ILSI India | K-FFIG

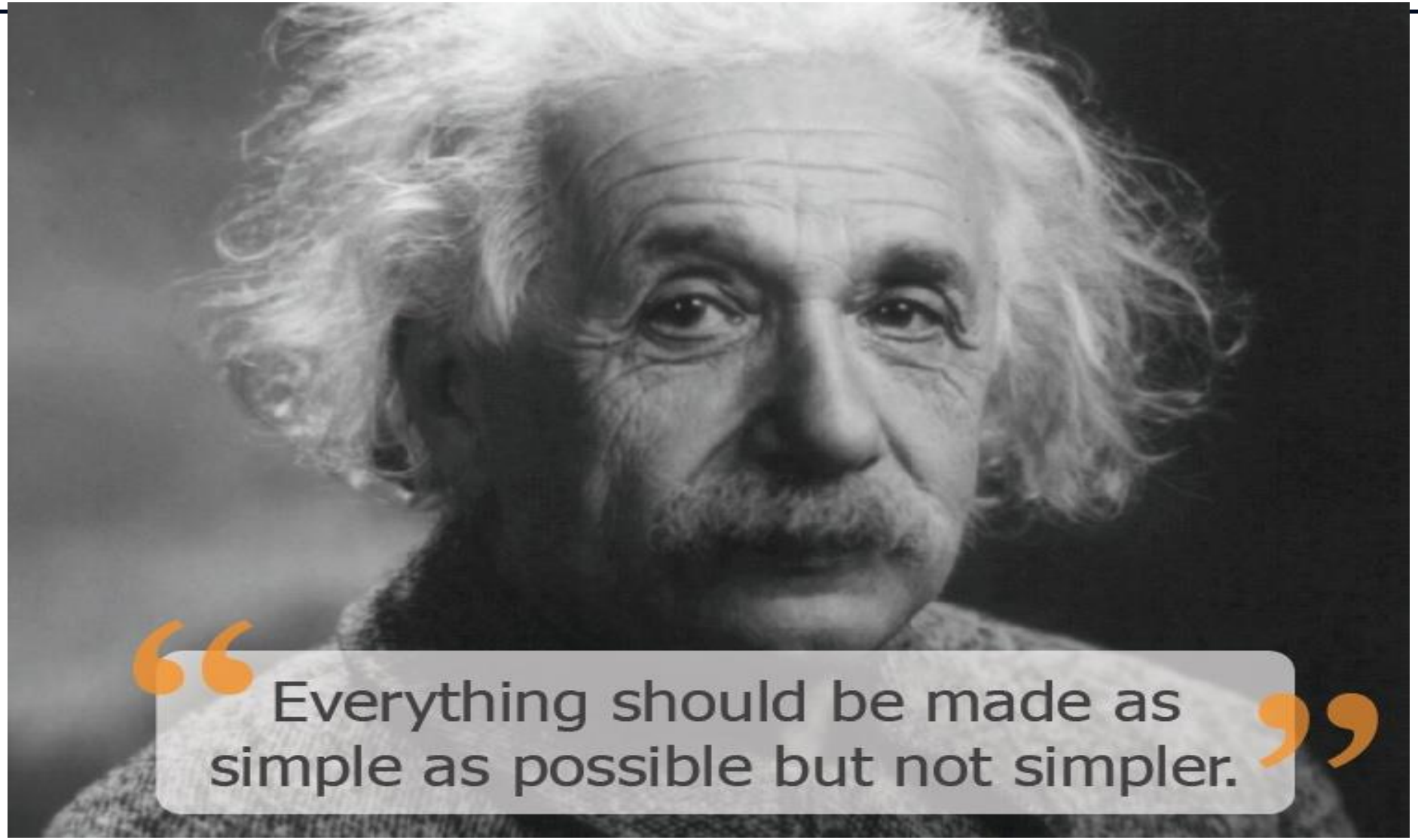
Seminar on
Clinical Evaluation/Intervention Studies for New Food & Food Ingredients

Current status and way forward

Study planning , Design, Methology, Statistical Considerations and registration process for conductiing Human Studies

by

Dr. M. Vishnu Vardhana Rao, *M.Sc.(stat),* PhD(stat), M.Tech(IT), FSMS, FTAS
Former Director, ICMR-NIMS
Fomer HOD AI cell, ICMR
New Delhi

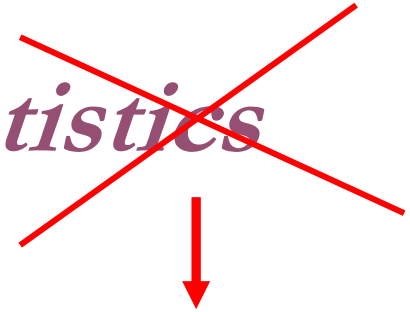

Everything should be made as simple as possible but not simpler.

Variability

- Patients vary.
- Physicians vary.
- Nurses vary.
- Hospitals vary.
- Measurements vary.
- Disease states vary.
- Immune response varies.
- Drug adherence varies……..

There are three kinds of lies:

Lies, Damned Lies and Statistics



Misused statistics

Benjamin Disraeli

THE LANCET

LONDON: SATURDAY, JANUARY 2, 1937

MATHEMATICS AND MEDICINE

STATISTICS are curious things. They afford one of the few examples in which the use, or abuse, of mathematical methods tends to induce a strong emotional reaction in non-mathematical minds. This is because statisticians apply, to problems in which we are interested, a technique which we do not understand. It is exasperating, when we have studied a problem by methods that we have spent laborious years in mastering, to find our conclusions questioned, and perhaps refuted, by someone who could not have made the observations himself. It requires more equanimity than most of us possess to acknowledge that the fault is in ourselves.

A health minister was intrigued by the statement in the report submitted by **a** statistician that 3.2 persons out of 1000 suffering from **a** disease died during the last year. He asked his private secretary, and administrator, how 3.2 persons can die. The secretary replied,

Sir, when a statistician says 3.2 persons died, he means that 3 persons actually died and ***2*** are at the point of death.

Systematic errors

You have a very serious disease. Of ten persons who get this disease only one survives. But do not worry. It is lucky you came to me, for I have recently had nine patients with this disease and they all died of it.

If clever enough you'll learn how to avoid such mistakes ...

Solving equation by one Blondie:

$$\frac{1}{n}\sin x = ?$$

$$\frac{1}{n}\sin x =$$

$$six = 6$$

The correct use of statistics is not just good for science — it is essential.

(Nature Journal editorial)

Treatment of King Charles II

At eight o'clock on Monday morning of February 2, 1685, King Charles was being shaved in his bedroom. With a sudden cry he fell backward and had a violent convulsion. He became unconscious, rallied once or twice, and after a few days died. Seventeenth-century autopsy records are far from complete, but one could hazard a guess that the king suffered with an embolism—that is, a floating blood clot which has plugged up an artery and deprived some portion of his brain of blood—or else his kidneys were diseased.

The Treat given was as follows:

- An emetic and purgative were administered, and soon after a second purgative.
- Was followed by an enema containing antimony, sacred bitters, rock salt, mallow leaves, violets, beet root, camomile flowers, fennel seeds, linseed, cinnamon, cardamom seed, saphron, cochineal, and aloes. The enema was repeated in two hours and a purgative given.
- The king's head was shaved and a blister raised on his scalp. A sneezing powder of hellebore root was administered, and also a powder of cowslip flowers "to strengthen his brain." The cathartics were repeated at frequent intervals and interspersed with a soothing drink composed of barley water, licorice and sweet almond. Likewise white wine, absinthe and anise were given .

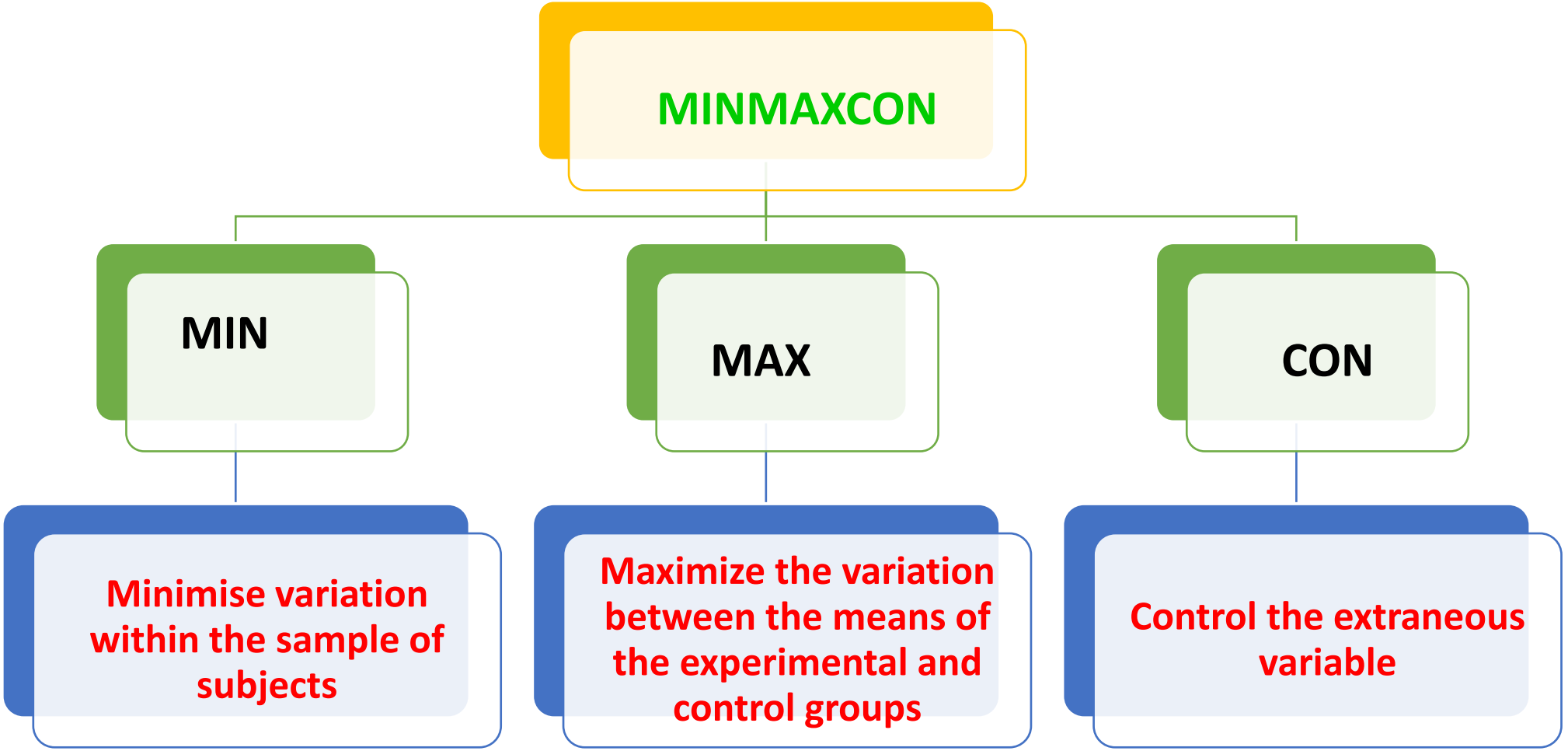
- For external treatment a plaster of Burgundy pitch and pigeon dung was applied to the feet. The bleeding and purging continued, and to the medicaments were added melon seeds, manna, slippery elm, black cherry water, an extract of flowers of lime, lily-of-the-valley, peony, lavender, and dissolved pearls Later came gentian root, nutmeg, quinine, and cloves.
- The king's condition did not improve, indeed it grew worse, and in the emergency forty drops of extract of human skull were administered to allay convulsions. A rallying dose of Raleigh's antidote was forced down the king's throat; this antidote contained an enormous number of herbs and animal extracts.
- Finally bezoar stone was given. Then says Dr.Scarburgh: "Alas! after an ill-fated night his serene majesty's strength seemed exhausted to such a degree that the whole assembly of physicians lost all hope and became despondent , and ammonia was forced down the throat of the dying king.

From this time and distance there are comical aspects about this observational study describing the "treatment" given to King Charles. It should be remembered that his physicians were doing their best according to the state of their knowledge. Our knowledge has advanced considerably, but it would be intellectual pride to assume that all modes of medical treatment in use today are necessarily beneficial. This example illustrates that there is a need for sound scientific development and verification in the biomedical sciences.

Why design studies

I. Formulating clear Research question
II. Setting up a procedure to select the population of interest
III. Selecting an appropriate sample
IV. Selecting relevant variables and appropriate instruments for measuring those variables
V. Assigning treatments to subjects in a systematic, unbaised fashion
VI. Planning for analysis of data

Designing of experiment



Basic requirements of a research problem

- A clearly stated problem should permit clear description of overall goals and specific aims.
- All hypotheses (structured ideas) should be testable.
- The problem should be amenable to data collection, and the methods selected should be those most efficient in testing the hypotheses.

WHAT IS A HYPOTHESIS?

A well-formulated hypothesis will be both quantifiable and testable, that is, involve measurable quantities or refer to items that may be assigned to mutually exclusive categories.

Eg. For males over 40 suffering from chronic hypertension, a 100- mg daily dose of this new drug lowers diastolic blood pressure an average of 10mmHg."

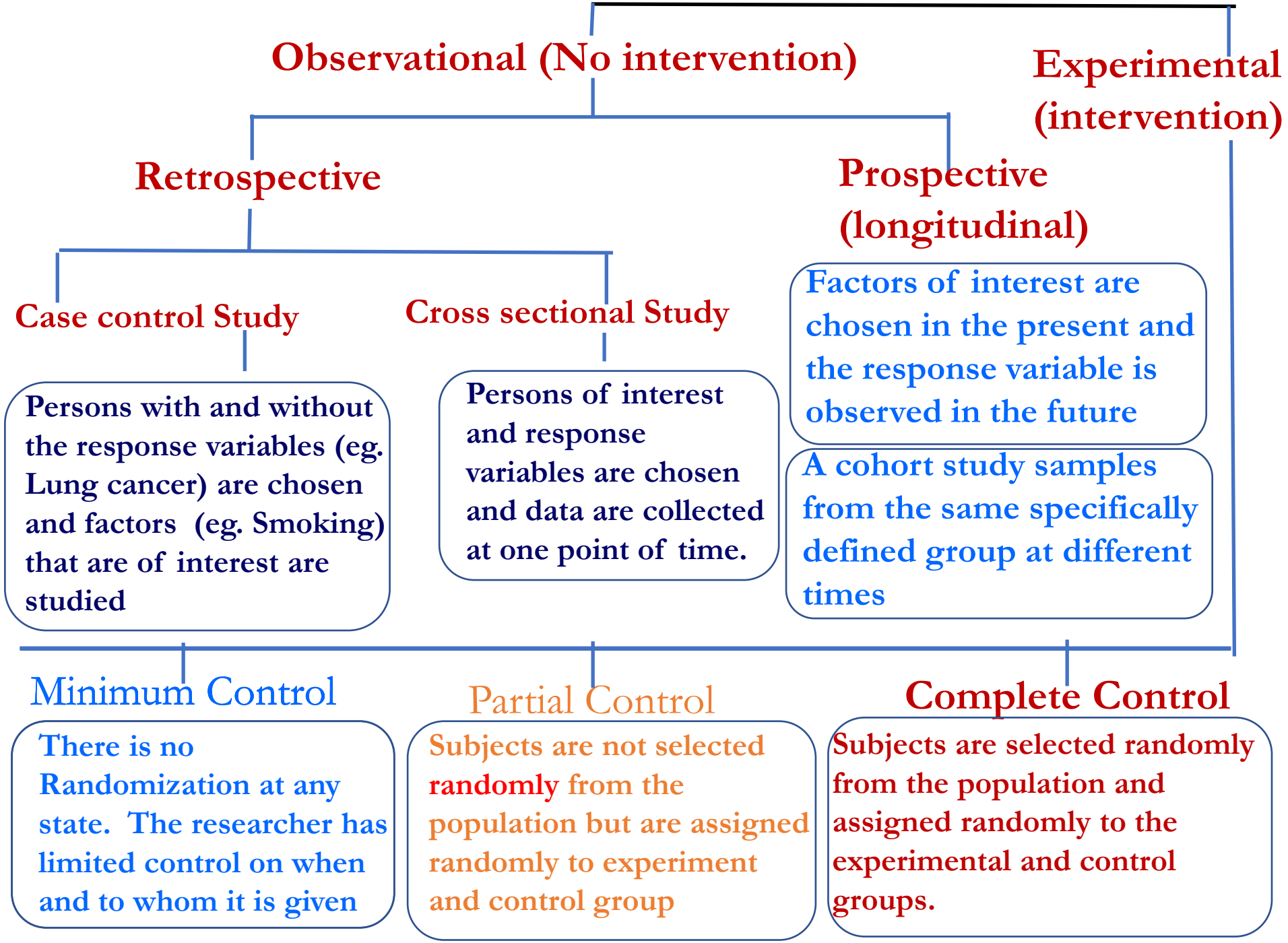
- From *Archives of Surgery* article, August 2000:
  - "**Hypothesis:** Surgeon-directed institutional peer review, associated with positive physician feedback, can decrease the morbidity and mortality rates associated with carotid endarterectomy."

Two type of investigations

Observational : In which we simply observe a phenomenon using an appropriate measuring instrument
e.g. a questionnaire to assess knowledge about AIDS, a check list to extract information from medical records, or a scale to determine weights of individuals.

Experimental: some particular variable is manipulated to determine the effect of the manipulation on a response variable

e.g., feeding different quantities of food (independent or treatment variable) to animals and determining the weight gain (response variable)


Observational (No intervention)
Experimental (intervention)
Retrospective
Prospective (longitudinal)
Case control Study
Cross sectional Study
Factors of interest are chosen in the present and the response variable is observed in the future
Persons with and without the response variables (eg. Lung cancer) are chosen and factors (eg. Smoking) that are of interest are studied
Persons of interest and response variables are chosen and data are collected at one point of time.
A cohort study samples from the same specifically defined group at different times
Minimum Control
Partial Control
Complete Control
There is no Randomization at any state. The researcher has limited control on when and to whom it is given
Subjects are not selected randomly from the population but are assigned randomly to experiment and control group
Subjects are selected randomly from the population and assigned randomly to the experimental and control groups.

OPEN ACCESS Freely available online PLOS MEDICINE

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies

Erik von Elm[1*], Douglas G. Altman[2], Matthias Egger[1,3], Stuart J. Pocock[4], Peter C. Gøtzsche[5], Jan P. Vandenbroucke[6] for the STROBE Initiative

CONSORT 2010 statement: extension to randomised pilot and feasibility trials

BMJ 2016; 355 doi: https://doi.org/10.1136/bmj.i5239 (Published 24 October 2016)Cite this as: *BMJ* 2016;355:i5239

TYPE OF STUDIES

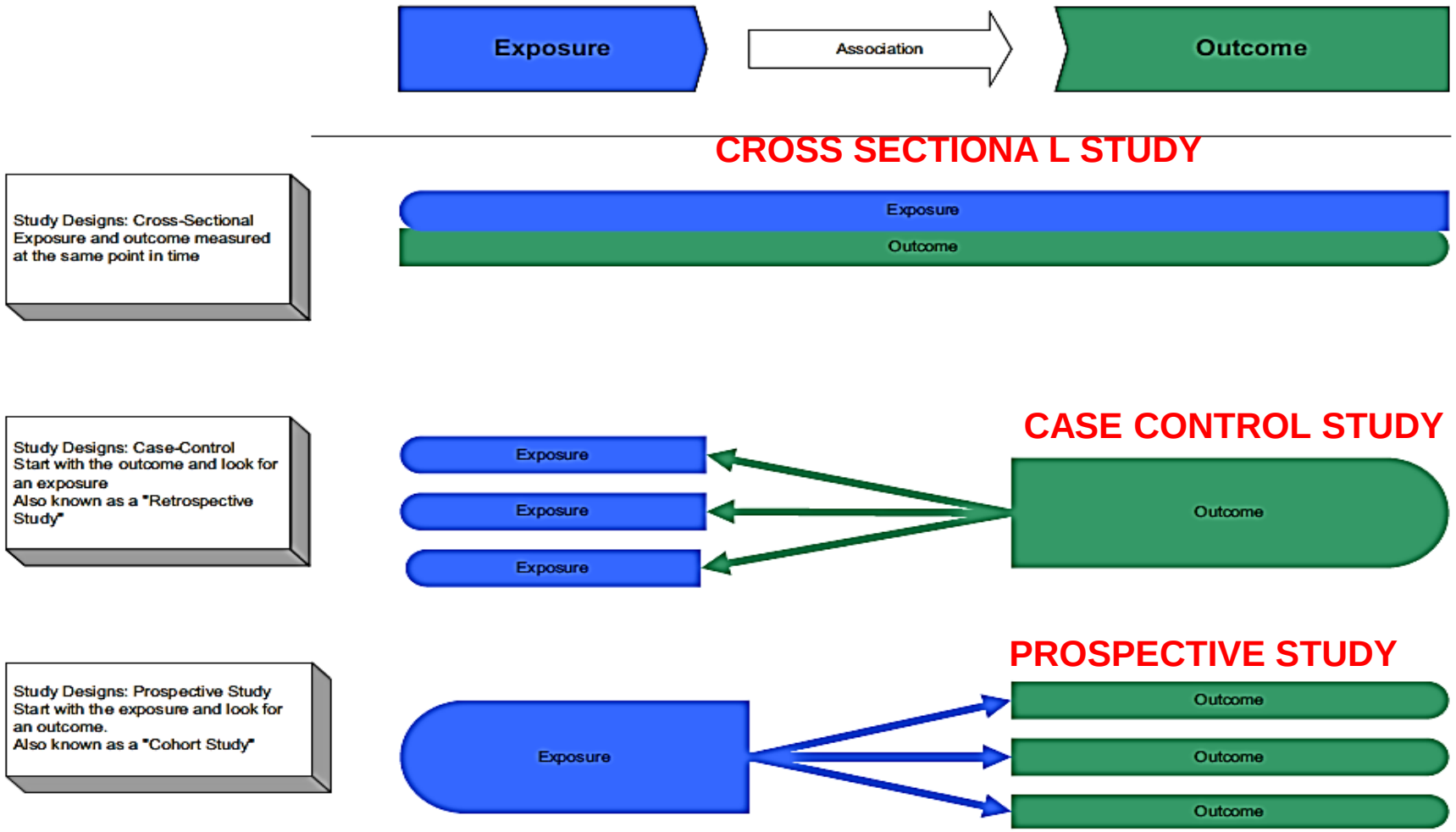
Observational

1. Correlational study
2. Case reports and case series
3. Cross sectional survey
4. Case-control study
5. Cohort study

Experimental

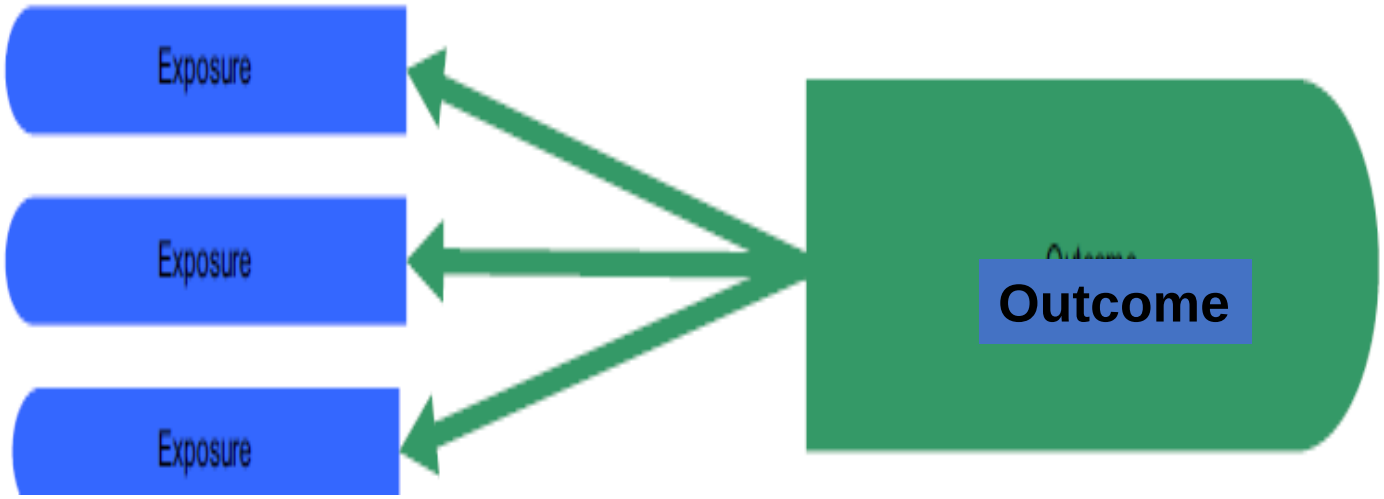
1. Community trials
2. Clinical trials – individuals

Schematic of Study Designs



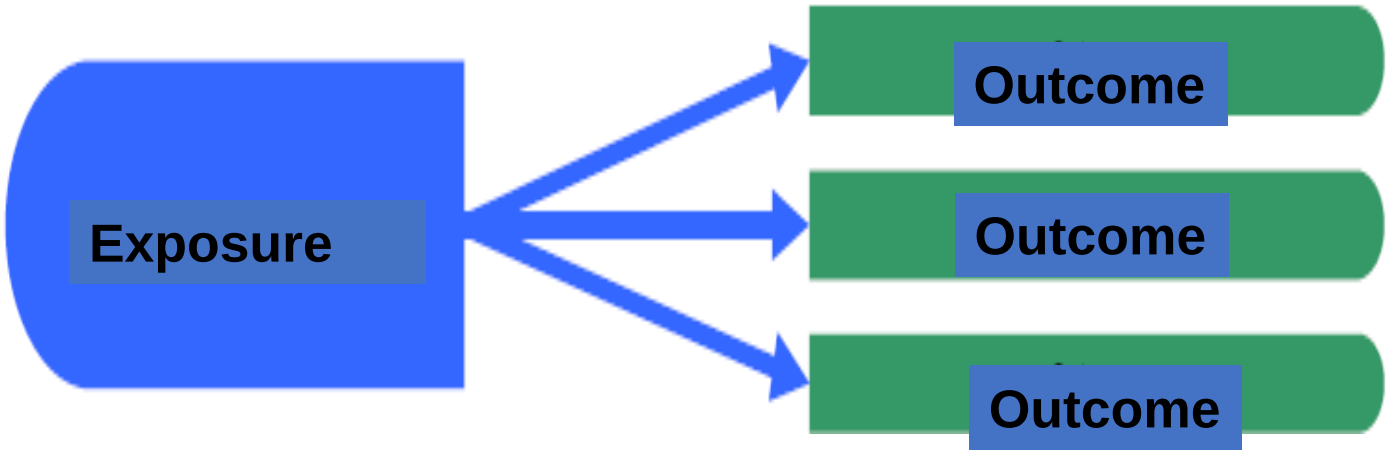
Case-control study

Study Designs: Case-Control
Start with the outcome and look for an exposure
Also known as a "Retrospective Study"

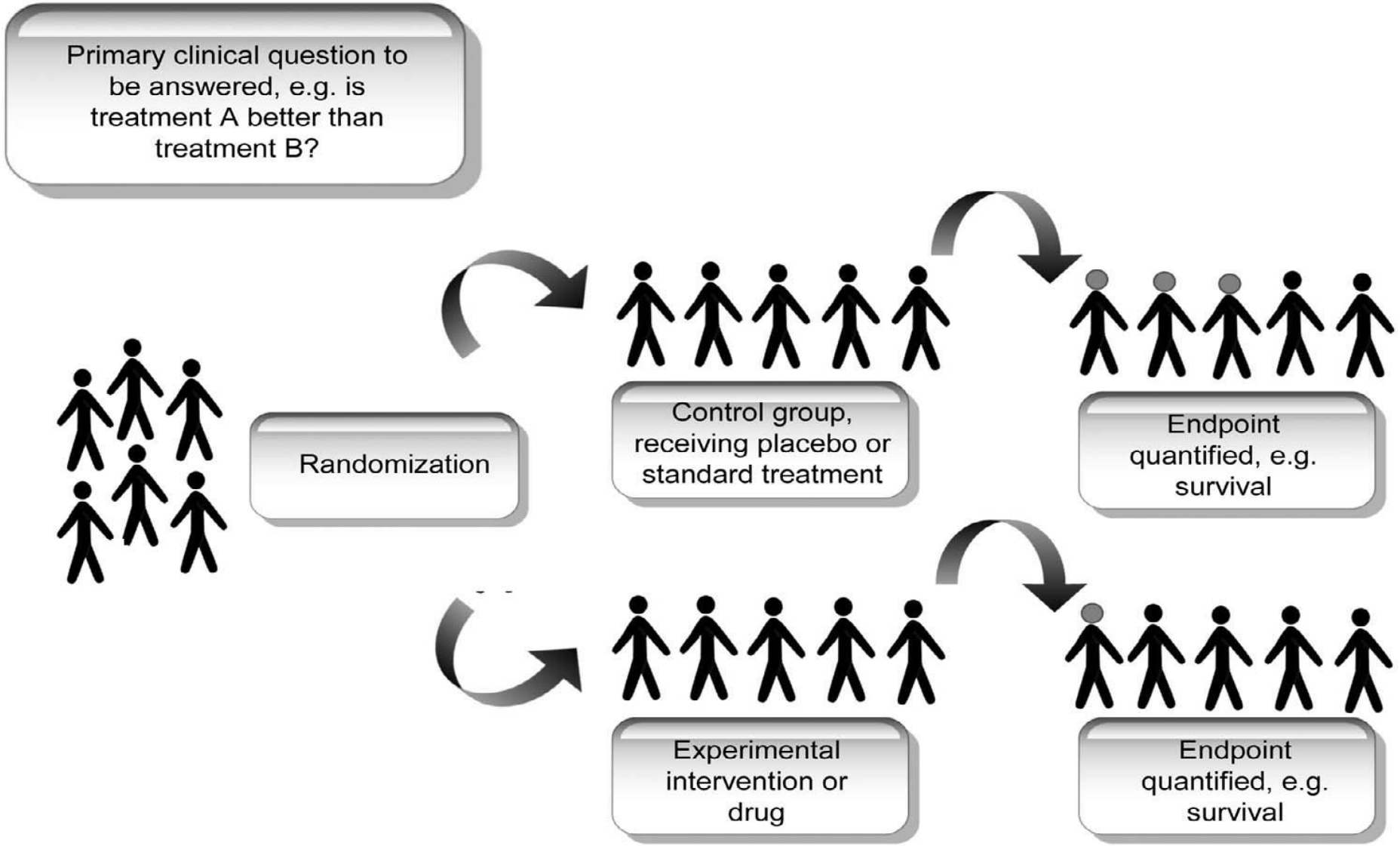


Cohort/prospective study

Study Designs: Prospective Study
Start with the exposure and look for an outcome.
Also known as a "Cohort Study"



RANDOMIZED CONTROLLED TRIALS



Case Study: The Problem

- Woman (a friend) asked me for advice regarding her current pregnancy
- History of neonatal death in her first pregnancy (due to prematurity and respiratory distress in the new-born child)
- Likelihood of premature delivery again
- Doctor's advice to try a short course of cortico-steroids to prevent neonatal death
- Will steroids help ?

The Problem: rephrased as an answerable question

The Question

Mothers at High Risk of Premature Delivery will be — **Population ?**

Short Course Of Corticosteroids — **Intervention?**

Compared to **No Steroids** — **Comparison ?**

Prevent Neonatal Deaths? — **Outcome ?**

Time point(s)?

Architecture of a focused 4-part review question

Richardson et al. The well-built clinical question: a key to evidence-based decisions. ACP Journal Club 1995;A-12
Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. Ann Intern Med 1997;127:380-7.

P - Who is the patient or what problem is being addressed?

I - What is the intervention or exposure?

C – What is the comparison group?

O - What is the outcome or endpoint?

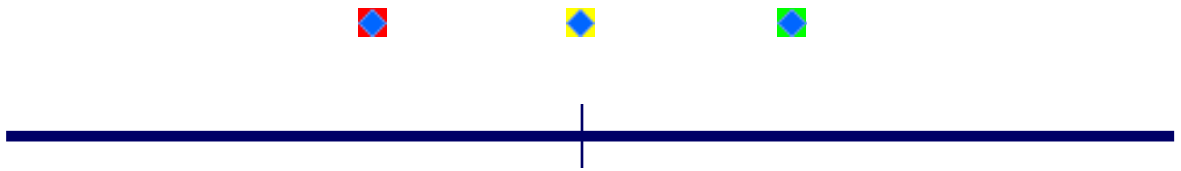
+ study design

Different types of hypothesis testing problems

- ***Test for Equality***: **Here the goal is to detect a clinically meaningful difference/effects is such a difference/effects exists**
- ***Test for Non-inferiority***: To demonstrate that the new drug is as less effective as the standard treatment (ie the difference between the new treatment and the standard is lesn the smallest clinically meaningful
- ***Test for Superiority***: To demonstrate that the new treatment is more superior that standard treatment (ie the difference between the new treatment and the standard is greater than the smallest clinically meaningful difference).
- ***Test for equivalence*****:** To demonstrate the difference between the new treatment and standard treatment has no clinical importance

Point estimate of the difference

- **If T=R, d=T-R=0**
- **If T>R, d=T-R>0**
- **If T<R, d=T-R<0**



d < 0
Negative effect

d = 0
No difference

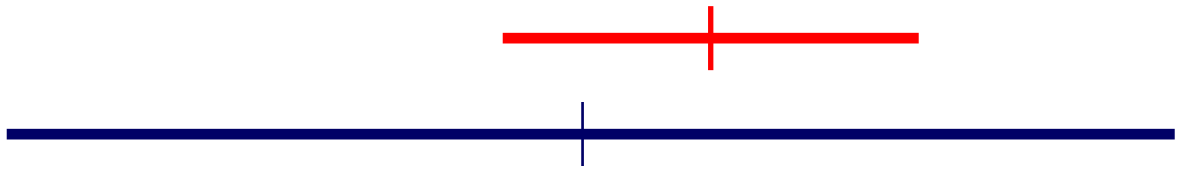
d > 0
Positive effect

Estimation with confidence intervals in a superiority trial

It is not statistically significant!

Because the CI includes the d=0 value

Confidence interval 90% - 95%



d < 0
Negative effect

d = 0
No difference

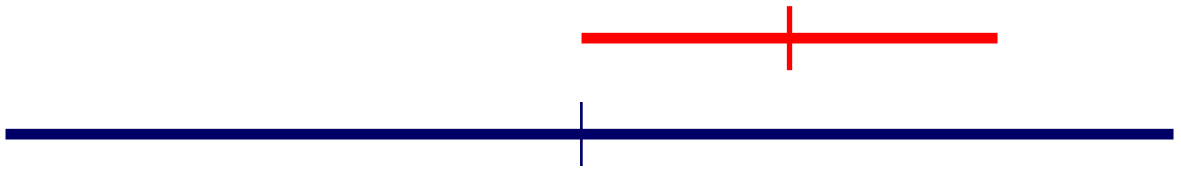
d > 0
Positive effect

Estimation with confidence intervals in a superiority trial

It is statistically significant with P=0.05

Because the boundary of the CI touches the d=0 value

Confidence interval 90% - 95%

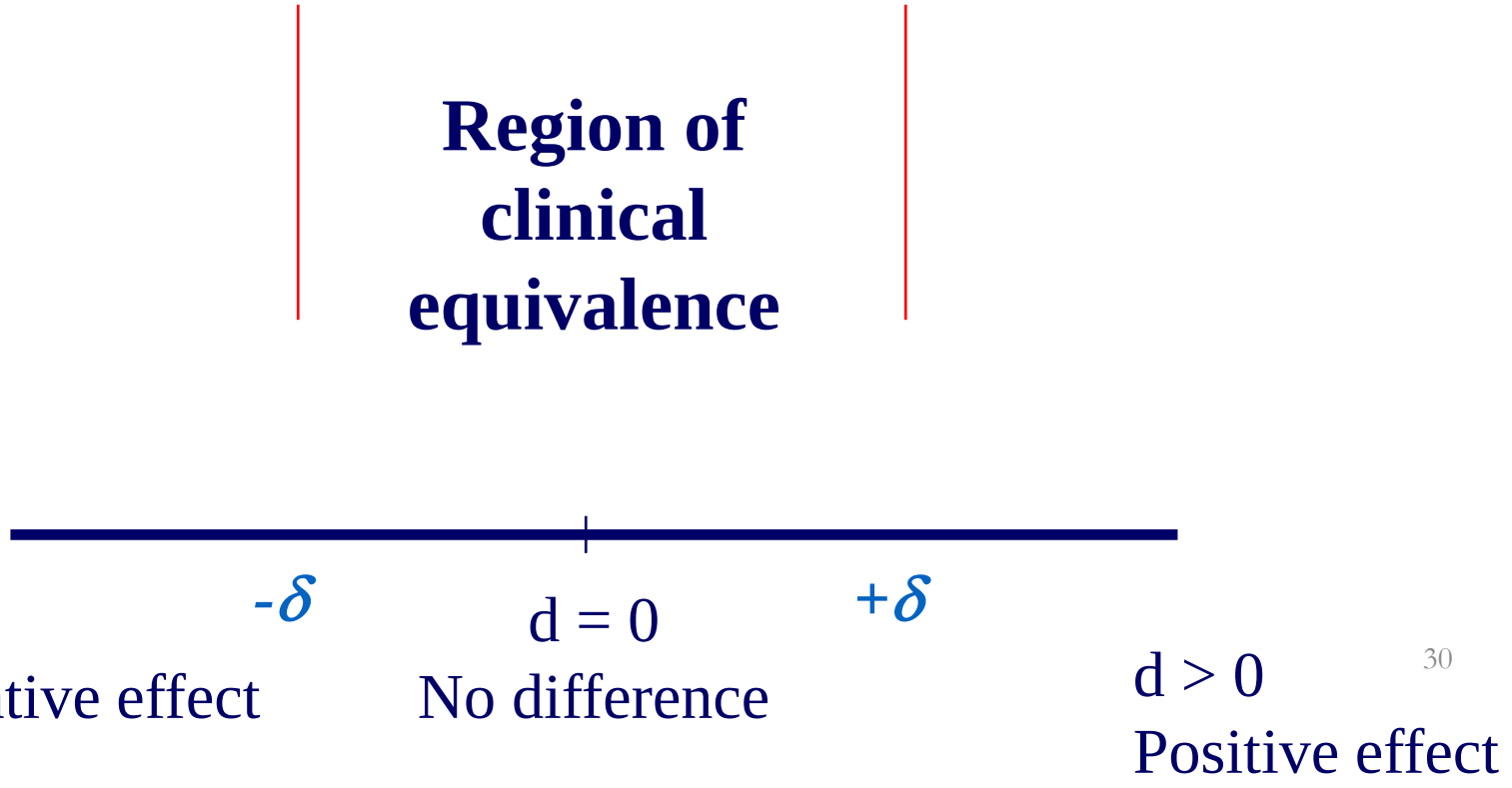


d < 0
Negative effect

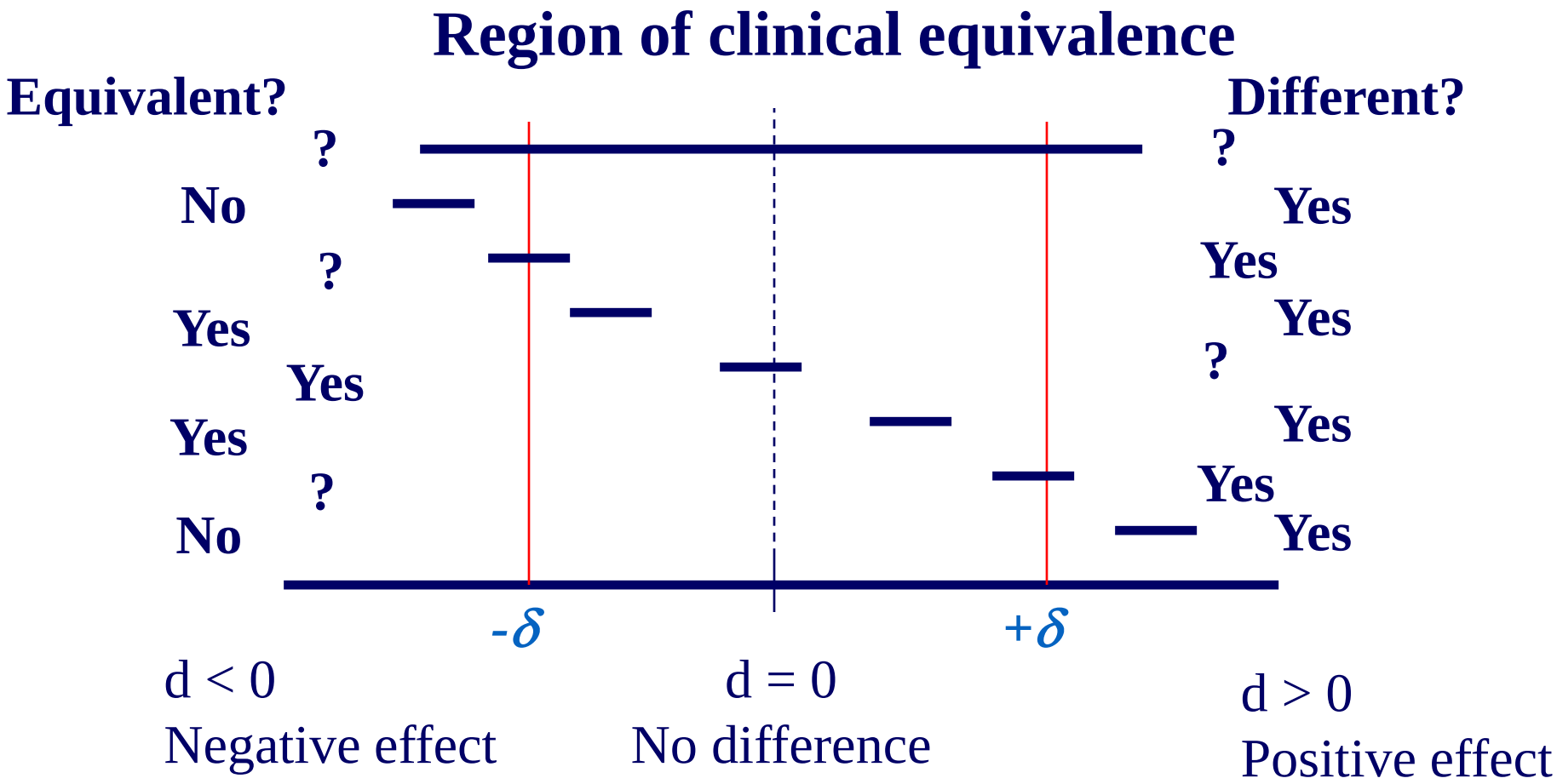
d = 0
No difference

d > 0
Positive effect

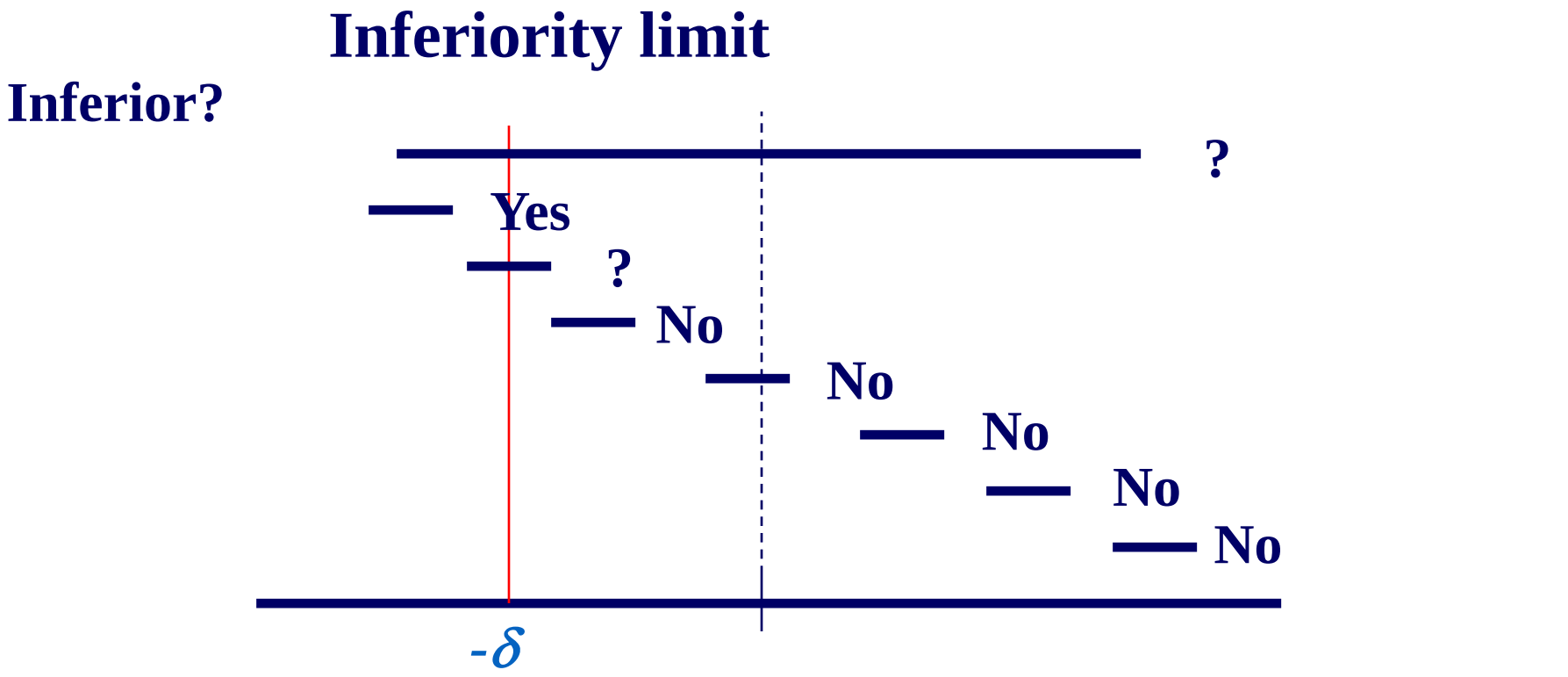
Equivalence study



Equivalence vs. difference



Non-inferiority study



Superiority study (?)

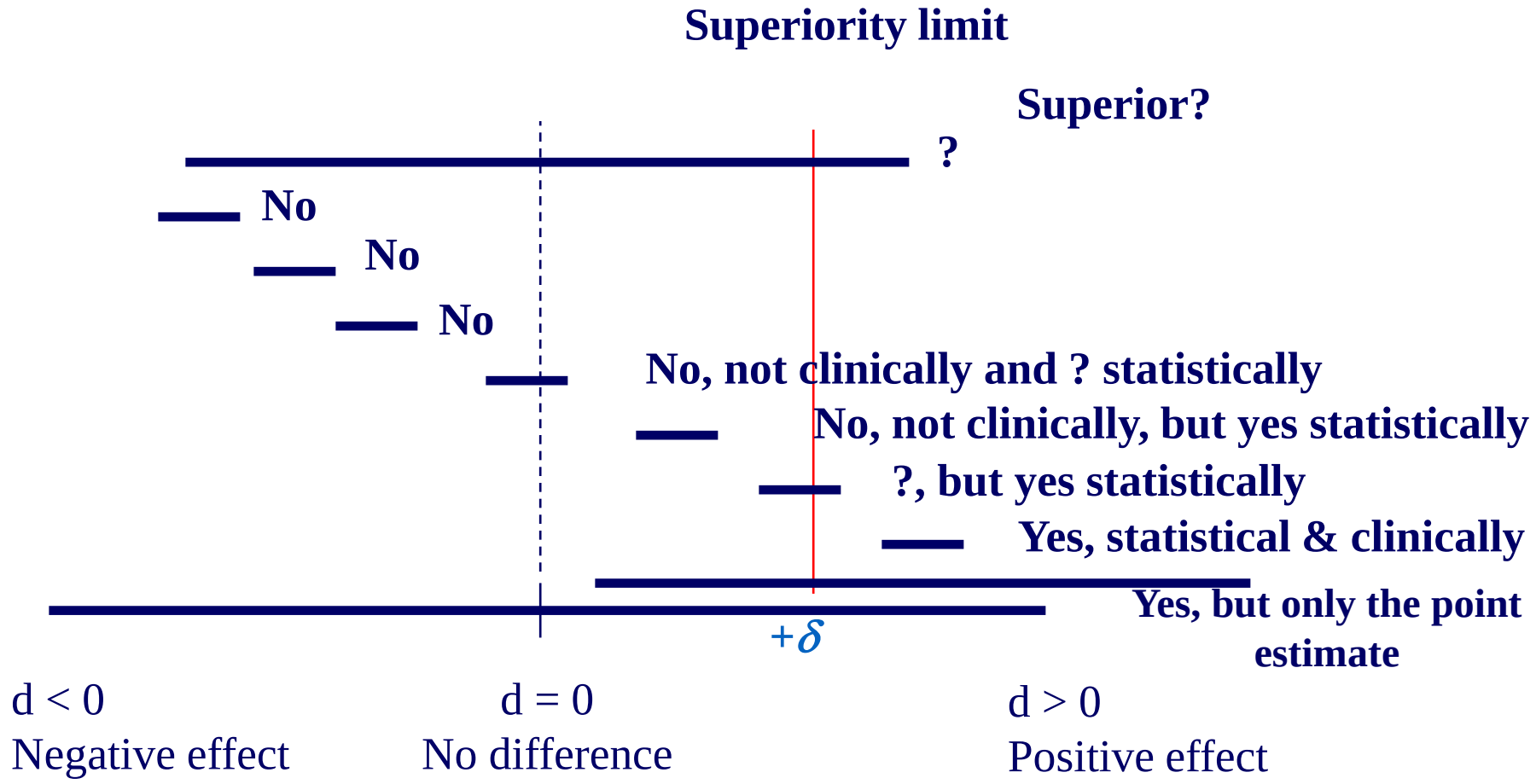


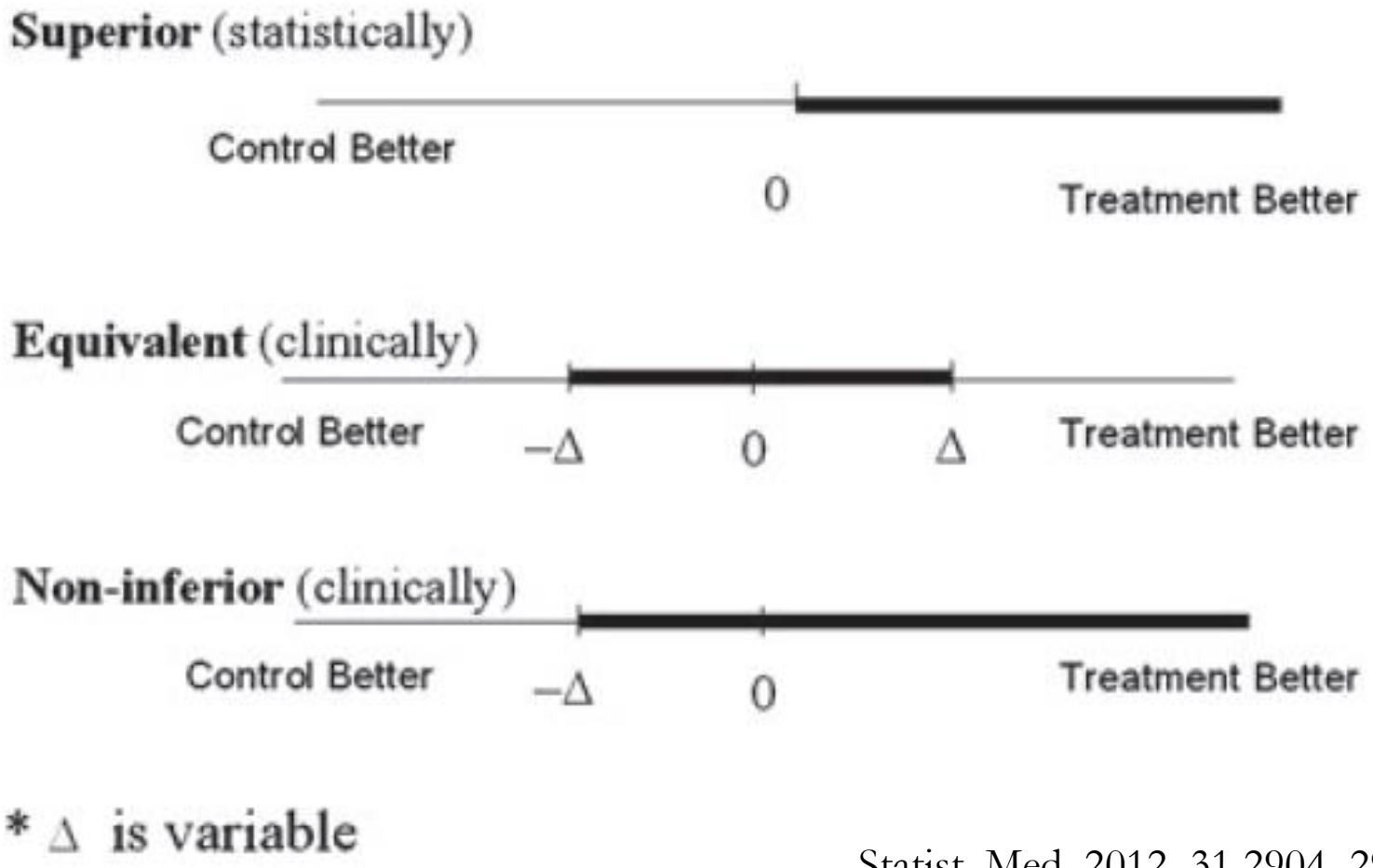
Table XII. Non-inferiority margins for different control response rates.

	Non-inferiority margin	
Response rate	FDA*	CHMP†
⩾ 90	−10%	−10%
80–89%	−15%	−10%
70–79%	−20%	−10%

*Food and Drug Authority.

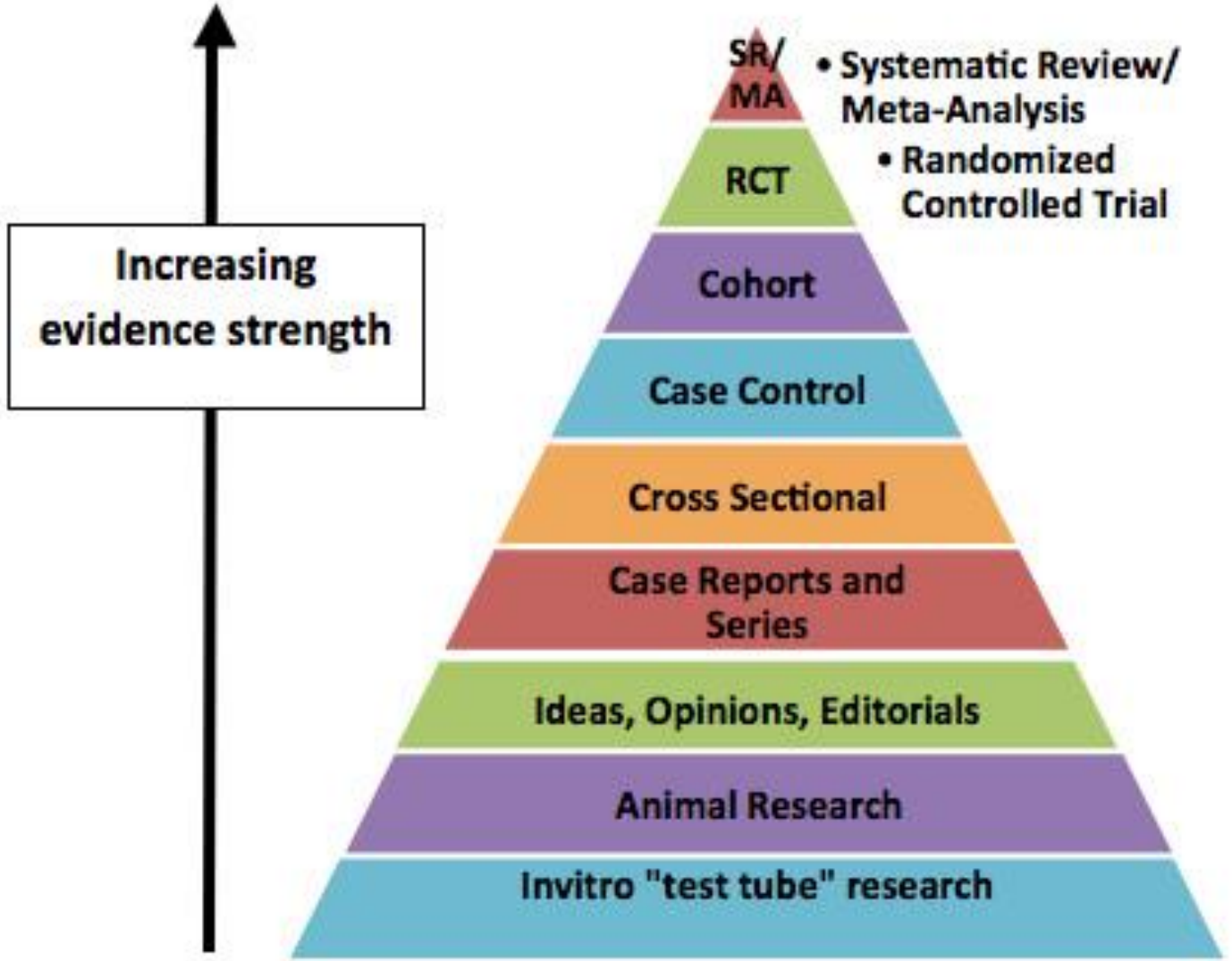
†Committee for Health and Medicinal Products (CHMP; formerly Committee for Pharmaceutical and Medicinal Products (CPMP)).

An illustration of the difference between superiority, equivalence and non-inferiority trials: the dark line in the figure is the confidence interval while delta is the non-inferiority or equivalence limit



Statist. Med. 2012, 31 2904–2936

Study designs

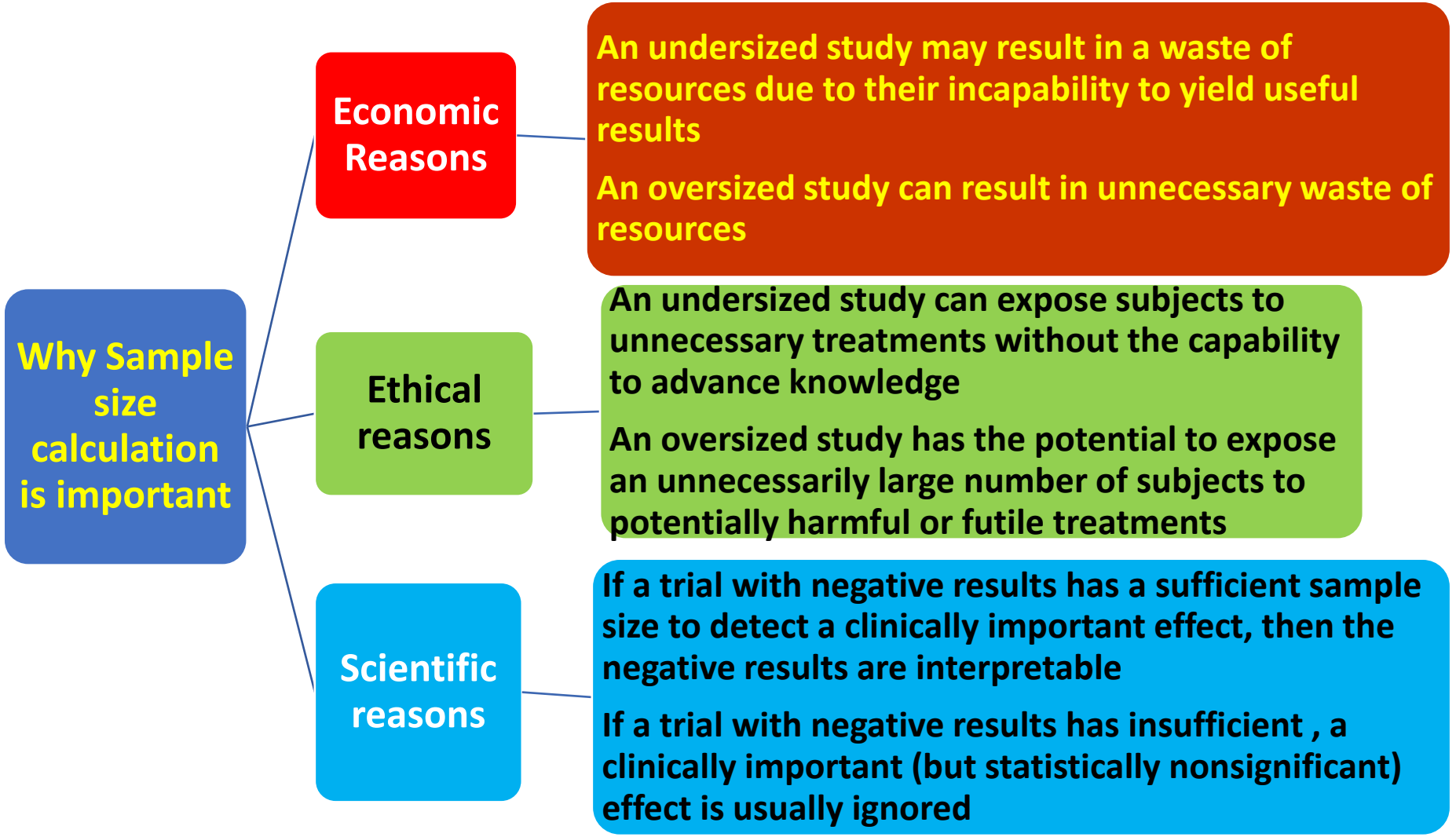


Suitable Study Design

Issues	Study Design
Diagnosis	Cross sectional
Therapy	RCT (Non-RCT)
Prognosis	Prospective cohort
Cause	Cohort Case control
Description	Case Series Cross Sectional

- However, more than one study design can be used to answer any given question of causal association

Why sample size calculation is important



Assumptions needed about the conditions of a study to complete sample size calculations.

Values needed to estimate sample size	Example
1. Choose the main endpoint of interest and the method by which it will be measured.	Difference in average calcium intakes from food between two groups using a two sample t test.
2. Specify the size of the difference between the experimental groups that is meaningful to detect.	Meaningful difference would be 225 mg, an amount equivalent to about 6 oz milk.
3. Estimate the expected variability (ie, the estimated standard deviation).	Based on pilot data the standard deviation for a group that likes milk is 540 mg and the group that doesn't like milk is 430 mg.

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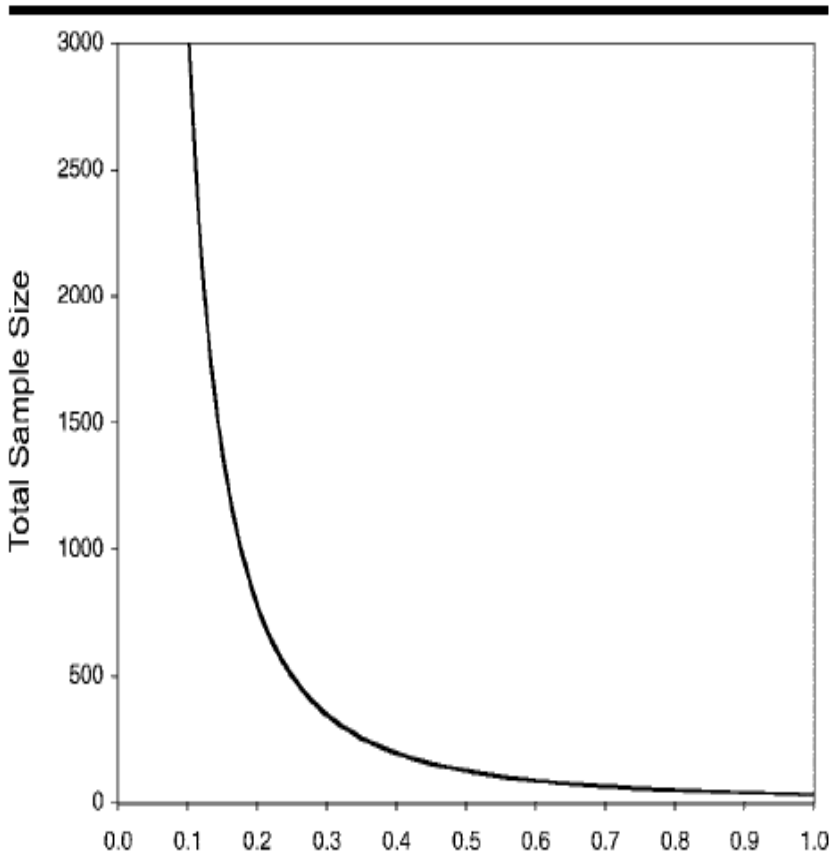
Factors That Decrease Sample Size	Factors That Increase Statistical Power
Lower desired statistical power	Larger sample size
Larger meaningful difference (effect size)	Larger meaningful difference (effect size)
Smaller standard deviation	Smaller standard deviation
Less stringent significance criterion	Less stringent significance criterion

Study design characteristics that affect sample size and statistical power.

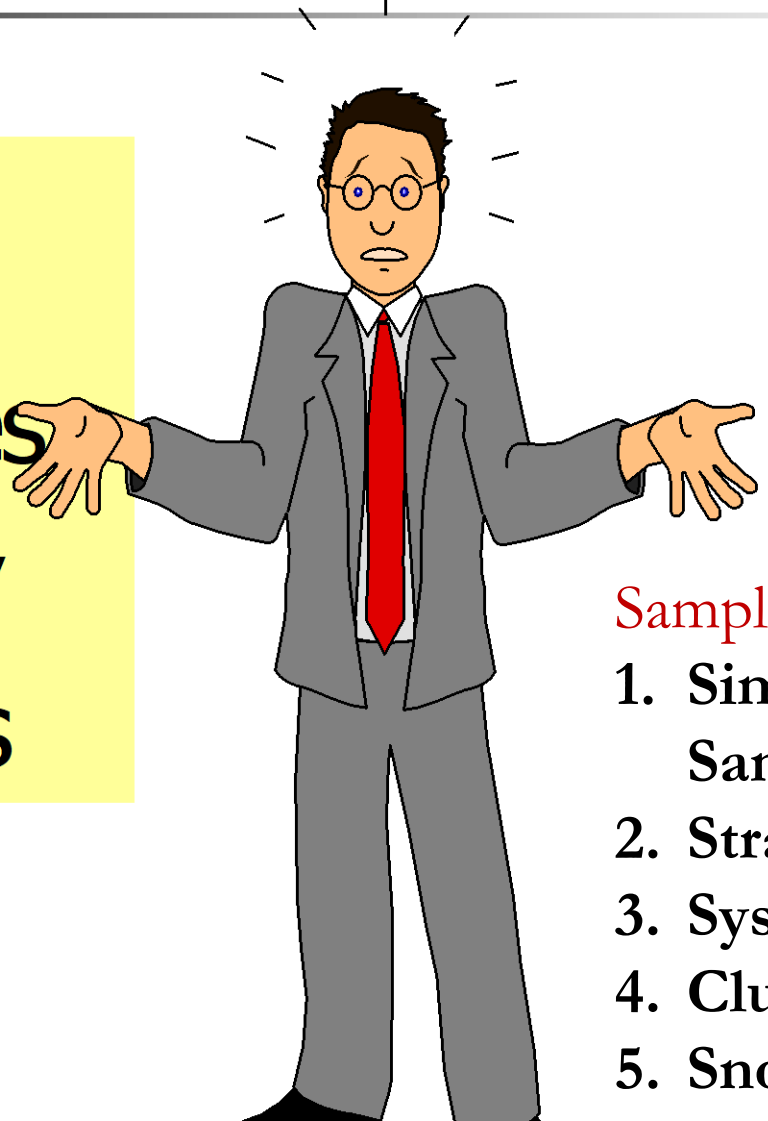


Ration of meaningful difference to standard deviation

SAMPLE SIZE

Too Big:

- Requires too many resources



Too small:

- Won't do the job

Sampling:

1. Simple Random Sampling
2. Stratified sampling
3. Systematic sampling
4. Cluster Sampling
5. Snow ball sampling

Misleading Sample size

- $33\frac{1}{3}\%$ of the mice used in the experiment were cured by the test drug
- $33\frac{1}{3}\%$ of the test population were unaffected by the drug and remained in moribund condition
- The third mouse got away

Big is not beautiful

- One day there was a fire in a wastebasket in the office of the Dean of Sciences. In rushed a physicist, a chemist, and a statistician.
- The physicist immediately starts to work on how much energy would have to be removed from the fire to stop the combustion.
- The chemist works on which reagent would have to be added to the fire to prevent oxidation.
- While they are doing this, the statistician is setting fires to all the other wastebaskets in the office. "What are you doing?" the others demand. The statistician replies, "Well, to solve the problem, you obviously need a larger sample size.

Kinds of research approaches

Description	Comparison of group means	Determining the relationship among the variables		Determining the effect of intervention
		Association	Prediction	
Simple Descriptions [1]	Comparison with values given in the literature[2]	Two categorized variables[5]	The values of one Variable from another[8]	Doing experiments [9]
	Comparison of two groups[3]	One categorized variables and one continuous variable[6]		
	Comparison of three or more groups[4]	Continuous data[7]		

Vocabulary for variables used in statistics

Definition	Name of variable	
The variable measures subject response	Response or out come variable	Dependent variable
The variable which will explain the response variable	Explanatory	Independent Variable
Some times researchers intervene and conduct experiments	Outcome	Response
The type of intervention	Treatment	Factor

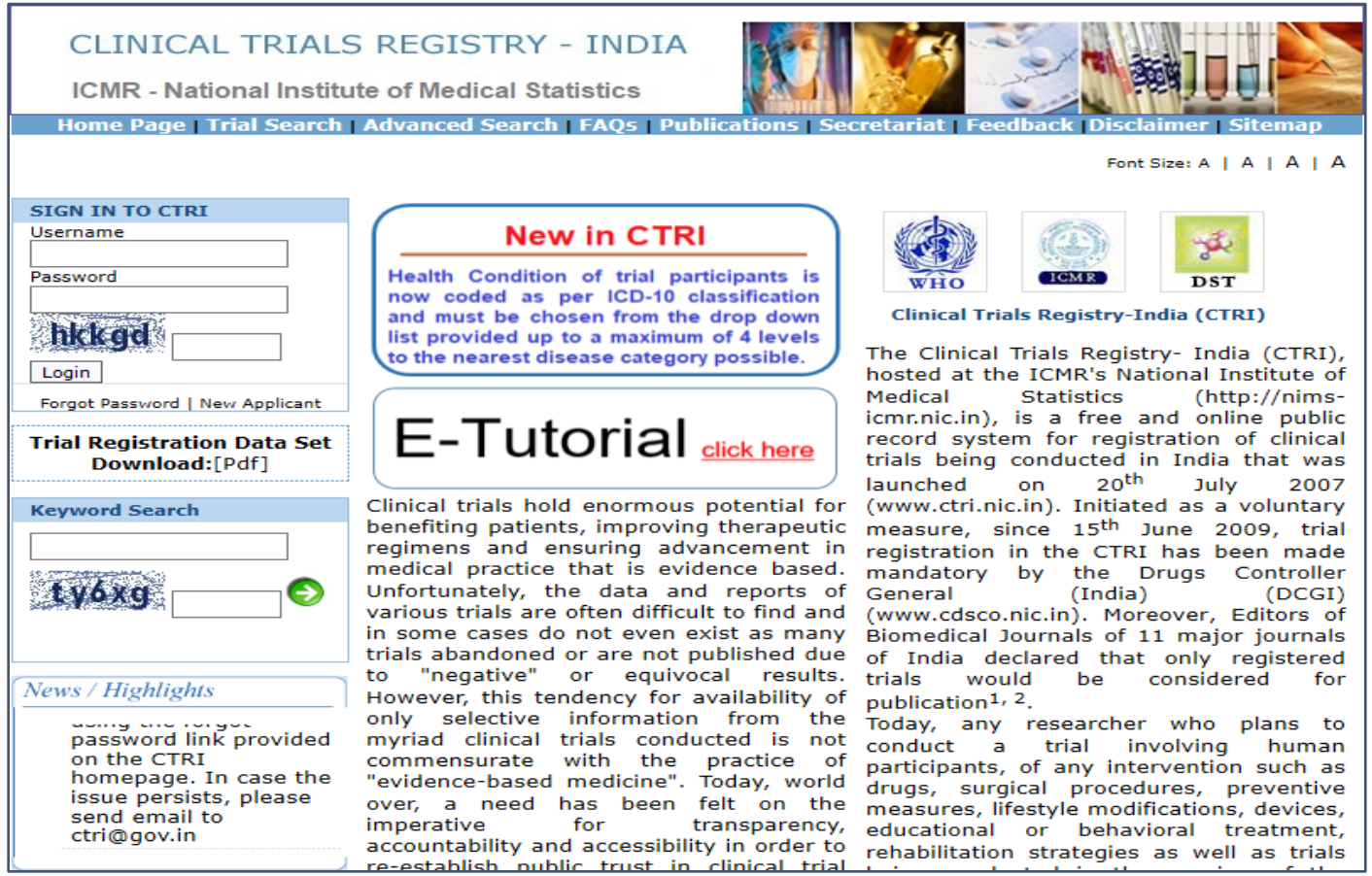
Finally, I must stress the need for active collaboration between statisticians and experimental scientists. A statistician can help the scientist in designing efficient experiments to yield the maximum information on the questions raised by the scientist and providing the scientist guidelines for examining his hypotheses and modifying them if the data indicate contrary evidence. ***As Fisher, the father of modern experimental designs said:***

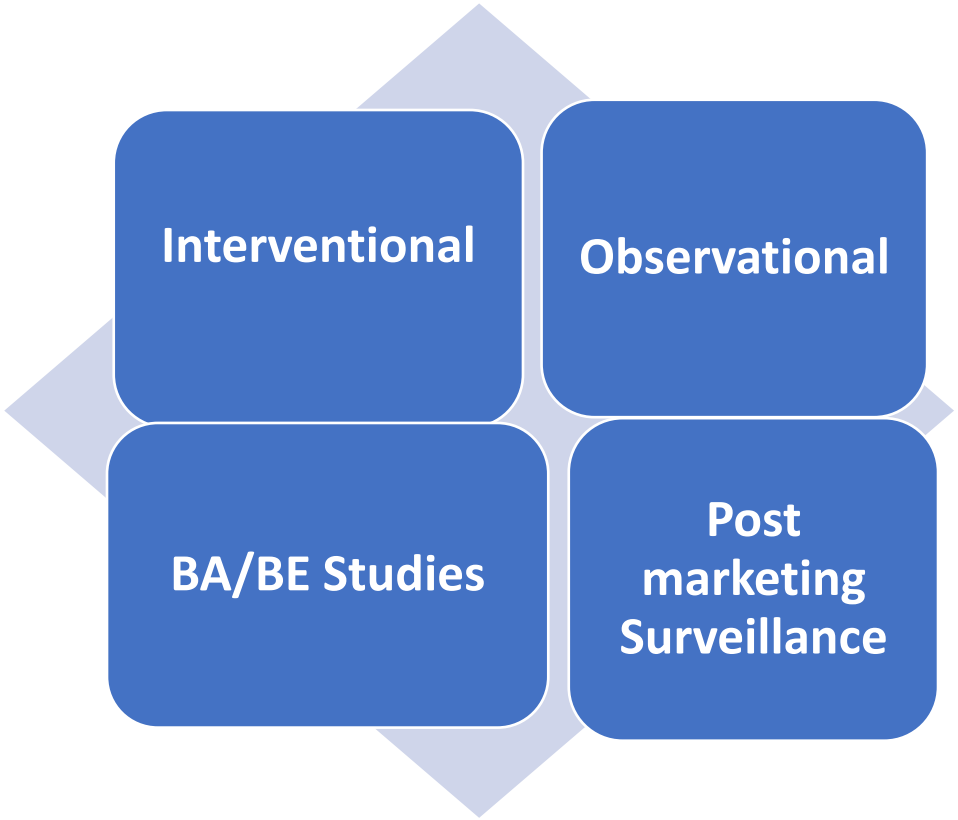
Clinical trials registration process

Introduction & Genesis

- Clinical trials - valuable sources of evidence - safety and efficacy of health interventions
- Evidence should be based on Correct information about ongoing, completed and published clinical trials
- To ensure transparency , accountability and to increase public trust in the conduct of clinical research, all clinical trials should be registered at inception and all results made publicly available.
- 58th World Health Assembly held on 25th May 2005 WHO proposed the setting up of an International Clinical Trial Registry Platform (ICTRP), a one-stop search portal for searching registers worldwide.
- Also in 2005 only, the International Committee of Medical Journal Editors (ICJME), implemented a policy whereby a scientific paper on clinical trial results would be published only if the trial had been registered in a publicly-accessible registry.
- In the 59th General Assembly of the World Medical Association, 2008, emphesised that: Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject
- The registration of all interventional trials is a scientific, ethical and moral responsibility (WHO) . When in doubt, register (WHO)

www.ctri.nic.in





Trial Registration Dataset Items

1. **Public Title of Study***
2. **Scientific Title of Study,* Acronym, if any**
3. **Secondary IDs, (UTN, Protocol No etc.)***
4. **Principal Investigator's Name and Address**
5. **Contact Person (Scientific Query)***
6. **Contact Person (Public Query)***
7. **Source/s of Material or Monetary Support***
8. **Primary Sponsor***
9. **Secondary Sponsor***
10. **Countries of Recruitment***
11. **11. Site/s of study***

12 Name of Ethics Committee and approval status*

13. Regulatory Clearance obtained from DCGI*

14. Health Condition/Problem studied*

15. Study Type*

16. Intervention and Comparator agent*

17. Key inclusion/Exclusion Criteria*

18. Method of generating randomization sequence

19. Method of allocation concealment

20. Blinding and masking

21. Primary Outcome/s*

22. Secondary Outcome/s*

23. Target sample size*

24. Phase of Trial*

25. Date of first enrollment*

26. Estimated duration of trial

27. Status of Trial*

28. Publication Details

29. Brief Summary*

30. Data Sharing Plan*

Thank You

dr_vishnurao@yahoo.com
menduvishnuvardhanarao@gmail.com