Designing a Research Protocol

Dr. Nicole Lewis

lewiscn2@etsu.edu

Introduction

- The protocol is the detailed plan of the study.
- Every research study should have a protocol
- The protocol should be written.

Goals of Protocol

1. Overcoming the limits of the current knowledge in a determinate field with the aim of bridging a “knowledge gap.”

2. Bringing something new in a scarcely explored field.

3. Validating or nullifying previous results obtained in limited records by studies on a wider population.

Written Protocol

- Forces the investigators to clarify their thoughts and to think about all aspects of the study
- Is a necessary guide if a team (not a single investigator) is working on the research
- Is essential if the study involves research on human subjects or is on experimental animals, in order to get the institution's ethical approval
- Is an essential component of a research proposal submitted for funding.

Violations

- Once a protocol for the study has been developed and approved, and the study has started and progressed, it should be adhered to strictly and should not be changed.
- This is particularly important in multi-center studies.
- Violations of the protocol can discredit the whole study.
- If the violations are minor, at least that part of the study should be excluded from the analysis.

Operational Manuals

- An additional step, after writing the protocol, particularly in large studies with teams of investigators, is to develop what may be called the operations manual for the study.

- This will include detailed instruction to the investigators to assure a uniform and standardized approach to carrying out the study with good quality control.

Well-Written Protocol

1. Is it adequate to answer the research question(s), and achieve the study objective?

2. Is it feasible in the particular set-up for the study?

3. Does it provide enough detail that can allow another investigator to do the study and arrive at comparable conclusions?

Protocol Format

- General Information
- Project title
- Project summary
- Project description:
  - Rationale
  - Objectives
  - Methodology
- Data management and analysis
- Ethical considerations
- Gender issues
- References

- More Detailed Format: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6172884/table/T1/?report=objectonly

Project Description: Rationale

- This is equivalent to the introduction in a research paper.
- It puts the proposal in context.
- It should answer the question of why and what.
- A brief description of the most relevant studies published on the subject should be provided to support the rationale for the study.

Project Description: Objective(s)

- Specific objectives are statements of the research question(s).
- Objectives should be simple (not complex), specific (not vague), and stated in advance (not after the research is done).
- After statement of the primary objective, secondary objectives may be mentioned.

Project Description: Methodology

- It should include information on the research design, the research subjects, interventions introduced, observations to be made and sample size.

- Research Design: The choice of the design should be explained in relation to the study objectives.
  - Observational
  - Experimental

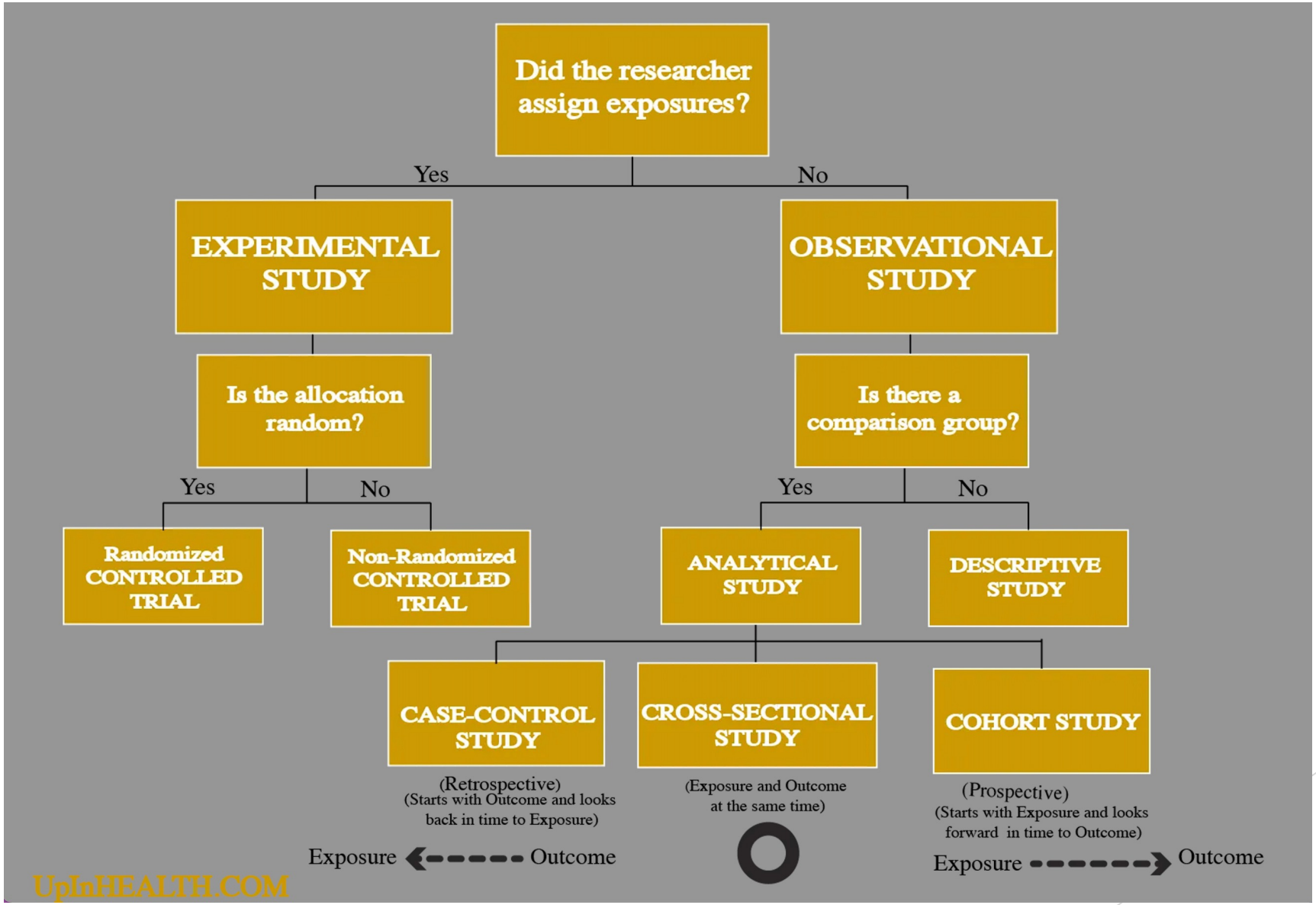
Observational Example

- A researcher wants to know why individuals in Community A have a higher rate of a rare form of cancer when compared to those living in Community B. To find out the reasons for the differences in cancer rates in these two communities, the investigator surveyed residents about their lifestyle, noted the types of businesses that were present in the community and searched medical records. The researcher found that the headquarters for the Toxico Chemical Plant is located in Community A, there is a higher rate of cigarette smoking in this community and residents tended to delay or skip going to the doctor for an annual checkup. In Community B, the largest employer was a department store and on average, residents did not smoke as much as residents from Community A. However, like individuals from Community A, Community B residents tended to delay or skip their annual checkup with their doctor.

Experimental Example

- A fitness instructor wants to test the effectiveness of a performance-enhancing herbal supplement on students in her exercise class. To create experimental groups that are similar at the beginning of the study, the students are assigned into two groups at random (they can not choose which group they are in). Students in both groups are given a pill to take every day, but they do not know whether the pill is a placebo (sugar pill) or the herbal supplement. The instructor gives Group A the herbal supplement and Group B receives the placebo (sugar pill). The students' fitness level is compared before and after six weeks of consuming the supplement or the sugar pill. No differences in performance ability were found between the two groups suggesting that the herbal supplement was not effective.

Pictorial View



Project Description: Methodology

- Research Subjects: Depending on the type of the study, the following questions should be answered:
  - What are the criteria for inclusion or selection?
  - What are the criteria for exclusion?
  - In intervention studies, how will subjects be allocated to index and comparison groups?
  - What are the criteria for discontinuation?

Project Description: Methodology

- Interventions: If an intervention is introduced, a description must be given of the drugs or devices to be used, and whether they are already commercially available, or in phases of experimentation.

- For drugs and devices that are commercially available, the protocol must state their proprietary names, manufacturer, chemical composition, dose and frequency of administration.

- For drugs and devices that are still in the experimental stage (or that are commercially available but are being used for a different indication or in a different mode of administration), additional information should be provided on available pre-clinical investigations in animals and/or results of studies already conducted on humans.

Project Description: Methodology

- Observations: Information should be provided on the observations to be made, how they will be made, and how frequently will they be made.
- If the observation is made by a questionnaire, this should be appended to the protocol.
- Laboratory or other diagnostic and investigative procedures should be described.
- For established procedures, reference to appropriate published work is enough.
- For new or modified procedures, an adequate description is needed, with a justification for their use.

Project Description: Methodology

- Sample size: The protocol should provide information and justification about sample size.
- A larger sample size than needed to test the research hypothesis increases the cost and duration of the study and will be unethical if it exposes human subjects to any potential unnecessary risk without additional benefit.
- A smaller sample size than needed can also be unethical if it exposes human subjects to risk with no benefit to scientific knowledge.
- The basis on which sample size is calculated should be explained in the methodology section of the protocol.

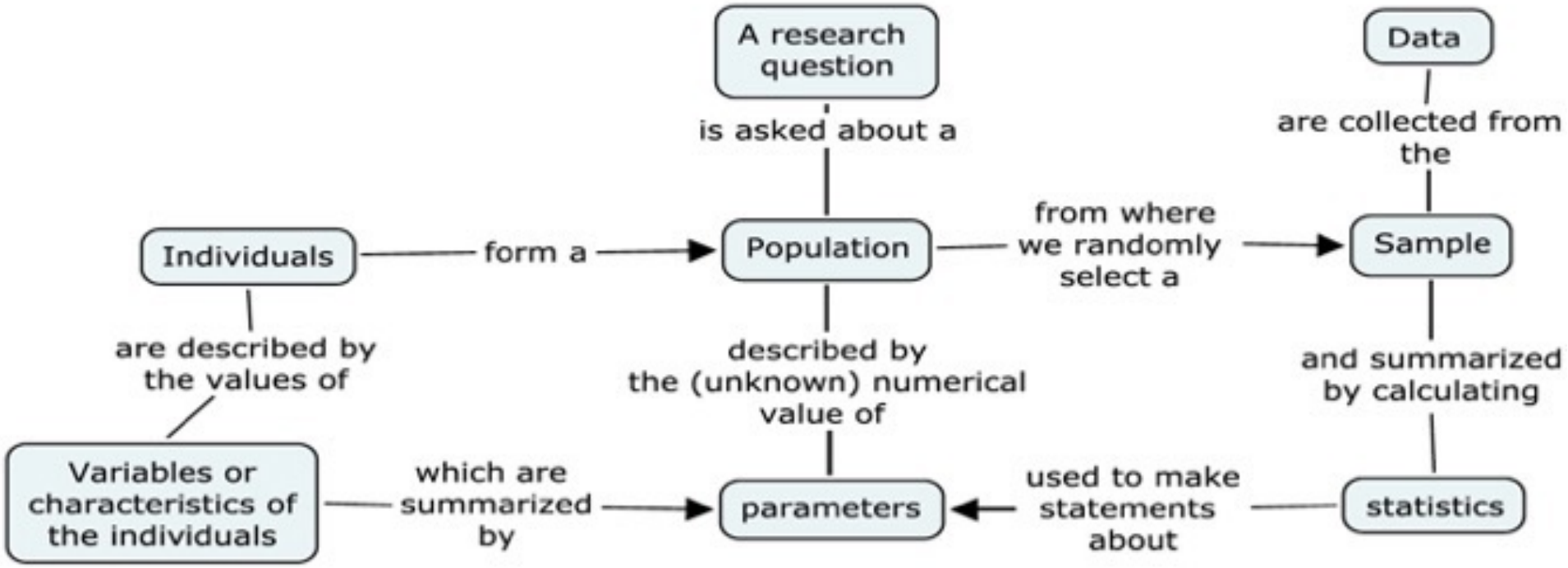
Data Management and Analysis

- The protocol should provide information on how the data will be managed, including data coding for computer analysis, monitoring and verification.
- Information should also be provided on the available computer facility and computer software.
  - R, SAS, SPSS, Prism, Excel, …
- The statistical methods used for the analysis of data should be clearly outlined.

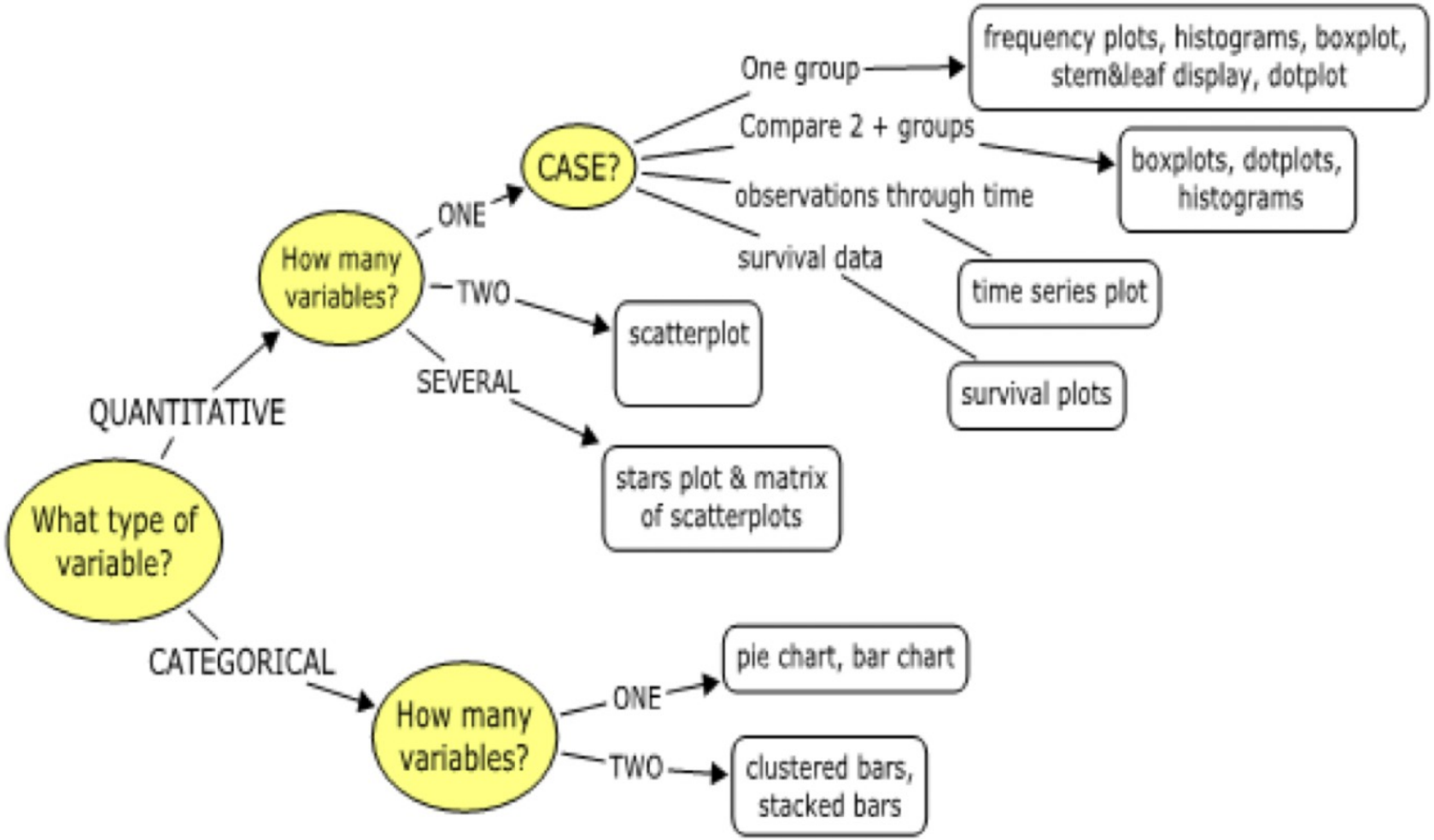
Data Management and Analysis

- It is important that your protocol communicate an appropriate statistical approach to analyze your outcomes.
- In reviewing your data analysis plan, the IRB needs to know that there is a plan that will provide some kind of valid generalizable knowledge (the main benefit of most research studies).
- An expert analysis plan is always preferred and communicates that this study is well-positioned to meet its goals; however, even a rudimentary analysis plan can be sufficient to meet this generalizable knowledge standard.

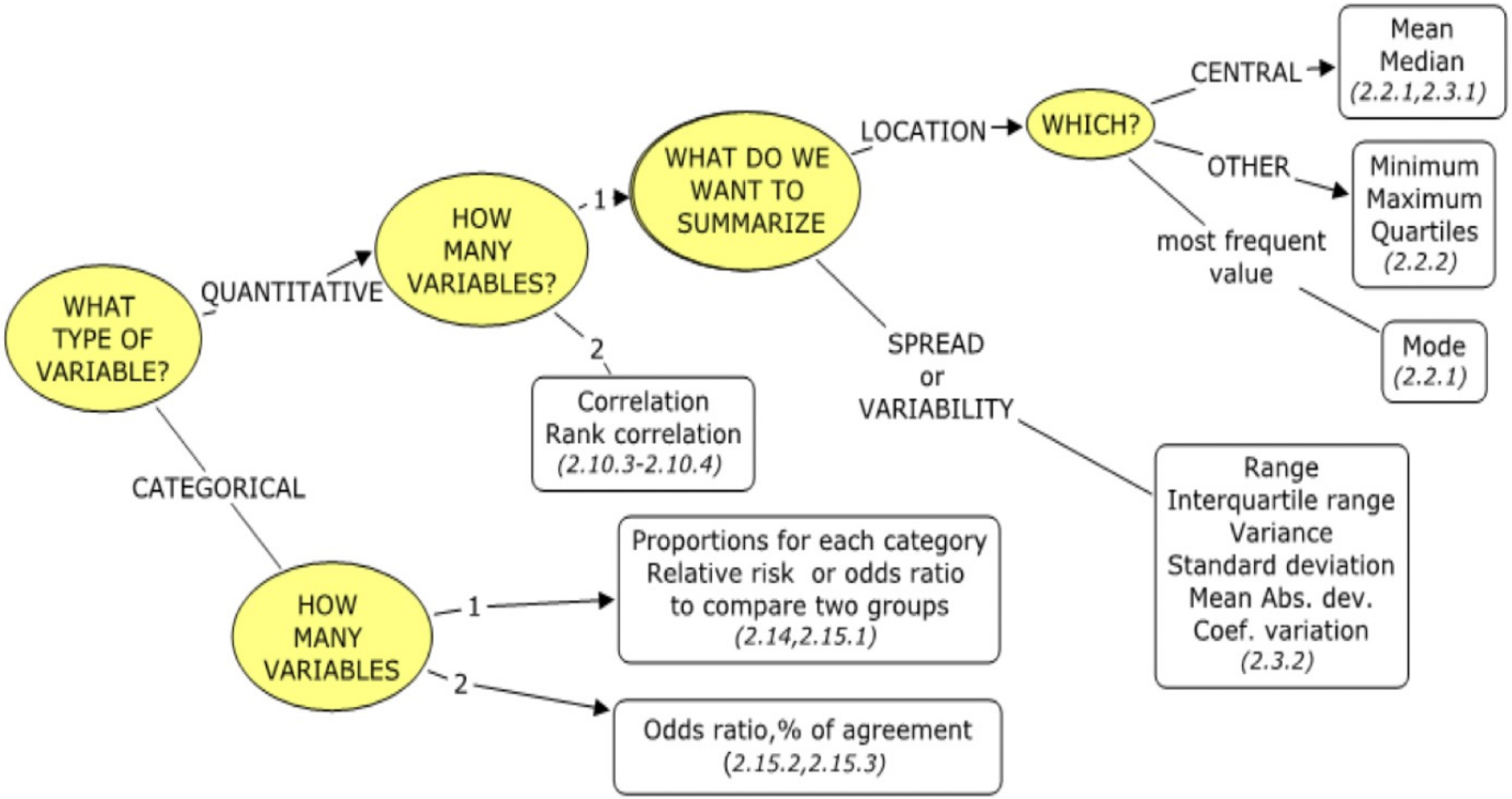
The Big Picture

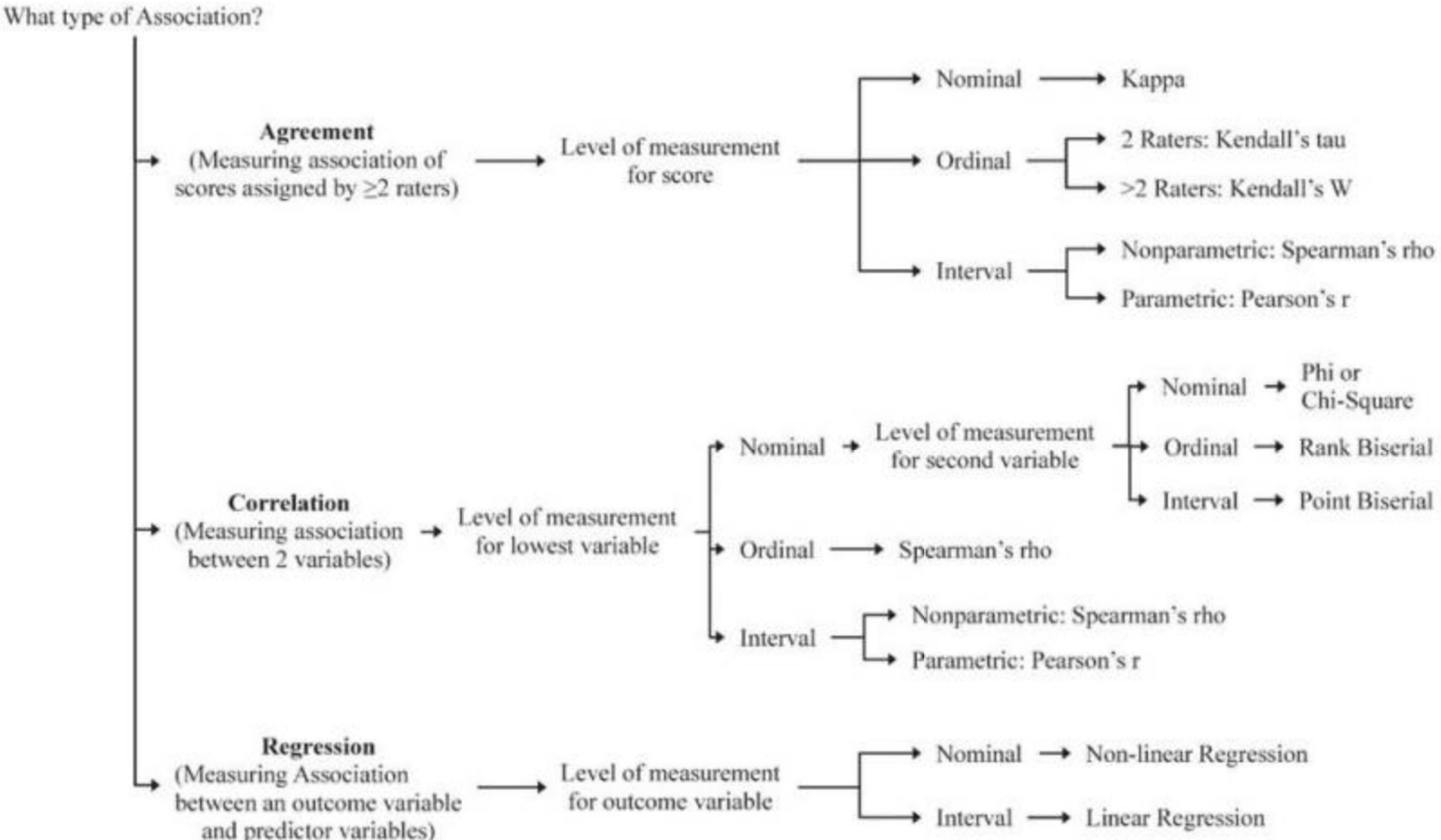


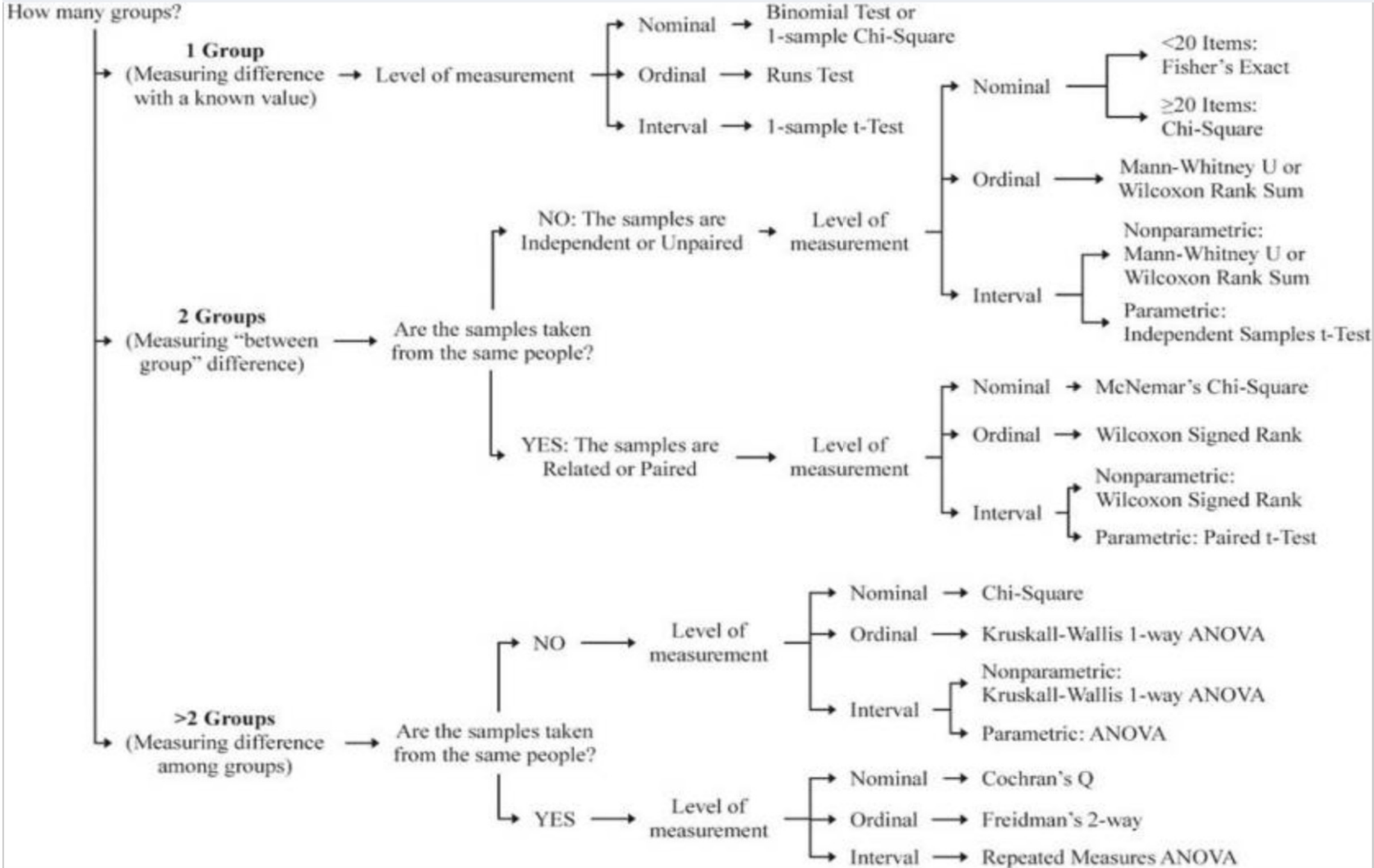
What Type of Graph to Use?



What Type of Statistic to




What type of Association?
Agreement
(Measuring association of scores assigned by ≥2 raters)
Level of measurement for score
Nominal
Kappa
Ordinal
2 Raters: Kendall's tau
>2 Raters: Kendall's W
Interval
Nonparametric: Spearman's rho
Parametric: Pearson's r
Correlation
(Measuring association between 2 variables)
Level of measurement for lowest variable
Nominal
Level of measurement for second variable
Nominal
Phi or Chi-Square
Ordinal
Rank Biserial
Interval
Point Biserial
Ordinal
Spearman's rho
Interval
Nonparametric: Spearman's rho
Parametric: Pearson's r
Regression
(Measuring Association between an outcome variable and predictor variables)
Level of measurement for outcome variable
Nominal
Non-linear Regression
Interval
Linear Regression


How many groups?
1 Group
(Measuring difference with a known value)
Level of measurement
Nominal
Binomial Test or 1-sample Chi-Square
Ordinal
Runs Test
Interval
1-sample t-Test
2 Groups
(Measuring "between group" difference)
Are the samples taken from the same people?
NO: The samples are Independent or Unpaired
Level of measurement
Nominal
<20 Items: Fisher's Exact
≥20 Items: Chi-Square
Ordinal
Mann-Whitney U or Wilcoxon Rank Sum
Interval
Nonparametric: Mann-Whitney U or Wilcoxon Rank Sum
Parametric: Independent Samples t-Test
YES: The samples are Related or Paired
Level of measurement
Nominal
McNemar's Chi-Square
Ordinal
Wilcoxon Signed Rank
Interval
Nonparametric: Wilcoxon Signed Rank
Parametric: Paired t-Test
>2 Groups
(Measuring difference among groups)
Are the samples taken from the same people?
NO
Level of measurement
Nominal
Chi-Square
Ordinal
Kruskall-Wallis 1-way ANOVA
Interval
Nonparametric: Kruskall-Wallis 1-way ANOVA
Parametric: ANOVA
YES
Level of measurement
Nominal
Cochran's Q
Ordinal
Freidman's 2-way
Interval
Repeated Measures ANOVA

Ethical Considerations

- Involved in both experimental and observational
- Experimental: is carried out on patients who may expect a potential benefit from their participation, or is of a purely scientific nature for which human subjects volunteer to advance medical science but will not draw any therapeutic or diagnostic benefit.
- Observational: can be as intrusive on the individual's privacy and even on communities.

Ethical Considerations

1. Written approval of the appropriate ethics review committee, together with a written form for informed consent, where appropriate.

2. A special section, preferably in the format of a checklist, to address all possible ethical concerns.

Informed Consent

- A consent form, where appropriate, must be developed and attached to the protocol.
- It should be written in the prospective subjects' native tongue.
- The consent form has two parts:
  - a statement describing the study and the nature of the subject's involvement
  - a certificate of consent attesting to the subject's consent.

Ethics Checklist

- Is the research design adequate to provide answers to the research question?
- It is unethical to expose subjects to research that will have no value?
- Is the method of selection of research subjects justified?
- Are interventions justified, in terms of risks/benefits ratio?
- For observations made, have measures been taken to ensure confidentiality?

Gender Issues

- "Ensure, where indicated, that clinical trials of pharmaceuticals, medical devices and other medical products include women with their full knowledge and consent and ensure that the resulting data is analyzed for sex and gender differences."

- It is well known that genetic and hormonal factors modify the prevalence, behavior and treatment of diseases of body systems in men and women.

- But what is less known is that culturally evolved gender-related differences in lifestyle behavior are also powerful determinants of women's health and account for major differences in the disease burden between males and females, probably more than genetic or hormonal factors.

- Both biological and gender-related differences can influence the outcome of the research for men and women.

References

- The protocol should end with relevant references on the subject.

Appendix: Glossary of Terms

ANOVA (analysis of variance): Parametric statistic used to compare the means of 3 or more groups that are defined by 1 or more variables.

- 1-way ANOVA: Uses 1 variable to define the groups for comparing means. This is similar to the Student *t* test when comparing the means of 2 groups.
- Kruskall–Wallis 1-way ANOVA: Nonparametric alternative for the 1-way ANOVA. Used to determine the difference in medians between 3 or more groups.
- *n*-way ANOVA: Uses 2 or more variables to define groups when comparing means. Also called a "between-subjects factorial ANOVA".
- Repeated-measures ANOVA: A method for analyzing whether the means of 3 or more measures from the same group of participants are different.
- Freidman ANOVA: Nonparametric alternative for the repeated-measures ANOVA. It is often used to compare rankings and preferences that are measured 3 or more times.

Appendix: Glossary of Terms

Binomial test: Used to determine whether the observed proportion is significantly different from a known or hypothesized proportion. The variable is dichotomous (nominal-level data with 2 options).

Biserial correlation (rank or point): Correlation technique when one of the variables is dichotomous (or measured at the nominal level).

Chi-square (χ^2) test: Nonparametric test used to determine whether a statistically significant association exists between rows and columns in a contingency table.

- Fisher exact: Variation of chi-square that accounts for cell counts < 5.
- McNemar: Variation of chi-square that tests statistical significance of changes in 2 paired measurements of dichotomous variables.
- Cochran Q: An extension of the McNemar test that provides a method for testing for differences between 3 or more matched sets of frequencies or proportions. Often used as a measure of heterogeneity in meta-analyses.

Appendix: Glossary of Terms

Descriptive statistics: Numeric or graphic summaries (or descriptions) of a variable.

Inferential statistics: Measures the difference between 2 variables or subgroups of a variable. Allows the investigator to make inferences about another group on the basis of information generated from the study data.

Kappa (κ): Measures the degree of nonrandom agreement between observers or measurements for the same nominal-level variable.

Kendall tau (τ): Nonparametric alternative for the Spearman correlation. Used when measuring the relationship between 2 ranked (or ordinal-level data) variables.

Mann–Whitney *U* test: Nonparametric alternative for the independent *t* test. One variable is dichotomous (e.g., group A versus group B) and the other variable is either ordinal or interval.

Pearson correlation: Parametric test used to determine whether an association exists between 2 variables measured at the interval or ratio level.

Phi (ϕ): Used when both variables in a correlation analysis are dichotomous.

Runs test: Used to determine whether a series of data occurs from a random process.

Spearman rank correlation: Nonparametric alternative for the Pearson correlation coefficient. Used when the assumptions for Pearson correlation are violated (e.g., data are not normally distributed) or one of the variables is measured at the ordinal level.

Appendix: Glossary of Terms

***t* test:** Parametric statistical test for comparing the means of 2 independent groups.

- 1-sample: Used to determine whether the mean of a sample is significantly different from a known or hypothesized value.
- Independent-samples *t* test (also referred to as the Student *t* test): Used when the independent variable is a nominal-level variable that identifies 2 groups and the dependent variable is an interval-level variable.
- Paired: Used to compare 2 pairs of scores between 2 groups (e.g., baseline and follow-up blood pressure in the intervention and control groups).

Wilcoxon rank–sum test: Nonparametric alternative to the independent *t* test based solely on the order in which observations from the 2 samples fall. Similar to the Mann–Whitney *U* test.

Wilcoxon signed-rank test: Nonparametric alternative to the paired *t* test. The differences between matched pairs are computed and ranked. This test compares the sum of the negative differences and the sum of the positive differences.