

# *How to Design Post-Marketing Comparative Evaluations*

---

*2008 International Health Technology  
Assessment Symposium*

*Taipei, Taiwan  
August 11, 2008*



uOttawa

L'Université canadienne  
Canada's university

*George A Wells*

# *Post-Marketing Comparative Evaluations*

## *Why are these needed?*

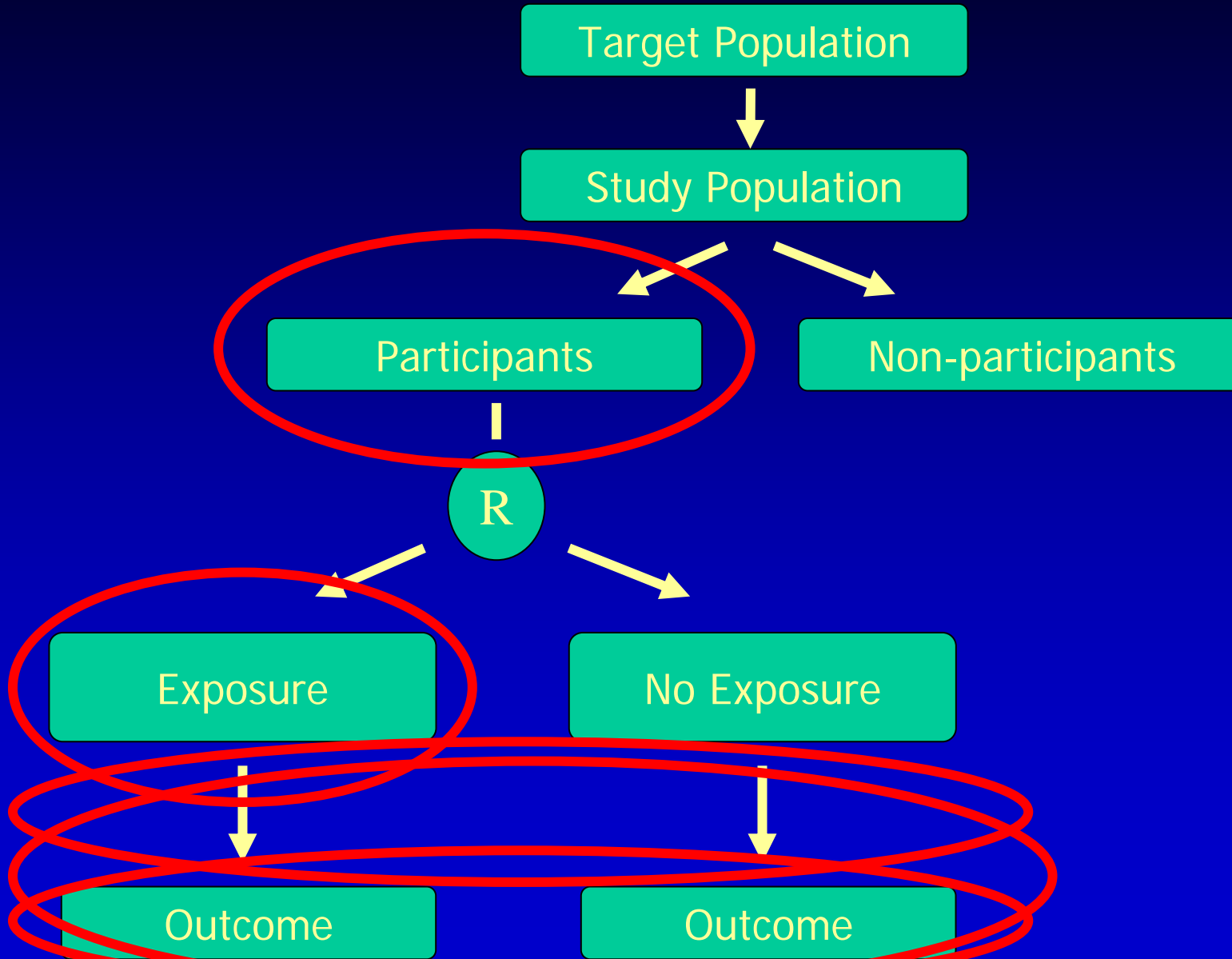
---

- RCT design yields the most robust evidence, but extrapolation of this evidence may not be realized
- Need for
  - post-marketing (routine care)
  - comparative (head-to-head)
  - evaluation (effectiveness)

(S. Schneeweiss, Clinical Pharmacology & Therapeutics, 2007)

# Structure: Randomized Controlled Trial

---



# *Limitations of Randomized Trials*

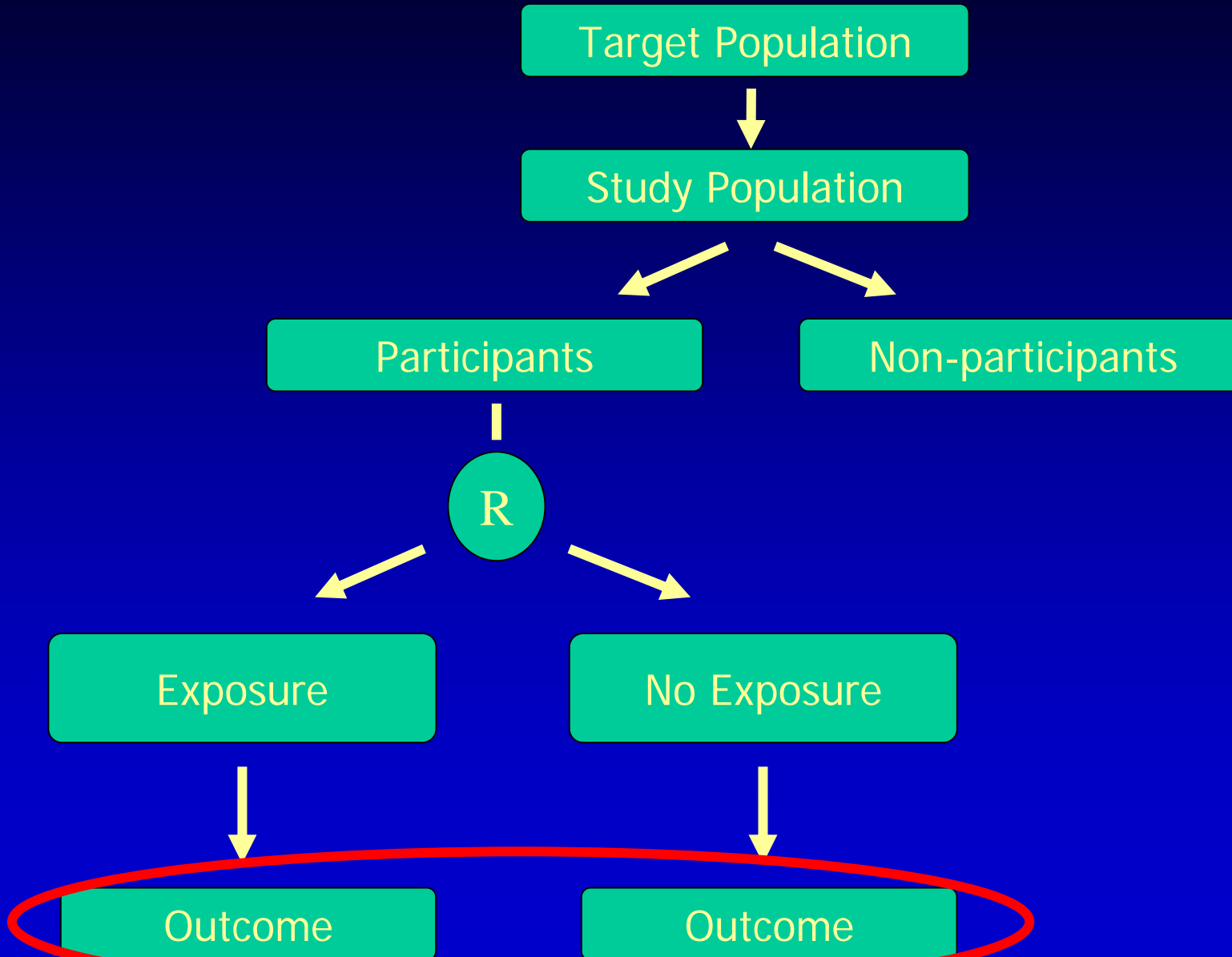
## *Issues to consider*

---

- **Choice of primary efficacy outcome**
- **Choice of duration of trial**
- **Inclusion of complicated patients**
- **Detection of adverse events**
- **Guidance on 'varying' the intervention**

# Structure: Randomized Controlled Trial

---



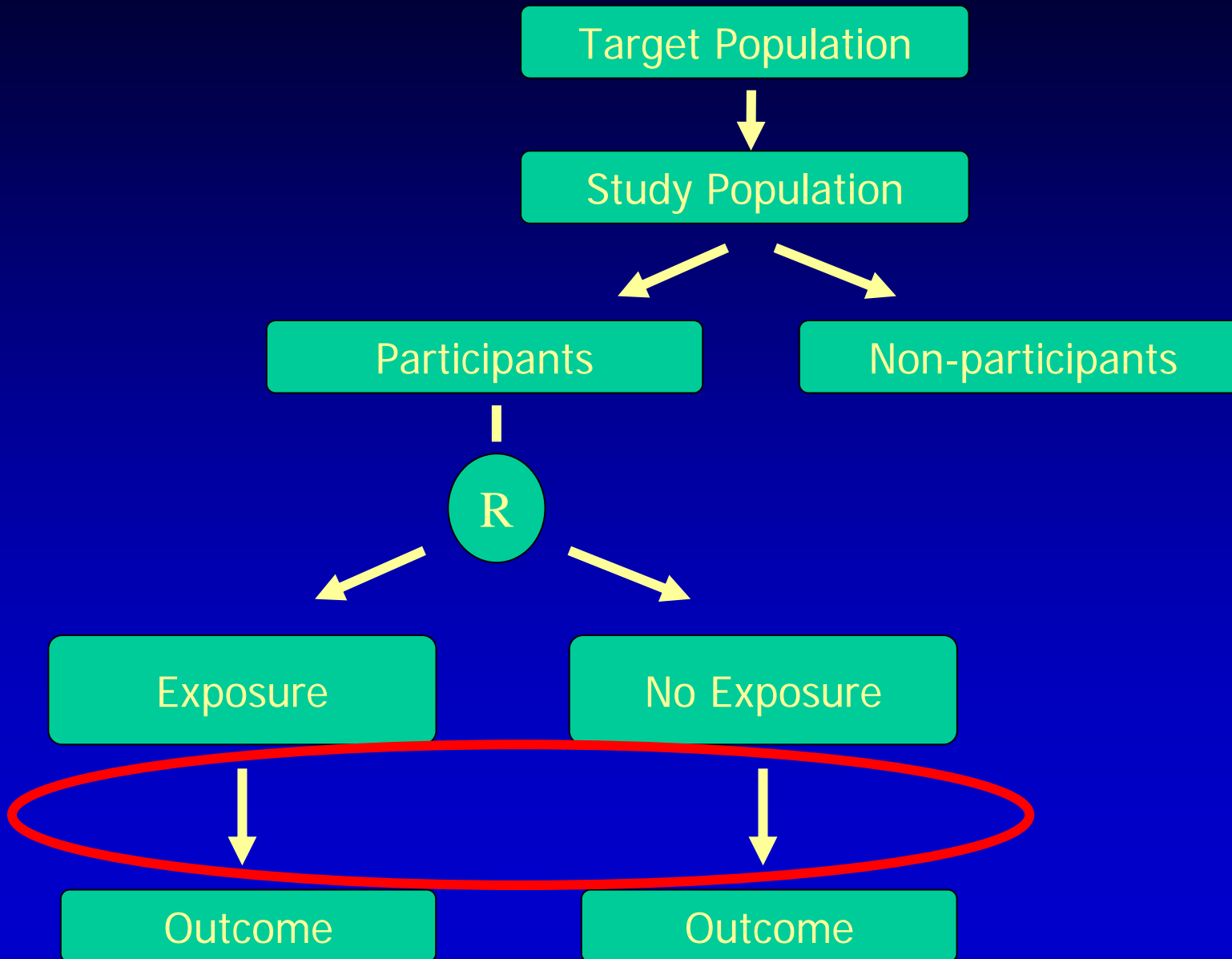
# *Limitations of Randomized Trials*

## **1. Primary efficacy outcome**

- may not be optimum choice (cost / duration)
- sometimes not relevant for clinical decision-making
- Example: surrogate markers in clinical trials

# Structure: Randomized Controlled Trial

---



# *Limitations of Randomized Trials*

## **2. Duration of trial**

---

- duration of trials often short because of cost and feasibility
- only short-term efficacy of treatments can be appropriately inferred

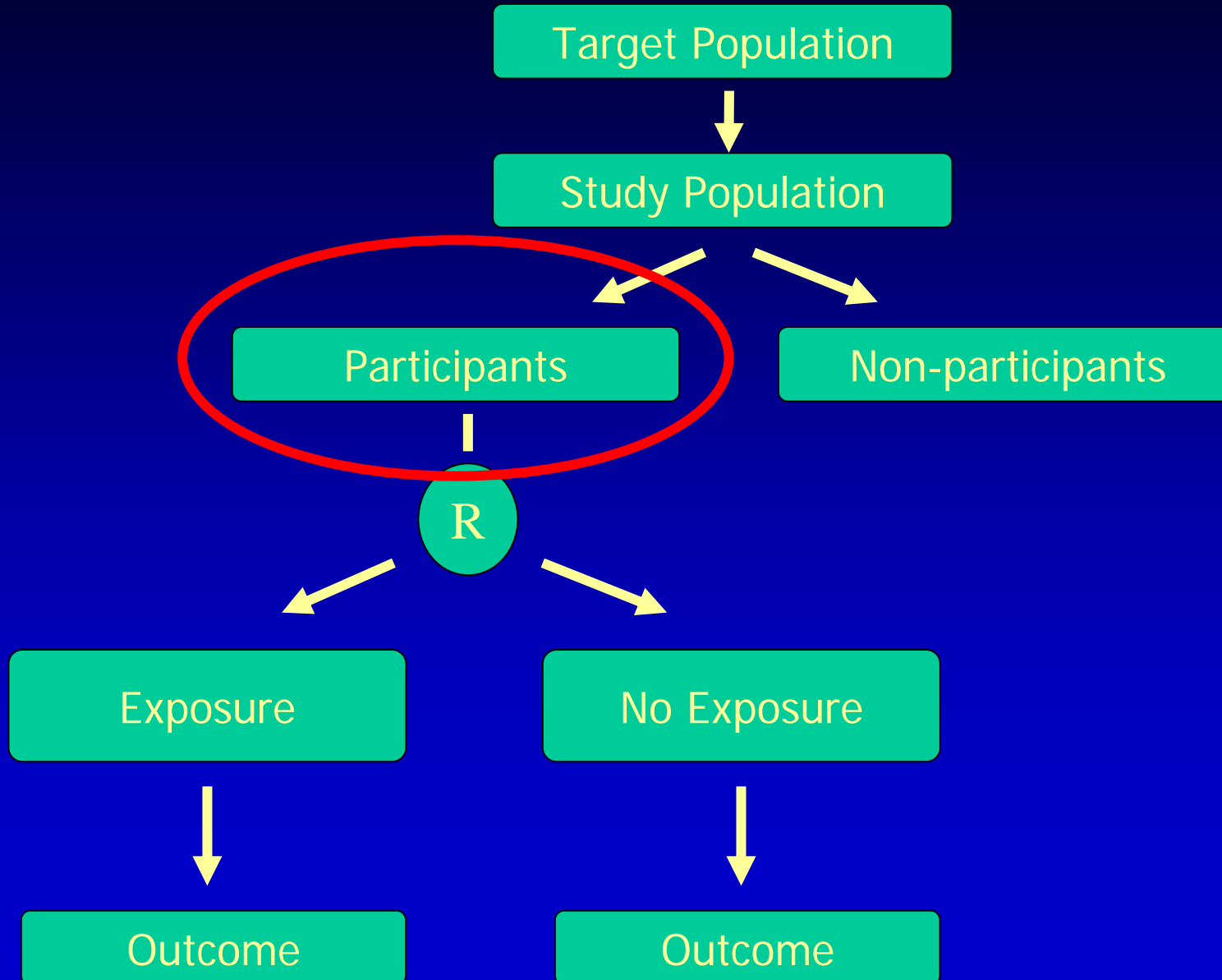
### **Over Time**



- feasibility
- noncompliance, withdrawals, and losses to follow-up
- change in 'standards' of treatment

# Structure: Randomized Controlled Trial

---



# *Limitations of Randomized Trials*

## ***3. Complicated patients***

---

- often exclude very young, the elderly, those with concurrent disease, those on concurrent medication
- can constitute a large proportion of those to be treated by clinician

# *Limitations of Randomized Trials*

## *Complicated patients*

---

The Food and Drug Administration's Code of Federal Regulations (CFR)

The CFR indicates only that the subjects treated in efficacy trials must have the condition being studied; there is no discussion of exclusion criteria (21 CFR 314.126)

(Posternak et al., 2002): since principal aim of most efficacy trials is to demonstrate drug-placebo differences, patients believed to have high placebo response rates or low drug response rates (*e.g.*, presence of comorbid disorders) are generally excluded

# *Limitations of Randomized Trials*

## *Complicated patients*

---

**Example: Exclusion Criteria Used in Antidepressant Efficacy Trials (AETs): Consistency Across Studies and Representativeness of Samples Included\***

**Impact of different sets of exclusion criteria on representativeness of subjects treated in AETs is unknown**

**Applied eligibility criteria used in published AETs to patients evaluated in routine clinical practice to evaluate the range and extent of the representativeness of samples treated in AETs**

\*The Journal of Nervous and Mental Disease: Volume 192(2) February 2004 pp 87-94

# *Limitations of Randomized Trials*

## *Complicated patients*

---

Example ...

AETs: 39 recently published AETs

Patient Sample: 503 outpatients with DSM-IV major depressive disorder (MDD) or bipolar depression, with nonpsychotic, unipolar MDD

Eligibility criteria used in the 39 AETs were applied to determine how many patients from the sample would have qualified for each AET had they applied

# *Limitations of Randomized Trials*

## *Complicated patients*

---

### **Example ...**

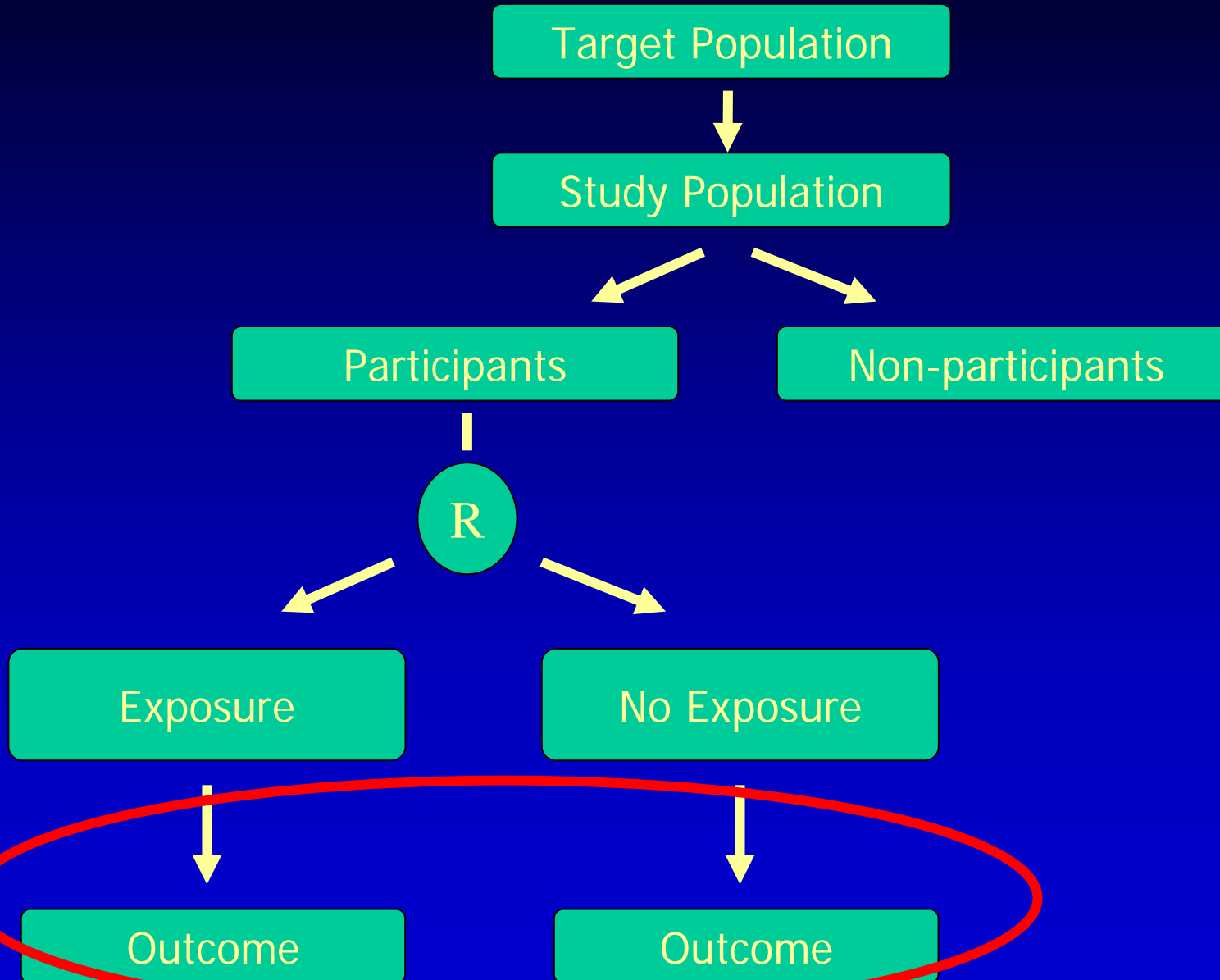
**Rates of exclusion ranged from 0% to 95.0% (mean 65.8%)**

**Findings suggest that:**

- there is much variability in the generalizability of AETs**
- in general, subjects treated in AETs represent only a minority of patients treated for MDD in a community-based psychiatry outpatient practice**

# Structure: Randomized Controlled Trial

---



# *Limitations of Randomized Trials*

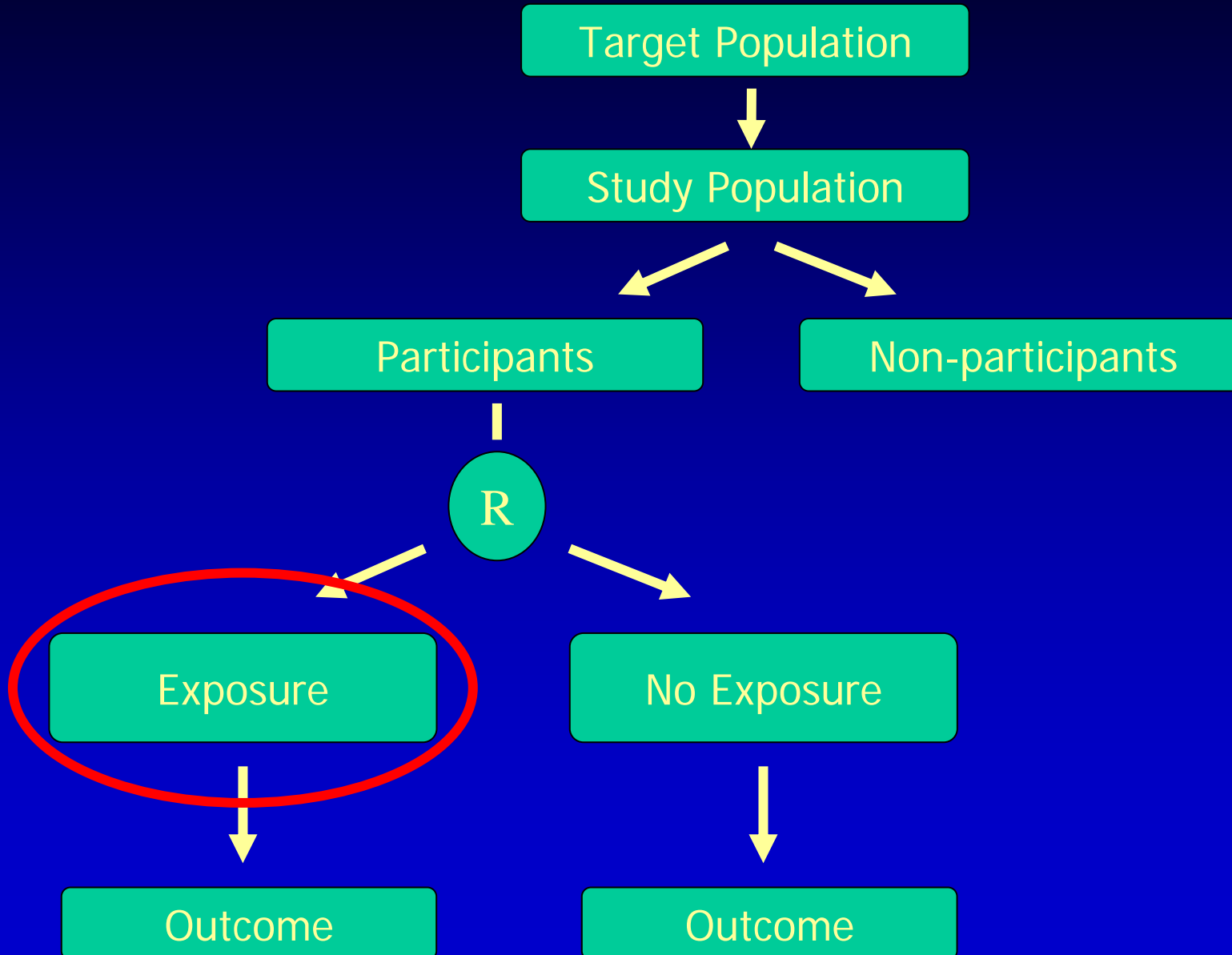
## *4. Adverse events*

---

- **low power to detect important differences in**
  - **adverse event rates**
  - **adverse event profiles**
  - **new but rare adverse events**

# Structure: Randomized Controlled Trial

---



# *Limitations of Randomized Trials*

## *Issues to consider*

---

- **Choice of primary efficacy outcome**
- **Choice of duration of trial**
- **Inclusion of complicated patients**
- **Detection of adverse events**
- **Guidance on 'varying' the intervention**

# *Post-Marketing Comparative Evaluations*

## *Health Care Utilization Databases*

---

### **Setting:**

- Electronic pharmacy claims are an important source of information on utilization of marketed drugs
- Pharmacy claims can be electronically linked to claims from physician services and hospitalizations, and information from vital statistics agencies and disease registries
- Databases contain records of medical service encounters and pharmacy dispensings for a large number of patients over long periods of time
- Each encounter is recorded with
  - coded diagnoses
  - dates when each service provided

# *Post-Marketing Comparative Evaluations Health Care Utilization Databases*

---

## **Advantages:**

- low cost and availability
- representative of routine care (effectiveness)
- large population possibly yielding a sufficient number of users of a marketed drug
- data prospectively collected and patient non-response and recall bias non-existent

# *Post-Marketing Comparative Evaluations Health Care Utilization Databases*

---

## **Disadvantages:**

- reliance on data generated primarily for administrative purposes (timing, detail and accuracy of data collection beyond control of investigator)
- record is generated only if there is an encounter with the health-care system that is accompanied by a diagnosis and procedure(s), including prescribing of drugs
- encounter must be filed, coded accurately and with complete information (including diagnosis)

# *Post-Marketing Comparative Evaluations*

## *Non-randomized Study Design*

---

- Choosing among non-randomized study designs
- Utilization patterns in routine care will provide guidance on choice of design
- Three fundamental ways to vary drug exposure status:
  - Examine outcomes of varying drug exposure between patients
  - Examine outcomes of varying drug exposure in the same patient over time
  - Examine outcomes of varying drug exposure between patient groups

# *Post-Marketing Comparative Evaluations*

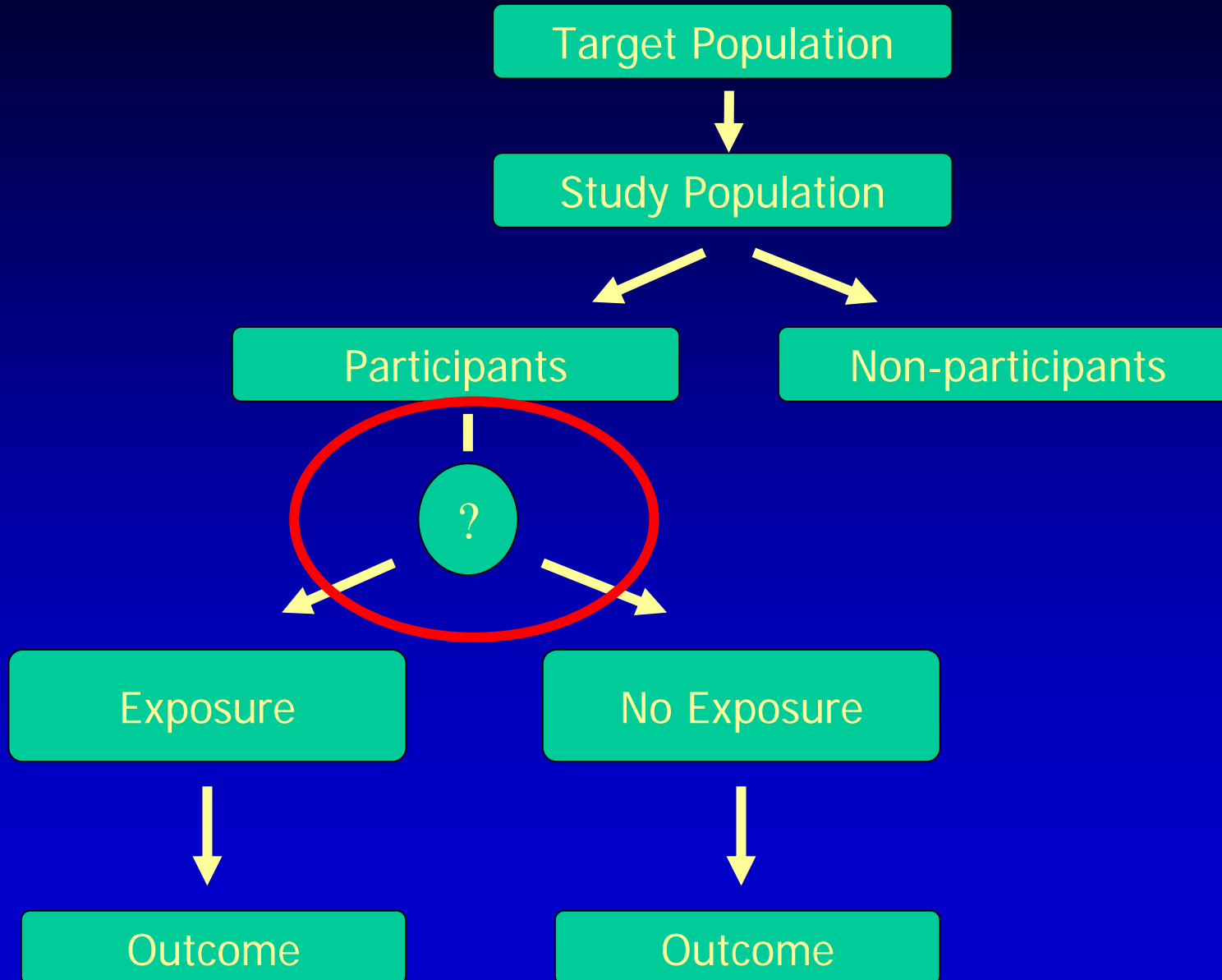
## *Non-randomized Study Design*

---

- **Examine outcomes of varying drug exposure between patients**
  - One group of patients will be exposed to a new drug and another group to a comparison drug
  - Assume patients in both groups are on average comparable with regard to their patient characteristics
  - Basis for an epidemiological cohort study
- **Cohort study design**

# Structure: Cohort Study Design

---



# *Post-Marketing Comparative Evaluations*

## *Cohort Study Design*

---

### Distinguishing Features:

Groups of persons (cohorts) to be studied are defined in terms of characteristics that manifest prior to outcome under study (exposed and not exposed)

Groups observed over period of time to determine frequency of outcome among them

### **Then**

rate for outcome for those exposed is compared to the corresponding rate for those not exposed

### **If**

rates are significantly different then an association is said to exist between the exposure and outcome

# Post-Marketing Comparative Evaluations

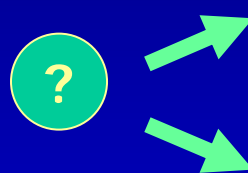
## Cohort Study Design

---

Data:

Outcome

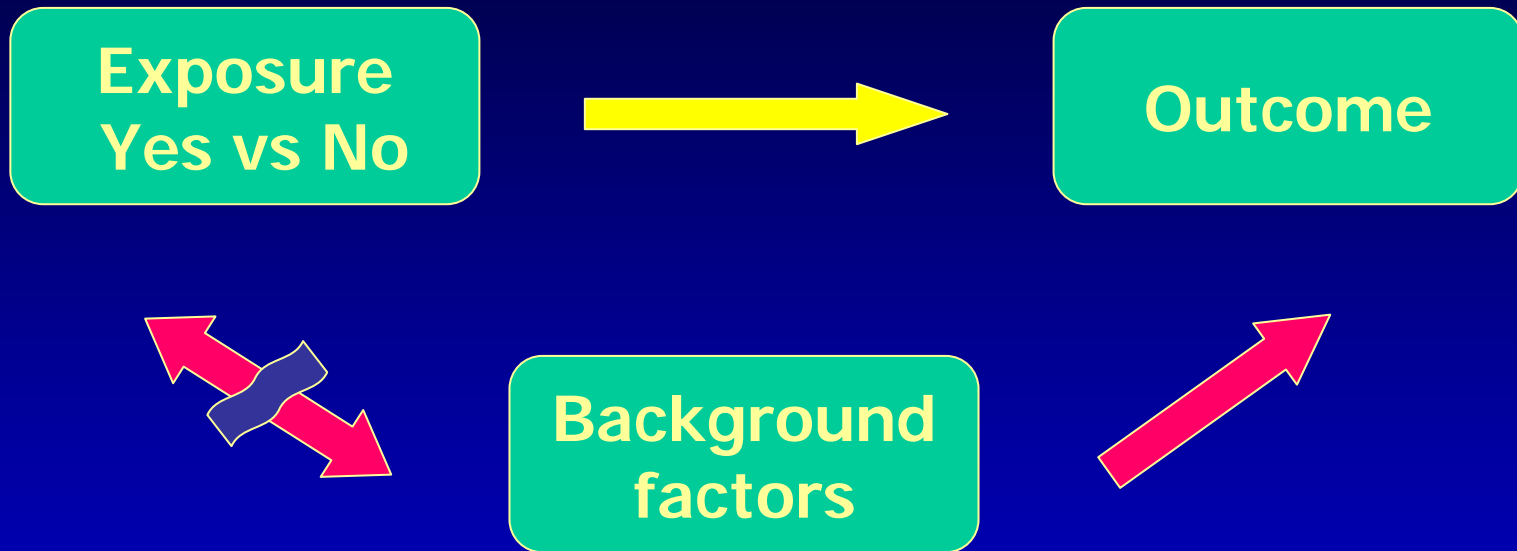
Exposure	Yes	No
Exposed	a	b
Not exposed	c	d



# *Post-Marketing Comparative Evaluations*

## *Making Comparisons*

---



1. Design

- match
- stratified sampling
- restrict inclusion

2. Analysis

- standardize
- stratify (subgroups)
- adjust (statistical model)

3. Randomize

# *Post-Marketing Comparative Evaluations*

## *Strategies to Reduce Confounding*

---

- **Strategies to reduce confounding**
  - Design: restrict inclusion
  - Analysis: stratify and adjust
- **Restrict Inclusion**
  - Restrict eligibility for being a member of study cohort
  - Makes cohort more homogeneous on patient factors
  - Reduces cohort size (databases large so loss in precision small)
  - Useful restrictions
    - Restrict to patients that are new users
    - Restrict to patients without contraindications
    - Restrict to patients that adhere to treatment

# *Post-Marketing Comparative Evaluations*

## ***Confounding – Restrict Inclusion***

---

### **Restrict to patients that are new users**

- All users (patient treated with study drug at least once)
  - consists of prevalent and incident users with balance depending on average duration of drug use
  - prevalent users have persisted in their drug use, which may correlate with better outcome and different patient characteristics
- New users (only patients initiating study drug)
  - resolves issues related to prevalent users
  - ensures patient characteristics are assessed before the start of study drug

# *Post-Marketing Comparative Evaluations*

## *Confounding – Restrict Inclusion*

---

### **Restrict to patients without contraindications**

- Exclude patients who have a clear contraindication to study drug since will not be treated and will not provide information
- Even if patients receive the study drug despite a contraindication, only involve a few and experience unusual
- Determining contraindications using diagnostic codes recorded in health care utilization databases may be difficult
  - propensity scores may be a better approach
    - estimate patient's probability of treatment given all measured covariates
    - low propensity for receiving treatment likely non-users having a contraindication for the study drug and these patients should be deleted from the study population

# *Post-Marketing Comparative Evaluations*

## *Confounding – Restrict Inclusion*

---

### **Restrict to patients that adhere to treatment**

- In routine care, adherence to drugs is substantially lower than in RCTs
- Starting follow-up after a certain number of refills of the study drug in new user cohorts will exclude patients who are least adherent
  - such a restriction may be more appropriate when effectiveness occurs with some delay

# *Post-Marketing Comparative Evaluations*

## *Strategies to Reduce Confounding*

---

- **Strategies to reduce confounding**
  - Design: restrict inclusion
  - Analysis: stratify and adjust
- **Stratify**
  - Identify patient subgroups (strata)
  - Get treatment effect estimates for all strata and combine them into one weighted summary effect measure
  - Stratified analyses will provide unbiased treatment effects in the absence of effect measure modification and assuming that all confounding factors were measured
  - Many such subgroup analyses usually possible because databases large

# *Post-Marketing Comparative Evaluations*

## *Strategies to Reduce Confounding*

---

- **Strategies to reduce confounding**

- Design: restrict inclusion
- Analysis: stratify and adjust

- **Adjust**

- Traditional regression based models adjusting treatment effect for measured confounding factors
- Also regression adjustment, matching, and stratification using propensity scores are widely used techniques to compare groups
  - Propensity score is the conditional probability of a patient receiving study drug based on pretreatment variables
  - Objective is to balance the treatment groups so to reduce bias of treatment selection
  - Check distribution of propensity scores by treatment group for sizeable overlap, demonstrating groups are comparable

# *Post-Marketing Comparative Evaluations*

## *Confounding by Indication*

---

### **Setting:**

- Drugs are prescribed based on diagnostic and prognostic information
- Factors influencing prescribing involve clinical, functional, and patient characteristics
- If these factors are also predictors of the study outcome, then failing to control for such factors can lead to confounding
- Confounding thus results from an informed selection based on indications and contraindications and is referred to as **confounding by indication**

# ***Post-Marketing Comparative Evaluations***

## ***Confounding by Indication***

---

- Ideally, can stratify patients of similar baseline risk and compare users of study drug within these strata
- However, physicians often prescribe considering subtle risk factors that are not recorded and so are unmeasured confounders
- Most non-randomized studies using claims data with limited patient information will not be able to fully measure and adjust for confounders and may be unable to show an effect because of residual confounding

# *Post-Marketing Comparative Evaluations*

## *Confounding by Indication*

---

**Confounding by indication is further complicated for newly approved drugs**

- Often marketed for being more effective in treating the condition or reducing risk of safety concerns
- Physicians will consider prescribing these newer drugs to sicker patients and patients at higher risk for adverse effects
- Studies not fully adjusting for these considerations may underestimate the benefits of newly marketed drugs and overestimate their risks

# *Post-Marketing Comparative Evaluations*

## **Cohort Studies**

---

### Types of Cohort Studies:

**Prospective cohort studies:** classifying subjects without the outcome of interest on the basis of exposure status; follow cohort longitudinally into the future to determine outcome

**Retrospective cohort studies:** historical cohort reconstructed from existing data sources at the beginning of the study; subjects classified by exposure status; determine outcome status (possible follow-up)

# *Post-Marketing Comparative Evaluations*

## *Selection of Cohorts*

---

- Selection of Study Cohort:

- Special exposure cohort
- Special resources that may facilitate ascertainment of exposure and / or follow-up of outcome

- Selection of Comparison Group:

- Internal comparisons (exposure level categories)
- Comparison with population outcome rates
- Comparison cohort (selection of cohort similar to exposed but not exposed)

- Health care utilization databases allow extraction of between patient drug exposure data

# ***Post-Marketing Comparative Evaluations***

## ***Selection of Cohorts***

---

### **Health care utilization databases allow extraction of between patient drug exposure data**

- need to identify imbalances in prescribing by tabulating measured patient characteristics by drug exposure group
- differences in measured patient factors between drug exposure groups often leads to confounding, if these factors are also risk factors for the study outcome
- Such factors need to be adjusted in further analyses
- Instead of considering each factor individually, it is possible to combine all patient characteristics into a single propensity score which is the estimated probability of treatment, given all covariates

# *Introduction to Observational Study Designs*

## ***Cohort Studies***

---

### **Potential Strengths**

demonstrate appropriate temporal sequence between exposure and outcome

permit direct calculation of incidence rates in exposed and unexposed groups

allow multiple outcomes to be evaluated

provide indication of latency period of outcome

suitable for studying rare exposures

outcome status determination unlikely to bias exposure status determination

can help establish cause-effect relationships

# *Introduction to Observational Study Designs*

## *Cohort Studies*

---

### Potential Weaknesses

loss to follow-up bias

exposure misclassification due to changes in exposure during follow-up period or because of inadequate information in retrospective designs

outcome misclassifications when advances in detection during follow-up phase question earlier classifications or knowledge of exposure status biases assessment of outcome status

# *How to Design Post-Marketing Comparative Evaluations*

---

*2008 International Health Technology  
Assessment Symposium*

*Taipei, Taiwan  
August 11, 2008*



uOttawa

L'Université canadienne  
Canada's university

*George A Wells*

# *Post-Marketing Comparative Evaluations*

## *Non-randomized Study Design*

---

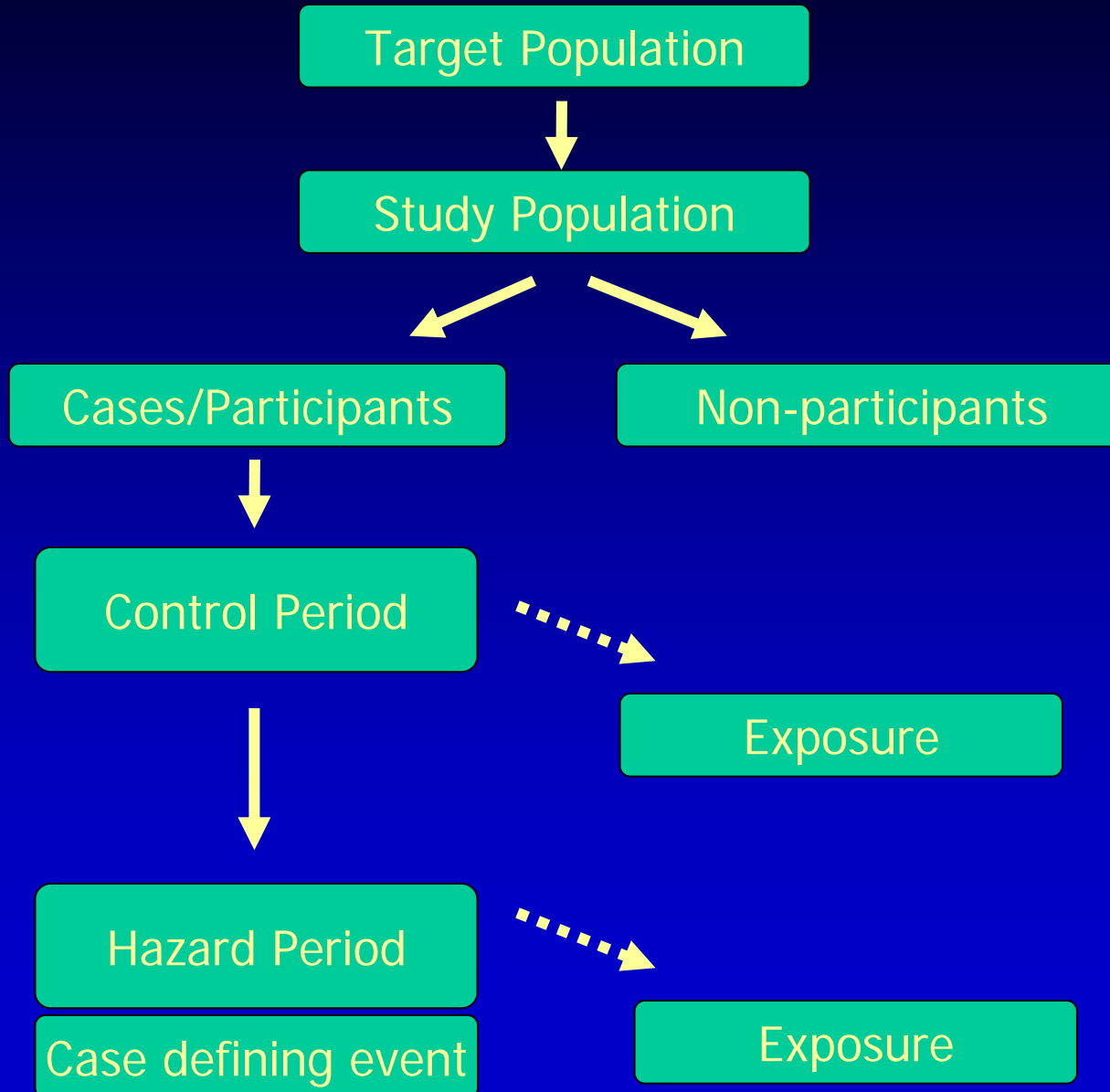
Examine outcomes of varying drug exposure in the same patient but over time

- Patient becomes own control, and all non-time-varying patient characteristics are kept constant by design
- Basis for case-crossover study

### Case-Crossover Study Design

# Structure: Case-Crossover Study Design

---



# *Post-Marketing Comparative Evaluations*

## *Case-Crossover Study Design*

---

### Distinguishing Features:

Group of patients assembled in terms of having have the outcome under study (case)

Define the "case component" as the hazard period which is the time period right before the outcome; and the "control component" as control period which is a specified time interval other than the hazard period

The information of the case exposed to a certain agent during the hazard period and control period will be compared

# *Post-Marketing Comparative Evaluations*

## *Case-Crossover Study Design*

---

Data:

Control Period

Hazard Period	Exposure	Not exposure
Exposed		b
Not exposure	c	

# ***Post-Marketing Comparative Evaluations***

## ***Selection of Cases and Periods***

---

**Health care utilization databases allow extraction of within patient drug exposure data**

- longitudinal strings of information in database on health service and dispensing
- since service tied to reimbursement, recorded time of service and dispensing highly reliable
- with dispensing date and supply information, a drug exposure calendar can be established, and variation of drug exposure within a patient over time can be studied

# *Post-Marketing Comparative Evaluations*

## *Non-randomized Study Design*

---

Examine outcomes of varying drug exposure between groups of patients

- Some physicians prescribe one drug over another independent of patient characteristics, because treatment preference
- Basis for instrument variable (IV) analyses of cohort studies

**Cohort study with IV analysis**

# *Post-Marketing Comparative Evaluations*

## *Cohort Study Design with IV Analysis*

**Cohort Study Design** (as discussed above)

### **Instrument variable (IV) analyses**

- Traditional risk adjustment methods rely on observable measures, whereas IV methods factor in unmeasured factors as source of confounding
- Goal of IV analyses is to find instruments that are correlated with treatment selection but are not directly correlated with the study outcome
- When variables are found, the IV creates variance to estimate the effect of treatment on the outcome
- PROC QLIM IN SAS ETS®

# *Post-Marketing Comparative Evaluations*

## *Cohort Study Design with IV Analysis*

---

**Health care utilization databases allow extraction of between patient group drug exposure data**

- databases well suited to understand properties and predictors of physicians' prescribing decisions
- physician id and some physician characteristics can be linked to their patients, making it possible to identify provider subgroups that are more likely to prescribe one drug over another
- if such a prescribing preference is largely independent of patient characteristics, it can be used as a substitute for exposure in an IV analysis

# *Post-Marketing Comparative Evaluations*

## *Unmeasured Confounders*

---

- Utilizing variation in drug exposure within patients
  - crossover designs
- Utilizing proxies (propensity scores)
- Utilizing additional clinical information in patient sub-samples
- Utilizing variation in drug preference between providers
  - IV estimation

# ***How to Design Post-Marketing Comparative Evaluations***

---

***2008 International Health Technology  
Assessment Symposium***

***Taipei, Taiwan  
August 11, 2008***



uOttawa

L'Université canadienne  
Canada's university

***George A Wells***