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• You may submit questions anytime during this live webinar using the chat feature, if time remains, questions will be addressed either during or at the end of the presentation.
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In research, types of studies depend on the purpose of the study, data collection strategy, and other factors.

**Types of Study:**

I. **Observational study (Cohort Study)**
   1.1 Cross-sectional study
   1.2 Case-control study
   1.3 Observational study

II. **Non-randomized Controlled Trial**
   *Randomized Controlled Trial (Clinical Trial)*
   - Phase I
   - Phase II
   - Phase III
   - Phase IV

III. **Systematic Review and Meta-analysis**

[Diagram showing types of observational studies with Prospective Observational Study and Retrospective Observational Study as branches, Weak and Stronger Evidence indicators]
**HIERARCHY OF RESEARCH EVIDENCE**

1. Systematic reviews and meta-analysis
2. Randomized controlled trial (clinical trial)
3. Non-randomized controlled trials
4. Case-control or cohort studies
5. Systematic reviews for descriptive and qualitative or cross-sectional studies
6. Single descriptive, qualitative or cross-sectional study
7. Opinion of authorities or report of expert committees
DIAGRAM 1
OVERVIEW OF TEST HYPOTHESES

Outcome

Is the outcome continuous, categorical, or survival data?

Continuous outcome

Is the continuous outcome normally distributed?

Continuous outcome is normally distributed.

Continuous outcome is NOT normally distributed.

Appropriate tests are:
- One sample t-test
- Two sample t-test
- Paired t-test
- ANOVA
- ANCOVA
- Pearson’s correlation
- Linear regression

Appropriate tests are:
- Wilcoxon rank sum test
  (equivalent to two sample t-test)
- Wilcoxon signed rank test
  (equivalent to paired t-test)
- Kruskal-Wallis test
  (equivalent to ANOVA)
- Spearman’s correlation

Categorical outcome

Appropriate tests are:
- Chi-square ($\chi^2$) test
- Fisher’s exact test
- McNemar’s $\chi^2$ test
- Logistic regression

Survival outcome

Appropriate tests are:
- Survival analysis
- Cox proportional hazards analysis

ANOVA – Analysis of variance
ANCOVA – Analysis of covariance

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DIAGRAM 2: TEST HYPOTHESES FOR CONTINUOUS OUTCOME

Continuous Outcome

Is the continuous outcome normally distributed?

Continuous outcome is normally distributed. (Parametric Method)

Is the outcome independent or dependent variable?

Objective 1: To compare the means of the outcome
   - One sample t-test (one group)
   - Two sample t-test (two groups)
   - ANOVA (three or more groups)
   - ANCOVA (three or more groups controlling by another variable)

Objective 2: To quantify the relationship between two continuous outcomes
   - Pearson’s correlation

Objective 3: To predict the continuous outcome by other variables
   - Linear regression analysis

Objective 4: To compare the means of the outcome measured before vs. after the intervention
   - Paired t-test (before vs. after)

Objective 5: To compare the means of the outcome measured more than twice repeatedly over time
   - Repeated measures ANOVA

Continuous outcome is NOT normally distributed. (Non-Parametric Method)

Is the outcome independent or dependent variable?

Objective 6: To compare the means of the outcome
   - Wilcoxon rank sum test

Objective 7: To quantify the relationship between two continuous outcomes
   - Spearman’s correlation

Objective 8: To compare the means of the outcome measured before vs. after the intervention
   - Wilcoxon signed rank test (before vs. after)

Objective 9: To compare the means of the outcome measured more than twice repeatedly over time
   - Kruskal – Wallis test

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Diagram 3
Test Hypotheses for Categorical Outcome

Categorical Outcome

Is the outcome independent or dependent variable?

Independent variable

Is one of the numbers in a 2x2 table less than 5?

Yes

Objective 10: To compare the proportions from two independent samples when all of the numbers in a 2x2 table is less than 5
  • Fisher’s exact test

No

Objective 11: To compare the proportions from two independent samples when all of the numbers in a 2x2 table is greater than or equal to 5
  • Chi-square ($\chi^2$) test

Dependent variable

Objective 13: To compare the proportions from two dependent samples (or a matched pair data) test
  • McNemar’s $\chi^2$ test

Objective 12: To predict the probability of success (or an event) by other variables
  • Logistic regression analysis

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Diagram 4
Test Hypotheses for Survival Outcome

1. Survival Outcome (Time to event)
   - Is there any adjustment for the other variable(s)?
     - Yes
       - Objective 14: To compare the chance to survive during a specific time period between two groups without an adjustment for the other variable(s)
         - Cox Proportional Hazard Regression
     - No
       - Objective 15: To compare the chance to survive during a specific time period between two groups without an adjustment for the other variable(s)
         - Log-rank test
       - Objective 16: To predict a chance to survive during a specific time period
         - Survival analysis

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BIASES IN RESEARCH

Why do we need to know about bias?

- Understanding research bias allows readers to critically and independently review the scientific literature and avoid treatments which are potentially harmful or lack of true benefit.
- Bias can occur in the planning, data collection, analysis, and publication phases of research.
- A thorough understanding of bias and how it affects study results is essential for the practice of evidence-based medicine.

What is Bias?

- A bias is a systematic error, or deviation from the truth in results or inferences.
- Biases can operate in either direction: Different types of bias can lead to underestimation or overestimation of the true intervention effect.

BIASES IN RESEARCH

Before Bias occurs before starting the study
Selection Bias
Sampling Bias

During Bias occurs as the study proceeds
- Placebo Effect
- Recall Bias
- Hawthorne Effect

After Bias occurs as the study is completed
- Detection Bias
- Loss to follow up Bias
- Reporting Bias
### BIAS OCCURS BEFORE STARTING THE STUDY

<table>
<thead>
<tr>
<th>Source of Bias</th>
<th>Type of Bias</th>
<th>Strategies for Reducing Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Treatment and control patients differ in prognosis, in demographic, in socioeconomic status, in hereditary component, and/or other factors</td>
<td>Selection bias</td>
<td>- Randomization</td>
</tr>
<tr>
<td>- Systematic difference in baseline characteristics between the groups that are compared</td>
<td></td>
<td>- Statistical adjustment for prognostic factors in the analysis data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Randomize with stratification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Matching</td>
</tr>
</tbody>
</table>

**Sources:**
# BIAS OCCURS BEFORE STARTING THE STUDY

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<th>Strategies for Reducing Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>The study subjects do not represent the population of interest</td>
<td>Sampling bias</td>
<td>▪ Choose the study subjects to represent the population of interest</td>
</tr>
<tr>
<td>Systematic difference between groups in how outcomes are assessed</td>
<td>Detection bias</td>
<td>▪ Make sure the outcomes are measured the same way such as use the same lab or same instrument for both groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Blind the data collectors, nurses, interviewers etc.</td>
</tr>
</tbody>
</table>

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<th>Strategies for Reducing Bias</th>
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<tbody>
<tr>
<td>Patients believe or felt improvement in health or behavior not attributable to a medication or invasive treatment</td>
<td>Placebo effect</td>
<td>Blind the patients</td>
</tr>
<tr>
<td>Patients could not recall what they have been exposed to or which treatment they received</td>
<td>Recall bias</td>
<td>Rely on medical records or well documented evidence rather than rely on the patient’s memory</td>
</tr>
<tr>
<td>Patients change their behavior because they are being studied</td>
<td>Hawthorne Effect</td>
<td>Blind the patients</td>
</tr>
</tbody>
</table>

## BIAS OCCURS AS THE STUDY IS COMPLETED

<table>
<thead>
<tr>
<th>Source of Bias</th>
<th>Type of Bias</th>
<th>Strategies for Reducing Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bias occurs as the study has already completed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Loss to follow-up</td>
<td>Loss to follow-up bias</td>
<td>Make sure patients complete the study</td>
</tr>
<tr>
<td>▪ Stop the study early because of a large effect</td>
<td>Bias due to early stopping</td>
<td>Complete study as initially planned unless there is a life threatening side effect</td>
</tr>
<tr>
<td>▪ Choose to report those analyses with statistically significant differences between treatment and control groups</td>
<td>Reporting bias or selective reporting bias</td>
<td>Have a third party to analyze the data and form a Data Monitoring Committee</td>
</tr>
</tbody>
</table>

**Sources:**
**RANDOM ERROR AND VALIDITY**

**Bias:**
- A systematic error in the design, recruitment, data collection or analysis that results in a mistaken estimation of the true effect of the exposure and the outcome.

**Confounding:**
- A situation in which the effect or association between an exposure and outcome is distorted by the presence of another variable.

Accuracy describes how close a measurement is to the true value of a given quantity.

Precision describes the reproducibility of the measurement.

Systematic errors cause by lack of controlling of biases:

1. **Selection Bias**: Non-random assignment to study group commonly happens in clinical trial

2. **Recall Bias**: Knowledge of presence of disorder alters recall by subjects commonly happens in retrospective study and case-control study.

3. **Sampling Bias**: Subjects are not representative relative to general population; therefore, results are not generalizable.
Systematic errors cause by lack of controlling of biases: (continued)

4. **Lead-time Bias**: Information gathered at an inappropriate time. Early detection is mistakenly lead to increasing survival time.

5. **Procedure Bias**: Subjects in different groups are not treated the same e.g. more care given to patient in the treatment group or stimulating greater compliance in the treatment group more than control group

6. **Hawthorn Effect**: Subjects change their behaviors to improve the outcome. This could be considered as a confounding factor.
Lead-time Bias: Bias in Survival Analysis

- Early detection is mistakenly lead to increasing survival time.
- Lung cancer-specific survival is measured from the time of diagnosis of cancer to the time of death.

LEAD-TIME BIAS

BIAS IN META-ANALYSIS: FUNNEL PLOT

Meta-analysis:
- Meta-analysis is a quantitative, formal, epidemiological study design used to systematically assess previous research studies to derive conclusions about that body of research.

Each dot represents sample size and effect of a treatment or exposure from a published article.

“A funnel plot is used as a way to assess publication bias in meta-analysis.”

FIGURE A1. Funnel plot for meta-analysis anxiety and risk for incident cognitive impairment in the community. \( P = 0.47 \) for Egger’s regression intercept.
FIGURE A2. Funnel plot for meta-analysis anxiety and risk for incident dementia in the community. $P = 0.88$ for Egger’s regression intercept.
FIGURE A3. Funnel plot for meta-analysis anxiety and risk for conversion to dementia in memory-clinics. P = 0.46 for Egger’s regression intercept.
Confounding:

- A situation in which the effect or association between an exposure and outcome is distorted by the presence of another variable such as smoking.

Sources:
- https://www.slideshare.net/AndrewMertens1/422-confounding-classical-approach
- https://www.slideshare.net/IllllIkrAmKhanIllll/bias-and-confounding-75591012
PLACEBO EFFECT AND HAWTHORN EFFECT

- **Placebo effect** is the phenomenon whereby a patient’s symptoms can be alleviated by an ineffective treatment; most likely because the individual expects or believes that the treatment will work.

- **Hawthorn effect** is the phenomenon whereby a patient change behavior after they know that they are randomized to a experimental group. For example, diabetic patients started to exercise after they know they are randomized into the experimental treatment group to test a new drug to treat diabetes.

Methods to Prevent Biases:

1. Randomization: To avoid selection bias
2. Blinding: To avoid procedure bias and placebo effect
3. Crossover study: To avoid underlying differences among patients in treatment and control group
Methods to Prevent Biases: (Continued)

4. Use the same method or instrument to measure the outcome
5. Evaluate confounding factors in the analysis
6. Rely on medical records or reliable documents rather than patient’s memory to avoid recall bias
**Randomization**: To provide equal opportunity to every patient to be in the investigational or control group and avoid selection bias. Every patient recruited to participate in a clinical trial must have an equal opportunity to be assigned to an investigational or control group.

**BLINDING**

**Blind or blinded experiment**

- Blinding is a scientific experiment where some of the persons involved are prevented from knowing certain information that might lead to conscious or unconscious bias on their part, invalidating the results.
- Blinding conceals the assignment of receiving experimental treatment or control the patients from the certain groups of people.

BLINDING

Five groups of people that should be blinded:

<table>
<thead>
<tr>
<th>Group</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>To avoid placebo effects</td>
</tr>
<tr>
<td>Clinicians</td>
<td>To prevent differential administration of therapies that affect the outcome of interest</td>
</tr>
<tr>
<td>Data collectors</td>
<td>To prevent bias in data collection</td>
</tr>
<tr>
<td>Adjudicators of outcome</td>
<td>To prevent bias in decisions about whether or not patient has had an outcome of interest.</td>
</tr>
<tr>
<td>Data analysts</td>
<td>To avoid bias in decisions regarding data analysis.</td>
</tr>
</tbody>
</table>

CROSS OVER CLINICAL TRIAL

Randomization

Treatment Group

Control Group

Wash out period

USING THE MEDICAL LITERATURE TO PROVIDE OPTIMAL PATIENT CARE

Evidence Based Medicine follows the following steps:

1. Formulate a clear clinical question from a patient's problem
2. Search the literature for relevant clinical articles
3. Evaluate (critically appraise) the evidence for its validity and usefulness
4. Implement useful findings in clinical practice

Identify your problem
Define a structured question
Find the best evidence (original primary study or evidence summary)
How valid is the evidence?
What are the results?
How should I apply the results to patient care?

Sources:
“External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision.”

THANK YOU!