ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΕΡΓΑΣΤΗΡΙΟ ΒΙΟΜΑΘΗΜΑΤΙΚΩΝ

ΚΑΤΗΓΟΡΙΕΣ ΙΑΤΡΙΚΗΣ ΕΡΕΥΝΑΣ ΚΑΙ Η ΠΥΡΑΜΙΔΑ ΤΩΝ ΕΝΔΕΙΞΕΩΝ

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Ακαδημαϊκός Υπότροφος

ΑΠΟΔΕΙΚΤΙΚΗ ΙΑΤΡΙΚΗ

- Evidence-Based Medicine (EBM)

«Είναι η εμπεριστατωμένη, σαφής και συνετή χρήση των τρεχουσών άριστων ενδείξεων για τη λήψη αποφάσεων σχετικών με τη φροντίδα συγκεκριμένων ασθενών»

(“evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”)

SACKETT DL, ROSENBERG WM, GRAY JA, HAYNES RB, RICHARDSON WS. Evidence based medicine: What it is and what it isn’t. BMJ 1996, 312:71–72

ΑΠΟΔΕΙΚΤΙΚΗ ΙΑΤΡΙΚΗ

- Evidence-Based Medicine (EBM)
- Τεκμηριωμένη Ιατρική
- Ιατρική βασιζόμενη σε ενδείξεις (αποδείξεις)

Evidence

“the best available external evidence from systematic research”

Εννοείται

«η άριστη διαθέσιμη εξωτερική ένδειξη από συστηματική έρευνα»

David Lawrence Sackett

Evidence

- ***Άριστη:*** όχι όλες οι ενδείξεις την ίδια ισχύ
- ***Διαθέσιμη****:* δεν υπάρχουν ενδείξεις για όλα τα προβλήματα
- ***Εξωτερική:*** έξωθεν προερχόμενη συλλογική εμπειρία (έρευνα) ǂ εσωτερική (προσωπική εμπειρία του ιατρού)
- ***Συστηματική έρευνα***: μεθοδική έρευνα

The Hierarchy of Evidence

ΕΙΔΗ ΙΑΤΡΙΚΗΣ ΕΡΕΥΝΑΣ

Types of Clinical Trials

- **Clinical trial/study:**

Any investigation in human subjects intended to discover or verify

a) the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s),
b) to identify any adverse reactions to an investigational product(s),
c) to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

The terms clinical trial and clinical study are synonymous

Study Designs

DESCRIPTIVE	***ANALYTICS***
designed to describe **occurrence of disease** by **time, place, person**	designed to examine **etiology and causal associations**

DESCRIPTIVE

designed to describe **occurrence of disease** by **time**, **place**, **person**

- Prevalence surveys
- Case-series
- Surveillance data
- Descriptive analyses of routinely collected data (registries, mortality data, etc.)

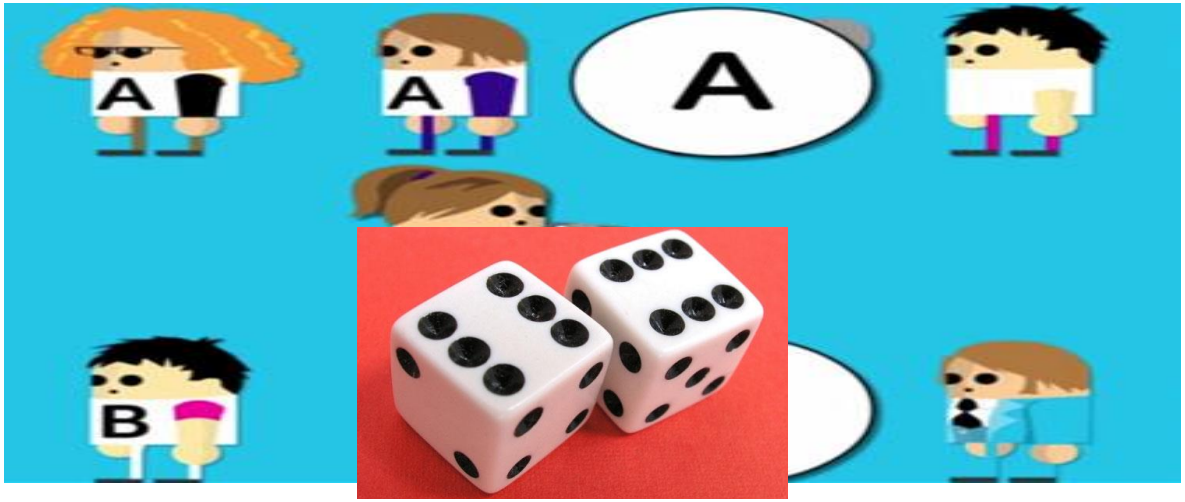
ANALYTICS

Interventional	Non-Interventional
Selected population	Non-selected population
"Perfect conditions"	"Real life conditions"
Exclusion of special populations/sub-groups	Very specific patients/conditions are excluded
Short observational period	Extended observational period
Not applicable in rare diseases or diseases with long life cycle	Applicable in rare diseases or diseases with long life cycle

UNCONTROLLED	***CONTROLLED***
trials **without** control/ comparison groups	trials **with** control/ comparison groups

Randomization (Τυχαιοποίηση)
Ισότιμη κατανομή χωρίς προκατάληψη

- *Individuals are allocated at random to receive one of several interventions (at least two at total)*



- ***gold standard of EBM***

Randomization Allocation

- Covariates are distributed equally across the groups at baseline
- Affects both measured and unmeasured variables

Note: the risk of the imbalance remains even after properly executed randomization

Generation of allocation sequence

- ***Simple Randomization***

– ***Analogous to a repeated fair coin tossing***

- ***Restricted randomization - Blocking***

– ***Done to ensure equal balance of arms throughout all portions of the study***

– ***i.e. blocks of six would have 3 active/3 control***

- ***Stratified randomization***

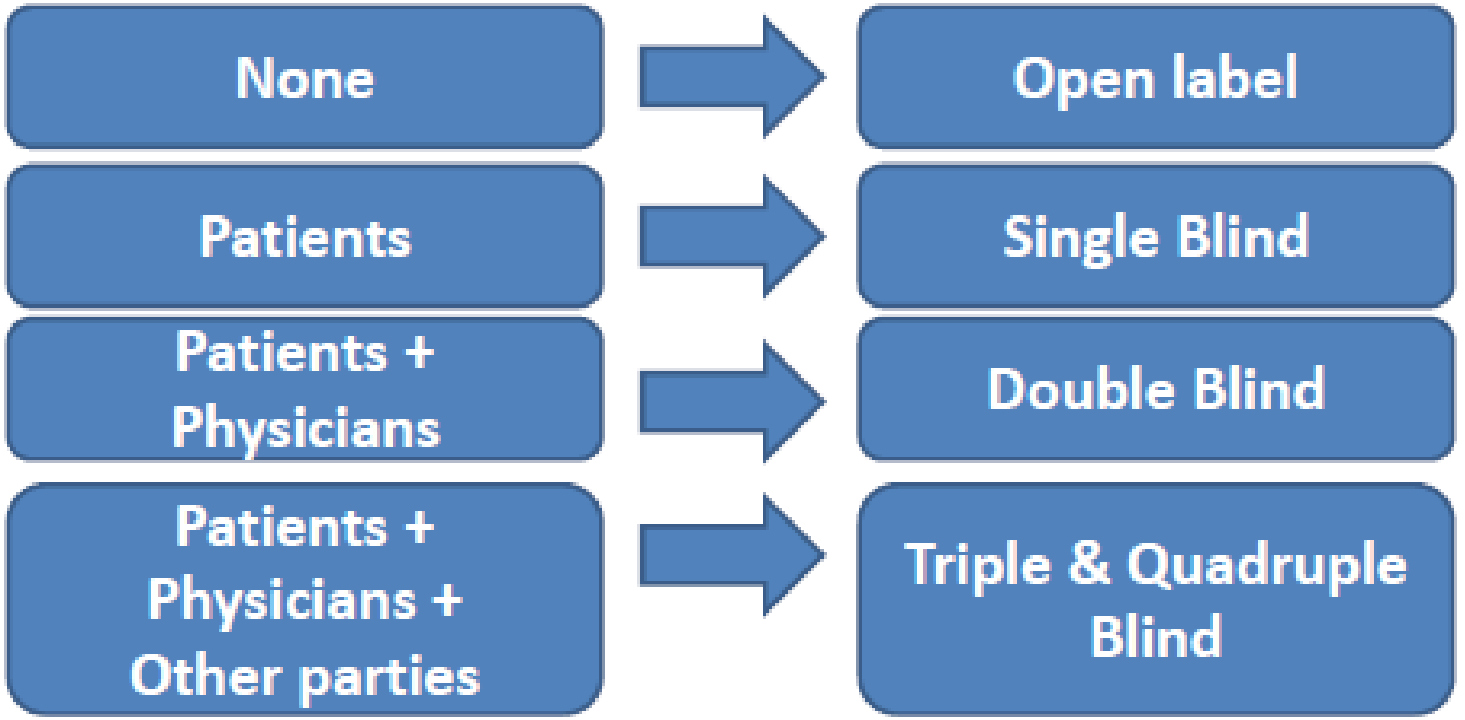
– ***Individuals are identified based on important covariates (sex, age, etc.) and then randomization occurs within the strata***

Classification Schemes for RCTs

- Based on whether investigators and/or participants know which **intervention is being studied (BLINDING)**
- Based on **how participants are exposed** to interventions
- Based on **the type of interventions** being evaluated
- Based on **the number of participants**
- Based on whether **the goal** is evaluation of superiority, equivalence or non-inferiority

Blinding

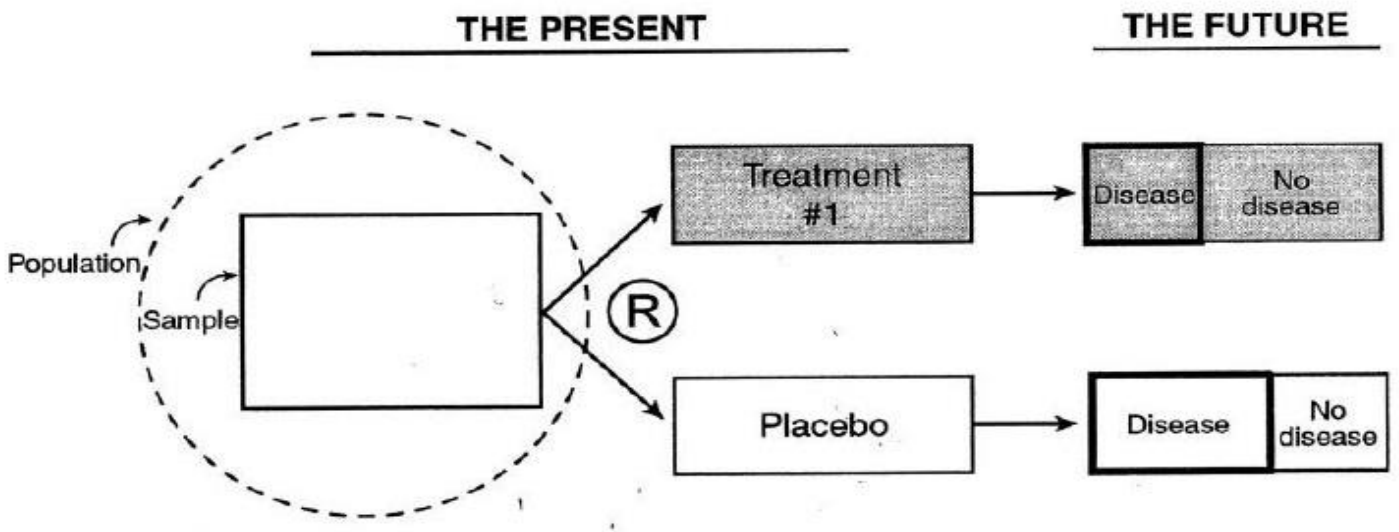
- Classification based on whether investigators and/or participants know which intervention is being studied



Classification based on how participants are exposed to interventions

- Parallel Trials
- Crossover Trials
- Trials with Factorial Design

Simple, two-arm (parallel) RCT

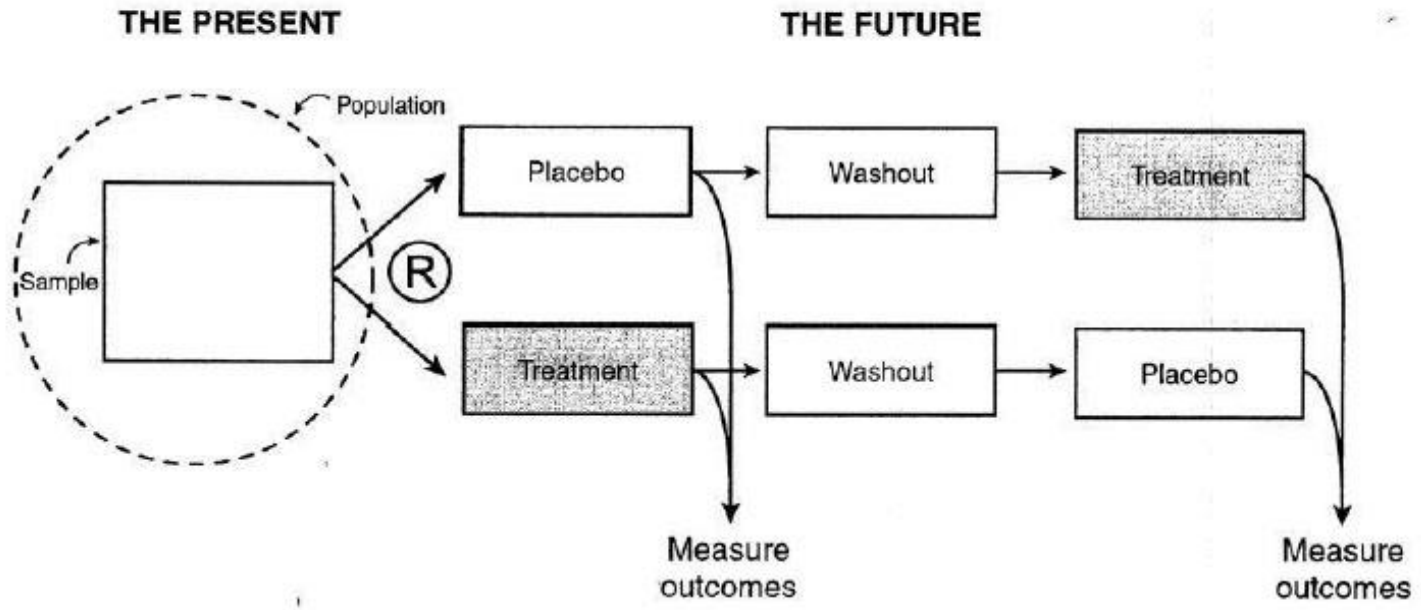


■ **FIGURE 10.1**

In a randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions (one should be a blinded placebo, if possible), (e) follows up the cohort, (f) measures outcome variables (blindly, if possible) and analyzes the results.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

Cross-over RCT design

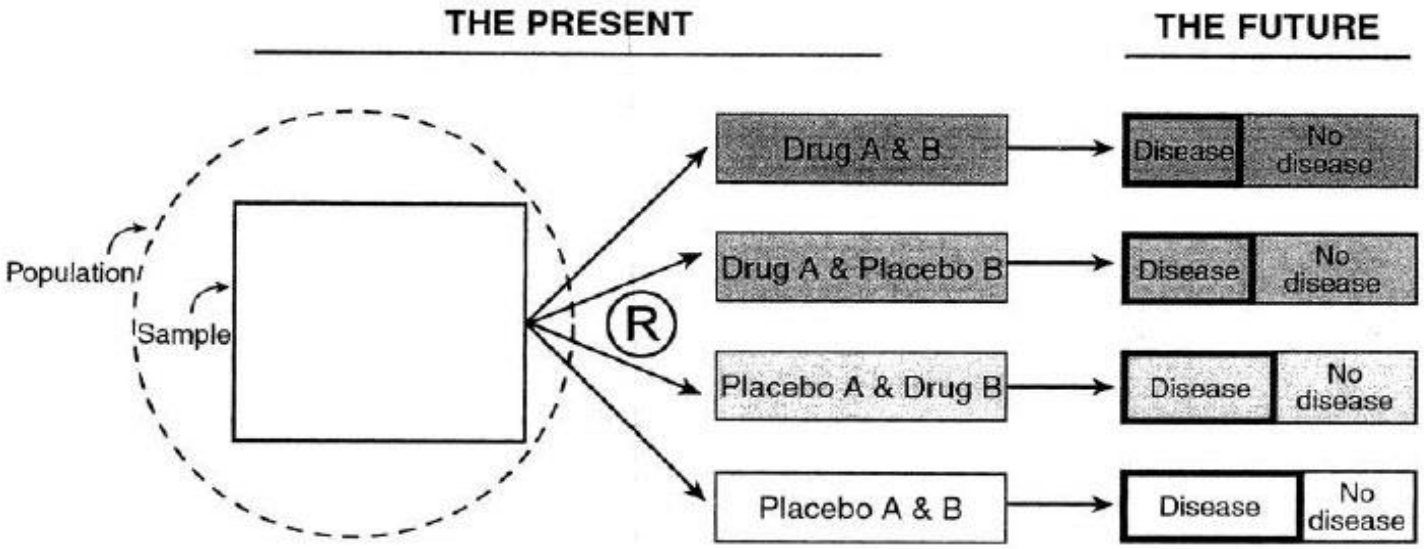


■ **FIGURE 11.4**

In the cross-over randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions, (e) measures outcome variables, (f) allows washout period to reduce carryover effect, (g) applies intervention to former placebo group, (h) measures outcome variables again.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

Factorial RCT design



■ **FIGURE 11.2**

In a factorial randomized trial, the investigator (a) selects a sample from the population; (b) measures baseline variables; (c) randomly assigns two active interventions and their controls to four groups, as shown; (d) applies interventions; (e) follows up the cohorts; (f) measures outcome variables.

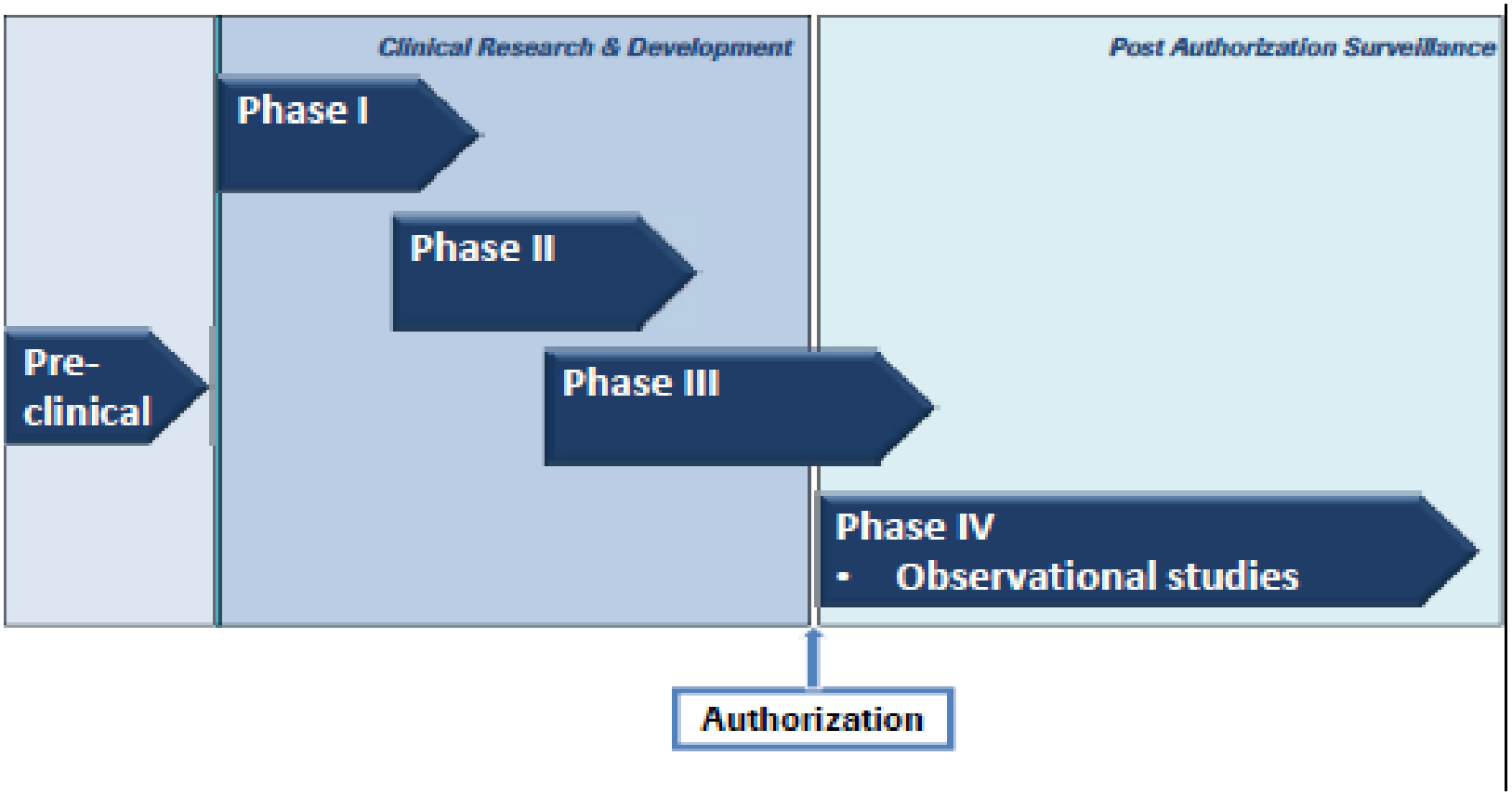
Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

- Factorial clinical trials test the effect of two or more treatments simultaneously using various combinations of the treatments. The simplest factorial design is known as a 2x2 factorial design, whereby participants are randomly allocated to one of four combinations of two interventions.

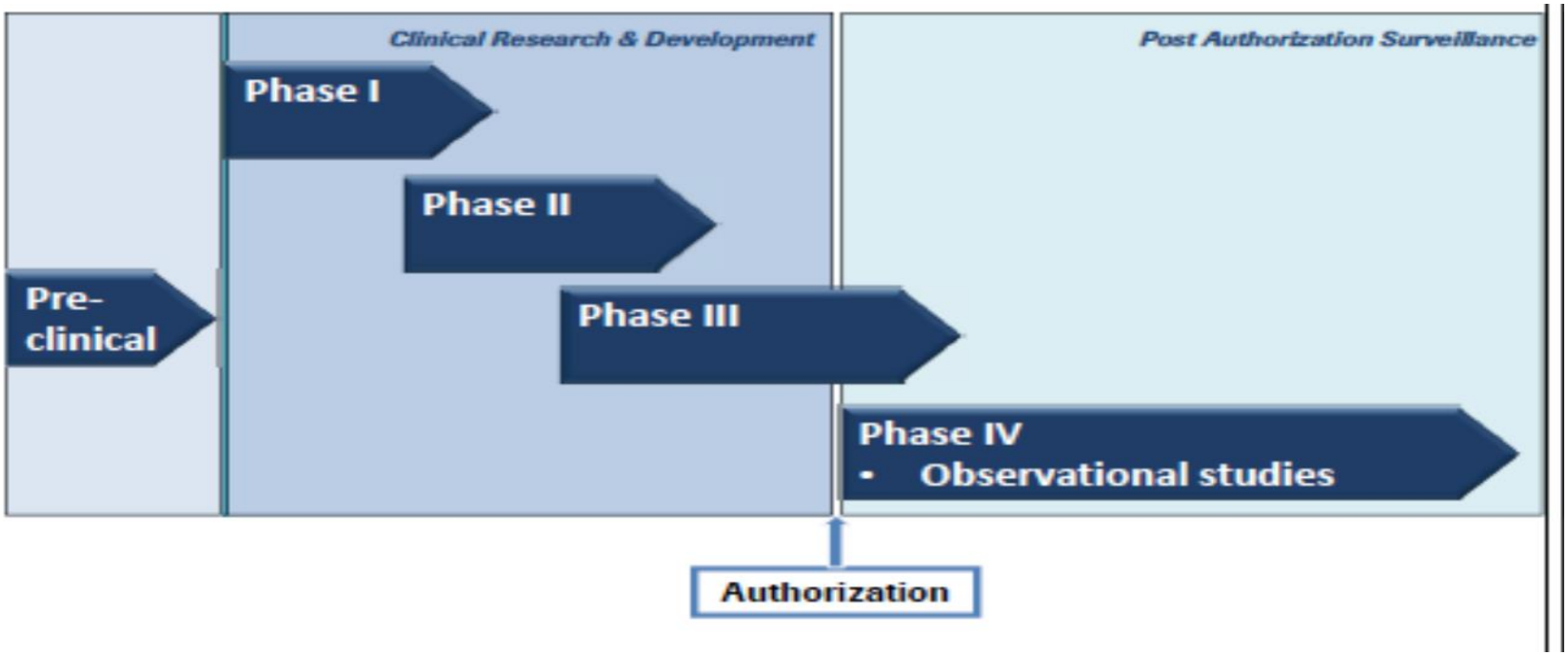
Classification based on the number of the participants

- Fixed Size: number of participants is determined based on *a priori* sample size calculations
- N-of-1 trials: consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions
- Mega-trials: trial powered to address subgroup differences/interactions/secondary analyses
- Sequential Trials: number of participants is NOT specified before the trial begins; participants are recruited until the question is answered (or it becomes clear that there is no possibility to detect a difference between the arms)

Drug development phases

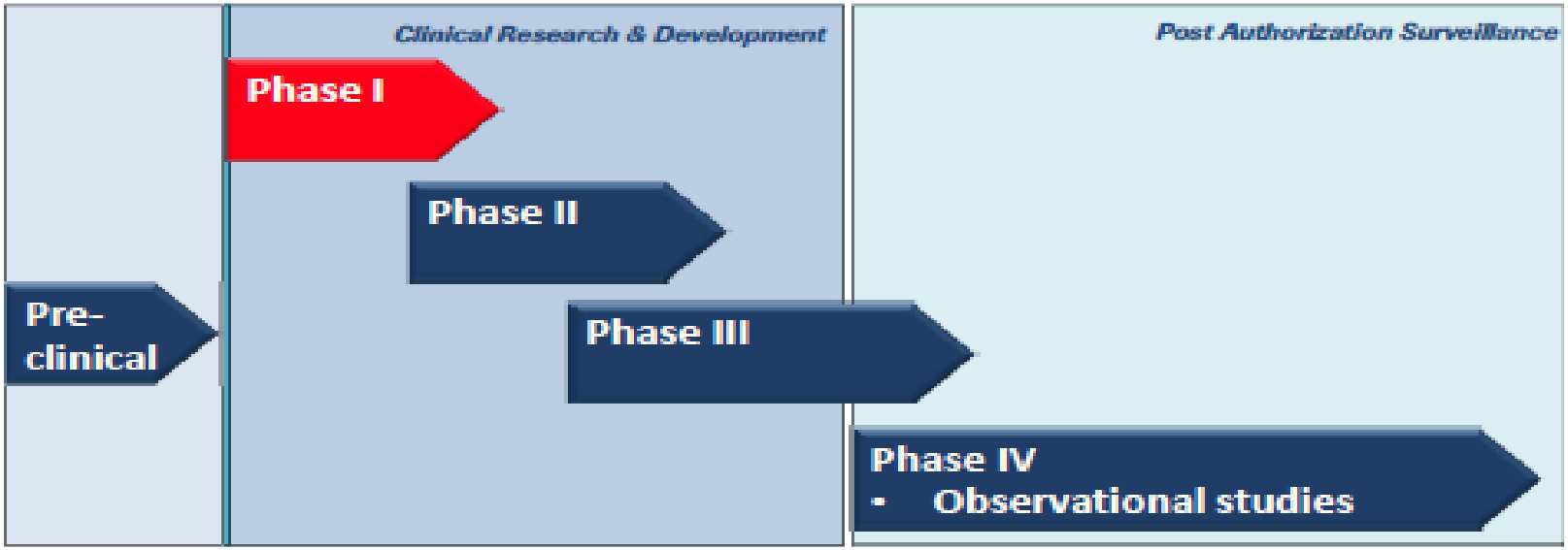


Phase 0 (Exploratory IND series)

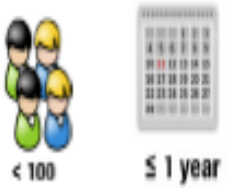


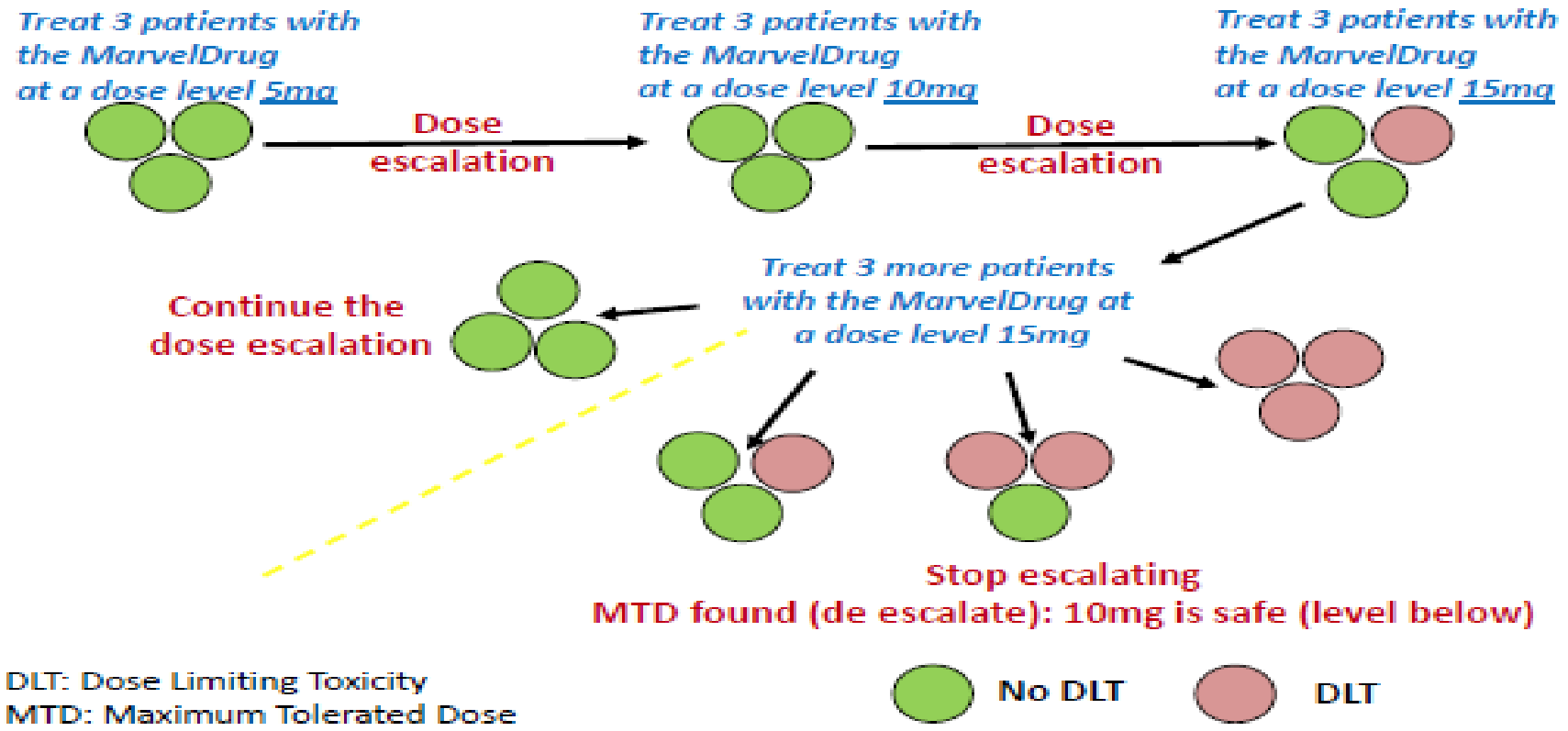
- the first clinical trials done among people.
- Aim: how a drug is processed in the body and how it affects the body.
- a very small dose of a drug is given to about 10 to 15 people.

Phase I



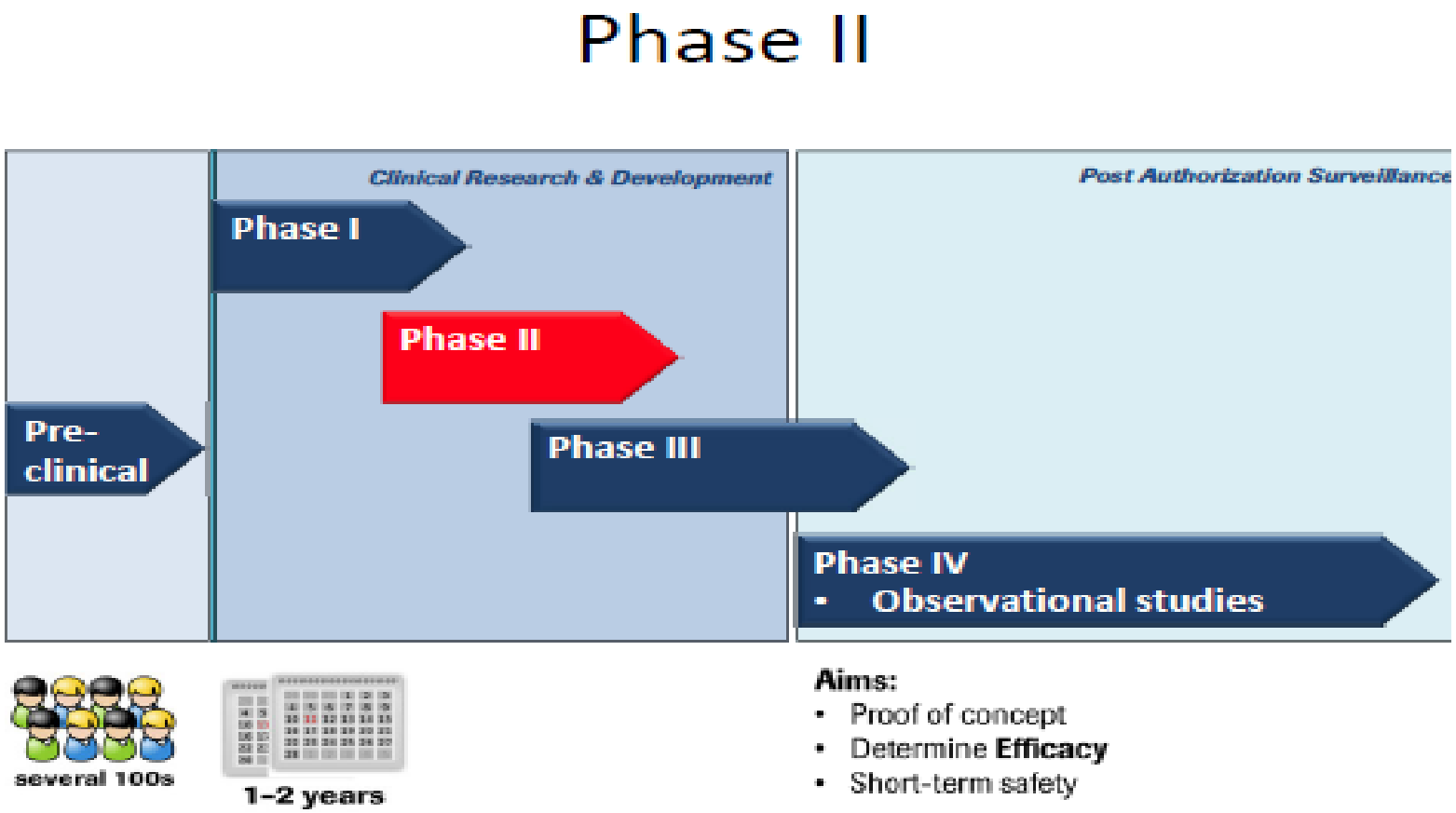
- ***Aim***: drug's safety → human tolerance- dose range
- Pharmaco-kinetics/-dynamics.
- Administered form (pill, solution, patch)
- small group of 15 to 30 patients (<100).





DLT: Dose Limiting Toxicity
MTD: Maximum Tolerated Dose

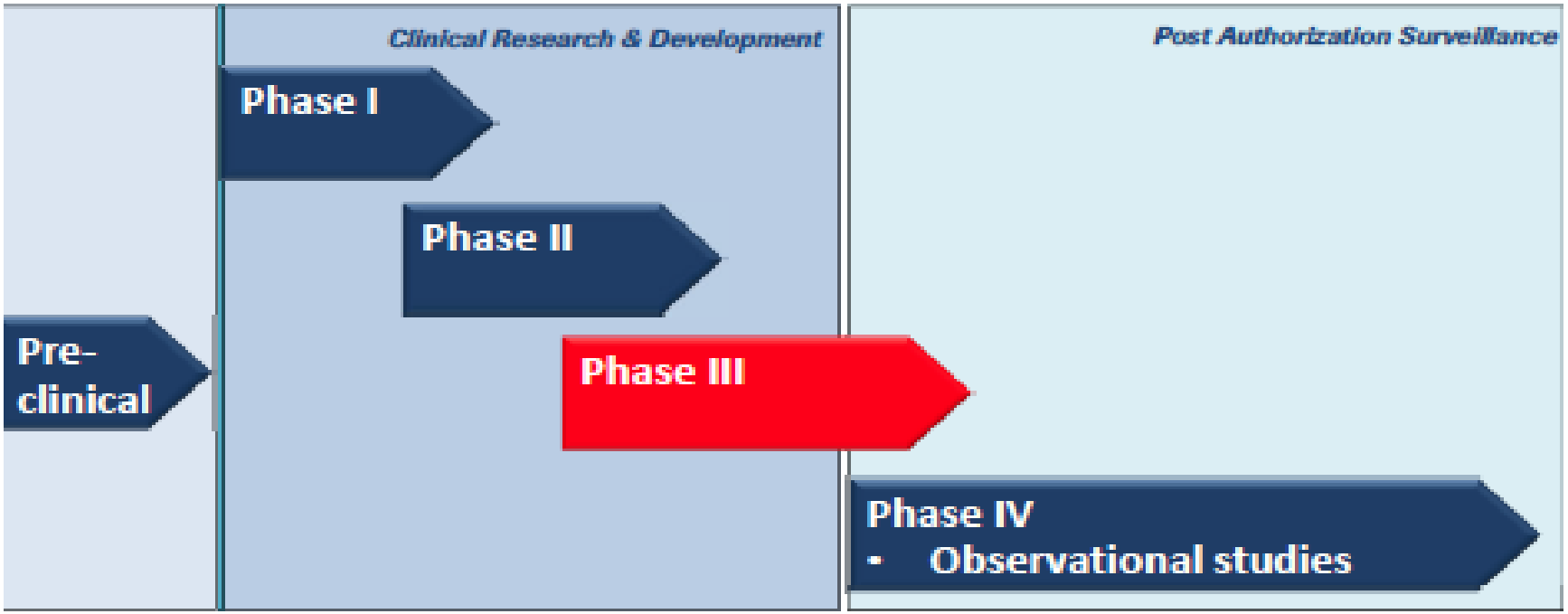
Phase II


Phase II
Clinical Research & Development
Post Authorization Surveillance
Phase I
Phase II
Pre-clinical
Phase III
Phase IV
• Observational studies
several 100s
1–2 years
Aims:
• Proof of concept
• Determine Efficacy
• Short-term safety

Objective: to show that more than 20% of the patient treated with the MarvelDrug will respond

(i.e. a response rate ≤20% would suggest inactivity, usually level of activity is determined on clinical grounds)

Phase III

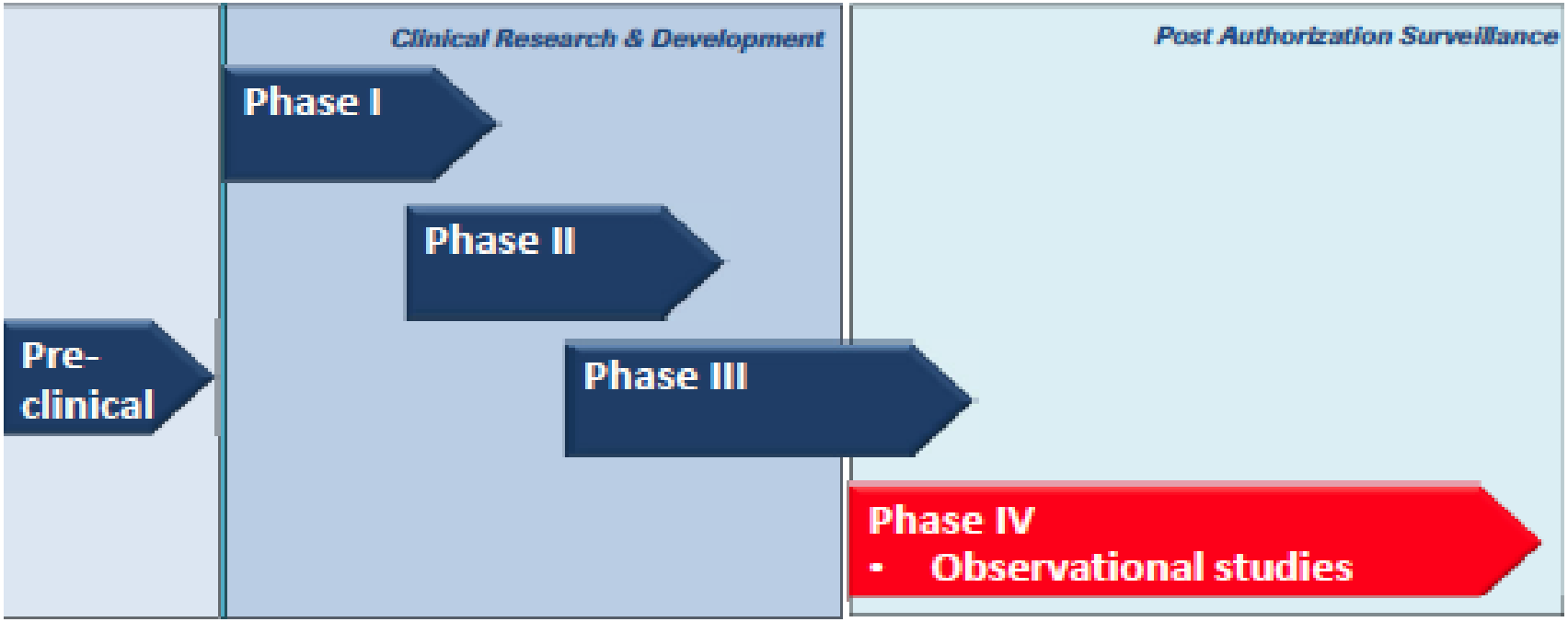


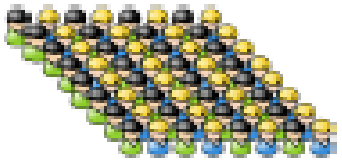
Aims:

- Confirms efficacy (effectiveness)
- Definition of adverse events
- Key Information for label and marketing approval

Superiority Trial / Equivalence / Non-Inferiority

Phase IV





Aims:

- New formulations and indications
- Long – term safety
- Identification of rare adverse events in comparison to other standard treatment

Superiority trials

Purpose

- To detect a difference between two drugs

Goals

- Establish new drug is statistically superior to active control (and/or placebo)
- Establish new drug is clinically superior to active control (and/or placebo)

Equivalence Trials

Purpose

- To confirm the absence of a meaningful difference between treatments

Pharmaceutical equivalence

- Pharmaceutical equivalence (= bioequivalence)
- By itself does not necessarily imply therapeutic equivalence:
  - Absence of a **greater-than-allowable** difference in PK between two drugs
  - This is formalized by bioequivalence margins (see later slides)

Therapeutic equivalence

Pharmaceutically equivalent

+

Same safety and efficacy profiles after administration of same dose

Non-Inferioriy (NI) Trials

- Purpose:

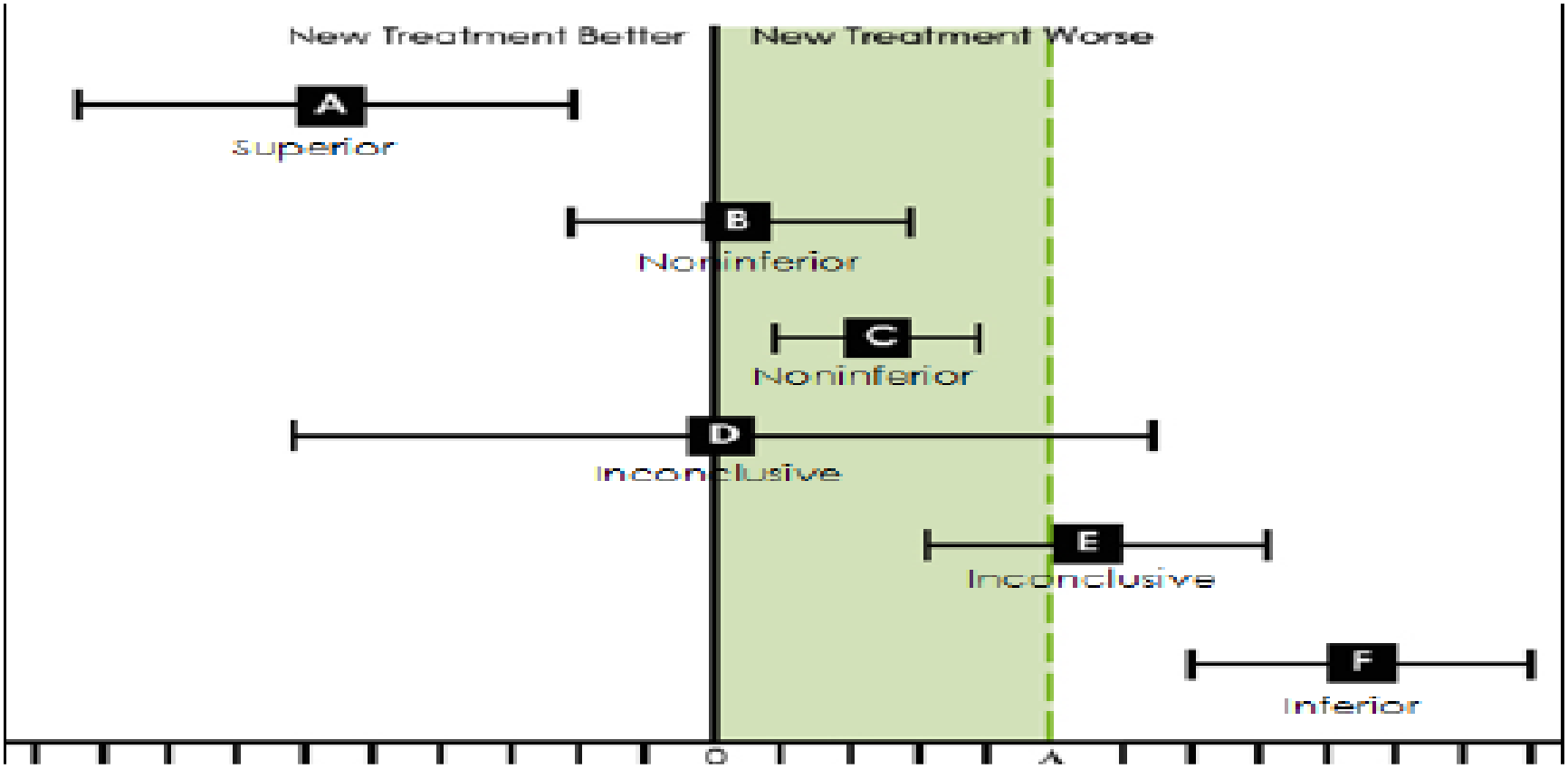
To demonstrate that a new drug is not worse than an active comparator by more than a pre-specified amount*

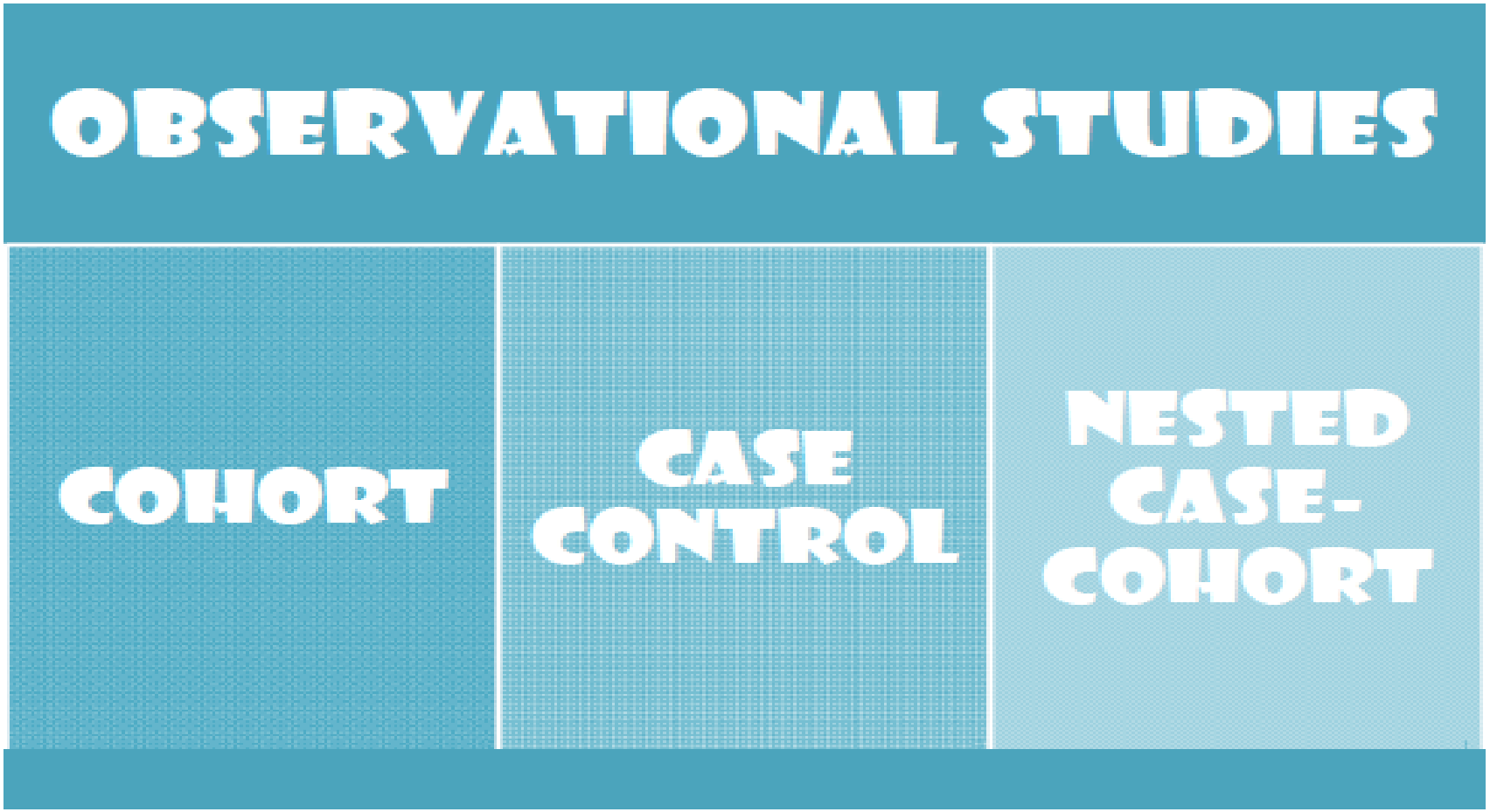
- Non inferiority margin delta (Δ), δ

- NOT equivalent
- NOT inferior to active comparator

- NI margin must be determined by combination of clinical considerations and statistical methods

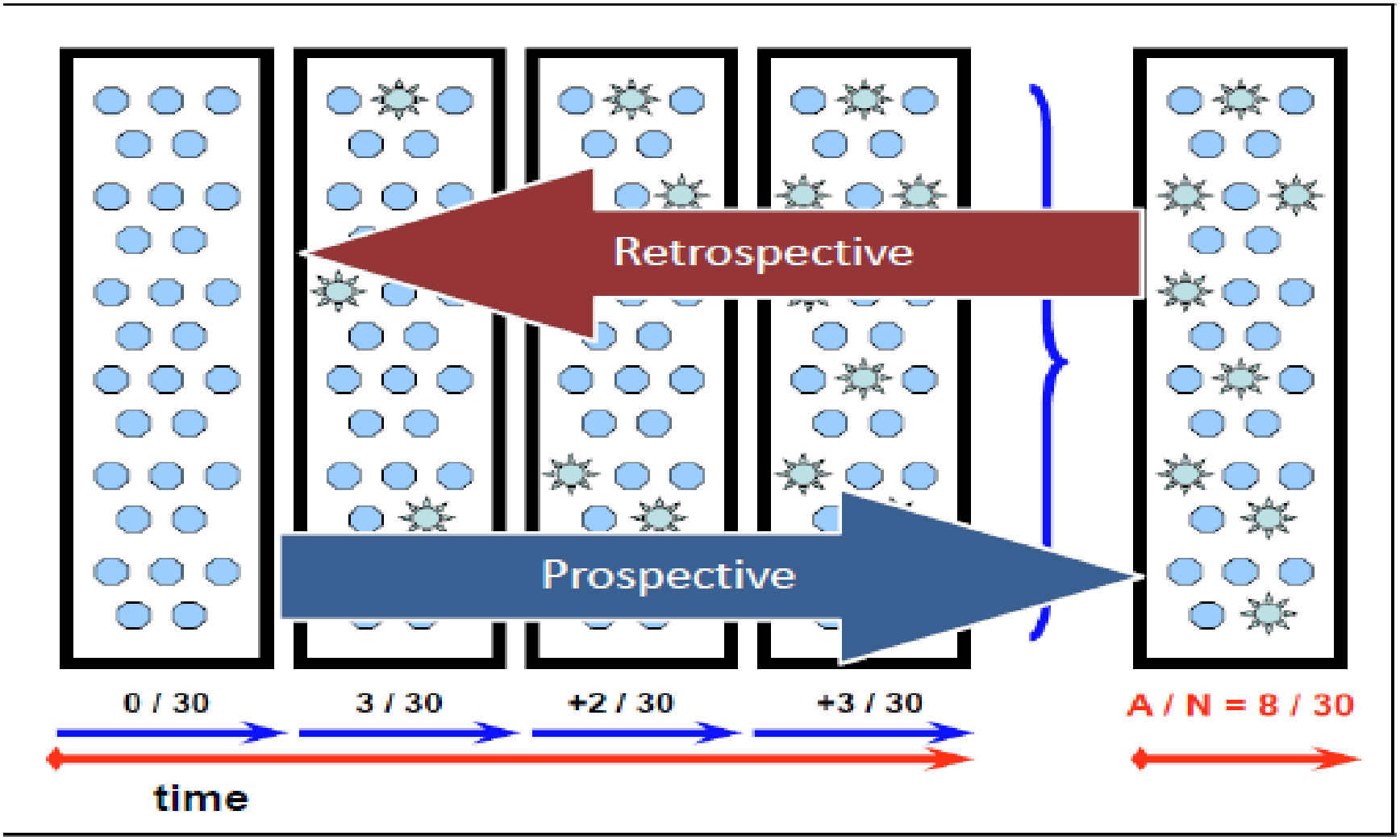
Pros	Cons
Useful when placebo control is inappropriate	Not recommended when the reference treatment is not well established, or is inconsistent when compared with placebo
Not limited to pharmaceutical therapy	
Appropriate for comparing a specific intervention to itself (dose vs. dose or formulation vs. formulation)	
Provides evidence for inferiority, noninferiority OR superiority claims	


New Treatment Better
New Treatment Worse
A
Superior
B
Noninferior
C
Noninferior
D
Inconclusive
E
Inconclusive
F
Inferior
0
Δ


OBSERVATIONAL STUDIES
COHORT
CASE CONTROL
NESTED CASE-COHORT

COHORT

- **Cohors**: subdivision of Roman Legion (300-600 legionnaire)
- **Group of individuals with common characteristics**

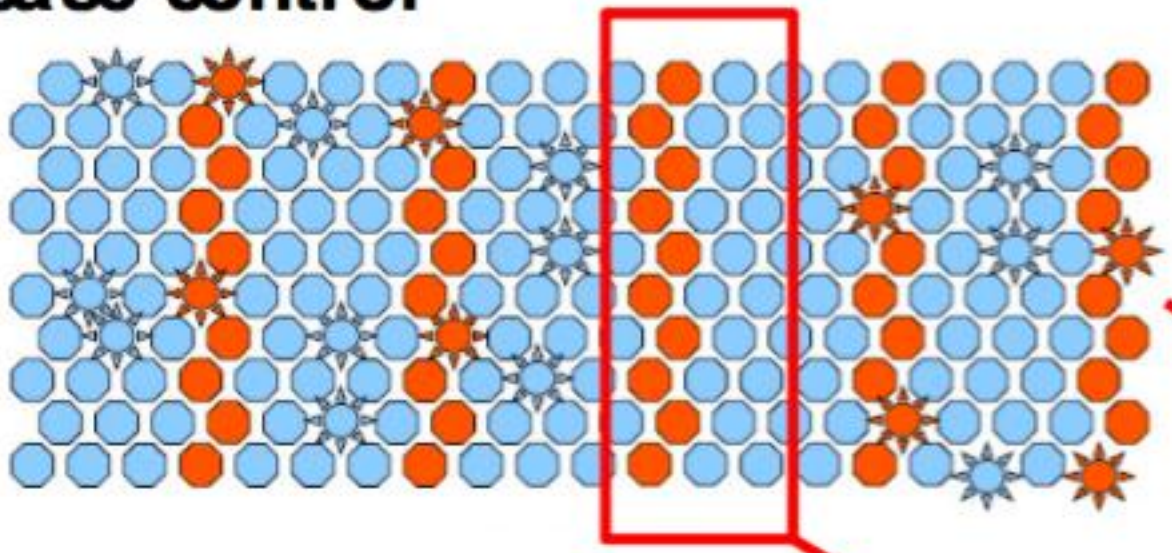

Retrospective
Prospective
0 / 30
3 / 30
+2 / 30
+3 / 30
A / N = 8 / 30
time

- Give direct information on the sequence of happenings (ideal for demonstrating causality)
- Permit the direct calculation of incidence rates in both the exposed and unexposed groups (calculation of risk or rate ratios, or differences)
- Permit multiple outcomes to be assessed in the same study
- Can be used to study exposures that are relatively uncommon (enable an adequate number of exposed and unexposed subjects at the study outset)

- Expensive and time-consuming (large sample size requirements and long follow-up periods)
- Withdrawals and losses to follow-up (selection bias) (connected or unconnected to the disease)
- Exposure misclassification (measurement bias). Subjects may change their exposure status during the follow-up period. Periodic reassessments of exposure status are necessary
- Outcome misclassification. Advances in the ability to detect a particular disease during the course of follow-up may bring prior classifications of outcome status into question and lead to incorrect study results
- Diagnostic suspicion bias. Knowledge of a subject's exposure status may influence the accuracy with which outcome status is determined
- Inefficient for rare diseases

The Prospective Cohort Study
is the method of choice for an observational study and when a clinical trial is not feasible

case-control



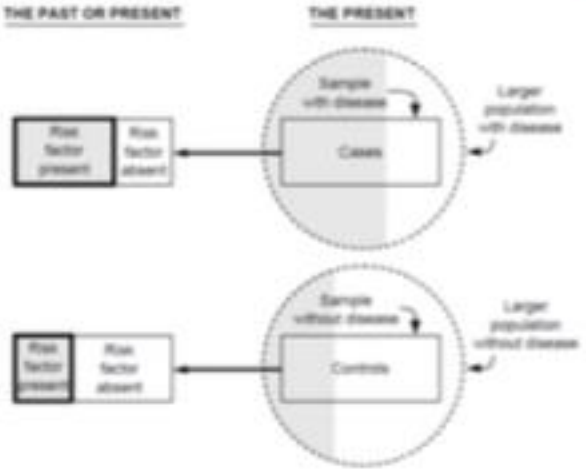
disease

non-disease

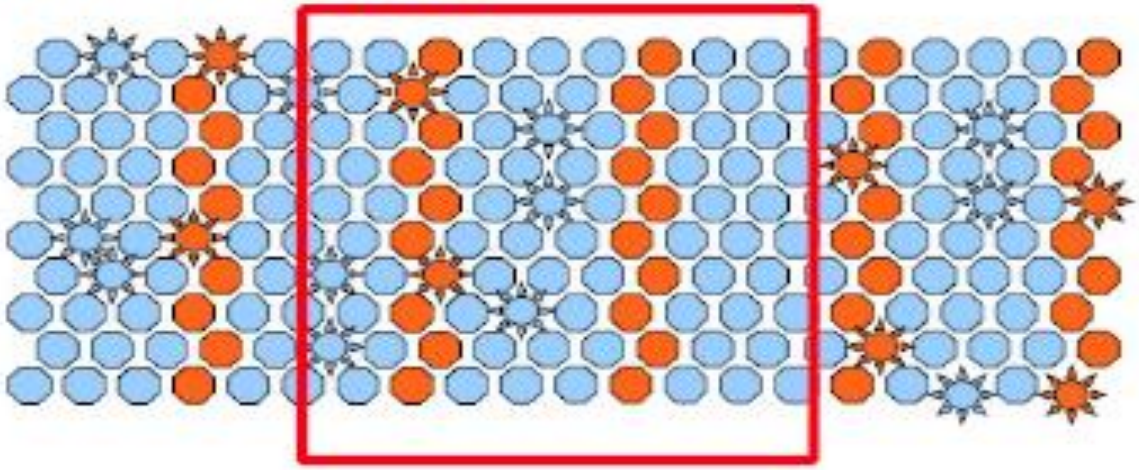
exposure

non-exposure

disease



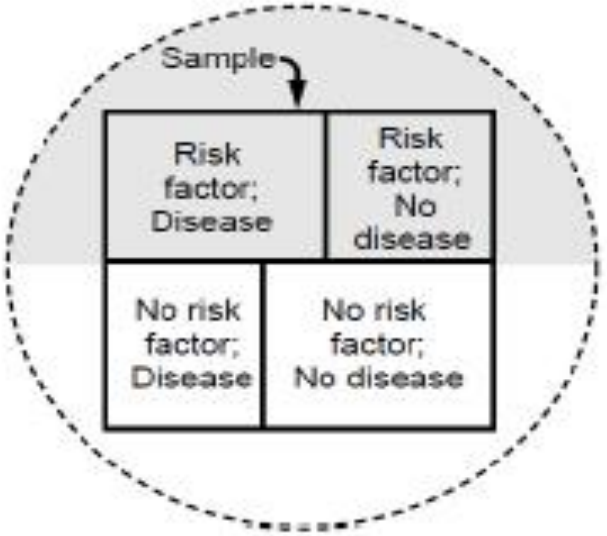
cross-sectional



exposure

non-exposure

disease



Nested Case-Control / Case-Cohort Studies