Randomized Experimental Design

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Randomized Experimental Designs

Three Design Principles:

1. Replication

2. Randomization

3. Blocking

Randomized Experimental Designs

1. Replication

- Allows estimation of *experimental error,* against which, differences in treatments are judged.

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Replication

- Allows estimation of *expt'l error,* against which, differences in trts are judged.

Experimental Error:

- Measure of random variability.
- Inherent variability between subjects treated alike.

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True Replication

- Each treatment is applied to several experimental units.
- Multiple measurements obtained on each experimental unit is <u>not</u> true replication. This is referred to as subsampling.

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If you don't *replicate* . . .

. . . You can't *estimate*!

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Example

- In a clinical trial investigating a new therapy for seizure control in epileptics, **50** patients are given (randomized to) the new (experimental) therapy and **50** are given the standard therapy.

- Each treatment is replicated **50** times.

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To ensure the ***validity*** of our estimates of treatment effects we rely on ...

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. . . Randomization

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2. Randomization

- leads to **unbiased** estimates of *treatment effects*

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Randomization

- leads to **unbiased** estimates of *treatment effects*
- *i.e.*, estimates free from systematic differences due to uncontrolled variables

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Without randomization, we may need to adjust analysis by

- stratifying
- covariate adjustment

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Example

- In our epilepsy example, we would ***randomly*** assign ½ the patients to the new drug and ½ the patients to the standard drug.

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3. Blocking

- Arranging subjects into similar groups (blocks) to account for systematic differences.

- e.g., clinic site, gender, or age.

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- **Blocking**

- leads to increased *sensitivity* of statistical tests by *reducing* expt'l error.

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Blocking

- **Result**: More *powerful* statistical test

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Blocking

Example

- To achieve the desired sample size of 50 per treatment group, we may need to conduct the epilepsy study at 10 different study centers.
- Each center would be considered a ***block***.

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Blocking

- There would be a separate randomization plan at each center (block).
- Study centers are almost always considered **blocks** in clinical trial designs, since it is expected that systematic differences exist among them.

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Blocking

Example

- Animal litters are often viewed as blocks containing several similar experimental units (eu), i.e., siblings.

- A complete replication of the treatments would normally occur within a litter (*block*).

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Summary:

- **Replication** – allows us to estimate **Expt'l Error**
- **Randomization** – ensures **unbiased** estimates of treatment effects
- **Blocking** – increases **power** of statistical tests

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Three Aspects of Any Statistical Design

- *Treatment* Design
- *Sampling* Design
- *Error Control* Design

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1. Treatment Design

- How many *factors*
- How many *levels* per factor
- *Range* of the levels
- Qualitative vs quantitative factors

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Example 1 Headache Relief

Suppose we wish to compare the effects of popular analgesics for reducing headaches.

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Example 1 Headache Relief

Suppose we wish to compare the effects of popular analgesics for reducing headaches.

Factor – Type of Analgesic (Number of levels = 3)

– Treatment 1: Aspirin (Qualitative levels)

– Treatment 2: Tylenol

– Treatment 3: Placebo

Example 2 Dose Response

Suppose we wish to compare the pharmacokinetics of a new compound for treating pneumonia in the elderly.

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Example 2 Dose Response

Suppose we wish to compare the pharmacokinetics of a new compound for treating pneumonia in the elderly.

Design:

Four groups of dogs (3 in each group) with induced pneumonia are randomly assigned to one of the 4 dose levels: 0, 10, 100, 1000 mg

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Example 2 . . .Dose Response

The treatment ***factor*** is dosage.

The treatment ***levels*** are the dosages:

0, 10, 100, 1000

Dosage is an example of a ***quantitative*** factor

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Three Aspects of Any Statistical Design

- *Treatment* Design
- ***Sampling* Design**
- *Error Control* Design

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2. Sampling or Observation Design

Determines the level at which observations are made.

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2. Sampling or Observation Design

Is observational unit (OU) = experimental unit ?

or,

is there *subsampling* of EU ?

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Examples of Subsampling (OU)

Example 1: Blood Pressure Study (OU $\neq$ EU)

- Resting blood pressure may be measured twice in a 5-minute interval.

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Examples of Subsampling (OU)

Example 2: Study of New Antibiotic (OU $\neq$ EU)

- A microbiologist may measure bacterial concentrations from several areas on a petri dish.

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Three Aspects of Any Statistical Design

- *Treatment* Design
- *Sampling* Design
- ***Error Control* Design**

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3. Error Control Design

- concerned with actual *arrangement of the expt'l units*
- How treatments are assigned to eu's

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Error Control Design

Goal: Decrease experimental error

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Error Control Design

Examples:

- Completely Randomized Design (CRD)
- Randomized Complete Block Design (RCB)
- Cross-Over and Repeated Measures Designs

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Error Control Design

- **Completely Randomized Design (CRD)**
  - All subjects have an *equal* chance of receiving any particular treatment
  - The headache relief study uses a completely randomized design.

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Error Control Design

- **Randomized Complete Block Design (RCB)**
  - Groups of similar subjects (blocks of eu's) are formed
  - Treatments are assigned completely at random to subjects within blocks
  - The epilepsy study uses a RCB design where (centers = blocks)

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Error Control Design

- **Cross-over Design**
  - Each subject receives all treatments in a pre-determined order.
  - Subjects are randomized to sequences of trts
  - Washout period separates treatment periods

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- **Cross-over Design**

Sequence	Period 1	Washout	Period 2
AB	Trt A	- - -	Trt B
BA	Trt B	- - -	Trt A

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Error Control Design

- **Repeated Measures Design**
  - Each subject is repeatedly measured over time.
  - Time and its interaction with treatment become factors to be studied.
  - Missing values can become major issue in analysis

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Example: Repeated Measures

- Study effect of ***d=3*** drugs on heart rate
- At study start, ***n=30*** subjects randomly assigned to each drug
- After administration, heart rate measured every 5 minutes for a total of ***t=24*** times

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Summary of Design Components:

- **Treatment Design** – Arrangement of treatments
- **Sampling Design** – Nature of observations
- **Error Control** – How are trt's randomized to eu
  - CRD
  - RCB
  - Crossover / Repeated Measures

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Threats to Study Validity:

- **Bias**
- **Confounding**
- **Regression to the Mean**

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Bias

- Any effect that produces results that depart systematically from the true value.
- Has effect on association between exposure (i.e., treatment) and outcome:
  - Creates apparent associations
  - Obscures real associations
  - Usually can’t be corrected with analysis

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Confounding Variable

- A variable that is associated independently with both exposure and outcome.
- A treatment effect may be masked or totally indistinguishable from the effect of a confounder

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Confounding

- Has effect on association between exposure and outcome:
  - The association is real, but it is not due to cause and effect
  - Like bias, confounding can also obscure real associations
  - Can be addressed with analysis

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Regression to the Mean

- Tendency of an observation that is extreme on its initial measurement to be closer to normal (the mean) on subsequent measurement.

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Addressing Regression to the Mean:

- Include concurrent controls
- If a cut-point criterion used for entry, require that criterion be met on two consecutive measurements.

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Combating Threats to Study Validity:

- **Randomization**
- **Masking**
- **Concurrent Controls**

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Randomization

- principal method available for reducing selection bias
- Tends to balance groups with respect to known and unknown confounders

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Masking (Blinding)

- Reduces assessment bias
- Three types of masking:
    - single
    - double
    - triple

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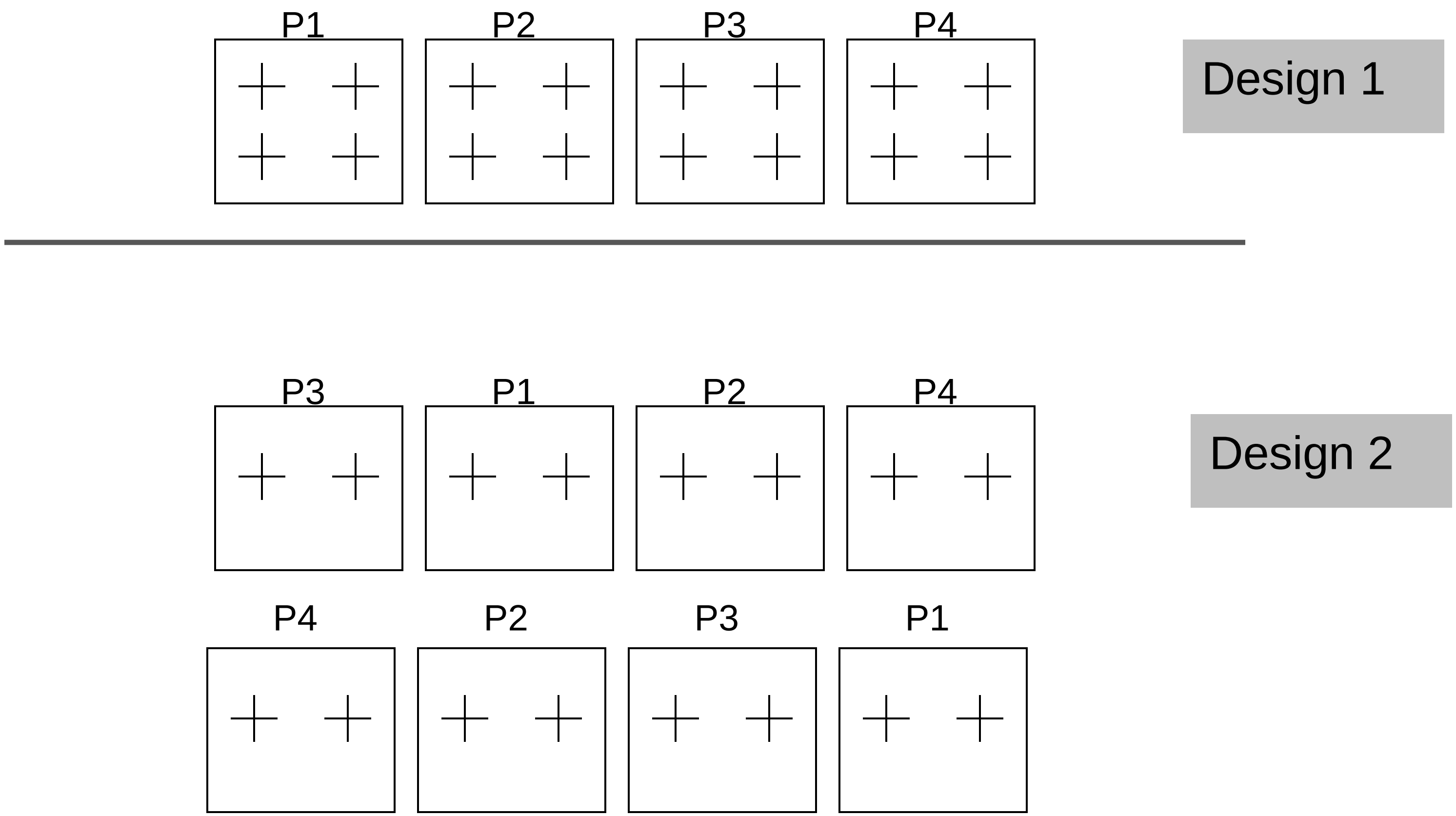
Concurrent Controls

- Resource intensive method, but very effective at reducing bias
- Eliminates confounding of treatment with calendar time
- Facilitates use of randomization

Four Design Scenarios



Four Design Scenarios