The Research Question

- **Success depends upon turning a clinical problem into a research question**
- **Must be answerable**
- **Foundation for everything empirical**
- **Increases likelihood of finding a solution**
- **Helps choose the correct methodology**
- **Drives the nature of statistical analysis**

Where do research questions come from?

- **Answerable, appropriate, meaningful, and purposeful**
  - **Clinical experience**
  - **Etiology/risk**
  - **Differential dx**
  - **Dx tests**
  - **Prognosis**
  - **Therapy**
  - **Prevention**

Characteristics of a Research Question

- **Hulley et al. (2013) use the FINER acronym**
  - **Feasible**
  - **Interesting**
  - **Novel**
  - **Ethical**
  - **Relevant**

Feasible

- **Answered in the clinical/empirical/academic environment?**
- **Time frame?**
- **Adequate time and resources?**
- **Competency and experience?**
- **Financial and political contingencies?**
- **Adequate pool of participants?**
- **Scope of the question**
  - **Deductive vs. Inductive**

Feasibility

- **Pilot study**
- **Modify inclusion and exclusion criteria**
- **Use observational research designs**
- **Choose established predictors and outcomes**
- **Measure for large effect sizes**
- **Collaborate with experienced researchers**

Interesting

- **This is YOU**
- **Genuine interest**
  - **Personally and professionally rewarding?**
- **Peers and Mentors**
- **Funding agencies**
- **Serves an immediate patient need**
  - **Buy-in from stakeholders, collaborators, patients**

Novel

- **NEW information, findings, interventions**
- **Replication of methods to new populations**
- **Discussion and implications**
- **MASTERY of the existing literature**
- **Make a meaningful contribution**
  - **"Fill a gap"**

Ethical

- **Institutional Review Board (IRB)**
- **BEFORE you collect any data or talk to potential participants, you must have IRB approval**

Relevant

- **"So what?"**
- **What is the impact?**
  - **Protocols, patient safety, QI**
  - **Influence clinical practice**
  - **Meet needs of patient population**
  - **Guide future research**

Refining and Framing the Research Question

- **Easily understood and overtly stated**
- **Specific, simple, clear, and concise**
- **PICO**
  - **Population**
  - **Intervention**
  - **Comparator Intervention**
  - **Outcome**

PICO

- **P**
  - **Patient, population, predicament, or problem**
- **I**
  - **Intervention, exposure, test, or agent**
- **C**
  - **Comparison intervention, exposure, test, or agent**
- **O**
  - **Outcome of clinical importance, including time when relevant**
  - **increases**

Evidence-Based Medicine (EBM)

- **Asking**
  - **"Foreground" questions**
    - **Specific questions that inform upon clinical decisions**
    - **PICO**
  - **PICO generates high yield search queries**

Secondary Research Questions

- **It is normal to have several research questions**
- **Have a primary research question to focus the study and conduct a power analysis**
- **Secondary, tertiary, and ancillary questions**
  - **Predictors, confounders, and outcomes yielded from literature or clinical experience**

Flow of Research

1. Research Question
   - Literature Review
   - Peers, mentors, clinical experience
   - "So what?" → FINER, PICO
     - Secondary, Tertiary, and Ancillary Research Questions
2. Research Hypotheses
   - Null and Research Hypotheses
3. Research Design

3a. What design will answer the research question?
- Case study, cross-sectional, observational, RCT

3b. Population and Sampling Methodology
- Inclusion and Exclusion Criteria
- Sampling Technique

3c. Variables and Measurement
- Predictor, Confounding, and Outcome variables
- How were the variables chosen?
- Scales of Measurement

4. Power Analysis
   - Effect Size
     - Literature, clinical experience, best "educated guess"
5. Database Management and Codebook
   - Database structure and Data Entry
6. IRB Application and Approval
7. Data Collection
8. Statistical Analysis
9. Publication and Presentation of Findings

Despite the valiant efforts of the research group, the insulin suppository still had one major drawback.

Examples

- **Between-groups (independent)**
  - **How does "Group A" differ from "Group B" on the "outcome?"**
- **Within-groups (repeated)**
  - **How does "Group A" change in the "outcome" after receiving the "treatment?"**
- **Mixed-design (independent and repeated)**
  - **How does the "outcome" change for "Group A" versus "Group B" after receiving "treatment?"**

Examples

- **Correlational (Social Sciences)**
  - **What is the relationship between "Variable A" and "Variable B?"**
- **Cross-sectional (Survey)**
  - **How do members of the "population" rate themselves on the "outcome?"**
- **Multivariate**
  - **What is the effect of the "predictor" on the "outcome" when controlled for other "confounding variables?"**

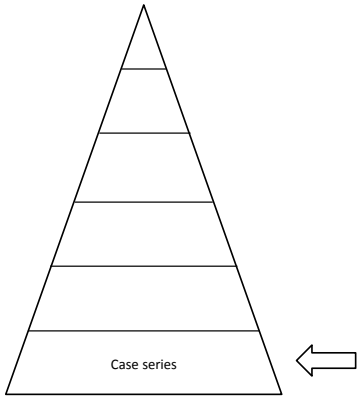
Activity

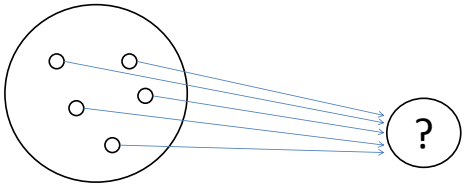
- **Using your handout, work through the FINER and PICO mnemonics**
- **Write out a research question.**

Research Design

Common Terms

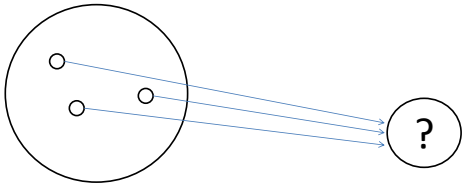
- **Reliability/precision/confidence**
  - **Consistency**
- **Validity/accuracy/magnitude**
  - **Interpretable**
- **Prospective/retrospective**
- **Observational/experimental**
  - **Randomized selection and allocation**
- **Internal validity**
  - **Integrity of the study to show a causal link between exposure and outcome**
  - **History, mortality, maturation, diffusion, learning effects**
- **External validity**
  - **Ability to generalize findings back to populations of interest**
  - **Bias, confounding, observational design, lack of randomization**
- **Confounding**
  - **Outcome association versus exposure association**
- **Selection bias**
- **Observation bias**





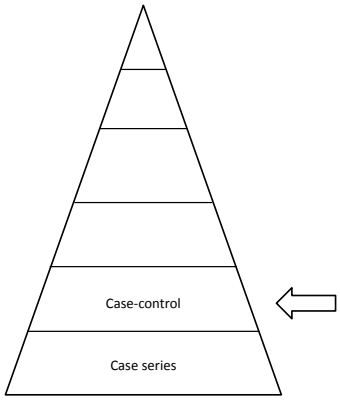
Case Series

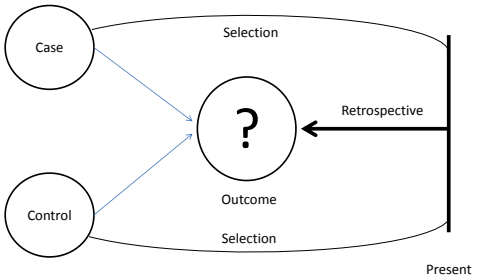
- **Individual cases with similar clinical characteristics, exposures, treatments, and/or outcomes are selected from a population**
- **Phenomena are measured and analyzed in a descriptive fashion**
- **Weakest type of observational design**
- **Good for hypothesis generation and extremely rare outcomes**



Case Series -- GHB

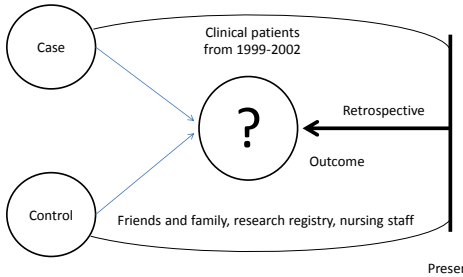
- GHB-dependency is not all that prevalent
- However, when presenting in general hospitals, they are often going through severe withdrawal symptoms
- Very hard to manage
- Found three cases where pharmaceutical GHB was administered after a high dose benzo did not do the job





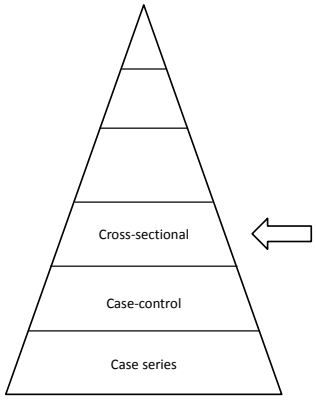
Case-Control

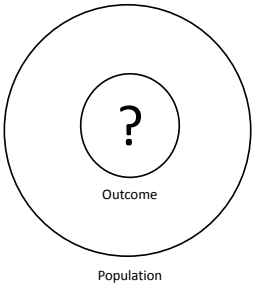
- Retrospective
- Find outcome and compare on predictor variables
- Odds ratio
- No cause and effect, good for rare outcomes
- Selection of cases and controls can introduce bias



Case-control -- MH Dx

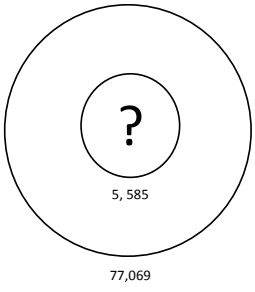
- Mental health and urological pain syndromes are not prevalent
- Direct comparison of rates of MH Dx and urological pain
- Selection biases and observation biases
- Odds ratios are generated
- Cases were more likely to have MH Dx, $$$ = less MH Dx





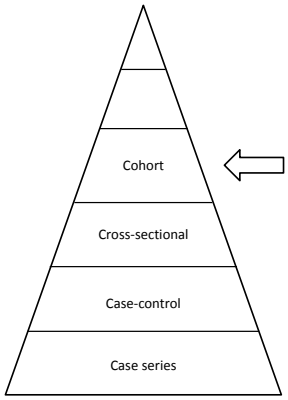
Cross-sectional -- HPV

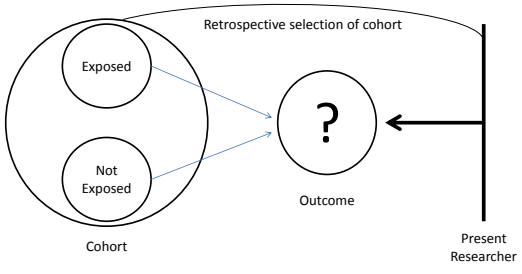
- Select a population and take a measure of an outcome at one point in time
- Prevalence
- Describe population
- Hypothesis generation



Cross-sectional -- HPV

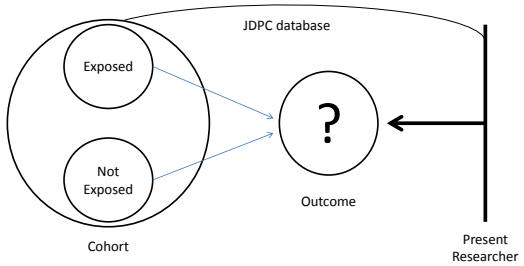
- 5,585 / 77,069 women in Pearl River Delta Region of Southern China
- Prevalence of HPV
- HPV 16, HPV 33, HPV 58, and HPV 31 , multiple genotype infection, increased risk of cytology abnormalities





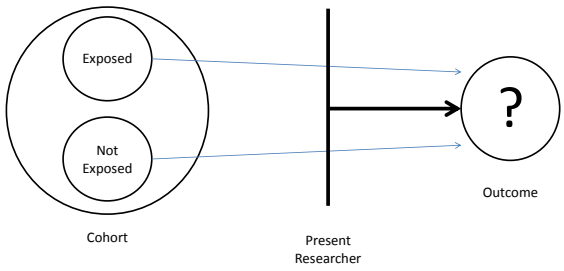
Retrospective Cohort

- Assemble a retrospective cohort of individuals with similar clinical characteristics
- Comparison of exposure to non-exposure in relationship to outcome
- Relative risk
- Prevalence
- Selection bias, information bias



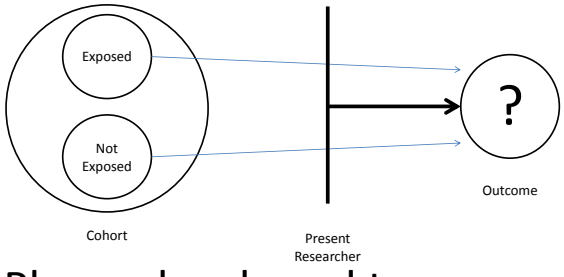
Pneumonia and case volume

- Assembled a retrospective cohort of individuals from a nationwide database
- Defined inclusion and exclusion critieria
- Relative risk of pneumonia when controlled for various other predictors



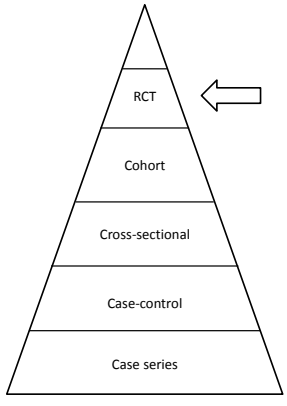
Prospective Cohort

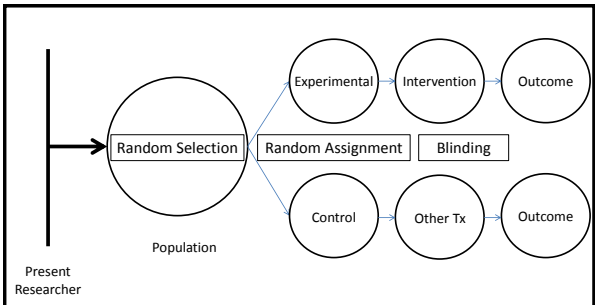
- Relative Risk
- Incidence
- Baseline data is taken and members of the cohort are followed longitudinally
- Etiology of disease, association between exposure and subsequent outcomes
- No outcomes have occurred yet



Plasma levels and trauma

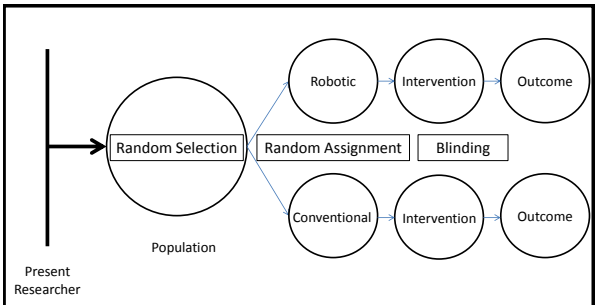
- Department of Traumatic Surgery
- Determined inclusion and exclusion criteria
- Followed longitudinally and did an observation at 1 month, three months, and six months
- Transfusion, ISS, and HMGB1 (day 7) > 60 mg/mL were associated with PTSD





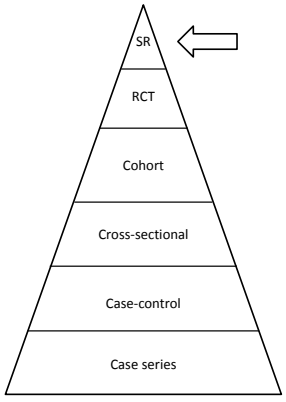
Randomized controlled trial

- Random selection and assignment
- Cause and effect
- Blinding of patients and clinicians
- Treatment for controls
- Follow-up and attrition

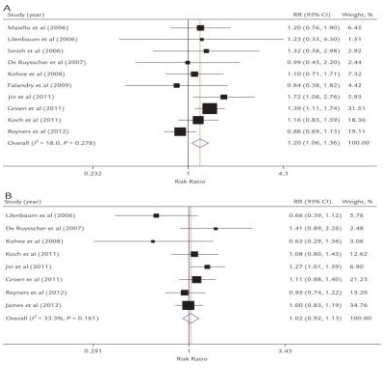


RAT and Cerebral palsy

- Random selection and assignment of participants to groups
- Blinded assessment by independent raters
- Differences at baseline occur due to chance
- Cause and effect can be inferred



- Highest form of empirical evidence
- Meta-analysis is the statistic conducted in a systematic review
- Generally shown in a forest plot
- Look for:
  - Homogeneity of effect
  - Pooled result
  - 95% CI



Celecoxib treatment

Activity

- **Choose which research design will best answer your research question.**
- **Define your population of interest**
  - **Inclusion criteria**
  - **Exclusion criteria**
  - **Sampling methodology**
  - **Sampling pool**
  - **Recruitment**

Measurement

Foundations

- **Research Question**
  - **FINER**
  - **PICO**
- **Research Design**
  - **Observational vs. Experimental**
  - **Retrospective vs. Prospective**
  - **Population – Inclusion and Exclusion Criteria**
  - **Next?**

Foundations

- **Will answer the research question**
- **Appear in the literature**
- **"Gold standard"**
- **Precision/Consistency/Reliability**
- **Accuracy/Interpretable/Validity**
- **Existing instruments**

Variables

- **Independent (predictor)**
- **Dependent (outcome)**
- **Confounding**
- **Demographic**
- **Selection of variables**
  - **Research question**
  - **Clinical experience**
  - **Literature**

SCALES OF MEASUREMENT

Impact of Measurement

- **Measurement DIRECTLY influences:**
  - **Statistical power**
  - **Sample size**
  - **Nature of effect size**
  - **Statistical tests**
  - **Database management**

Nominal/Categorical

- **"Naming" something with a code or assignment to a category**
- **Popular in medical literature**
  - **Limited variability**
  - **Less precision and accuracy**
  - **Less statistical power**
  - **Larger sample sizes**
  - **Less powerful statistics**
  - **Weaker inferences**

0 1

Examples of Nominal Variables

- **Race**
- **Gender**
- **Treatment Versus Control**
- **Pain – Yes or No**
- **Survival – Yes or No**
- **Dx – Yes or No**
- **Recurrence – Yes or No**
- **Type of Bandage – Gauze, Bandaid, Tegaderm**

Ordinal

- **"Order"**
- **Measure subjective feelings or perceptions of phenomena**
  - **Cross-sectional designs**
  - **Surveys**
  - **Instruments**
  - **Likert scales**

Examples of Ordinal Variables

- **Grade in school**
- **Placement in a race**
- **Stage of cancer**
- **APGAR Score**
- **ACT, SAT, GRE, MCAT**
- **Pain: No pain, little pain, mild pain, moderate pain, severe pain**
- **Frequency: Never, rarely, sometimes, often, always**
- **Agreement: Strongly disagree, disagree, neither agree nor disagree, agree, strongly agree**

1 2 3 4 5

Scale/Continuous

- **Strongest scale of measurement.**
  - **Measure of distance and magnitude**
  - **Absolute zero**
- **Increased precision and accuracy**
- **More statistical power**
- **Smaller sample sizes**
- **More powerful statistics**
- **Stronger inferences**

Examples of Scale/Continuous Variables

- **A1C**
- **Age**
- **Height**
- **Number of readmissions**
- **Blood Loss**
- **Amount of a drug given**
  - **All have a TRUE ZERO**

0 ——————— ∞

0 1

1 2 3 4 5

0 ——————— ∞

Activity

- **Describe a primary outcome variable and specify its scale of measurement**
- **Describe a primary predictor variable and specify its scale of measurement**
- **Describe various predictor, confounding, demographic, and clinical variables you would also want to assess**

POWER ANALYSIS

Statistical Power

- **Chance of finding a significant *p*-value!!!**
  - **Probability that a test will reject the null hypothesis**
- **Dependent upon:**
  - **Significance or alpha level (*p*=.05, .01, or .001)**
  - **Effect size (Large vs. small)**
  - **Sample size (Large vs. small)**
  - **Precision and accuracy of variables (Categorical vs. continuous)**
- **Most studies are powered at .80**

Effect Size

- **Difference expected between groups or observations of an outcome**
- **Association between variables**
- **HARDEST part of planning a study**
- **Often times, you're trying to find it out!**
  - **Literature review, clinical experience, educated guess**
- **Continuous vs. Categorical**
  - **Continuous -> Difference in means and standard deviations**
  - **Categorical -> Difference in proportions**

Sample Size

- **In empirical research, we draw representative samples from given populations to make INFERENCES about the populations**
- **Consider sampling techniques**
  - **Random/probability**
  - **Purposive**
  - **Convenience**
- **Always try to maximize sample size**

Statistical Power Reasoning

- **Measurement**
  - **Continuous -> More statistical power**
  - **Categorical -> Less statistical power**
- **Effect Size**
  - **Large effect size -> More statistical power**
  - **Small effect size -> Less statistical power**
- **Sample Size**
  - **Larger sample size -> More statistical power**
  - **Small sample size -> Less statistical power**

G*Power

- **G*Power is a power analysis software program that is available to everyone via download**
- **Researchers can conduct power analyses based on many different types of statistical tests**

Between-subjects

- **Does Remifentanil temporarily improve renal function in adult patients with chronic kidney disease undergoing orthopedic surgery?**
- **Drug group vs. control group**
- **Positive fluid balance is the outcome**
- **Drug group – M = 2210, SD = 1123.8**
- **Control group – M = 2058.9, SD = 895**
- **How many people do I need in my study?**

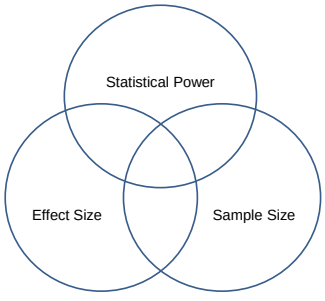
Within-subjects

- **What is the effect of a single-incision sling at the time of robotic sacrocolpopexy on pain levels at 1-year follow-up?**
- **Change in pain as measured by the UDI-6 from baseline to 1 year is the outcome**
- **Baseline – M = 34.8, SD = 25.1**
- **1 year – M = 6.7, SD = 11.2**
- **How many people do I need in my study?**

Proportions

- **What is the effect of bariatric surgery on urinary incontinence (UI)?**
- **UI is the outcome**
- **Bariatric group vs. non-bariatric group**
- **Bariatric – 62.4% positive response**
- **Non-bariatric – 42.1% positive response**
- **How many people do I need in my study?**

Isomorphism in Research



Strategies to Increase Statistical Power

- **Utilize continuous variables**
- **Use within-subjects design**
- **Measure for large effect sizes**
- **Collect a large sample**

Activity

- **Specify your effect size according to the scale of measurement of your outcome**
- **Specify the individual values**
- **What are you doing to increase your statistical power?**

DATA MANAGEMENT

Database and Codebook

- **Based on variables and scales of measurement**
- **Excel formatted database**
- **Word document with variable names, explanations, and codifications**
- **Share with ALL research team members**

Data Formatting

- **Patients go in the "rows"**
- **Variables go in the "columns"**
- **Data structuring changes according to the type of study**
- **Importance of "rows" and "columns" CANNOT be overlooked**

Data Formatting cont'd

- **Research design and database structure**
  - **Between-subjects**
  - **Within-subjects**
  - **Mixed or multivariate designs**

Stacked

- **Used in between-subjects (independent) designs**

Participant	Group	Age	Outcome
1	1	52	0
2	0	51	0
3	1	65	1
4	1	46	1
5	1	59	1
6	0	64	1
7	0	55	1
8	0	61	1
9	1	57	0
10	0	53	0
11	1	59	1
12	0	54	1
13	0	57	1
14	1	56	1
15	1	55	0
16	0	62	0
17	0	60	0
18	0	50	1
19	1	58	1
20	0	52	0

Side-by-Side

- **Used in within-subjects (repeated) designs**

Participant	Administration 1	Administration 2	Administration 3
1	6	8	7
2	5	6	4
3	2	3	8
4	6	4	7
5	9	6	1
6	5	3	2
7	7	6	1
8	9	3	4
9	1	6	7
10	5	9	8
11	6	1	2
12	8	4	6
13	2	1	4
14	6	3	6
15	9	4	5
16	3	4	3
17	4	7	1
18	2	6	5
19	9	8	4
20	1	3	2

Combination

- **Used in mixed or multivariate designs**

Participant	Group	Age	Outcome	Administration 1	Administration 2	Administration 3
1	1	52	0	6	8	7
2	0	51	0	5	6	4
3	1	65	1	2	3	8
4	1	46	1	6	4	7
5	1	59	1	9	6	1
6	0	64	1	5	3	2
7	0	55	1	7	6	1
8	0	61	1	9	3	4
9	1	57	0	1	6	7
10	0	53	0	5	9	8
11	1	59	1	6	1	2
12	0	54	1	8	4	6
13	0	57	1	2	1	4
14	1	56	1	6	3	6
15	1	55	0	9	4	5
16	0	62	0	3	4	3
17	0	60	0	4	7	1
18	0	50	1	2	6	5
19	1	58	1	9	8	4
20	0	52	0	1	3	2

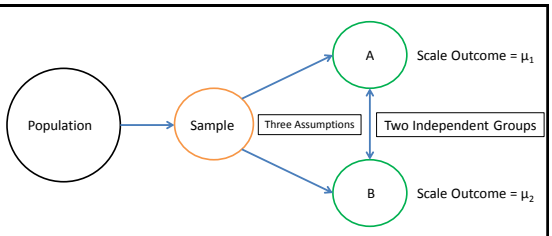
Data Entry

- **Use the codification scheme**
  - **If any changes/additions need to be made, make everyone aware of them**
- **Train research colleagues how to enter data**
- **Minimize "missingness" and data entry errors**

Activity

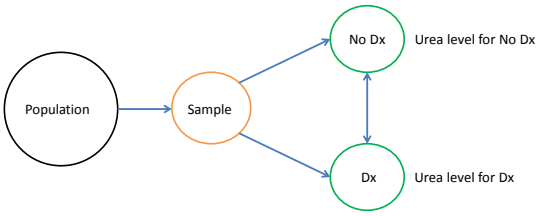
- **What type of database design will you use?**
- **Write your variables into the provided database.**
- **Write out your codebook.**

Group Comparisons



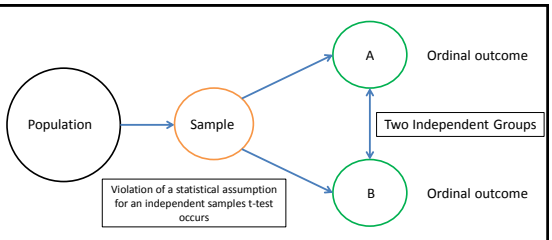
Independent samples t-test

- **Research Question – Comparison of two group means**
  - **Two independent groups**
  - **Scale outcome**
- **Assumptions**
  - **Independence of observations**
  - **Normality**
  - **Homogeneity of variance**



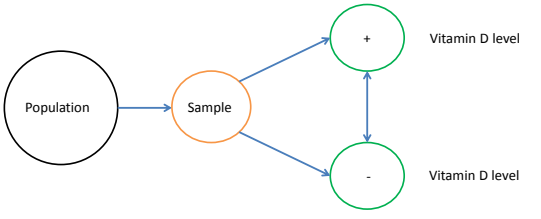
Salivary urea levels and depression

- **Assess the relationship between sialochemical alterations and depression**
  - **Two independent groups – People with depressive history and controls**
  - **Continuous outcome – Salivary urea levels**



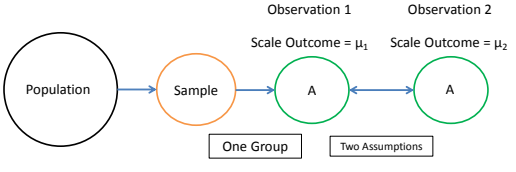
Mann-Whitney U test

- **Research Question – Comparison of two group medians**
  - **Two independent groups**
  - **Ordinal outcome**
- **Violation of statistical assumptions of independent t-test**
  - **Independence of observations**
  - **Normality**
  - **Homogeneity of variance**
  - **Small sample sizes**



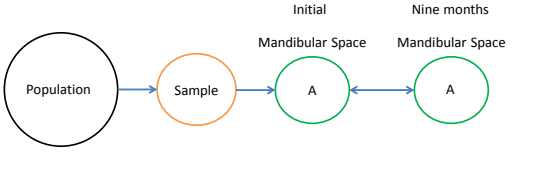
Vitamin D and Monospot tests

- **Research Question – Comparison of two group medians**
  - **Two independent groups – Acute Pharyngitis vs. Control**
  - **Ordinal outcome – Vit D level is not normally distributed**



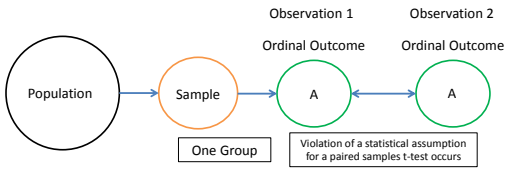
Paired samples t-test

- **Research Question – Comparison of one group measured at two time points**
  - **One Group**
  - **Scale outcome measured at two points in time (pre and post)**
- **Assumptions**
  - **Independence of observations**
  - **Normality of difference scores**



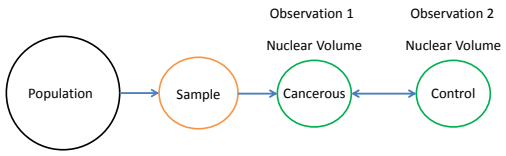
Premature loss of primary first molars

- **Research Question – Comparison of one group measured at two time points**
  - **People that prematurely lost their primary first molars**
  - **Scale outcome measured at two points in time – Mandibular space at initial and 9 months**



Wilcoxon

- Research Question – Comparison of one group measured at two time points
  - One Group
  - Ordinal outcome
- Violation of statistical assumptions of a paired samples t-test
  - Independence of observations
  - Normality of difference scores
  - Small sample sizes

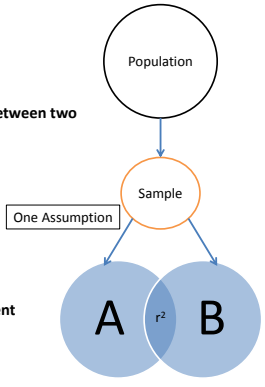


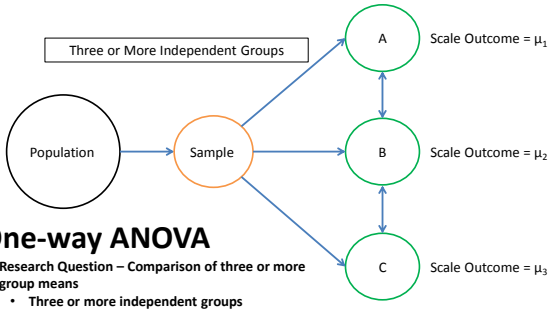
Mean Nuclear Volume in Prostate Cancer

- Research Question – Comparison of one group measured at two time points
  - One Group measured at two time points – 74 radical prostatectomies
  - Ordinal outcome – Mean Nuclear Volume (not normally distributed)

Correlation

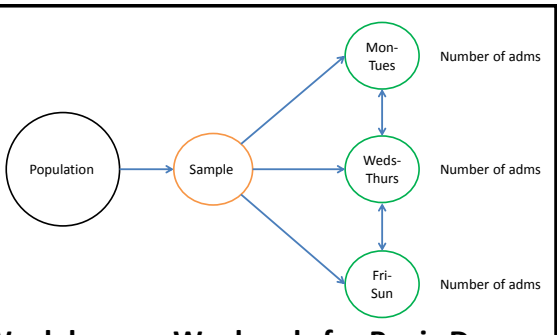
- Research Question – The association between two constructs
- Assumptions
  - Normality
- Scale of measurement
  - Scale to Scale – Pearson
  - Scale to Ordinal – Biserial
  - Scale to Nominal – Point Biserial
  - Ordinal to Ordinal – Spearman
  - Ordinal to Nominal – Rank Biserial
  - Nominal to Nominal – Phi-coefficient
- Coefficient of Determination – r^2





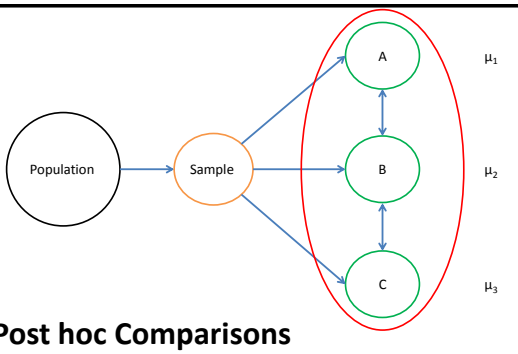
One-way ANOVA

- Research Question – Comparison of three or more group means
  - Three or more independent groups
  - Scale outcome
- Assumptions
  - Independence of observations
  - Normality
  - Homogeneity of variance



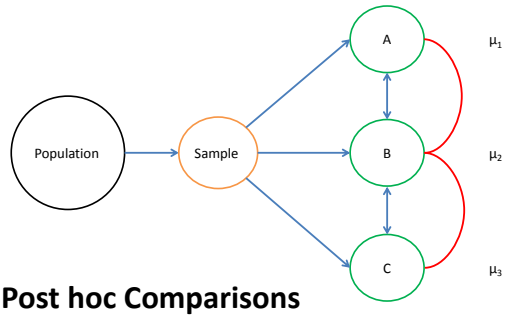
Weekdays vs. Weekends for Panic Dx

- Research Question – Comparing time periods on number of Panic Dx admissions
  - Three or more independent groups – Mon-Tues, Weds-Thurs, Fri-Sun
  - Scale outcome – Number of admissions to ER with Panic Dx symptoms



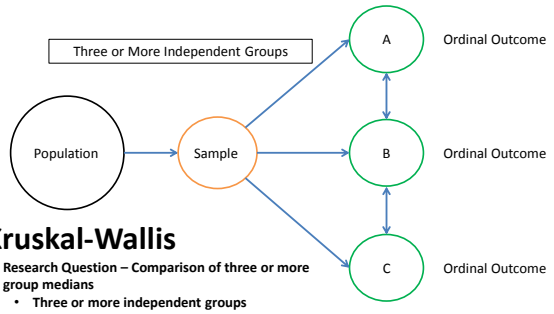
Post hoc Comparisons

- Research Question – We found a significant main effect ($p < .05$) for our one-way ANOVA. What are the differences amongst the individual groups?



Post hoc Comparisons

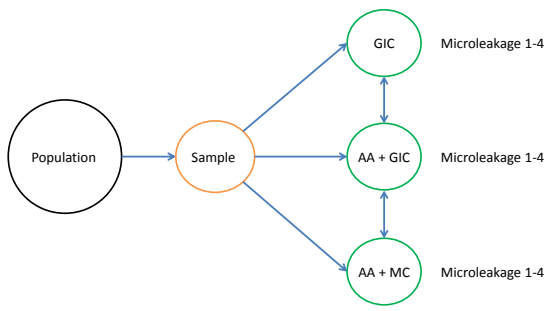
- **Post hoc tests**
  - **Tukey's HSD test**
  - **Bonferroni**
  - **Scheffe test**



Kruskal-Wallis

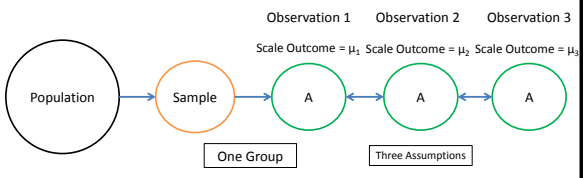
- **Research Question – Comparison of three or more group medians**
  - **Three or more independent groups**
  - **Ordinal outcome**
- **Violation of statistical assumptions of an ANOVA**
  - **Independence of observations**
  - **Normality**
  - **Homogeneity of variance**
  - **Small sample sizes**

Violation of a statistical assumption for an ANOVA occurs



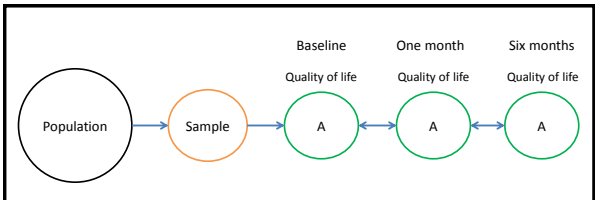
Air Abrasion Preconditioning

- **Research Question – Compare microleakage between groups**
  - **Three or more independent groups – Different preconditioning techniques**
  - **Ordinal outcome – Microleakage rated on a scale of 1 - 4**



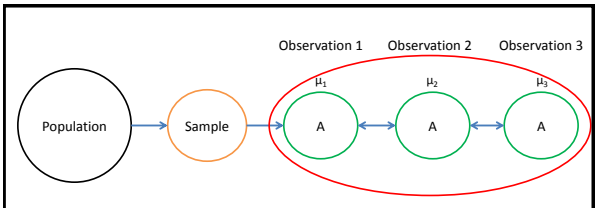
Repeated-measures ANOVA

- **Research Question – Comparison of one group measured at three or more time points**
  - **One Group**
  - **Scale outcome measured at three or more points in time (pre, post, maintenance)**
- **Assumptions**
  - **Independence of observations**
  - **Normality of difference scores**
  - **Sphericity**
    - **Greenhouse-Geisser correction**



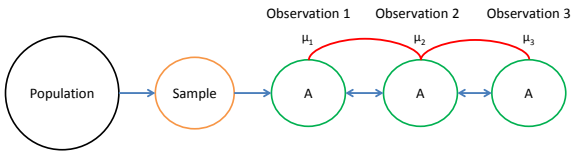
Repeated-measures ANOVA

- **Research Question – Comparison of one group measured at three or more time points**
  - **One Group – People with disordered eating**
  - **Scale outcome measured at three or more points in time (pre, post, maintenance) – Quality of life as measured by the Medical Outcomes Study Short Form Survey**



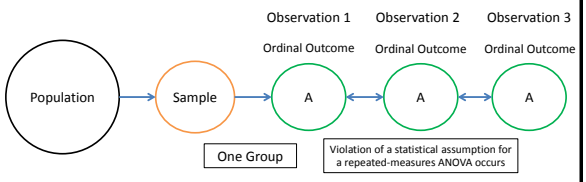
Post hoc Comparisons

- **Research Question – We found a significant main effect for the repeated-measures ANOVA. What are the differences amongst the individual groups?**



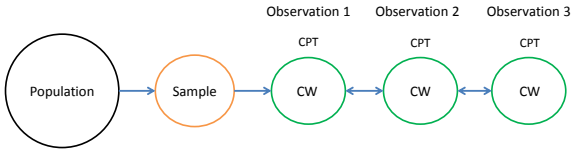
Post hoc Comparisons

- **Post hoc tests**
  - **Tukey's HSD test**
  - **Bonferroni**
  - **Scheffe test**



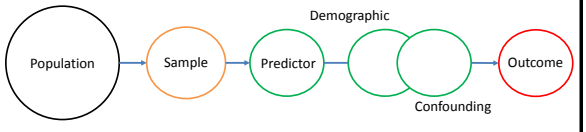
Friedman's ANOVA

- **Research Question – Comparison of one group measured at three or more time points**
  - **One Group**
  - **Ordinal outcome measured at three or more points in time (pre, post, maintenance)**
- **Violation of statistical assumptions of a repeated-measures ANOVA**
  - **Independence of observations**
  - **Normality of difference scores**
  - **Small sample sizes**



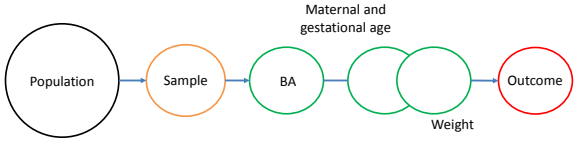
Friedman's ANOVA

- **Research Question – Comparison of one group measured at three or more time points**
  - **One Group – Individuals with Chronic Whiplash**
  - **Ordinal outcome measured at three or more points in time (pre, post, maintenance) – Cold pain threshold at three time points**



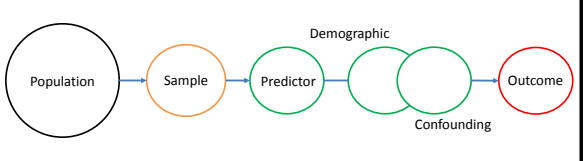
Logistic regression

- **Research Question – What is the association between the predictor variable and the dichotomous outcome variable when controlling for other variables?**
  - **Primary predictor**
  - **Demographic and confounding variables**
  - **Dichotomous categorical outcome**
  - **Multivariate extension of Chi-square**
  - **ADJUSTED ODDS RATIOS WITH 95% CIs**



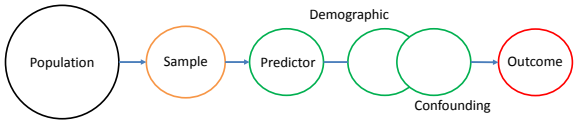
Logistic regression

- **Research Question – What is the relationship between increase in bile acid level and adverse pregnancy outcomes?**
  - **Primary predictor – 10 unit increase in BA level**
  - **Maternal age, gestational age, birth weight were confounders**
  - **Outcome – Adverse neonatal outcome or no adverse outcome**
  - **When controlling for maternal age, gestational age, and birth weight, for every 10 unit increase in bile acid level, women were 1.15 times more likely (95% CI 1.03-1.28) to have spontaneous preterm birth.**



Multiple regression

- **Research Question – What is the association between the predictor variable and the continuous outcome variable when controlling for other variables?**
  - **Primary predictor**
  - **Demographic and confounding variables**
  - **Continuous outcome**
  - **Multivariate extension of ANOVA**
  - **R^2**



Multiple regression

- Research Question – What is the association between type of breast reconstruction and satisfaction, when controlling for other variables?
  - Primary predictor – Autologous, alloplastic, LD/implant
  - Time, age, BMI, bilaterality, invasive disease, adjuvant therapy
  - Continuous outcome – Level of satisfaction
  - When controlling for covariates, type of reconstruction had no association with satisfaction. Chemotherapy had a negative effect on satisfaction.
  - $R^2 = .38$

Activity

- **What type of inferential statistic will you use to answer your research question?**
- **What statistics will you use for your other questions?**
- **What non-parametric statistics will you use?**

2x2 Tables

2x2 Tables

Predictor	Outcome: Yes	Outcome: No
Yes	100	30
No	20	70

Odds ratio

Predictor	Outcome: Yes	Outcome: No
Yes	100 (A)	30 (B)
No	20 (C)	70 (D)

- Research Question:
- What is the association between the nominal predictor and outcome variable?
- Retrospective
- Case-control
- Odds ratio
- Prevalence
- Measure of strength of association
- NO *p*-value
- 95% Confidence Interval is the inference
  - ((A x D)/(B x C))
  - ((100 x 70)/(30 x 20))
  - (7000)/(600)
  - 11.67
  - People with the predictor were 11.67 times more likely to have the outcome

95% Confidence Interval

$$95\%\ CI = OR \pm 1.96 * \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

$$95\%\ CI = 11.67 \pm 1.96 * \sqrt{\frac{1}{100}+\frac{1}{30}+\frac{1}{20}+\frac{1}{70}}$$ OR = 11.67, (11.02 – 12.31)

$$95\%\ CI = 11.67 \pm 1.96 * \sqrt{\frac{1}{10}+\frac{1}{3}+\frac{1}{2}+\frac{1}{7}}$$ OR = 11.67, (9.63 – 13.70)

The width of the confidence interval is 100% dependent upon the sample size!

95% CI Interpretation

- **OR 3.96 (3.21 – 5.63)**
- **OR .78 (.66 – 1.03)**
- **OR .23 (.19 – .29)**
- **OR 7.1 (1.3 – 78.9)**
- **OR 13.8 (.67 – 47.91)**
- **OR .57 (.14 – .92)**

Relative Risk

Predictor	Outcome: Yes	Outcome: No
Yes	100 (A)	30 (B)
No	20 (C)	70 (D)

- **Research Question:**
- **What is the association between the nominal predictor and outcome variable?**
- **Prospective**
- **Cohort - Incidence**
- **Relative risk**
- **Measure of strength of association**
- **NO *p*-value**
- **95% Confidence Interval is the inference**
  - **((A/A+B)/(C/C+D))**
  - **((100/130)/(20/90))**
  - **(.77)/(.22)**
  - **3.5**
  - **People with the predictor were 3.5 times more at risk for the outcome**

Epidemiology

Epidemiologic Measures

Intervention	Event: Yes	Event: No
Yes	133 (A)	1127 (B)
No	198 (C)	1028 (D)

- **Research Question:**
- **Does the treatment work?**
- **Control Event Rate (CER)**
  - **(C / (C+D))**
  - **198/1226 = .162**
- **Experimental Event Rate (EER)**
  - **(A / (A+B))**
  - **133/1260= .106**
- **Absolute Risk Reduction (ARR)**
  - **|CER – EER|**
  - **.056**
- **NNT**
  - **(1/ARR)**
  - **18**

Epidemiologic Measures

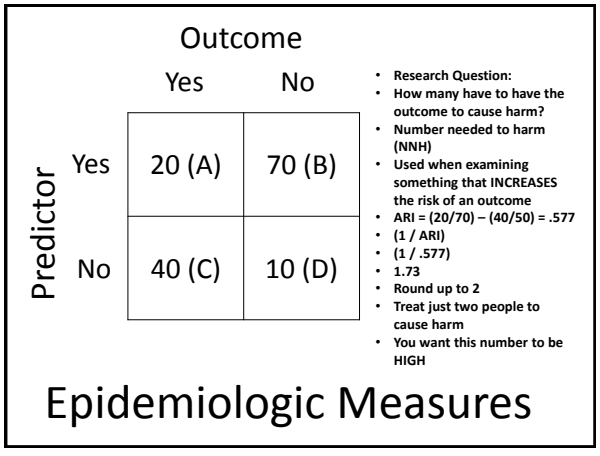
Predictor	Outcome: Yes	Outcome: No
Yes	100 (A)	30 (B)
No	20 (C)	70 (D)

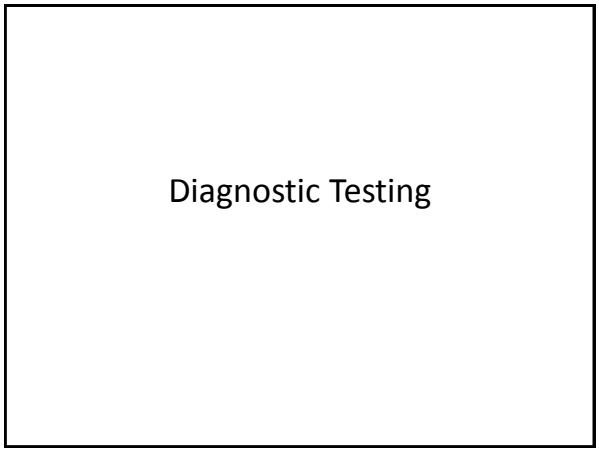
- **Research Question:**
- **How many have to have the outcome to prevent one case of the disease?**
- **Number needed to treat (NNT)**
- **Prevention, NOT treatment**
- **(1 / ARR)**
- **(1 / .547)**
- **1.83**
- **Round up**
- **Treat just two people to prevent a case**
- **You want this number to be LOW**

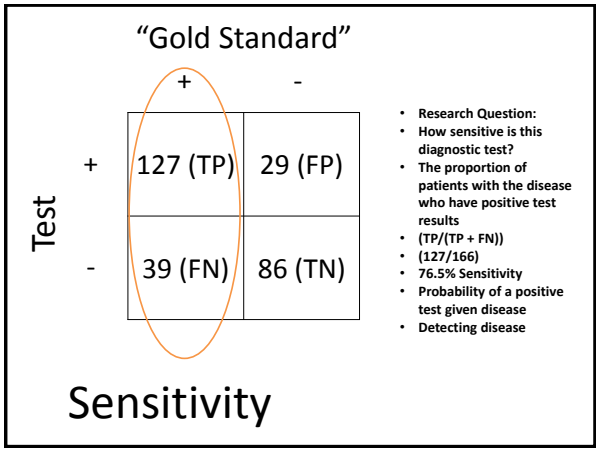
Epidemiologic Measures

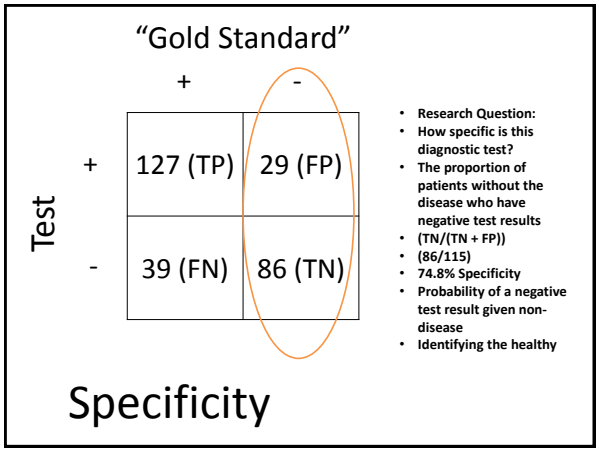
Intervention	Event: Yes	Event: No
Yes	267 (A)	1003 (B)
No	46 (C)	901 (D)

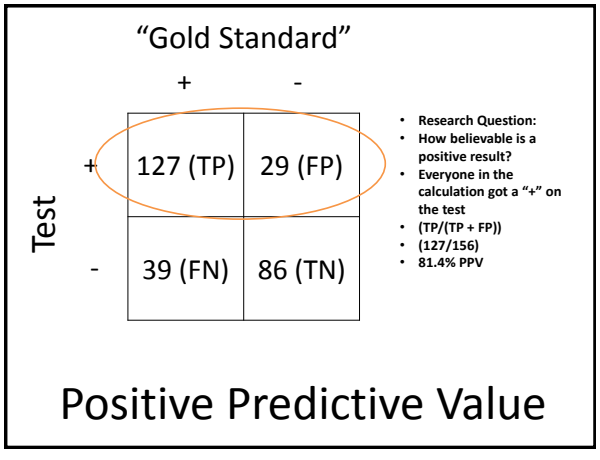
- **Research Question:**
- **Does the treatment work?**
- **Control Event Rate (CER)**
  - **(C / (C+D))**
  - **46/947 = .05**
- **Experimental Event Rate (EER)**
  - **(A / (A+B))**
  - **267/1270= .21**
- **Relative Risk Increase (RRI)**
  - **(|CER – EER|/CER)**
  - **.16/.05**
  - **3.2**
- **Absolute Risk Increase (ARI)**
  - **|CER – EER|**
  - **.16**
- **NNH**
  - **(1/ARI)**
  - **6**

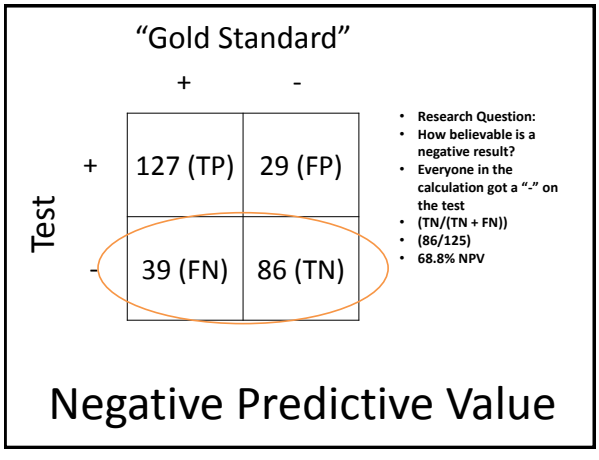

Outcome
Yes
No
Predictor
Yes
No
20 (A)
70 (B)
40 (C)
10 (D)
Epidemiologic Measures
Research Question:
How many have to have the outcome to cause harm?
Number needed to harm (NNH)
Used when examining something that INCREASES the risk of an outcome
ARI = (20/70) – (40/50) = .577
(1 / ARI)
(1 / .577)
1.73
Round up to 2
Treat just two people to cause harm
You want this number to be HIGH


Diagnostic Testing


"Gold Standard"
+
-
Test
+
-
127 (TP)
29 (FP)
39 (FN)
86 (TN)
Sensitivity
Research Question:
How sensitive is this diagnostic test?
The proportion of patients with the disease who have positive test results
(TP/(TP + FN))
(127/166)
76.5% Sensitivity
Probability of a positive test given disease
Detecting disease


"Gold Standard"
+
-
Test
+
-
127 (TP)
29 (FP)
39 (FN)
86 (TN)
Specificity
Research Question:
How specific is this diagnostic test?
The proportion of patients without the disease who have negative test results
(TN/(TN + FP))
(86/115)
74.8% Specificity
Probability of a negative test result given non-disease
Identifying the healthy


"Gold Standard"
+
-
Test
+
-
127 (TP)
29 (FP)
39 (FN)
86 (TN)
Positive Predictive Value
Research Question:
How believable is a positive result?
Everyone in the calculation got a "+" on the test
(TP/(TP + FP))
(127/156)
81.4% PPV

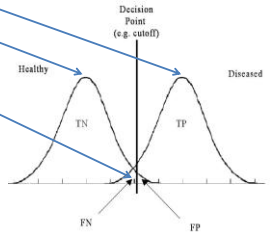

"Gold Standard"
+
-
Test
+
-
127 (TP)
29 (FP)
39 (FN)
86 (TN)
Negative Predictive Value
Research Question:
How believable is a negative result?
Everyone in the calculation got a "-" on the test
(TN/(TN + FN))
(86/125)
68.8% NPV

Test	"Gold Standard" +	"Gold Standard" -
+	127 (TP)	29 (FP)
-	39 (FN)	86 (TN)

- Research Question:
- What is the overall accuracy for this diagnostic test?
- Overall correctness
- ((TP + TN) / (TP + FP + FN + TN))
- (213) / (281)
- 75.8% overall accuracy

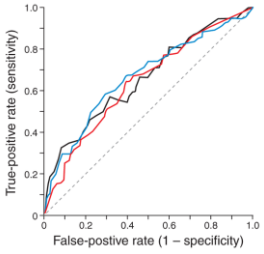
Accuracy

- Point of optimum specificity and PPV
- Point of optimum sensitivity and NPV
- Point of highest accuracy
- There is an inverse relationship between sensitivity and specificity
  - Sensitivity ↑ Specificity ↓
  - Sensitivity ↓ Specificity ↑
  - Sensitivity ↑ PPV ↓
  - Specificity ↑ PPV ↑
- Balance of cut-off point
- Clinical implications
- Youden index
  - (Sensitivity + Specificity) – 100%
  - <50% is a poor test



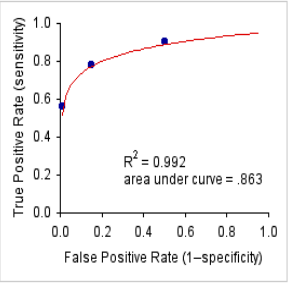
Diagnostic Reasoning

- Comparison of the tests
- Test with most area under the curve (AUC) and is closest to the upper left-hand corner is best



ROC Curves

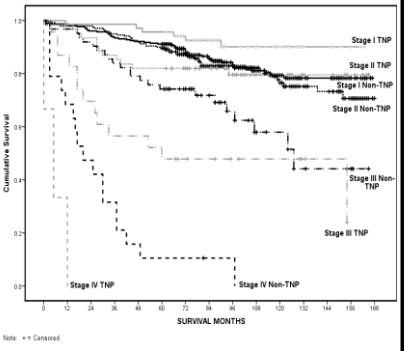
- Choose different cut-off points along the curve
- Balance of sensitivity and specificity in the clinical setting



ROC Curves

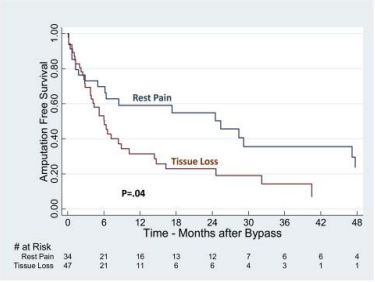
Survival Analysis

- Research Question:
- What is the difference in "time-to-event" for different groups?
- Bivariate comparison of predictor (group) and outcome (mortality)
- Censored observations are people that fell out of the study
- Follow-up
- Three things needed:
  - Groups
  - Dichotomous outcome
  - Time signature



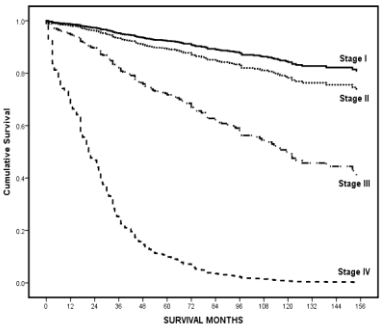
Kaplan-Meier curve

- Research Question:
- What is the difference in "amputation-free survival" for people that had a rest pain indication and those with tissue loss?
- Indication -> AFS
- Follow-up of four years
- There was a significant difference in the AFS between the groups, p = .04.



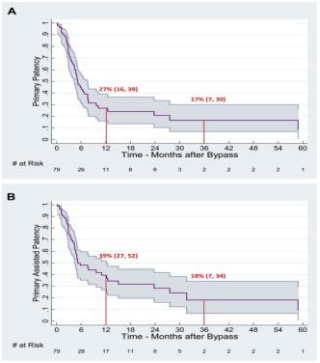
Kaplan-Meier curve

- Research Question:
- What is the difference in "time-to-event" for different groups, when controlling for confounders and other variables?
- Multivariate comparison of predictor (group) and outcome (mortality)
- Follow-up
- Hazard ratios
- Three things needed:
  - Groups
  - Dichotomous outcome
  - Confounding variables
  - Time signature



Cox Regression

- Research Question:
- What is "time to amputation" in critical limb ischemia patients, when controlling for confounders and other variables?
- Cohort of CLI patients
- Follow-up for five years
- Significant predictors of limb salvage was postoperative warfarin, .4 (.2-.8), dyslipidemia, .4 (.2-.9)



Cox Regression

Activity

- **Are you going to use measures of risk, epidemiology, or survival?**
- **Specify how these analyses may help you answer your research question**

Evidence-Based Medicine (EBM)

The Practice of EBM

- **Convert "knowledge gap" into an answerable question**
- **Find the best evidence to answer the question**
- **Critically appraising the evidence for its validity, impact, and applicability**
- **Integrate the evidence according to the patient's biology, values, and circumstances**
- **Evaluating the effectiveness and efficiency of EBM treatments**
  - **Asking, acquiring, appraising, apply, assess**

Incorporating EBM

- **"Doing" mode – The first four steps are completed**
- **"Using" mode – Literature searches are limited to evidence resources that have already been critically appraised**
- **"Replicating" mode – Decisions of respected opinion leaders are followed**

Asking

- **"Background" questions**
  - **Ask for general knowledge about a condition, test, or treatment**
    - **Have two essential components:**
      - **A question root (who, what, where, when how, why) and a verb**
      - **A disorder, test, or treatment**
- **"Foreground" questions**
  - **Ask for specific knowledge to inform clinical decisions**
    - **Four components:**
      - **"P" or patient, population, or problem**
      - **"I" or intervention, exposure, or test**
      - **"C" or comparison intervention, exposure, or test**
      - **"O" or outcomes**

Cognitive Dissonance

- **"Not knowing"**
- **Powerful motivator for learning**
- **Filling "knowledge gaps" becomes a standard practice of asking questions and seeking out answers**

Where and How?

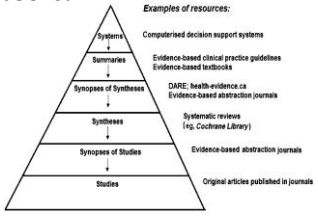
- **Clinical findings**
- **Etiology/risk**
- **Clinical manifestations of disease**
- **Differential diagnosis**
- **Diagnostic tests**
- **Prognosis**
- **Therapy**
- **Prevention**
- **Experience and meaning**
- **Improvement**

Why bother?

- **Ask more specific questions**
- **More searching for evidence**
- **More detailed searches are more precise answers**
- **Time**
- **Communication to patients**
- **Stronger clinicians**

Acquiring

- **Find the current best evidence related to managing clinical problems**
- **BURN your textbooks!**
- **6S approach**



Systems

- **Integrates and summarizes all relevant evidence related to a clinical problem**
- **Linked to EMR**
- **Related to patient's circumstances**
- **DOES NOT tell clinicians what to do**
- **Synopsis linked to syntheses and studies**
- **Available at point of care**

Summaries

- **Clinical Evidence**
- **Physicians Information and Education Resource (PIER)**
- **Dynamed**
- **Up-To-Date**
- **Harrison's Practice**
- **Database of Abstracts of Reviews of Evidence (DARE)**

Synopses of Syntheses

- **Carefully edited "snippets" of pre-appraised articles that report sound research with clinically relevant and newsworthy findings**
- **These do a lot of "heavy lifting" in EBM**

Syntheses

- **Cochrane Collaboration**
- **EvidenceUpdates**
- **DARE**

Synopses of studies

- **The reports of single studies are described**

Studies

- **SUMSearch**
- **Turning Research Into Practice (TRIP)**
- **Cochrane Central Register of Controlled Trials (CENTRAL)**
- **MEDLINE**
- **PubMed**
- **Google**

Appraising RCTs

- Therapy articles
- Individual RCT studies
  - Was the assignment of patients to treatment randomized?
  - Was the randomization concealed?
  - Were the groups similar at the start of the trial?
  - Was follow-up of patients sufficiently long and complete?
  - Were all patients analyzed in the groups to which they were randomized?
  - Were patient, clinicians, and study personnel kept blind to treatment?
  - Were groups treated equally, apart from the experimental therapy?

Appraising RCTs

- Therapy articles
- Individual RCT studies
- What is the magnitude of the treatment effect?
- Experimental event rate (EER)
- Control event rate (CER)
- Relative risk reduction (RRR)
  - (EER – CER / CER)
- Relative benefit increase (RBI)
  - (CER – EER / CER)
- Absolute risk reduction (ARR)
  - |EER – CER|
- Absolute risk increase (ARI)
  - |CER – EER|
- Number needed to treat (NNT)
  - (1 / ARR)
- Number needed to harm (NNH)
  - (1 / ARI)

Appraising RCTs

- **Therapy articles**
- **Individual RCT studies**
- **How precise is the estimate of the treatment effect?**
- **Confidence intervals**
  - **Larger sample sizes = smaller CIs**
  - **Smaller sample sizes = larger CIs**

Applying RCT Evidence

- **Therapy articles**
- **Individual RCT Studies**
- **Are the results applicable to the patient?**
  - **Is the patient so different from those in the study that its results cannot apply?**
  - **Is the treatment feasible in our setting?**
  - **What are our patient's potential benefits and harms from the therapy?**
  - **What are our patient's values and expectations for both the outcome we are trying to prevent and the treatment we are offering?**

Appraising Systematic Reviews

- **Therapy articles**
- **Reports of systematic reviews**
  - **Is this a systematic review of randomized trials?**
  - **Does it describe a comprehensive and detailed search for relevant trials?**
  - **Were the individual studies assessed for validity?**
  - **Were individual patient data or aggregate date used in the analysis?**
  - **Are the results consistent across studies?**
  - **What is the magnitude of the treatment effect?**
  - **How precise is the treatment effect?**

Applying SR Evidence

- **Therapy articles**
- **Reports of systematic reviews**
  - **Are the results applicable to the patient?**
  - **Is our patient so different from those in the study that its results cannot apply?**
  - **Is the treatment feasible in our setting?**
  - **What are our patient's potential benefits and harms from the therapy?**
  - **What are our patient's values and expectations for both the outcome we are trying to prevent and the adverse effects we may cause?**

Levels of Evidence for Therapy

- **Levels of evidence for therapy studies**
  - **1a – Systematic review with homogeneity of RCTs**
  - **1b – Individual RCT with narrow confidence interval**
  - **2a – Systematic review with homogeneity of cohort studies**
  - **2b – Individual cohort study**
  - **3a – Systematic review with homogeneity of case-control studies**
  - **3b – Individual case-control study**
  - **4 – Case series**
  - **5 – Expert opinion**

Appraising

- **Diagnosis and screening articles**
- **There are three prevailing questions that can be applied to any article about diagnostic tests:**
  - **Is this evidence about the accuracy of the diagnostic test valid?**
  - **Does this evidence show that the test is useful at all?**
  - **How can I apply the test to my specific patient?**

Appraising Dx Evidence

- **Diagnosis and screening articles**
- **Is this evidence about the accuracy of the diagnostic test valid?**
  - **Was the diagnostic test evaluated in an appropriate spectrum of patients?**
  - **Was the reference standard ascertained regardless of the diagnostic test's result?**
  - **Was there an independent, blind comparison with a gold standard?**

Appraising Dx Evidence

- **Diagnosis and screening articles**
- **Can the test accurately distinguish between patients who do and don have a specific disorder?**
  - **Sensitivity – Probability of a positive test given disease**
  - **Specificity – Probability of a negative test given no disease**
- **Likelihood ratio**
  - **Probability of positive test given disease / probability of a positive test given no disease**

Appraising Dx Evidence

- **Diagnosis and screening articles**
- **Is the test useful at all?**
- **Youden index**
  - **Sensitivity + Specificity – 100**
  - **Must be greater that 0 and be at least 50**

Appraising Dx Evidence

- **Diagnosis and screening articles**
- **Can the test rule in or rule out?**
- **When either sensitivity and specificity are high and the other is low:**
  - **Tests with high sensitivity and a negative result rules out a diagnosis**
  - **Tests with high specificity and a positive result rules in a diagnosis**
  - **Likelihood ratio for a positive result**
    - **Sensitivity / (1 – specificity)**
  - **Likelihood ratio for a negative result**
    - **(1 – sensitivity) / specificity**

Applying Dx Evidence

- Diagnosis and screening articles
- Can I apply this diagnostic test to my patient?
  - Is the diagnostic test available, affordable, accurate, and precise in our setting?
  - Can we generate a clinically sensible estimate of our patient's pre-test probability?
  - Are the study patients similar to our patient?
  - Is it unlikely that the disease probabilities have changed since the evidence was gathered?
  - Will the resulting post-test probabilities affect our management and help our patient?
  - Could it move us across a test-treatment threshold?
  - Would our patient be a willing partner in carrying it out?
  - Would the consequences of the test help our patient reach his or her goals?

Appraising Prognosis Evidence

- **Prognosis articles**
- **Was a defined, representative sample of patients assembled at a common point in the course of their disease?**
- **Was follow-up of study patients sufficiently long and complete?**
- **Were objective outcome criteria applied in a "blind" fashion?**
- **If subgroups with different prognoses are identified:**
  - **Was there adjustment for important prognostic factors?**
  - **Was there validation in an independent group of "test-set" patients?**

Applying Prognosis Evidence

- **Prognosis articles**
- **How likely are the outcomes over time?**
- **How precise are the prognostic estimates?**
- **Is our patient so different from those in the study that its results cannot apply?**
- **Will this evidence make a clinically important impact on our conclusions about what to offer or tell our patient?**

Appraising Harm Evidence

- Harm articles
- Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment or other cause?
- Were treatments/exposures and clinical outcomes measured in the same ways in both groups?
- Was the follow-up of the study patients sufficiently long and complete?
- Do the results of the harm study fulfill some of the diagnostic tests for causation?
  - Is it clear that the exposure preceded the onset of the outcome?
  - Is there a dose-response gradient?
  - Is there any positive evidence from a "dechallenge-rechallenge" study?
  - Is the association consistent from study to study?
  - Does the association make biological sense?

Applying Harm Evidence

- Harm articles
- What is the magnitude of the association between the exposure and outcome?
- What is the precision of the estimate of the association between the exposure and the outcome?
- Is our patient so different from those included in the study that its results cannot apply?
- What are our patient's risks of benefit and harm from the agent?
- What are our patient's preferences, concerns, and expectations from the treatment?
- What alternative treatments are available?

Assessing

- **Asking**
  - **Am I asking any clinical questions at all?**
  - **Am I asking focused questions?**
  - **Am I locating and acknowledging knowledge gaps?**
- **Acquiring**
  - **Am I searching at all?**
  - **Do I know the best sources of current evidence for my clinical discipline?**
  - **Do I have easy access to the best evidence for my clinical discipline?**
  - **Am I an efficient searcher?**

Assessing

- **Appraising**
  - **Am I critically appraising external evidence at all?**
  - **Is my critical appraisal accurate and efficient?**
  - **Am I creating any appraisal summaries?**
- **Applying**
  - **Am I integrating my critical appraisals into my practice at all?**
  - **Am I becoming more accurate and efficient?**
  - **Can I explain my decision in the context of the evidence?**

Assessing

- **Practice Improvement**
  - **When evidence suggests a change in practice, am I identifying barriers and facilitators to the change?**
  - **Have I identified a strategy to implement the change?**
  - **How will evidence impact clinical outcomes?**
  - **Is the change sustainable?**