What is Clinical Research?
- Clinical research is the systematic study of new drugs, devices, procedures, or technologies that may or may have not yet been approved for use.
- These studies use human volunteers as their subjects
  - Informed consent

Why Do Clinical Research?
- Usually to answer a specific question about a medical condition or disease; e.g.:
  - Is a certain behavior related to risk of a certain disease?
  - Is a new product or technology more effective in treating a disease or condition than an existing one?

Types of Studies
- Randomized, blinded prospective clinical trial
- Retrospective review
- Cohort Study
- Case series
- Isolated case reports

Prospective, Double Blinded, Randomized Control Study
- This trial design is the gold standard
- Usually prospective, well-organized trial
- Usually has two or more “arms” with one being a control arm to either use the standard of care or a sham procedure where nothing is done such as a placebo if a medication is utilized, or a plain dressing in the case of wound care
- Typically blinded so that the researcher or at least the patient does not know that they are receiving the prescribed treatment and they cannot enter in any bias
**Retrospective Study**
- Has less clinical significance than a trial because there is bias that can be looked at from a reviewer's standpoint.
- Is useful in not wasting clinical information that has already been obtained with real patients.
- Does have greater significance when compared to a case series or case report that utilizes typically a large cohort group.

**Cohort Study**
- A type of analytical study undertaken to obtain additional evidence to refute or support existence of association between suspected cause and diseases.
- Other names:
  - Longitudinal study
  - Incidence study
  - Prospective (forward looking) study

**Case Series**
- At least two or more anecdotal reports of an observation.
- Can be very powerful in that it can start the wheels turning toward development of the clinical trial, or at least a large retrospective review.
- Does have limited clinical validity.

**Case Report**
- Should be taken very skeptically, but should begin a thought process in developing further interest in a certain area.
- Needs to be reproduced by someone else but again, has limited clinical validity.

**The Language of Clinical Research**
- Type 1 Error
- Type 2 Error
- Cohort
- Prospective
- Stratified
- Controlled
- Cross-sectional
- Placebo
- Case series
- Case study
- Retrospective
- Randomized
- Bias
- Blinded
- P-values
The Study Hypothesis

- What is the expected answer to the question being addressed by the study?
  - The Study Hypothesis
    - That there is a link between the behavior and the risk of disease
    - That the new product is more effective than the old one

The Null Hypothesis

- The flip side of the coin…
  - Null Hypothesis:
    - That there is NOT a link between a behavior and the risk of disease
    - That the new product is NOT MORE EFFECTIVE than the old one

Clinical Studies Assume the Null Hypothesis Applies Until Proven Otherwise by the DATA...

- The data gathered in the study will allow the researchers to reject the null hypothesis OR
- The data gathered in the study will NOT allow the researchers to reject the null hypothesis.

How are Clinical Studies Designed?

- Types of clinical study design
  - Observational - watching one group of patients at a time
    - Case-control studies
    - Cohort studies
  - Controlled, simultaneous comparisons - watching two or more groups of patients at the same time
    - Randomized clinical trials (RCT)

The “External” Anatomy of a Clinical Research Paper

Standard sections in a published paper
- Abstract
- Introduction
- Materials & Methods
- Results
- Discussion
- References
- Figures & Tables

The “Internal” Anatomy of a Clinical Research Paper

- Key pieces of information about how the study was performed
- Which help determine the strength of evidence provided by the data
**“PIPE CROMBS”**
Acronym for the Key Points to look for in a paper:
- ** Patients **
- ** Inclusion/exclusion criteria **
- ** Power **
- ** Error types **
- ** Controls **
- ** Randomization **
- ** Outcomes **
- ** Measurements **
- ** Blinding **
- ** Statistics **

### Patients
Who are the study subjects (patients)?
- Elderly, pediatric, elective surgery, emergent surgery, men, women?
- Are they a representative sample of the population you are interested in?

### Inclusion/Exclusion Criteria
**Inclusion criteria**
- Characteristics or conditions that the patient must possess in order to be enrolled in the study, e.g.:
  - Age of the patient
  - Presence of the condition or disease
  - Adequate nutritional status
  - Wounds of a particular type or duration

**Exclusion criteria**
- Characteristics which will exclude the patient from the study if present, e.g.:
  - Infection
  - Use of certain drugs
  - Poor nutrition

### Power of the Study
**How many patients were in the study?**
- Sample size
- Recruit enough patients (get enough data) to show a difference between the treatment group and the control group

**Power Calculation**
- A statistical method that calculates how many patients are enough

A study must be appropriately powered (examine enough patients) to show a meaningful difference

Underpowered studies (NOT enough patients) can give misleading results

Underpowered studies are common because it takes time and money to recruit, follow, and analyze large numbers of patients...

### Error Sources
**Type 1 Error**
- False positive conclusions

**Type 2 Error**
- False negative conclusions
**Controls**
- Usually want to know if a new treatment is as good as, better or worse than a control or standard treatment
- What was the control treatment?
- Was it the same for all patients in the control group?

**Randomization**
- Refers to how the patients were assigned to treatment and control groups
- Assignment should be random to minimize bias
- Assignment should not be predictable in any way
  - Random numbers, sealed envelopes
  - Not coin toss, day of week, even-odd

**Outcomes**
- **Quantitative**
  - # wounds closed
  - Time to reach complete closure or 50% or x% closure
  - % reduction of original wound area or volume
  - Cost of care
- **Qualitative**
  - Pain reduction
  - Increased quality of life
  - Prevention of recurrence or complications
  - Ease of use

**Measurements**
- How were the outcomes measured?
- Was the measurement objective? i.e., was the measurer blinded as to what the treatment was?
- How often were the measurements taken?

**Blinding**
- Blinding means that either the patient or the clinician or both did not know which treatment was which
- Minimizes bias
- In instances where the 2 treatments are obviously or visibly different, the evaluator may be blinded

**Statistics**
- Statistical analysis enables researchers to determine if the measured differences between groups are more than a chance occurrence.
- In other words, if patients taking product A experienced more improvement than those taking product B, was this because drug A is truly more efficacious than product B, or was it just a fluke?
- There are a number of different methods statisticians use to analyze and report study results. The most common is the $P$ value.
The P value, also known as the level of statistical significance, is a numerical estimate of the probability of error of a particular result. The smaller the P value, the less likely the results occurred by error or chance.

For example, a P value of 0.05 indicates that there is a 5% probability that the results occurred by chance, whereas a P value of 0.03 indicates there is only a 3% probability the results occurred by chance.

For most studies, a P value < 0.05 indicates statistical significance, meaning the results are unlikely to have occurred by chance and are likely to be due to the intervention (ie, the device or drug being tested).

A confidence interval is a range around a measurement that conveys how precise the measurement is. Confidence intervals are used because a study recruits only a small sample of the overall population so by having an upper and lower confidence limit we can infer that the true population effect lies between these two points. Most studies report the 95% confidence interval (95%CI).

The term clinically significant is used when the treatment benefit is expressed in medical terms, without regard to questions of statistical significance. For example:

- A patient's blood pressure may be statistically significantly lower than baseline following administration of the drug being tested.
- But if the change is still within the normal limits of the test, this result, although statistically significant, is not clinically significant.

The average number of patients that need to be treated to cause one positive effect, or prevent one additional bad outcome (e.g., the number of patients that need to be treated for one to benefit compared with a control).

The lower the NNT the better.
Number Needed to Harm (NNH)

- The average number of patients that need to be treated or exposed to a risk factor to cause harm in a patient who would not otherwise have been harmed.
- The higher the NNH the better

Strength of Evidence Ratings

A. Results of two or more randomized controlled clinical trials
B. Results of two or more controlled trials in animal models to provide indirect support
C. One of the following:
   1) Results of one control trial
   2) Results of at least two case series
   3) Descriptive studies
   4) Expert opinion

(adapted from guide to clinical preventative services by the US Preventative Service task force 1989)

Categorization of Treatment Effects

- Beneficial
- Likely to be beneficial
- Trade-off between benefits and harm
- Unknown effectiveness
- Unlikely to be beneficial
- Likely to be ineffective or harmful

(from clinical evidence British Medical Journal publishing group)

How do you take a journal article or new idea presented in a publication and incorporate it into clinical practice?

Assessing a Study in a Journal

1. First, read the abstract and see if it applies to your clinical practice
2. Evaluate the type of study and what is its statistical value
3. Assess the power of the study in its cohort group or its overall design and evaluate the methodology of analysis or statistics
4. Read the introduction of the paper and ask yourself why they chose to develop the hypothesis they did

Assessing a Study in a Journal

5. Read the data section of the paper to see if you can find any potential errors or potential biases that you have not thought of
6. Read the results of the paper and critically evaluate their analysis of this (be the devil's advocate)
7. Read the conclusion and, at this point, form your own conclusion and ask yourself, would this change my clinical practice?