Objectives of the Session

- Define types of research approach
- Identify key considerations for selecting study approach
- List steps to select study design
- List and define types of study design in research
- Define unique characteristics of different types of study designs
- List advantages and disadvantages of different types of study designs
- Analyze and interpret data from cohort, cross-sectional, and case-control designs
- Demonstrate how to select study design for an identified research question
## Components of a Study Protocol

<table>
<thead>
<tr>
<th>Element</th>
<th>Purpose</th>
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</thead>
<tbody>
<tr>
<td>Research questions</td>
<td>What questions will the study address?</td>
</tr>
<tr>
<td>Significance (background)</td>
<td>Why are these questions important?</td>
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<tr>
<td><strong>Design</strong></td>
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<tr>
<td>Time frame</td>
<td>How is the study structured?</td>
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<tr>
<td>Approach</td>
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</tr>
<tr>
<td>Subjects</td>
<td>Who are the subjects and how will they be selected?</td>
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<tr>
<td>Selection criteria</td>
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<tr>
<td>Sampling design</td>
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<tr>
<td>Variables</td>
<td>What measurements will be made/recorded?</td>
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<tr>
<td>Predictor variables</td>
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<tr>
<td>Confounding variables</td>
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<tr>
<td>Outcome variables</td>
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<tr>
<td>Statistical issues</td>
<td>How large is the study and how will it be analyzed?</td>
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<tr>
<td>Hypotheses</td>
<td></td>
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<tr>
<td>Sample size</td>
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<tr>
<td>Analytic approach</td>
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</tbody>
</table>

## Types of Research

**“Primary, Secondary, and Tertiary Research”**

<table>
<thead>
<tr>
<th>Research Approach</th>
<th>Study Plan</th>
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</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Collect and analyze new data</td>
</tr>
<tr>
<td>Secondary</td>
<td>Analyze existing data</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Review and synthesize the literature</td>
</tr>
</tbody>
</table>
# Key Considerations

<table>
<thead>
<tr>
<th>Study Approach</th>
<th>Key Questions to Ask</th>
</tr>
</thead>
</table>
| • Collection and analysis of new data | • What are possible source populations?  
  • Will it be possible to recruit enough participants? |
| • Analysis of existing data  | • What are possible sources of usable data files?  
  • What questions can be explored with the available data? |
| • Review of the literature   | • Does the researcher have access to adequate library resources?  
  • Can the researcher reasonably expect to acquire all of the needed articles? |

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## Analyze published articles
- Collect new data
- Use existing data
- Review literature
- Meta-analysis

## Analyze population-level data
- Case series
- Cross-sectional study
- Case-control study
- Cohort study
- Experimental study
- Qualitative study

## Analyze individual-level data
- Ecological study
  - Case series
  - Cross-sectional study
  - Case-control study
  - Cohort study
  - Experimental study
Common Study Designs

1. Experimental studies
2. Cohort studies
3. Case control studies
4. Cross-sectional surveys
5. Case series
6. Correlational (ecological) studies
7. Systematic Reviews / meta-analyses
8. Qualitative studies

Summary of Study Approaches

<table>
<thead>
<tr>
<th>Study Approach</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review/meta-analysis</td>
<td>Synthesize existing knowledge</td>
</tr>
<tr>
<td>Correlational (ecological) study</td>
<td>Compare average levels of exposure and disease in several populations</td>
</tr>
<tr>
<td>Case series</td>
<td>Describe a group of individuals with a disease</td>
</tr>
<tr>
<td>Cross-sectional survey</td>
<td>Describe exposure and/or disease status in a population</td>
</tr>
<tr>
<td>Case-control study</td>
<td>Compare exposure histories in people with disease (cases) and people without diseases (controls)</td>
</tr>
<tr>
<td>Cohort study</td>
<td>Compare rates of new (incident) disease in people with different exposure histories or follow a population forward in time to look for incident diseases</td>
</tr>
<tr>
<td>Experimental study</td>
<td>Compare outcomes in participants assigned to an intervention or control group</td>
</tr>
<tr>
<td>Qualitative study</td>
<td>Seek to understand how individuals and communities perceive and make sense of the world and their experiences</td>
</tr>
</tbody>
</table>
Considerations when choosing a Study Design

- A good clinical study starts with a good question based on good hypothesis that is based on good and comprehensive review of the available evidence from pre-clinical and clinical data.

- **Type of design depends on the question to be answered**
  - Each research question requires a judgment about which design is the most efficient way to get a satisfactory answer.
  
  A common sequence for studying a topic:
  - **Descriptive studies**
    - How common is estrogen treatment in women after menopause?
  - **Analytic studies** to evaluate associations and discover cause-and-effect relationships
    - Is taking estrogen after menopause associated with lower risk of CHD?
  - **Clinical trial** to establish the effects of an intervention
    - Does hormone treatment alter the incidence of CHD?

### Steps for Selecting Study Design

```
Did investigator assign exposures?

Yes

Experimental study

Random allocation?

Yes

Randomised controlled trial

No

Non-randomised controlled trial

No

Observational study

Comparison group?

Yes

Analytical study

Direction?

Yes

Descriptive study

No

Cohort study

Case-control study

Cross-sectional study
```

Grimes & Schulz, 2002
**Hierarchy of Study Design**

- Case reports
- Case series
- Ecologic studies
- Cross-sectional studies
- Case-control studies
- Cohort studies
- Randomized controlled trials

**Experimental Design**

"Randomized Clinical Trials"

- **Definition:**
  - A clinical trial is a prospective study comparing the effect of intervention against a control in humans.

- **Phases:**
  - Most trials that involve new drugs go through a series of steps:
    - Experiments in the laboratory
    - Once deemed safe, go through 1-4 phases
      - Phase I
      - Phase II
      - Phase III
      - Phase IV
Phases of Clinical Trials

• **Phase I**: Small group to evaluate safety, determine safe dosage range and identify side effects [20-100 subjects, followed for months]

• **Phase II**: Large group to confirm efficacy, monitor side effects and further evaluate safety [several 100 subjects followed for months up to 2 years]

• **Phase III**: Larger group to fulfill all of Phase II objectives and compare it to other commonly used treatment and collect data that will allow it to be used safely [i.e., definitive comparative trial. Designed to determine efficacy and its role in clinical practice] [several 1000s subjects, followed for 1-4 years]

• **Phase IV**: Done after drug has been marketed - studies continue to test drug to collect data about effects in various populations and side effects from long term use.

Uses of Randomized Trials

• Evaluate new drug and other treatment of disease
  – Clinical trial
• Test new health and medical care technology
• Assess new program for screening and early detection
• Assess new ways of organizing and delivering health services
Statement of the Research Questions in Clinical Trials

• Example:
  – **Research question:**
    • Is intensive therapy, including more frequent insulin injections and blood glucose monitoring, superior to standard therapy for diabetes mellitus?
  – **Assess treatment efficacy**
    • End point
      – Measure length of survival or percent survived
      – Measure quality of life
      – Complication rate
      – Recurrent symptoms
  – **Possible outcome measures**
    • Percentage of patients surviving following the treatment
    • Patients ability to maintain an active lifestyle
    • The risk of having a major complication from treatment
    • The risk of experiencing one of the vascular events associated with diabetes mellitus
    • Measurement of hemoglobin A1C
      – An indicator of the degree to which blood insulin levels have risen over the previous month
    • Blood glucose levels

Intervention Trials – General Structure

• Researcher selects and randomly assigns individuals (or groups) to treatment or non-treatment groups.
• Participants are followed forward in time.
• Incidence of outcome (i.e., disease, survival, death) are compared between groups.
Factorial Design

For example, the WHI. Women separately assigned to HRT or placebo (ignoring diet) and to low fat diet or not (ignoring HRT).

The goal here is mostly efficiency, if it works, get 2 trials for the price of one.

Summary

• Advantages
  – Gold standard for evaluating efficacy of therapeutic or preventive measures.
  – Provides strongest evidence for causality.
  – Reduces influence of other determinants of exposure and outcome (confounding) due to randomization.

• Disadvantages
  – Expensive, time-consuming.
  – Subjects may not be representative of all people who might eventually be put on the treatment.
  – Ethical considerations – believe new treatment is at least as good as old treatment or placebo.
Observational Studies: Cohort Study

- Cohort studies begin with identification of a population, assessment of exposure (e.g., lipid or BP levels)
- Follow-up to the occurrence of outcomes (CHD events)
- **Useful for:**
  - Finding causes and estimating incidence of disease
  - Identification of risk factors
  - Following natural history, determining prognosis

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**Advantages and Disadvantages of Cohort Studies**

**Advantages:**
- Can establish population-based incidence
- Accurate relative risk (risk ratio) estimation
- Temporal relationship can be inferred (prospective design)
- Can be used where randomization is not possible
- Magnitude of a risk factor’s effect can be quantified
- Selection and information biases are decreased
- Multiple outcomes can be studied (smoking, lung cancer, COPD, larynx cancer)

**Disadvantages:**
- Lengthy and expensive; and may require very large samples
- Not suitable for rare diseases and for diseases with long-latency
- Non response, migration and loss-to-follow-up biases
- Sampling, ascertainment and observer biases are still possible
Observational Studies: Case-Control Study

• Compare a group with the outcome to a group without the outcome
• Controls must be free of outcome and susceptible to outcome
• Steps:
  – Identify source population
  – Identify cases
  – Identify controls
  – Determine the exposure in the cases and the controls
  – Information about exposure is determined after the observation of the outcome

• Designed to assess the association between disease occurrence and an exposure

• **Does not prove causality**
• Can provide *suggestive evidence* of a causal relationship

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Observational Studies: Case-Control Study (Cont.)

• Can be carried out in a shorter time with a smaller sample size (less expensive)
• Only practical approach for identifying risk factors for rare diseases
• Relies on historical information to obtain exposure status (and information on confounders)
• **Useful for:** Hypothesizing causes of disease and Identifying risk factors
Advantages of Case-Control Studies

**Advantages**
- Inexpensive, easy and quick studies
- Multiple exposures can be examined
- Rare diseases and diseases with long latency can be studied
- Used when randomization is unethical (alcohol/ pregnancy outcome)
- Efficient in the study of rare disease and more feasible

**Disadvantages**
- Subject to bias (selection, recall, misclassification)
- Temporal relationship is not clear
- Multiple outcomes cannot be studied

Observational Studies-- Cross-Sectional Study

- Both exposure and outcome are determined *simultaneously* for each subject.
  - Snapshot of the population at a certain point in time
  - A slice through the population, capturing levels of cholesterol and evidence of CHD at the same time
  - Cases are PREVALENT cases

- Example
  - Research question: relationship of increased serum cholesterol level to ECG evidence of CHD
    - What is the exposure [independent variable]? What is the outcome [dependent variable]?
**Observational Studies: Cross Sectional Study**

- Examines association between two factors (Example: an exposure and a disease state) assessed at a single point in time.
- **Example**: Prevalence of a known condition, association of risk factors with prevalent disease.
- **Useful for**:
  - Disease description
  - Diagnosis and staging
  - Describing disease processes, mechanisms
- **Conclusions**: Associations found may suggest hypotheses to be further tested, but are far from conclusive in proving causation
- **Advantages**: cheap and simple and ethically safe

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**Case Reports and Case Series**

- Provides evidence about a treatment or adverse reaction
- Often with significant detail not available in other study designs
- May generate hypotheses, help in designing a clinical trial.
- Several reports forming a “case series” can help establish efficacy of a drug, or through adverse reports, cause its demise (example: statin fatal cases of rhabdomyolysis).
Studies making observations on groups of individuals

- Studies using group level data are usually called **ecological studies**
- Two main weaknesses:
  - ecological fallacy
  - very limited control of confounding
- One (sometime) strength:
  - some exposures may be best measured at area or group level

Ecological Fallacy

- Cannot tell whether the relationship between the predictor and the outcome at the group level holds at the individual level
- Example: Are the individuals in the cohorts eating more saturated fat the same individuals experiencing more CHD deaths?
- Sometimes called confounding at the group level
**Systematic Review**

**What is a Systematic Review?**

“A review that is conducted according to clearly stated, scientific research methods, and is designed to minimize biases and errors inherent to traditional, narrative reviews.”

**Significance of Systematic Reviews**

- The large amount of medical and nursing literature requires clinicians, nurses and researchers alike to rely on systematic reviews in order to make an informed decision.

- **Systematic Reviews minimize bias.** “A systematic review is a more scientific method of summarizing literature because specific protocols are used to determine which studies will be included in the review.”
Systematic Reviews is Necessary

• “The volume of published material makes it impractical for an individual clinician to remain up to date on a variety of common conditions.

• This is further complicated when individual studies report conflicting conclusions, a problem that is prevalent when small patient samples and retrospective designs are used.”

Characteristics of Systematic Reviews

• Formulates a Question
• Clearly stated title and objectives
• Comprehensive strategy to search for relevant studies (unpublished and published)
• Explicit and justified criteria for the inclusion or exclusion of any study
• Refines the search by applying predetermined inclusion and exclusion criteria
• Clear presentation of characteristics of each study included and an analysis of methodological quality
• Comprehensive list of all studies excluded and justification for exclusion
Characteristics of Systematic Reviews (cont.)

- Extracts the appropriate data and assess their quality and validity
- Clear analysis of the results of the eligible studies
  - statistical synthesis of data (meta-analysis) if appropriate and possible;
  - or qualitative synthesis
- Synthesizes, interprets, and reports data
- Structured report of the review clearly stating the aims, describing the methods and materials and reporting the results

- Sources: Cochrane Collaborative
  - www.Cochrane.org

Meta-Analysis

- Meta-analysis is a statistical technique for combining the results of independent, but similar, studies to obtain an overall estimate of treatment effect.
  - While all meta-analyses are based on systematic review of literature, not all systematic reviews necessarily include meta-analysis.

- If a meta-analysis will be included in a systematic review, an experienced statistician or an epidemiologist should be consulted during all phases of the study.
Steps of Meta-analysis

• Define the Research Question
• Perform the literature search
• Select the studies
• Extract the data
• Analyze the data
• Report the results

• Sources: Cochrane Collaborative
  – www.Cochrane.org

Meta-analysis of radiotherapy for early breast cancer

• Meta-analysis of 40 RCTs
• Central review of individual-level data; N = 20,000
• Breast cancer mortality reduced (20-yr ARR 4.8%; P = .0001)
• Mortality from other causes increased (20-yr ARR -4.3%; P = 0.003)
