Research in Multiple Sclerosis

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Presentation outline

* Introduction
* Research Question?
* Hypotheses
* Study Design
* Tools/Variables
  * EDSS
  * 25 FW
  * MRI
  * Relapses
  * Demographics
* Collection of Data/SPSS
* Sample Size & Power
* Normal vs. Non-Normal Distribution
* Results
  * Descriptive statistics
  * Logistic regression
  * Correlation
  * Discussion
  * Strengths & Limitations (see example)

Introduction

* We hope that you will enjoy this workshop!
* Heidi and I do not have anything to disclose in regards to this program.
* We included the basics of Research, a critique application of research and example of how to do a research study from the question to the analysis!
* This is an overview of research data – you will need assistance with your first & second study…

Research Principles

* **Research is Fun!**
* **Discovering new data and applying it into practice is exciting!**
* Nursing Research focus on patients, caregivers, symptoms management & others in a holistic manner!
* **Research requires work, interest & curiosity!**
* **Outcomes can change practice!**
* Publishing your data – empower you as a clinician & as a nurse!

Research: What to Study?

* Will your study address an important question that will improve clinical practice?
* Has this study question been researched in the past? If yes, is there room for change & improvement?
* What major outcomes are you interested in?
* Would funding sources be interested?
* Can your results be generalized to all people with MS?

What is your Question? Problem?

* What is your interest?
* What is your broad question?
* What is your specific question?

1. Focus Your Question

* **Interest**: Exercise in MS
  - **Broad scope**: What exercise types are used by people with multiple sclerosis?
* **Narrow scope**: What is the **relationship** between aerobic exercise *(independent variable)* and fatigue *(outcome or dependent variable)* in women with RRMS *(target population)*?

2. Focus Your Question

* **Interest**: Nutrition in MS
  - **Broad scope**: What diet types are used by people with multiple sclerosis?
* **Narrow scope**: What is the **relationship** between Gluten Free Diet *(independent variable)* and disability in MS *(outcome or dependent variable)* in women and men with RRMS *(target population)*?

3. Focus Your Question

* **Interest**: Cognition in MS
  - **Broad scope**: What cognitive remediation programs are used by people with multiple sclerosis?
* **Narrow scope**: What is the **effect** of Dalfampridine (Ampyra) *(independent variable)* on cognitive function *(outcome or dependent variable)* in women and men with all types of MS *(target population)*?

Research Question & Hypotheses

* Next 2 slides:
* An example of
  * Research Question
  * Hypotheses

Research Question?

* Develop a question that you have not seen an answer for and a topic that you are passionate about!!!
* **Research Relationship or association?**
* What is the relationship between Smoking & progression of MS as measured by the Expanded Disability Status Scale, the 25 Foot Walk, relapse rate, and the Magnetic Resonance Imaging (MRI) films ?

Hypothesis

* A statement of predicted, **testable**, difference between groups
* Expressed as a null hypothesis:
  * There is no relationship between the variables
  * The means of both populations are equal
* Researchers attempt to reject the null hypothesis& want to show that - There is difference between the variables tested and the means are not equal
* Decision to accept or reject the null hypothesis is based on the probability of the study

Study Hypotheses

* **Null Hypothesis**
  * There is no relationship between smoking & progression of Multiple Sclerosis (MS)
* **Alternate Hypotheses**
  * There is positive or negative relationship between smoking and progression of MS
  * People who are current smokers, former or never smokers will have different MS disease progression
  * People with MS who are current smokers, former or never smokers will have different EDSS change, T25FW change, Number of relapses change, & changes on MRI

Significance

* Why is your study important?
* Will your study make a difference?
* Will your study will contribute new knowledge?
* Who will care about the study?
* Example – Your study will minimize the impact of depression in MS by early screening and treating depression effectively with medication and psychotherapy.

Literature Search

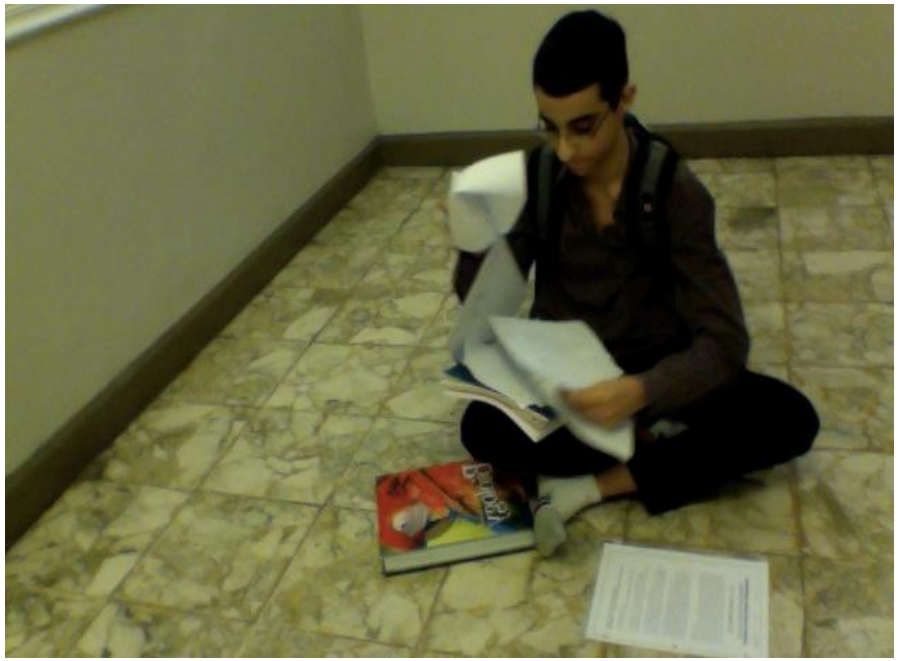
* Literature search about your topic
* Research an interesting topic for you and important topic for your practice
* Search engines to use for literature search:
  * Pubmed
  * CINHAL (Nursing Journals)
  * Google Scholar
  * Psych Info
  * Others

Engine Research Terms

- PubMed & others (See previous slide)
- Narrow the review to the past five years or ten years
- Search strategy: compiling key words
  - Smoking, nicotine, cigarette smoking and MS
  - Use Mesh terms
  - 34 articles found using key terms of cigarette smoking & MS
  - Identify duplicates when searching PubMed and CiNHAL for example
  - Refine your search for specific types of MS if has too many articles
  - Identify articles based on your interest – only relapsing or progressive forms of MS
  - If interested in emotional or psychological problem – search PsychInfo engine

Review of the Literature

* Summary of current knowledge about your question or practice problem
* Includes
  * what is known and not known about the question & problem
  * knowledge gaps



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Literature Review

* Evaluate existing knowledge
* Critically review the literature
* Review different engines for review of literature
* Specify existing gaps that your research is intended to fill
* Discuss the importance and relevance of your research question and aims

Literature Search

* Primary sources: original research articles
* Secondary sources: summaries of primary sources
* Integrative reviews: syntheses of independent primary research studies
* Meta-analysis: statistical analyses of multiple study findings

Research Design

* **Qualitative Research**
* **Definition:** Aim to explore when little is known – in depth understanding - Aim to develop an hypothesis
  * **Example:**
  * **The Lived Experience of Relapsing Multiple Sclerosis: A Phenomenological Study – Colleen Miller JOURNAL OF NEUROSCIENCE NURSING 29(5):294-304 · OCTOBER 1997**
* **Quantitative Research**
* **Definition:** Aim to test an hypothesis usually relationships between variables or testing medications vs. placebo
  * **Example:**
  * **Association between alcohol and MS (Poster AAN 2015)**
  * **Diaz-Cruz C et al. Abstract P2.213. Does Alcohol and Red Wine Consumption Play a Role in Multiple Sclerosis Disease Course? Presented at: American Academy of Neurology Annual Meeting 2015; April 18-25, 2015. Washington, D.C.**

Qualitative Research

* What was your family response and experience to the diagnosis of MS?
* What was your experience while living with MS in the workplace?
* What were the role and social changes that you had to make while living with MS?

Qualitative Research Methods

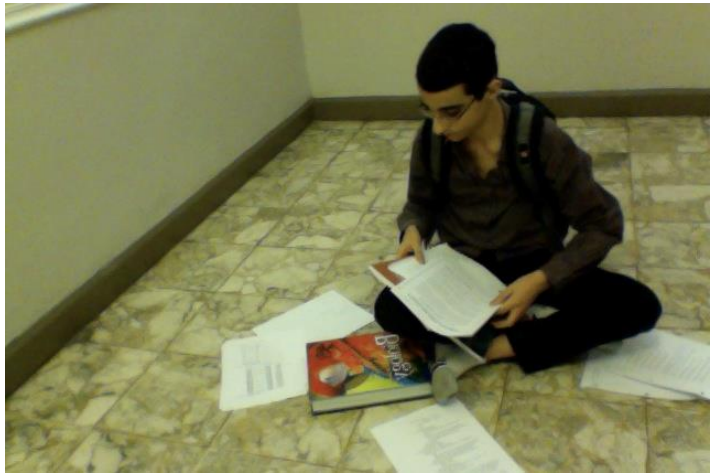
* In depth interviews – face-to-face or telephone – optimal for collecting data on individuals' personal histories, perspectives, and experiences, particularly when sensitive topics are being explored.

* Focus Groups – 7 – 12 patients with MS in a group - effective in eliciting data on the cultural norms of a group and in generating broad overviews of issues of concern to the cultural groups or subgroups represented

* Participant Observation - appropriate for collecting data on naturally occurring behaviors in their usual contexts

Quantitative Research Rationale

* Gain more information
* Develop theories
* Identify problems
* Justify practice



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Quantitative Research Methods

* Quantitative experiments use a standard format of generating a hypothesis to be proved or disproved. This hypothesis must be provable by mathematical and statistical means
* Randomization of any study groups is essential, and a control group should be included, wherever possible
* Research Methods
  * Survey
  * Questionnaires
  * Instruments
    * Interval (Temperature scale) /Ratio scales (Weight)
    * Ordinal Scales (Expanded Disability Status Scale=EDSS)

Difference between Qualitative & Quantitative Research

* Their analytical objectives
* The types of questions they pose
* The types of data collection instruments they use
* The forms of data they produce
* The degree of flexibility built into study design

Quantitative Research: Observational & Experimental Studies

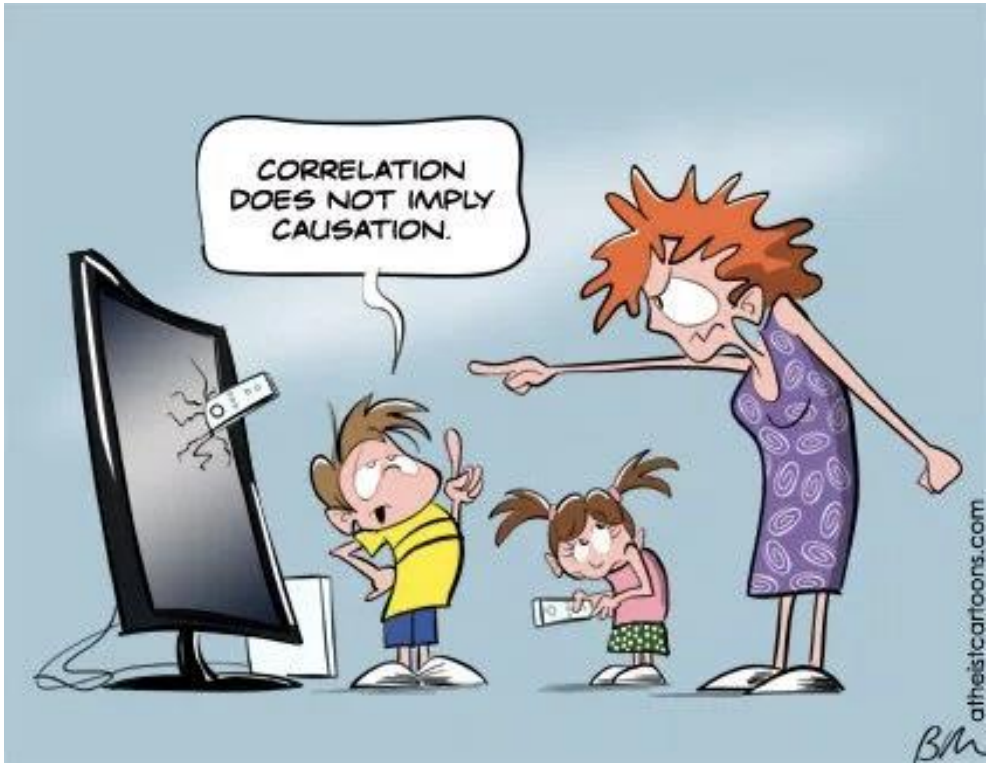
* Observational
  * Passive (although systematic) observation
  * Control extraneous influences that bias observation
* Experimental
  * Active manipulation
  * Randomization to balance extraneous influences

Study Design

* Purpose: maximizes the chance of obtaining valid answers to a research question or hypothesis
* **Correlational design**- examines relationships among the variables
* **Experimental or quasi-experimental design**- tests a treatment
* **Qualitative or Descriptive design**- generates theory

Causality versus Association

* Causality
  * Cause and effect
  * Independent and dependent variable
* Multicausality
  * CAM effect on EDSS
  * CAM effect on QOL
* Bias
* Probability
  * Chance that a given event will occur



Elements of a Strong Design

* Controlling the Environment
* Controlling the characteristics of subjects (example: getting similar subjects in both treatment and control arms)
* Controlling the treatment
* Controlling the measurement (example: same clinician testing the study participants – at time can be unrealistic)
* Controlling extraneous variables (confounders)

Defining the Confounder

* A confounder is related to the variables being tested – the independent and the dependent variable (outcome)
* A confounder is a third variable that may affect the relationship between the 2 variables that are being tested
* A situation in which the effect or association between a variable (Western diet) and outcome (colon cancer) is distorted by the presence of another variable (family History).

Is This a confounder?

* Example: In a study of diet and Cardiovascular Disease, you see that Cholesterol is the variable leading to cardiovascular disease and not the general diet.
* This confounder is called mediator because it is the middle of the pathway

Descriptive Design

* Typical descriptive design: examines a single sample
* Comparative descriptive design: describes variables and examines their differences
* Time dimensional design
  * Longitudinal design
    * Cohort study (Prospective study)
    * Case-Control study (Prospective & Retrospective)
  * Cross-sectional design (One time snap shot, Polls)
* Case study: Intensive exploration of a single unit or few cases

Correlational Design

Examine relationship of two or more variables in a single or multiple groups

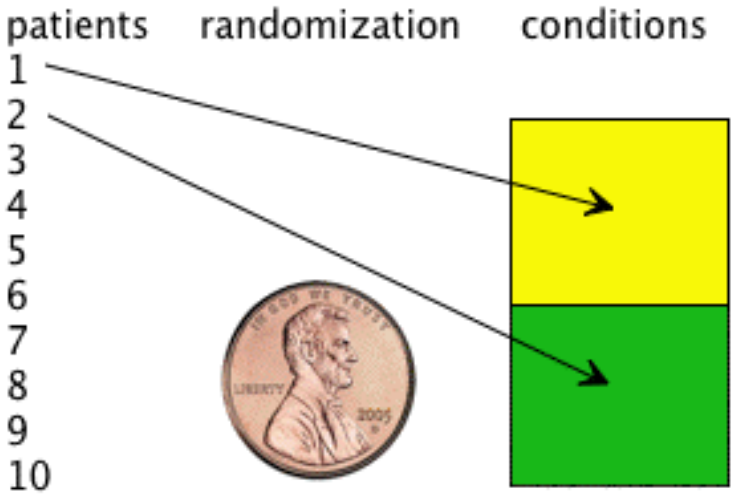
- Descriptive Correlational Design: Describes relationship between and among variables
- Predictive Correlational Design: predicts relationship between and among variables

Quasi-experimental Designs

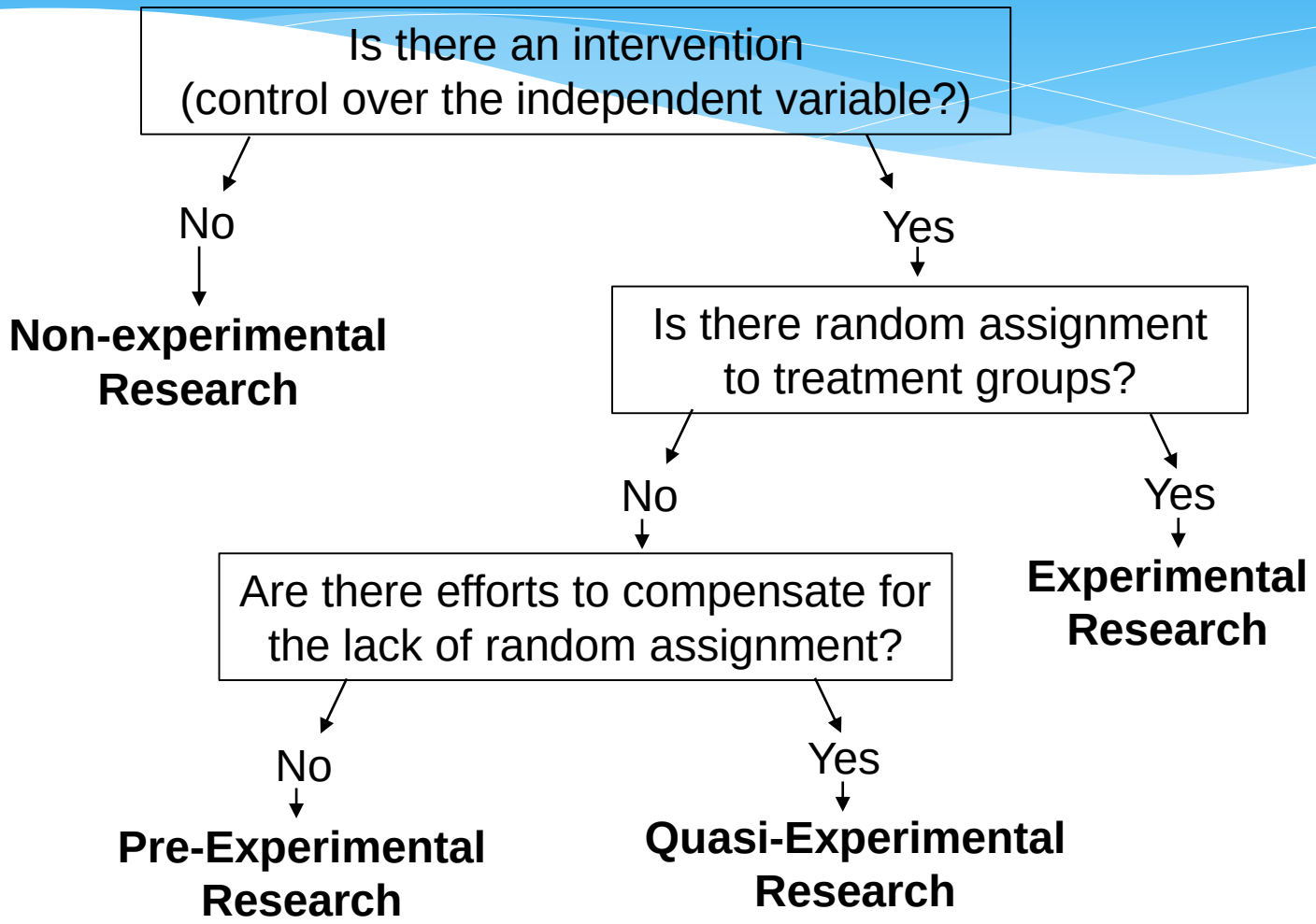
* Non-equivalent control group designs - control group not selected by random means as opposed to experimental design which has randomized sample of both groups – treatment & control
* Examples of quasi-experimental design:
  * One group post-test only design (without pre-test findings for comparison)
  * One-group pretest-posttest design
  * Untreated control group design with pretest and posttest

Experimental Study Designs

* Randomization
* Control groups
* Manipulation of treatment



Quantitative Research Design Characteristics



Polit & Beck (2004), p. 182

Qualitative Research Sampling

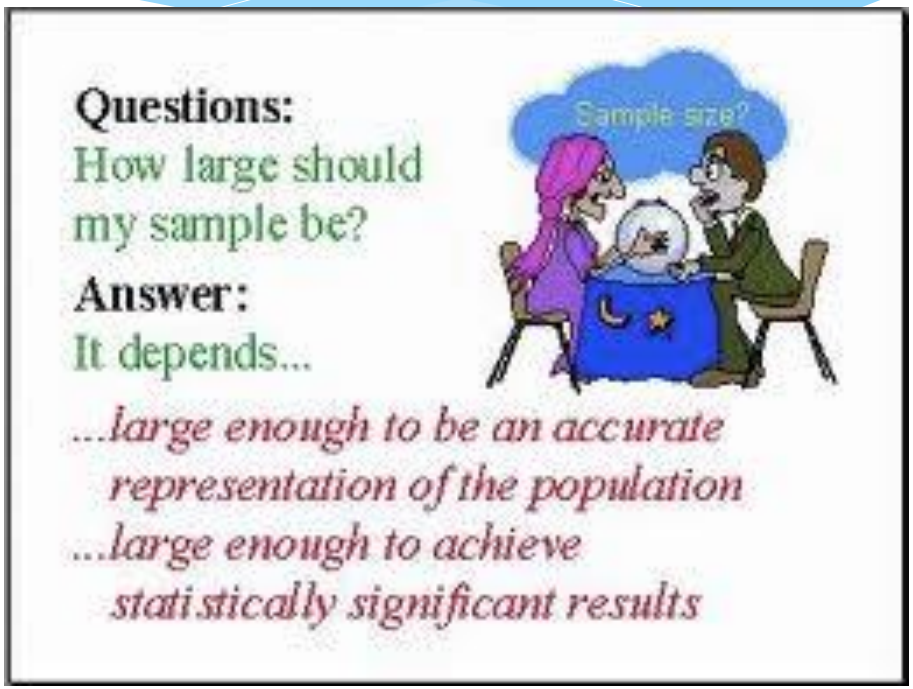
* **Purposive sampling** - participants according to preselected criteria relevant to a particular research question (for example, HIV-positive women in Capital City).
* **Quota sampling** – deciding how many people with which characteristics to include as participants. Characteristics might include age, place of residence, gender, class, profession, marital status, HIV status, etc.
* **Snowball sampling** - participants or informants with whom contact has been made & use their social networks to refer the researcher to other people who could potentially participate or contribute to the study

Quantitative Research Sampling

* Randomized sampling (every participant has equal opportunity to enroll into the treatment arm vs. control arm)
* Non-Randomized samples
  * Assigning participants to case group or control group based on presence or absence of illness
  * Convenience sampling – Participants available on day of recruitment and enrolling into the study
  * Sampling by matching of characteristics between the groups (Block design & others)

Sample Size & Power

* A Power level of 80%
* A level of significance of 0.05
* Distribution & type of variables
* Sample size in similar studies
* G-Power software (free download) to determine sample size
* http://www.gpower.hhu.de/



*** Usually with determining Statistics – Power-test-sample size – You will need assistance initially**

Theoretical or Conceptual Framework

* Gives your study a context
* Provide a conceptual perspective for your phenomenon that is being studied
* Solidifies your proposal
* A **pathophysiological framework** - the effect of Gray matter atrophy on cognitive dysfunction: decreased brain tissue…. .. increased inflammatory disease…..decreased cognitive function

The Research Process Question to Hypothesis

Currently there is no evidence that specific diet has an impact on progression of disability in MS

* **Research question:** What is the relationship between specific diets and disability in people with multiple sclerosis?
* **Hypothesis:** People with multiple sclerosis who are on a specific diet, will have lower disability status scores.
* **Aim:** to understand the relationship between specific diets and disability status scores in people with multiple sclerosis

Inclusion & Exclusion Criteria Example

* **Inclusion**
* Dx of Multiple Sclerosis
* Have at least 2 MRI with interval of 1 year
* Have a full neurological exam for the EDSS
* Have a few 25FW
* Duration of disease – at least 5 years of illness

* **Exclusion**
* Patients with possible MS or variant of MS
* Patients with uncontrolled multiple autoimmune diseases
* Patients without the required parameters i.e. EDSS, 25FW

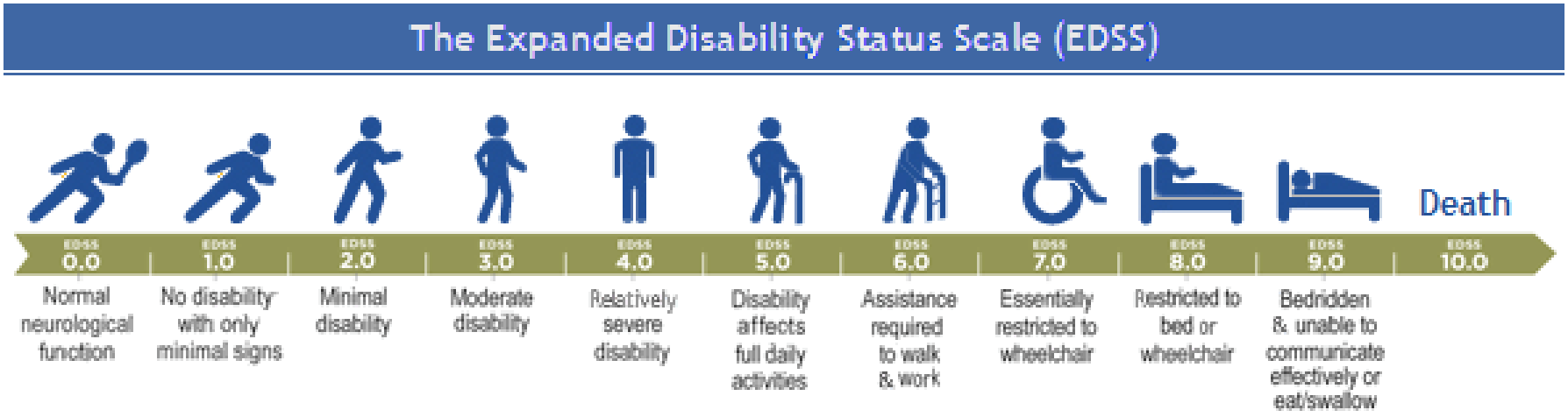
Collection of Data

* **Retrospective or Prospective data collection**
* **Specify dates of data collection**
* **Describe the procedure of data collection**
* **Specify instruments' use**
  * **Demographic sheet data**
  * **Different scales (EDSS & others)**
* **Baseline data & follow up data**
* **Input data into SPSS or SAS computer programs**
* **You will need assistance on your first project using these computer programs!**

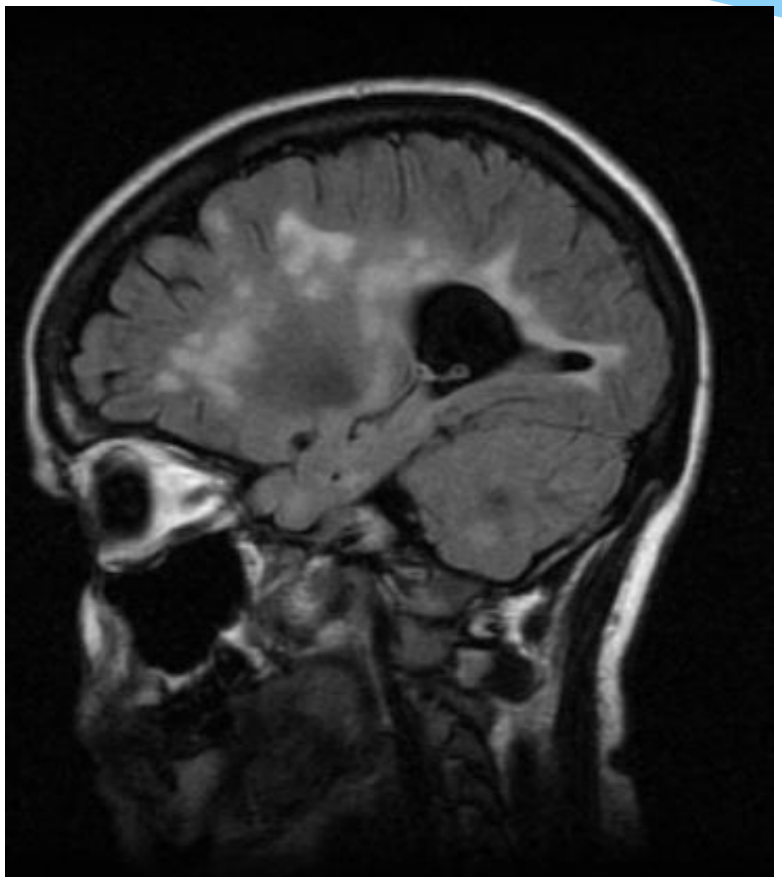
Definition of Variables

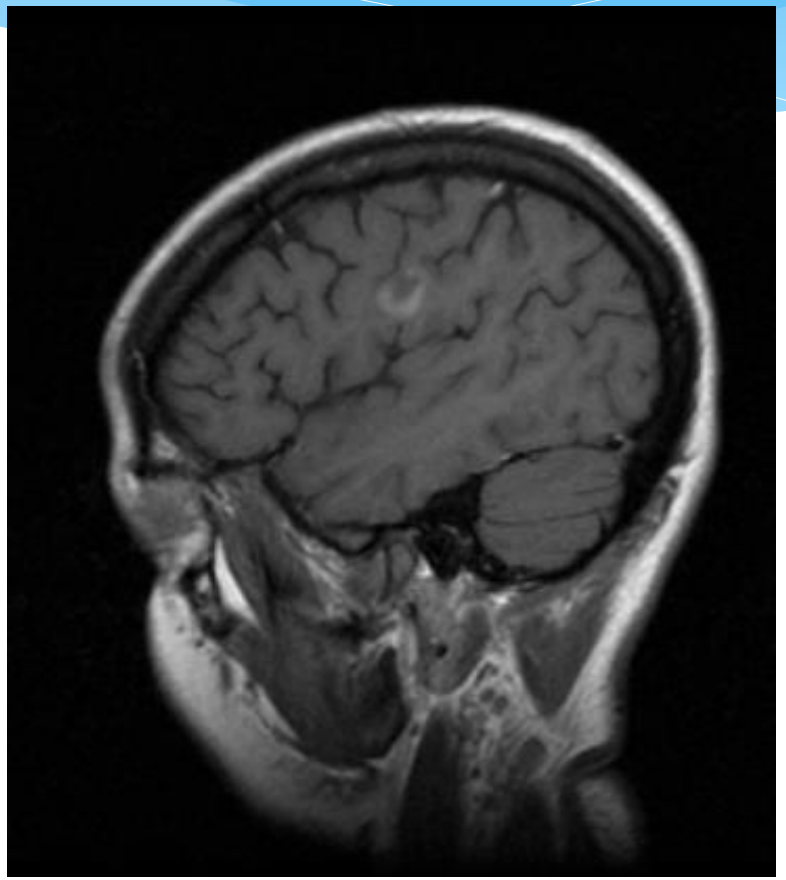
* Define your variables clearly
* Identify the instruments used in your research study
* Discuss their validity and reliability
  * Validity – it truly measures what it says it measures
  * Reliability – Multiple raters use the instrument and get the same results or repeatedly the same rater evaluates participants and get similar results

Variable: Disability
Expanded Disability Status Scale (EDSS)



Variable: Disability
Brain MRI Changes:
Sagittal FLAIR view & GAD view





Other Independent Variables

* Age
* Gender
* Ethnicity/race
* Education level
* Work
* Marital status
* Living alone or with others
* Type of MS
* Type of DMT
* Smoking
* Alcohol
* Vitamin D

Reliability and Validity

* Internal and External Validity
  * Internal Validity – The study has valid content – the design of your study is appropriate for data collection and the analysis
  * Need to address any bias (selection bias – for example if you use convenience sample – enroll patients on certain days that you are available)
  * External Validity – Generalizability of the data – the data can be extracted to the general MS population from your study
* Reliability – Inter-rater reliability & repeatedly of testing - instruments are reliable and testing same patients a few times with same instruments provide same results.
* Need to address different clinicians measuring the study participants with the instruments used

Describing Data

* **Continuous variables (Numeric variables)**
  * Age, test score
* **Categorical variables**
  * Eye color, MS Subtype (RRMS, SPMS, PPMS)
* **Measures of Central Tendency:**

  Mean: mathematical average – continuous data

  Median: middle score when scores are ordered from smallest to largest – example: 1, 2, 2, 4, 5 – 2 is the median

  Mode: most frequently occurring value – categorical data – example – 1, 3 , 4, 3, 3, 5 – 3 is the mode

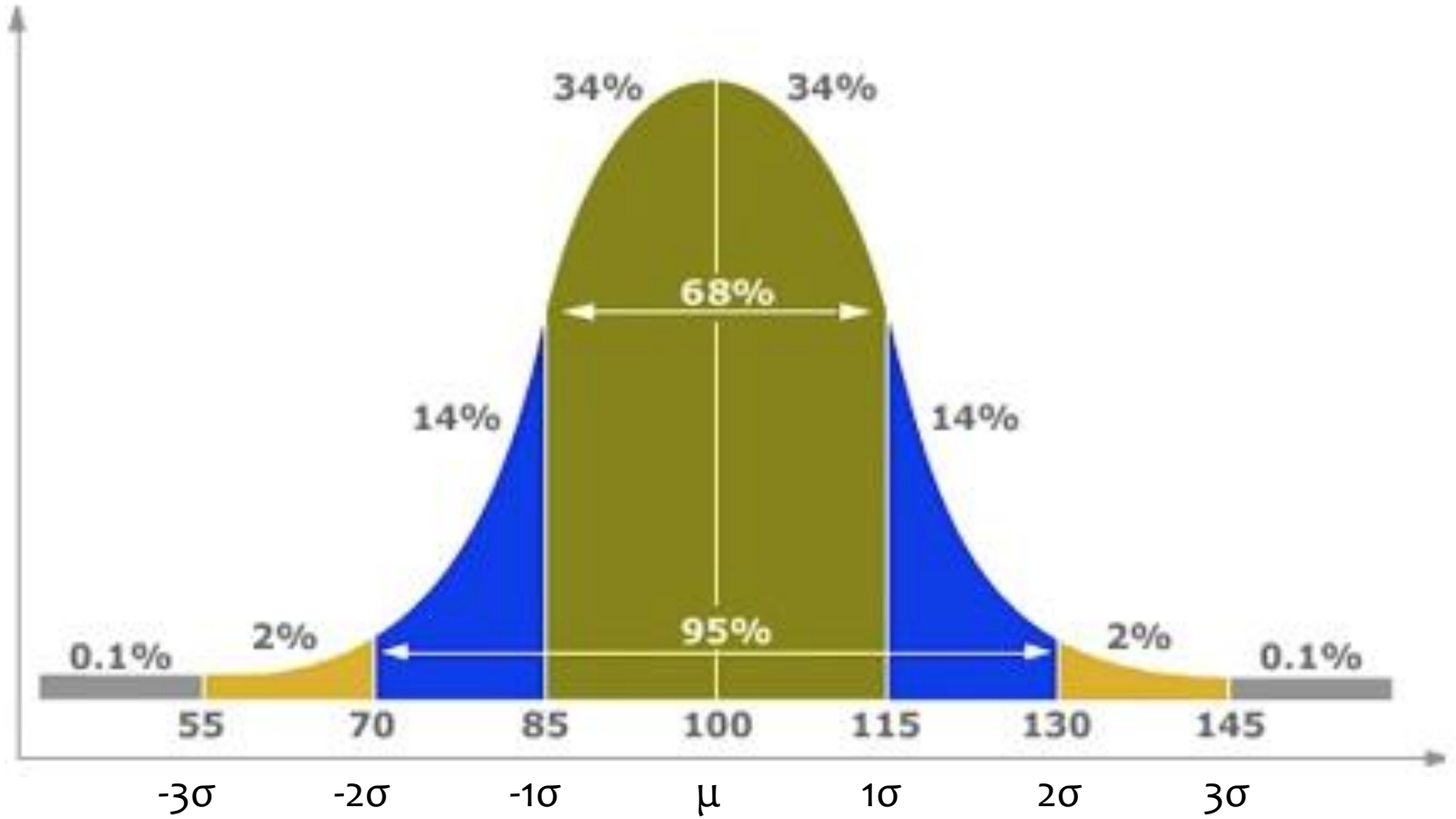
Inferential Statistics

* Probability Theory
  * The likelihood that an event will occur
  * probability that an event can be accurately predicted
  * probability that subjects in experimental group are the same as control group
  * Ranges from 0 to 1
  * Expressed as a decimal

Significance

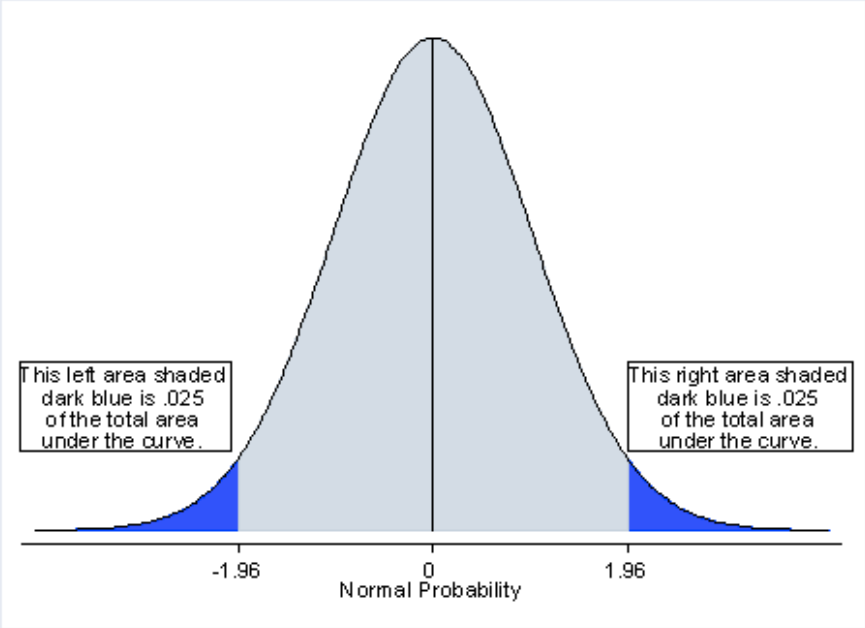
* Significance levels show you how likely a pattern in your data is due to chance.
* The most common level used is .95 - the finding has a 95% chance of being true.
* It will show ".05," meaning that the finding has a five percent (.05) chance of not being true, which is the converse of a 95% chance of being true.
* A value of ".01" means that there is a 99% (1-.01=.99) chance of it being true.

Normal Curve



Significance Testing

* Level of Significance: cut-off point that tests the assumption that there is *no* difference between groups
* Cut-off point is called *alpha* or a probability level at which statistical analysis detects a significant difference between groups (α=.05)
* P value: probability that results are due to chance alone – NOT due to your manipulation (p=.05)



Hypothesis Testing

Type I Error=There is no true difference,
But the null was rejected falsely
(+difference decided)

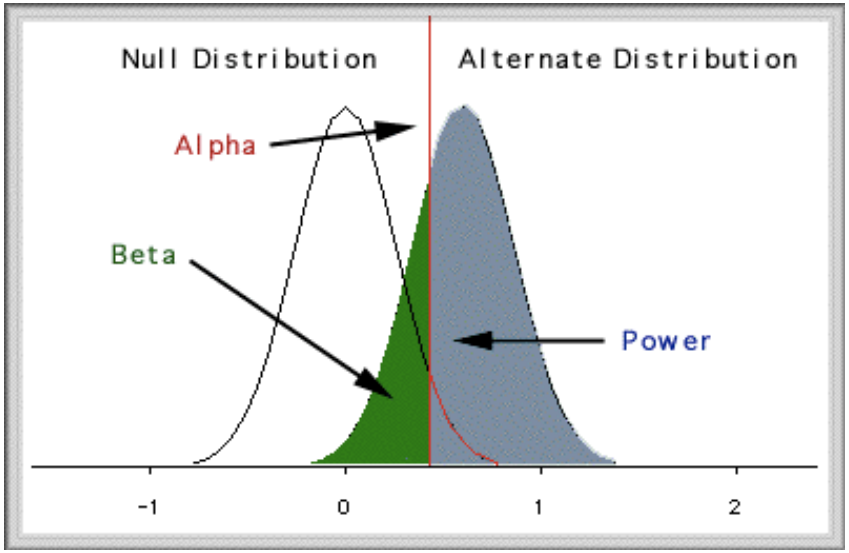
Type II Error= There is true difference
Between the two or more groups
But the null was not rejected (no
Difference decided)

Decision based on sample	Truth about the population: H_0 true	Truth about the population: H_a true
Reject H_0	Type I error	Correct decision
Accept H_0	Correct decision	Type II error

In statistical hypothesis testing, a type I error is the incorrect rejection of a true null Hypothesis (a "false positive"), while a type II error is the failure to reject a false null hypothesis (a "false negative").

Statistical Concepts

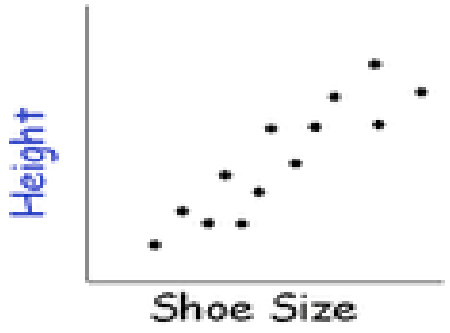
* **Power:**
  * Probability that statistical test will detect a significant difference
  * Type II error is more likely to occur when power is low
  * Power analysis



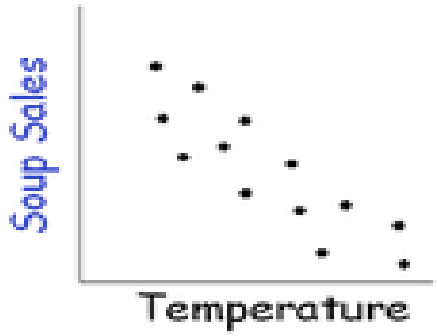
Statistics to Examine Relationships

* ***r*** is a correlation coefficient with a value between -1 and +1
  - 0.1 to 0.29 is a weak relationship
  - 0.3 to 0.5 is a moderate relationship
  - > 0.5 is a strong relationship

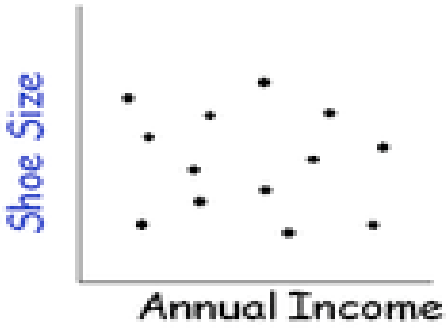
r = 0.55



r = -0.45



r = 0.00



Statistics to Predict

* **Regression Analysis:** used with dependent interval level variable to predict value of one variable while controlling for other variables – Linear relationship
* Outcome is regression coefficient: R
* R^2 indicated the amount of variance in the data that is explained by the relationship
* $R^2 = 0.85$ or 85% of the variance in length of stay can be predicted by combined effect of age, and post op complications i.e. infections
* **Logistic Regression** used with outcome (dependent) categorical variable i.e. progression of disease – yes/no

Statistics to Examine Causality

* ***t*- Tests:** tests showing difference between means of independent or related **two groups**
* **Analysis of Variance (ANOVA):** tests significance of differences between means; examines data between two or **more groups**
* **Analysis of Covariance (ANCOVA)**
  * Allows researcher to sort out potentially confounding variables. Removes certain variables by regression analysis before an ANOVA is performed – comparison between means of **3 groups**

Overview of Common Statistical Tests

Outcome Variable	Are the observations correlated?		Assumptions
	Independent	Correlated	
Continuous (e.g. blood pressure, age, pain score)	T-test ANOVA Linear correlation Linear regression	Paired t-test Repeated-measures ANOVA Mixed models/GEE modeling	Outcome is normally distributed (important for small samples) Outcome and predictor have a linear relationship
Binary or categorical (e.g. breast cancer yes/no)	Chi-square test Relative risks Logistic regression	McNemar's test Conditional logistic regression GEE modeling	Chi-square test assumes sufficient numbers in each cell (>=5)
Time-to-event (e.g. time-to-death, time-to-fracture)	Kaplan-Meier statistics Cox regression	NA	Cox regression assumes proportional hazards between groups

Continuous Outcome (Means)

Outcome Variable	Are the observations correlated?		Alternatives if the normality assumption is violated (and small n)
	Independent	Correlated	
Continuous (e.g. blood pressure, age, pain score)	**T-test:** compares means between two independent groups **ANOVA:** compares means between more than two independent groups **Pearson's correlation coefficient** (linear correlation): shows linear correlation between two continuous variables **Linear regression:** multivariate regression technique when the outcome is continuous; gives slopes or adjusted means	**Paired t-test:** compares means between two related groups (e.g., the same subjects before and after) **Repeated-measures ANOVA:** compares changes over time in the means of two or more groups (repeated measurements) **Mixed models/GEE modeling**: multivariate regression techniques to compare changes over time between two or more groups	<u>Non-parametric statistics</u> **Wilcoxon sign-rank test:** non-parametric alternative to paired t-test **Wilcoxon sum-rank test** (=Mann-Whitney U test): non-parametric alternative to the t-test **Kruskal-Wallis test:** non-parametric alternative to ANOVA **Spearman rank correlation coefficient:** non-parametric alternative to Pearson's correlation coefficient

Findings

* Describe your demographics (i.e. 60% women, 80% RRMS, etc.)
* Describe the relationship you identifies with or without statistical significance
* Identify negative or positive associations between the variables
* Describe any predicative analysis obtained oin your study
* Summarize limitations & strengths of your study

Protecting your Subjects: The Institutional Review Board (IRB)

* The purpose of the IRB is to protect *human* subjects
* All human research MUST be submitted to the IRB
* IRB looks to see that you uphold the principles of the Belmont Report
  * Respect
  * Beneficence
  * Justice

IRB: Protecting your Subjects

* IRB determines whether your research involves "greater than minimal risk" or is "exempt"
* IRB especially scrutinizes proposals involving vulnerable populations
  * Children
  * Pregnant women
  * Prisoners
  * Mentally disabled
  * Elderly
  * Economically disadvantaged

Protecting Your Subjects: The IRB Process

* Submit your initial review for approval
* Follow protocol - obtaining informed consent
* Record data while maintaining HIPAA regulations
* Submit continuing reviews annually
* Record and submit any protocol deviations, significant adverse events, or protocol amendments
* Maintain meticulous records – IRB can audit your study at any time
* Study closure and archiving

Thank You!

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