

ABC of Statistics

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Use of Statistics in Research

- Estimation of parameter
- Descriptive statistics
  - Knowledge of a distribution based on observed values

- Inference
- Association of variables of interest, i.e.,
  - Effect of smoking in the incidence of lung cancer (Epidemiological Study)
  - Effect of treatment and outcome (Intervention: Clinical Trial)

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European School of Oncology

What Are Descriptive Statistics?

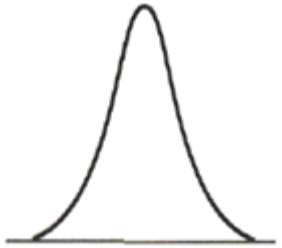
- Descriptive statistics are used to **describe or summarize** data in ways that are meaningful and useful.
- Descriptive statistics are at the heart of all quantitative analyses.
- So how do we describe data?
  - **measures of central tendency** and
  - **measures of variability**, or **dispersion**.

http://study.com/academy/lesson/what-is-descriptive-statistics-examples-lesson-quiz.html

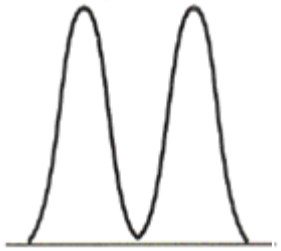
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Measures of Central Tendency

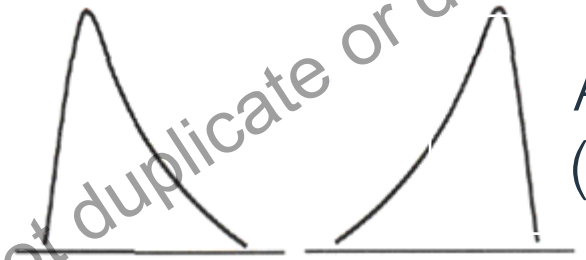
Choice of most appropriate measure of central tendency for a specific dataset depends on their *distribution*:



Symmetric, unimodal → Mean, Median, Mode: identical



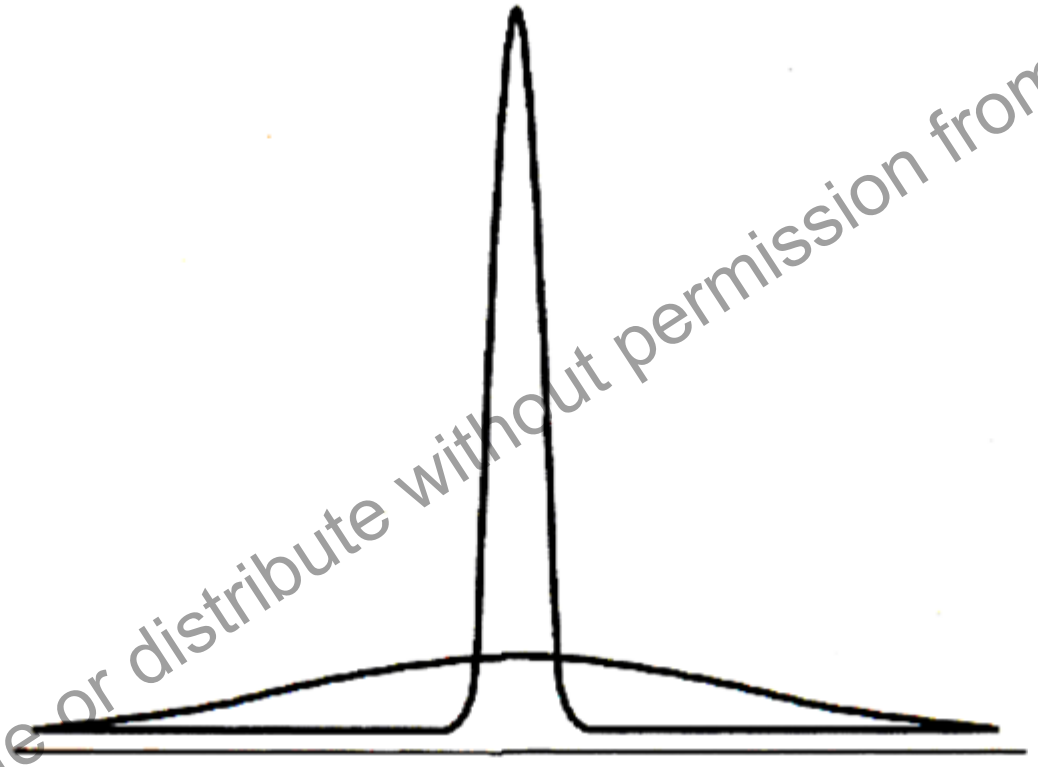
Symmetric, bimodal → Mean ≈ Median
Better to report 2 modes



Asymmetry (left or right) → Median is preferable

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Measures of Dispersion

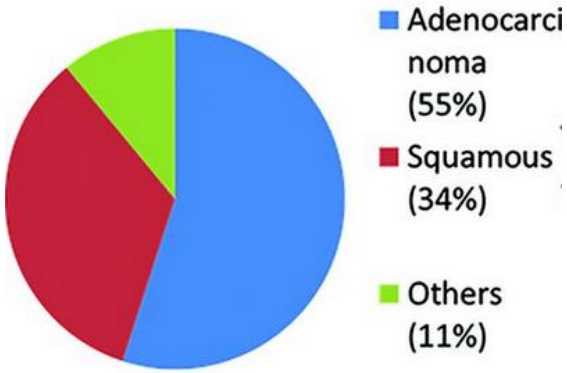


Two datasets with identical means, medians and modes

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Description of Distribution (plots)

Histology based subtyping



Rolfo et al, The Journal of the American Board of Family Medicine 2015

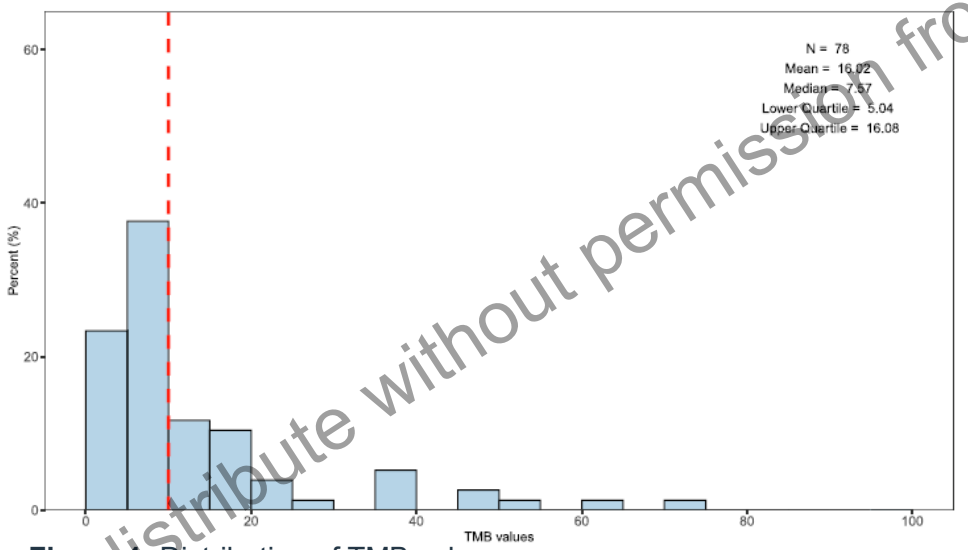
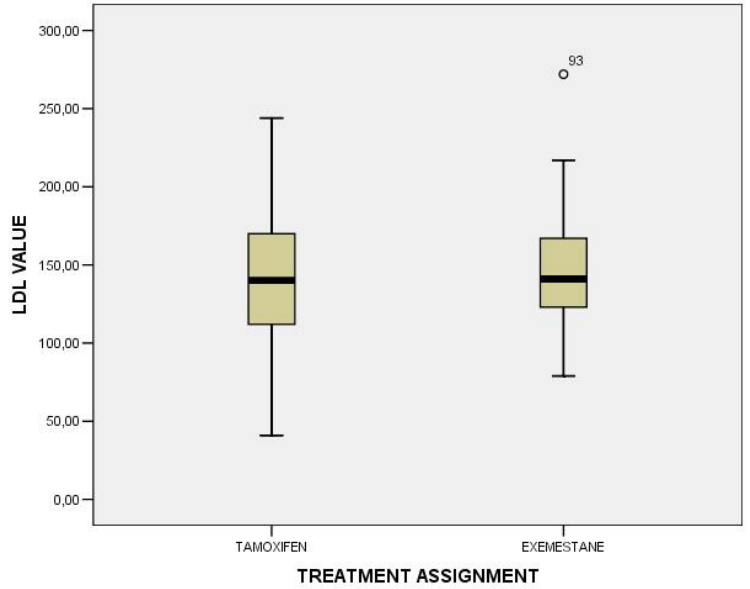


Figure 1: Distribution of TMB values
Note: *The red dashed line indicates the cut-off value of 10 Muts/Mb used for the classification of TMB.*

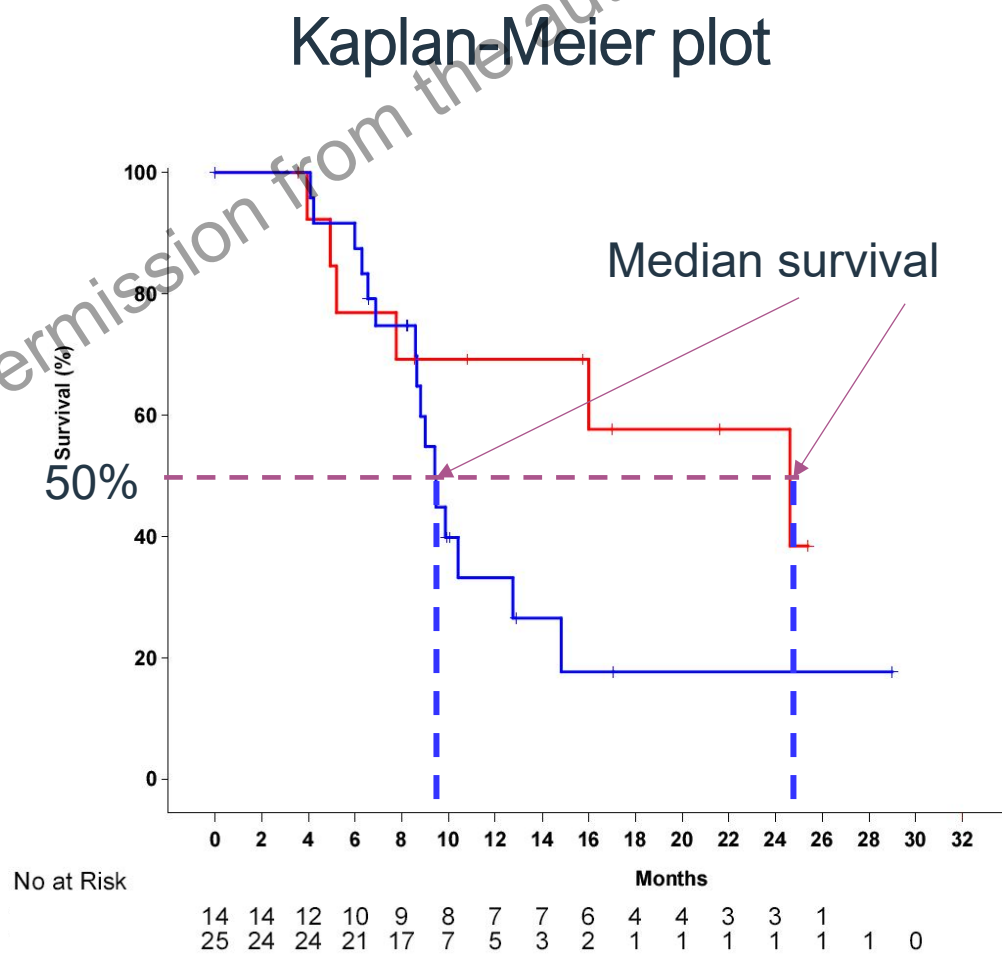
Bubendorf et al, Lung Cancer 2022



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Description of Distribution (plots)

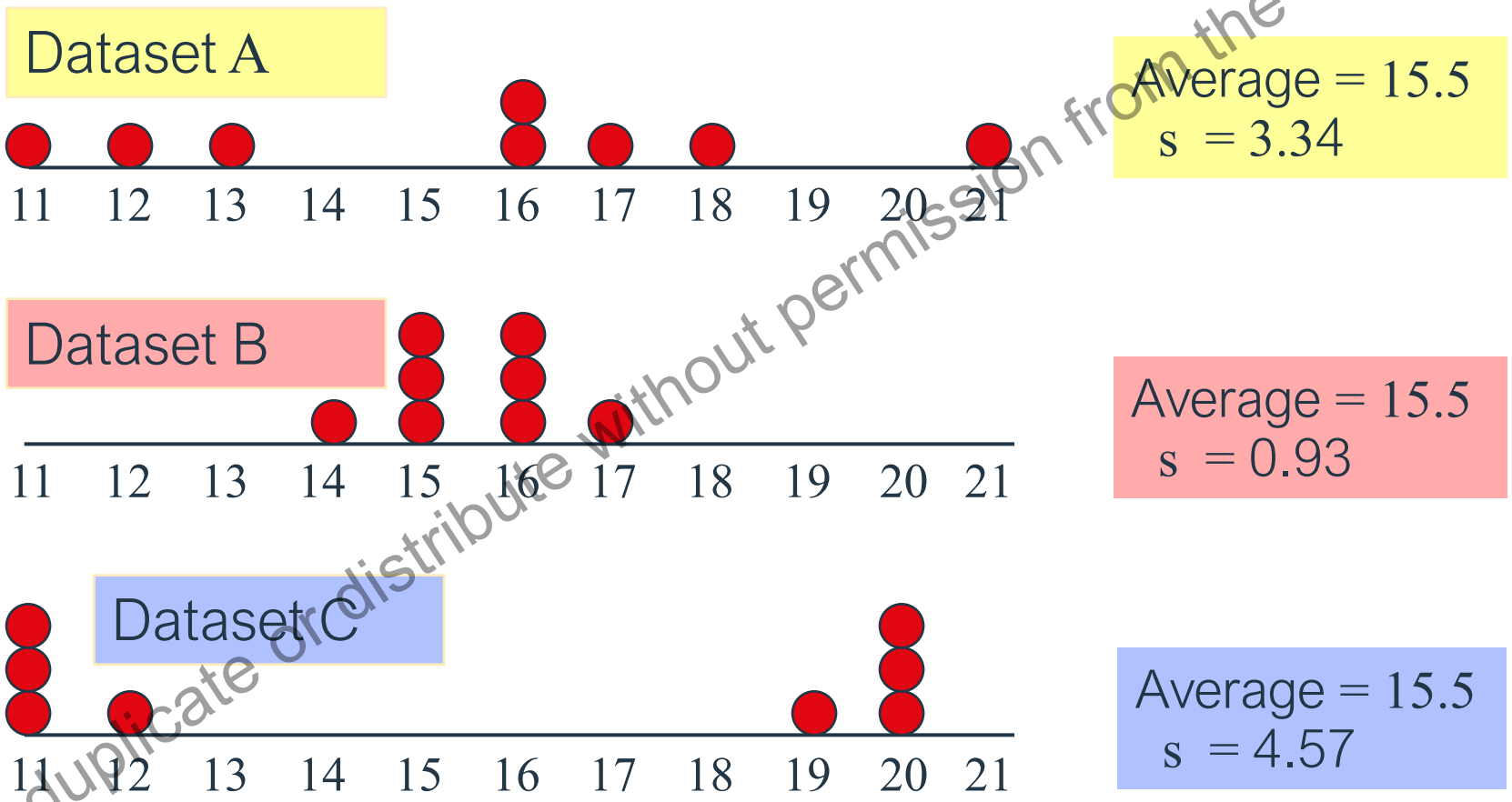
- Measure of central tendency
- 50% of the observations are below this value
- Contrary to the mean, not influenced by outliers
- Calculation based on the ranked series of observations



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Measures of Dispersion

Same average - Different Standard deviations



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SIMULATIONS
TRUE HR = 0.70; Power=0.80

50,000 trials

39,808 (79.6%) significant

10,192 (20.4%) non-significant

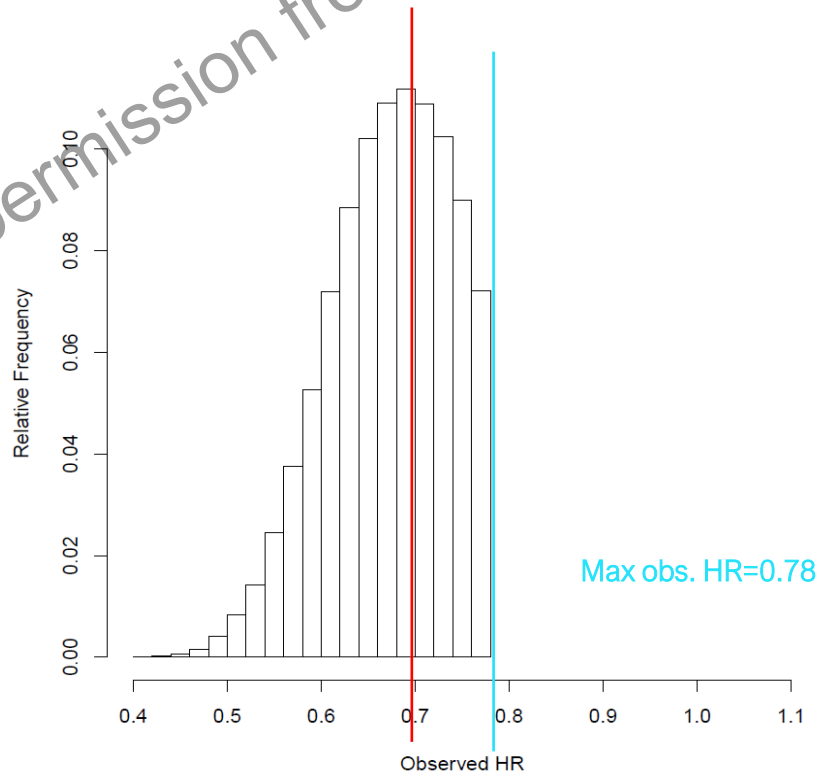
All trials *(50,000 simulated trials)*



HR<0.70: 24,949 (~50%)

TRUE HR targeted

Only significant trials (39,808; 79.6%)



Max obs. HR=0.78

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Baseline Table

Table 1. Baseline patient characteristics

Characteristic	Osimertinib/bevacizumab (n = 78)	Osimertinib (n = 77)	All patients (N = 155)	P value
Age at randomisation, years				0.76[a]
Median (range)	68 (34-85)	66 (41-83)	67 (34-85)	
Sex, n (%)				0.74[b]
Male	31 (39.7)	28 (36.4)	59 (38.1)	
Female	47 (60.3)	49 (63.6)	96 (61.9)	
Ethnicity, n (%)				>0.99[b]
Asian	32 (41.0)	31 (40.3)	63 (40.6)	
Non-Asian	46 (59.0)	46 (59.7)	92 (59.4)	
ECOG performance status, n (%)				0.60[b,c]
0	22 (28.2)	25 (32.5)	47 (30.3)	
1	51 (65.4)	48 (62.3)	99 (63.9)	
2	5 (6.4)	4 (5.2)	9 (5.8)	
Smoking status, n (%)				0.41[b,d]
Current (still smokes cigarettes)	4 (5.1)	1 (1.3)	5 (3.2)	
Former (smoked ≥100 cigarettes in the past during the whole life)	30 (38.5)	27 (35.1)	57 (36.8)	
Never smoker (smoked 0-99 cigarettes during the whole life)	44 (56.4)	49 (63.6)	93 (60.0)	

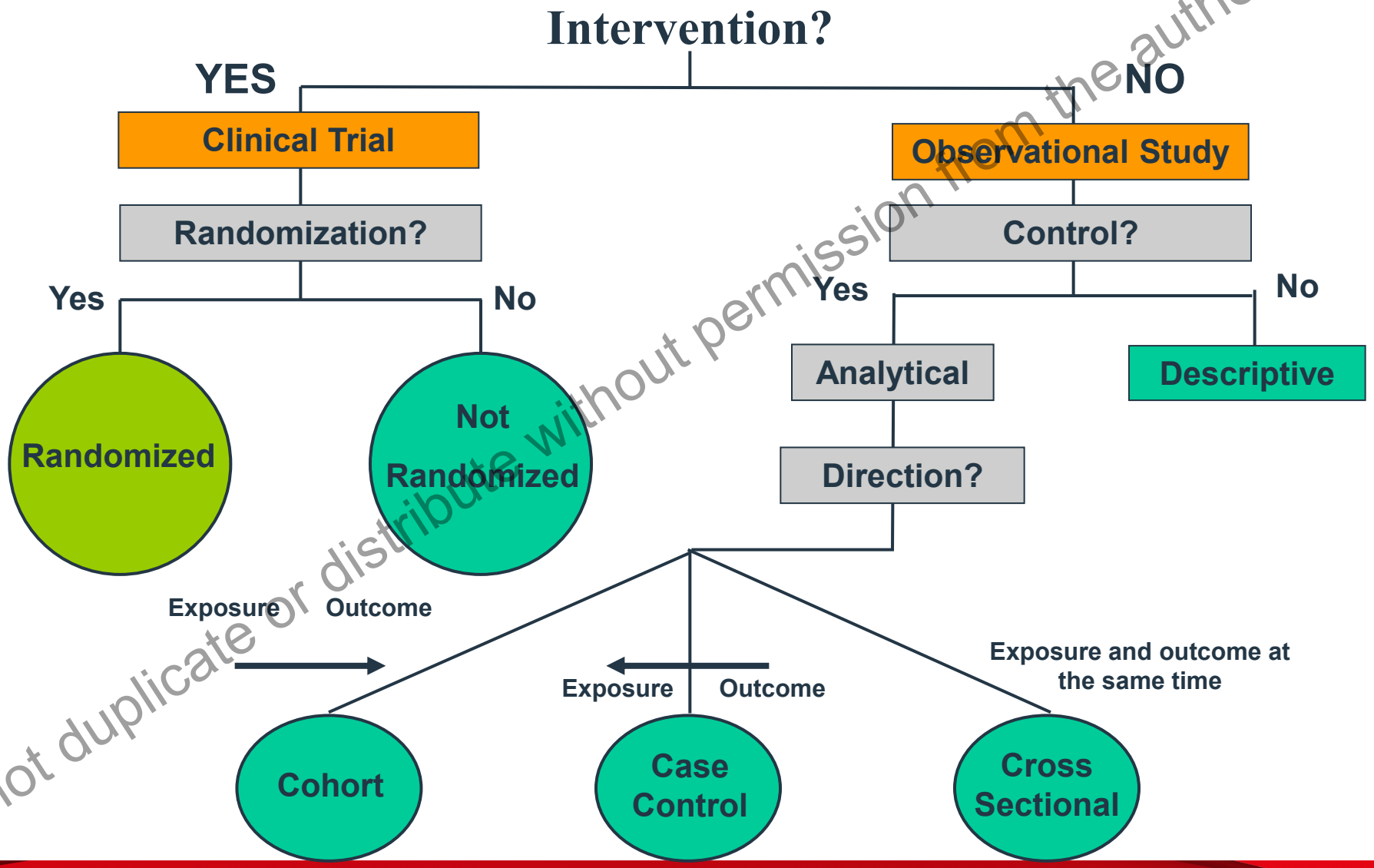
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Types of Studies Researching an Association

- Case Reports: Detailed description of one or few patients.
- Case Series: Similar to above, but with more patients.
- Database Analyses: Typically, on existing databases.
- Observational Studies: (no treatment interventions imposed):
  - Cross-sectional Studies: Observe each patient at 1 time point.
  - Case-Control Studies: Subjects selected by disease status and compared with controls for possible causes.
  - Cohort Studies: Subjects observed over time. Cohort studies can focus on treatment as a determinant of course of disease.
- Clinical Trials: The treatment assignment is by design. Endpoints and analyses planned in advance.

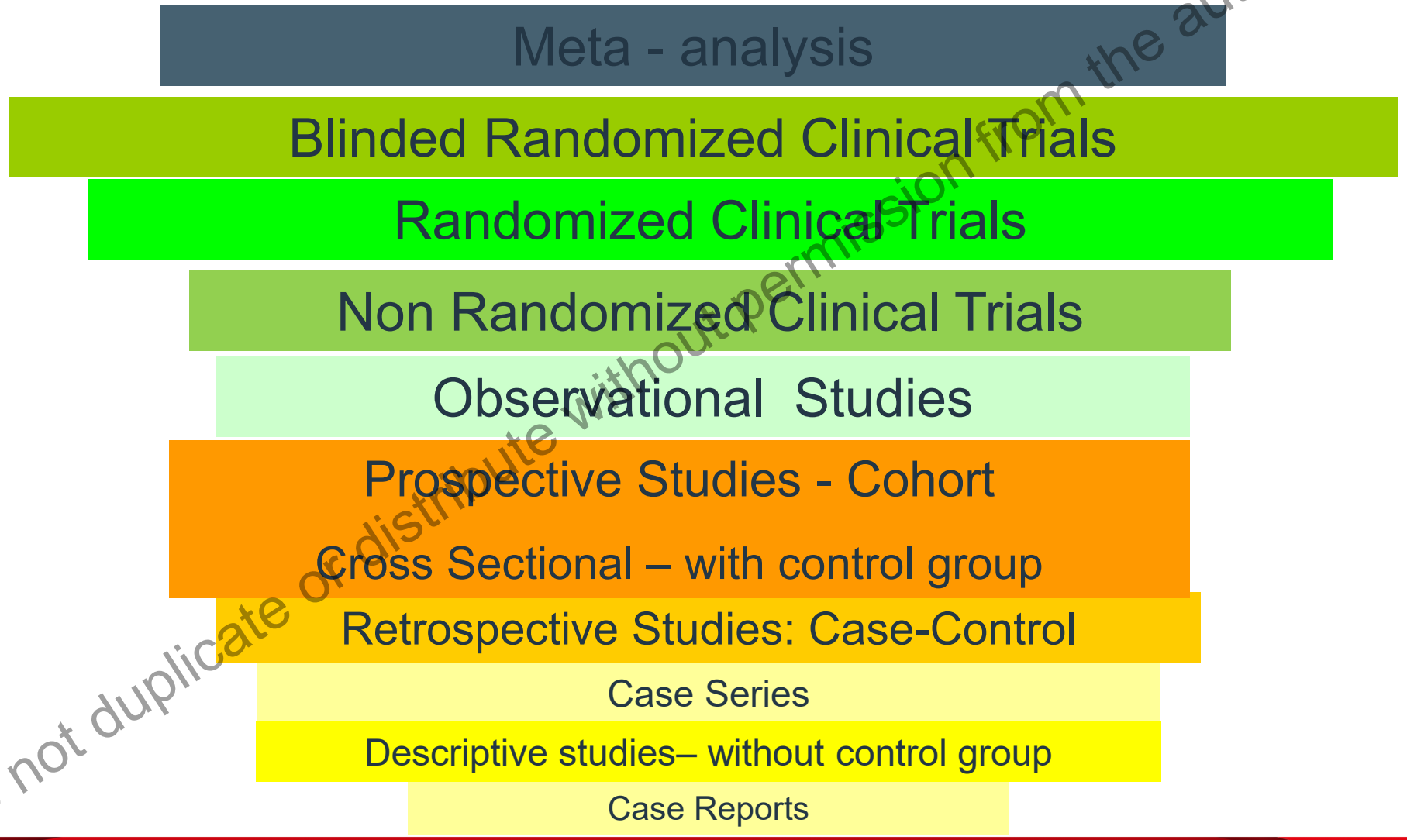
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Types of Studies Researching an Association



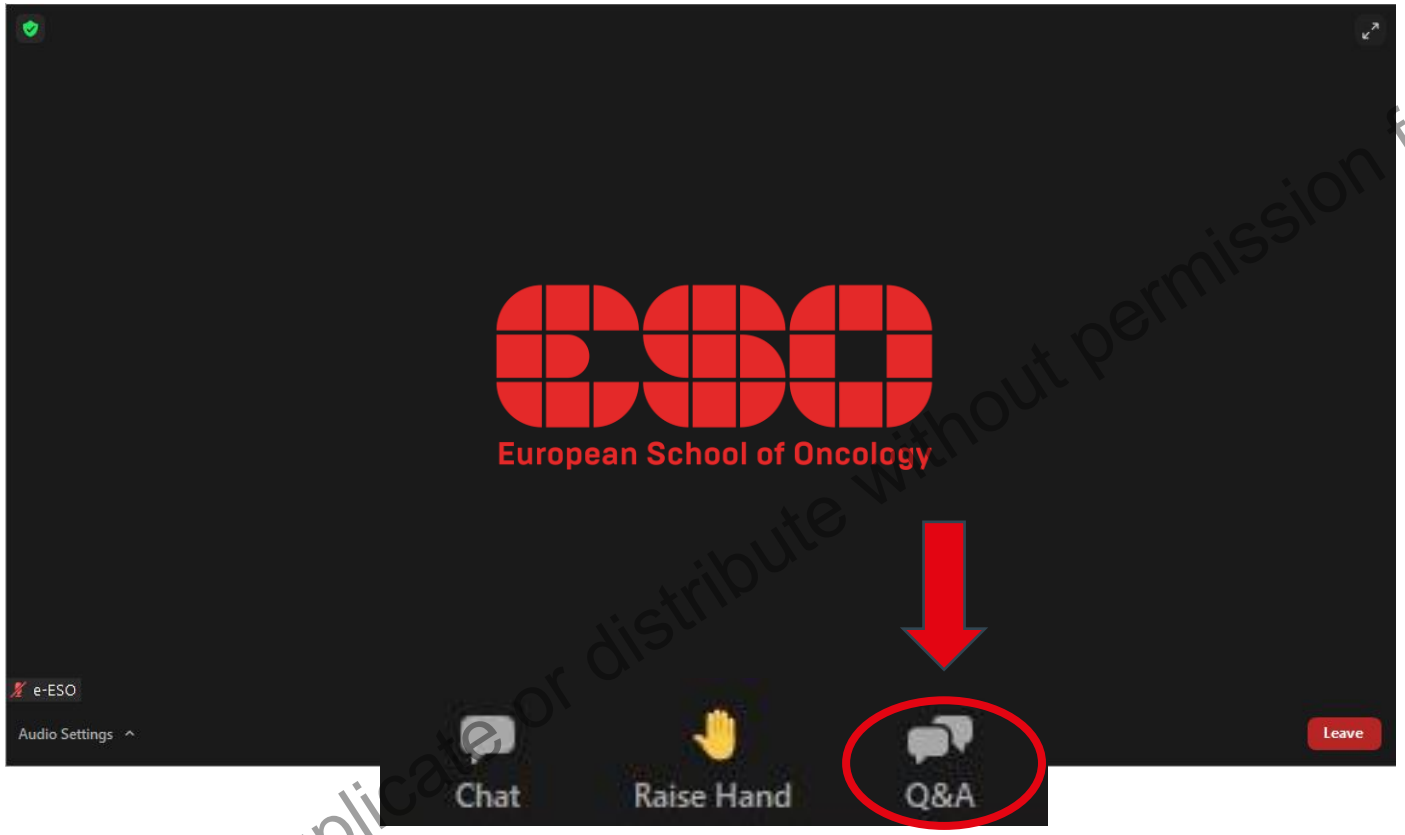
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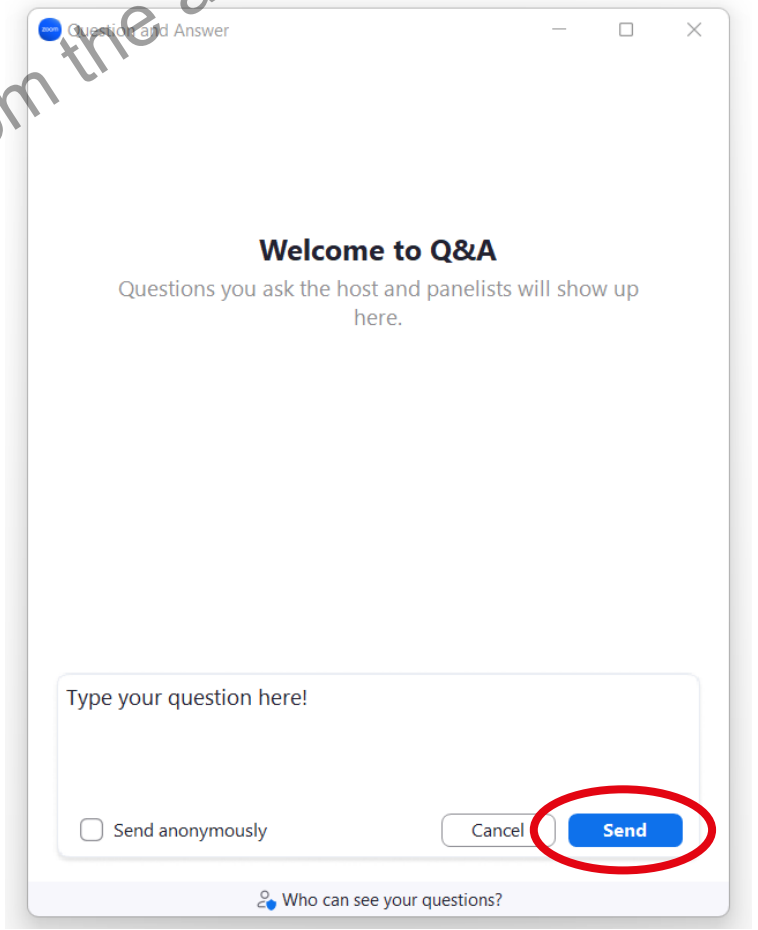
Ranking the Quality of Evidence



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Remember that you can ask questions and send comments at any time.





Click on the Q&A button
to send your questions and comments

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Clinical Trials



- Lab & animal studies
- Safety study
- 20-80 people
- Safety study
- Identify side effects
- Measure effectiveness
- 100-300 people
- Measure effectiveness
- Monitor side effects
- 1,000-3,000 people
- Monitor long-term side effects

A ***clinical trial*** is a controlled **experiment** *testing r*

Phase III: Compare new treatment to standard therapy or placebo.

DECLARATION OF HELSINKI – ETHICAL PRINCIPLES F
HUMAN SUBJECTS (1964)
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

http://www.msra.org.au/next-20-article-clinical-trials-phase-1

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Basic Concepts

- Variability and Bias
- Non-inferiority and Superiority Trials
  - Hypothesis Testing:
  - Sample Size, Power, Type I & II Errors
  - Clinical Significance vs Statistical Significance
    - http://hedwig.mgh.harvard.edu/sample_size/size.html
    - http://cancer.unc.edu/biostatistics/program/
    - https://stattools.crab.org/
- Prognostic/Predictive Factors
- Multiplicity Problem

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Scientific Question

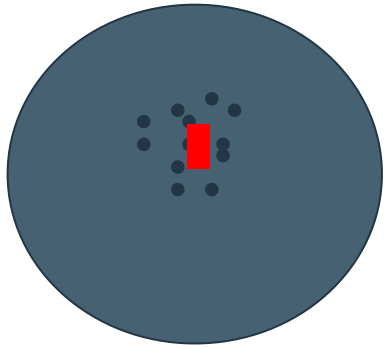
- Experiments answer a scientific question by isolating the intervention and the outcome from extraneous influences
- **Goals:**
  - Minimize random error (increase precision, decrease variability)
    - inaccuracy of results due to sampling
  - Eliminate systematic error (Bias)
    - any effect rendering the observed results not representative of the treatment effect.
  - Ensure the generalizability of study results

Study Design is the methodology for achieving these goals

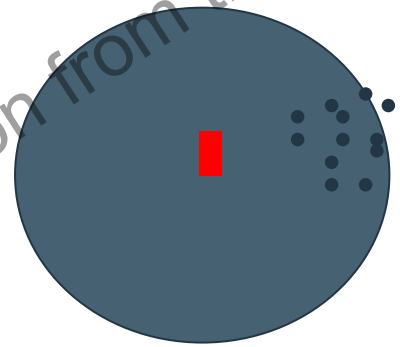
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Bias - Variability

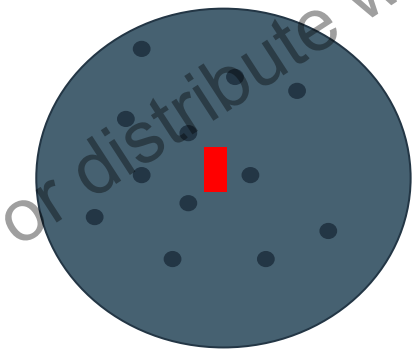
No bias, small variability



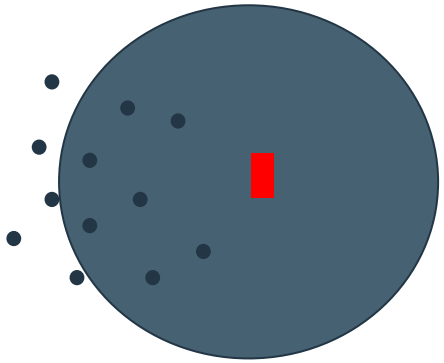
Bias, small variability



No bias, larger variability



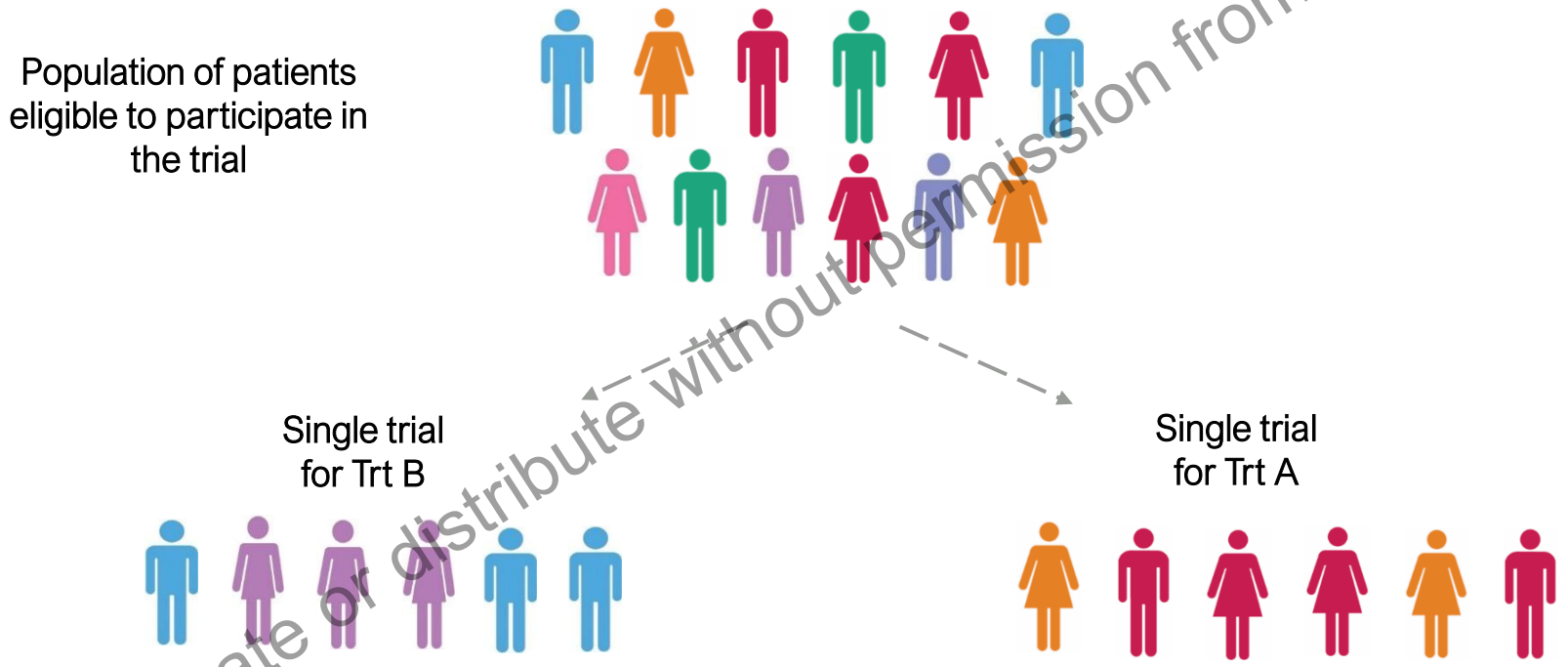
Bias, larger variability



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Non-randomized studies

Single arm - No control arm

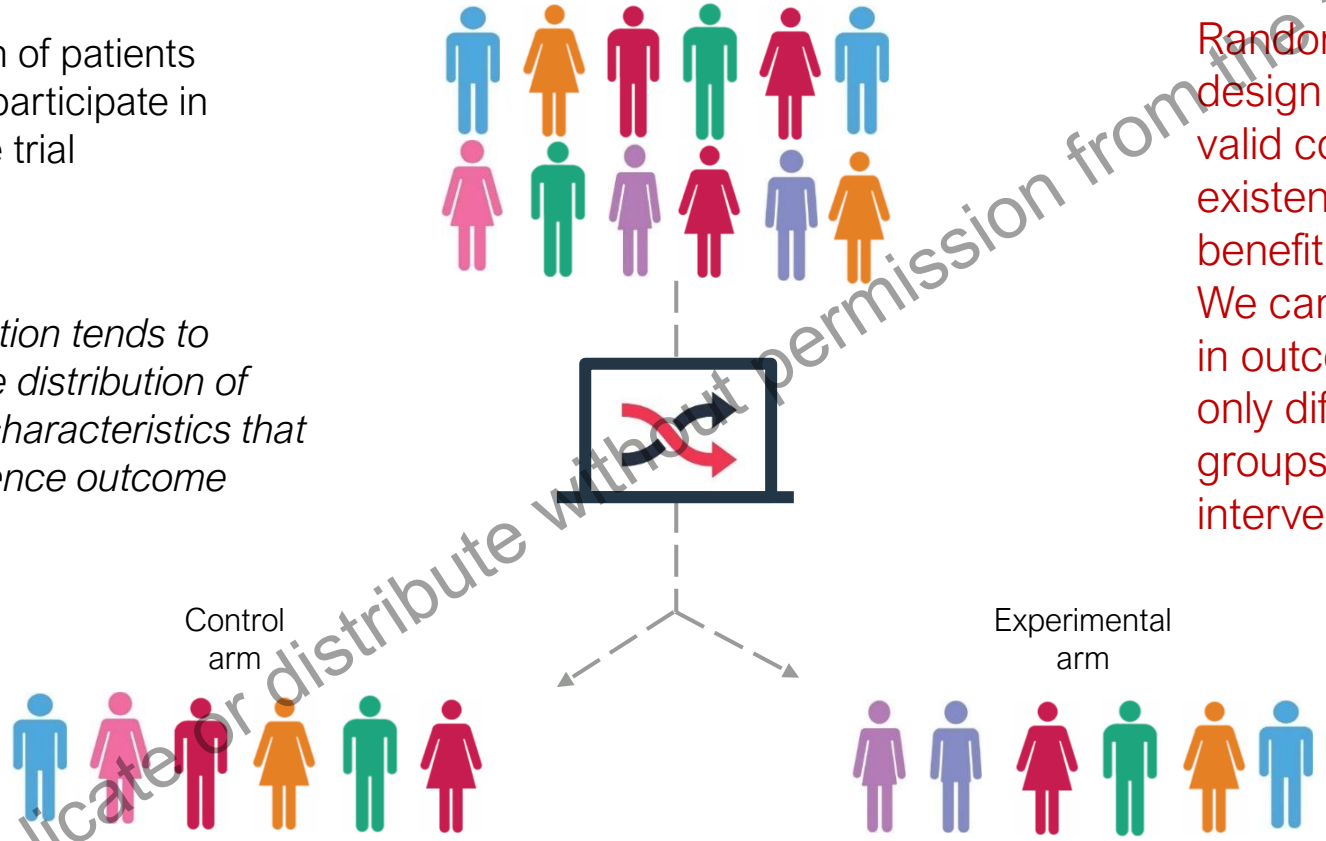


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Randomization

Population of patients eligible to participate in the trial

Randomization tends to balance the distribution of important characteristics that might influence outcome



Randomized design is the only design that allows us to reach a valid conclusion relative to the existence of a treatment benefit.
We can claim that a difference in outcome is derived from the only difference between groups, i.e., the difference in intervention.

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Important Design Elements

- To **address bias** of the estimate, the design needs to include <u>at least</u>:
  - ❑ Randomization

- To **address variability** of the estimate, the design needs to include :
  - ❑ Adequate Sample Size

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Sample Size Determination

- Experiments with **more patients** than needed violate the individual human rights of the specific patients
- Experiments with **less patients** than needed violate human rights of the whole society

- **ETHICAL to use appropriate sample size**

- **Sample Size**: To estimate the sample size one needs to consider
  - the *clinically significant difference* (Δ)
  - the *power* (1-β),
  - the *significance level* (α), and
  - the magnitude of the variation of the measure (S or S^2)

Declaration of Helsinki:
http://oss-sper-clin.agenziafarmaco.it/normativa/direttive_OsSC-000122-000000.pdf

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Phase III - Parallel Design

- Superiority Trials
- Non-Inferiority Trials

- *Null hypothesis or* H_0 is a statement we would like to reject and generally we do not want to be true.
  - *Superiority Trial* H_0 : "no effect" or "no difference"
  - *Non-inferiority Trial* H_0 : "different effect" or "difference"
- *Alternative hypothesis or* H_1 is the statement we would like to prove if true
- Our final conclusion will always be one of these:
  - Reject the null hypothesis or
  - Fail to reject the null hypothesis

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Hypothesis Testing: Errors

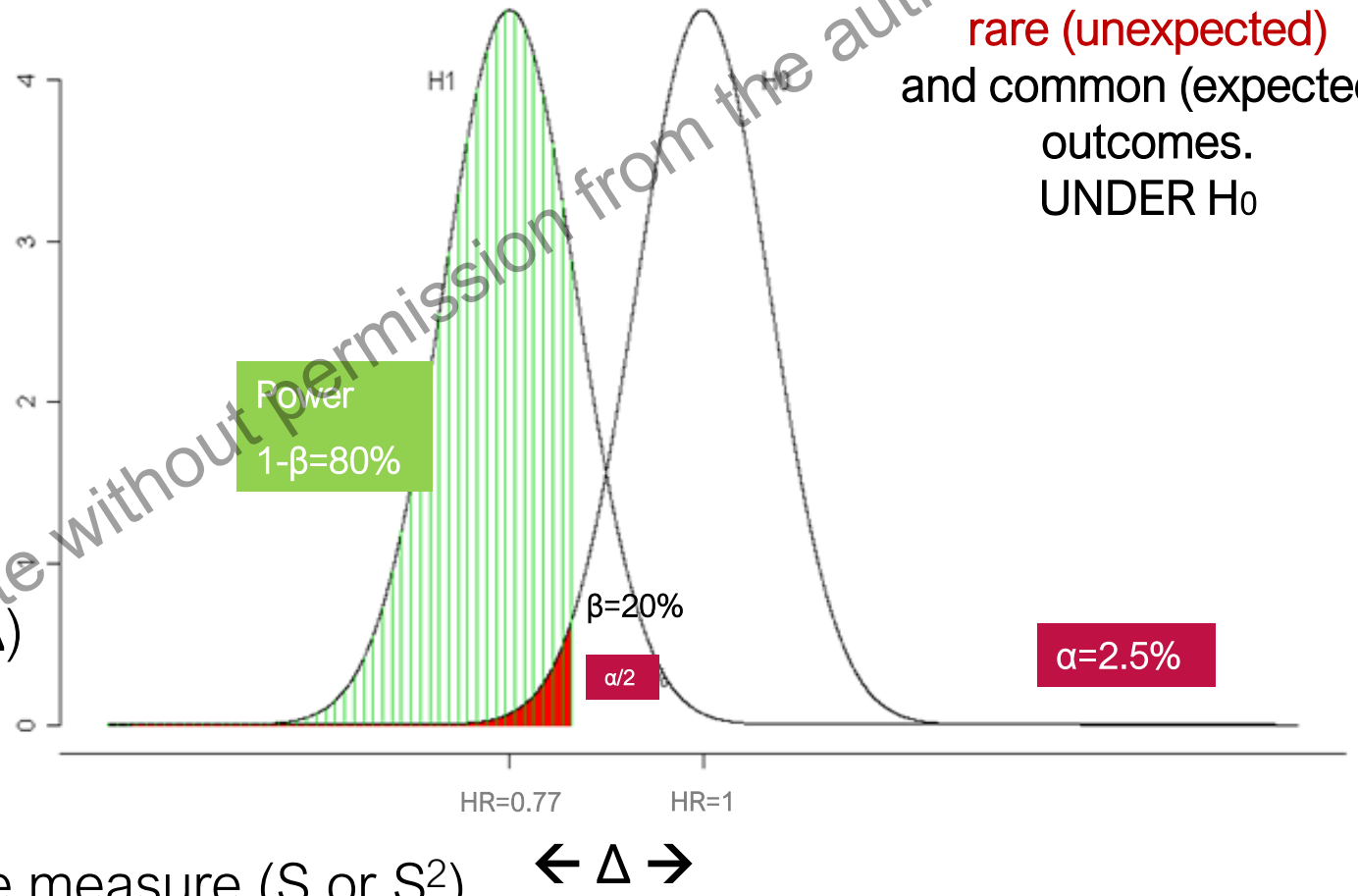
We can enumerate the possible outcomes of a hypothesis testing in a table:

		True State	
		H_0 True	H_0 False
Test Result	**Do not reject H_0** $\Delta = 0$ $\ln(HR) = 0$, $HR = 1$ $\ln(\lambda_T) - \ln(\lambda_S) = 0$	✓ $(1-\alpha=97.5\%)$	**FALSE NEGATIVE** Type II error $(\beta=20\%)$
	Reject H_0 $\Delta < 0$, $HR < 1$	***FALSE POSITIVE*** ***Type I error*** ***$(\alpha=2.5\%)$***	✓ ***Power*** ***$(1-\beta=80\%)$***

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Superiority Trials

- **Aim:** To demonstrate the superiority of a new therapy compared to an established therapy or placebo



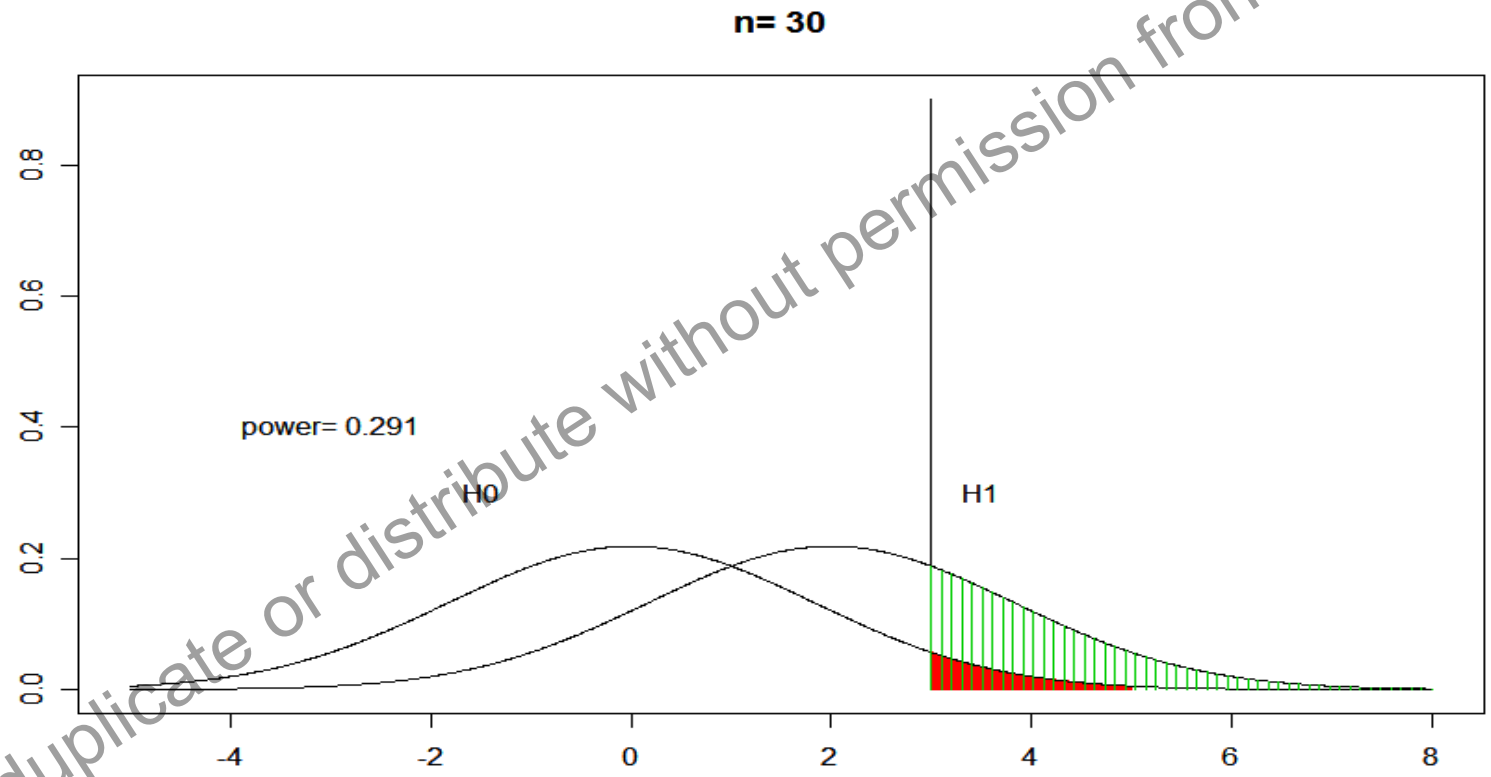
We discriminate between rare (unexpected) and common (expected) outcomes.
UNDER H_0

- the *clinically significant difference* (Δ)
- the *power* (1-β),
- the *significance level* (α), and
- the magnitude of the variation of the measure (S or S^2)

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Sample size = 30,Power = 29%

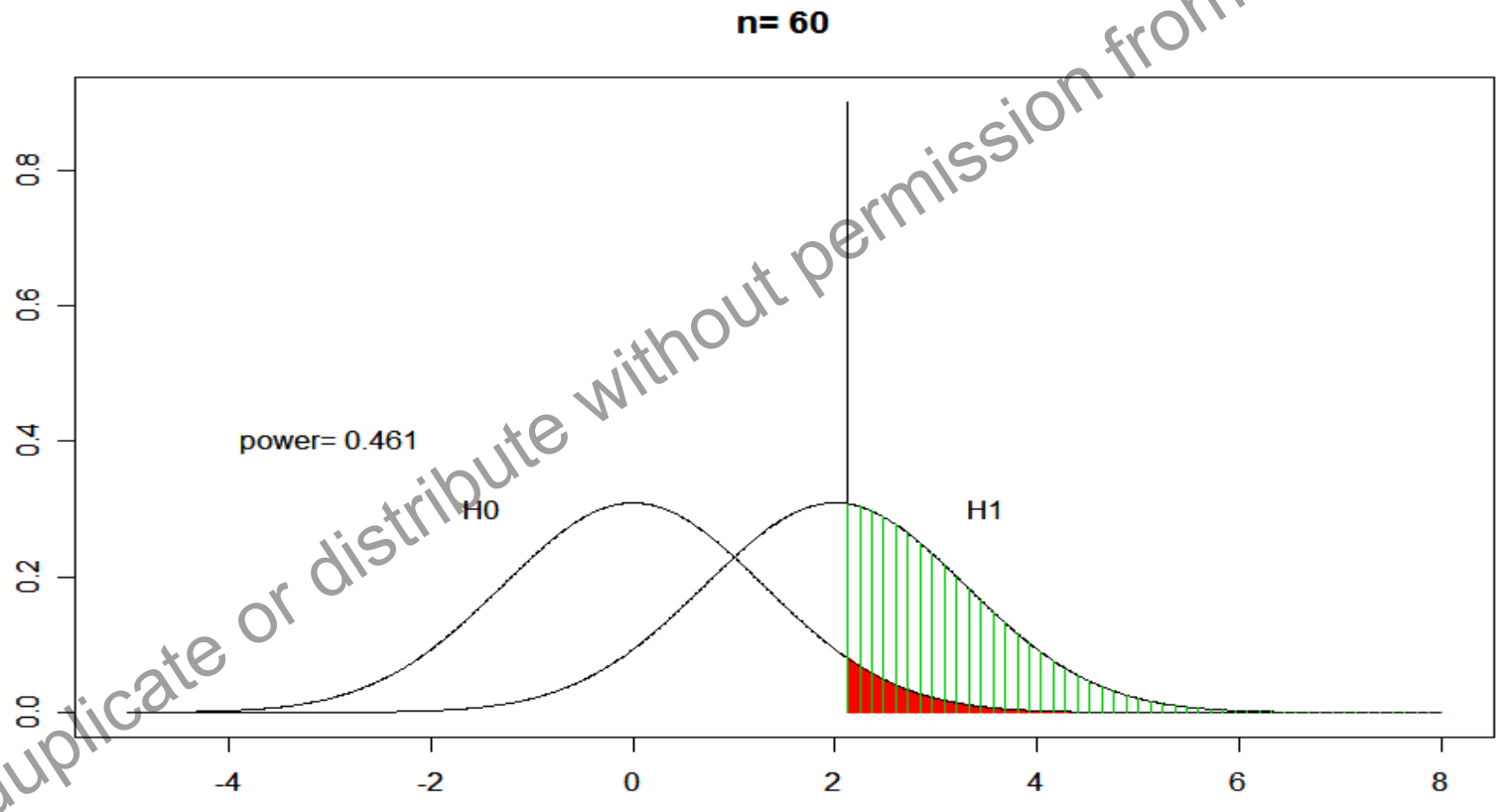
Sampling distn under H_0: $\mu_1 - \mu_2 = 0$ Sampling distn under H_1: $\mu_1 - \mu_2 = 2$



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Sample size = 60,Power = 46%

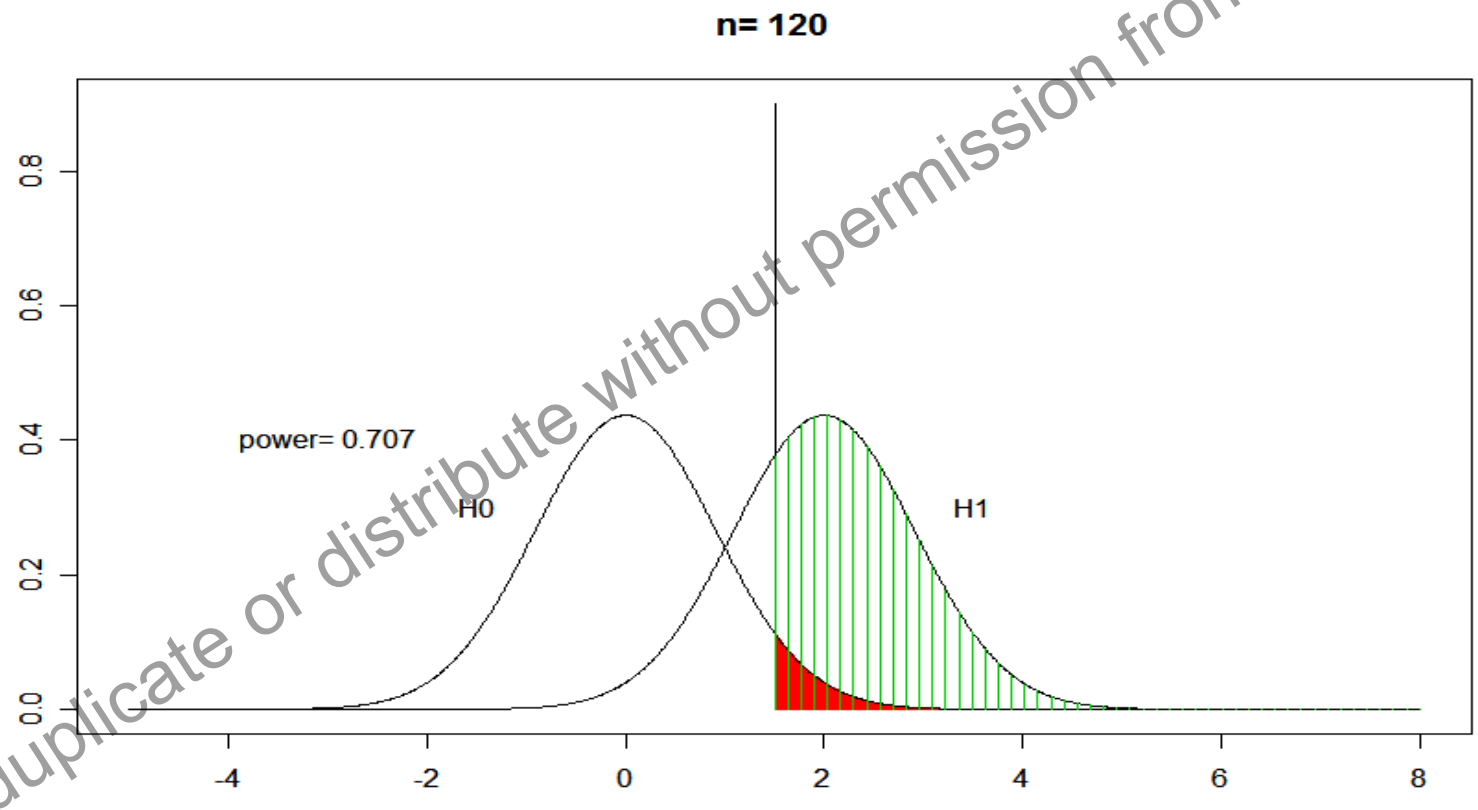
Sampling distn under H_0: $\mu_1 - \mu_2 = 0$ Sampling distn under H_1: $\mu_1 - \mu_2 = 2$



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Sample size = 120,Power = 71%

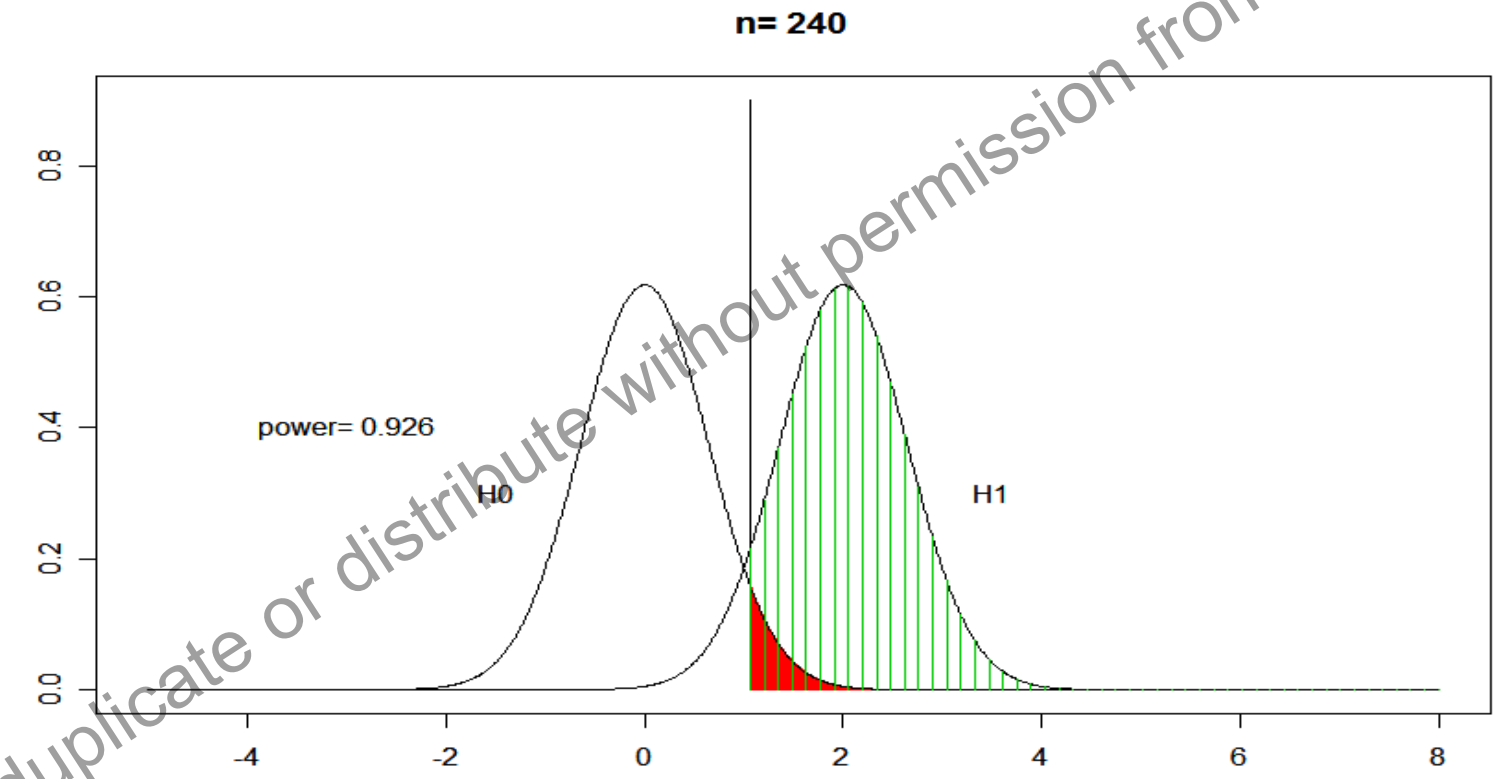
Sampling distn under H_0: $\mu_1 - \mu_2 = 0$ Sampling distn under H_1: $\mu_1 - \mu_2 = 2$



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Sample size = 240, Power = 93%

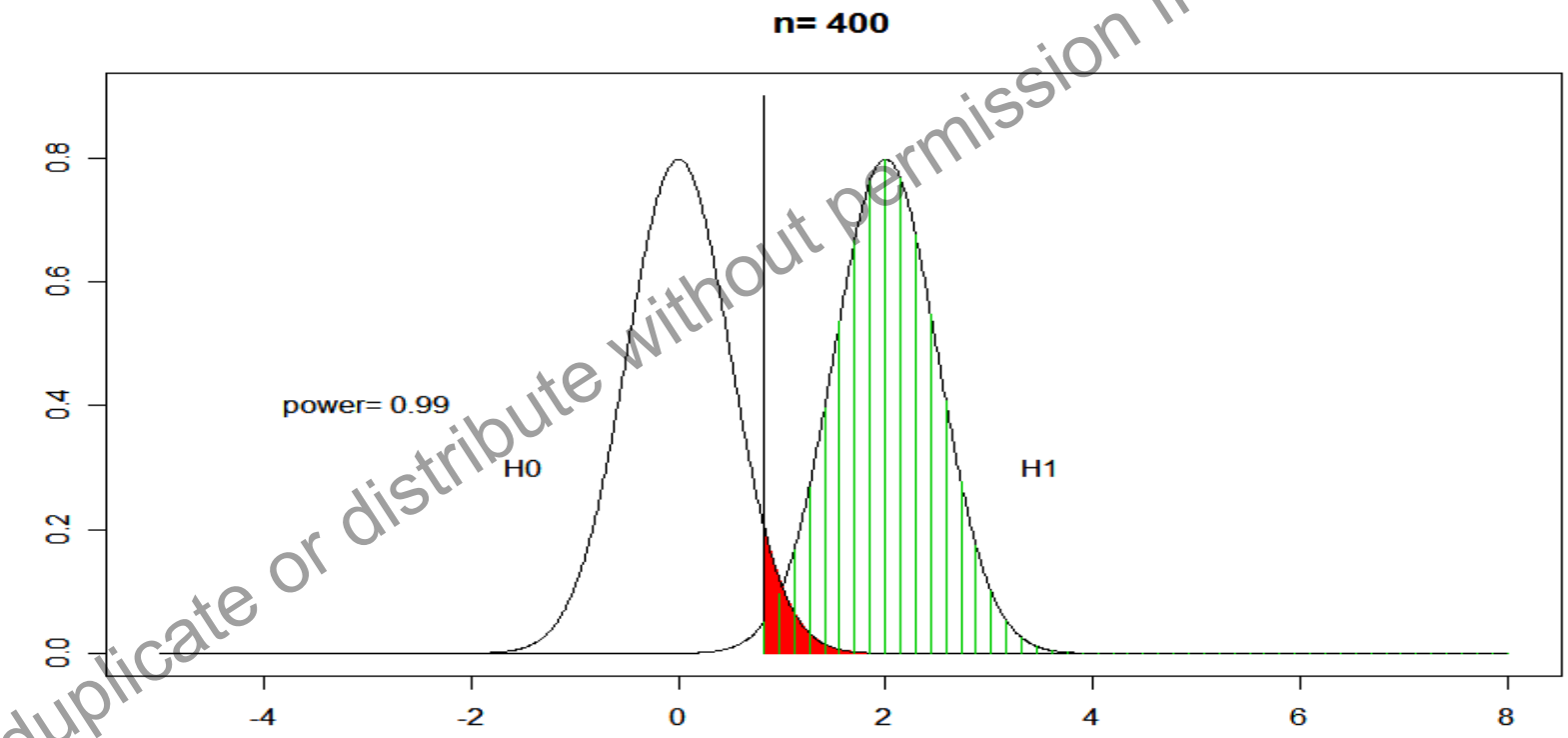
Sampling distn under H_0: $\mu_1 - \mu_2 = 0$ Sampling distn under H_1: $\mu_1 - \mu_2 = 2$



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Sample size = 400, Power > 99%

Sampling distn under H_0: $\mu_1 - \mu_2 = 0$ Sampling distn under H_1: $\mu_1 - \mu_2 = 2$



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Final Conclusion in a Superiority Trial

- Reject the null hypothesis:

  reject equivalence

  accept significant difference

- Fail to reject the null hypothesis:

  FAILURE TO REJECT the Null hypothesis should not be confused with PROOF OF EQUIVALENCE

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Question

- In a clinical trial, to **address variability** of the estimate, the design needs to include :
  - ❑ Randomization
  - ❑ Stratification & Blinding
  - ❑ Adequate Sample Size
  - ❑ Randomization & Stratification & Blinding

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Answer

- In a clinical trial, to **address variability** of the estimate, the design needs to include :
  - ❑ Randomization
  - ❑ Stratification & Blinding
  - ❑ **Adequate Sample Size**
  - ❑ Randomization & Stratification & Blinding

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Equivalence or Non-Inferiority Trial

- The objective for equivalence trials is to demonstrate that a new treatment **is equivalent** to a standard therapy with regard to a specific clinical end point and has an intrinsic benefit for other clinical end points
- A non-inferiority trial refers to a study in which the primary objective is to evaluate whether the new treatment **is not inferior** to or as effective as the standard therapy for a particular end point

Non-Inferiority Margin

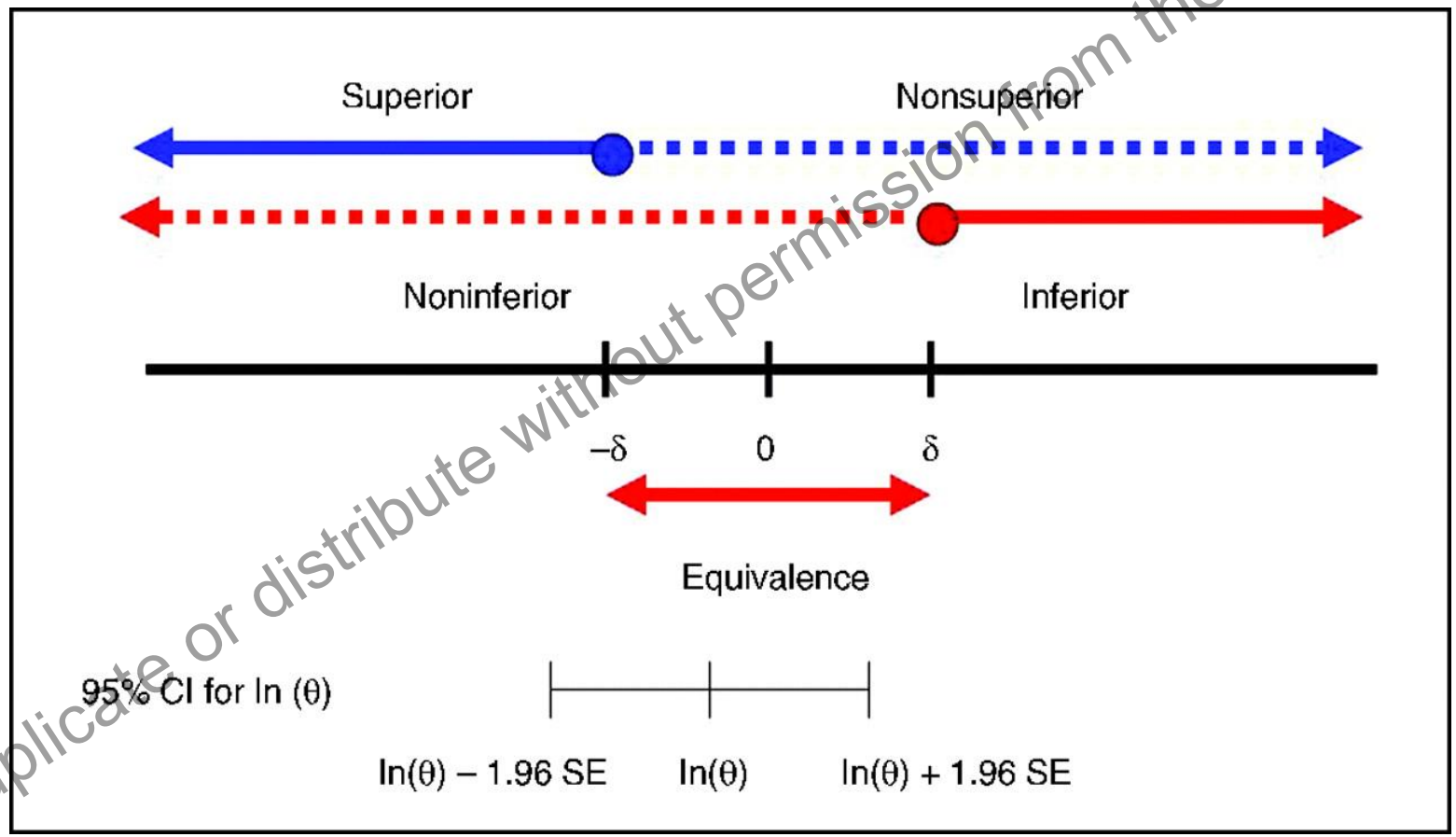
Predefined tolerance: **δ**

Zee, B. C.-Y. J Clin Oncol; 24:1026-1028 2006

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Equivalence and Non-Inferiority Trial

Prespecified quantity δ: equivalence limit or non-inferiority margin



Zee, B. C.-Y. J Clin Oncol; 24:1026-1028 2006

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Final Conclusion in a Phase III Trial

Superiority trial

- Reject the null hypothesis:

  reject equivalence

  accept significant difference

- Fail to reject null hypothesis : not to be confused with PROOF OF EQUIVALENCE or non-inferiority

Non-inferiority trial

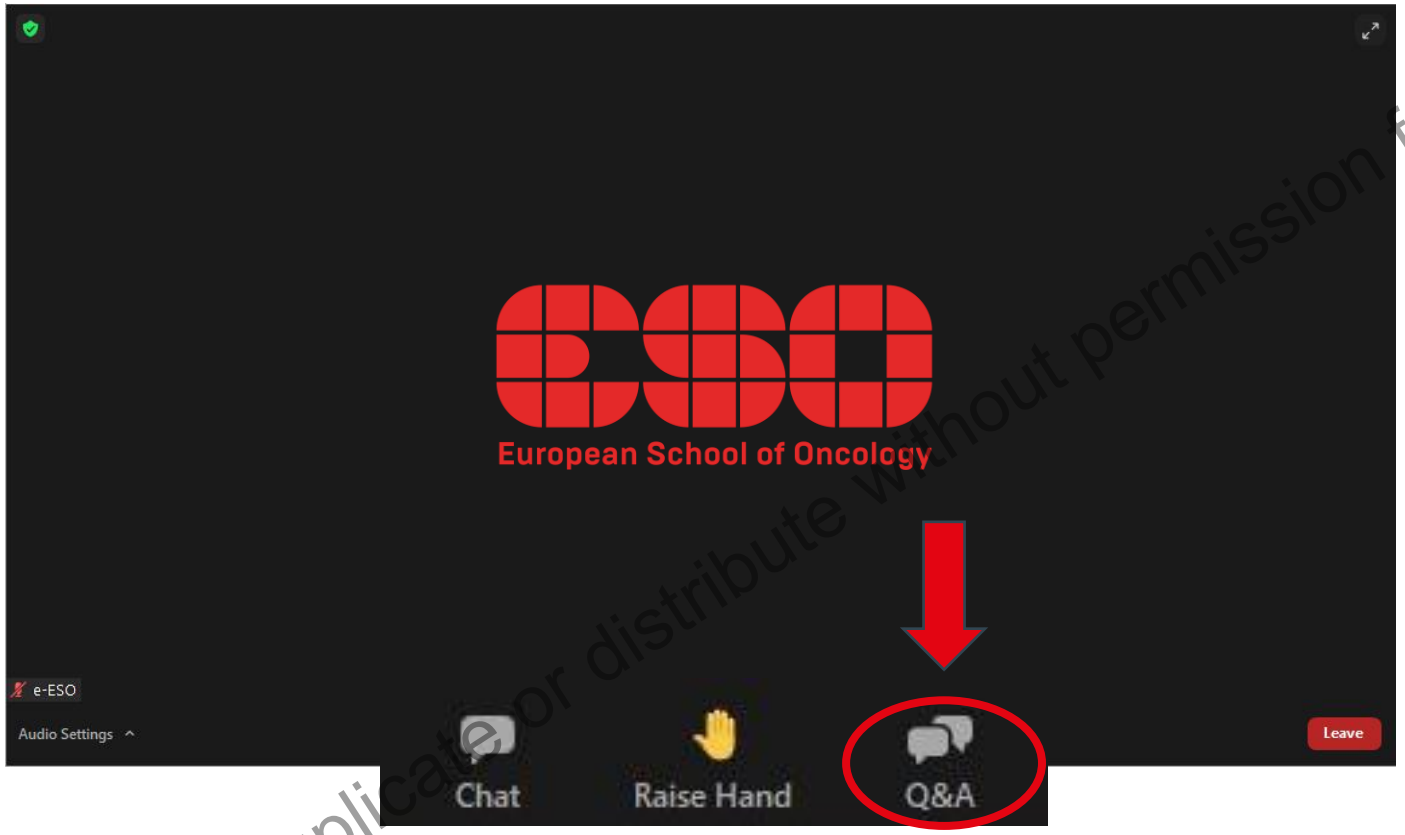
- Reject the null hypothesis:

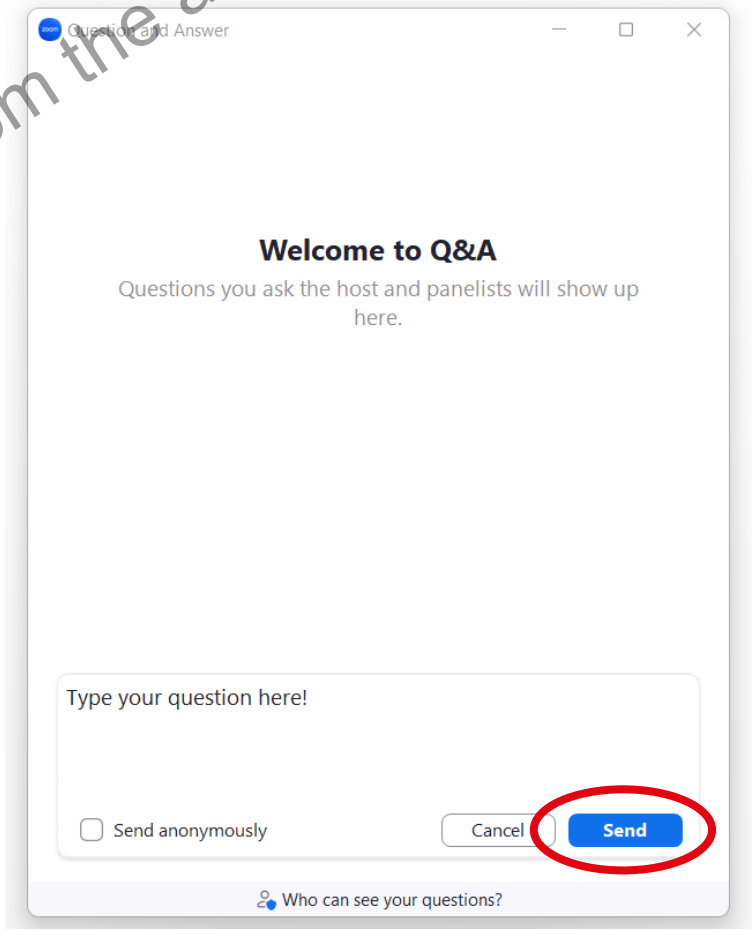
  reject inferiority

  accept non-inferiority

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Your views are important!
Remember that you can ask questions and send comments at any time.





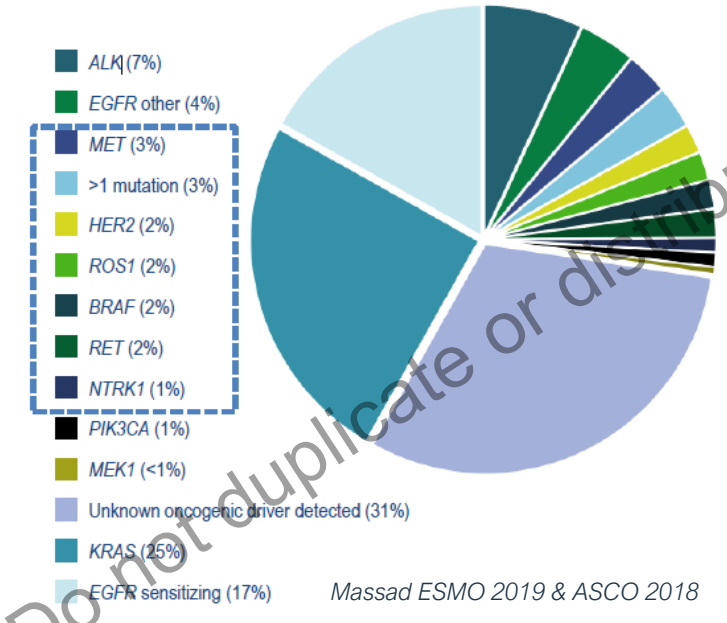
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Design of Biomarker-based Clinical Trials

Treatment

Chemotherapy
↓
TARGETED
therapies
&
IMMUNOTHERAPY



Massad ESMO 2019 & ASCO 2018

All comers (stratified by marker status) designs

All patients meeting the eligibility criteria, without exploring the biomarker status in question, are entered

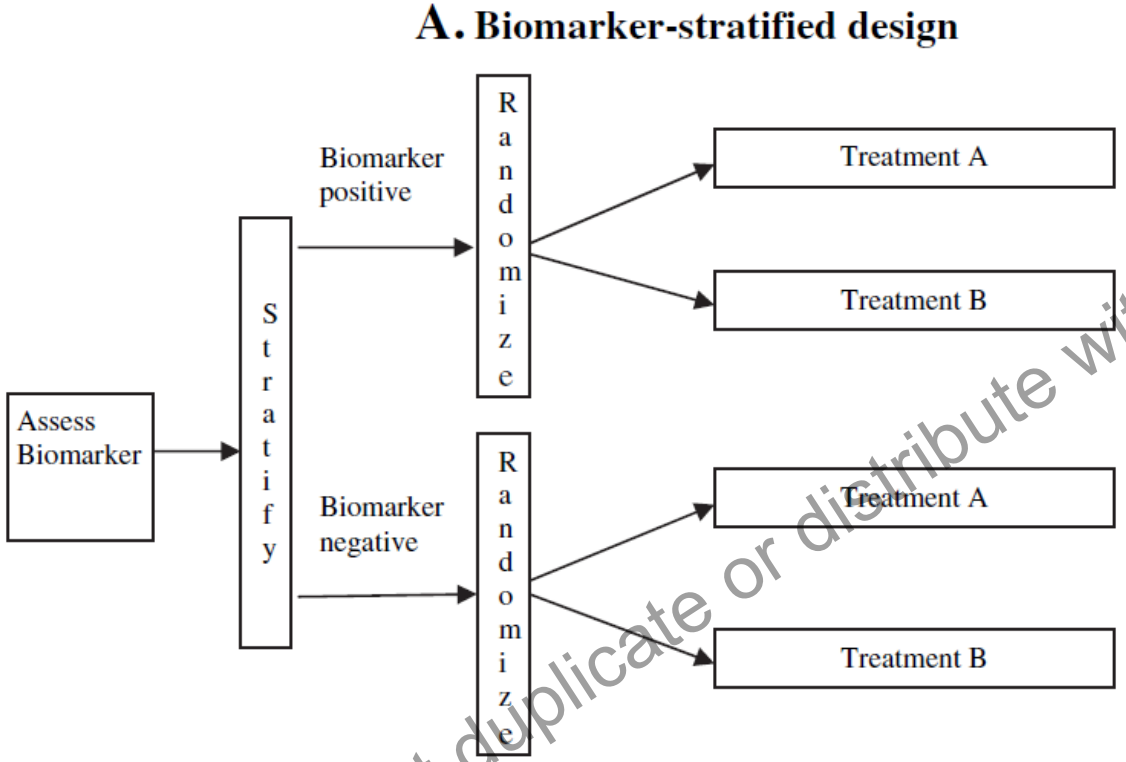
Enrichment designs

Patients are screened for the presence or absence of a biomarker profile and only those who either have or do not have the profile are included

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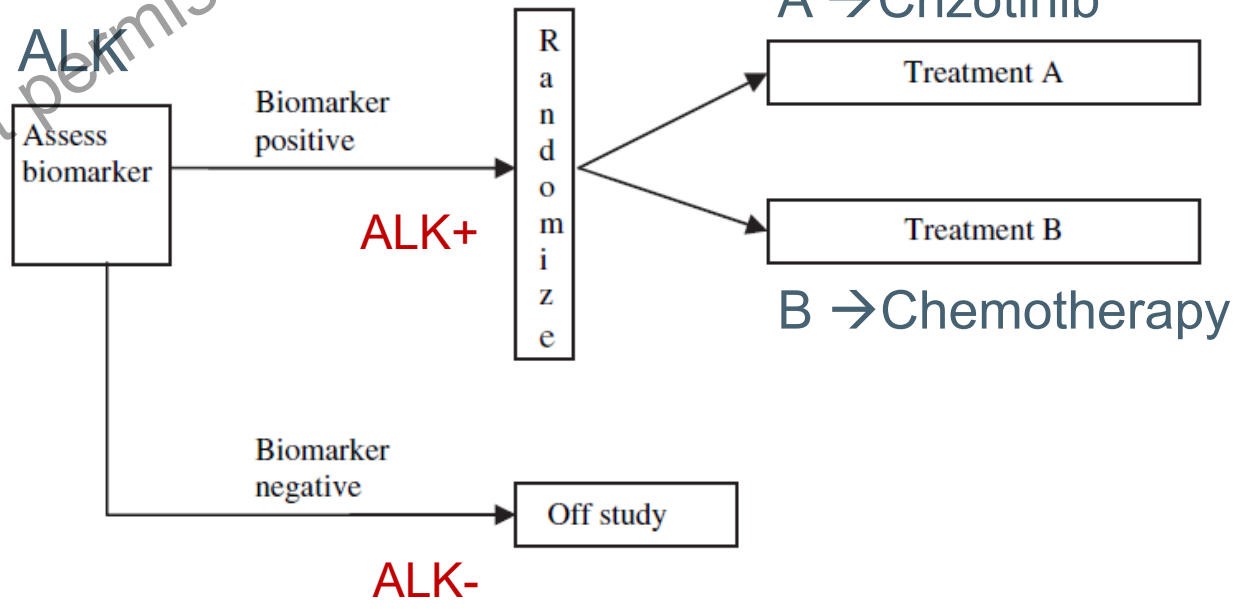
Design of Biomarker-based Clinical Trials

All comers



Freidlin,, J Natl Cancer Inst 2010

Enrichment Design



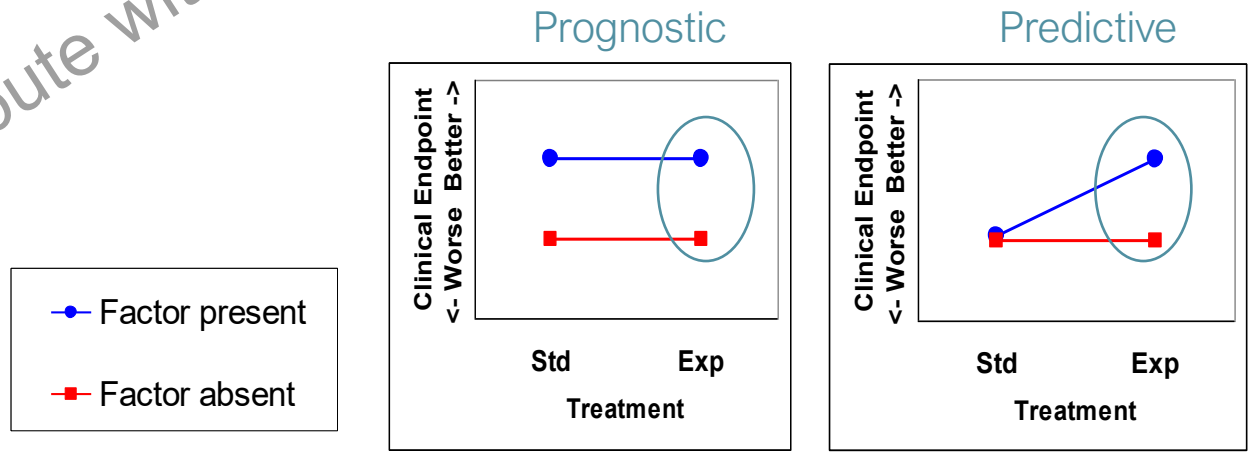
Shaw et al, NEJM 2013

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Precision Medicine needs Randomized Trials

- Certain problems cannot be addressed when relying on efficacy results from uncontrolled clinical trials

→ Improvements in outcomes in a single arm trial, cannot answer on whether the apparent benefit reflects the prognostic nature of the target, rather than a true treatment effect.



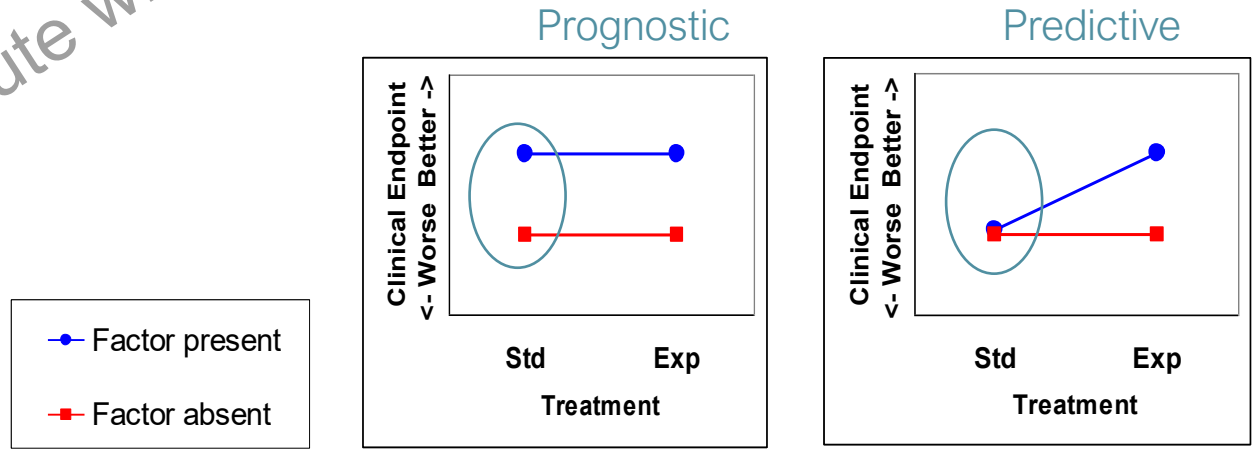
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Precision Medicine needs Randomized Trials

- Certain problems cannot be addressed when relying on efficacy results from uncontrolled clinical trials

→ Improvements in outcomes in a single arm trial, cannot answer on whether the apparent benefit reflects the prognostic nature of the target, rather than a true treatment effect.

Predictive role of biomarker can be definitely ascertained only through randomly assigning patients to the standard treatment arm.



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Subgroup Analysis:

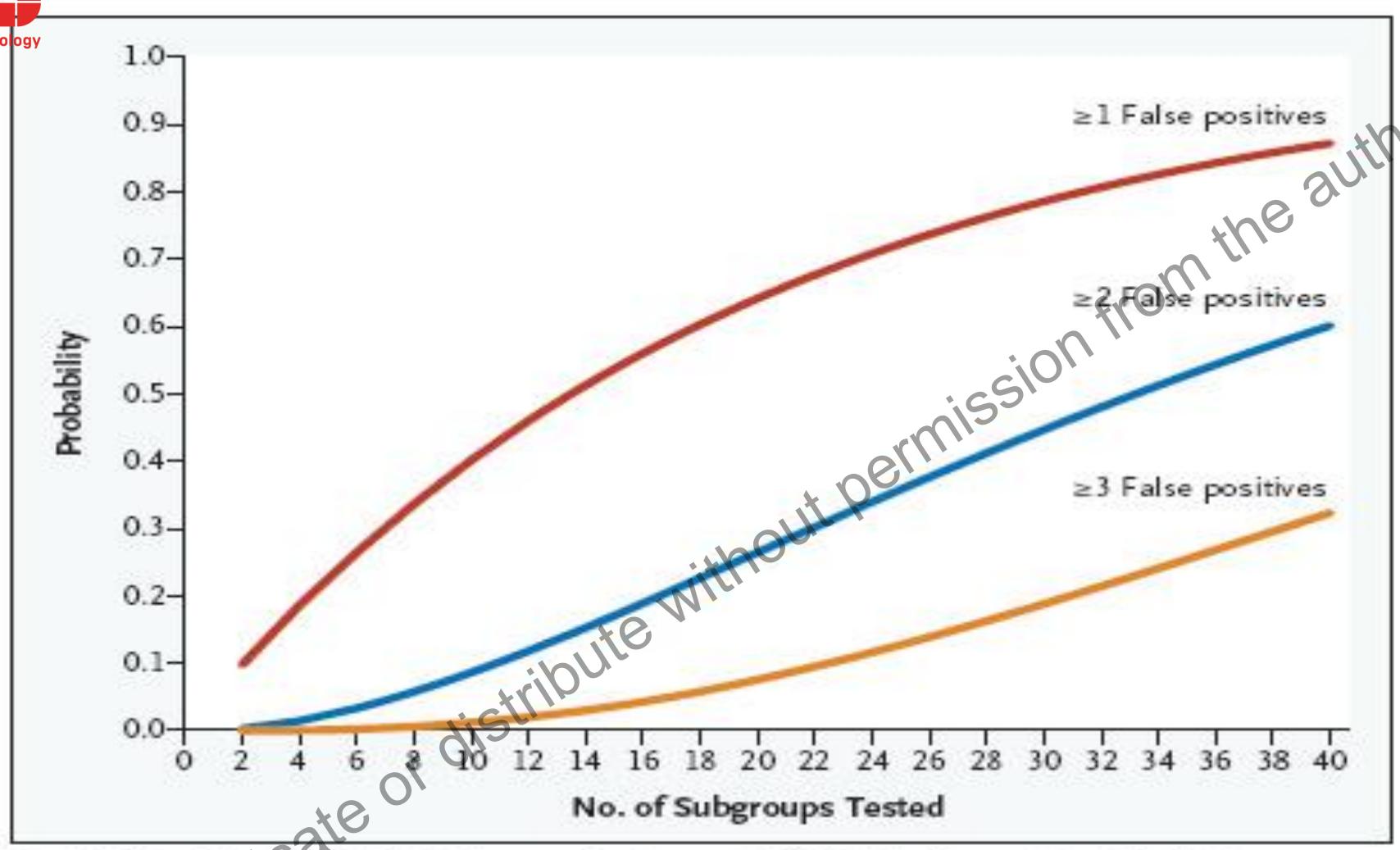
Identification of Factors affecting the outcome

Curse of multiplicity

- Common practice to perform multiple subgroup analyses
- The probability of a false positive finding (type-I error) increases as the number of subgroup analyses increases
- **10 analyses conducted ⟶ 40% chance at least 1 yields p ≤ 0.05**
- 14 analyses conducted ⟶ 50% chance at least 1 yields p ≤ 0.05

Easy to find one subgroup in which the treatment appears to work!!

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Probability That Multiple Subgroup Analyses Will Yield at Least One (Red), Two (Blue), or Three (Yellow) False Positive Results.

Presented by Gelber; Wang, Lagakos

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Summary

- Errors in Scientific Conclusions (Type I & II)

  → Trial Design and Sample Size

- Addressing Bias → Randomization
- Superiority vs Non-Inferiority Trial Conclusions
  - Lack of rejection of Null Hypothesis DOES NOT EQUAL ACCEPTANCE
- Predictive vs Prognostic Factors
- Multiplicity Problem → Adjust type I error / report all analyses

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