Experimental Study

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Concepts

Experiment

- A set of **observations**, conducted under **controlled circumstances**, in which the scientist **manipulates** the conditions to ascertain what effect, if any, such manipulation has on the observations

Rothman KJ, Greenland S, Lash TL. Modern Epidemiology 3rd ed, 2008.

Experiment

A study of

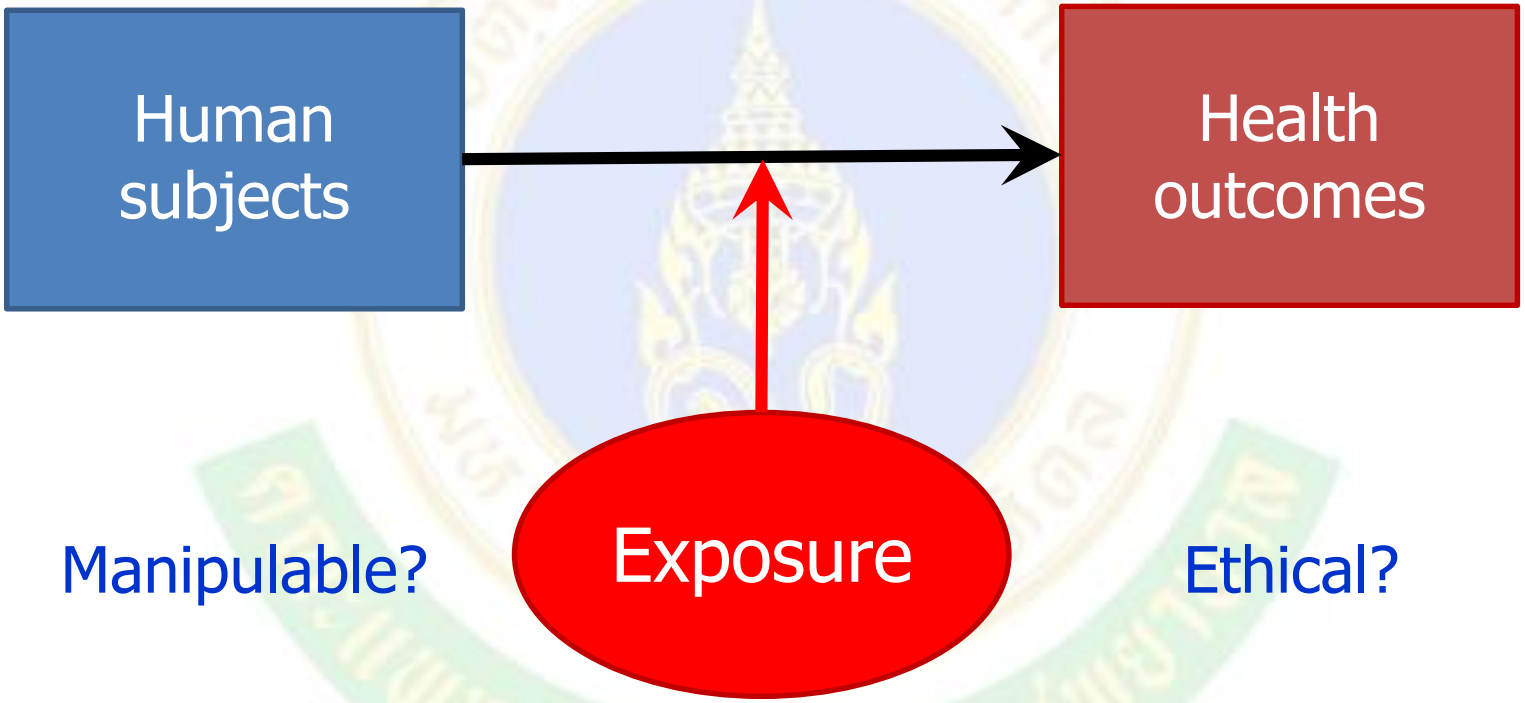
CAUSE-EFFECT association

Validity for Causal Inference

Validity Ranking	Types of Study Design
Highest	**Experimental study**
	Quasi-experimental study
	Prospective cohort study
	Retrospective cohort study
	Nested case-control study
	Time-series analysis
	Cross-sectional study
	Ecologic study
	Case study
Lowest	Anecdote

Adapted from Environmental Health Perspectives 1997;15:1079.

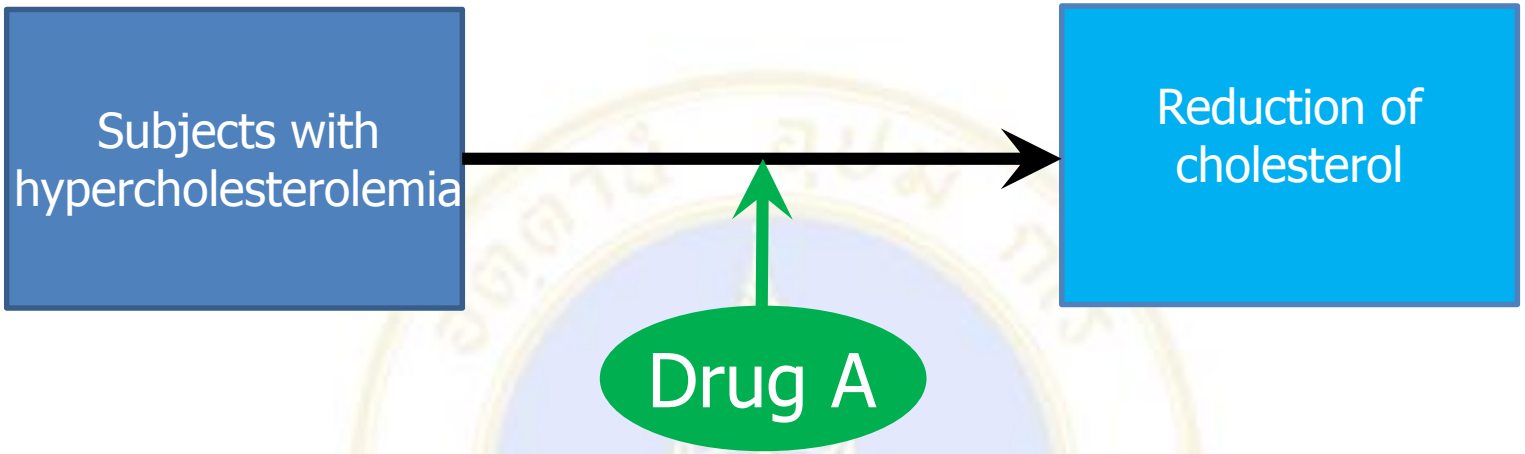
Health Sciences



Causal association?

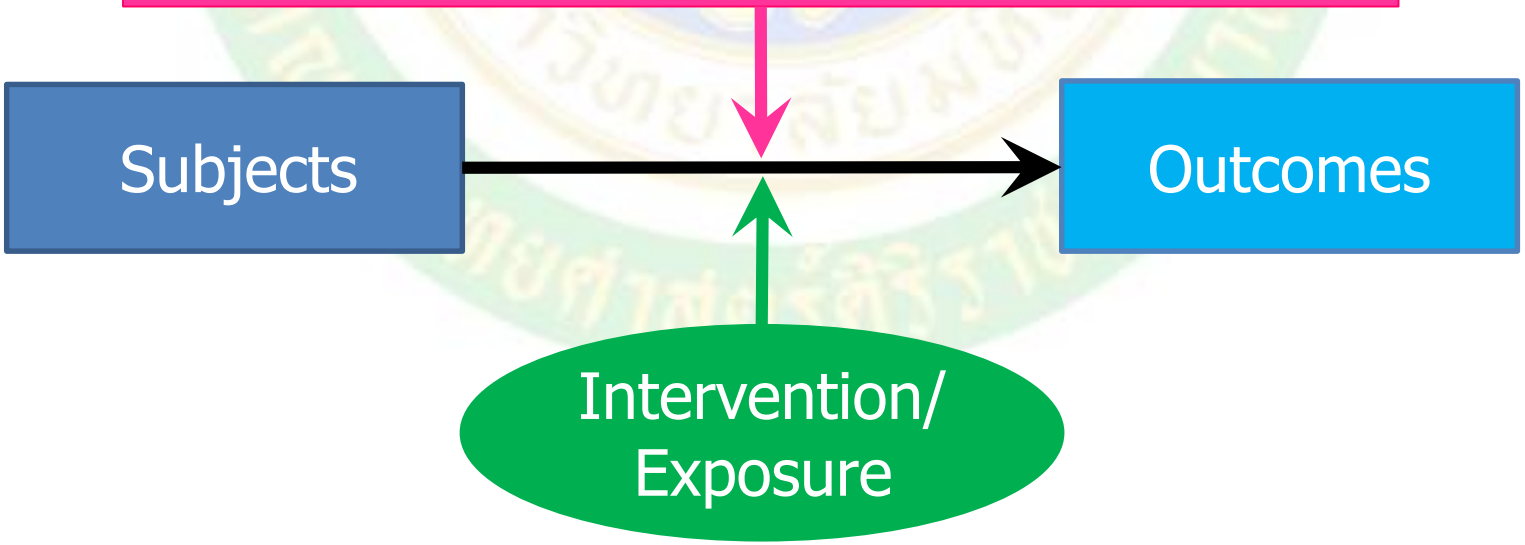
Experimental Study

- Exposure conditions must be amenable to manipulation
- Exposure assignments must be expected to cause no harm
  - Therapeutic or preventive interventions



- Possible factors other than drug A that may be related to cholesterol reduction (Extraneous or confounding factors)
  - Other co-interventions: Lifestyle modifications
  - Regression to the mean phenomenon

- **Extraneous Factors**
  - Other co-interventions
  - Regression to the mean phenomenon
  - Natural course
  - Learning effect if measurement is done more than one time
  - Change in properties of the measurement tools over time
  - Placebo effect
  - Various unknown factors



Experimental Study

Main features

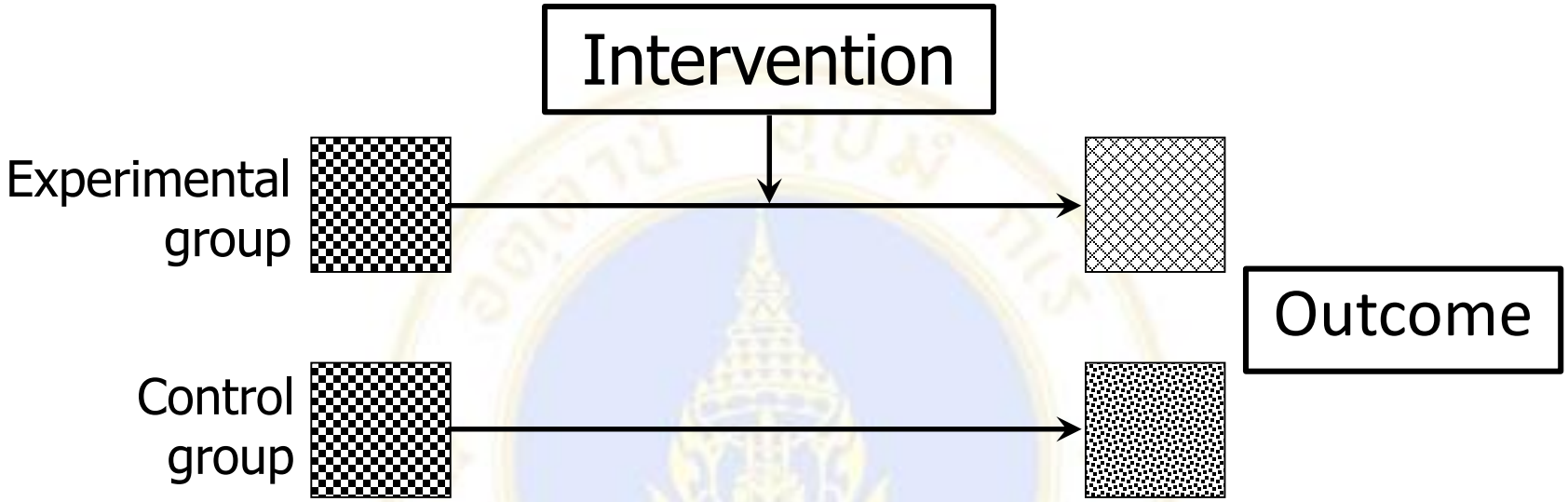
- There must be a control group
  - Not a unique feature of experimental study

Physicians' Health Study

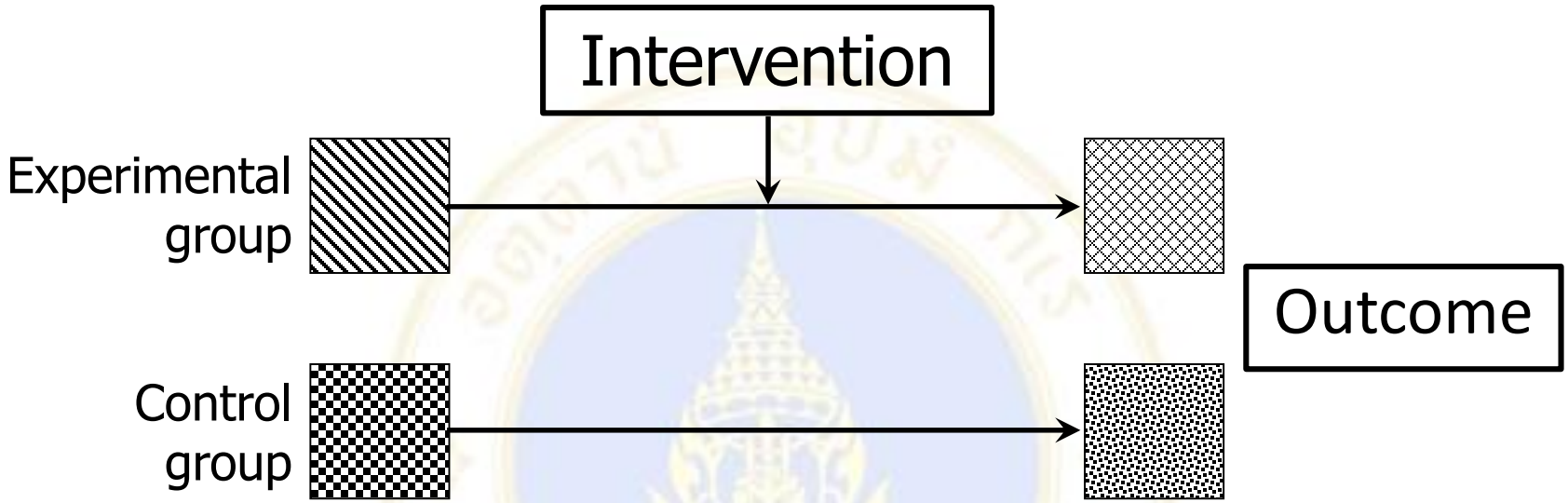
Side effects	Aspirin (%)	Control (%)	p value
GI symptoms	34.8	34.2	0.48
Upper GI ulcers	1.5	1.3	0.08
Bleeding problems	27.0	20.4	<0.00001

Without control group, one might conclude that aspirin causes GI symptoms and upper GI ulcers

N Engl J Med 1989;321:129-35.



- Difference in outcome **<u>can</u>** be attributed to intervention **<u>only if</u>** both groups are similar at the beginning
  - Similar prognosis



- Difference in outcome **cannot** be attributed solely to intervention as both groups differ at the beginning

Experimental Study

Main features

- There must be a control group
  - Not a unique feature of experimental study
- Experimental and control groups must have similar pre-intervention risk of developing the outcomes (i.e. similar prognosis)
- Investigators manipulate the assignment of exposure to study participants to ensure similar prognosis between groups
  - The unique feature of experimental study

Experimental Study: Basic Structure

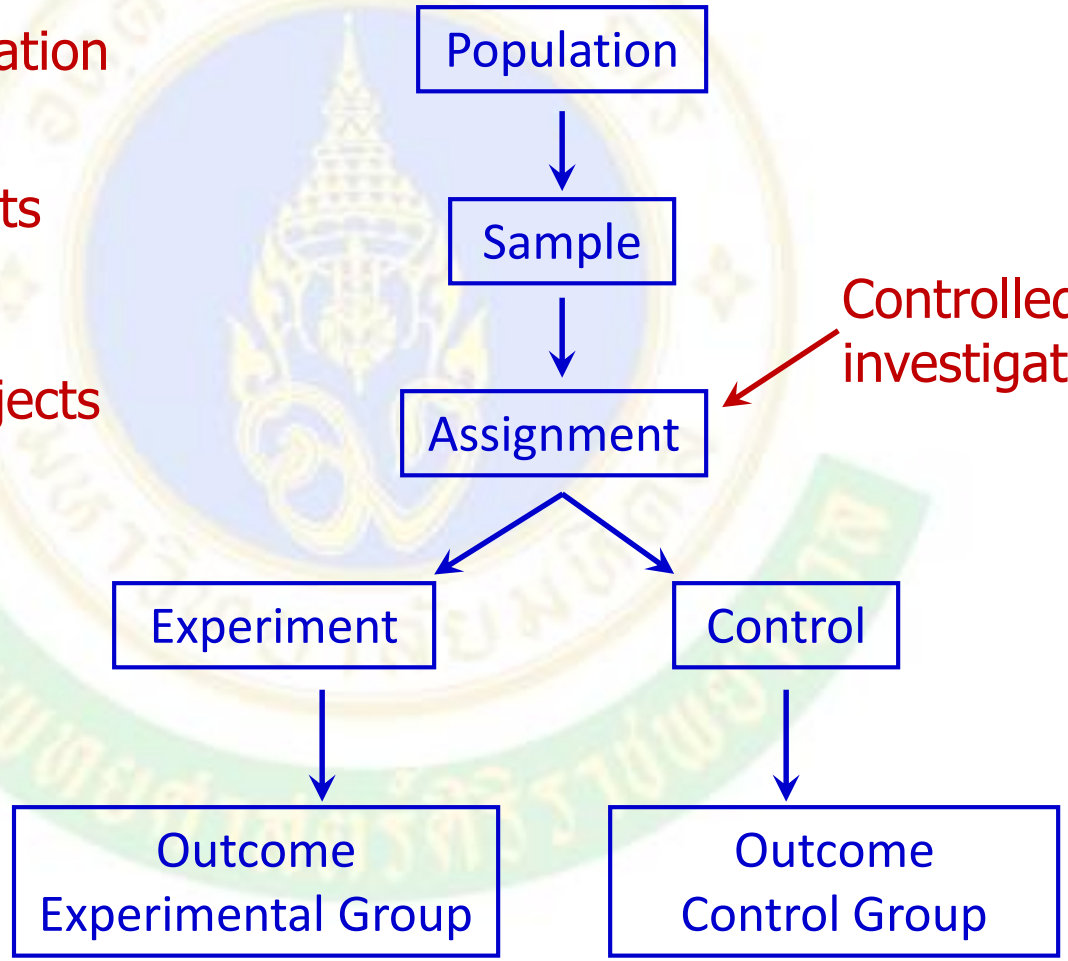
Definition of population

Selection of subjects to be studied

Assignment of subjects to study group

Administration of intervention

Measurement of outcome



Experimental Study

- Clinical trials
  - Patients as subjects
- Field trials
  - Healthy individuals as subjects
- Community intervention trials
  - Groups of people in communities as subjects

Methodology

Design Considerations

- Research question
- Selection of participants
- Selection of intervention and control
- Selection of outcomes (endpoints)
- Data analysis and sample size
- Measures to reduce bias
- Ethical considerations

Research Question

- Effectiveness of therapeutic or preventive interventions
  - Pharmacotherapy
  - Surgical procedures
  - Physical therapy
  - Lifestyle interventions
  - Educational programs
  - Vaccine
  - Etc.

Research Question

- Primary research question
  - The most important question that the study wants to answer.
  - The answer is intended to be and can be conclusive.
  - There is usually 1 primary research question.
- Secondary research question
  - The answer can only be hypothesis-generation.
  - There are usually many secondary research questions.

Good Research Question: FINER

- **F**easible
  - Adequate number of subjects
  - Adequate technical expertise
  - Affordable in time and money
  - Manageable in scope
- **I**nteresting
- **N**ovel
  - Provides new findings
  - Confirms, refutes or extends previous findings
- **E**thical
- **R**elevant
  - To scientific knowledge
  - To clinical and health policy
  - To future research

Research Question: Components

PICO

- **P**atients / Population
- **I**ntervention
- **C**omparison intervention (Control)
- **O**utcome

- Each component must be defined as specifically and clearly as possible

Research Question

- Should be as clear and specific as possible
  - Not "Is drug A better than drug B?"
  - But "In population W, does drug A at daily dose X reduce outcome Z over a period of time T more than drug B at daily dose Y by the magnitude C?"

Design Considerations

- Research question
- **Selection of participants**
- Selection of intervention and control
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Selection of Participants

- Eligibility criteria
  - Identify a population in which it is feasible, ethical and relevant to study the impact of the interventions on outcomes

Selection of Participants

- Eligibility criteria
  - Inclusion criteria
    - Define the main characteristics of the target population that pertain to the research question
  - Exclusion criteria
    - Specific characteristics rendering individuals not suitable to enter the study
    - Should be parsimonious (enhance generalizability)

Reasons for Exclusion

- Study treatment is clearly indicated
  - ACEI is indicated in congestive heart failure
- Study treatment is contraindicated or would be harmful
  - Unacceptable risk of adverse reaction
  - Pregnant or lactating women
  - Severe renal or hepatic impairment
- Unlikely to benefit form study treatment
  - High likelihood of non-adherence or being lost to follow-up
  - Short life expectancy
  - Not likely to respond to treatment due to some characteristics
- Practical problems with participating in the protocol
  - Impaired mental status
  - Language barrier

Design Considerations

- Research question
- Selection of participants
- **Selection of intervention and control**
- Selection of outcomes (endpoints)
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Selection of Intervention

- Intensity, duration and frequency
  - Balance effectiveness and safety
    - Serious conditions: Effectiveness may be the primary concern
      - Highest tolerable dose
    - Mild conditions or prevention: Safety may be the primary concern
      - Lowest effective dose
  - Generalizability
    - Simple interventions are better

Selection of Control

- Concurrent standard of care
  - No treatment
  - Placebo
  - Active treatment control

  } + Supportive care
- Allowance or restriction of co-interventions

Design Considerations

- Research question
- Selection of participants
- Selection of intervention and control
- **Selection of outcomes (endpoints)**
- Data analysis and sample size
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Outcome (Endpoint)

- Primary outcome
  - To address primary research question
- Secondary outcome
  - To address secondary research question(s)
- Adverse outcomes

Outcome

- Single event
  - Total mortality, Cause-specific mortality, hospitalization, occurrence of a condition e.g. MI, stroke, recurrence of cancer, etc.
- Combination of events: Composite outcome
  - Should be capable of meaningful interpretation such as being related through a common underlying conditions
    - Example: Cardiovascular death, non-fatal MI, recurrent severe angina or unplanned revascularization

Composite Outcome

- Advantages
  - Reduce sample size
  - Reduce bias
- Disadvantages
  - Assume equal importance of each component
    - Death, MI, Angina
  - Assume similar effect of the intervention on each component
    - Complicate interpretation

Outcome

- Choice of outcome for a clinical trial
  - Responsiveness to intervention
  - Relevance
    - Clinical or "hard" outcome preferable to "surrogate" or "physiologic" outcome (patients & physicians)
    - Quality of life (patients & physicians)
    - Economic outcome (government, policy makers, payers of health care cost)
  - Credibility
    - Assessment can be objective and unambiguous

Outcome

- Capability of being assessed in all participants, in an unbiased fashion, and as completely as possible
  - Similar outcome for all subjects
  - Similar technique of measurement
  - "Hard" outcome or outcome with objective criteria
  - Blind assessment
  - Outcome that can be assessed without co-operation of subjects

Adverse Outcomes

- Hardly any intervention is 100% safe
- Though rarely specified as primary outcome in most clinical trials, adverse outcome is very important
- Most clinical trials are not designed for the purpose of addressing adverse outcome
  - Inadequate sample size, short duration of follow-up, restricted subject selection
  - Statistical requirements for comparison of adverse outcome should not be too strict

Adverse Outcomes

- Definitions
  - Difficult to define clearly as there are many possibilities and some are unexpected
  - However, important adverse outcomes should be well-defined
- Ascertainment
  - Systematic elicitation using checklist and lab tests
    - Standardization
  - Spontaneous report by subjects
    - Clinically important events
    - Unexpected events

Design Considerations

- Research question
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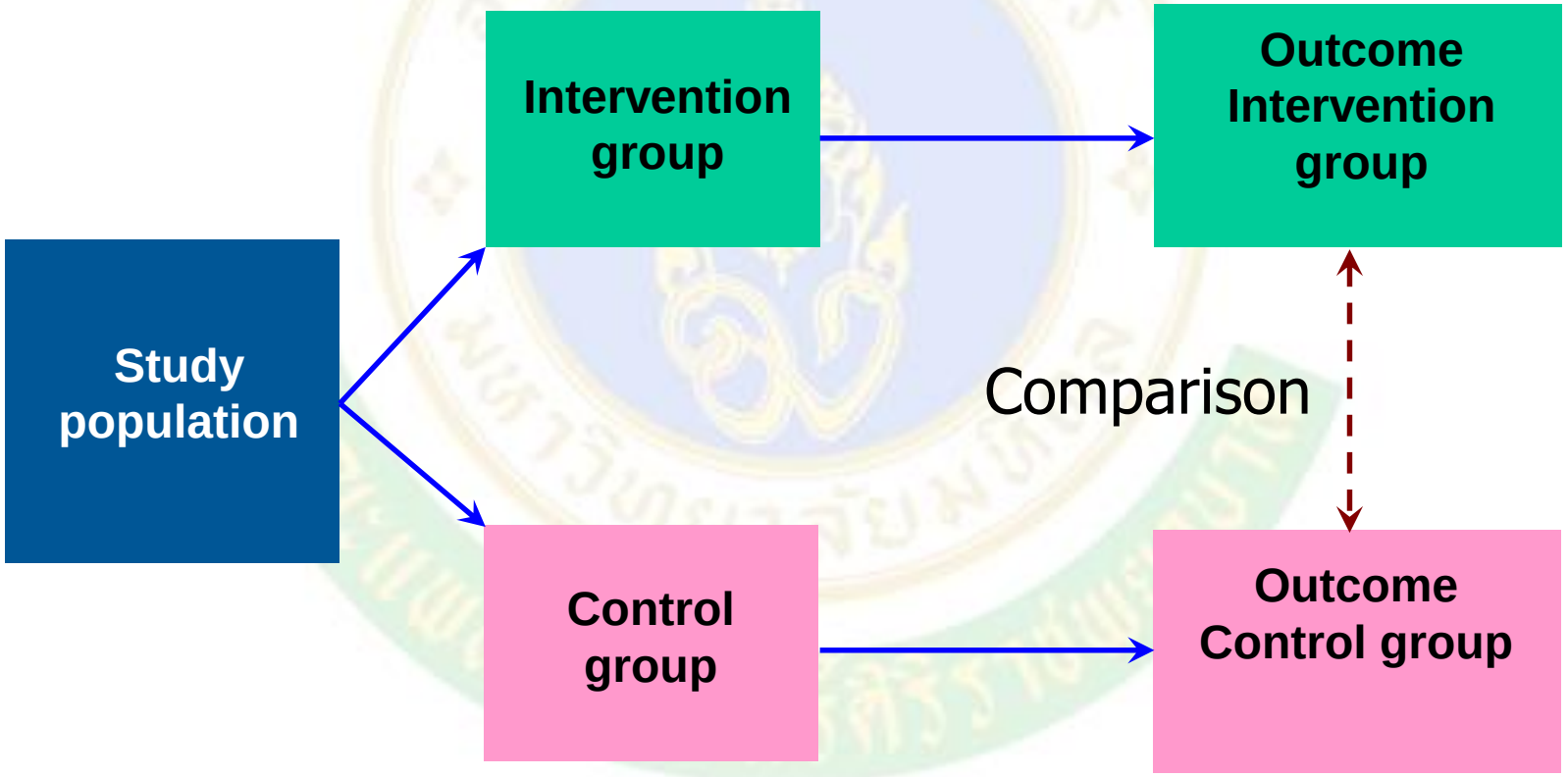
Is the intervention effective?
(Does the intervention make any difference?)



Comparison of Outcome Between Groups

- Absolutely no difference
  - The intervention is not effective
- Some degree of difference
  - What is the probability that the observed difference is only a "chance" finding?
    - That probability is called "p value" (Hypothesis testing)

Comparison of Outcome Between Groups

Type of Outcome	Statistical Test
Categorical	Fisher's Exact Chi-Square (Approximate)
Time-to-Event	Log-rank (Survival analysis)
Continuous	Student's t

What is the magnitude of effect?

- Measure of effect
  - Parameter estimation
    - Point estimate
    - Interval estimate (95% confidence interval)

Magnitude of effect: Binary outcome

	Treatment ($n = N_T$)	Control ($n = N_C$)
Outcome+	$p_T = n_T/N_T$	$p_C = n_C/N_C$

Measures	Formula
Risk Difference (RD) or Absolute risk reduction (ARR)	$p_C - p_T$
Relative Risk (RR)	p_T/p_C
Relative Risk Reduction (RRR)	1 - RR
Number needed to treat (NNT)	100/ARR (%)
Odds Ratio (OR)	$[p_T/(1-p_T)]/[p_C/(1-p_C)]$
Hazard Ratio (HR)	Cox regression model
Relative Hazard Reduction (Frequently presented as RRR)	1 - HR

Sample Size Estimation

- Too small sample size can prove nothing
  - Probability of type II error
  - Wasteful, unethical, may mislead conclusions
- A clinical trial should have sufficient statistical power to detect clinically important effect
- Calculation of sample size with provision for adequate levels of significance and power is an essential part of planning

Sample Size Estimation

- Parameters required for calculation
  - Acceptable type I error (level of significance)
  - Acceptable type II error (complement of "power")
  - Smallest clinically important effect that needs to be detected
  - Expected variability of outcome variable
    - From other trials or a pilot study
  - Expected magnitude of outcome in one group (usually the control)
    - From other trials or a pilot study

Sample Size Formula

- Binary outcome, 2 groups, equal sample size in each group

$$n\ (per\ group) = \frac{\left[z\alpha_{/2}\sqrt{2\bar{\pi}(1-\bar{\pi})} + z_{\beta}\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}\right]^2}{(\pi_1-\pi_2)^2}$$

- π_1 = Proportion of outcome in group 1
- π_2 = Proportion of outcome in group 2
- $\pi_1 - \pi_2$ = Smallest clinically important difference
- $\bar{\pi} = (\pi_1 + \pi_2)/2$

$$n\ (per\ group) = \frac{\left[z\alpha_{/2}\sqrt{2\bar{\pi}(1-\bar{\pi})} + z_{\beta}\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}\right]^2}{(\pi_1-\pi_2)^2}$$

- Drug A to reduce mortality of avian influenza
- Mortality rate = 60%
- Gr 1 = Control (No drug A)
- Gr 2 = Drug A
- α = 0.05 → $z_{\alpha/2}$ = 1.96
- Power = 90% → β = 0.01 → z_{β} = 1.28
- π_1 = 0.6, π_2 = ?

$$n\,(per\ group) = \frac{\left[z\alpha_{/2}\sqrt{2\bar{\pi}(1-\bar{\pi})} + z_{\beta}\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}\right]^2}{(\pi_1-\pi_2)^2}$$

- $\pi_1 = 0.6$, $\pi_2 = ?$
  - Define $\pi_1 - \pi_2$
  - If $\pi_1 - \pi_2 = 0.1$, then $\pi_2 = 0.5$
- $\bar{\pi} = (0.6 + 0.5)/2 = 0.55$

$$n\,(per\ group)$$

$$= \frac{\left[1.96\sqrt{2 \times 0.55 \times 0.45} + 1.28\sqrt{0.6 \times 0.4 + 0.5 \times 0.5}\right]^2}{(0.6-0.5)^2}$$

$$= 517.5 = 518$$

Total N = 2 x 518 = 1036

Sample Size Formula

- Continuous outcome, 2 groups, equal sample size in each group

$$n\,(per\ group) = 2\left[\frac{\left(z\alpha_{/2} + z_{\beta}\right)\sigma}{\mu_1 - \mu_2}\right]^2$$

- μ_1 = Mean value of outcome in group 1
- μ_2 = Mean value of outcome in group 2
- $\mu_1 - \mu_2$ = Smallest clinically important difference
- σ = Standard deviation of outcome

$$n\,(per\ group) = 2\left[\frac{\left(z\alpha_{/2} + z_{\beta}\right)\sigma}{\mu_1 - \mu_2}\right]^2$$

- Drug B to reduce cholesterol in hypercholesterolemia
- Mean $\pm$ SD cholesterol = 250 $\pm$ 40 mg/dL
- Group 1 = Control (No drug B)
- Group 2 = Drug B
- α = 0.05 → $z_{\alpha/2}$ = 1.96
- Power = 90% → β = 0.01 → z_{β} = 1.28
- μ_1 = 250, μ_2 = ?

$$n\,(per\ group) = 2\left[\frac{\left(z\alpha_{/2} + z_{\beta}\right)\sigma}{\mu_1 - \mu_2}\right]^2$$

- $\mu_1 = 250$, $\mu_2 = ?$
  - Define $\mu_1 - \mu_2$
  - If $\mu_1 - \mu_2 = 30$, then $\mu_2 = 220$
  - Unnecessary to know μ_1 and μ_2 at all

$$n\,(per\ group) = 2\left[\frac{(1.96 + 1.28) \times 40}{30}\right]^2$$

$$= 37.3 = 38$$

Total N = 76

Design Considerations

- Research question
- Selection of participants
- Selection of intervention and control
- Selection of outcomes (endpoints)
- Data analysis and sample size
- **Measures to reduce bias**
- Ethical considerations

Measures to Reduce Bias

- Treatment allocation by randomization
- Concealment of randomization
- Blinding of treatment allocation
- Maximizing adherence and follow-up
- Analysis using intention-to-treat principle

Randomization

- A process analogous to coin tossing
  - Subjects are equally likely to be assigned to either the intervention or control group
  - The best method for obtaining comparability of groups

Randomization

- Merits of randomization
  - More likely than other methods to balance the distribution of prognostic factors (both known and unknown) between the intervention and control groups
  - Avoid "selection bias": allocation of treatment based on physician or patient preference, which (either consciously or unconsciously) is usually based on many prognostic factors
  - Guarantee the validity of statistical tests

Experimental Study = Randomized Controlled Trial (RCT)

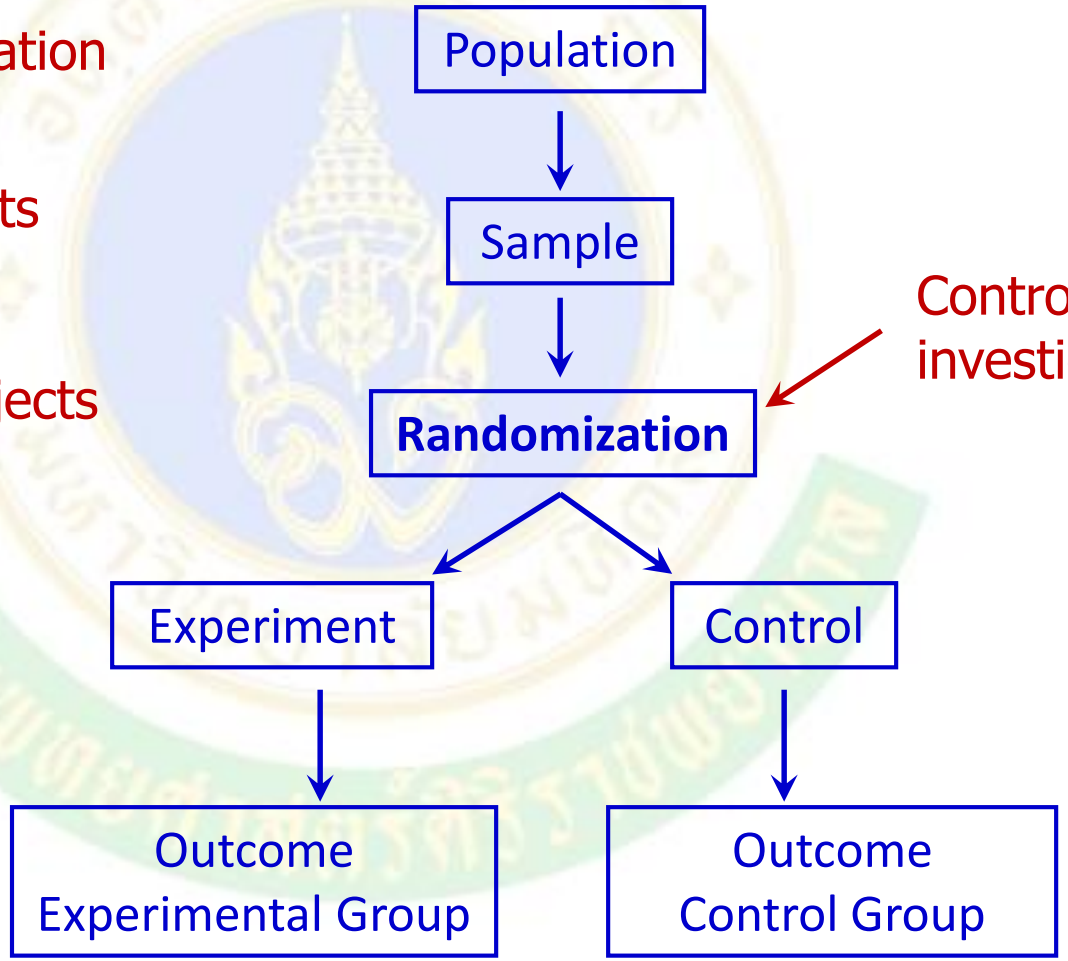
Definition of population

Selection of subjects to be studied

Assignment of subjects to study group

Administration of intervention

Measurement of outcome



Randomized Controlled Trial

- The best study design to evaluate efficacy/effectiveness of a therapeutic / preventive intervention
- Matching instead of randomization?
  - Possible only for known prognostic factors
  - Low feasibility with increasing numbers of prognostic factors to be matched

Randomization Process

- Simple randomization
- Blocked randomization
- Stratified randomization
- Adaptive randomization
- Cluster randomization

Simple Randomization

- Procedures equivalent to "coin tossing"
  - Random-number table
  - Computer generated randomization list
- Advantage
  - Easy
- Disadvantages (esp. for small sample size)
  - Risk of imbalance number of subjects between groups
  - Risk of imbalance prognosis between groups

Blocked Randomization

- Avoid serious imbalance in the number of subjects assigned to each group
- Guarantee that
  - at no time during randomization will the imbalance be large
  - at certain points the number of subjects in each group will be equal

Blocked randomization

Block of 4	TCTC	CTTC	CCTT	CTCT	TTCC	TCCT	. . . .
Block of 6	TCCTCT	CCTCTT	TTTCCC	TCTCCT	. . . . .		

- At the end of each block the number of subjects in each group will be equal
- Order of treatment within the block and order of consecutive blocks are randomized
- Assignment to the last person in each block can be known if treatment is not blind
  - Solution: randomly varying block size

Stratified Randomization

- Avoid imbalance in prognosis (baseline characteristics) between groups
- Subjects are classified into stratum based on stratification factor(s)
  - Important prognostic factors regarding the outcome
- Randomization (blocked) is performed for each stratum separately

Stratified Randomization

- Important prognostic factors that should not be imbalance between groups
  - Age: 40-49, 50-59, 60+
  - History of MI: Yes, No

Stratified Randomization

Strata	Age	History of MI	Assignment
1	40-49	Yes	TCCT CTCT
2	40-49	No	TCTC CCTT
3	50-59	Yes	etc.
4	50-59	No	
5	60+	Yes	
6	60+	No	

Stratified Randomization

- Numbers of prognostic factors used for stratification should be kept minimum, otherwise there would be too many strata and some of them would contain only a few subjects if the sample size is small
- In most multi-center clinical trials, randomization is usually stratified by centers

Adaptive Randomization

- Randomization procedures that change allocation probability as the study progresses, based on imbalance in numbers of subjects, in prognosis, or in response to treatment
  - Baseline adaptive randomization
    - Correct imbalance in number or prognosis
  - Response adaptive randomization
    - Maximize the number of subjects on the superior intervention

Cluster randomization

- Randomization with naturally occurring groups or cluster of participants as units of randomization (schools, physicians' practices, communities, etc.)
  - All subjects in the same cluster receive the same intervention
  - Suitable for interventions that cannot be delivered to individual subjects

Measures to Reduce Bias

- Treatment allocation by randomization
- **Concealment of randomization**
- Blinding of treatment allocation
- Maximizing adherence and follow-up
- Analysis using intention-to-treat principle

Concealment of randomization

- Concealed randomization
  - Inability to predict the next assignment
- Unconcealed randomization
  - Awareness of the next assignment may result in sicker or less sick patients being systematically enrolled to either intervention or control groups, resulting in groups with different prognosis

Concealment of randomization

- Commonly used methods of concealed randomization
  1. Central (or remote) randomization, usually by using a telephone call
  2. Preparation of blinded medication in a pharmacy
  3. Sealed, opaque envelope containing randomization list

Pseudo- (or Quasi-) Randomization

- Superficially similar to randomization, but it is systematic
  - alternate treatment allocation
  - allocation according to birth date, chart or ID number, day of the week, attending physicians, etc.
- Lack of concealment of randomization
- The factor used for assignment of intervention may somehow relate to prognosis
  - Patients presenting on Monday may in general be sicker than those presenting on other days

Measures to Reduce Bias

- Treatment allocation by randomization
- Concealment of randomization
- **Blinding of treatment allocation**
- Maximizing adherence and follow-up
- Analysis using intention-to-treat principle

Blinding of treatment allocation

- Unawareness of treatment assignment after randomization
- Ensure comparability between intervention and control groups after randomization
- Should be considered whenever it is possible to blind participants
  - Blinding is not always possible
    - surgical trials, devices, behavioral intervention, etc.

Blinding of Treatment Allocation

Avoid bias due to

- Placebo effect
- Fake response in order to please the physician or investigators
- Differential co-intervention
- Differential interpretation of lab results
- Differential follow-up procedure and schedule
- Differential effort to detect outcomes
- Differential verification of outcomes

Five groups that should be blind to treatment assignment, if possible

Participants	Purposes
Patients	To avoid placebo effects
Clinicians	To prevent differential administration of therapies that affect the outcome of interest (co-intervention)
Data collectors	To prevent bias in data collection
Adjudicators of outcome	To prevent bias in decisions about whether or not a patient has had an outcome of interest
Data analysts	To avoid bias in decisions regarding data analysis

Blinding of Treatment Allocation

- Achieved by
  - Placebo
  - Sham procedures
  - Blind adjudication committee

Difference between Blinding and Concealment of Randomization

- Blinding
  - Unawareness of treatment allocation after randomization
- Concealment of randomization
  - Unawareness of treatment allocation before randomization

Measures to Reduce Bias

- Treatment allocation by randomization
- Concealment of randomization
- Blinding of treatment allocation
- **Maximizing adherence and follow-up**
- Analysis using intention-to-treat principle

Adherence and Follow-up

- Nonadherence (noncompliance) and lost to follow-up
  - Loss of power of the trial
  - Biased results
- Subjects not adherent to the protocol or lost to follow-up have different prognosis from others
- Efforts to maximize adherence and follow-up should be carried out

Coronary Drug Project

Compliance	5-Y Mortality (%)	
	Clofibrate	Placebo
Total group	20.0	20.9
Good (≥ 80%)	15.0	15.1
Poor (< 80%)	24.6	28.3

Even in the placebo group, those with good compliance had better prognosis than those with poor compliance.

N Engl J Med 1980;303:1038-1041.

Follow-up

- In general, if lost to follow-up is **≥20%**, the study validity is **usually** considerably compromised
- If lost to follow-up is **<20%**, the study validity **may or may not** be considerably compromised
  - If want to be sure, do the sensitivity analysis assuming the worst case scenario

When does loss to F/U seriously threaten validity?

	Trial A		Trial B	
	Treatment	Control	Treatment	Control
Number of patients randomized	1000	1000	1000	1000
Number (%) lost to F/U	30 (3%)	30 (3%)	30 (3%)	30 (3%)
Number (%) of deaths	200 (20%)	400 (40%)	30 (3%)	60 (6%)
RR not counting patients loss to F/U	0.2/0.4 = **0.5**		0.03/0.06 = **0.5**	
RR for worst case scenario	0.23/0.4 = **0.57**		0.06/0.06 = **1.0**	

Follow-up

- Consider the proportion of number lost to follow-up to the number of outcome events
  - No. lost to F/U << No. outcome events
    - Small effect of bias
  - No. lost to F/U ≈ No. outcome events
    - Considerable effect of bias

Adherence and Follow-up

- Efforts to maximize adherence and follow-up should be carried out
  - Run-in period
    - Placebo run-in
    - Active treatment run-in
  - Incentives
    - Monetary and non-monetary
  - Social events

Measures to Reduce Bias

- Treatment allocation by randomization
- Concealment of randomization
- Blinding of treatment allocation
- Maximizing adherence and follow-up
- **Analysis using intention-to-treat principle**

Analysis

- Intention-to-treat analysis
  - Analysis of outcomes based on the treatment arm to which patients were randomized rather than which treatment they actually received
- Preserve the value of randomization
- Results reflecting true population effect when the intervention is widely used in real practice

Analysis

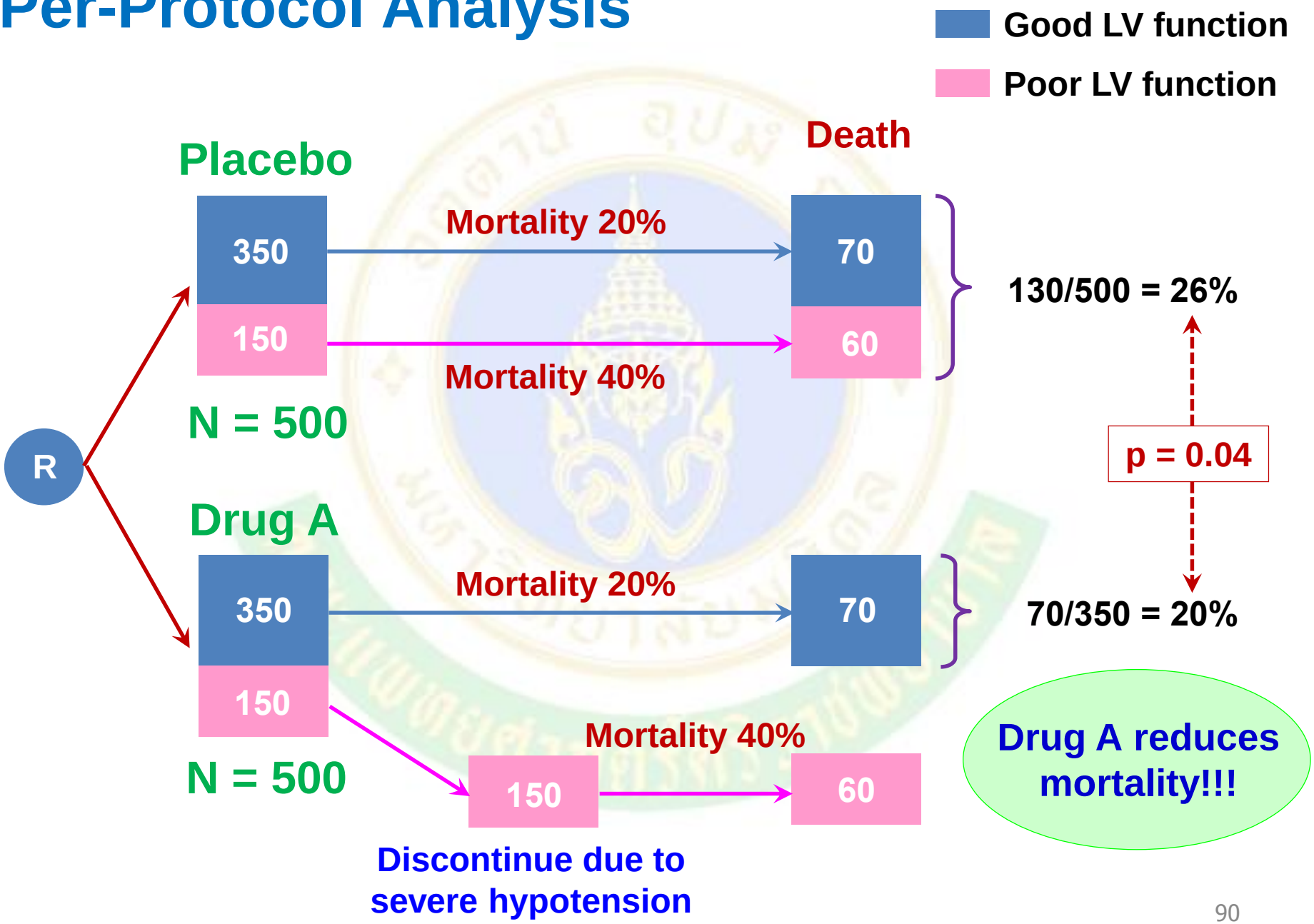
- Per-Protocol analysis
  - Analysis restricted to subjects who comply to the study protocol
  - Can introduce bias (See example)

Analysis

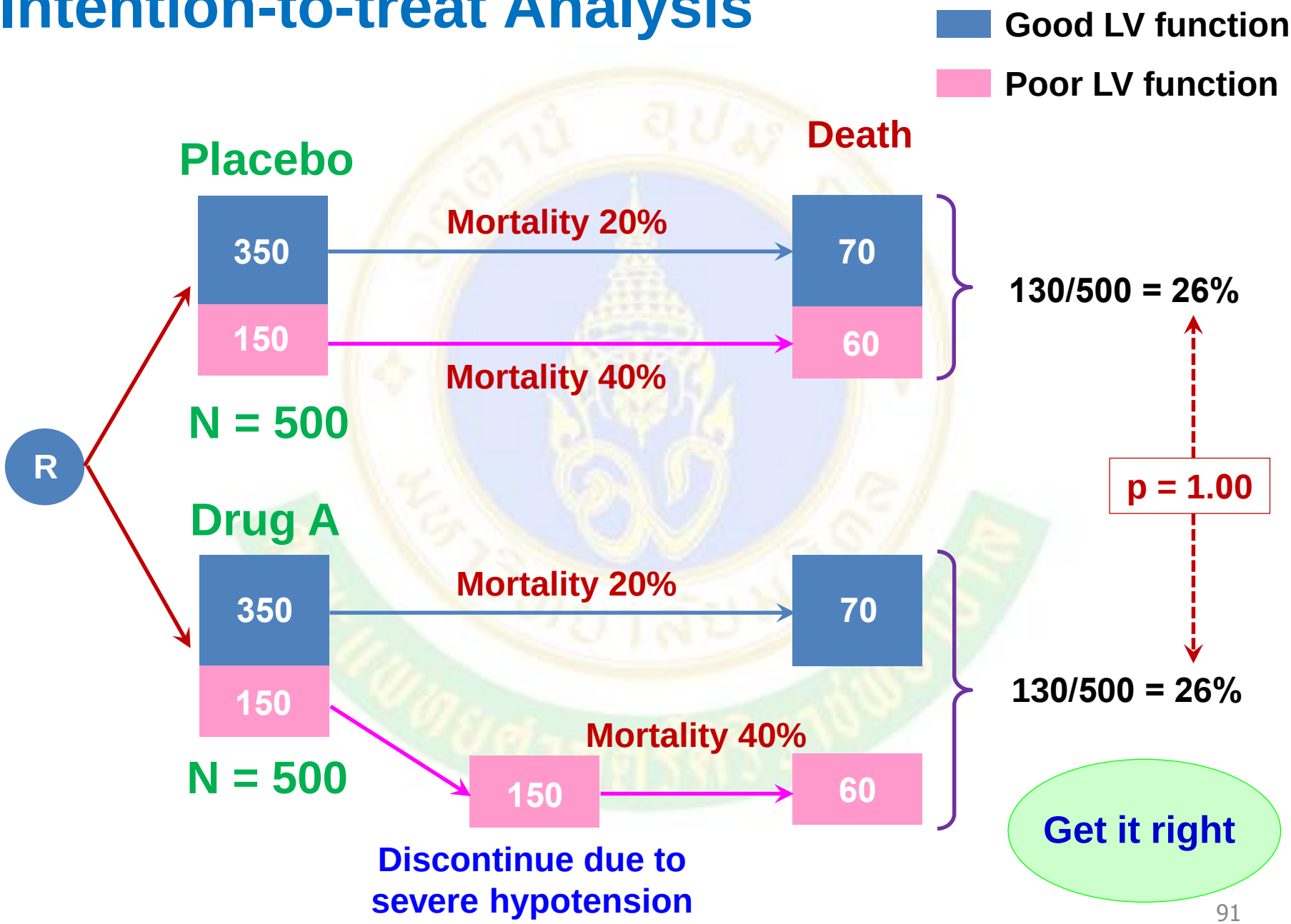
Example

- Drug A in acute STEMI to reduce in-hospital mortality
- Drug A can cause severe hypotension in subjects with poor left ventricular function
- Truth: Drug A has no effect in acute STEMI regarding in-hospital mortality.

Per-Protocol Analysis



Intention-to-treat Analysis



Design Considerations

- Research question
- Selection of participants
- Selection of intervention and control
- Selection of outcomes (endpoints)
- Data analysis and sample size
- Measures to reduce bias
- **Ethical considerations**

Ethical Issues

- Is randomization ethical?
- Is using placebo ethical?
- IRB or EC approval
- Informed consent

Ethical Issues

- Is randomization ethical?
  - Withholding a drug from patients
- "Randomization is ethical only when we do not know whether drug A is better than drug B"
- Equipoise
  - The state of uncertainty about the relative merits of new treatment and standard treatment
  - Current evidence does not prove that either arm is superior

Ethical Issues

- "Studies are only ethical if they have a reasonable likelihood of producing the correct answer to the research question, and randomized studies are more likely to lead to a conclusive and correct result than nonrandomized designs"
- Is it ethical "not to randomize"?

Ethical Issues

- Is using placebo ethical?
  - "Pure placebo" is not ethical if there is a standard treatment for the condition
  - Standard treatment must be provided to all patients; experimental treatment is then compared to placebo on top of the standard treatment

IRB or EC Approval

- Risk minimization
- Risks are reasonable in relation to anticipated benefits
- Informed consent
- Maintenance of confidentiality

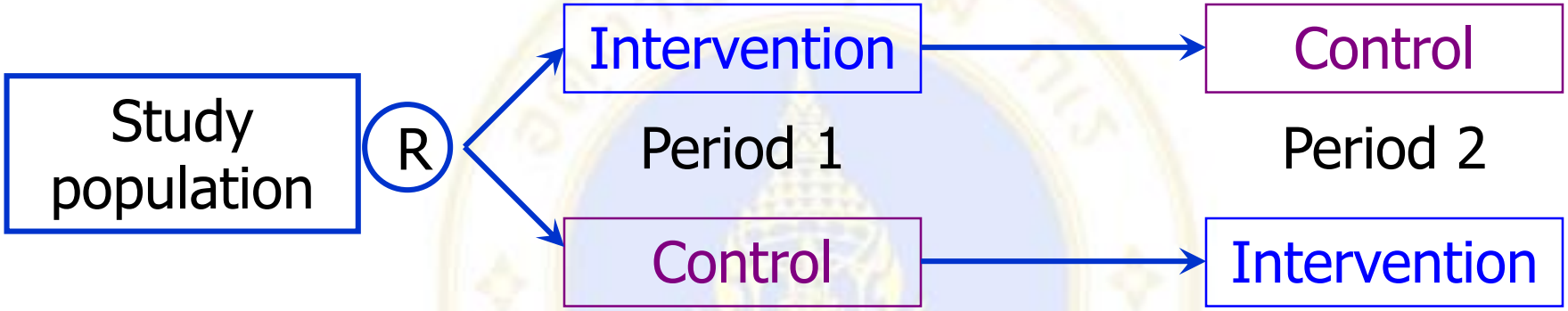
Informed Consent

- Consent provided after subjects fully understand the objectives, procedures, anticipated benefits and risks of the study
- "Written" consent is standard
- "Verbal" consent is acceptable in some situations
- Decision to participate must be made free of any influence

Other Forms of Experiment

- Randomized cross-over design
- Factorial design

Cross-Over Design



- Each subject serves as his/her own control
- Reduced variability, resulting in smaller sample size
- Suitable for
  - Chronic, stable diseases, episodic conditions
  - Treatment is non-curative
- Based on the assumption that there is no "carry over" effect

Factorial Design

- Evaluate 2 or more interventions in a single trial (save cost and time)
- Interaction between the 2 (or more) interventions
  - Absence: much smaller sample size than conducting 2 separate trials
  - Presence: the only trial design that enables assessment of interaction

Factorial design: ISIS-2 Trial

	Aspirin (ASA)	ASA Placebo
Streptokinase (SK)	SK + ASA	SK
SK Placebo	ASA	Nothing

- Absence of interaction
  - Effect of SK: (SK+ASA combined with SK) vs. (ASA combined with Nothing)
  - Effect of ASA: (SK+ASA combined with ASA) vs. (SK combined with Nothing)

Conclusions

- Experimental study (= RCT) is most suitable for studying the effectiveness of a therapeutic or preventive intervention
- Main features
  - Control group
  - Similar prognosis between experimental and control groups
  - Investigators manipulate or control assignment of subjects to groups using randomization technique (unique for experiment study)

Conclusions

Measures used to reduce bias

- Treatment allocation by randomization
- Concealment of randomization
- Blinding of treatment allocation
- Maximizing adherence and follow-up
- Analysis using intention-to-treat principle