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Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

RANDOMIZED CONTROLLED TRIALS (RCT)

Julie E. Buring, ScD

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Totality of Evidence

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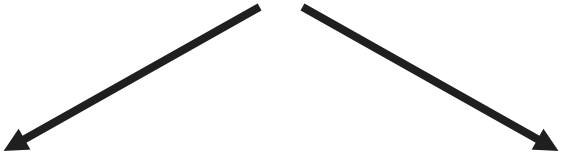
- Basic Research
- Epidemiologic Studies



Descriptive studies

Who? What? Where? When?

- Correlational or ecologic study
- Case reports/series
- Cross-sectional study

Analytic studies

Why?

- Observational study
  - case-control
  - cohort

Intervention study
e.g., randomized clinical trial

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Analytic Studies

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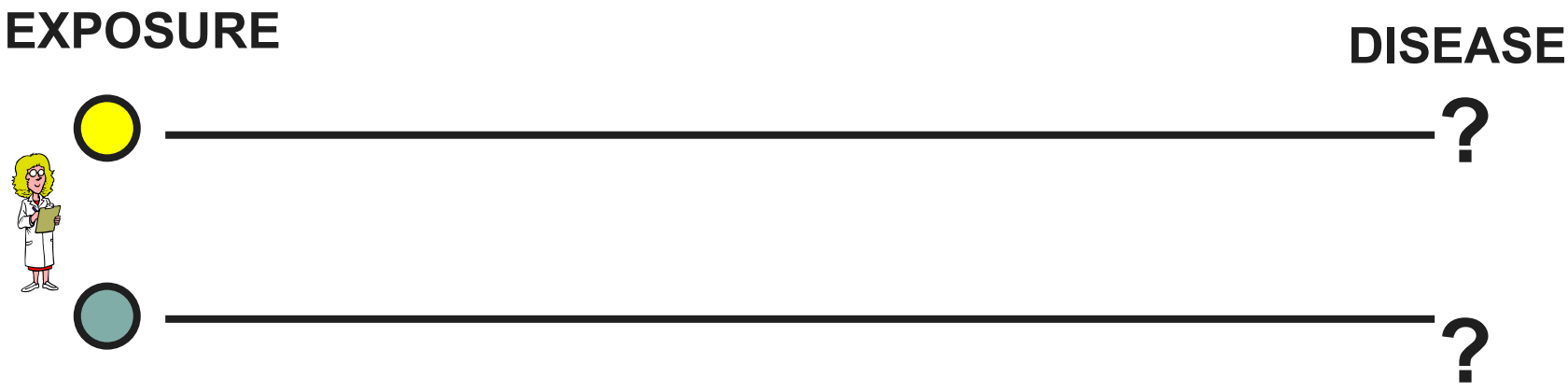
1. **Observational Studies**
   - **Case-control (initial selection on basis of disease status)**
   - **Cohort (initial selection/classification on basis of exposure status)**
   - **Exposures are self-selected**
2. **Intervention Studies (e.g., randomized clinical trials)**
   - **Initial classification on basis of exposure status**
   - **Exposures are allocated by investigators (not self-selected)**

Intervention Study: Structure of cohort study, but exposure is allocated by investigator



PRESENT

ABSENT

} Exposure is allocated to participants at beginning of study. Not self-selected; not observational study.

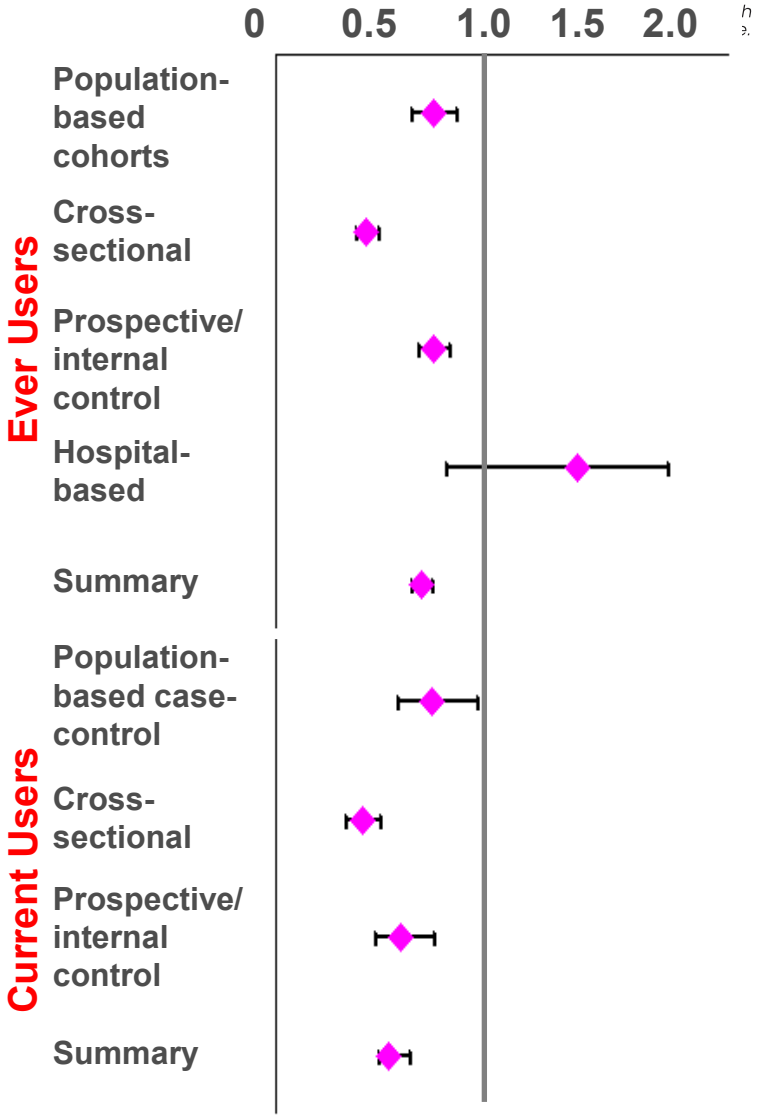
INVESTIGATOR at beginning of study

What is an Observational Study?

Women free of disease at start of study, classified as users or nonusers of hormone therapy → **Are followed over time** → **To compare who does and does not develop the CVD among the exposed and nonexposed groups**

Postmenopausal Hormone Therapy (HT) and CHD: Meta-Analysis of Observational Studies

Based on more than 40 observational studies of HT and CHD, the summary relative risk was 0.64 (95% CI, 0.59-0.68) for ever use of HT and 0.50 (95% CI, 0.45-0.59) for current use, compared with never users.



From: Grodstein F, Stampfer MJ. *Prog Cardiovasc Dis* 1995; 38:199.

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Limitations of Observational Studies of HRT

- **Women who take hormones for an extended time differ from those who don't in many ways that could be related to the outcome of interest. Also, why are they taking? Could there be confounding by indication?**
- **In observational studies, estrogen users were leaner, less likely to smoke, more physically active, more likely to see doctors, and more educated.**

These differences could explain the lower rates of heart disease among hormone users seen in observational studies.

What is a Clinical Trial?

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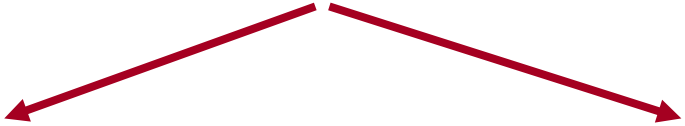
In a randomized, placebo-controlled clinical trial:

Participants who are eligible are randomly assigned to



Hormone Use | **Placebo**

They are followed over time to see how many develop disease in one group compared to the other group.

Randomization with large sample size ensures hormone group will be similar to placebo group in lifestyle factors, medical and family history, and other factors

Randomized Clinical Trials

- **Every trial feature is designed to minimize alternative explanations of chance, bias and confounding: large sample size, randomized, double-blind, placebo-controlled, high compliance, low loss-to-follow-up, intention-to-treat analysis, etc.**
- **None of this would be necessary if the effect size was large (e.g., penicillin). But we are not usually evaluating magic bullets. Evaluating 10%, 20%, 30% differences, statistically difficult to assess but clinically meaningful.**
- **Unique niche of RCT's: optimal to detect statistically small to moderate, but clinically worthwhile, treatment effects because of ability to reduce noise in study.**

Bottom Line

- **RCTs are more logistically difficult, more expensive, and have more issues related to ethical considerations than any other epidemiologic design strategy.**
- **But if ethically appropriate, and if well designed and conducted, they provide a level of assurance about the effect of the intervention itself on the outcome that cannot be achieved by any other epidemiologic design strategy.**

Types of RCTs

- Treatment Trials = Secondary Prevention
- Prevention Trials = Primary Prevention
- Individual randomization vs. group randomization (e.g., communities, schools)

Special Issues in RCTs

- **Costs, feasibility and ethics.**
- **Ethics: Equipoise: enough belief to give, enough doubt to withhold.**
- **Can't randomize to demonstrate harm.**
- **Is doing a trial ethical? Is not doing a trial ethical?**
- **Key issue of timing: "window of opportunity". Issues of logistics, willingness to be randomized.**

Physicians' Health Study

- Randomized trial, designed to test the effects of low-dose aspirin (325 mg QOD) and beta carotene (50 mg QOD) (vegetable form of vitamin A) in the primary prevention of CVD and cancer among 22,071 U.S. male physicians, aged 40-84 at baseline.
- Funded by the NIH; drugs provided by industry.

Women's Health Study

- Randomized trial, designed to test the effects of lower-dose aspirin (100 mg QOD) and vitamin E (600 IU QOD) in the primary prevention of CVD and cancer among 39,876 U.S. female health professionals, over age 45 at baseline.
- Funded by the NIH; drugs provided by industry.

Preliminary Work

- Piloting an RCT is KEY.
- Bioavailability study to confirm proposed doses of aspirin are adequate to irreversibly inhibit platelets in both men (325 mg qod PHS) and women (100 mg qod WHS).
- Pilot study needed to show feasibility of every study procedure (pilot study in 1000 physicians: identify, mail, rates of response, eligibility, willingness, etc).
- Need an IND (Investigational New Drug) from FDA – established drug, but not for this new indication.

Population Hierarchy

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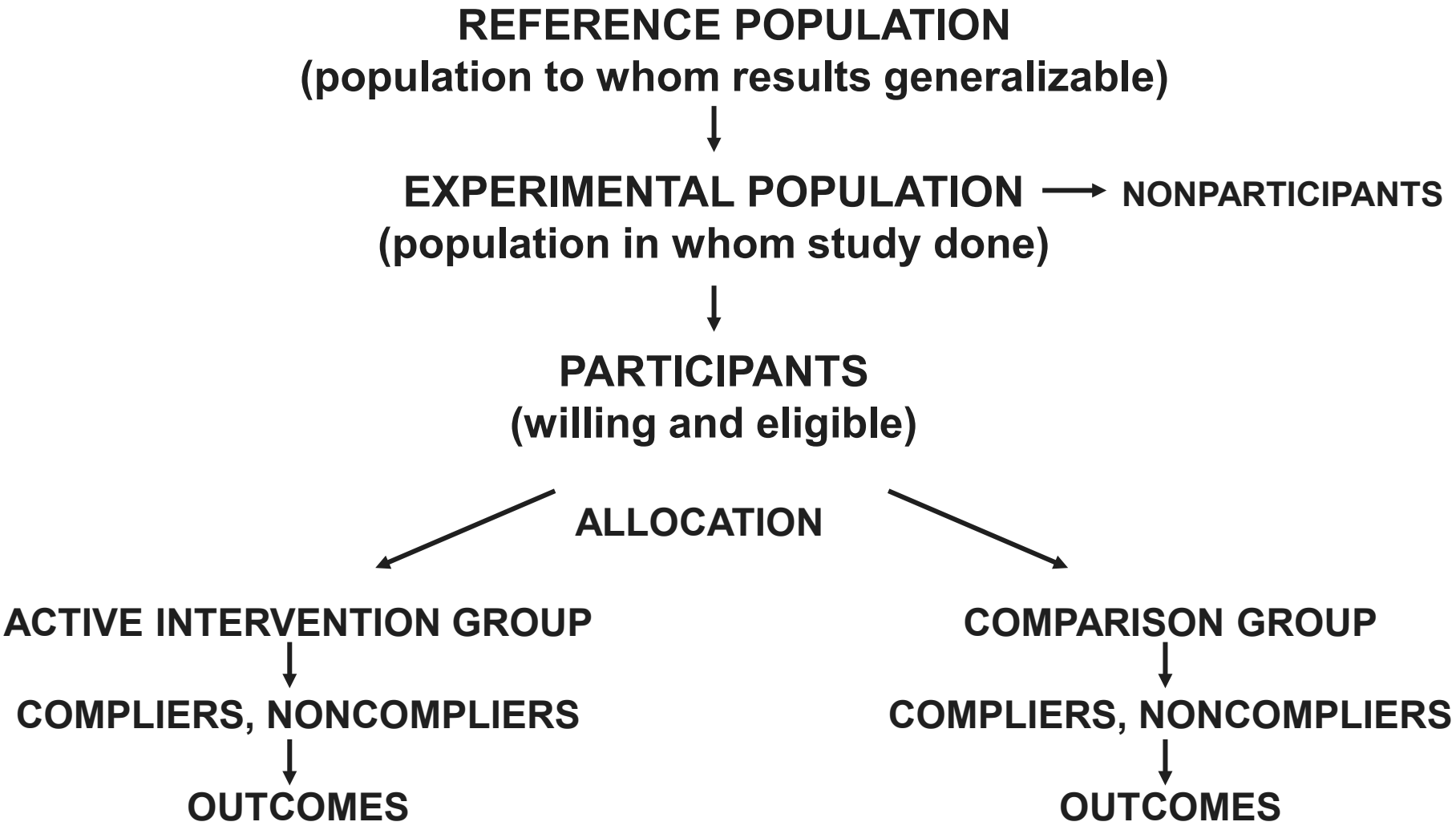

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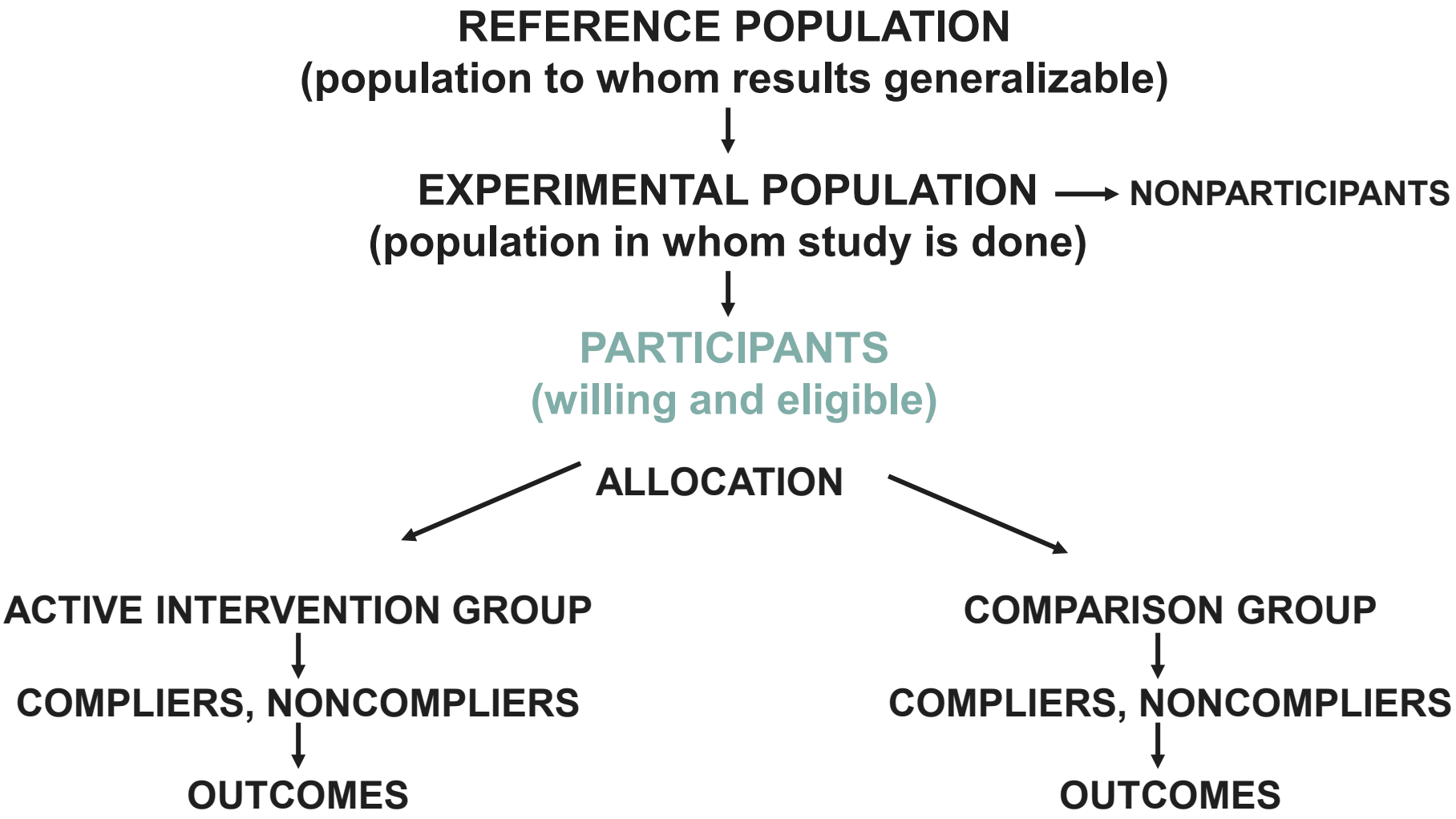

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Physicians' Health Study

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261,248

U.S. male physicians mailed invitational letter and questionnaire

↓

112,528

Questionnaires returned

↓

59,285

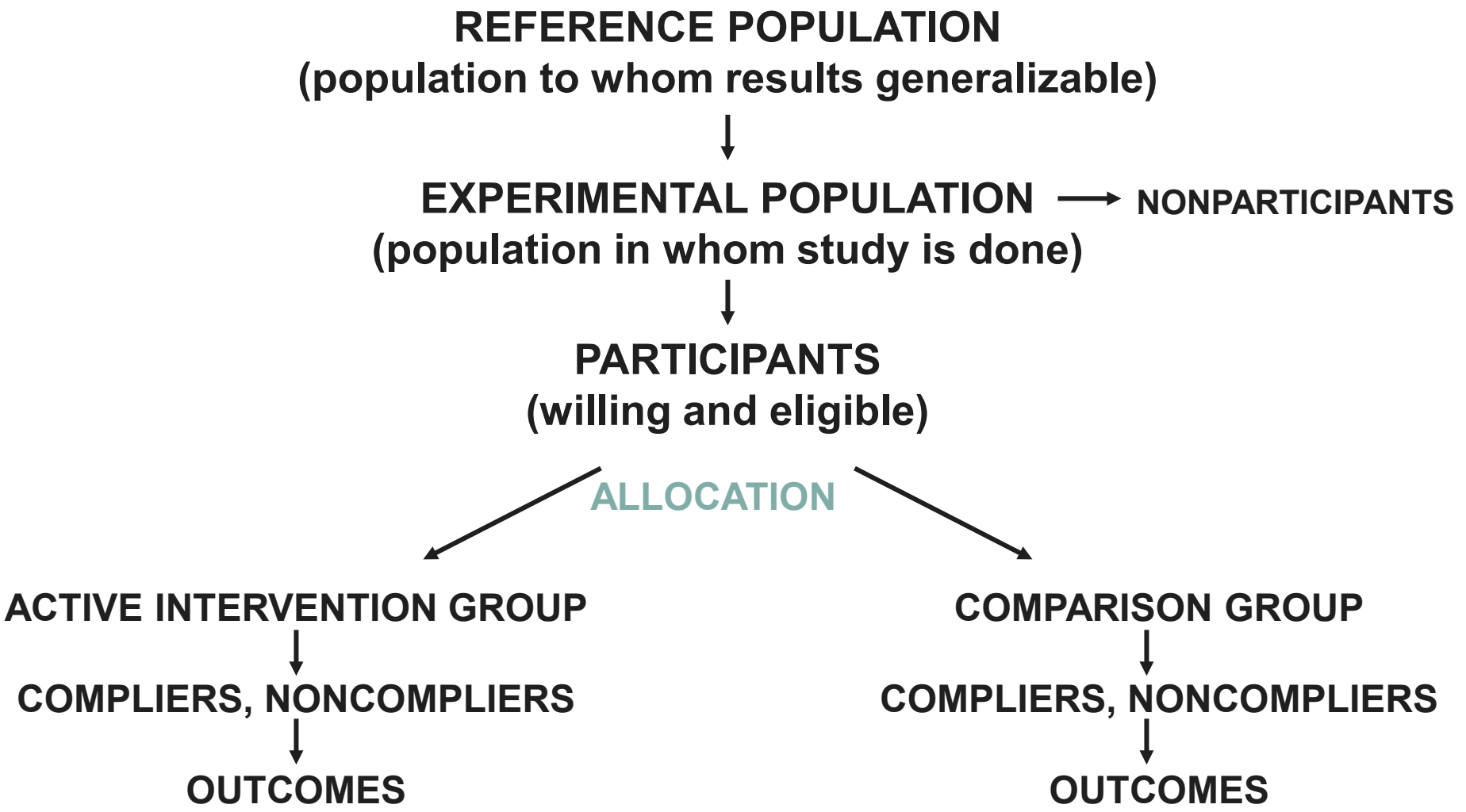
Willing to participate

↓

33,223

Eligible and enrolled in 18-week run-in (practice period)

Population Hierarchy



Allocation of Study Regimens

- Optimal way is randomization (treatment group allocated at random; by computerized random number generator, opaque envelopes, call-in randomization center).
  - Strength is unpredictability
  - All confounders - known and unknown - are on average distributed equally among the study groups
  - Works "on average" - so if going to do a trial, do it big
  - Minimizes selection bias and confounding

Baseline Characteristics - Medical History

	Aspirin (n=11,037)	Placebo (n=11,034)
Age (yrs)	53.2 ± 9.5	53.2 ± 9.5
History of hypertension (%)	13.5	13.6
Systolic BP (mmHg)	126.1 ± 11.3	126.1 ± 11.1
Diastolic BP (mmHg)	78.8 ± 7.4	78.8 ± 7.4
History of high cholesterol (%)	17.5	17.3
Cholesterol level (mg)	212.1 ± 44.2	212.0 ± 45.1
History of diabetes (%)	2.3	2.2
History of angina (%)	1.3	1.2
Parental MI (%)	13.0	13.1

Physicians' Health Study

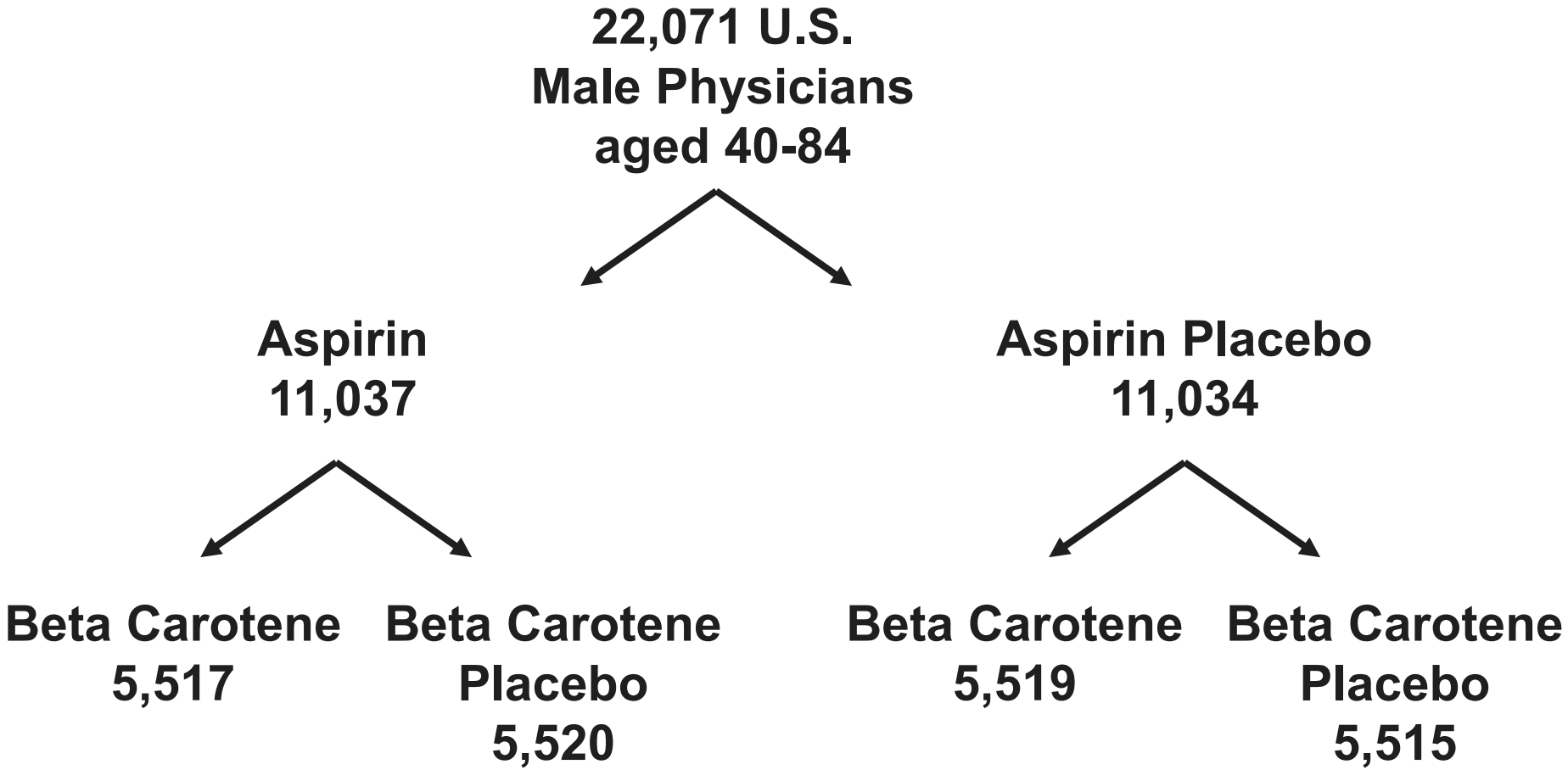
Baseline Characteristics - Health Habits

	Aspirin (n=11,037)	Placebo (n=11,034)
Current smoking (%)	11.0	11.1
Past smoking (%)	39.4	39.1
Daily alcohol (%)	24.9	25.0
Exercise >1/week (%)	71.7	71.2
Body mass index (kg/m^2)	24.9 ± 3.1	24.9 ± 3.0
Multivitamin	19.9	19.9

Allocation of Study Regimens

- **Crossover RCT – before/after where individuals serve as own historical control.**
  - **Advantage is perfect matching – no issues with confounding.**
  - **Requires individual's condition can't change over time.**
  - **Has to be able to have adequate washout period (can't be long-lasting effects or irreversible outcomes).**

Physicians' Health Study
Randomization Scheme: 2x2 Factorial Design



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Population Hierarchy

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REFERENCE POPULATION
(population to whom results generalizable)

↓

EXPERIMENTAL POPULATION → **NONPARTICIPANTS**
(population in whom study is done)

↓

PARTICIPANTS
(willing and eligible)

ALLOCATION

ACTIVE INTERVENTION GROUP	COMPARISON GROUP
↓	↓
COMPLIERS, NONCOMPLIERS	COMPLIERS, NONCOMPLIERS
↓	↓
OUTCOMES	OUTCOMES

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Nature of Comparison Group

- Cannot give less than standard of care
- Usual care
- Other doses of same treatment
- Other treatments
- Placebo
  - Inert agent that looks indistinguishable from active agent

Minimizing Bias in Ascertainment of Outcomes

- Use of placebo
  - minimizes observation bias
  - depends on subjectivity of outcome
  - placebo or blinding may not be practicable, or cannot be done in some situations (medical vs surgical, drugs with characteristic effects)

Minimizing Bias in Ascertainment of Outcomes

- **Blind (participant) and double-blind (investigator) techniques (also termed masked, double-masked). Also blinding in assessment of outcome. Adds credibililty, but also complexity and cost.**

- **Objective criteria in determining outcome (especially important if can't use blinding and/or placebo).**

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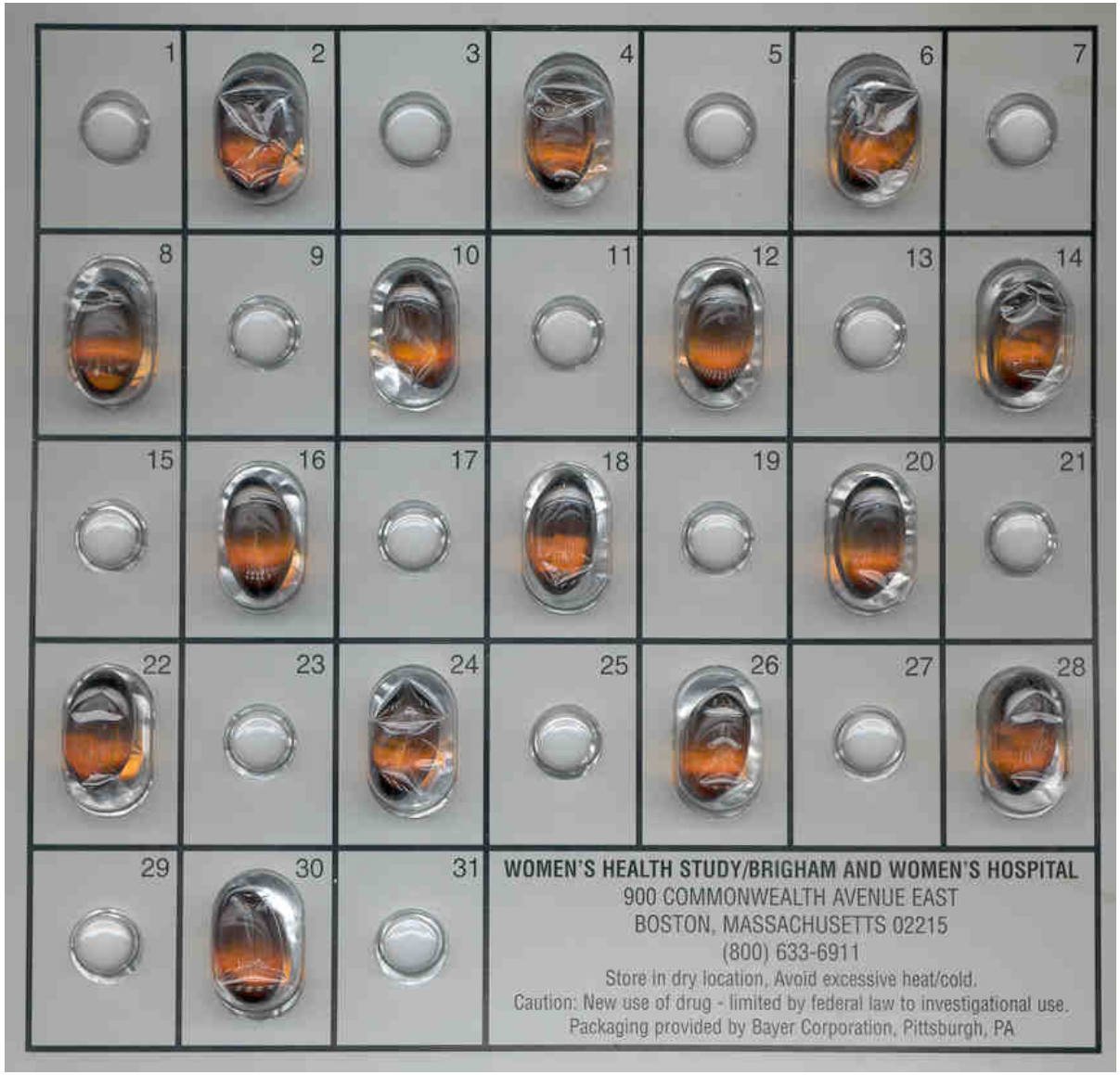
Compliance in Randomized Trials

- Crucial to ability of trial to demonstrate a true effect.
- Noncompliance will bias relative risk towards the null value.
- Need for ascertainment of compliance (e.g., spot blood/urine checks in PHS/WHS).
- Methods to maintain high compliance critical. Allocating regimen = taking regimen. (e.g., using calendar packs – double blinded, costs).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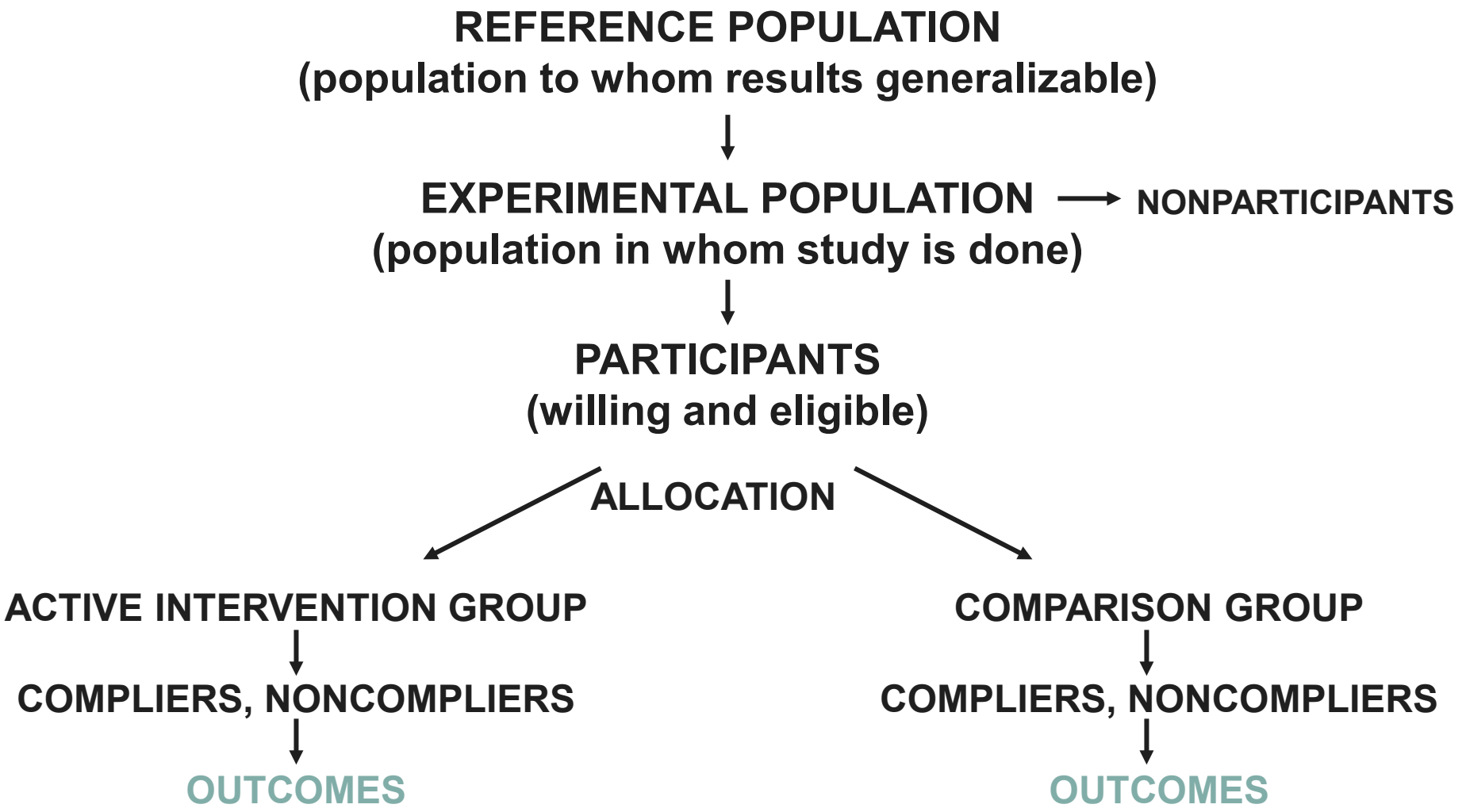

Physicians' Health Study: Endpoints Ascertainment

- If participant self-reported a trial endpoint, request permission to obtain relevant medical records; reviewed by an Endpoints Committee of physicians blinded to randomized treatment assignment, using prespecified objective criteria (i.e., WHO criteria for MI).
- Only confirmed endpoints were included in the final analyses.

Data and Safety Monitoring Board

- Independent group with expertise in various disciplines
  - independence is key: scientific and financial
- Charge to safeguard the participants in the trial
  - protecting from unexpected harm or benefit that has not been communicated (change in equipoise)
  - ensuring integrity of trial
- Review progress of trial and unblinded data on outcomes. Consider early stopping rules, for unexpected benefit, unexpected harm, futility.
- Can recommend modification or termination based on information from trial; from other trials; new basic science information.

Analysis

- Basic analysis, similar to cohort study: compare rate of outcome in treated ("exposed") versus comparison ("unexposed") group.
- But first table will be to ascertain if randomization "worked" - are the treatment groups comparable with respect to baseline characteristics (i.e., potential confounders). If not, need to control known confounders in the analysis - but cannot count on randomization to control unknown.

Analysis

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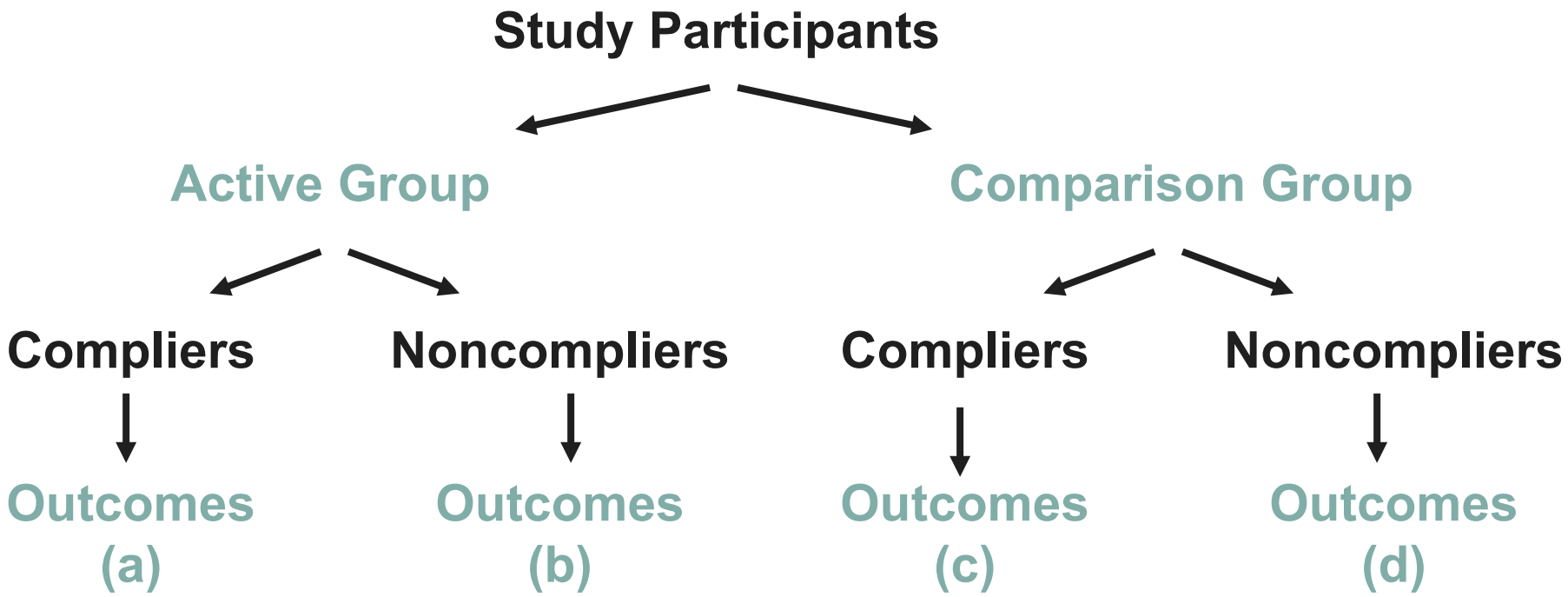
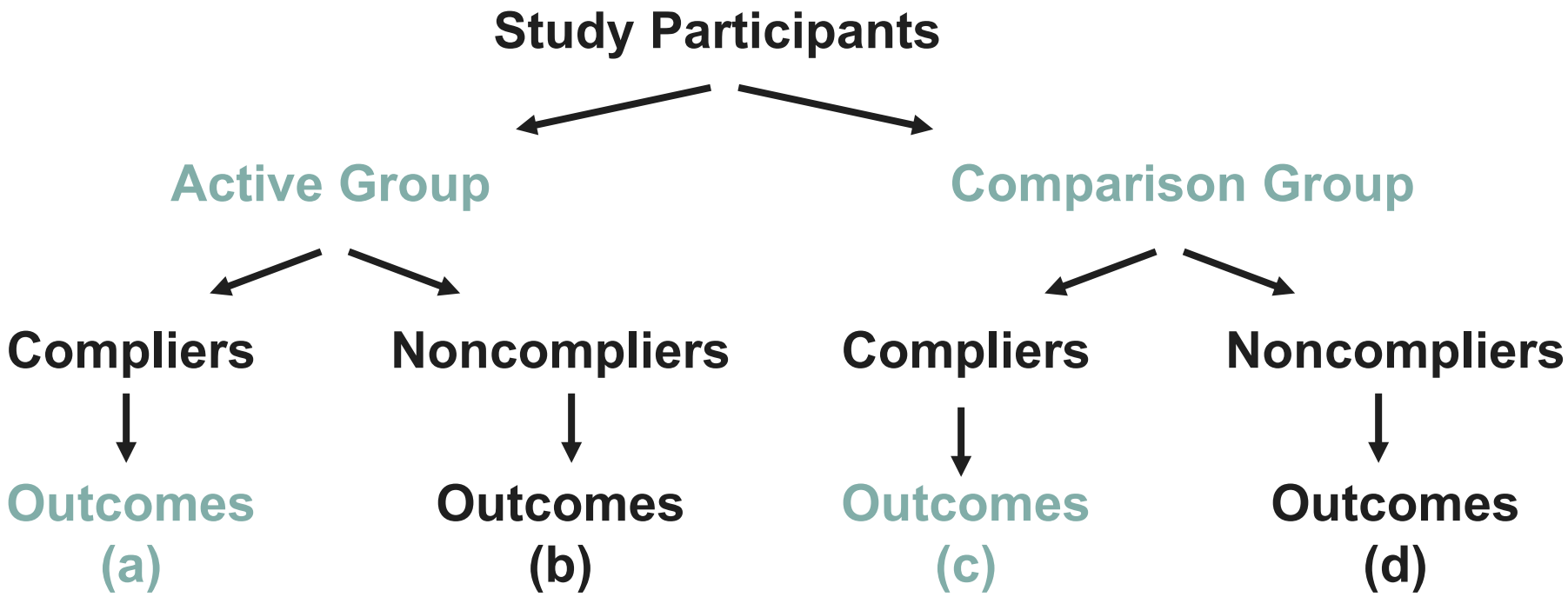


Primary Analysis: **Intention-to-treat (ITT) analysis.**

"Once randomized, always analyzed", regardless o compliance: (a+b) vs (c+d)

Most comparable in terms of equality of baseline characteristics. Have power of randomization.

Analysis



Secondary Analysis: **Compliers-only analysis: (a) vs (c).**

But beware - this is not a randomized comparison. Have to control confounders in analysis yourself. Do both – but what if differ?

Coronary Drug Project
(Clofibrate in reduction of mortality post-myocardial Infarction)

	Clofibrate	Placebo
• 5 Year Mortality	18.0%	19.5%
• Compliance ≥80%	15.0%	15.1%
• Compliance <80%	24.6%	28.2%

Source: N Engl J Med 1980; 303:1038

Effective Sample Size in an RCT

Effective sample size is not number of participants, but number of ENDPOINTS.

MI in The Physicians' Health Study

	Aspirin Group	Placebo Group	RR	95% CL
Total MI	139	239	0.56	(0.45-0.70)
Hemorrhagic Stroke	23	12	2.14	(0.96-4.77)

Trials of Primary Prevention of Cardiovascular Disease

	Men	Women
Sample size	22,000	40,000
Age (years)	>40	>45
Cost	1.75×10^6 ($82/participant/year)	3.52×10^6

Intervention Studies

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- Type of cohort study, in which the exposure is allocated by the investigator
- Strengths:
  - optimal for detecting small to moderate-sized effects
  - greater degree of control over exposure
  - if randomized, minimizes selection bias and confounding by known and unknown factors
  - through placebo, blinding or objective outcome definition, minimizes observation bias
- Limitations:
  - ethical issues
  - costs and feasibility
  - compliance, losses-to-follow-up
- There is a fundamental trade-off of internal validity with external validity (generalizability).

Bottom Line

- **RCTs are more logistically difficult, more expensive, and have more issues related to ethical considerations than any other epidemiologic design strategy. Recruitment is harder than anticipated, event rates often lower than expected.**
- **But if ethically appropriate, and if well designed and conducted, they provide a level of assurance about the effect of the intervention itself on the outcome that cannot be achieved by any other epidemiologic design strategy.**

Bottom Line

- **RCTs serve as a theoretical gold standard design for observational studies.**

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