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Randomized Clinical Trials

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Section A

Experimental Study

Objectives of Epidemiological Investigation

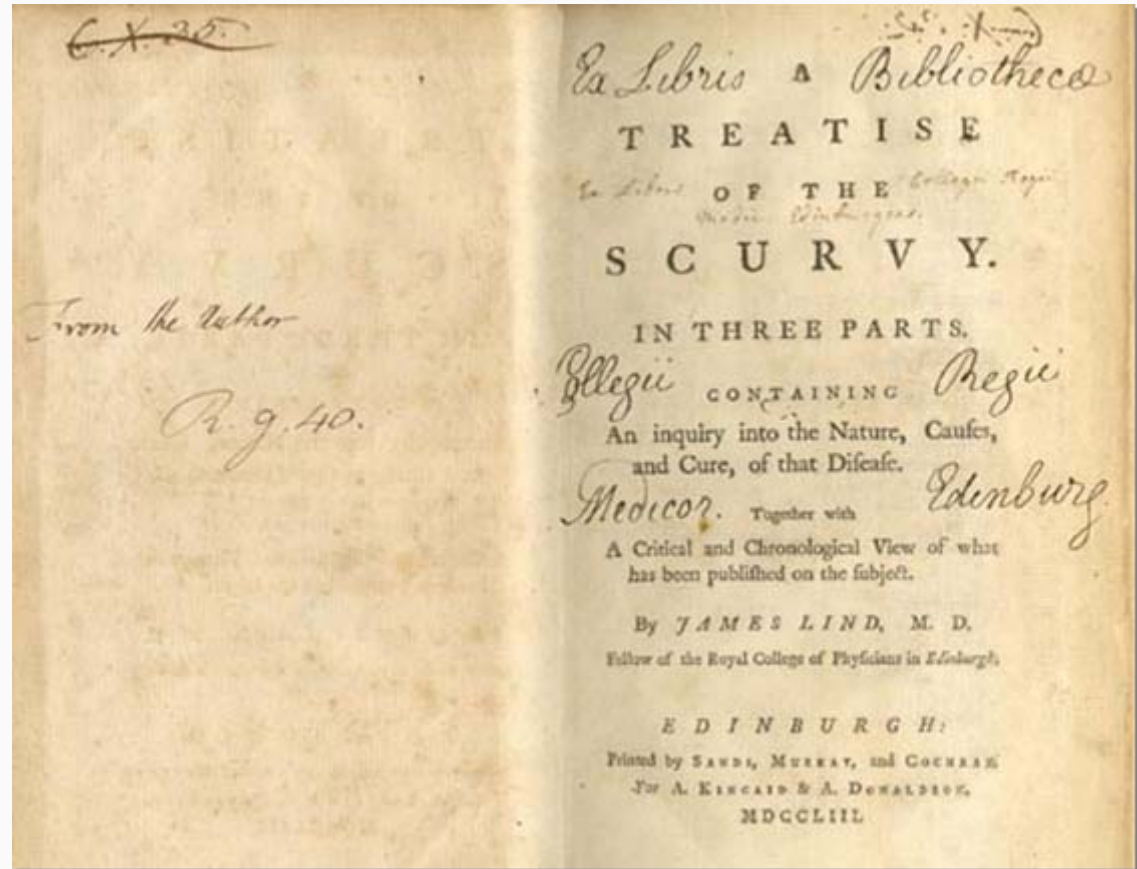
- Investigate the etiology of disease and modes of transmission
- Determine the extent of disease problems in the community
- Study the natural history of disease
- **Evaluate new preventive and therapeutic measures and modes of health care delivery**
- Provide a foundation for developing public policy and regulatory decisions

- Observational study
 - The investigators use the data observed in the population to make inference on the relationship between the variables
- **Experimental study**
 - **The investigators intervene in the natural history by actively altering one of the variables and then making inference on the relationship between the variables based on the outcomes**

Historical Example of an Experimental Study



James Lind,
1716–1794



Passages from A Treatise of the Scurvy

The following are the experiments.

On the 20th of *May* 1747, I took twelve patients in the scurvy, on board the *Salisbury* at sea. Their cases were as similar as I could have

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have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all, *viz.* water-gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times puddings, boiled biscuit with sugar, &c.; and for supper, barley and raisins, rice and currants, sago and wine, or the like. Two of these were ordered each a quart of cyder a-day. Two others took twenty-five gutts of *elixir vitriol* three times a-day, upon an empty stomach; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a-day, upon an empty stomach; having their gruels and their other food well acidulated with it, as also the gargle for their mouth. Two of the worst patients, with the tendons in the ham rigid, (a symptom none of the rest had), were put under a course of sea-water. Of this they drank half a pint every day, and sometimes more or less as it operated, by way of gentle physic. Two others had each two oranges and one lemon given them every day. These they eat with green
dines,

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dines, at different times, upon an empty stomach. They continued but six days under this course, having consumed the quantity that could be spared. The two remaining patients, took the bigness of a nutmeg three times a-day, of an electuary recommended by an hospital-surgeon, made of garlic, mustard-seed, *rad. raphan.* balsam of *Peru*, and gum myrrh; using for common drink, barley-water well acidulated with tamarinds; by a decoction of which, with the addition of *cremor tartar*, they were gently purged three or four times during the course.

The consequence was, that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of six days fit for duty. The spots were not indeed at that time quite off his body, nor his gums found; but without any other medicine, than a gargism of *elixir vitriol*, he became quite healthy before we came into *Plymouth*, which was on the 16th of *June*. The other was the best recovered of any in his condition; and being now deemed pretty well, was appointed nurse to the rest of the sick.

B b

Next

“On the 20th of May 1747, I took twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all. ... Two of these were ordered each a quart of cider a day. Two others took twenty-five gutts of elixir vitriol three times a day, ... and so on. They continued but six days under this course. ... The consequence was that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of six days fit for duty.”

— James Lind, 1747

Interventions that Can Be Evaluated

- New drugs and new treatment of diseases
- New medical and health care technology
- New methods of primary prevention
- New programs for screening
- New ways of organizing and delivering health services
- New community health programs
- New behavioral intervention programs

Comparison Groups in an Experimental Study

- Therapy vs. no therapy
- Therapy vs. placebo or sham
- Therapy A vs. Therapy B

Historical and Simultaneous Control Groups

- Historical controls
- Simultaneous controls
 - Simultaneous non-randomized controls
 - Simultaneous randomized controls

Results of a Trial of BCG Vaccination

Vaccinations were selectively performed

	Cases	TB deaths	
		Number	Percent
Vaccinated	445	3	0.67
Controls	545	18	3.30

Results of a Trial of BCG Vaccination

Alternate children were vaccinated

	Cases	TB deaths	
		Number	Percent
Vaccinated	556	8	1.44
Controls	528	8	1.52



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Section B

Randomized Clinical Trials

About Randomization

- Sir R.A. Fisher first developed the concept of experimental randomization in 1925
- J.B. Amberson and B.T. McMahon (1931) randomized patients by using a coin flip to see who received treatment for tuberculosis
- Sir Austin Bradford Hill introduced the use of random numbers in the allocation of patients in the study of streptomycin and tuberculosis

“The 24 (tuberculosis) patients were then divided into two approximately comparable groups of 12 each. The cases were individually matched, one with another, in making this division. ... Then by a flip of the coin, one group became identified as group I (treated group) and the other as group II (control). The members of the separate groups were known only to the nurse in charge of the ward and to two of us. The patients themselves were not aware of any distinctions in the treatment administered.”

— Amberson, et al., 1931

- **Randomization** is the process by which allocation of subjects to treatment groups is done by chance, without the ability to predict who is in what group

Randomized Clinical Trial

- A **trial** is an experiment
- A **clinical trial** is a controlled experiment having a clinical event as an outcome measure, done in a clinical setting, and involving persons having a specific disease or health condition
- A **randomized clinical trial** is a clinical trial in which participants are randomly assigned to separate groups that compare different treatments

Design of a Randomized Clinical Trial

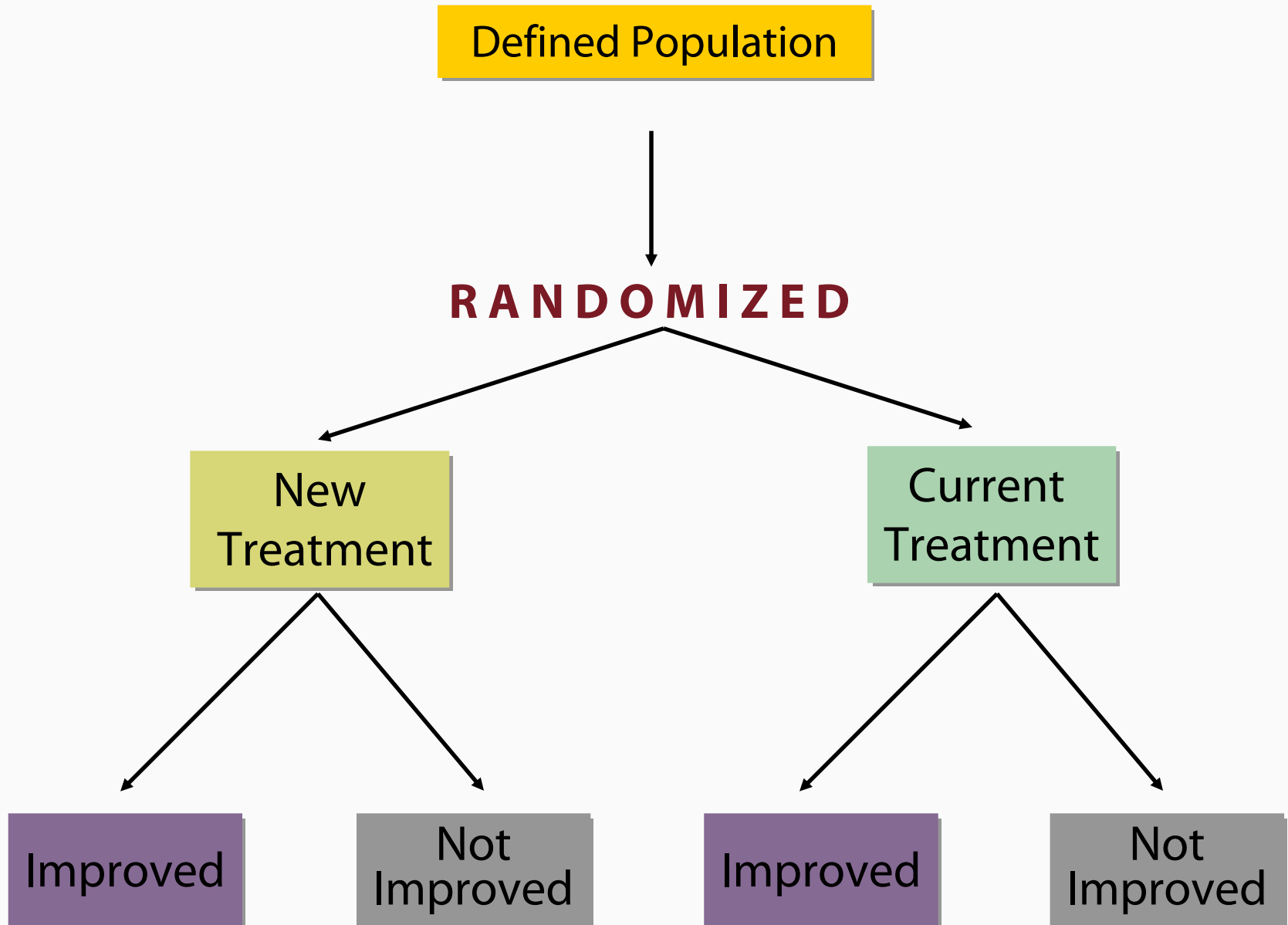


Table of Random Numbers

		Column			
		00–04	05–09	10–14	15–19
Row	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

Allocation Scheme

- A simple example using a one-digit random number
- **If two treatment groups are being studied:**
 - **If digit is:** **assign to:**
0–4 Treatment A
5–9 Treatment B
- **If three treatment groups are being studied:**
 - **If digit is:** **assign to:**
1–3 Treatment A
4–6 Treatment B
7–9 Treatment C
(0 ignore)

Example (2 groups)

6	1	1	4	7
7	8	9	1	0
Translated to				
B	A	A	A	B
B	B	B	A	A

Example (3 groups)

6	1	1	4	7
7	8	9	1	0
Translated to				
B	A	A	B	C
C	C	C	A	—

Other Sources of Random Numbers

- Computers or calculators
 - Pseudo-random numbers
 - Based on a mathematical formula or a predetermined list
- Random number Web sites, such as <http://random.org/>
 - True random numbers
 - Based on true randomness (entropy) outside of the computer, such as time to radioactive decay or atmospheric noise from radio

Purpose of Randomization

- Primary purpose
 - **Prevent bias in allocating subjects to treatment groups (avoid predictability)**
- Secondary purpose
 - Achieve comparability between the groups (there is no guarantee)

Gold Standard of Study Designs

- Randomized trials are gold standard of study designs because the potential for bias (selection into treatment groups) is avoided

Non-Randomized Observational Study

- A comparative study of an intervention in two groups of patients with MI shows that the mortality between the two groups differs

Intervention
n = 1,000

No Intervention
n = 1,000

Total deaths

180

300

Mortality

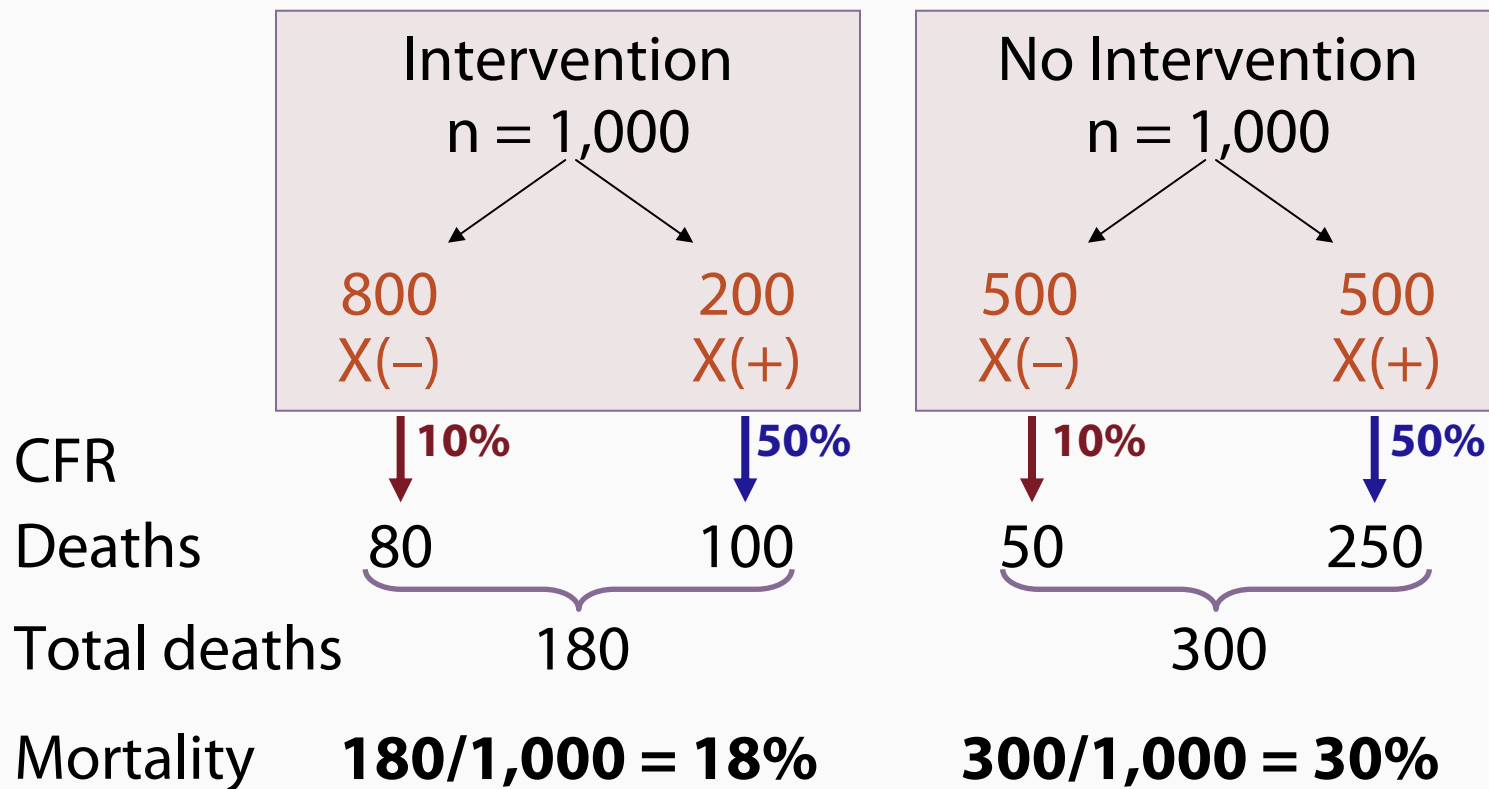
$180/1,000 = 18\%$

$300/1,000 = 30\%$

Conclusion?

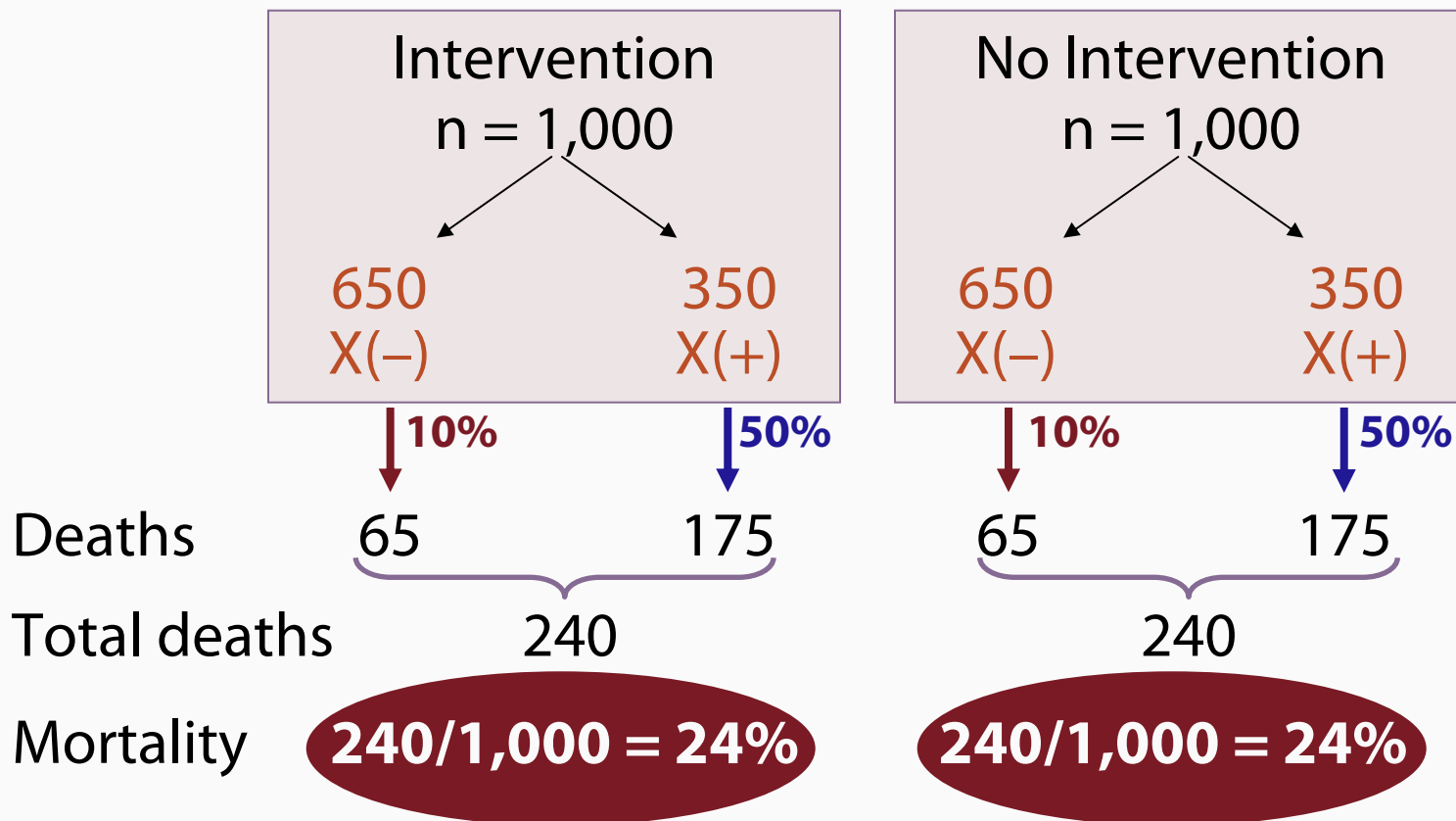
Non-Randomized Observational Study

- Proportions of patients with the arrhythmia X in the two groups differ



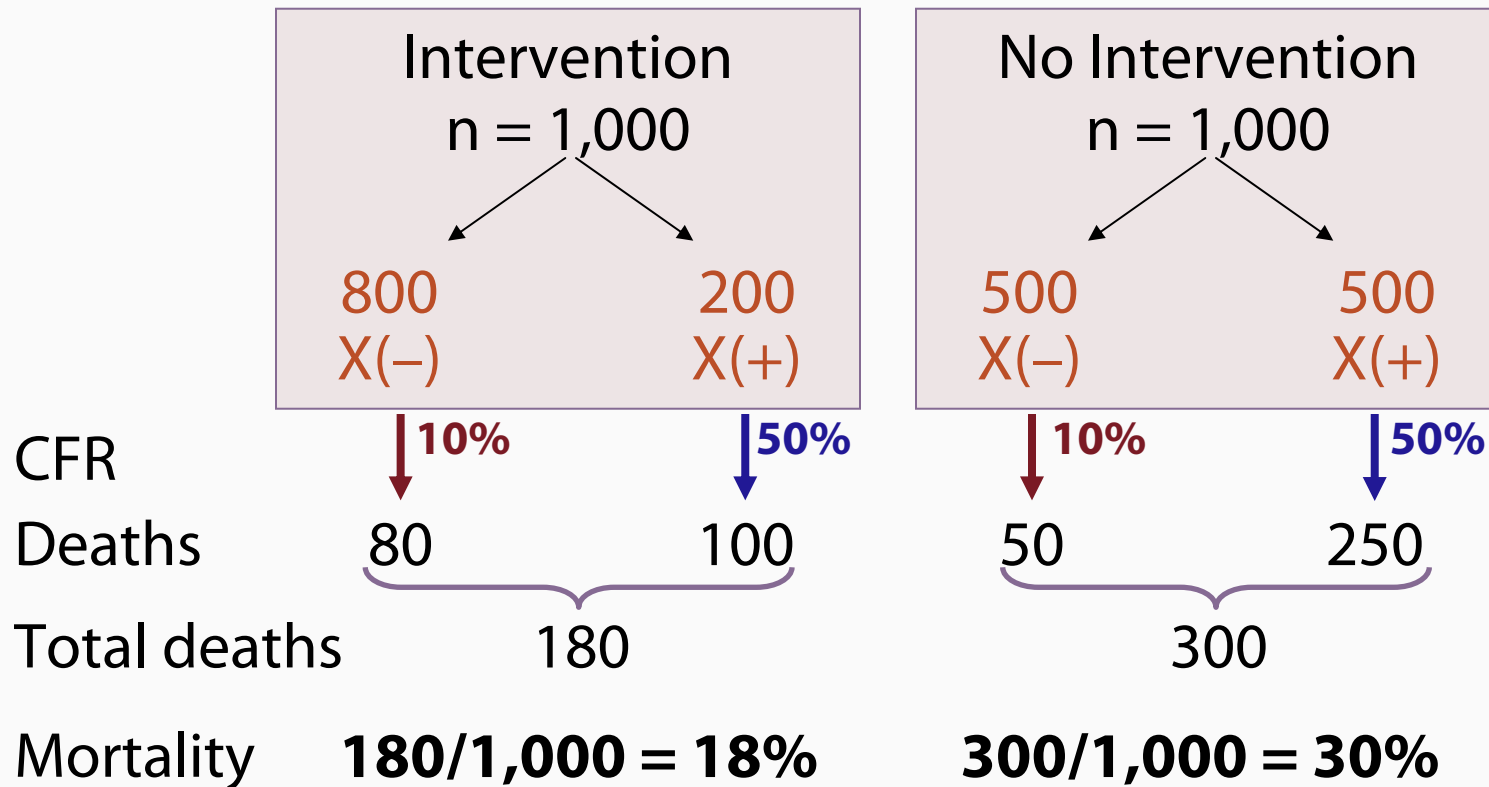
Randomized Experimental Study

- Proportions of patients with the arrhythmia X in the two groups are likely to be similar



Randomized Experimental Study

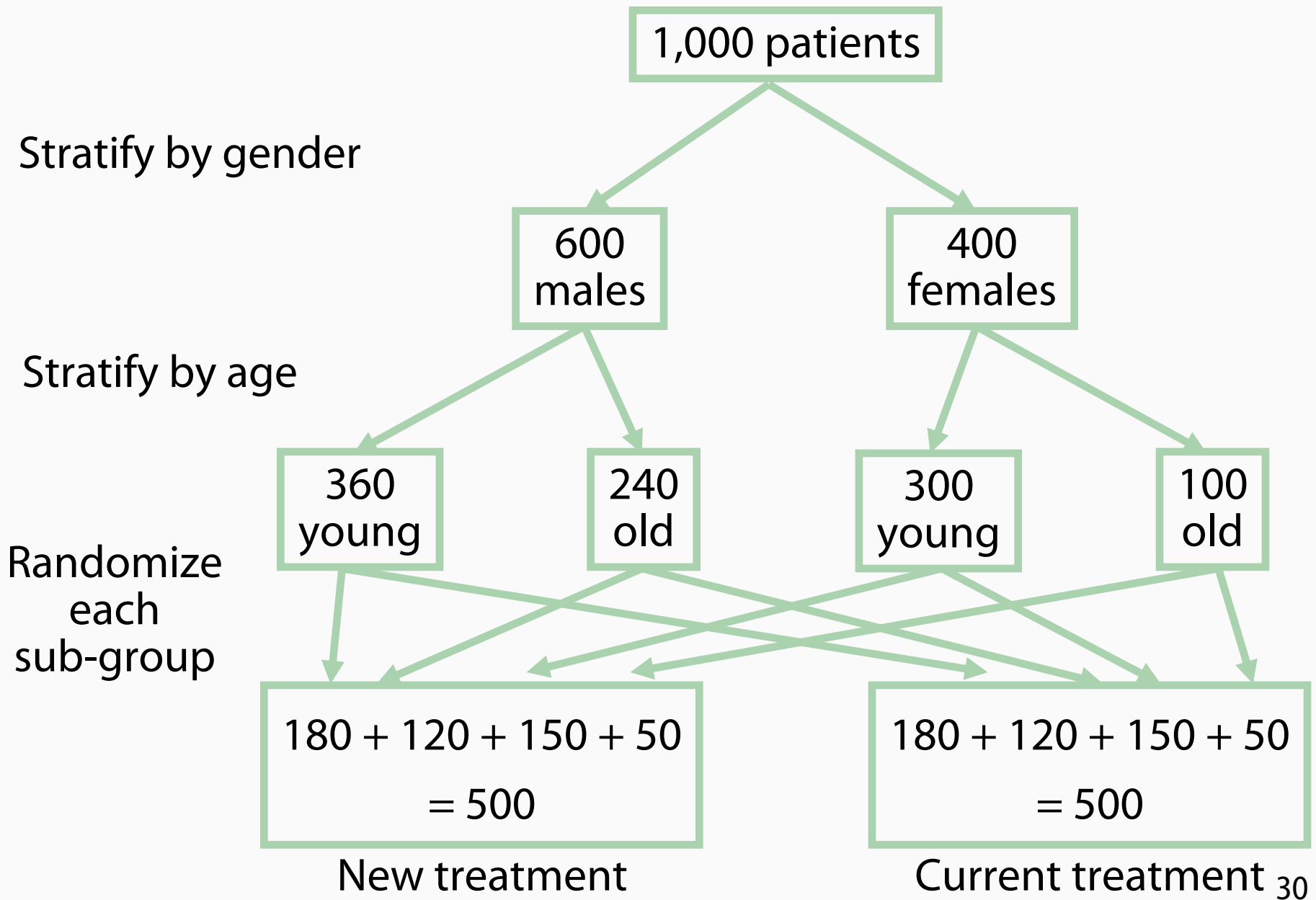
- Proportions of patients with the arrhythmia X in the two groups **may differ** (similarity is not guaranteed)



Stratified Randomization

- **Stratified randomization** is random assignment within groups defined by participant characteristics, such as age or disease severity, intended to ensure good balance of these factors across intervention groups

Diagram of Stratified Randomization



Data Collection and Documentation

- Treatment
 - Assigned and received
- Outcomes
 - Including beneficial and adverse effects
- Prognostic profile at entry
- Randomization procedure
 - Method used to generate the random allocation sequence
 - Method used to implement the random allocation
 - Personnel who generated the allocation sequence, enrolled participants, and assigned participants to groups

Masking or Blinding

- **Masking or blinding** is used to increase the objectivity of the persons dealing with the randomized study (to prevent prejudice)
- Subjects who can be masked/blinded
 - Study participants
 - Caregivers/treaters
 - Data collectors/assessors of outcome
 - Data analysts
 - Investigators
- Level of masking/blinding
 - Non-blinded (open)
 - Single
 - Double
 - Triple

- A **placebo** (from the Latin for “I will please”) is a medical treatment (operation, therapy, chemical solution, pill, etc.), which is administered as if it were a therapy, but which has no therapeutic value other than the placebo effect
- A **nocebo** (from the Latin for “I will harm”) is treatment like a placebo but which has a harmful result

Placebo and Blinding

- Results of a questionnaire on a prophylactic drug ingested by each volunteer

Actual drug	Suspected Drug			Total
	Vitamin C	Placebo	Unknown	
Vitamin C	40	12	49	101
Placebo	11	39	39	89
Total	51	51	88	190

Note: $p < 0.001$

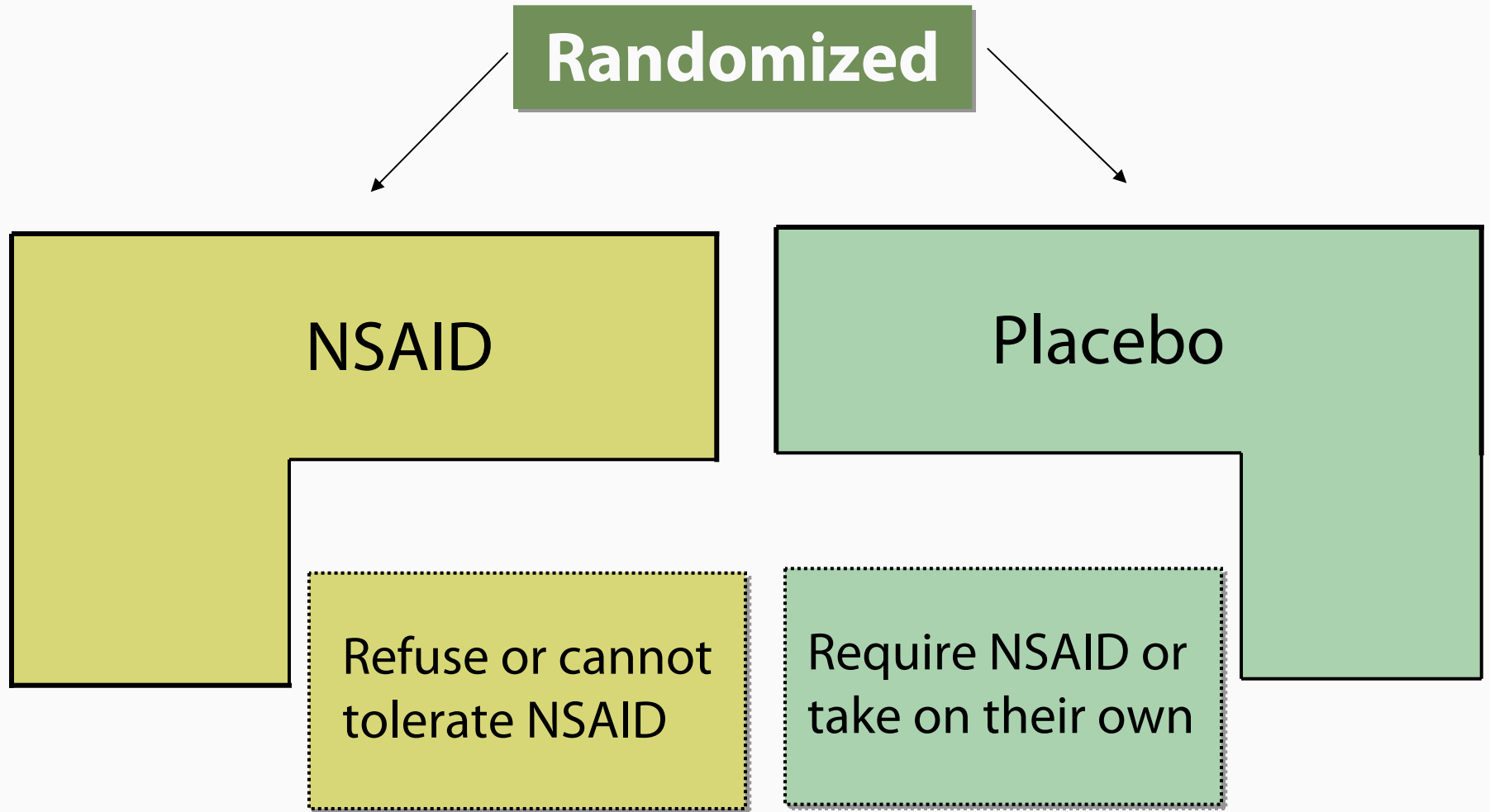
Placebo and Side Effects

- Side effect results from the Women's Health study

Side Effect	Aspirin	Placebo	P-value
GI bleeding	910 (4.6%)	751 (3.8%)	<0.001
Peptic ulcer	542 (2.7%)	413 (2.1%)	<0.001
Hematuria	3,039 (15.2%)	2,879 (14.4%)	0.02
Easy bruising	10,561 (53%)	8,494 (42.6%)	<0.001
Any report of gastric upset	11,856 (59.5%)	11,915 (59.7%)	0.59

- **Compliance** is the willingness of the participants to carry out the procedures according to the established protocols (adherence)
- **Drop-outs** are the participants who do not adhere to the experimental regimen during follow-up
- **Drop-ins** are the participants who do not adhere to the control regimen during follow-up

Non-Adherence during Follow-Up



- Primary: **intention to treat**
 - Analyze according to original allocation
 - Net effect of non-compliance is to reduce the observed differences
- Secondary: actual treatment received
 - Based on observed data
 - No benefit of randomization

Example of Subgroup Analysis

	Number of Patients	Five-Year Mortality
Clofibrate	1,065	18.2%
Placebo	2,695	19.4%

Compliance Analysis

	Number of Patients	Five-Year Mortality
Clofibrate		
Poor complier	357	24.6%
Good complier	708	15.0%
Placebo	2,695	19.4%

Compliance Analysis

	Number of Patients	Five-Year Mortality
Clofibrate		
Poor complier	357	24.6%
Good complier	708	15.0%
Placebo		
Poor complier	882	28.2%
Good complier	1,813	15.1%

Dealing with Non-Compliance

- Monitor compliance
 - Observe treatment directly
 - Count pills
 - Conduct blood or urine tests to confirm compliance
- Use of “run-in” period

Example of Run-in from the Physicians' Health Study

“The 33,223 willing and eligible physicians were enrolled in a **run-in phase** during which all received active aspirin and placebo beta-carotene. After 18 weeks, participants were sent a questionnaire asking about their health status, side effects, compliance, and willingness to continue in the trial. A total of 11,152 changed their minds, reported a reason for exclusion, or did not reliably take the study pills. The remaining 22,071 physicians were then randomly assigned.”

- Define
 - Randomization
 - Placebo
 - Intention to treat
 - Drop-in and drop-out
 - Run-in period
- What is the primary purpose of randomization?



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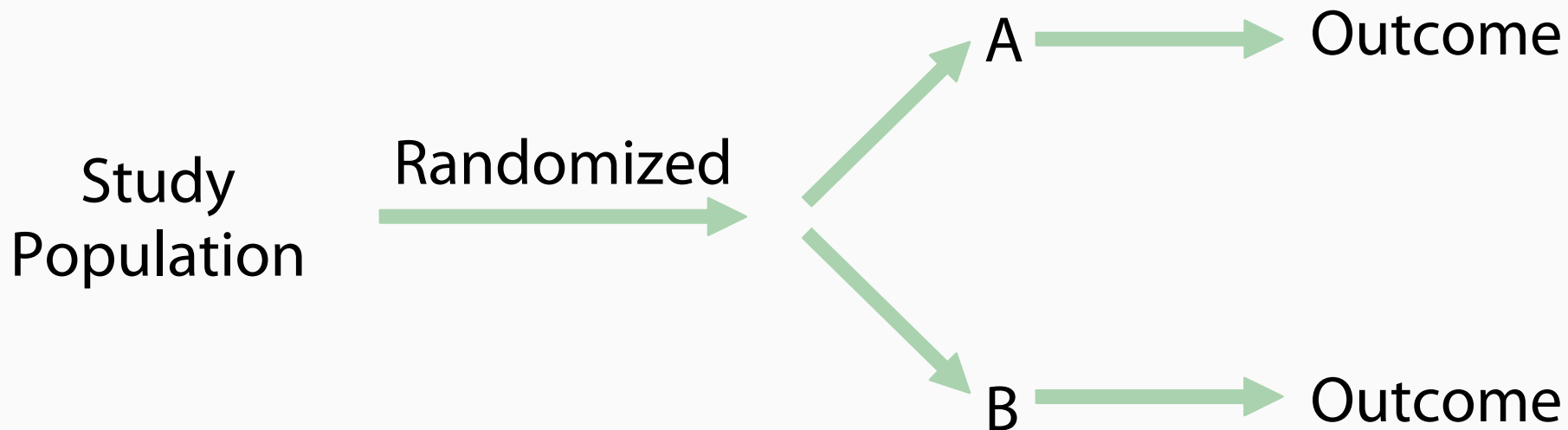
Section C

Types of Clinical Trials

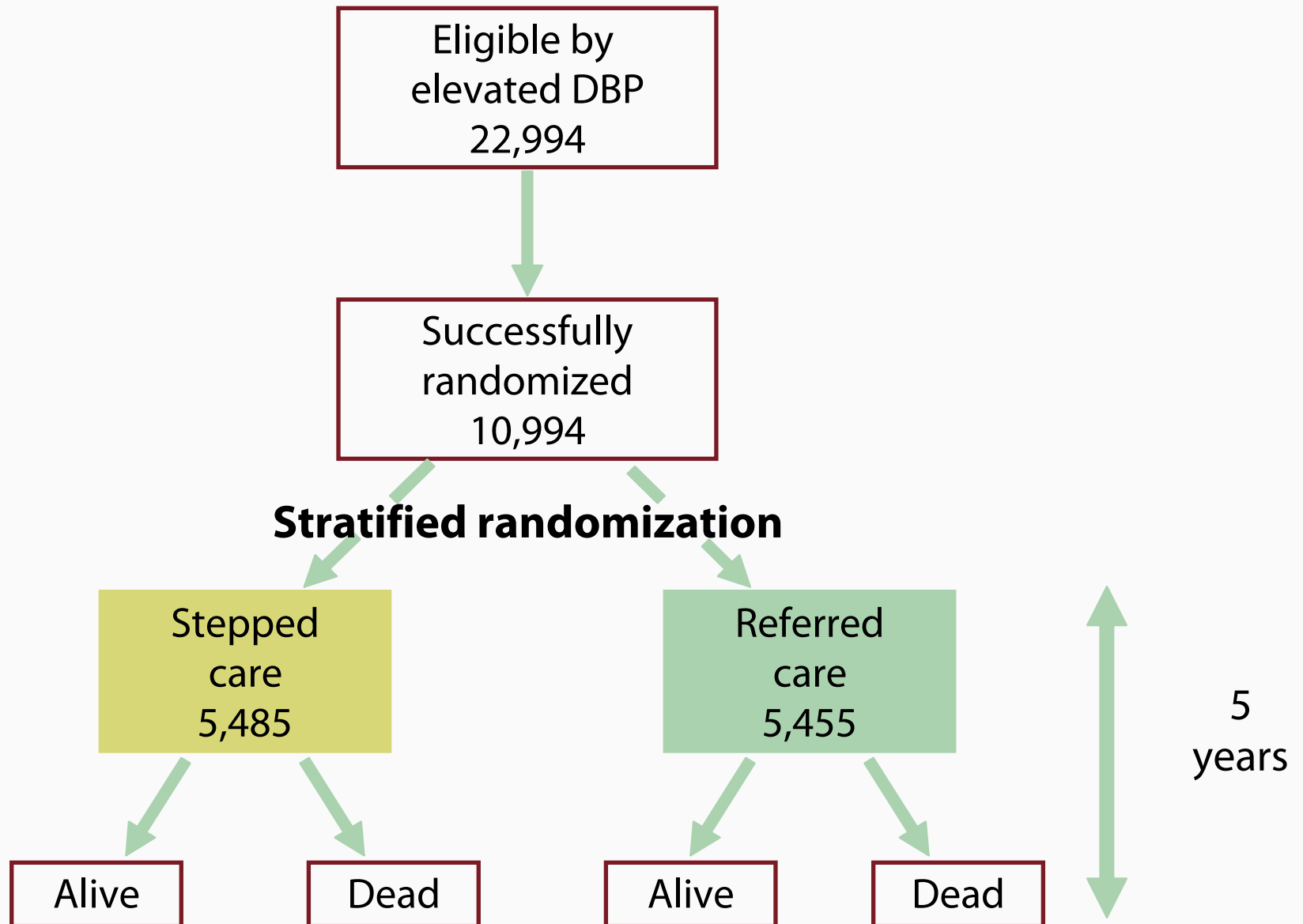
Randomized Trials: Study Designs

- Parallel treatment or simple, non-crossover
- Crossover
 - Planned crossover
 - Unplanned crossover
- Factorial

Parallel Treatment or Simple, Non-Crossover Trial



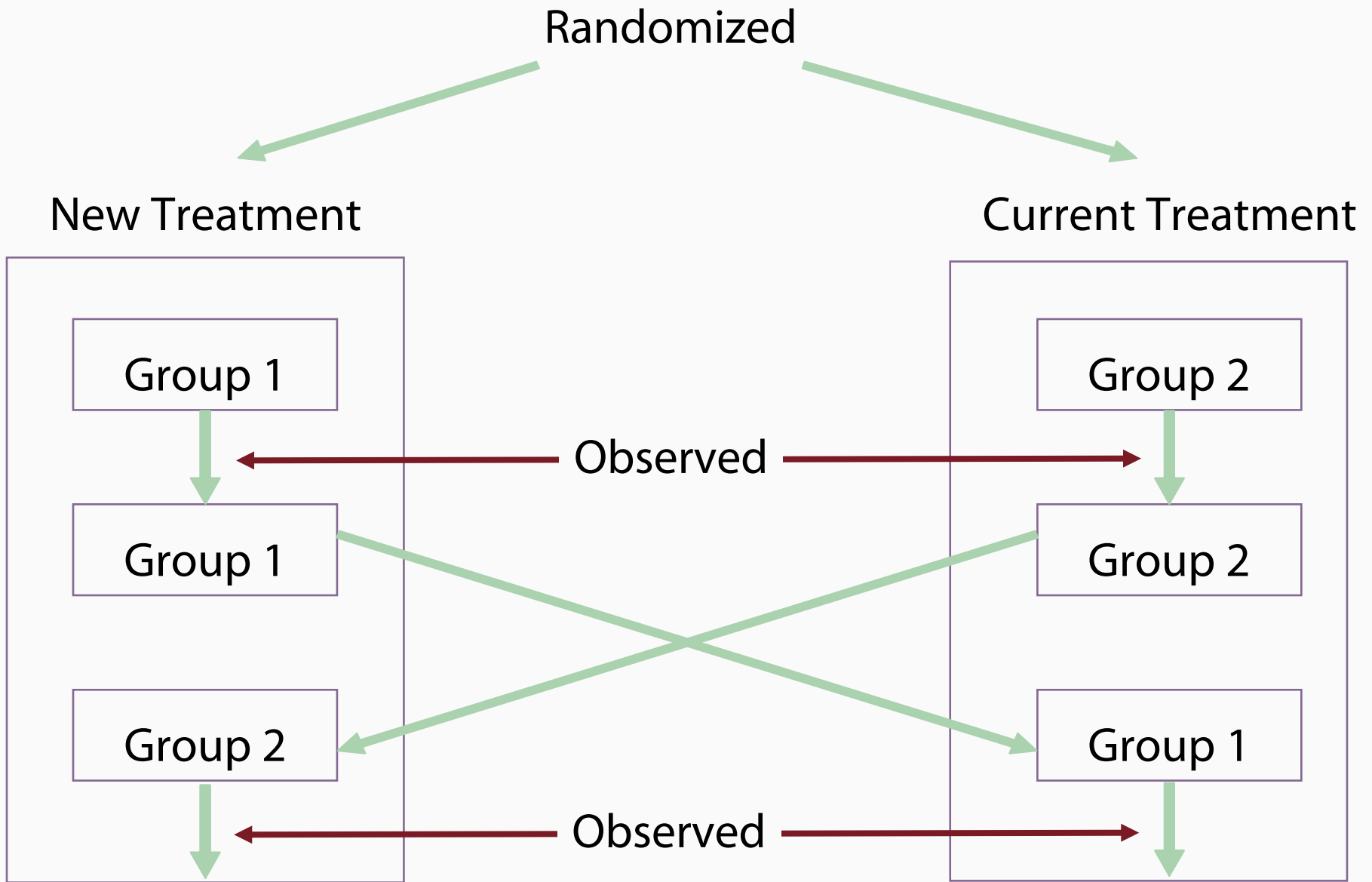
The Hypertension Detection and Follow-Up Program



Mortality from All Causes During the HDFP

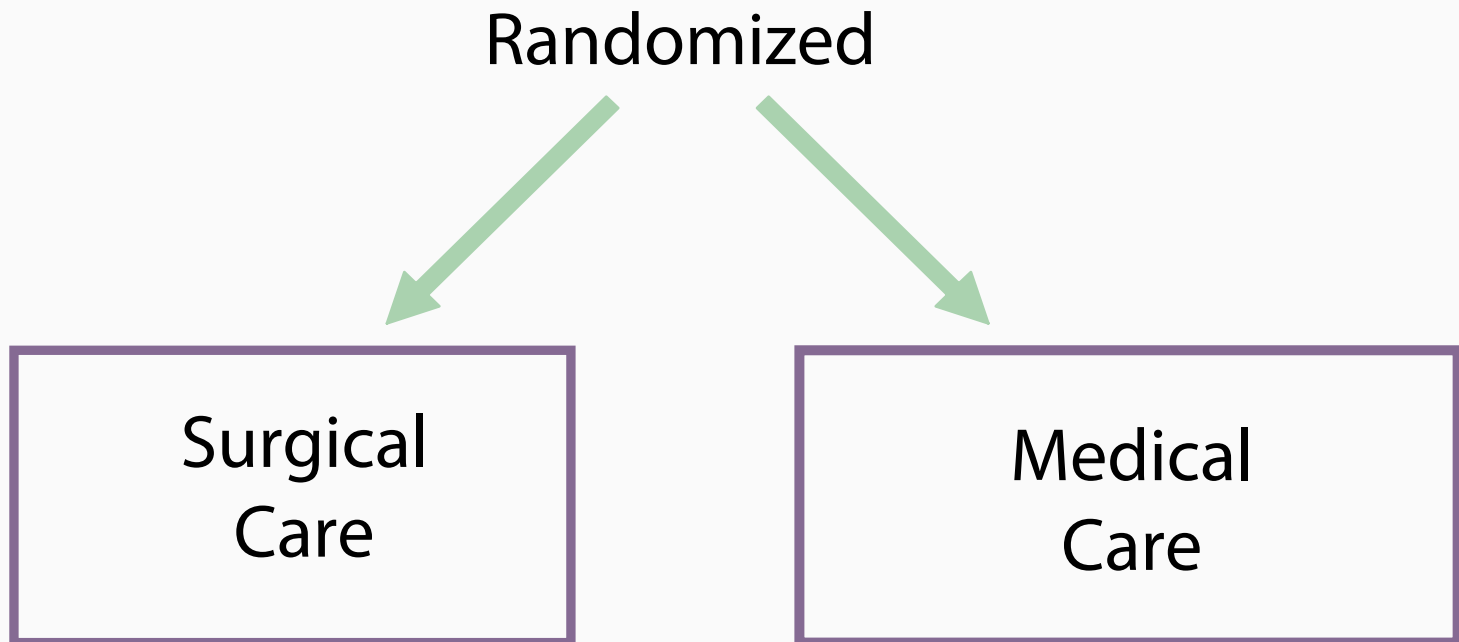
Diastolic Blood pressure at entry (Mm hg)	Stepped care (SC)	Referred care (RC)	5-year death rate		Percent mortality reduction in SC group
			SC	RC	
90–104	3,903	3,922	5.9	7.4	20.3
105–114	1,048	1,004	6.7	7.7	13.0
≥ 115	534	529	9.0	9.7	7.2
Total	5,485	5,455	6.4	7.7	16.9

Planned Crossover Trial

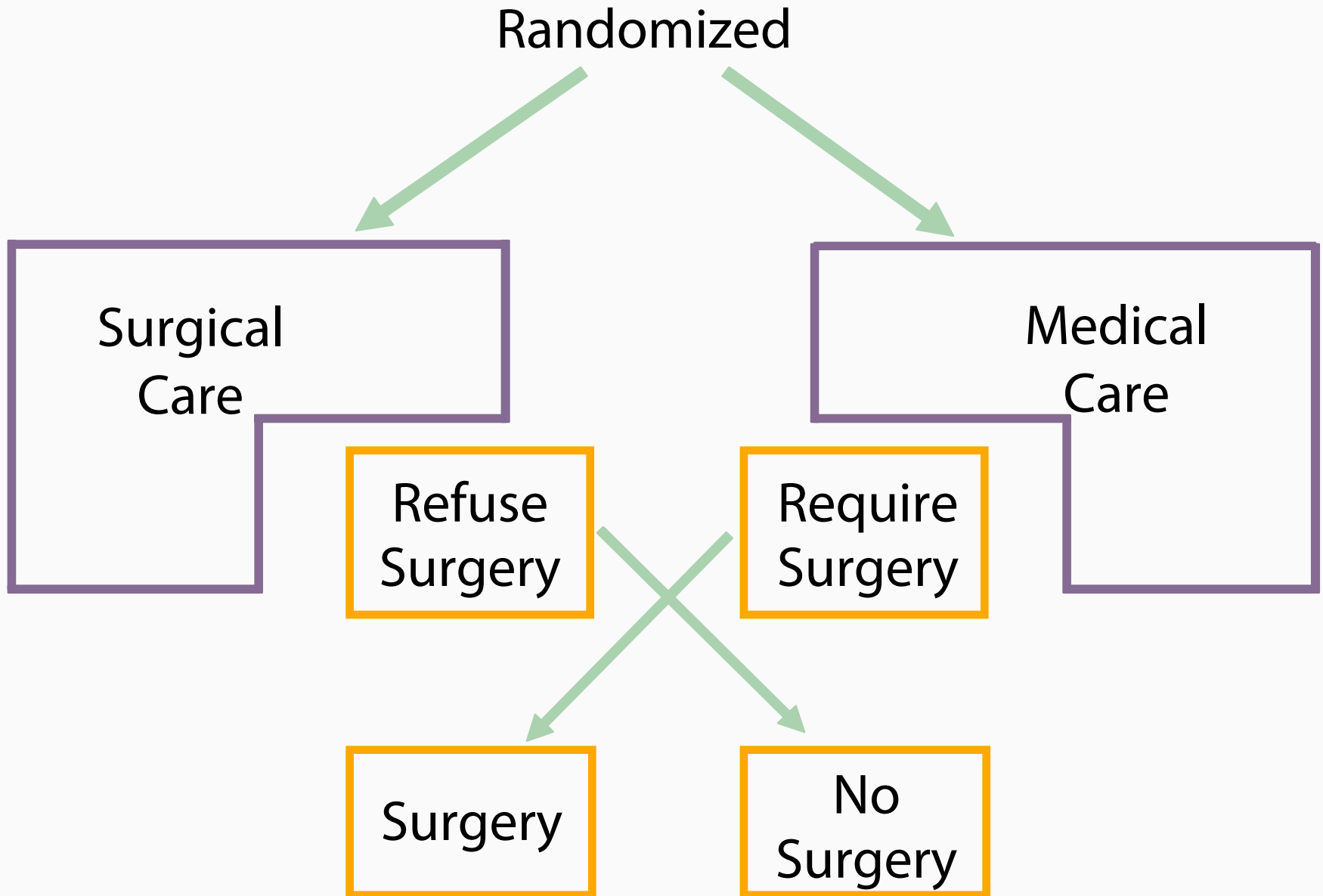


Cardiac Bypass Surgery Study

Original Study Design



Reality: Unplanned Crossover



Treatment B

+

-

Treatment A

+

Both A
and B

A only

-

B only

Neither A
nor B

Factorial Design Trial

Study of treatment A

Treatment B

+

-

Treatment A

+

Both A
and B

A only

-

B only

Neither A
nor B

Study of treatment B

Treatment B

+

-

Treatment A

+

Both A
and B

A only

-

B only

Neither A
nor B

Objectives of the Physicians' Health Study

- Does aspirin prevent first myocardial infarction?
- Does beta carotene prevent cancer?

Physicians' Health Study

- 22,071 physicians, 40–84 years old
- Randomly assigned in 1982 to one of four groups
 1. Aspirin only (beta-carotene placebo)
 2. Beta carotene only (aspirin placebo)
 3. Aspirin and beta carotene
 4. Neither (both placebos)

Factorial Design Used in the Physicians' Health Study

		Aspirin	
		+	-
Beta carotene	+	Both aspirin and beta carotene	Beta carotene only
	-	Aspirin only	Neither aspirin nor beta carotene

Physicians' Health Study Results

- Randomized aspirin component terminated early on January 25, 1988, with a positive effect (44% reduction in risk of MI)
- Randomized beta-carotene component continued as originally scheduled and terminated on December 31, 1995, and produced neither benefit nor harm for cancer

Physicians' Health Study II

- **Physicians' Health Study II (PHS II)** is a randomized, double-blind, placebo-controlled trial enrolling 15,000 willing and eligible physicians aged 55 years and older
- PHS II will utilize a 2 x 2 x 2 x 2 factorial design to test alternate day beta carotene, alternate day vitamin E, daily vitamin C, and a daily multivitamin in the prevention of total and prostate cancer, CVD, and the age-related eye diseases (cataract and macular degeneration)
- Randomization began in 1997
- Study is scheduled to continue until 2007

Results of Randomized Trials

- Efficacy = reduction in risk

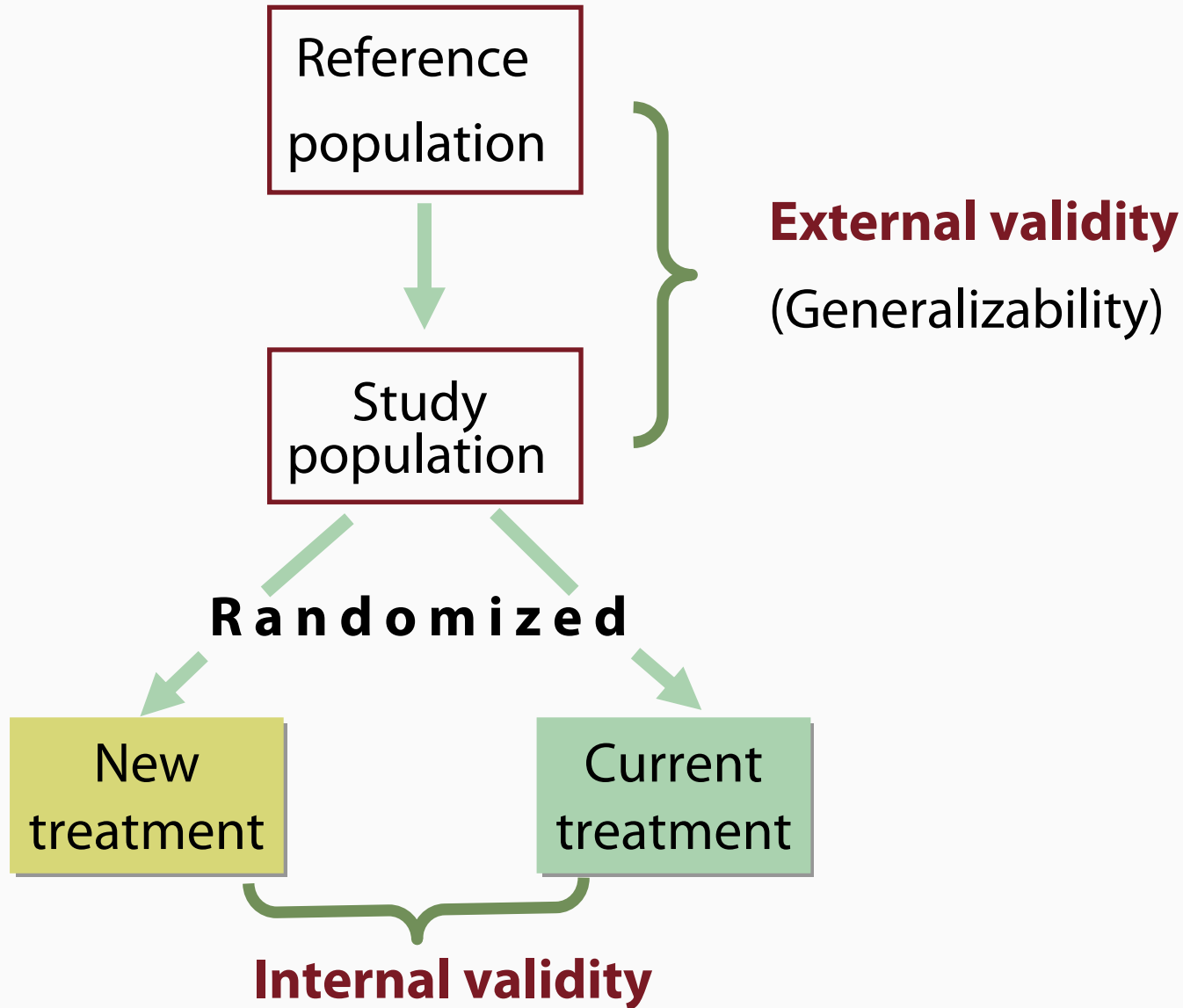
$$\begin{aligned}\text{Efficacy} &= \frac{\text{Rate in placebo} - \text{Rate in treated}}{\text{Rate in placebo}} \\ &= 1 - \frac{\text{Rate in treated}}{\text{Rate in placebo}}\end{aligned}$$

Example of Results of a Randomized Trial

- From the Physicians' Health Study (unadjusted result),
 - Rate of MI in the treated group = $139/54,560 = 254.8$ per 100,000 per year
 - Rate of MI in the placebo group = $239/54,355.7 = 439.7$ per 100,000 per year

$$\begin{aligned}\text{Efficacy} &= \frac{439.7 - 254.8}{439.7} \\ &= 1 - \frac{254.8}{439.7} = 1 - 0.5795 = 42.05\%\end{aligned}$$

Internal and External Validity in a Randomized Trial



External Validity (Generalizability)

- Physicians' Health Study
 - Aspirin reduced the risk of MI (reduction in risk = 44%) in **men** 50 years or older who did not have clinical evidence of coronary disease (primary prevention)
- Can the findings be generalized to **women**?

From the **Women's Health study**

Aspirin has no significant effect on the risk of MI in women 65 years or older who did not have history of cardiovascular disease

Phases in Testing of New Drugs

- **Phase I studies** (clinical pharmacologic studies)
 - Test new drug or treatment in a small group of people (20–80) for the first time to evaluate its safety
 - ▶ Determine levels of toxicity, metabolism, pharmacological effect, and safe dosage range
 - ▶ Identify side effects
- **Phase II studies** (efficacy studies)
 - The drug or treatment is given to a larger group of people (100–300) for efficacy and to further evaluate its safety

Phases in Testing of New Drugs (II)

- **Phase III studies** (effectiveness studies)
 - The drug or treatment is given to a large group of people (1,000–3,000) to confirm its effectiveness, compare it to commonly used treatments, and monitor side effects
- **Phase IV studies** (post-marketing clinical trials)
 - The drug or treatment is monitored to gather more information on risks, benefits, and optimal use

Some Ethical Issues in Randomized Clinical Trials

- Is randomization ethical?
- Can truly informed consent be obtained?
- When can placebo be used?
- Under what conditions should a randomized clinical trial be stopped earlier than originally planned?