Randomized Clinical Trials

Pediatrics Resident Research Course

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Objectives

- Why randomized clinical trials (RCT) are so important
  - Strengths and Weaknesses
- Overview of RCT designs
- Principles of RCT design
  - Asking the right study question
  - Choosing a study population
  - Reducing bias
  - Sample size
  - Ethics & logistics
- Analysis

Why are Pediatric Randomized Clinical Trials Crucial?

Limitations of Observational Data

- No control of baseline variables or exposure
- Cannot establish causality
  - Can only identify associations or correlations

- Confounding: Unmeasured/unknown variable influences exposure & outcome
- Selection bias: Study population may not represent target population
- Observer bias: Personal perspectives influence how data is interpreted
- Hawthorne effect: Participants being observed change behaviour
- Measurement error/Missing data: Especially if retrospective

Why Pediatric RCTs are Essential

- Children are not small adults
  - Metabolize drugs & respond to treatments differently
- Provide high-quality evidence
  - Most rigorous study design
- Ensure safety & efficacy
  - Required by regulatory agencies
- Reduce ‘off-label’ use
  - Medications are used in children without Health Canada approval
- Guide clinical practice & policy
  - Societies & policymakers use results to update treatment guidelines

Off-Label Drug Use in Children

- Drug used outside the terms of regulatory approval
  - Unapproved age, indication, dose, formulation, route
- Prevalence
  - 50% – 80% of all medications prescribed to children
  - In NICU can exceed 90%
- Reasons
  - Physiologic differences
  - Lack of clinical trials
  - Limited suitable formulations
  - Small market size
  - Inadequate labelling

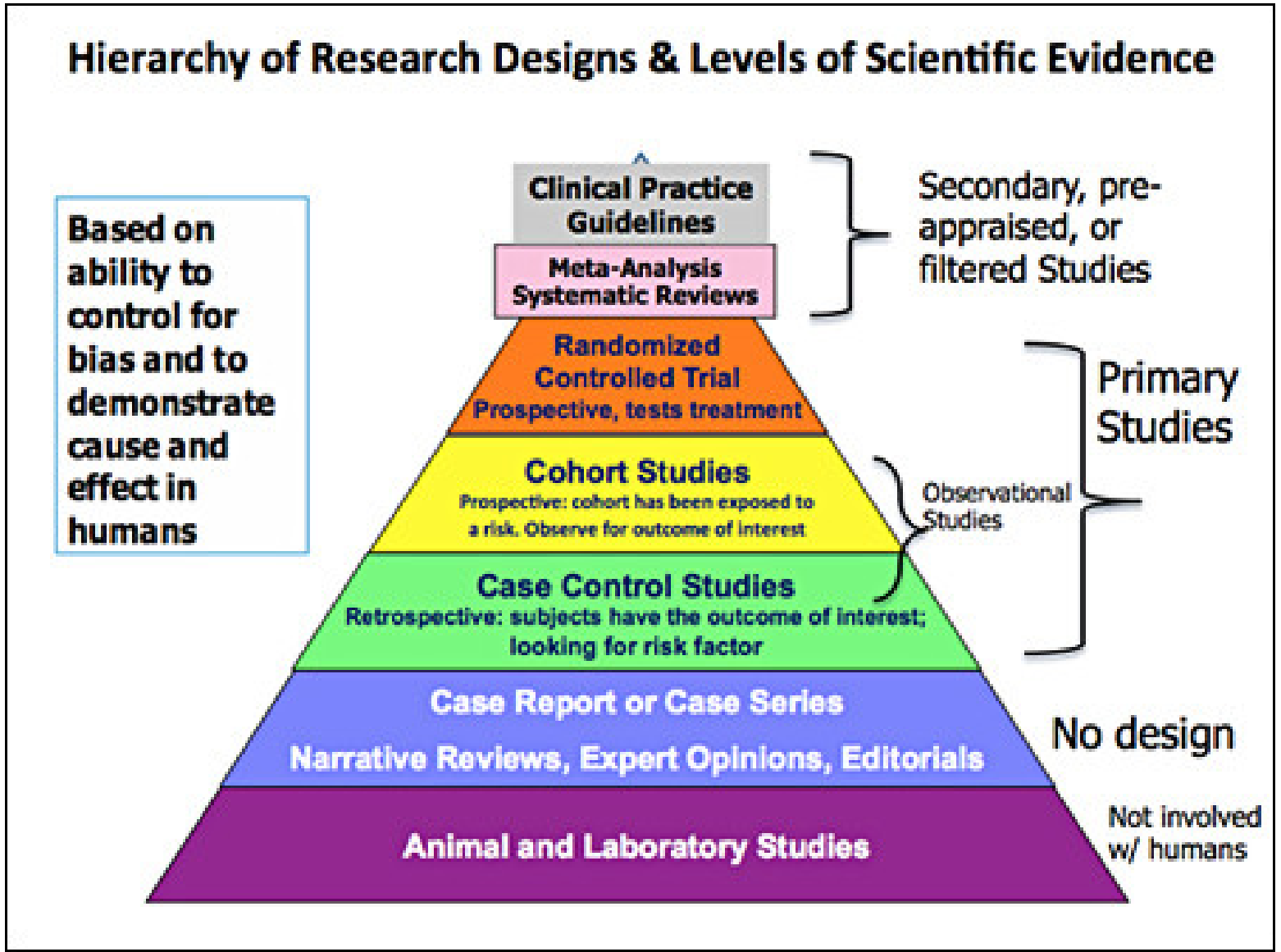
Ondansetron Licensed

Indications in Children?

Pediatrics (4-18 years of age)

Post-Chemotherapy Induced Nausea and Vomiting

Pyramid of Evidence



Clinical Trial Designs

AbbVie Clinical Trials

WHAT ARE THE CLINICAL TRIAL PHASES?

SAFETY

Is the investigational medication/treatment safe?

- Are there side effects?
- How does it affect or move through the body?
- Is it safe to use at the same time as other medications?

Who's in it?

Small group of healthy people—generally less than 100

PHASE 1

PHASE 2

EFFICACY

Is the investigational medication/treatment effective in treating the targeted condition?

- Does it relieve, reverse or stop the progression of the condition?
- How safe is it?
- What is the most effective dosage?

Who's in it?

Generally 100-300 people with the exact condition being studied

PHASE 4

PHASE 3

FOLLOW UP

After the investigational medication/ treatment is approved, how does it work for other patients with the condition?

- More safety/efficacy information is gathered
- Are there long-term benefits?
- Are there long-term risks?

Who's in it?

Often several thousand people who have been prescribed the investigational medication

CONFIRMATION

How does the investigational medication/ treatment compare to the standard treatment for the condition?

- More effective, less effective, or the same?
- Longer-term adverse effects?
- How does it affect quality of life, or survival?
- How might it be used along with existing treatments?

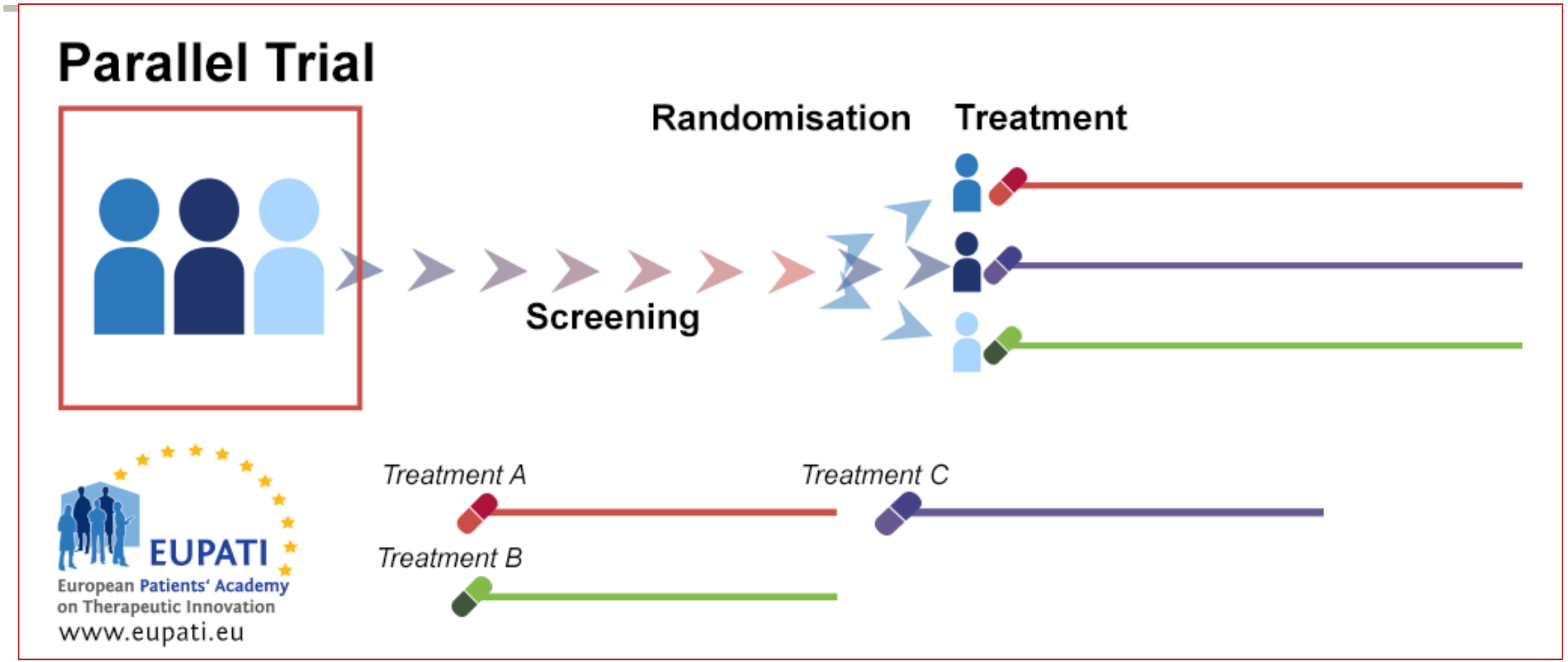
Who's in it?

Often 300-3,000 people with the exact condition being studied

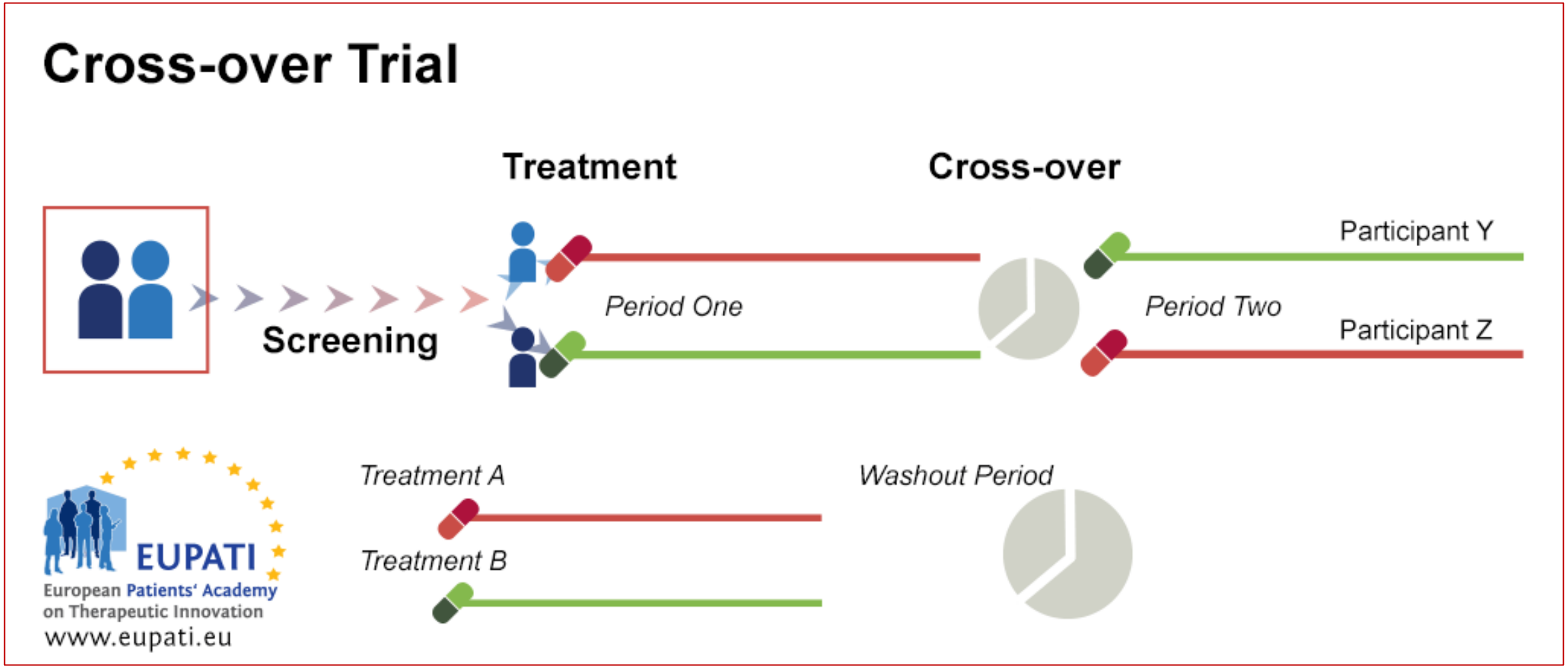
Learn about All Trials Available

Visit AbbvieClinicalTrials.com | Visit ClinicalTrials.gov | Talk to your healthcare provider

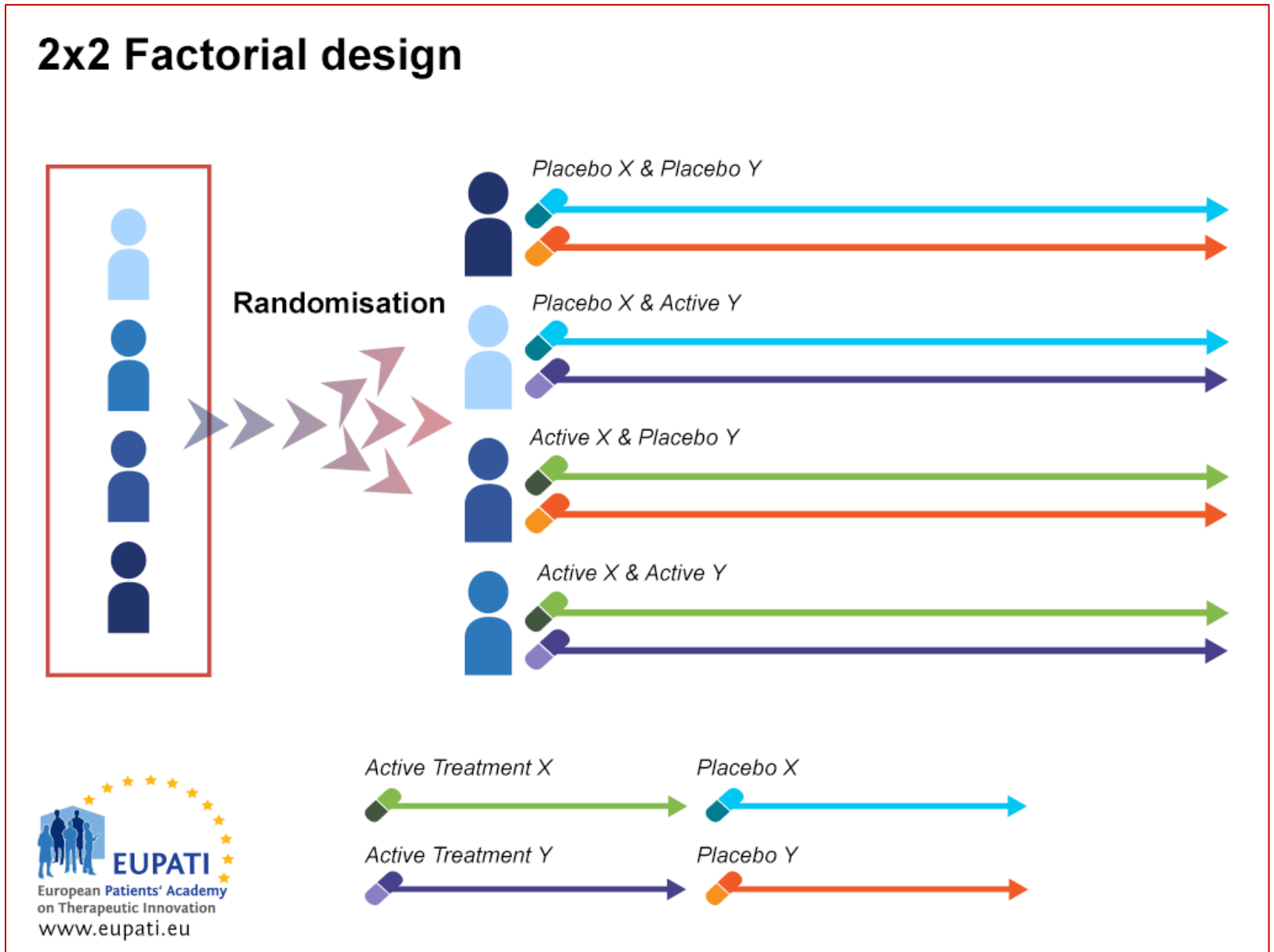
Parallel Trial



Crossover Trial



Factorial Trial



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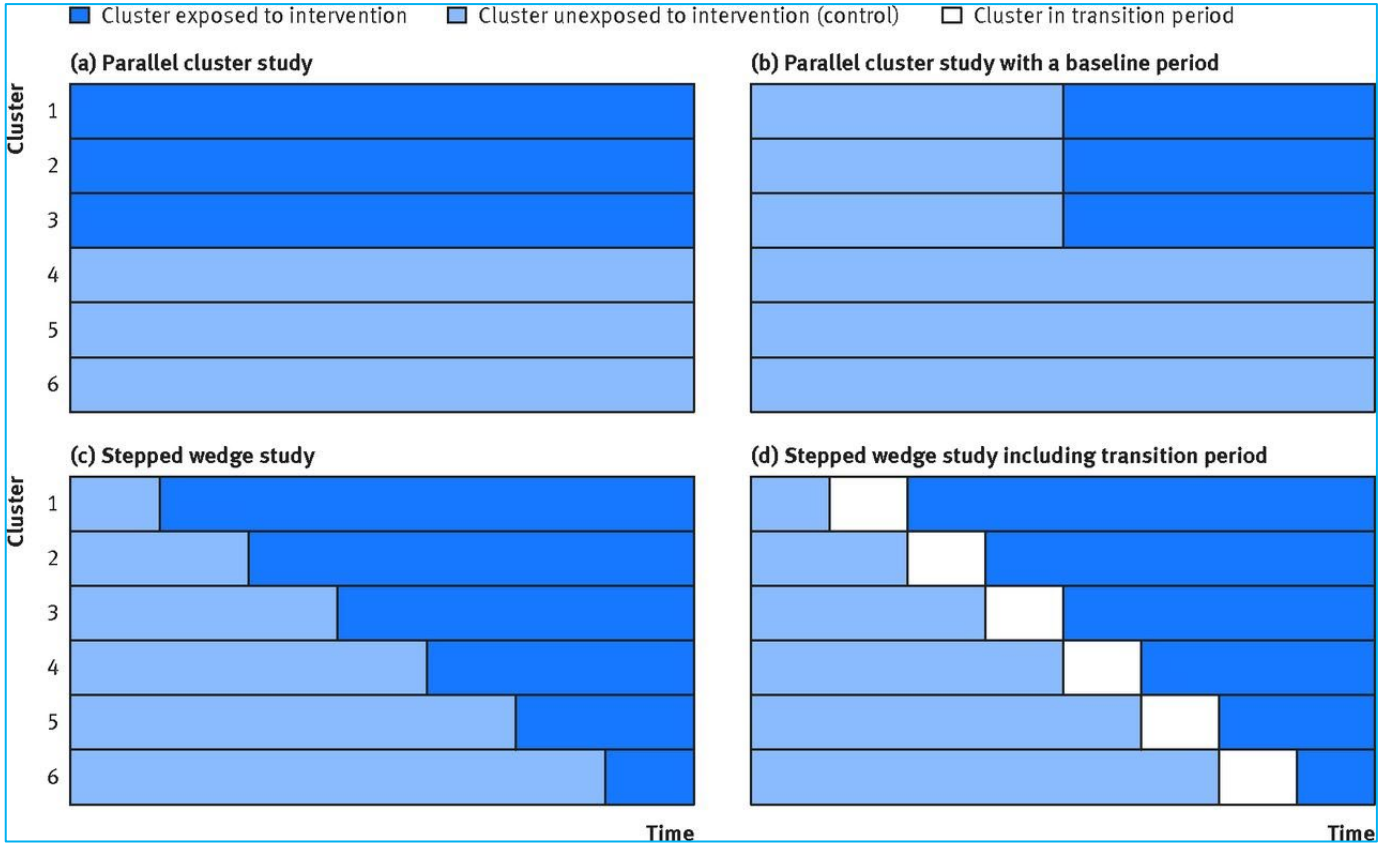
Cluster Randomized Trial

- Groups of individuals are randomly assigned to intervention or control group

- When to use
  - When intervention is applied to a group
  - To prevent contamination
  - For logistical or administrative purposes

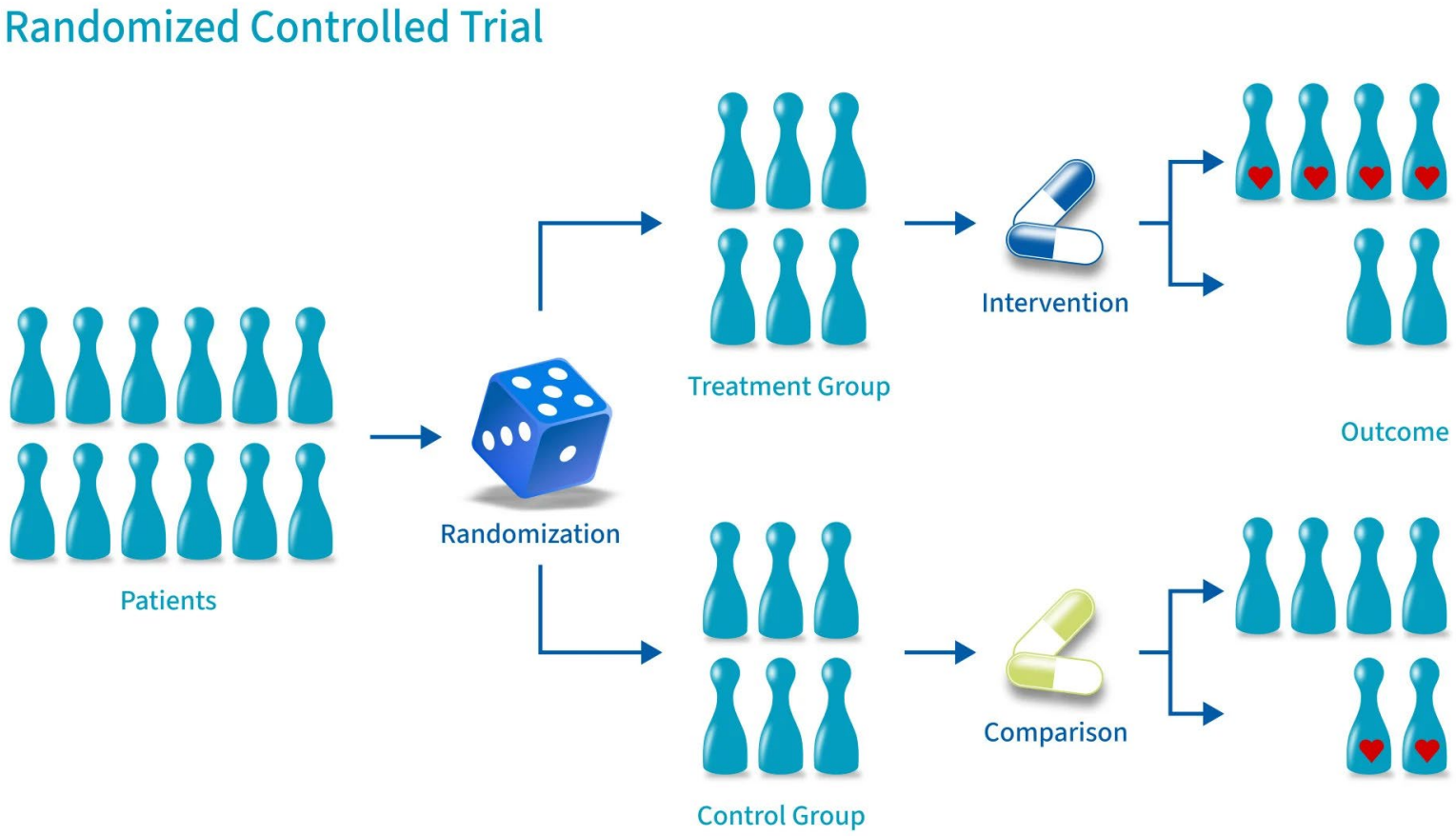
- Design types
  - Parallel
  - Stepped wedge



Randomized Clinical Trial Definition

- Scientific study in which participants are assigned by chance (randomization) to one of two or more treatment or intervention groups

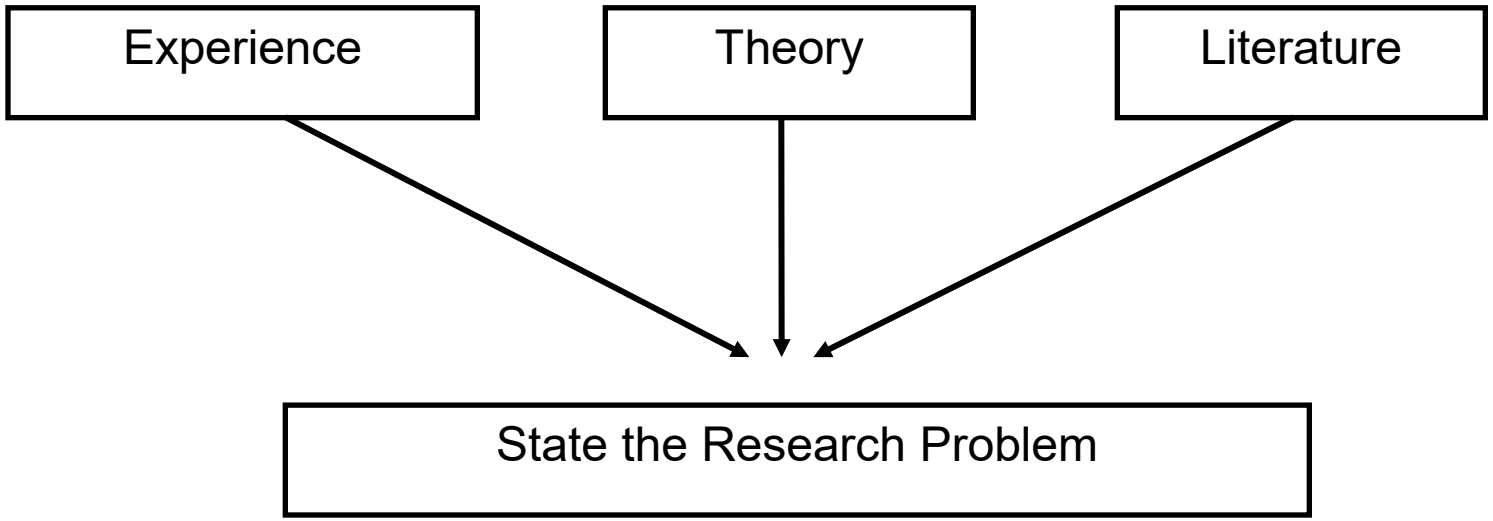
- Key features
  - Random assignment
  - Comparison groups
  - Blinding
  - Outcome measurement



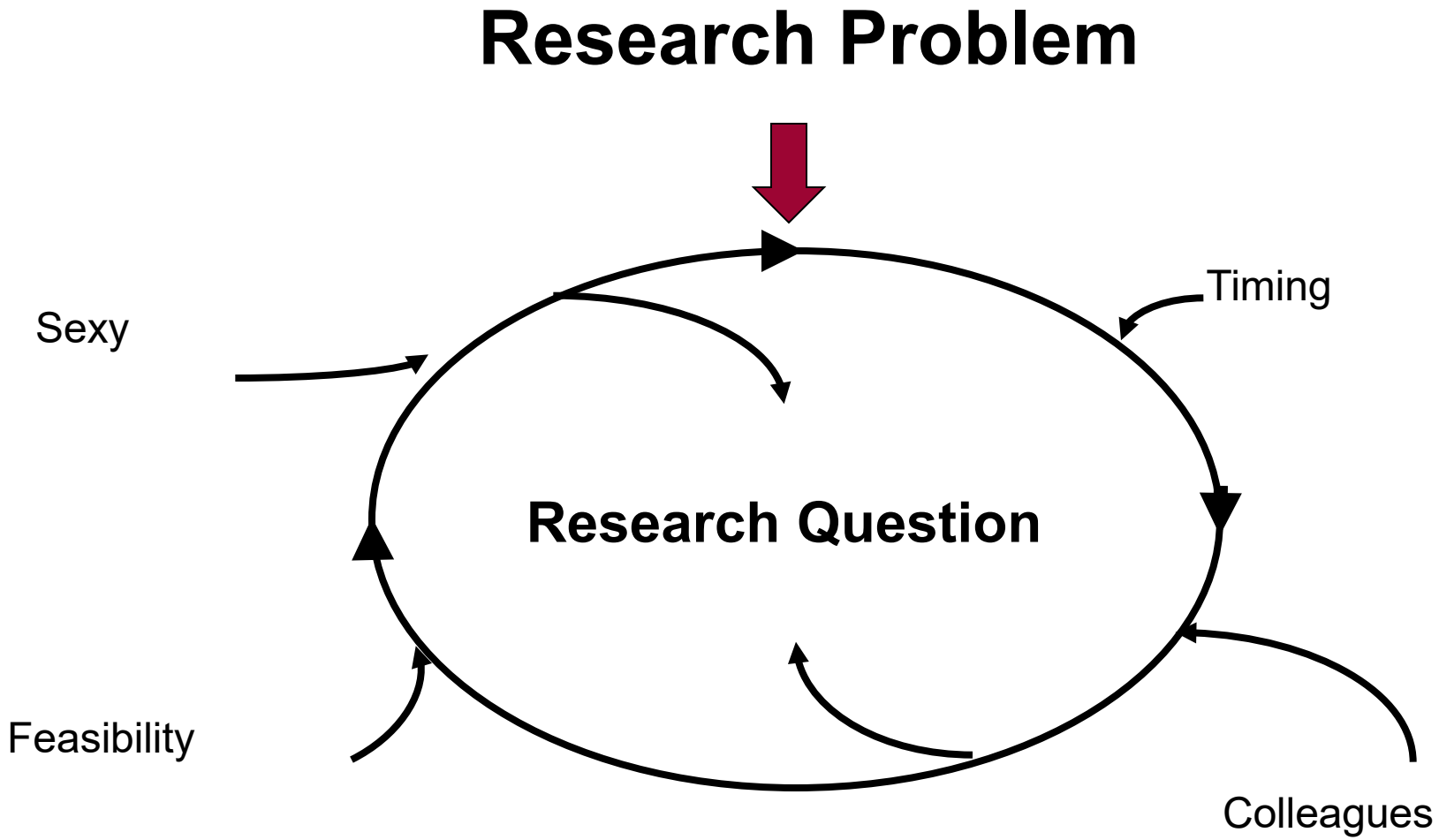
Randomized Clinical Trial Design Details

Primacy of the Research Question

Where do questions come from?



Define/Refine a Research Question



Literature

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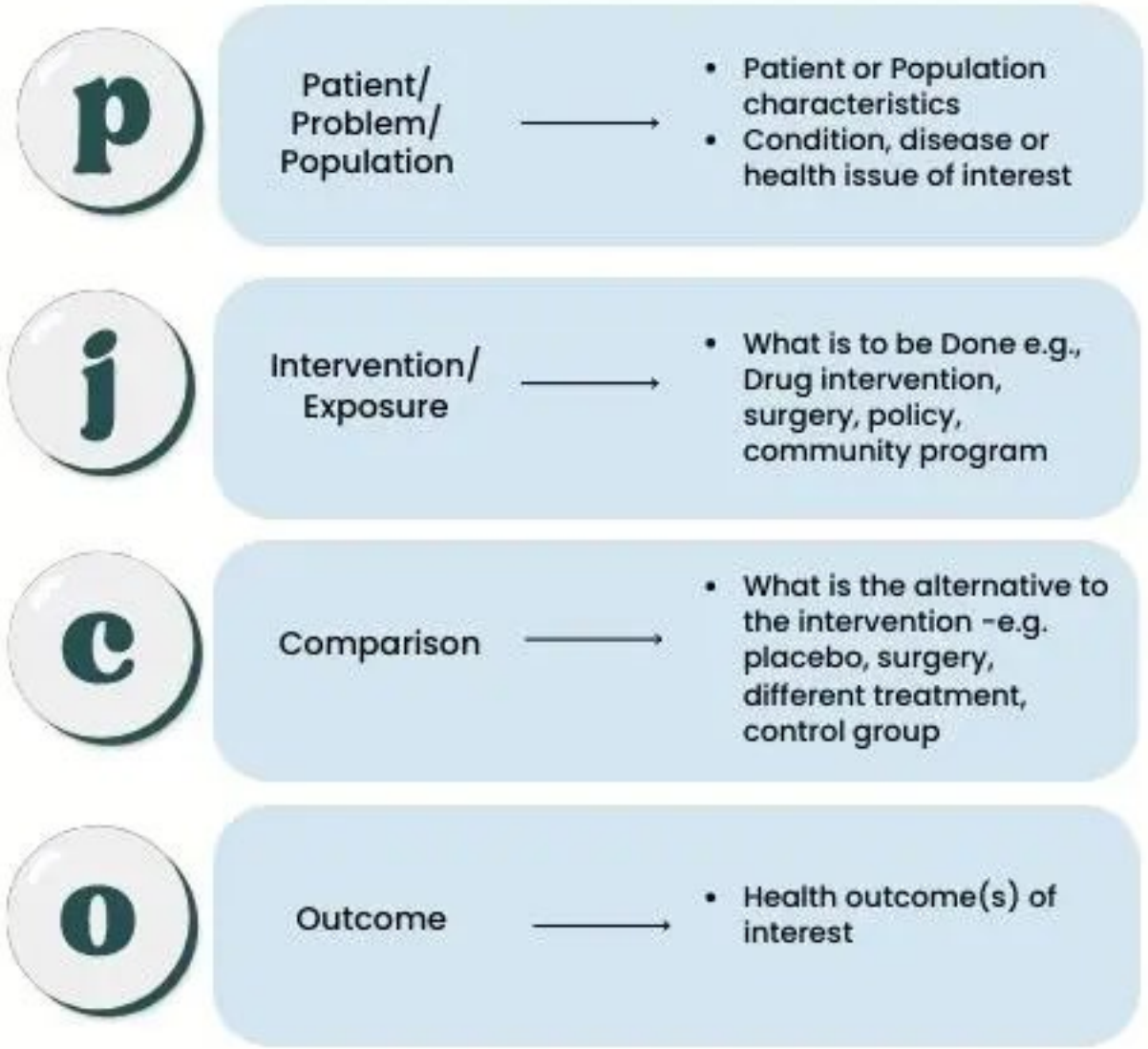
The Research Question



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multidose Ondansetron after Emergency Visits in Children with Gastroenteritis

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ABSTRACT

BACKGROUND

Ondansetron improves outcomes when administered in emergency departments to children with acute gastroenteritis–associated vomiting. It is commonly prescribed at discharge to reduce symptoms, but evidence to support this practice is limited.

METHODS

We conducted a double-blind, randomized superiority trial involving children 6 months to less than 18 years of age with acute gastroenteritis–associated vomiting in six pediatric emergency departments. Caregivers were provided with six doses of oral ondansetron or placebo to administer in response to ongoing vomiting during the first 48 hours after enrollment. The primary outcome was moderate-to-severe gastroenteritis, defined by a score of 9 or higher on the modified Vesikari scale (scores range from 0 to 20, with higher scores indicating greater severity), during the 7 days after enrollment. Secondary outcomes included the presence of vomiting, the duration of vomiting (defined as the time from enrollment to the last vomiting episode), the number of vomiting episodes within 48 hours after enrollment, unscheduled physician visits within 7 days after enrollment, and receipt of intravenous fluids.

Freedman, NEJM, 2025

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Eligibility Criteria – Key Considerations

- **Scientific Objectives and Study Design**
  - Target population
  - Minimizing confounding
  - Homogeneity vs. Generalizability
- **Participant Safety and Risk**
  - Risk-Benefit Assessment
  - Vulnerable Populations - children, elderly, pregnant/lactating women
  - Ability to consent - understand study details, risks, and benefits
- **Ethical and Regulatory Requirements**
  - Fair and equitable Selection
  - Diversity representation
- **Operational and Practical Feasibility**
  - Overly restrictive criteria can hinder recruitment
  - Ensure screening data criteria are available
  - Consider ability to meet study requirements

Multi-Dose Ondansetron Study

Inclusion

- 6 months - < 18 years of age
- Diagnosis of acute gastroenteritis
- 3 vomit episodes within 24 hours
- Symptom onset < 72 hours ago
- Vomit during 6 hours pre-enrollment
- Received ondansetron as part of ED care

Exclusion

- Hematemesis
- Bilious vomiting
- Allergy to ondansetron, serotonin receptor antagonist, ingredient of active/placebo meds
- Long QT syndrome or ventricular arrhythmia in participant or 1st degree relative
- Complex congenital heart disease
- G6PD deficiency
- Taking medication that prolongs the QT interval
- Previously enrolled in the trial
- No commitment to complete follow-up

Methods of Bias Reduction

Design

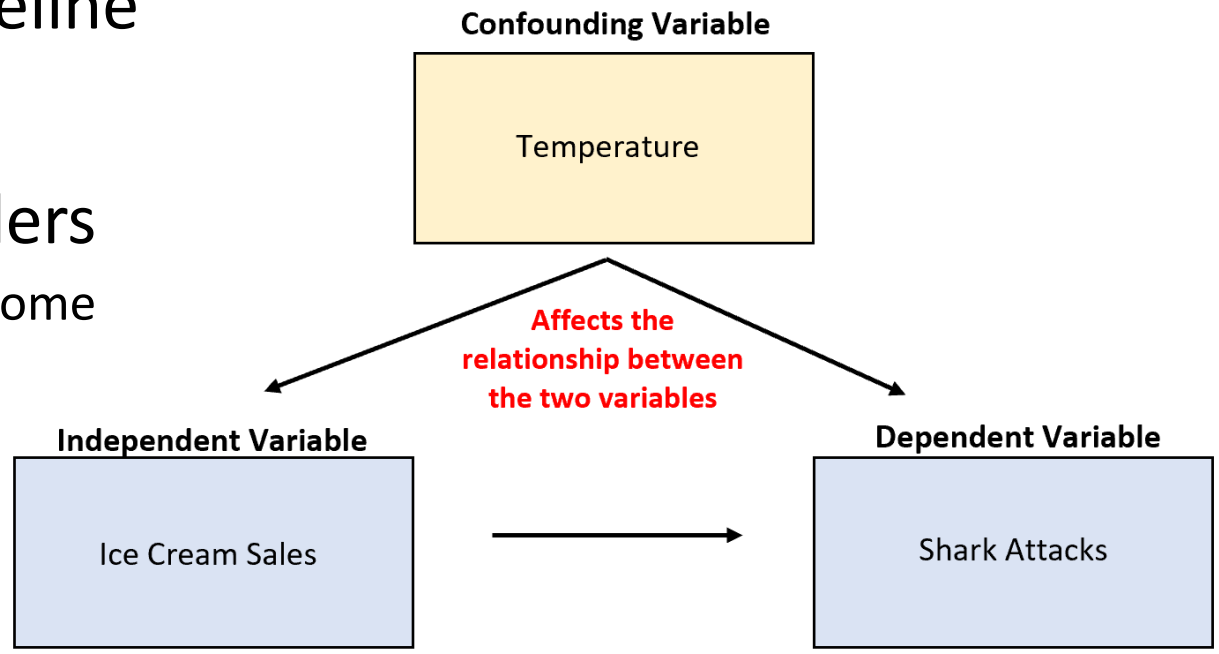
- Randomized treatment allocation
- Allocation concealment
- Blinding/Masking
- Completeness of data collection
- Completeness of follow-up

Analysis

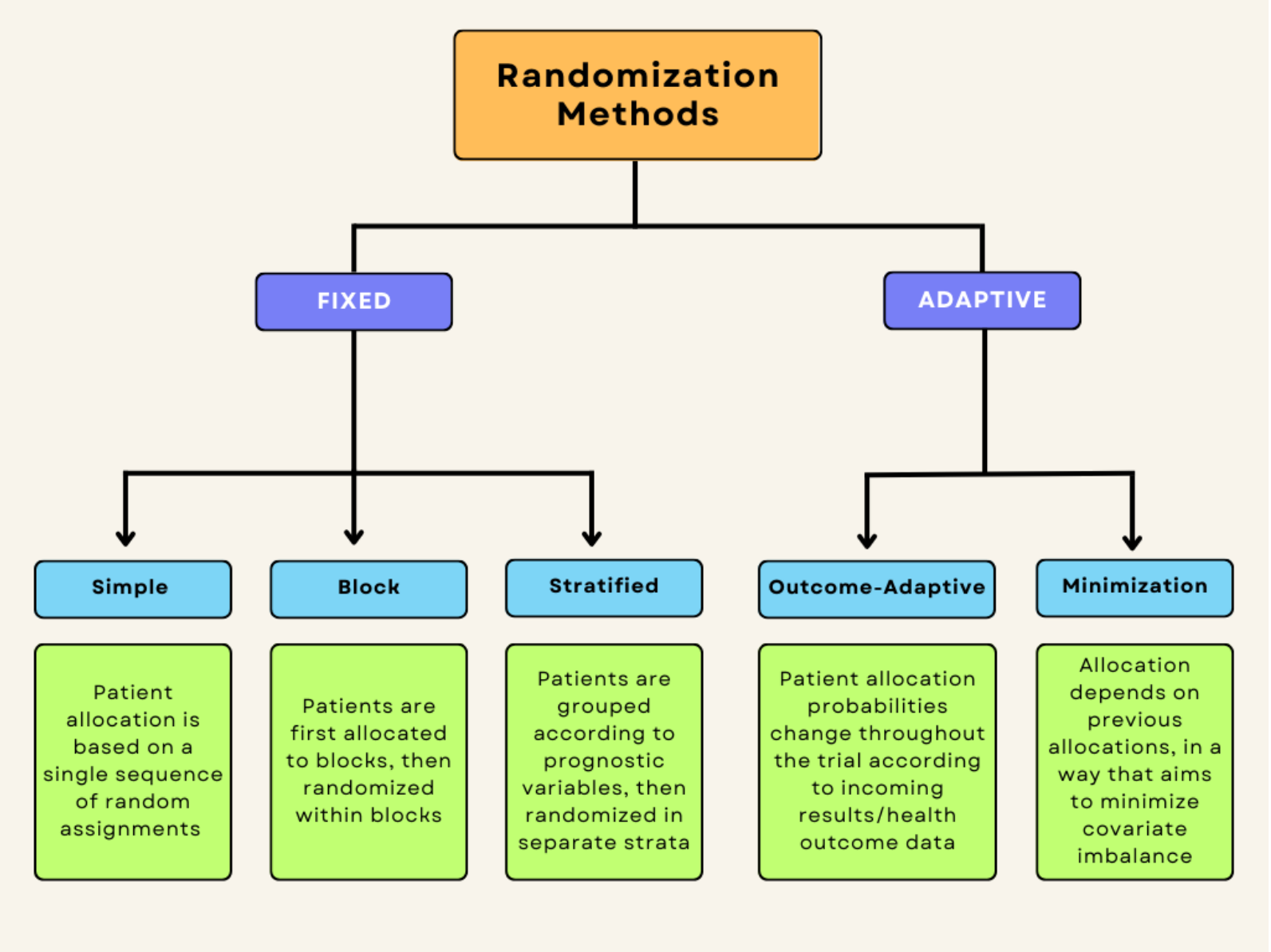
- Intention to treat versus per protocol

The Magic of Randomization

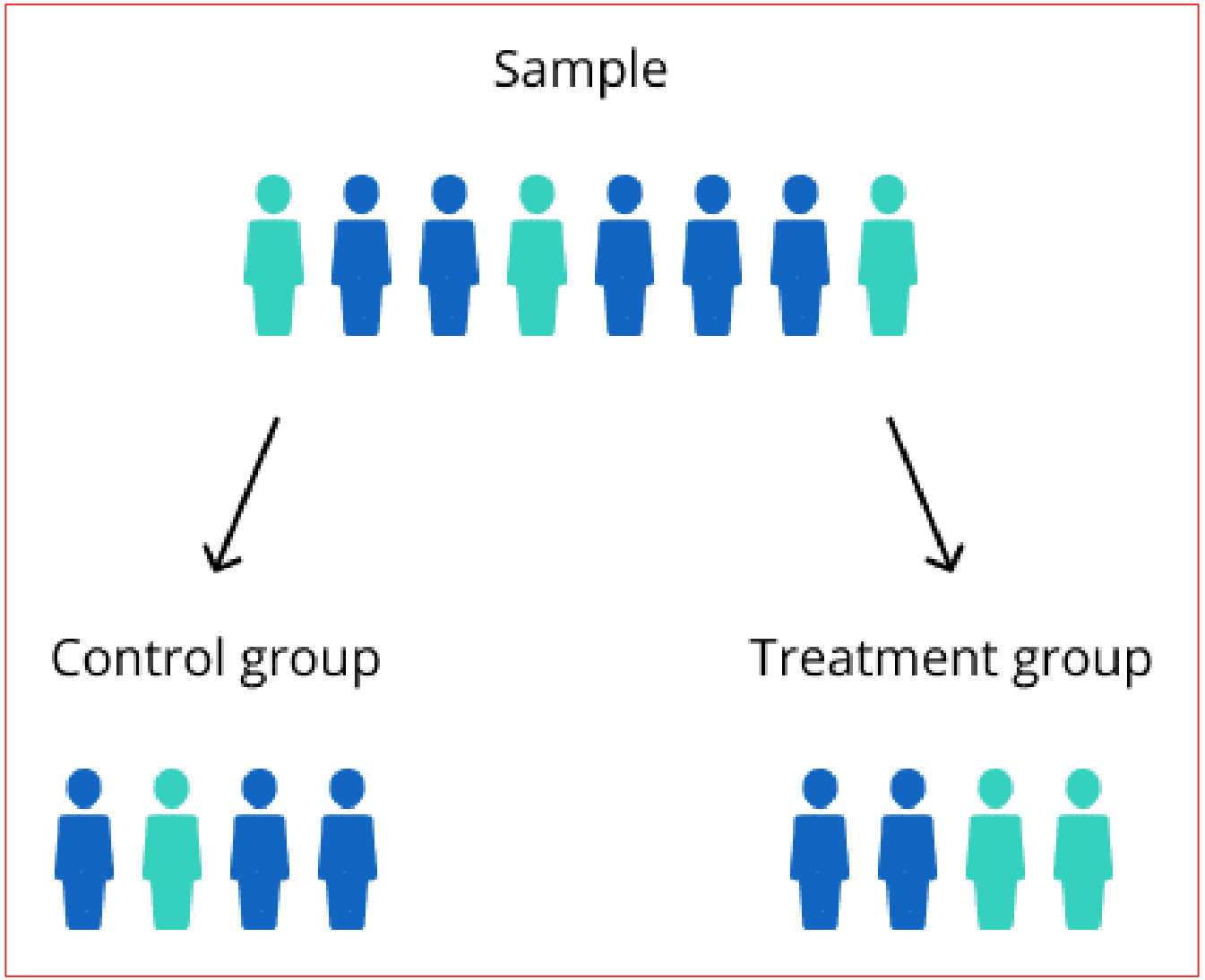
- Minimizes selection bias
  - Prevents assigning participants with specific prognoses to a particular treatment
  - Every participant has an equal chance of being in any group
  - Removes systematic differences in baseline characteristics that could skew results
- Ensures groups are comparable at baseline
- Balances known & unknown confounders
  - Confounding variable: factor that influences outcome independent of treatment



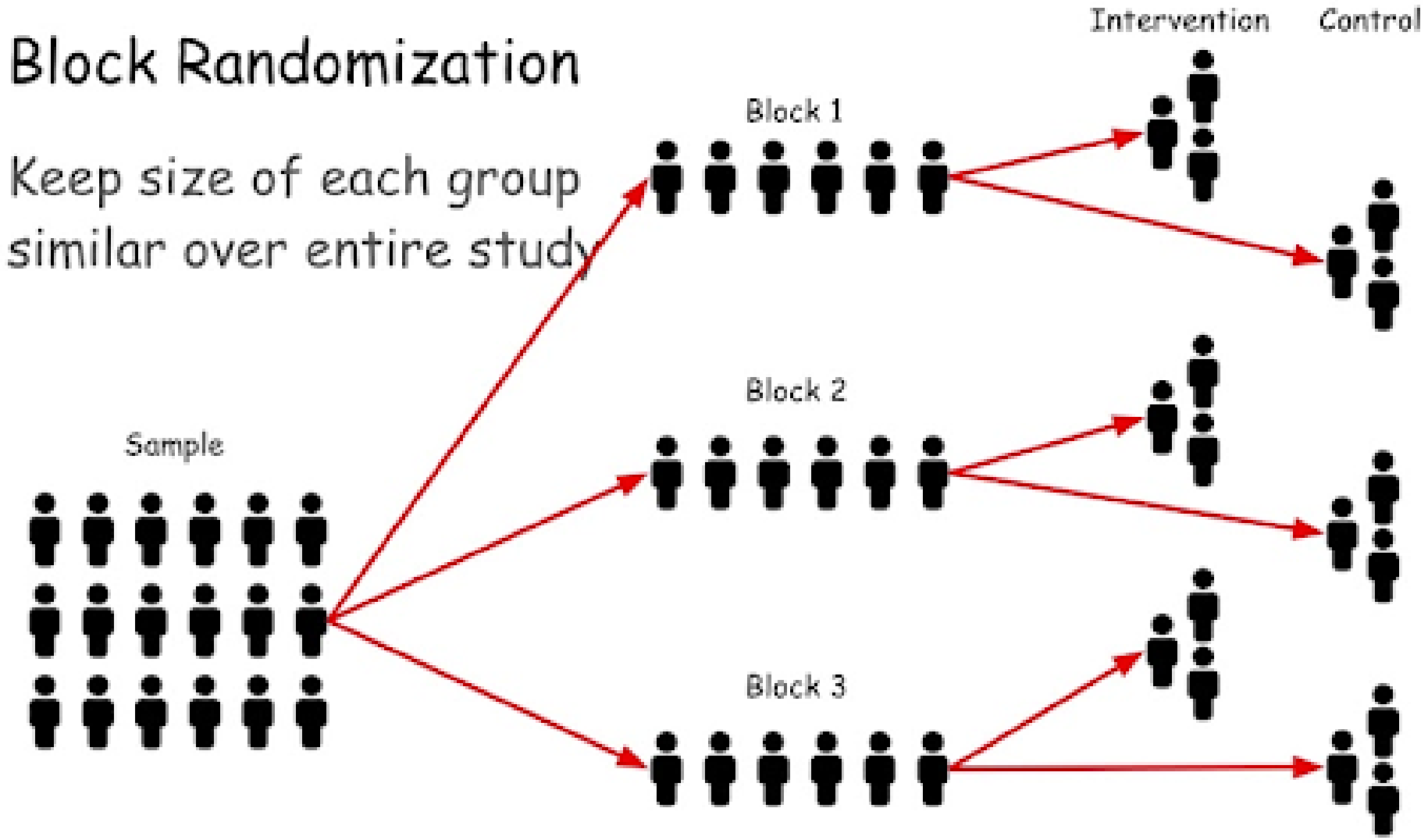
Types of Randomization



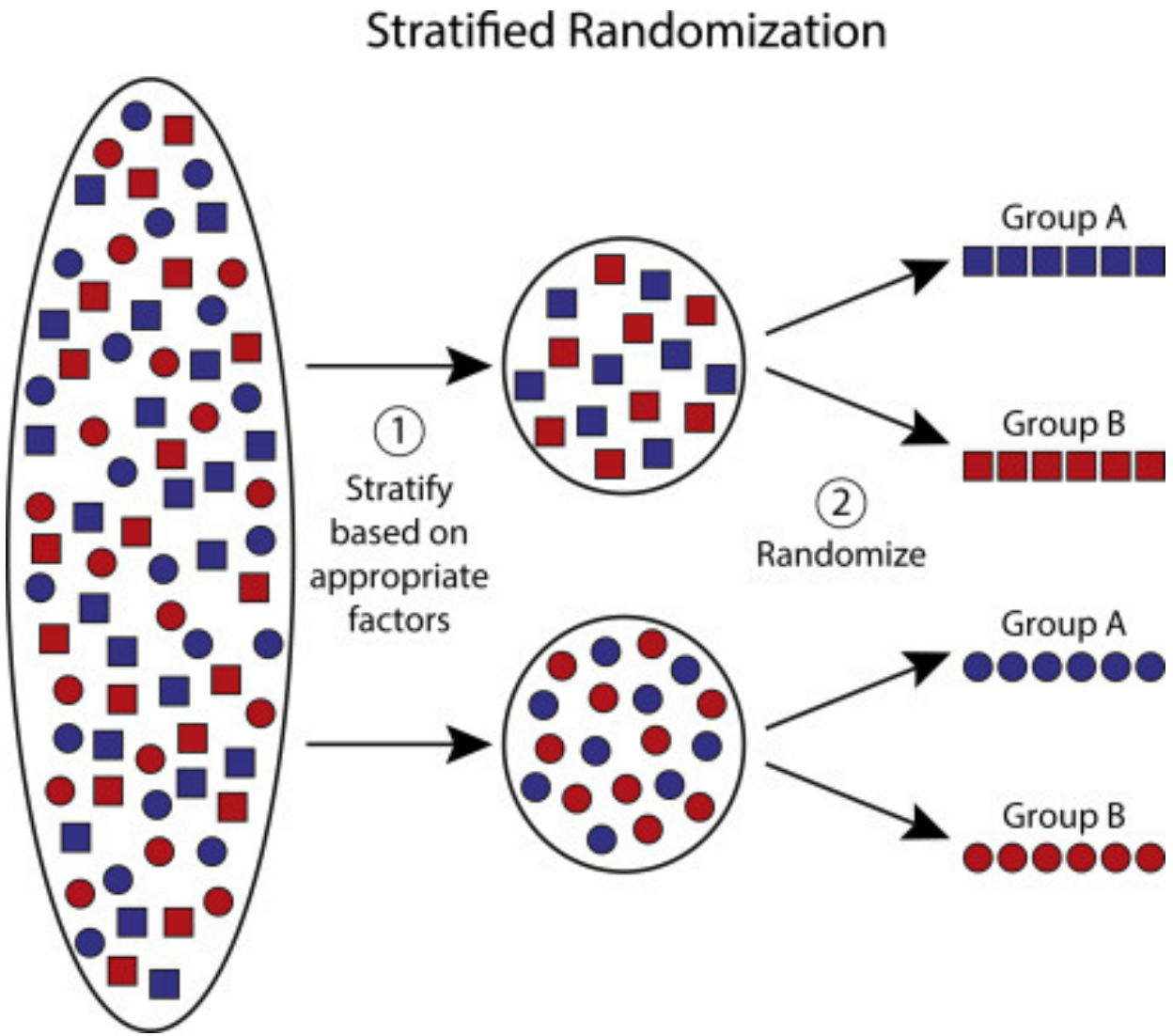
Simple Randomization



Block Randomization



Stratified Randomization



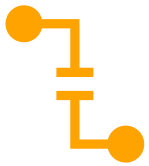
Allocation Concealment

Allocation Concealment

Process of protecting randomization sequence

Prevent selection bias before participants are enrolled

Ensures that researchers and participants cannot predict/influence who gets assigned to which treatment group.



Methods

Central randomization by a third party – www.randomize.net

Sequentially numbered, opaque, sealed envelopes

- Tampering and subversion
- Predictability
- Transillumination

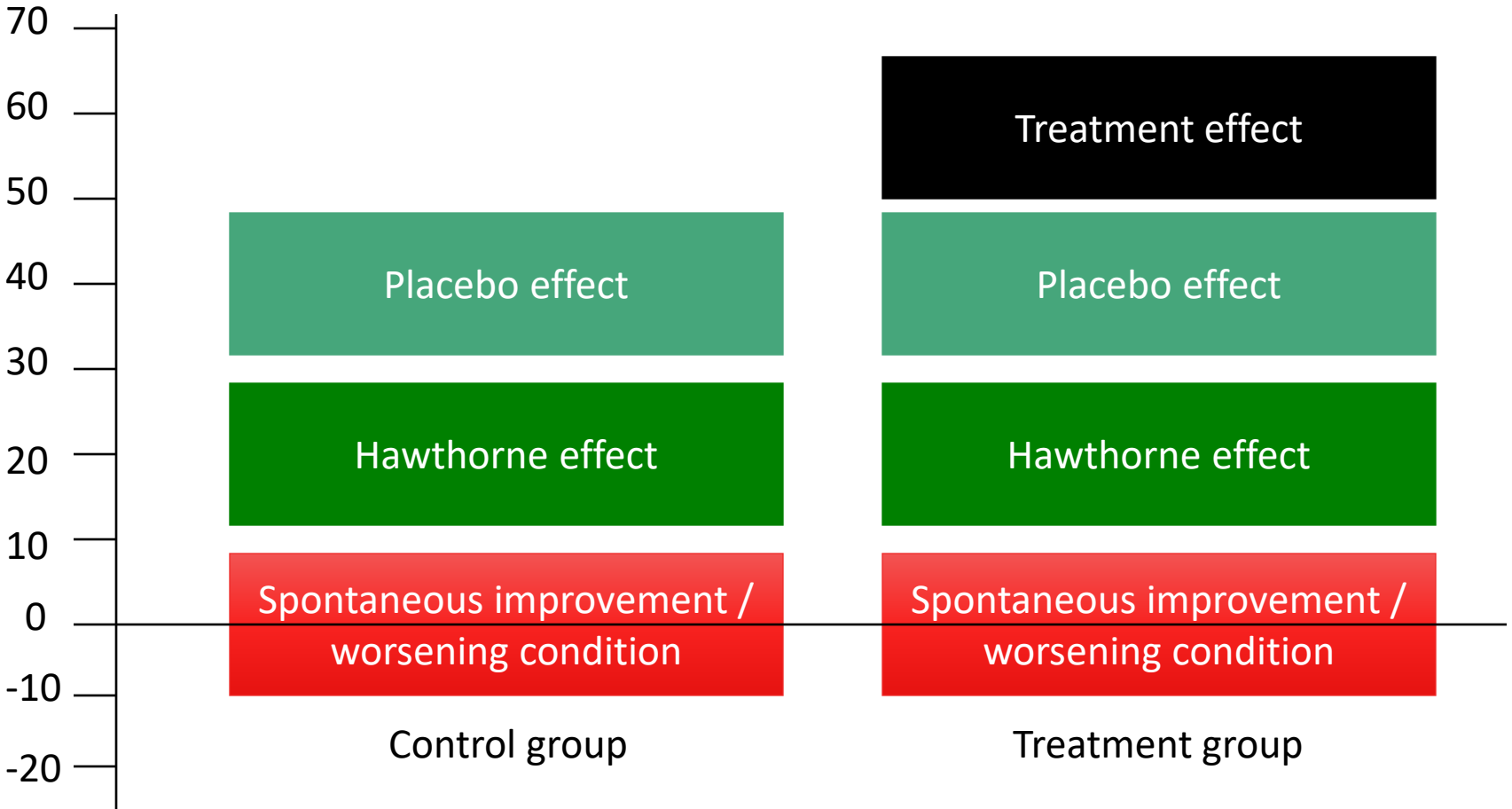
Distinct from blinding

Occurs after enrollment

Hides treatment assignment from participants and researchers

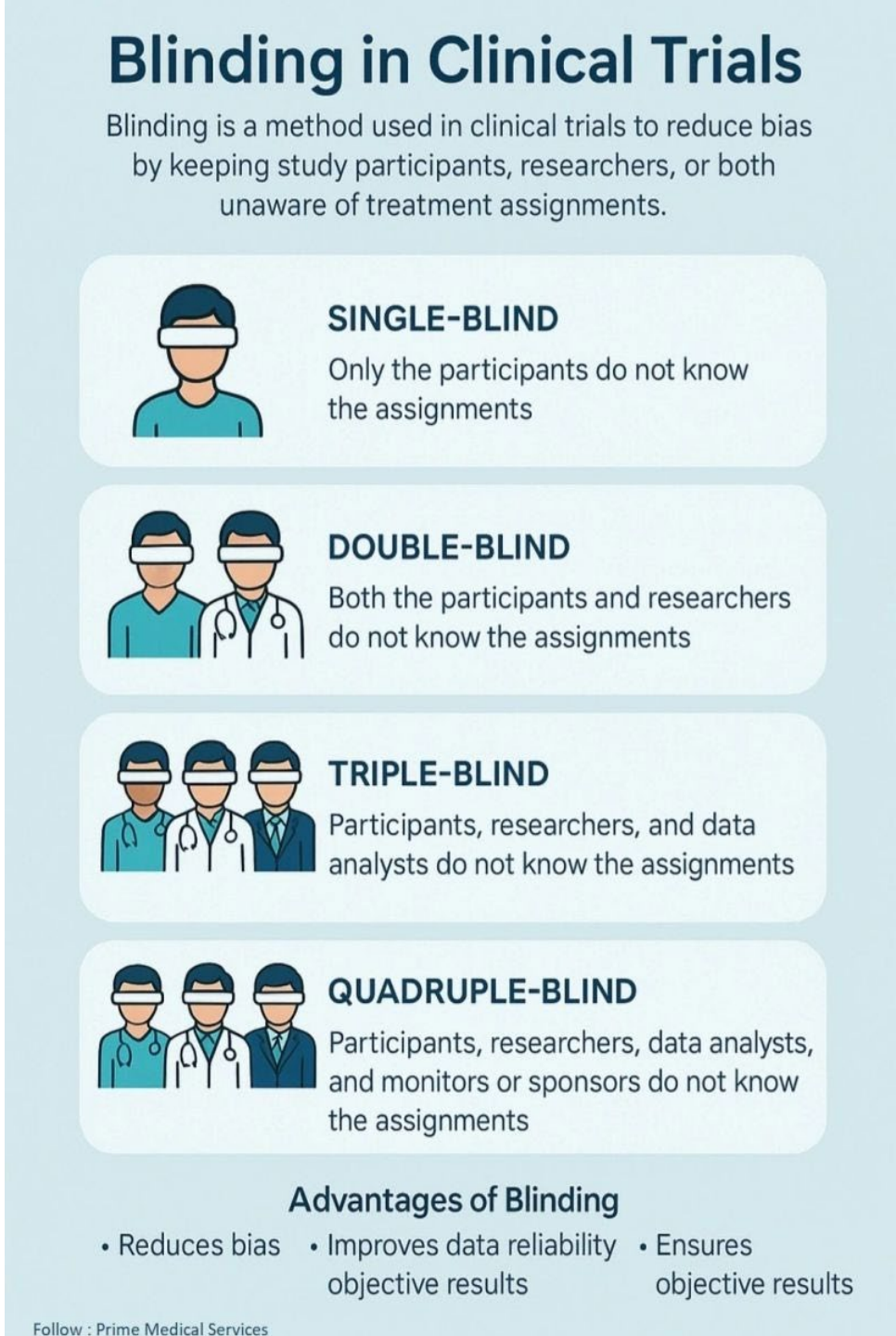
Rationale for Blinding

Allows for quantification of actual treatment effect size



Blinding

- Concealing information about which participants are receiving which treatments
- Reduces bias
  - Prevents participants from changing their behavior
  - Prevents influence on researcher assessments & interactions
- Increases objectivity
  - Eliminates subjective components
- Ensures credibility
  - Ensures knowledge of intervention does not influence assessment of outcomes



How Blinding is Acheived

Placebo	Inactive substance or sham intervention Similar appearance, smell, taste
Coding group assignments	Assign codes to treatment groups so assignment is hidden until the study is complete
Specialized equipment	Use opaque tubing or plastic sleeves for infusion bags to hide the contents

Types of Control Groups

Placebo Control Group

- "dummy" treatment/no active ingredients, physically identical to experimental treatment
- Goal is to account for placebo effect

Active Control Group

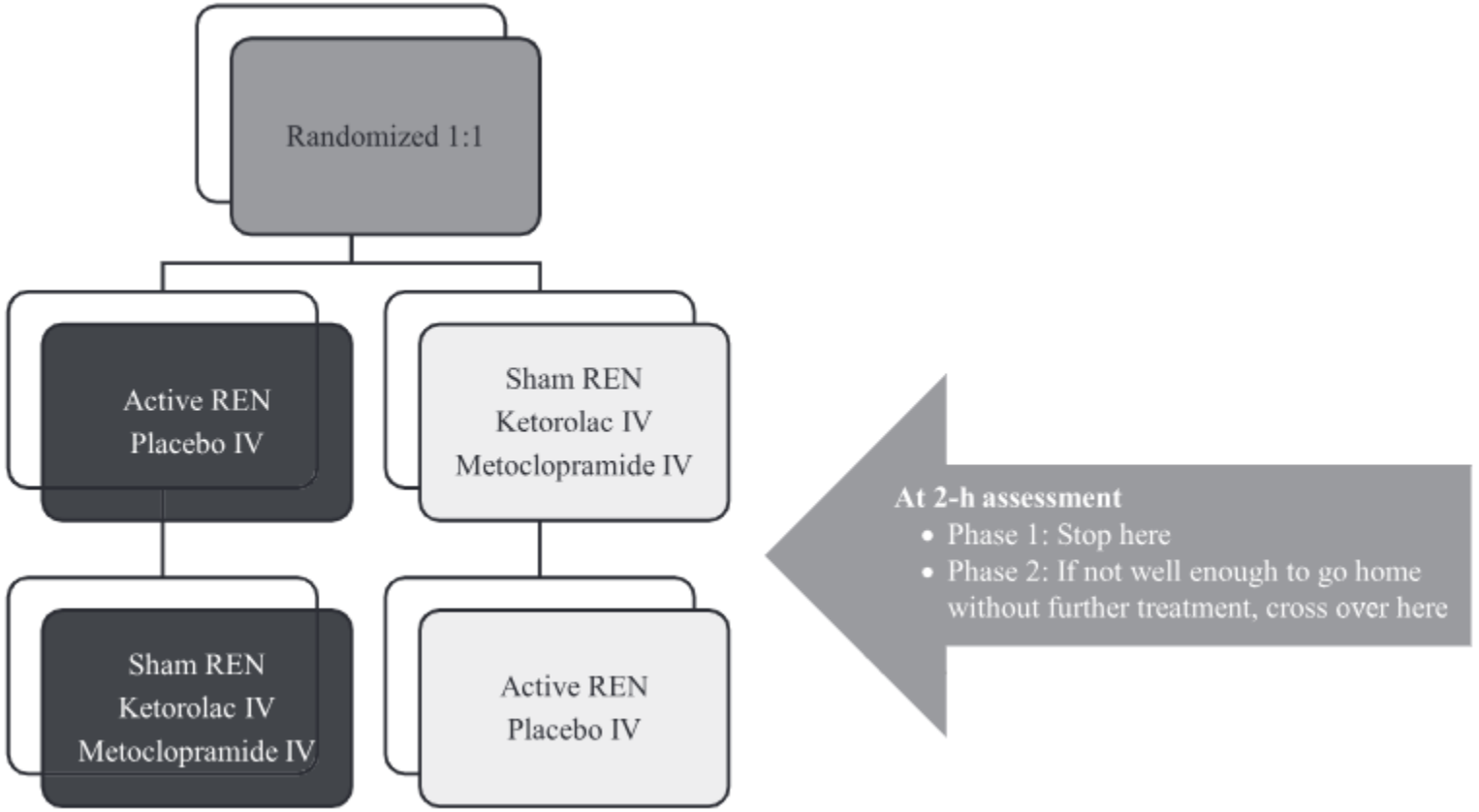
- New treatment is compared against existing/known effective treatment/standard of care
- Used when it is unethical to withhold an effective treatment

No-Treatment Control Group

- Participants in this group receive no intervention at all
- Used when objective outcomes are measured, blinding is impractical/impossible, and no standard treatment exists

Double Dummy Design

- When you need to double-blind a study comparing two active treatments that have different appearances
  - Two active drugs
  - Different dosage forms



Orr. Headache, 2025

Incomplete Data

Introduces bias and reduces reliability of findings

Participant-related reasons

- Withdrawal
- Missed visits
- Non-adherence
- Refusal to respond

Study-related reasons

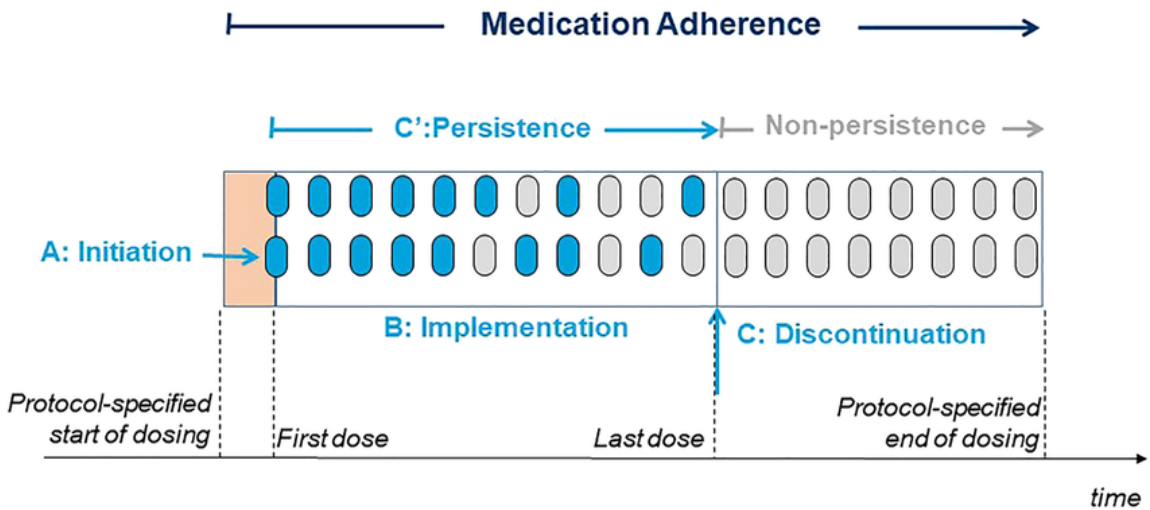
- Data collection and recording errors
- Investigator/clinician decisions
- Endpoint assessment challenges

Trial design

- Longer trials
- Pragmatic trials – rely on real-world data

Non-Adherence

- Participants fail to follow the protocol
- Phases
  - Non-initiation
    - Participant does not take first dose of the allocated drug
  - Suboptimal implementation
    - Participant takes wrong dose, misses doses, takes medication at the wrong times
  - Non-persistence
    - Participant prematurely discontinues investigational drug
- Consequences
  - Skewed results and reduced power
  - Compromised safety evaluation
  - Wasted resources



Loss to Follow-Up

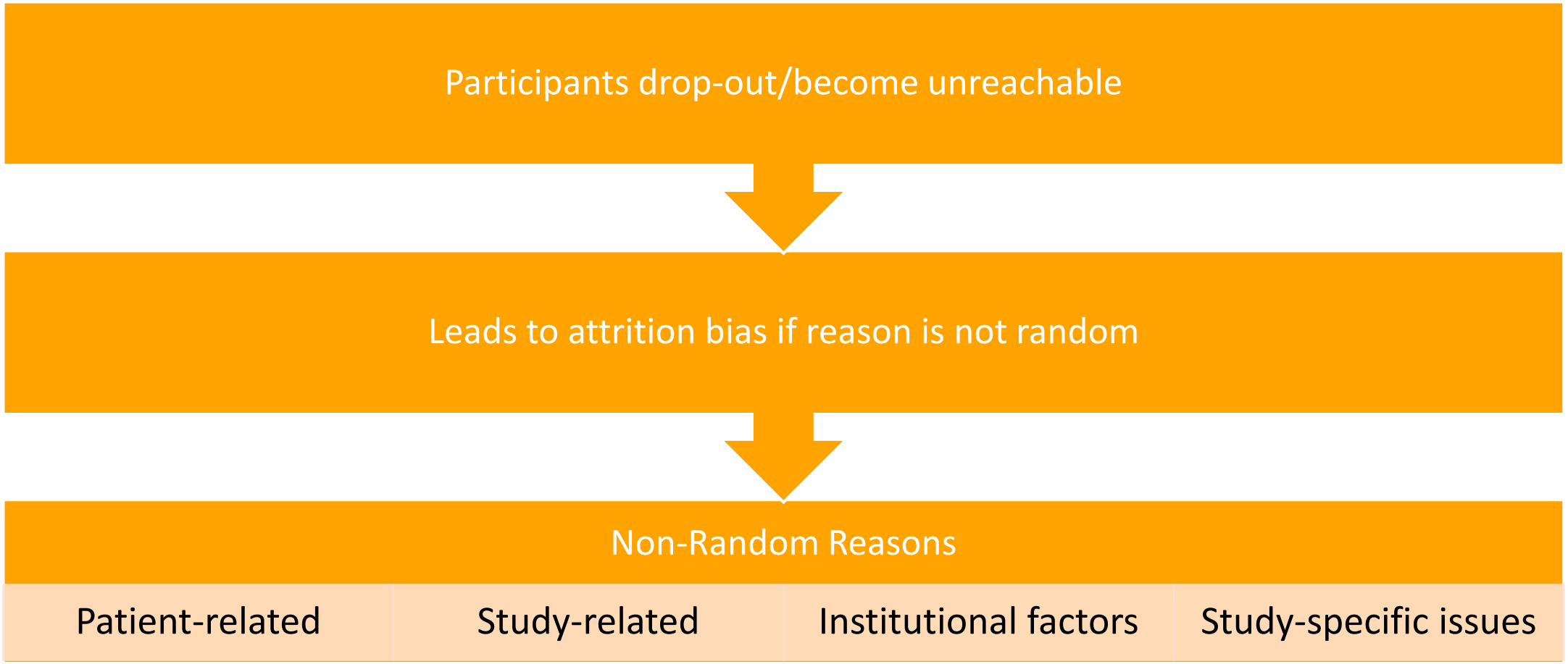


Table 1. Eight Ideas for Limiting Missing Data in the Design of Clinical Trials.

Target a population that is not adequately served by current treatments and hence has an incentive to remain in the study.
Include a run-in period in which all patients are assigned to the active treatment, after which only those who tolerated and adhered to the therapy undergo randomization.
Allow a flexible treatment regimen that accommodates individual differences in efficacy and side effects in order to reduce the dropout rate because of a lack of efficacy or tolerability.
Consider add-on designs, in which a study treatment is added to an existing treatment, typically with a different mechanism of action known to be effective in previous studies.
Shorten the follow-up period for the primary outcome.
Allow the use of rescue medications that are designated as components of a treatment regimen in the study protocol.
For assessment of long-term efficacy (which is associated with an increased dropout rate), consider a randomized withdrawal design, in which only participants who have already received a study treatment without dropping out undergo randomization to continue to receive the treatment or switch to placebo.
Avoid outcome measures that are likely to lead to substantial missing data. In some cases, it may be appropriate to consider the time until the use of a rescue treatment as an outcome measure or the discontinuation of a study treatment as a form of treatment failure.

Little, NEJM, 2012

Table 2. Eight Ideas for Limiting Missing Data in the Conduct of Clinical Trials.

Select investigators who have a good track record with respect to enrolling and following participants and collecting complete data in previous trials.
Set acceptable target rates for missing data and monitor the progress of the trial with respect to these targets.
Provide monetary and nonmonetary incentives to investigators and participants for completeness of data collection, as long as they meet rigorous ethical requirements.[15,16]
Limit the burden and inconvenience of data collection on the participants, and make the study experience as positive as possible.
Provide continued access to effective treatments after the trial, before treatment approval.
Train investigators and study staff that keeping participants in the trial until the end is important, regardless of whether they continue to receive the assigned treatment. Convey this information to study participants.
Collect information from participants regarding the likelihood that they will drop out, and use this information to attempt to reduce the incidence of dropout.
Keep contact information for participants up to date.

Little, NEJM, 2012

Ethical Considerations When Standard Therapy Exists

- Controversial because it may deprive participants of effective care
- Declaration of Helsinki
  - States that participants should receive **best proven intervention** available
- Equipoise
  - Research is considered ethical if there is uncertainty about which treatment is better or whether any treatment works at all
  - If a standard therapy is **known** to be effective, equipoise is violated by using a placebo group that receives no active treatment
- Solutions
  - Active-Controlled Trials
  - "Add-on" Designs
  - "Rescue" therapy

Outcome Measures

Primary

Most important measure used to determine success

Main variable that the study is designed to test

Basis for sample size calculations

Secondary outcomes

Additional measures that provide supporting evidence or extra information

- E.g., Safety data or long-term effects

Do not drive design or sample size

Outcome Measures – Key Considerations

Clinically meaningful

Should reflect a meaningful change in health

Directly related to study objective

Should be important for making decisions regarding an intervention

Objective

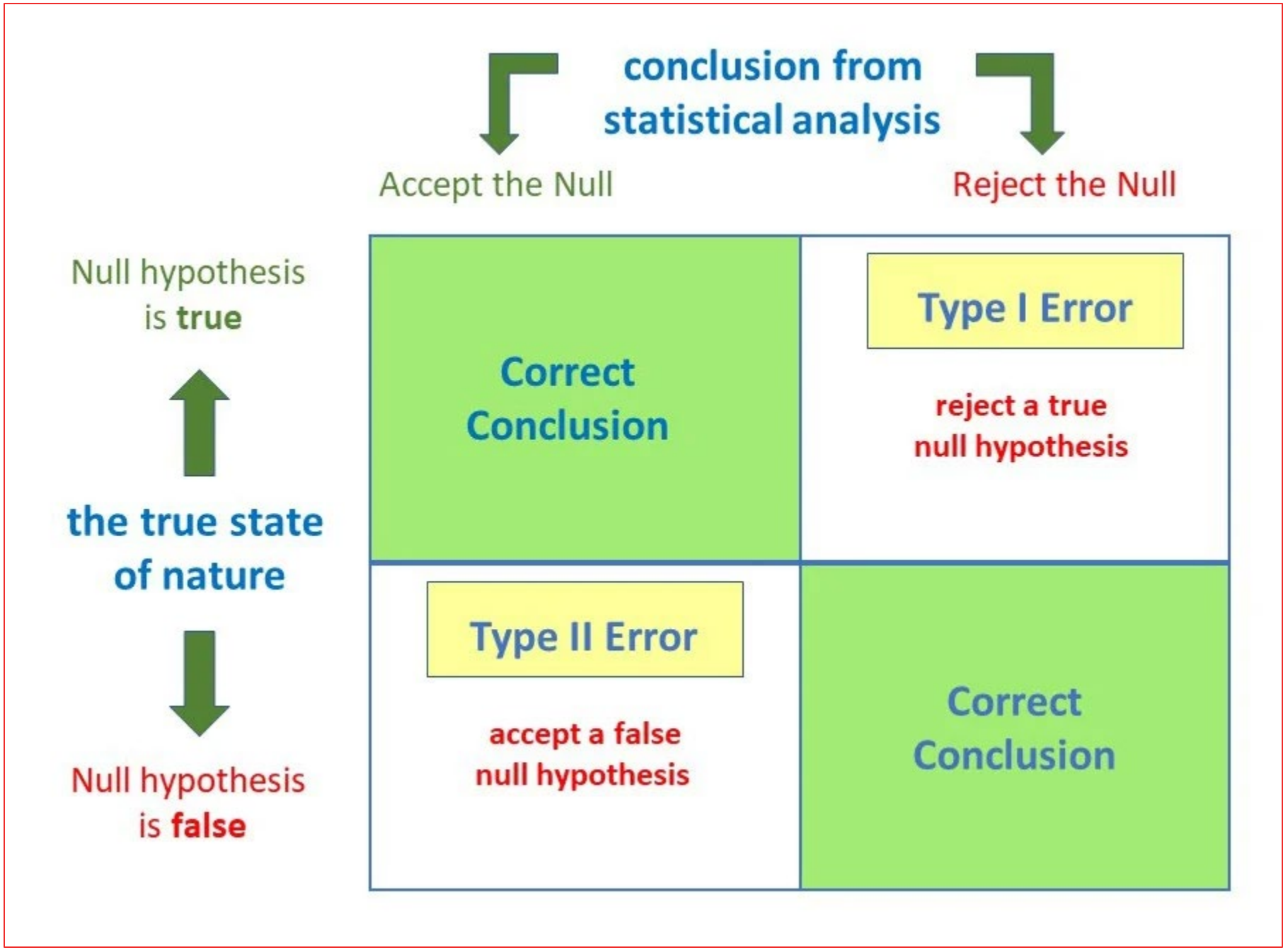
Free from bias of researcher & patient

Clearly defined and measurable

Validation

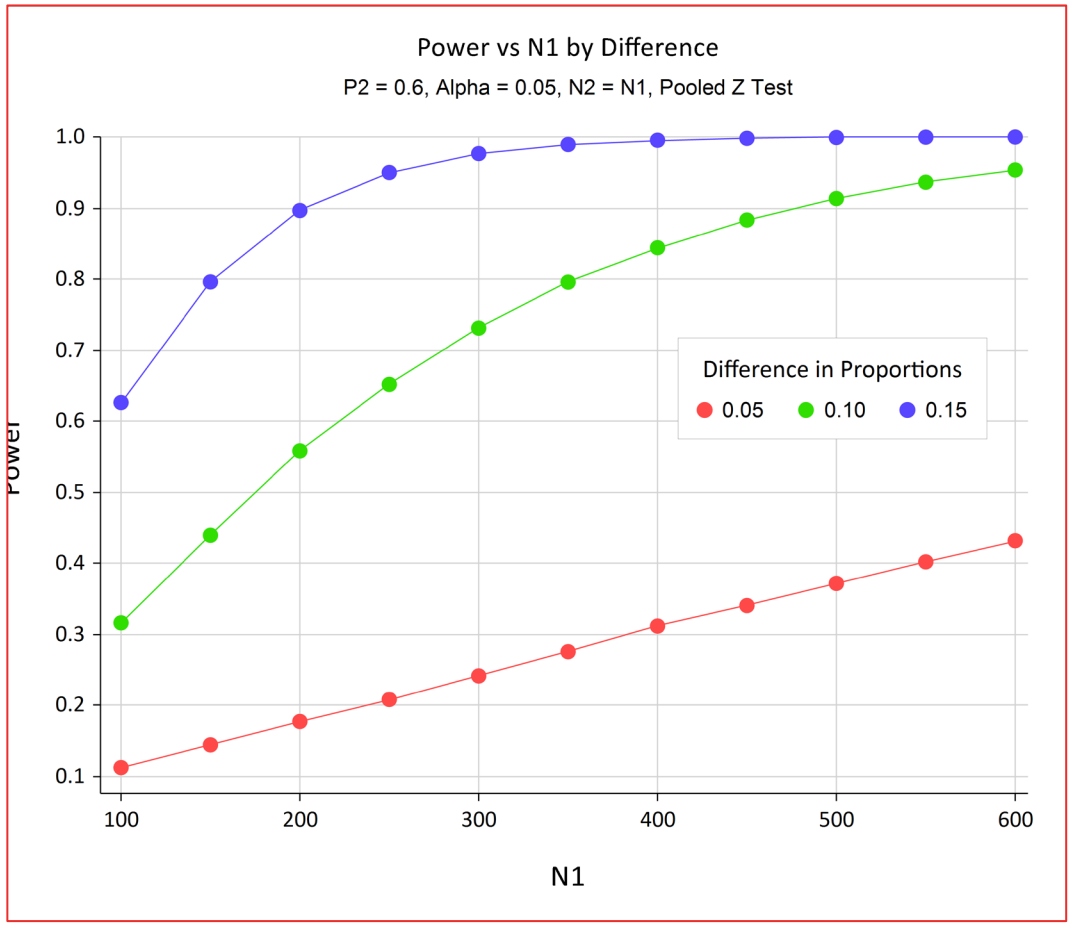
Accurate and consistently measure the concept it is designed to assess

Previously tested/validated scales/tests


conclusion from statistical analysis
Accept the Null
Reject the Null
Null hypothesis is true
the true state of nature
Null hypothesis is false
Correct Conclusion
Type I Error
reject a true null hypothesis
Type II Error
accept a false null hypothesis
Correct Conclusion

Sample Size & Power

- Sample size
  - Number of participants needed to detect a significant difference between groups
- Power
  - Probability study will detect a true effect if one exists
- Larger sample size = higher power
- Sample size must be calculated before trial begins



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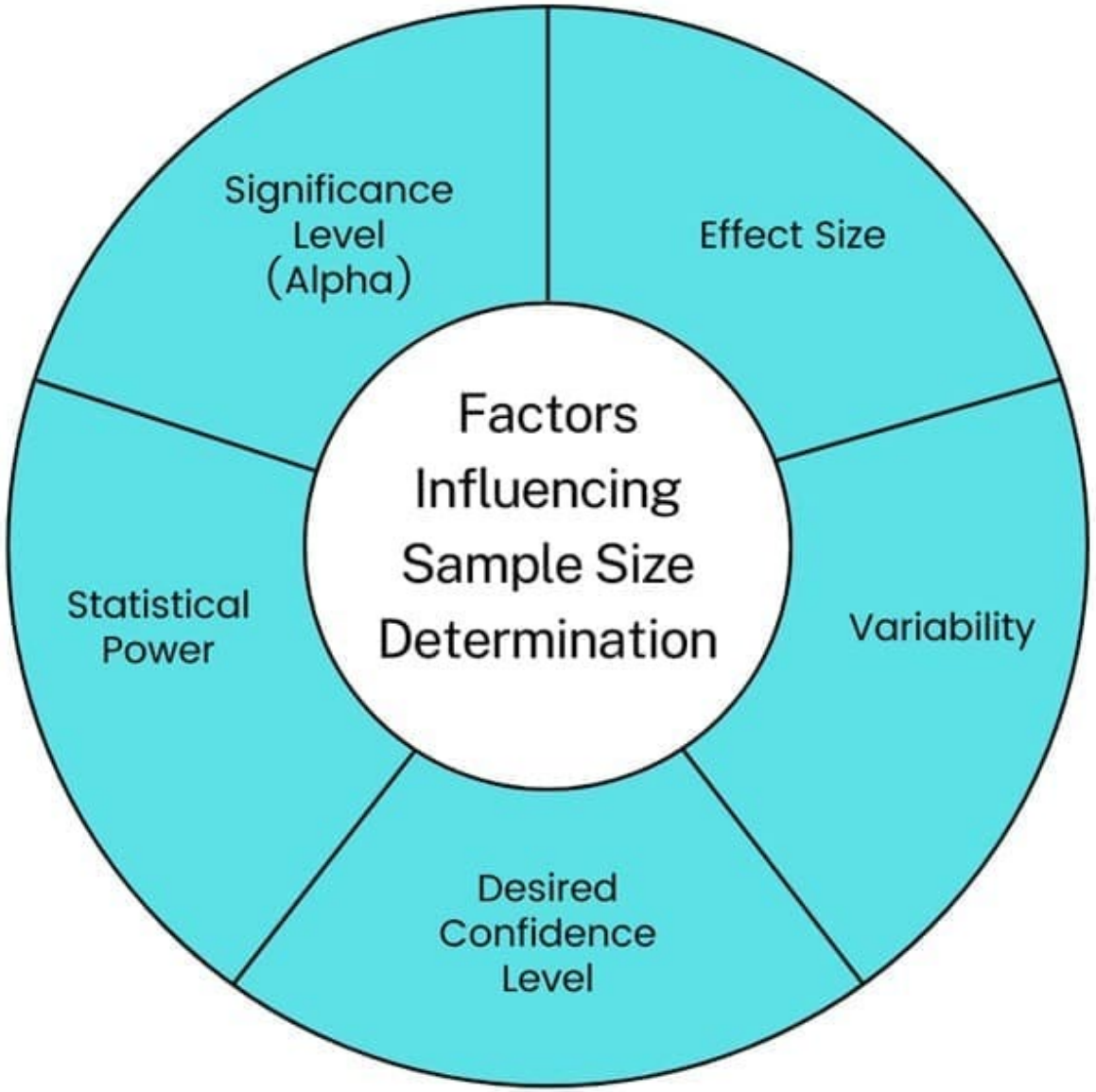
Probability of making a Type I error (false positive).
Lower significance levels require larger sample sizes.

Magnitude of difference study aims to detect.
Smaller effect sizes require larger sample sizes to achieve the same level of statistical power.



Probability of correctly rejecting null hypothesis when it is false.
Higher power increases likelihood of detecting a true effect and requires a larger sample size.

Extent of variability or dispersion in data.
Higher variability necessitates larger sample size to accurately estimate population parameters.

Probability that confidence interval contains true population parameter.
Higher confidence levels require larger sample sizes.

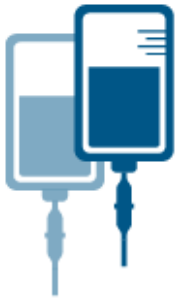
Pediatric Trials - Ethical and Consent Considerations

- Ethical and consent considerations - UofC guidelines (Microsoft Word - CHREB Guidance - Mature Minor and Assent - Dec2024)
  - <7 years of age: parental consent
  - 7 - <14 years of age: seek assent from child AND consent from parent/guardian
  - 14 – 17 years old: might be mature minors & can give full consent
    - Depends on decision-making capacity
- Family burden
  - Entire family is effectively enrolled
  - Fears and misconceptions may impede participation (e.g., no benefit, complex, cultural)
- Balancing risks & benefits
  - Protecting children from research risks while developing safe and effective treatments

Trials in Emergency Situations - Canada

- Deferred consent is acceptable if…
  - Serious threat – immediate intervention needed
  - Lack of standard of care or possible direct benefit
  - Risk vs. benefit – risk cannot be greater than standard of care
  - Inability to get timely consent

- Additional requirements
  - REB approval
  - Promptly seek consent
  - Not a substitute for full consent
  - Continued participant autonomy



PRoMPT BOLUS

PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FlUid in Sepsis

Pediatric Trials
Unique Design & Procedural Considerations

Adaptations for children	• Procedures and settings must be adapted to physical, emotional, and cognitive needs • Formulations that address dosing accuracy, palatability, ease of administration
Age-appropriate measures	• Outcome measures must be developmentally appropriate for different age group
Risk assessment	• REBs need to ensure a favourable risk-benefit ratio
Research setting	• Must be sensitive to the needs of child and family

Pediatric Trials
Scientific & Logistical Considerations

Physiological differences	• Children absorb, distribute, metabolize, and excrete drugs differently than adults
Developmental variation	• Physiological and cognitive development change rapidly across age groups
Small sample sizes	• Lower prevalence of many diseases can lead to underpowered studies
Long-term effects	• Trials may require long follow-up periods to assess developmental effects

Recruitment Barriers
Placebo

Patient concerns

Fear of receiving an inactive treatment

Perception that standard care is better

Desire for an active intervention

Ethical concerns and fear of being a "guinea pig“

Difficulty understanding informed consent

Clinician concerns

Equipoise

Aversion to perceived risk without benefit

Recruitment Barriers
Logistics

- Travel and distance
- Time commitment and scheduling
- Financial burden
- Complexity of procedure
- Resource and infrastructure issues at sites
- Investigational product management

Potential Limitations of RCTs

Practical & resource issues

- High cost and time
- Difficult for certain interventions
- Challenges with rare diseases

Validity & generalizability issues

- Selection and sampling bias → limited generalizability
- Lack of long-term data
- Challenges with blinding

Ethical & statistical issues

- Ethical concerns
- Statistical power limitations
- Difficulty assessing harms

Efficacy versus Effectiveness

Efficacy studies

Tightly controlled RCT!

Works there!

Therapy works in a tightly controlled environment

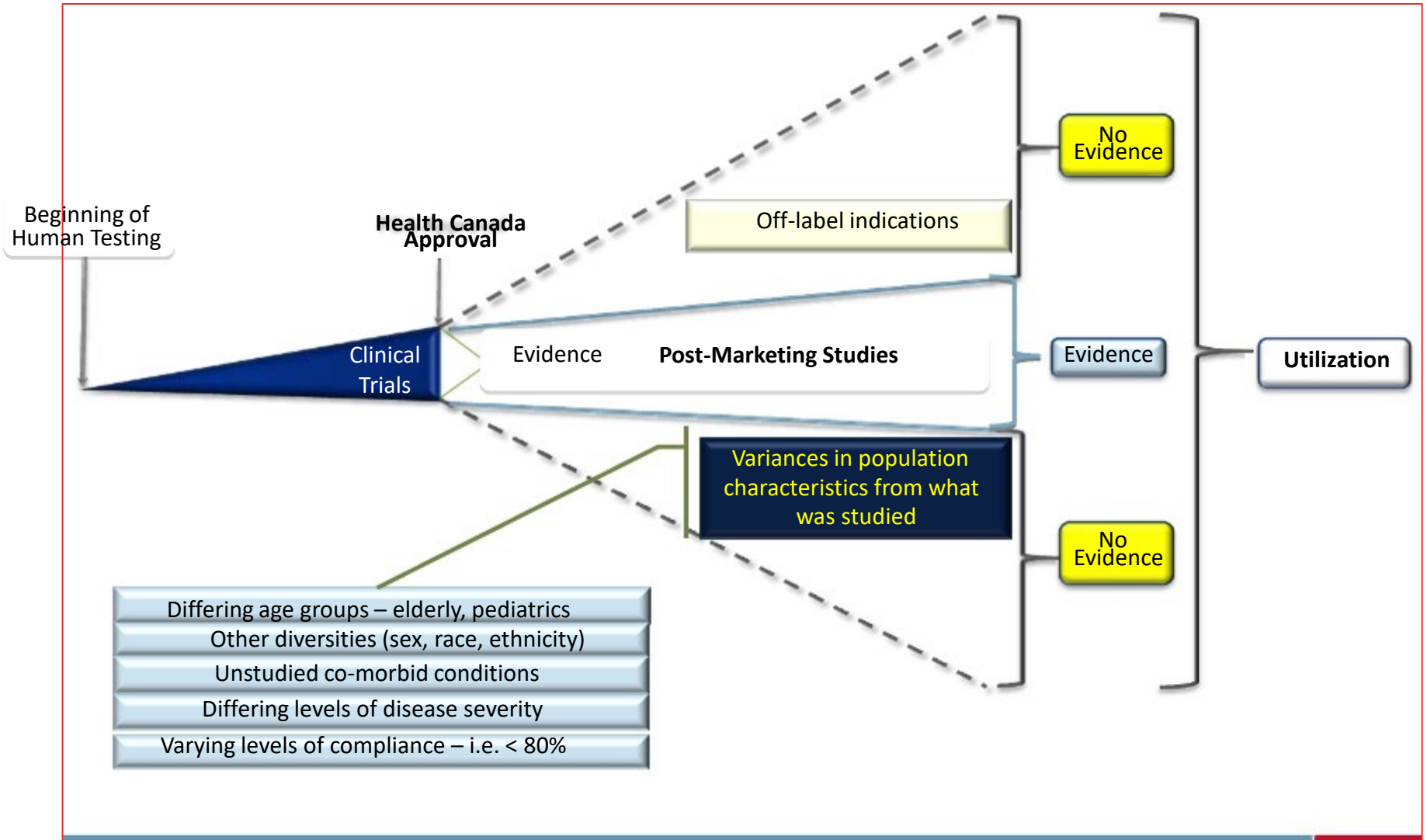
Effectiveness studies

Will it work here?

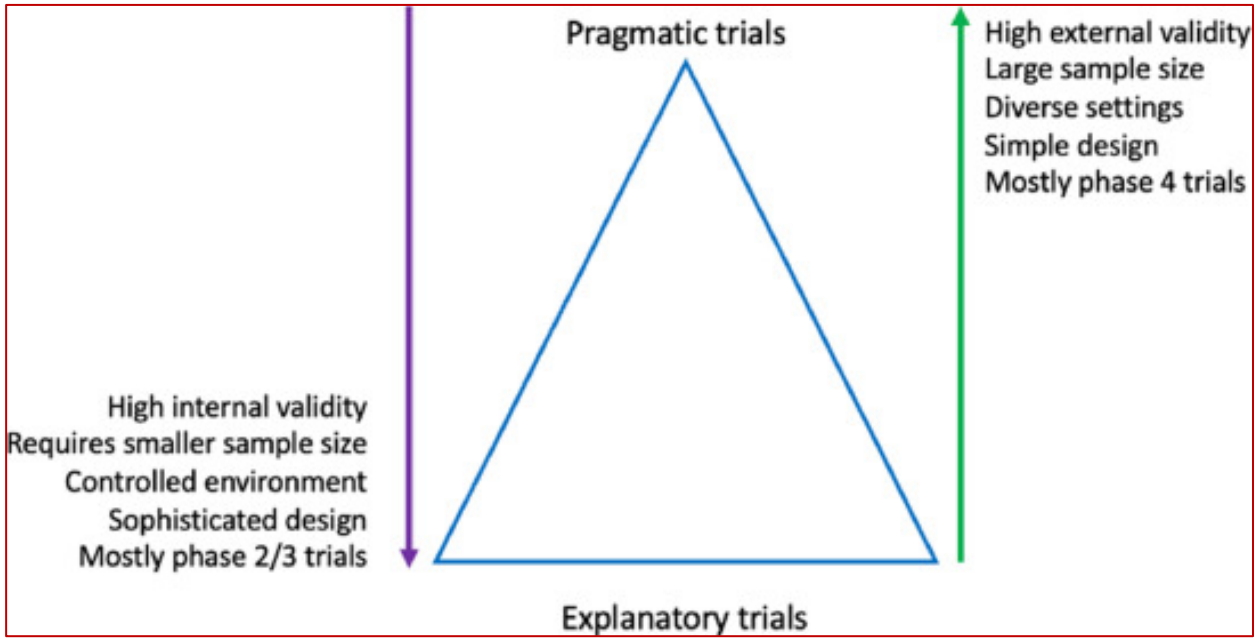
Phase-4 cluster RCT!

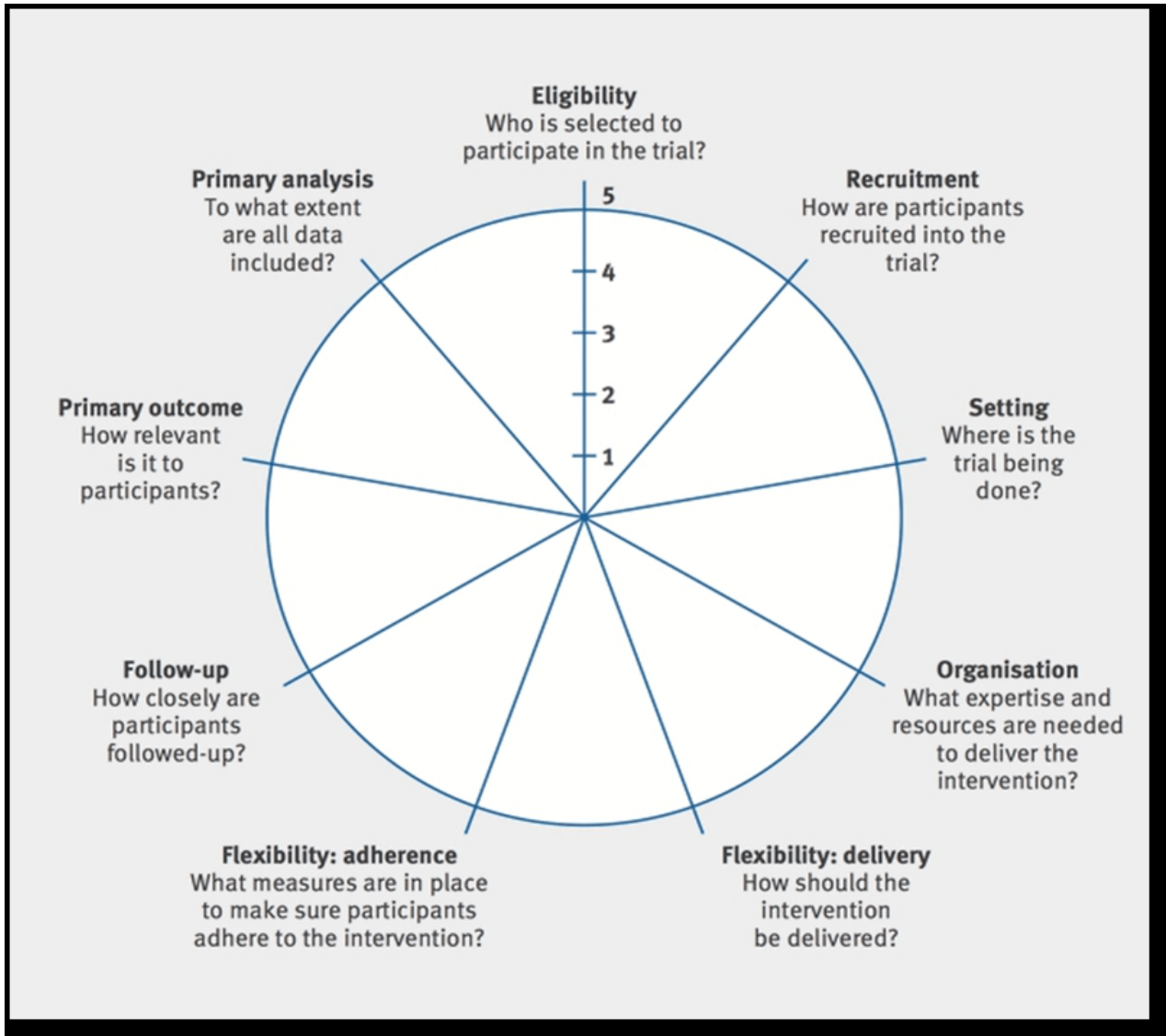
Therapy may not work in a setting closer to the real-world clinical practice

From RCTs to Clinical Practice



Pragmatic vs. Explanatory Clinical Trials





Analysis of RCTs

Statistical Analysis of RCTs

Write a Statistical Analysis Plan!

- Hypothesis
  - Superiority, non-inferiority, or equivalence
- Sample size calculation
- Outcome definitions
  - Adverse events monitoring
  - Stopping rules
- Model choice and variables to include
  - Intention to treat versus per-protocol analysis
- Subgroup analyses
- Sensitivity analyses

Freedman. Trials, 2020

UPDATE Open Access

A pragmatic randomized controlled trial of multi-dose oral ondansetron for pediatric gastroenteritis (the DOSE-AGE study): statistical analysis plan

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Abstract

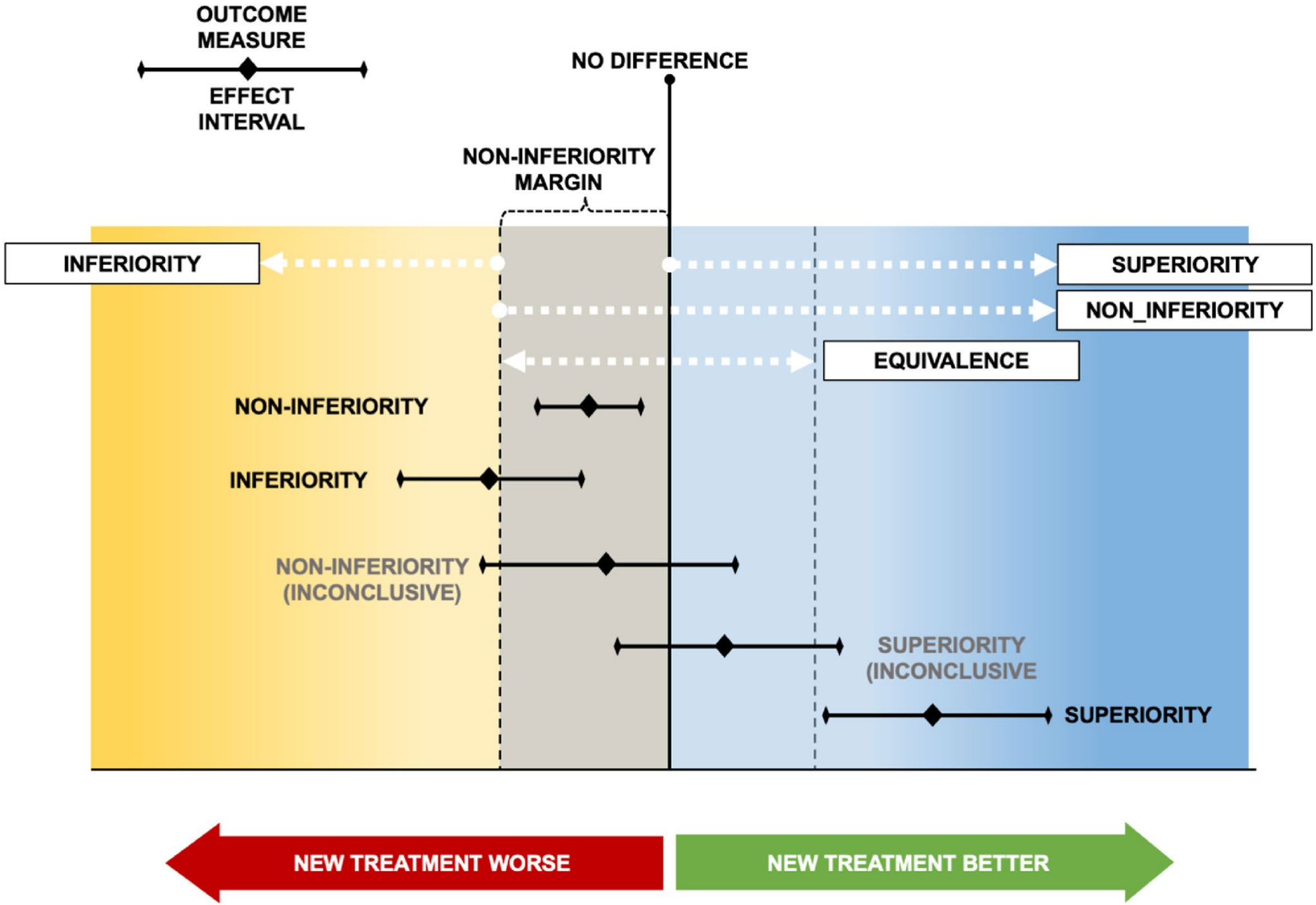
Background: Acute gastroenteritis is a leading cause of emergency department visits and hospitalizations among children in North America. Oral-rehydration therapy is recommended for children with mild-to-moderate dehydration, but children who present with vomiting are frequently offered intravenous rehydration in the emergency department (ED). Recent studies have demonstrated that the anti-emetic ondansetron can reduce vomiting, intravenous rehydration, and hospitalization when administered in the ED to children with dehydration. However, there is little evidence of additional benefit from prescribing ondansetron beyond the initial ED dose. Moreover, repeat dosing may increase the frequency of diarrhea. Despite the lack of evidence and potential adverse side effects, many physicians across North America provide multiple doses of ondansetron to be taken following ED disposition. Thus, the Multi-Dose Oral Ondansetron for Pediatric Gastroenteritis (DOSE-AGE) trial will evaluate the effectiveness of prescribing multiple doses of ondansetron to treat acute gastroenteritis-associated vomiting. This article specifies the statistical analysis plan (SAP) for the DOSE-AGE trial and was submitted before the outcomes of the study were available for analysis.

Methods/design: The DOSE-AGE study is a phase III, 6-center, placebo-controlled, double-blind, parallel design randomized controlled trial designed to determine whether participants who are prescribed multiple doses of oral ondansetron to administer, as needed, following their ED visit have a lower incidence of experiencing moderate-to-severe gastroenteritis, as measured by the Modified Vesikari Scale score, compared with a placebo. To assess safety, the DOSE-AGE trial will investigate the frequency and maximum number of diarrheal episodes following ED disposition, and the occurrence of palpitations, pre-syncope/syncope, chest pain, arrhythmias, and serious adverse events. For the secondary outcomes, the DOSE-AGE trial will investigate the individual elements of the Modified Vesikari Scale score and caregiver satisfaction with the therapy.

(Continued on next page)

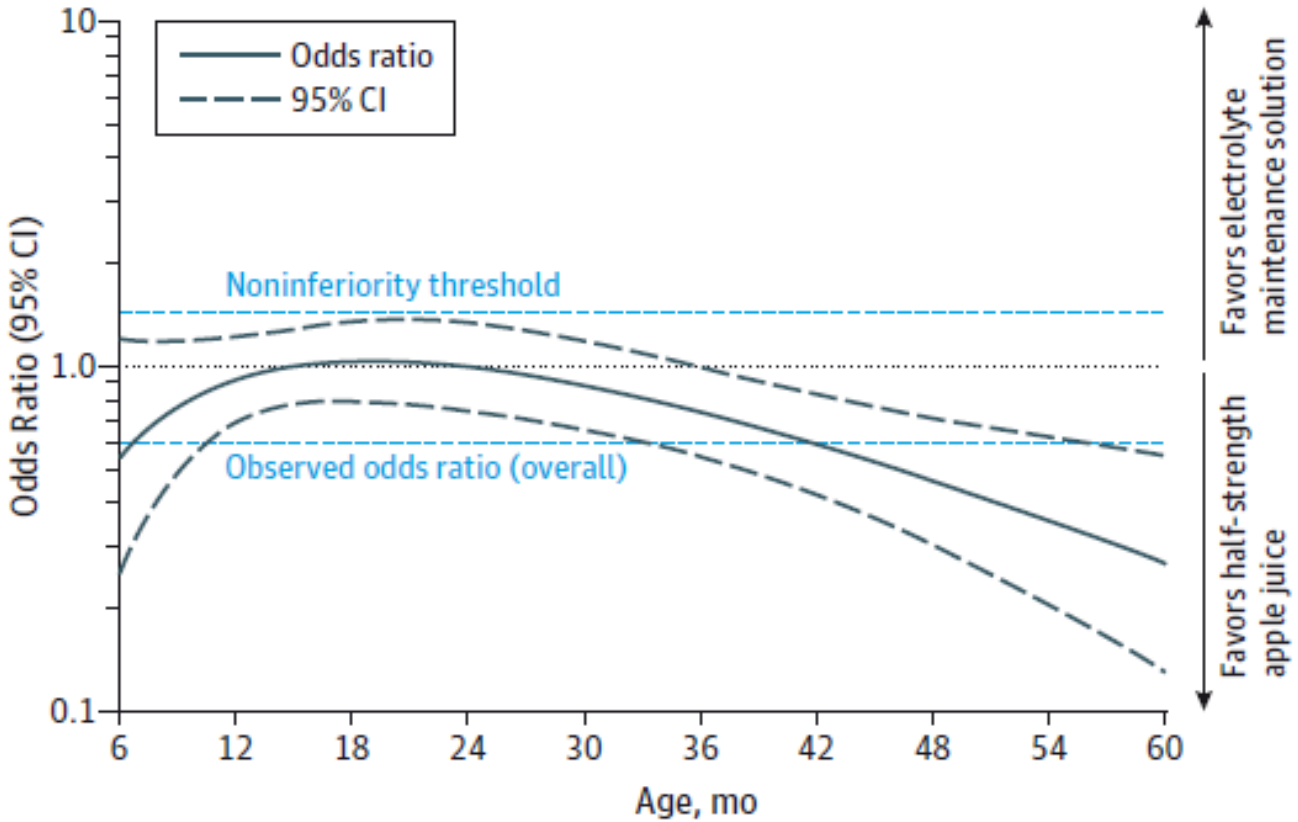
Superiority vs Non-inferiority Trials

	Superiority Trial	Non-Inferiority Trial
Primary Goal	To show the new treatment is significantly better than the standard treatment	To show the new treatment is not unacceptably worse than the standard treatment
Hypothesis	Null: No difference or the new treatment is worse. Alternative: The new treatment is better	Null: The new treatment is worse than the standard by more than a pre-defined margin (delta). Alternative: The new treatment is not worse than the standard by more than the margin
Statistical Test	Often uses a two-sided test	Always uses a one-sided test.
Sample Size	Typically requires a larger sample size to detect a small difference	Requires a smaller sample size than a superiority trial, as it is testing against a margin of non-inferiority
When to Use	When a new treatment offers a clear advantage in efficacy or safety	When a placebo cannot be used, and the new treatment may have other benefits like being easier to take or having fewer side effects


OUTCOME MEASURE
EFFECT INTERVAL
NO DIFFERENCE
NON-INFERIORITY MARGIN
INFERIORITY
SUPERIORITY
NON_INFERIORITY
EQUIVALENCE
NON-INFERIORITY
INFERIORITY
NON-INFERIORITY (INCONCLUSIVE)
SUPERIORITY (INCONCLUSIVE
SUPERIORITY
NEW TREATMENT WORSE
NEW TREATMENT BETTER

Half-Strength Apple Juice vs. Electrolyte Solution

Figure 2. Treatment Failure Comparing Half-Strength Apple Juice/ Preferred Fluids Therapy and Electrolyte Maintenance Solution Groups as a Function of Age



Freedman et al. JAMA. 2016

Statistical vs. Clinical Significance

- Statistical significance
  - Measured by a p-value
  - If there were truly no effect, how likely is it that we would see these results by chance?
  - **The cutoff:** Typically set at 0.05
- Clinical significance
  - Informed by a confidence interval (CI)
  - Tells you if results are meaningful for your patient
  - Range of values within which true treatment is likely to fall
  - **Typical:** 95%
    - If study were repeated 100 times, 95 of the resulting CIs would contain true population effect
  - Does entire range of CI represent a clinically meaningful effect for your patient?

statistical significance ≠ clinical significance

Examples

- A new anticoagulant shows a 95% CI for absolute risk reduction of [10%, 14%]. The p-value is 0.001. The CI is narrow and represents a meaningful risk reduction for a patient.
  - **Clinically and statistically significant**
- An antidepressant study with thousands of patients shows a 95% CI for a change in depression score of [0.5, 1.5] on a 100-point scale. The p-value is <0.001 due to the large sample size. The effect is real, but a 0.5–1.5-point improvement is unlikely to be noticed by a patient.
  - **Statistically significant, not clinically significant**
- A small pilot study on a new therapy for chronic pain shows a 95% CI for pain reduction of [0, 14%] with a p-value of 0.06. Although not statistically significant (the range includes zero), the CI shows that a meaningful effect is still plausible. The clinical potential here warrants a larger trial, as opposed to abandoning the therapy.
  - **Clinically significant, not statistically significant**

Analytic Approaches to Handle RCT Challenges
Intention-to-Treat, Per-Protocol, As-Treated

Intention-to-Treat

All randomized patients are included in the analysis, based on allocation

Includes differences in individuals' adherence

Estimated effect reflects inherent effect of treatment AND proportion of patients that receive it

Per-Protocol

Only analyzes data from participants who follow the protocol

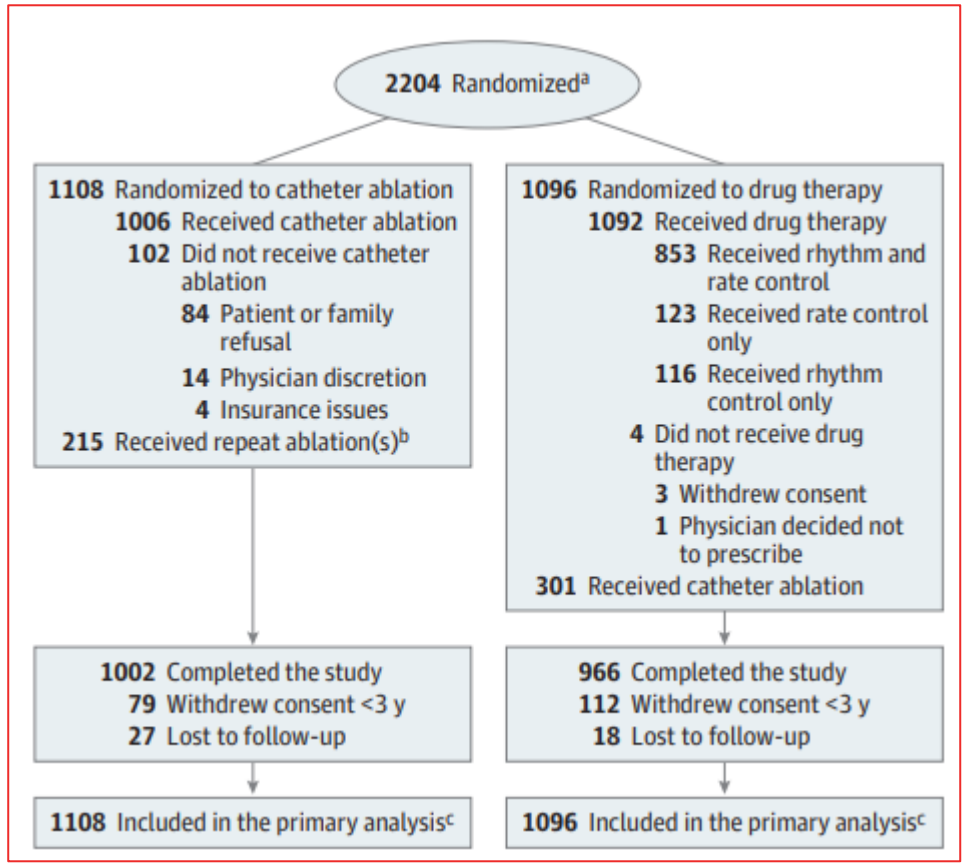
Excludes data after participants become nonadherent

As-Treated

Considers treatment actually received without regard to adherence

Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation

- Primary outcome
  - Death, disabling stroke, serious bleeding, or cardiac arrest
- Intention-to-Treat
  - HR ablation vs. drug: 0.86 (0.65, 1.15)
- Per-Protocol
  - HR ablation vs. drug: 0.74 (0.54, 1.01)
- As-Treated
  - HR ablation vs. drug: 0.67 (0.50, 0.89)



Packer. JAMA, 2019

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Exercise

Design a Randomized Clinical Trial

Anaphylaxis Management in the ED

UNIVERSITY OF CALGARY

Summary

Topics Covered

Why randomized clinical trials (RCT) are so important

Strengths and Weaknesses

Principles of RCT design

Asking the right study question
Choosing a study population
Reducing bias
Analysis methods

Not covered today

Ethics and Good Clinical Practice

Assessing feasibility – pilot studies

Novel RCT Designs

Details of Analysis methods, early stopping rules

Clinical trial management

Grant-writing for success

Critical appraisal

Opportunities to Learn and be Involved

Formal training – MDCH 641: Introduction to Clinical Trials

SPOR Pragmatic Clinical Trials Program

Contribute as a learner to ongoing studies

Observership on grant review panels

Clinical Research Fellowship in Pediatric Emergency Medicine

Thanks!

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