Randomized Controlled Trial

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OBJECTIVES of THE COURSE

After completion of the course, participants are expected to be able to:

1. Recognize types of clinical trial
2. Comprehend characteristics of RCT
3. Conduct a study using RCT design
   a. **Subjects selection**
   b. **Treatment and control**
   c. **Random allocation**
   d. **Sample size**
   e. **Blinding**
   f. **Informed consent and ethical clearance**
4. Analyze RCT data

STEPS of DRUG TESTING-1

I. **Preclinical Phase:** *in vitro, in vivo*, and animal studies.

- Mode of action
- Pharmacokinetics: absorption, distribution, metabolism, and excretion.
- Lethal dose (LD_{50})
- Teratogenicity
- Toxicity and organ or tissue damage
- Carcinogenic effect

II. **Clinical Phase**

STEPS of DRUG TESTING-2

II. Clinical Phase

- Phase I
- Phase II
- Phase III
- Phase IV

PHASE I CLINICAL TRIAL

- Initial evaluation of drugs in human
- Primary objective: tolerance and adverse effects
- Metabolism and *bioavailability*
- Effectiveness is not evaluated, but safety is.
- The subjects are volunteer
- From 20 to 80 are usually required

PHASE II CLINICAL TRIAL

- Evaluate potential ***effectiveness*** of drugs
- Evaluate ***safety***.
- Screen the most potential drugs
- No control group (***case series***)
- No. of subjects 100 to 200 volunteers

PHASE III CLINICAL TRIAL

1. The new drug is compared with the existing one (the standard treatment)
2. Evaluate relative effectiveness and adverse effects
3. Sample size must be calculated
4. The treated and control group must be assigned randomly
5. It is well known as randomized controlled (or clinical) trial, RCT

PHASE IV CLINICAL TRIAL

- A new drug should always be monitored after widely used.
- It is known as *a post marketing surveillance.*
- Primary objective: adverse effect undetectable on phase III clinical trial, or long-term side effects, as well as morbidity and mortality
- It takes for 5 or more years.

GENERAL CHARACTERISTICS

1. Subjects are randomly assigned into two groups
2. The first group may be considered as the treated and the second as the control (or the opposite)
3. Both groups should be comparable except for the treatment (random allocation guarantees this comparability)
4. Both groups should be followed from the beginning to the end of the study
5. Blinding is an important thing to consider

TREATMENT and CONTROL

- Treatment: new drug, new dosage, new approach, new method etc.
- Control: Standard drug, existing method, conventional way, old protocol or placebo
- Placebo may not be used in certain RCT
  - Study of antibiotics
  - Study of contraception
  - Study of anti-hypertensive or anti-cancer drugs

PROTOCOL of the STUDY

1. Title of the study
2. Background
3. Objective
4. Hypothesis
5. Eligibility criteria
6. Study design
7. Sample size
8. Treatment and control
9. Process and evaluation
10. Data collecting and analisis
11. Informed consent and ethical clearance

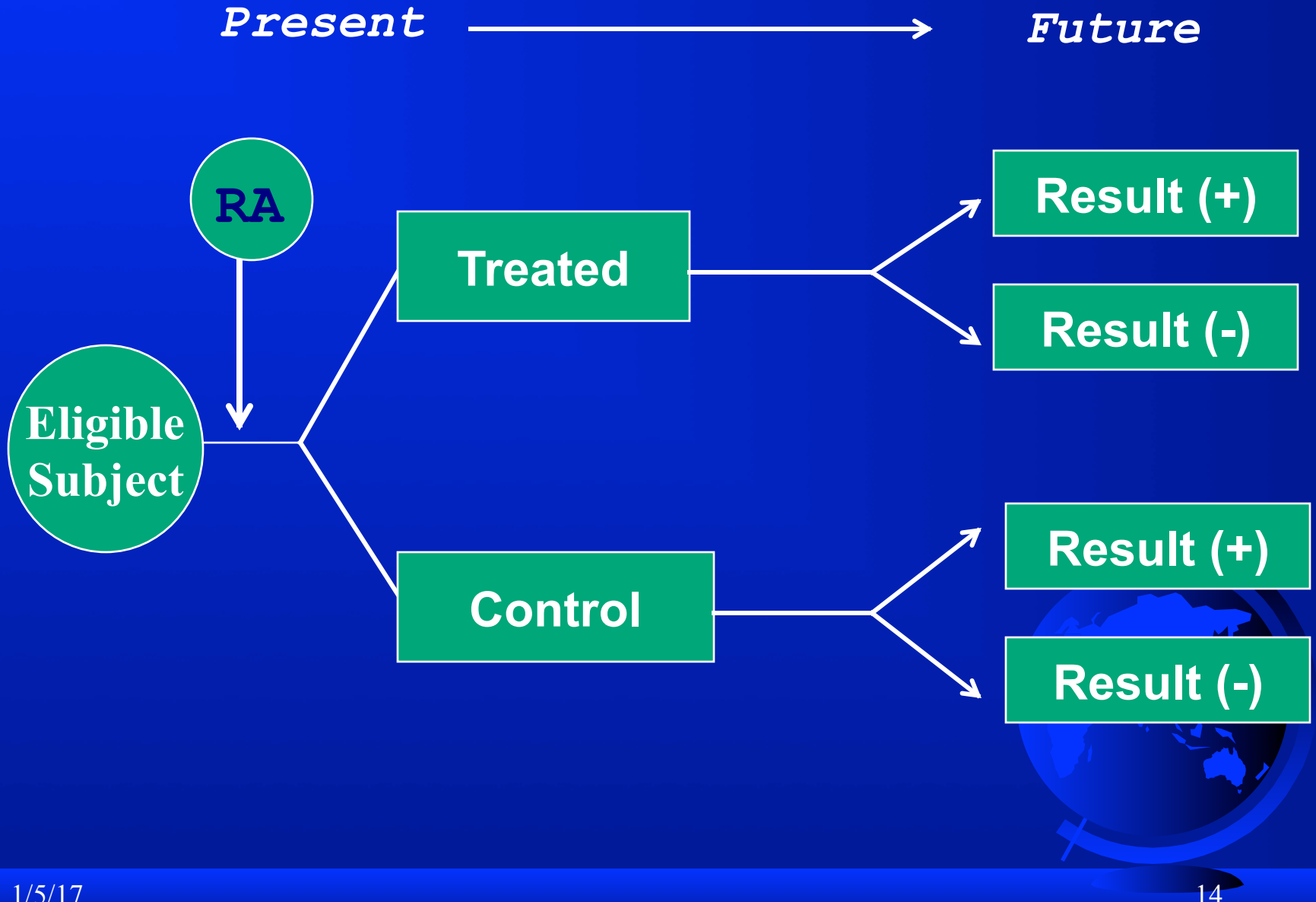
ELIGIBILITY CRITERIA

- Inclusion criteria
- Exclusion criteria
- Reduce heterogeneity or produce homogeneity
- Internal validity
- External validity (generalization)

BASIC DESIGNS

- Paralel design or between subject design
- Cross over design
- Paired design

PARALEL DESIGN-1 (Scheme)



PARALEL DESIGN-2 (Advantages)

- The most common RCT design
- Simple and easy
- Each subject receives one treatment
- Can be used for all treatments and diseases, acute or chronic
- No influence (contamination) from the compared drugs or treatment

PARALEL DESIGN-3 (Disadvantages)

- Heterogeneity between subjects is uncontrollable
- Individual drug response varies considerably
- Large sample size

CROSS OVER DESIGN-1 (Characteristics)

- Each group receives both treatments
- Two periods of cross-over is usually used
- The first period, the first group receives one treatment and the second group receives the other treatment
- Wash out period is needed
- The second period, it is switched (crossed over) to the alternative treatment.

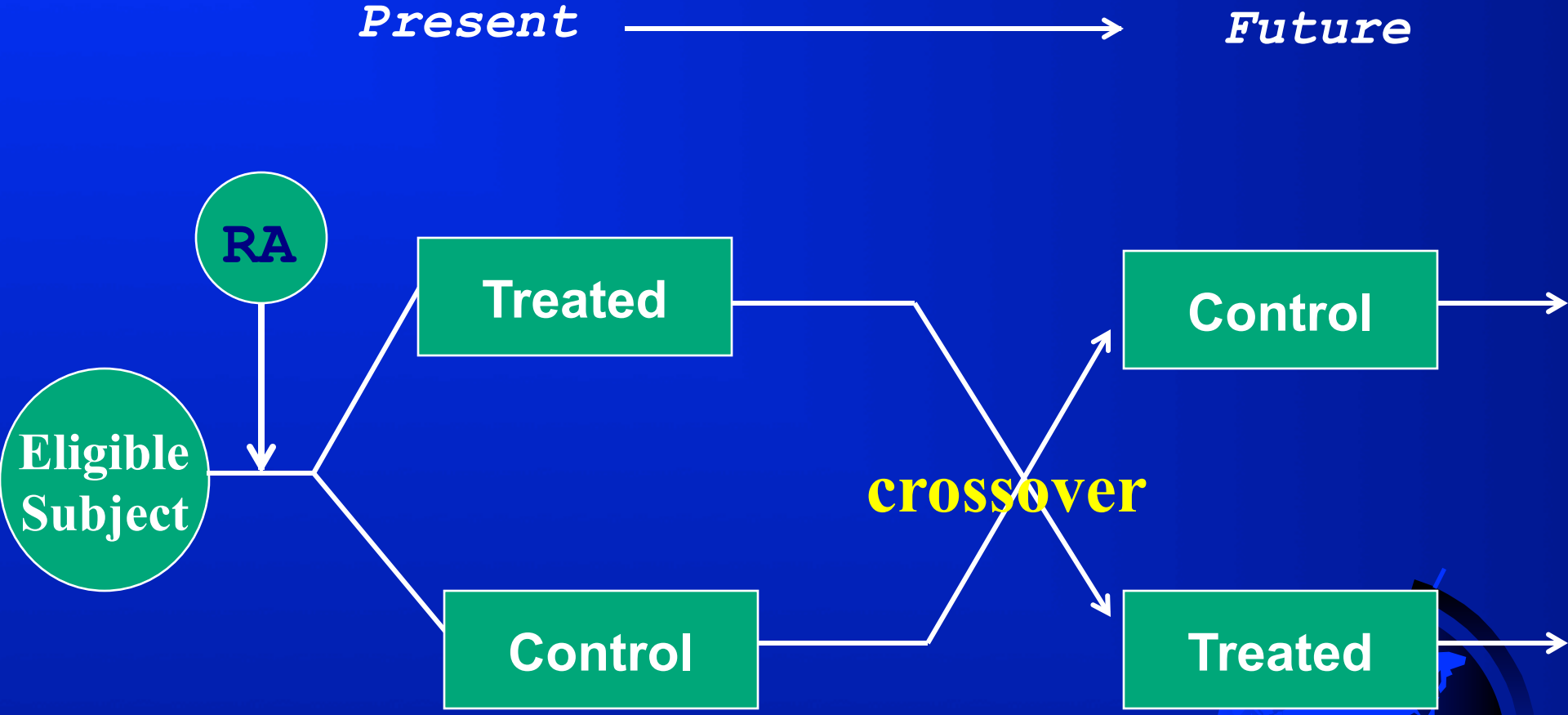
CROSS OVER DESIGN-2
(Advantages)

1. Efficient, few participants are needed
2. Variation and response to the treatment are minimal

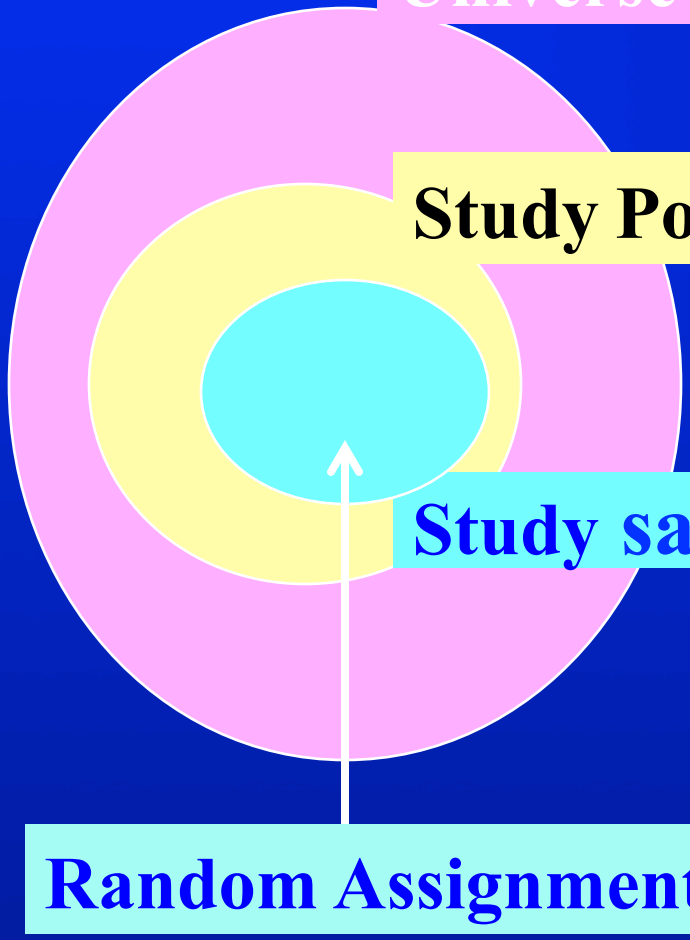
CROSS OVER DESIGN-3 (Disadvantages)

1. Not suitable for acute diseases, when the outcome is finished (e.g. antibiotic treatment).
2. Not suitable for surgical procedures.
3. Not suitable if death or pregnancy are the outcome of interest.
4. The effect of the first treatment must not carry over into the second period (carryover effect).Washout period may minimize the carryover effect
5. The length of carryover effect varies considerably
6. During the washout period the disease may worse

CROSSOVER DESIGN-1 (Scheme)



STUDY POPULATION



Inclusion criteria

Exclusion criteria

Sample size

ELLIGIBILITY CRITERIA -1

Objective

1. Assure homogeneity
2. Obtain expected outcomes
3. Outcomes are related to treatment

Two component:

1. Inclusion criteria
2. Exclusion criteria

ELLIGIBILITY CRITERIA- 2 (Exp)
Study in family planning (pills)

Inclusion criteria

1. Healthy women, age 20-40 years
2. Proven to be fertile (at least one child)
3. Married (sexually active)
4. Do not want to get pregnant at least during the study period
5. Clear last mensis period

ELLIGIBILITY CRITERIA- 2 (Exp)
Study in family planning (pills)

Exclusion criteria

1. Overweight
2. Hypertension (>140/90)
3. Unexplained bleeding
4. Breast lump
5. Diabetes mellitus

RANDOM ASSIGNMENT

Objectives

1. Gives an equal chance of being assigned to the treated or control group
2. Assures comparability
3. Comparability assures significant statistical test

Method

1. Random number table
2. Computer generated random number

BLINDING

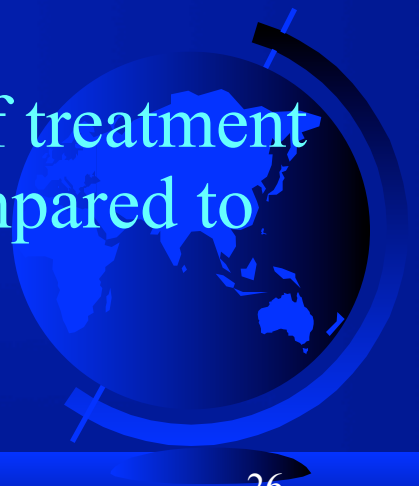
Objective:

1. Avoid bias (systematic error)
2. To get objective outcomes

Level:

1. Single blind (patient or investigator)
2. Double blind (patient and investigator)
3. Triple blind (patient, investigator and evaluator)

Note: An RCT may not be blinded, if mode of treatment is different (exp: operative procedure compared to medical treatment)



Determining sample size for discrete data What are needed?

Incidence of the exposed group (P1)

Incidence of the control group

Type one error (alpha)

Type two error (beta)

Number of participant expected to be loss to follow up

Type I and II error (α and β)

Exposure	Effect	
	Yes	**No**
Yes	Yes and Yes. (Tru yes)	Yes and No. (Type I error= α)
No	No and Yes (Type II error= β)	No and No (True no)

Note:

1. Type I error (α): If α is 5%, it means, if we find an effect, we are 95% sure that is effect is true and not by chance. Only 5% this happens by chance. (there is no effect)
2. Type II error (β):Find no effect but in fact there is an effect. If β is 0,2 means that if we find no effect it means we are sure that 80% is really no effect or only 20% that there is effects. So if our study find no effects it is possible that our study is not big enough to detect such an effect.

SAMPLE SIZE (Nominal data)

$$N/group = \frac{1}{(1-f)} \times \frac{2pq\,(z_\alpha + z_\beta)^2}{(p_1 - p_2)^2}$$

p_1 = incidence of the exposed group in decimal

p_2 = incidence of the control group in decimal

$\alpha = 0.05 \longrightarrow z_\alpha = 1.65$ (one sided) or 1.96 (two sided)

$\beta = 0.20 \longrightarrow z_\beta = 0.84$

$p = (p_1 + p_2)/2$; and $q = (100 - p)$

f = No of subjects expected loss to follow up (decimal)

Determining sample size for continuous data What are needed?

Mean of the control group

Mean of the exposed group

Standar deviation control group (P1)

Type one error (alpha)

Type two error (beta)

Number of participant expected to be loss to follow up

SAMPLE SIZE (Continuous data)

$$N/group = \frac{1}{(1-f)} \times \frac{2\,s_c^2\,(z_\alpha + z_\beta)^2}{(x_c - x_t)^2}$$

s_c = standard deviation of the control group

x_c = mean of the control group

x_t = mean of the treated group (expected)

$\alpha = 0.05 \longrightarrow z_\alpha = 1.65$ (one sided) or 1.96 (two sided)

$\beta = 0.20 \longrightarrow z_\beta = 0.84$

f = No of subjects expected loss to follow up

TABLE of α and Z_α

α	Z_α 1 sided	Z_α 2 sided
0,1	1,28	1,65
0,05	1,65	1,96
0,025	1,96	2,24
0,01	2,33	2,58

TABLE of β and Z_β

β	Z_β	Power
0,50	0,00	0,50
0,40	0,25	0,60
0,30	0,53	0,70
0,20	0,84	0,80
0,15	1,03	0,85
0,10	1,28	0,90
0,05	1,65	0,95
0,025	1,98	0,975
0,01	2,33	0,99

SAMPLE SIZE (Exp. Nominal. data)

A study is planned to find out whether combination of clavulanic acid and amoxicillin has a greater cure rate compared with amoxicillin alone in the treatment of acute gonorrheal urethritis. Literature review shows that 85% of acute gonorrheal urethritis can be cured by the administration of 500 mg amoxicillin for 5 days. Suppose that the addition of clavulanic acid will increase the cure rate to 95%, and the investigator want to be sure that 95% of the difference can be detected with the power of the study as high as 0.8, how many participants have to be recruited when about 10% of the participants are anticipated to be loss to follow up?.

SAMPLE SIZE (Exp, Nominal data)

$$\text{N/group} = \frac{1}{(1- 0.1)} \times \frac{2x90 \times 10\ (1.65+ 0.84)^2}{(95- 85)^2} = 131$$

$p_1 = 95$ $p = 90$

$p_2 = 85$ $q = 10$

$\alpha = 0.05 \longrightarrow z_\alpha = 1.65$ (one sided)

$\beta = 0.20 \longrightarrow z_\beta = 0.84$

f = No of subjects expected loss to follow up

SAMPLE SIZE (Exp. continuous. data)

A new anti-anemia drug, is claimed to be more superior to the conventional one, ferrous sulfate. An RCT is designed to prove the claim. The previous study showed that ferrous sulfate can increase hemoglobin level by 2.44 g/dL during three months period with the standard deviation 1.10. The new drug should be able to increase at least a quarter higher, or 0.61 mg/dL. If the investigator wants to detect at 95% level of confidence and the power of the study is as high as 0.8, how many participants have to be recruited when about 10% of the participants are anticipated to be loss to follow up?

SAMPLE SIZE (Continuous data)

$$N/group = \frac{1}{(1- 0.1)} \times \frac{2 \times Sc \ (Z\alpha+Z\beta)^2}{(Xc- Xt)^2} = 49$$

s_c = std dev control

x_c= mean control

x_t = mean treated (expected)

$\alpha = 0.05 \longrightarrow z_\alpha = 1.65$ (one sided)

$\beta = 0.20 \longrightarrow z_\beta = 0.84$

$f = 0.1$

SAMPLE SIZE (Continuous data)

$$\text{N/group} = \frac{1}{(1- 0.1)} \times \frac{2 \times 1.1^2 \ (1.65+ 0.84)^2}{(2.44- 3.05)^2} = 49$$

$s_c = 1.10$

$x_c = 2.44$

$x_t = 3.05$ (expected)

$\alpha = 0.05 \longrightarrow z_\alpha = 1.65$ (one sided)

$\beta = 0.20 \longrightarrow z_\beta = 0.84$

$f = 0.1$

RCT (Analysis: Comparability, discrete data

	Treated	Control	P value *)
Education Low High	 a b	 c d	p1
Sex Male Female	 a b	 c d	p2

*) Computed with Chi square

RCT (Analysis: Comparability, continuous data)

	Treated Mean ± SD	Control Mean ± SD	P value*)
Age (years)	30.24 5.97	27.29 7.41	p1
Hb level (g/dL)	14.56 4.55	12.21 3.66	p2
Cholesterol (mg/dL)	269.23 16.44	178.89 25,34	p3

***) Computed with t-test**

RCT (Analysis: Comparability, continuous data)

T-test

$$t = \frac{x_1 - x_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

Where:

x_1 = mean of the first group (treated)

x_2 = mean of the second group (control)

s_1 = standard deviation of the first group

s_2 = standard deviation of the second group

RCT- Analysis
(Two by to Table, Chi Square Test)

	Result (+)	Result (-)	Percent
Treated	a	b	a/(a+b)
Control	c	d	c/(c+d)

Computing the Chi square (X^2)

$$X^2 = \frac{\{|ad-bc|-N/2\}^2 \times N}{(a+b)\,(c+d)\,(a+c)(b+d)}$$

RCT- Analysis, Relative Risk

	Result (+)	Result (-)	Percent	RR (95%CL)
Treated	a	b	a/(a+b)	
Control	c	d	c/(c+d)	

Computing the Relative Risk and Confidence Limit

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

$$95\%CL = RR^{1 \pm \frac{1.96}{\sqrt{X^2}}}$$

Analysis of discrete data
Relative Risk

Variabel	Effect		Percent of effect yes	RR (95% CI)	P Value
	Yes	No			
Exposed	a	b	a/(a+b)	[a/(a+b)]/ [c/(c+d)]	-
Control	c	d	c/(c+d)	1	

Number Needed to Treat (NNT) and Number Needed to Harm (NNH)

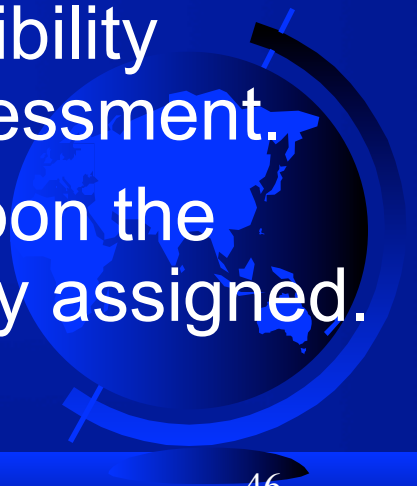
$$AR = \frac{a}{a+b} - \frac{c}{c+d}$$

$$NNT = \frac{1}{AR}$$

AR = Attributabel Risk, incidence of exposed – Incidence of control
NNH = the same formula as NNT

RANDOMIZED CLINICAL TRIAL-1 (Advantages)

1. Random allocation guarantees comparability and avoids bias
2. The most powerful design
3. Strong causal effect relationship can be detected
4. The investigator may actively determine type of intervention (dose variation, comparison between two drugs etc)
5. An RCT allows standardization of eligibility criteria, treatments, and outcome assessment.
6. Many statistical analysis are based upon the assumption that subjects are randomly assigned.



RANDOMIZED CLINICAL TRIAL-2 (Disadvantages)

1. Expensive and time consuming
2. Ethical issues may limit the use
3. Informed consent and ethical clearance must be obtained
4. It may be subject to a lack of representativeness. Participants volunteer to the study may be different from those whom the results are intended.

- Random assignment reduces confounding bias
- Concealment reduces selection bias
- Blinding reduces biased measurement