**Exam Format:**

* 1.5 hours to complete exam
* Closed book, closed notes
* May use calculator
  + Program calculator with notes

# **Potential Topics Covered:**

## **General concepts for clinical trial design:**

### Studypopulation**:**

* + - *Selecting eligibility criteria*
      * Characteristics that must be shared by all participants
      * Could include age, gender, medical history, and current health status.
    - *benefits and drawbacks of broad vs. narrow population*
      * Narrow population is more likely to be homogeneous and thus have more concise results. This is hard to recruit, however.
      * Broad population allows for easier recruitment, and potentially more participants for higher *n*. Higher prob of lacking in similarity between enrollees.

### Primary vs. secondary objectives/endpoints: What is the purpose of each?

* + - Objectives are specific goals. Endpoints refines objectives into a specific variable that can be evaluated; should be measurable in all patients.
    - These should be defined before any research begins.
    - *Primary Objective/endpoint*
      * Patients are followed until primary endpoint is reached.
      * Response variable should be ascertained as completely as possible
      * Can sometimes be more than one (but it makes things challenging)
    - *Secondary Objective/endpoint*
      * Other endpoints that don’t have to be followed for the extent of the trial.
      * Can be a surrogate outcome

### Surrogate endpoints

* + - These are outcomes that point to a longer term primary outcome. EX: tumor remission as a sub for longer survival. The former implies the latter.

### Randomization: What is it, benefits and drawbacks

* + - Process by which all participants are equally likely to be assigned to either intervention or control group
    - *Benefits*
      * Protects against bias
      * Makes groups comparable. Balancing both known and unknown prognostic factors.
      * Guarantees validity of statistical tests to judge of treatment effect is real
    - *Drawbacks*
      * Only 50% of the patients receive promising intervention
      * Investigators who believe very strongly in the efficacy of the new intervention would have to stay out to avoid introducting bias.

### Blinding: Types of blinding (single vs. double), benefits and drawbacks.

* + - Single blinding: Treatment assignment unknown to patients
    - Double blinding: Treatment assignment unknown to patient AND evaluator
    - *Benefits:*
      * Avoid placebo in patient knowing their getting new treatment
      * Avoids bias in what the patient/evaluator thinks of the treatment
      * Maintains objectivity in the evaluators
    - *Drawbacks:*
      * Ethics of not treating half the patients could be sus
      * Makes informed consent a little sus
      * Makes administration harder

## Phase 1 trials:

* + Purpose: Find maximum tolerated dose (MTD) for further study
    - First study in which a new drug is administered to human subjects (not animals)
    - Determines if its safe and MTD. Intended to be efficient and quick.
  + Common methods to find MTD: 3+3, CRM. – **DO PRACTICE PROBLEM FOR 3+3 IN HW**
    - *3+3*
      * Patients treated in cohorts of size 3. Start at lowest dose level.
      * For current cohort:
        + If 0/3 toxicities, escalate to next dose and treat next cohort
        + If 1/3 toxicities, treat additional 3 subjects at the same dose

If 1/6, then escalate to next dose and treat next cohort

If >= 2/6, STOP

* + - * + If >= 2/3 toxicities – STOP
    - CRM (Continual Reassessment Method)
      * Patients treated one at a time. Dose-toxicity curve is refit after each patient.
      * Curve is used to estimate the MTD and treat the next patient at the dose closest to the MTD. USE R.

## Phase 2 trials:

* + Purpose: Evaluate whether signal of treatment benefit exists
    - Determines if the treatment should be studied in a phase III large-scale study.
    - Usually single-arm, common dose for ALL patients.
  + Approaches to evaluate signal:
    - Estimate outcome with a CI that is sufficiently narrow
    - Formal hypothesis test of outcome against historical value
  + Determining sample size needed for these approaches
* Phase 3 trials:
  + Methods for randomization: Simple randomization, permuted block randomization, stratified randomization
  + Sample size calculations when comparing two groups on:
    - Normal outcome
    - Binary outcome