JOHNS HOPKINS
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Study Designs, Objectives, and Hypotheses

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Section A

Variations in Study Designs

Many Designs Available

- Parallel
- Cross-over
- Factorial
- Cluster
- Others

Categories of Trials

- Phases
- Control groups
- Chronic vs. short-term treatment
- Single vs. multiple centers
- Exploratory vs. confirmatory

Study Designs

- Focus on trials intended to provide primary evidence of safety and efficacy (“pivotal” trials)
- Regulations permit substantial flexibility (“adequate and well-controlled trials”)

Selecting a Study Design

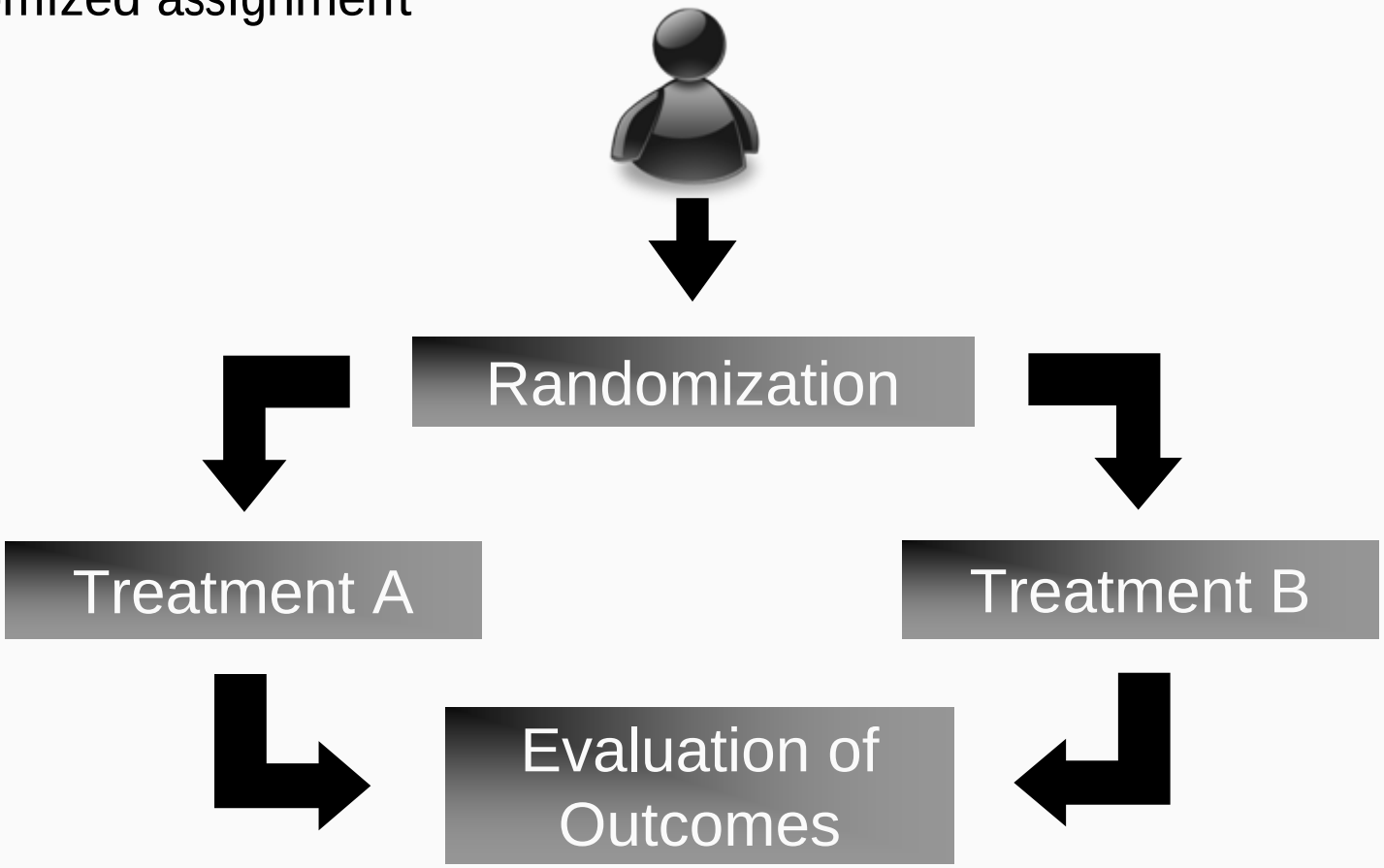
- What are the objectives?
- What are the expectations?
  - Major advance
  - Modest advance
  - Reduction in side effects
- What are the practicalities?
  - Available population
  - Relevant population
  - Potential impact on medical practice
  - Ability to blind/mask

Parallel Groups

- Multiple concurrent experimental arms
  - Different treatments
  - Different doses
- Control arm(s)
  - Placebo, active control
- Balance/imbalanced randomization

Parallel Design

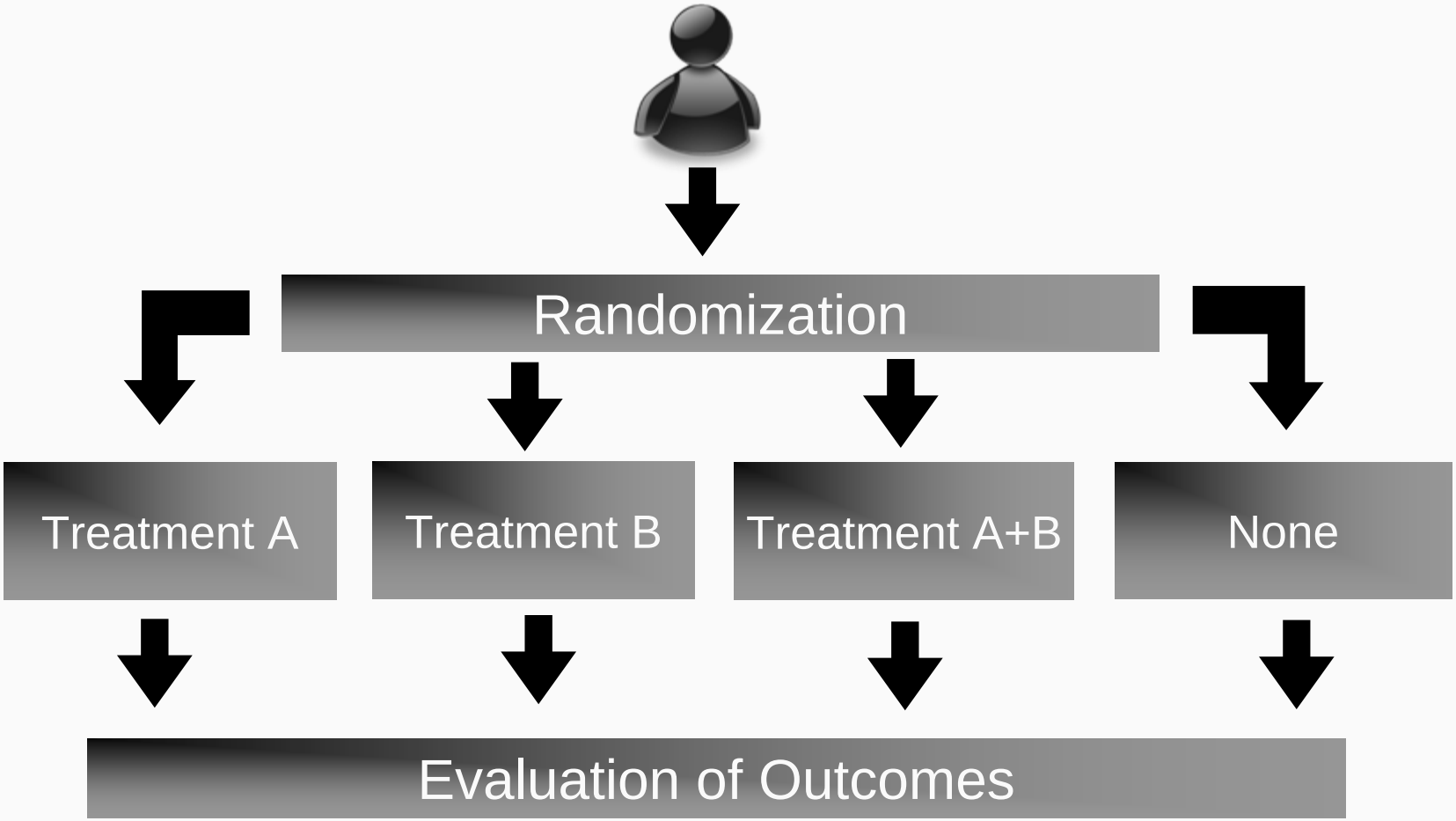
- Classical clinical trial approach
- Two study groups
- Randomized assignment



Adapted from Tinmouth A, Hebert P. Interventional trials: an overview of design alternatives. *Transfusion.* 2007;47:565-67.

Factorial Designs

- Evaluates multiple factors simultaneously
- 2 X 2 most practical, but little used
- Sometimes a combination cannot be given (incomplete factorial)



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ISIS-3 Design

Fibrinolytic agent

Anti-thrombotic agent	SK	tPA	APSAC
Aspirin			
Aspirin and heparin			

Source: *Lancet*. (1992). 339: 753-70.

Factorial Design

- Evaluates two interventions simultaneously
- Four possible treatment combinations
- Efficient approach in some circumstances
- Potentially more informative approach
- Increases proportion getting active treatment
- Major concern: interaction of interventions

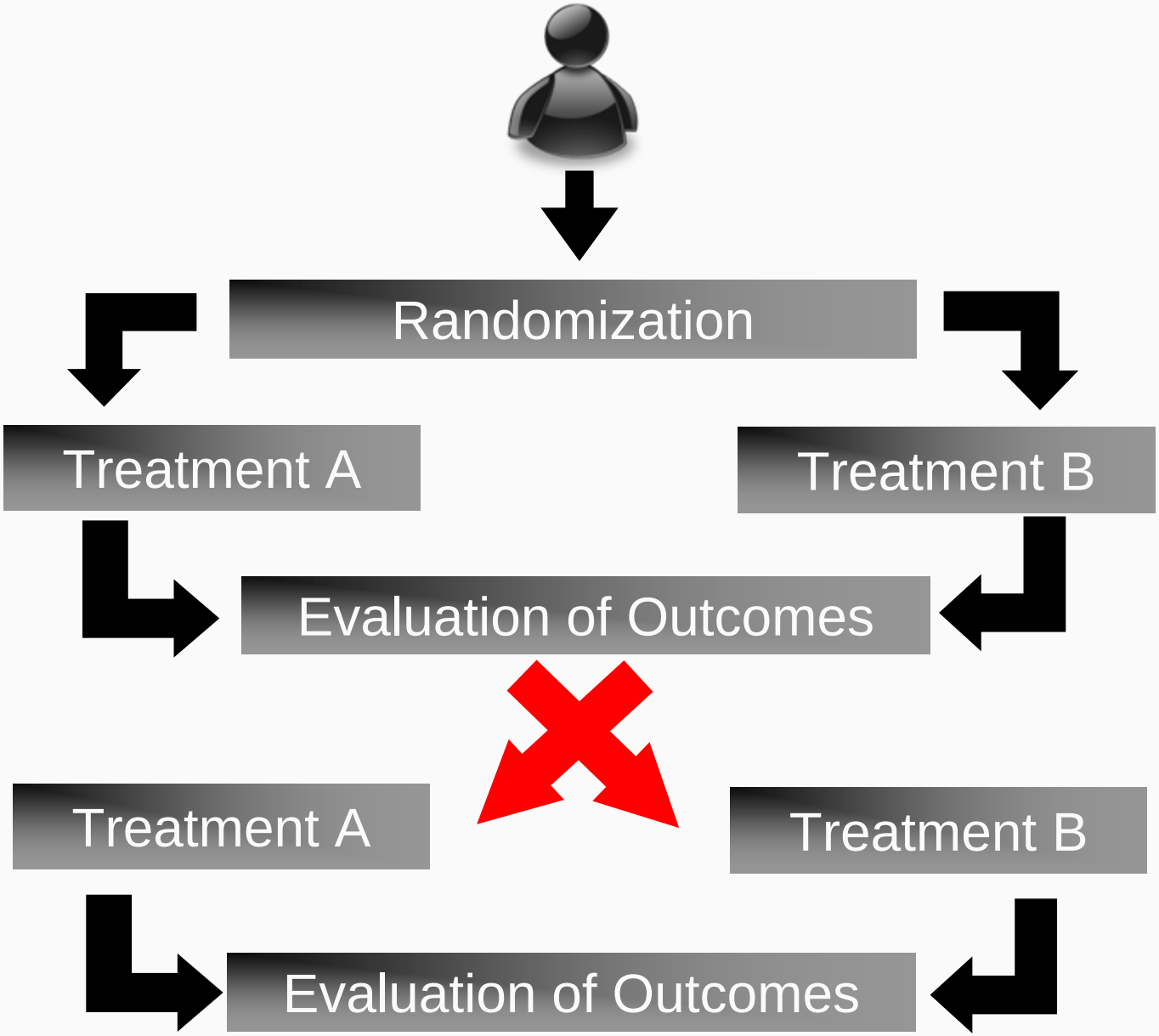
Problems with Factorial Design

- Patients must be willing and able to take any of the treatment combinations
- Optimal dose modification strategy for toxicity may be hard to determine
- May require burdensome administration scheme if blinded
- Interaction complicates interpretation of treatment effects

Bottom Line on Interaction

- You can't rely on detecting modest interactions if studies are powered for main effects
- Interaction is important to study if agents are likely to be used together

Crossover Designs



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Advantages of Cross-Over Designs

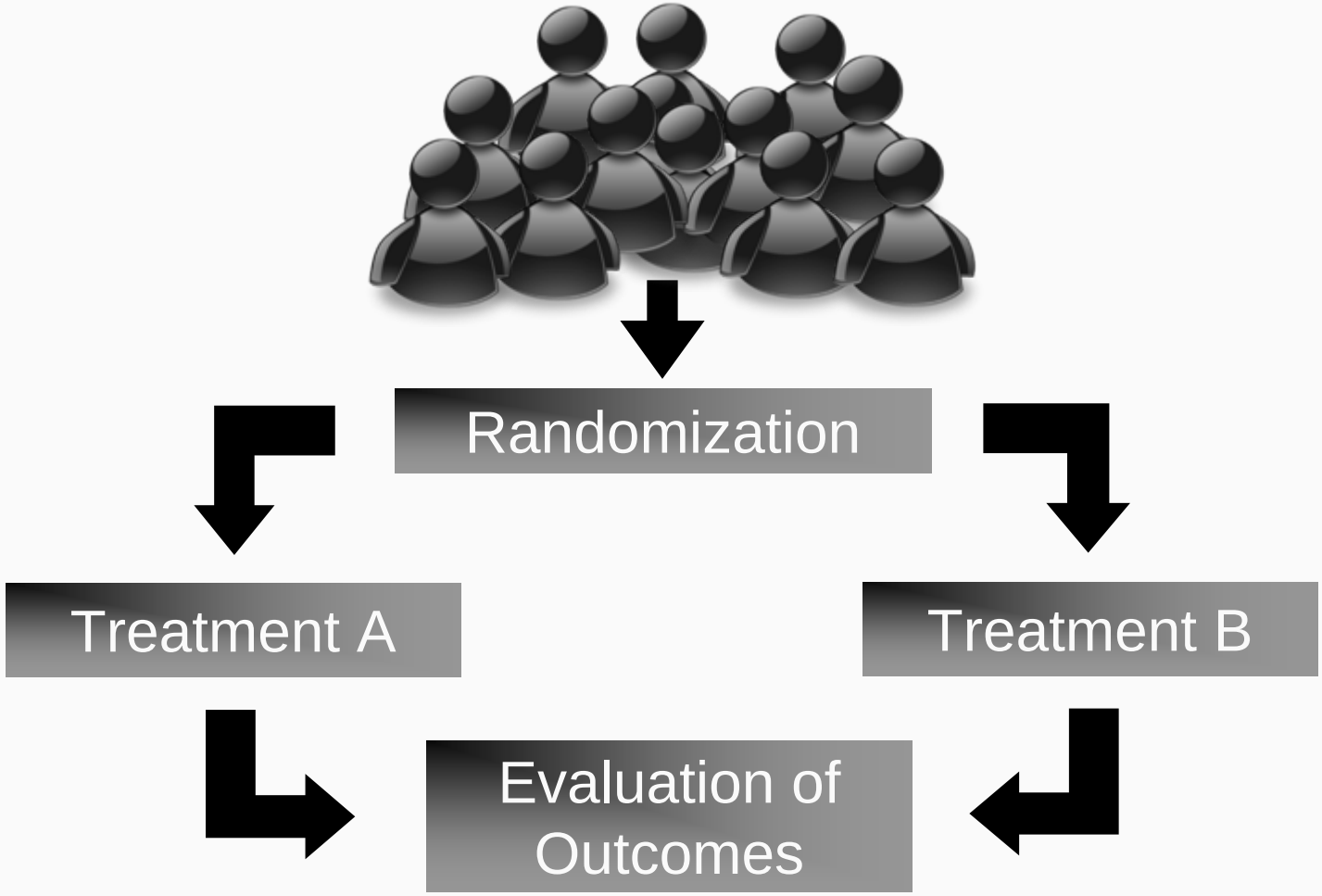
- Address question of major interest
  - Will this patient do better on drug A or drug B?
- Removes “patient effect” thereby reducing variability and increasing precision of estimation
- Opportunity to receive both treatments (or be assured of receiving active treatment at some point) is attractive to patients
- Under assumption of no carryover effect, design provides more information than simple parallel design

Disadvantages of Cross-Over Designs

- Assumption of no carryover effects is difficult to test
- May be difficult to determine appropriate length of washout period so as to avoid carryover effects
- There may be “period” effects in addition to carryover effects
  - Progression of disease
  - Dropouts

Cluster Design

- Groups or clusters randomly assigned, not individuals
  - Examples: villages, classrooms, platoons



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Study Designs

- Treatment allocation method
- Blinding of assigned treatment
- Choice of control group
  - ICH E10

In the Next Lecture Section We'll Look at . . .

- Objectives and hypotheses
  - How to meet objectives
  - Hierarchy of strength of evidence
  - Phases of trials

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Section B

Objectives and Hypotheses

In the Beginning

- Begin with a clear statement of the major scientific questions posed by the study, usually conveyed in quantitative terms

Objectives by Phase

- Phase I
  - Determine optimal or tolerable dose
  - Describe adverse event or PK profile
  - Establish feasibility of treatment approach
- Phase II
  - Estimation of activity
  - Comparison of doses or schedules
  - Estimation of factors for Phase III
- Phase III
  - Demonstrate superiority or non-inferiority
  - Estimate rates of adverse events
- Phase IV
  - Address remaining outstanding issues

Examples

- To select the optimal dose that satisfies specific criteria
- To demonstrate that the two year mortality rate on treatment A is less than on treatment B

The Objective Is to . . .

- Classify
- Order
- Estimate differences
- Estimate rates

Cohesive Driving Force

- All other properties of the trial, the study population, the primary endpoint, the sample size, the primary analysis, flow from the study objective

Study Hypotheses

- The study objective corresponds to the primary hypothesis of the study, e.g., the null hypothesis, H_0
  - The two year mortality rate on treatment A equals the two year mortality rate on treatment B

In the Next Lecture We'll Look at . . .

- Study populations
  - Who should we recruit?
  - Who do we actually recruit?
  - Eligibility criteria
  - To whom do the results apply?