**Study Design**

**Hierarchy of Study Design**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Best Type of Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology/Harm</td>
<td>Systematic Review/Meta-analysis of RCTs &gt; single RCT &gt; Cohort &gt; Case Control &gt; Case Series</td>
</tr>
<tr>
<td>Prevention</td>
<td></td>
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<tr>
<td>Therapy</td>
<td></td>
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<tr>
<td>Prognosis</td>
<td>Cohort &gt; Case Control &gt; Case Series</td>
</tr>
<tr>
<td>Clinical Exam</td>
<td>Prospective, blind comparison to a gold standard</td>
</tr>
<tr>
<td>Diagnostic Test</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Economic Analysis</td>
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</tbody>
</table>

Adapted from UNC SILS “Evidence-Based Medicine and the Medical Librarian” fall, 2004

**Risk Analysis**

<table>
<thead>
<tr>
<th>Exposure/Intervention</th>
<th>Disease/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>a</td>
</tr>
<tr>
<td>-</td>
<td>c</td>
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</table>

Odds Ratio (OR) = how many times more likely were those with the disease exposed to a risk factor compared to those without the disease (derived from retrospective case-control study)

$$OR = \frac{(a/b)}{(c/d)}$$

Relative Risk (RR) = how many times more likely are those exposed to the risk factor to develop a disease compared to those not exposed to the risk factor (derived from prospective cohort study)

$$RR = \frac{a/(a+b)}{(c/(c+d))}$$

Absolute Risk Reduction (ARR) = the difference in the rate of outcome between intervention group vs. control group (intervention could either reduce harm or increase benefit compared to control)

$$ARR = \frac{c/(c+d) - a/(a+b)}{a/(a+b)}$$

Number Needed to Treat (NNT) = the number of patients that need to be treated in order to prevent one adverse outcome, or for one patient to benefit

$$NNT = \frac{1}{ARR}$$

Relative Risk Reduction (RRR) = the percent reduction in outcome in the intervention group compared to the control group outcome rate

$$RRR = \frac{ARR}{c/(c+d)}$$

Note: ARR and NNT are much more important in clinical decision making than the RRR.

E.g. the rate of developing cancer in the control group is 1/500, and the rate of developing cancer in the intervention group is 1/1000. The intervention has a RRR of 50%, thus making the intervention appear powerful. But, due to the overall low risk of developing cancer, the ARR is only 0.001 and NNT is 1000, so the intervention is actually not very useful.

**Prevalence, Incidence and Case Fatality**

**Prevalence (P)** = Number of existing cases of a disease at a specific point in time. Often expressed as a proportion of entire population at risk, e.g. 1 in 100,000. It is useful for determining the burden of the disease.

$$P = \frac{\text{total number of cases at a specific time}}{\text{total population at risk \times (10}^{\text{a}}\text{)}}$$

**Incidence (I)** = Number of new cases of a disease over a certain period of time. Often expressed as a rate.

$$I = \frac{\text{number of new cases in a fixed period of time}}{\text{population at risk \times (10}^{\text{b}}\text{)}}$$

**Case fatality** = Measure of severity of a disease

$$\text{Case fatality (%) = } \frac{\text{[# of deaths from a disease in a specific period of time]}}{\text{[# of diagnosed cases in the same period]}} \times 100\%$$
**Sensitivity and Specificity**

<table>
<thead>
<tr>
<th></th>
<th>Disease Present</th>
<th>Disease Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Positive</td>
<td>a (TP)</td>
<td>b (FP)</td>
</tr>
<tr>
<td>Test Negative</td>
<td>c (FN)</td>
<td>d (TN)</td>
</tr>
</tbody>
</table>

TP = true positive; FN = false negative; FP = false positive; TN = true negative

**Sensitivity** = What fraction of all individuals with disease test positive?

\[ \text{Sensitivity} = \frac{TP}{TP+FN} \]

In a highly sensitive test:
- High proportion of those with disease are detected
- Low false negative rate: Sensitivity is inversely associated with false Negatives

SnNOut = On a highly Sensitive test, a Negative result rules the disease OUT (this is because a sensitive test would have found a true case).

- **Specificity** = What fraction of all individuals without disease test negative?

\[ \text{Specificity} = \frac{TN}{FP+TN} \]

In a highly specific test:
- Only those with the disease detected
- Low false positive rate
- Specificity is inversely associated with false Positive rate

SpPin = On a highly Specific test, a Positive result rules the disease IN. (The logic: a specific test detects only that disease, so a positive result rules it in).

**False Negative rate** = (FN/FN+TP), how many cases are missed by the test?

**False Positive rate** = (FP/FP+TN), how many are falsely classified as having the disease?

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**Predictive values**

Given a positive (or negative) test result, what is the probability of disease?

**Positive Predictive Value (PPV)** = Probability that a positive test score is a true positive
\[ \text{PPV} = \frac{TP}{TP+FP} \]

**Negative Predictive Value (NPV)** = Probability that a negative test score is a true negative
\[ \text{NPV} = \frac{TN}{TN+FN} \]

PPV and NPV depend on prevalence of disease. As prevalence ↓, PPV ↓ and NPV ↑

**Pretest, Post-test Probabilities and Likelihood Ratios**

**Pretest Probability** = prevalence of disease.
- **Post-test probability** = how much the result on a diagnostic test changes the probability that a patient has a disease.

- **Positive post-test probability** = PPV
- **Negative post-test probability** = 1 - NPV

**Likelihood ratios (LR)** = How many times more (or less) likely are patients with a disease to have a particular result than patients without the disease?
\[ \text{LR for positive test} = \frac{\text{Sensitivity}}{1-\text{specificity}} = \frac{a/(a+c)}{b/(b+d)} \]
\[ \text{LR for negative test} = \frac{1-\text{Sensitivity}}{\text{specificity}} = \frac{c/(a+c)}{d/(b+d)} \]

**Post-test odds** = **pre-test odds** * LR

**Note:** For very high and very low pretest probabilities, LR cannot add much more information, so diagnostic testing is most useful in the intermediate pretest probability range (i.e., 30-70%). Here the test result may be useful to rule in disease.

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**Statistical Significance**

- The likelihood that the difference found between groups could have occurred by chance alone, and so would not occur if study was done again.
- By convention, result is statistically significant if the difference could have occurred by chance alone in less than 1 time in 20
- Expressed as a **p value** < 0.05

**REMEMBER:** A trivial difference can be statistically significant if the number of subjects is large enough!

**Clinical Significance (or Importance)**

- Is a matter of clinical judgment and has little to do with statistics
- Answers the question "Is the difference between groups large enough to be worth achieving?"

**REMEMBER:** Studies can be statistically significant yet clinically insignificant!

**Effect Size**

- Can be used to determine clinical significance
- Measures the magnitude of a treatment effect
- Unlike significance tests, it is independent of sample size.

**Power**

- The probability of detecting a given effect size (i.e., a clinically relevant difference between the treatment & control group) if a difference actually exists
- Well designed studies may fail to detect a real, possibly clinically significant, association if the sample size is too small to give the test enough power to detect a given effect
- This can lead erroneous conclusions that interventions may not work (an idea close to false negative test results). Hence, careful consideration of the results of "negative studies" should be taken.
- Meta-analysis is one way of dealing with the problem of insufficient power by combining studies

[http://www.musc.edu/dc/crebm/statisticalsignificance.html](http://www.musc.edu/dc/crebm/statisticalsignificance.html)