Department of Clinical Sciences

Temple Clinical Research Institute

School of Medicine
TEMPLE UNIVERSITY®

Designing The *Right* Study

…..*Observational & Experimental Designs*

Susan G. Fisher, M.S., Ph.D.
Chair, Department of Clinical Sciences

October, 2015

Asking the Right Question

A Good Research Question is:

- Relevant and interesting
- Feasible
- Ethical
- *Novel…maybe!*
- Well-built

Start with a research question:

Is statin use associated with an increased risk of type II diabetes?

Formulate a hypothesis:

Null Hypothesis (H_0) :

There is no association between statin use and risk of diabetes.

Alternate Hypothesis (H_A) :

There is an association between statin use and diabetes.

Refining the Research Parameters

Population

- High cholesterol
- Previous cardiac event
- Presence of risk factors of diabetes
- Normal glycated hemoglobin (HbA_{1C})

Independent Variable: statin use

- Specific type/drug
- Dose
- Length of time on drug

Dependent Variable: diabetes

- Onset of newly diagnosed diabetes
- Changes in HbA_{1C}

Strength of Evidence

Strength		Design
Weak	Descriptive	Case Report
		Case Series
		Ecological Study
		Cross-sectional Survey
	Analytic	Case-control Study
		Cohort Study
Strong		Clinical Trial

Case Report / Case Series

- Anecdotal Reports of Interesting Observations
  - Unusual cluster of symptoms
  - Departure from a normal pattern of known disease
  - Repetitive disease occurrence among people with a specific exposure
- Cluster of observations in short time period or small geographic area
  - New epidemic of known disease
  - New disease occurrence
  - New cause of existing disease

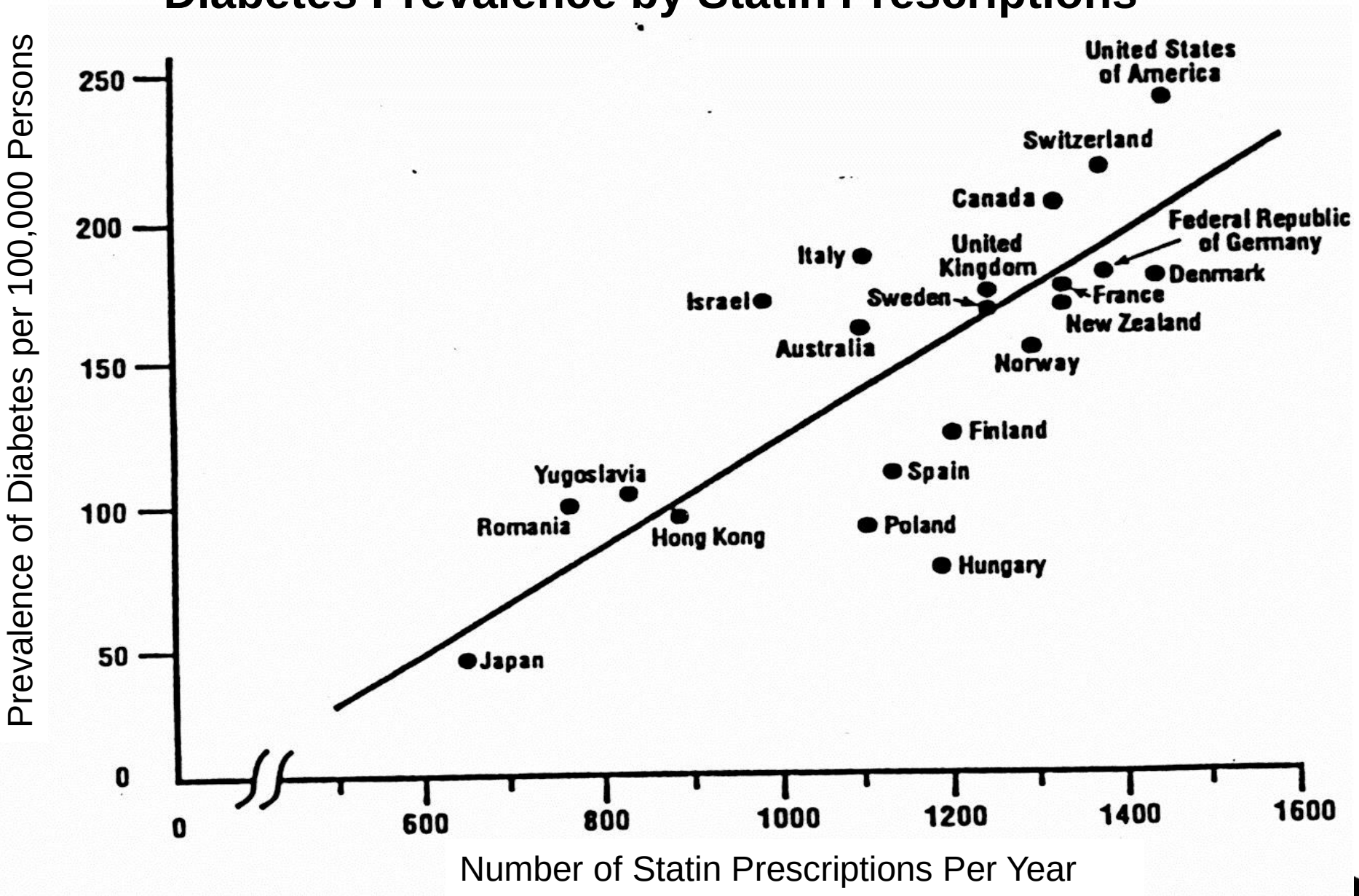
[Example: Three well-controlled diabetic patients prescribed statins over the last 6 months have unexpected elevations in HbA1C]

Ecologic Studies

- Evaluation of associations between exposures and outcomes in populations rather than individuals
- *Ecological Fallacy*

  -results from making causal inferences about individual phenomena based on observations of group

Diabetes Prevalence by Statin Prescriptions



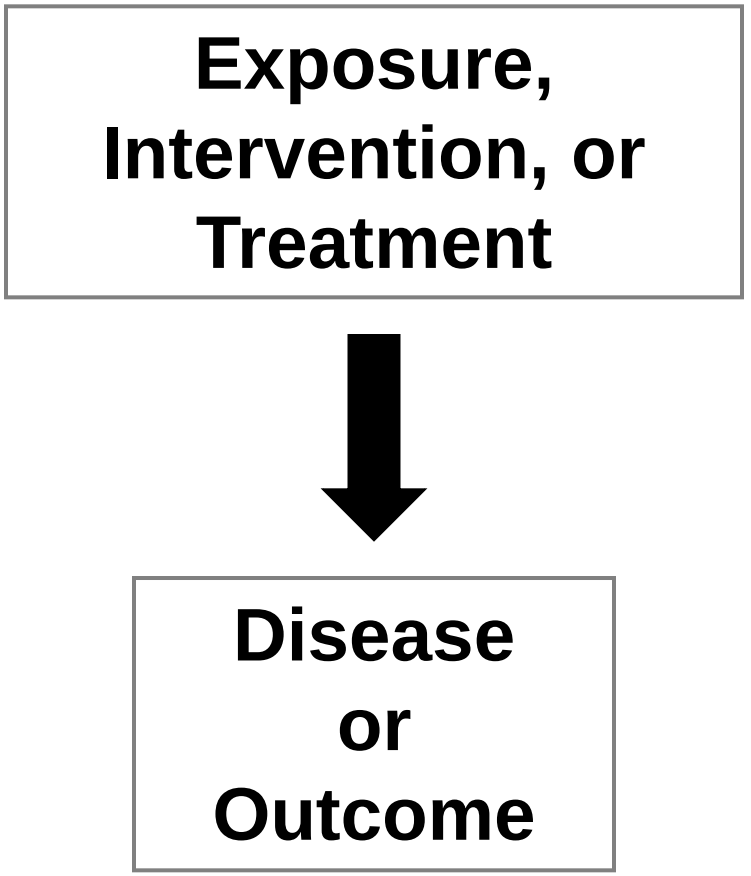
Cross-Sectional Studies

- Provide “snapshots” of the health of a specified population at one moment in time.
- Usually descriptive in nature
- Often used to determine ‘prevalence’ of a condition or correlation between 2 variables
- Temporality cannot be determined → ‘chicken or egg problem’
- Low cost and no loss to follow-up

[Example: Identify 200 males over age 40; obtain history of statin use and measure their HbA1C level.]

Analytic (Observational) Studies

- **Case Control study**
- **Cohort Study**



Case Control Study

- Select subjects with outcome/disease of interest (Cases)
- Select similar group of individuals without disease/outcome of interest (Controls)
- Determine exposure status of all subjects

	Cases (Diabetes)	Controls (No Diabetes)
Exposed (Statins)	a	b
Unexposed (No Statins)	c	d
Total	a + c	b + d

Case Control Study Advantages

- Quick and easy
- Able to study multiple risk factors simultaneously
- Efficient for rare diseases
- Requires ‘small-ish’ sample sizes

Case Control Study Disadvantages

- Cannot address causality
- Only investigates 1 disease outcome
- Can only compare odds of exposure; not incidence of outcome
- High, **HIGH** likelihood of bias

Control Sources

- General population controls
- Hospitalized individuals
- Neighborhood residents
- Spouses / relatives/ friends of case

ODDS RATIOS

In a case control study, we use the **ODDS RATIO** to estimate the odds of a case being exposed versus the odds of a control being exposed.

ODDS RATIO (OR) = AD/BC

	Cases (Disease)	Controls (No Disease)
Exposure	**A**	**B**
No Exposure	**C**	**D**

OR = Odds of case exposed / Odds of control exposed $= \frac{A}{C} \Big/ \frac{B}{D}$ or $= AD/BC$

Interpreting an Odds Ratio

If OR = 1

- Odds of exposure is equal between groups (no association)

If OR > 1

- Odds of exposure is greater in cases than in controls (positive association);

If OR < 1

- Odds of exposure in cases is less than odds of exposure in controls (negative association; possibly protective)

Example of an Odds Ratio

Role of Statins in Risk of New Onset of Diabetes

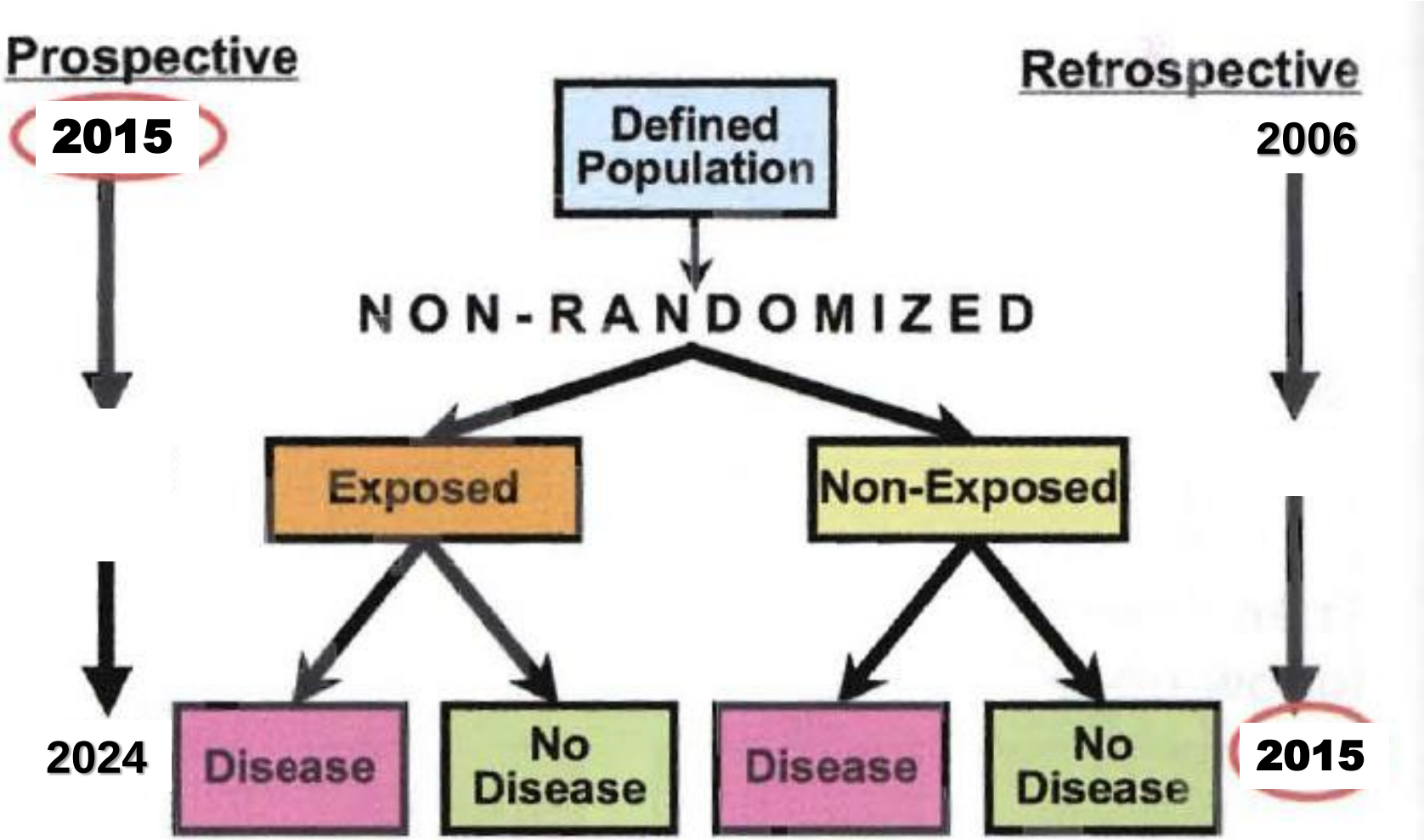
	CASES Diabetes	CONTROLS No Diabetes
Statin Use for > 2 yrs (before dx)	25	10
No Hx of Statin Use	50	80
Total	75	90

$$OR = \frac{ad}{bc} = \frac{25*80}{50*10} = \frac{2000}{500} = 4.0$$

Cohort Studies

- Designed to address a specific hypothesis;
- Select a group of subjects exposed to factor of interest and a group **not** exposed
- **OR** select a group of subjects and then categorize them by presence or absence of risk / exposure / treatment
- Prospectively follow both the exposed and unexposed group to determine occurrence of outcome of interest

Prospective & Retrospective Cohort Studies



Cohort Study

Role of Statins in Risk of New Onset of Diabetes

	Diabetes		Incidence
	Yes	**NO**	
Exposed (Statin Use)	a	b	a/(a+b)
Unexposed (No Statin Use)	c	d	c/(c+d)

Relative Risk (RR) = incidence of disease in exposed divided by incidence of disease in the unexposed

$$RR = (a/a+b) / c/c+d)$$

Interpreting the Relative Risk of a Disease

If RR = 1

- Risk in exposed equal to risk in unexposed (no association)

If RR > 1

- Risk in exposed greater than risk in unexposed (positive association);

If RR < 1

- Risk in exposed less than risk in unexposed (negative association; possibly protective)

Cohort Study

Role of Statins in Risk of New Onset of Diabetes

	Diabetes		Incidence
	Yes	**NO**	
Exposed (Statin Use)	30	270	30/300=.10
Unexposed (No Statin Use)	25	475	25/500=.05

RR = (a/a+b) / c/c+d)

RR = 0.10 / 0.05 = 2.00

Advantages of Cohort Studies

- Cases are incident cases and may be more representative of all cases of the disease
- Provides more information on the natural history of a disease
- Incidence rates are available
- Fewer sources of bias
- Temporal relationship between exposure and disease can be established
- Able to study a rare exposure and a common disease

Disadvantages of Cohort Studies

- Duration may be long with difficulty maintaining consistent study methods and staff
- Expensive
- Large population required
- Exposure may not have been measured at baseline or may change
- Rare diseases cannot be studied

When is a Prospective Observational Study the RIGHT Design?

- Good evidence of an association between an exposure and a disease exists;
- Attrition of study population can be minimized;
- Ample funds are available;
- The investigator has a long life-expectancy

Randomized Clinical Trial: What?

- Experimental design to test a specific hypothesis involving a new intervention(s);
- Controlled and randomized;
- Assign a group of subjects to one of two or more interventions;
- Follow subjects *prospectively* to determine outcome of interest.

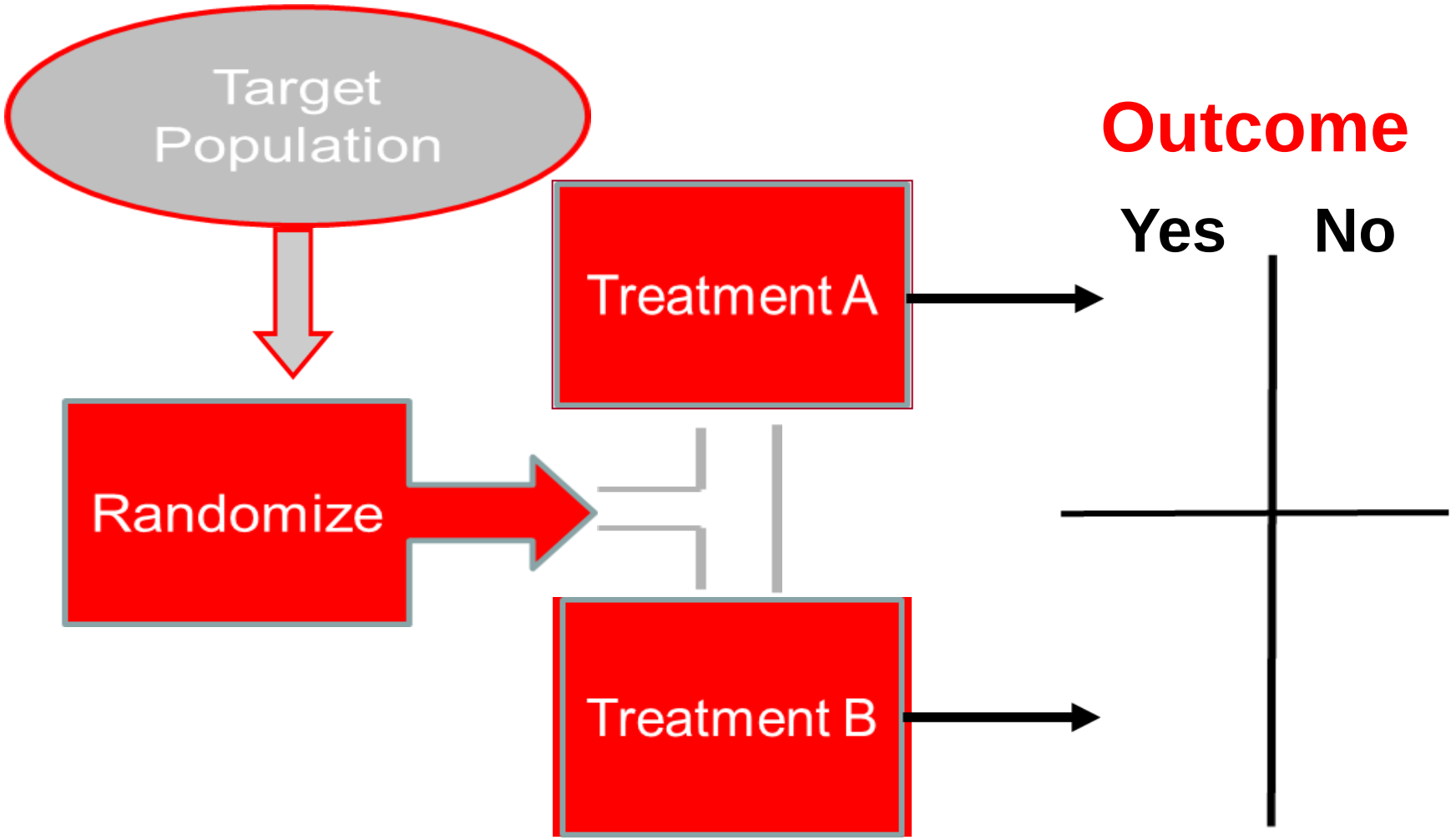
Randomized Clinical Trial: When?

- Exposure or treatment of interest is modifiable;
- Individuals are willing to relinquish control;
- Legitimate uncertainty exists about benefit of treatment;
- Health condition and/or outcome is reasonably common or detrimental.

Randomized Clinical Trial: WHY?

- Best method for providing evidence related to direct treatment benefit
- “Clinical equipoise”

Randomized Clinical Trial



Hallmark #1: Randomization

- Randomization is the process of assigning subjects to different treatments by using a predetermined, random scheme;
- Eliminates bias in treatment assignments;
- Balances known and unknown prognostic factors between treatment groups;

Hallmark #2: Blinding

- Process in which the identity of the treatment being received is unknown to certain individuals.

- Single blind → patient
- Double blind → patient & physician
- Triple blind → patient, physician, & reviewer

Hallmark #3: Validity of Results

- Inclusion criteria provide defined, homogeneous population;
- Treatments/interventions administered with a systematic, planned approach;
- Treatment groups provided similar care and follow-up;
- Outcomes/endpoints are defined and objectively assessed;
- Statistical analyses carefully planned *a priori.*

Pitfalls of Randomized Trials

- Numerous exclusion criteria leads to decreased generalizablilty;
- Lack of treatment choice, inflexible schedule lead to decreased accrual;
- Expensive & lengthy;
- Measurement of medical endpoints rather than patient-centered outcomes .

Randomized Clinical Trials

- Designed to provide best available care to patients;
- Maximize patient safety;
- Optimize data integrity;
- Minimize study bias;
- Provide compelling evidence of treatment efficacy.

If Research Were So Easy, EVERYONE would do it!