Experimental Design and Statistical Analysis Seminar

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EXPERIMENTAL DESIGN AND STATISTICAL ANALYSIS SEMINAR:
STUDY DESIGNS

1. Classification of Study Designs
2. Essential Design Features of a Controlled Clinical Trial
3. Quality Assurance
4. Computer Facility
5. Data Security Precautions
6. Preparation of Analysis Files
7. **Broader classifications of study designs**
8. Randomization
9. Activities By Stage Of Clinical Trial

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6: Preparation of Analysis Files

1. Create an analysis dataset
2. Data can be rearranged in the analysis dataset easier to meet data analysis requirements
3. It reduces the number of times the database is accessed for data analysis
4. The database can be updated regularly, but not the analysis dataset
5. Have a policy of if/when the Analysis dataset should be synced with the Database
6. Create multiple backups for the dataset as its content changes.

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7: Broader classifications of study designs

Randomized Controlled Trial (RCT):
Subjects are randomly assigned to interventions (e.g., drugs) or control groups. Independent Concurrent Controls; Crossover Studies

Factorial Design: Evaluates two or more treatments simultaneously in different combinations (e.g., Treatment A, Treatment B, both, or neither). It is efficient for studying independent or interactive effects. Independent Concurrent Controls

Single-Arm Trial: All participants receive the experimental therapy. Used primarily for preliminary efficacy and safety data when randomization is not ethical or feasible. Uncontrolled, No randomization

Block Design: Participants are grouped into blocks based on certain pre-specified characteristics such as age or disease stage. Within each block, participants are randomly assigned to a treatment group, independent of the treatment assignments in other blocks.

Basket/Platform/Umbrella Trials: Multiple interventions for 'one' disease/condition or 'one' intervention for multiple diseases/conditions. (Biomarker and Genetic)

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7: Broader classifications of study designs

Basket design clinical trial: Tests a single targeted therapy or drug across multiple, distinct disease types (or subtypes) that all share the same common, actionable mutation or biomarker.

Umbrella Study Design:

- Subjects with a single type of cancer with multiple mutations are given different treatments/interventions based on the variant.
- Umbrella designs allow for efficient testing of multiple treatments in patients with specific genetic mutations.

Platform Study Design:

- This is a type of trial that uses a common infrastructure and patient population to test multiple interventions simultaneously against a common control group.
- This design allows for the efficient testing of multiple interventions and the sharing of resources.
- Platform trials are carefully designed with pre-specified rules for adaptation to allow for the addition of new arms, removal of ineffective or undesirable arms, and multiple interim analyses or data looks.

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7: Broader classifications of study designs

Adaptive Design:

- An adaptive design is a clinical trial design that allows for modification of a structured plan in a clinical trial based on data accumulated during pre-planned interim analyses while maintaining trial integrity.
- Study design is modified according to pre-specified criteria (e.g., high dropout rate, high SE).
- These trials can more quickly identify therapeutic effects and minimize the number of participants exposed to less effective or unsafe treatments.
- Requires careful planning to maintain validity and avoid bias, as selecting populations based on interim data can lead to overestimated effects.

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7: Broader classifications of study designs

Adaptive Design:

- Adaptive designs are broadly classified into two categories:
- **Covariate-adaptive randomization**: Subjects are randomly assigned to treatment groups based on the cumulative results of the baseline characteristics of the previously enrolled subjects.
- **Randomization ratio and response-adaptive randomization**: A new randomization ratio is computed based on the results of previously enrolled subjects using interim analysis.
- Most frequently used in clinical trials for oncology diseases, followed by neurology, and autoimmune/inflammatory diseases.
- Disadvantages: Adjustment for Type I error must be considered when designing an adaptive design.
- A common method is to estimate the type I error rate using simulation methods

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7: Broader classifications of study designs

Parallel-Group: Participants are randomized to one of two or more arms.

Pragmatic Trial: Evaluates effectiveness in real-world settings rather than ideal conditions. (Effectiveness)

Decentralized/Remote Trials: Uses technology (telemedicine, wearables) to conduct research outside of traditional clinic settings.

Cluster Randomized Trial: Randomizes groups (e.g., hospitals, counties) rather than individuals.

Community trial (cluster-randomized): Subjects are grouped into those with and without disease. They are assigned to different intervention/experiment groups.

Field trial (preventive): Subjects without the disease are assigned to different preventive intervention groups.

Dose Escalation Design: Starts with a low dose of the treatment and slowly gives participants stronger doses to attempt to find the maximum tolerated dose. (drug development).

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7: Broader classifications of study designs

Non-Inferiority Trial:

- Non-inferiority trials are a type of clinical research study designed to determine whether a new treatment is not significantly worse than an established or standard treatment by a predefined margin.
- It is used to show that the new interventions may offer additional benefits such as improved safety profiles, ease of administration, or cost-effectiveness
- They are also useful in situations where it may not be practical or ethical to conduct traditional superiority trials.
- This design requires defining a non-inferiority margin or the maximum difference they consider clinically acceptable.
- Statistical analyses to show whether the new treatment falls within this margin compared to the standard treatment. =non-inferior.

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7: Broader classification of study designs

Matched Design / Matched Pair Design:

- Subjects are matched based on their similarities in certain characteristics such as age or disease stage, or on a more complex technique like propensity scores.
- The goal of this design is to ensure that the groups are as similar as possible, reducing the potential for bias.
- Factors used for matching must account for a good amount of inter-subject variability in treatment effect.
- Works best with only two interventions; when one is a control, then they are a type of Randomized Control Trial.
- Subjects are then randomly assigned such that the two pair members are on different interventions.
- This study design serves a similar purpose to a crossover design but can be used when a crossover design is not feasible.
- It can be used for retrospective or observational datasets to create “balanced” samples of each intervention from the data.

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7: Broader classifications of study designs

3+3 Design:

- A form of dose escalation design, used in Phase I trials for oncology.
- First, 3 participants are given a low dose of the experimental treatment and monitored for pre-specified toxicity events.
- If 0 participants experience any toxicity events, then the next group of 3 participants is enrolled at a higher dose.
- If 1 participant experiences toxicity, another group of 3 participants is enrolled at the same dose.
- If 2 or 3 participants experience toxicity, then the next group of 3 participants is enrolled at a lower dose (or the study ends).
- At the next level, if 1 or more of those participants experience toxicity, then the dose is lowered, and the study ends.
- Otherwise, if 0 of the additional participants experience toxicity, the next group is enrolled at a higher dose.
- 3+3 designs do not accurately determine the maximum tolerated dosage in many circumstances, and other, modified designs (such as accelerated titration) are more effective.

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7: Broader classifications of study designs

Enriched Design:

- Subject recruitment is biased in favor of, or restricted to, individuals who are expected to benefit from the intervention being tested.
- Advantages: Increased Study Power, by reducing population variability;
  Smaller sample sizes = Faster recruitment = lower overall costs.
- Disadvantage: Limited generalizability.

- Key features:
  - Targeted Enrollment: Only including biomarker-positive or specific, high-response-probability patients. (different from "prognostic enrichment," which targets patients with the highest disease severity).
  - Predictive Enrichment: Selecting patients more likely to respond to the treatment to increase efficiency by using baseline biomarkers or patient characteristics to select individuals most likely to respond to a new therapy.
  - Prognostic Enrichment: Choosing patients at high risk of a clinical outcome (i.e., the highest disease severity), ensuring enough events occur.
  - Adaptive Enrichment: Using interim data to modify study criteria, such as limiting recruitment to a subgroup showing early benefit.

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7: Broader classifications of study designs

Enriched Design:

- Subject recruitment is biased in favor of, or restricted to, individuals who are expected to benefit from the intervention being tested.
- It is used to increase the study efficiency by focusing on the population most likely to benefit from the intervention.
- Increased Study Power: By reducing population variability (noise), smaller trials can sometimes identify treatment efficacy.

- Key features:
  - Prognostic Enrichment: Choosing patients at high risk of a clinical outcome (i.e., the highest disease severity), ensuring enough events occur.

  Benefits:

  Smaller sample sizes
  Faster recruitment and
  lower overall costs.

  Trade-offs:

  Limited generalizability.

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7: Broader classification of study designs

Enriched Design:
Adaptive Enrichment: Using interim data to modify study criteria, such as limiting recruitment to a subgroup showing early benefit.
Key Characteristics of Adaptive Enrichment

- Dynamic Enrollment: It may start by enrolling a broad group, but then restrict future recruitment to a specific biomarker-positive subgroup if early signals show they benefit the most.
- Efficiency and Ethics: These trials can achieve statistical power with smaller sample sizes and shorter durations, while protecting less-responsive patients from potentially ineffective treatments or side effects.
- Biomarker Validation: They are particularly valuable in personalized medicine, where they help validate whether a specific biomarker truly predicts a patient's response to a targeted therapy.
- Regulatory Flexibility: The U.S. Food and Drug Administration (FDA) supports these designs as a way to modernize drug development and improve the success rates of late-phase confirmatory trials.
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7: Broader classification of study designs

N-of-1 trial:

- An N-of-1 trial is a type of trial in which a single patient receives a series of interventions in a randomized, crossover design.
- This design is used to determine the best treatment for an individual patient.
- Subject serves as their own control.
- The treatment periods are typically repeated multiple times to gather sufficient data for analysis.
- An N-of-1 trial narrows focus to treat an individual patient's well-being and health as the primary concern of the trial.
- These trials aim to provide personalized evidence regarding the effectiveness of a treatment for a particular patient.
- They are particularly useful in cases where individual variation in treatment response or rare conditions makes it challenging to apply generalized research findings to an individual's specific situation.
- The data collected from N-of-1 trials can help guide treatment decisions by providing detailed information about how an individual responds to a specific intervention.

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3: Broader classification of study designs

1. Randomized Controlled Trial (RCT)
2. Factorial Design
3. Single-Arm Trial
4. Block Design
5. Basket design clinical trial
6. Umbrella Study Design
7. Platform Study Design
8. Adaptive Randomization Design
9. Parallel-Group
10. Pragmatic Trial (Effectiveness)
11. Decentralized/ Remote Trials
12. Cluster Randomized Trial
13. Community trial (cluster-randomized)
14. Field trial (preventive or prophylactic
15. Dose Escalation Design
16. Non-Inferiority Trial
17. Matched Design / Matched Pair Design
18. 3+3 Design
19. Enriched Design
20. N-of-1 trial

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Intent-to-Treat Principle (ITT):

- This principle requires that all subjects be analyzed according to the group to which they were originally assigned, regardless of whether they completed the study or remained on the assigned treatment or not.
- ITT analysis requires continuing to follow and measure subjects who withdraw from treatment or drop out of the study, which may pose difficulties.
- ITT prevents bias by keeping everyone in the final results.
- Subjects often dropped out due to side effects or lack of efficacy.
- Excluding these "failures" leads to overly optimistic results.

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Intent-to-Treat Principle (ITT):

- **Advantage:**
  - ITT analysis is often desired or required by regulatory authorities.
  - It keeps the original sample size, which avoids reducing the study's power to detect differences.
  - It helps keep the "fairness" of the original randomization by ignoring treatment crossover or dropout by subjects who are not responding to treatment.
  - A less biased analysis of treatment effects, as it may reduce the possibility of bias introduced by treatment changes during the study.
- **Disadvantage:**
  - Ignoring issues with treatment adherence or protocol deviations may also obscure some effects; for instance, if a subject assigned to active treatment is accidentally given a placebo during the study, ITT analysis will underestimate the true effect of the treatment.

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Meta-Analyses Design:

- Analyses of existing scientific literature on a particular topic, providing a comprehensive and robust summary of the available evidence.
- Heavily depends on the quality of the included studies.
- Requires:
  1. A structured approach to identify and select relevant studies that address a specific research question.
  2. Predefined criteria and methodology for a systematic review of studies and their analyses.
  3. Use multiple databases to search for studies.
  4. Following established guidelines and methodological standards to ensure the reliability and validity of findings.

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Meta-Analyses Design:

- It involves pooling the data from individual studies to calculate:
  - Summary effect sizes
  - Estimating the overall treatment effect or association between variables.
- Increases statistical power and precision by analyzing a larger sample size than any single study, which can lead to more reliable and generalizable conclusions.
- Draw more robust conclusions about the effectiveness of interventions, the prevalence of conditions, or the associations between variables.

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9. Activities By Stage of Clinical Trial

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8: Randomization

- **Research:** Research is the empirical investigation of the relationship between or among several variables.
- There are three basic goals in any research:
  1. To collect data that are free of bias.
  2. To draw valid conclusions concerning the effects of an independent variable.
  3. To make valid generalizations to populations and settings of interest.

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8: Randomization

- It is one of the fundamental principles of experimental study designs and ensures scientific validity.
- Prevent bias in the results due to subject selection.
- Ensures comparability between groups as most baseline characteristics are similar before randomization.
- Helps to interpret the results regarding the intervention/ experiment group without bias.
- There are various ways to randomize.
- Simple as 'flip of a coin' to use computer software and statistical methods.
  - Simple, Block, Stratified randomizations
  - Minimization randomization
  - Cluster-randomization
  - Equipoise-Stratified randomization
  - The stepped wedge cluster randomized trial

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8: Randomization

Simple Randomization:

- The subjects are randomly allocated to experiment/intervention groups based on a constant probability (1:1)
- This can be performed in multiple ways: 'flip of a coin' or using random tables or numbers.
- Disadvantage:
  - It could result in an imbalance in the number allocated to each group in the prognostic factors (e.g., Age, Severity of symptoms) between groups.
  - It is more challenging in studies with a small sample size.

Block randomization:

- The subjects of similar characteristics are classified into blocks.
- Objective: balance the number of subjects allocated to each group
- It helps to control the balance between the experiment/intervention groups.
- Disadvantage:
  - There is still a component of predictability in the selection of subjects.
  - The randomization of prognostic factors (e.g., Age, Severity of symptoms) is not performed.

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8: Randomization

Stratified randomization:

- Subjects are defined based on certain strata, such as, prognostic factors (e.g., Age, Severity of symptoms).
- The specified population can be randomized within each strata group related to an experiment/intervention group.
- **Advantage**:
  - ❖ Balance between experiment/intervention groups → results in more efficient analysis.
- **Disadvantage**:
  - ❖ The strata factor needs to be measured and determined before the randomization process.
  - ❖ A larger sample size might be needed.
- The sample size will help determine the number of strata that would need to be chosen for a study.
- Strata could be classified as covariates.

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8: Randomization

Minimization randomization:

- Similar to block and stratified randomizations.
- Objective: To minimize the imbalance in each randomized arm based on pre-specified strata.
- A new subject is hypothetically added to each arm, one at a time, and the imbalance score of that arm is calculated based on a pre-determined equation.
- The arms are then weighted so that the subject is more likely (or required) to be randomized to the arm(s) with the lowest imbalance score.
- This technique is particularly useful in small studies with several characteristics of interest where randomization alone may not be sufficient to achieve balance.
- The lower the imbalance scores, the more likely it is that this subject will be randomized to that arm.

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8: Randomization

Minimization randomization:

- **Advantages**: Superior for controlling for multiple prognostic factors compared to stratified randomization.
- **Disadvantages**: More complex to implement, and if not done properly (e.g., fully deterministic), it can lead to selection bias.
- Minimization is frequently utilized in multi-center trials with small sample sizes to ensure valid statistical comparisons.
- Example: Criteria for minimization randomization: Age (< 60, ≥ 60) and Pain Severity score (Low Pain or High Pain).
  - ❖ A new subject aged 65 years old and with a high level of Pain is enrolled.
  - ❖ The algorithm will temporarily assign the subject to each treatment arm, one at a time, and calculate an imbalance score.
  - ❖ Arms that have fewer subjects aged ≥ 60 and a high level of pain will have lower imbalance scores, and it is more likely that this subject will be randomized to that arm.

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8: Randomization

Cluster-randomization:

- Subjects are grouped into clusters—such as Counties, healthcare facilities, or Clinics.
- Each cluster is randomized to a single treatment.
- **Advantage:**
- A more holistic perspective on the effects of interventions can overcome obstacles that impede the traditional approach.
- Minimized Contamination: By randomizing entire groups (e.g., County or Clinic) to a single intervention, it prevents members of the other group from accidentally receiving information about the other group's intervention.
- It can be more cost-effective to conduct surveys or treatments at centralized locations (e.g., a specific Clinic or County) to reduce travel and management overhead.
- This design is more feasible when dealing with real-world settings where it may be logistically challenging or ethically inappropriate to randomize individuals.
- It optimizes statistical power.

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8: Randomization

The stepped wedge cluster randomized trial:

- The design involves random and sequential crossover of clusters from control to intervention until all clusters are exposed.
- The early stepped wedge designs were sometimes described in other terms, such as "waiting list designs" or "phased implementations."
- The design includes an initial period in which no clusters are exposed to the intervention.
- Subsequently, at regular intervals (the "steps") one cluster (or a group of clusters) is randomized to cross from the control to the intervention under evaluation.
- This process continues until all clusters have crossed over to be exposed to the intervention.
- At the end of the study, there will be a period when all clusters are exposed

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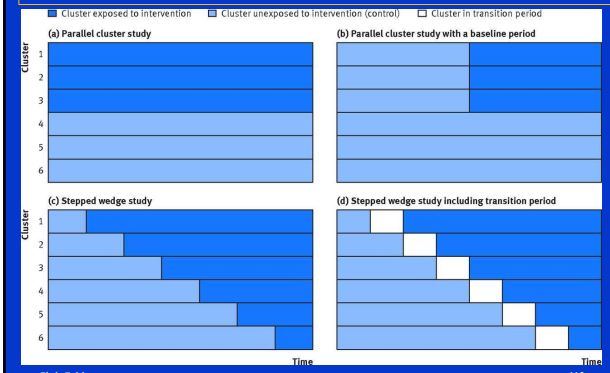
8: Randomization: Stepped wedge cluster randomized trial



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8: Randomization

Equipoise-Stratified Randomization

- The total group of subjects is stratified into subgroups (strata) defined by the treatments they chose to be randomized among, or their clinician is genuinely uncertain which option is best (equipoise).
- The subjects who would consider only one treatment are excluded from the trial.
- The inclusion of the strata factor in the analysis will serve to account for possible differences among the patients associated with the decision about which treatment options are acceptable.
- For example, with a total of 4 treatments, there are 11 possible strata (see the Table below).
- These include
  - a stratum in which the subjects allow randomization to all 4 groups,
  - Four possible strata of those who allow randomization to 3 treatments,
  - Six possible strata of those who allow randomization to 2 treatments

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8: Randomization: Equipoise-Stratified Randomization

- A series of pairwise comparisons will be performed.
- For example, for the Treatment A versus Treatment B comparison, strata numbers 1, 2, 3, and 6 will be pooled (see above for explanation).
- Or for the Treatment C versus Treatment D comparison, strata numbers 1, 4, 5, and 11 will be pooled.
- The strata factor will be eliminated if the interaction of strata and Treatment and the main effect of the strata are not significant.

		Stratum	ES%	N per option	Total N
1	Any of the 4 Medications	A,B,C,D	30%	34	136
2	Any of the 3 Medications	A,B,C	10%	15	45
3		A,B,D	10%	15	45
4		A,C,D	10%	15	45
5		B,C,D	10%	15	45
6	Any of the 2 Medications	A,B	5%	11 *	22/23
7		A,C	5%	11*	22/23
8		A,D	5%	11*	22/23
9		B,C	5%	11*	22/23
10		B,D	5%	11*	22/23
11		C,D	5%	11*	22/23

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