Clinical trials

Research Skill II

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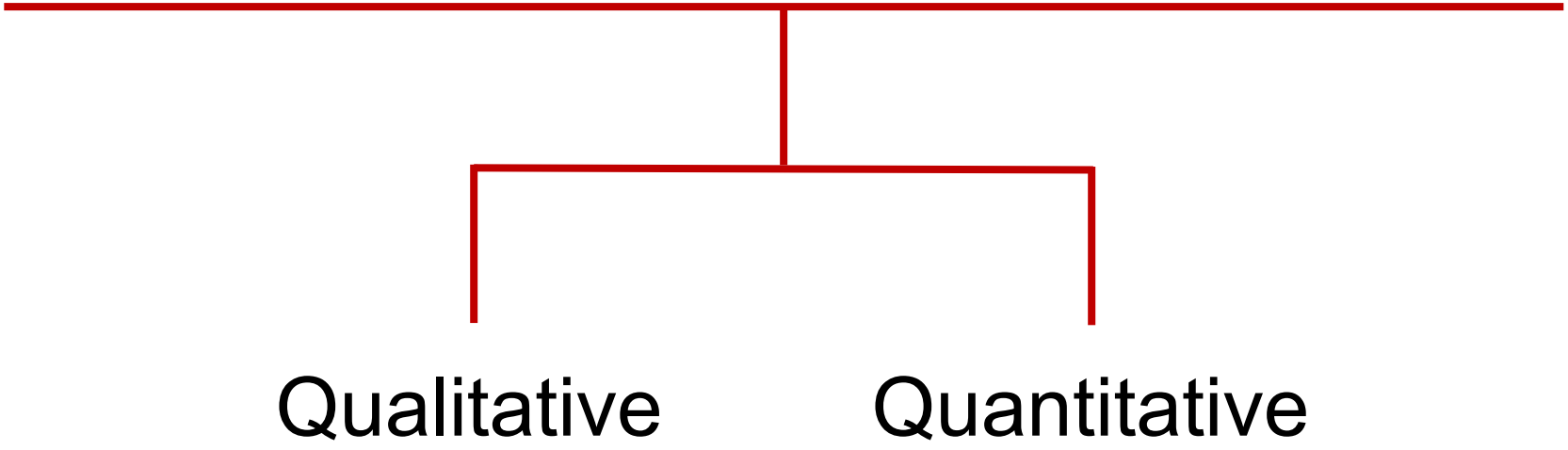
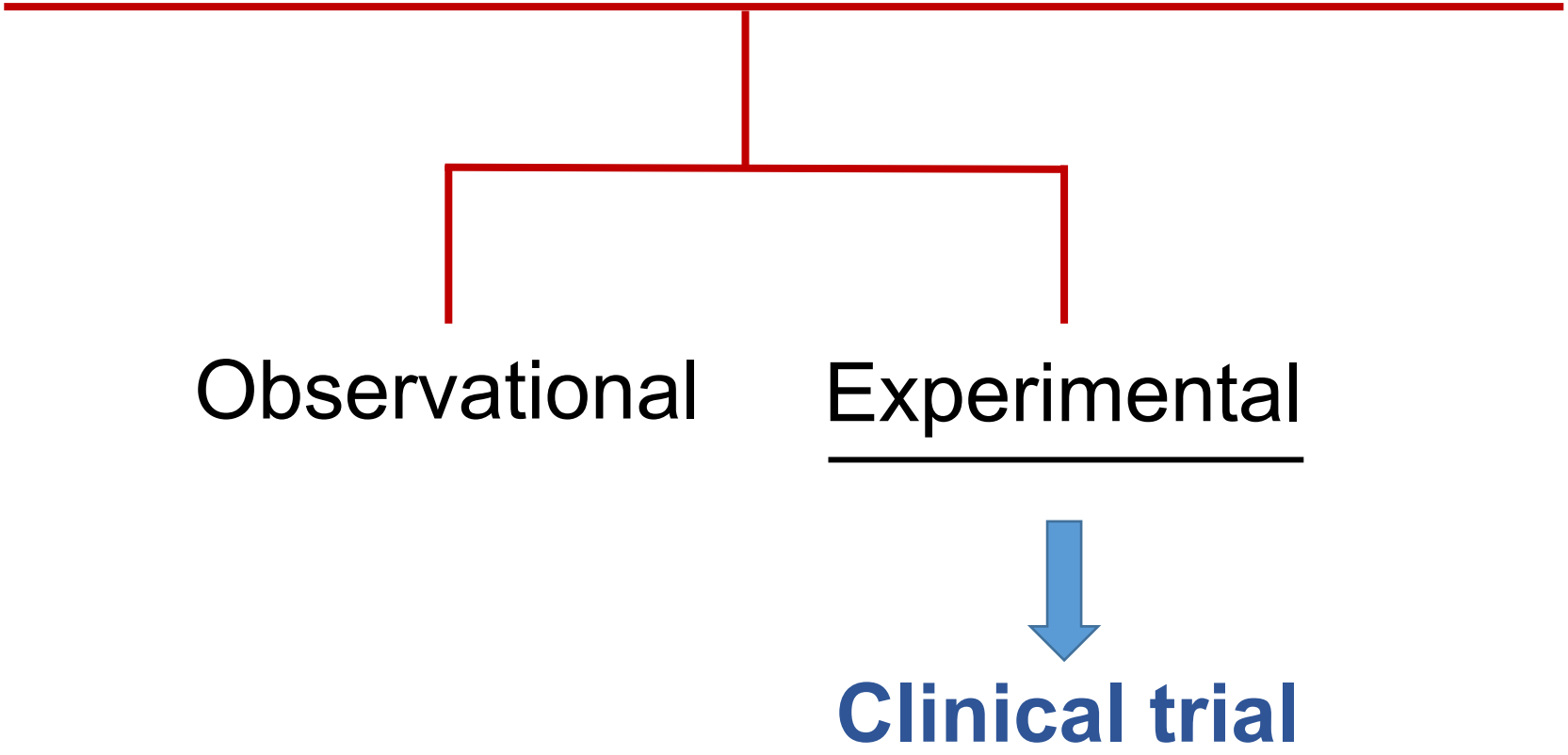
3 November 2020

Research design

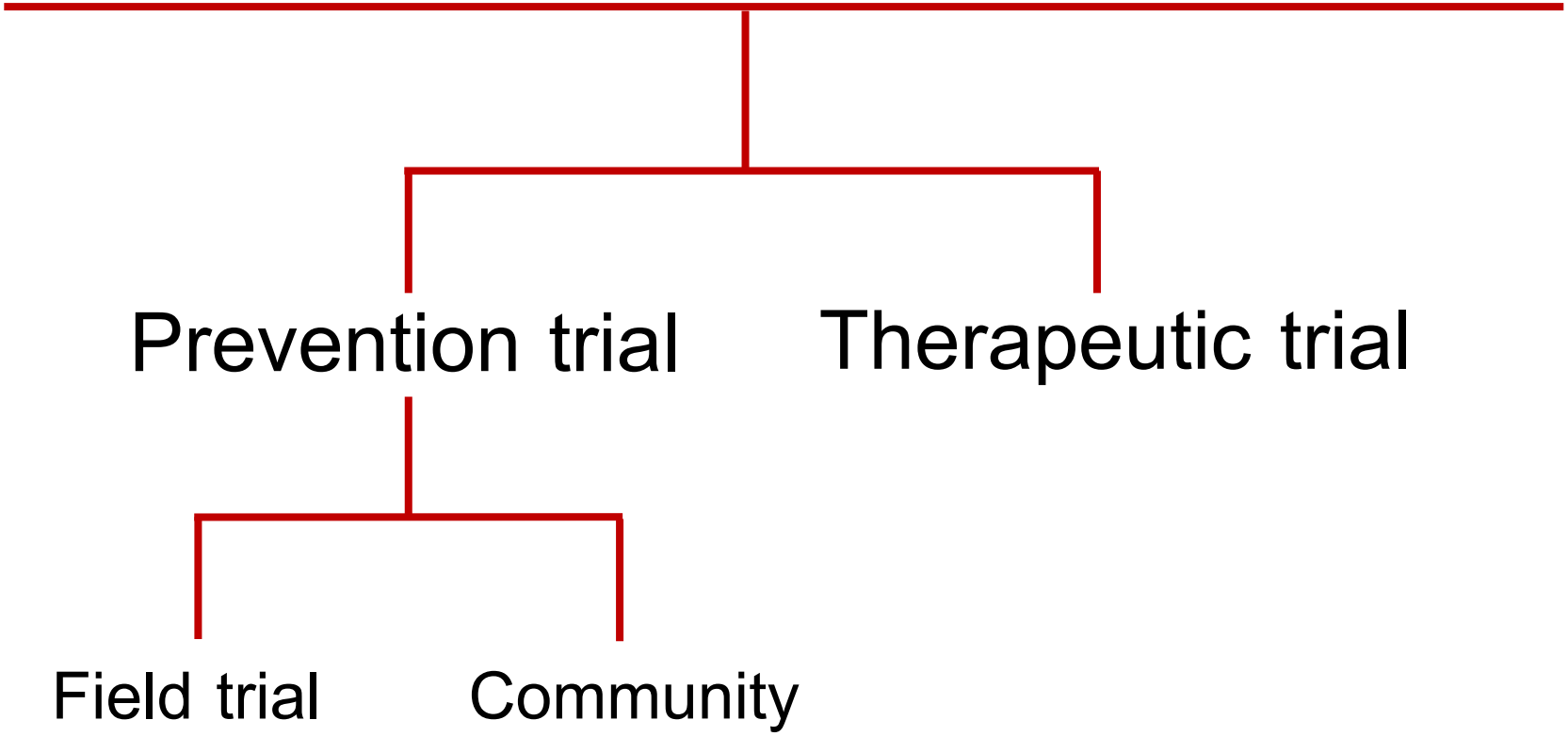


Quantitative research design



James Lind and Scurvy experiment (1747)

Clinical trial

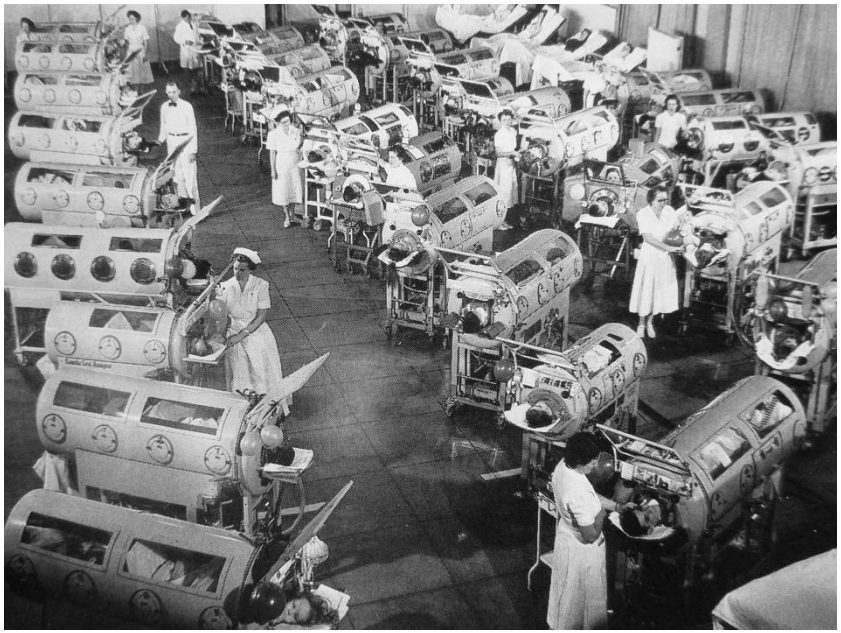


Prevention (primary prevention) trial

- Experiment to find if an intervention helps reduce risk of developing disease in healthy people
- **Field trial** (Individual prevention trial): unit of measurement is individual
- **Community prevention trial**: unit of measurement is group of people / community

Dr. Jonas Salk and Polio vaccine (1955)

Field trial



Patients in iron lungs during 1952 epidemic

Therapeutic (Secondary prevention) trial

- Experiment in patients who are getting sick with the disease of interest
- Intervention could be new medications, surgery, etc.
- To see if the intervention help improve clinical course or outcomes of treatment

Symbols use to explain the study designs

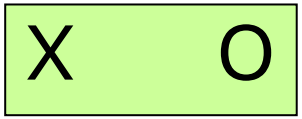
O = Observation, Measurement

X = Intervention

N = No randomization

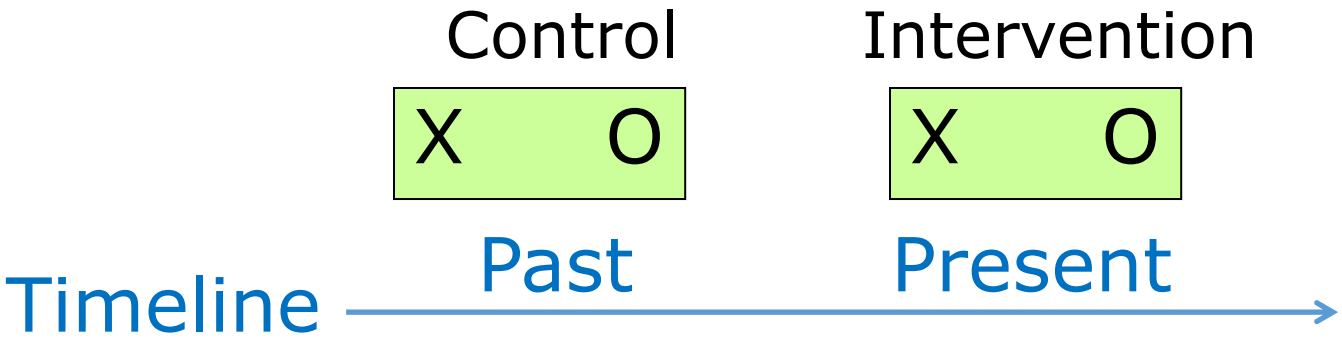
R = Randomization

Studies without comparison



- **No control group**
- **Hard to conclude whether the improvement is the result of the intervention**
- **Case study, case series**

Historical Controls



- **Use patients and treatment in the past as control**
- **Differences may cause from better data collection, other factors that has changed through time**
- **Can be used in uniformly fatal disease (e.g., Rabies)**

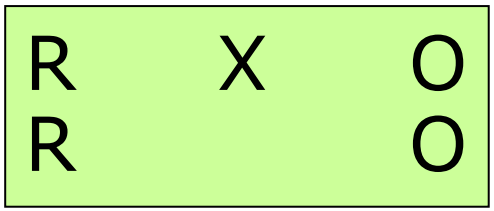
Non-randomized design

N	X	O
N		O

Quasi experiment

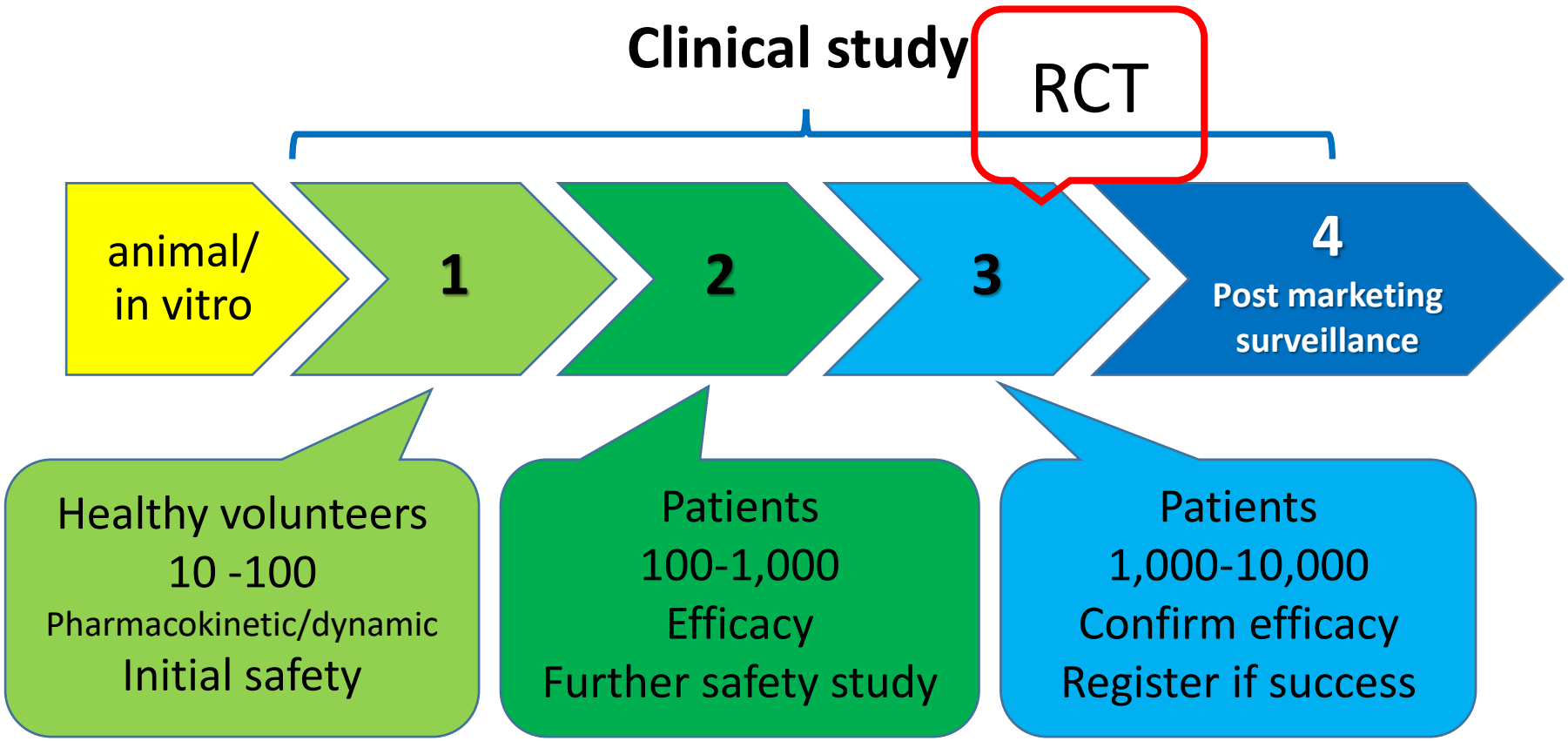
- **Has control group**
- **Non-randomized, assignment is predictable**
- **The results may be confounded by other factors.**

Randomized controlled trial (RCT)



- **Has control group**
- **Assignment is unpredictable (randomized)**
- **Confounding is negligible if random properly and sample size is large enough**

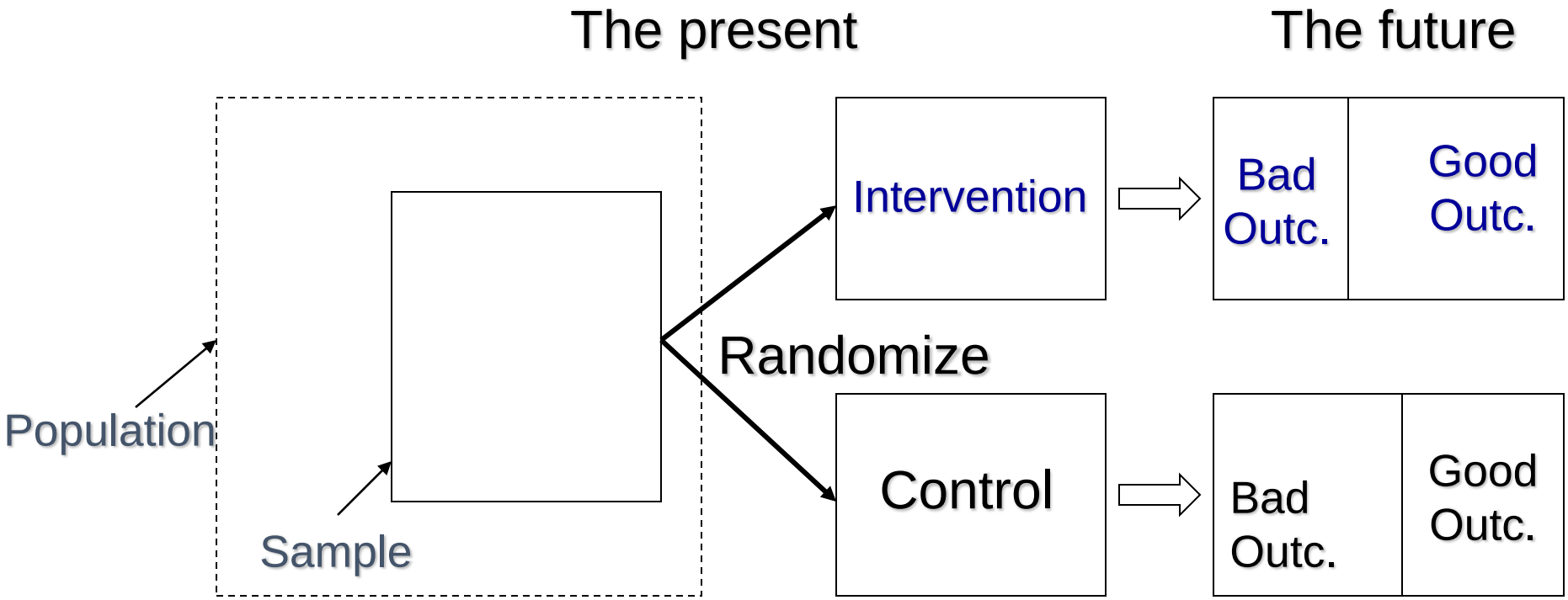
Phases of clinical trial



Randomized controlled trial (RCT)

- Current gold standard of clinical study design
- Most phase III clinical trial are RCTs.
- Best design to explain cause and effect between variables
- Characteristics
  - Randomization
  - Control group comparison
  - Blinding

Randomized controlled trial (RCT)



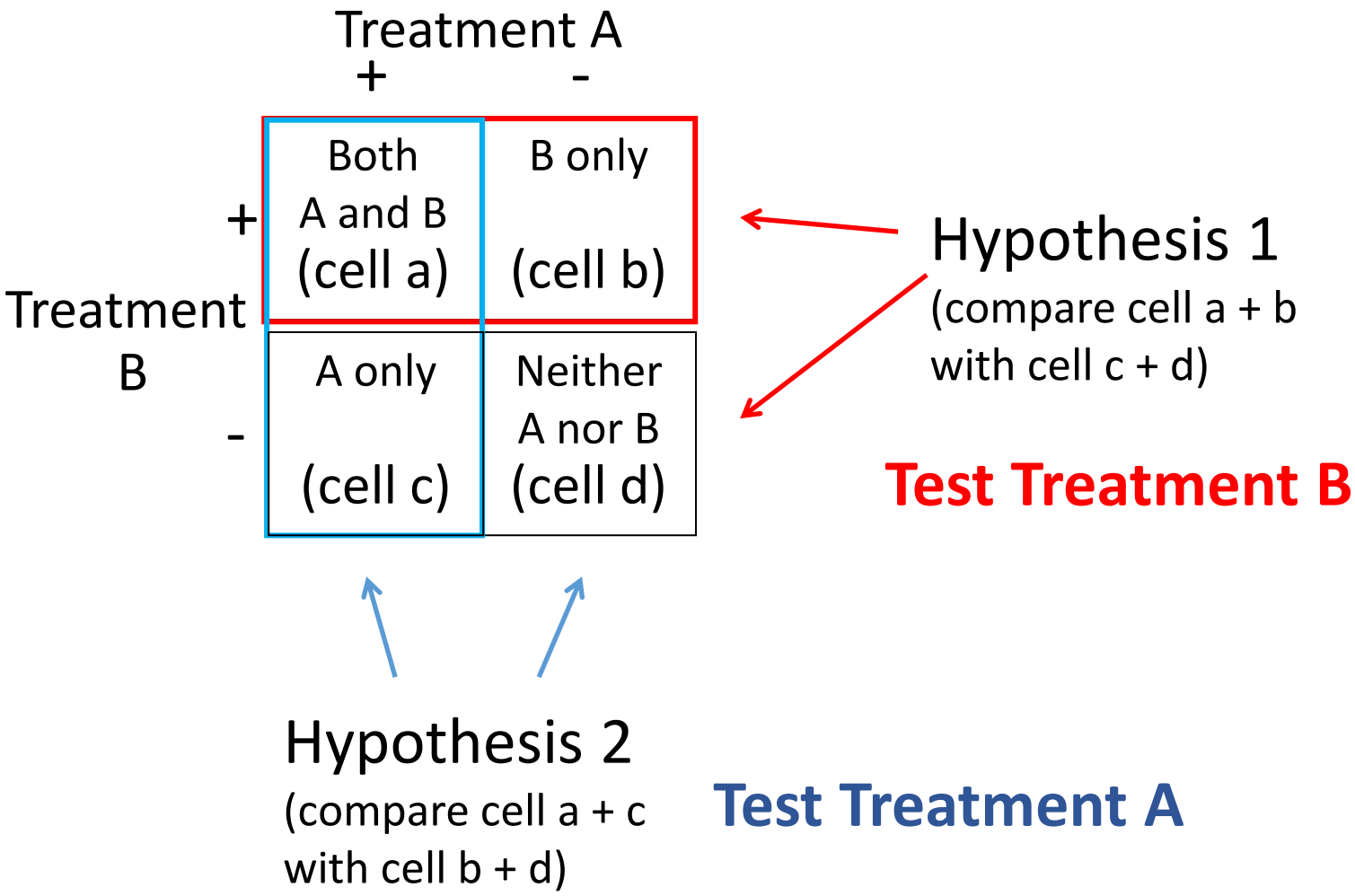
1. Select a sample from the population
2. Measure baseline variables
3. Randomize
4. Apply interventions (one should be a blinded placebo, if possible)
5. Follow up the cohorts
6. Measure outcome variables

Special designs: Factorial

		Treatment A +	Treatment A -
Treatment B	+	Both A and B (cell a)	B only (cell b)
	-	A only (cell c)	Neither A nor B (cell d)

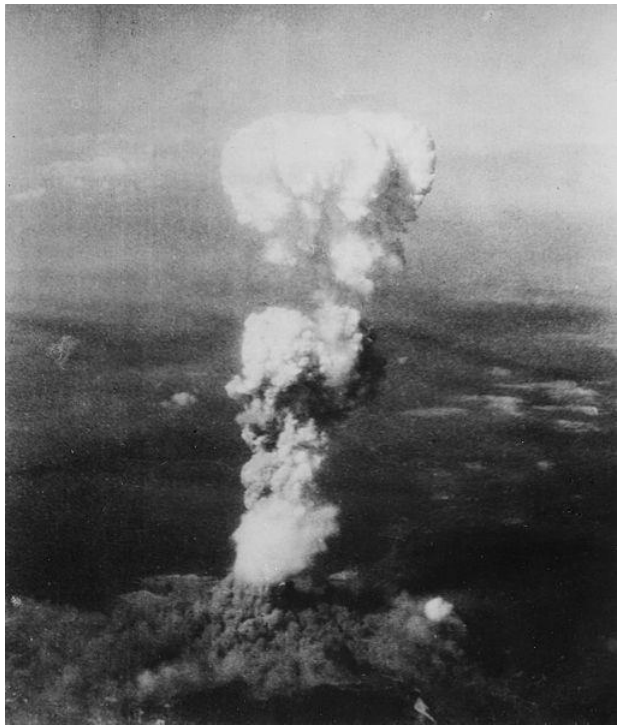
- Study two treatments in one study
- The mode of actions and outcomes must be independent.
- Effective and cost saving
- Burden of side effects in ‘cell a’

Special designs: Factorial

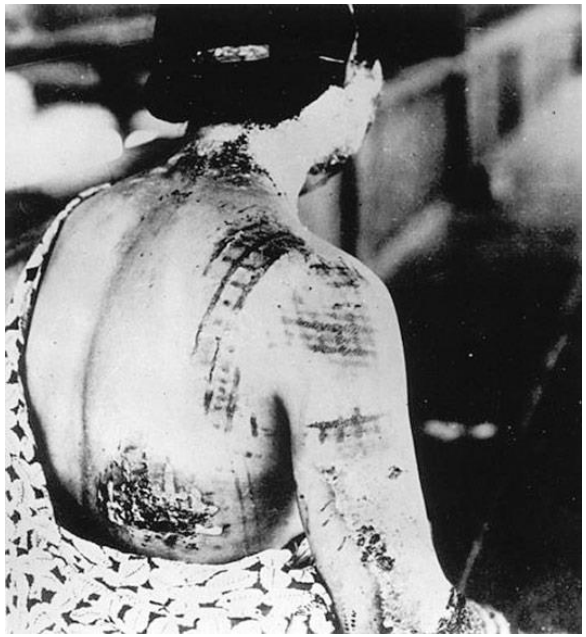


Special designs: Natural experiment

- The researcher does not assign the exposure.
- The intervention was done by the others.
- Most textbooks don’t define this as real experiment.



Clinical studies among atomic bomb victims

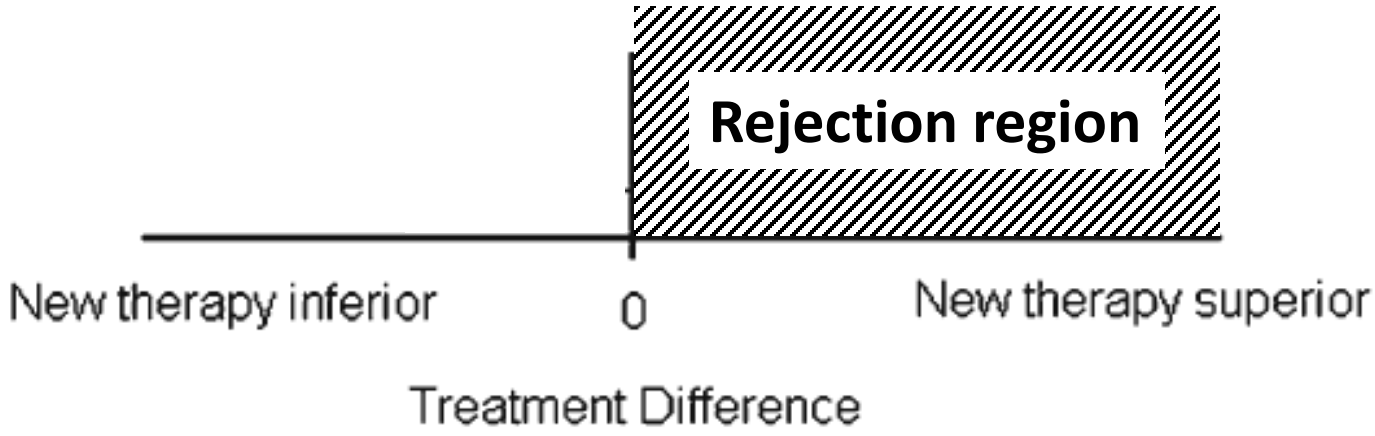


Hypothesis setting in clinical trials

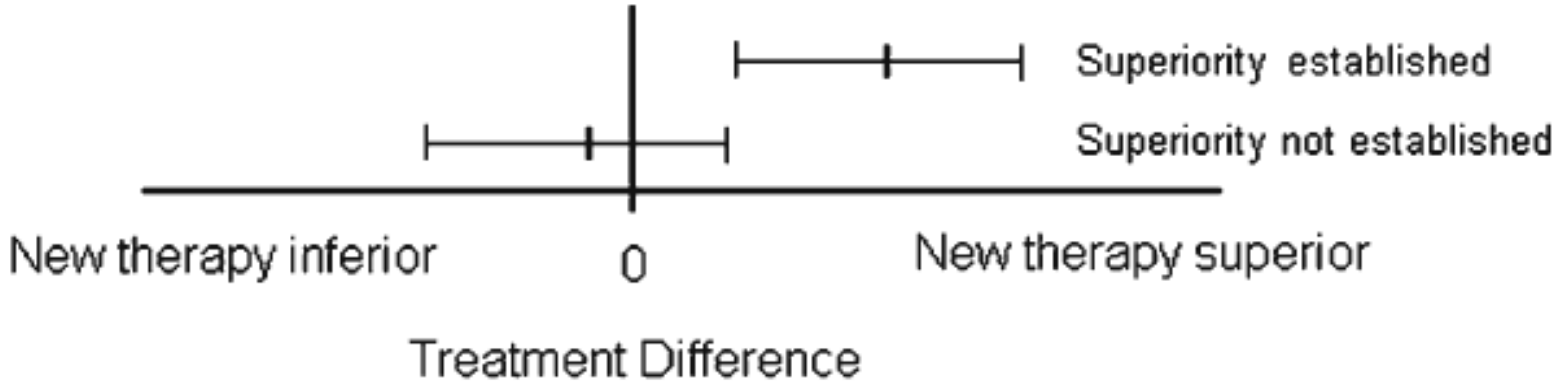
Type of study	Null hypotheses	Alternative hypothesis
Traditional comparative	There is no difference between the therapies	There is a difference between the therapies
Equivalence	The therapies are not equivalent	The new therapy is equivalent to current therapy
Noninferiority	The new therapy is inferior to the current therapy	The new therapy is not inferior to the current therapy

Walker E and Nowacki AS, 2010

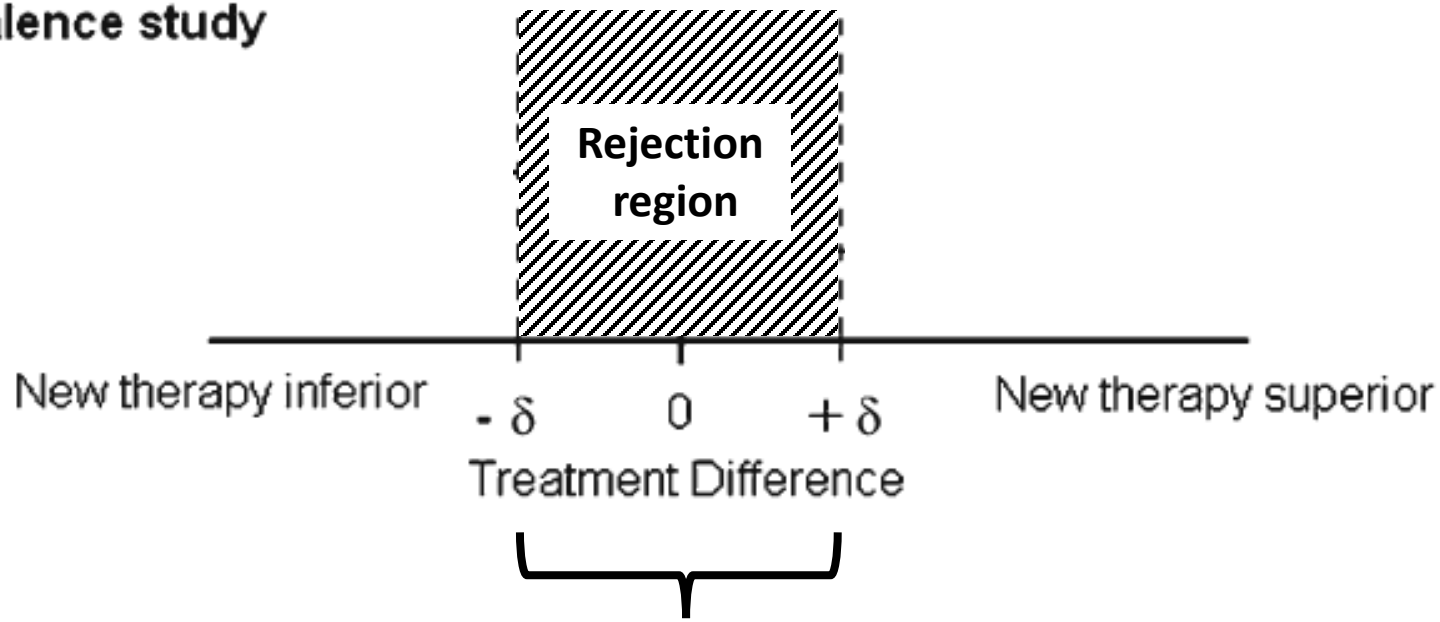
Traditional comparative study



Traditional comparative study

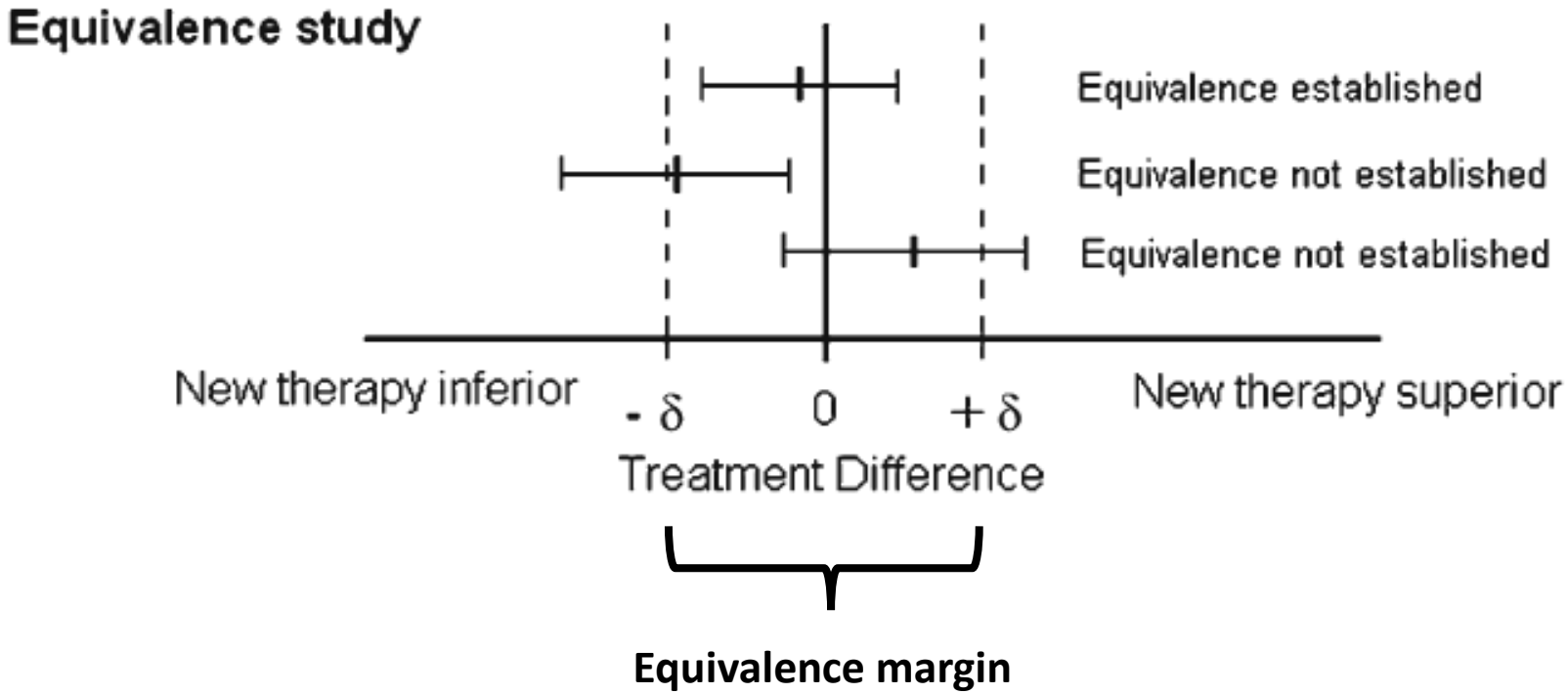


Equivalence study

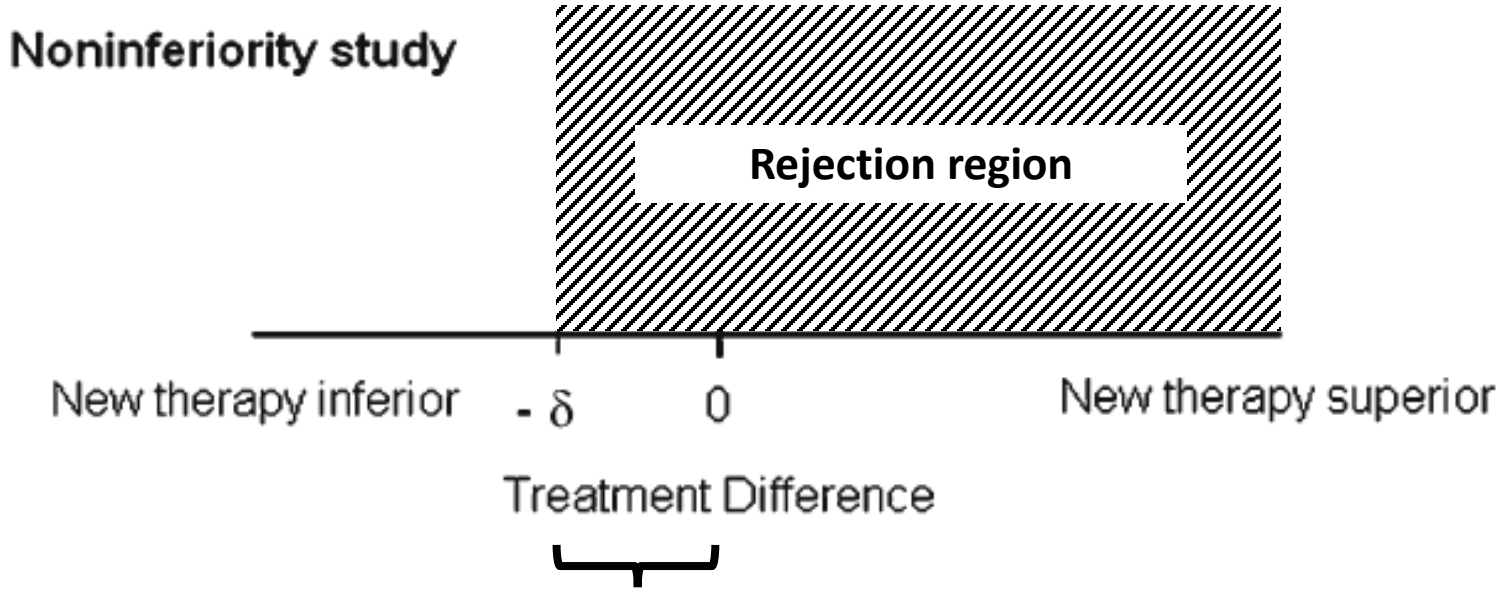


Equivalence margin

“A range of values for which the efficacies are “close enough” to be considered equivalent”



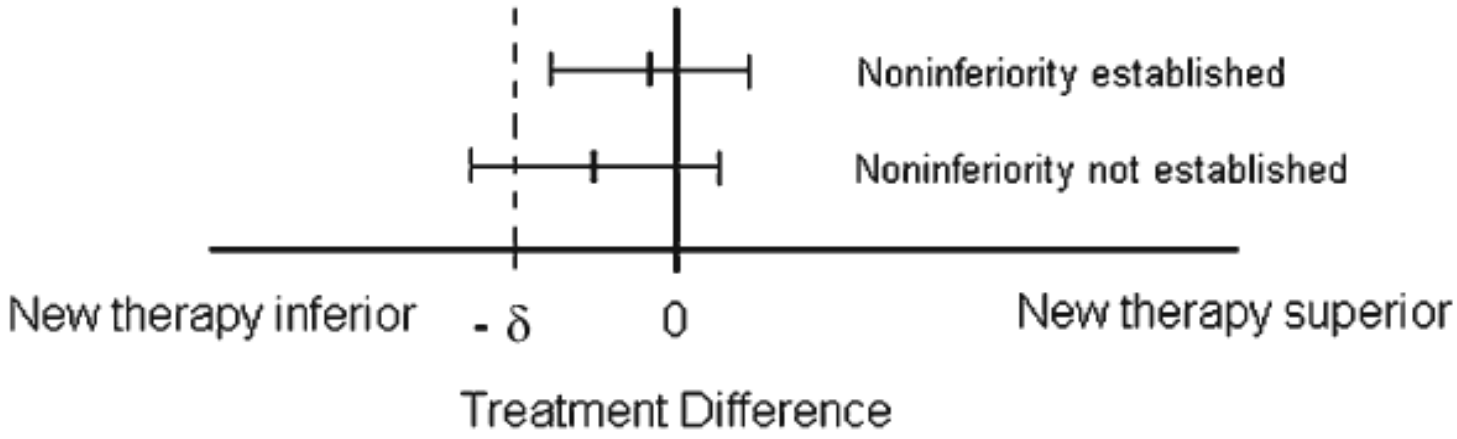
Equivalence margin



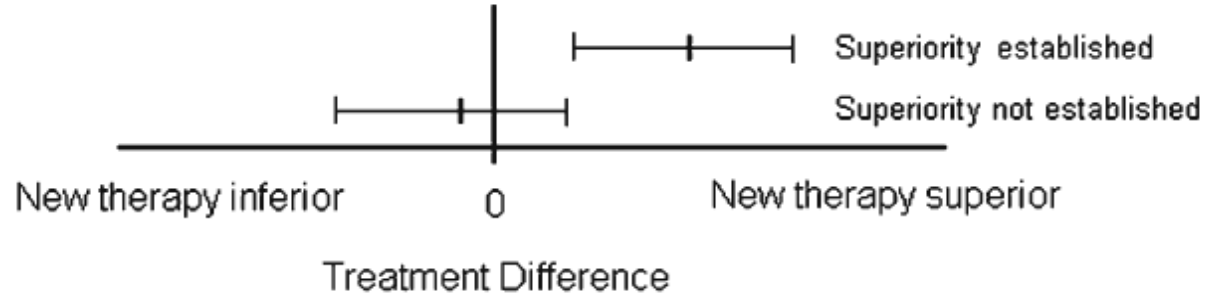
Noninferiority margin

“A range of values for which the efficacies are “close enough” to be considered noninferior”

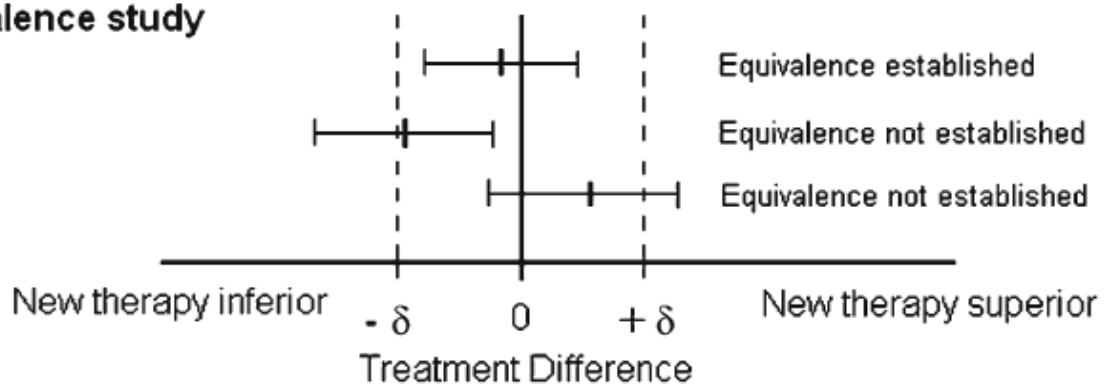
Noninferiority study



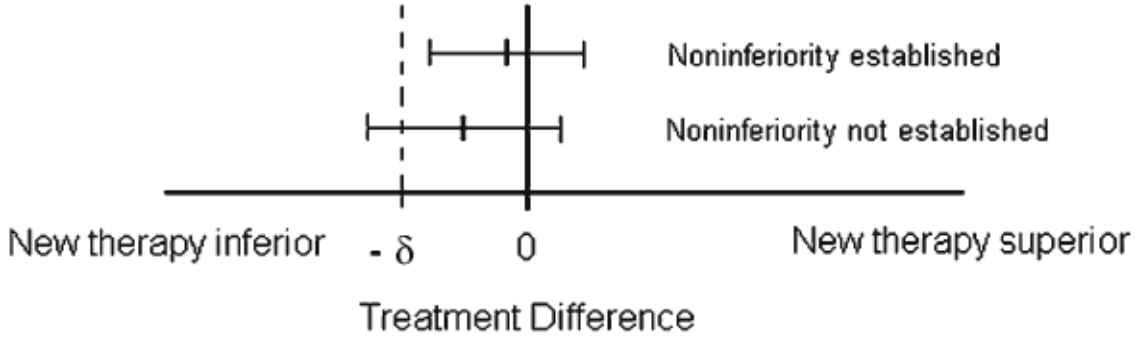
Traditional comparative study



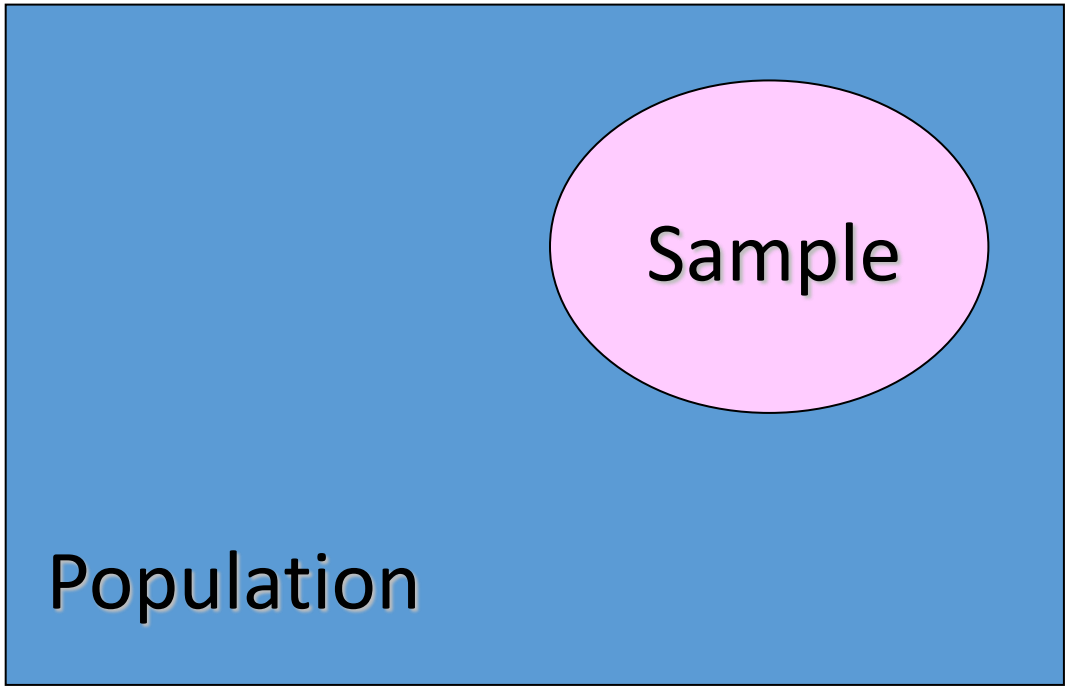
Equivalence study



Noninferiority study



Population and sample



Inferential statistics ⟺ Probability and randomness

Why sample size estimation is needed?

- Clinical research needs a sample size that “just large enough” to answer the research question reliably.
- It is worthless to conduct a study which is known from the outset that the sample size is too small the get the answer.
- Too large sample:
  - Excess risk from exposure to the intervention by unnecessary additional volunteers
  - Statistically significant but not clinically significant
- Safe time and budget

Factors affecting sample size

- **Effect size:** smallest difference or association which the investigator wants to detect
- **Type I error** (α error): probability of false positive
- **Type II error** (β error) probability of false negative
  - Statistical power (1 - β)
- **One-sided or Two-sided**
- **Variability**

Factors affecting sample size

- **Effect size:** smallest difference or association which the investigator wants to detect
  - Detecting small difference needs larger sample size
  - Detecting large difference needs smaller sample size
- Clinical significance should be considered when determining proper effect size

Measure of associations used to determine effect size in variety of study designs

Study designs	Measure of associations
Cross-sectional	Prevalence Ratio
Cohort	Incidence rate, Hazard ratio
Case-control	Odds Ratio
RCT	Efficacy (%), Differences

Estimating Effect size

- Clinically significance difference
- Results of previous studies
- Small pilot study

Example

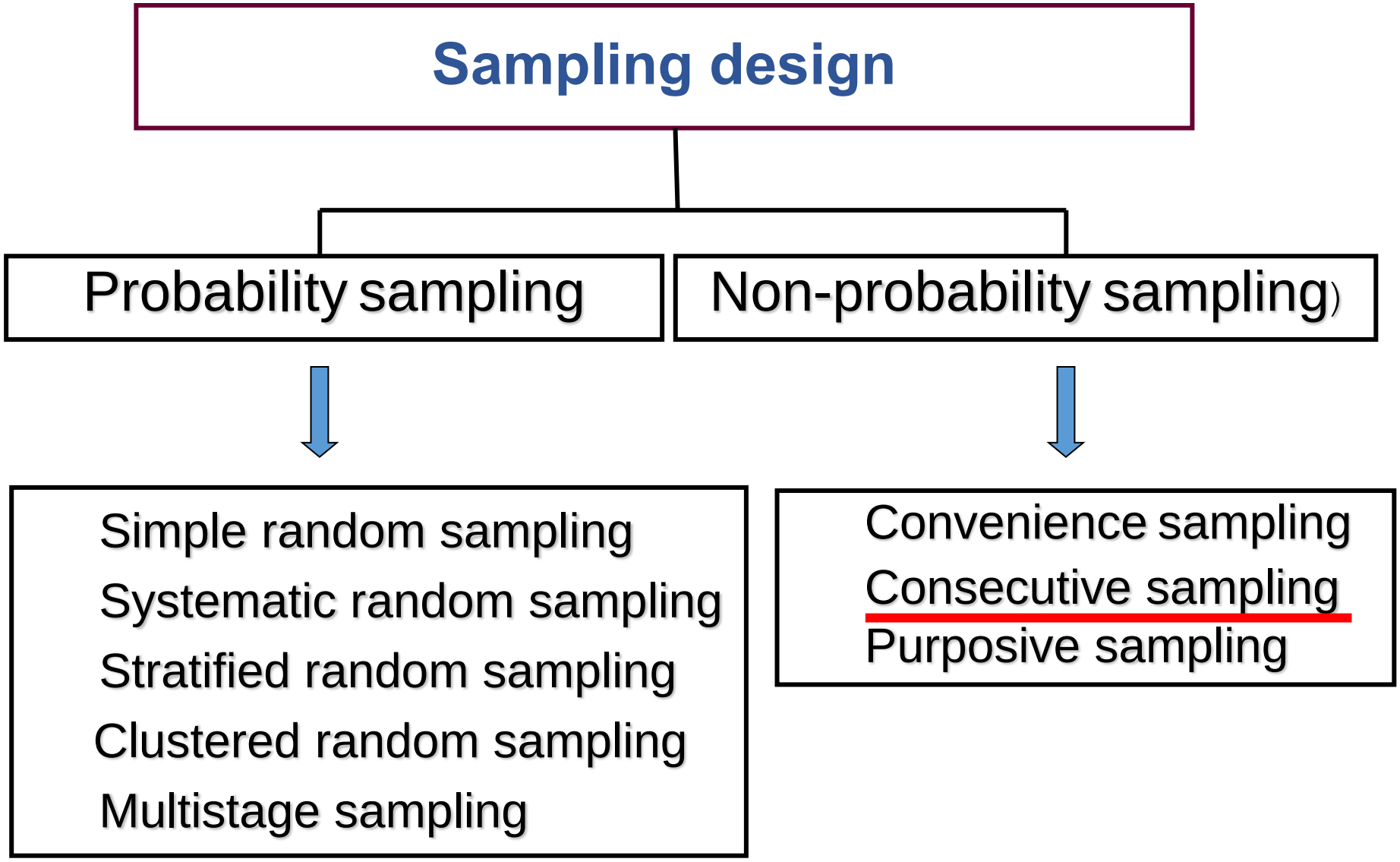
- Effect size
  - Efficacy of standard treatment = 40%
  - Expect new treatment to have efficacy of 60%
  - Effect size = 20%
- α = 0.05
- Statistical power = 0.80
- Two-sided test

TABLE 8-4. **Number of Patients Needed in Each Group to Detect Various Differences in Cure Rates; $\alpha = .05$; Power $(1 - \beta) = .80$ (Two-sided Test)**

Lower of the Two Cure Rates	DIFFERENCES IN CURE RATES BETWEEN THE TWO TREATMENT GROUPS													
	.05	.10	.15	.20	.25	.30	.35	.40	.45	.50	.55	.60	.65	.70
.05	420	130	69	44	36	31	23	20	17	14	13	11	10	8
.10	680	195	96	59	41	35	29	23	19	17	13	12	11	8
.15	910	250	120	71	48	39	31	25	20	17	15	12	11	9
.20	1,090	290	135	80	53	42	33	26	22	18	16	12	11	9
.25	1,250	330	150	88	57	44	35	28	22	18	16	12	11	—
.30	1,380	360	160	93	60	44	36	29	22	18	15	12	—	—
.35	1,470	370	170	96	61	44	36	28	22	17	13	—	—	—
.40	1,530	390	175	97	61	44	35	26	20	17	—	—	—	—
.45	1,560	390	175	96	60	42	33	25	19	—	—	—	—	—
.50	1,560	390	170	93	57	40	31	23	—	—	—	—	—	—

Adapted from Gehan E: Clinical trials in cancer research. Environ Health Perspect 32:31, 1979.

97 subjects for each group are needed

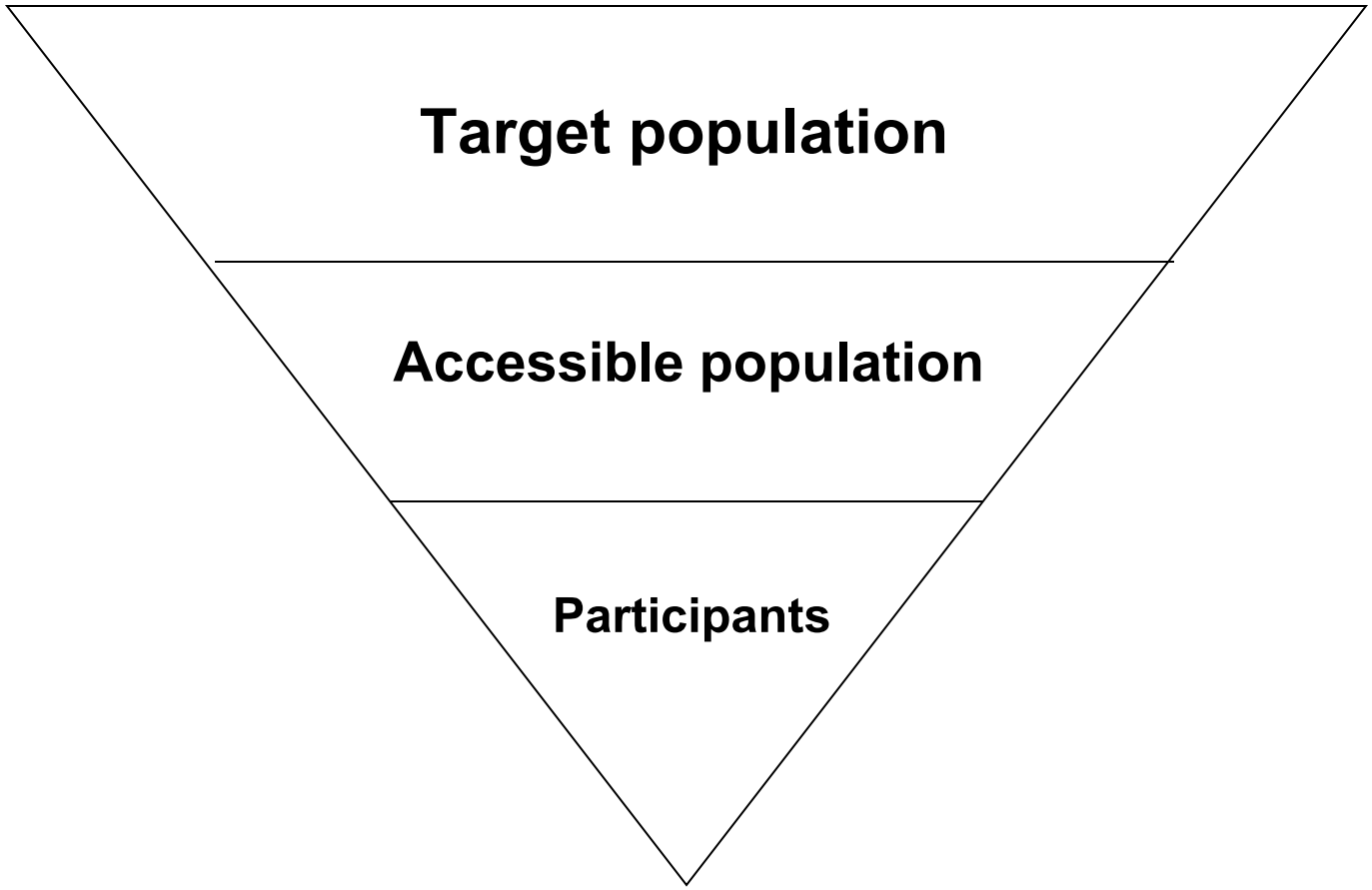

Sampling design
Probability sampling
Non-probability sampling)
Simple random sampling
Systematic random sampling
Stratified random sampling
Clustered random sampling
Multistage sampling
Convenience sampling
Consecutive sampling
Purposive sampling

Consecutive sampling

- The most frequently use sampling technique in clinical trials
- Study all potential participants who are eligible
- Potential participants are invited to join the study in chronological order.
- Stop recruiting subjects when the targeted sample size is reached, or time is up

Subject selection and exposure allocation

Population and sample



Eligibility criteria

- List of characteristics that the participants need to be met in order to be enrolled into the study
- For clinical trials, this helps ensure that all participants are similar, and the outcome are results of the intervention not from other factors
- Comprise of 2 parts
  - **Inclusion criteria**
  - **Exclusion criteria**

Eligibility criteria

- **Inclusion criteria:**
  - Specifications of the subjects
  - Characteristics of the group of people that the study would like to infer the results to
  - Determine target population and accessible population
- **Exclusion criteria:**
  - Comply with inclusion criteria but could not be enrolled into the study due to
    - Risk of invalidity
    - Incompleteness of the data
    - Potential harms to the subjects

RCT to study efficacy of circumcision in prevention of HIV infection

	Characteristics	Example
Inclusion criteria	**People who are fit to the research question**	
Target population	Demographics	Male, sexually active
	Clinical	HIV negative, uncircumcised
Accessible population	Geographic	Live in the study area
	Timing	No plan to move to other places within the study period
Exclusion criteria	**People who can't be enrolled into the study due to**	
	Tendency to loss to follow up	Drug addict
	Clinical	Hemophilia
	Ethical	Need to be circumcised

Randomization

- Assignment to be in intervention or in control arm of each subject must be by random (Random allocation)
- For consecutive sampling, the investigator must be able to predict the assignment of the next subject
- Is the most important characteristic of RCT
- Minimize confounding for the study
- Results of randomization usually be showed in table 1 of research article.

	Mode of delivery allocation	
	Caesarean section (n=188)	Vaginal delivery (n=220)
Mean (range) age (years)	28·5 (18–40)	28·1 (16–43)
Country		
Italy	137 (72·9%)	175 (79·5%)
France	27 (14·4%)	27 (12·3%)
Spain/other	24 (12·8%)	18 (8·2%)
Acquisition of HIV-1 infection		
Injection-drug user	65 (34·6%)	96 (43·6%)
Heterosexual	91 (48·4%)	100 (45·4%)
Other	9 (4·8%)	8 (3·6%)
Unknown	23 (12·2%)	16 (7·3%)
Parity		
None	121 (64·4%)	144 (65·4%)
One	45 (23·9%)	49 (22·3%)
Two or more	22 (11·7%)	24 (10·9%)
Unknown	0	3 (1·4%)
CD4 cell count (per mL)		
<200	17 (9·0%)	17 (7·7%)
200–499	88 (46·8%)	100 (45·4%)
⩾500	76 (40·4%)	92 (41·8%)
Unknown	7 (3·7%)	11 (5·0%)
Antiretroviral therapy before pregnancy		
No	147 (78·2%)	165 (75·0%)
Yes	40 (21·3%)	52 (23·6%)
Unknown	1 (0·5%)	3 (1·4%)
Antiretroviral therapy during pregnancy		
Yes	131 (69·7%)	128 (58·2%)
No	56 (29·8%)	91 (41·4%)
Unknown	1 (0·5%)	1 (0·4%)

Table 1: **Baseline characteristics of women at randomisation**

The European Mode of Delivery Collaboration, 1999

Randomization techniques

- **Simple randomization**
  - Assign subjects to each group purely randomly for every assignment
  - May produces imbalances between groups, especially small study
- **Block randomization**
  - Divide potential patients into *m* blocks of size *2n*, randomize each block such that *n* patients are allocated to A and n to B.
  - This will ensure a balance in sample size across groups over time
- **Stratified randomization**
  - Strata are constructed based on values of prognostic variables and a simple randomization is performed for each stratum.
  - To prevents imbalance between groups for known factors that influence prognosis or treatment outcomes.

Randomization techniques (continue)

- **Covariate adaptive randomization**
  - The probability of treatment assignment changes according to the specific covariates and previous assignments of participants.
  - Allocation of patients is determined by the current balance of the treatment groups to balance covariates between groups
- **Unequal randomization**
  - Unequal ratio of treatment and control, for example 2:1
  - Help save cost or maximize benefits of the intervention

Outcome assessment

Outcome variables, Clinical end points

- The investigator compares results of treatment or prevention between intervention and control group
- This is called clinical outcomes or clinical end points
- In case of more than one outcomes
  - The most important one is called **primary end point**
  - The other(s) is/are called **secondary end point(s)**

Types of outcomes

- Quantitative: data is figures such as birth weight, cholesterol
- Qualitative: dichotomous data, only 2 possible outcomes such as death/alive, cure/not cure
- Survival data: time to event

How to design and measure outcome properly?

- Use outcome that relevant to the research question
- Measurement and outcome should be objective than subjective
  - Objective: measure, count (laboratory results)
  - Subjective: feeling, attitude, (pain, perception)
- Outcome must be observed and measured continuously and completely.
- Reduce bias in outcome measurement to the minimum.

Surrogate outcome

- Alternate proxy outcome which is used instead of the ultimate outcome, especially when the real main clinical outcome need long time to occur or happen very rarely
- Example: the investigator used **intraocular pressure** as a surrogate outcome to study the efficacy of new eye drops in preventing recurrent glaucoma **instead of** waiting for **glaucoma** itself

Adverse outcome

- Negative effects of the intervention
- The investigator always have to plan the measurement to cover possible adverse outcomes.
- Any negative consequences happen to the subject, if severe enough, need to be investigated whether it is the result of the intervention.

Interim analysis

- Analysis of data that is conducted before data collection has been completed.
- If the results is statistically significant, the study can be stopped early.
- This help reduces cost and time.
- For ethical aspects, the subjects in control arm will have a chance to have access to new medication sooner.

Global HIV prevention study to stop early after ViiV Healthcare's long-acting injectable formulation of cabotegravir dosed every two months shows higher efficacy than daily oral PrEP

Published: May 18, 2020

May 18, 2020 06:17 UTC

- ***Interim analysis from HPTN 083 study shows investigational, long-acting injectable cabotegravir (CAB LA) administered every two months is 69% more effective than daily pills in preventing HIV acquisition***
- ***Participants who were in the daily oral emtricitabine/tenofovir***

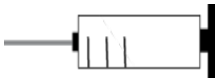
Blinding (Masking)

- People who get involve in the study do not know whether each subject are in which study arm
  - **Single-blind** the participant don't know
  - **Double-blind** both participants and investigators don't know
  - **Triple-blind** participants, investigators, and the person who analyze the results don't know
  - **Un-blind** un-code when the study is finished or in emergency

Placebo

- A simulated or otherwise medically ineffectual treatment for a disease or other medical condition intended to deceive the recipient
- Use to blind (mask) the participant from knowing that he/she is in the control arm
- Placebo can sometimes improve a patient's condition simply because the person has the expectation that it will be helpful. This is called “placebo effect”.

Cabotegravir injection



Cabotegravir placebo injection

Concerns in clinical trials

- **Compliance**
  - The participants have to comply with the regimens.
- **Co-interventions**
  - Application of additional therapeutic procedures to members of either the study group or control group.
- **Contamination**
  - Receipt of active intervention amongst participants in the control arm
- **Retention**
  - The study needs to keep high retention rate. Drop out of participants from the study will reduce the power of the study to detect the difference in results.

Retention of subjects

HPTN
HIV Prevention
Trials Network

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Network Performance Awards Winners Announced

HPTN 083
an HIV prevention clinical trial

Estimated Retention – Honorable Mention

CMU HIV Prevention CRS, Chiang Mai, Thailand

For an HPTN 083 study visit completion rate of 98.5% (2905/2949 expected study visits).

Efficacy, Effectiveness, and Efficiency

- **Efficacy:** Effect of intervention in ideal situations such as in research. The results of clinical trials are considered as efficacy
- **Effectiveness:** Effect of intervention in real life situations such as in clinics
- **Efficiency:** Economic aspects of intervention. Does it cost effective?

Types of analysis of clinical trial results

- Intention-to-treat analysis
- Per-protocol analysis

Intention-to-treat (ITT) analysis

- Analysis of the results of an experiment is based on the initial treatment assignment and not on the treatment eventually received.
- ITT analysis provides information about the potential effects of treatment policy.
- Keep the effect of randomization.
- Widely accepted as the standard way to analysis the results of controlled clinical trials

Per-protocol analysis

- Analysis only be restricted to the participants who fulfil the protocol in the terms of the eligibility, interventions, and outcome assessment.
- Shows biological effect of the intervention
- Does not show the practical value of the new treatment

Intention-to-treat analysis

Per-protocol analysis

	Infection status		Odds ratio (95% CI)
	Negative	Positive	
Allocated mode			
Vaginal delivery	179 (89·5%)	21 (10·5%)	1·0†
Caesarean section	167 (98·2%)	3 (1·8%)	0·2 (0·1–0·6)
Actual mode			
Vaginal delivery	150 (89·8%)	17 (10·2%)	1·0†
Caesarean section	196 (96·5%)	7 (3·5%)	0·4 (0·2–0·9)
Elective	165 (97·6%)	4 (2·4%))	0·3 (0·1–0·8)
Emergency	31 (91·2%)	3 (8·8%)	1·0 (0·3–3·7)

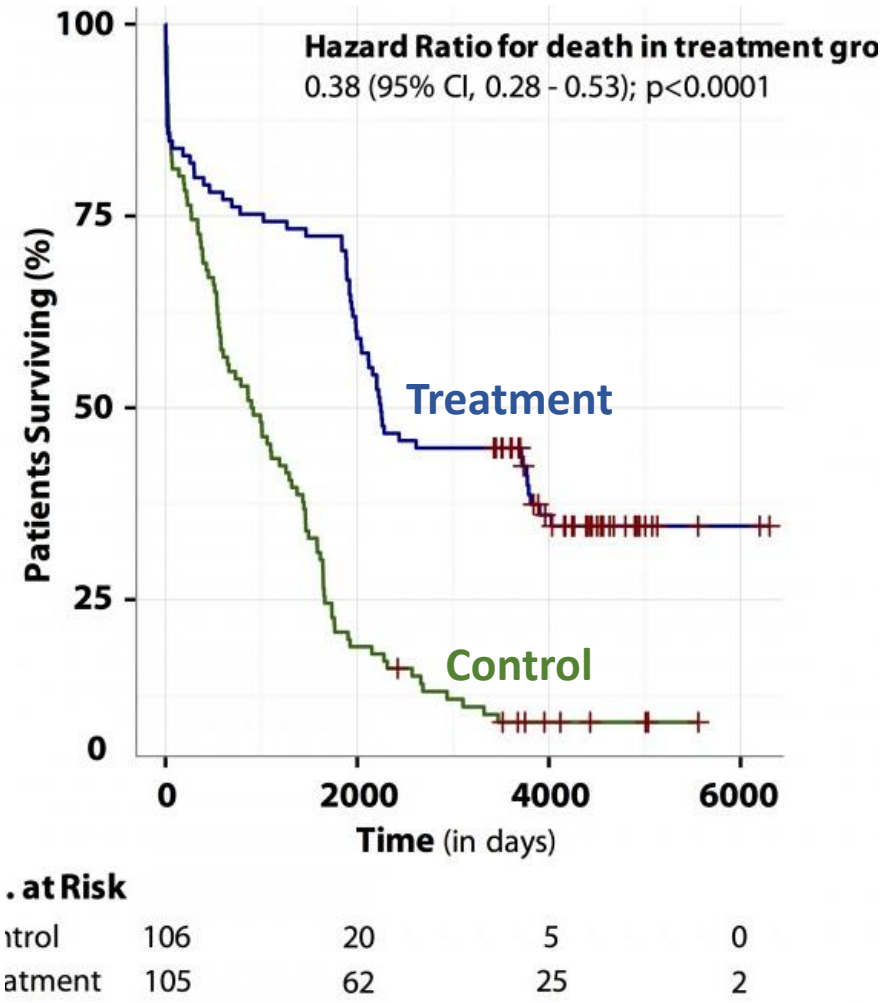
*Multivariate estimate including terms for calendar period at delivery and zidovudine use in pregnancy. †Reference category.

Table 2: **HIV-1 infection status of children according to allocated and actual mode of delivery**

Presentation of clinical trial results

- Multiplicative scale
  - Relative risk
  - Odds ratio
  - Hazard ratio
  - Others
- Additive scale
  - Absolute risk reduction
  - Relative risk reduction

Kaplan-Meier curve and Hazard ratio



(cochrane.org)

Treatment efficacy

- Typically present as relative risk reduction (RRR)
- How much the risk is reduced in the experimental group compared to a control group
- Example:

  Intensive insulin therapy in DM patients help reduce risk of developing diabetes retinopathy when compared to oral medication treatment

Calculating relative risk reduction (RRR)

- Experimental event rate (EER): EER is the experimental group event rate
  - 13% of DM patients receiving insulin injection developed diabetic retinopathy

- Control event rate (CER): CER is the control group event rate
  - 38% DM patients receiving oral medication developed diabetic retinopathy

Relative risk reduction (RRR)

$$|EER - CER| / CER = |13 - 38| / 38 = 66\%$$

Number needed to treat (NNT)

- The number of patients that would need to be treated to prevent one additional bad outcome
- The smaller the better

Absolute risk reduction (ARR)

- The absolute difference in outcome rates between the control and treatment groups

$$\begin{aligned} ARR &= |EER - CER| \\ &= |13 - 38| \\ &= 25\% \end{aligned}$$

Calculating Number needed to treat (NNT)

- = inverse of ARR
- ARR used has to be converted into probability first

$$\begin{aligned} NNT &= 1 / ARR \\ &= 1 / 0.25 \\ &= 4 \end{aligned}$$

Treatment risk

- How much the risk is reduced in the experimental group compared to a control group
- Relative risk increase (RRI)
- Example

  Increase of hypoglycemia in DM patients receiving intensive Insulin therapy compared to the patients receiving oral medication

Calculation relative risk increase (RRI)

- Experimental event rate (EER): EER is the experimental group event rate
  - 57% of patients receiving intensive insulin therapy had hypoglycemia
- Control event rate (CER): CER is the control group event rate
  - 23% of patients receiving oral medication had hypoglycemia

Relative risk increase (RRI)

$$|EER - CER| / CER = |0.57 - 0.23| / 0.23$$
$$= 148\%$$

Number needed to harm (NNH)

- The number of patients that would need to be treated to cause one additional adverse outcom
- The larger the better

Absolute risk increase (ARI)

- The absolute difference in adverse outcome rates between the control and treatment groups

$$
\begin{aligned}
\text{ARI} &= |\text{EER} - \text{CER}| \\
&= |0.57 - 0.23| \\
&= 0.34 \\
&= 34\%
\end{aligned}
$$

Calculation NNH

- = inverse of ARI
- ARI used has to be converted into probability first

NNH = 1 / 0.34
= 3

Limitations of Clinical trials

- Expensive
- Take long time
- Ethical issues
- Not suitable for rare disease (not enough subjects)
- Difficulty in studying
  - Rare events
  - Outcomes in distant future