Health System Research

- *Pharmacy: the art, practice, or profession of preparing, preserving, compounding, and dispensing medical drugs and provision of drug related information to the public*

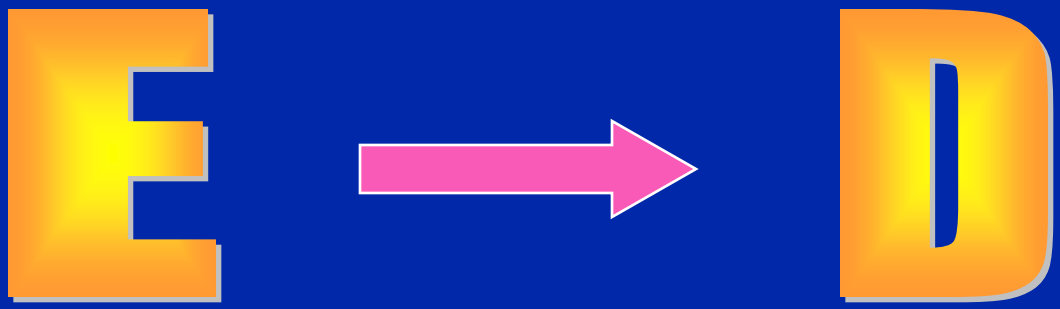
- *Research: studious inquiry or examination; especially: investigation or experimentation aimed at the discovery and interpretation of facts, revision of accepted theories or laws in the light of new facts, or practical application of such new or revised theories or laws*

Types of primary studies

- **Descriptive studies**
  - **describe occurrence of outcome**
- **Analytic studies**
  - **describe association between exposure and outcome**

Basic Question in Analytic Epidemiology

- Are exposure and disease linked?



Exposure **Disease**

Basic Questions in Analytic Epidemiology

- Look to link exposure and disease
  - **What is the exposure?**
  - **Who are the exposed?**
  - **What are the potential health effects?**
  - **What approach will you take to study the relationship between exposure and effect?**

Wijngaarden

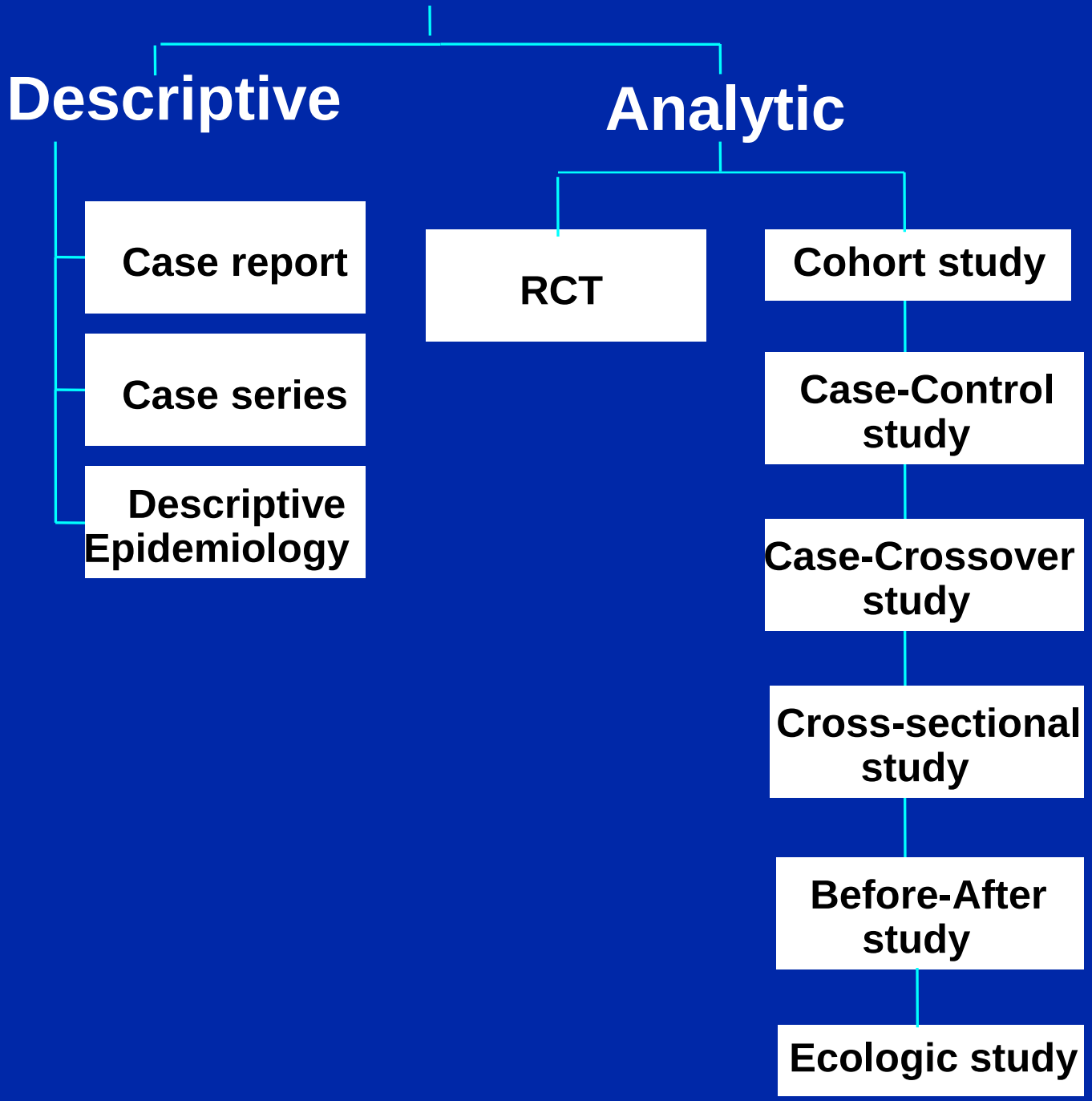
Basic Research Study Designs and their Application to Epidemiology

Big Picture

- To prevent and control disease
- In a coordinated plan, look to
  - identify hypotheses on what is related to disease and may be causing it
  - formally test these hypotheses
    - Study designs direct how the investigation is conducted

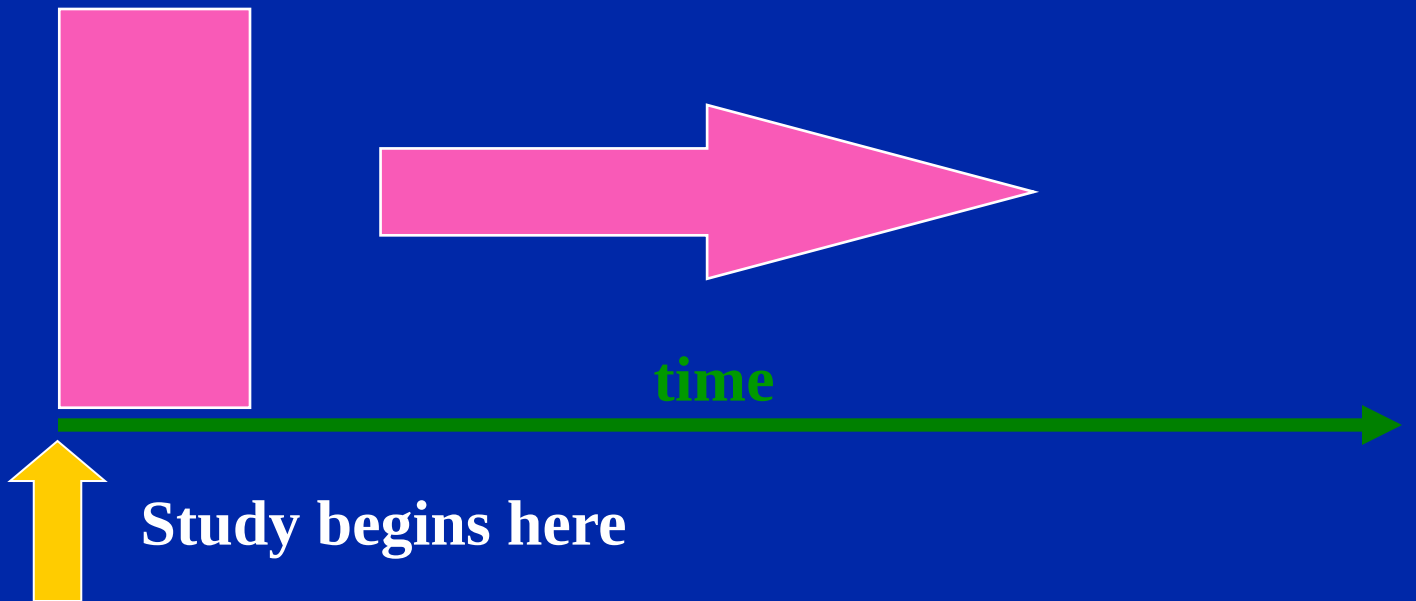
What designs exist to identify and investigate factors in disease?

Study Designs



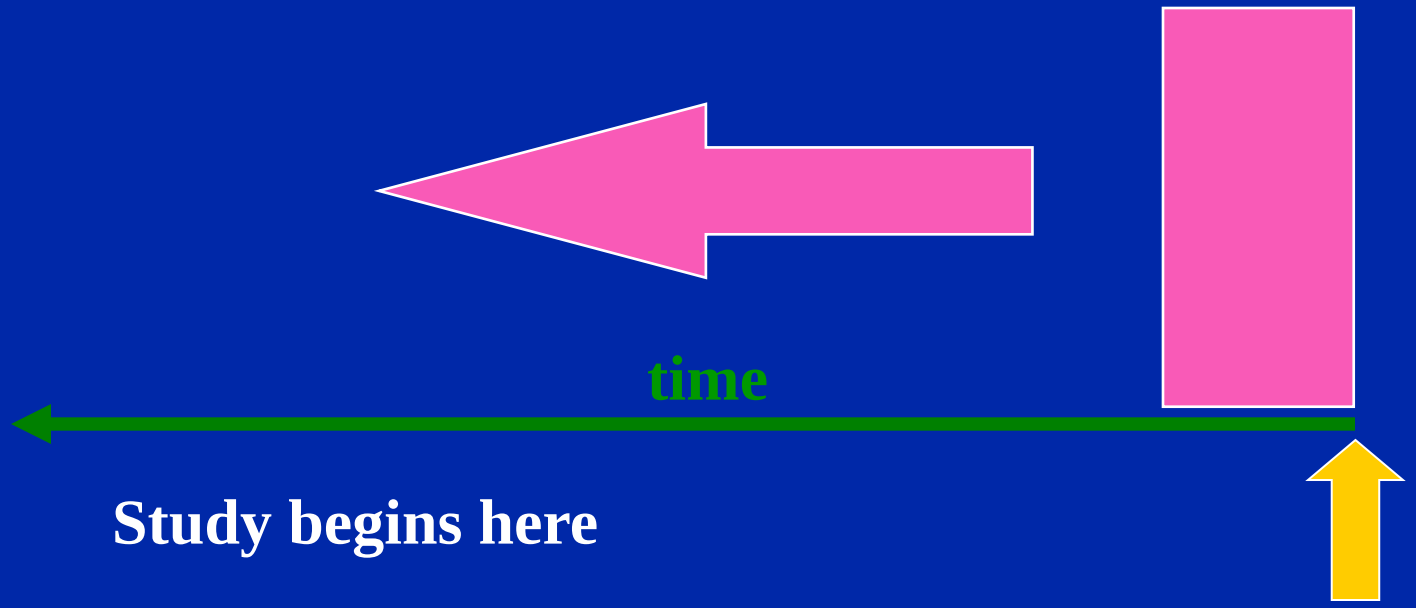
Timeframe of Studies

- **Prospective Study - looks forward, looks to the future, examines future events, follows a condition, concern or disease into the future**

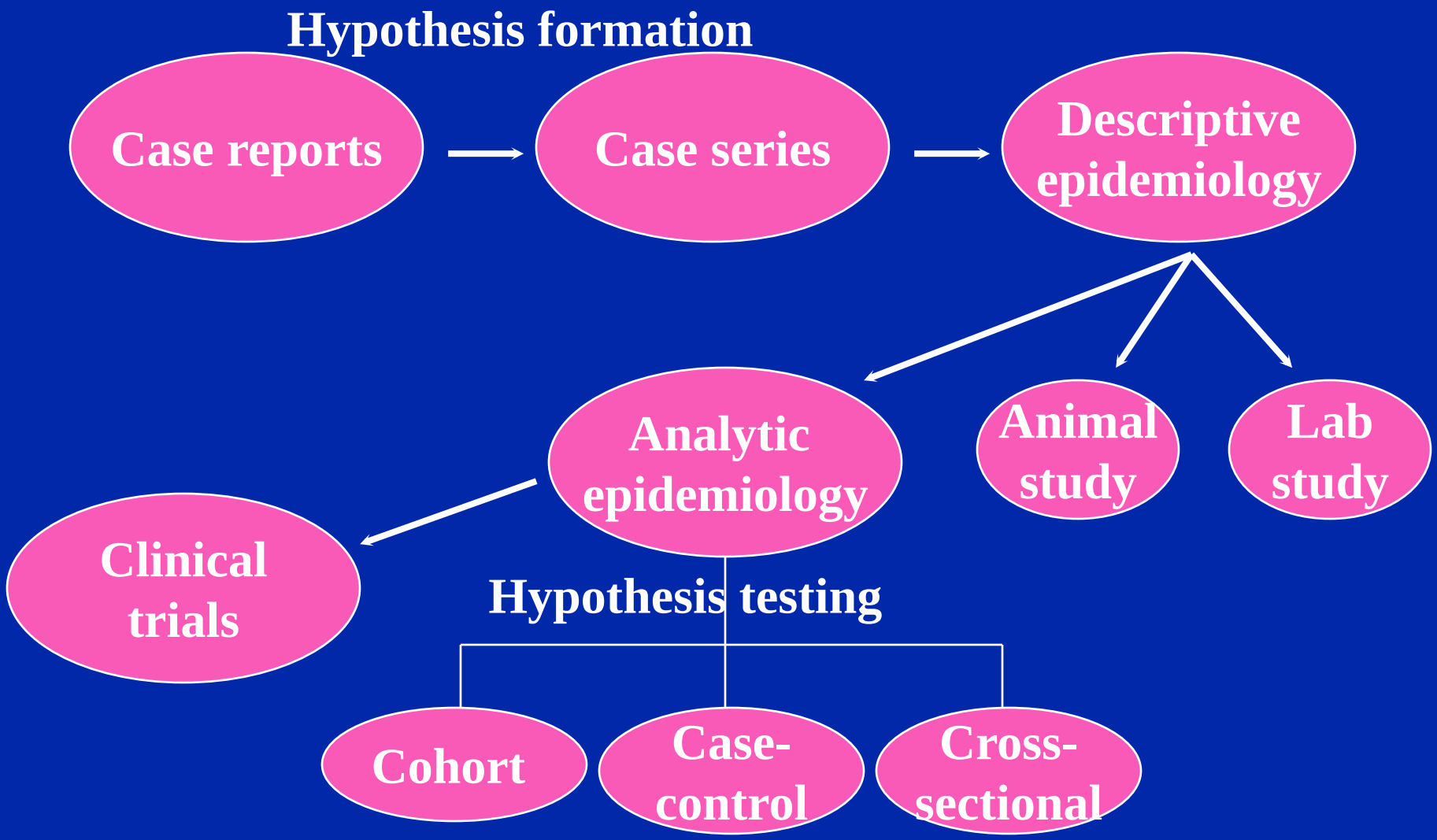


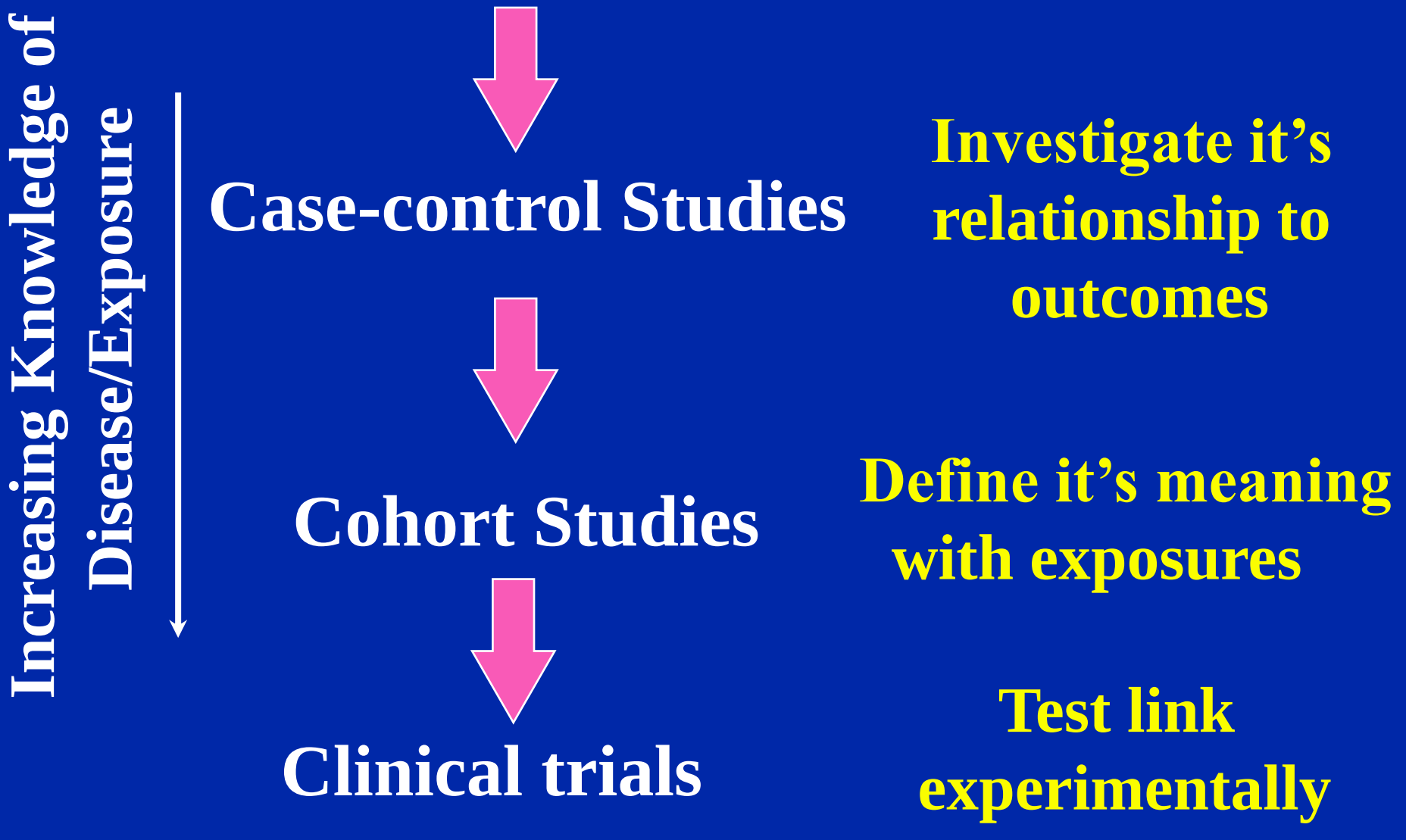
Timeframe of Studies

- **Retrospective Study** - **“to look back”, looks back in time to study events that have already occurred**



Study Design Sequence




Descriptive Studies
Develop hypothesis
Increasing Knowledge of Disease/Exposure
Case-control Studies
Investigate it's relationship to outcomes
Cohort Studies
Define it's meaning with exposures
Clinical trials
Test link experimentally

Descriptive Studies

Case Reports

- Detailed presentation of a single case or handful of cases
- Generally report a new or unique finding
  - e.g. previous undescribed disease
  - e.g. unexpected link between diseases
  - e.g. unexpected new therapeutic effect
  - e.g. adverse events

Case Series

- Experience of a group of patients with a similar diagnosis
- Assesses prevalent disease
- Cases may be identified from a single or multiple sources
- Generally report on new/unique condition
- May be only realistic design for rare disorders

Case Series

- **Advantages**
  - **Useful for hypothesis generation**
  - **Informative for very rare disease with few established risk factors**
  - **Characterizes averages for disorder**
- **Disadvantages**
  - **Cannot study cause and effect relationships**
  - **Cannot assess disease frequency**

Case Report → **One case of unusual findings**

Case Series → **Multiple cases of findings**

Descriptive Epidemiology Study → **Population-based cases with denominator**

Analytical Studies

Study Designs - Analytic Epidemiology

- Experimental Studies
  - Randomized controlled clinical trials
  - Community trials
- Observational Studies
  - Group data
    - Ecologic
  - Individual data
    - Cross-sectional
    - Cohort
    - Case-control
    - Case-crossover

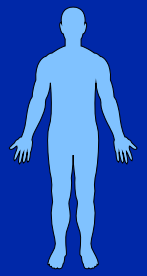
Experimental Studies

- **treatment and exposures occur in a "controlled" environment**
- **planned research designs**
- **clinical trials are the most well known experimental design. Clinical trials use randomly assigned data.**
- **Community trials use nonrandom data**

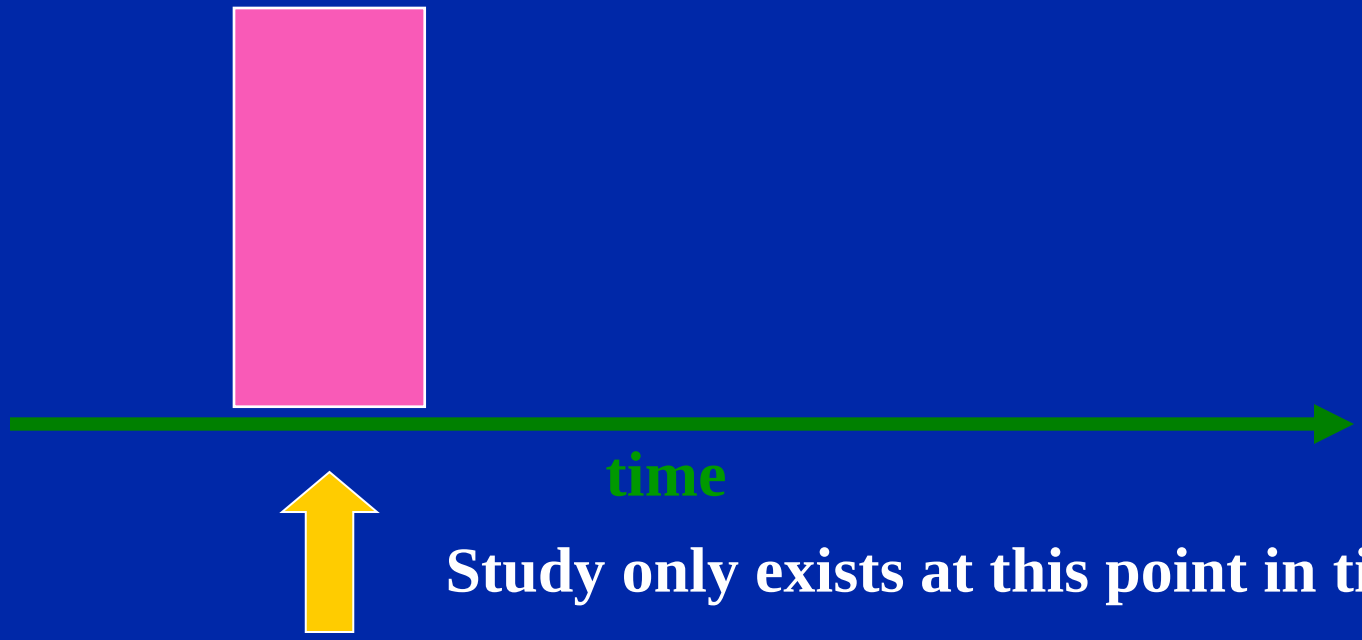
Observational Studies

- non-experimental
- observational because there is no individual intervention
- treatment and exposures occur in a “non-controlled” environment
- individuals can be observed prospectively, retrospectively, or currently

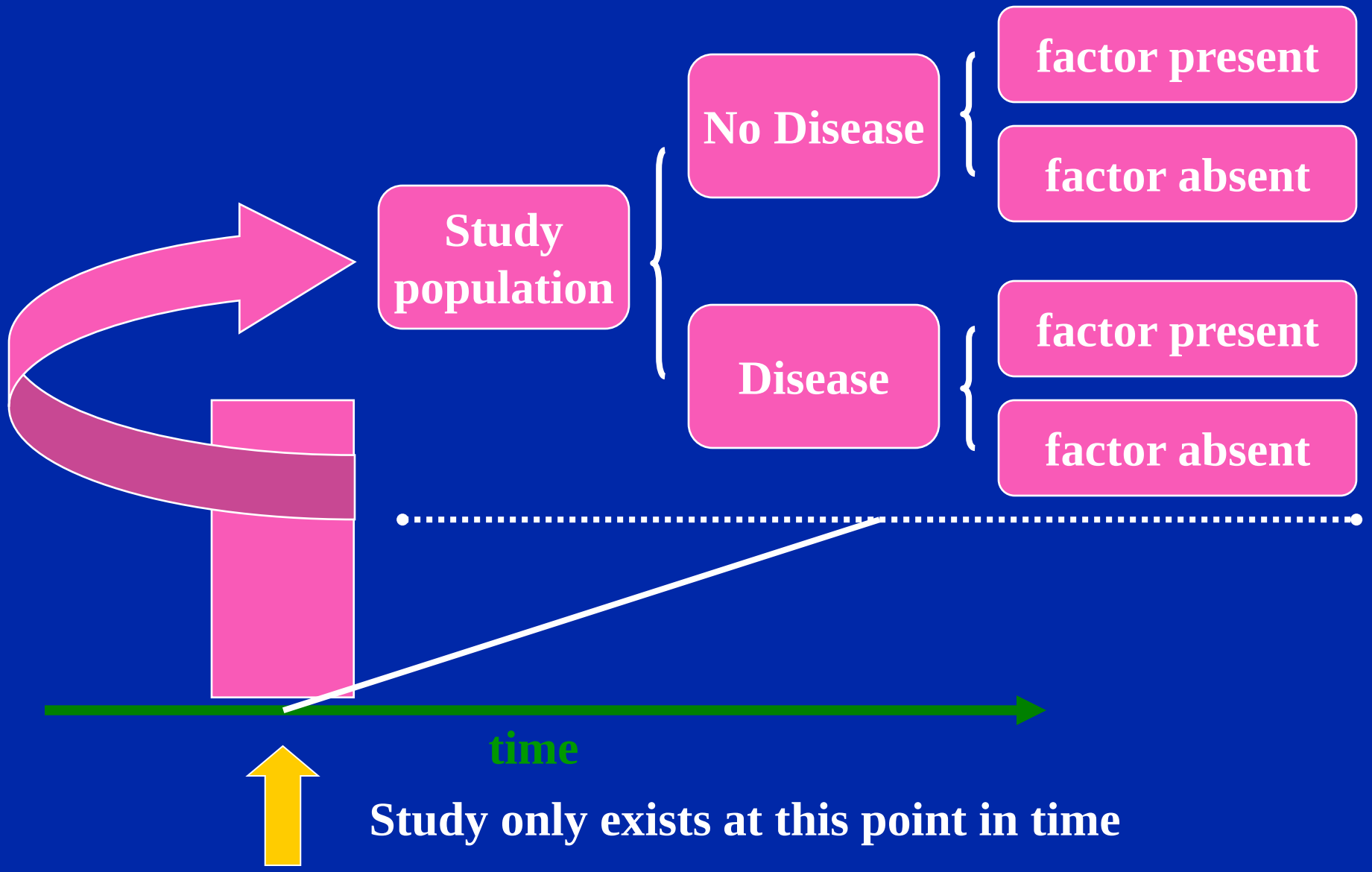
Cross-sectional studies



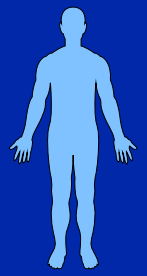
- An “observational” design that surveys exposures and disease status at a single point in time (a cross-section of the population)



Cross-sectional Design

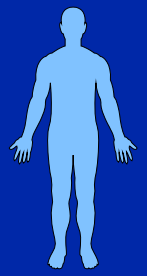


Cross-sectional Studies



- Often used to study conditions that are relatively frequent with long duration of expression (nonfatal, chronic conditions)
- It measures prevalence, not incidence of disease
- Example: community surveys
- Not suitable for studying rare or highly fatal diseases or a disease with short duration of expression

Cross-sectional studies



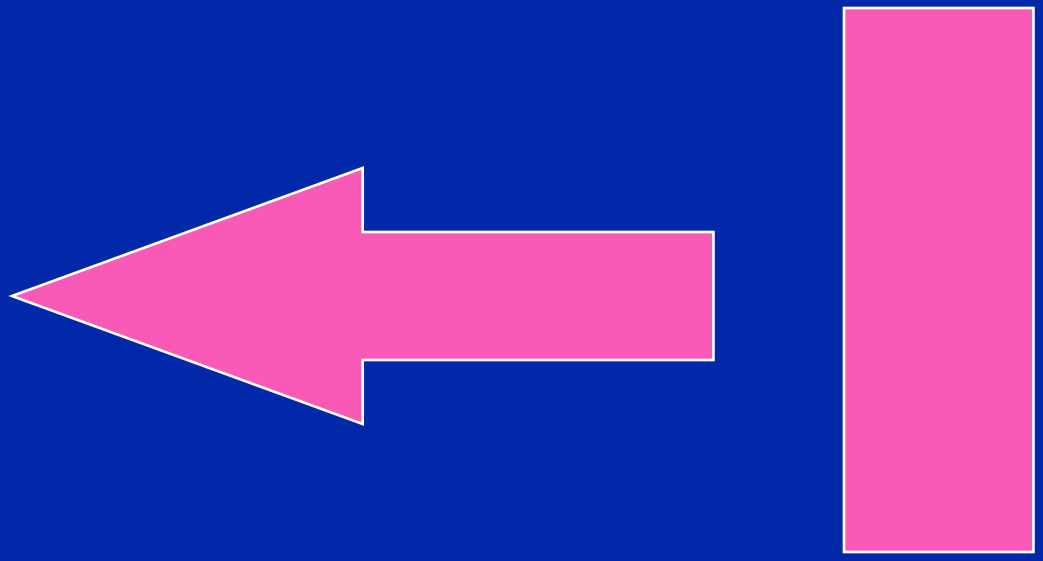
- **Disadvantages**
  - **Weakest observational design, (it measures prevalence, not incidence of disease). Prevalent cases are survivors**
  - **The temporal sequence of exposure and effect may be difficult or impossible to determine**
  - **Usually don't know when disease occurred**
  - **Rare events a problem. Quickly emerging diseases a problem**

Epidemiologic Study Designs

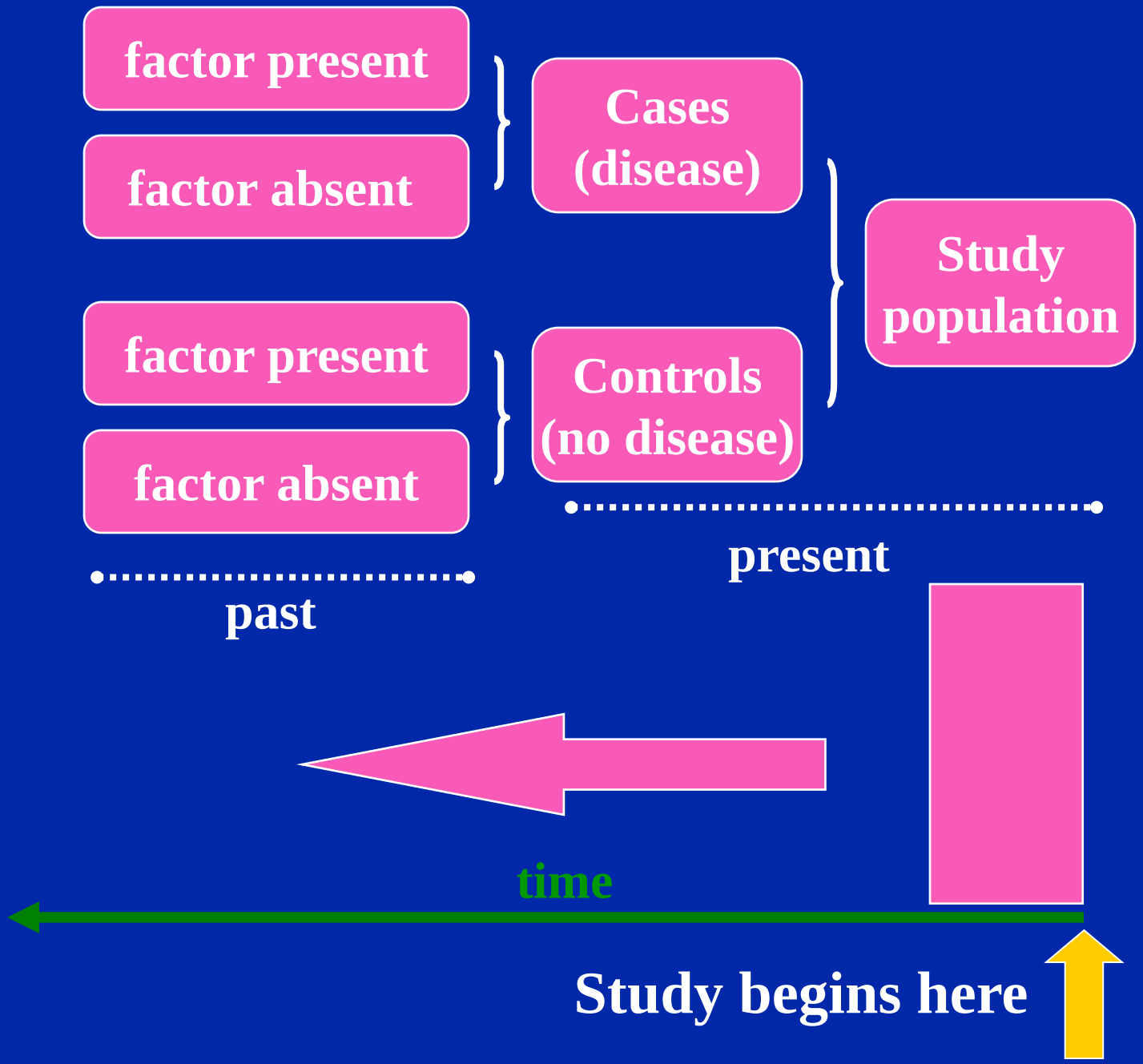
- **Case-Control Studies**
  - **an "observational" design comparing exposures in disease cases vs. healthy controls from same population**
  - **exposure data collected retrospectively**
  - **most feasible design where disease outcomes are rare**

Case-Control Studies

Cases: Disease
Controls: No disease



Case-Control Design



Case-Control Study

- **Strengths**
  - **Less expensive and time consuming**
  - **Efficient for studying rare diseases**
- **Limitations**
  - **Inappropriate when disease outcome for a specific exposure is not known at start of study**
  - **Exposure measurements taken after disease occurrence**
  - **Disease status can influence selection of subjects**

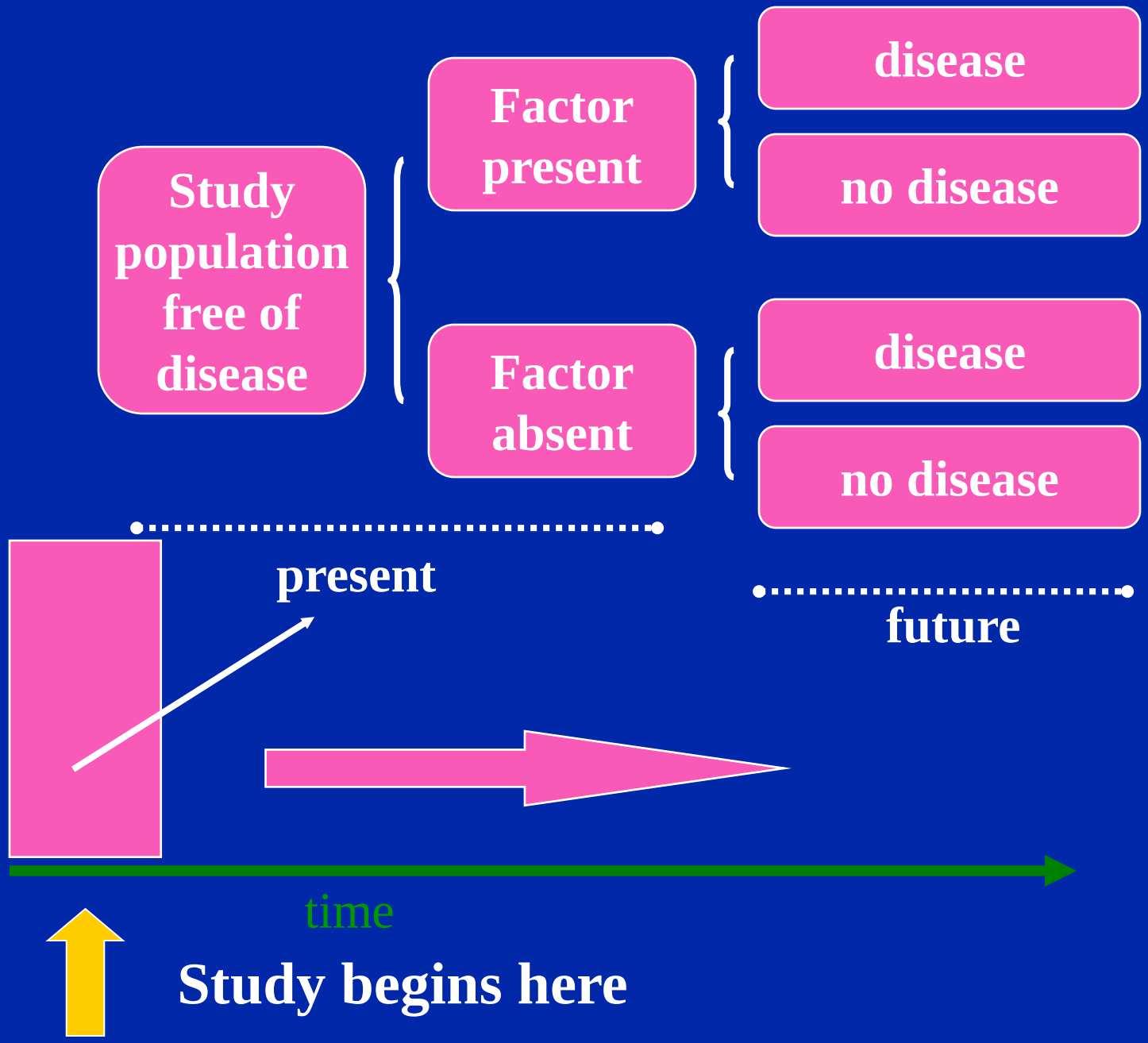
Hypothesis Testing: Case-Crossover Studies

- Study of “triggers” within an individual
- ”Case" and "control" component, but information of both components will come from the same individual
- ”Case component" = hazard period which is the time period right before the disease or event onset
- ”Control component" = control period which is a specified time interval other than the hazard period

Epidemiologic Study Designs

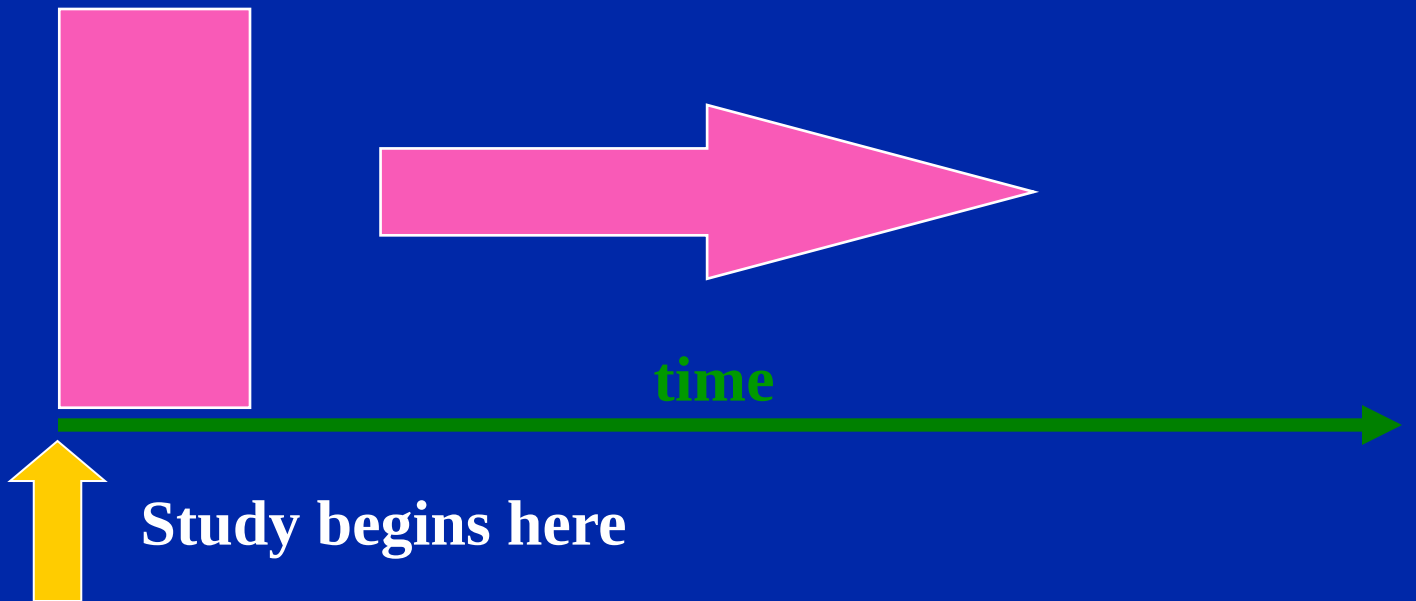
- **Cohort Studies**
  - **an "observational" design comparing individuals with a known risk factor or exposure with others without the risk factor or exposure**
  - **looking for a difference in the risk (incidence) of a disease over time**
  - **best observational design**
  - **data usually collected prospectively (some retrospective)**

Cohort Design

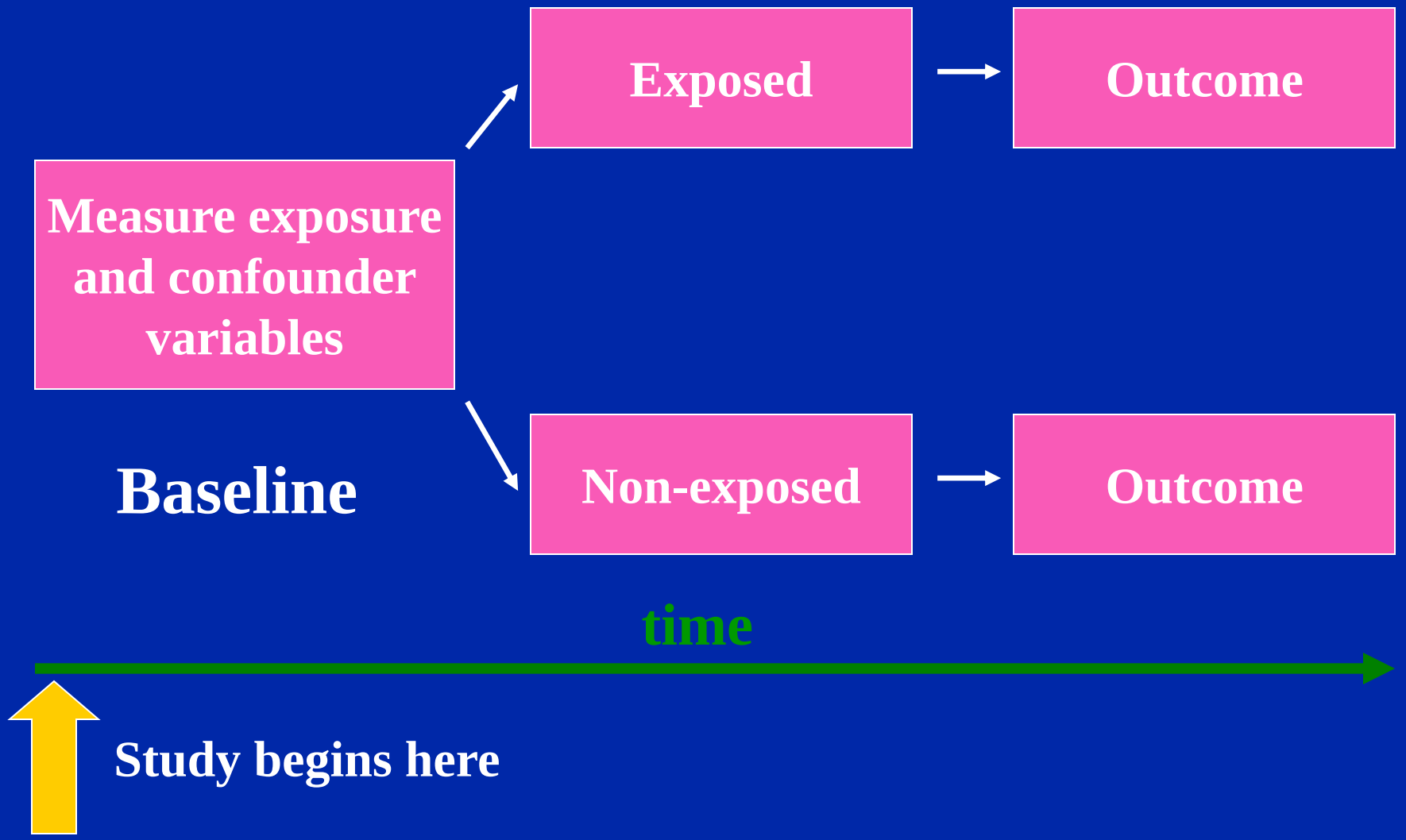


Timeframe of Studies

- **Prospective Study - looks forward, looks to the future, examines future events, follows a condition, concern or disease into the future**

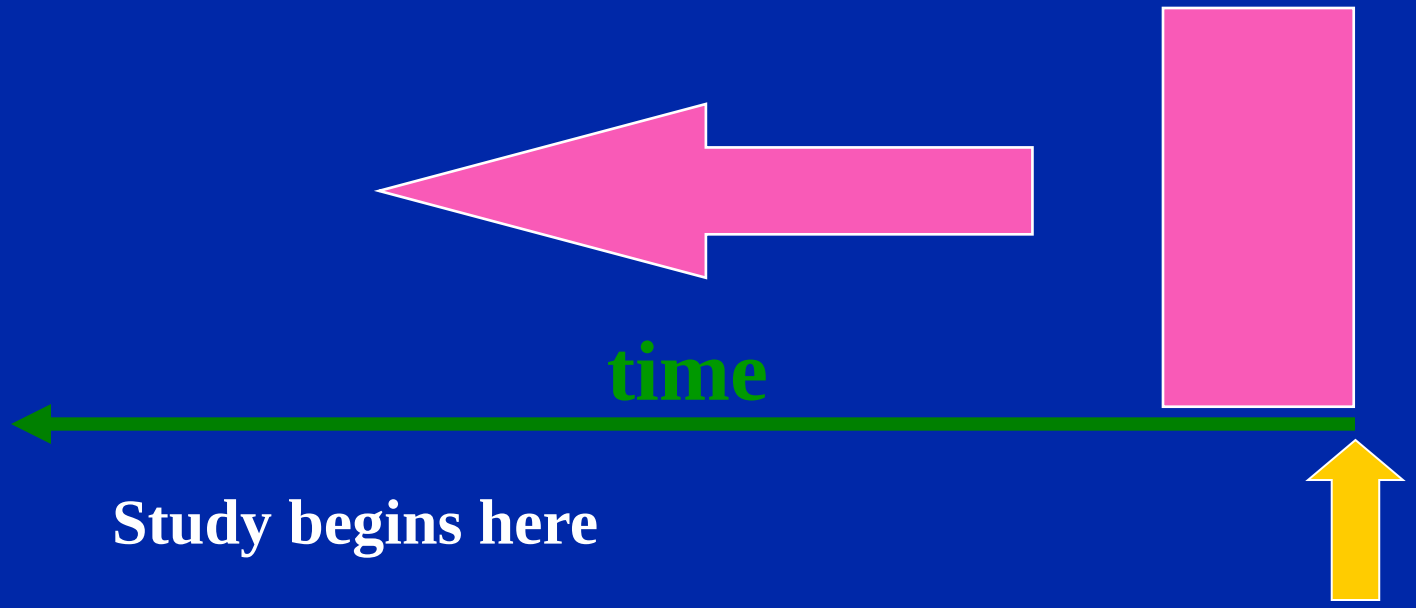


Prospective Cohort study

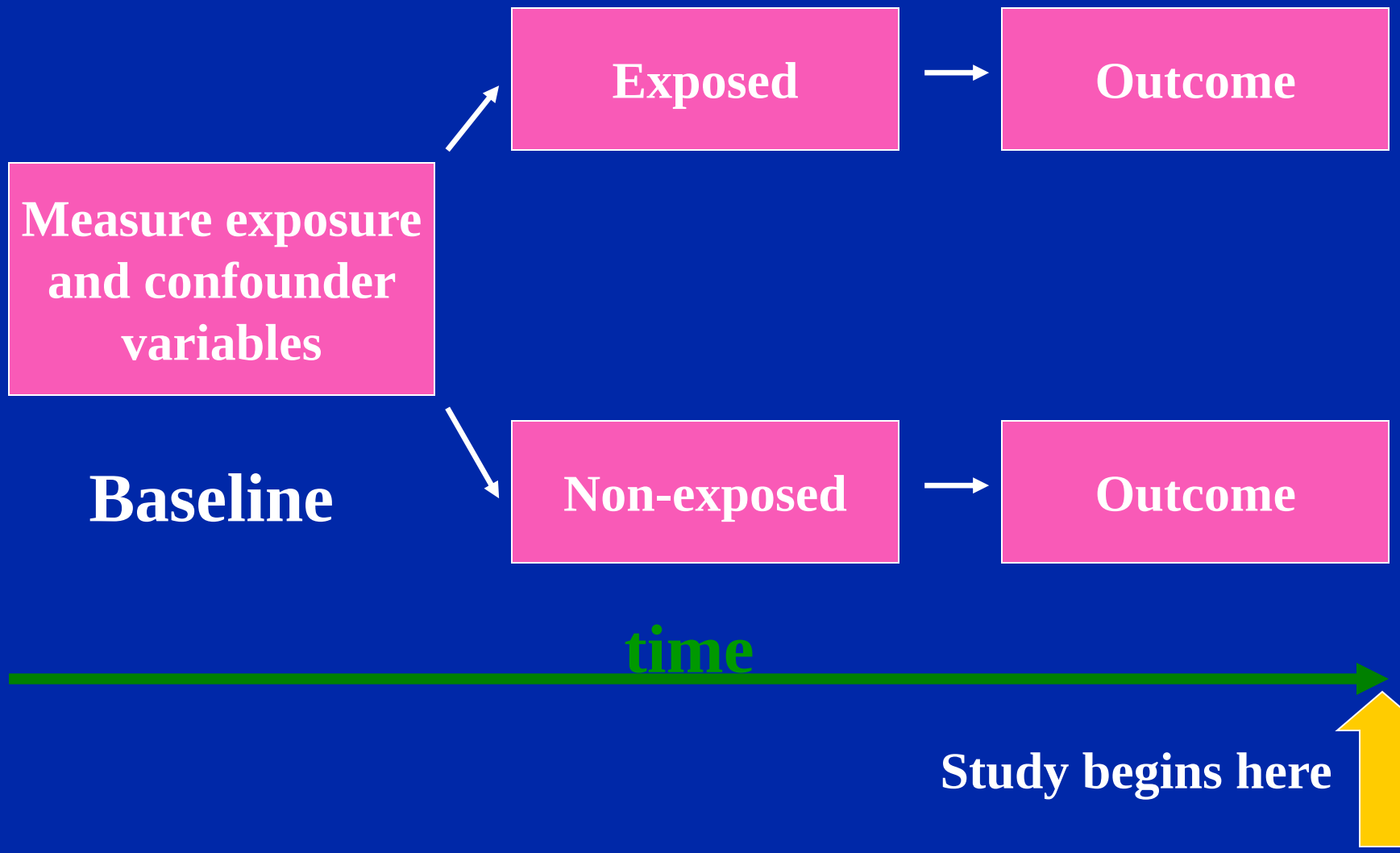


Timeframe of Studies

- **Retrospective Study** - **“to look back”, looks back in time to study events that have already occurred**



Retrospective Cohort study



Cohort Study

- **Strengths**
  - **Exposure status determined before disease detection**
  - **Subjects selected before disease detection**
  - **Can study several outcomes for each exposure**

- **Limitations**
  - **Expensive and time-consuming**
  - **Inefficient for rare diseases or diseases with long latency**
  - **Loss to follow-up**

Experimental Studies

- investigator can “control” the exposure
- akin to laboratory experiments except living populations are the subjects
- generally involves random assignment to groups
- clinical trials are the most well known experimental design
- the ultimate step in testing causal hypotheses

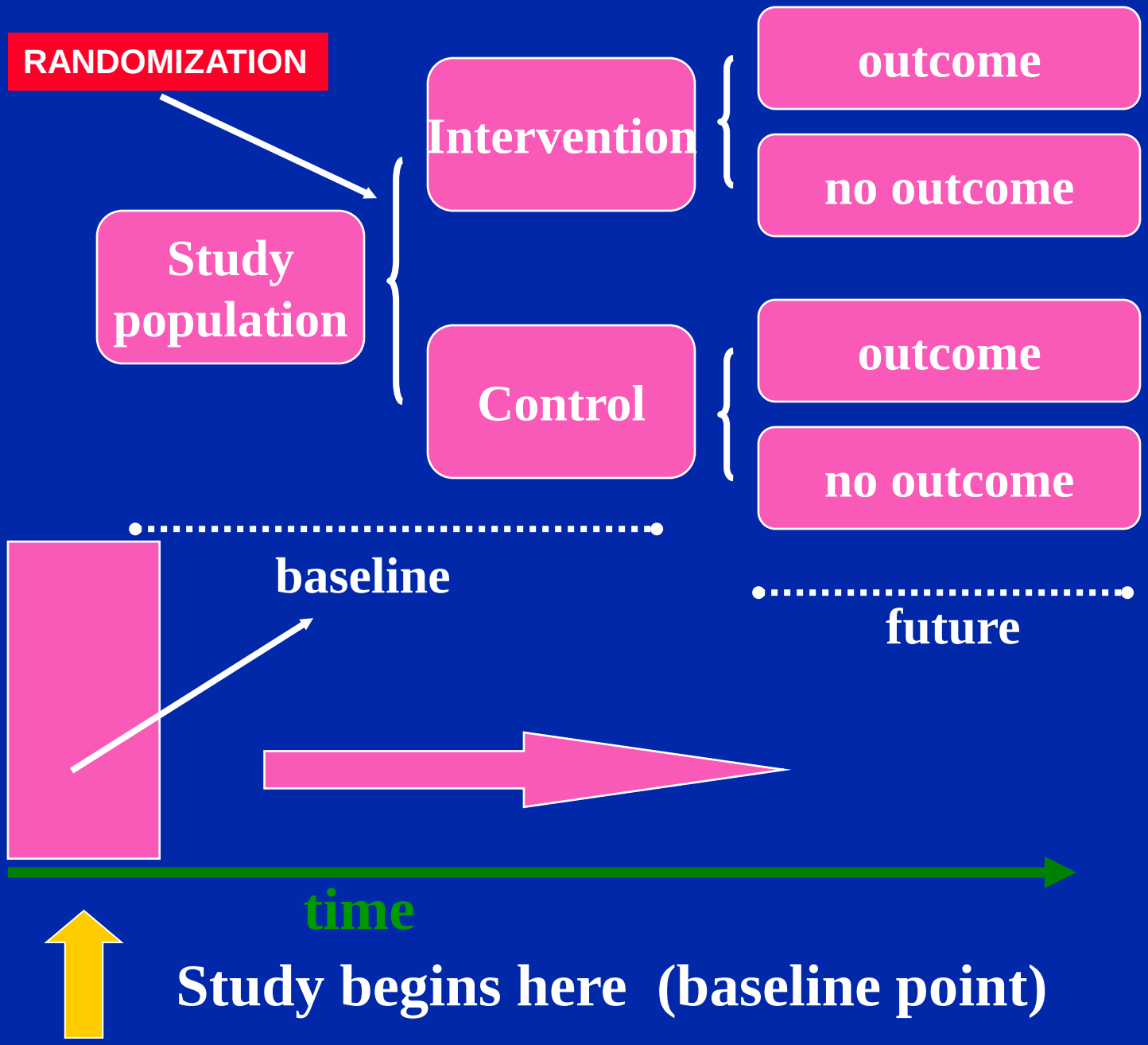
Experimental Studies

- **In an experiment, we are interested in the consequences of some treatment on some outcome.**
- **The subjects in the study who actually receive the treatment of interest are called the treatment group.**
- **The subjects in the study who receive no treatment or a different treatment are called the comparison group.**

Epidemiologic Study Designs

- **Randomized Controlled Trials (RCTs)**
  - **a design with subjects randomly assigned to "treatment" and "comparison" groups**
  - **provides most convincing evidence of relationship between exposure and effect**
  - **not possible to use RCTs to test effects of exposures that are expected to be harmful, for ethical reasons**

Experimental Design



Epidemiologic Study Designs

- **Randomized Controlled Trials (RCTs)**
  - **the "gold standard" of research designs**
  - **provides most convincing evidence of relationship between exposure and effect**

Randomized Controlled Trials

- **Disadvantages**
  - **Very expensive**
  - **Not appropriate to answer certain types of questions**
    - **it may be unethical, for example, to assign persons to certain treatment or comparison groups**

Pharmacovigilance

- Pharmaco + Vigilance (Medicines) (To Watch) According to WHO-:
- Science and activities relating to the detection, assessment, understanding and prevention of adverse effects and any other drug related problems.
- This applies throughout the life cycle of a medicine equally to the pre-approval stage as to the post approval.

Adverse Reaction

- “A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man”
- Adverse event: Any new clinical experience that occurs after starting a medicine, not necessarily a response to a medicine, and is recorded without judgement on its causality.

Causality assessment

- Causality assessment is the assessment of relationship between a drug treatment and the occurrence of an adverse event.
- It is also used to evaluate and to check that the particular treatment is the cause of an observed adverse event or not.

- It is an essential part of ADR report and important task, conducted by National Pharmacovigilance Programme in each country

Objectives of Causality Assessment

- Provide relationship between the drug and events.
- Signal detection(“a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously".)

- Provide better evaluation of the benefit/harm profiles of drugs.
- Plays as an essential part of evaluating ADR reports in early warning systems and for regulatory purposes.

How The Causality Assessment is Performed ?

- (Methods Of Causality Assessment) Many researchers developed various methods of causality assessment by using different criteria like- Chronological relationship between the administration of the drug and the occurrence of the ADR, Screening for drug and non drug related causes, Confirmation of the reaction by in vivo or in vitro test, Previous information on similar events etc.

- But there is No universally accepted method for assessing causality of ADRs.

Uppsala Monitoring Drug Interaction Probability Centre (UMC) causality Scale(DIPS)

- World Health Organization (WHO) - Uppsala Monitoring Centre (UMC) causality assessment criteria
- Widely and globally accepted method.
- WHO-UMC system provides practical tool for assessment of case reports for International drug monitoring

- System is used to detect unknown and unexpected adverse drug reaction. Assessment is based on following four criteria-: a) Time relationships between the drug use and the adverse event. b) Absence of other competing causes (medications, disease process itself).

- c) Response to drug withdrawal or dose reduction (de-challenge). d) Response to drug re-administration (re-challenge).
- the level of causal association is grouped into four categories which are based on a number of the above criteria being met

Causality association

- Certain
- Probable
- Possible
- Unlikely

Validity: 1) Sensitivity

- Probability (proportion) of correct classification of **cases**
  - **Cases found / all cases**

Validity: 2) Specificity

- Probability (proportion) of correct classification of **noncases**
  - **Noncases identified / all noncases**