Basic Statistical Concepts and Methods for Research Studies

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Discussion Point

What does the word
"Statistics"
mean to you?

The discipline of Statistics

- Wikipedia: Statistics is the study of the collection, organization, and interpretation of data.
- American Heritage Science Dictionary: The branch of mathematics that deals with the collection, organization, analysis, and interpretation of numerical data.
- Merriam-Webster Dictionary: A branch of mathematics dealing with the collection, analysis, interpretation, and presentation of masses of numerical data.
- Dictionary.com: the science that deals with the collection, classification, analysis, and interpretation of numerical facts or data, ...

Planning your Study

- Define the questions of interest.
- Determine the appropriate populations (people/animals/etc) that will allow the questions to be answered.
- Create a plan to sample the populations. Randomization may be required.
- Determine what information is needed from the sample to answer the questions.
- Create an appropriate analysis plan.

Statisticians can help

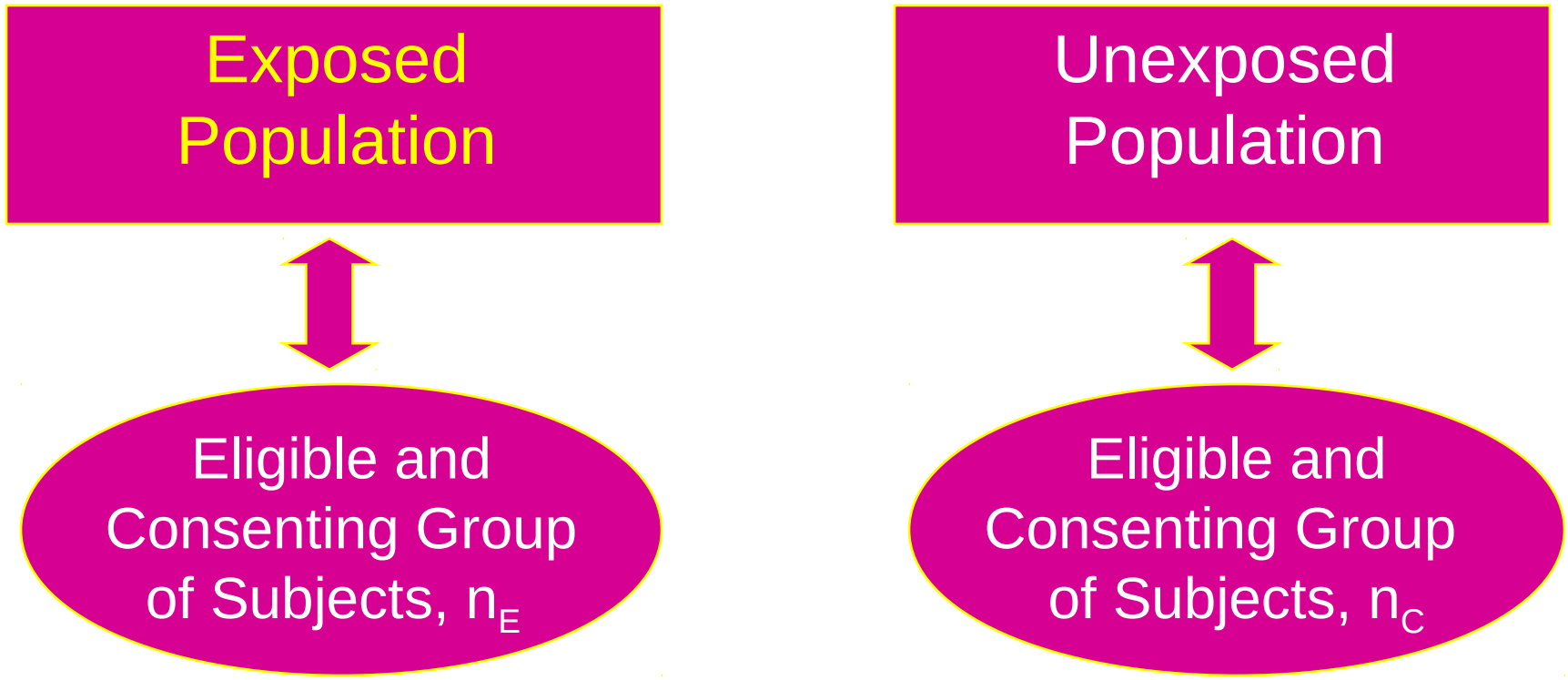
- Focus and clarify the objectives
- Design an appropriate sampling plan
- Provide a randomization scheme
- Design an appropriate analysis plan

➔ Talk to a statistician before you collect data !!!

Two Types of Research Studies

- Observational Studies
  - In epidemiology and statistics, an observational study draws inferences about the possible effect of a treatment on subjects, where the assignment of subjects into a treated group versus a control group is outside the control of the investigator.
- Controlled Experiments
  - There are many forms of controlled or designed experiments. A relatively simple one randomly assigns research subjects or specimens into two groups: an experimental group and a control group.

A Two-Group Observational Study



Observational Studies: Some Issues

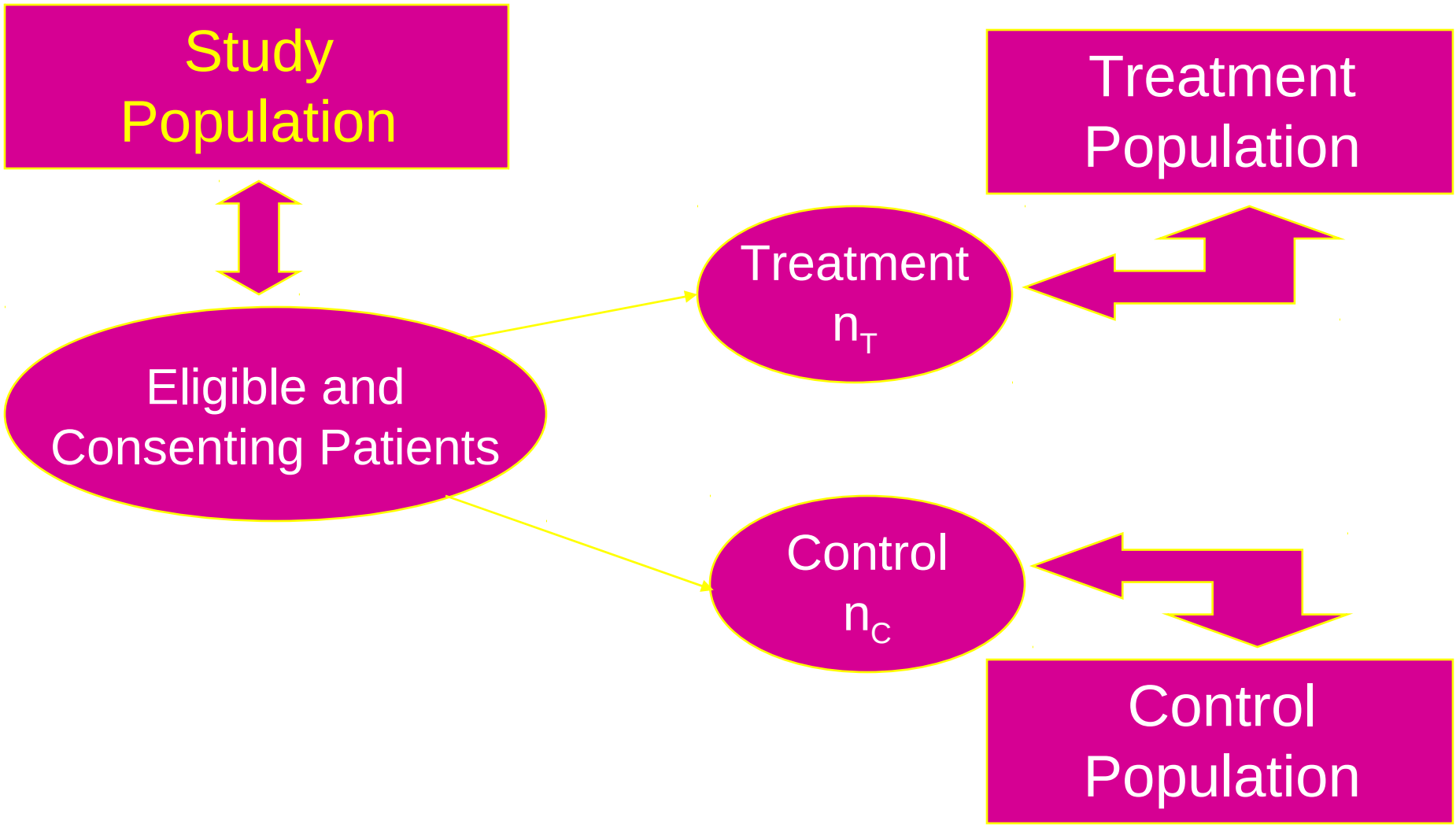
- Describing differences is straightforward
  - Examination of associations with exposure
- Confounding is a major issue
  - Differences could be due to a factor other than exposure that differs across the groups
  - Analyses must adjust for such confounders
- Analyses can suggest, but not establish causality
  - Bradford Hill's criteria for causality
- If based on samples, are samples representative?

Confounding Example

- Kidney Stones
- The table shows the success rates and numbers of treatments for treatments involving both small and large kidney stones, where Treatment A includes all open procedures and Treatment B is percutaneous nephrolithotomy:

	Treatment A	Treatment B
Small Stones	**93% 81/87**	87% 234/270
Large Stones	**73% 192/263**	69% 55/80
Both	78% 273/350	**83% 289/350**

A Two-Armed Clinical Trial



Clinical Trials: Some Issues

- Ethics of experimentation.
  - Cannot force someone to smoke
- Choice of control: nothing, placebo or active.
  - The placebo effect
  - ethically must treat if one already exists
- Blinding of subjects and evaluators.
  - subconscious effects
- Target population versus study population.

Defining the Question

- Make sure questions are clear and focused.
- All questions should be based on the same populations or perhaps a subset.
- Each question should define a single hypothesis to test or quantity to measure.
- “Does Betaseron decrease the relapse rate in relapsing-remitting MS patients?”
- “What is the change in relapse rate between relapsing-remitting MS patients treated with Betaseron and those who are not.”

Multiple Questions

- The more questions the greater the overall type 1 error rate (familywise error rate).
- Worse case scenario: Independent events
  - P(A & B) = P(A)*P(B)
- Suppose a researcher is trying to find a molecule that would be good biomarker for a given disease. If they look at 5, 10 or 20 markers with $\alpha = 0.05$ then the probability of at least 1 false positive = 0.23, 0.40 or 0.64 respectively.
- Using a Bonferroni correction ($\alpha^* = \alpha/n$) with 5, 10 or 20 biomarkers then $\alpha^* = 0.01$, 0.005 or 0.0025 and the probability of at least 1 false positive = 0.049 in all cases.

Multiple Question: cont

- Hypotheses in same study are usually not independent
- Bonferroni is conservative and leads to a larger sample size to maintain the same power
  - if n=64 is needed to detect a difference of 1/2 a standard unit with power = 0.80 for a single question in a two-sample t-test, then with 5, 10, 20 questions the sample size becomes 96, 109, 122 respectively
- Less conservative methods are available such as False Discovery Rate
- Recommendations: limit the number of questions or select a few questions as primary

The Sampling Plan

- Quite often the sample is based on the available population for experiments and observational studies.
  - clinical trials or case-control studies.
- Are sampled units independent?
  - Most analyses make this assumption.
- Does the sample represent the population?
  - This is who is sampled not how many.
  - This is statistical accuracy.
- Does the sample give enough precision or power?
  - This is how many are sampled.
  - Precision for estimation, power for testing.

Randomization

- Should assign a subject or specimen to any treatment or control group with probability based on relative sample size within those groups.
- Controls bias in the study.
- Does not guarantee that the groups are "matched" or equivalent, only that any differences are due to chance.
- Randomization should be used to balance the experiment as much as possible if several factors are considered
- Can be combined with some observational components such as gender or age.
- Randomization should be used to remove order effects within a subject if using repeated measures under different conditions

Experimental Unit

- The level of randomization or sampling.
- Sampling unit does not always equal the experimental unit
- The level of independent observations.
- Pseudoreplication are observations within an experimental unit: repeated measures
  - results in over exaggeration of statistical significance
  - some pseudoreplicates are hard to detect.
- Discussion Point: 100 mice are assigned to 20 cages. Each cage is fed a diet which contains either treatment or placebo. What is the experimental unit and why?

Sample Size Considerations

- Most statistical analysis depend on a reasonable sample size to be valid
- As sample size increases
  - statistical power of a hypothesis test increases
  - precision of estimates increases by the square root law
  - distribution of statistics become more predictable
    - Central limit theorem -> normal distribution
  - statistical accuracy does not change
- Demonstration **http://onlinestatbook.com/stat_sim/sampling_dist/index.html**

Sample Size/Power example

two sample t-test: detecting a 1/4 standard unit difference

N	Power
20	11.7%
40	19.6%
60	27.4%
80	34.9%
100	42.0%

two sample t-test: detecting a 1/2 standard unit difference

N	Power
20	33.8%
40	59.8%
60	77.5%
80	88.1%
100	94.0%

The Data

- Data must answer your questions
- Blind collectors to avoid bias
- Accuracy of measurements
- Accurate data entry
- Dealing with missing data
- Data issues should be resolved before analysis begins
- Data should be finalized and locked before analysis.
- Discussion Point: Why should the data be finalized before analysis begins?

Types of variables

- Numeric variables
  - Continuous variables (interval or ratio)
  - Discrete variables (binary or counts)
- Categorical variables (always discrete)
  - ordinal (can be ordered or ranked)
  - nominal (categories without order)
- Binary data can be treated as numeric, ordinal or nominal
- Response variables (dependent variables)
- Explanatory variables (independent variables)

Common Analyses

- Continuous response variable:
  - t-test, paired t-test, rank tests
  - regression, ANOVA, linear models, survival analysis
- Discrete numeric response variable:
  - Count: Poisson regression (possibly over-dispersed)
  - Binary: logistic regression
  - Contingency tables: Chi Squared or Fishers Exact tests
- Categorical responses are more complicated
  - Ordinal: Proportional odds models
  - Nominal: multinomial models
- Pseudoreplication complicates the analysis
  - Mixed effects models, repeated measures analysis

Model Assumptions

- Every model is based on a set of assumptions
- Most important assumption is data are i.i.d.
  - independent and identically distributed
  - required for most common statistical models and test
- Many models assume normally distributed errors
  - t-test, regression, ANOVA
  - with large sample size not a critical assumption
- Other distributions for logistic or Poisson regression models
- non-parametric tests make no assumptions about distribution
- effect of violating assumptions heavily depends on the situation
- some violations are more critical than others
- Assumptions should be checked if possible

Hypothesis test

- Define null and alternative hypothesis
  - Null Hypothesis: the default condition
    - Absence of evidence is not evidence of absence
  - Alternative Hypothesis: what we want to show
- Determine threshold needed to reject null
  - usually based on α (false positive probability)
- Collect data needed to test hypothesis
  - sample size determined by power analysis
- Analyze data to determine result
  - Null is true, do not reject null: correct decision
  - Null is true, reject null: Type 1 error
  - Alt is true, do not reject null: Type 2 error
  - Alt is true, reject null: correct decision (power)

The End

Questions?