Lecture 7 Experimental study--- Randomized trial

Lina Wang, MD, Ph.D

Department of Epidemiology and Biostatistics
School of Public Health
Southeast University
Phone: 025-83272569 (o)
E-mail: lnwang@seu.edu.cn

Southeast University

School of Public health

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检索试验

项目筛选条件

注册题目		正式科学名		研究课题代号(代码)	
注册状态	不限	注册号		在其它机构的注册号	
	筛选结果 更多筛选				

共检索到26051个符合检索条件的试验。

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历史版本	ChiCTR1900026601	高频和低频脑深部电刺激治疗帕金森病冻结步态的疗效差异分析 首都医科大学附属北京天坛医院	干预性研究	2019/10/15
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历史版本	ChiCTR1900026599	肥胖与择期心脏手术患者预后相关性：一项前瞻性队列研究 四川大学华西医院		2019/10/15
历史版本	ChiCTR1900026598	双任务步行训练对卒中患者运动及认知功能的影响 华北理工大学	干预性研究	2019/10/15
历史版本	ChiCTR1900026597	傅小娟医师：请上传完整版伦理审批文件。 罗沙司他对腹膜透析患者残肾功能的影响 成都医学院第一附属医院	干预性研究	2019/10/15
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Introduction

Experimental studies are conducted to assess the effect of a treatment using a drug, or intervention using a preventive agent, etc.

- Treatment/Intervention
- Prevention
- Early detection/screening
- Diagnostic
- Quality of life/supportive care

Experimental studies

- Randomized trial
- Field trial
- Community trial

Randomized Trial

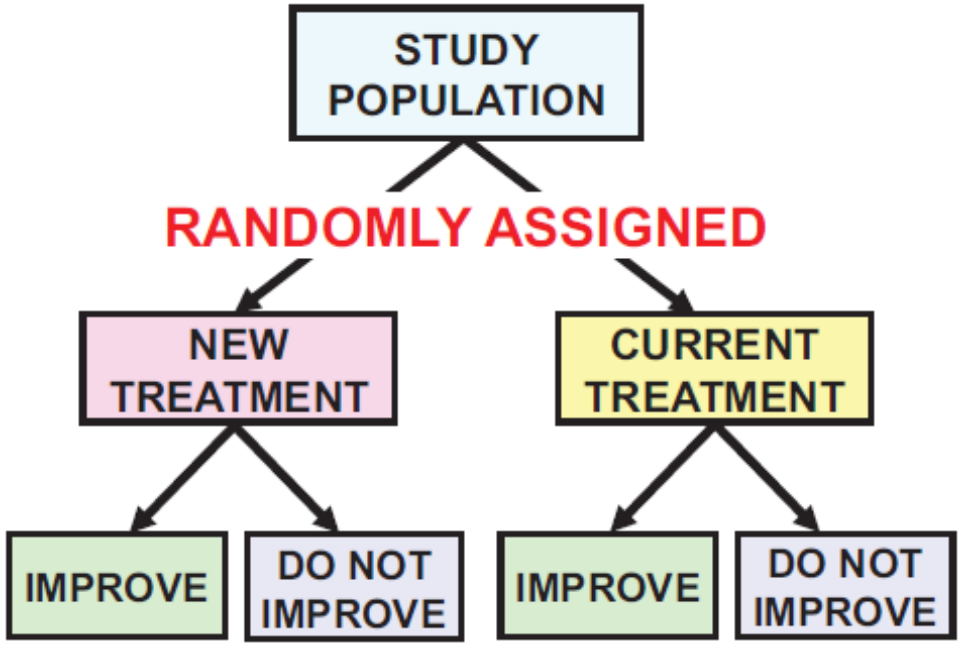
- Randomized trial: The ideal design for evaluating both the effectiveness and the side effects of new forms of intervention.
- Purpose:
  - evaluation of new drugs and other treatments of disease
  - assess new programs for screening and early detection
  - assess new ways of organizing and delivering health services

- Since the randomized trial design has major applicability to studies outside the clinical setting, such as community-based trials, we will refer to the term “randomized trial”, rather than “randomized *clinical* trial” in this lecture.

Definiton of RCT:

- A study design in which the investigator actively controls who is exposed and who is not. Subjects are randomly assigned to various treatment groups and followed to observe outcomes.

Basic design of a randomized trial



- Begin with a defined population that is randomized to receive new treatment or current treatment.
- Follow the subjects in each treatment arm.
- Compare the outcome (how many are improved) in the new and current treatment groups.
- Other possibilities:
  - may compare more than two groups
  - may compare “new treatment” with “no treatment”, but only if ethical

Steps in conducting randomized clinical trials

1.Specify Hypothesis

2.Specify target and source of populations

3 Define endpoints/possible side effects of intervention

4.Selection of subject(inclusion and exclusion criteria)

5. Obtain informed consent from those willing to participate

6.Randomize to treatment

7.Data collection on subjects(blindness)

8.Follow-up study groups for outcomes

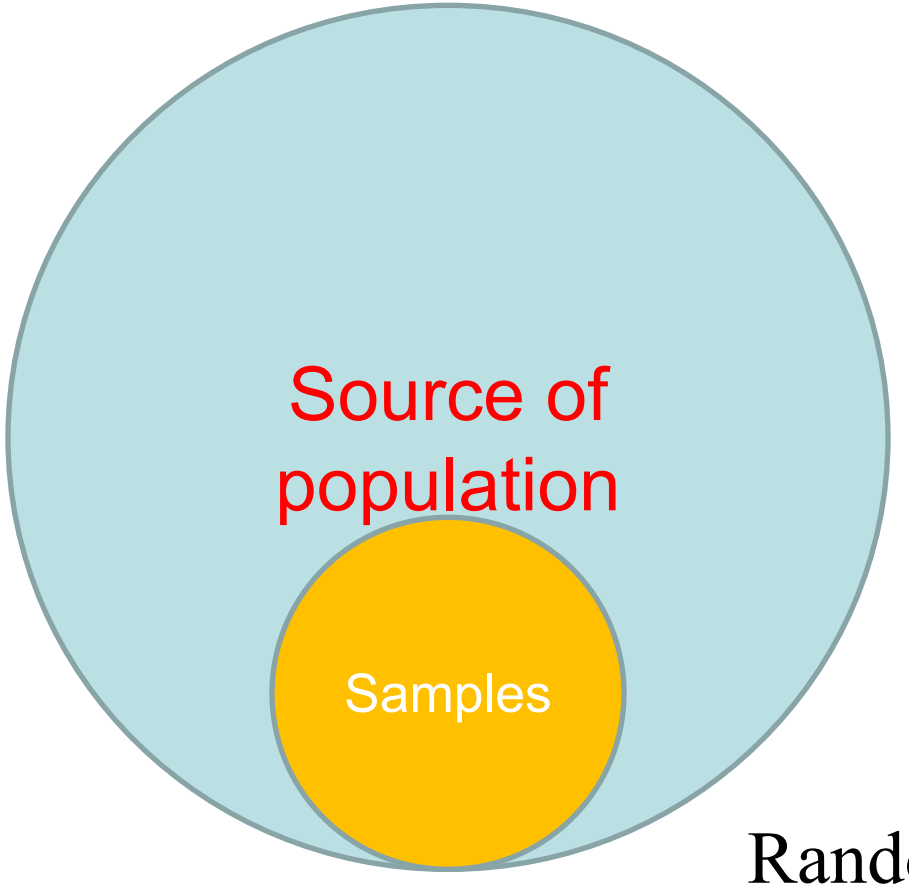
9. Analyze results: Use “Intention to treat” analyses

10. Establish procedures for terminating the trial and informing subjects of results.

1. Specify Hypothesis

- Purpose:
  - evaluation of new drugs and other treatments of disease
  - assess new programs for screening and early detection
  - assess new ways of organizing and delivering health services

- **2. Specify target and source of populations:**



Random Selection

3. Define endpoints/possible side effects of intervention:

Table 7–1. Types and examples of end points used in clinical trials.

Type of End Point	Example
Quality of life	Ability to perform usual daily tasks
Survival	Percentage of patients alive 1 year after entering trial
Complications	Percentage of patients who develop serious allergic reactions
Intermediate measures	Percentage of patients who have recurrence of symptoms

4.Selection of subject(inclusion and exclusion criteria)

- The inclusion and exclusion criteria must be *written* in great precision *before the study begins*.
  - Must be replicable by others.(randomization)
  - No subjective decision-making on the part of the investigator in deciding who is included or not included in the study.

5. Obtain informed consent from those willing to participate:

1. **Informed consent:**

   An agreement (signed) that the subject understands the benefits and risks of the study.

2. **Human Subjects Protection Committees:**

   act as watchdogs…review research applications the be sure they comply with issues pertaining to protection of human subjects. To receive research money from NIH (and other agencies), these committees must approve grand proposals. Require that all subjects must read and sign “Informed Consent” form.

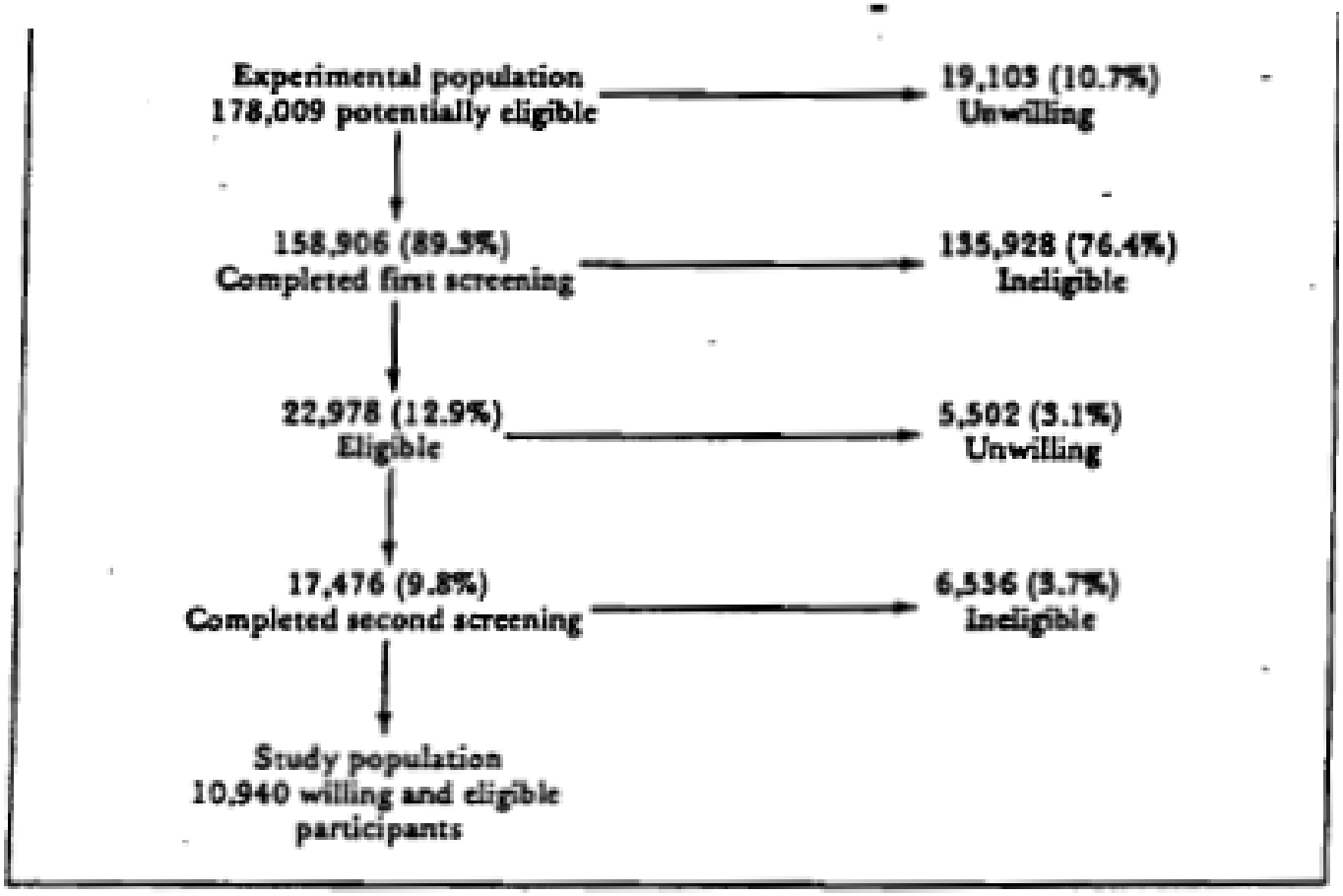
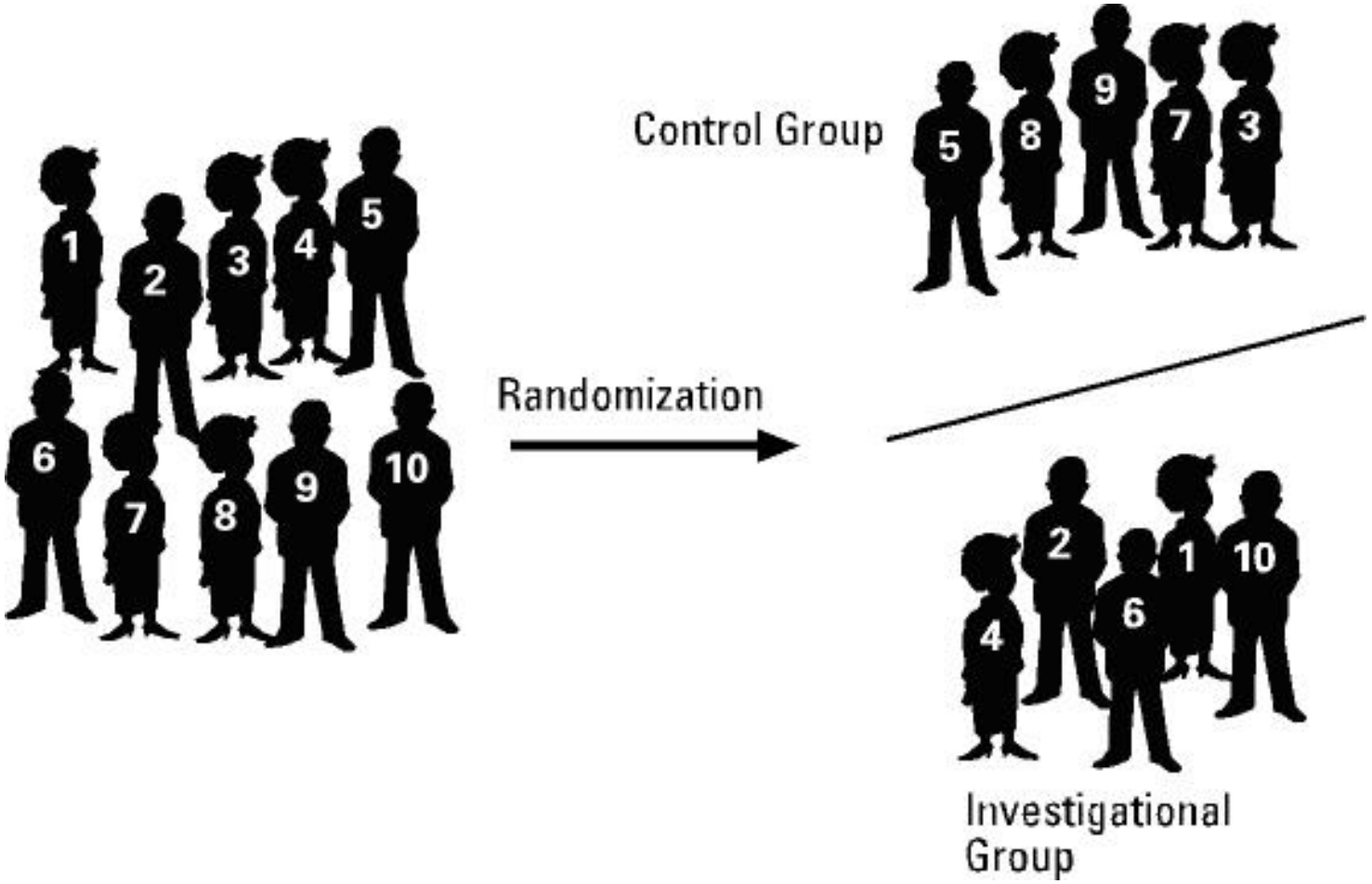


Fig. 8-2. Population hierarchy for hypertension detection and follow-up program. (From Hypertension Detection and Follow-up Program Cooperative Group, Five-year findings of the Hypertension Detection and Follow-up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *J.A.M.A.* 242:2562, 1979.)

6. Randomize to treatment

1. Experimental treatment.
2. Alternative treatment ("controls"):
   a. The current standard treatment:
   b. Placebo:
      1) Defined: An inert substance prepared to look as similar as possible to the experimental treatment.
      2) Placebo effect: Am improvement on health, symptoms, due to fact of being treated…and not due to the treatment!

Randomization



Allocating subjects to treatment groups:

- without randomization

- Studies without comparison: ***Case study, case series***

- Problem of inferring a causal relationship without comparison:
  - If we administer a drug and the patient improves, can we attribute the improvement to the administration of the drug?

Allocating subjects to treatment groups:

◆ Without randomization

- Studies with comparison: ***Historical controls***
  - To test a new therapy on a group of patients, compare with a group from the past.
  - Use the records of patients with the same disease who were treated before the new therapy was available.

- Problem:
  - The quality and completeness of the data obtained in the past should be comparable to the current data.
  - The observed difference may be a result of the new therapy, or of other factors that may change over calendar time.

Allocating subjects to treatment groups:

◆ Without randomization

- Studies with comparison: ***Simultaneous nonrandomized controls***
  - Instead of historic controls, use simultaneous controls that are not selected in a randomized manner.
  - Example: Study of BCG vaccination against tuberculosis.

    Physicians divided eligible children into a group to be immunized, and a comparison group who were not immunized. However, investigators selected children of the more intelligent and cooperative parents to be vaccinated, and the others as controls. Lower mortality rate observed in the vaccinated group may be due to the vaccination itself, or because those families were more health-conscious.

TABLE 7-1. **Results of a Trial of Bacillus Calmette-Guérin (BCG) Vaccination: I**

	Number of Children	TUBERCULOSIS DEATHS	
		Number	%
Vaccinated	445	3	0.67
Controls	545	18	3.30

Data from Levine MI, Sackett MF: Results of BCG immunization in New York City. Am Rev Tuberculosis 53:517–532, 1946.

Allocating subjects to treatment groups:

- **using randomization**

  - Randomization: Unpredictability of the next assignment is critical.
  - Methods:
    - Selection from a table of random numbers.
    - Today, mostly carried out using a computer.
  - Important to spell out in writing, what approach is selected, before the actual randomization is performed.

TABLE 7-3. **A Table of Random Numbers**

	00–04	05–09	10–14	15–19
00	56348	01458	36236	07253
01	09372	27651	30103	37004
02	44782	54023	61355	71692
03	04383	90952	57204	57810
04	98190	89997	98839	76129
05	16263	35632	88105	59090
06	62032	90741	13468	02647
07	48457	78538	22759	12188
08	36782	06157	73084	48094
09	63302	55103	19703	74741

TABLE 7-4. **Examples of Using a Random Numbers Table for Allocating Patients to Treatment Groups in a Randomized Trial**

If we plan to compare two groups:

- We decide that even digits designate treatment A, odd digits designate treatment B, *or*
- We decide that digits 0 to 4 designate treatment A, digits 5 to 9 designate treatment B

If we plan to compare three groups:

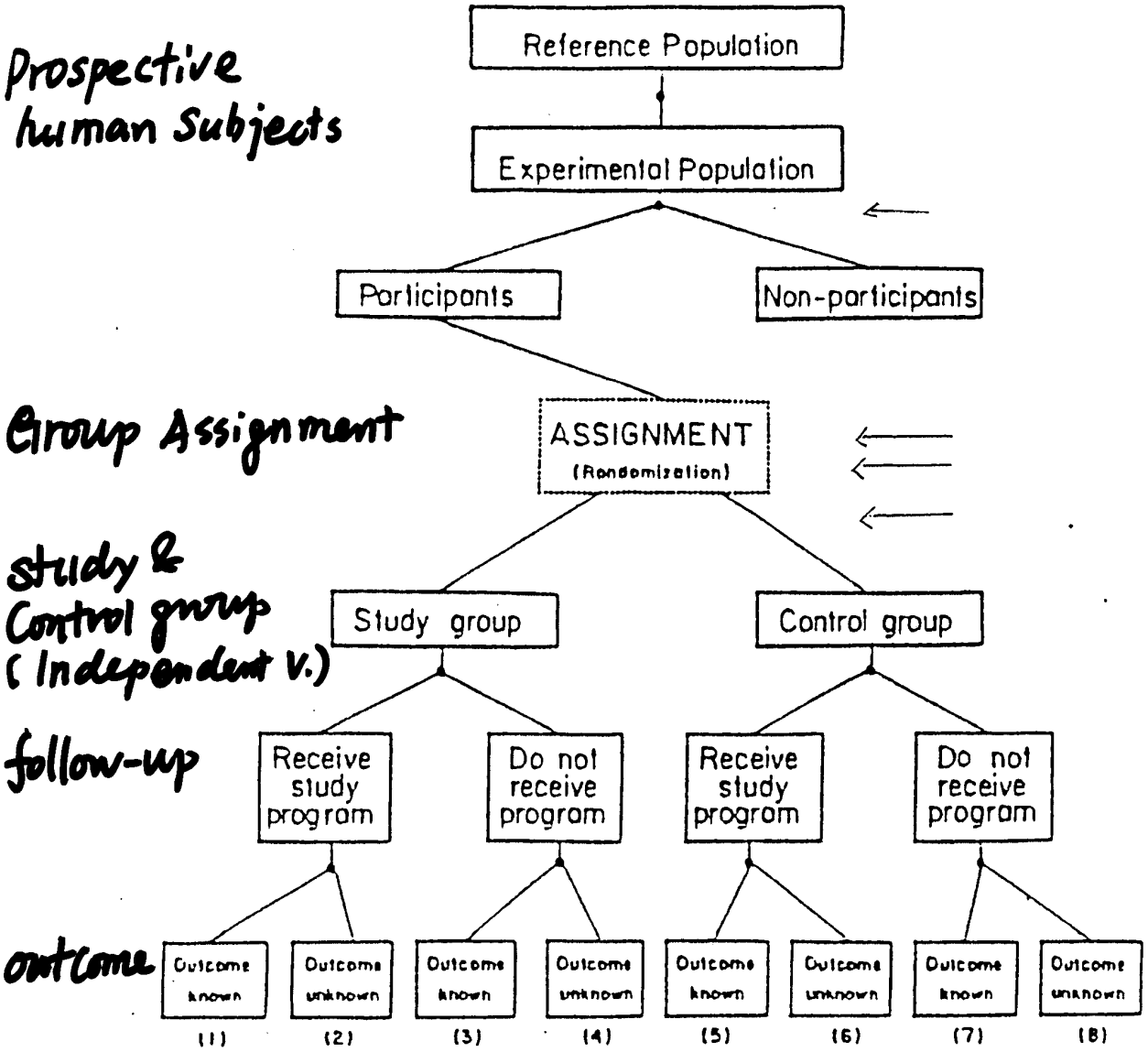
- We decide that digits 1 to 3 designate treatment A, digits 4 to 6 designate treatment B, digits 7 to 9 designate treatment C, and digit 0 would be ignored

TABLE 7-2. **Results of a Trial of Bacillus Calmette-Guérin (BCG) Vaccination: II**

	Number of Children	TUBERCULOSIS DEATHS	
		Number	%
Vaccinated	556	8	1.44
Controls	528	8	1.52

Data from Levine MI, Sackett MF: Results of BCG immunization in New York City. Am Rev Tuberculosis 53:517–532, 1946.

Prospective human subjects



Group Assignment

study & Control group (Independent V.)

follow-up

outcome

Figure 33

Steps in the selection of participants in a controlled intervention study. (Adapted from Hutchison [173].)

Random allocation/ randomization

1. Defined:

   A procedure for assigning patients to experimental treatment and other treatment groups so that chance alone is responsible for the group assignment…each subject **has an equal chance of being in any of the treatment groups.**

2. Purpose of randomization:

   To (attempt to) assure **comparability of the study groups** with respect to factors which may be related to outcome.

Random allocation/ randomization

3. **IMPORTANT: Randomization is done after informed consent is obtained!!!**

Random allocation/ randomization

4. **Do Not** Confuse Random Allocation with Random Selection!!!

Random **selection** of subjects:

A procedure for **selecting** subjects so that each has the same chance of being included in the study. When we can't afford to use all possible subjects in the source population.

Purpose:

To assure representativeness of subjects (of source pop.)

When used?

In any type of study design where a sample of the population is being selected.

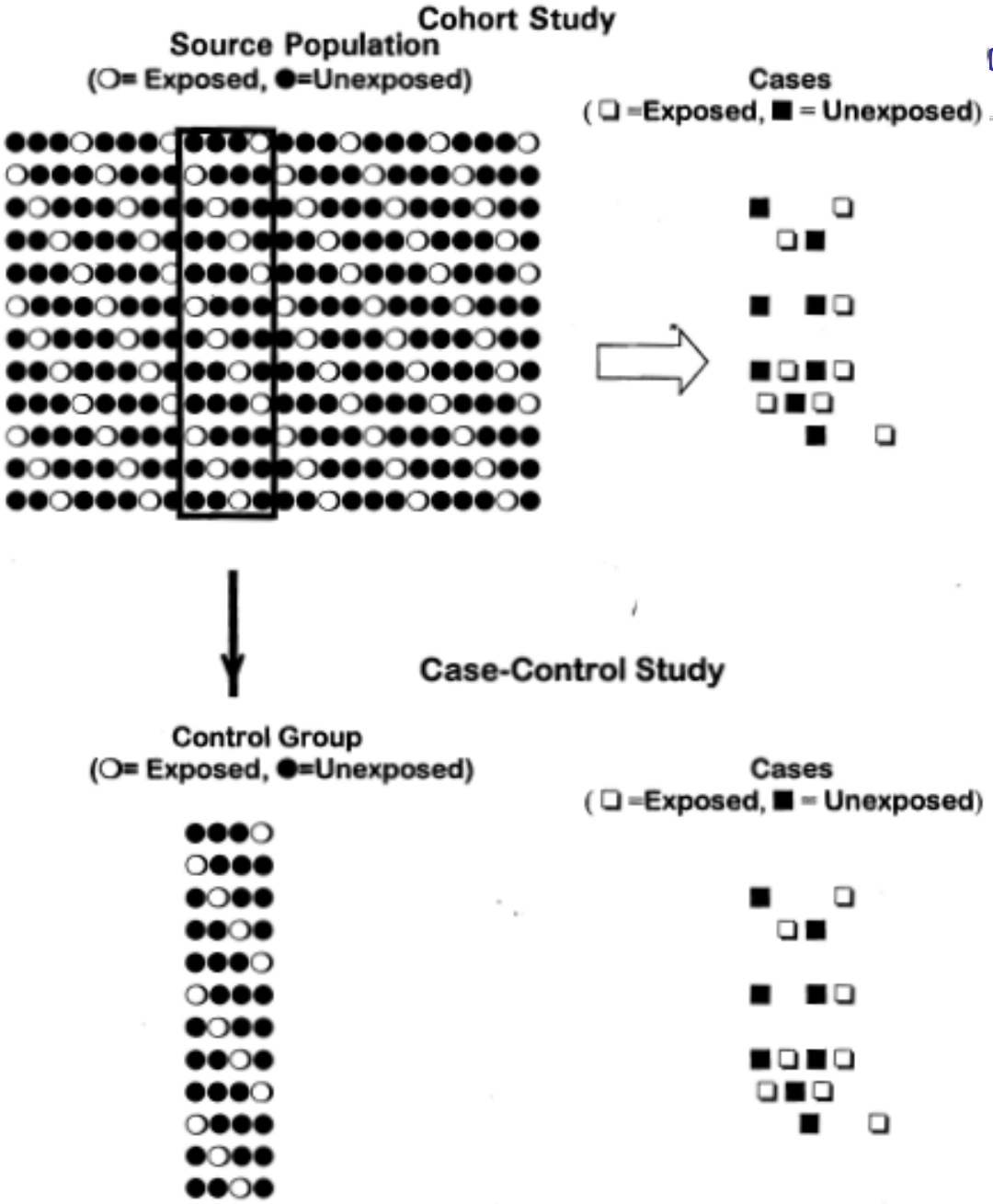


Figure 4–3. Schematic of a cohort study and a nested case-control study within the cohort showing how the control group is sampled from the source population.

Goals of randomization

- With proper randomization, we achieve…
  - Nonpredictability of the next assignment.
  - Prevent potential biases from the investigators in the assignment of treatment type for each participant.
  - Treatment groups are comparable to each other in regards to characteristics which we may be concerned (e.g. sex, age, race, severity of disease, etc.), *if the study is large enough*.
- Randomization does ***not*** guarantee **comparability of groups** since chance may play a role in the process of random treatment assignment.
- However, if the study is large enough, they will be similar in the long run.

Random allocation/ randomization

5. Randomization does not **guarantee** similarity of groups

Table 7–11. Baseline characteristics in a randomized clinical trial of the prevention of osteoporosis.

Characteristic	Level	Experimental	Control
Age (years)	Mean value	67	65
Race	% black	28	24
Body weight	% over ideal	64	42
Calcium supplements	% users	54	60
Exercise	% daily	46	38

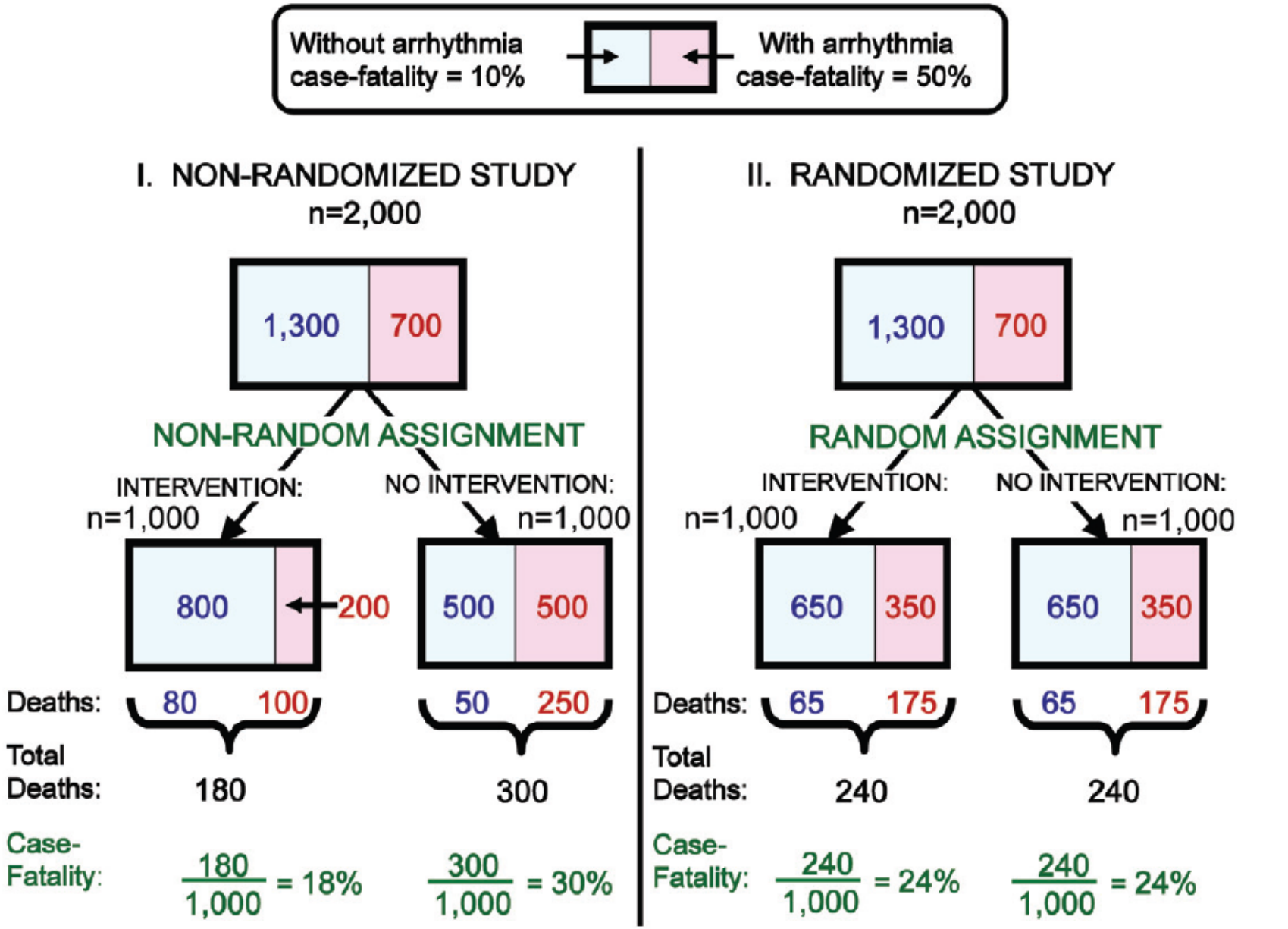


Figure 7-3. Nonrandomized versus randomized studies. I, If the study is not randomized, the proportions of patients with arrhythmia in the two intervention groups may differ. In this example, individuals with arrhythmia are less likely to receive the intervention than individuals without arrhythmia. II, If the study is randomized, the proportions of patients with arrhythmia in the two intervention groups are more likely to be similar.

Q: Why not just match the groups on specific variables we are concerned about, rather than randomizing?

A: We can only match on variables that we know about and can measure.

- **Example: Cannot match on an individual's genetic constitution, immune status, or other unknown variables.**

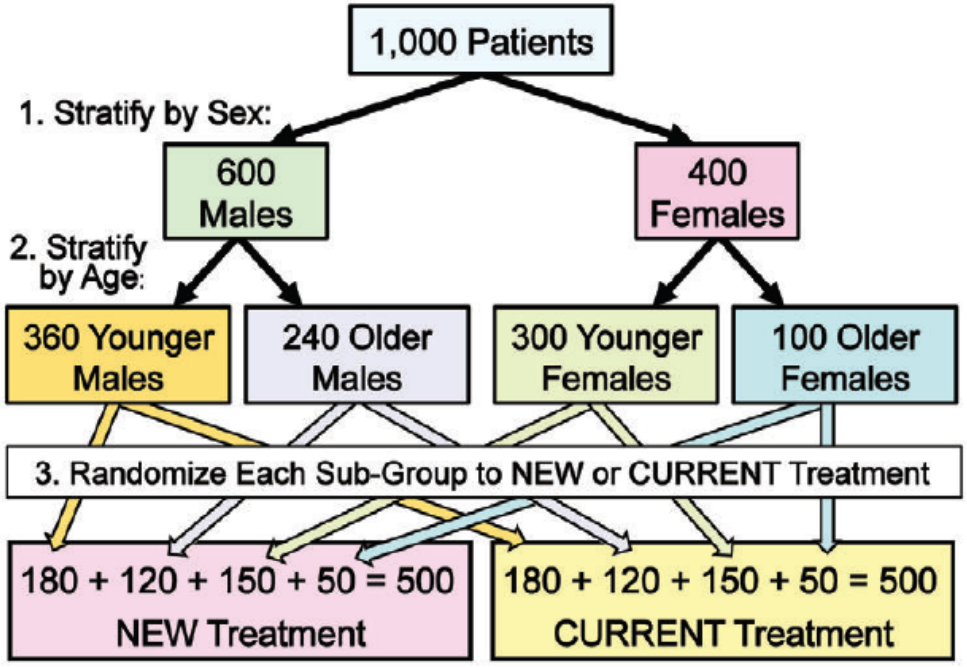
- **Randomization will increase the likelihood of comparability of variables (that we know and do not know) (that we can measure and cannot measure).**
- **However, keep in mind that randomization *does not guarantee comparability* of the groups being studied.**

Stratified randomization

- Recall: Randomization does not guarantee comparability.

- Stratified randomization can increase the likelihood of comparability of different study groups, especially, for one or more important characteristics that may influence the response to therapy in the groups being studied.

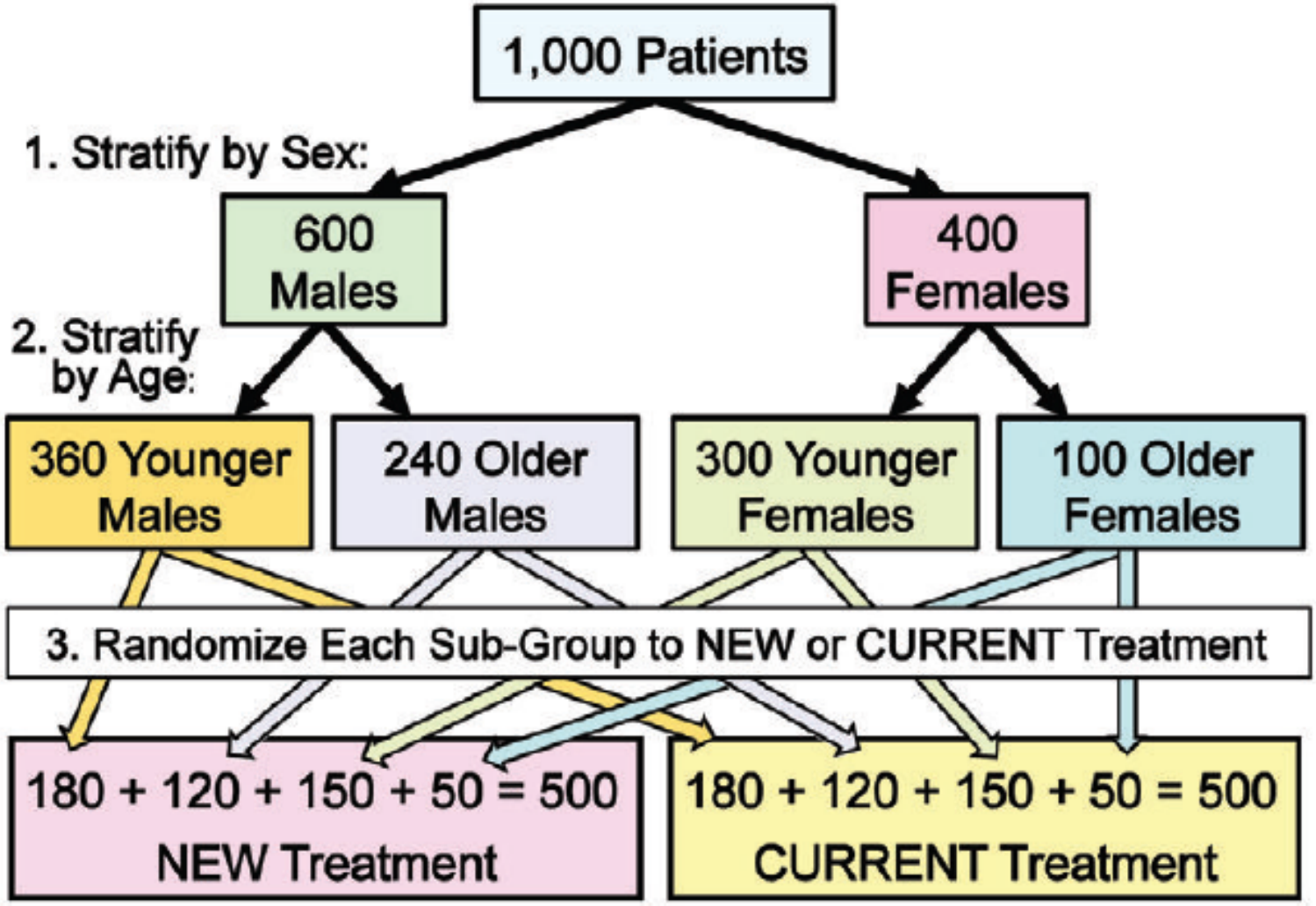
Example of stratified randomization



1) Stratify our study population by each variable we consider important.
2) Randomize individuals to different treatment groups within each stratum.

Result:

Treatment groups are comparable in terms of sex and age.


1,000 Patients
1. Stratify by Sex:
600 Males
400 Females
2. Stratify by Age:
360 Younger Males
240 Older Males
300 Younger Females
100 Older Females
3. Randomize Each Sub-Group to NEW or CURRENT Treatment
180 + 120 + 150 + 50 = 500
NEW Treatment
180 + 120 + 150 + 50 = 500
CURRENT Treatment

Three advantages of the randomized design:

- Randomization removes the potential of bias in the allocation of subjects to the intervention group or to the control group;
- Randomization tends to produce comparable groups; that is, the measured or unknown prognostic factors and other characteristics of the subjects at the time of randomization will be, on the average, evenly balanced between the intervention and control groups;
- The internal validity of statistical tests of significance is guaranteed.

7. Data collection on subjects

- Treatment (assigned and received):
  - Which treatment group was the patient assigned to?
  - What treatment did the patient actually receive?

- A patient may refuse to comply to their assignment, or may fail to comply without realizing it.

7. Data collection on subjects

- Measurements of outcome:
  - The desired effect of the treatment
  - Any side effects that may appear

- In order to ensure comparability in all treatment groups, we need to explicitly state the criteria for all outcomes to be measured in a study.
  - Blinding (masking) may prevent this problem, but may not be always possible.

7. Data collection on subjects

- Prognostic profile at entry
  - We want to verify that randomization has provided comparability of known risk factors for the outcome between treatment groups.
  - Example: We want to verify if randomization has resulted in groups that are comparable for age.

- Data for prognostic factors should be obtained at the time of entry in the study.

Blinding (Masking)

- Blinding (masking)
  - Masking of the subjects: they do not know their treatment group.
  - Masking of the observers or data collectors: in regards to which group a study participant is in.

- The masking of both participants and study personnel is called “double blinding”

Blindness

- **Fundamental Point**: To avoid potential problems of bias during data collection and assessment a clinical trial.

- **Unblinded**: In an unblinded or open trial, both the subject and the investigator know to which intervention the subject has been assigned. The studies involving most surgical procedures, changes in life style (eating habits, exercise, smoking) or learning techniques can be conducted only in this manner.

The **advantage** is that it is usually simpler to carry out and the **disadvantage** is the possibility of bias.

Blindness

- **Single-Blind**: Patient does not know which treatment group he/she is in. Only the investigator is aware of which intervention each subject is receiving. The advantage and disadvantage are similar to those of unblinded trials.

- **Double-Blind**: Neither the subjects nor the investigators responsible for following the subjects know which intervention the subject has been assigned. Such designs are usually restricted to trials of drug efficacy.

The **advantage** is that the risk of bias is reduced.
The **disadvantage** is that certain responsibilities, which in open or single-blind studies could be accomplished by the investigators, must be taken over by others in order to maintain the blindness.

Blindness

- **Triple-Blind**: Neither the subjects, nor the investigators, nor the committee monitoring response variables is told the identity of the groups. The theoretical **advantage** is to allow the monitoring committee to evaluate the response variable results more objectively. The **disadvantage** is that in a trial where the monitoring committee has an ethical responsibility to ensure subject safety, such a design may be counterproductive.

Blindness

Table 7–4. Summary of various types of blinding to assignment of treatment in clinical trials.

Blinding	Knowledge of Treatment Assignment	
	Patient	Investigator
None	Yes	Yes
Single	No	Yes
Double	No	No

Blinding (cont.)

b. Purpose of blinding:

To prevent biases in assessing outcome, which may be influenced by knowledge of treatment group.

c. Blinding is most important when

d. Blinding is less important when

e. Not always possible to blind subjects and/or investigators

TABLE 7-5. **A Randomized Trial of Vitamin C and Placebo for the Common Cold: Results of a Questionnaire Study to Determine Whether Subjects Suspected Which Agent They Had Been Given**

	Suspected Drug		
Actual Drug	***Vitamin C***	***Placebo***	**Total**
Vitamin C	40	12	52
Placebo	11	39	50
Total	51	51	102

$P < 0.001$.

From Karlowski TR, Chalmers TC, Frenkel LD, et al: Ascorbic acid for the common cold. JAMA 231:1038, 1975. Copyright 1975, American Medical Association.

Blinding of a study participant

- Use of a placebo.
- Important for studying the rates of side effects and reactions (in addition to the main effects of an agent).
  - Example: The Physicians' Health Study: Side effects of aspirin.

TABLE 7-6. **Physicians' Health Study: Side Effects According to Treatment Group**

Side Effect	Aspirin Group (%)	Placebo Group (%)	*P*
Gastrointestinal symptoms (except ulcer)	34.8	34.2	0.48
Upper gastrointestinal tract ulcers	1.5	1.3	0.08
Bleeding problems	27.0	20.4	<0.00001

Data from Steering Committee of the Physicians' Health Study Research Group: Final report on the aspirin component of the Ongoing Physicians' Health Study. N Engl J Med 321:129–135, 1989.

Noncompliance: *dropouts*

- Overt noncompliance
  - Participants articulate their refusal to comply or stop participating in the study ("dropouts").

- Covert noncompliance
  - Participants just stop taking the assigned treatment without telling the investigator or study staff.
  - Checks for compliance should be built in the study.
  - Example: urine tests for a metabolite of the agent

Noncompliance: *drop-ins*

- Participants in one treatment arm inadvertently take the agent assigned to the other group ("drop-ins").
  - Example: In a randomized trial testing the effect of aspirin for the prevention of MI, many of the control patients took aspirin without knowing it due to the vast number of over-the-counter preparations that contain aspirin.
  - How to address the problem:
    - Controls were provided with a list of aspirin-containing over-the-counter preparations that they should avoid.
    - Urine tests for salicylates for carried out for both treatment groups.

Noncompliance

- People who do not comply or who do not participate in studies differ from those who do.
  - In terms of many demographic, social, psychological, and cultural variables (that may affect the outcome).
- These are forms of selection bias.
- Randomization, or some other approach that reduces selection bias, is essential in a valid clinical trial.

8. Follow-up study groups for outcomes

9. Analyze results: Use "Intention to treat" analyses

1. Defined:

   Data are analyzed so that subjects remain in groups as originally assigned…even if subjects do not comply or change treatments on their own.

   This means that, even if the day after a subject was assigned to the control group, he starts the experimental treatment on his own…the outcome for that patient is analyzed as if he were still in the control group! …..In short: **"Once randomized, always analyzed."**

9. Analyze results: Use “Intention to treat” analyses

2. Why we must use intention to treat analyses:
   a. The results reflect what happens in the real world when the treatment is offered.
   b. The trial concerns whether the offering of a new treatment is more effective.
   c. Non-compliers are often different with respect to outcome, so likely to be less bias in keeping them in original groups than analyzing data in other ways.
   d. Though final results must reflect intention-to-treat analysis, investigators should look at compliers and non-compliers and their possible effect on the results.

10. Establish procedures for terminating the trial and informing subjects of results.

To Protect the welfare of subjects, data must be monitored regularly and analyzed for any obvious benefits or clear risks to subjects. If either occurs, the trial must be stopped and appropriate action taken (if there is a benefit, then controls must be offered new treatment. If a risk, experimentals must be taken of exper. treatment.

10. Establish procedures for terminating the trial and informing subjects of results.

Caveat: Small, transient differences between the groups may be observed early in the trial. So there must be a balance between a long-enough follow-up to see whether true benefits occur vs. depriving the controls of a better treatment.

A. Randomized clinical trial (RCT):

1. **Defined (phase III):**

   An experimental study where the effectiveness of the intervention is being tested on individuals.

Phase I trials

- How does the agent affect the human body?
- What dosage is safe?

Phase II trials

- Does the agent or intervention have an effect on the disease?

Phase III trials

- Is the new agent or intervention (or new use of a treatment) better than the standard?
- Participants have an equal chance to be assigned to one of two or more groups

Four Phases in Testing New Drugs in the United States

- **Phase I trials**: These trials are clinical pharmacologic studies—small studies of 20 to 80 patients that look at safety issues with the new drug or other treatment. Toxic and pharmacologic effects are examined, including safety, safe ranges of human dosage, and the side effects observed with the new treatment. If the drug passes these studies, it then undergoes phase II studies.

- **Phase II trials:** Phase II studies consist of clinical investigations of **100 to 300 patients** in order to evaluate the efficacy of the new drug or treatment and to further assess its relative safety. If the drug passes phase II studies, it is then tested in phase III trials.

- **Phase III trials:** These studies are large-scale randomized controlled trials for efficacy and relative safety. These studies often include 1,000 to 3,000 or more participants. When recruitment difficulties are anticipated from the beginning, the study may be designed in its planning stage as a multicenter trial. If the drug passes phase III testing, it can be approved and licensed for marketing.

- **Phase IV studies:** Phase IV studies, which are also called postmarketing surveillance, are important for monitoring new agents as they come into general use by the public. **Phase IV studies are not randomized studies and are not really trials at all, unlike phase I, II, and III trials.** Since phase IV studies ascertain side effects of a new treatment after the drug has been marketed, participants are not randomized. For the findings from such postmarketing surveillance to be valid, a very high-quality system for reporting of adverse effects is essential.

Example: hypertension detection and follow-up program

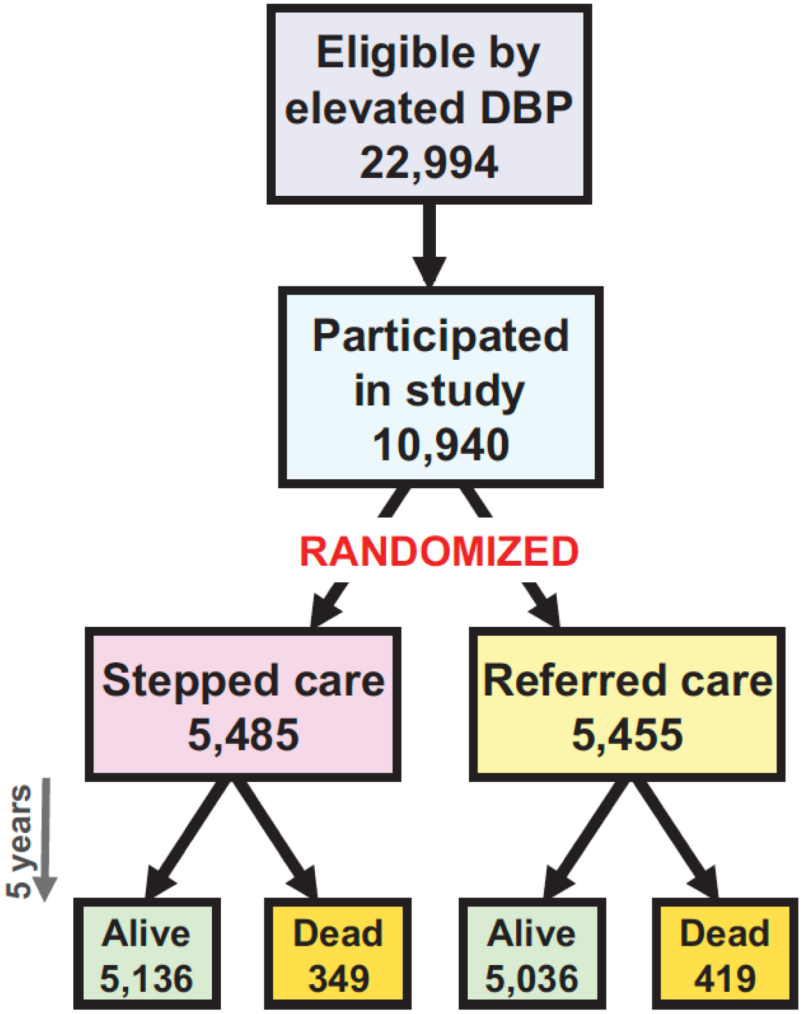


Fig. 11.10 Design of the Hypertension Detection and Follow-up Program. *DBP*, Diastolic blood pressure.

Example: hypertension detection and follow-up program

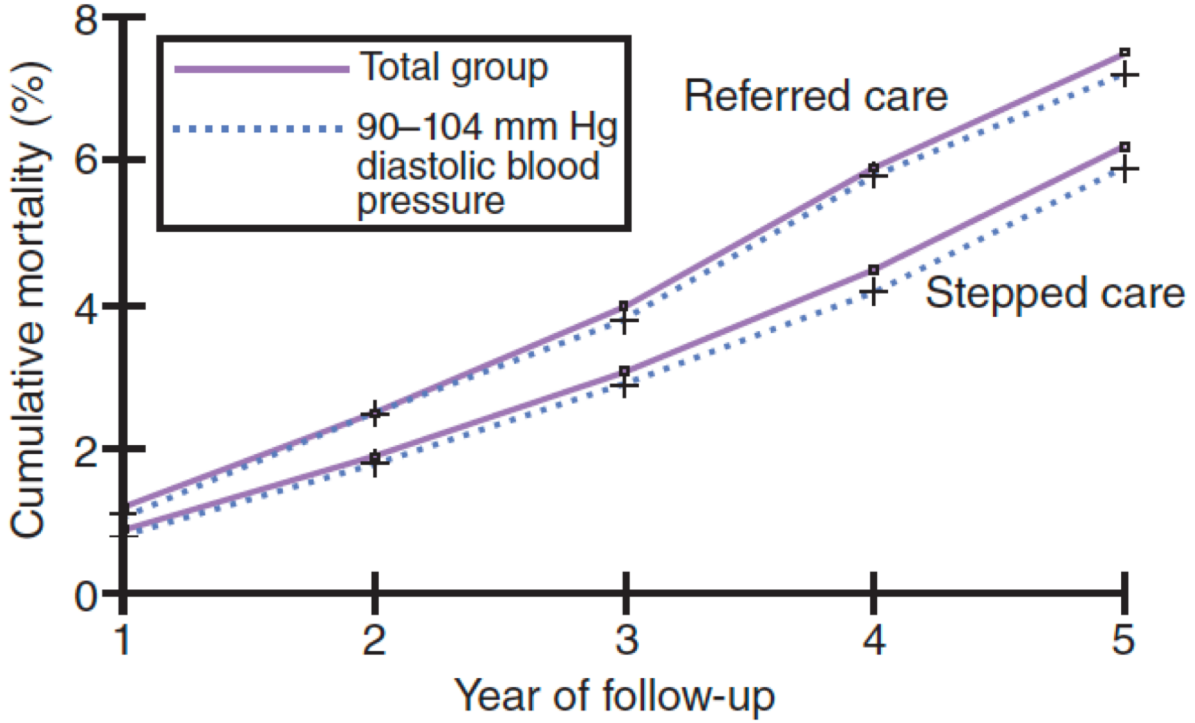


Fig. 11.11 Cumulative all-cause mortality by blood pressure status and type of care received in the Hypertension Detection and Follow-up Program. (Modified from Hypertension Detection and Follow-up Program Cooperative Group: Five-year findings of the Hypertension Detection and Follow-up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA*. 1979;242:2562–2571.)

Example: hypertension detection and follow-up program

TABLE 11.4 Mortality From All Causes During the Hypertension Detection and Follow-Up Program

Diastolic Blood Pressure at Entry (mm Hg)	Stepped Care	Referred Care	5-YEAR DEATH RATE		Mortality Reduction in SC Group (%)
			SC	RC	
90–104	3,903	3,922	5.9	7.4	20.3
105–114	1,048	1,004	6.7	7.7	13.0
≥115	534	529	9.0	9.7	7.2
Total	5,485	5,455	6.4	7.7	16.9

RC, Referred care; *SC,* stepped care.

From Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA.* 1979;242:2562–2571.

Community trial

1. Defined:

   An experimental study where the effectiveness of an intervention is tested on a community.

2. Example of a community trial: fluoridation of water.

Fluoridation of Water

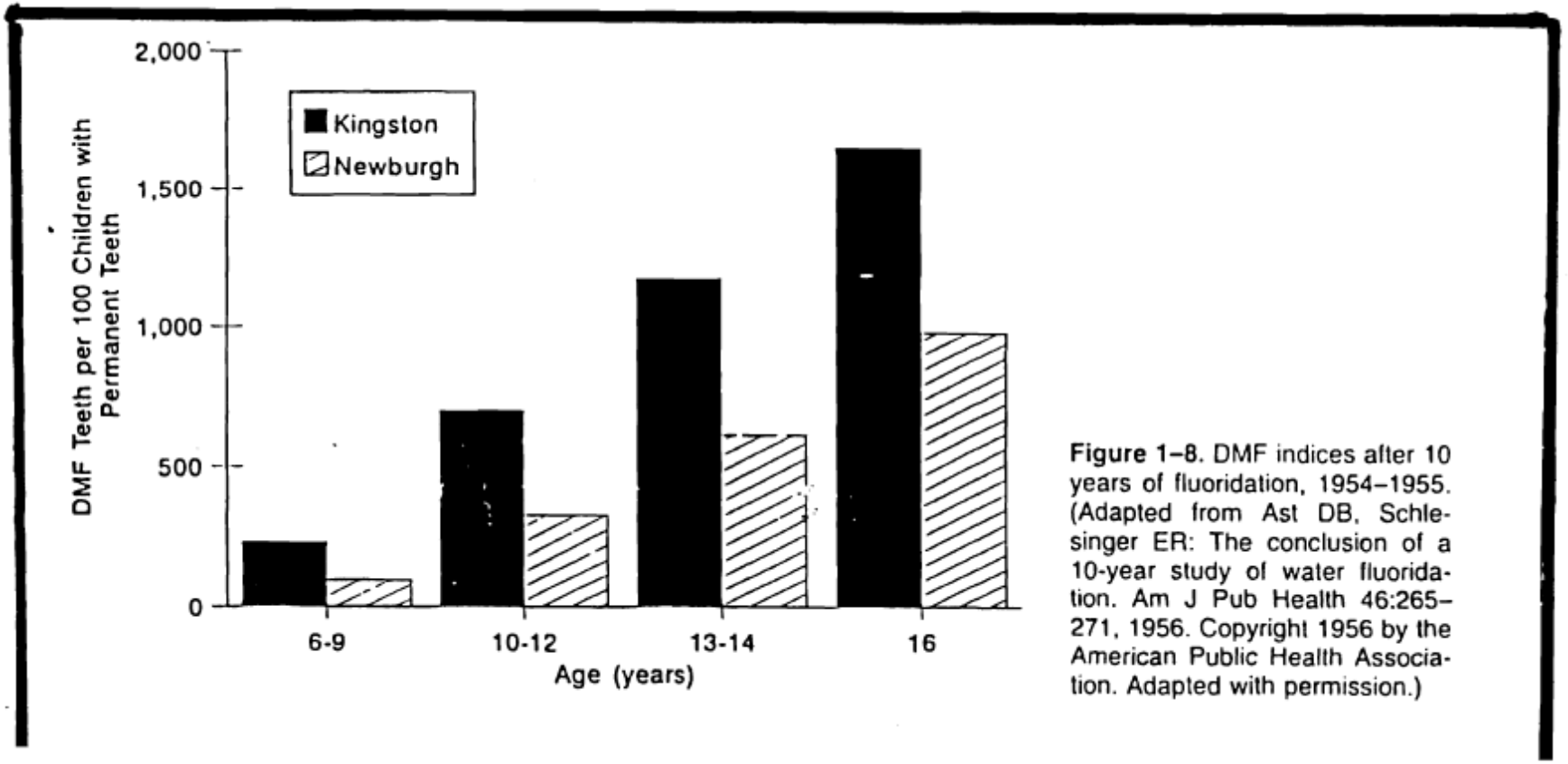


Figure 1–8. DMF indices after 10 years of fluoridation, 1954–1955. (Adapted from Ast DB, Schlesinger ER: The conclusion of a 10-year study of water fluoridation. Am J Pub Health 46:265–271, 1956. Copyright 1956 by the American Public Health Association. Adapted with permission.)

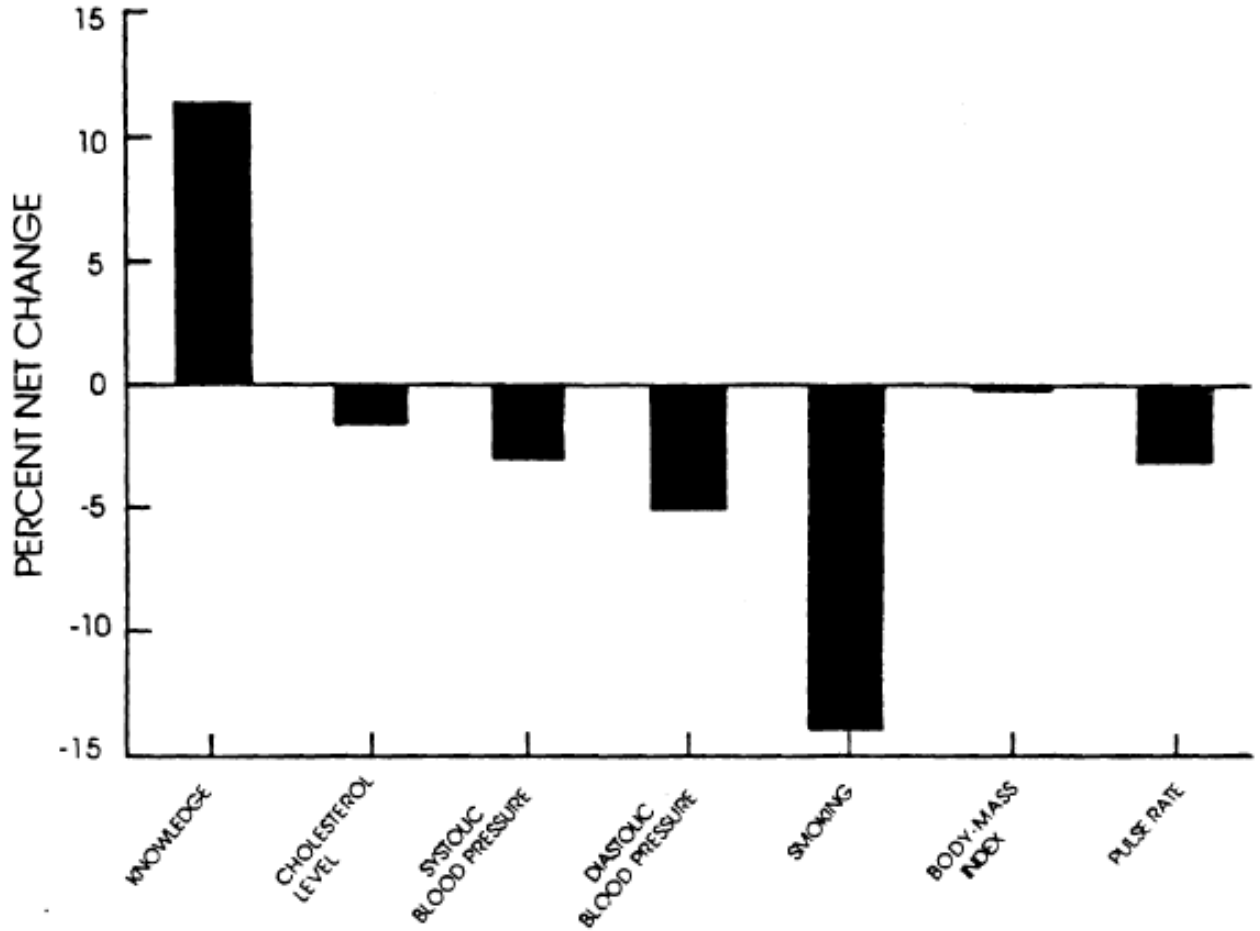


Figure 9–3. Net percentage changes in the intervention communities in knowledge and risk factors for persons 25 to 74 years old in the Stanford Five-City Project. *Source:* Farquhar et al. (1990).

Community trial

3. Problems of conducting community trials:
   a. Obtaining an appropriate control group:
      1) Same community before and after intervention
      2) A control community: similar to experimental community with respect to possible confounders.
   b. Other problems:
      1) It is hard to get individual's informed concent
      2) Intervention not at individuals level
      3) Collaboration of communities

Experimental studies compared to cohort studies

1. **Similarities between cohort and experimental studies. Both:**
   a. Subjects must be **free** of the outcome at the start of the study.
   b. People are grouped into “exposed”/ “not exposed” categories.
   c. Groups are followed for a period of time to determine outcome.
   d. Yield incidence data so allow the calculation of risk and related measures.
   e. Susceptible to lost-to-follow-up bias.

Experimental studies compared to cohort studies

2. Differences between cohort and experimental studies:

a. Experimental studies involve active manipulation of exposure (treatment/alternative treatment), whereas in cohort studies, the investigator must merely observe the effect of exposure.

b. Random allocation (or randomization) is an essential part of a good experimental study. Not possible in a cohort.

c. Ethical issues often a major issue in experimental epidemiological studies.

d. Compliance with study protocol is an important concern in experimental studies.

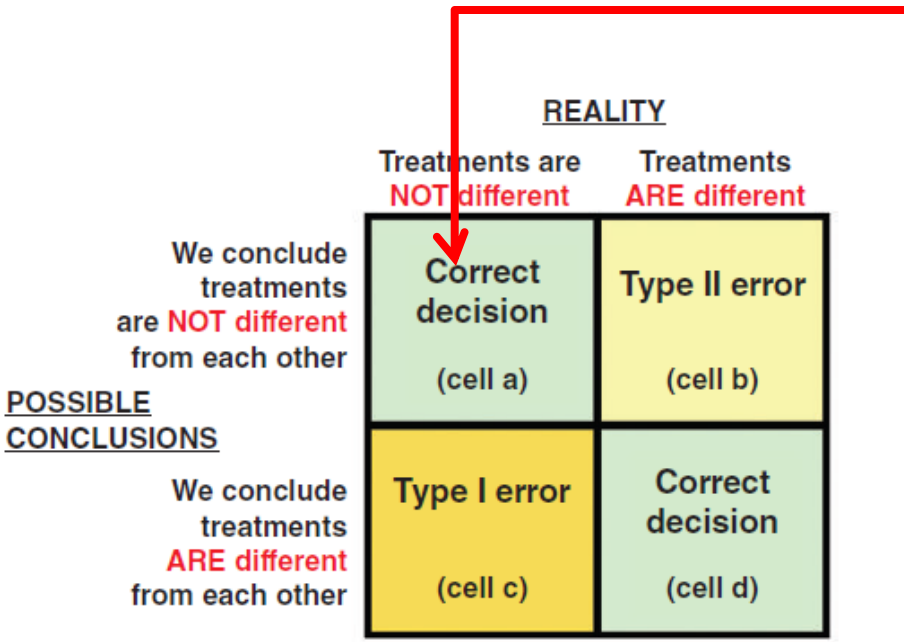
Some Further Issues in Randomized Trials

Four possible conclusions when testing whether or not treatments differ

- When in reality, the treatments do NOT differ:
  1. We correctly conclude that they do not differ.
  2. We conclude that they do differ by error.

- When in reality, the treatments DO differ:
  3. We conclude that they do not differ by error.
  4. We correctly conclude that they do differ.

The four possibilities in a 2x2 table

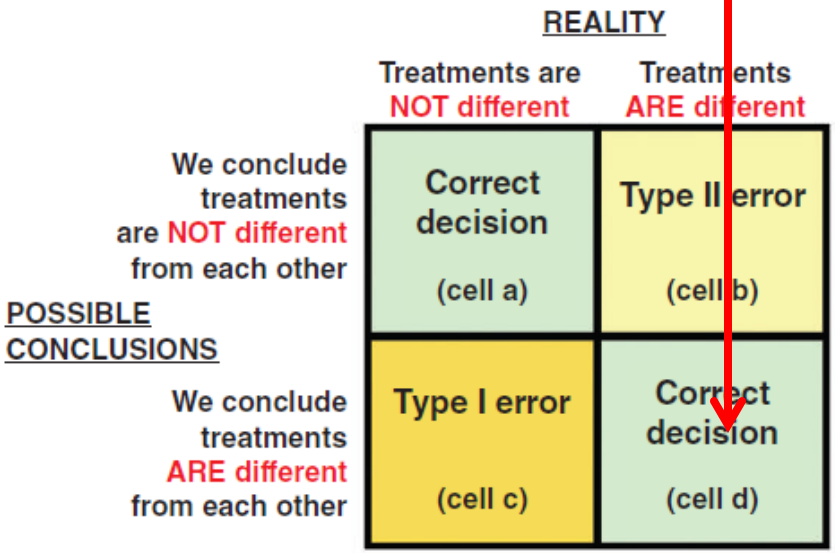


[Cell a]

- Reality: treatments are not different.
- Conclusion from study: treatments are not different.

⇒ Correct decision!

The four possibilities in a 2X2 table (continued)

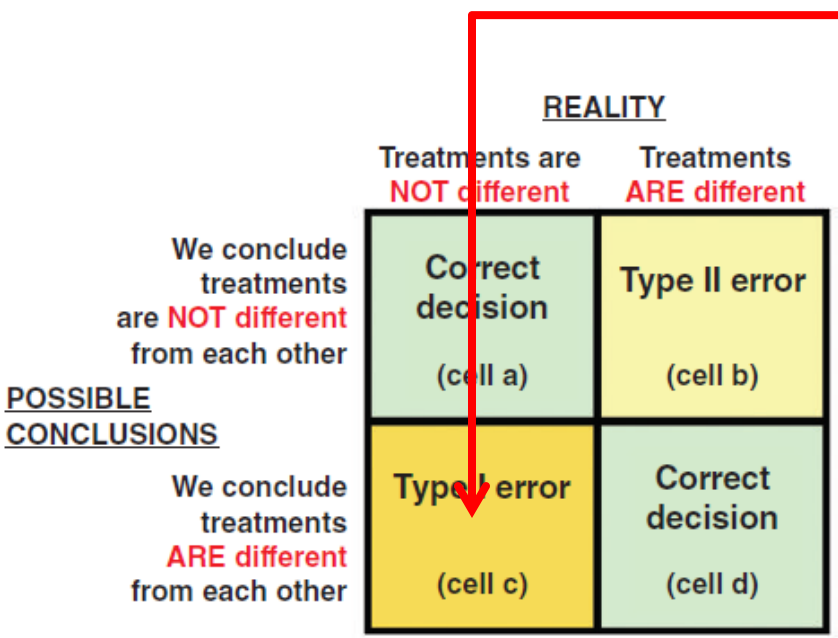


[Cell d]

- Reality: treatments are different.
- Conclusion from study: treatments are different.

⇒ Correct decision!

The four possibilities in a 2X2 table (continued)



[Cell c]

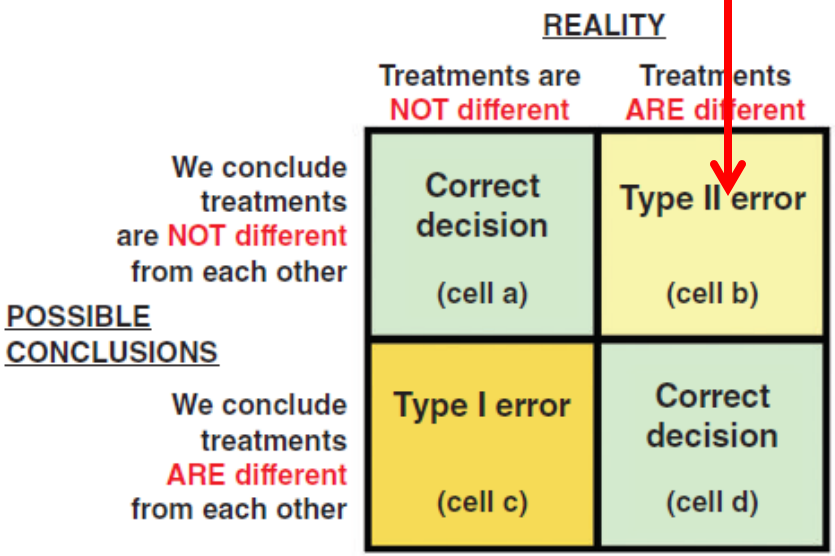
- Reality: treatments are not different.
- Conclusion from study: treatments are different.

⇒ Incorrect decision!

⇒ Called Type I error

⇒ Probability of making a Type I error is α.

The four possibilities in a 2X2 table (continued)



[Cell b]

- Reality: treatments are different.
- Conclusion from study: treatments are not different.

⇒ Incorrect decision!

⇒ Called Type II error

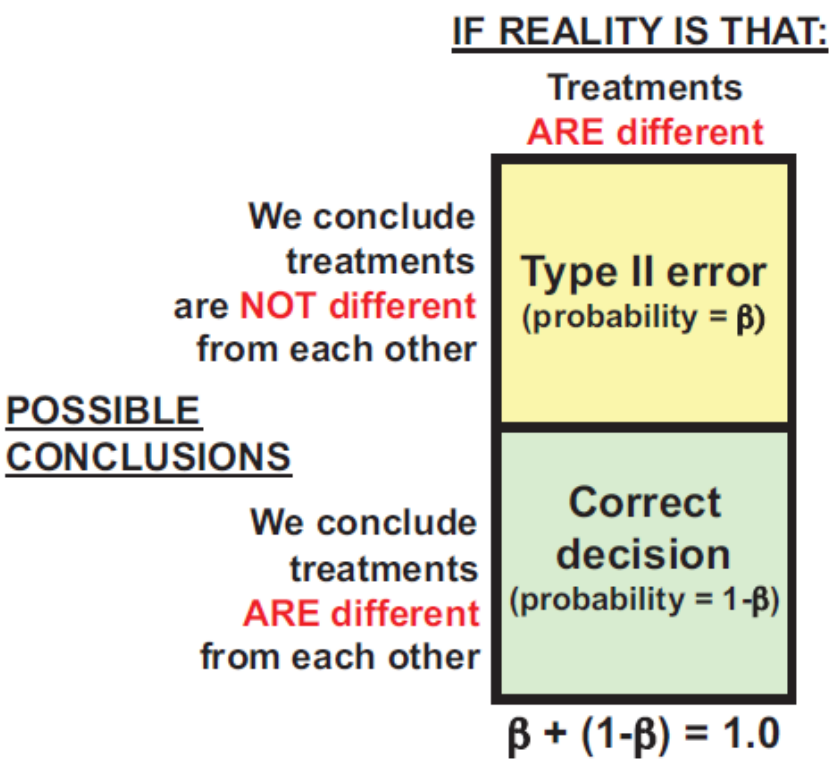
⇒ Probability of making a Type II error is β.

α and the P-value

- Recall: Probability(Making a Type I error)=α

- "P < 0.05": used in many published papers, is in reference to α.
- It means the probability that an observed difference could have arisen by chance alone, and that this difference between our groups does not reflect any true difference, is only 0.05, or 5%.

(1- β) and the power of the study



- Recall: Probability(Making a Type II error)= β
- In other words, the probability that we correctly say there is a difference, when there is indeed a difference is 1-β.
- This probability, (1-β), is called the **power** of the study.
- It tells us how likely is our study not to miss a difference if one exists.

TABLE 11.1 Summary of Terms

Term	Definitions
α	= Probability of making a type I error = Probability of concluding the treatments differ when in reality they do not differ
β	= Probability of making a type II error = Probability of concluding that the treatments do not differ when in reality they do differ
Power	= 1 – Probability of making a type II error = 1 – β = Probability of correctly concluding that the treatments differ = Probability of detecting a difference between the treatments if the treatments do in fact differ

Sample size

- "How many people do we have to study in a clinical trial?"

- What needs to be specified:
  - The difference in response rates (rate of cure, rate of improvement) to be detected.
  - An estimate of the response rate in one of the groups.
  - Level of statistical significance (α)
  - The desired power of the study ($1-\beta$)
  - Whether the test should be one-sided or two-sided.

Recruitment and retention of study participants

- Major challenge is to recruit a sufficient number or eligible and willing volunteers.
- (Within the limits of a randomized trial) participants must be fully informed of the risks and what arrangements have been made for their compensation.
- Paying large incentives may lead to biases.
- Investigators should avoid being overly zealous in promising the study subjects benefits that have not yet been conclusively demonstrated.
- Should develop measures to prevent losses to follow-up.

Ways to express the results of RT

- Efficacy: How well a treatment works under "ideal" conditions.
  - Is different from effectiveness, or how well a treatment works in "real-life".

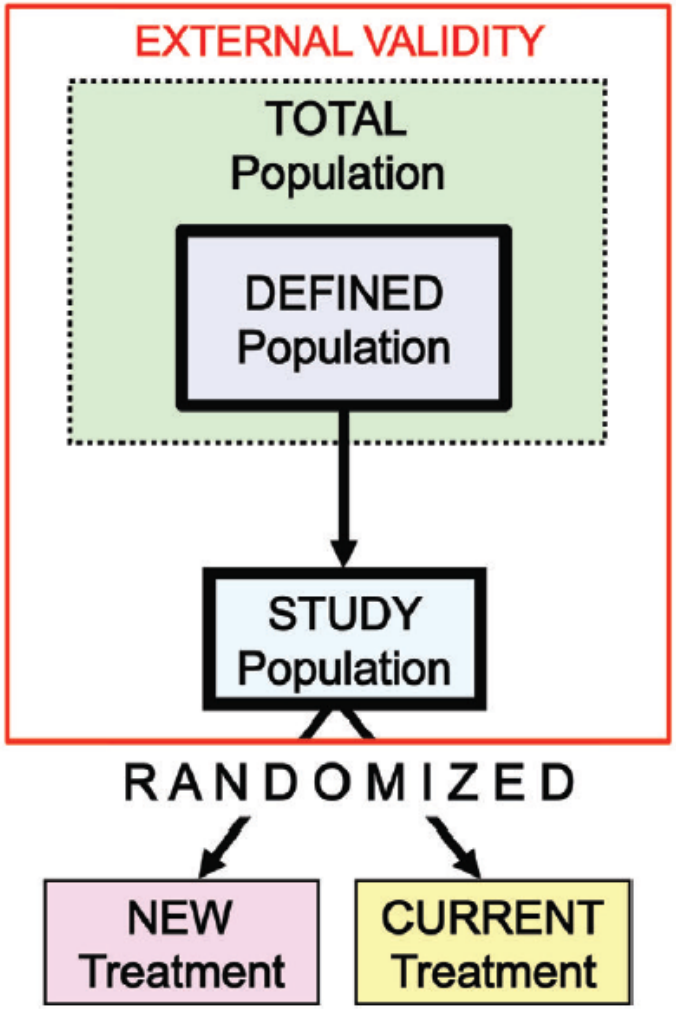
$$\text{Efficacy} = \frac{\left(\begin{array}{c}\text{Rate in those who}\\ \text{received the placebo}\end{array}\right) - \left(\begin{array}{c}\text{Rate in those who}\\ \text{received the vaccine}\end{array}\right)}{\text{Rate in those who received the placebo}}$$

Ways to express the results of RT (continued)

- Ratio of the risks (RR)
- Comparison of survival curves for each treatment.
- Number of patients who need to be treated (NNT) to prevent one adverse outcome.

$$\text{NNT} = \frac{1}{\left(\begin{array}{c}\text{Rate in}\\ \text{untreated group}\end{array}\right) - \left(\begin{array}{c}\text{Rate in}\\ \text{treated group}\end{array}\right)}$$

External validity: Generalizability

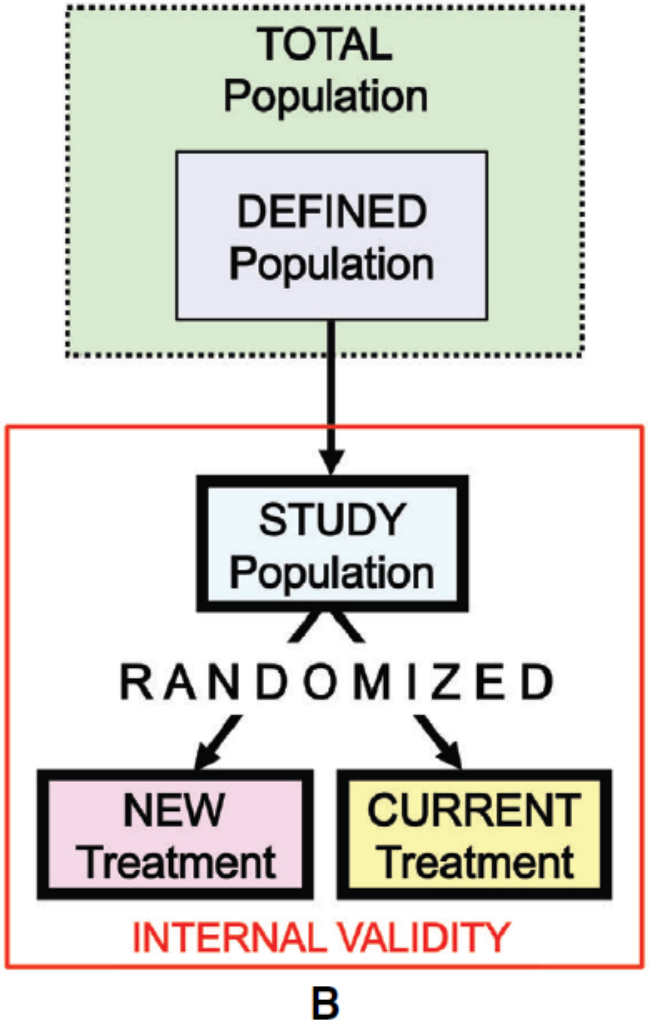


A

- Ultimate objective is to generalize the results beyond the study population.
- Example: Test a drug for disease "X"
  - Total population: all patients with "X"
  - Defined population: all patients with "X" in our community
  - Study population: patients with "X" that receive medical care from one of several clinics in our community
  - If new treatment is better than current treatment in our study, we want to say that the new treatment is better for the disease regardless of where they are treated at.

⇒ ***Generalizability, or external validity***.

Internal validity



- RT is **internally valid** if the randomization has been done properly and the study is free of other biases, without major methodologic problems.
- RT is the gold standard of study designs because of randomization.
- If study is large enough, randomization leads to comparability between treatment groups.

Example of a major randomized trial in the US: Study of breast cancer prevention using Tamoxifen

- Observation: Women treated with Tamoxifen for breast cancer had lower incidence of cancer in the other breast.
- Hypothesis: Tamoxifen might help prevent breast cancer.
- RT: Initiated in 1992. 13,388 women, 35 years or older, enroll in the trial by 1997. Randomized to receive a placebo or 20 mg/day of tamoxifen for 5 years.

Example of a major randomized trial in the US:
Study of breast cancer prevention using Tamoxifen

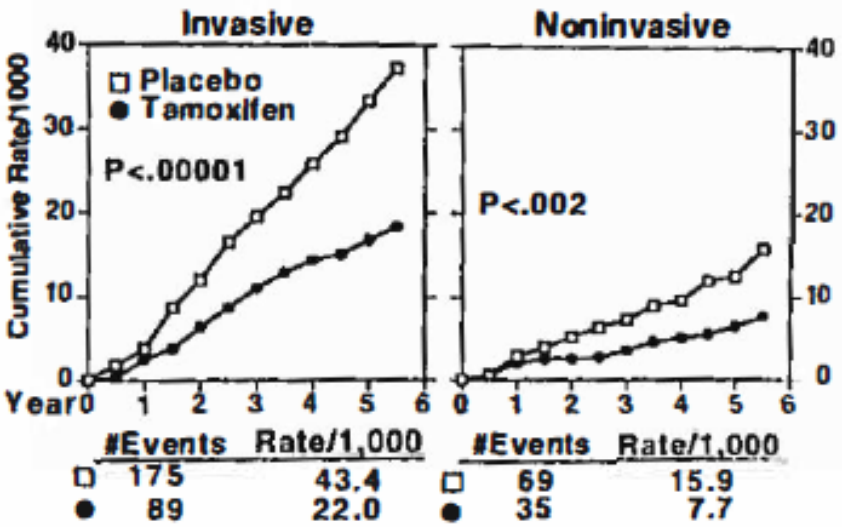


Figure 8-14. Cumulative rates of invasive and noninvasive breast cancer occurring in participants receiving placebo or tamoxifen. (From Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90:1371–1388, 1998.)

- Data monitoring committee decide that the evidence of reduction in breast cancer was sufficiently strong to stop the trial.
  - Cumulative rates of both invasive and noninvasive breast cancer were markedly reduced in treatment group.

Example of a major randomized trial in the US:

Study of breast cancer prevention using Tamoxifen (continued)

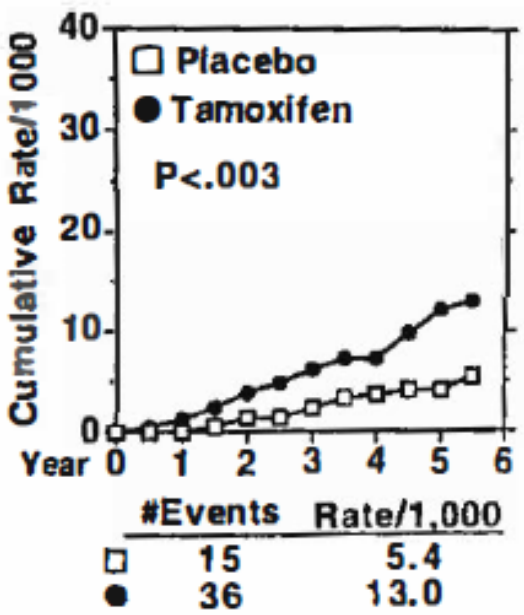
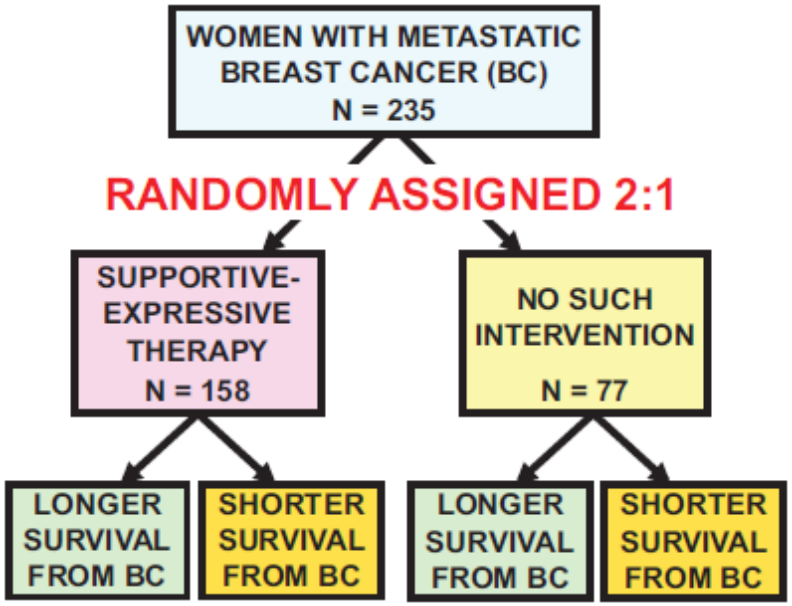


Figure 8-15. Cumulative rates of invasive endometrial cancer occurring in participants receiving placebo or tamoxifen. (From Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90:1371–1388, 1998.)

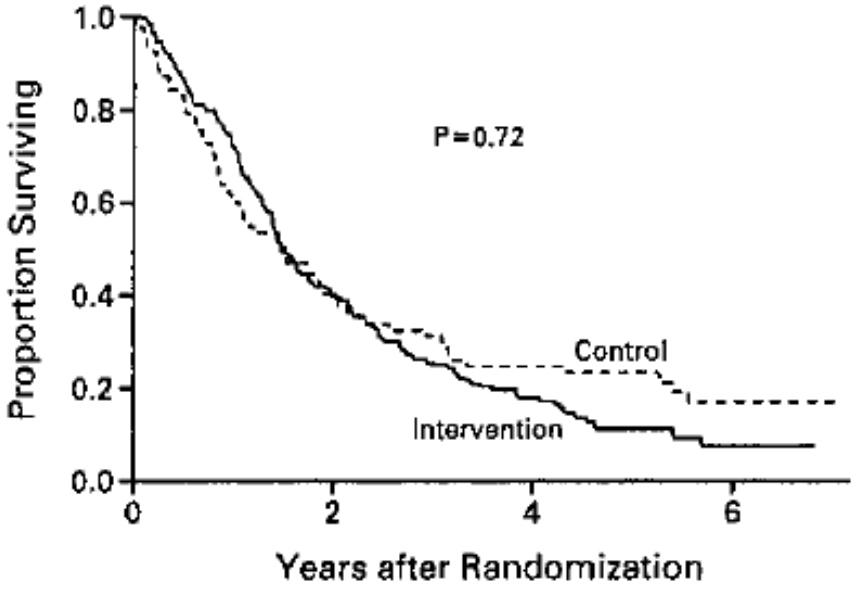
- However, rates of invasive endometrial cancer is increased in the tamoxifen treated group.
- Conclusion: The potential benefits of tamoxifen must be weighed against the increased risk of endometrial cancer.

Example: Effect of group psychosocial support on survival of patients with metastatic breast cancer.

- Women with metastatic breast cancer were randomly assigned to supportive-expressive group therapy or control.
- Supportive-expressive therapy is a standardized treatment for life-threatening illness, to express their feeling and concerns.



Example: Effect of group psychosocial support on survival of patients with metastatic breast cancer.



- Results: Survival is not prolonged in patients who receive supportive-expressive therapy.
- However, mood and pain perception were improved, especially in more distressed women.
- The results suggest there are no survival benefit from this intervention.

Registration of clinical trials

- Not all results of clinical trials are published.
  - If clinical trials showing beneficial results are published, but trials with negative results are not, it may seem (erroneously) that all studies of the new drug show clear benefit. ⇒ ***publication bias***
  - Researchers, journals, and drug companies are less eager to publish results that show no or less benefit of a new drug.
  - Therefore, the International Committee of Medical Journal Editors adapted a policy, where ALL clinical trials of medical interventions must be registered in public trials registry before recruiting participants.

Ethical Considerations

- Is randomization ethical?
  - Randomization is ethical only when we do not know *for certain* if drug A is better than drug B.
- Is it ethical not to randomize?
  - Questions of harm: unnecessary toxic effects and raising false hopes, often at huge expense.
- Is true informed consent obtained?
  - At a time of distress (right after diagnosis, which is often the protocol for inclusion of the study), they may not be capable of giving truly informed consent.
- When should a trial be stopped earlier than originally planned?
  - When sufficient evidence of benefit or harm is observed.

Some measures of effect in experimental studies

A. Risk ratio: I_C / I_T

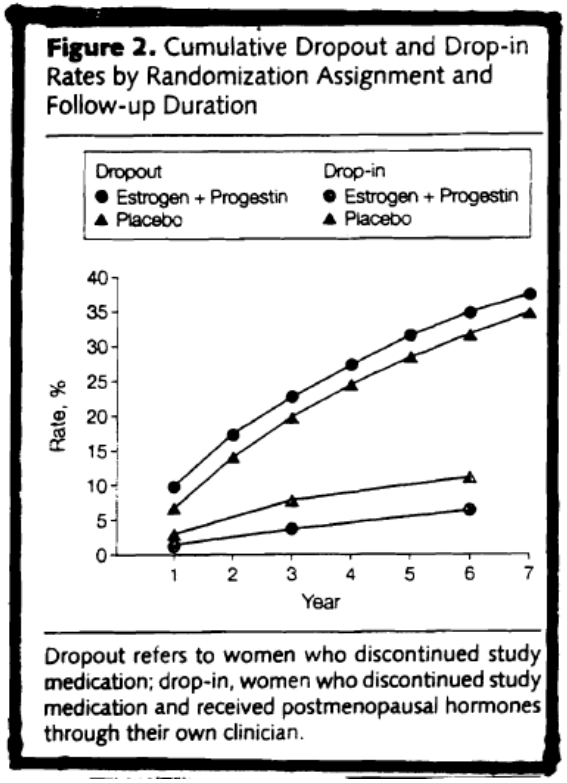
B. Risk difference: $I_C - I_T$

C. Efficacy:

$$\frac{Ic - It}{Ic} \times 100\%$$

Major potential biases in experimental studies:

- Lost-to-follow-up
- Compliance/adherence to study's protocol, e.g., WHI:



Reasons for non-compliance:

1. Misunderstanding of instructions.
2. Inconvenience of participation.
3. Side effects of treatment.
4. Cost of participation.
5. Forgetfulness.
6. Disappointment with results.
7. Preference for another treatment.

Ways to improve compliance:

1. Select motivated persons.
2. Pretest ability and willingness of participants to comply.
3. Provide simple and lucid instructions to subjects.
4. Offer incentives to comply (e.g., no charge for therapeutic intervention and associated examinations).
5. Provide positive reinforcements to subjects for adherence to treatment regimen.
6. Maintain frequent contract with participants and remind them about importance of adherence to the regimen.
7. Measure adherence through pill counts or sampling of biologic specimens.
8. Limit duration of intervention.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