- Literature summary
- Basic statistics
- Objective/Predetermined Inclusion Criteria

- Can be Level I, II, or III depending on the types of Advanc84T-1 Q a 1Q a 408

Study Type	Key Words	Level of Evidence
( )	- Random Treatment Assignment - Control Group - Prospective - Unmeasured covariates randomly distributed	- Level 1 if follow up > 80% - Level 2 if follow up < 80%

II.   Levels of Evidence

The levels of evidence is/are a ranking system used in evidence based practices which determines the clinical value of a study. Keep in mind both the study design and the endpoints measured determine the level of evidence. Definitions to make the chart easier to understand are included below.

Level of Evidence	Therapeutic Studies	Prognostic Studies	Diagnostic Studies
Level I	- High quality RCT - Systematic review of level 1 RCT w/ homogenous results	- High quality prospective study - Systematic review of level 1 studies	- Testing of previously developed diagnostic criteria on consecutive patients (w/universally applied gold standard) - Systematic review of level I studies
Level II	- Lesser quality RCT - Prospective Cohort Study - Systematic review of level II studies w/ heterogenous results	- Retrospective study - Untreated controls from RCT - Lesser quality prospective study - Systematic review of level II studies	- Development of previously developed diagnostic criteria on consecutive patients (w/universally applied gold standard) - Systematic review of level II studies
Level III	- Case control study - Retrospective cohort study - Systematic review of level III studies	- Case control study	- Study of non-consecutive patients without universally applied reference gold standard - Systematic review of level III studies

Level IV
- Case Series
- Case series
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III.   Sources of Bias

Bias and Study Errors

There are more types of bias than those described in this booklet, but the ones included are quite common and are important to be familiar with.

Types of Bias When Recruiting Participants

Selection Bias

Four Characteristics of Selection Bias:

1. Nonrandom sampling or assignment to treatment.
2. The sample does not effectively represent the population of interest.
3. Patients are lost in follow up.
4. The study produces a different results than expected if the study included the entire target population.

2. Assignment to Treatment: Assignment of subjects or smaller defined groups of subjects to treatment groups must be random.

Types of Bias When Performing the Study

Recall Bias

Characteristics of Recall Bias:

1. Sample population self-reports data. (ex. As a child, did your house have lead paint?)
2. One group either intentienally or unintentially misremembers a piece of information about exposure to a risk factor due to their being in the treatment group. (ex. Response: My house did not have lead paint — but it actually did.)
3. Because the subjects misremembered their exposure or non-exposure, they are incorrectly sorted into the control group or treatment group. (ex. Control group did not have lead paint in their houses as children, Treatment group did have lead paint in their houses — This particular subject is incorrectly sorted into the control group.)

Risk Factors for Recall Bias:

1. The disease or event in question is significant or critical (ex. cancer)
2. A particular exposure is thought of by the patient as a risk factor for a high burden disease.
3. A scientifically ill-established association is made public by the media.
4. The exposure under investigation is socially undesirable (ex. AIDS).
5. The event in question took place a long time ago.

How to Reduce Recall Bias:

1. Use a well constructed, standardized questionnaire.
2. Use a double-blind study: blind subjects and data collectors to the hypothesis of the study.

3. Use any available proxy sources of reported data

1. Non-random treatment assignment — Patients and/or physicians responsible for treatment assignment.

2. Subjects in different groups are treated differently.

How to Reduce the Chances of Procedure Bias:

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Interpreting Results

Confounding Bias

Confounding Variable: A variable other than the independent variable(s) that has an impact on the dependent variable.

Characteristics of Confounding Bias:

1. An relationship exists between the confounding variable and the outcome that is independent of the exposure.
2. The confounding variable is not a proxy for the exposure, but is associated with the exposure.
3. A confoundint variable is not an intermeditate between the exposure and the outcome.

How to Reduce the Chances of Confounding Bias:

1. Measure and report all potential confounding variables including diagnostic features, comorbidities, and any factor that may impact patient outcome
2. Routinely assess the role of confounding factors and adjust for them in analyses
- Restriction: Incusion criteria prevents confounders- if age is a confounder, set age boundaries for subjects (ex. 28-34 yrs old) OR stratification
- Multivariate analysis: Allows for adjustment of multiple variables simultaneously via mathematical modeling, mathematical controls
3. Report adjusted and crude estimates of association and discuss limitations
- If adjusted estimate is greater than or equal to 10% of the crude estimate, the variable can be considered a confounder

Lead-time Bias

Lead-time: The length of time between the detection of a disease and its diagnosis.

Characteristics of lead-time bias:

1. Disease is diagnosed earlier than usual, typically due to a novel screening method.

2. Early treatment often allows for earlier and more treatment than usual .

3. Disease runs its regular course but due to the early diagnosis, it is believed that the survival time has increased due to the extra treatment.

How to Reduce the Chances of Lead-time Bias:

1. Evalate severity of disease at time of diagnosis.

2. Compare survival times from different stages of the disease rather than survival times from diagnosis.

3. Measure "back-end" survival (adjust survival according to the severity of disease at the time of diagnosis).

IV.   Measures of Disease

Term	Definition
Inflow	Proportion of people developing a condition over a period of time.
Pool	Total number of cases at a period of time.
Incidence	A measure of the number of new cases of a characteristic (such as illness or risk factor) that arise in a population over a given period.
Prevalance	The proportion of a population who have (or had) a specific characteristic in a given time period.

V.

and absolute risk reduction (ARR) are given in prospective studies (prospective cohort, clinical trials) as measures of association.

Risk:

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Term	Definition
Standard Error	More reliable estimate of the variabilty for non-normal/ skewed data
Statistical Hypotheses	
Null Hypothesis H_0	Hypothesis of no difference: population values are not significantly different.
Alternative Hypothesis H_a	Hypothesis of some difference: population values are significantly different.
Hypothesis Testing	
Significance Level	The probability of rejecting the null hypothesis when it is true. A .05, 0.01, or 0.001 significance level is common. The null hypothesis is rejected if the p-value is less than the significance level.
Confidence Interval	A range of values so defined that there is a specified probability that the value of a parameter lies within it.
95% confidence interval	If a population was sampled many times, a confidence interval drawn from 95% of those samples will contain the true population parameter (mean).
p-value	The probability, under the null hypothesis , of obtaining a result at least as extreme as the result obtained.
$p\text{-value} < 0.05$	There is less than a 5% chance of obtaining a result at least this extreme, given the null hypothesis is true.
Correlation coefficient, r	Measure of association between the independent and dependent variables.
Coefficient of determination, r^2	Percentage of variability in the dependent variable accounted for by independent variable.

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Test	Description	Conditions
Two-sample paired t-test	- Used to compare the mean responses of groups of individuals who experiences both conditions of the variable of interest.	- Paired differences are normally distributed or there are at least 30 differences - Sample of paired differences is random
ANOVA	- Used to compare the means of 2 or more groups. - Categorical predictor(s), numerical response - H0: mean is the same between all groups - Ha: mean is different between 2 or more groups	- The errors are normally distributed and the errors are independent.
Chi-square	- Tests the association between 2 categorical variables - H0: No association - Ha: Some association - Compares the observed frequencies with the frequencies that would be expected if the null hypothesis of no association was true. - By assuming the variables are independent, we can predict an expected frequency for each cell in the contingency table	- Independence - Sample size/distribution: Each particular scenario (Cell count) must have at least 5 expected cases OR no more than 20% of the cells has an expected frequency less than 5 and no empty cells
Fisher's exact test	- Used the same way as chi-square, but functions even when chi-square conditions are not met. - 2 categorical independent variables tested against 2 categorical dependent variables	- Observations are independent - The row and column totals are fixed

Test	Description	Conditions
Kruskall Wallace Test	- If ANOVA conditions are not met, this test compares the median(s) of 2 or more groups of categorical variable(s)	- Observations in each group come from populations with the same shape of distribution
Logistic Regression	- Binary dependent variable - Continuous and/or categorical independent variable(s) - Used to determine OR - The empirical logit plot can be used to determine the OR for any level of the independent variable(s).	- Errors are independent - Independent variables are linearly related to the log odds - Sample size >10 per independent variable

III.   Power

Power: The power of a study is the probability that one will correctly reject the null hypothesis if the alternative hypothesis is actually true.

Why is Power Important?

- Power is used to decide before initiation of a clinical study to descide whether it is worthwhile given the cost, effort, and patient involvement. Often times to have enough patients to run a high power study, you need a lot of money and many patients.

- A hypothesis test with little power will likely yield large p values and large confidence intervals. Thus when the power of a proposed study is low, even when there are real differences between treatments under investigation, the most likely result of the study will be that there is not enough evidence to reject the H0 and meaningful clinical differences will remain in question.

The following terms are commonly used when discussing power.

IV.   Miscellaneous
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Likelihood Ratio

- Defined as the probability of a person who has the disease testing positive divided by the probability of a person who does not have the disease testing positive.

- P(T|D) / P(T|D') which is = Sensitivity/ (1 - Specificity), since Specificity = P(T'|D') and Sensitivity = P(T|D)

- Likelihood ratio positive = sensitivity / (1 – specificity)

Accuracy vs. Precision

Accuracy

- The difference between the measurement and the actual value.

Precision

- The variation between repeated measurements when using the same device.

Validity vs. Reliability

Validity:

- Measuring what is intended to be measured.