CLINICAL TRIALS 101:

Fundamentals for Orthopaedic Surgeons

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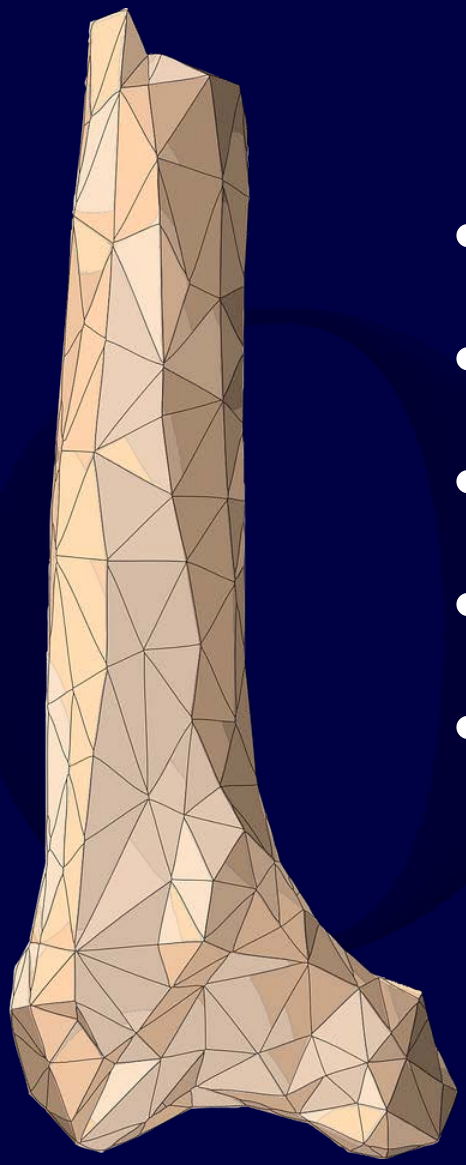
- McMaster Orthopaedics

Outline



- Why research?
- Study designs
- Outcome measurement
- Treatment effects
- Planning a trial

Why Research

Evidence Based Medicine (...and ortho)

1967 — 1991 — 2000 — 2003

Dr. Sackett

Founded the 1st Department of Clinical Epidemiology and Biostatistics

Dr. Guyatt

Coined the term "Evidence Based Medicine"

Dr. Swiontowski

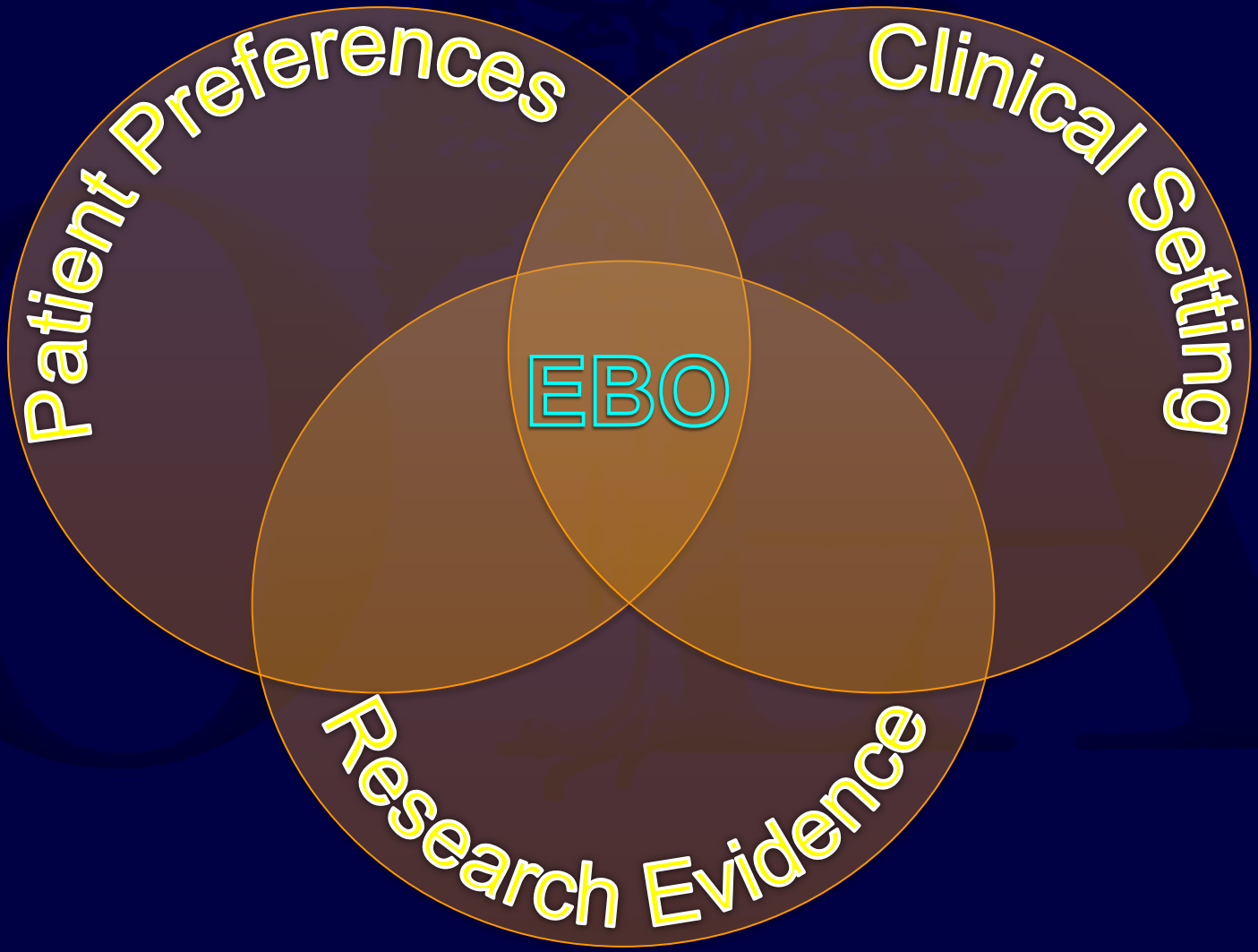
Introduced "Evidence Based Orthopaedics" to JBJS

Dr. Bhandari

Introduced "Evidence Based Orthopaedics" to JOT

Why Research

Evidence Based Orthopaedics (EBO)



Why Research

The Role of Clinical Trials in EBO

The 5 A's of of Evidence-Based Medicine[1]

Formulate the question	Search for the best evidence	Assess the quality of the evidence	Use the best applicable evidence	Combine the evidence with patient and provider preferences
Ask	**Acquire**	**Appraise**	**Apply**	**Act**

CLINICAL TRIALS

1. Bhandari, M., & Giannoudis, P. V. (2006). Evidence-based medicine: What it is and what it is not. *Injury*, *37*, 302–306.

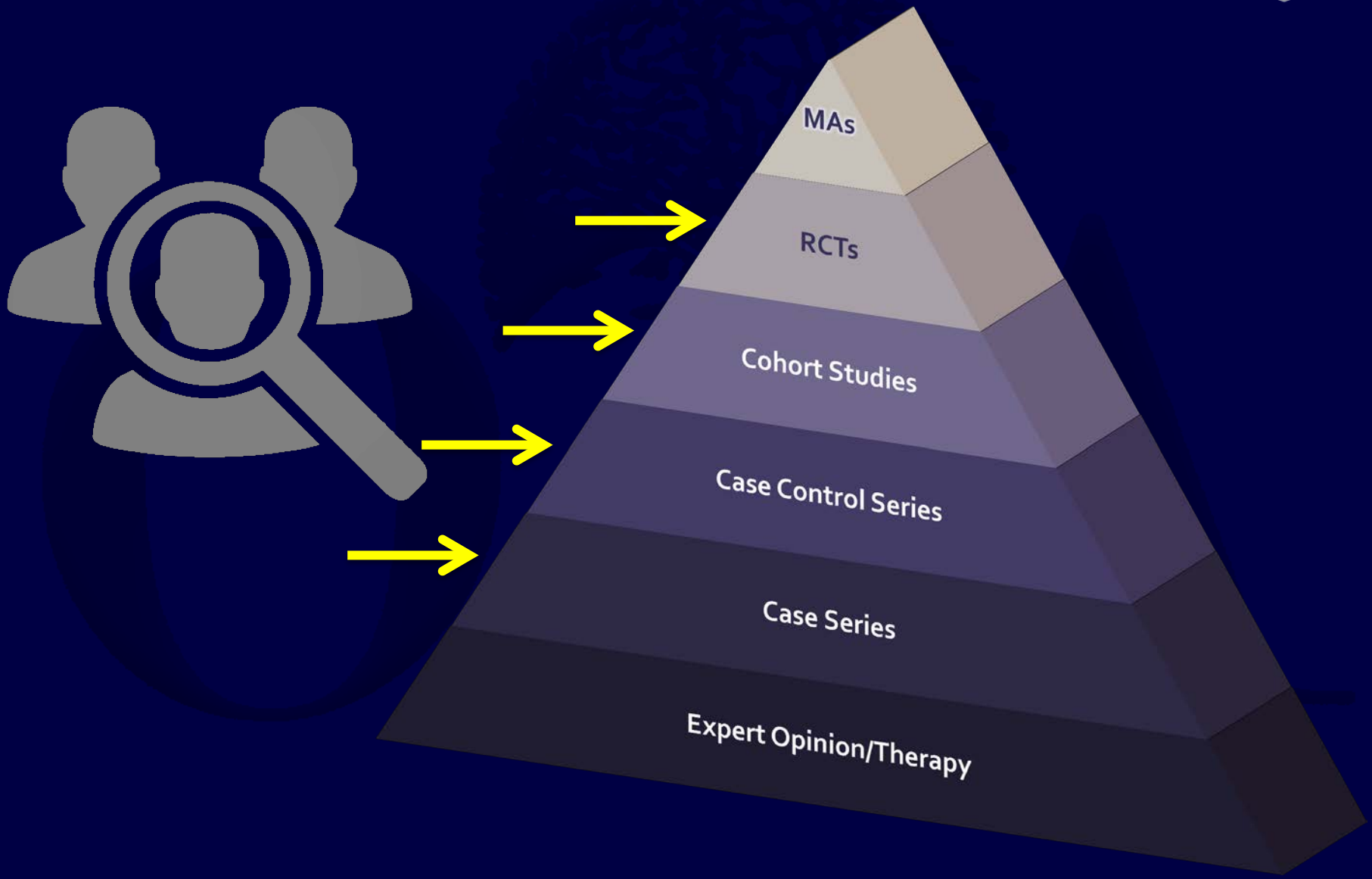
Why Research

Hierarchy of evidence

For therapeutic studies investigating a treatment intervention (i.e. a novel surgical technique)

Schunemann HJ, bone L. Part IV. Evidence-based orthopaedics: a primer. Clin Orthop Relat Res 2003; 413: 117-132

Clinical Trial Designs



Clinical Trial Designs

Types of Bias

Selection Bias

- Systematic error due to difference in study groups in measured and unmeasured characteristics, leading to differential prognosis of outcome

Recall Bias

- The increased likelihood of patients with an adverse outcome to recall exposure compared to those who do not sustain an adverse outcome

Detection Bias

- Differential assessment of outcome between groups influenced by knowledge of treatment allocation by assessors

Performance Bias

- Systematic differences in care provided to study groups independent of intervention under investigation

Attrition Bias

- Systematic difference in Individuals who drop out of a study compared to those who remain

Expertise Bias

- Differential ability or conviction of treatment providers (surgeons) in one intervention under investigation compared to another

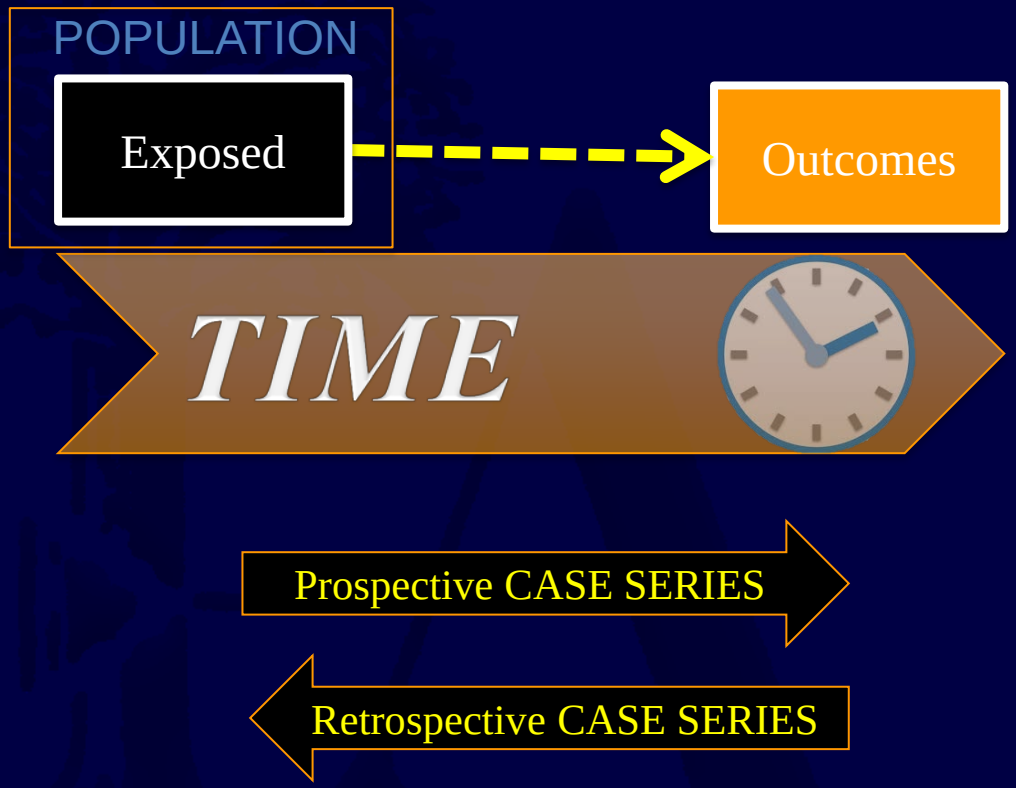
Clinical Trial Designs

Clinical Case Series

Level IV evidence
- No comparison arm
- Can be prospective or retrospective

Advantages
- Easy to perform
- Require few resources

Disadvantage
- Prone to selection bias, recall bias, performance bias and expertise bias
- Cannot derive an estimate of treatment effect

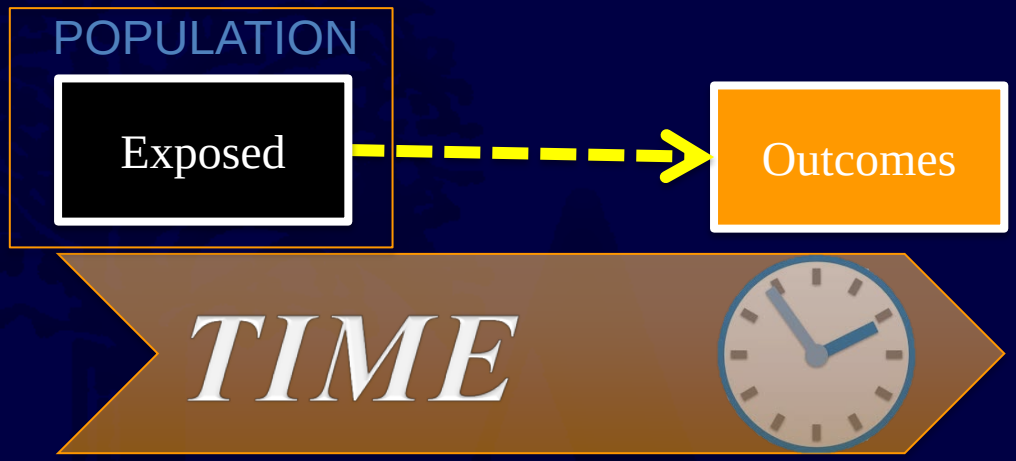


Clinical Trial Designs

Clinical Case Series

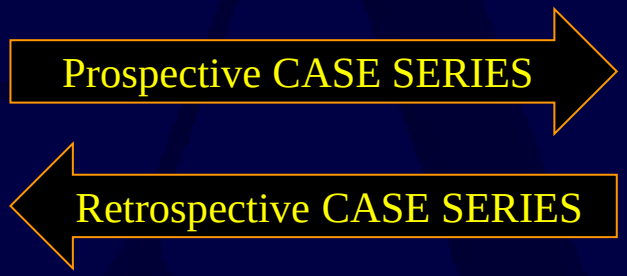
Useful for

- Evaluating novel surgical techniques
- Assessing feasibility prior to a more advanced trial
- Providing baseline data to inform sample size



Well designed case series have

- *A priori* study protocol
- Clear inclusion/exclusion criteria
- Prospective data collection
- Consecutive patient enrollment
- High follow-up
- Clinically relevant outcome measures



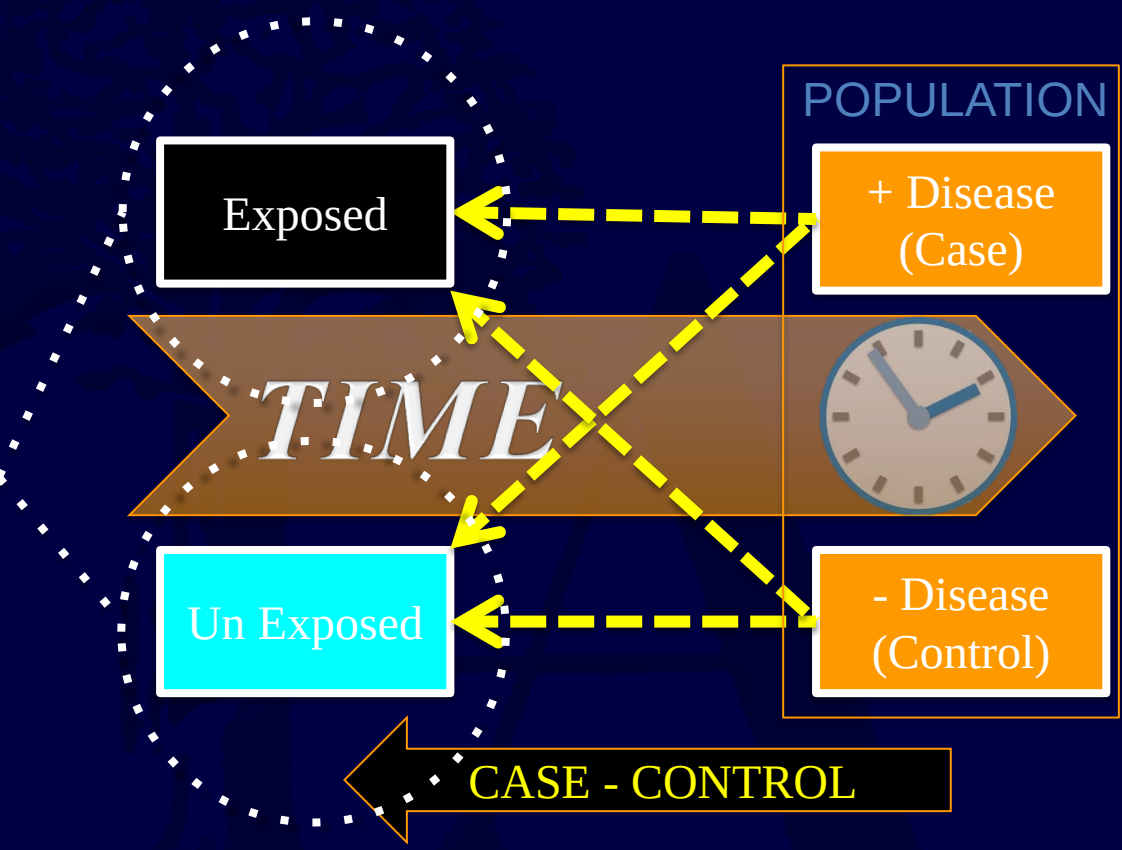
Clinical Trial Designs

Case-Control

Two groups
- Cases (+ outcome)
- Controls (– outcome)

Analyzed retrospectively
- Compared for ***exposure to risk factors***
  - Patient characteristics
  - Fracture characteristics
  - Treatment options

Measure the strength of association between the risk factors and outcome
- Odds ratio (OR)



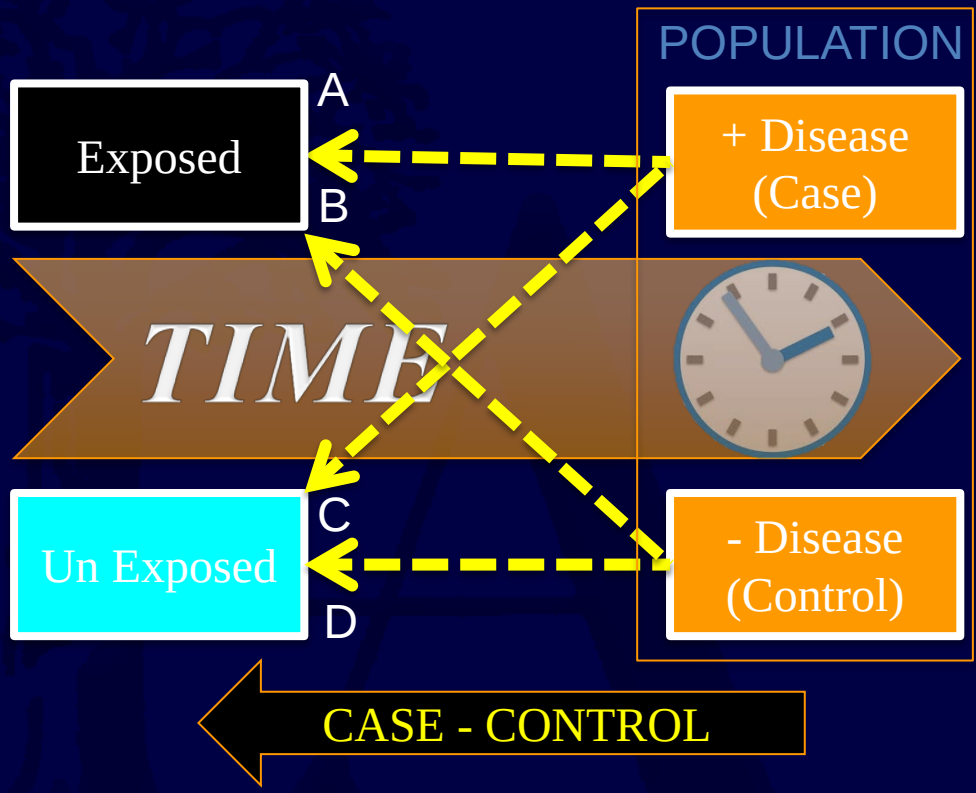
Clinical Trial Designs

Case-Control

Odds ratio (OR)

	OUTCOME	
EXPOSURE	+ (Case)	- (Control)
Yes	A	B
No	C	D
Odds of Exposure	A/C	B/D

$$(OR) = \frac{A/C}{B/D} = \frac{AD}{BC}$$



- The OR can be 0 to ∞ (OR of 1 = no difference)
- Multiple regression techniques can assess the strength of association of a particular risk factors while controlling for others

Clinical Trial Designs

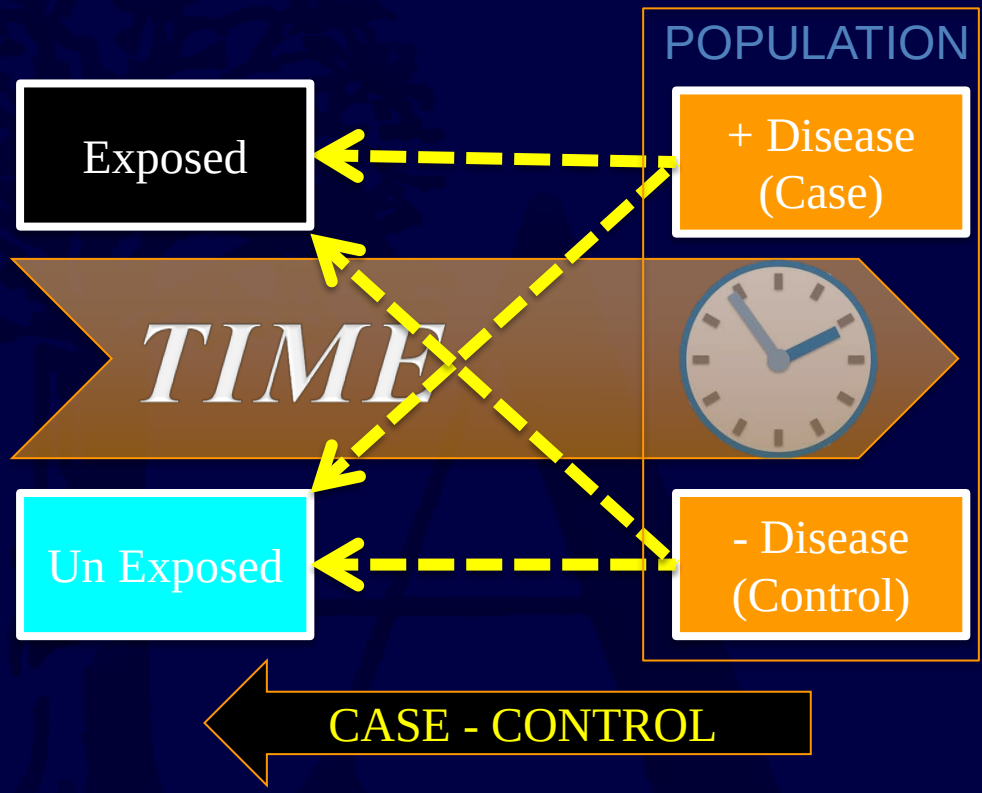
Case-Control

Advantages

- useful for rare outcomes, or outcomes that develop over a long time
- Simple to conduct
- Relatively low cost

Disadvantages

- Subject to multiple bias'
  - Selection bias
  - Recall bias
  - Performance bias
  - Confounding
- May "over-match" the control group

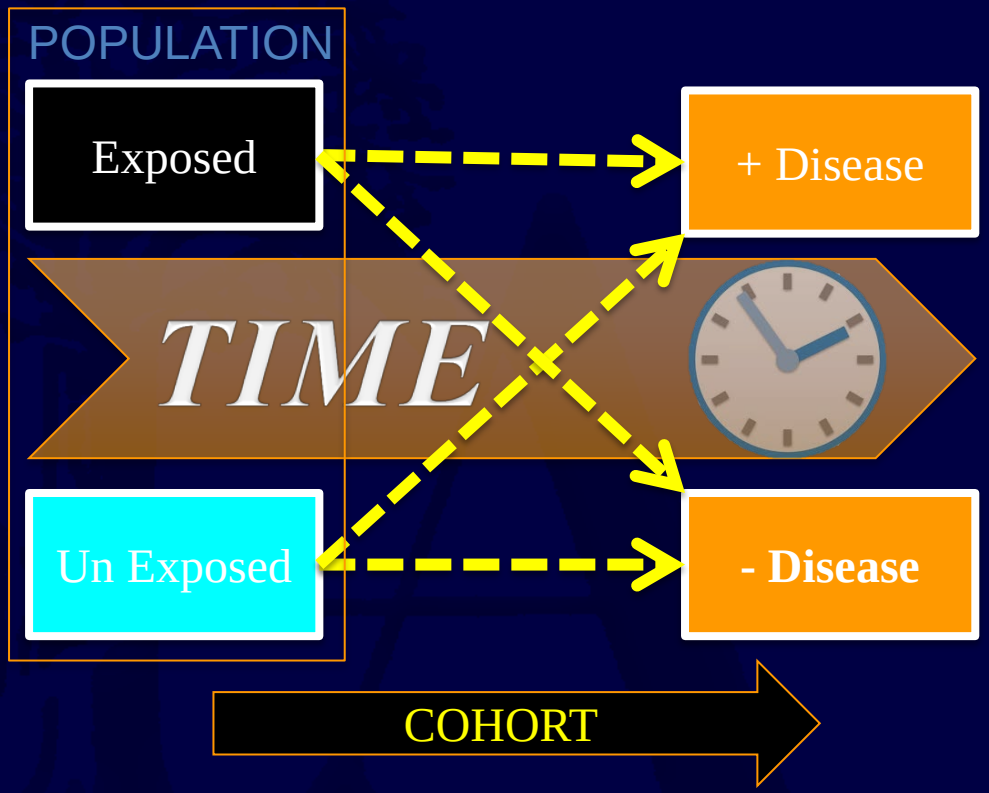


Clinical Trial Designs

Prospective Cohort*

Two groups
- Exposed
- Unexposed

- *allocated "naturally" at baseline*
- Followed prospectively for outcomes of interest



*can also have a retrospective cohort, where exposure characteristics are identified retrospectively (ie by type of treatment) and followed forward for the development of the outcome interest

Clinical Trial Designs

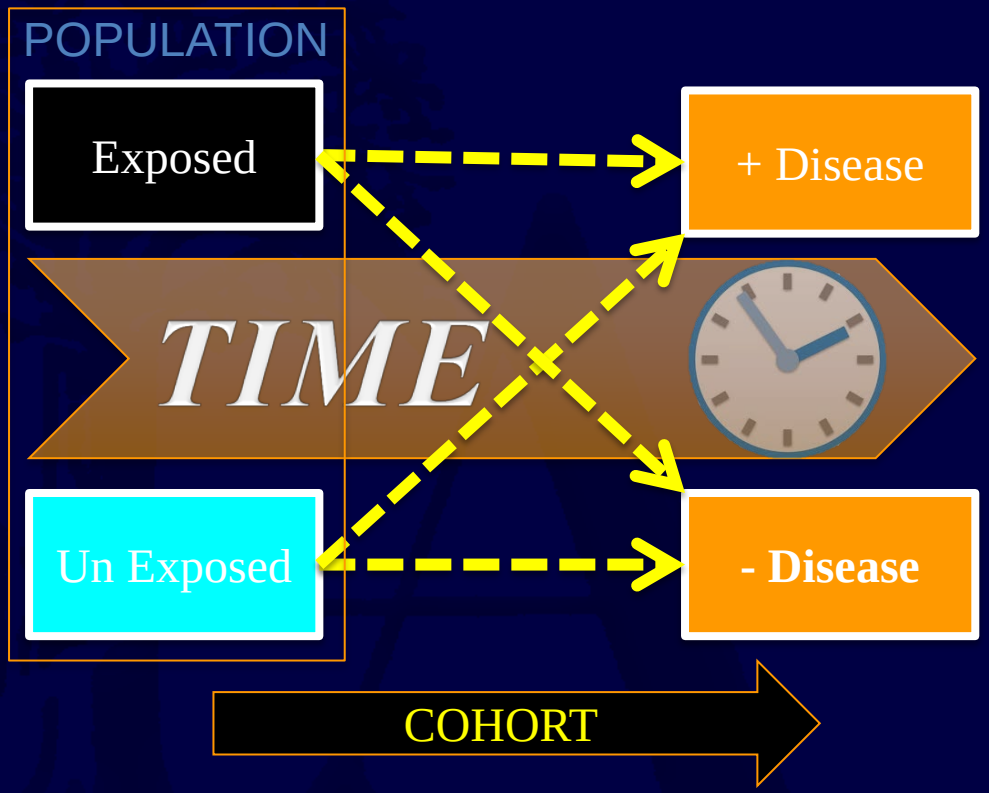
Prospective Cohort

Advantages

- Resistant to recall bias
- Timeline of progression is evident
- Can match groups for known confounding variables
- Can standardize eligibility
- Can standardize outcomes

Disadvantages

- Resource intensive
- Less strength in treatment effect inferences (vs RCTs)
- Subject to selection bias, detection bias, performance bias, confounding & attrition



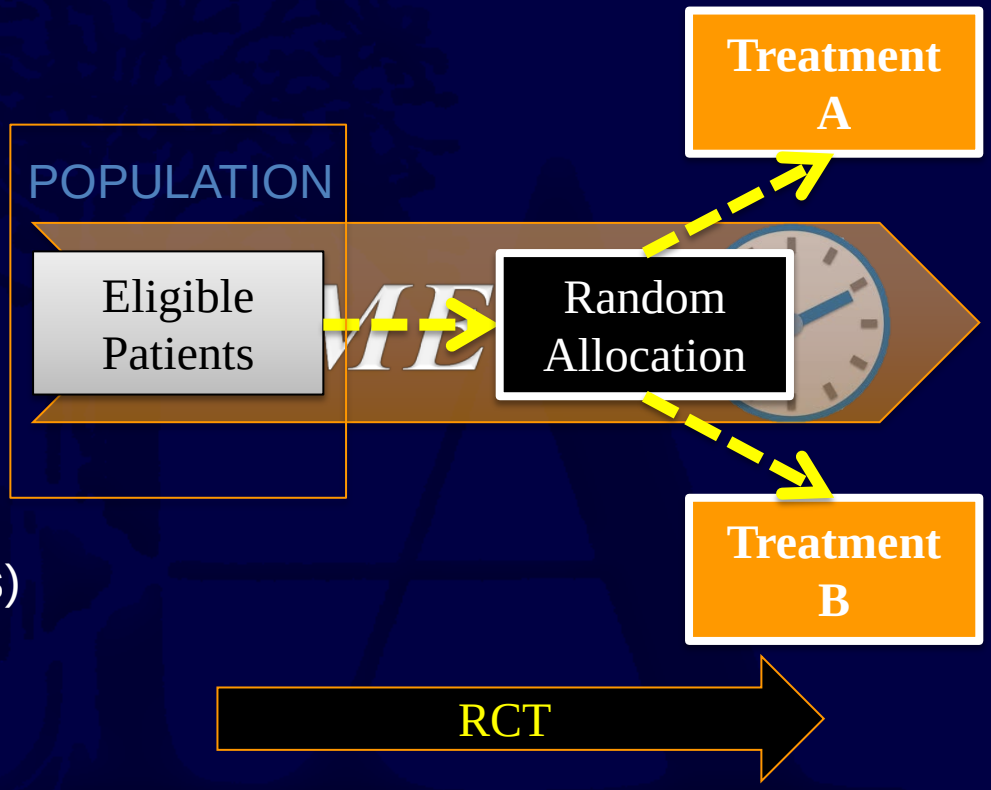
Clinical Trial Designs

Randomized Controlled Trial

- Represent the highest quality of evidence

- A population of eligible patients is identified prospectively with inclusion/exclusion criteria
  - Explanatory trial (efficacy)
    - Strict criteria
  - Pragmatic trial (effectiveness)
    - Less stringent criteria

- randomly allocated
  - Mitigates *selection bias*
  - Balances groups on confounders (known and unknown)
  - Isolates the treatment effect

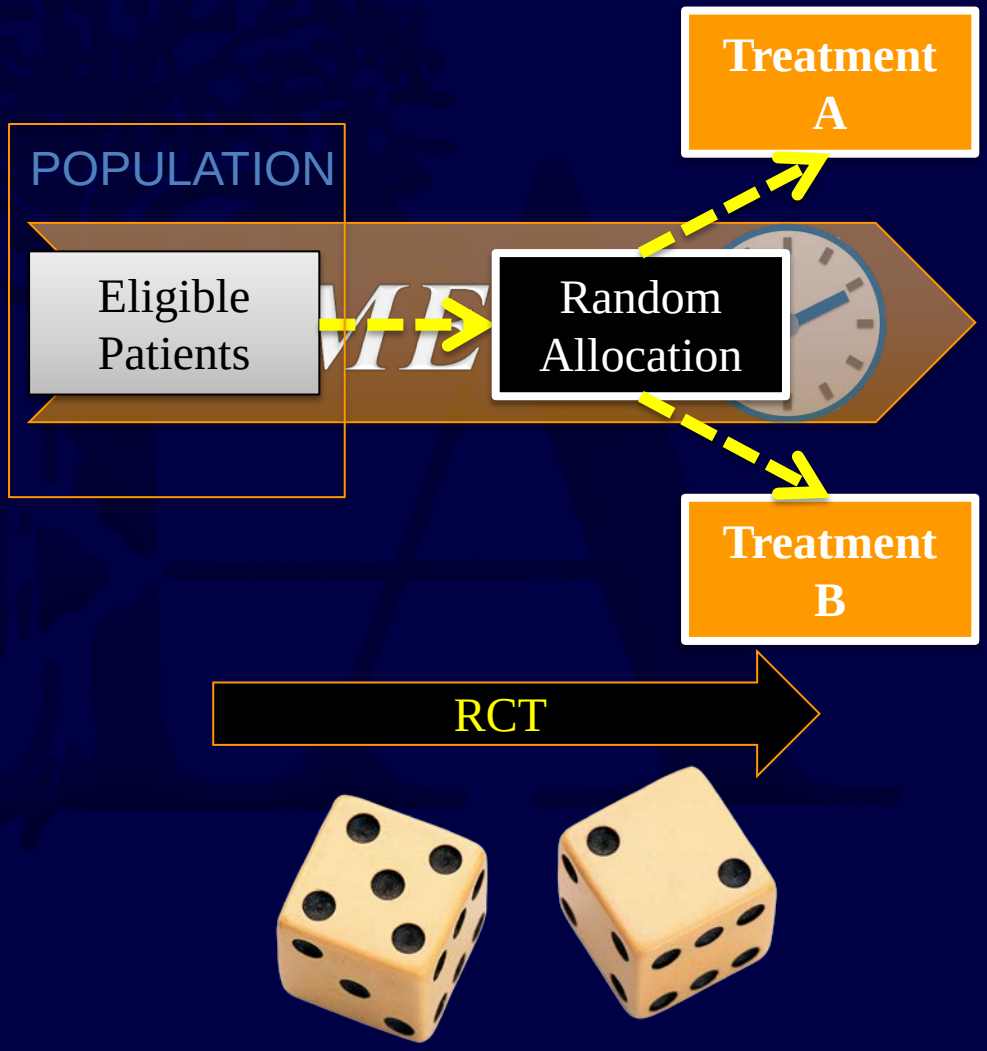


Clinical Trial Designs

Randomized Controlled Trial

Further steps to protect against *Selection Bias*

- Concealment
  - Individual identifying eligible patients unaware of which treatment arm patient will be allocated to
  - Avoids preferential enrollment and allocation of patients with favorable prognostic characteristics
  - Best done centrally (off-site from the center of enrollment), and with variable blocks *(more later)*



Clinical Trial Designs

Randomized Controlled Trial

Further steps to protect against *Detection/performance Bias*

- Blinding
  - Keeping one (or more) individuals unaware of treatment allocation
  - Can blind:
    - The patient
    - Treating clinicians (surgeons)
    - Other clinicians
    - Data collectors
    - Outcome assessors
    - Data analysts
    - Manuscript team

Clinical Trial Designs

Randomized Controlled Trial

Further steps to protect against *Other Bias*

- Blinding
  - Feasibility of who can be blinded will vary based intervention being investigated
  - Pharmacologic interventions
    - Blinded with use of placebos
  - Surgical interventions
    - Blinded with use of sham surgery

The New England Journal of Medicine

VOLUME 347 JULY 11, 2002 NUMBER 2

A CONTROLLED TRIAL OF ARTHROSCOPIC SURGERY FOR OSTEOARTHRITIS OF THE KNEE

J. BRUCE MOSELEY, M.D., KIMBERLY O'MALLEY, PH.D., NANCY J. PETERSEN, PH.D., TERRI J. MENKE, PH.D., BARUCH A. BRODY, PH.D., DAVID H. KUYKENDALL, PH.D., JOHN C. HOLLINGSWORTH, DR.P.H., CAROL M. ASHTON, M.D., M.P.H., AND NELDA P. WRAY, M.D., M.P.H.

RCT of 180 patients that assessed the arthroscopic surgery of knee OA by randomizing patients to either arthroscopic surgery or sham surgery arms

Clinical Trial Designs

Randomized Controlled Trial

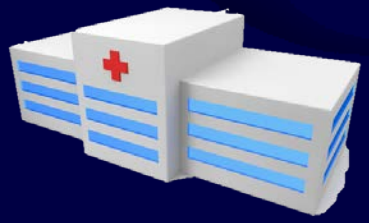
Possible Units of Randomization

By patient

Eligible Patients → Random Allocation → **Treatment A** / **Treatment B**

By expert (ie Surgeon)

Eligible Patients → Random Allocation → **Surgeon (A) Performs Treatment A** / **Surgeon (B) Performs Treatment B**



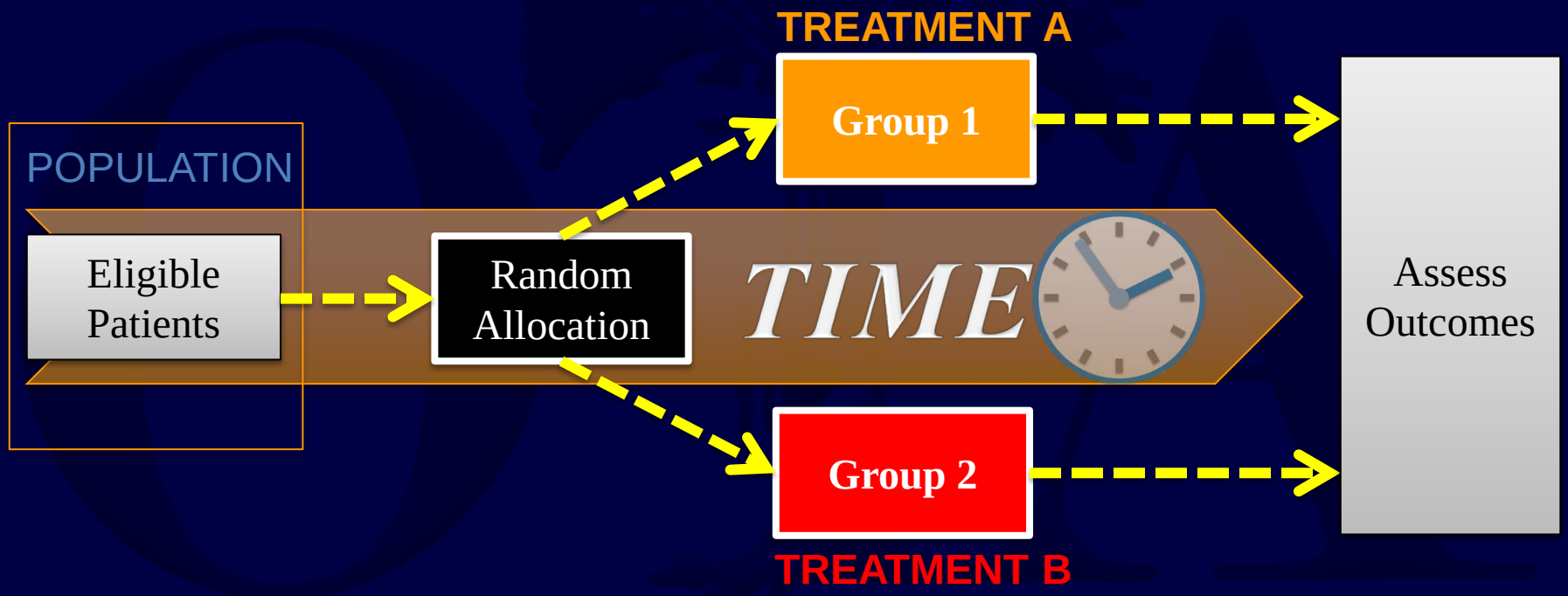
By Cluster (ie Trauma Center)

Participating trauma centers → Random Allocation → **Trauma Center (A) Provides Treatment A** / **Trauma Center (B) Provides Treatment B**

Clinical Trial Designs

Randomized Controlled Trial

Parallel Trial Design

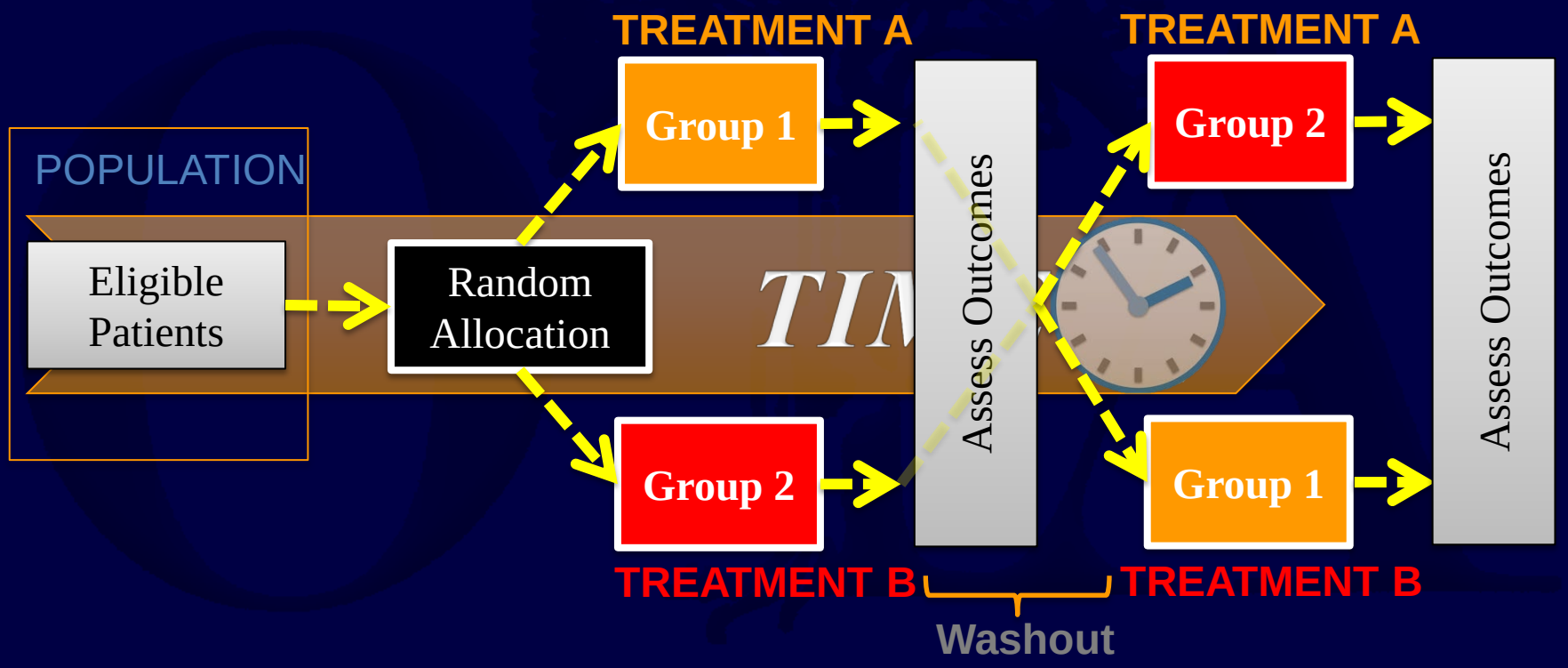


Busse JW, Bhandari M, Schemitsch EH. Randomized trails in surgery. Tech Orthop 2004; 19:77-82

Clinical Trial Designs

Randomized Controlled Trial

Cross-over Trial Design



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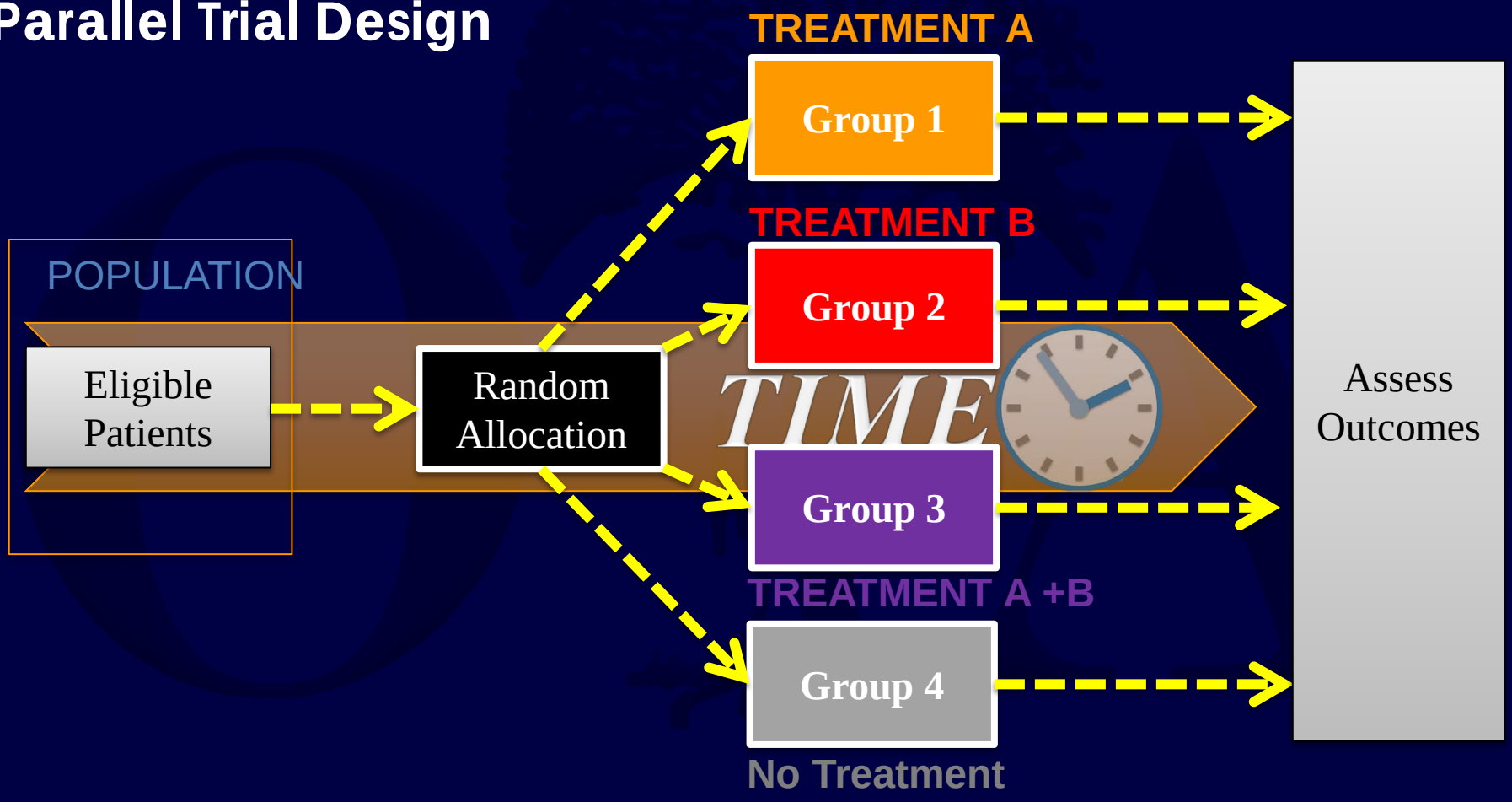
Clinical Trial Designs

Randomized Controlled Trial

Parallel Trial Design



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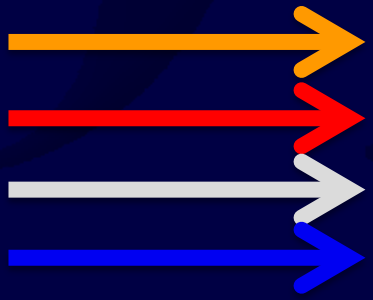
Clinical Trial Designs

Randomized Controlled Trial

RCT Trial Designs

		✓	✗
• Parallel		• Simple design • Easy to apply to most interventions/injuries	• Each (additional) intervention studied requires a large incremental sample size increase
• Crossover		• Smaller sample size required • All baseline characteristics distributed evenly	• Prone to carryover and period effect • Can only test rapid acting treatment in chronic conditions
• Factorial		• Can assess the effect of combined therapies	• Prone to interaction effects

Busse JW, Bhandari M, Schemitsch EH. Randomized trails in surgery. Tech Orthop 2004; 19:77-82

Outcome Assessment

Types of Outcomes

The effectiveness of an intervention is dependent on the outcome by which it is measured

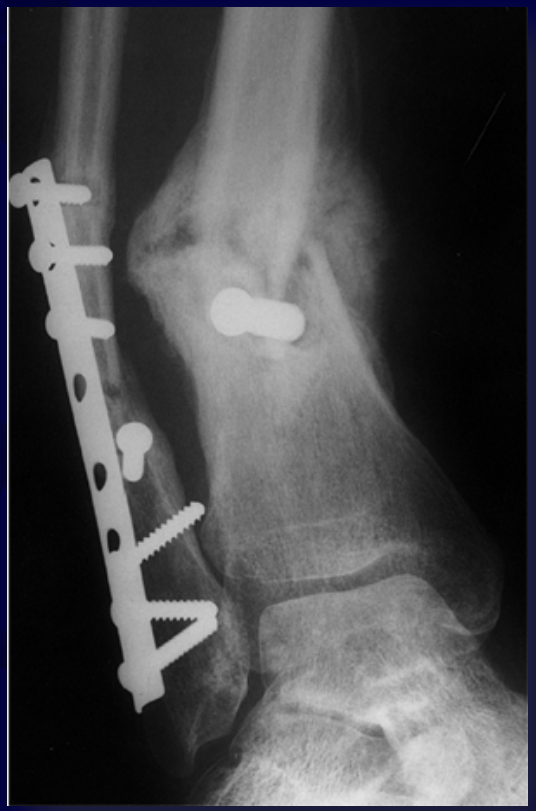
CLINICAL OUTCOMES

- Blood Loss
- Time to fracture healing
- Surgical time
- Range of Motion

continuous

- Adverse events
  - Non-union
  - Mal-union
  - Reoperation/Revision
  - Death

dichotomous



Outcome Assessment

Types of Outcomes

Increased emphasis is placed on patient important outcomes

HEALTH RELATED QUALITY OF LIFE

Generic

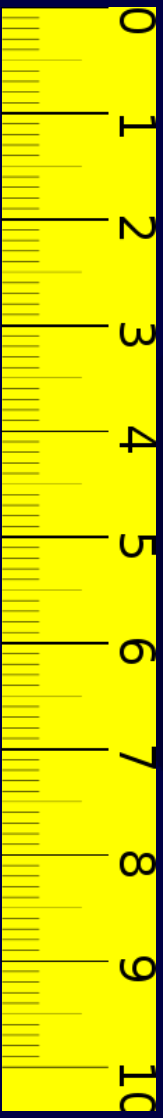
- Measure of general health status
- Reflective of physical symptoms, function and emotional dimensions of health

Disease Specific

- Inquire about specific aspects of a disease (injury or limb)
- More comprehensive

Outcome Assessment

Outcome Characteristics



RELIABILITY

Does a tool repeatedly give the same results in a stable population

- when used by the same user **(Intra-observer Test-rest)**
- different users **(inter-rater)**

VALIDITY

Face Validity - an instrument appears to measure what it intends to

Content Validity - the components of a tool reflect the components of what the tool sets out to measure

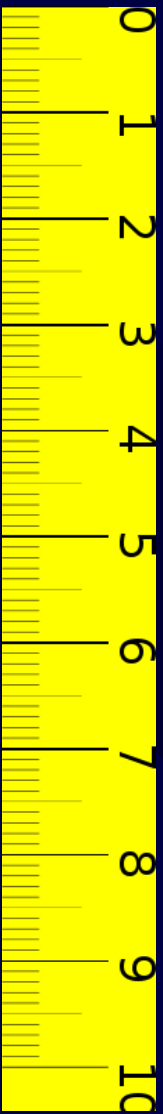
Construct Validity - the measurements of a tool reflect the direction and magnitude of observation as expected

RESPONSIVENESS

The ability of a tool to reflect the underlying changes in a population and discriminate between treatment effects

Outcome Assessment

Outcome Characteristics



RESPONSIVENESS

100 (Perfect Health)

Ceiling effect

Floor effect

0 (Worst Health)

Outcome Assessment

Common Examples

Generic Measures

SF-36

SF-12

SIP

Utility Measures

HUI

EQ5D

SF-6

Disease Specific Measures

DASH

SST

MEPS

WOMAC

HHS

KOOS

AOFAS…

Treatment Effects

Presentation of Results

	Non-union	Union
Treatment	**10** (A)	**90** (B)
Control	**50** (C)	**50** (D)

Treatment Event Rate (TER)
A/(A+B) = 10/100 = 10%

Control Event Rate (CER)
C/(C+D) = 50/100 = 50%

Relative Risk (RR)

TER/CER = 10/50 = 0.2

Relative Risk Reduction (RRR)

1 – RR = 1-0.2 = 0.8 or 80% -> *Treatment reduces the risk of non-union by 80%*

Absolute Risk Reduction (ARR)

CER – TER = 50%-10% = 40%

Number Needed to Treat (NNT)

1/ARR = 1/0.40 = 2.5 -> *for every 2.5 patients treated, one non-union can be avoided*

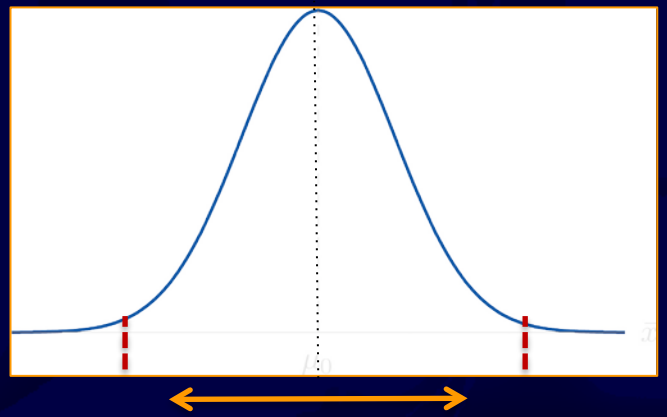
Odds Ratio (OR)…see earlier slides

AD/BC = (10 x 50)/(90 x 50) = 0.11 -> *The odds of non-union in the treatment group compared to the controls is 0.11*

Treatment Effects

Confidence Intervals (CI)

- Range of values around an effect estimate, within which the true (unknown) population effect lies
- Effected by:
  - Variability within the sample population
  - Sample Size
  - Level of confidence defined (commonly 95%CI)



- The effect estimate will lie outside of the defined CI only by chance (commonly 5% of the time)

Treatment Effects

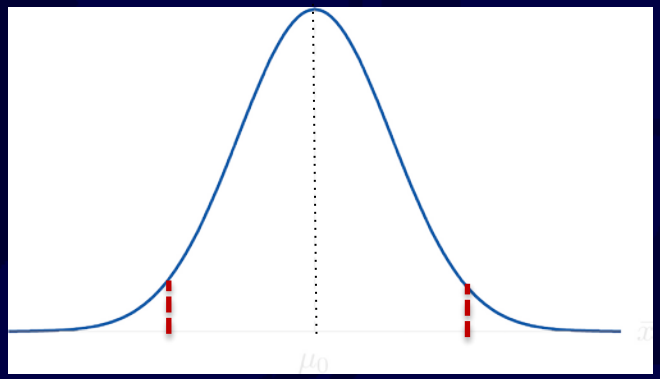
Hypothesis Testing

Null Hypothesis (H_0)

The statement that the investigator is studying and possibly trying to disprove

- For therapeutic trials H_0: Treatment A = Treatment B *(effect size = 0)*

$$\mu_A = \mu_B$$



μ = Mean Treatment effect of treatment group

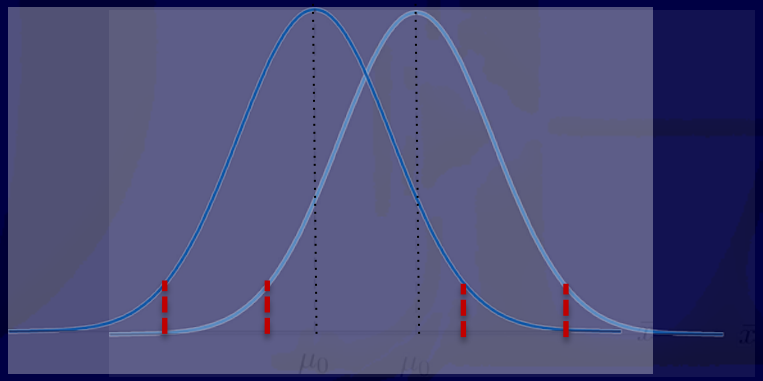
Treatment Effects

Hypothesis Testing

Null Hypothesis (H_0)

- Not likely that results from two groups tested will be exactly equal
  - As they diverge, at what point can we say the two groups are not equal (i.e. reject H_o)

$\mu_A = \mu_B$



Treatment Effects

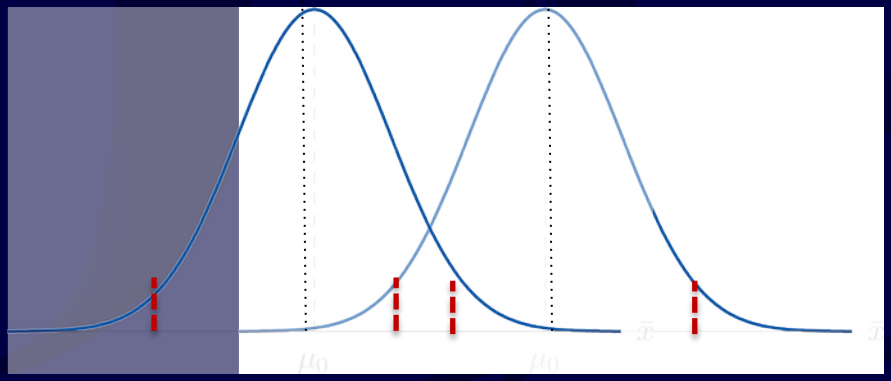
Hypothesis Testing

Alternate Hypothesis (H_A)

Once the effect estimates fall outside of the defined CI, we can reject H_o, and accept the alternate hypothesis (H_A)

- For therapeutic trials H_A: Treatment A ≠ Treatment B

$\mu_A \neq \mu_B$

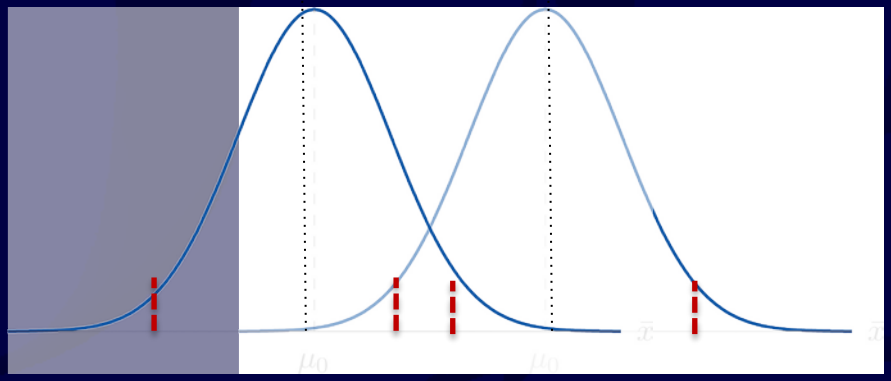


Treatment Effects

P value

- The probability (assuming that no difference), of finding a result that falls outside of the confidence interval (typically 0.05)
- "statistically significant" = unlikely to observe a value this extreme due to chance alone

$\mu_A \neq \mu_B$



- Statistical significance ≠ Clinical significance

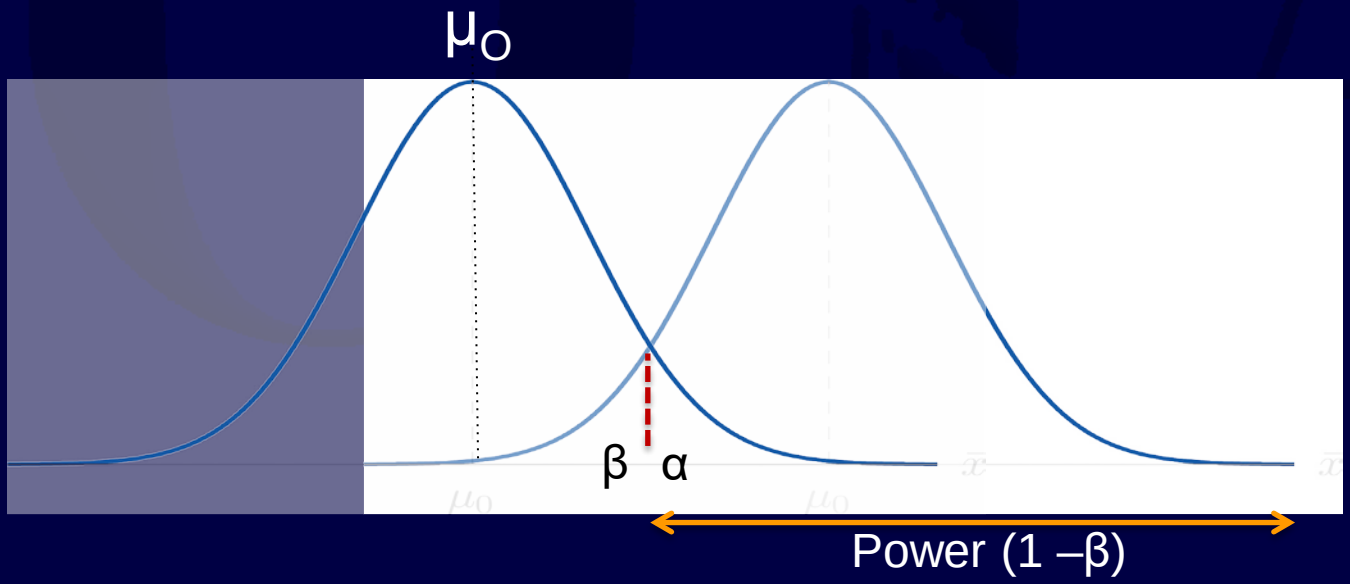
Treatment Effects

Understanding Error

	TRUTH	
STUDY	Difference	No Difference
Difference	Correct $(1 - \beta)$	Type I Error (α)
No Difference	Type II Error (β)	Correct

α = probability of false rejection of the null hypothesis

β = probability of false acceptance of the null hypothesis



Trial Planning

1. Ask a clinically important question

- **P** – Population
- **I** – Intervention
- **C** – Comparator
- **O** – Outcome

Trial Planning

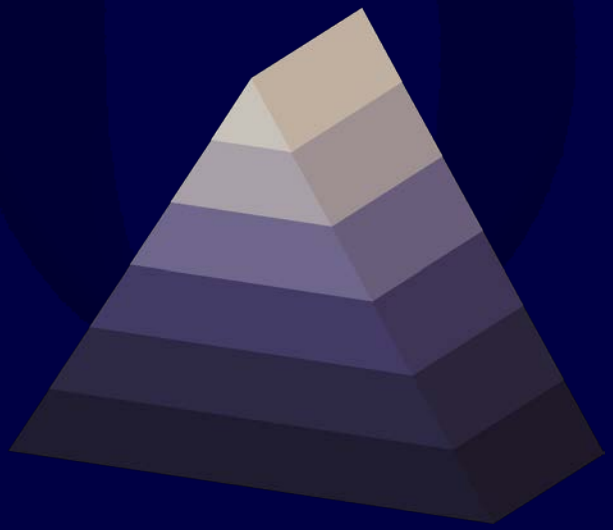
2. Conduct a comprehensive literature search

- Systematically search known databases
  - Cochrane
  - Pubmed
  - Embase
- Determine the gap in the literature
- Establish the need for the trial

Trial Planning

3. Select the Correct Study Methodology and Design

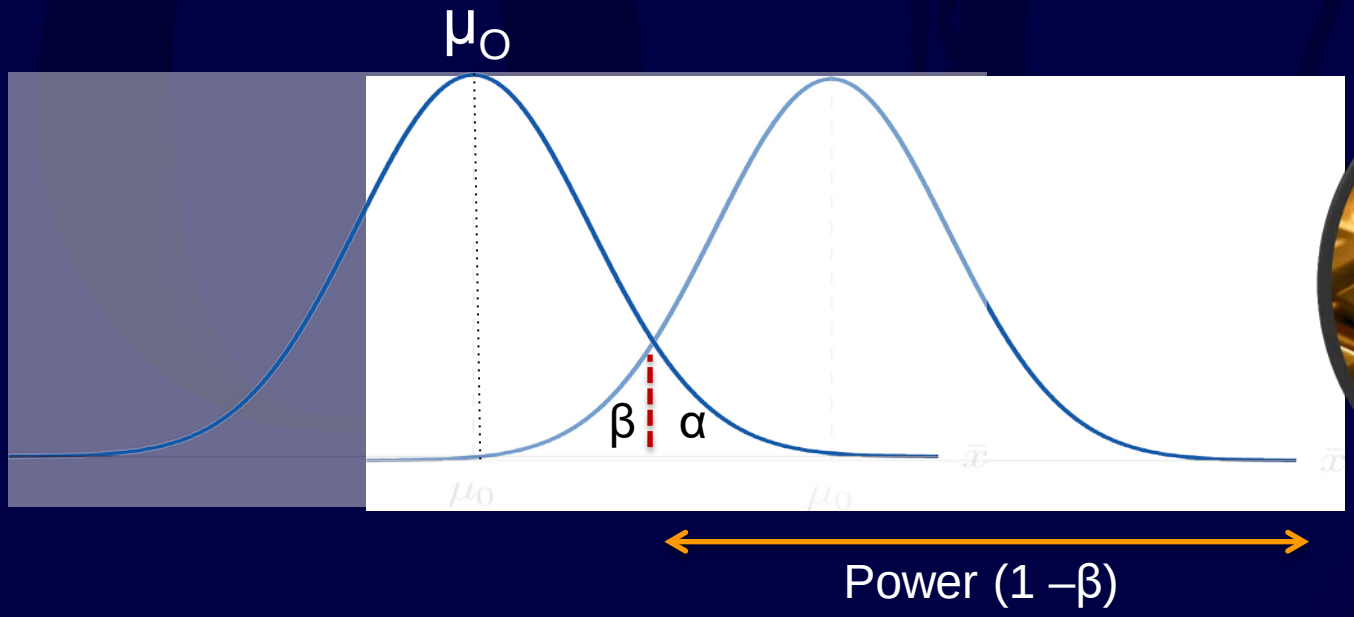
- Select the correct study design from the hierarchy of evidence
  - Choose the highest level of evidence that can be feasibly used to address the question
- Select the appropriate Outcome instruments based on the characteristics of the question



Trial Planning

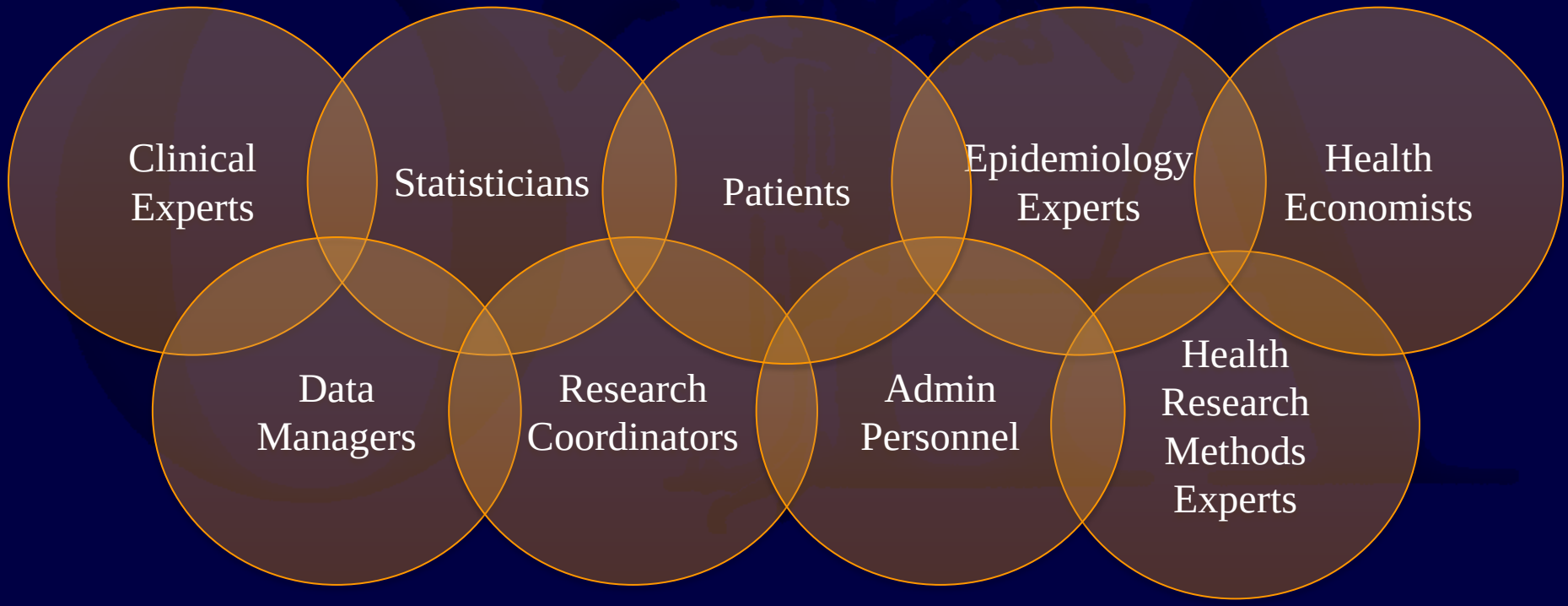
4. Determine the required sample size

- Set desired Power (1 –β)
  - Likelihood of determining a difference if one truly exists
- Set Type I error (α)
  - Chance of identifying a difference when one doesn't exist
- Set Delta (Δ)
  - Clinically important difference to detect



Trial Planning

5. Assemble Study Team



Good Luck!