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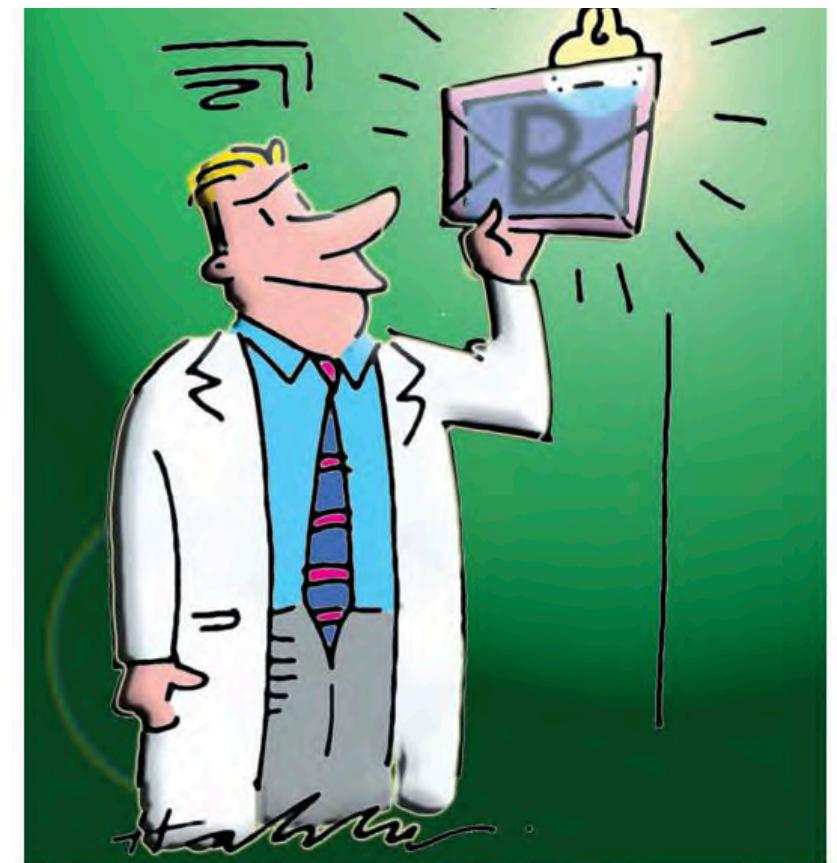
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Allocation concealment versus blinding

Lakshmi Gopalakrishnan

Allocation concealment

- Person randomizing the patient/participant ***does not know*** what the next treatment allocation will be.
- Prevents selection bias affecting which patients are given which treatment (*the bias randomization is designed to avoid*)
 - Possible in all trials including unblinded trials
- E.g., using patient date of birth (e.g., odd/even) or alternating treatments as the randomization scheme means that the allocation is not concealed but is open to all → subject to selection bias
- Without allocation concealment, the purpose of a RCT is defeated. Recommended ways of doing allocation concealment:
 - Centralized service
 - Third party randomization by phone / pharmacy
 - Sequentially numbered opaque sealed envelope



Examples – Trials for Drug A (Claire) and Drug B (Cliff)

- Claire is designing a trial to see whether her new drug A, is more effective than a placebo at reducing pain. She comes up with an randomization sequence using a random number generator. So far so good.
- She posts her carefully planned sequence on a bulletin board, allowing everyone involved in the trial to see the upcoming allocations. The lack of allocation concealment allows the trial investigators – intentionally or unintentionally – to direct participants towards which group they believe is most suitable.
- The trial investigators select participants with a better potential for pain relief for the Drug A group. This introduces selection bias and makes Drug A seem far more effective than it actually is.
- Cliff is also doing a trial for his new pain killing drug, Drug B. He makes an unpredictable randomization sequence just like Claire did.
- Cliff tells the trial investigators to ring a number when a new participant has given their consent to enter into the study. When the number is called, an automated system takes the details of the new participant and assigns them to a group, as per Cliff's randomization sequence.
- Since the trial investigators have no way of knowing which participant will go in which group, they have no influence on the randomization. The results give a fair representation of how efficacious Drug B is.

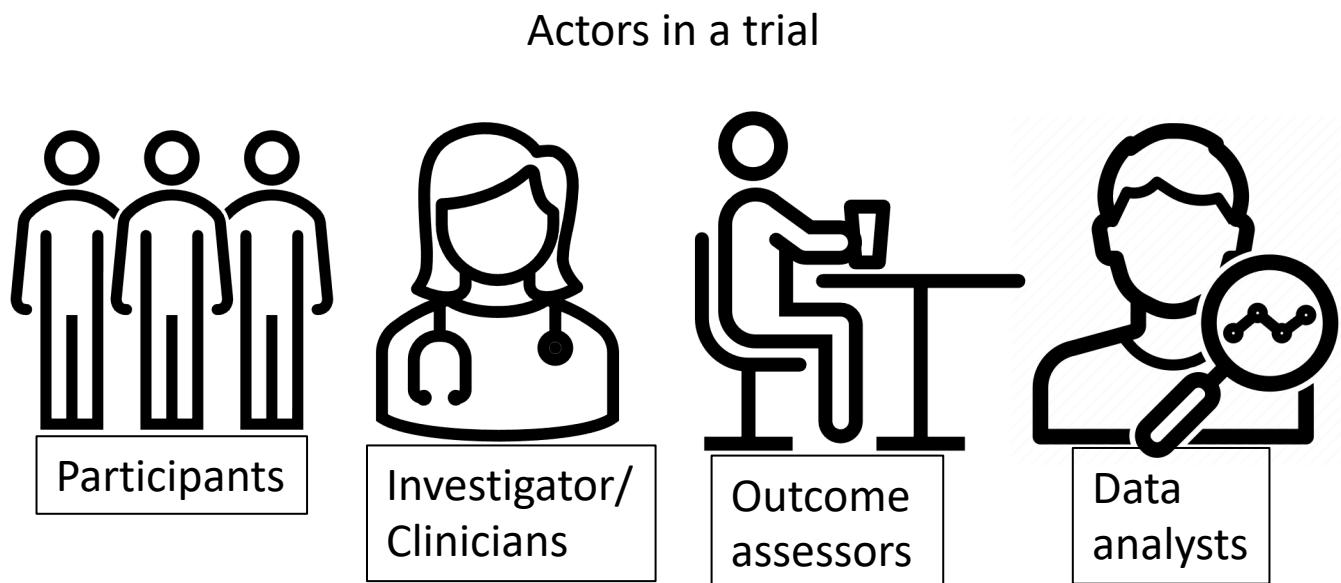
Blinding (who knows what?)

- Keeping people in a trial unaware of which treatment arms our study participants have been assigned to after randomization has occurred.
- Used to prevent conscious or unconscious bias in the ***design of a clinical trial*** and how it is carried out
- Minimize the likelihood of differential treatment or assessments of outcomes



Types of blinding

- **Single-blinded:** The participants (usually) or the investigators assessing outcome (alternately) do not know the assignments
- **Double-blinded:** Two groups do not know—usually it is the participants and the outcome assessors/investigators
- **Triple / Quadraple-blinded:** Three or four of the relevant groups mentioned here are not aware of the treatment assignment



Key takeaways

	Allocation concealment	Blinding
Purpose	Conceals randomization sequence	Makes participant or investigator or both unaware of the treatment received
Time in the trial	Done when the patient enters the trial (during recruitment)	Occurs after the patient has entered the trial (after recruitment)
Bias prevented	Selection bias (systematic differences that occurs when individuals or groups in a study differ systematically from the population of interest leading to a systematic error in an association or outcome)	Performance bias (Performance bias is specific to differences that occur due to knowledge of interventions allocation, in either the researcher or the participant)

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Simple, Blocked, and Stratified Randomization

Lakshmi Gopalakrishnan

Slides adapted from Fall 2018 GSI slide deck

Objective

- Randomization
- Simple randomization
- Block/blocked randomization
- Stratified randomization

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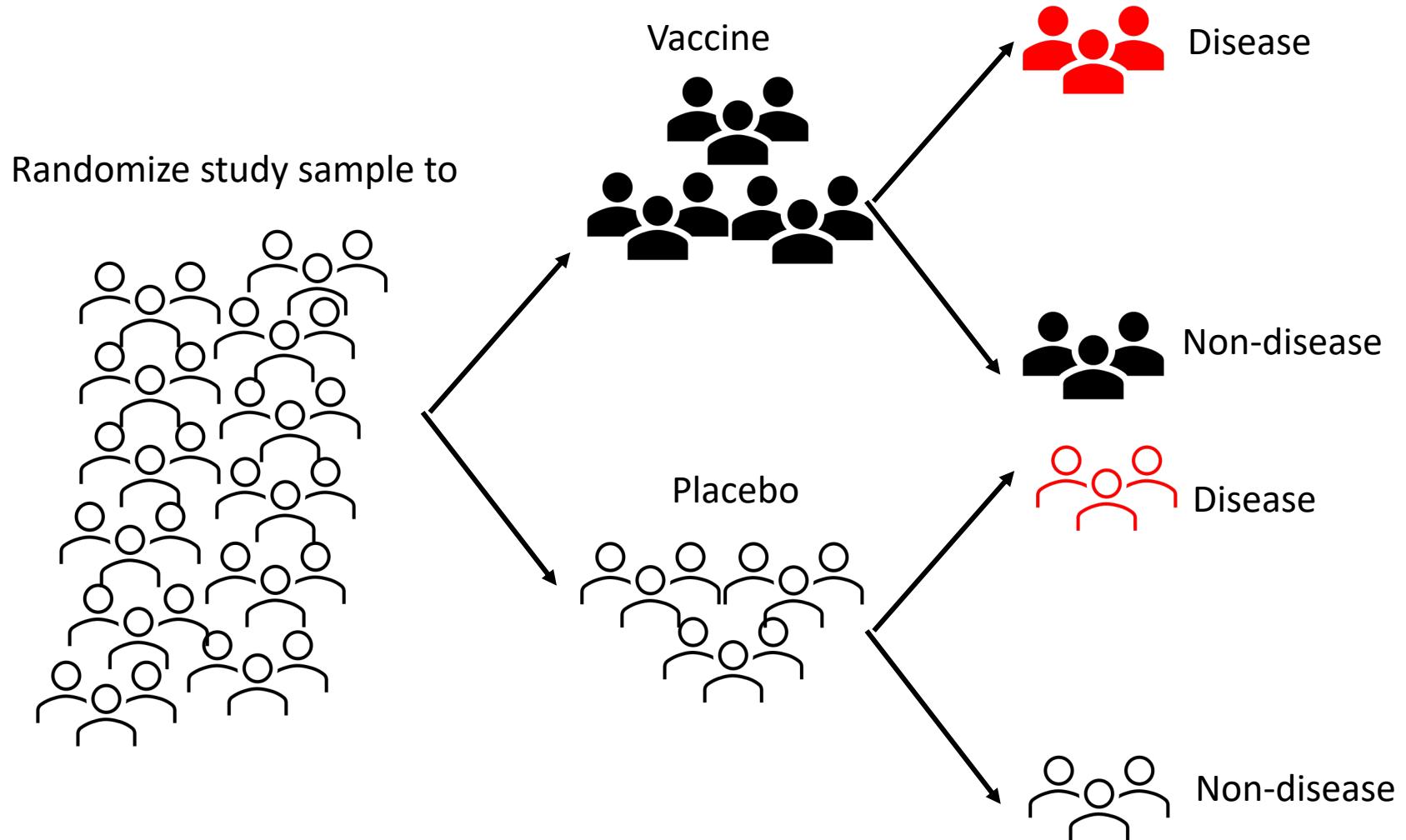
By SCOTT ADAMS

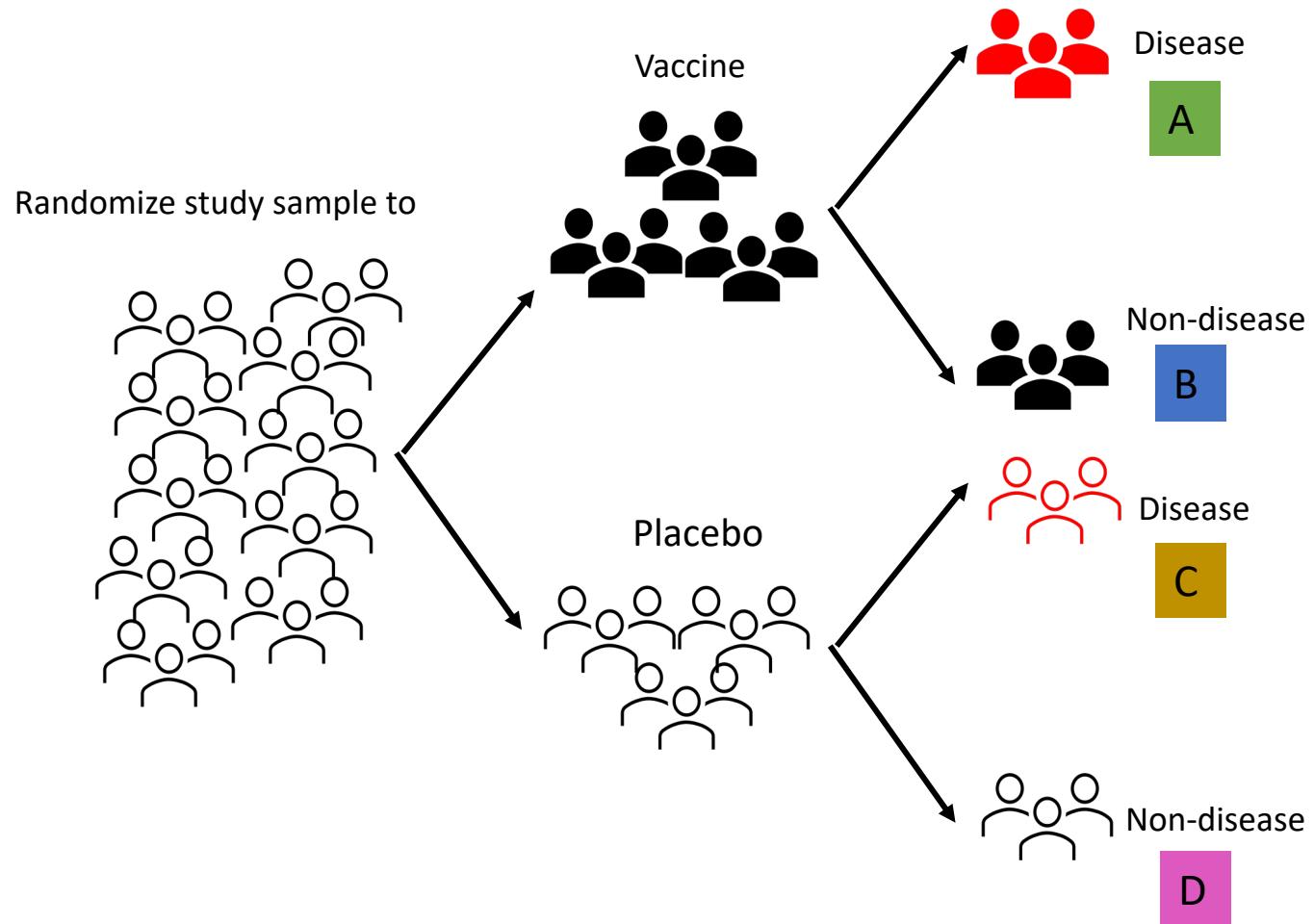


Randomization

- Process of assigning **the participants to treatment and control groups assuming that all participants have a fixed probability of assignment into each group** (not necessarily equal across groups).
 - All participants have a **fixed probability** of assignment to each group (not necessarily equal across groups)
 - Allocation is not predictable based on a pattern
 - Allocation not determined by investigator, clinician or participant
 - **Goals:**
 - Ensure that participants are as similar as possible across groups at the start of the study (baseline) – also called exchangeability
 - Reduce the chance of imbalance in measured and unmeasured (known and unknown) confounders

Randomization





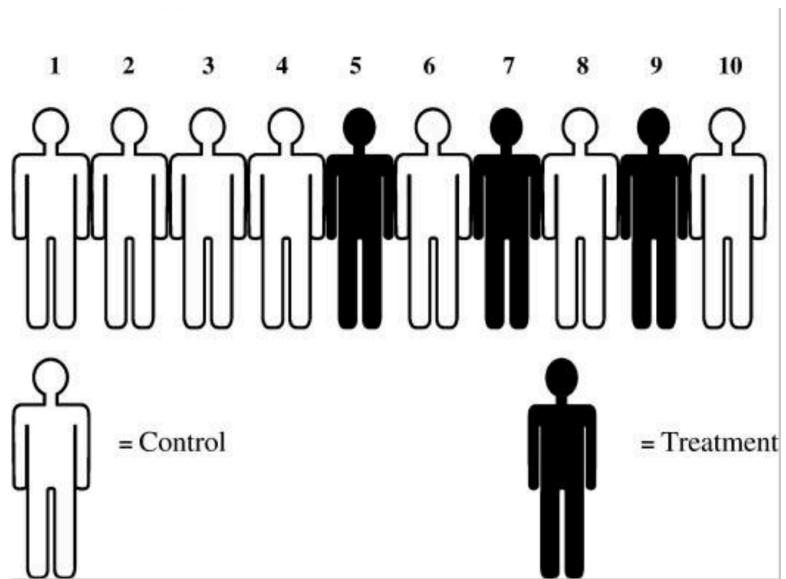
	Disease	No disease
Vaccine	A	B
Placebo	C	D

We can calculate risk ratio using the formula:
 $RR = \text{Risk of disease in the exposed} / \text{Risk of disease in the unexposed}$

$$RR = A / (A+B) \text{ divided by } C / (C+D)$$

If $RR < 1$, then exposure to vaccine is protective.

$$\text{Vaccine efficacy} = (1-RR) * 100$$



Method of randomization: Simple randomization

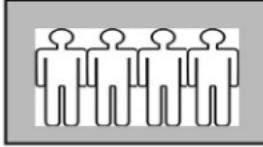
- Simple randomization of participants
 - Coin flip
 - Random number generator
- Pros:
 - Simple, easy to implement
- Cons:
 - Can get imbalanced in smaller trials
 - Reduces statistical power

Block randomization

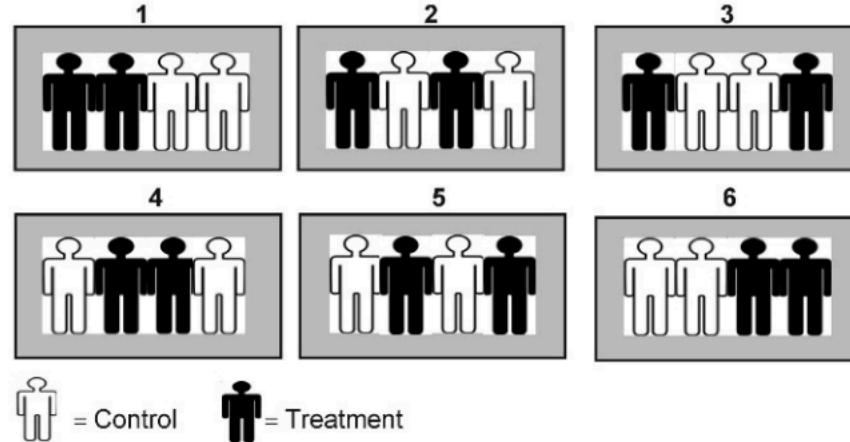
- What is block randomization?
 - Treatment is assigned in blocks that are a multiple of the number of treatment groups
 - Used to avoid imbalance of the number of participants in each treatment group and ensures equal allocation within blocks
- How does it work?
 - Divide potential patients into m blocks of size $2n$
 - Randomize by block, such that n patients are allocated to treatment T, n patients to control C, and then choose blocks randomly
- Must have variety of block sizes – otherwise evident pattern resulting in bias (also called permuted block randomization)

Example of block randomization for a clinical trial with control and treatment groups involving 40 participants

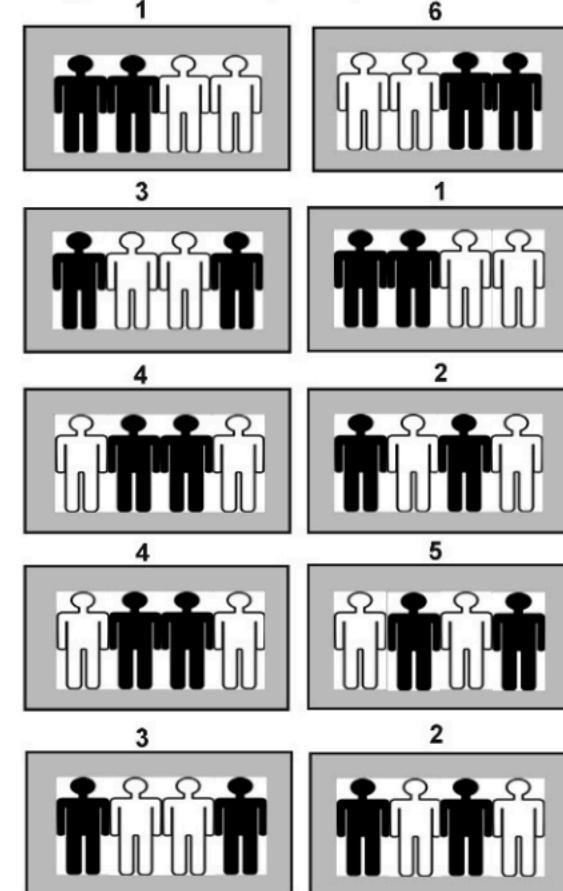
A) Block size



B) Possible balanced combinations (ie, 2 to control group, 2 to treatment group)



C) Random selection of blocks (ie, 1, 3, 4, 4, 3, 6, 1, 2, 5, 2)
Assignment of all 40 participants



Stratified randomization

- Stratified randomization is achieved by generating a separate block for each combination of covariates, and participants are assigned to the appropriate block of covariates. After all participants have been identified and assigned into blocks, simple randomization occurs within each block to assign participants to one of the groups.
 - Separate randomization scheme for each factor to ensure that the groups are balanced within each stratum but too many strata will lead to sparse data in some cells (keep the number of strata to a minimum)
- Address the need to control and balance the influence of covariates and keep characteristics of the participants (that is, age, weight, or gender) as similar as possible across the study groups
- Identify factors (or strata) that are known to be related to the outcome of the study identified by researcher

Example of stratified randomization for a clinical trial with control and treatment groups involving 40 participants

2 Covariates:

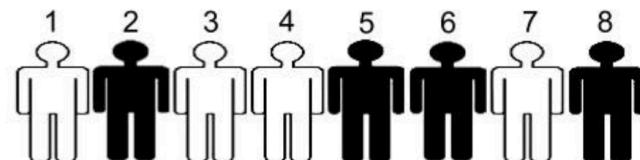
Sex (2 levels: male, female)

Body mass index (3 levels: underweight, normal, overweight)

		Sex		Marginal total
		Male	Female	
Body mass index	Underweight	7	5	12
	Normal	8	8	16
	Overweight	7	5	12
Marginal total		22	18	40



Random assignment of “male” and “normal”: simple randomization by flipping a coin



Source: Kang M, Ragan BG, Park J-H. Issues in Outcomes Research: An Overview of Randomization Techniques for Clinical Trials. *J Athl Train.* 2008;43(2):215–21.



Key takeaways

- Randomization is considered the gold standard in most clinical trials
 - Reduces selection bias
 - Ensures balance of sample size between groups and balance of baseline characteristics
 - Improves exchangeability between treatment and control groups (and allows us to approximate the counterfactual experiment)
- Know what type of randomization method to apply depending on your study size, balance in covariates or both

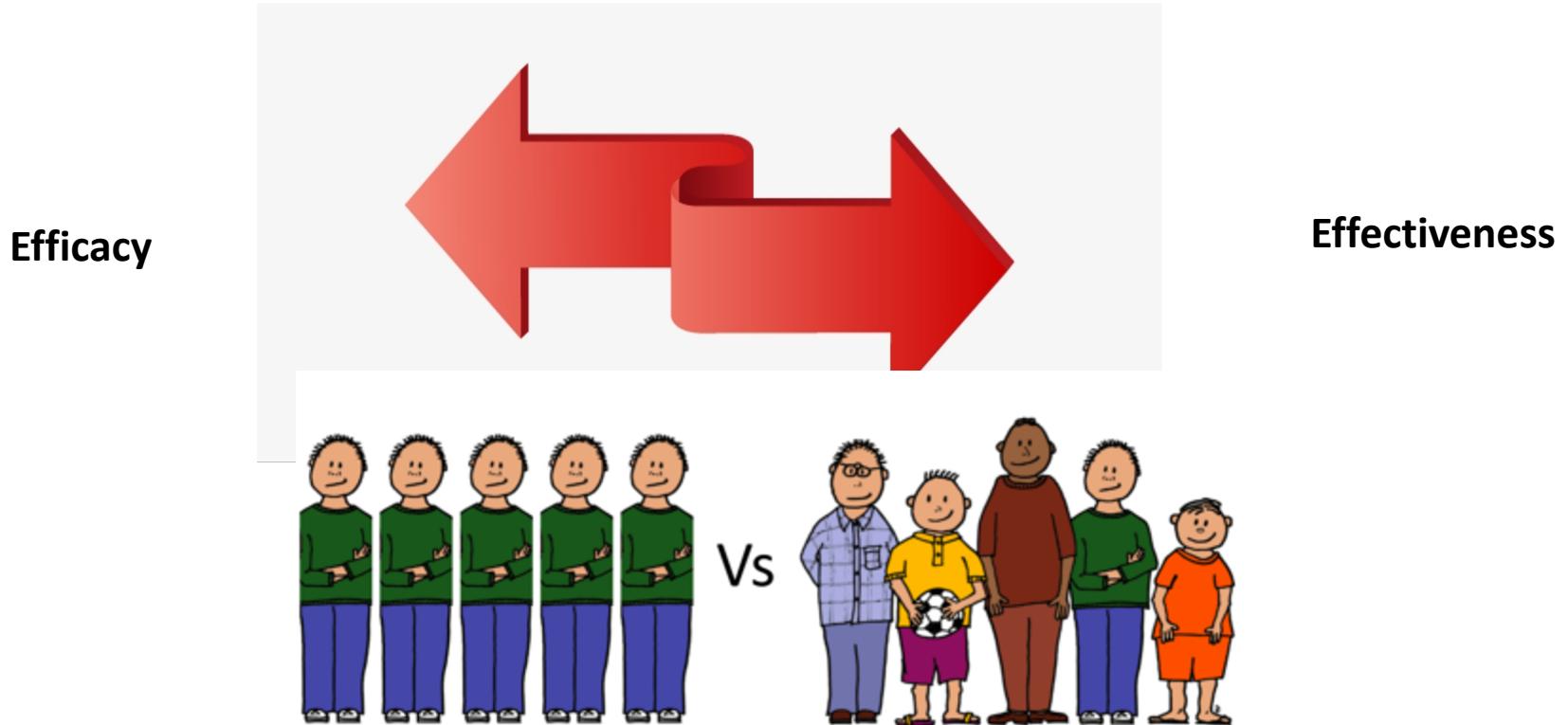
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Efficacy versus effectiveness trials (Trials)

Lakshmi Gopalakrishnan

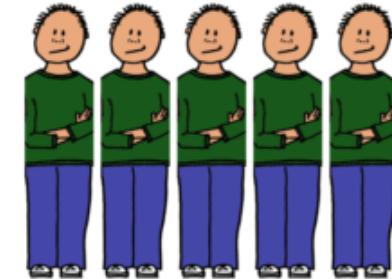
Understand the difference b/w efficacy and effectiveness trials



Efficacy trials (or Explanatory trials)

- Whether the treatment works under ideal and controlled circumstances?

- Resource-intensive ‘ideal’ setting
- Highly selected, homogenous population
- Strictly defined exclusion and inclusion criteria
- Compliance monitored closely, minimal loss to follow-up
- Highly experienced and trained providers
- Standardized intervention
- No concurrent interventions
- Analysis usually ITT with per-protocol as possibility for secondary analysis



Effectiveness trials (also called pragmatic trials)

- Does the treatment work under circumstances similar to the real world?
- Pragmatic trials measure effectiveness—that is, the benefit of treatment in clinical practice.
 - Real world setting
 - Heterogenous populations
 - Representative usual providers
 - Adherence may vary
 - Feasible interventions
 - Analysis usually ITT with per-protocol as possibility for secondary analysis



Example: COVID vaccine trials

You read that Pfizer vaccine with an efficacy of 90% in a trial – What does this mean?

90% reduction in cases of disease in the vaccinated group compared to the unvaccinated (or placebo) group.

But does 90% efficacious mean it will be 90% effective? Likely NOT.

How can we measure effectiveness of vaccine trials?

- Surveillance data – what proportion of population has received the vaccine and when people receive the vaccines, dosage, etc.
- Stepped wedge design / phased-in / phased implementation
 - Sequential rollout of an intervention to participants (individuals or clusters) over a number of time periods.
 - Useful when we have an efficacious treatment but want to figure out an implementation strategy
- Observation studies – due to ethical reasons
 - Case-control studies (we'll learn more about case-control studies next week)

Key Takeaways

- Efficacy – Does the drug work under ideal circumstances?
- Effectiveness – Does the drug work under real world circumstances?

Additional references

- Singal AG, Higgins PDR, Waljee AK. A Primer on Effectiveness and Efficacy Trials. *Clin Transl Gastroenterol.* 2014;5(1):e45. doi:[10.1038/ctg.2013.13](https://doi.org/10.1038/ctg.2013.13)
 - Authors describe the differences between efficacy and effectiveness trials. Compared across a variety of metrics from study population, intervention delivery, analysis, etc.
- Sedgwick P. Explanatory trials versus pragmatic trials. *BMJ.* 2014 Nov 13;349:g6694.
 - Authors describe the difference b/w explanatory and pragmatic trials with examples
- Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ.* 2015 Feb 6;350:h391.
 - Authors explain the concept behind a stepped wedge cluster RCT

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Extra slides - Trials

PHW250B
October 5, 2020

Review - The Basics: Study Design

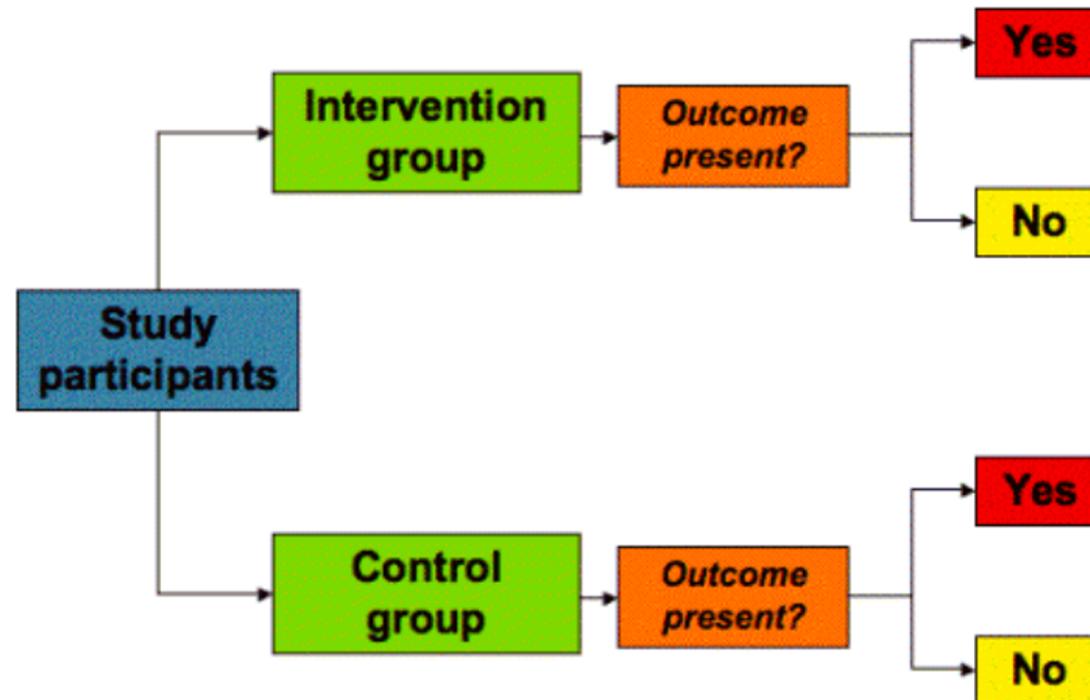
- Cannot observe counterfactual outcomes to directly assess causality
- Epidemiologists design studies to approximate the counterfactual experiment (balance ideal study and practical constraints). We consider:
 - What design will best answer the study question?
 - What design is most feasible given limitations of budget, etc?
 - What are the relative strengths and disadvantages of each study design?

Review - Study Designs

- Generally, 2 major categories of epidemiologic designs
 - Experimental
 - Randomized Controlled Trial (RCT)
 - Non-experimental
 - Cohort
 - Case-control
 - Cross-sectional
 - Ecologic

Randomized Controlled Trials

- Exposure/treatment is randomly assigned
 - Exposure determined by goal of the study, not individual preferences
- Trials are experiments with human subjects



RCTs: The Big Picture

- Ethical constraints limit where experiments with humans are allowable
- Ethical principles (Belmont Report)
 - Respect for persons/Autonomy
 - Beneficence
 - Justice
- Adherence to protocol cannot conflict with subjects best interests

RCTs: The Big Picture

- Equipoise
 - There is genuine uncertainty about which treatment is more effective
 - No placebo allowed if there is an accepted preventive remedy - standard of care provided as an alternative to placebo

RCTs: The Big Picture

- Often thought of as the “gold standard” in epidemiologic research
- This is true in certain applications **if and only if** randomization works perfectly (i.e., no confounding) AND they are free from information and selection bias (e.g. non-adherence, loss to follow-up)
- RCTs are not appropriate for interventions that cannot or should not be controlled by an investigator or for very rare outcomes

Exposure Assignment

- Key element of an intervention trial is that the **investigator assigns the exposure**
- Randomization (the ‘gold standard’): when exposure/treatment is randomly assigned
 - All participants have a fixed probability of assignment to each intervention group (not necessarily equal across groups)
 - Allocation is not predictable based on a pattern

Randomization

- When we compare treated to untreated participants, what is the ideal comparison we seek to make?
 - Counterfactual
- Randomization approaches this ideal comparison by reducing confounding
 - Exchangeability – treated and untreated groups are equivalent except for exposure
 - Attempts to assure that participant characteristics are as similar as possible across groups at baseline
 - Unobserved AND observed variables

Randomization

- Imbalance is possible even after randomization due to random chance within a finite sample
- Differences in baseline covariates do not have to be statistically significant to affect the trial result
- Differences that are meaningful in context of the particular study can be taken into account in analysis

Baseline Balance

- Assess whether randomization worked by comparing the treated and untreated groups
- Table 1 in most RCT papers
- P-values should not be reported in Table 1
- Statistical tests are less meaningful than qualitative differences

	Control group (N=1382)	Water group (N=698)	Sanitation group (N=696)	Handwashing group (N=688)	Combined water, sanitation, and handwashing group (N=702)	Nutrition (N=699)	Combined water, sanitation, handwashing, and nutrition group (N=686)
Maternal							
Age (years)	23.6 (5.0)	23.7 (5.2)	23.7 (5.2)	23.8 (5.5)	24.3 (5.5)	23.7 (5.1)	23.8 (5.5)
Years of education	5.9 (3.4)	5.8 (3.4)	5.8 (3.5)	5.8 (3.3)	5.9 (3.3)	5.8 (3.5)	5.6 (3.5)
Paternal							
Years of education	4.9 (4.0)	4.9 (4.1)	5.0 (4.2)	4.6 (4.1)	5.0 (4.2)	4.8 (4.0)	4.7 (3.9)
Works in agriculture	414 (30%)	224 (32%)	204 (29%)	249 (36%)	216 (31%)	232 (33%)	207 (30%)
Household							
Number of people	4.7 (2.3)	4.6 (2.2)	4.7 (2.1)	4.7 (2.2)	4.7 (2.1)	4.7 (2.2)	4.7 (2.1)
Has electricity	784 (57%)	422 (60%)	408 (59%)	405 (59%)	426 (61%)	409 (59%)	412 (60%)
Has a cement floor	145 (10%)	82 (12%)	85 (12%)	55 (8%)	77 (11%)	67 (10%)	72 (10%)
Acres of agricultural land owned	0.15 (0.21)	0.14 (0.20)	0.14 (0.22)	0.14 (0.20)	0.15 (0.23)	0.16 (0.27)	0.14 (0.38)
Drinking water							
Tubewell primary water source	1038 (75%)	500 (72%)	519 (75%)	482 (70%)	546 (78%)	519 (74%)	504 (73%)
Stored water observed at home	666 (48%)	353 (51%)	341 (49%)	347 (50%)	304 (43%)	301 (43%)	331 (48%)
Sanitation							
Daily defecation in the open							
Adult men	97 (7%)	39 (6%)	52 (8%)	64 (9%)	54 (8%)	59 (9%)	50 (7%)
Adult women	62 (4%)	18 (3%)	33 (5%)	31 (5%)	29 (4%)	39 (6%)	24 (4%)
Children aged 8 to <15 years	53 (10%)	25 (9%)	28 (9%)	43 (15%)	30 (10%)	23 (8%)	28 (10%)
Children aged 3 to <8 years	267 (38%)	141 (37%)	137 (38%)	137 (39%)	137 (38%)	129 (39%)	134 (37%)
Children aged 0 to <3 years	245 (82%)	112 (85%)	117 (84%)	120 (85%)	123 (79%)	128 (85%)	123 (88%)
Latrine							
Owned	750 (54%)	363 (52%)	374 (54%)	372 (54%)	373 (53%)	377 (54%)	367 (53%)
Concrete slab	1251 (95%)	644 (95%)	610 (92%)	613 (93%)	620 (93%)	620 (94%)	621 (94%)
Functional water seal	358 (31%)	183 (31%)	177 (30%)	162 (28%)	152 (26%)	183 (31%)	155 (27%)
Visible stool on slab or floor	625 (48%)	350 (53%)	332 (52%)	335 (52%)	289 (44%)	331 (51%)	298 (46%)
Owned a potty	61 (4%)	27 (4%)	28 (4%)	35 (5%)	27 (4%)	36 (5%)	30 (4%)
Human faeces observed							
In the house	114 (8%)	65 (9%)	56 (8%)	70 (10%)	48 (7%)	58 (8%)	49 (7%)
In child's play area	21 (2%)	6 (1%)	6 (1%)	8 (1%)	7 (1%)	8 (1%)	7 (1%)
Handwashing							
Within six steps of latrine							
Has water	178 (14%)	83 (13%)	81 (13%)	63 (10%)	67 (10%)	62 (10%)	72 (11%)
Has soap	88 (7%)	50 (8%)	48 (8%)	34 (5%)	42 (7%)	32 (5%)	36 (6%)
Within six steps of kitchen							
Has water	118 (9%)	51 (8%)	51 (8%)	45 (7%)	61 (9%)	61 (9%)	60 (9%)
Has soap	33 (3%)	18 (3%)	14 (2%)	13 (2%)	15 (2%)	23 (3%)	18 (3%)
Nutrition							
Household is food secure*	932 (67%)	495 (71%)	475 (68%)	475 (69%)	482 (69%)	479 (69%)	485 (71%)

Data are n (%) or mean (SD). Percentages were estimated from slightly smaller denominators than those shown at the top of the table for the following variables due to missing values: father works in agriculture, open defecation, latrine has a concrete slab, latrine has a functional water seal, visible stool on latrine slab or floor, ownership of child potty, observed faeces in the house or child's play area, handwashing variables. *Assessed by the Household Food Insecurity Access Scale.²⁵

Table 1: Baseline characteristics

Tofail et al, 2018

Methods of Randomization

- Simple randomization of each individual (coin flip, random number generator, etc.)
- Blocked randomization: treatment is assigned in blocks that are a multiple of the number of treatment groups
 - E.g. 2 treatment groups, block size=4, 6 possible block combinations (AABB, ABAB, BAAB, BABA, BBAA, ABBA)
 - Used to avoid imbalance of the number of participants in each treatment group
- Stratified randomization; stratify participants on one or more characteristics that you want to balance (e.g. sex, age)
 - Assign treatment randomly within strata

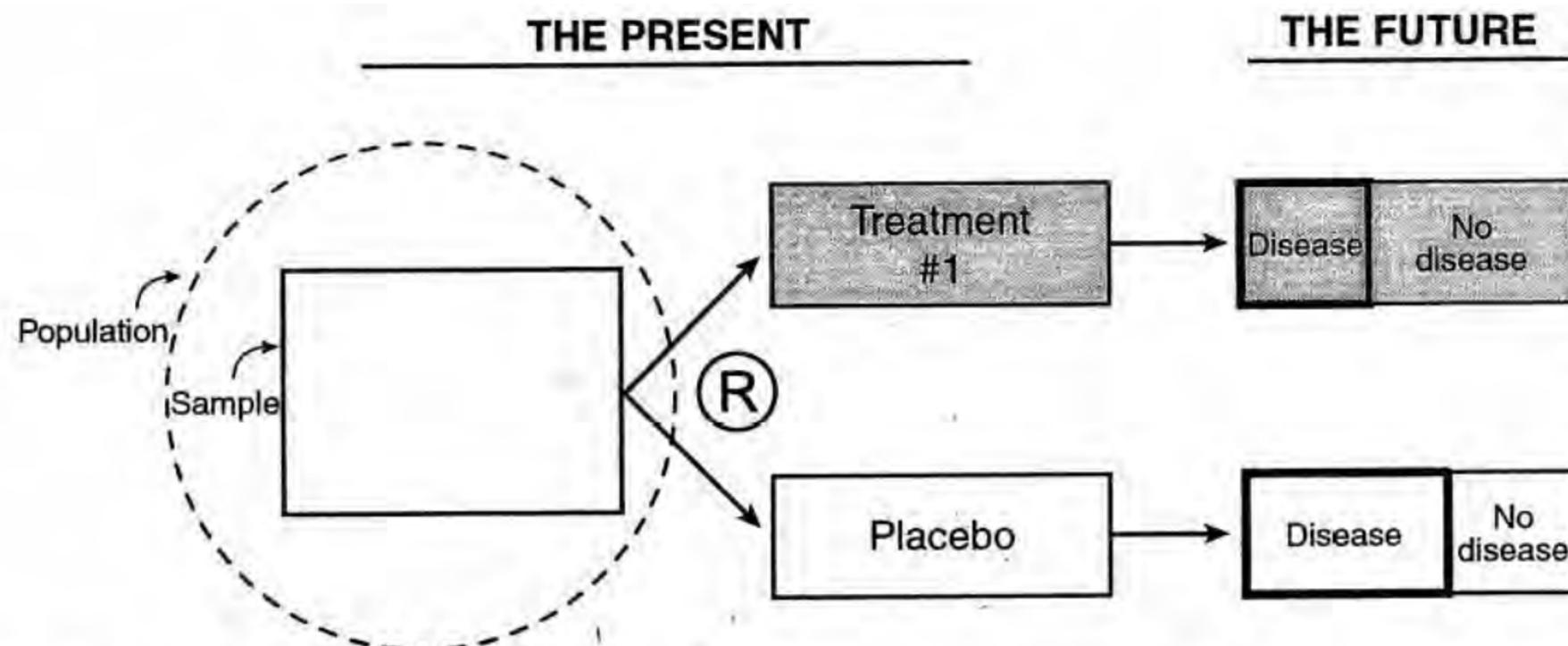
Characteristics of Intervention Trials

- Many different (not mutually exclusive) ways of categorizing/describing trials
 - Types of trials
 - How treatment was assigned
 - Parallel, crossover, factorial
 - Number of participants
 - N-of-1, megatrials, sequential
 - Blinding

Types of Intervention Trials

- **Clinical trial:** goal is to cure or prevent disease progression among people with disease
- **Field trial:** focus is on prevention of disease in general population
- **Explanatory trials:** goal is to see if an intervention works under ideal conditions - highly homogeneous study population
- **Pragmatic trials:** goal is to see if intervention works under circumstances similar to clinical practice

Parallel Design



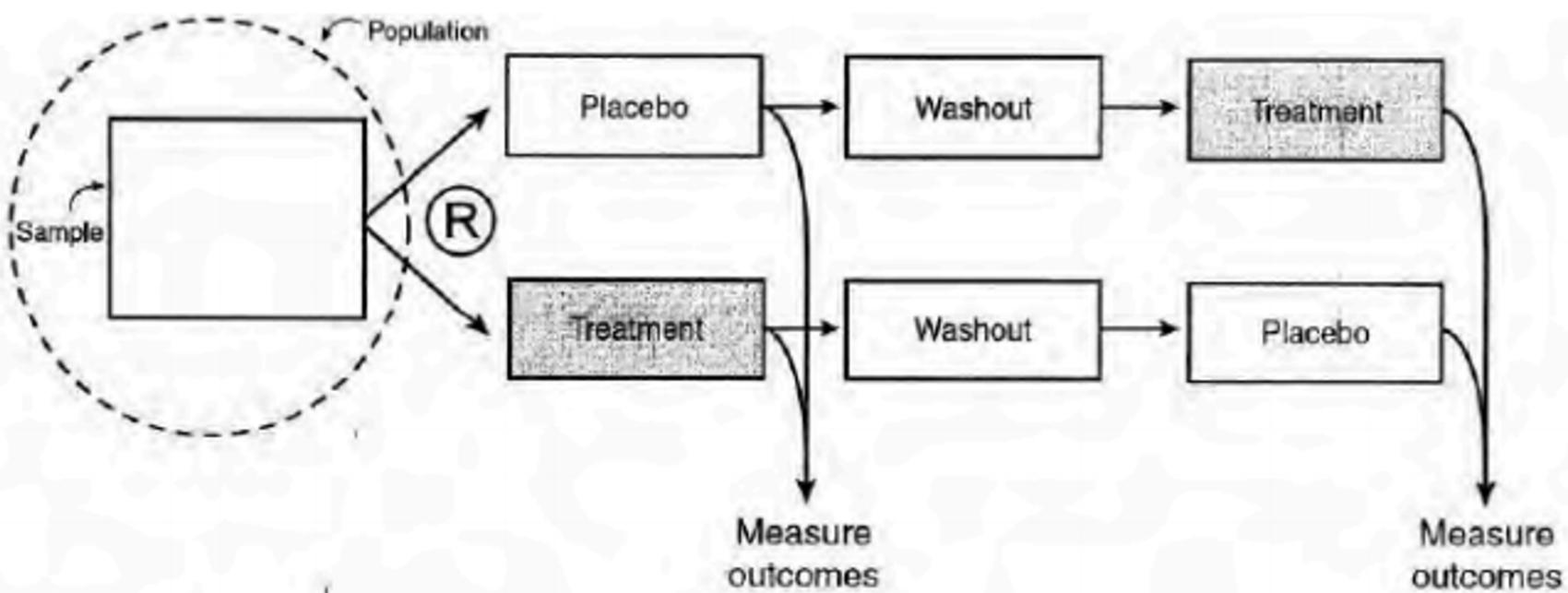
■ FIGURE 10.1

In a randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions (one should be a blinded placebo, if possible), (e) follows up the cohort, (f) measures outcome variables (blindly, if possible) and analyzes the results.

Crossover Design

- Each subject serves as their own control
 - Treatment/control periods are separated by a wash out period
 - Order of treatment/control can be randomized
 - Good for transient exposure/outcome
- N of 1: crossover trial of one person
 - Used in medicine to determine if a treatment is safe and effective for a particular patient

Crossover Design



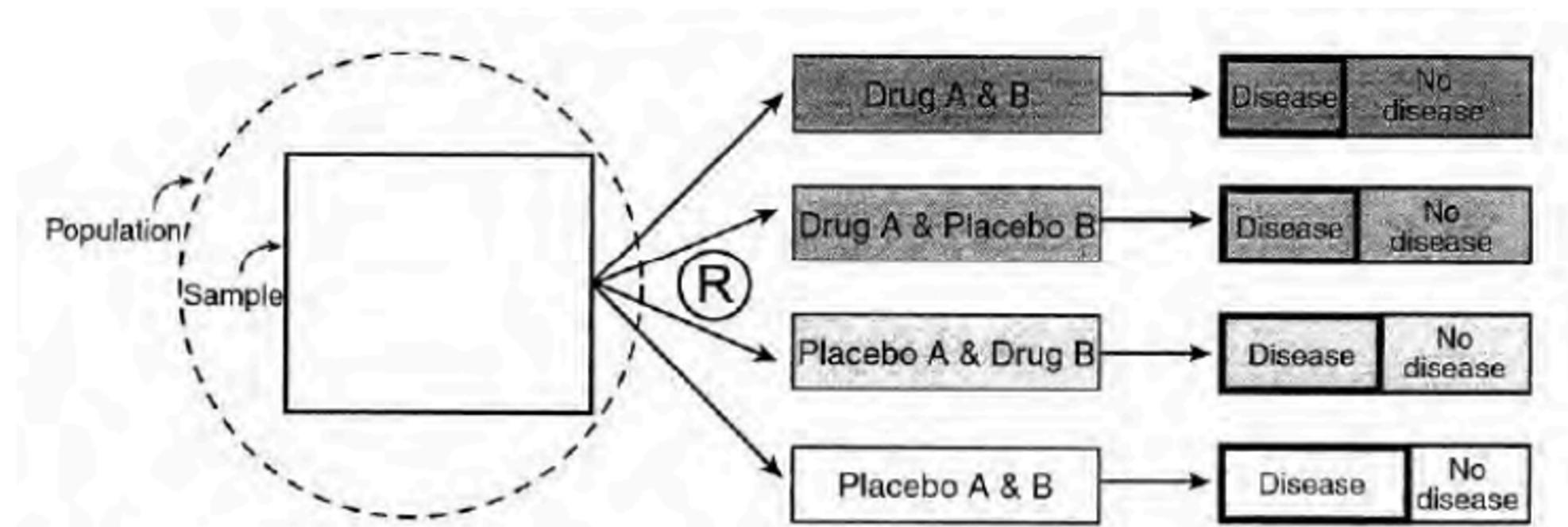
■ FIGURE 11.4

In the cross-over randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions, (e) measures outcome variables, (f) allows washout period to reduce carryover effect, (g) applies intervention to former placebo group, (h) measures outcome variables again.

Factorial Design

- Two active interventions assigned
 - A+B
 - A
 - B
 - Placebo
- Same design used in two ways
 - Efficient way to test 2 hypotheses in 1 trial if the interventions do not interact in any way
 - Method to explicitly study potential synergy between 2 interventions that are believed to interact

Factorial Design



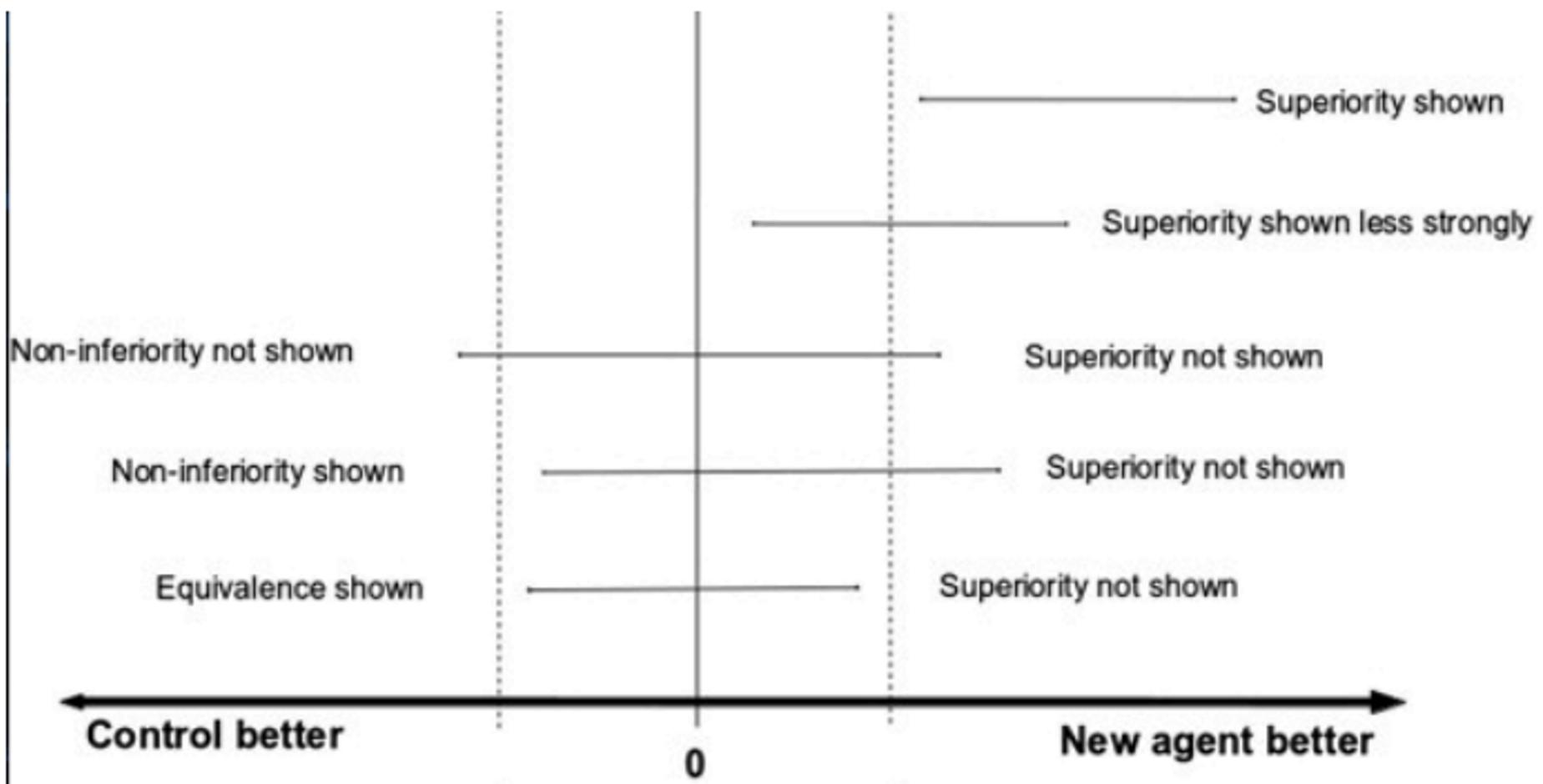
■ FIGURE 11.2

In a factorial randomized trial, the investigator (a) selects a sample from the population; (b) measures baseline variables; (c) randomly assigns two active interventions and their controls to four groups, as shown; (d) applies interventions; (e) follows up the cohorts; (f) measures outcome variables.

Types of Intervention Trials

- **Superiority trials:** intended to determine that new treatment is better than placebo or active control
 - H_0 : there is no difference between treatment A and B
 - H_A : treatment B is better than A
- **Non-inferiority trials:** intended to determine that new treatment is *no worse* than existing
 - H_0 : B is inferior to A by some margin Δ
 - H_A : B is not inferior to A, within margin Δ
- **Equivalence trials:** intended to determine that new treatment is *no different* than active control
 - H_0 : difference between A and B is greater than some margin $+/- \Delta$
 - H_A : difference between A and B is within $+/- \Delta$

Types of Intervention Trials



Cluster Randomized Trials (CRTs)

- Nature of intervention requires community-level implementation (group interventions)
 - E.g. sanitation, media campaigns, schools
- Group effect on disease of applying intervention at community level (individual interventions where group effects important)
 - E.g. reduction of transmission of infectious disease

Cluster Trial Motivations

- Component of intervention delivered at community or group level
- Avoid contaminations between individuals
 - Still concerned about contamination between clusters based on geographic or social proximity
- Increased administrative efficiency and lower cost
- Allows for estimation of within and between cluster variation

Reducing Bias: Allocation Concealment

- Allocation is the method through which treatment is assigned to study participants
- Allocation concealment prevents those who admit patients into a trial from knowing each person's treatment assignment
- One aspect of blinding
- “Trials in which the allocation sequence had been inadequately concealed yield larger estimates of treatment effects (ORs exaggerated, on average, by 30-40%) compared with trials which authors reported adequate allocation concealment”

Reducing Bias: Blinding

- Blinding keeps the treatment assignments unknown, so that relevant groups cannot be influenced by knowledge of assignment
 - Many different groups in a trial - participants, study managers, clinicians, investigators/analysts, data safety monitoring boards - can be blinded
 - Single, double, triple or quadruple blinding possible
 - Placebos are a form of blinding
 - Discrepancies in size, shape, color, sheen, texture, taste, or odor can unblind a study
 - In non-drug trials, the placebo may not be immediately obvious

Efficacy vs. Effectiveness

- **Efficacy:** does the treatment work under ideal circumstances?
- **Effectiveness:** does the treatment work under circumstances similar to those found in daily practice (*in the real world*)?

Adherence

- A key reason efficacy is often higher than effectiveness, major problem in healthcare and epidemiology
- Patient knowledge of treatment regimen can affect adherence - part of motivation for blinding and placebo
- No widely accepted criterion for high or low adherence
 - Some over 80%
- A range of direct and indirect measures of adherence can be used
 - Patient self-report, blood draw, etc.
- Best to estimate in advance and increase sample size accordingly

Analysis of Trial Data

- Intention-to-Treat Analysis (ITT)
 - Analyze subjects according to treatment assignment (i.e., as randomized)
 - Variation from randomized exposure biases results toward no difference between groups
 - Quantifies effectiveness
 - Note than ITT analysis of an exploratory trial will quantify effectiveness in the highly selected explanatory trial population - some would argue this should be viewed as quantifying efficacy

Analysis of Trial Data

- Per Protocol
 - Alternative to ITT
 - Analyze subjects according to treatment received (their actual behavior, taking adherence into account)
 - Variation from randomization exposure will eliminate all benefits gained from randomization
 - Introduces bias!
 - Measures efficacy of a treatment
 - Not generally used in pragmatic trial

Strengths and Challenges

Strengths of RCTs

- Randomization of treatment reduces confounding
- Study design more closely resembles the counterfactual ideal experiment than observational study designs
- Results from randomized trials are generally perceived to carry more weight than observational designs (although arguable point)
- Trials may be the only study design available in some cases - e.g., for new medical devices or drugs
- Blinding reduces biases

Strengths and Challenges

Challenges

- Question must be one that can be addressed feasibly and ethically with a RCT design
- Loss to follow-up
- Non-adherence to treatment
- Expense, feasibility, and participant burden repeated data collection
- Inefficient for rare outcome (rare in the trial population)
- In cluster-randomized trials, must increase sample size to account for correlation within clusters
- Generalizability - trial participants are different from the general population
 - Trials often have strict eligibility criteria
 - Volunteers may be very different from general population