Epidemiological Methods and Management

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Methods of Measuring effectiveness of public/ health services

- **Definition of terms:** Randomization, accuracy, blinding, cluster, conflict of interest, confounding, follow up, biological plausibility
- **Measuring the efficacy and effectiveness of preventive and therapeutic interventions:** Preventive and Therapeutic Trials- Randomized Clinical trial, Field Trial and Community Trial, estimation and quantification of impacts- attributable risk and population attributable risk

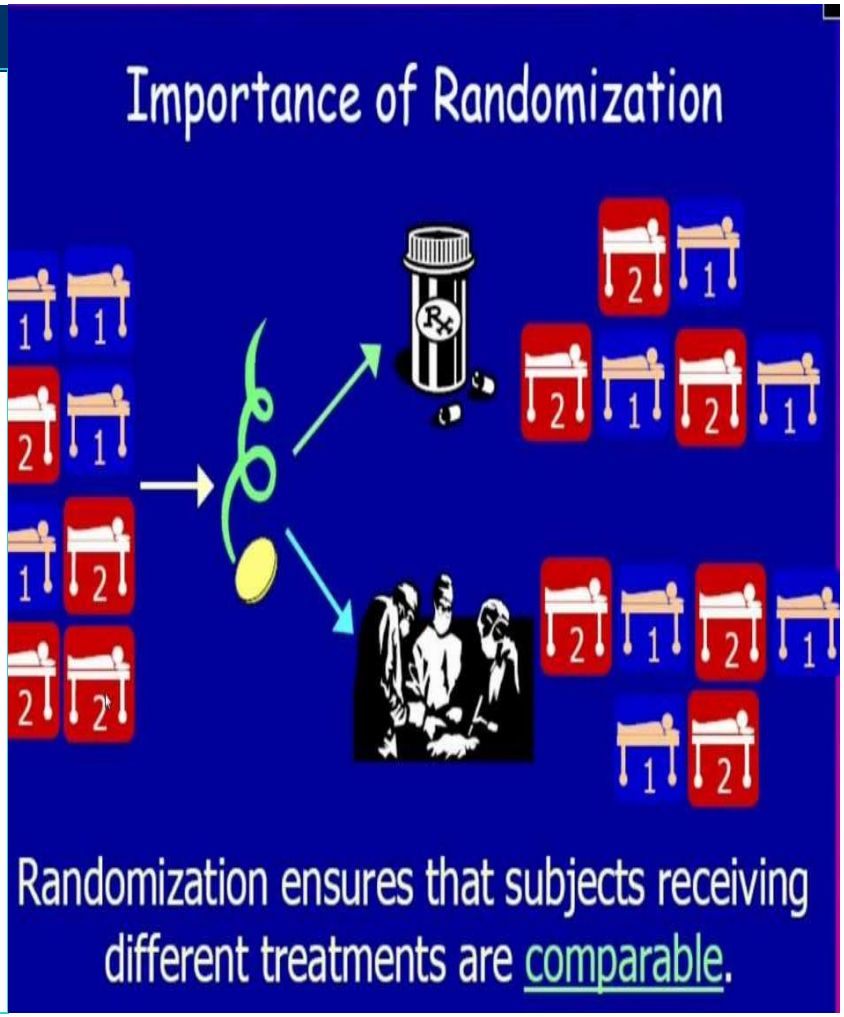
  Strengths and limitations of experimental studies
- **Methods of synthesis and quantification of evidences in epidemiology**

  Concept of systematic review and meta-analysis

Definition of terms

Randomization

- Randomization is the process of making something random. Randomization is not haphazard; instead, a random process is a sequence of random variables
- The process by which participants in clinical trials are assigned by chance to separate groups that are given different treatments or other interventions.
- Neither the researcher nor the participant chooses which treatment or intervention the participant will receive.



Randomization.....

- Process by which each participant has the same chance of being assigned to either intervention or control group
- Assure the compatibility of characteristics among Treatment and Control group
- Eliminates the source of bias like investigator bias
- Facilitates blinding the type of treatments to the investigator, participants, and evaluators

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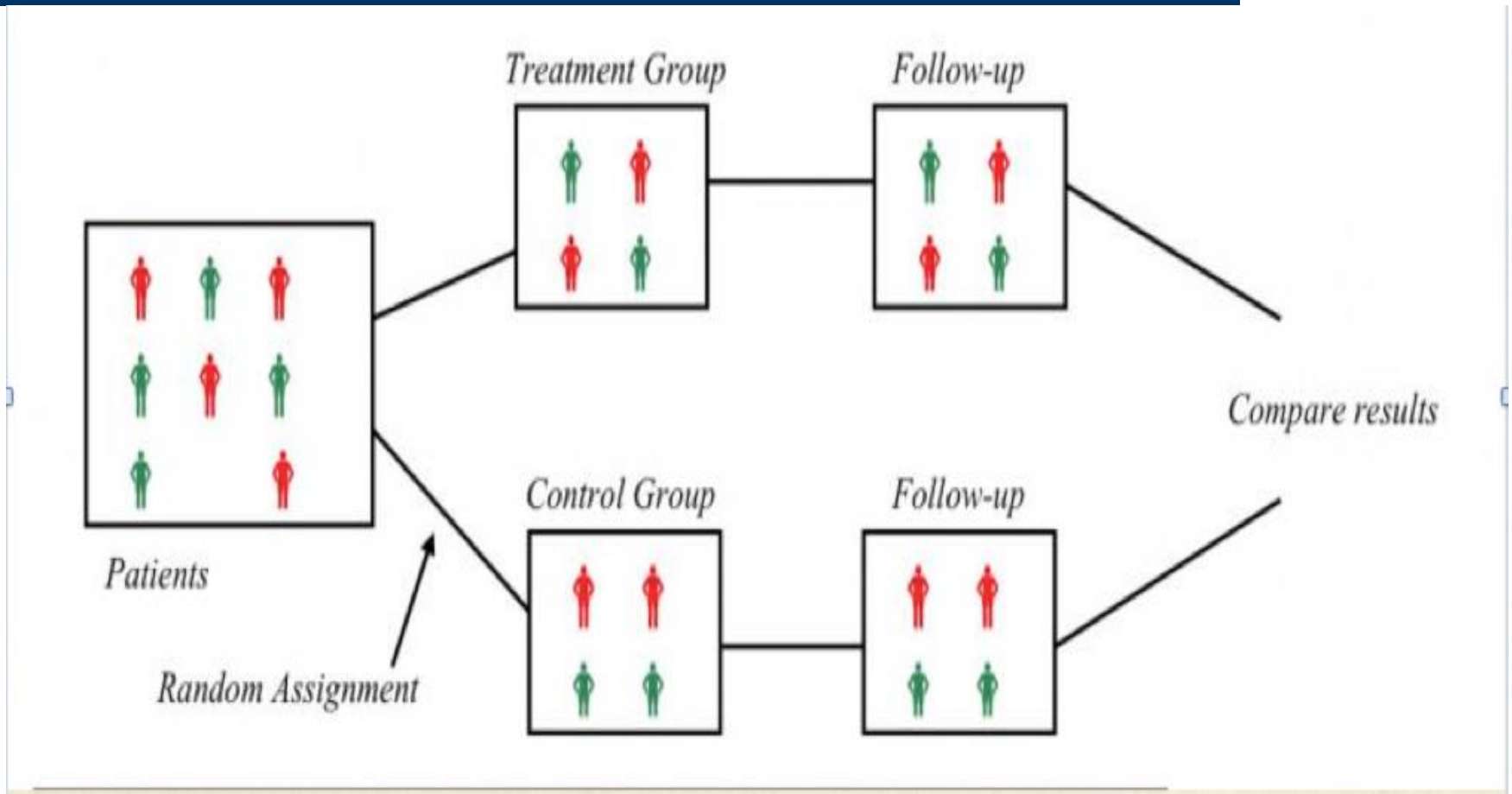

Treatment Group
Follow-up
Compare results
Control Group
Follow-up
Patients
Random Assignment

Types of Randomization

- Simple: Randomization based on a single sequence of random assignments is known as simple randomization. This technique maintains complete randomness of the assignment of a subject to a particular group.

- Blocked Randomization: The block randomization method is designed to randomize subjects into groups that result in equal sample sizes. This method is used to ensure a balance in sample size across groups over time.

- Stratified Randomization: refers to the situation in which strata are constructed based on values of prognostic variables and a randomization scheme is performed separately within each stratum.

Accuracy

Accuracy refers to the closeness of the measured value to the correct value (marked as “reference”, “criterion” or “gold standard ”).

- Accuracy is how close a given set of measurements are to their true value, while precision is how close the measurements are to each other.

- Accuracy is the degree to which an expression or measurement conforms to a true value. It also has to do with correctness or absence of error.

Blinding

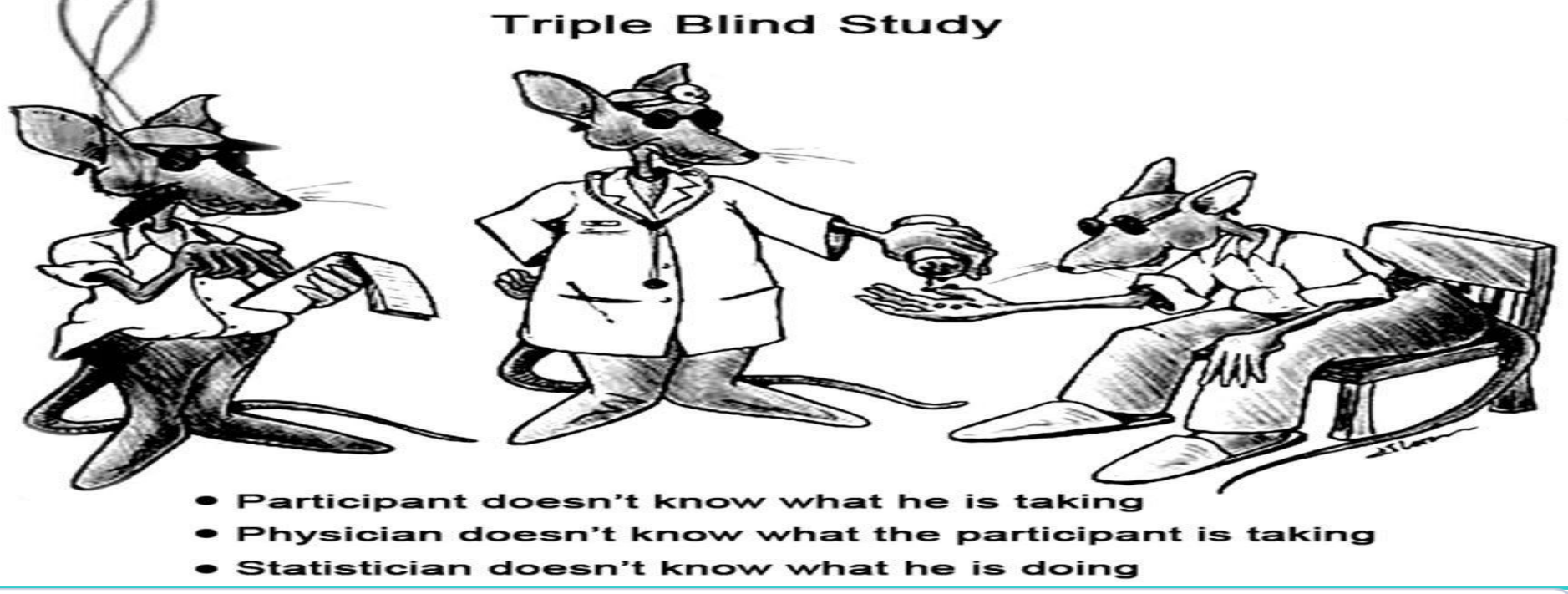
- To reduce the possible error while attempting epidemiological studies, a process in which one or more person concerned with experiment are unknown or blind about the status of study participants is called blinding.

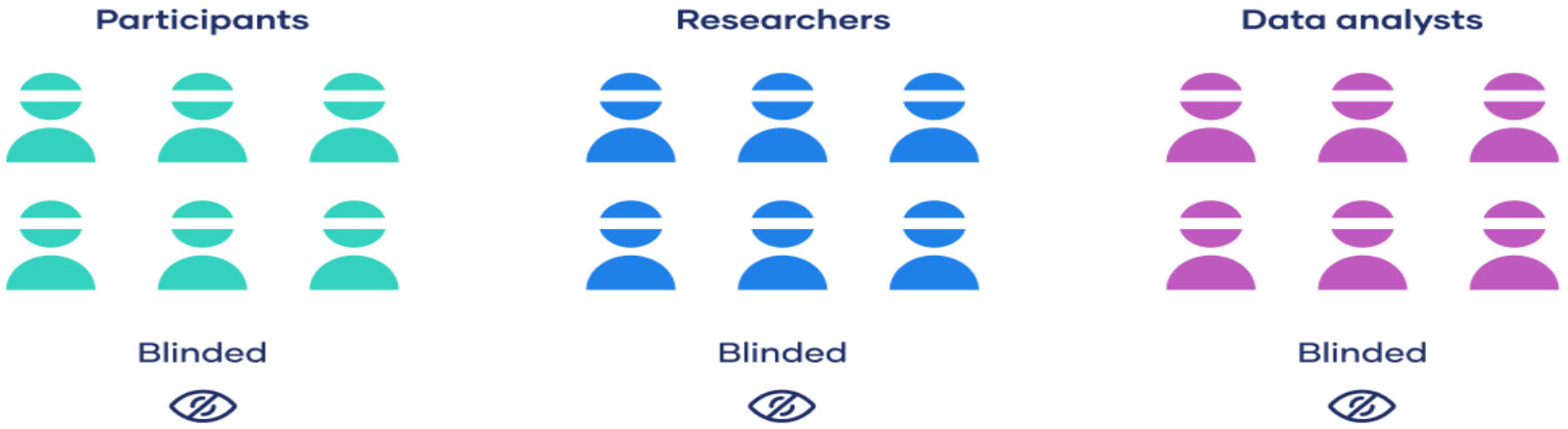
Blinding can be classified into three types

- Single blinding: the trial is so planned that the participants are not aware whether they belongs to experiment or placebo group.

- Double blinding: The trial is so planned that neither the doctor nor participants are aware of group allocation and treatment received.

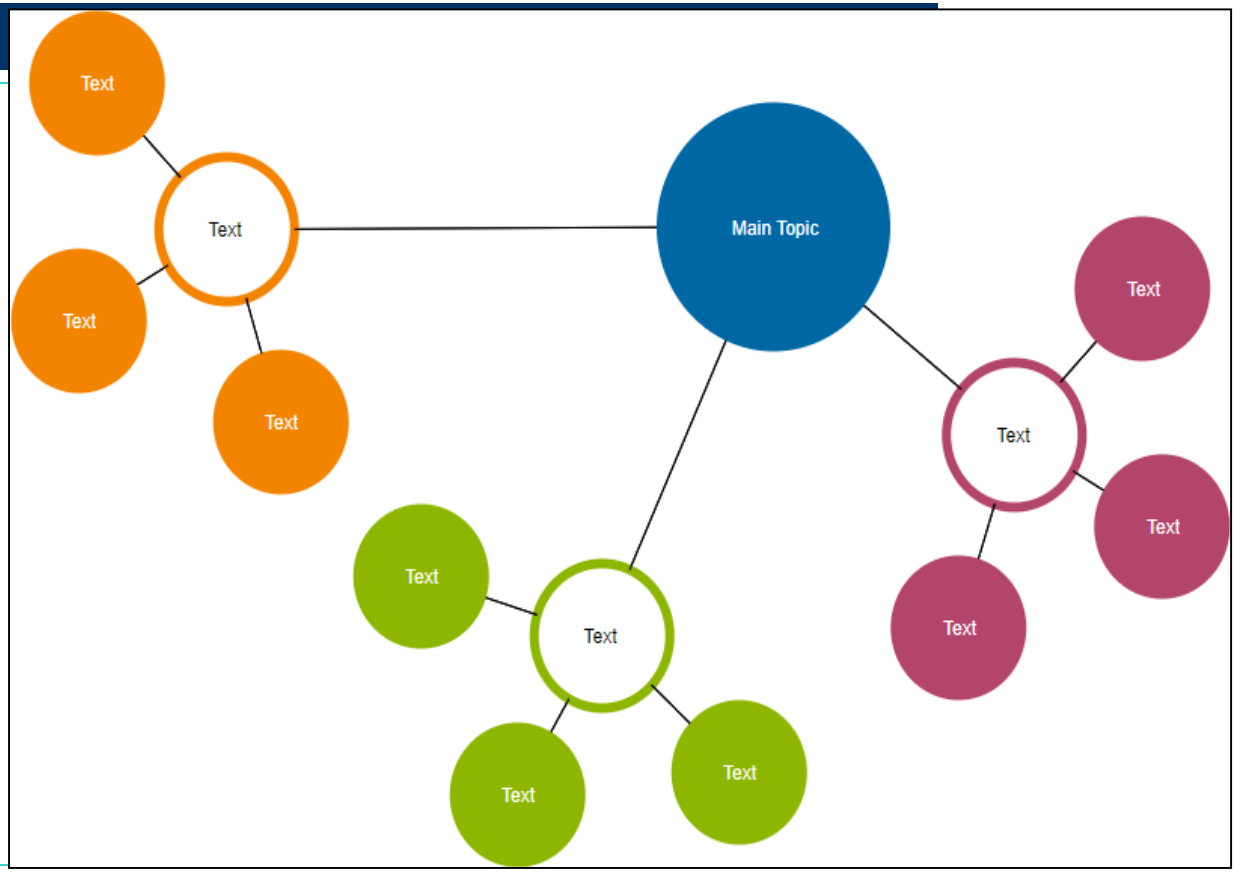
- Triple Blinding: The participants, investigator and the person analyzing the data are all blind. Ideally of course, triple blinding should be used in RCT.


Triple Blind Study
• Participant doesn't know what he is taking
• Physician doesn't know what the participant is taking
• Statistician doesn't know what he is doing


Triple-blind study
Participants
Researchers
Data analysts
Blinded
Blinded
Blinded

Cluster

- A cluster of people or things is a small group of them close together.



Conflict of interest

- Conflict of interest (COI) in research represents the situation where professional decisions regarding the primary responsibilities of a researcher may be at risk of being wrongly influenced by a secondary benefit, such as financial gain or career advancement.

- Conflicts of interest may be actual, potential or perceived and involve financial and non-financial benefits. Conflicts of interest may affect, or be perceived to affect, a researcher's impartiality and judgement, which can erode confidence in the research.

Contd…

- The term “conflict of interest (COI) in research” refers to situations in which financial or other personal considerations may compromise or have the appearance of compromising an investigator's professional judgment in conducting or reporting research.

Conflict of Interest in Research

- Conflicting Financial Interests
- Impartiality in Performing Official Duties
- Misuse of Position
- Representation
- Gifts
- Activities with Outside Organizations
- Seeking Other Employment

Examples

- A conflict of interest can occur when you, or your employer, or sponsor have a financial, commercial, legal, or professional relationship with other organizations, or with the people working with them, that could influence your research.

- A conflict of interest is anything that interferes with, or could reasonably be perceived as interfering with, the full and objective presentation, commissioning, peer review, editorial decision-making, or publication of research or non-research articles submitted to Publishing Journals.

Confounding

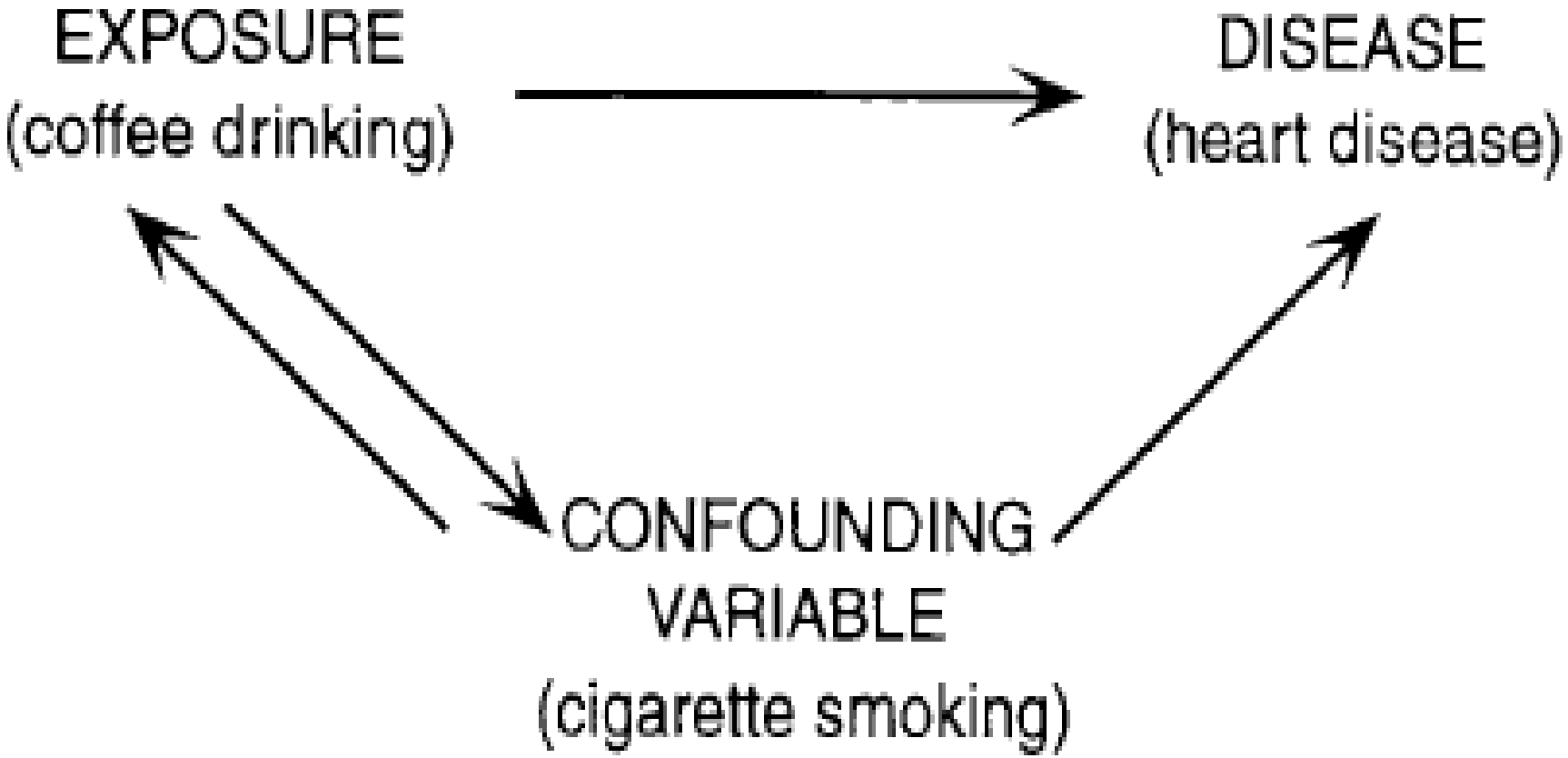
- A special type of bias which has independent importance in epidemiological study.

- Confounding refers to the effect of an extraneous variable that entirely or partially explains the apparent association between the study exposure and the disease.

Contd…

- Confounding occurs when two factors are associated with each other and the effect of one is confused with the effect of other.

Illustration



The most common concern is that it may create the appearance of a cause – effect relationship that in reality does not exist.

Follow up

- This implies examination of the study subjects at defined interval of time in standard manner, with equal intensity.

- The follow up may be short or may require many years depending upon the study undertaken.

Biological plausibility

- A term referring to the results of research or a trial which are believable in terms of current scientific biological knowledge.
- The fact that a hypothesis and the relationship that it proposes are in harmony with existing scientific information

Hill's Viewpoints

- **Biological Plausibility**
  - An hypothesized relationship between an exposure and a health outcome makes sense in the context of current biological knowledge
  - Not a necessary criterion since "…the association we observe may be new to science or medicine and we must not dismiss it too light-heartedly as just too odd." (Hill)

Measuring the efficacy and effectiveness of preventive and therapeutic interventions:

- Evaluating the broader quality of health service interventions is multi-dimensional and shaped by complex interactions between setting, personnel, accessibility, financial sustainability, and of course efficacy and effectiveness.

- Intervention studies can be placed on a continuum, with a progression from efficacy trials to effectiveness trials. Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under 'real-world' conditions.

Types of Trials

- Preventive Trials (vaccine trials)
- Risk factors Trials (e.g cancer risk factors)
- Therapeutic Trials(drug trials)
- Health service Evaluation Trials

Contd…

- Interventions can be classified into two broad categories:
  - Preventive interventions are those that prevent disease from occurring and thus reduce the incidence (new cases) of disease
  - Therapeutic interventions are those that treat, mitigate, or postpone the effects of disease

Contd…

- Clinical trials are a type of research that studies new tests and treatments and evaluates their effects on human health outcomes.
- People volunteer to take part in clinical trials to test medical interventions including drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments and preventive care.
- Clinical trials in individuals can be classified as either preventive or therapeutic.

Contd…

- ***Preventive Trials:***
  - Healthy or high-risk individuals are tested to determine whether a treatment prevents disease, e.g.,
  - Does the drug tamoxifen prevent development of breast cancer in women who have a high risk of developing breast cancer?
  - How effective is this year's influenza vaccine in preventing the flu?
  - Does a Mediterranean diet reduce the incidence of cardiovascular disease?

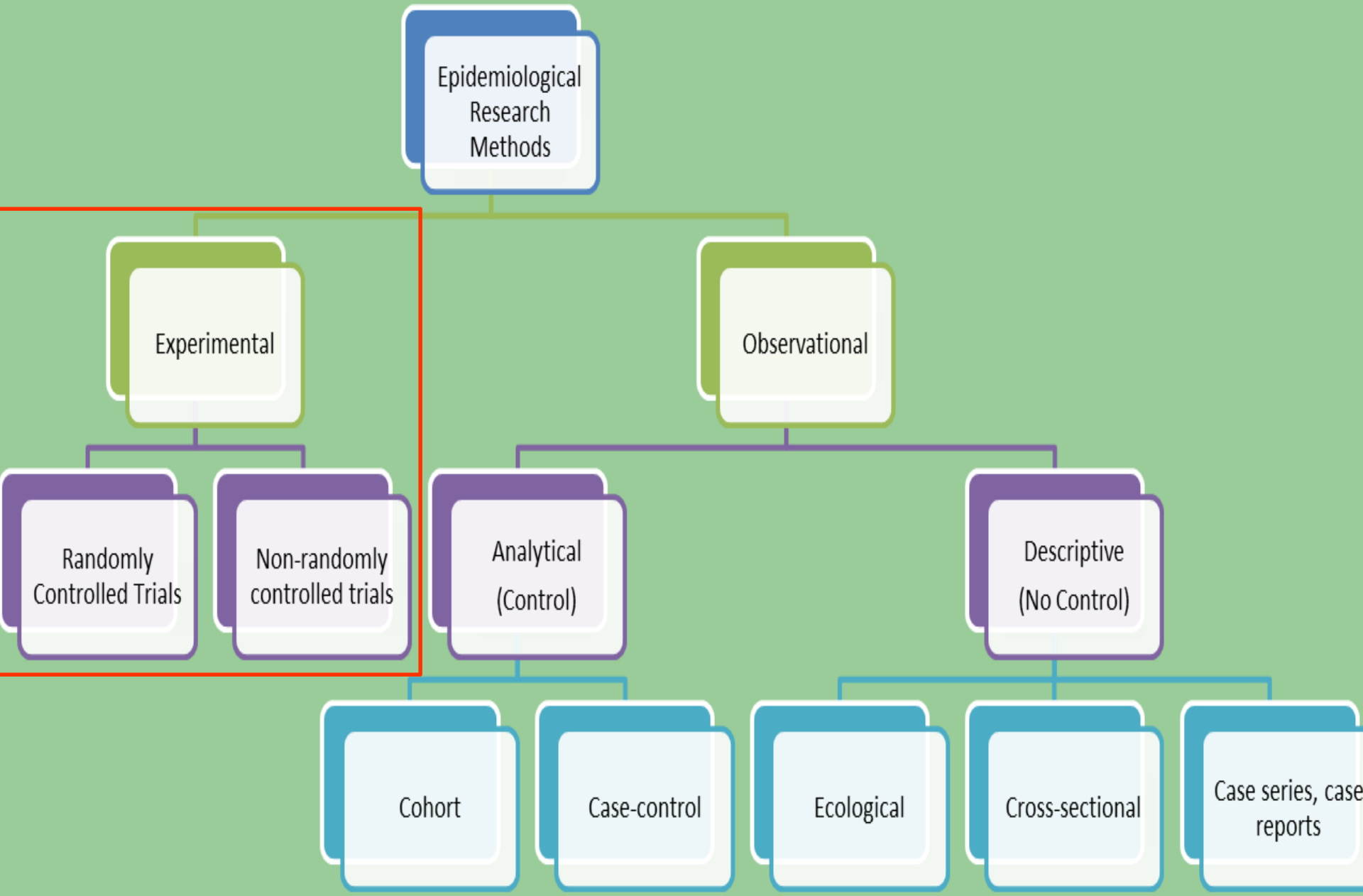
Contd….

- ***Therapeutic Trials:***
  - New treatments are tested for the effectiveness in treating disease, e.g.,
  - Does the drug herceptin improve survival in women already diagnosed with breast cancer?
  - Does treatment with Tamiflu shorten the duration and improve survival in patients with bird flu?

Contd…

Intervention Types – Therapeutic vs Preventive

- Preventive trials seek the best way to prevent a disease from developing
- Therapeutic trials seek to determine the best treatment of people with a disease or condition
- One classic therapeutic trial is the Beta-blocker Heart Attack Trial (B-HAT). In this study, men who had a heart attack were assigned to receive propranolol or a placebo
- Those receiving treatment had improved survival times compared to those receiving a placebo
  - (The β-Blocker Heart Attack trial. *JAMA* 11/6/1981;246(18):2073)


Epidemiological Research Methods
Experimental
Observational
Randomly Controlled Trials
Non-randomly controlled trials
Analytical (Control)
Descriptive (No Control)
Cohort
Case-control
Ecological
Cross-sectional
Case series, case reports

A Classification of Experimental Design

Experimental Design

Pre-Experimental

One-shot case study

One Group Pretest-Posttest

Static Group

True-Experimental

Pretest-Posttest Control Group

Pretest: Only Control Group

Solomon Four-Group

Statistical

Time series

Multiple Time series

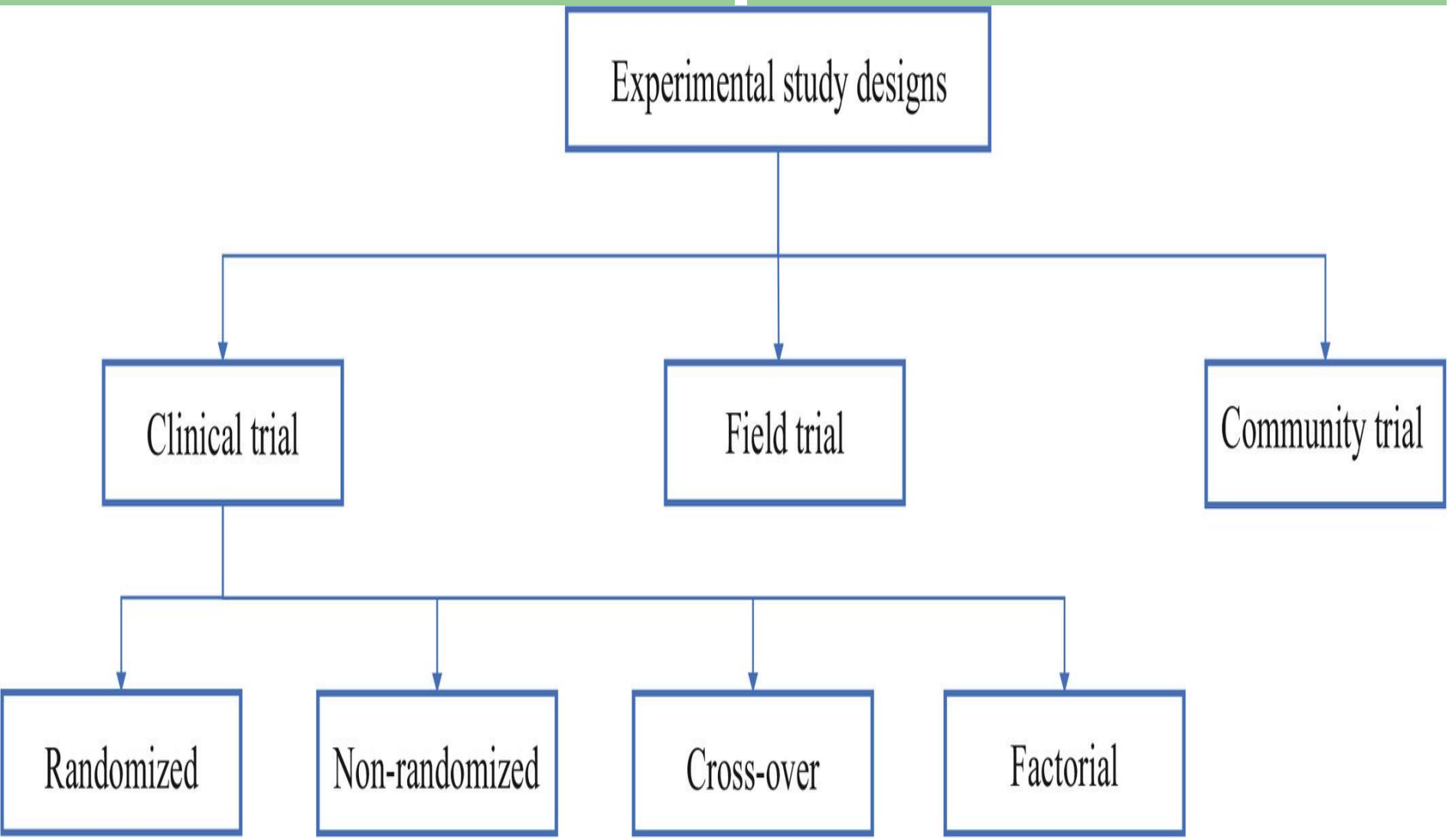
Quasi Experimental

Randomized Blocks

Latin Square

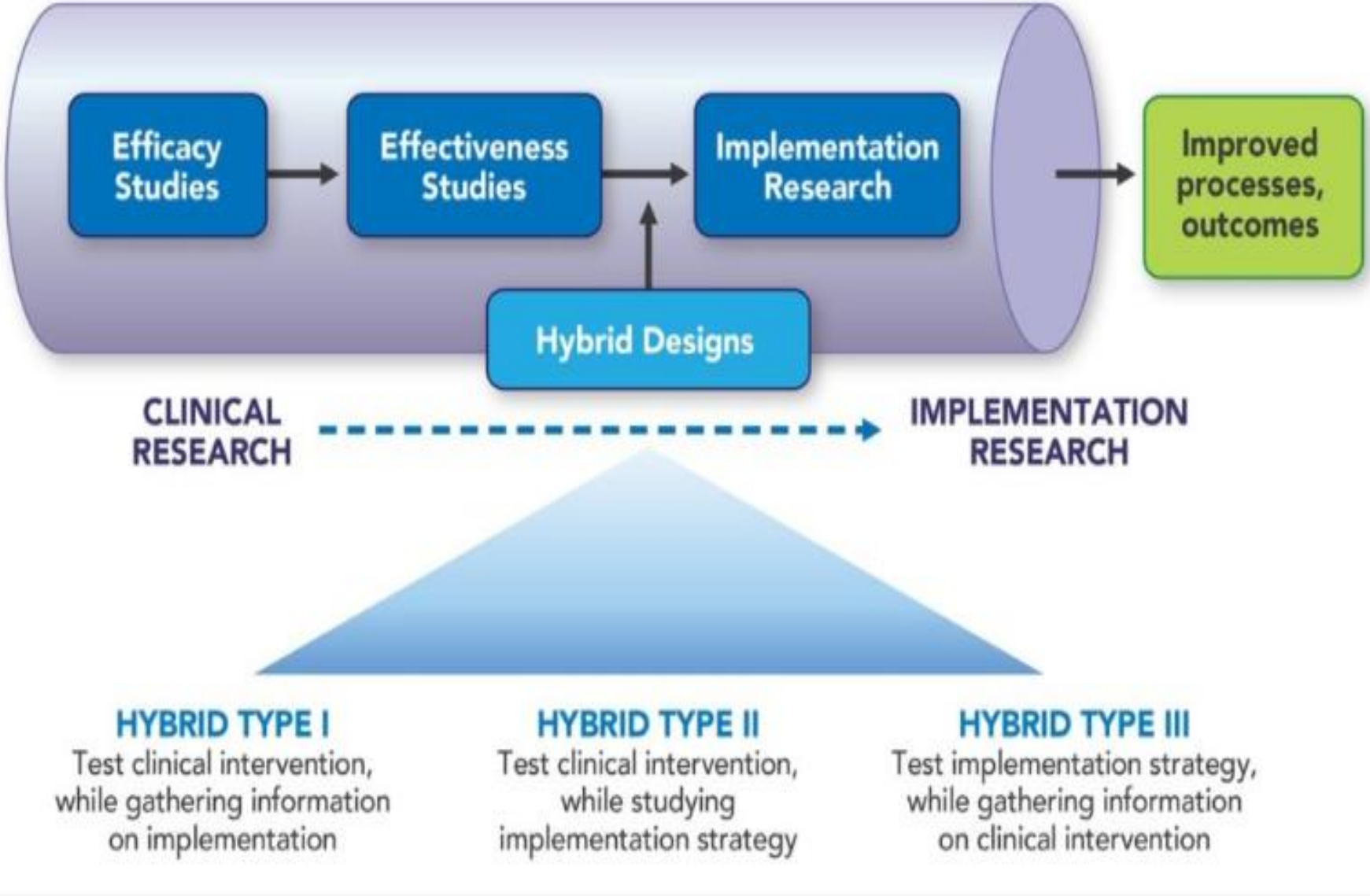
Factorial Design

Clinical research study designs



Source : Pediatric Investigation, Volume: 3, Issue: 4, Pages: 245-252, First published: 21 December 2019, DOI: (10.1002/ped4.12166)

Figure 1. Research Pipeline and Hybrid Designs[8,12]



https://www.evidera.com/white-paper-implementation-science/

Randomized controlled trials

- **Randomized controlled trials** are considered the gold standard type of study to assess the efficacy and safety of medications because they have defined endpoints and a set protocol

Contd….

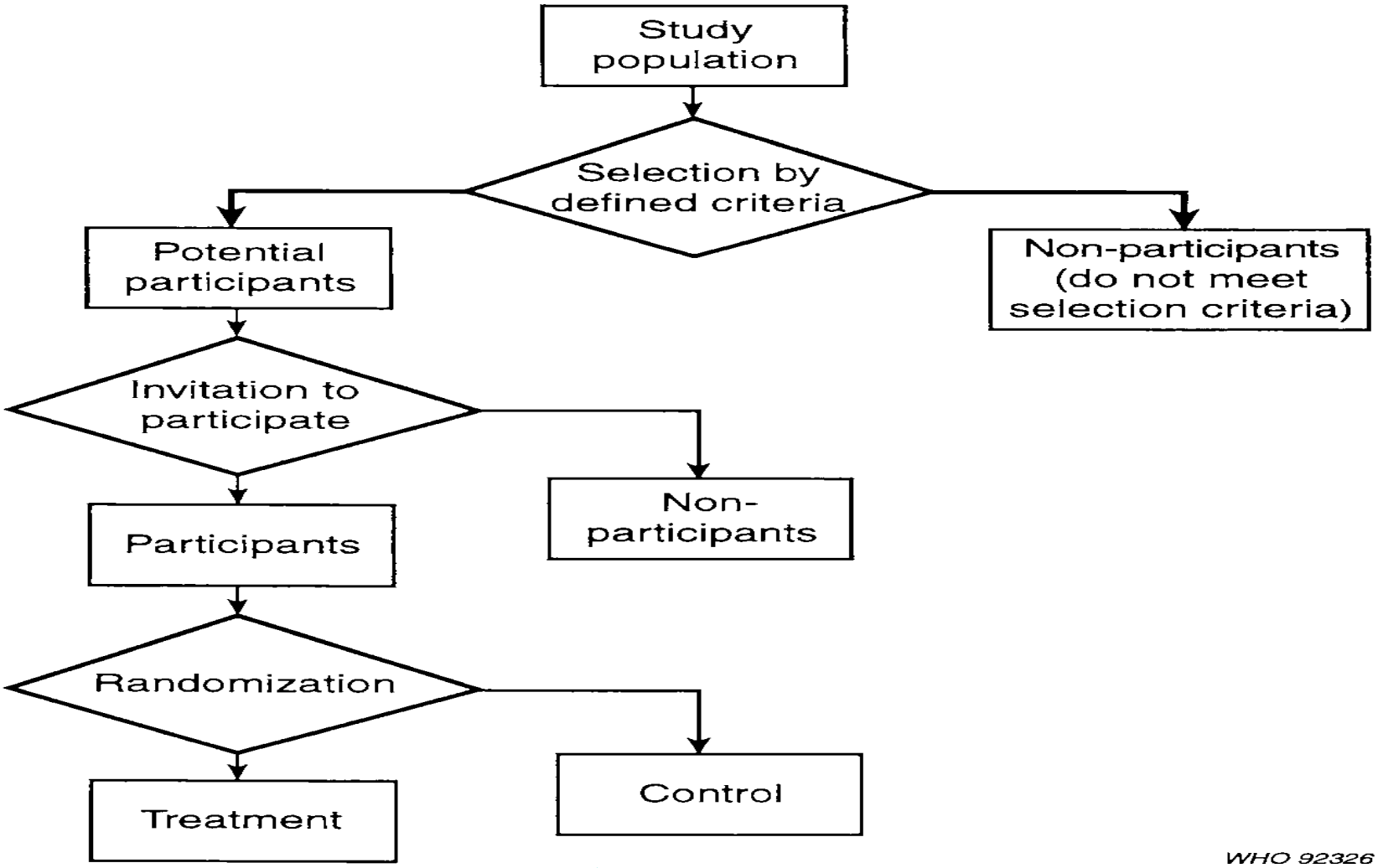
- Important scientific method to evaluate the effectiveness of interventions or preventive or therapeutics (treatments).

- An epidemiological experiment to study a new preventive or therapeutic regimen.

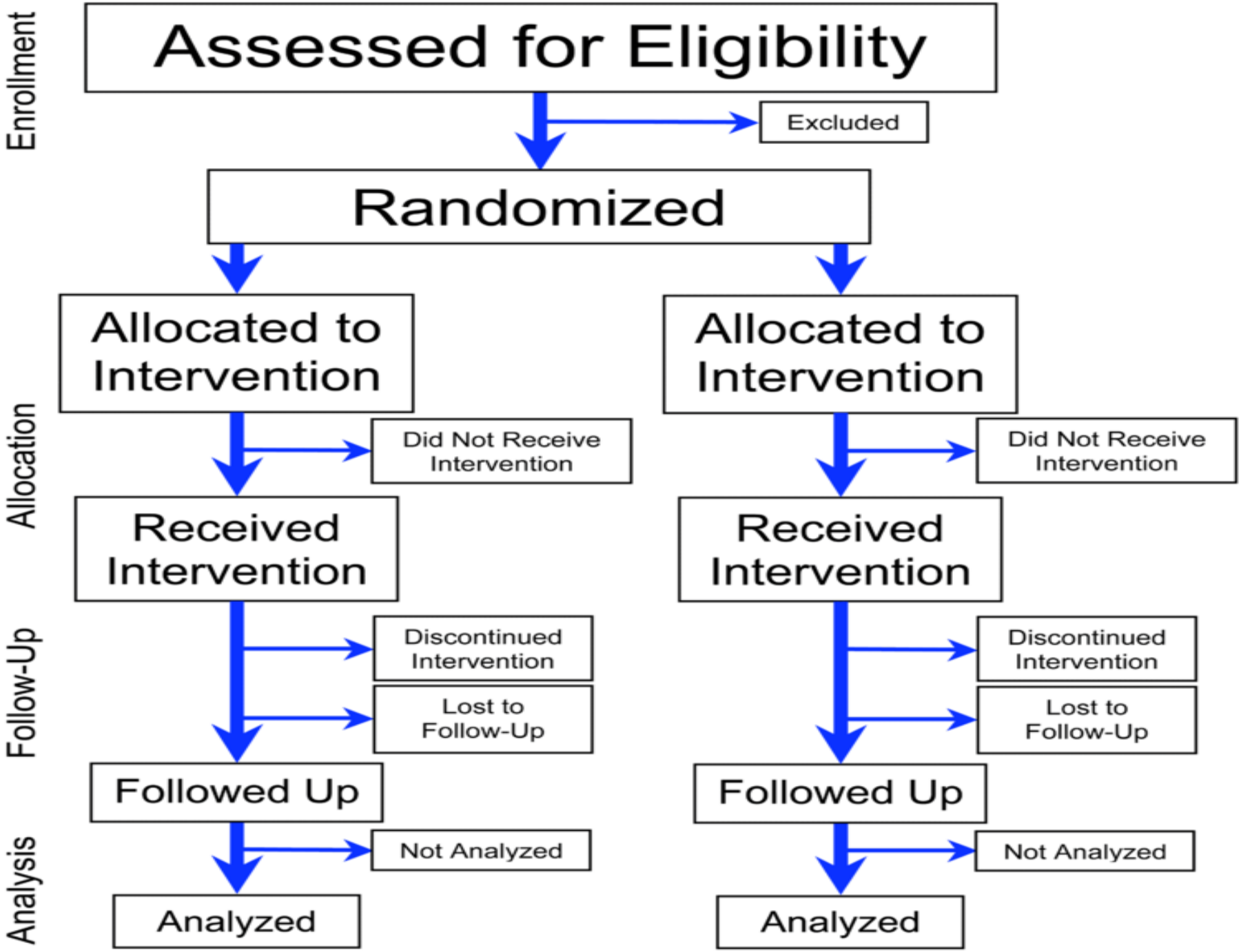
Contd…

- Subjects in a population are randomly allocated to groups, usually called treatment and control groups and the results are assessed by comparing the outcome in the two or more groups.

Design of RCT



Comparison


Enrollment
Assessed for Eligibility
Excluded
Randomized
Allocation
Allocated to Intervention
Did Not Receive Intervention
Received Intervention
Allocated to Intervention
Did Not Receive Intervention
Received Intervention
Follow-Up
Discontinued Intervention
Lost to Follow-Up
Followed Up
Discontinued Intervention
Lost to Follow-Up
Followed Up
Analysis
Not Analyzed
Analyzed
Not Analyzed
Analyzed

Steps in carrying out Randomized controlled trial

1. Drawing up a protocol
2. Selecting reference and experiment population
3. Randomization
4. Manipulation or intervention
5. Follow up
6. Assessment of outcome

Drawing up a Protocol

- Performed under strict protocol.
- The protocol specifies,
  - the aim and objectives of the study;
  - criteria for selection of study and control groups,
  - sample size,
  - procedure for allocation of subjects
  - treatments to be applied.

Selecting reference and experiment population

a. Reference population

- It is the population to which the findings of trial, if found successful are expected to be applicable.

- The reference population may comprise the population of a whole city or a population of school children and so on according to the nature of the study.

Contd..

b. Experimental or study population

- It is the actual population that participates in experimental study.

- Ideally, it should be randomly chosen from reference population, so that it has similar characteristics as the reference population.

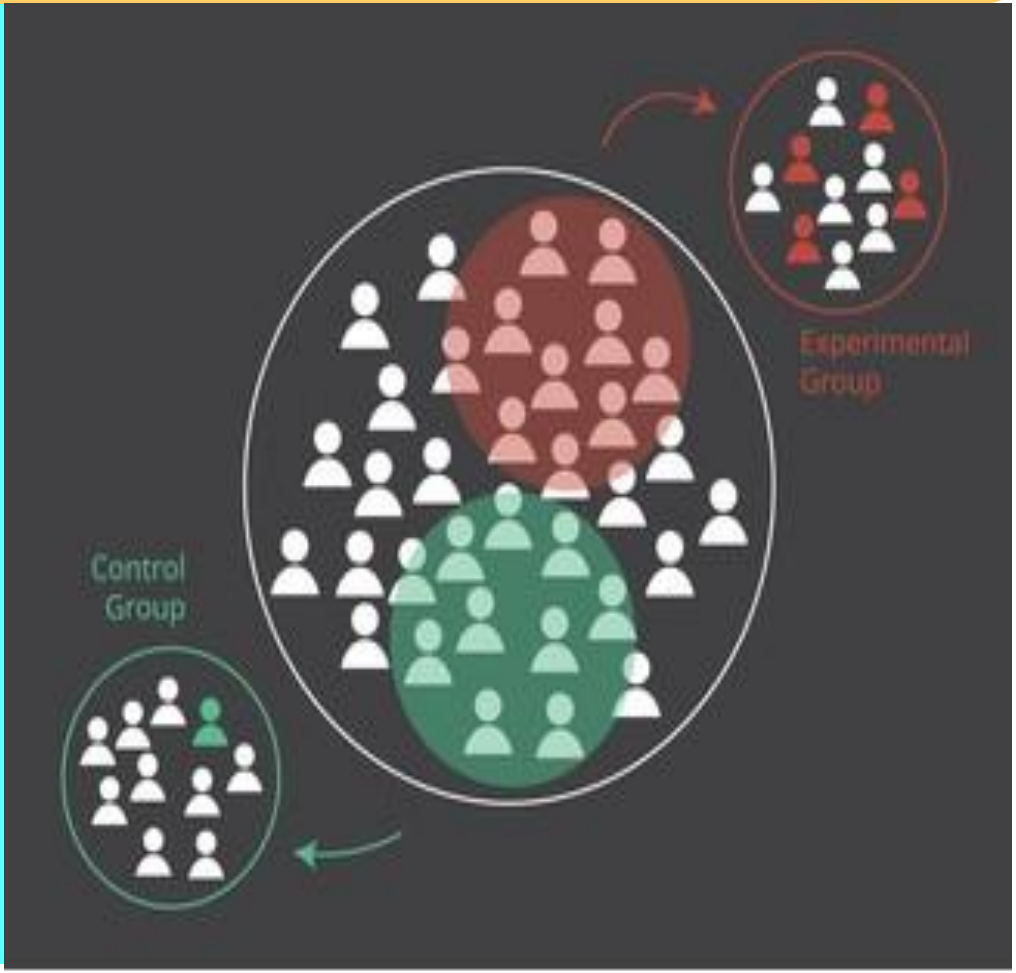
Contd…

The participants or volunteers must fulfill the following criteria,

- Must give informed consent
- Must be representative of population
- Qualify or eligibility for trial

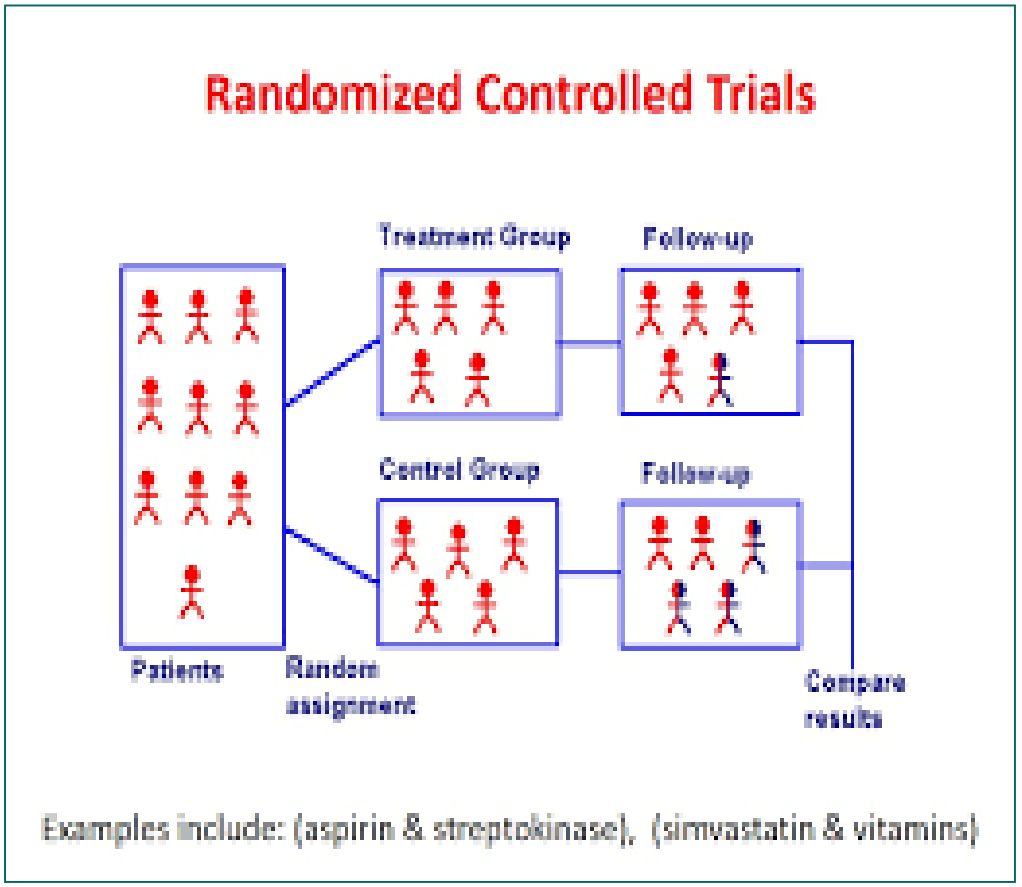
3. Randomization

- It is a statistical procedure by which the participants are allocated into groups usually called study and control or placebo group to receive or not to receive an experimental or preventive or therapeutic procedure.



Contd…

- Randomization is an attempt to eliminate bias or error.
- It is heart of the controlled trial.
- It will give the greatest comparability so that like can be compared with like.
- Randomization is done only after the participants have entered into the study.



4. Manipulation or intervention

- The manipulation creates an independent variable whose effect is then determined by measurement of final outcome which constitutes the dependent variable.

5. Follow up

- This implies examination of the experimental and control group subjects at defined interval of time in standard manner, with equal intensity.
- The follow up may be short or may require many years depending upon the study undertaken.

6. Assessment of Outcome

- The final step is to assess the outcome of trial in terms of positive results; that is benefits of experiment or effectiveness of intervention.
- Negative results is observed in terms of increase in severity, frequency and side effects and complications .
- The incidence of results rigorously compared in between experiment and placebo group.

Blinding

- To reduce the possible error while attempting epidemiological studies, a process in which one or more person concerned with experiment are unknown or blind about the status of study participants is called blinding.

Blinding can be classified into three types

- Single blinding: the trial is so planned that the participants are not aware whether they belongs to experiment or placebo group.
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POPULATIONS FOR ANALYSIS

Intention to Treat Analysis

All randomized patients are included in final data analysis

Per Protocol Analysis

Only patients who complete the trial according to protocol are analyzed

POPULATIONS FOR ANALYSIS

- Intention-to-treat population
  - All patients randomized regardless of follow-up or receipt of study intervention
- Per-protocol population excludes those who
  - Did not receive sufficient study intervention
  - Did not return for adequate follow-up
  - Had major violations of inclusion criteria
    - e.g., did not have the disease being studied
  - Had major violations during the study

INTENTION-TO-TREAT ANALYSIS
Example

- Comparison of radiology procedure (TIPS) vs. drug (β-blocker) for prevention of recurrent variceal bleeding with death as the primary endpoint

- If a patient is randomized to get TIPS and dies from bleeding before the procedure can be done, should the patient be included in the final data analysis?

POPULATIONS FOR ANALYSIS

- Choose the most conservative analysis
  - Less likely to favor intervention, be overly optimistic
- Superiority study
  - Per-protocol assesses intervention under optimal circumstances (not real world, ignores study quality)
    - e.g., excluded if non-adherence, protocol violations, drop-out
  - ITT avoids bias to treatment difference and superiority
- Non-inferiority study
  - ITT can bias to no treatment difference (non-inferiority)
    - e.g., non-adherence, drop-outs, misclassified subjects/endpoints
  - Per protocol analysis should be included

Outcome/s measurement

- Predefine presentation of data
  - Proportions vs. time-to-event curves
  - Mean vs. median
- Predefine statistical analyses
  - Comparisons for primary, additional outcomes
  - Subgroup analyses
  - Other analyses
    - e.g., multivariable analyses, sensitivity analyses

Contd…

- Null hypothesis
  - “True” proportion of success with treatment equals “true” proportion of success with control
- If the null hypothesis is correct and treatments are equally effective, p-value indicates
  - Probability of observing a difference between treatment and control at least this large
    - Probability that difference at least this large is due to chance

Drug trials

- Used to test new therapy or to compare the efficacy of new drugs with respect to gold standard available
- There are 4 Phases in the drug trial
- Conducted in human after the animal experimentation, if found safe.

PHASE-I(Clinical Pharmacology and Toxicity)

- Concerned with drug safety
- Performed among normal human population
- Objective is to determine an acceptable level of drug dose
- Studies metabolism, bioavaliability
- Takes up to 1 months
- Participants : 20-80

PHASE-II (Initial Investigation of effects)

- Small scale study of safety and efficacy
- Requires close monitoring of patients
- To study the genuine potential of drug
- Participants : 100-200/300
- Takes several months

PHASE-III (Full scale evaluation of drug)

- Most rigorous and extensive clinical investigation
- Done if the drug is found to be safe and effective in phase II.
- Comparison with gold standard methods available/placebo
- Sample size is based on statistical parameters

PHASE-IV(Post marketing surveillance)

- In this phase, monitoring of long term effects, morbidity and mortality due to drug
- Pharmaco-epidemiology, pharmaco-economics, efficiency, drug interactions can be studied.

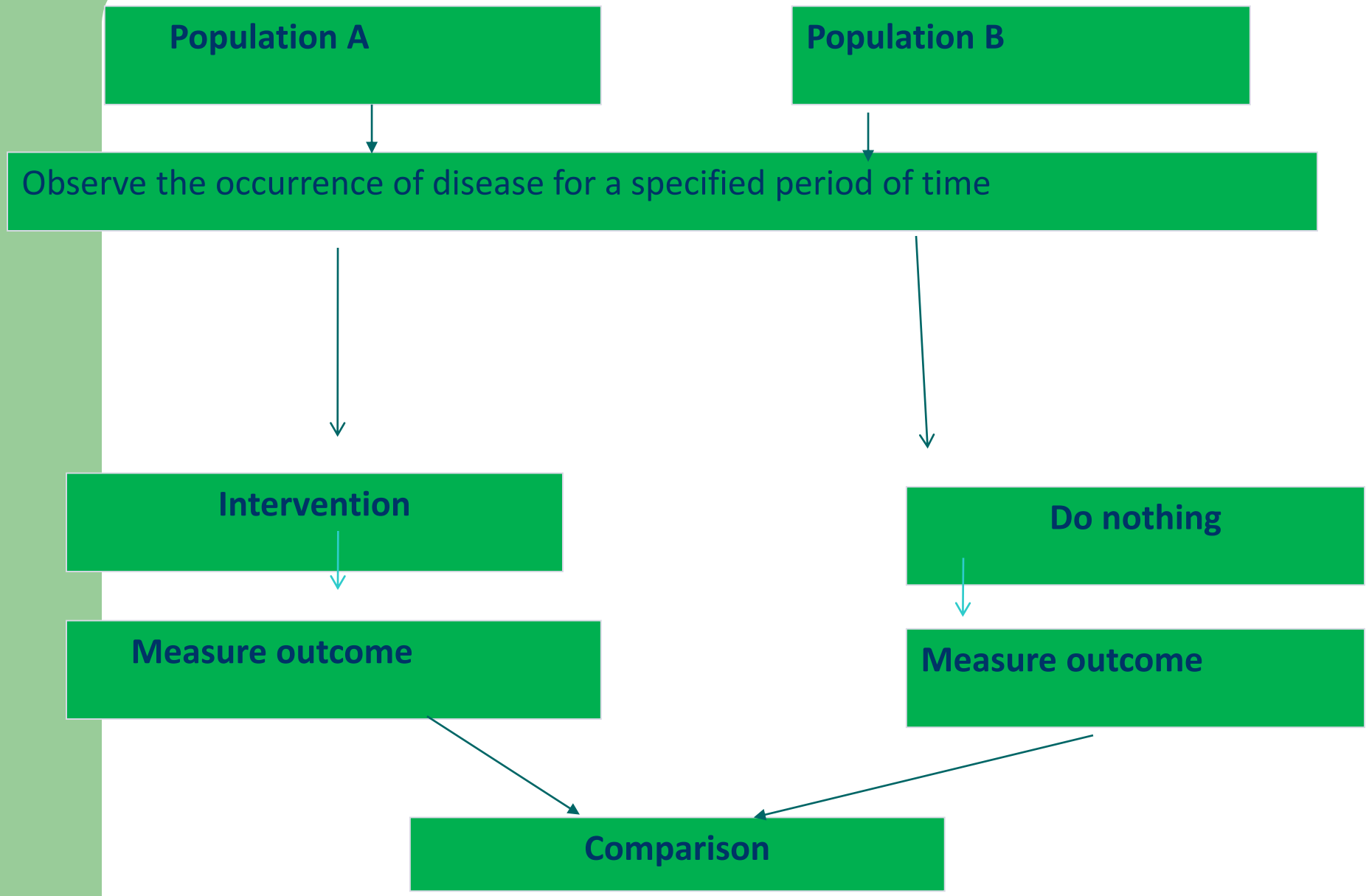
Community Trial

- Community interventions are types of experimental study designs that greatly enhance the potentials to make widespread impact on health of population.
- Typical community interventions are oriented towards education and behavior change.
  - Eg. Stopping smoking and control of alcohol abuse etc.

Contd…

- The treatment groups are communities rather than individuals.
- Appropriate for diseases that have their origins in social conditions
  - E.g. Cardiovascular disease
- A limitation: random allocation of communities is not practicable.

Community Trial….



Field Trials

- Involve people who are disease free but presumed to be at risk; data collection takes place in the field.

- Since the subjects are disease free and the purpose is to prevent the occurrence of diseases that may occur with relatively low frequency.

Contd…

- Are used to evaluate interventions aimed at reducing exposure without necessarily measuring the occurrence of health effects.

- Such intervention studies can often be carried out on a small scale at low cost.

  - E.g. one of the largest field trials ever undertaken was that of the Salk vaccine for the prevention of poliomyelitis, involving over million children.

Estimation and quantification of impacts

- Can be Measured by:
  - Relative Risk
  - Odds Ratio
  - Attributable Risk
  - Population Attributable Risk

Attributable risk:

- Also called an excess risk or absolute risk or risk difference.
- The extent to which the occurrence of a disease or other outcome variables can be attributed to a particular factor.

Contd…

- It is the difference between the incidence rates of outcome of interest among exposed group to the incidence rate among non exposed groups.
- It is denoted by AR.

AR = Incidence among exposed group – incidence among non expose

- Importance: It is useful measure of the extent of the public health problem caused by exposure.

Attributable fraction

- Attributable fraction or etiological fraction is the ratio of risk differences to the rate of occurrence of disease among exposed group.

AF= Attributable risk / Incidence among exposed group.

- It is the proportion of the diseased population that would be eliminated in the absence of exposure.
- Attributable fraction is the useful tool for assessing priorities for public health action.

Attributable Risk (Risk Difference)

Interpretation:

- AR = 0: Risk in exposed is same as unexposed
- AR > 0: Exposure is harmful
- AR < 0: Exposure is protective

Note:

It is useful in public health to eliminate exposure to what is known to cause disease for a large proportion of the population.

Example

Attributable Risk: Interpretation

- % AR_{exp} = 83%
- If we remove exposure, the risk of the outcome in the exposed would be reduced by 83%, from 1.8% to 0.3%.
- But, can't say that this exposure caused the outcome in only this 83%. Might have been the cause in 100% of the exposed.

Population Attributable Risk(PAR)

- It is the difference in the incidence of specific health problem in the general population to the non exposed group.
- Denoted by PAR
- Calculated as,

Incidence of disease in general population – incidence of disease among non exposed.

or (IR in population –IR in non exposed)

Population Attributable Risk (PAR)

Prospective Study

Contingency (or 2 x 2) Table

	Cases	Controls	Total
Exposed	a	b	a+b
Unexposed	c	d	c+d
Total	a+c	b+d	a+b+c+d

$$PAR = [IT - IU] / IT$$
$$= [p_e(RR-1)] / [p_e(RR-1)+1]$$

(p_e = exposure rate in the general population)

Note: IT= incidence in total; IU= Incodence in unexposed
RR= relative Risk or RIsk Ratio

Implications

- It is useful for determining the relative importance of exposure for entire population
- It is the proportion by which incidence rate of outcome in the population would be reduced if exposures are eliminated

Population attributable fraction

Population Attributable fraction is the ratio of risk differences in IR in population and the non exposed group to the rate of occurrence of disease among population. It is also called the Population Attributable Proportion or Attributable Proportion among the total population.

PAF= PAR / Incidence among general population

Population Attributable Risk (PAR)

$$PAR = I_{total} - I_{nonexposed}$$

Diabetes

Weight	Yes	No	
Obese	850	3650	4500
Slim	250	5250	5500
	1100	8900	10000

$I_T = 1100 / 10000$

$= 0.11 = 110 / 1000$

$I_{NE} = 250 / 5500$

$= 0.0455 = 45.5 / 1000$

(background risk)

$$PAR = (110 - 45.5) / 1000 = 64.5 / 1000$$

Note: The PAR% quantifies the contribution of the risk factor to the outcome and can thus help direct interventions. The higher the PAR%, the greater the proportion of the outcome that is attributable to the risk factor.

Overview of Attributable Risk Measures

General Interpretation

Attributable Risk: The risk of an outcome attributed to a given risk factor ***among those with that factor***

Attributable Fraction: The ***proportion*** of cases of an outcome attributable to a risk factor ***in those with the given risk factor***

Pop. Attributable Risk: The risk of an outcome attributed to a given risk factor ***in the population as a whole***

Pop. Attributable Fraction (PAF): The proportion of cases of an outcome attributable to a risk factor **in the population as a whole**

Strengths and limitations of experimental studies

Strengths
Confounders factors affect poorly
Blinding supports validity of study
Facilitate statistical calculation
Strongest study, most scientific

Limitations
More ethical issues
Costly
Time consuming
Requires more expertise and skills

Methods of synthesis and quantification of evidences in epidemiology

KNOWLEDGE SYNTHESIS: AN ENGINE FOR TRANSLATIONAL EPIDEMIOLOGY

- Knowledge synthesis is a systematic approach to reviewing the evidence on what we know and what we do not know, and how we know it.
- Knowledge synthesis methods, such as meta-analysis, are becoming standard in developing evidence-based recommendations for practice (T2 research).
- The Cochrane Collaboration
- Other independent groups, such as the US Preventive Services Task Force

The Emergence of Translational Epidemiology: From Scientific Discovery to Population Health Impact. Khoury M J et al. Am. J. Epidemiol. 2010;172:517-524

Meta-analysis

- Evidence synthesis is a type of research method that allows researchers to bring together all relevant information on a research question.
- This can be useful to identify gaps in knowledge, establish an evidence base for best-practice guidance, or help inform policymakers and practitioners.

Contd….

- Evidence synthesis includes literature review, systematic review and meta-analysis to combine various sources of quantitative evidence.

- Appropriate methods will depend on the purpose of the synthesis, the number and similarity of studies included in the review, the level of detail available from the studies, the nature of the results reported in the studies, the expertise of the synthesis team and the resources available.

Establish evidence needs (data, time frame); formulate research question

Establish knowledge synthesis approach (e.g. systematic review); draft review protocol

Conduct systematic electronic literature search

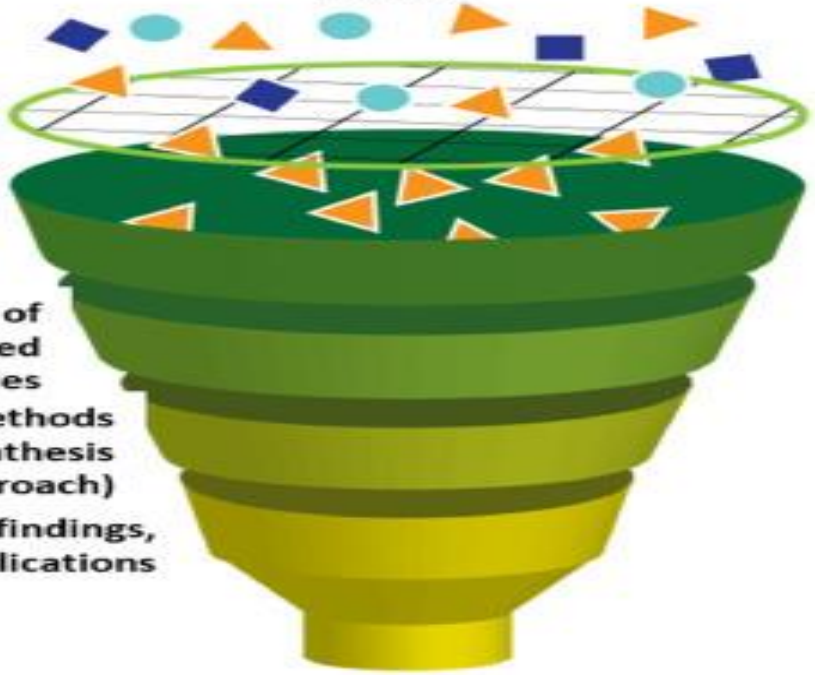
Carefully screen and select studies for inclusion

Gather data from included studies

Appraise the risk of bias of included studies

Synthesize evidence (using methods appropriate to knowledge synthesis approach)

Interpret findings, discuss implications



Develop summary report of review; disseminate to end users (using publications, presentations and other means of knowledge translation)

https://www.youtube.com/watch?v=FK8NkpLWJeI

Systematic Review and Meta-analysis

Systematic Review

- A systematic review is defined as “a review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyze data from the studies that are included in the review.”

Contd…

- Systematic reviews aim to identify, evaluate and summarize the findings of all relevant individual studies, thereby making the available evidence more accessible to decision makers. When appropriate, combining the results of several studies gives a more reliable and precise estimate of an intervention's effectiveness than one study alone.

- Systematic reviews adhere to a strict scientific design based on explicit, pre-specified and reproducible methods. Because of this, when carried out well, they provide reliable estimates about the effects of interventions so that conclusions are defensible

Contd….

- A systematic review attempts to collect and analyze all evidence that answers a specific question.
- The question must be clearly defined and have inclusion and exclusion criteria.
- A broad and thorough search of the literature is performed and a critical analysis of the search results is reported and ultimately provides a current evidence-based answer to the specific question.

What is the significance of Systematic Reviews?

- The large amount of medical literature requires clinicians and researchers alike to rely on systematic reviews in order to make an informed decision.

- Systematic Reviews minimize bias. “A systematic review is a more scientific method of summarizing literature because specific protocols are used to determine which studies will be included in the review.”

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD, “Clinical Perspective: A Practical Guide to Meta-Analysis.” The Journal of Hand Surgery. Vol. 31A No.10 December 2006. p.1671

Key Characteristics of Systematic Reviews

- Clearly stated title and objectives
- Comprehensive strategy to search for relevant studies (unpublished and published)
- Explicit and justified criteria for the inclusion or exclusion of any study
- Clear presentation of characteristics of each study included and an analysis of methodological quality
- Comprehensive list of all studies excluded and justification for exclusion

Contd…..

- Clear analysis of the results of the eligible studies
  - statistical synthesis of data (meta-analysis) if appropriate and possible;
  - or qualitative synthesis

- Structured report of the review clearly stating the aims, describing the methods and materials and reporting the results

An author of a good Systematic Review…

- Formulates a Question
- Conducts a Literature Search
- Refines the search by applying predetermined inclusion and exclusion criteria
- Extracts the appropriate data and assess their quality and validity
- Synthesizes, interprets, and reports data

Hypothesis

- “A systematic review should be based on principles of hypothesis testing, and the hypotheses must be conceived a priori.

Focus of the Question

- The structured question will determine the inclusion and exclusion criteria:
  - What is the population of interest?
  - What are the interventions?
  - What are the outcomes of interest?
  - What study designs are appropriate?

Inclusion/Exclusion Criteria

- “Once the study question is formalized, the authors must compose a comprehensive list of inclusion and exclusion criteria.”
- “To avoid selection bias, inclusion and exclusion criteria should be agreed upon and formalized before data extraction and analysis.”

Literature Search

- “A comprehensive and reproducible literature search is the foundation of a systematic review.”

Literature Search Challenges

- **Database Bias** - “No single database is likely to contain all published studies on a given subject.”
- **Publication Bias** - selective publication of articles that show positive treatment of effects and statistical significance.
  - Hence, it is important to search for unpublished studies through a manual search of conference proceedings, correspondence with experts, and a search of clinical trials registries.

Contd….

- **English-language bias** - occurs when reviewers exclude papers published in languages other than English

- **Citation bias** - occurs when studies with significant or positive results are referenced in other publications, compared with studies with inconclusive or negative findings

Data Collection

- “The list of data to be extracted should be agreed upon a priori consensus during the design stage of the study.”

- Collected data includes:
  - Study characteristics
  - Sample demographics
  - Outcome data

Contd…

- “It is necessary to design a review-specific data extraction form, so that the same data are extracted from each study and missing data are clearly apparent.”

- “To ensure that data extraction is accurate and reproducible, it should be performed by at least two independent readers.”

Quality Assessment

- "The validity of a systematic review ultimately depends on the scientific method of the retrieved studies and the reporting of data."

- Randomized Controlled Trials (RCT):
  - RCT are considered to be more rigorous than observational studies
  - A review based on well-designed RCT will likely be more valid and accurate than a review based on observational studies or case reports

Contd….

- “The most common way to assess and report study quality has been using a composite, numerical scoring instrument.”

- “More than 35 different quality assessment instruments have been published in the literature, and most are designed for randomized clinical trials.”

Jadad score & Chalmers score

- "The Jadad score and the T.C. Chalmers score are two examples of quality assessment instruments."

Jadad Score:

- **Randomization (2 points possible)**
  - 1 point if study described as randomized
  - Add 1 point if randomization method described and appropriate (e.g. random numbers generated)
  - Deduct 1 point randomization described and inappropriate
- **Double-blinding (2 points possible)**
  - 1 point if study described as double-blinded
  - Add 1 point if method of double-blinding described and appropriate
  - Deduct 1 point if double-blinding described and inappropriate
- **Withdrawals (1 point possible)**
  - Give 1 point for a description of withdrawals and drop-outs

Jadad Score Example

Study	Randomization	Blinding	Drop-out
1	++	+	++
2	+	++	0
3	++	0	+
4	+	++	++
5	0	++	+

Data Synthesis

- “Once the data have been extracted and their quality and validity assessed, the outcomes of individual studies within a systematic review may be pooled and presented as summary outcome or effect”
- The authors summarize heterogeneous data qualitatively
  - “Data that are very conflicting and widely variable should not, under most circumstances, be combined numerically.”

Meta-Analysis

- “Meta-analysis is a statistical technique for combining the results of independent, but similar, studies to obtain an overall estimate of treatment effect.”

- “While all meta-analyses are based on systematic review of literature, not all systematic reviews necessarily include meta-analysis.”

Contd…

- “If a meta-analysis is to be included in a systematic review, an experienced statistician or an epidemiologist should be consulted during all phases of the study.”

- “Protocols for the reporting of meta-analysis results were developed for RCTs (Quality of Reports of Meta-analysis [QUOROM] and Observational Studies in Epidemiology [MOOSE].”

Protocols

- The purpose of QUOROM and MOOSE guidelines is to provide proper procedures for conducting a meta-analysis and to standardize the methods of reporting a meta-analysis.

Steps of Meta-analysis

- Define the Research Question
- Perform the literature search
- Select the studies
- Extract the data
- Analyze the data
- Report the results

Meta-analysis: The Research Question

- “Common questions addressed in meta-analysis are whether one treatment is more effective than another or if exposure to a certain agent will result in disease.”

Meta-analysis: Performing the Literature Search

- “The literature search is a critical step in the meta-analysis and often the most difficult part.”
- MEDLINE to ensure a comprehensive search.”
- EMBASE, and CINAHL.
- Search for unpublished clinical trials in the Cochrane Central Register of Controlled Trials

Meta-analysis: Study Selection

- "The inclusion and exclusion criteria for studies needs to be defined at the beginning, during the design stage of the meta-analysis."
  - "Factors determining inclusion in the analysis are study design, population characteristics, type of treatment or exposure, and outcome measures."

- Meta-analysis needs to be documented
  - "One should keep track of the studies included and excluded at each step of the selection process to document the selection process."

Contd…

- “The QUOROM guidelines for reporting a meta-analysis requests that investigators provide a flow diagram of the selection process.”

The Validity of a Meta-analysis

- “The validity of a meta-analysis depends on the quality of the studies included, and an assessment of quality is a necessary part of the process.”

Meta-analysis: Extracting the Data

- “The type of data to be extracted from each study should be determined in the design phase and a standardized form is constructed to record the data.”

Meta-analysis: Data

- What are the examples of data commonly extracted?
  - Study design, descriptions of study groups, diagnostic information, treatments, length of follow-up evaluation, and outcome measures.
  - “The difficulty with data extraction is that studies often use different outcome metrics, which make combining the data awkward. The data should be converted to a uniform metric for pooling.”

Meta-analysis: Analyzing the Data

- There are 2 statistical models used in a meta-analysis:
  - Fixed effects
  - Random effects

The Fixed Effects Model

- “The fixed-effects model assumes that the true effect of treatment is the same for every study.”

The Random Effects Model

- “The random effects model assumes that the true effect estimate for each study vary.”

Meta-analysis: Reporting the Results

- A meta-analysis should include:
  - A title, abstract, an introduction
  - Methods, results, and discussion sections

The Introduction

- “The introduction should indicate the clinical question of interest, the hypothesis being tested, the types of treatment or exposure being studied, the study designs to be included, and a description of the study population.”

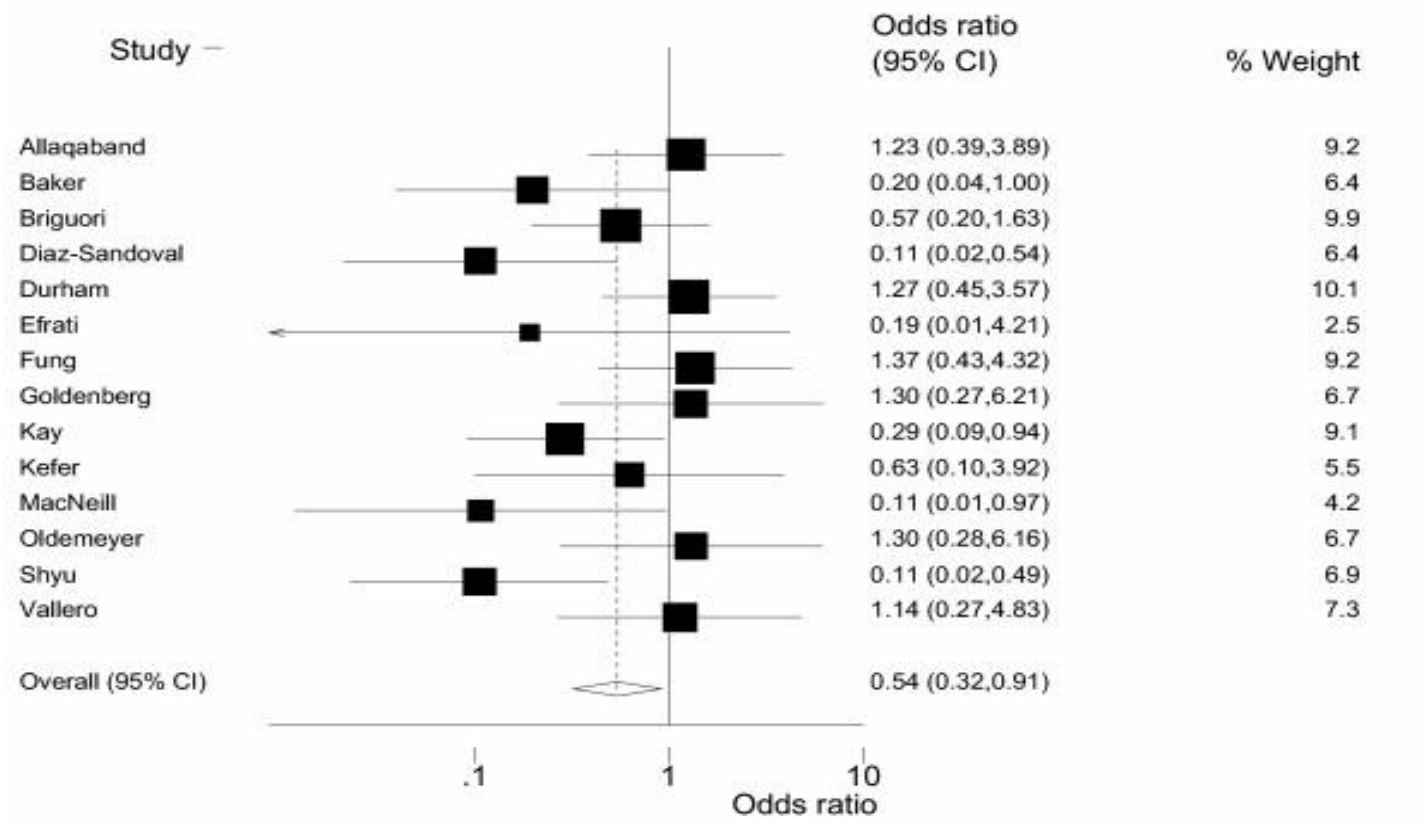
The Methods Section

- “The methods section should
  - describe the literature search, specifically the databases used, and if the search was restricted in any way.
  - The selection process for articles, quality assessment, methods of data abstraction, and synthesis.”

The Results Section

- The results section should
  - Include a flow chart of studies included
  - A figure displaying the results from each individual study (forest plot), results of heterogeneity testing, overall summary statistic, and results of a sensitivity analysis and meta-regression, if performed.

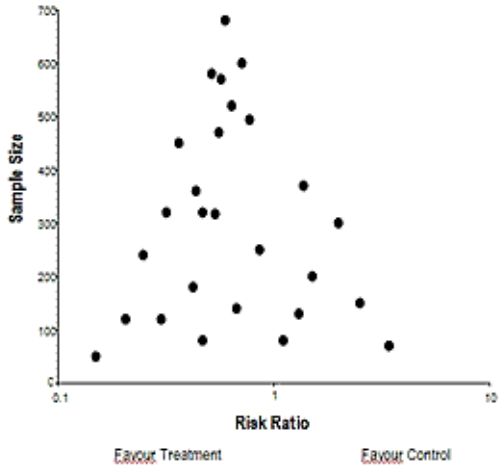
A Forest Plot

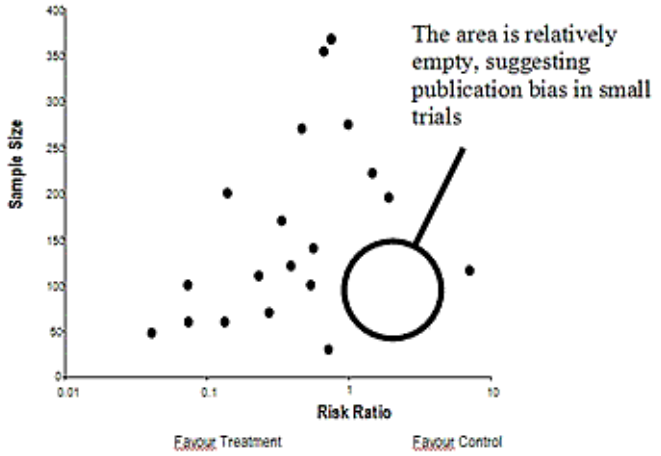


A Funnel Plot

- "A funnel plot is used as a way to assess publication bias in meta-analysis."

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1676





Systematic review Vs Literature search

	Systematic Review	Literature Review
Definition	High-level overview of primary research on a focused question that identifies, selects, synthesizes, and appraises all high quality research evidence relevant to that question.	Qualitatively summarizes evidence on a topic using informal or subjective methods to collect and interpret studies.
Goals	Answer a focused clinical question Eliminate bias	Provide summary or overview of topic
Question	Clearly defined and answerable clinical question Recommend using PICO as a guide	Can be a general topic or a specific question
Components	Pre-specified eligibility criteria Systematic search strategy Assessment of the validity of findings Interpretation and presentation of results Reference list	Introduction Methods Discussion Conclusion Reference list
Number of Authors	Three or more	One or more
Timeline	Months to years Average eighteen months	Weeks to months
Requirements	Thorough knowledge of topic Perform searches of all relevant databases Statistical analysis resources (for meta-analysis)	Understanding of topic Perform searches of one or more databases
Value	Connects practicing clinicians to high quality evidence Supports evidence-based practice	Provides summary of literature on a topic

Relationship of different reviews

Literature Review

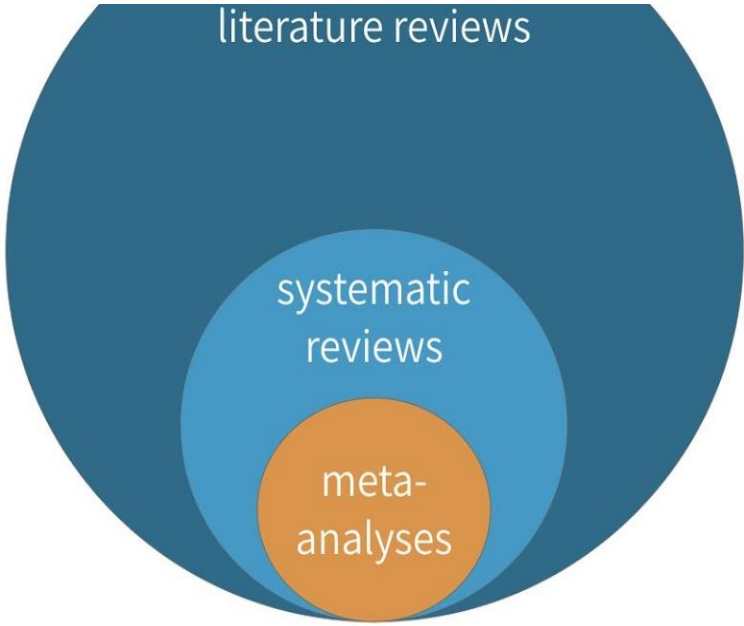
- **Summarizes** a topic that is **broad** in scope (e.x. cancer treatment)
- **Qualitative**
- May use sources that are **biased**
- Does **not** define what types of studies will be included (looks at everything)

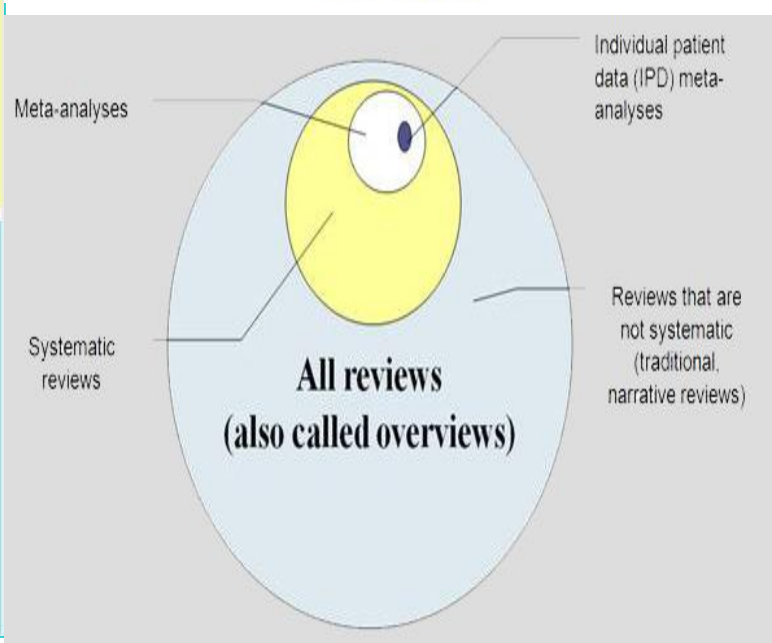
Systematic Review

- Answers a **specific clinical question** (e.x. **PICO**) (e.x. Is Vitamin C or Chemotherapy a better cancer treatment in patients over the age of 40?)
- **Defines** a specific search strategy; lists what will be **included and excluded** in articles selected
- Can include a meta-analysis within the review (but no necessary)

Meta-Analysis

- Looks at studies from a systemic review
- Purpose: Combines similar studies and pulls **data** to get a **statistically** significant result
- Important because **statistical analysis** may overturn results of smaller clinical trials






thank
you