Biostatistics & Clinical Application Review

A presentation for HealthTrust Members

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Speaker Disclosures

- The presenter has no real or perceived conflicts of interest related to this presentation.

- Note: This program may contain the mention of suppliers, brands, products, services or drugs presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand, product, service or drug.

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Objectives

- Describe different types of study design
- Complete statistical calculations including number needed to treat/harm, odds ratio and absolute risk reduction
- Evaluate trial results for statistical significance and clinical relevance

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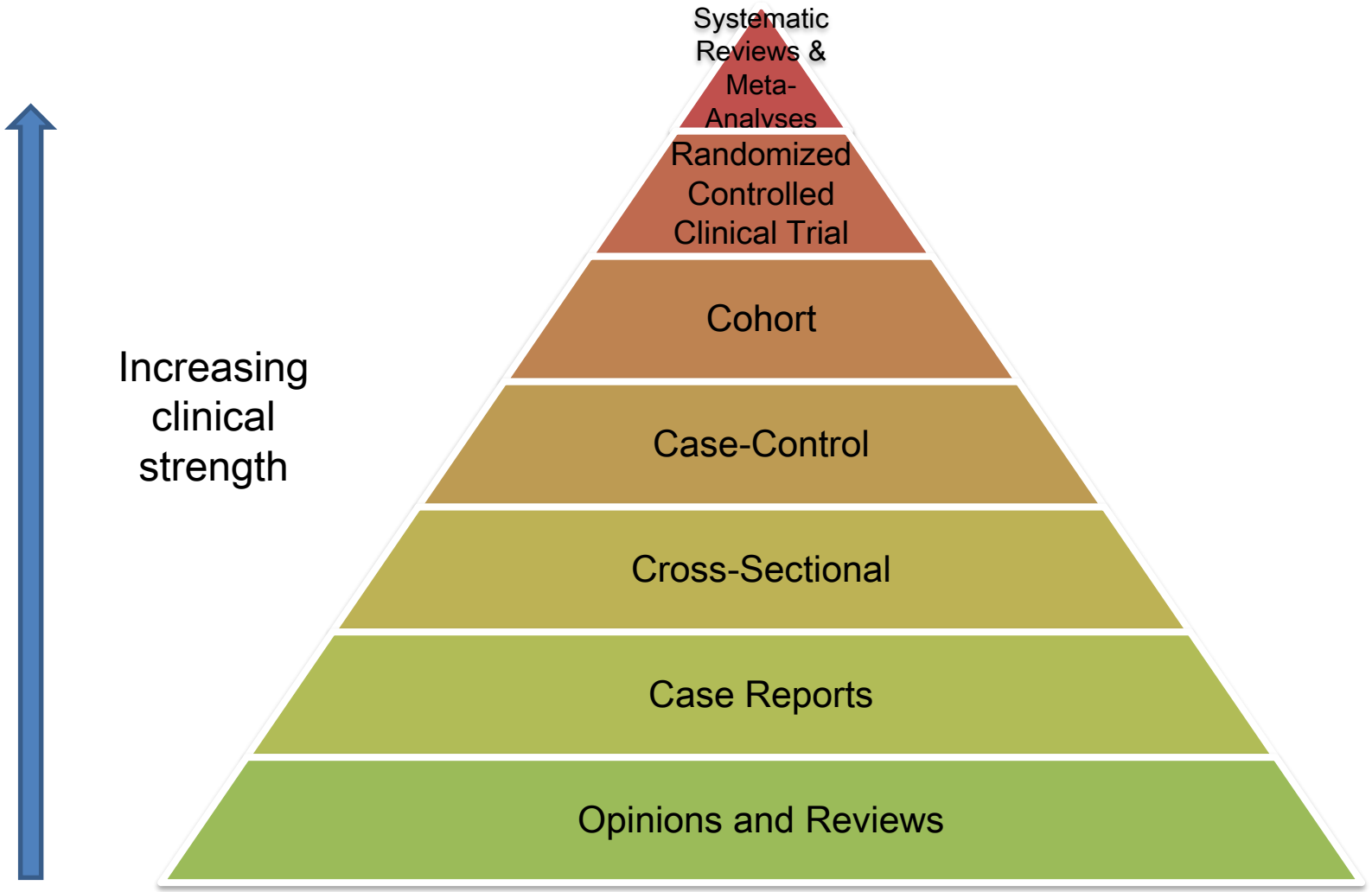
Research Types



Source: Dawson B, Trapp RG. Basic & clinical biostatistics, 5e. 2019.

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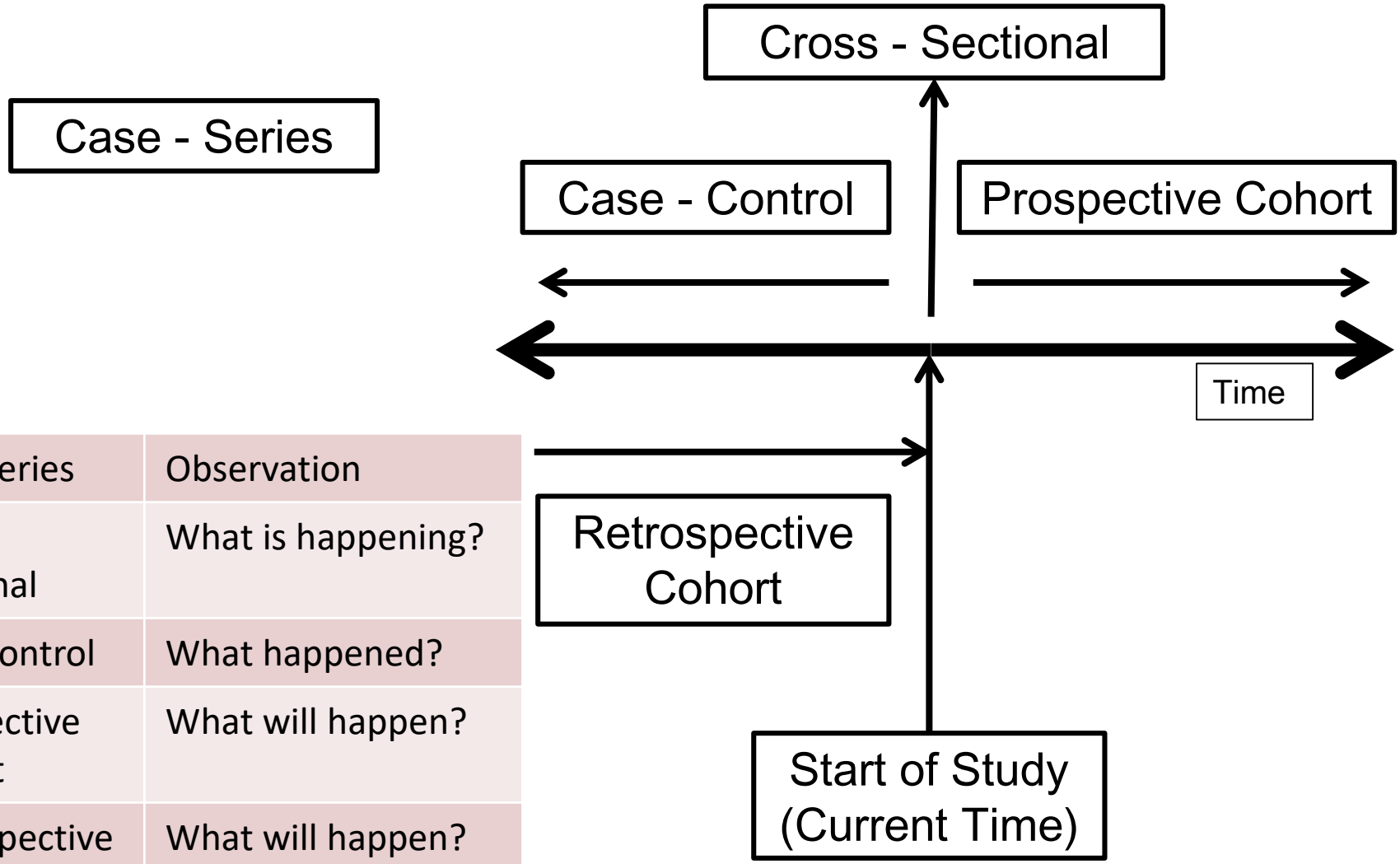
Observational Studies



Case-series	Observation
Cross-sectional	What is happening?
Case-control	What happened?
Prospective Cohort	What will happen?
Retrospective Cohort	What will happen? (modified)

Sources: Dawson B, Trapp RG. Basic & clinical biostatistics, 5e. 2019.
Kier KL. Pharmacotherapy. 2011;31:9-22

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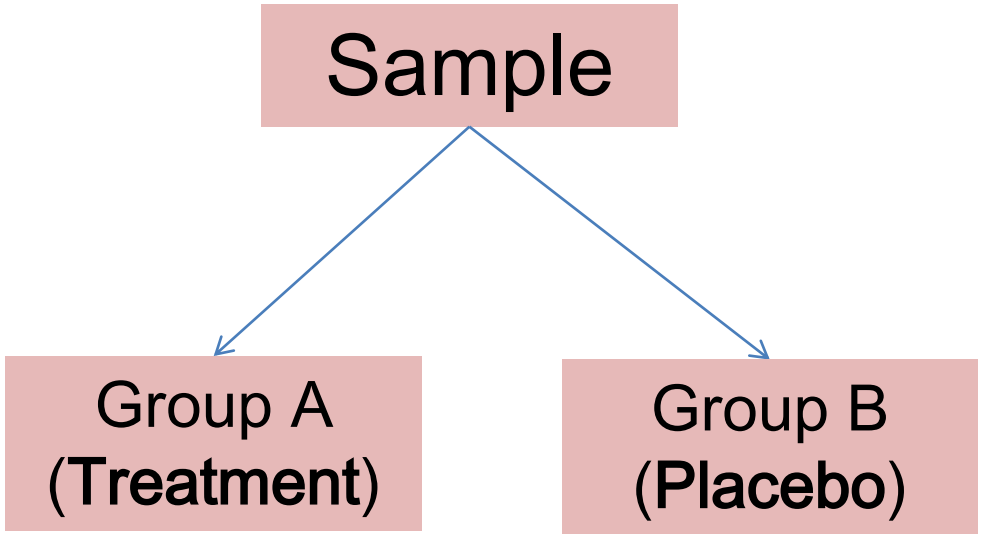
Controlled Clinical Trials: Concurrent Controls



Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.

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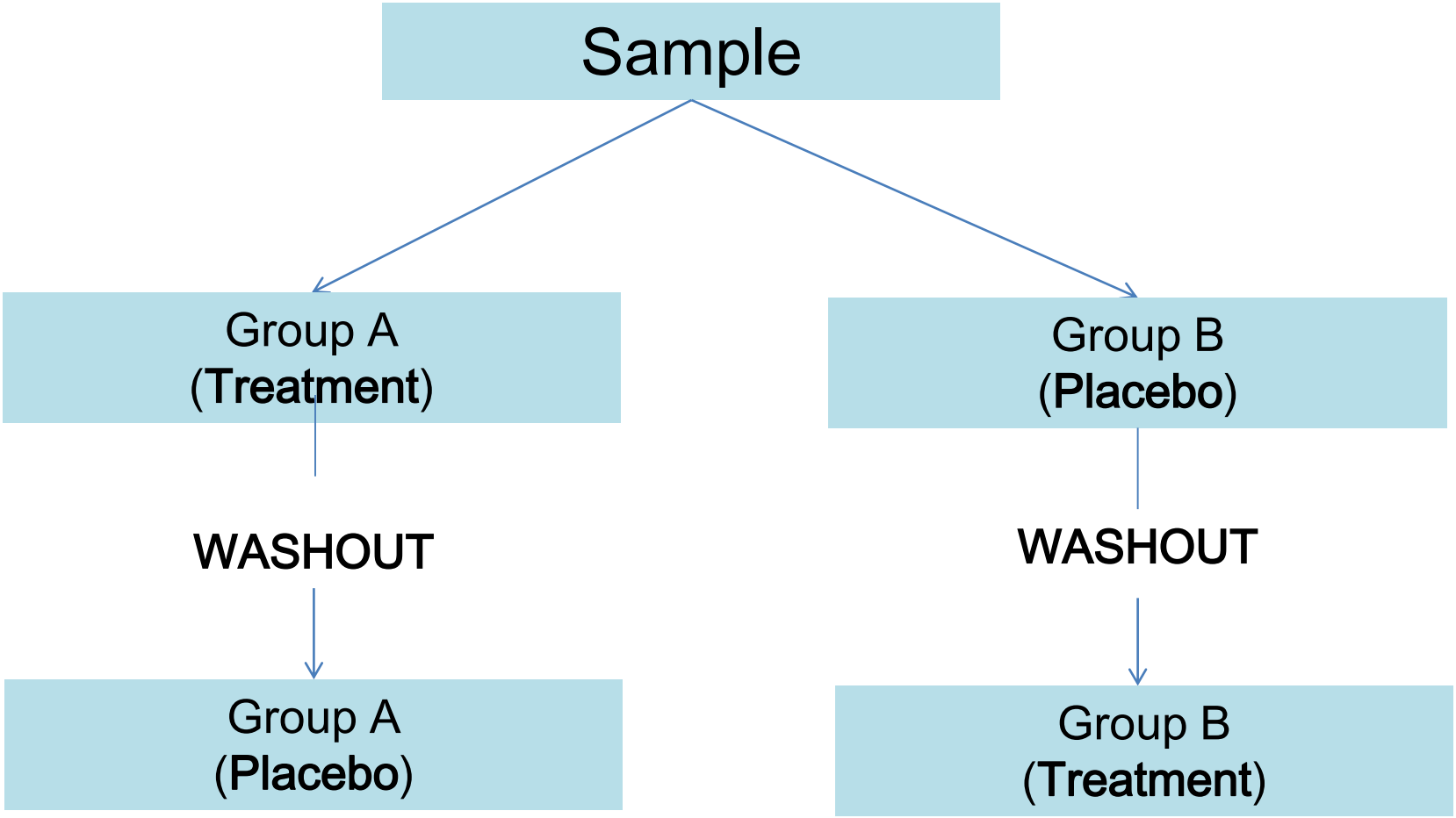
Controlled Clinical Trials: Self Controls



Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.

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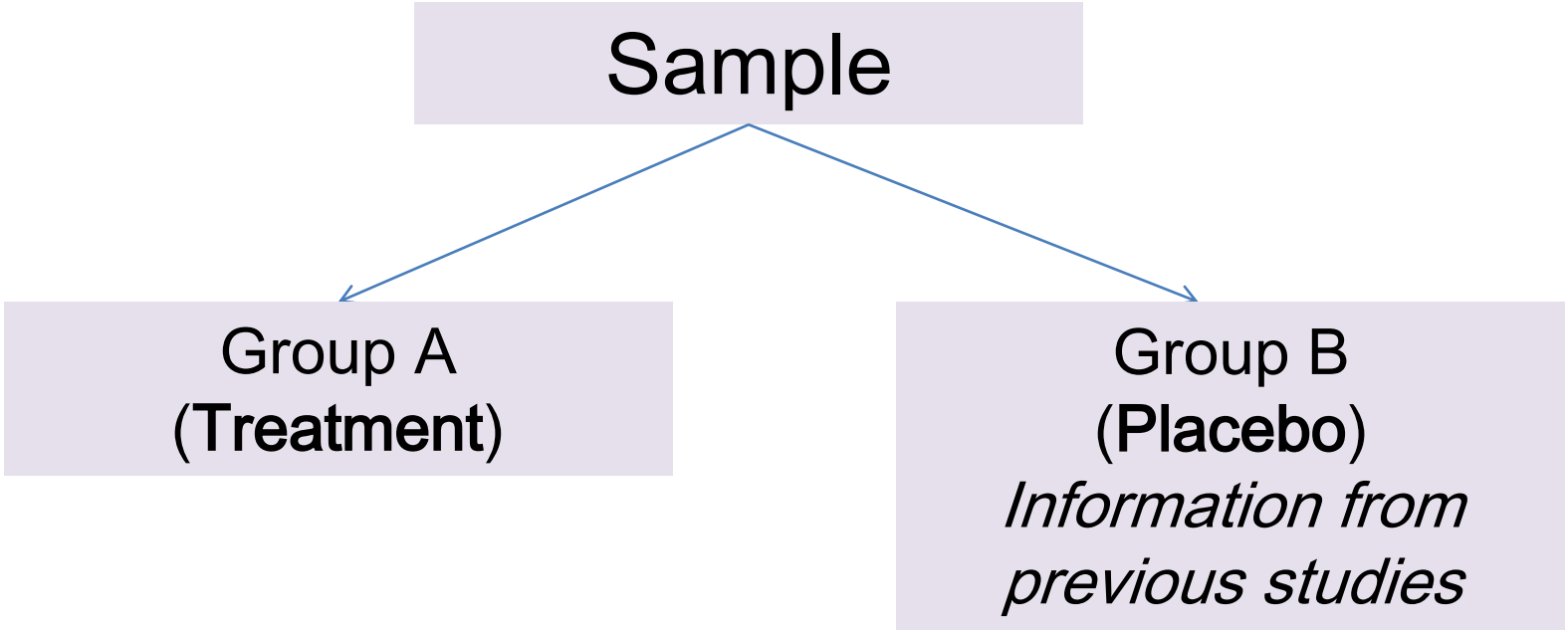
Controlled Clinical Trials: External Controls



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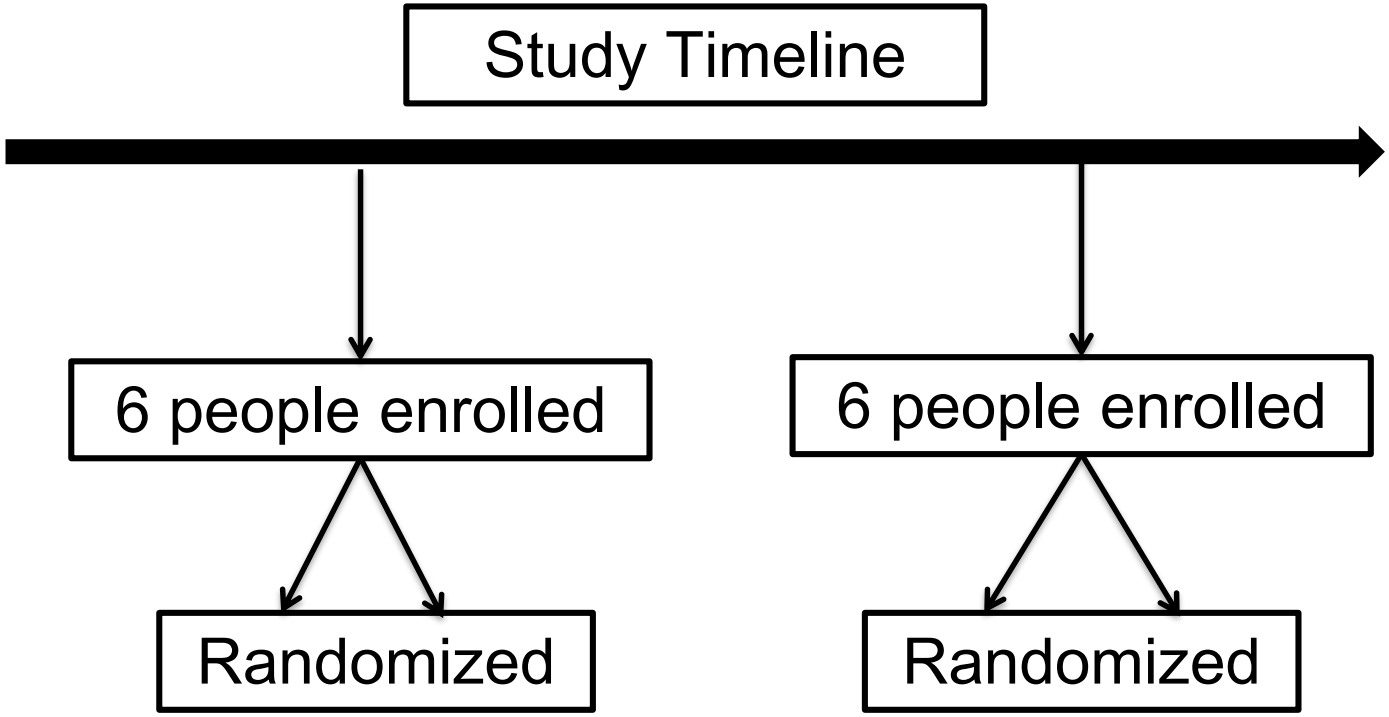
Controlled Trial Terminology



Blinding	Randomization	Other
Single vs. Double	Cohort vs. block	Double-dummy

Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.

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Trial Design

- Per-protocol
  - All patients who have completed the study and followed the study protocol
- Intent to treat
  - All patients randomized into the study
- Modified intent to treat
  - Similar to intent to treat, but patients have to have met the "modified" criteria (i.e. at least one dose of the study drug)
- As treated
  - Patients are placed into the study group of the drug they were in at completion

Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.

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Types of Data

Nominal	Ordinal	Continuous
Yes/No	Consistent order but no consistent magnitude	Constant and defined units of measure
Stroke vs. no stroke Death vs. no death BP > 140 mmHg vs. BP < 140 mmHg	Likert Scale Pain faces Cancer staging	Blood pressure Temperature Weight

Source: Dawson B, Trapp RG. Basic & clinical biostatistics, 5e. 2019.

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Statistical Tests: Descriptive Statistics

Type	Examples
Measures of Central Tendency	Mean (continuous data) Median (ordinal data) Mode (nominal data)
Measures of variability, dispersion, spread	Range, standard deviation (SD), variance – (continuous) Ratios, proportions, rates – (ordinal and nominal)

Source: Dawson B, Trapp RG. Basic & clinical biostatistics, 5e. 2019.

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Parametric vs. Nonparametric

- Parametric
  - Normal distribution
  - Need a large enough sample (usually >30)
  - Continuous data
- Nonparametric
  - Nominal and ordinal data
  - Continuous data with non-normal distribution

Source: Kier KL. Pharmacotherapy. 2011;31:9-22

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Statistical Tests

Data Comparing	Parametric Tests	Non-parametric Tests
Mean difference between 2 groups (continuous)	Student *t* Test	
Difference between 2 groups (ordinal, nominal, non-parametric)		Mann-Whitney U Test X^2 Test Fischer Exact Test
Difference between 3 or more groups	Analysis of Variance (ANOVA)	Kruskai- Wallis One-way ANOVA
Relationships between 2 or more variables	Regression and Correlation Linear Regression	Contingency Coefficient Logistic Regression
Survival analysis between 2 groups	Kaplan- Meier Method Cox Proportional Hazard Model	
Combining multiple studies	Meta-analysis	

Sources: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.
Kier KL. Pharmacotherapy. 2011;31:9-22

Important Study Numbers

Statistic	Definition
Alpha	Probability of having a type 1 error *(probability that results were due to chance)*
Beta	Used to calculate Power (Power = 1 – beta) Probability of having a type 2 error
Delta	Anticipating difference between the two groups Determined by authors
N	Calculated number of patients needed to detect a difference
Non-inferiority Margin	Acceptable difference between groups in a non-inferiority trial

Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.

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Types of Error

- Type I- rejected null hypothesis because of a statistically significant difference between the groups, however the null hypothesis is true
  - False positive
- Type II- accept the null hypothesis because there is no statistically significant difference between the groups, however the null hypothesis is false
  - False negative

Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.

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Types of Error

	False H_0	True H_0
Reject H_0	X	Type I error
Accept H_0	Type II error	X

Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.

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Statistical Significance vs. Clinical Relevance

- Statistical significance
  - Meet statistical requirements
- Clinical relevance
  - More subjective
  - Evaluates statistical values and clinical relevance

Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.

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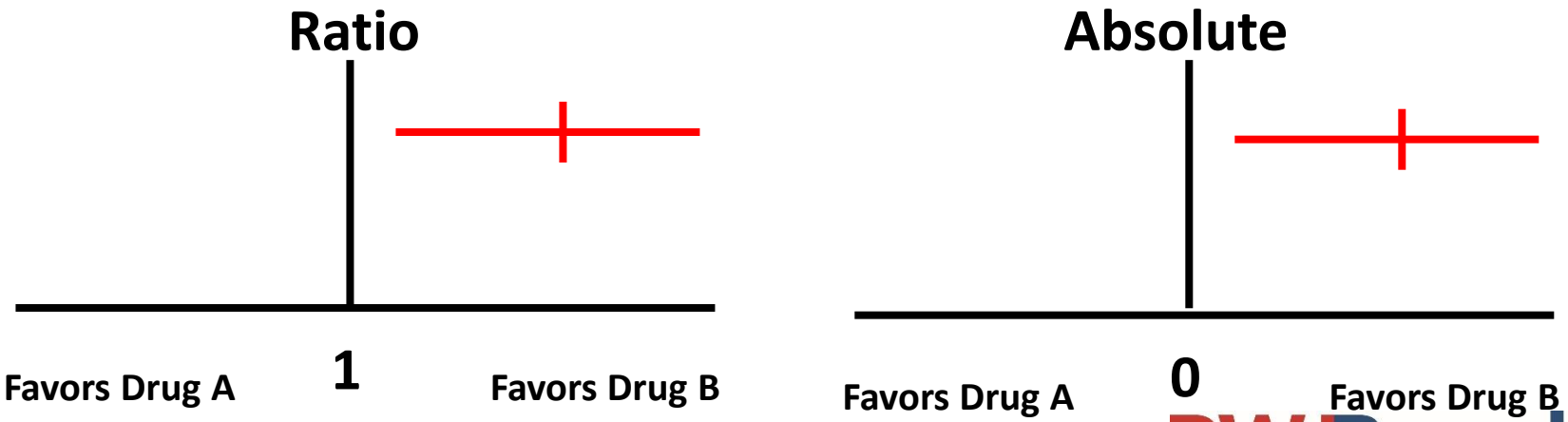
Statistical Significance: Forest Plot

- Results as ratio vs. absolute
  - Ratio: Line of NO significance = 1
    - Hazard ratio, relative risk, odds ratio
  - Absolute: Line of NO significance = 0
    - Absolute risk difference



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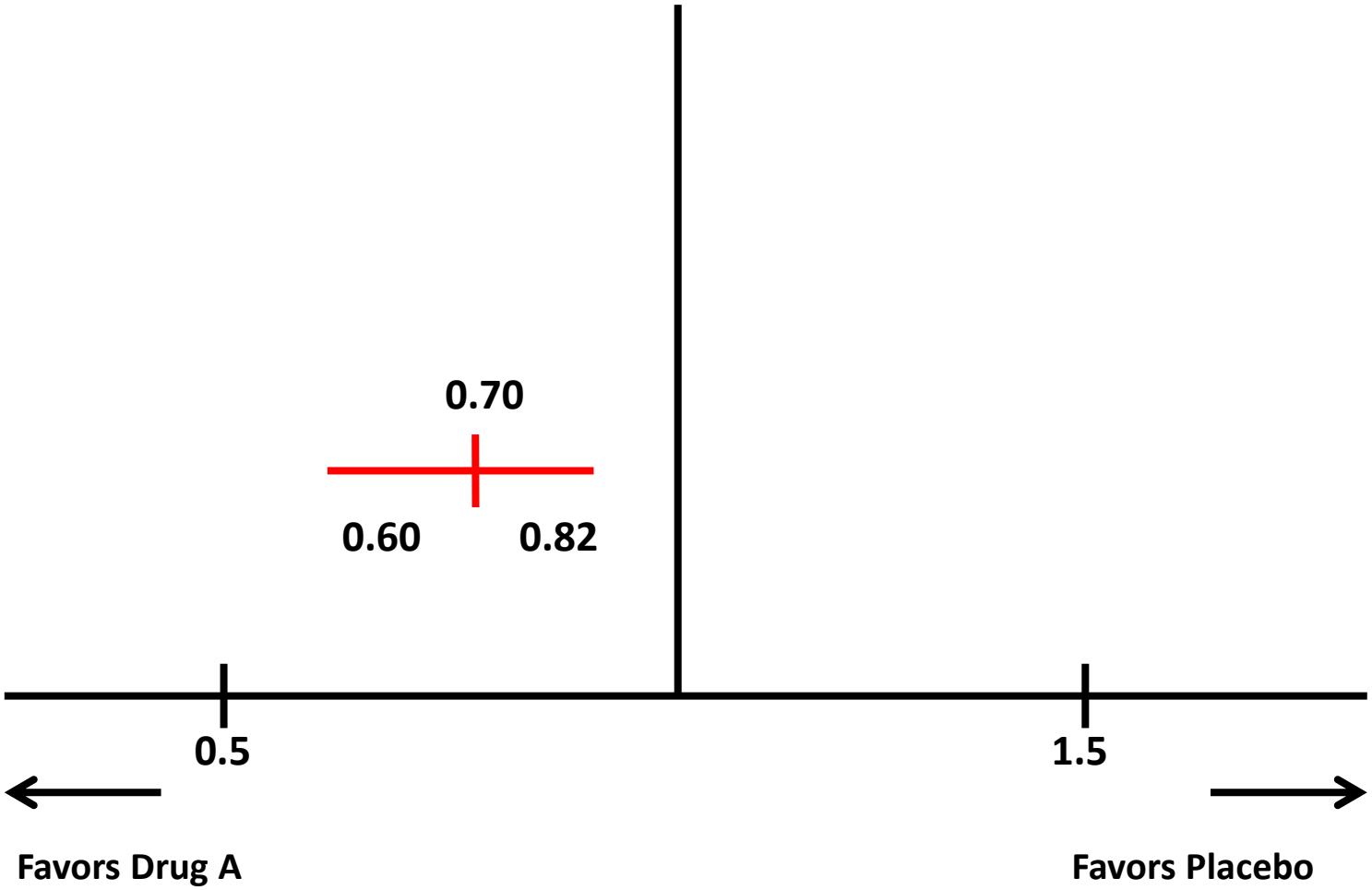
Is this statistically significant?



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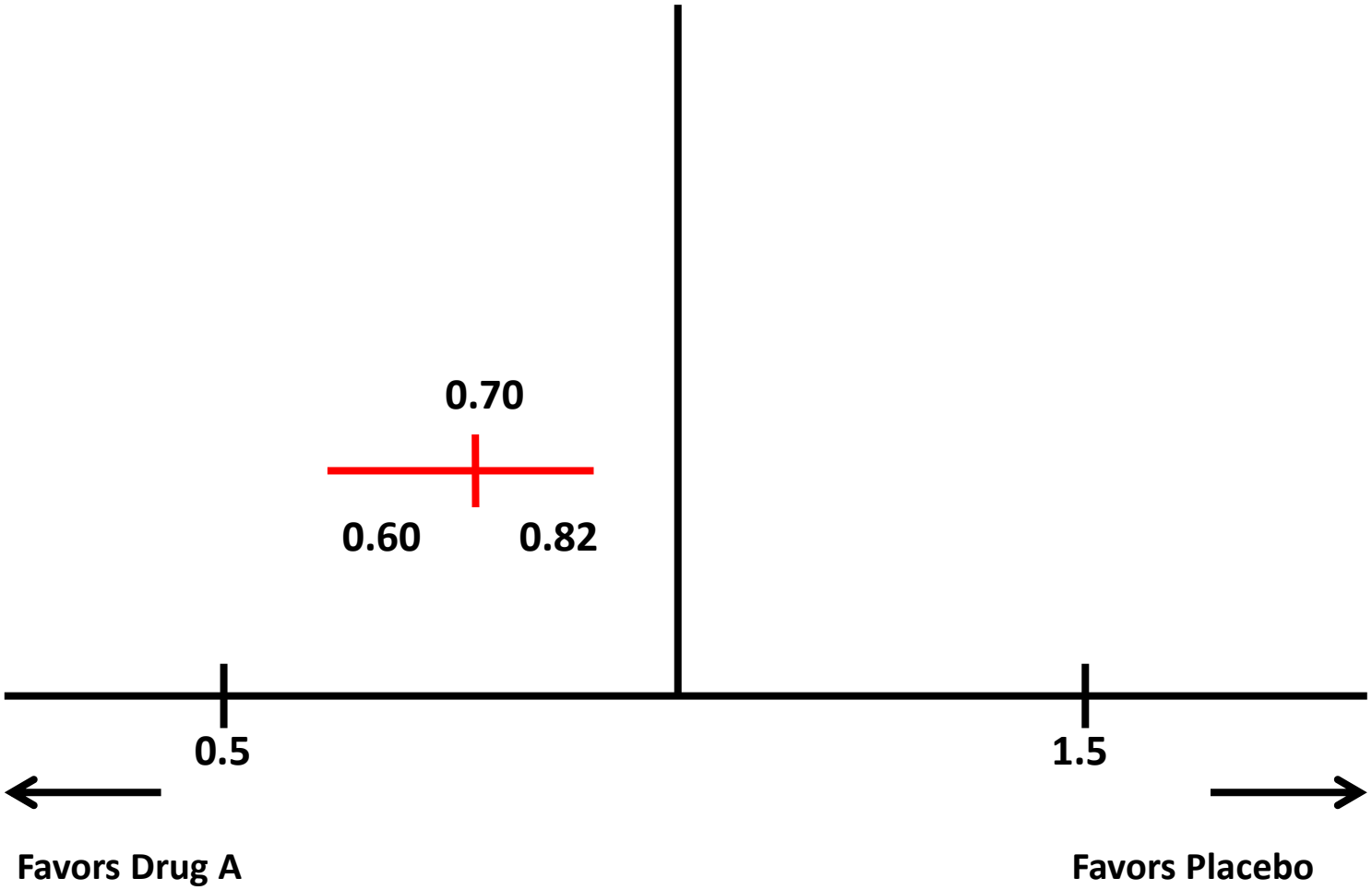
Is it clinically relevant?



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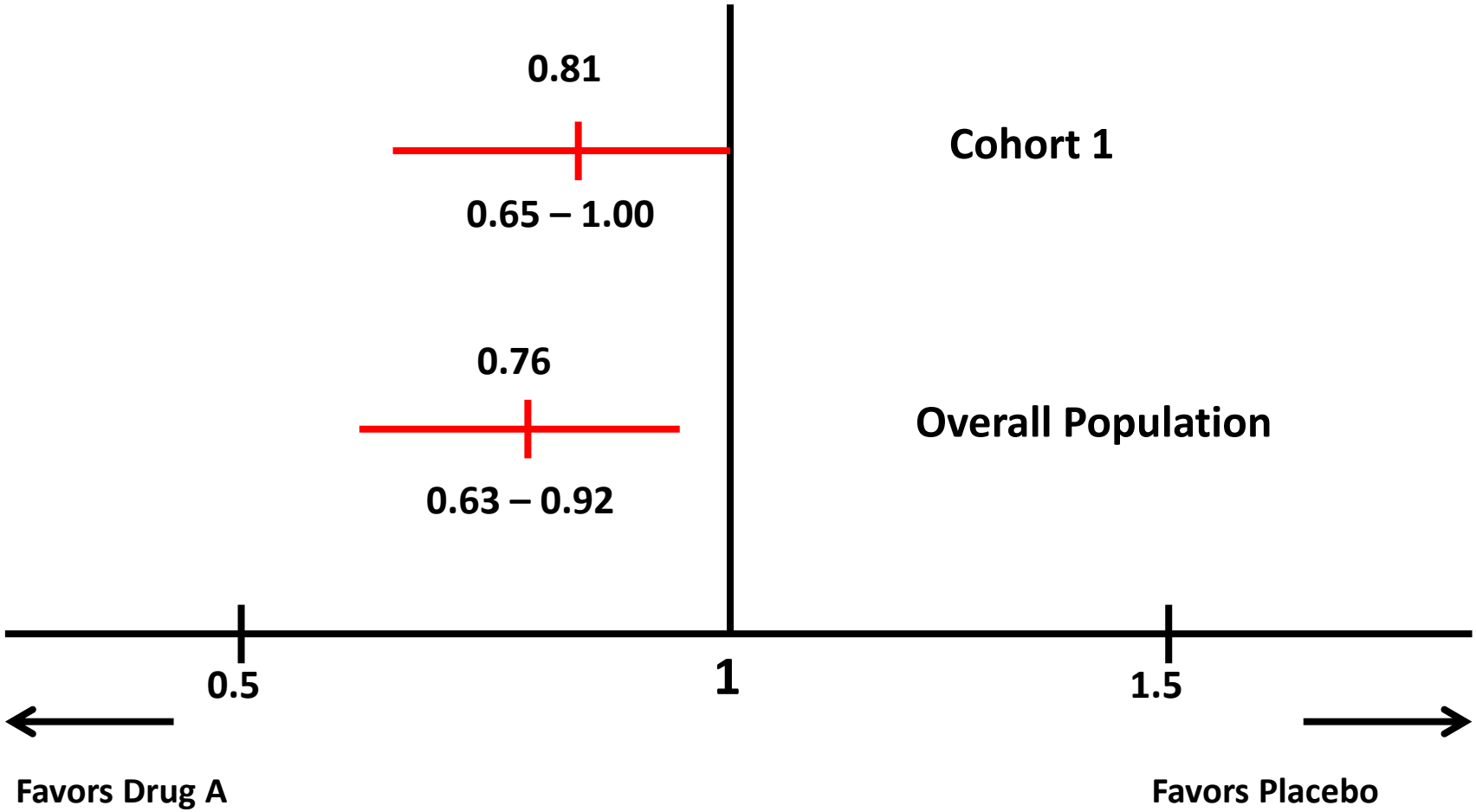
Is this clinically relevant?



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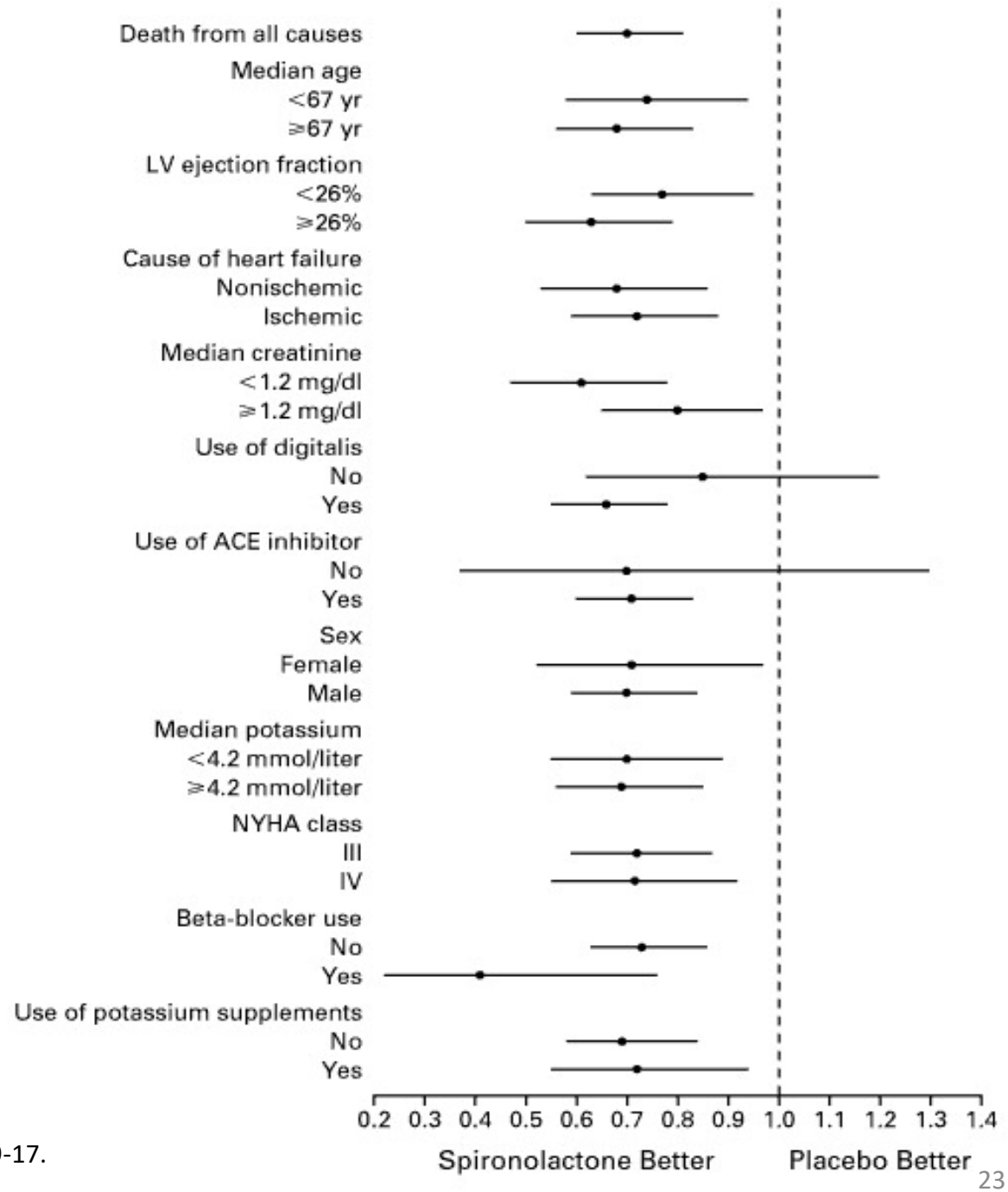
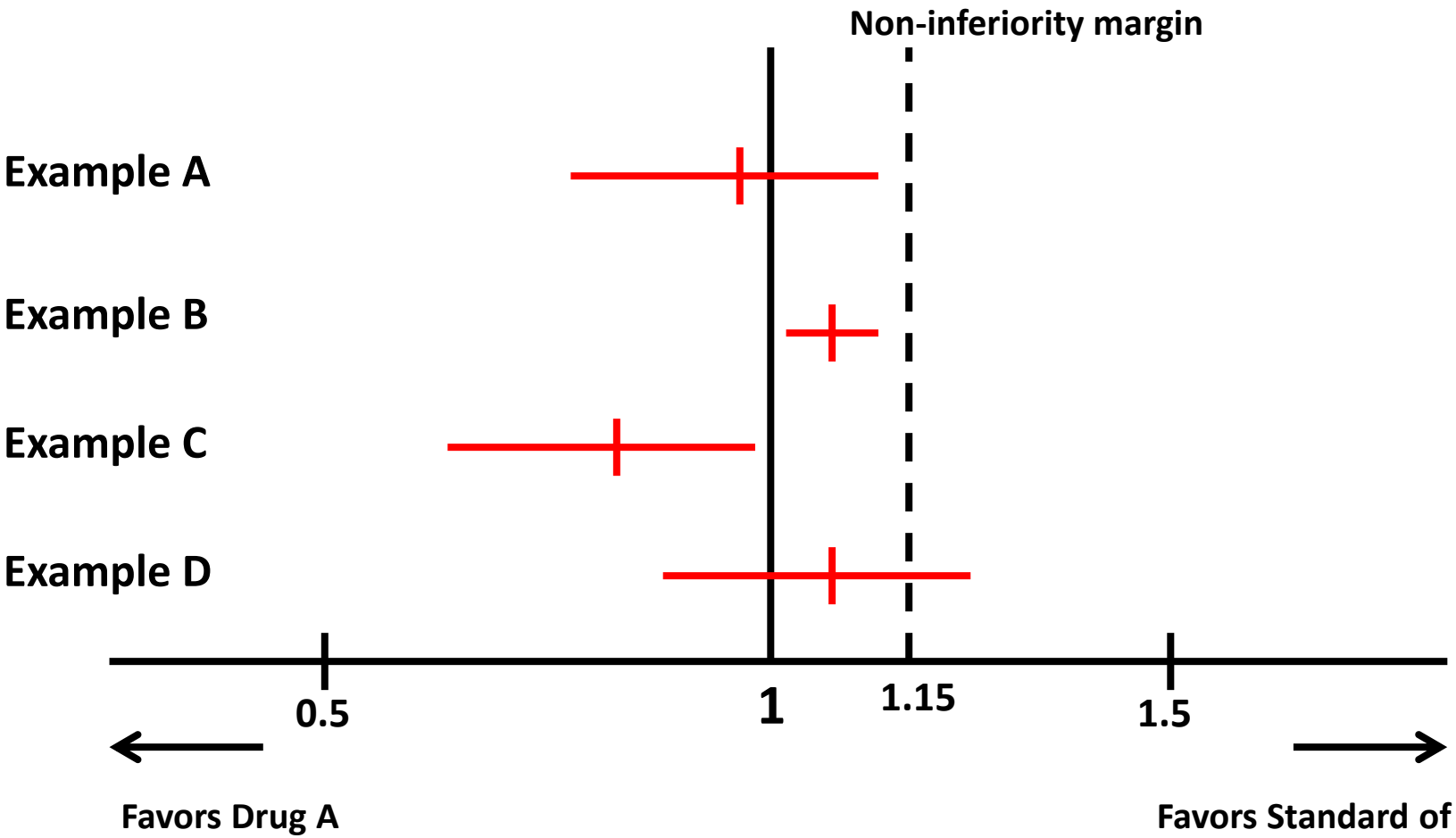
Subgroup Analysis

- Are there groups where spironolactone was better?
- Are there groups where placebo was better?



Source: Pitt B, et al. N Engl J Med. 1991;341:709-17.

Non-inferiority Forest Plot



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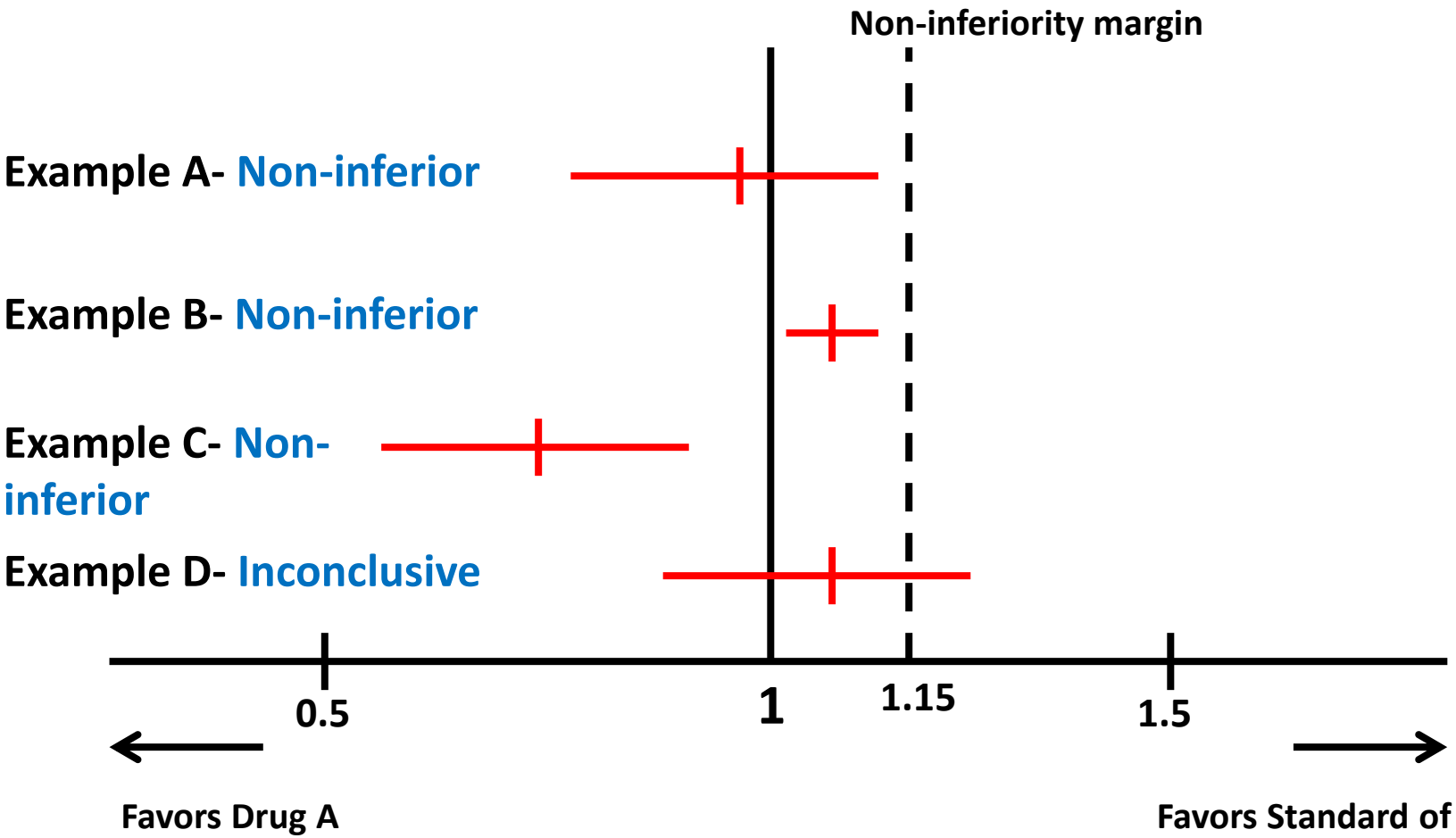
Non-inferiority Forest Plot



Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.

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Relative Risk

$$RR = \frac{\text{Probability of an event in } \textbf{study drug} \text{ group}}{\text{Probably of an event in } \textbf{control} \text{ group}}$$

Probability = # have event / total in group

Sources: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.
Kier KL. Pharmacotherapy. 2011;31:9-22

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Relative Risk Example

	Had event	Did not have event
Study Group	61 **A**	632 **B**
Control Group	207 **C**	483 **D**

$$RR = \frac{A/(A+B)}{C/(C+D)}$$

$$RR = \frac{61/(61+632)}{207/(207+483)} = \frac{61/693}{207/690} = \frac{0.09}{0.3} = \underline{\mathbf{0.3}}$$

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Hazard Ratio

- Refers to whether "hazard" of the event is increased or decreased with the intervention
  - Same calculation as relative risk
    - HR is at a particular point in time whereas RR is over the entire time
  - RR or HR <1 = intervention lowered the risk
  - RR or HR >1 = intervention increased risk of event
- Example: primary endpoint stroke, HR 0.75 (95% CI 0.68 – 0.84)
  - Patients in intervention group were 25% less likely to have a stroke
    - 1 – 0.75 = 0.25

Sources: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.
Kier KL. Pharmacotherapy. 2011;31:9-22

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Odds Ratio

$$\text{OR} = \frac{\text{Ratio of an event in } \textbf{study drug} \text{ group}}{\text{Ratio of an event in } \textbf{control} \text{ group}}$$

Ratio = # have event / # don't have event in group

Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.
Kier KL. Pharmacotherapy. 2011;31:9-22

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Odds Ratio Example

	Had event	Did not have event
Study Group	11 **A**	479 **B**
Control Group	237 **C**	305 **D**

$$\mathrm{OR} = \frac{\mathrm{A}/\mathrm{B}}{\mathrm{C}/\mathrm{D}}$$

$$\mathrm{OR} = \frac{11/479}{237/305} = \frac{0.02}{0.78} = \underline{\mathbf{0.03}}$$

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Absolute Risk Reduction

- The difference in the percentage of subjects developing the adverse event in the control group versus subjects in the intervention group
  - ARR = Control – Intervention
    - When no difference = 0

- Clinical trial comparing Superstatin and Placebo for the incidence of MI:
  - Placebo rate: 4%
  - Superstatin rate: 2%
- ARR = 4% - 2% = **2%**

Source: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.
Kier KL. Pharmacotherapy. 2011;31:9-22

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Relative Risk Reduction

- Estimates how many times greater (or lower) the risk of disease state development is in the patients exposed to the intervention compared to the control

$$\text{RRR} = \frac{\text{Incidence in Control} - \text{Incidence in Intervention}}{\text{Incidence in Control}}$$

Sources: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.
Kier KL. Pharmacotherapy. 2011;31:9-22

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Relative Risk Reduction

- When rates are the same, RRR = 1

- Clinical trial comparing Superstatin and Placebo for the incidence of MI:
  - Placebo rate: 4%
  - Superstatin rate: 2%

- RRR = $\frac{4\% - 2\%}{4\%} = \frac{2\%}{4\%} =$ **50% (0.5)**

Sources: Malone PM. Drug information: A guide for pharmacists, 6e. 2017.
Kier KL. Pharmacotherapy. 2011;31:9-22

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Number Needed to Treat

- Number Needed to Treat (NNT)
  - Number of people need to receive treatment to cause 1 episode of benefit
  - Smaller number = better
- Calculation:
  - NNT = $\frac{1}{\text{ARR}}$
    - ARR = Absolute risk reduction
    - Round answer **up**

Source: Kier KL. Pharmacotherapy. 2011;31:9-22

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Number Needed to Treat Example

- Study looking at medication to prevent death
  - 46% of patients on placebo died
  - 35% of patients on spironolactone died
- ARR = 46% - 35% =

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Number Needed to Treat Example

- Study looking at medication to prevent death
  - 46% of patients on placebo died
  - 35% of patients on spironolactone died
- ARR = 46% - 35% = 11%
  - NNT = $\frac{1}{\text{ARR}}$

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Number Needed to Treat Example

- Study looking at medication to prevent death
  - 46% of patients on placebo died
  - 35% of patients on spironolactone died
- ARR = 46% - 35% = 11%
  - NNT = $\frac{1}{0.11}$ = 9.09 = 10

Need to treat **<u>10</u>** patients to prevent 1 death

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Number Needed to Harm

- Number Needed to Harm (NNH)
  - Number of people needed to receive treatment to cause 1 episode of harm
  - Larger number = better
- Calculation:
  - NNH = $\frac{1}{\text{ARR}}$
    - ARR = Absolute risk reduction
    - Round answer **down**

Source: Kier KL. Pharmacotherapy. 2011;31:9-22

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Number Needed to Harm Example

In a trial for a novel chemotherapy agent, myocardial infarctions occurred in 32 of 598 patients in the experimental arm and 7 out of 596 patients in the control group.

Number Needed to Harm Example

In a trial for a novel chemotherapy agent, myocardial infarctions occurred in 32 of 598 patients in the experimental arm and 7 out of 596 patients in the control group.

- Rate of MI in control group = 7/596 = 1.17%
- Rate of MI in experimental group = 32/598 = 5.35%

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Number Needed to Harm Example

- Rate of MI in control group = 7/596 = 1.17%
- Rate of MI in experimental group = 32/598 = 5.35%

- ARR = 5.35% - 1.17% = 4.18%

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Number Needed to Harm Example

- ARR = 4.18%
- NNH = $\frac{1}{\text{ARR}}$
- NNH = $\frac{1}{0.0418}$ = 23.9

For every **<u>23</u>** patients treated, one will have a myocardial infarction.

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Question 1

A trial is planning on including all patients randomized in the trial who complete at least 2 follow-up visits in the final efficacy analysis. This analysis is best described as being:

A. Per protocol

B. Intent to treat

C. Modified intent to treat

D. As treated

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Response 1

A trial is planning on including all patients randomized in the trial who complete at least 2 follow-up visits in the final efficacy analysis. This analysis is best described as being:

A. Per protocol

B. Intent to treat

C. Modified intent to treat

D. As treated

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Question 2

A clinical trial reports that Drug A is associated with risk of death at a rate of 32% compared to drug B which has a rate of death of 17%. Therefore, Drug B has an absolute risk reduction of ____% compared to Drug A.

A. 3.1%

B. 15%

C. 17%

D. 32%

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Response 2

A clinical trial reports that Drug A is associated with risk of death at a rate of 32% compared to drug B which has a rate of death of 17%. Therefore, Drug B has an absolute risk reduction of ____% compared to Drug A.

A. 3.1%

B. 15%

C. 17%

D. 32%

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Question 3

Drug A had a 5% mortality rate compared to placebo which had 10% (95% CI 0.84-2.91; p=0.2) Is this statistically significant? Clinically relevant?

A. Statistically significant and clinically relevant

B. Statistically significant, but not clinically relevant

C. Not statistically significant, but clinically relevant

D. Not statistically significant or clinically relevant

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Response 3

Drug A had a 2% mortality rate compared to placebo which had 10% (95% CI 0.35-0.74; p=0.002)
Is this statistically significant? Clinically relevant?

A. Statistically significant and clinically relevant

B. Statistically significant, but not clinically relevant

C. Not statistically significant, but clinically relevant

D. Not statistically significant or clinically relevant

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References

1. Bryant PJ, McQueen CE. Literature Evaluation II: Beyond the Basics. In: Malone PM, Malone MJ, Park SK. eds. Drug Information: A Guide for Pharmacists. 6th ed. New York, NY: McGraw-Hill; http://accesspharmacy.mhmedical.com.proxy.libraries.rutgers.edu/content.aspx?bookid=2275&sectionid=177198100. Accessed September 26, 2019.
2. Dawson B, Trapp RG. Basic & Clinical Biostatistics. 4th ed. New York, NY: McGraw-Hill; 2004.
3. Kier KL. Biostatistical applications in epidemiology. Pharmacotherapy. 2011;31:9-22.
4. Pitt B, Zannad F, Remme WJ, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. N Engl J Med. 1991;341:709-17.

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Thank you!

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