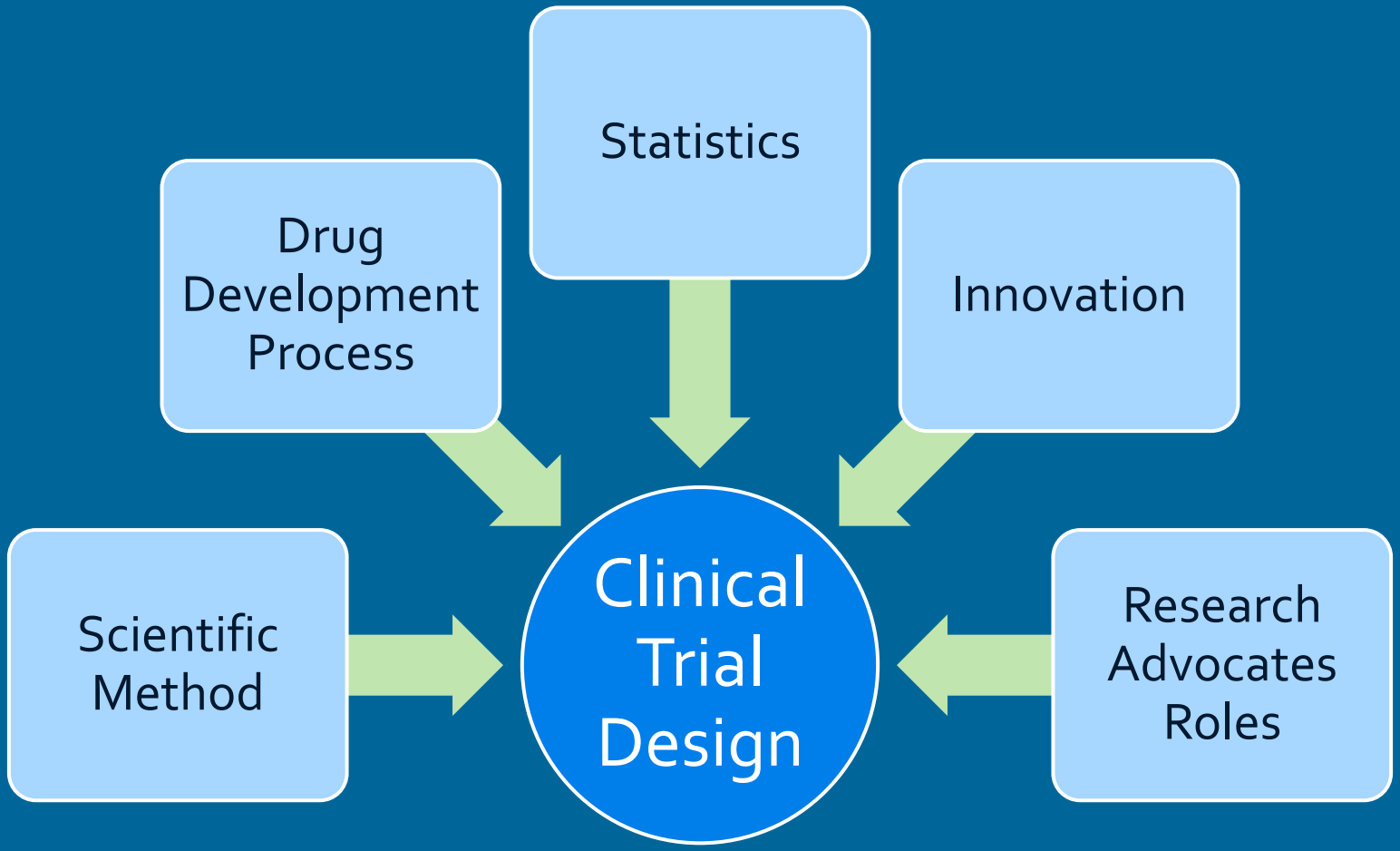
Research Advocacy Network
AdvocateInstitute

Understanding Clinical Trial Design: *A Tutorial for Research Advocates*

Part I

Jane Perlmutter
janep@gemini-grp.com

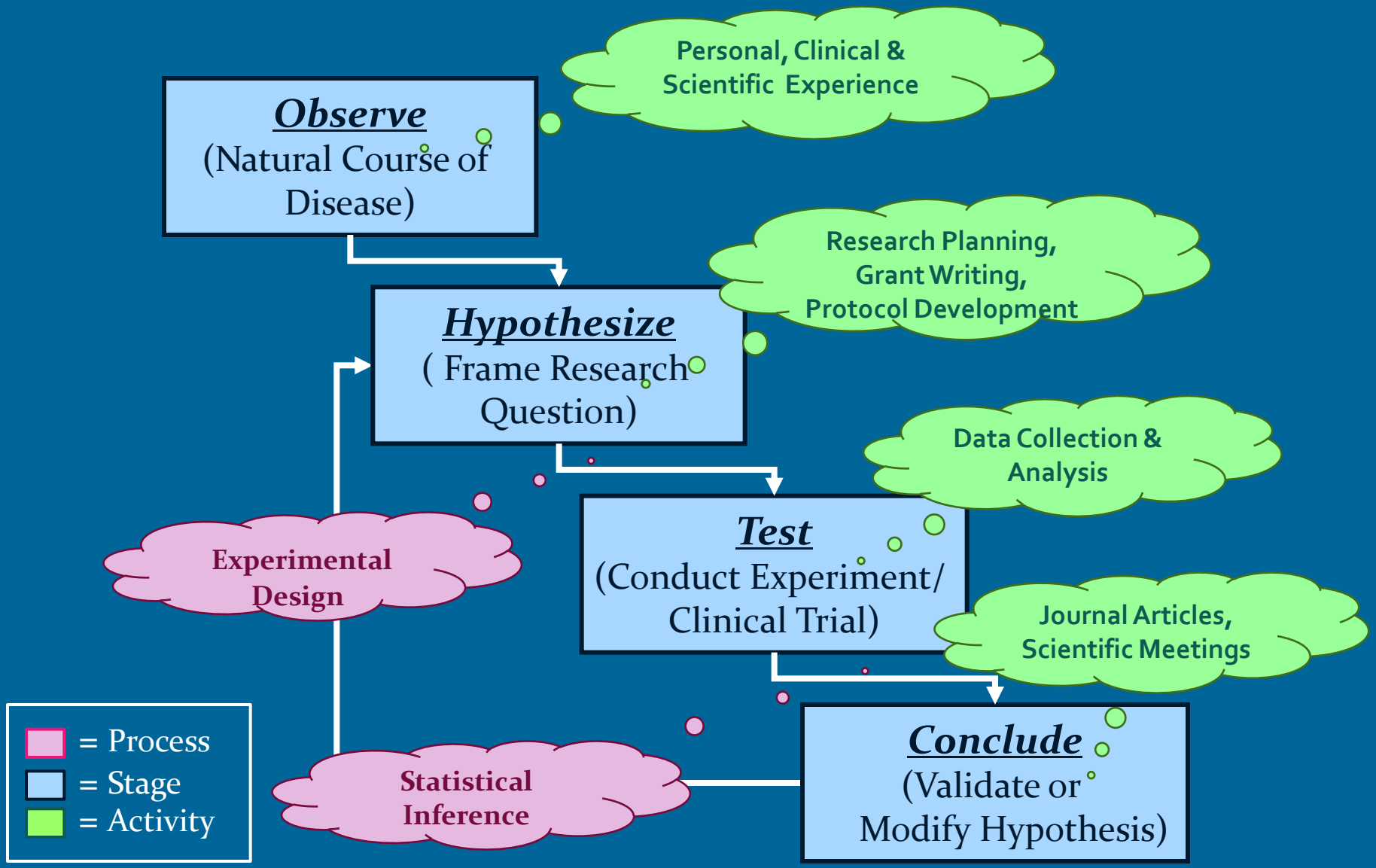
Clinical Trial Design



Part I Topics

- Scientific Method
- Drug Development Process
- Components of Clinical Trials
- Randomized Controlled Trials
- Statistical Inference—Hypothesis Testing

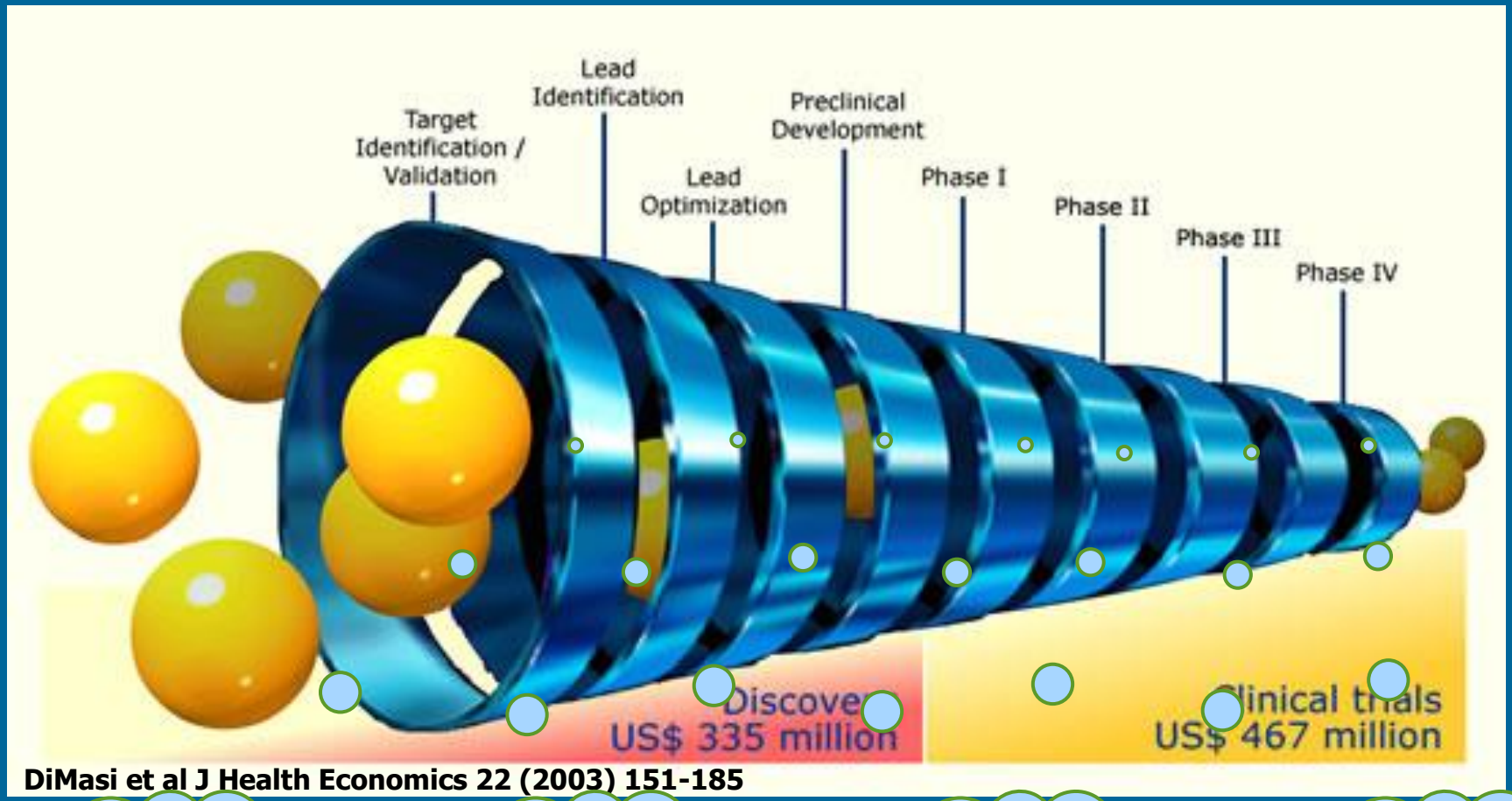
Scientific Method



Clinical Trials

- Experiments that assess the value of clinical interventions
  - New drugs, including combinations, doses, and schedules
  - Surgical procedures
  - Radiation protocols
  - Psychosocial interventions
  - Prevention strategies
  - Screening
  - Etc.

Drug Development Process



DiMasi et al J Health Economics 22 (2003) 151-185

Biology

Chemistr

In vitro & In vivo mode

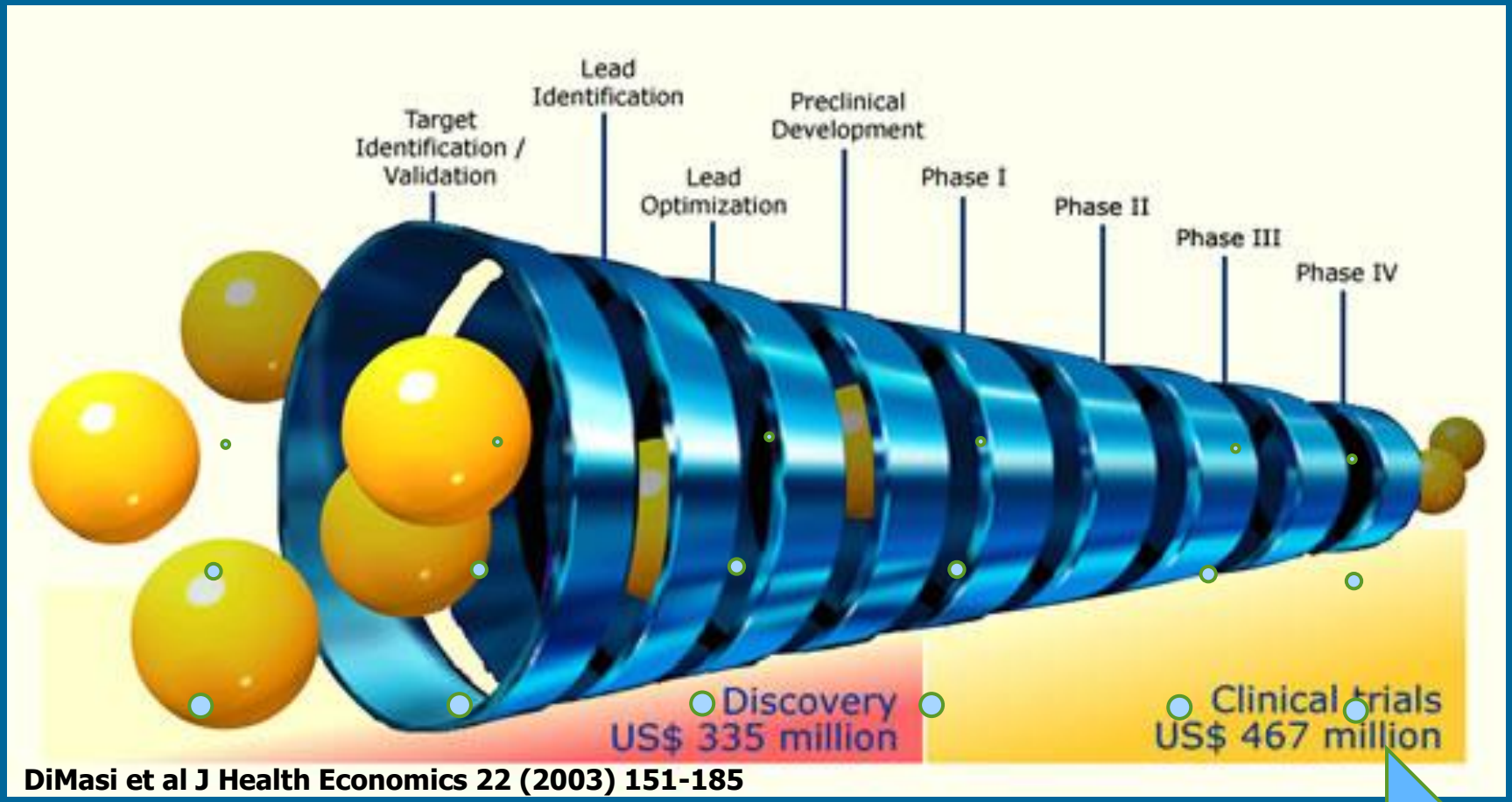
Safety (Maximun Tolerated Dose)

Activity

Efficacy

Post Marketing

Drug Development Process



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1,000,000 Screened → 1,000 Hits → 50 Leads → 10 Phase I Trails → 2 Phase III Trials → 1 New Drug

Drug Development

- Has many false starts
- Takes a long time
- Takes a lot of money
- Requires multiple clinical trials and many patient participants for approval

Clinical Trial Components: PICO

- ***P***atients
  - Eligibility requirements determine generalizability of results
- ***I***ntervention
  - Impact disease, but also other aspects of patients lives
- ***C***omparison
  - Must avoid bias to lead to unambiguous results
- ***O***utcomes
  - Clinical relevance
  - Measurement issues

Comparison Issues

- ***Avoid Bias:*** distortion that leads to ambiguous results

Type of Bias:	Confounding among variables being studied	Confounding between variables being studied and methods of collecting data
Example:	Patients assigned to the experimental arm have more advanced disease than patients in the control arm	Patients assigned to the experimental arm are from one hospital and those in the control are from
Prevention:	***Randomization:*** process by which patients are assigned by *chance* to separate groups	***Blinding:*** procedure in which one or more parties to the trial are kept unaware of the treatment assignment.

Outcomes Measures

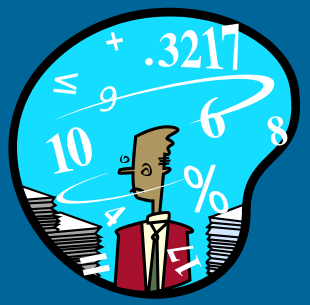
- ***Primary endpoints:*** main result that is measured—e.g., overall survival, disease free survival, response rate
- ***Secondary endpoints:*** outcomes that are of interest but of lesser importance than the primary endpoints –e.g., side effects, quality of life
- ***Surrogate endpoints:*** biomarker that is intended to substitute for a primary endpoint expected to predict clinical benefit

Randomized Controlled Trial

Experimental/ Investigational Group/Arm	***Comparison/ Control Group/Arm***
Experimental or Investigation Treatment, plus Standard of Care	Standard of Care

- Equal numbers of patients ***randomly*** assigned to two (or more) treatment arms
- Triple ***blinded*** (patients, healthcare providers, and searchers), if possible
- Single primary endpoint
- May require many trials to answer complicated questions

Statistical Inference



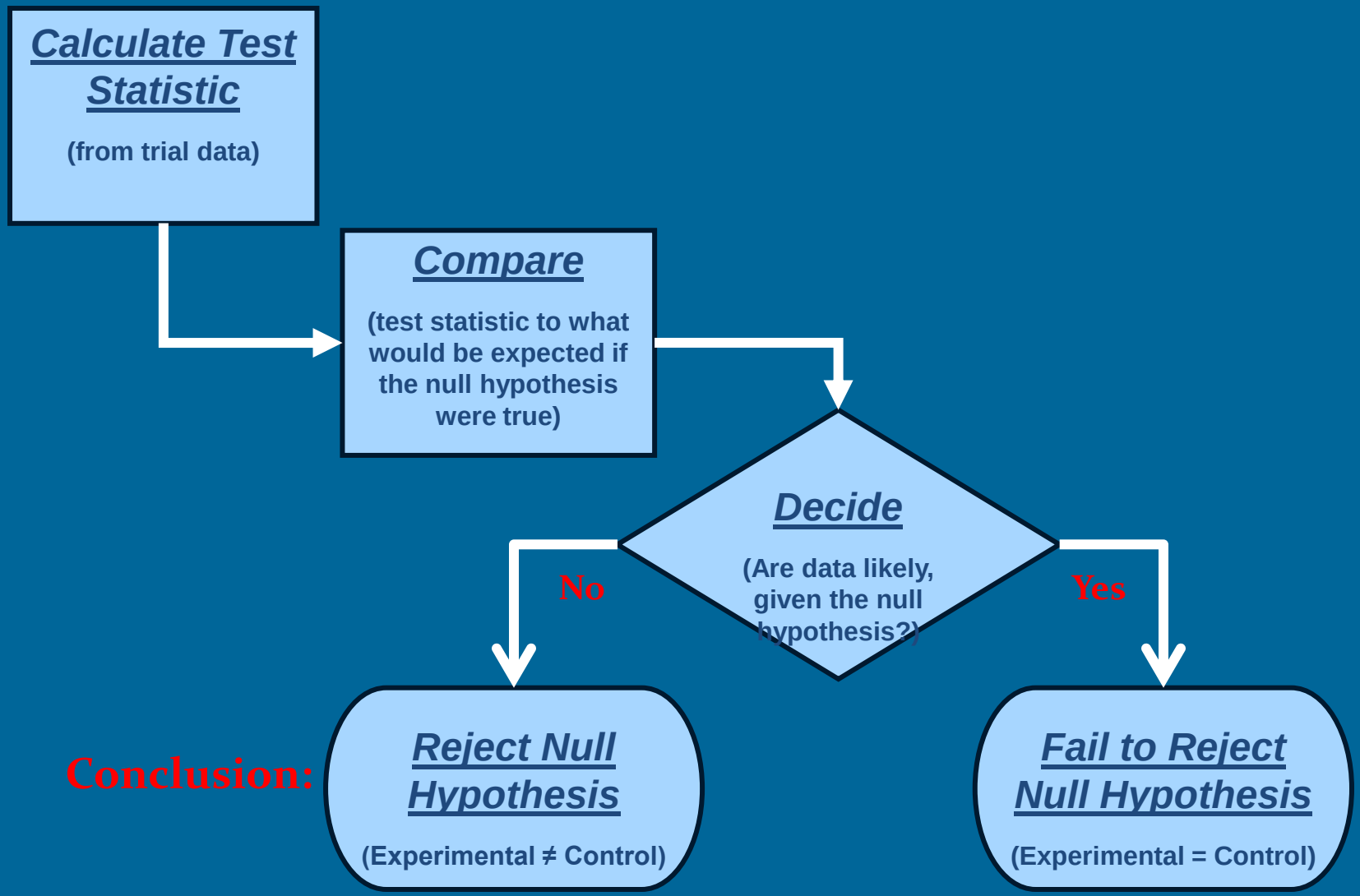
- Allows researchers to draw conclusions about populations of future patients from the limited sample of patients in their trials
- Traditional (frequentist) approach:
  - Determine whether trial results are evidence of a ***true difference*** between experimental and control intervention, or a ***chance*** occurrence
  - Errors will be made, but over the long run, the proportion of errors are controlled

Hypothesis Testing

- State a null hypothesis
  - What you are trying to disprove
  - Typically, that experimental (investigational) and control (standard of care) interventions are equivalent
- Determine whether trial results are evidence of a true difference, or a chance occurrence
  - If the difference would be very unlikely if the null hypothesis were true:
    - Reject the null hypothesis
    - Conclude the experimental and control interventions differ

Philosophy: It is relatively easy to prove something is false; much harder to prove something is true

Hypothesis Testing



Errors in Hypothesis Testing

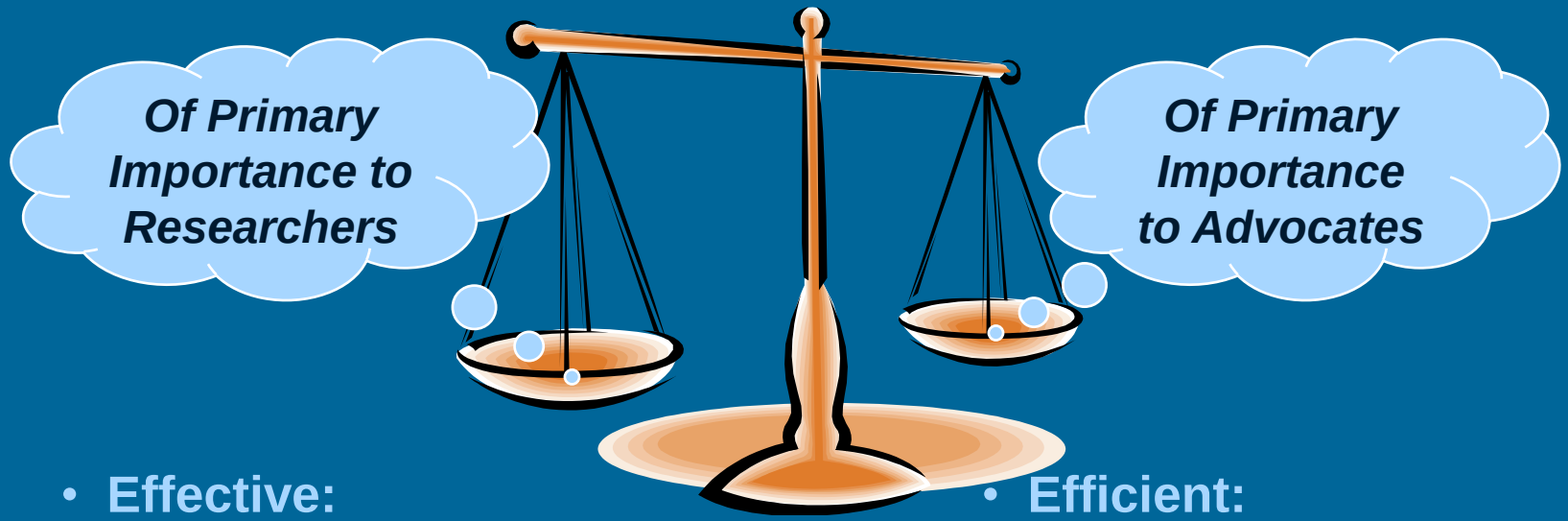
Decision \ Truth	H_o is True	H_o is False
Fail to Reject H_o	☺ Ex = Control	☹ Ex = Control
Reject H_o	☹ ☹ Ex ≠ Control	☺ ☺ Ex ≠ Control

α *or type I error (false positive)*

β *or type II error (false negative)*

Note: Power = 1- β

Clinical Trial Design: Balancing Multiple Priorities



- **Effective:**
  - Avoid errors
  - Answer the right primary question definitively
  - Provide evidence about secondary questions
- **Satisfy the Needs of Multiple Stakeholders**

- **Efficient:**
  - Minimize Costs
  - Speed Results
  - Increase Accrual
- **Ethical:**
  - Minimize harm and maximize benefit to participants

Clinical Trial Design