# Critical Appraisal

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# Objectives of the lecture:

- Show how to do critical appraisal and check the appropriateness of study design for the research question.
- Learn how to do careful assessment of the key methodological features of the research design.
- Learn how to check the potential conflicts of interest.
- Learn how to examine the suitability of the statistical methods used and their subsequent interpretation.
- Explain the implications of research findings for individual patients, elicit patients' own preferences and develop an appropriate management plan based on the combination of this information.

# What's A Paper on Therapy?

- Clinical Trial (Controlled) Compares

INTERVENTION
with
CONTROL

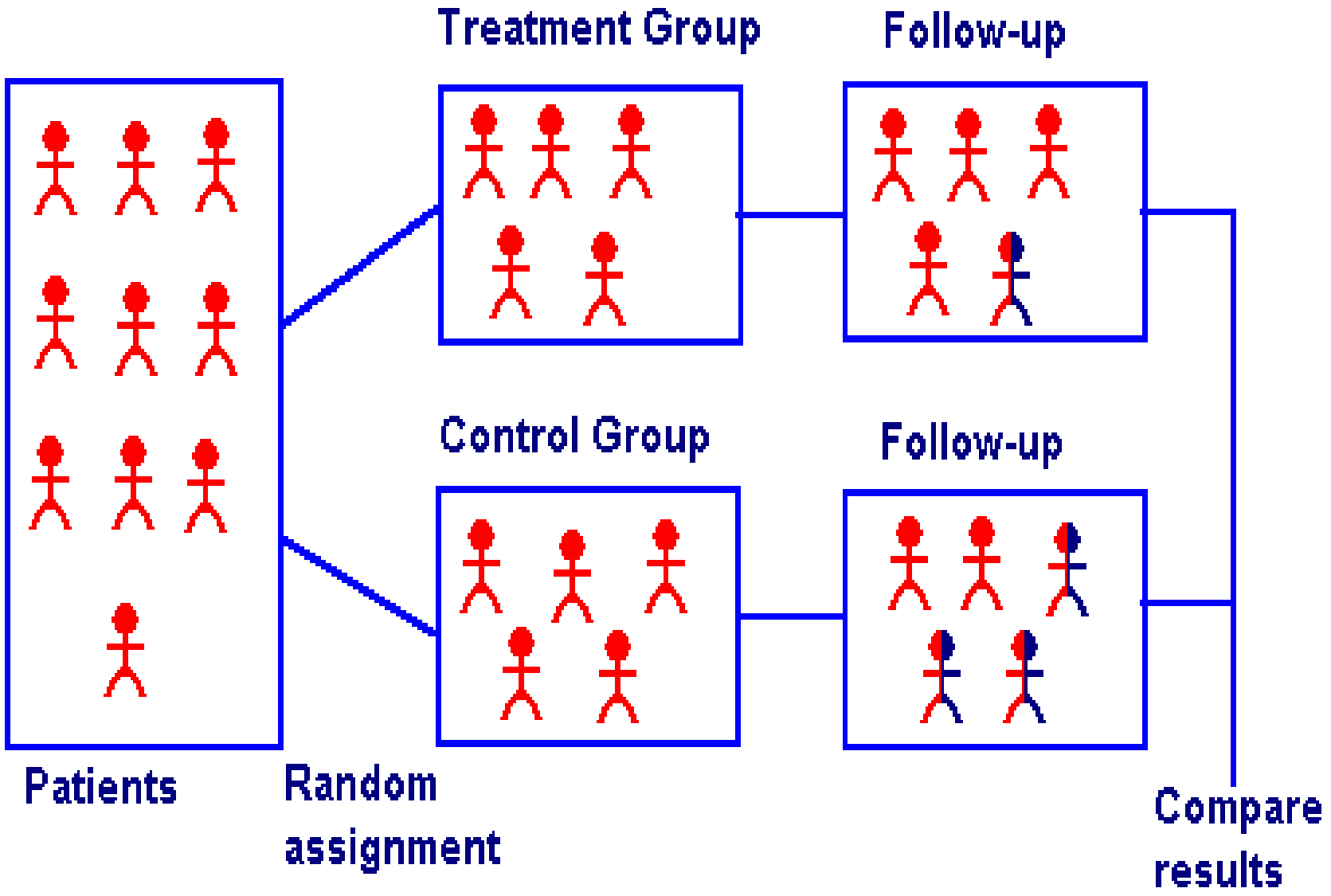
## Clinical Trial Compares

- **INTERVENTION**
  - Drug (New)
  - Structured exercise program (e.g. osteoporosis)
  - Surgical procedure

- **CONTROL**
  - Placebo, old drug or old intervention
  - Usual regular advise given (osteoporosis)
  - Another surgical procedure / No surgery

# Process of RCTs

- ✓ Preparation: Randomization, Computer generated list
- ✓ Eligibility assessment (Inclusion/exclusion)
- ✓ Consent
- ✓ Allocation to study arms (Concealment)
- ✓ Baseline assessment
- ✓ Initiation of intervention (Blind)
- ✓ Follow-up
- ✓ Outcome assessment
- ✓ Data analysis


Treatment Group
Follow-up
Control Group
Follow-up
Patients
Random assignment
Compare results

# Appraise the Evidence

- Assess **validity**? Correctness (likely to be true)
- What are the **results**? Clinically important
- Can we **apply** the results to our patient? Applicable in and useful for my patients

# Users' Guides to the Medical Literature

## A Manual for Evidence-Based Clinical Practice

The Evidence-Based
Medicine Working Group

Edited by
*Gordon Guyatt, MD*
*Drummond Rennie, MD*
*Robert Hayward, MD (interactive guides)*

AMA press

JAMA & ARCHIVES JOURNALS
American Medical Association

# VALIDITY

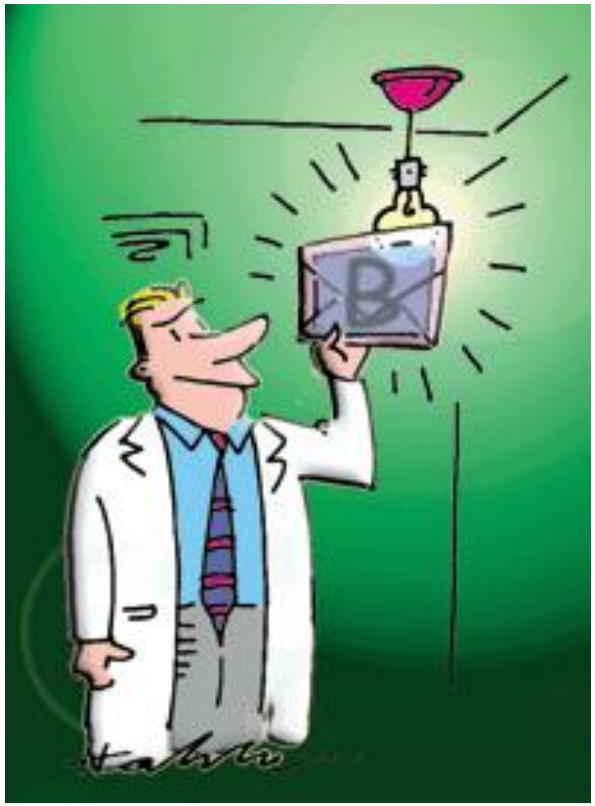
- Randomization.
- Concealment.
- Blindness.
- Follow up complete.
- Intention to treat.
- Similar groups at start.
- Both groups treated equally.

# Randomization

- Randomisation = similar groups at baseline
- Equal (50%) chance to be in either group
- How was it randomized?
- Was randomization concealed?
  - selection
  - allocation

# concealed allocation

- Did investigators know to which group the potential subject would be assigned before enrolling them?
- Trials with unconcealed allocation consistently overestimate benefit by ~40%



# Selection bias

Reduced by:

- ✓ centralised randomisation
- ✓ on-site computer system with group assignments in a locked file
- ✓ sequentially numbered, sealed, opaque envelopes

- ✗ Not: alternation, dates of birth, day of week.

# Blindness

- Who is Blind?

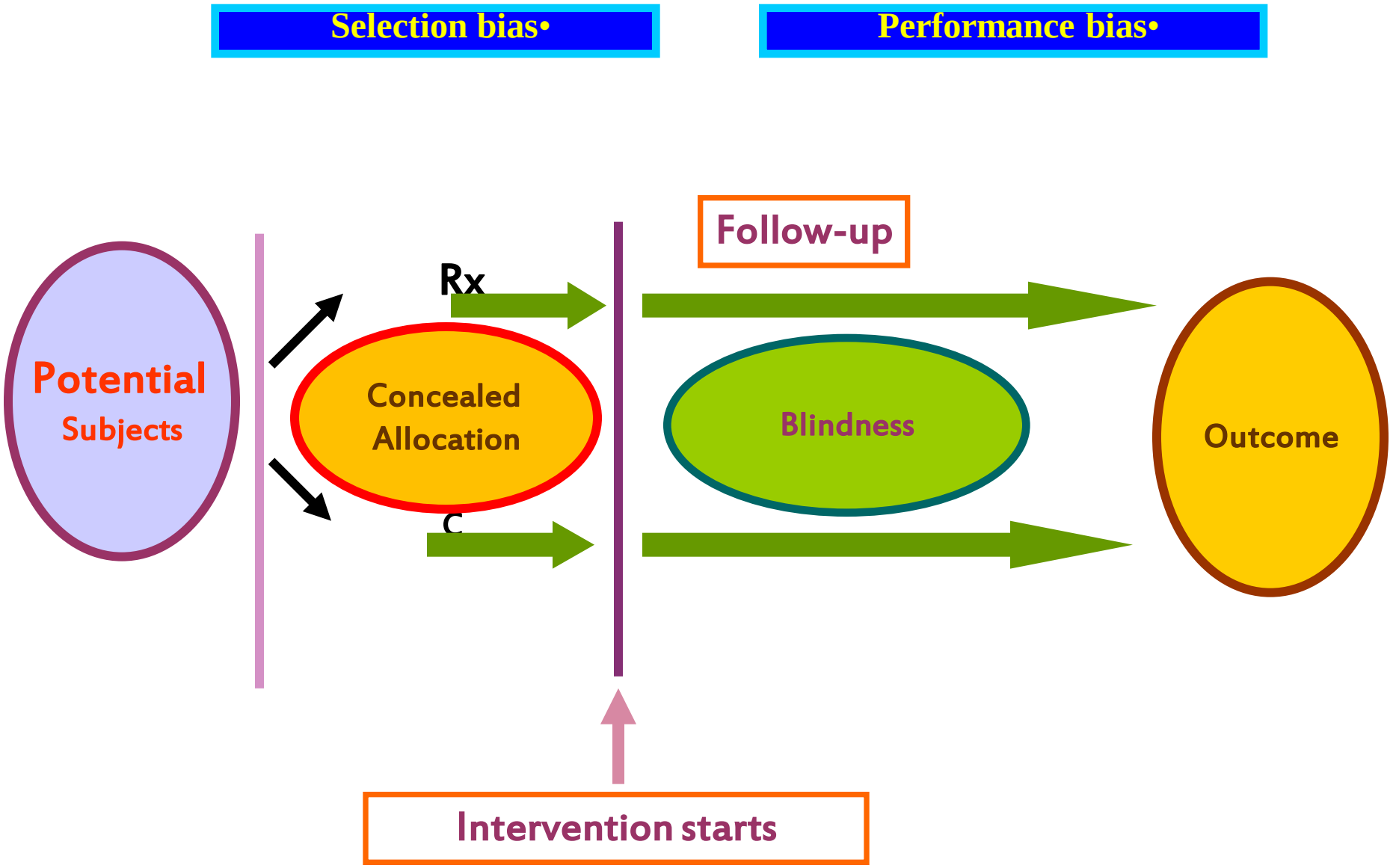
- - Physicians-Nurses-Patients-Data gathering staff- data analyzers.

- - Single, double…

# Blindness

- If patient knows: ***Placebo effect*** Those who are on effective treatment perform better than those who receive Placebo

- If Physician knows: ***Overestimate Treatment effect*** (More care, Co-intervention)


Selection bias•
Performance bias•
Follow-up
Rx
Potential
Subjects
Concealed
Allocation
C
Blindness
Outcome
Intervention starts

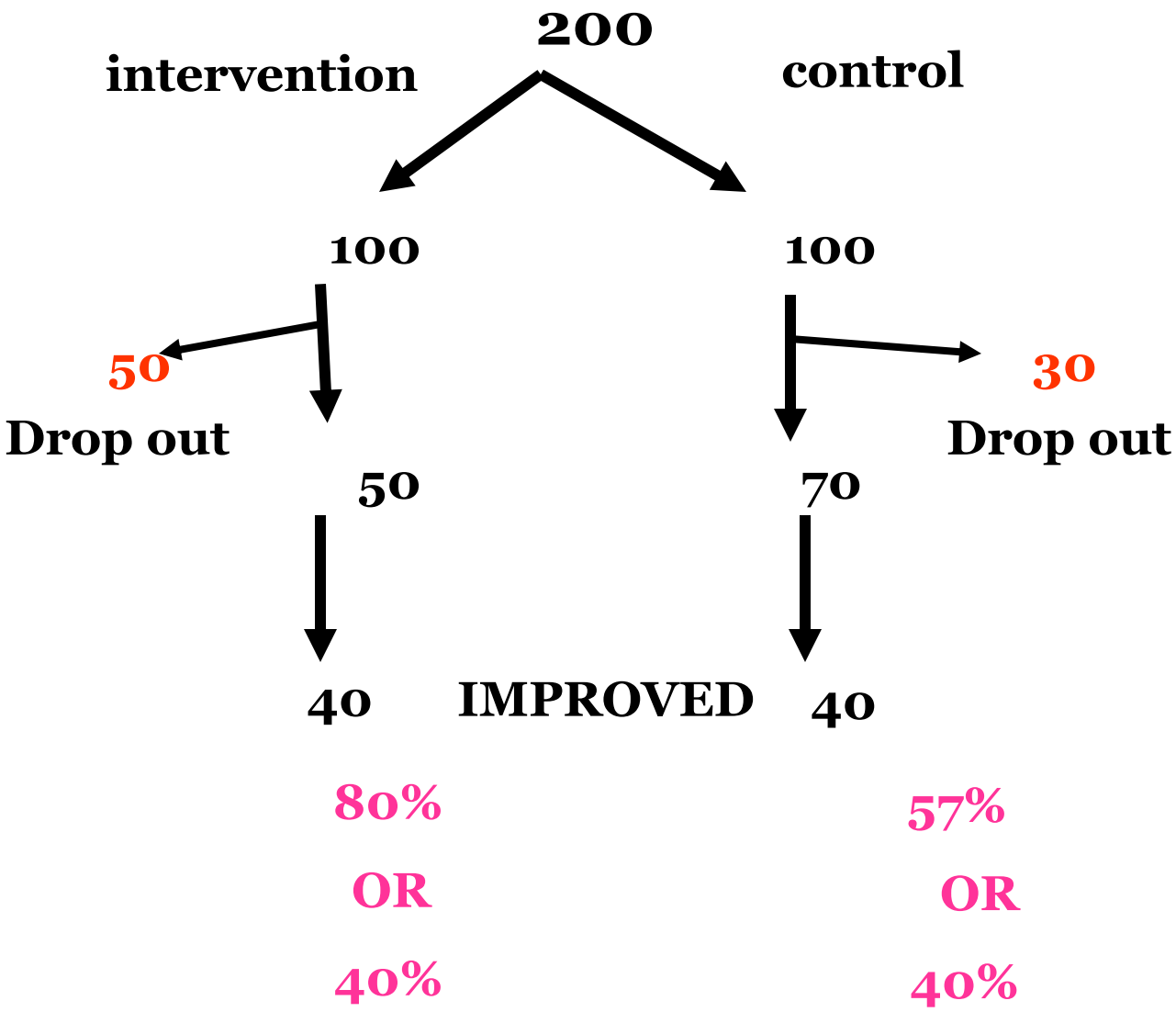
# Follow up

- duration of study.
- drop out < 20%.

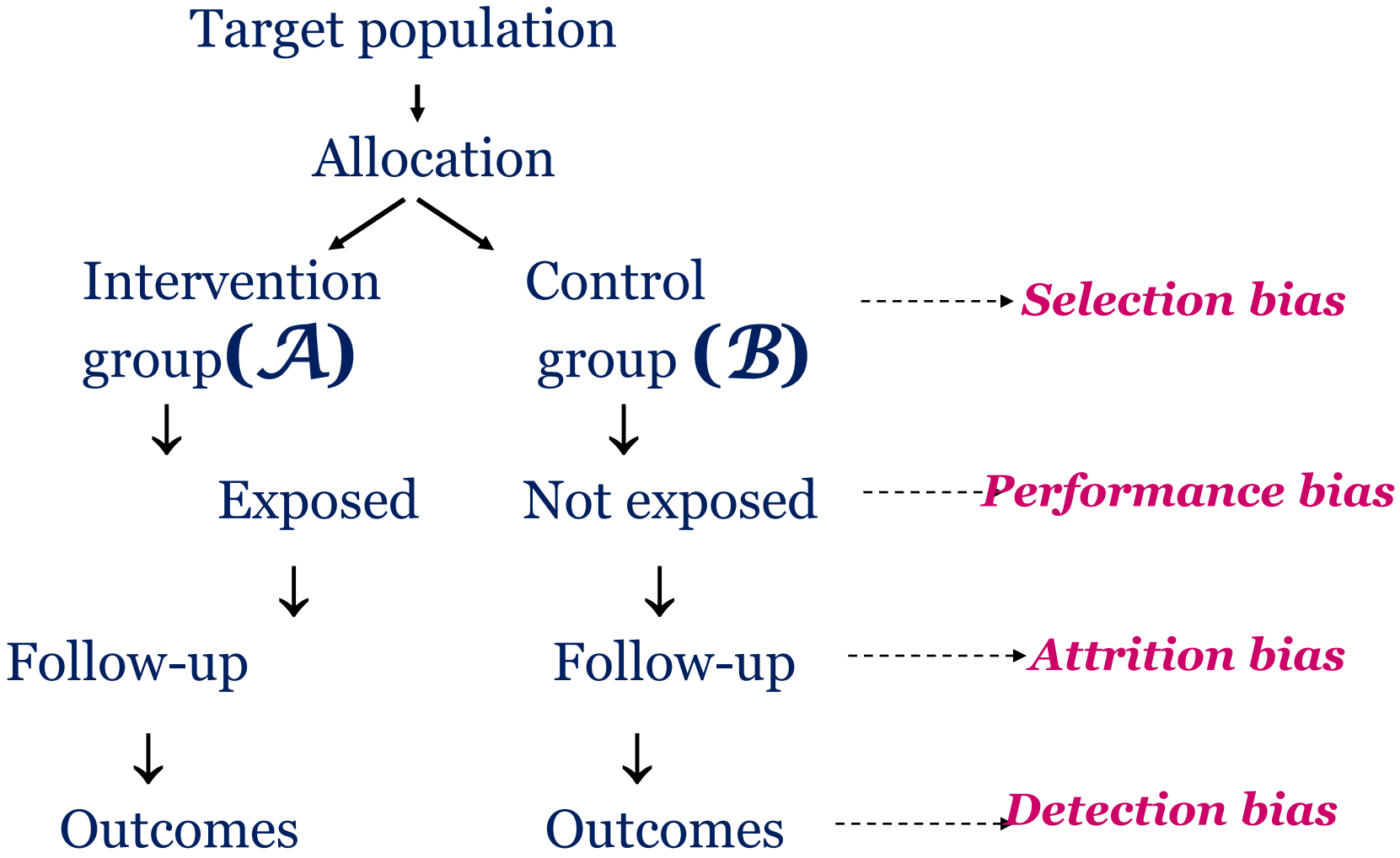
# INTENTION TO TREAT

**All patients analyzed in the groups to which they were allocated**

# INTENTION TO TREAT (ITT)



# Sources of bias in trials



# How RCTs differ from other designs

**Two balanced groups:**

- **Start Balanced:** All prognostic factors are equally distributed at the start (Concealed Randomization)
- **Run Balanced:** All prognostic factors are maintained balanced throughout the study (Blindness and the 3C)
- **End Balanced:** All prognostic factors are maintained balanced at the end of the study (ITT)

**Intervention**

**Figure 1.** Profile of the Estrogen Plus Progestin Component of the Women's Health Initiative

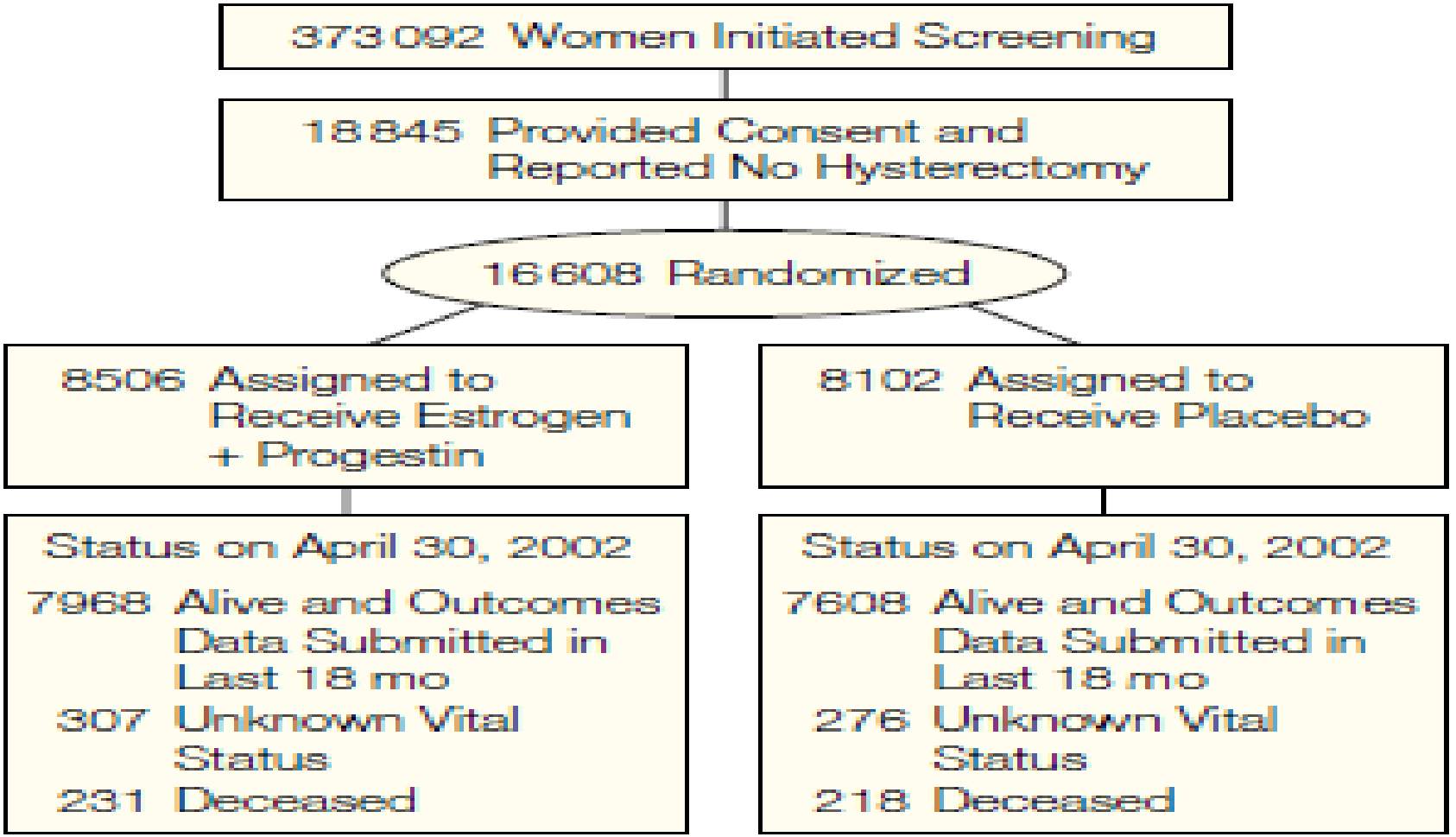
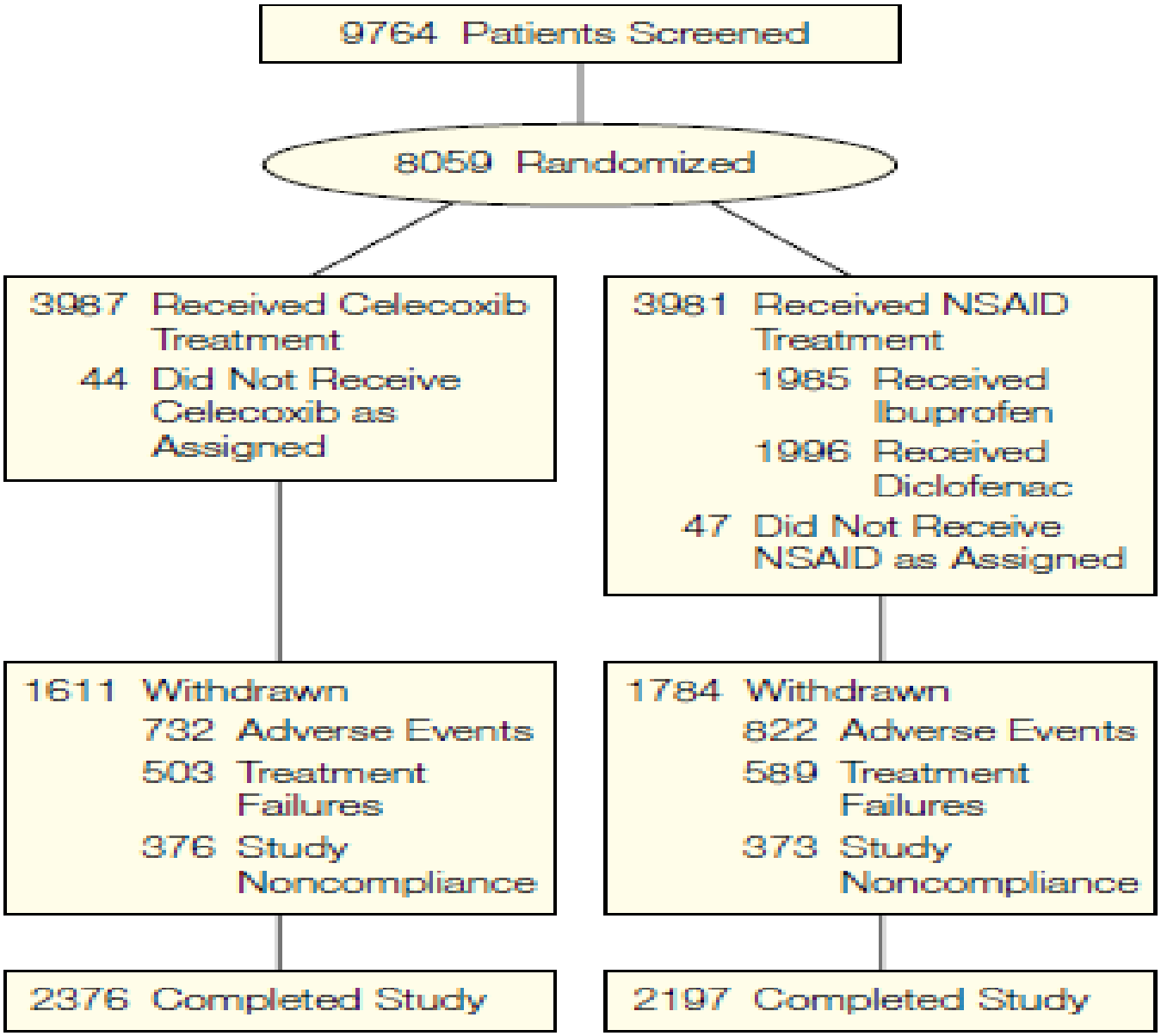


**Figure 1.** Flowchart of Patient Disposition at 6 Months



# Menerba® Phase 3 Advanced Clinical Trial Design

**PI: Wulf Utian, M.D., Ph.D. D.Sc.**
Founder and President Emeritus of the North American Menopause Society (NAMS)

**40 U.S. Clinical Sites Approved and Trained**

**Eligibility:**

- Postmenopausal women ages 40-65
- ≥ 7 moderate to severe hot flashes/day

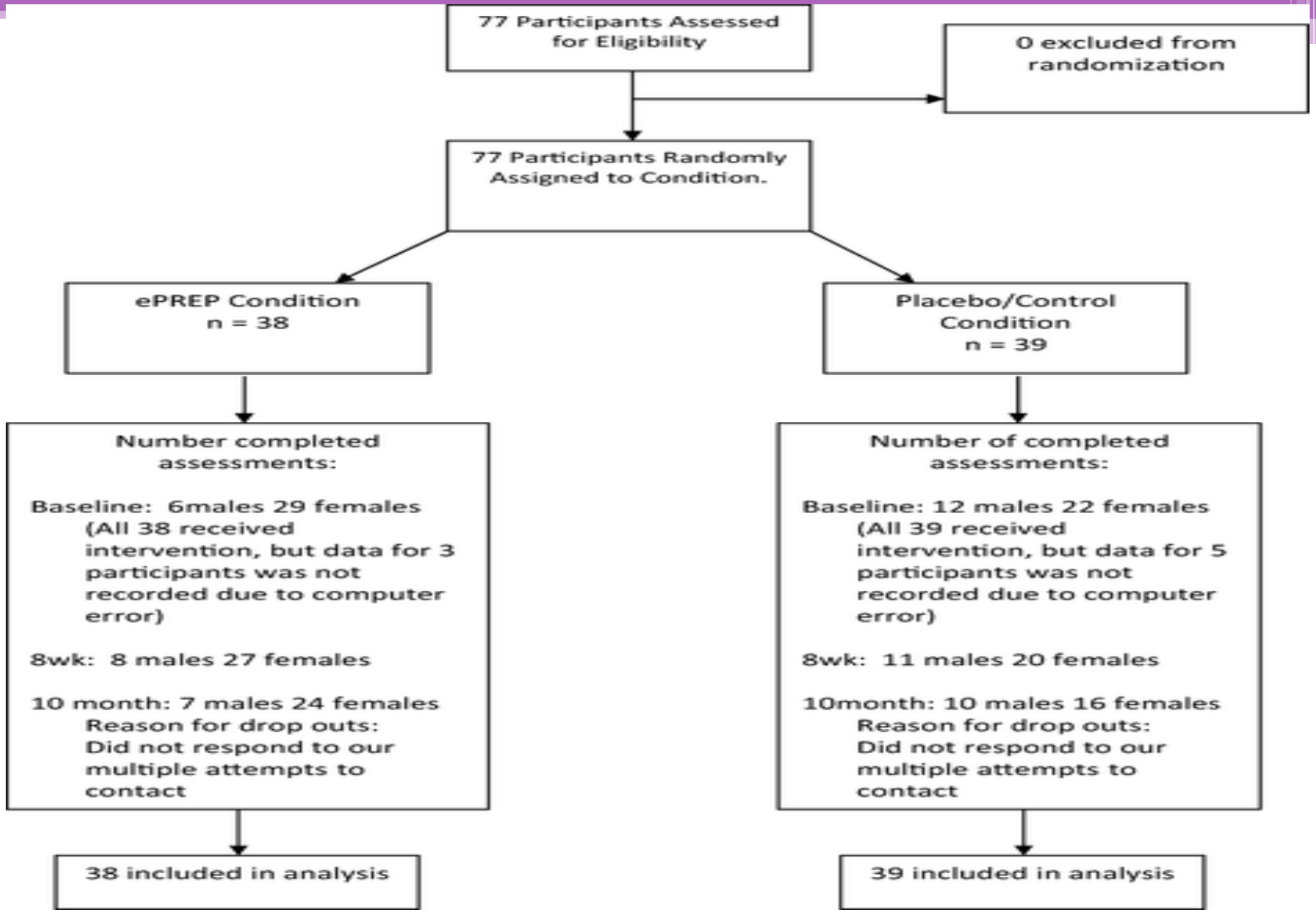
**Randomization:**

1200 patients to 12 weeks of treatment

- 400 Participants 5g/day
- 400 Participants 15 g/day
- 400 Participants Placebo

**Primary Endpoint:**

Change in frequency of moderate to severe hot flashes at 12 weeks


77 Participants Assessed for Eligibility
0 excluded from randomization
77 Participants Randomly Assigned to Condition.
ePREP Condition n = 38
Placebo/Control Condition n = 39
Number completed assessments:
Baseline: 6males 29 females (All 38 received intervention, but data for 3 participants was not recorded due to computer error)
8wk: 8 males 27 females
10 month: 7 males 24 females
Reason for drop outs: Did not respond to our multiple attempts to contact
Number of completed assessments:
Baseline: 12 males 22 females (All 39 received intervention, but data for 5 participants was not recorded due to computer error)
8wk: 11 males 20 females
10month: 10 males 16 females
Reason for drop outs: Did not respond to our multiple attempts to contact
38 included in analysis
39 included in analysis



"The police called, we're taking you out of the clinical trial and putting you in a criminal trial."

# WHAT DO WE LOOK FOR?

- VALIDITY
- IMPORTANCE
- APPLICATION

# VALIDITY

# Are the results of this single preventive or therapeutic trial valid?

| | |
|---|---|
| Was the assignment of patients to treatments randomised?<br><br>Was the randomisation list concealed? | |
| Was follow-up of patients sufficiently long and complete? | |
| Were all patients analysed in the groups to which they were randomised? | |
| Were patients and clinicians kept "blind" to treatment? | |
| Were the groups treated equally, apart from the experimental treatment? | |
| Were the groups similar at the start of the trial? | |

Was the assignment of patients to treatments randomised?

Was the randomisation list concealed?

# Ensuring Allocation Concealment

## BEST – most valid technique

- Central computer randomization

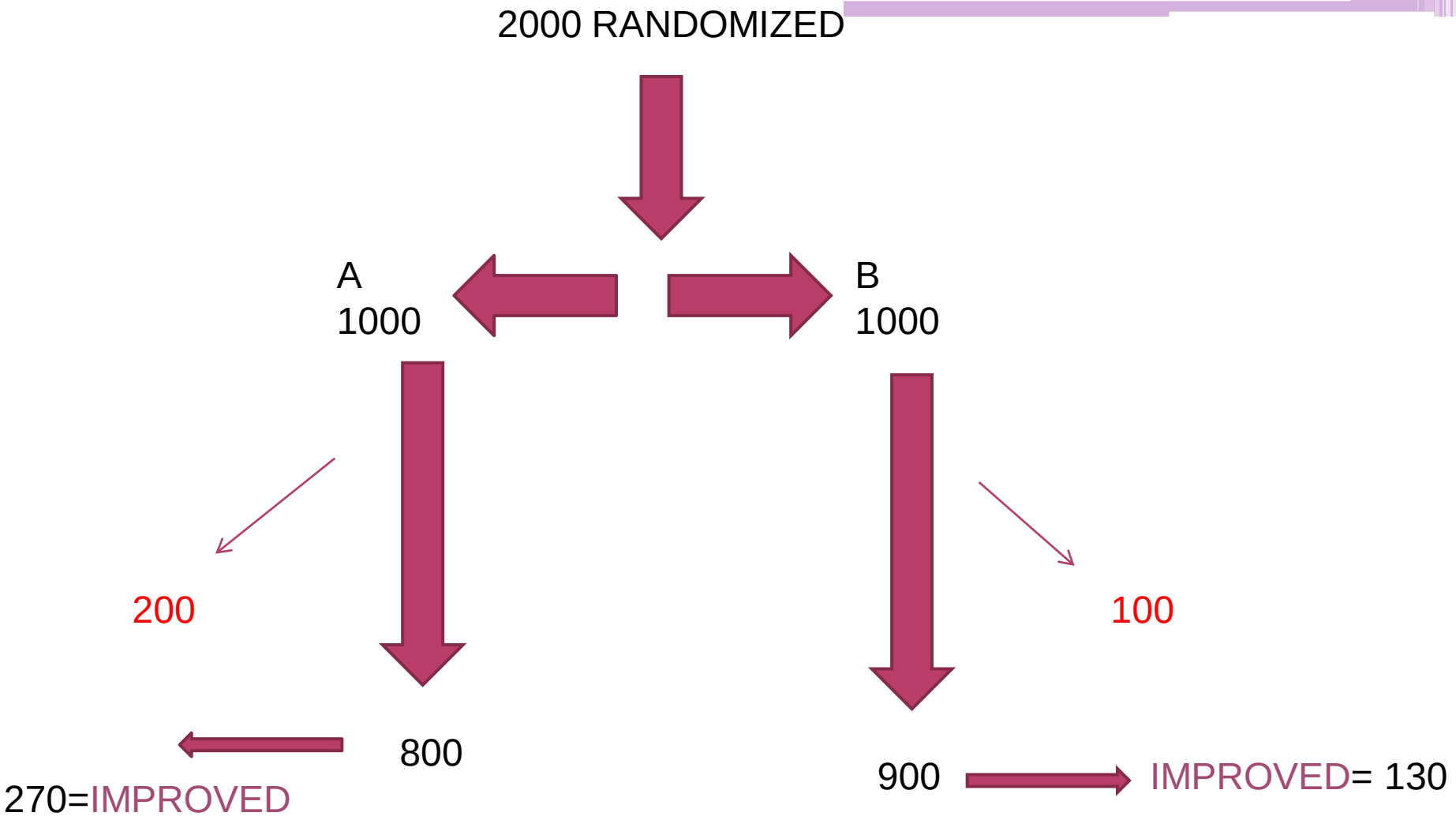
## DOUBTFUL

- Envelopes, etc

## NOT RANDOMIZED

Date of birth, alternate days, etc

Was follow-up of patients sufficiently long and complete?




EER= 270/?

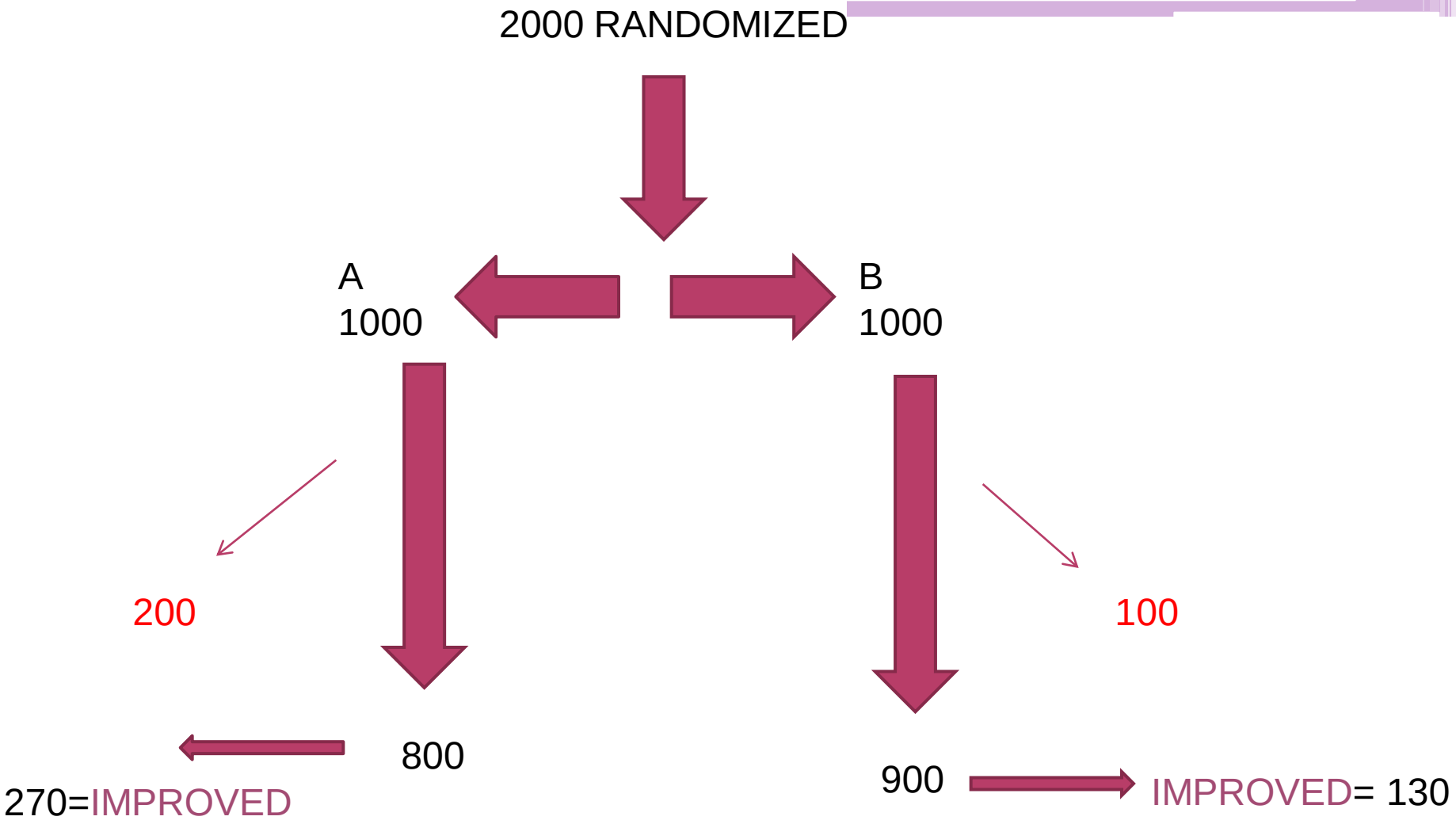
CER=130/?

# Losses-to-follow-up
## How many is too many?

"5-and-20 rule of thumb"

- 5% probably leads to little bias
- >20% poses serious threats to validity

Were all patients analysed in the groups to which they were randomised?




EER= 270/?

CER=130/?

# Intention-to-Treat Principle

## Maintaining the randomization

### Principle:

Once a patient is randomized, s/he should be analyzed in the group randomized to - even if they discontinue, never receive treatment, or crossover.

**Exception: If patient is found on BLIND reassessment to be ineligible based on pre-randomization criteria.**

Were patients and clinicians kept "blind" to treatment?

# Measurement Bias - minimizing differential

- Blinding – Who?
  - Participants?
  - Investigators?
  - Outcome assessors?
  - Analysts?

- Most important to use "blinded" outcome assessors when outcome is not objective!

- Papers should report WHO was blinded and HOW it was done

Figure 1: The authors: double blinded versus single blinded

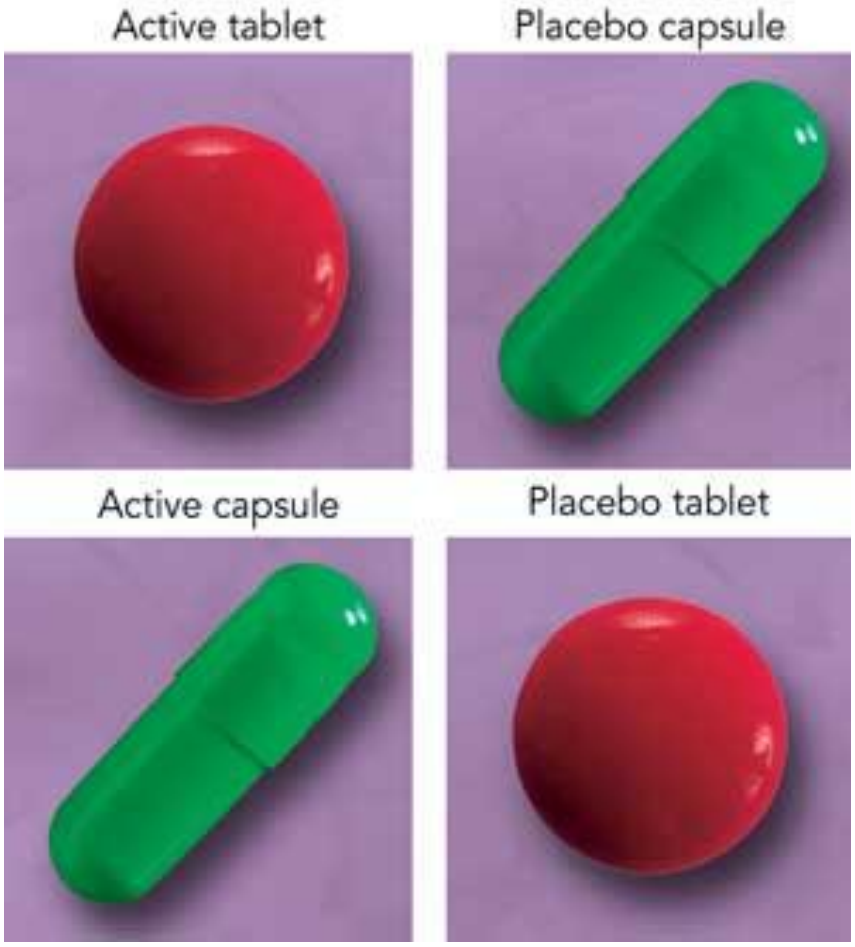
Figure 2: The authors blinded and masked

Schulz and Grimes. Lancet, 2002

# Best RCTs: Double Blind

- Subject doesn't know which he's getting.
- Researcher doesn't know which he's giving.

- Exit poll to see if patients could guess if they were in the placebo group


Active tablet
Placebo capsule
Active capsule
Placebo tablet

Were the groups treated equally, apart from the experimental treatment?

Were the groups similar at the start of the trial?

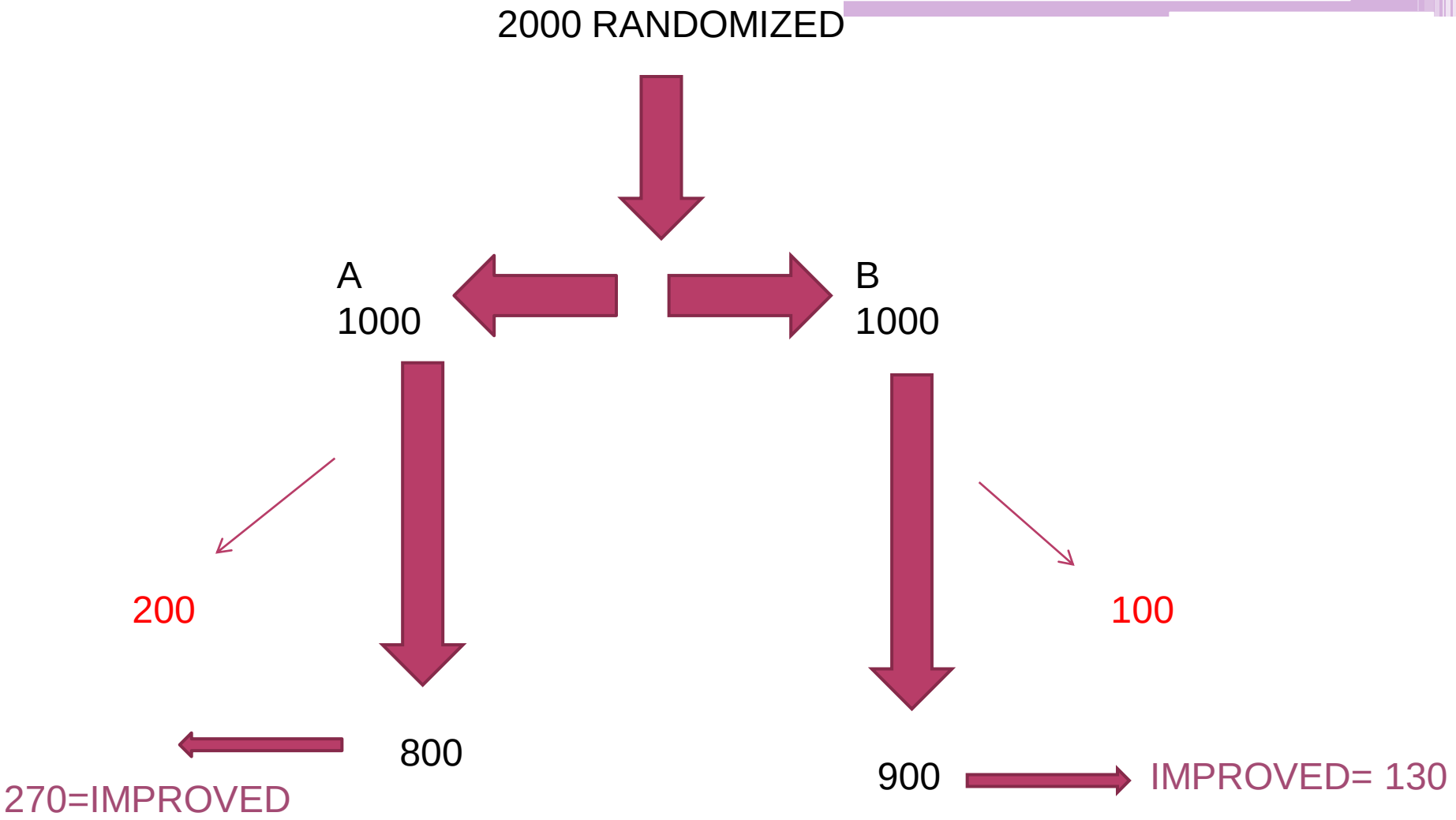
# IMPORTANCE

## MEASURES OF ASSOCIATION

# Definition

- Number Needed to Treat (NNT):
  - Number of persons who would have to receive an intervention for 1 to benefit.

NNT=1/ARR




EER= 270/?

CER=130/?

EER=270/800 = 33%= 0.33

CER= 130/900=14 %=0.14

ARR= 0.33-0.14= 0.19

NNT=1/0.19= 5.2=6

EER=270/1000=27%=0.27

CEER=130/1000= 13%=0.13

ARR=0.27-0.13=0.14

NNT=1/0.14=7


# NUMBER NEED TO HARM(NNH)

## WHAEN THE OUTCOME IS UNFAVOURABLE

# Therapy

- ARR
- RR
- RRR
- NNT
- CI

# Result

- **Result Experimental Event Rate (EER)**
  Risk (or chance) of outcome event in experimental group
- **Results control event rate (CER)**
  Risk (or chance) of outcome event in control group.

# Result

**Relative Risk (RR)**

- A measure of the chance of the event occurring in the experimental group relative to it occurring in the control group.

- **RR = EER / CER**

# Relative Risk Reduction (RRR ):.

- **RRR=CER-EER/CER**
- **A RRR of 25% means that the new treatment reduced the risk of death by 25% relative to that occurring among control patients; the greater the relative risk reduction, the more effective the therapy.**

# Absolute Risk Reduction (ARR)

- The absolute difference between the risk of the event in the control and experimental groups.

- ARR = CER – EER

# Number needed to treat (NNT)

- Measure of clinical significance
- How many pat's have to be treated with intervention in order one patient Would expected to benefit.
- **NNT=1/ARR**
- Conversely, can do number needed to harm
  - uses harmful outcomes, eg death, weight gain

## Magnitude (treatment effect):

- Absolute effects (ARR & NNT)
- Relative effects (RR, RRR )

## Precision:

- **P value.**
- Confidence interval?

# Result Tabulation

| | Event + Ve | Event - Ve | Total |
|---|---|---|---|
| Experimental | a | b | a+b |
| Control | c | d | c+d |

EER = Experimental Event Rate (a/a+b) •

CER = Control Event Rate (c/c+d) •

# Result Tabulation

| | Bleeding present | Bleeding Absent | Total |
|---|---|---|---|
| Drug A | 20 | 80 | 100 |
| Drug B | 40 | 60 | 100 |

- EER-A (Risk A) = 20/100 = 20% (0.2)
- CER-B (Risk B) = 40/100 = 40% (0.4)

# Calculations

- ARR = CER - EER
- NNT = 1 / ARR
- RR = EER/CER (Risk A/Risk B)
- RRR = 1- RR

# Result Tabulation

| | Bleeding present | Bleeding Absent | Total |
|---|---|---|---|
| Drug A | 20 | 80 | 100 |
| Drug B | 40 | 60 | 100 |

ARR = CER - EER

RR = EER/CER

- NNT = 1 / ARR
- RRR = 1- RR

# Calculations

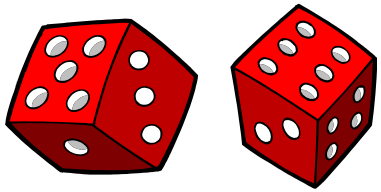
- ARR = CER – EER = 0.4 – 0.2 = 0.2 (20%)
- NNT = 1 / ARR = 1/0.2 = 5
- RR = EER/CER = 0.2/0.4 = 0.5
- RRR = 1- RR = 1- 0.5= 0.5 (50%)

# Confidence intervals?

- The range within which the likelihood of a true value is expected to be within a given degree of certainty, usually evaluated at 95% CI.

- Precision

# Confidence Intervals (Estimation) - in DVT study



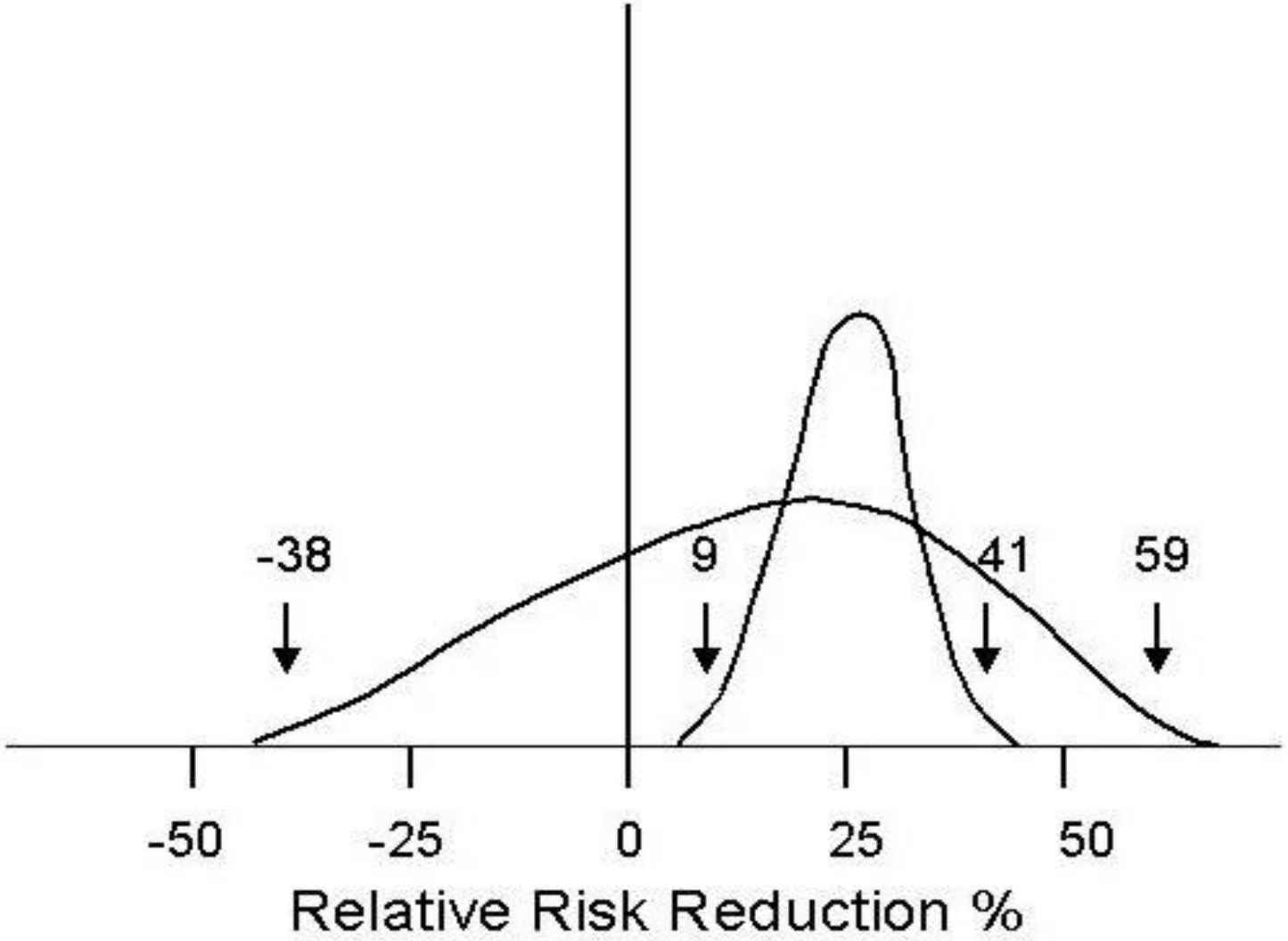
- Incidence of DVT
  - Stocking group - 0
  - No Stocking group - 0.12

Risk difference = 0.12 - 0 = 0.12

(95% CI, 0.058 - 0.20)

The true value could be as low as 0.058 or as high as 0.20 - *but is probably closer to 0.12*

**Since the CI does not include the 'no effect' value of '0' → the result is statistically significant**


-38
9
41
59
-50
-25
0
25
50
Relative Risk Reduction %

# APPLICABILITY

# CAN I APPLY THESE VALID, IMPORTANT RESULTS TO MY PATIENT?

- **Do these results apply to my patient?**
  - **IS OUR PATIENT SO DIFFERENT?**
  - **IS THE TREATMENT FEASIBLE?**
  - **POTENTIAL BENEFITS AND HARMS**

- **Are my patient's values and preferences satisfied by the intervention offered?**

# Summary

- Validity – is the paper likely to be true
- Importance – size of effect
  - NNT
  - Percision
- Applicability – can it work for me/my setting

http://www.ebm.med.ualberta.ca/Therapy.html

# Evidence Based Medicine Toolkit


- Home
- About EBM
- Domains
- Practice Guidelines
- Systematic Review
- Economic Analysis
- Glossaries
- JAMA User's Guide
- Links




## Therapy/Prevention Article Appraisal Guide

### Questions to Ask Yourself

**Are the results valid?**

1. Was the assignment of patients to treatment randomized?

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

- Was follow-up complete?
- Were patients analyzed in the groups to which they were randomized ?
- Intention to treat analysis?


WATCH
FOR
ICE

# Take-home messages:

- Different types of question require different study designs.
- Does the study address a clearly focused question?
- Did the study use valid methods to address this question?
- Are the valid results of this study important?
- Are these valid, important results applicable to my patient or population?

# Refrences


- Critical Appraisal tools and Work sheets http://www.cebm.net/critical-appraisal/
- Jane M Young & Michael J Solomo. How to critically appraise an article. Nature Reviews Gastroenterology and Hepatology 6, 82-91 (February 2009) | doi:10.1038/ncpgasthep1331
- What is a critical appraisal? http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/what_is_critical_appraisal.pdf
- The BMJ - How to Read a Paper http://www.bmj.com/about-bmj/resources-readers/publications/how-read-paper
- Evidently Cochrane http://www.evidentlycochrane.net/
- CEBM http://www.cebm.net/


Thank You!