INTRODUCTION & MEASUREMENT IN CLINICAL RESEARCH

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Pediatrics, Pediatric Cardiology
Emergency Medicine, Ped Emergency
Family Medicine
Section of Clinical Epidemiology and Biostatistics
Faculty of Medicine, Ramathibodi Hospital, Mahidol University
http://www.ceb-rama.org or http://med.mahidol.ac.th/ceb
3 modules in 1 Course

1. Clinical Epidemiology (mandatory)
2. Biostatistics for research (mandatory)
3. English for presentation and publication (optional)
Resident Basic Clinical Epidemiology & Biostatistics Course 2015:

<table>
<thead>
<tr>
<th>Date</th>
<th>Topic</th>
<th>Lecturer</th>
<th>Location</th>
<th>VDO</th>
<th>Handout</th>
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<td>1 06 Aug 2015</td>
<td>Introduction and measurement in Clinical Research</td>
<td>Dr. Sakda Arj-ong Vallipakorn, MD., PhD.</td>
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<td>Case Series, Descriptive, and Cross-Sectional Studies</td>
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<td>Case-Control Study</td>
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Agreement Criteria/Rules

- Must attend 70% of Mandatory class (Eligible for final examination)
  - Examination
  - Fast Track of consultation services
  - Received certify of EBM Certification from faculty of Medicine
- Examination
  - Divided in 2 Part (Passing > 60% in 2 attempts)
  - Clinical Epidemiology 15 ข้อ
  - Biostatistics 15 ข้อ

Note: Sorry! You fail the examination after twice attempts.
Final Examination Residents 2014

Fail, 15, 16%

All Exam = 92

Pass, 77, 84%

Pass Fail
# Final Examination Residents 2014

## Residents Data

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<tr>
<td>Surgery</td>
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Final Examination Residents 2014

Department's Exam Results

<table>
<thead>
<tr>
<th>Department</th>
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Legend: Exam, Pass, Fail
Final Examination Residents 2014

Department's Score

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<tr>
<td>Surgery</td>
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Shall we start ??
Types of Bio-medical Research

• Purposes
  • Exploratory VS. Confirmatory Research

• Resources
  • Laboratory VS. translational VS. Research

• Designs **
  • Observational VS. Experimental
  • Descriptive VS. Analytic

• Category of clinical question **
  • Therapy, diagnosis, causation (risk), prognosis
Clinical Research

NIH definition:
Research conducted with “human subjects (or on material with human origin)” for which an investigator directly interacts with human subjects

Excluded in Vitro studies that utilized human tissues that cannot be linked to living individual
Research

Good Question?

Require Research?

Design

Methodology?
Population?
Measurement?

Rethink – Feasibility?

STOP !!!
8 Steps to do research

• Research questions
• Review & Do literature search
• Create study design: Protocol writing * (ethic submit)
• Perform Data correction
  • Select Data base programing: Epidata, XLS, XLSX, SQL
  • Design Data base and variables
    (Clarify definitions: Variables & Outcomes)
• Data management
  • Entry, Validating (checking and cleaning)
• Data Analysis
• Results/Conclusion
• +/- Publication
## What research is made of?

<table>
<thead>
<tr>
<th>Elements</th>
<th>Purposes</th>
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<tr>
<td><strong>Research questions</strong></td>
<td>What questions will the study address?</td>
</tr>
<tr>
<td></td>
<td>If Answer known well → Change Question</td>
</tr>
<tr>
<td><strong>Significance (background)</strong></td>
<td>Why are the questions important?</td>
</tr>
<tr>
<td></td>
<td>→ Rational (e.g. Scientific rational)</td>
</tr>
<tr>
<td></td>
<td>→ Ease of use/Applications</td>
</tr>
<tr>
<td></td>
<td>→ Find gap of improvement/Best Practices/CPGs</td>
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<tr>
<td><strong>Design</strong></td>
<td>How is the study structured?</td>
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<tr>
<td></td>
<td>1. Descriptive</td>
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<td>2. Cross-sectional</td>
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<td>3. Case-Control</td>
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<td>4. Cohort</td>
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<td></td>
<td>5. Systematic Review/Meta analysis</td>
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<tr>
<td><strong>Subjects</strong></td>
<td>Who are the subjects and how will they be selected?</td>
</tr>
<tr>
<td><strong>Variables</strong></td>
<td>What measurements will be made?</td>
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<tr>
<td><strong>Statistical issues</strong></td>
<td>How large is the study and how will it be analyzed?</td>
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Statistical inference

Population

Real Parameters

Sample

Parameter

Infer

Statistical Analysis

Answer
Internal vs. External validity

Description

Selection

Comparison

Population

Sample

Study subject

Bias

Chance

Conclusion

External validity

Internal validity
The process of clinical research

- Research Questions
- Design
- Study Plan
- Implement
- Conduct Study
- Truth in The Universe
- Infer
- Truth in The Study
- Infer
- Findings in The Study

Hulley SB. Designing Clinical Epidemiology
How to conduct of Research Question?
Components of Research question

- Population being studied
- Intervention (exposure) being studied
- Control (comparison) being studied
- Outcome being measured
“All of steps of Research work should be aware... to What are Errors which concern?
Errors (Error-Bias) can occur during any stage of a study:

- during the literature review of the study question
- during the selection of the study sample
- during the measurement of exposure and outcome
- during the analysis of data
- during the interpretation of the analysis
- during the publication of the results
What are Errors which concern?

• Random error (Chance)
• Systematic error (Bias)
The process of clinical research

Research Questions
- Truth in The Universe

Design
- Random & Systematic error

Study Plan
- Truth in The Study

Implement
- Random & Systematic error

Conduct Study
- Findings in The Study

Infer

Hulley SB. Designing Clinical Epidemiology
Errors

- **Random error**
  - Type I Error (Alpha)
  - Type II Error (Beta)

- **Systematic error (Bias)**
  - A Process at any stages of inference tending to produce results that depart systematically from true values.
Random error

Urine output vs. Drug doses
Random error

Urine output

Drug dose
Random error

Urine output

Drug dose

Before

After
Random error

Urine output vs Drug dose

Before vs After
Random error

- Small sample size
- High variation in Samples/Subjects
- Measurement errors
  - One-time measure (e.g. BP)
  - Unreliable measure (No calibration)
  - Too many measurements
  - Non-standardized measurement
Strategies to reduce random error

• Appropriated sample size (Not largest sample size)
• Measure endpoints in a precise way
• Standardizing aspect of the protocol which impact on patient-to-patient variations
• Collecting data on key prognostic factors
• Choosing a homogenous group of patient
• Choosing the most appropriated design


\[ H_0 = u_{SBP(A)} = u_{SBP(B)} \]

\[ H_1 = u_{SBP(A)} \neq u_{SBP(B)} \]

<table>
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<tr>
<th>Statistical Testing</th>
<th>In Population Different exist (+)</th>
<th>No Different exist (-)</th>
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<tr>
<td>Different (+)</td>
<td>Power 1-Beta</td>
<td>False Positive (alpha)</td>
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<td><strong>Type I Error</strong></td>
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<td>True Negative 1-alpha</td>
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<td>No-Different (-)</td>
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<tr>
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<td><strong>Type II Error</strong></td>
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Tool to assess random error

• **The P value**: A numeric representative of the degree to which random variation alone could account for the difference observed between groups or data being compared, e.g. $P < 0.05$, $P < 0.01$

• **Confidence Interval**: Provide a plausible range within which the true association lies and provide all the information in P value and more.
Bias

• The systematic tendency of **any factors associated** with the Design Conduct Analysis Interpretation & Conclusion of the result of clinical study to **make the estimate of an effect deviate from its true value**.
Bias

• **Selection bias** should be aware to
  • Berkson Bias (Admission bias, hospital admission bias <> Gen population)
  • **Ascertainment bias** (incidence of diseases +/-)
  • Healthy worker effect (EGAT Good v.s Poor)
  • Volunteer Bias (Healthy or diseases sample e.g. MRI brain)
  • Non-Response Bias (eg. Questionnaire sexual issue, confidential issue, not interest issues)
Bias

• **Information bias**
  
  “It happens when estimated effect is distorted either by an error in measurement or by misclassifying the subject for exposure and/or outcome variables.

  • **Observer bias**
  
  • **Recall bias** esp. case control study
  
  • **Reporting bias** (synonym. Self report response bias)
Bias

• Ecological Bias (bias-different environment)
• Confounding Bias (Confound factor->outcome)
• Spectrum Bias (syn. Case mix bias)
• Publication bias
Is an unbiased study ever possible?

• “The skill of the...researcher, lies not conducting the perfect study, but in documenting and assessing the likely impact of its perfections.”

Silman A. Epidermiological Studies: A Practical Guide
Cambridge University Press 2002
Bias effect with Reliability and Validity of study
Population of patients with condition of interest

Sample

Description
Selection
Comparison
Describe
Effects

Bias
Chance
Conclusion

Internal validity
External validity
Population of patients with condition of interest

Sample

Sampling Bias

Sample

Description

Selection

Comparison

Bias

Measurement bias

Chance

Effects

Confounding bias

Conclusion
Confounding Factors/Bias

- A factors that distorts the true relationship of the study variables of interest by being related to the outcome of interest.
Confounding Factors

- A factors that distorts the true relationship of the study variables of interest by being related to the outcome of interest
Confounding Factors

• A factors that distorts the true relationship of the study variables of interest by being related to the outcome of interest

Confounding Factor (Confounder)

Study factor

Hot Tea

Drinking

Smoking

Outcome

CA. Stomach
Cohort study of worker & TCX

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<th>TCX</th>
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Relative Risk = 2.1
# Cohort study of worker & TCX

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Relative Risk = 1.5

## Non-Smoker

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Relative Risk = 1  No association

## Smoker

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<td>31</td>
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Relative Risk = 1.23  Confounder
A Priority criteria of confounder

- Clinically/Scientifically sensible
- Must be a risk factor
- Cannot be an intervening factor
- Must be associated with the exposure in the population (imbalance distribution)
- In analysis, crude estimate not equally to adjusted estimate
Study Designs

Exposure -
- Etiologic agent
- Risk factor
- Therapeutic measure
- Preventive measure

Outcome -
- Disease
- Biochemical change
- Pathophysiology
- Pathophysiologic change
Classification of study designs

• Classify by presence of **comparison group**
• Classify by **action of investigator**
  • Only observe → observational study
  • Assign intervention → Experimental study (Clinical trial)
Did investigator Assign exposure? 

Experimental Study

Random/Allocation? 

Yes

RCT

Yes → O

E → O

Yes → Cohort Study

No

Non RCT

O → E

Yes → Case control Study

Observational Study

Comparison group? 

Yes

Analytical Study

Yes → Cross-sectional Study

E = O 
(Same time)

Yes

Descriptive Study

No
Classification of study design

- **Observational study**
  - Descriptive or case-series
  - Case control studies (retrospective)
  - Cohort studies (prospective)
  - Historical cohort studies (retrospective)

- **Experimental study**
  - Controlled trials
  - Studies with no controls

- **Systematic Reviews/Meta-analysis**
Hierarchy of evidences

- Systematic Reviews
- RCT
- Cohort Study
- Case-Control study
- Cross-Sectional study
- Case Report
Logic of Cross Sectional Study

Population

Sample

Case with exposure + ve
Case with exposure - ve
Non-case with exposure + ve
Non-case with exposure - ve
Cross Sectional Study

- **Advantage**
  - In expensive, simple (no follow up)
  - No exposure, no drop out

- **Disadvantage**
  - Can establish association but not "conclusion"
  - Can not control confounder
  - Recall bias usually present
  - Incidence-prevalence bias
  - Different sample size among groups
Relative prevalence $O^+ = \frac{50}{100} / \frac{20}{100}$

= 1.67

Association ???
Logic of Case-Control Study

Population

Sample

Case with exposure + ve
Case with exposure - ve
Non-case with exposure + ve
Non-case with exposure - ve

Non-Disease
Logic of Case-Control Study

- Exposed
- Non-Exposed

Exposed - Disease/Outcome
Non-Exposed - No Disease/No Outcome

Time
Direction of study
Case Control Study

• **Advantage**
  - Quickly and Inexpensive
  - Feasible for rare disorder or long term follow up
  - May be required fewer subjects

• **Disadvantage**
  - Recall bias
  - More effect of confounder
  - Difficult to find control group

**Odds ratio calculation**

\[
\text{OR} = \frac{a/b}{c/d} = \frac{ad}{bc}
\]

where

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>✗</td>
<td></td>
</tr>
</tbody>
</table>
Logic of Prospective Cohort Study

Population

Exposure +ve

Exposure -ve

Disease

No Disease

Disease

No Disease
Prospective Cohort Study

Exposure

Non-Exposure

With outcome

Without outcome

Direction of study

Time
Retrospective Cohort Study

Direction of study: Expose

Time: Non-Expose

With outcome
Without outcome
With outcome
Without outcome
Cohort Study

• **Advantage**
  • Can be matched
  • Can be standardized in eligible criteria & outcome assessment
  • Can establish temporal association **

• **Disadvantage**
  • Usually expensive
  • Hard to blind
  • Long follow up period for rare disorder
  • Difficult to find controls and confounders
Randomized Control Trial

Population

Sample

Treatment

Control

Outcome

No-Outcome

Outcome

No-Outcome
Randomized Control Trial

Population

Sample

Randomization

Treatment

Control

Blind assessment

Outcome

No-Outcome

Outcome

No-Outcome
RCT Study

• **Advantage**
  • Confounding and variables can be balance by randomization
  • Blinding of subjects, medical staff and investigators are achievable

• **Disadvantage**
  • Cost in term of time and money
  • Dropout or loss to follow up are common event
  • Need time to final results.
### Accuracy of Test Result

<table>
<thead>
<tr>
<th>Test</th>
<th>Disease</th>
<th>Present (+)</th>
<th>Absent (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (+)</td>
<td>TP</td>
<td>a</td>
<td>FP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>Negative(-)</td>
<td>FN</td>
<td>c</td>
<td>TN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>d</td>
<td></td>
</tr>
</tbody>
</table>

\[
\text{Sensitivity} = \text{True positive rate} = \frac{a}{a+c} \\
\text{Specificity} = \text{True negative rate} = \frac{d}{b+d}
\]
### How to choose Sense VS. Specificity?

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
</table>
| 1. The ability of test to identify correctly those who have disease.  
2. Use to “rule out”  
3. There is a reason to suspect dangerous but treatable condition | 1. The ability of test to identify correctly those who do not have the disease  
2. Use to confirm “Rule in”  
3. Need when false-positive result can harm the patient physically, emotionally or financially. |

<table>
<thead>
<tr>
<th>SNout</th>
<th>SPin</th>
</tr>
</thead>
</table>
• Anti HIV Positive เป็นจริง ๆ หรือค่ะ ؟
• Negative ไม่เป็นแน่ค่ะ
• Anti HIV Positive เป็นจริง ๆ หรือค่ะ ? PPV
• Negative ไม่เป็นแน่ค่ะ NPV
The study design for diagnostic test

Patients suspected of target conditions → Diagnostic test → Gold standard test → Target condition (+/-)

The study for treatment/prevention

1. Random allocation (by chance): participants to interventions (Randomization)
2. Blind: Double, triple blind... etc
3. Placebo
4. Intention to treat analysis
5. Complete follow up > 80%
Risk study (Causation)

• Exposure & Outcome

Exposure
- Risk Factors
- Intervention
- Maneuver

Outcome
- Disease
- Health Problems

Independent variable

dependent variable
Cause

• A cause of disease event is an antecedent event, condition, or characteristic that was necessary for occurrence of disease at the moment of its occurrence, given that other conditions are fixed (Kenneth J. Rothman)

Association

• Is a statistical relationship between two or more events, characteristics or other variables.
Causal criteria
(Modified from Bradford-Hill AB)

<table>
<thead>
<tr>
<th>Temporality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
</tr>
<tr>
<td>Dose-response</td>
</tr>
<tr>
<td>Consistency</td>
</tr>
<tr>
<td>Biological plausibility</td>
</tr>
<tr>
<td>Reversibility</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Analogy</td>
</tr>
<tr>
<td>Experimental evidences</td>
</tr>
</tbody>
</table>
Criteria for judgment of causal associations (Hills’ Criteria)

• **Temporal sequence**: Did exposure precede outcome?

• **Strength of association**: How strong is the effect, measured as relative risk or odds ratio?

• **Coherence with existing knowledge**: Is the association consistent with available evidence?

• **Analogy**: Is the association similar to others

• **Experimental evidence**: has a randomized control
Research Design which assess cause?

- Cohort study +++
- Case-control +++
- Cross sectional study +
Other research with prognostic study

• A prediction of future course of diseases following its onset
• A group of patients having something in common are assembled and followed forward in time, and clinical outcomes are measured.
• “Natural history of disease”
Onset of Acute MI

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Prognostic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Male</td>
<td>female</td>
</tr>
<tr>
<td>Smoking</td>
<td>Smoking</td>
</tr>
<tr>
<td>HT</td>
<td>Hypotension</td>
</tr>
<tr>
<td>LDL</td>
<td>Anterior infarction</td>
</tr>
<tr>
<td>Inactively</td>
<td>CHF</td>
</tr>
<tr>
<td></td>
<td>Ventricular arrhythmias</td>
</tr>
</tbody>
</table>
Prognosis

• An inception cohort of persons, all initially free of outcome of interest
• Representative of sample
• Homogenous to prognostic risk
• Objective outcome measurement
• FU >= 80% of patients
Broad topics of Research

• **Diagnosis** – Demonstrate that new diagnosis test is valid/reliable
  Preferred “cross sectional study”

• **Causation or Risk** - Determine that agent is related to development of illness, preferred “Cohort or case-control study”

• **Therapy** – Testing the efficacy of intervention preferred “RCT”

• **Prognosis** - determine what happen to someone with some stage of disease, preferred “Prospective Cohort study”
Is the exposure or intervention under the control of investigator

Are the subjects followed up over time?

Are the subjects selected according to The outcome?

Experimental Study

Cohort Study

Case-Control Study

Cross sectional Study
## Key methodological strength and weakness

<table>
<thead>
<tr>
<th>Design</th>
<th>Starting point-Assessment</th>
<th>Strength</th>
<th>Frequency of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>E-O</td>
<td>Low susceptibility to bias</td>
<td>Feasibility, generalizability</td>
</tr>
<tr>
<td>Cohort</td>
<td>E-O</td>
<td>Feasible when randomization of exposure not possible</td>
<td>Susceptible to bias, limited validity</td>
</tr>
<tr>
<td>Case-Control</td>
<td>O-E</td>
<td>Overcomes temporal delays, may require small sample size</td>
<td>Susceptible to bias, limited validity</td>
</tr>
</tbody>
</table>
Thank You

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