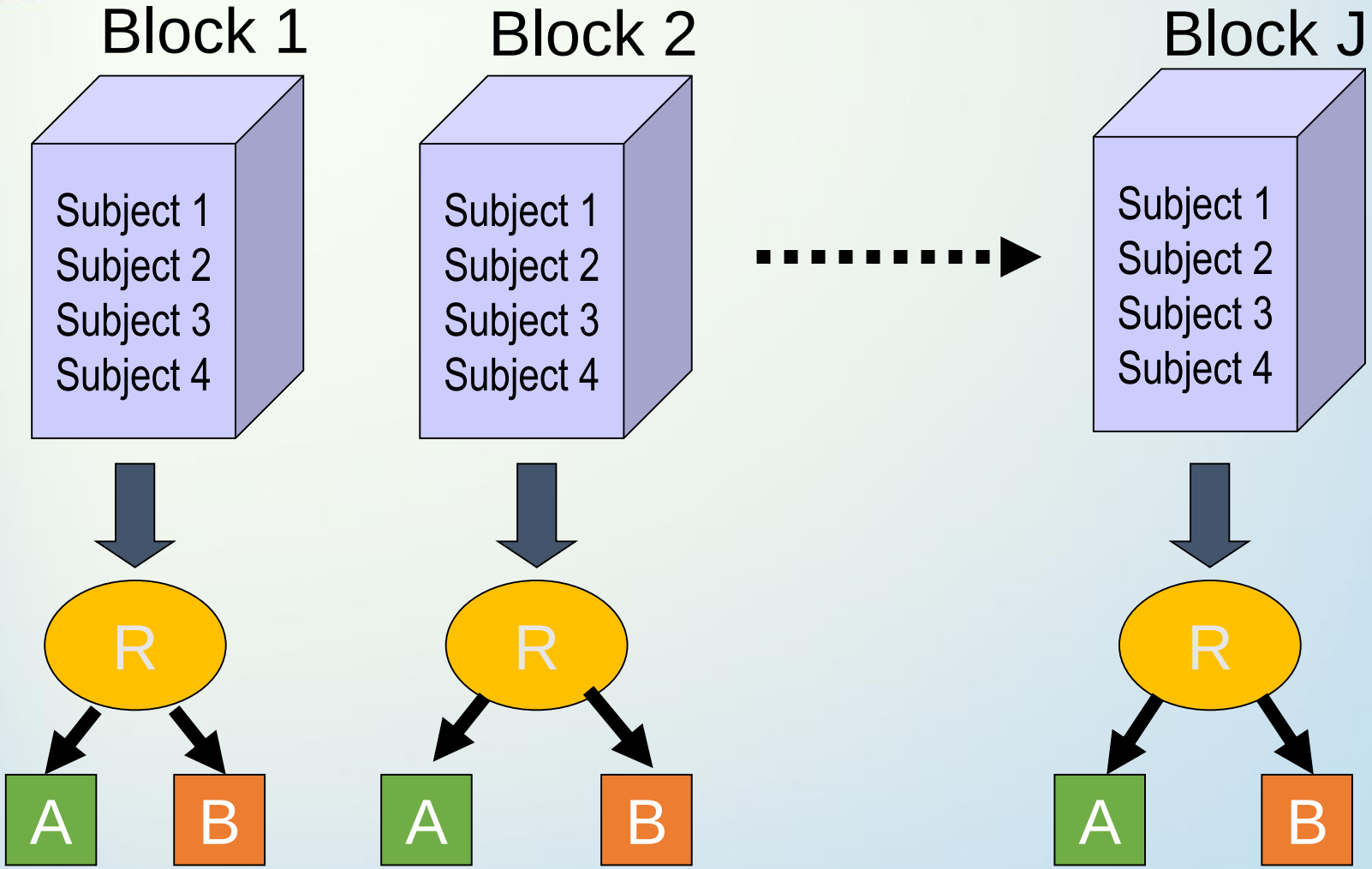
Patient No.	11	12	13	14	15	16	17	18	19	20
Treatment	A	B	A	B	B	B	B	B	B	B

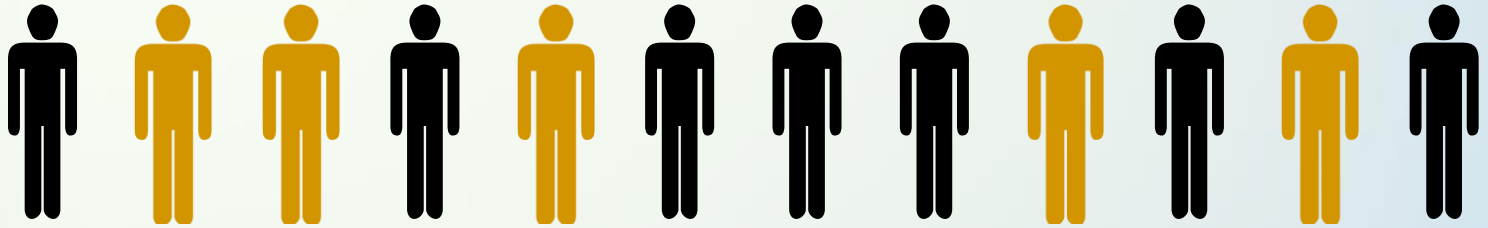
- **Advantages:**
  - Each assignment is completely unpredictable
  - Long run: tends to produce similar number of patients in both groups
- **Risks of simple randomization**
  - Imbalance of number of participants in each group
  - Imbalance of number of participants with and without confounding factors
  - Less number of participants – higher risk of imbalance

2. Restricted Randomization

- **Blocking**
- Block: list of treatment assignments that achieve the allocation ratio
  - A:B 1:1
  - Block of 4 should have 2A:2B
  - Possibility: AABB ABAB ABBA BABA BAAB BBAA
  - Block of 6 should have 3A:3B
  - Possibility: AAABBB …
- Randomization: Random block possibility

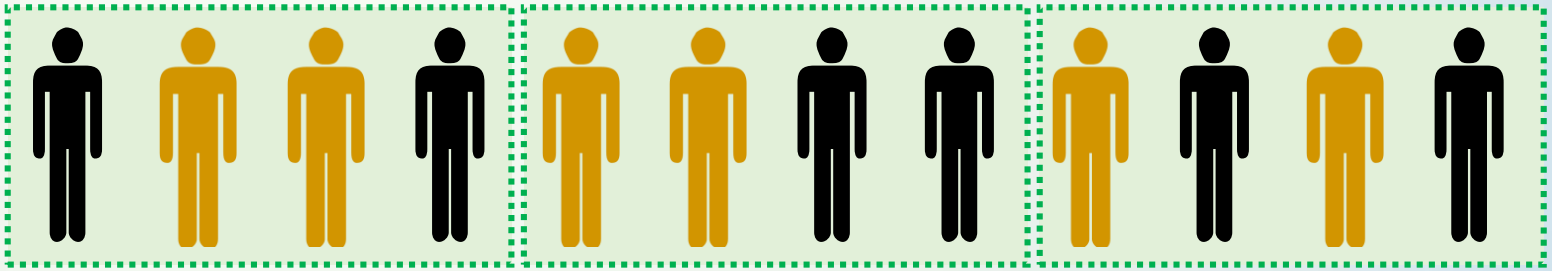
Block Randomization





Treatment A = 7

Treatment B = 5



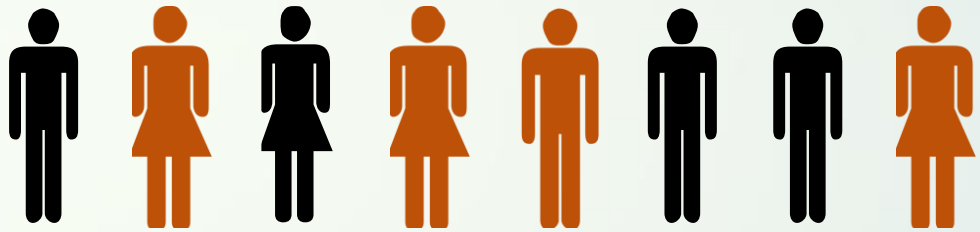
Treatment A = 6

Treatment B = 6

- **Advantages**
  - Ensure balance of treatments over time
  - Protect against time-related changes e.g. learning curve of surgeon
  - If trial is stopped early, we still have balanced groups
  - Analysis are more powerful
- **Disadvantages**
  - Prediction of next assignment
  - Especially unblinded trial
  - Possible solution: randomly varying more than one block size

- **Stratification**
- Ensure balance in treatment assignments within subgroups
  - Site of study
  - Gender
  - Age group

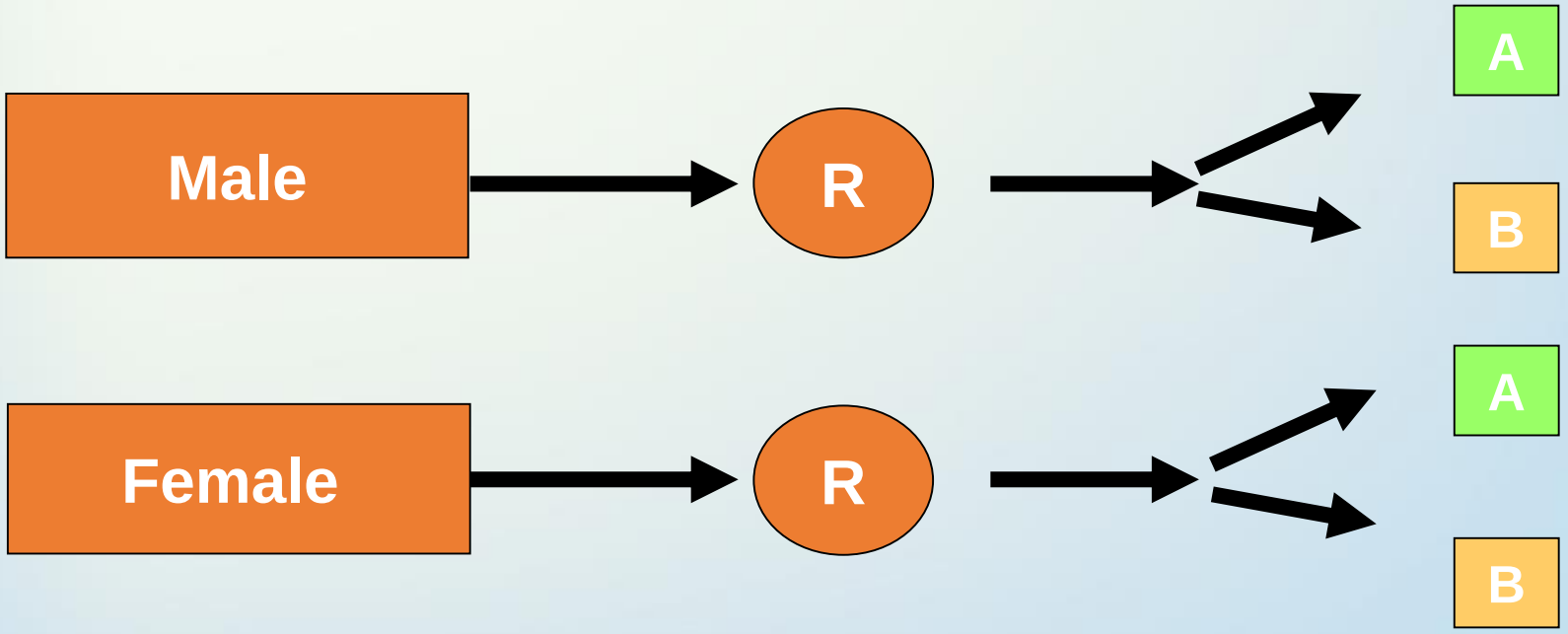
- **Disadvantages:** too many strata may lead to imbalances in overall treatment allocation



M 1:3
F 3:1

Stratification

- Example
  - Gender: Male or female

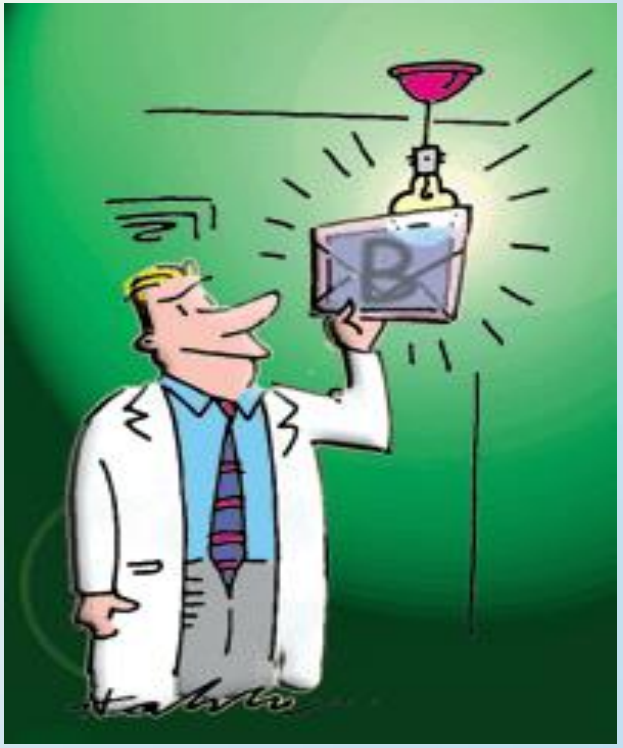


Allocation concealment

- Generation of an ***unpredictable randomized allocation sequence.***
- It represents the first crucial element of randomization in a RCT.
- Allocation concealment refers to the technique used to implement the sequence, not to generate it.
- Is not the same as blinding!

How to conceal?

- Local: Sequentially numbered, opaque envelopes
- Central: computer-based
- Emergency situation?

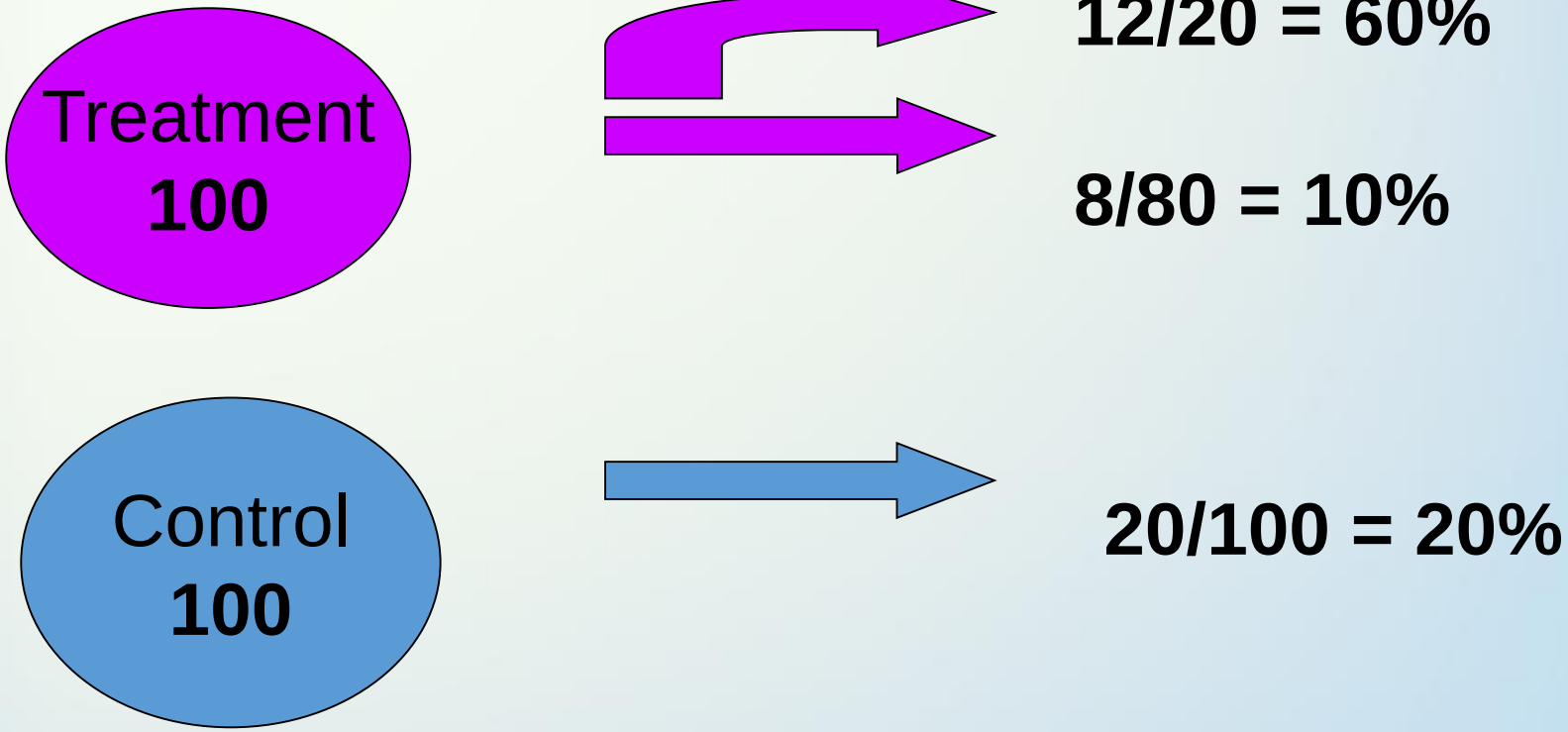


Sequentially numbered, opaque, sealed envelopes (SNOSE)

Per protocol analysis

- Analysis according to the treatment each patient actually received, regardless of the treatment to which they were randomized
- Dissimilarities between groups

Intention to treat vs. Per protocol analysis



Per protocol analysis

- Excluding noncompliant patients from the analysis leaves behind those who may be destined to have a better outcome.
- Destroys the unbiased comparison provided by randomization

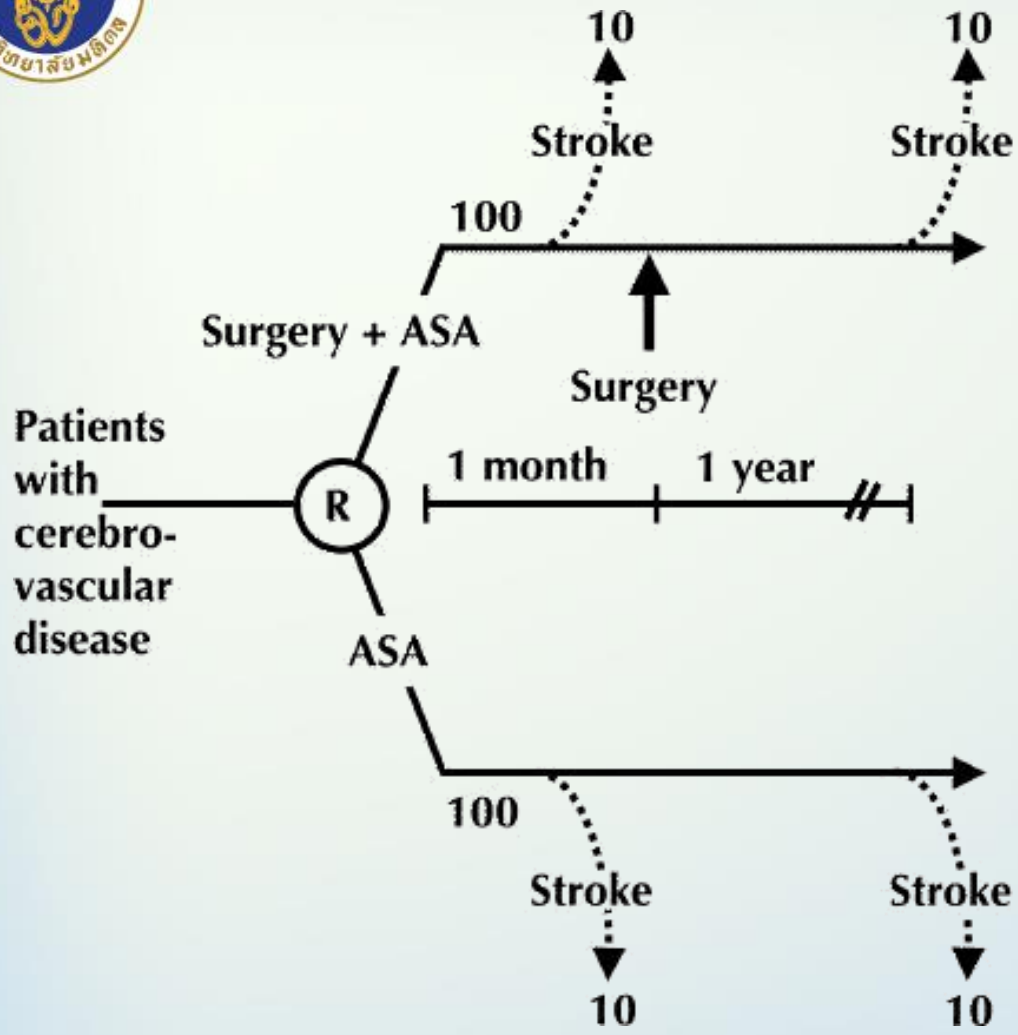
Intention to treat analysis

- Analysis according to the assigned group

Intention to treat analysis

- Includes every subject who is randomized according to randomized treatment assignment
- ITT analysis is usually described as **“once randomized, always analyzed”**
- Analyzed data based purely on randomization
- Ignore
  - Ineligibility
  - Complete nonadherence
  - Treatment termination
  - Treatment switches
  - Partial adherence

Perspect Clin Res. 2011 Jul-Sep; 2(3): 109–112



	Per protocol	Intention-to-treat
	10/90 = 0.11	20/100 = 0.20
RRR	0.45	0
	20/100 = 0.20	20/100 = 0.20

Blinding

Potential benefits of blinding

Individuals	Potential benefits
Patients	• Less likely to have biased psychological or physical responses to intervention • More likely to comply with trial regimens • Less likely to seek additional adjunct interventions
Clinicians	• Less likely to differentially administer co-interventions • Less likely to differentially adjust dose • Less likely to differentially withdraw participants • Less likely to differentially encourage or discourage participants to continue trial
Assessors	• Less likely to have biases affect their outcome assessments, especially with subjective outcomes of interest

What should you do when blinding is impossible?

- Strict to treatment protocol: to prevent unequal co-intervention
- Equally intense follow-up of experimental and control patients.
- External outcome adjudicators: to reduce biased outcome measurement

Comparison group

- No intervention
- Placebo treatment
- Standard treatment

Placebo

- An inert medication or procedure.
- The placebo effect (usually but not necessarily beneficial) is attributable to the expectation that the regimen will have an effect.

Outcome measurement

Surrogate outcome

- **Low-density lipoprotein (LDL)**
- **Proteinuria**

Clinical outcome

- **Death**
- **ESRD**

Surrogate outcome

- Laboratory or physiologic measurement used as a substitute for an outcome that measure directly
- A surrogate outcome will be consistently reliable only if there is a causal connection between change in surrogate and change in the clinically important outcome.

Composite outcome

- Combination of multiple endpoints e.g. combined death, MI or stroke
- Frequently used as primary outcome measures in RCT
- Increased statistical efficiency

Treatment effect

Control	Experimental	ARR	RRR	RR
80 KG	60 KG	20 KG	25%	75%
My past weight	My present weight	The absolute Weight I lost	The percent weight I lost	The percent weight that remained
Rc	Rt	Rc-Rt	(Rc-Rt)/Rc	Rt/Rc
My past risk	My present risk	The absolute risk I lost	The percent risk I lost	The percent risk remaining

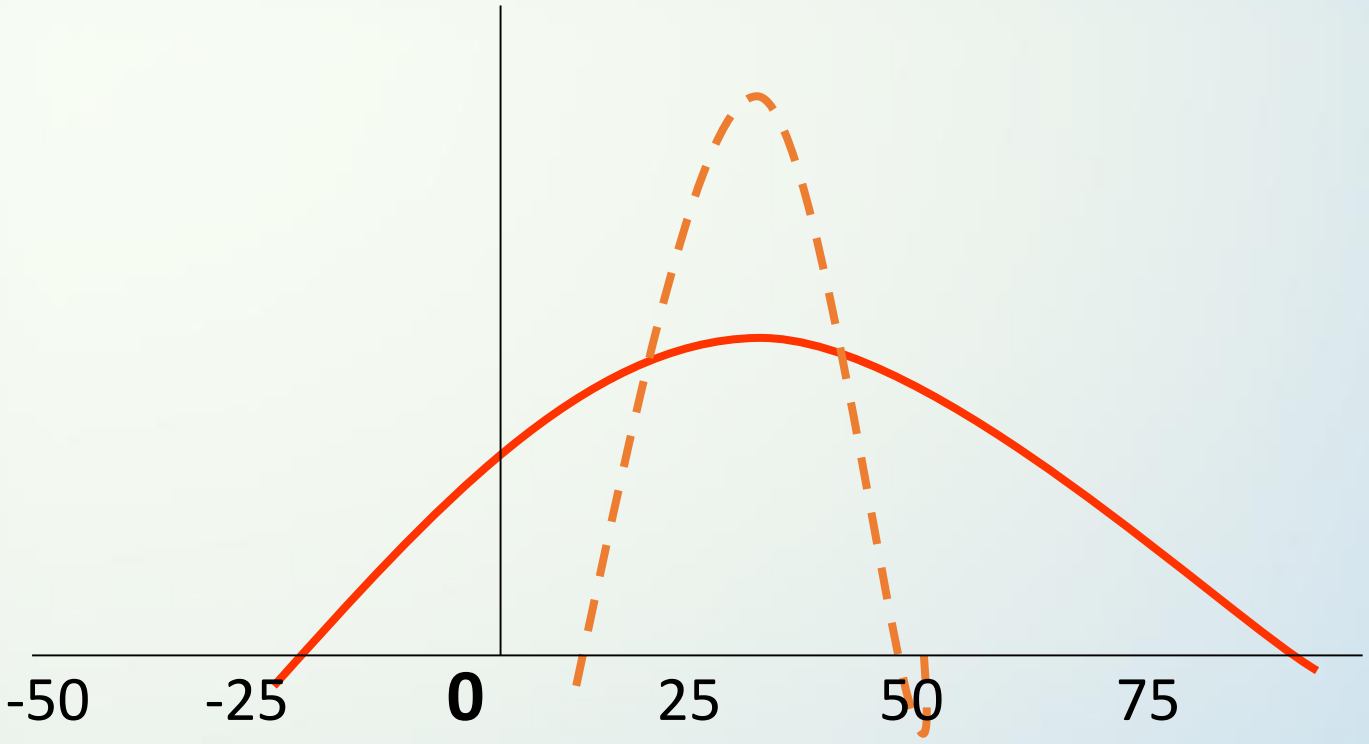
When does loss to follow-up seriously threaten validity?

	Trial A		Trial B	
	Treatment	**Control**	**Treatment**	**Control**
No. of patients randomized	1000	1000	1000	1000
No. of lost to F/U	30 (3%)	30 (3%)	30 (3%)	30 (3%)
No. of death	200 (20%)	400 (40%)	30 (3%)	60 (6%)
RRR not counting patient lost to F/U	0.2/0.4 = 0.50		0.03/0.06 = 0.50	
RRR for worst-case scenario	0.17/0.4 = 0.43		0.00/0.06 = 0	

How large was the treatment effect?

Incidence of contrast nephropathy		Absolute Risk Reduction ARR	Relative Risk Reduction RRR	Number Needed to Treat NNT
Hydration Control Event Rate CER	NAC Experimental Event Rate EER	CER - EER	CER - EER CER	1/ARR
9.6%	2.8%	0.10-0.05 = 0.05 = 5%	(0.10-0.05)/0.10 = 0.5 = 50%	

Confidence Intervals



Relative risk reduction(%)

Number needed to treat (NNT)
Number needed to harm (NNH)

Number needed to treat (NNT)

- Number needed to be treated to prevent one more event

$$NNT = 1/ (Risk_{control}-Risk_{treatment})$$
$$= 1/ARR$$

Number needed to harm (NNH)

- Number needed to be treated to harm one more of them

$$NNH = 1/ (R_{treatment}-R_{control})$$

Advantages/Disadvantages of RCT over Observational Study Design

Advantages

- Internal validity:
  - Avoid selection bias
  - Avoid confounding
  - Controls similar to exposure case
- Reduce information bias
  - Blinding
- Detect small to moderate effect

Disadvantages

- External validity:
  - "Selected" population
  - Rigid protocols
- Can't evaluate potentially harmful exposure
- Often too small to detect side effects
- Usually too short to see long term effect
- Expensive

Critical Appraisal of Therapeutic Studies

1. Are the results of the study valid?
2. What are the results?
3. How can you apply the results to patient care?

1. Are the results valid?

- Did intervention and control groups start with the same prognosis?

- Was prognostic balance maintained as the study progressed?

Did intervention and control groups start with the same prognosis?

- Were patients randomized?
- Was randomization concealed?
- Were patients analyzed in the groups to which they were randomized?
- Were patients in the treatment and control groups similar with respect to known prognostic variables?

Was prognostic balance maintained as the study progressed?

- Were patients blinded to group allocation?
- Were clinicians blinded to group allocation?
- Were outcome assessors blinded to group allocation?
- Was follow-up adequate?

2. What are the results?

- How large was the treatment effect?
- How precise was the estimate of the treatment effect?

3. How can you apply the results to patient care?

- Were the study patients similar to the patients in your practice?
- Were all clinically relevant outcomes considered?
- Are the likely treatment benefits worth the potential harm and costs?