Medical Statistics 101

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Presenter Disclosure Information

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The following relationships exist related to this presentation:

No Industry Relationships to Disclose

Salary support from and consultant to Harvard Clinical Research Institute, an academic research organization performing contracted research activities for stent and drug manufacturers

Outline

- **Data Measurement and Comparison**
  - Parametric versus non-parametric testing
- **Hypothesis Testing**
  - Alpha error
  - Beta error and power
  - Sample size calculations
  - Confidence intervals

Data Types

- **Continuous**
  - Data can assume all possible numerical value along a continuum within a specified range
  - Most quantitative measures are continuous
- **Categorical or Discrete**
  - Values can only fall into a limited number of separate categories with no possible intermediate levels
  - Dichotomous = Yes or no responses such as baseline characteristics or event status
  - Nominal = no inherent order (gender, blood type)
  - Ordinal = numerical ranking

Measuring Continuous Data

Suppose you want to assess late loss for a new DES

- Population of interest = all patients with coronary artery disease who may be candidates for DES
- Sample of this population is chosen for study
- Late loss is measured for each subject in sample

Two Measures of Interest for Analysis

- Central tendencies (signal of interest)
  - Mean
  - Median
- Data Dispersion (noise)
  - Variance

Measuring Continuous Data II

- **Example: Late loss values obtained for 200 patients ranging from -0.2 mm – 3.2 mm**
- **Central tendency**
  - Mean = Sum of all late loss values/N subjects
  - Median = 50th percentile (middle) value
- **Dispersion – Spread of data around the central tendency**

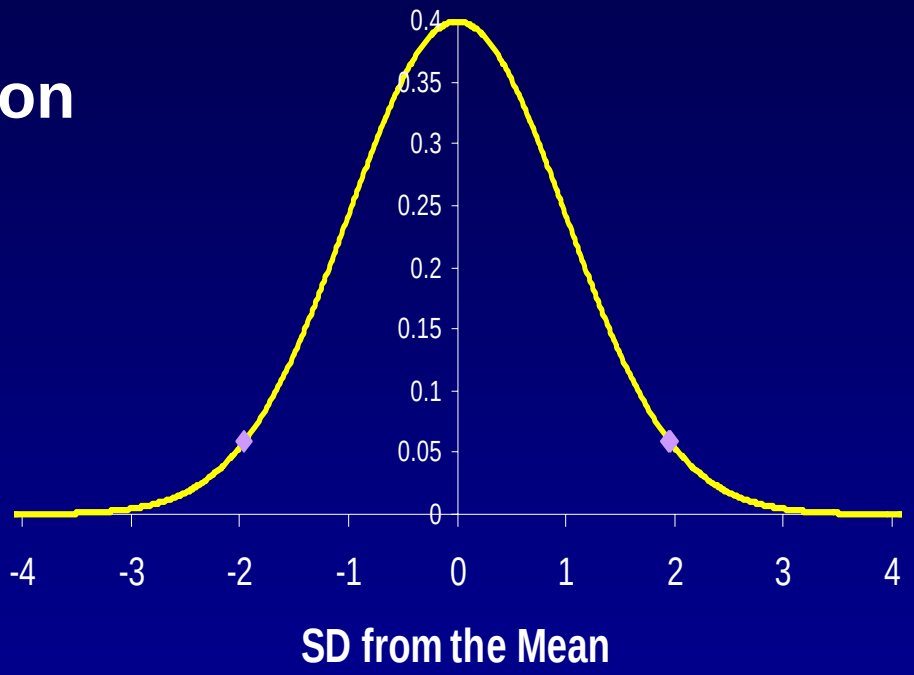
Dispersion for Means

$$\textit{Variance} = \frac{\sum_{i=1}^{n}\left(x_i - \bar{x}\right)^2}{n-1}$$

Standard deviation = $\sqrt{\text{variance}}$

Distribution of Continuous Data

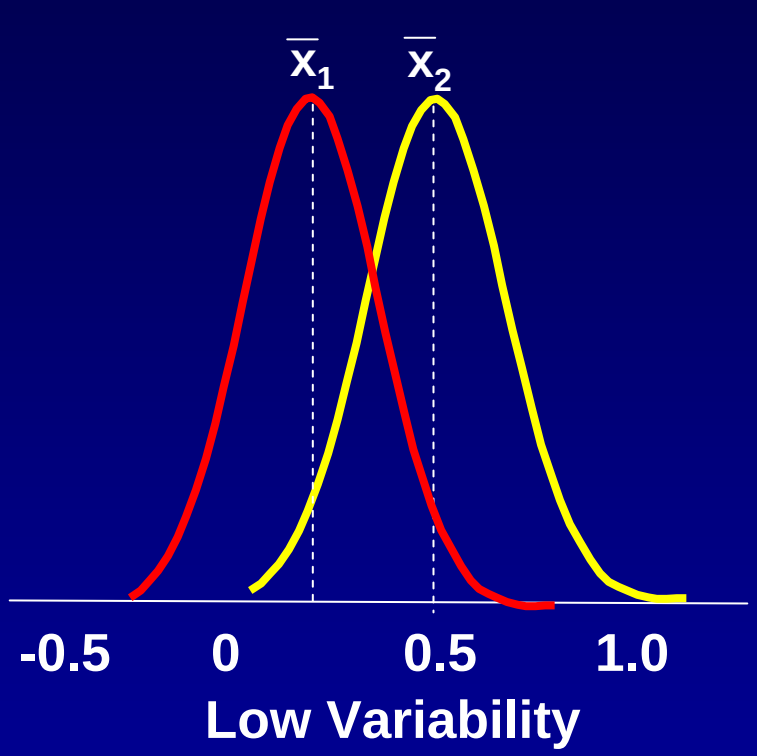
- Normal/Gaussian distribution
- Described by μ & σ
- Mean = Median
- Symmetrical
- Area under the curve sums up to 100%

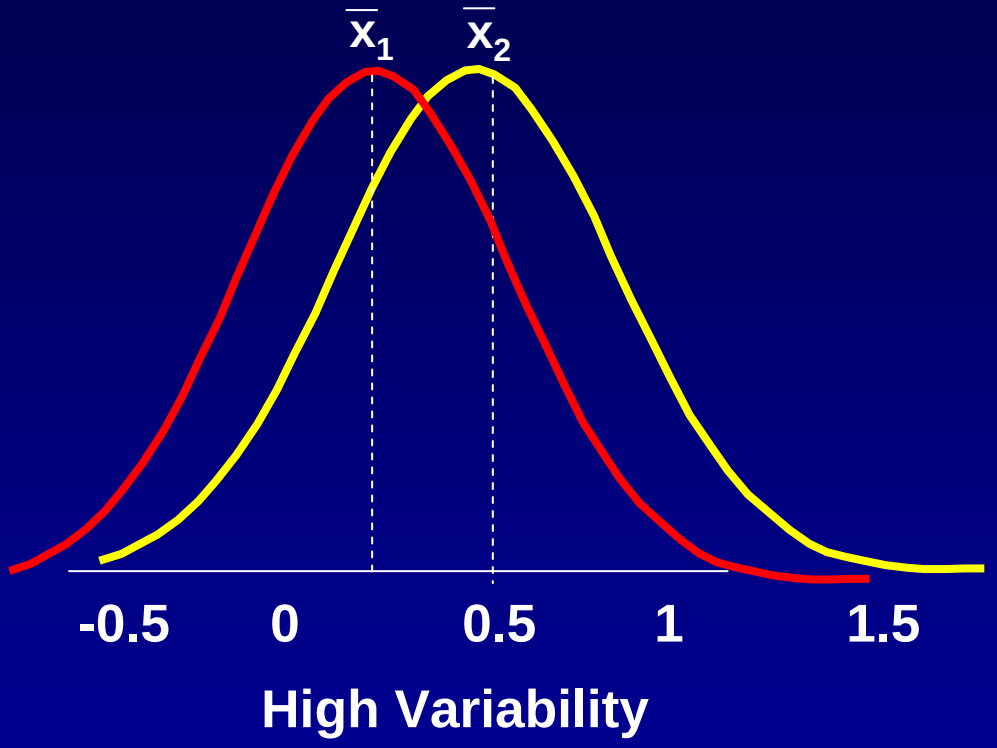


Standard Deviation =

- Zone from -1SD to 1SD covers 68.3% of the sample
- Zone from -1.96SD to 1.96SD covers 95% of the sample
- Zone from -2.58SD to 2.58SD covers 99% of the sample

Comparing Continuous Data





For data that are normally distributed, comparison of means as a function of variance
= Parametric Tests

Parametric Tests

Signal/Noise ratio = Differences in Means/Variability

- **t-Test – Useful for comparing 2 groups; Variability = SE of difference; calculates t statistic > look-up p value**

$$t = \frac{x1 - x2}{\sqrt{var1/n1 + var2/n2}}$$

Variances may be equal or unequal in the 2 groups

- **ANOVA - Analysis of Variance (test for differences in populations means based on variance); useful for comparing >2 groups; calculates F statistic> lookup p value**
- **Linear regression – tests for associations with variable of interest and other variables**

Non-Parametric Tests

If data are not normally distributed

- **Makes no assumptions about distribution of data**
- **Represented by median and interquartile range (25th and 75th percentile)**
- **Statistical tests based on ranking of data points and rank value per group**
- **Examples:**
  - Wilcoxon sign rank (2 correlated measures)
  - Mann Whitney (2 independent groups)
  - Kruskal-Wallis (multiple groups)
  - Spearman Correlation
- **Why not play it safe and just use non-parametric tests?**
  - Less powerful - more difficult to show difference

Measuring Discrete Data

- **Represented as number, frequency, or rates**
- **Rate or proportion = *probability* of success or failure**
- **Statistical tests for proportions assume a binomial distribution with mean = the proportion and variance directly related to p * (1-p) and inversely related to sample size**
- **Tests (based on observed vs expected rates)**
  - Chi-square
  - Fisher's exact (if any cell <5)

2 x 2 Table

	Yes	No	
Group 1	**a**	**b**	**a + b**
Group 2	**c**	**d**	**c + d**
	a + c	**b + d**	

Hypothesis Testing

- Null Hypothesis – H0: PA = PB
- Alternate Hypothesis – H1: PA ≠ PB
- Objective is to reject or fail to reject the null hypothesis. If null is rejected then accept the alternative hypothesis
- Alternative hypothesis implies difference in either direction (A better or worse than B); Two-sided test

Hypothesis Testing 2

- After comparison using statistical tests based on data type and distribution etc, obtain probability that observed result is due to random chance and consistent with the null hypothesis.
- By convention, probability of 5% is usually accepted as convincing evidence.
- The probability of this chance – rejecting the null hypothesis (claiming difference) when it is true (no difference) is termed alpha error
- Since 2-sided test, there is 2.5% chance for error in either direction

Hypothesis Testing 3

- **Since it is not possible to prove the null hypothesis there is some probability that an experiment will fail to reject the null hypothesis even though it is false**
- **This is termed beta error**
- **The power of a study (reject the null hypothesis when it is false and claim a difference) = 1 – beta**
- **Generally study designs include power of at least 80% or *20% probability of failure to reject even though false***

Sample Size

- **Often the most important factor to the success of a trial design**
- **Benefits of smallest possible sample size due to costs and time for enrollment**
- **Sample size dependent on:**
  - alpha error (usually fixed by convention)
  - treatment effect (should be fixed and reasonable)
  - variance (fixed if known)
  - beta error or power (becomes the major driver of sample size in design variations)

Sample Size 2

If you hold all the other variables constant,

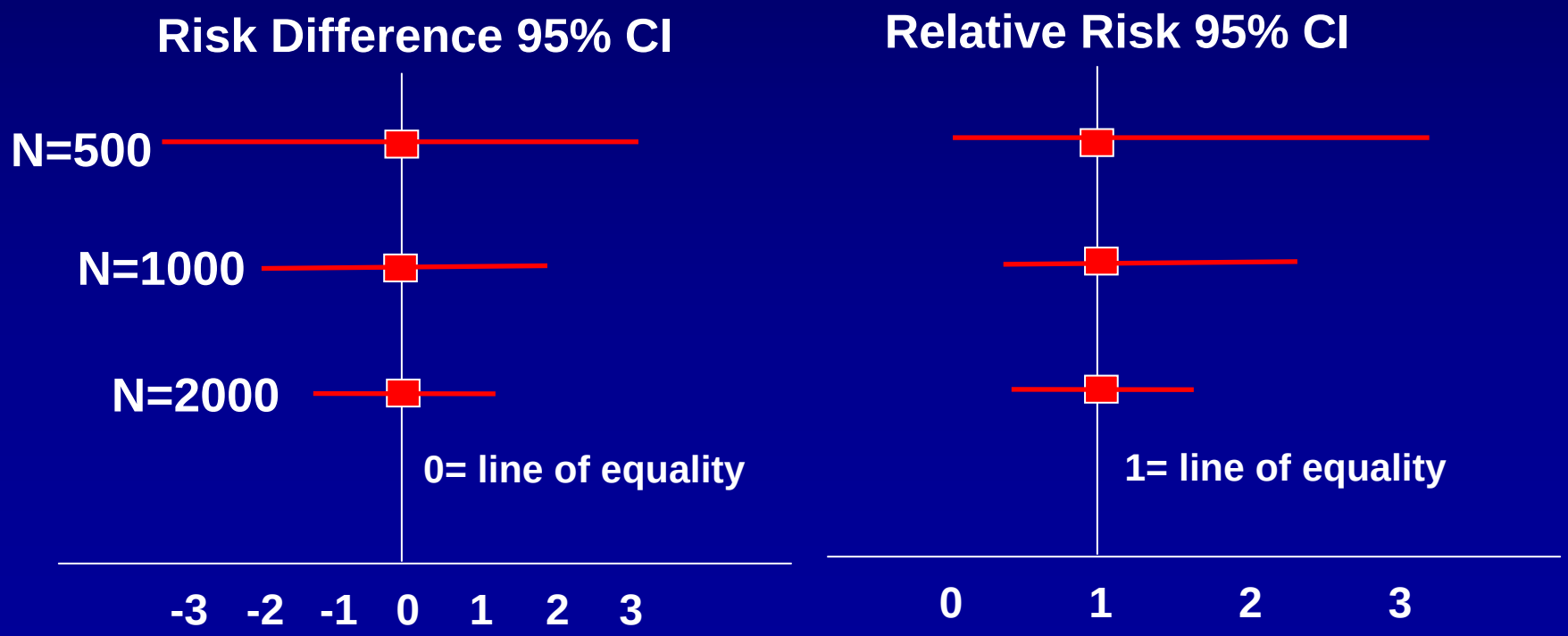
- If alpha decreases, then power decreases (i.e., it's harder to find a difference if you use a very stringent p-value).
- If the magnitude of difference sought increases, power increases (i.e., it's easier to detect a big difference, harder to detect a small difference).
- If the sample size increases, then power increases (i.e., it's easier to find a difference if you have a large sample).
- If the standard deviation of the variable in question increases, the power decreases (i.e., more noise, less power).

Confidence Intervals

- **Level of assurance that the results are reproducible and not due to chance**
- **Most common level is 95% (correlates with alpha error of 5%) interpreted as: If the same trial were conducted 100 times then 95 times the estimate would be within the specified interval**
- **Confidence intervals are calculated based on actual result, the desired level of assurance, and a measure of variance (standard error)**
- **Confidence intervals can be based on:**
  - Proportion or mean estimate (actual study result)
  - Risk difference (Group 1 – Group 2)
  - Relative risk

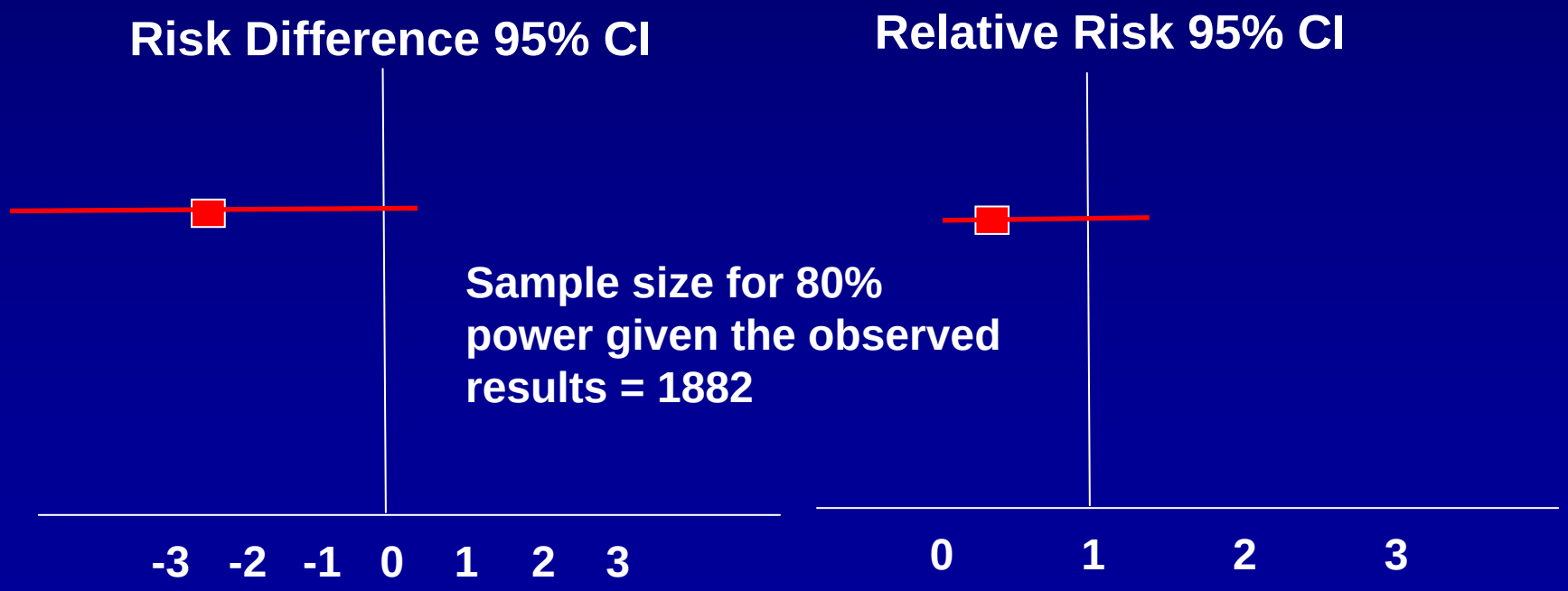
Confidence Intervals & Interpretation of Results

- Suppose a clinical trial with 250 pts in each of 2 arms has death or MI rate of 2% in each arm. The authors report no differences in safety – Is this true?



Confidence Intervals & Impact of Sample Size

- Suppose a clinical trial sponsor has new DES with expected 0% TLR; assume control DES = 5%, new DES =0.5%; sample size = 500
- Actual Results at 1 year: 3.2% vs. 1.2% (observed 62% relative risk reduction)



Beware of Underpowered Trials

Claims of "No Difference"

- **Failure to reject the null hypothesis does not equate equivalence or mean "not different"**
- **Possibilities**
  - Play of chance (80% power means 20% chance of failure to reject null when in fact is false, i.e. there is a difference)
  - Overly optimistic treatment effect in trial design
  - Failure to attain event rate assumptions
- **Confidence intervals help determine what difference can be excluded with specified assurance**
- **Requires formal non-inferiority trial design**