Randomized Controlled Trials

Lecture prepared by Dr. Hailey Banack, PhD

Looking Forward

- **Next few weeks will focus on study design:**
  - Randomized Controlled Trials
  - Cohort studies
  - Case control studies
  - Diagnostic studies
  - Cross/sectional, surveillance & ecological studies

What is a randomized controlled trial (RCT)?

A **prospective** study that compares the effects of at least two different interventions

- **Prospective:** follow-up of participants from a defined moment of their condition
- **Interventions:** may be drugs, surgical procedures, devices, behavioral treatments, and processess of health care. The experimental intervention is compared to to the the control intervention
- **Random allocation:** assignment to an intervention
  - This is the key feature of randomized trials

Why RCTs/RTs?

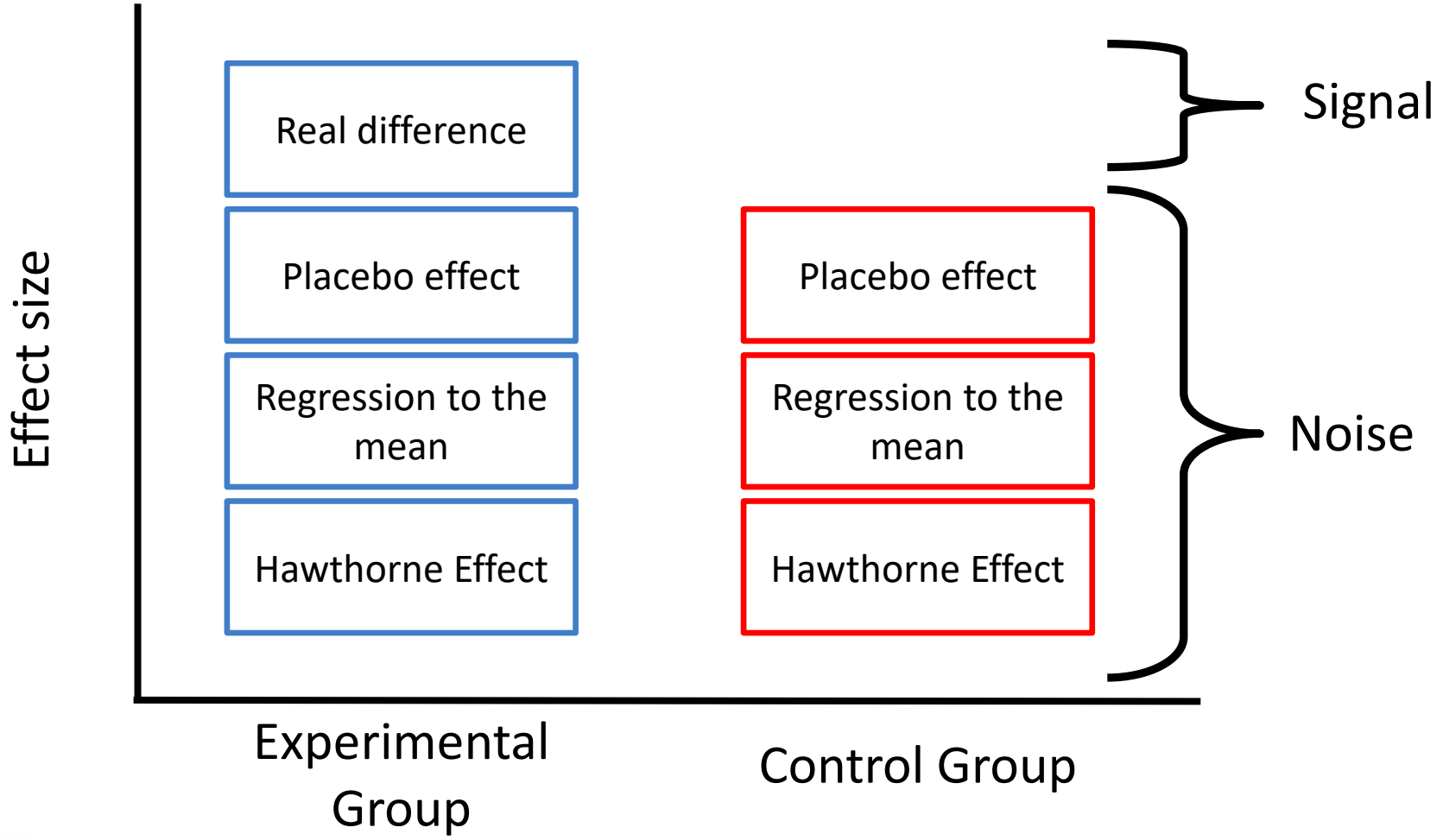
The best method to determine:

- Causal relation between exposure and outcome
- The direction and size of such effect

Helps to separate:

- **The signal:** true effect of the intervention
- **The noise:** other factors. different from the intervention may have similar effects – randomizing usually distributes known and unknown confounders between groups

RCTs are the BEST method to handle confounding

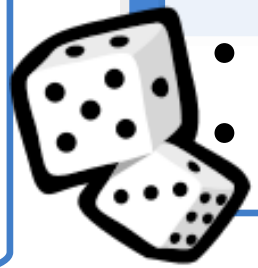


Structure of an RCT

Selection

Eligible subjects (meeting pre-specified inclusion/ exclusion criteria)

Random assignment to an intervention

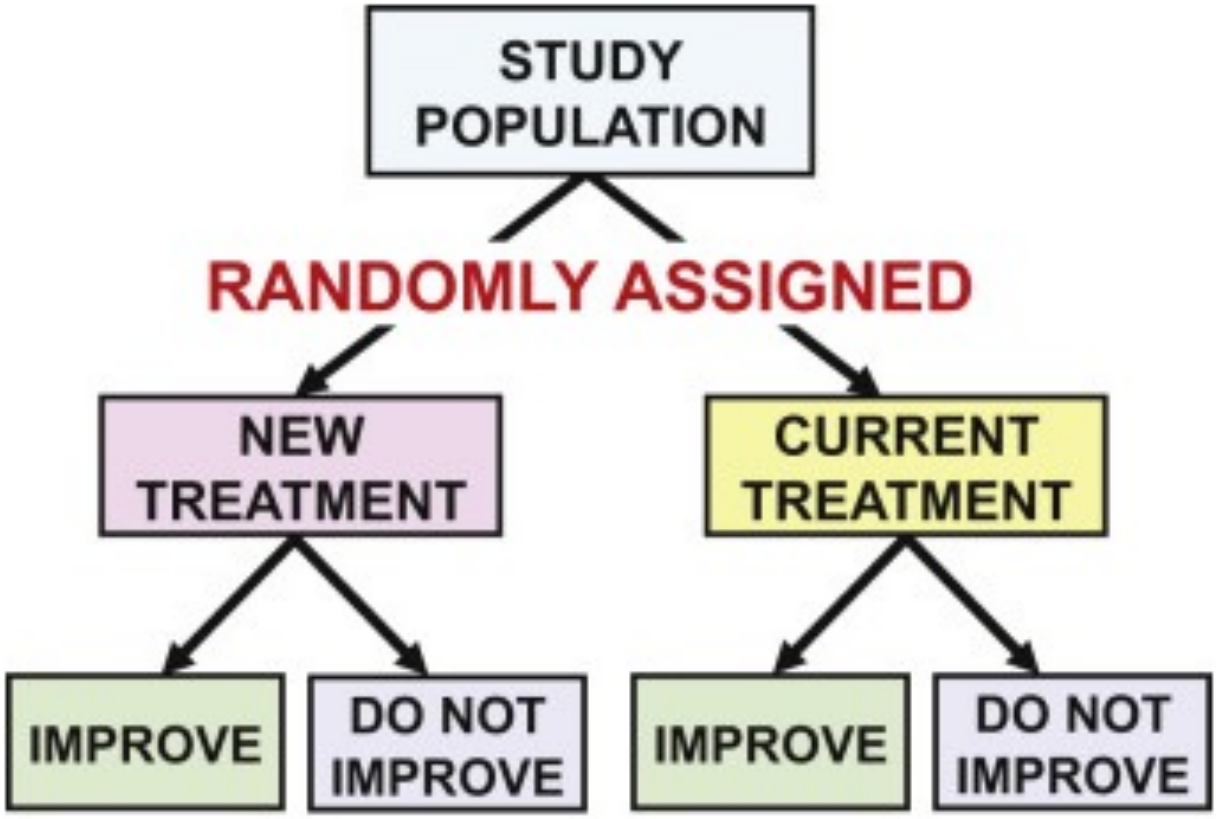


- Experimental group
- Control group

Follow-up to assess outcomes

Comparison of outcome frequency

RCT Design


STUDY POPULATION
RANDOMLY ASSIGNED
NEW TREATMENT
CURRENT TREATMENT
IMPROVE
DO NOT IMPROVE
IMPROVE
DO NOT IMPROVE

Types of trials

Basic trial design: 2-arm parallel trial

Advanced trial design:

- Cross-over
- Factorial
- Equivalence, non-inferiority
- Multiple arms
- Cluster
- Sequential

Developing a trial question

PICOT

- Population
- Intervention or exposure
- Control to which the intervention/exposure is compared
- Outcome(s) of interest
- Timing of the trial

Selecting Participants

- Must be decided before the study has started
  - There cannot be any subjectivity
  - Must be replicable
- Type of participants selected has important implications for the external validity (generalizability) of study results
  - Community based trial vs. hospital trial
  - Pregnant women, children, older adults
  - Under-represented minority groups

Eligibility Criteria

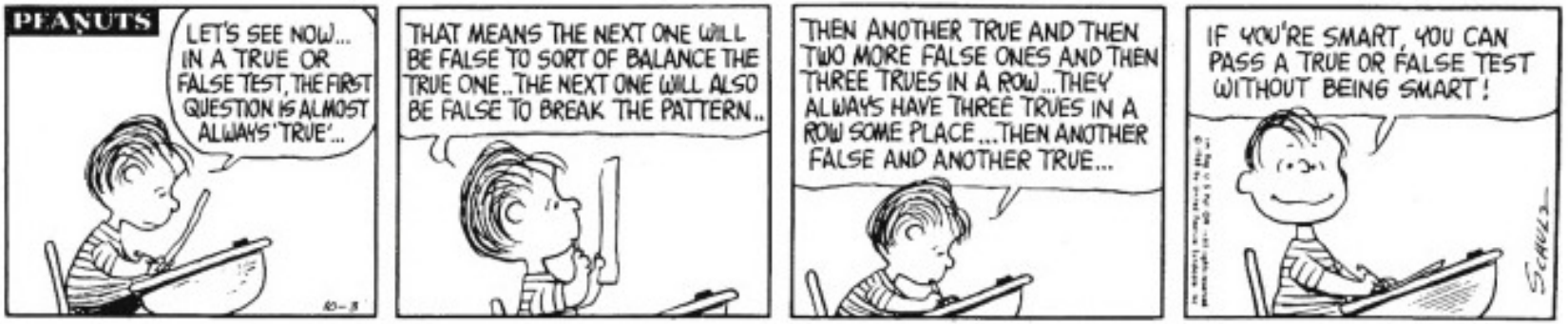
- Also called inclusion and exclusion criteria
- Characteristics that define the individuals you want to participate in the study
- Must be explicitly specified in a study protocol, before the study begins. Why?
  - Allows clear selection of the sample
  - Allows homogeneity of the sample
  - Allows others to reproduce the study, assess if the sample was appropriate for the research question, identifies the individuals to whom findings apply

Eligibility Criteria

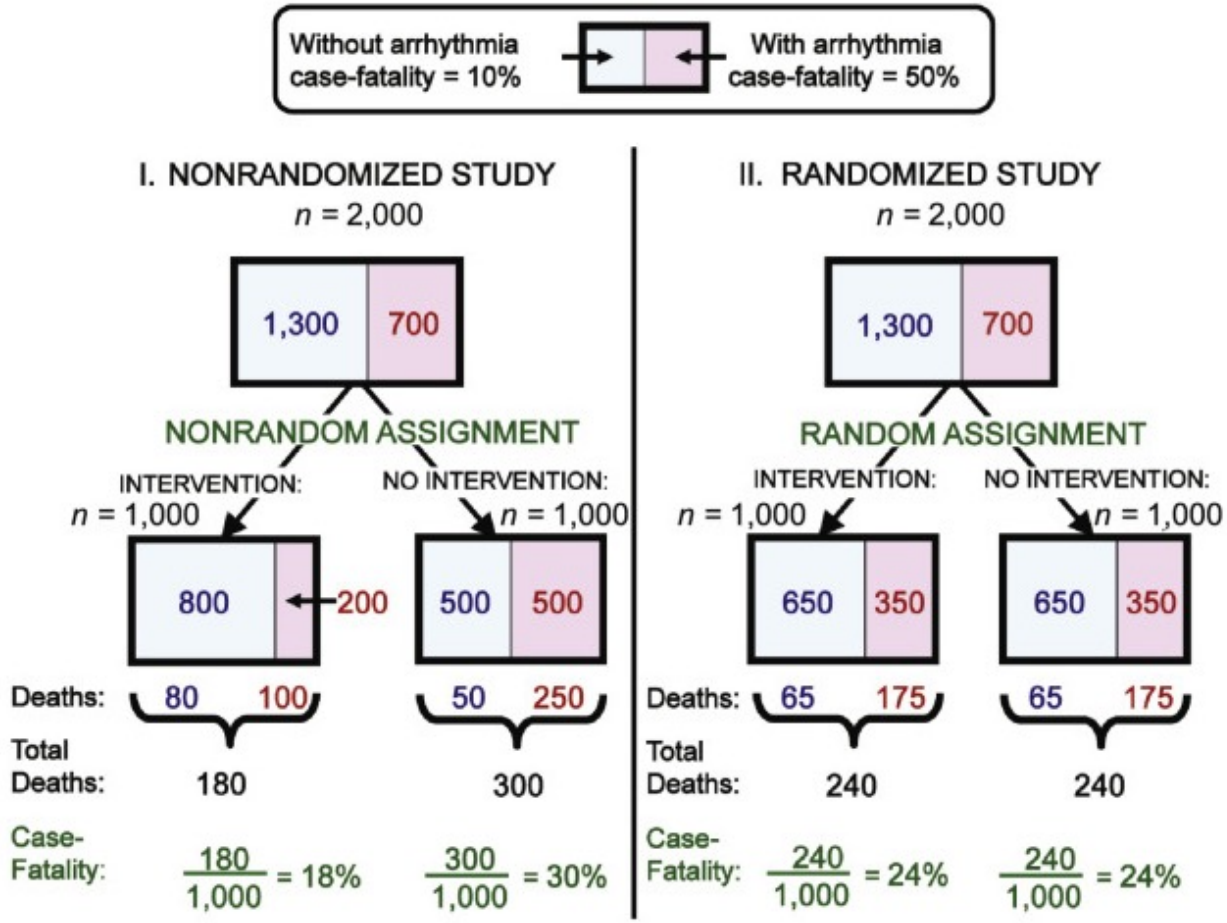
- **Inclusion criteria:** participants that have the potential to benefit from the intervention and have a high probability of developing the outcomes of interest
- **Exclusion criteria:**
  - Higher risk of unwanted events (allergic reactions, pregnant women, children)
  - Risk of not complying with the study protocol
  - Is not just the opposite of inclusion criteria

Allocation

- Process of allocating participants randomly to the study arm(s) -- allocate participants via randomization
- Each participant has a known likelihood of receiving any of the trial interventions (likelihood is usually the same)
  - Allocation is not determined by the investigator, clinicians, or participants
  - Allocation is not predictable based on a pattern



Lack of comparability



Why Randomize?

- Prevent bias related to group assignment, all decisions about treatment are removed from control of investigators (consciously or unconsciously)
- Balances known and unknown prognostic (confounding) factors, including time
  - Not a **guarantee** of comparability at baseline because there could be chance imbalances
- Facilitates blinding of participants, investigators, assessors
- Increases likelihood of exchangeability and comparability between study groups

RCT “Table 1”

- Table 1 in most RCTs will provide a comparison of treatment and comparison groups, with p-values
  - If randomization has been performed correctly, chance is the only explanation for any observed difference between groups
  - P-values comparing treatment groups are not informative, yet are widely used

Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients

The MENDS Randomized Controlled Trial

JAMA. 2007;298(22):2644-2653

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Table 1. Baseline Demographics of Patients Sedated With Dexmedetomidine vs Lorazepam[a]

Variable	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*P* Value
Age, y	60 (49 to 65)	59 (45 to 67)	.97
Men, No. (%)	30 (58)	23 (45)	.20
Severity of illness assessment scores			
APACHE II	29 (24 to 32)	27 (24 to 32)	.75
SOFA	10 (8 to 12)	9 (7 to 11)	.15
IQCODE at enrollment	3 (3 to 3)	3 (3 to 3)	.31
ICU type, No. (%)			.78
Medical ICU	37 (71)	35 (69)	
Surgical ICU	15 (29)	16 (31)	
Preenrollment history			
Total lorazepam exposure, mg	0.25 (0 to 4.25)	0 (0 to 3.0)	.69
Mechanical ventilator support prior to enrollment, h	22 (14 to 35)	17 (8 to 27)	.18
RASS score at enrollment	−3 (−4 to −1)	−4 (−4 to −1)	.21
Admission diagnosis, No. (%)			
Sepsis/acute respiratory distress syndrome	19 (37)	20 (39)	.78
Pulmonary (other)[b]	12 (23)	11 (22)	.85
Malignancies	4 (8)	4 (8)	.98
Airway/ear, nose and throat (otolaryngeal surgery)	3 (6)	1 (2)	.32
Acute lung injury	2 (4)	3 (6)	.63
Chronic obstructive pulmonary disease	2 (4)	2 (4)	.98
Cardiogenic shock	2 (4)	0 (0)	.16
Hemorrhagic shock	1 (2)	1 (2)	.99
Renal failure	1 (2)	0 (0)	.32
Other[c]	6 (10)	9 (17)	.38

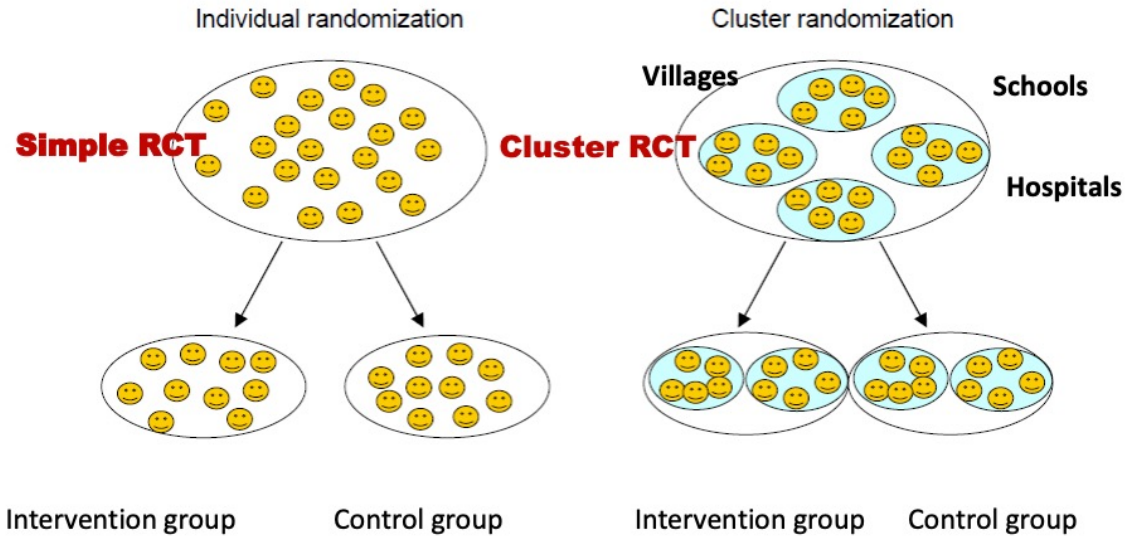
Quasi-Randomization

Studies are not considered randomized if the allocation is based on:

- Patient order of arrival (alternating)
- Day of the week
- Last digit of an ID or record number
- Date of birth

Individual vs. group randomization

- Can randomize individuals or groups
  - E.g., families, schools, towns, hospitals, communities
  - Special concerns about contamination in cluster randomization and loss of allocation concealment
  - Need special statistical techniques because individuals within the cluster are not independent of each other



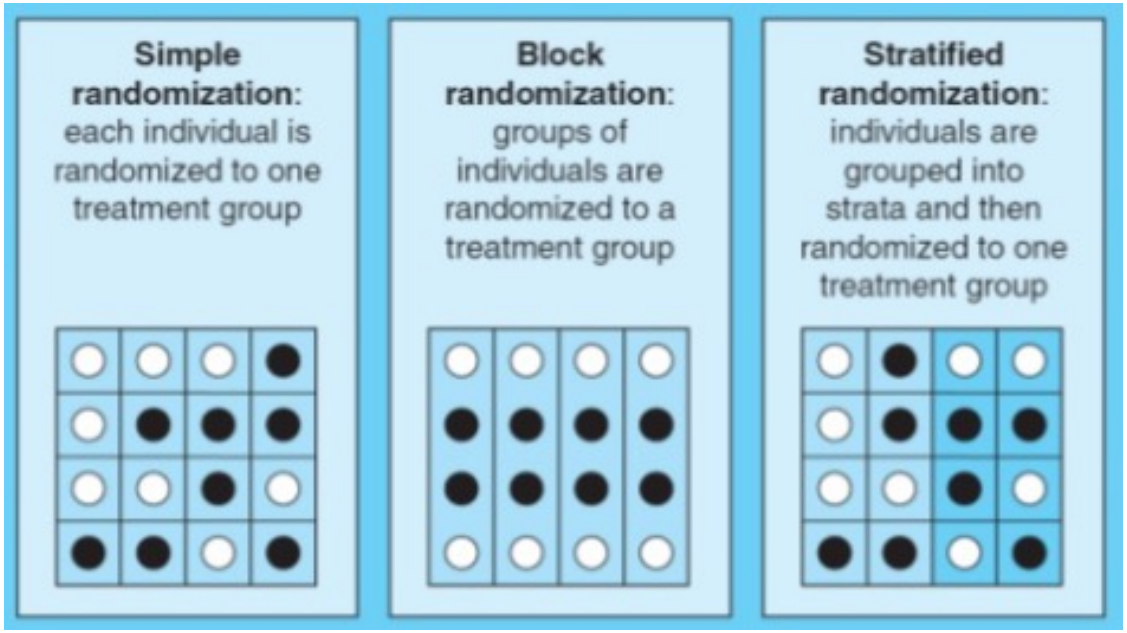
How do we randomize?

- Two steps:
  1. Generating allocation sequence
  2. Implementation of allocation (allocation concealment)
     - Critically important step- without allocation concealment, generating a randomized sequence isn't important.

- Different methods for randomization:
  - Simple randomization
  - Blocked randomization
  - Stratified randomization
  - Dynamic or adaptive randomization

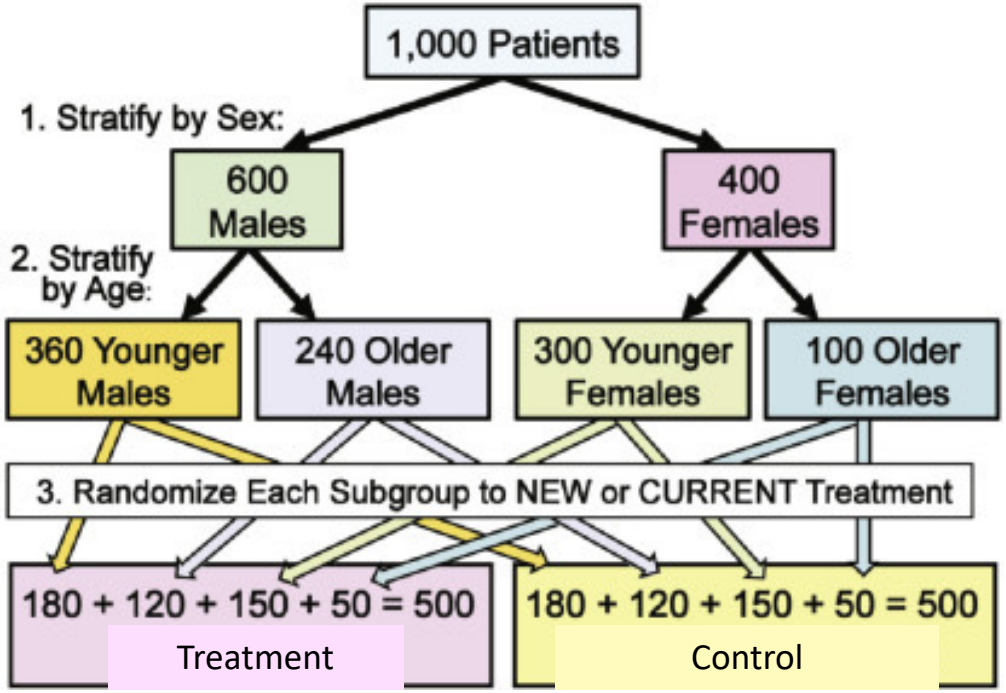
Implementing Randomization

- Simple randomization
  - Conceptually similar to flipping a coin
  - Usually done by a computer program
- Block randomization
  - Ensures equal balance of study arms throughout trial (block of 4 has 2 tx and 2 control)
- Stratified randomization
  - Identify specific characteristics (e.g., sex) and then randomization occurs within strata

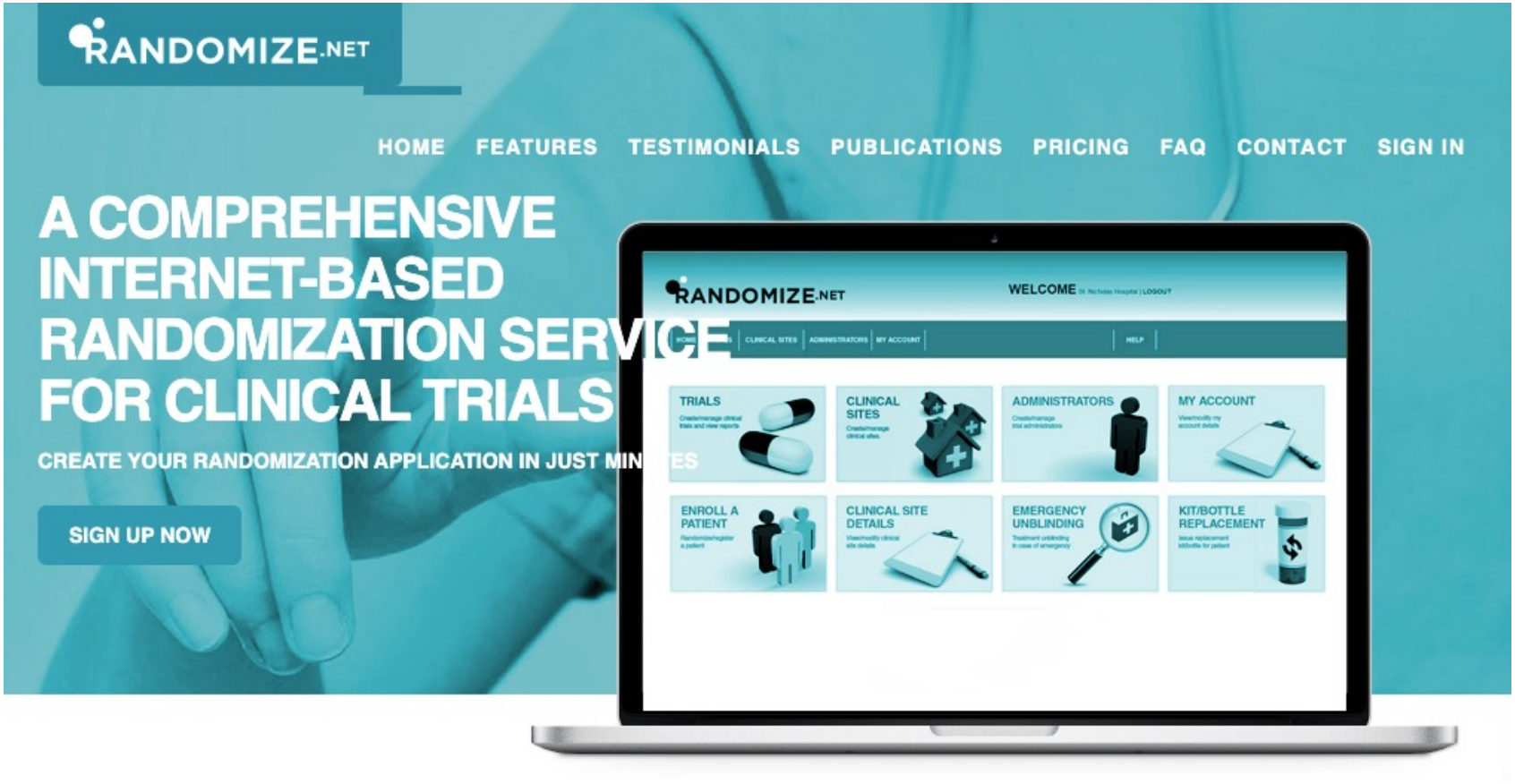


Stratified Randomization

- Strata = group
- Group study participants by specific variables that may affect the outcome and then use simple randomization within each stratum



Randomization Services

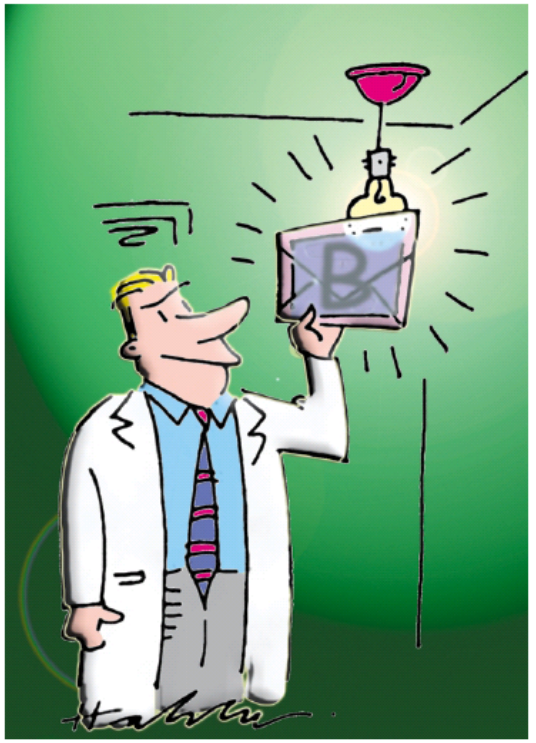


Concealment of allocation

- Need to ensure those making decisions about patient eligibility are not aware of the arm of the study to which the patient will be allocated
  - If randomization is unconcealed, they may systematically enroll sicker, or less sick, patients to either treatment or control groups
  - Defeats the purpose of an RCT
- Best practice: someone other than the investigator to prepare the randomization
- The time between the allocation of each subject and the application of the intervention should be as short as possible

Strategies for allocation concealment

- Sealed packages with the medications
- Randomization at central pharmacy
- Centralized telephone randomization
- Opaque envelopes, sealed and numbered in sequence



Deciphering the allocation concealment scheme

Allocation concealment in randomised trials: defending against deciphering

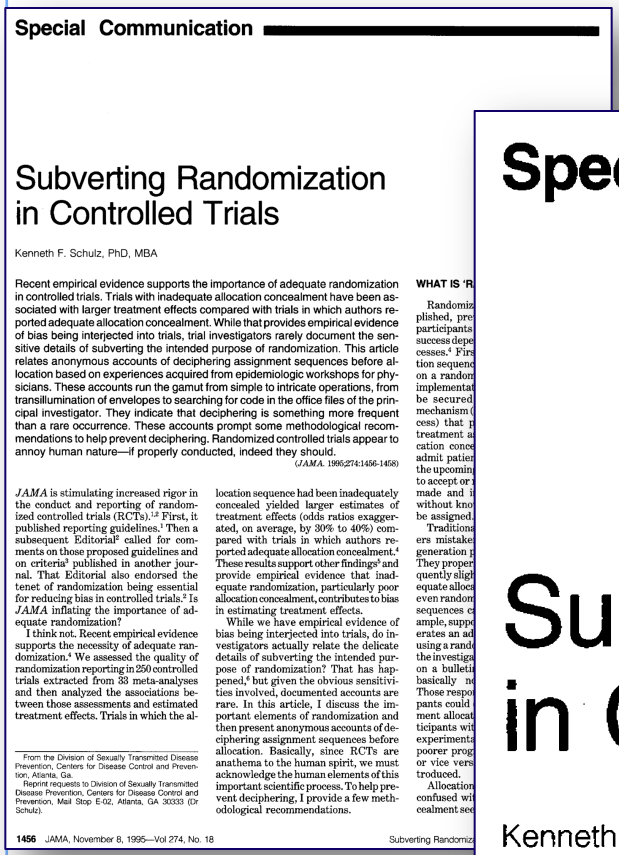
Kenneth F Schulz, David A Grimes

Lancet 2002; **359:** 614–18

Panel 2: **Minimum and expanded criteria for adequate allocation concealment schemes**

Minimum description of adequate allocation concealment scheme	**Additional descriptive elements that provide greater assurance of allocation concealment**
Sequentially numbered, opaque, sealed envelopes (SNOSE)	Envelopes are opened sequentially only after participant details are written on the envelope. Pressure-sensitive or carbon paper inside the envelope transfers that information to the assignment card (creates an audit trail). Cardboard or aluminum foil inside the envelope renders the envelope impermeable to intense light.
Sequentially numbered containers	All of the containers were tamper-proof, equal in weight, and similar in appearance.
Pharmacy controlled	Indications that the researchers developed, or at least validated, a proper randomisation scheme for the pharmacy. Indications that the researchers instructed the pharmacy in proper allocation concealment.
Central randomisation	The mechanism for contact—eg, telephone, fax, or e-mail—the stringent procedures to ensure enrolment before randomisation, and the thorough training for those individuals staffing the central randomisation office.

Subversion of Randomization



Special Communication

Subverting Randomization in Controlled Trials

Kenneth F. Schulz, PhD, MBA

Recent empirical evidence supports the importance of adequate randomization in controlled trials. Trials with inadequate allocation concealment have been associated with larger treatment effects compared with trials in which authors reported adequate allocation concealment. While that provides empirical evidence of bias being interjected into trials, trial investigators rarely document the sensitive details of subverting the intended purpose of randomization. This article relates anonymous accounts of deciphering assignment sequences before allocation based on experiences acquired from epidemiologic workshops for physicians. These accounts run the gamut from simple to intricate operations, from transillumination of envelopes to searching for code in the office files of the principal investigator. They indicate that deciphering is something more frequent than a rare occurrence. These accounts prompt some methodological recommendations to help prevent deciphering. Randomized controlled trials appear to annoy human nature—if properly conducted, indeed they should.

(*JAMA*. 1995;274:1456-1458)

JAMA is stimulating increased rigor in the conduct and reporting of randomized controlled trials (RCTs).[1,2] First, it published reporting guidelines.[1] Then a subsequent Editorial[2] called for comments on those proposed guidelines and on criteria[3] published in another journal. That Editorial also endorsed the tenet of randomization being essential for reducing bias in controlled trials.[2] Is *JAMA* inflating the importance of adequate randomization?

I think not. Recent empirical evidence supports the necessity of adequate randomization.[4] We assessed the quality of randomization reporting in 250 controlled trials extracted from 33 meta-analyses and then analyzed the associations between those assessments and estimated treatment effects. Trials in which the allocation sequence had been inadequately concealed yielded larger estimates of treatment effects (odds ratios exaggerated, on average, by 30% to 40%) compared with trials in which authors reported adequate allocation concealment.[4] These results support other findings[3] and provide empirical evidence that inadequate randomization, particularly poor allocation concealment, contributes to bias in estimating treatment effects.

While we have empirical evidence of bias being interjected into trials, do investigators actually relate the delicate details of subverting the intended purpose of randomization? That has happened,[5] but given the obvious sensitivities involved, documented accounts are rare. In this article, I discuss the important elements of randomization and then present anonymous accounts of deciphering assignment sequences before allocation. Basically, since RCTs are anathema to the human spirit, we must acknowledge the human elements of this important scientific process. To help prevent deciphering, I provide a few methodological recommendations.

From the Division of Sexually Transmitted Disease Prevention, Centers for Disease Control and Prevention, Atlanta, Ga.

Reprint requests to Division of Sexually Transmitted Disease Prevention, Centers for Disease Control and Prevention, Mail Stop E-02, Atlanta, GA 30333 (Dr Schulz).

Special Communication

Subverting Randomization in Controlled Trials

Kenneth F. Schulz, PhD, MBA

Table 1

Examples of Methods of Deciphering Allocation Concealment[10]

- Holding translucent envelopes up to bright lights to reveal upcoming assignment (even using the hot light in a radiology department for more opaque envelopes)
- Opening unsealed assignment envelopes
- Opening a well-sealed, opaque envelope in advance of consent
- Opening unnumbered envelopes until desired allocation found
- Determining different weights of the assignment envelopes (eg, the heavier envelope means intervention group)
- Asking a central randomization center for the next several assignments all at once
- Deciphering assignments to active drug or placebo based on appearance of drug container labels

Blinding

- Relevant groups (patients, investigators) do not know which group they are assigned to
  - Especially important when outcomes are subjective or self-report
  - Participants, investigators, assessors, analysts
  - E.g., pain symptoms, quality of life

- Blinded trial is the opposite of an open trial
  - Sometimes impossible to blind participants/investigator
  - E.g., trial of surgical intervention

- Options: single, double, triple/quadruple blinding

Benefits

Panel 1: **Potential benefits accruing dependent on those individuals successfully blinded**

Individuals blinded	Potential benefits
Participants	Less likely to have biased psychological or physical responses to intervention More likely to comply with trial regimens Less likely to seek additional adjunct interventions Less likely to leave trial without providing outcome data, leading to lost to follow-up
Trial investigators	Less likely to transfer their inclinations or attitudes to participants Less likely to differentially administer co-interventions Less likely to differentially adjust dose Less likely to differentially withdraw participants Less likely to differentially encourage or discourage participants to continue trial
Assessors	Less likely to have biases affect their outcome assessments, especially with subjective outcomes of interest

Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. Lancet. 2002 Feb 23;359(9307):696-700

Allocation concealment vs. blinding

- **Concealment of allocation:**
  - Procedure to protect the randomization process before the subject enters the trial
  - Concealment of allocation is ALWAYS feasible
  - If not done, results in selection bias (randomization benefits are lost, and treatment assignment is no longer truly random)
- **Blinding:**
  - Masking of the treatments after randomization (once trial begins)
  - Blinding is not always feasible
  - If not done, can result in patients biasing their responses because of their knowledge of treatment; can also lead to biased outcome assessment because investigators have knowledge of treatment

End of Module 1

Types of RCTs

- Based on the type of interventions being evaluated
  - Efficacy vs effectiveness trials
  - Superiority vs equivalence trials
  - Phase I, II, III, IV trials
- Based on how participants are exposed to interventions
- Based on the number of participants
- Blinded vs. open trial

Efficacy vs. Effectiveness

- Efficacy—does the intervention work in the people who actually receive it?
  - These trials tend to be explanatory
  - Goal here is high compliance
- Effectiveness—how does the intervention work in those offered it
  - Tend to be pragmatic
  - Real world considerations

Superiority vs. equivalence trials

- Superiority trials
  - Intended to determine if new treatment is different from (better than) placebo or existing treatment (active control)
  - Null hypothesis is that there is no difference between treatments.
  - Alternative hypothesis is that the new treatment is better than the control.
- Equivalence trials
  - Intended to determine that new treatment is no worse than active control
  - Null hypothesis and alternative hypotheses are reversed.
  - Null hypothesis is that difference between treatments is greater than X.
  - Alternative hypothesis is that difference between treatments is less than X

Why do an equivalence trial?

- Existing effective treatment (standard treatment)
- Placebo-controlled trial unethical
  - Life-threatening illness.
- New treatment not substantially better than existing treatment.
  - May have fewer side effects, greater convenience, lower cost, higher quality of life, or provide an alternative or second line therapy.

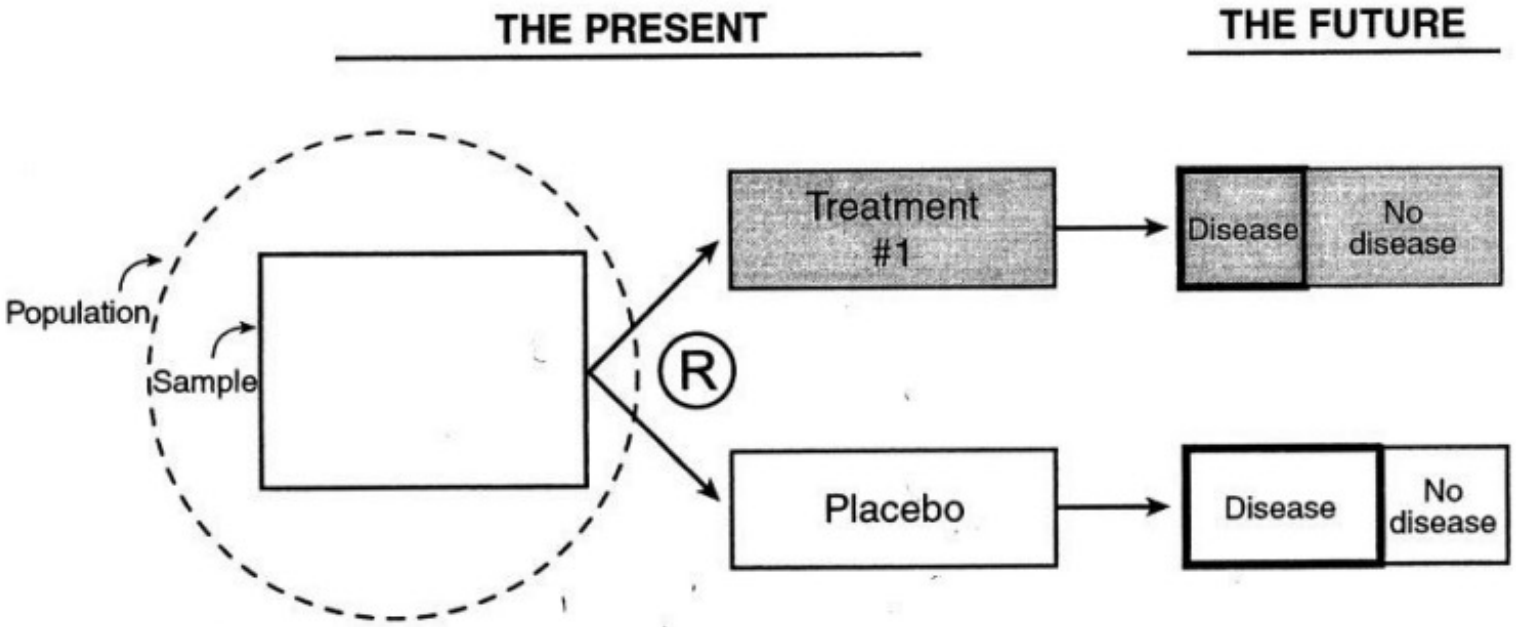
Types of trial design for pharmaceuticals

Phase	Goal	Dose	# patients	Comments
Phase I	Pharamcovigilence, tolerability, toxicity, some dose finding	Ascending	20-80	Determine if drug safe to check for efficacy
Phase II	Initial efficacy, toxicity, dose finding	Therapeutic	100-300	Determines final dose & if drug has true efficacy
Phase III	Testing for intended purpose in clinical practice	Therapeutic	1000-3000	Determines drug's efficacy
Phase IV	Post-marketing surveillance	Therapeutic	Anyone	Watches for drug long term AEs

Classification of trial type: participant assignment

- Parallel trials
  - Usually 2 arm RCT design, most common
- Crossover trials
  - Intervention switches to control or vice versa
- Trials with factorial design
  - Testing more than one intervention or treatment at the same time

Parallel Arm

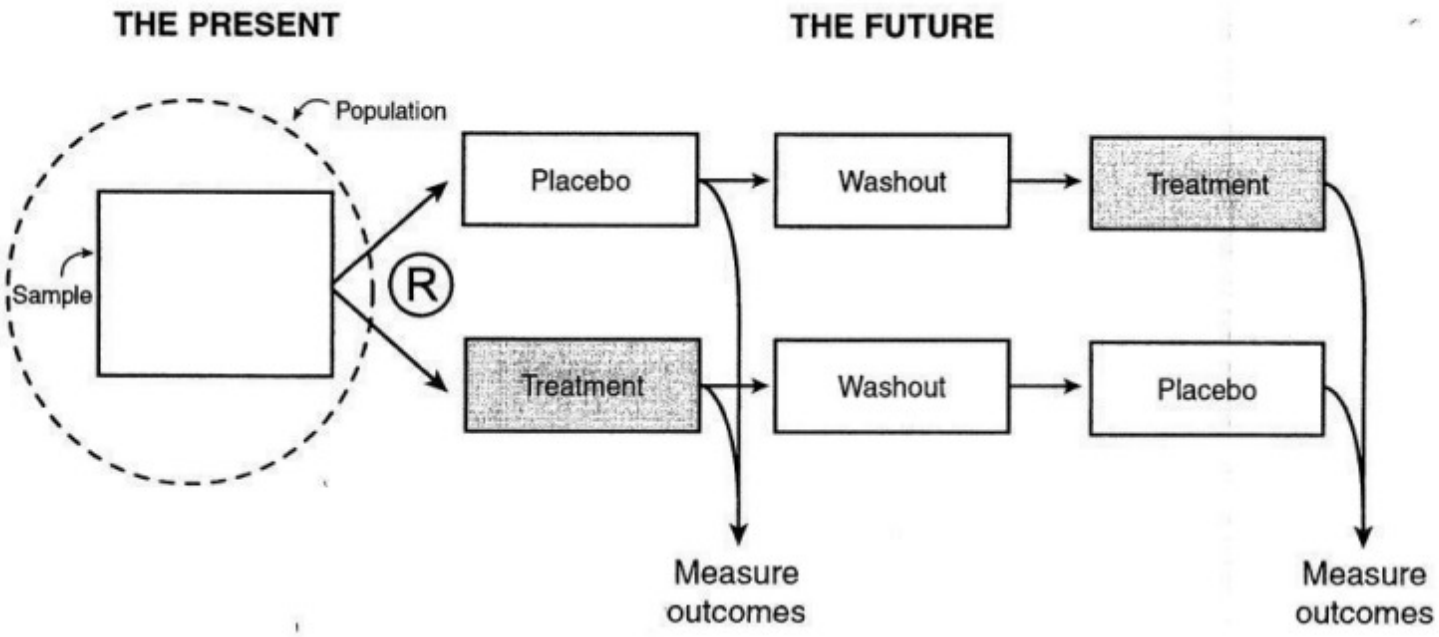


■ **FIGURE 10.1**

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.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

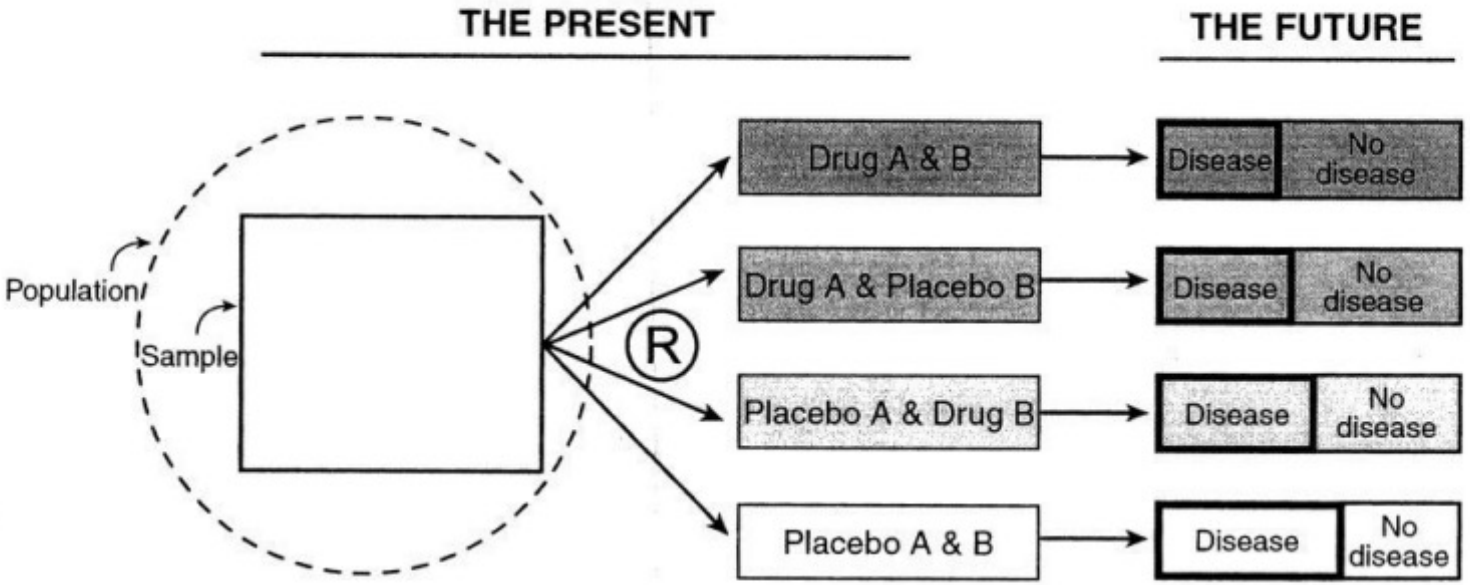
Cross-over RCT



■ **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



■ **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.

Type of Trial Outcomes

- Primary:
  - Usually single (or single cluster)
  - Dictates sample size
- Secondary:
  - May be multiple
  - Other important changes that are expected from intervention – e.g. adverse events

Choice of Primary Outcome

1. Clinical relevance and target audience (*what will change practice?*)
2. Likelihood of response to intervention
3. Supportive biological rationale
4. Easy to measure in a reliable, valid, non-biased, reproducible and economic manner

Special Considerations: Composite Outcomes

- Use of multiple possible outcomes of interest as one outcome which is achieved if any of the individual components is reached or realized (e.g. cardiovascular death, MI, CHF, stroke = one outcome)
- Measurement scale or index is a special type of composite outcome
- Disadvantages: may not make sense; over-interpretation; overlook important effects on individual variables

Special Considerations: Surrogate Outcomes

- An outcome that is often easier and faster to measure that is associated with the outcome of interest
  - CIMT in CVD trials
  - Viral load in HIV trials
    - Often faster to enroll, important in life-threatening trials
    - Risk of not capturing what is important if outcome also happens as AE – e.g. arrhythmia, diabetic, CHF drugs

The use of physiological surrogates should be limited to those with clear relation to important health outcomes

Ascertainment of Outcome Events

- Usually easy for objectively defined and determined events (e.g. death)
- Difficult for subjectively determined events (e.g. disease activity of Crohn's disease; patient satisfaction)
- Has it been validated?

- Improving ascertainment
    1. "Hard" outcome
    2. Clear and objective operational definition of outcome
    3. Blinded ascertainment of outcome
    4. Adjudication of events

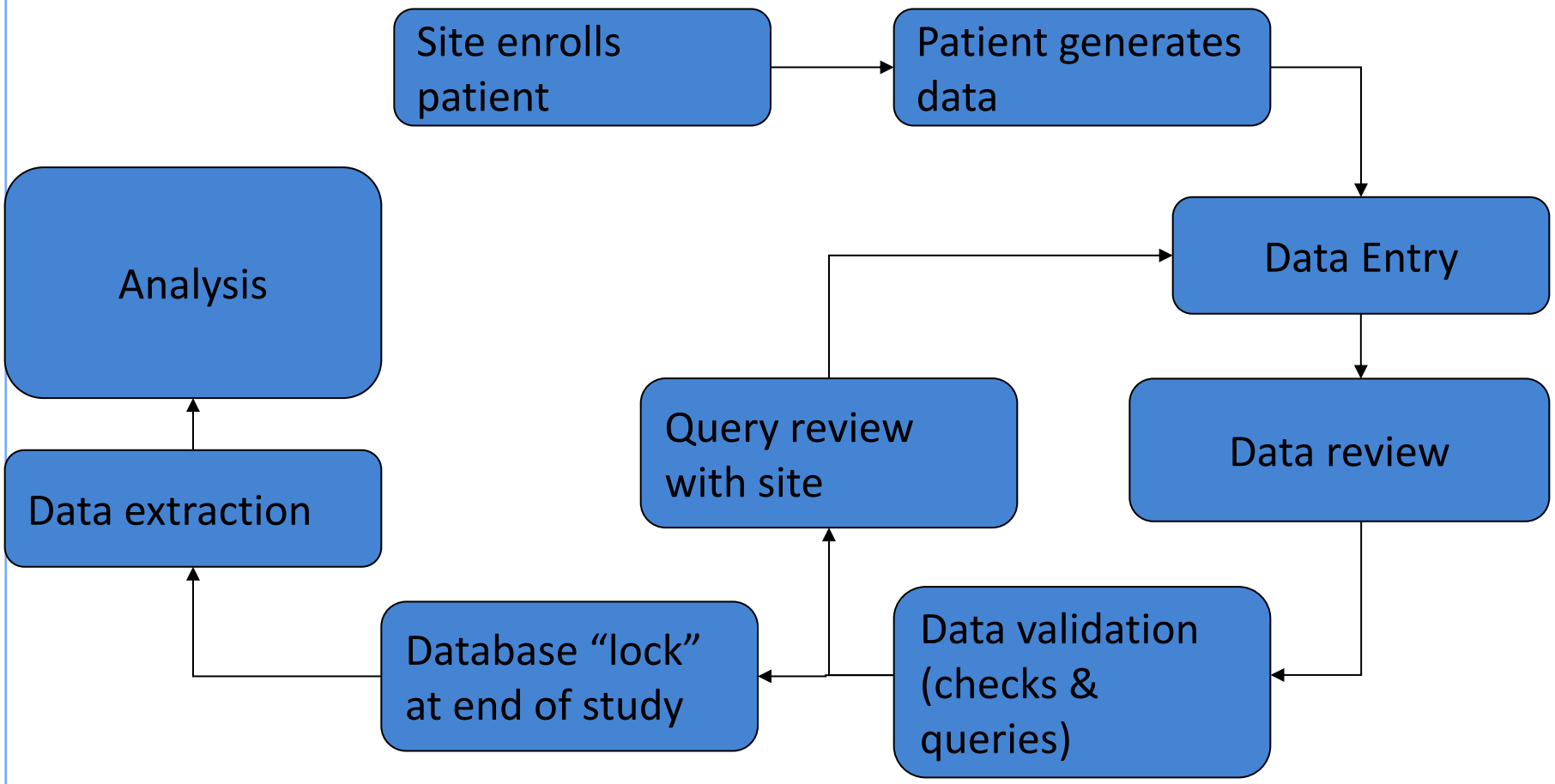
Ascertainment of Outcome Events (cont.)

- Must decide how to ascertain outcomes
  - Standardized f/u or patient-driven?
- Timing of assessments – figuring best time of follow-up?
- Who will ascertain?
  - Lab, clinicians, self-reported questionnaire?
- What happens when event happens?
  - Typically participant ends study but may continue for 2ndary outcomes

Data Collection

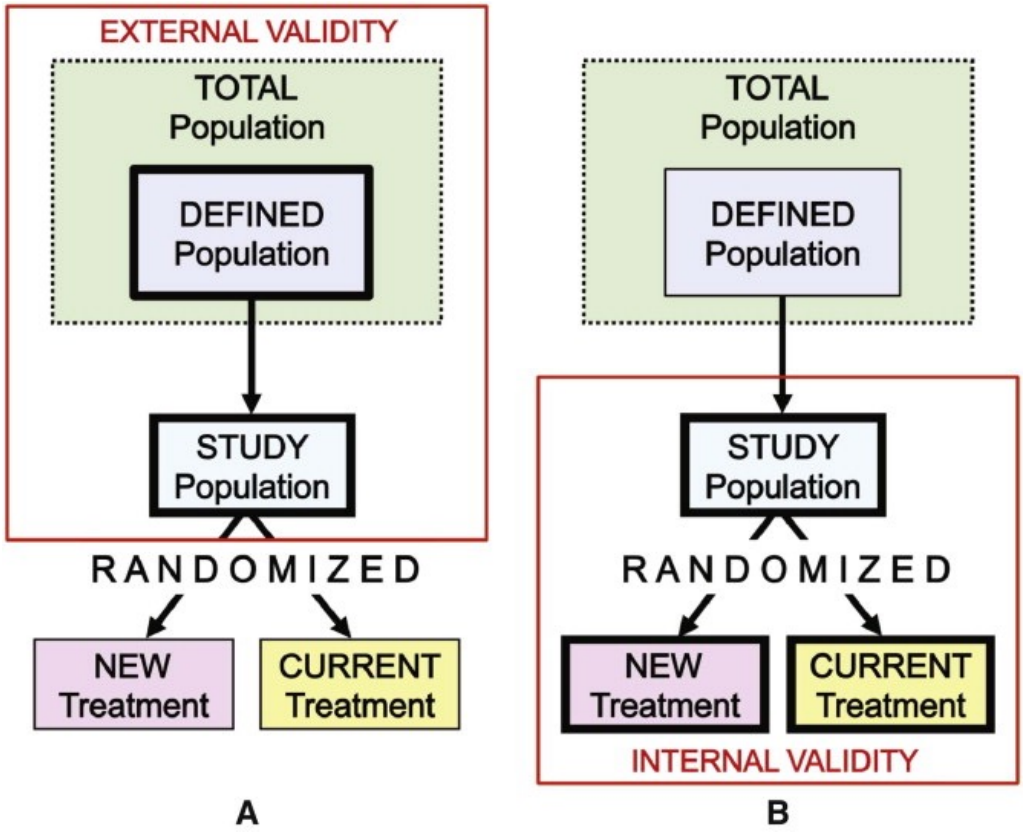
- Clinical trials generate reams of data!
- Data management is the process whereby this data is collected, reviewed and verified, and managed
- Information is reported using a “case report form”

Data Management

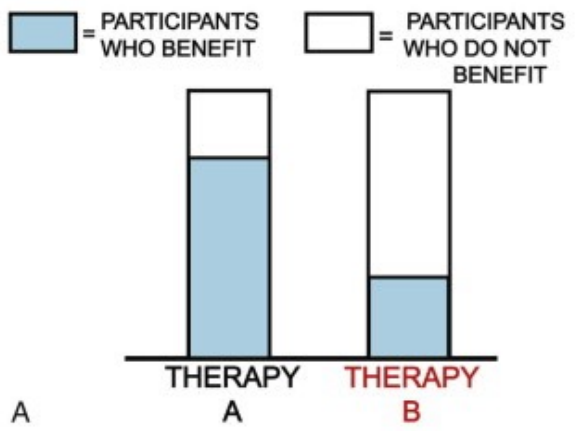


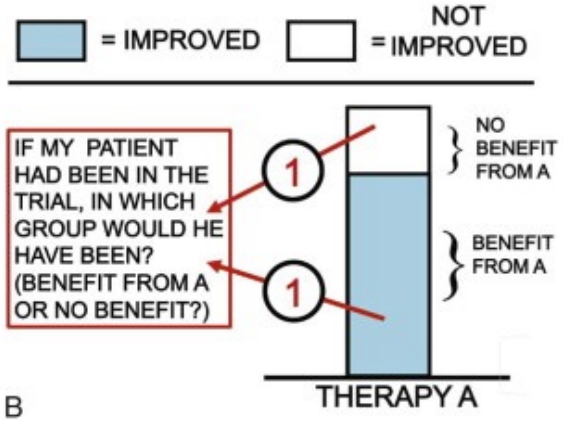
Interpreting results

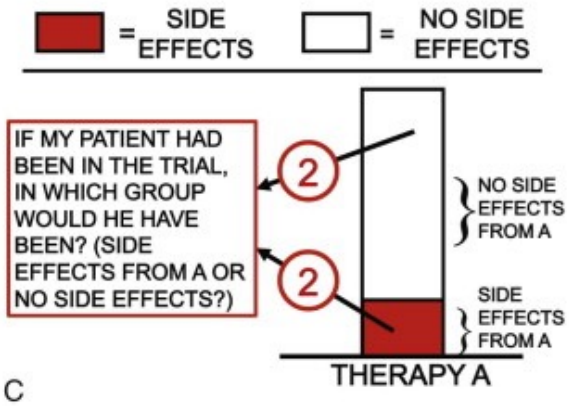
Goal is to generalize results beyond the study population

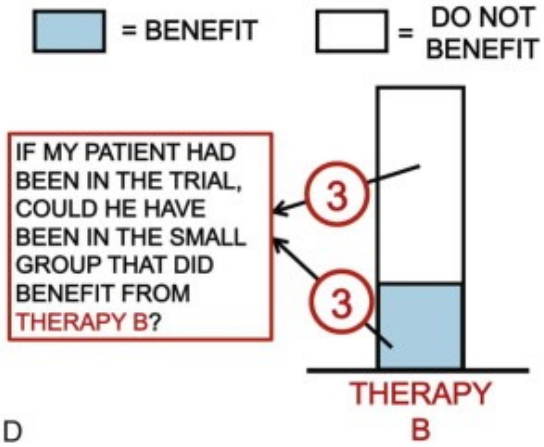


What can the results tell the treating physician?









Non-compliance

- Must carefully assess compliance with trial protocol
  - Non-compliance comes in several forms
    - Drop out or censoring
    - Failing to take assigned treatment
    - Drop-ins → choosing to take the treatment assigned to the other group
      - E.g., Aspirin trial: provided pts with list of medications to specifically avoid, urine tests to check
- Non-compliance reduces differences between study group, producing a bias toward the null
  - Groups will be less different than you wanted them to be
  - Attenuating true effect of treatment

End of Module 2

When is randomization ethical?

- There are many instances when we cannot randomize individuals
- There are two ‘moral’ considerations when answering the question of whether a trial is ethical
  - Uncertainty principle
  - Clinical equipoise

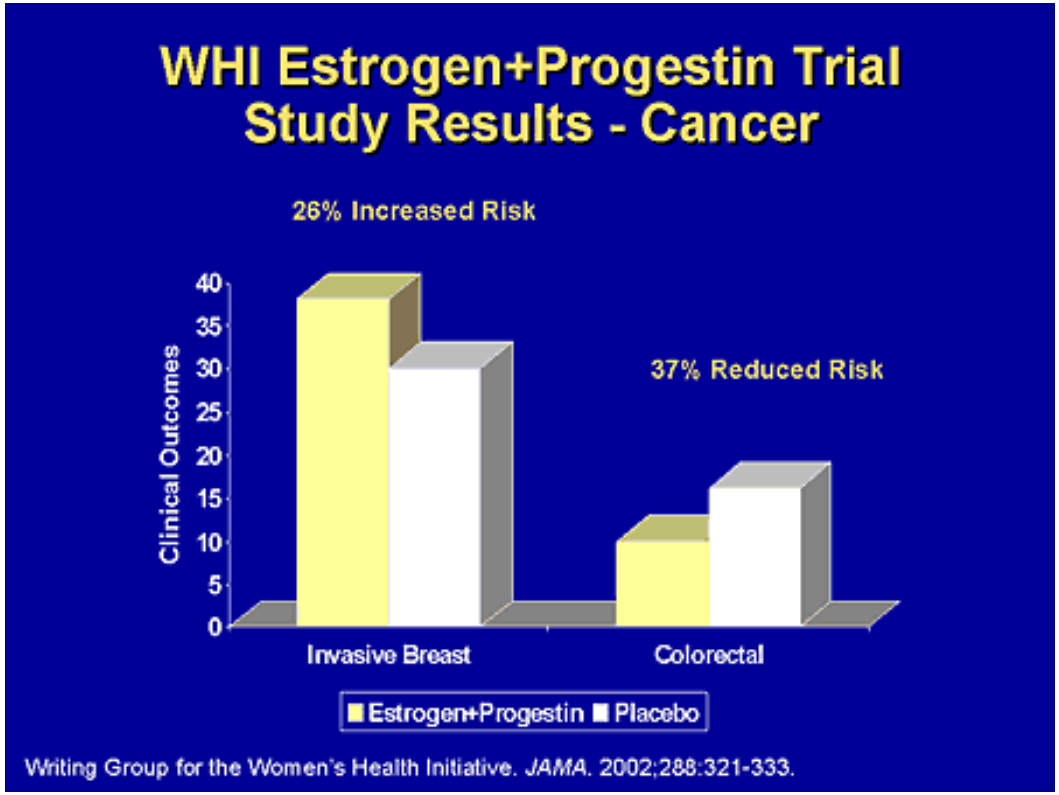
The uncertainty principle

"Physicians who are convinced that one treatment is better than another for a particular patient of theirs cannot ethically choose at random which treatment to give: they must do what they think best for the particular patient. For this reason, physicians who feel they already know the answer cannot enter their patients into a trial." –Richard Peto et al. (1976)

Clinical Equipoise

- Genuine uncertainty exists on the part of the relevant expert community about what therapy or therapies are most effective for a given condition
- This generates the need for a comparative study (possibly a trial)
- Provides a link between duty of care for a clinician and the need to do research
- Main endpoint for both = safety and effectiveness for whatever it is that is being offered

The Women's Health Initiative (WHI)



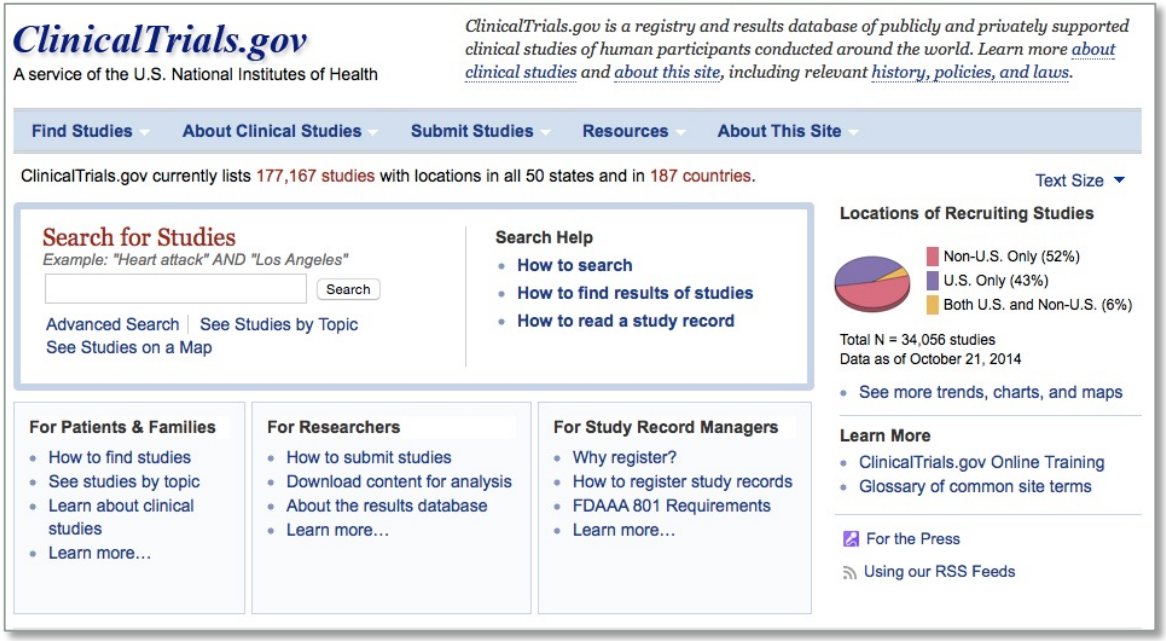
Ethical considerations

Is using a placebo ethical?

- Placebo-controlled trials
  - Use of an active treatment comparator in a clinical trial of a new therapy is generally the appropriate trial design when an established effective therapy exists
- Placebo ok in these circumstances:
  - No established therapy
  - Existing evidence raises significant doubt by medical experts regarding benefit of existing therapy
  - Patients are resistant to existing therapy due to previous history
  - Patient has provided informed refusal to therapy

Trial Registration

- Requires investigators to pre-register as a tool to avoid publication bias
- Null results are important too
- Prevents “fishing” for significant outcomes



Selective reporting of trial results

Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

Comparison of Protocols to Published Articles

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Context Selective reporting of outcomes within published studies based on the nature or direction of their results has been widely suspected, but direct evidence of such bias is currently limited to case reports.

Objective To study empirically the extent and nature of outcome reporting bias in a cohort of randomized trials.

Design Cohort study using protocols and published reports of randomized trials approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg, Denmark, in 1994-1995. The number and characteristics of reported and unreported trial outcomes were recorded from protocols, journal articles, and a survey of trialists. An outcome was considered incompletely reported if insufficient data were presented in the published articles for meta-analysis. Odds ratios relating the completeness of outcome reporting to statistical significance were calculated for each trial and then pooled to provide an overall estimate of bias. Protocols and published articles were also compared to identify discrepancies in primary outcomes.

Main Outcome Measures Completeness of reporting of efficacy and harm outcomes and of statistically significant vs nonsignificant outcomes; consistency between primary outcomes defined in the most recent protocols and those defined in published articles.

Results One hundred two trials with 122 published journal articles and 3736 outcomes were identified. Overall, 50% of efficacy and 65% of harm outcomes per trial were incompletely reported. Statistically significant outcomes had a higher odds of being fully reported compared with nonsignificant outcomes for both efficacy (pooled odds ratio, 2.4; 95% confidence interval [CI], 1.4-4.0) and harm (pooled odds ratio, 4.7; 95% CI, 1.8-12.0) data. In comparing published articles with protocols, 62% of trials had at least 1 primary outcome that was changed, introduced, or omitted. Eighty-six percent of survey responders (42/49) denied the existence of unreported outcomes despite clear evidence to the contrary.

Conclusions The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols. Published articles, as well as reviews that incorporate them, may therefore be unreliable and overestimate the benefits of an intervention. To ensure transparency, planned trials should be registered and protocols should be made publicly available prior to trial completion.

SELECTIVE PUBLICATION OF STUDIES with statistically significant results has received widespread recognition.[1] In contrast, selective reporting of favorable outcomes within published studies has not undergone comparable empirical investigation. The existence of outcome reporting bias has been widely suspected for years,[2-12] but direct evidence is limited to case reports that have low generalizability[13-15] and may themselves be subject to publication bias.

Our study had 3 goals: (1) to determine the prevalence of incomplete outcome reporting in published reports of randomized trials; (2) to assess the association between outcome reporting and statistical significance; and (3) to evaluate the consistency between primary outcomes specified in trial protocols and those defined in the published articles.

METHODS

JAMA 2004

Assessing the quality of RCTs

- CONSORT statement - improving the quality of reports on RCTS

Table. Checklist of Items to Include When Reporting a Randomized Trial

Section and Topic	Item #	Descriptor	Reported on Page #
Title and Abstract	1	How participants were allocated to interventions (eg, "random allocation," "randomized," or "randomly assigned").	
Introduction			
Background	2	Scientific background and explanation of rationale.	
Methods			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomization			
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).	
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	
Results			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group.	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat." State the results in absolute numbers when feasible (eg, 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (eg, 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
Comment			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes.	
Generalizability	21	Generalizability (external validity) of the trial findings.	
Overall evidence	22	General interpretation of the results in the context of current evidence.	

CONSORT Diagram

http://www.consort-statement.org/