انواع طراحی ها در کارآزمایی های بالینی
کارآزمایی در عرصه و در جامعه

RCT DESIGNS
FIELD AND COMMUNITY TRIALS

مهمترین انواع کار آزمایی‌های شاهد دار تصادفی

- طراحی موازی
  Parallel Design
- طراحی متقاطع
  Design Cross-over
- طراحی فاکتوریل
  Design Factorial
- کارآزمایی مگا
  Mega Design
- کارآزمایی متوالی
  Sequential Design
- کارآزمایی با اندازه ثابت
  Fixed size Design
- کارآزمایی باز Open Trial
- Withdrawal Study
- Run-In Design
- کارآزمایی یک سوکور
  Single Blind Trial
- کارازمایی دوسوکور Double Blind Trial
- کارآزمایی سه سوکور
  Triple Blind Trial
- کارآزمایی چهار سوکور
  Quartet Blind Trial
- کارآزمایی با طراحی زلن
  Zelen's Design
- کارآزمایی با طرح ونبرگ
  Venberg's Design

DESIGN

- The choice of design depends on the goal of the trial
- Choice also depends on the population, knowledge of the intervention
- Proper design is critical, analysis cannot rescue improper design

طراحی موازی: PARALLEL DESIGN

- اکثر کارآزمایی‌هاي بالیني تصادفي طراحي موازي دارند. در این مطالعات هر گروه از شرکت کنندگان در معرض یکي از مداخلات مطالعه قرار مي‌گیرند.

CROSS-OVER DESIGN:طراحی متقاطع

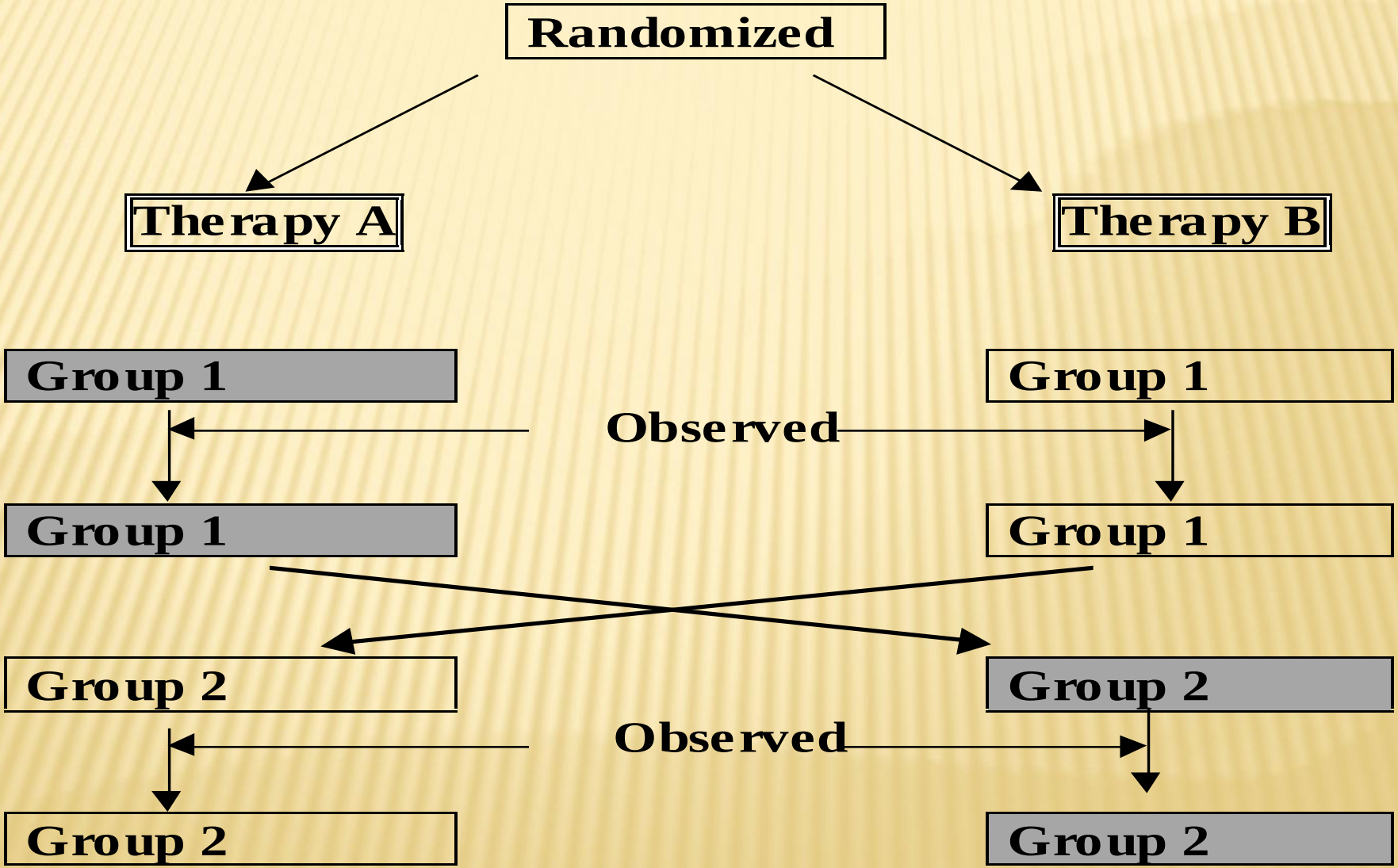
- يك RCT زماني طراحي متقاطع دارد كه هر يك از شركت‌كنندگان كليه مداخلات مطالعه را در دوره‌هاي متوالي دريافت كنند. اينكه كدام شركت كننده، كدام يك از مداخلات را دريافت كند بطور تصادفي معين مي‌شود. در طراحي متقاطع هر يك از شركت‌كنندگان خود شاهد خود مي‌باشند (شاهد و مورد يكي است).

ویژگی‌های طراحی متقاطع:

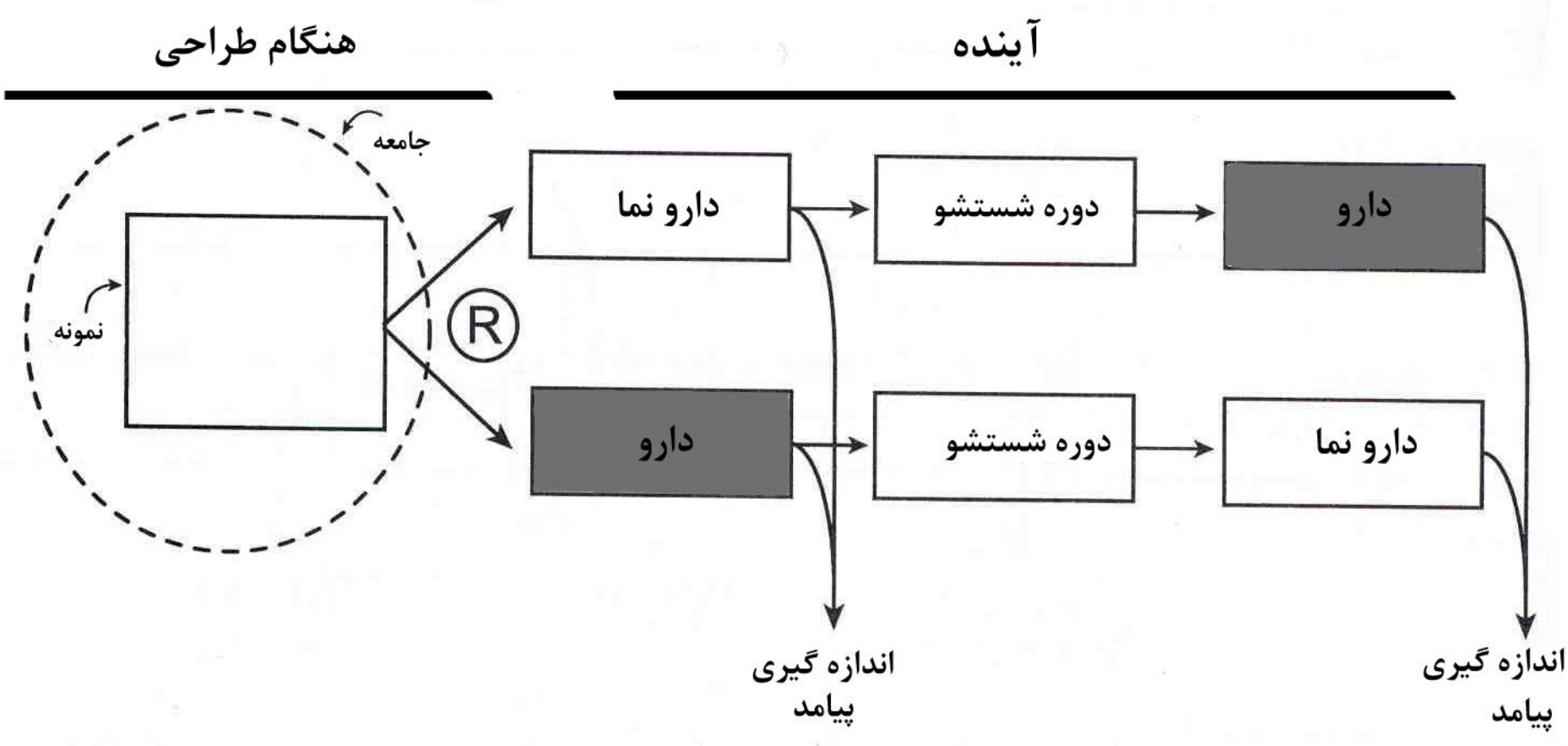
- -مداخلات بايد در بيماريهاي مزمن و غيرقابل درمان (سريع) استفاده شود.
- -اثرات يك مداخله بايد شروع سريع و دوره كوتاه داشته باشد.
- -وضعيت بيماري بايد ثابت باشد.

CROSSOVER DESIGN (PLANNED & UNPLANNED CROSSOVER TRIAL)

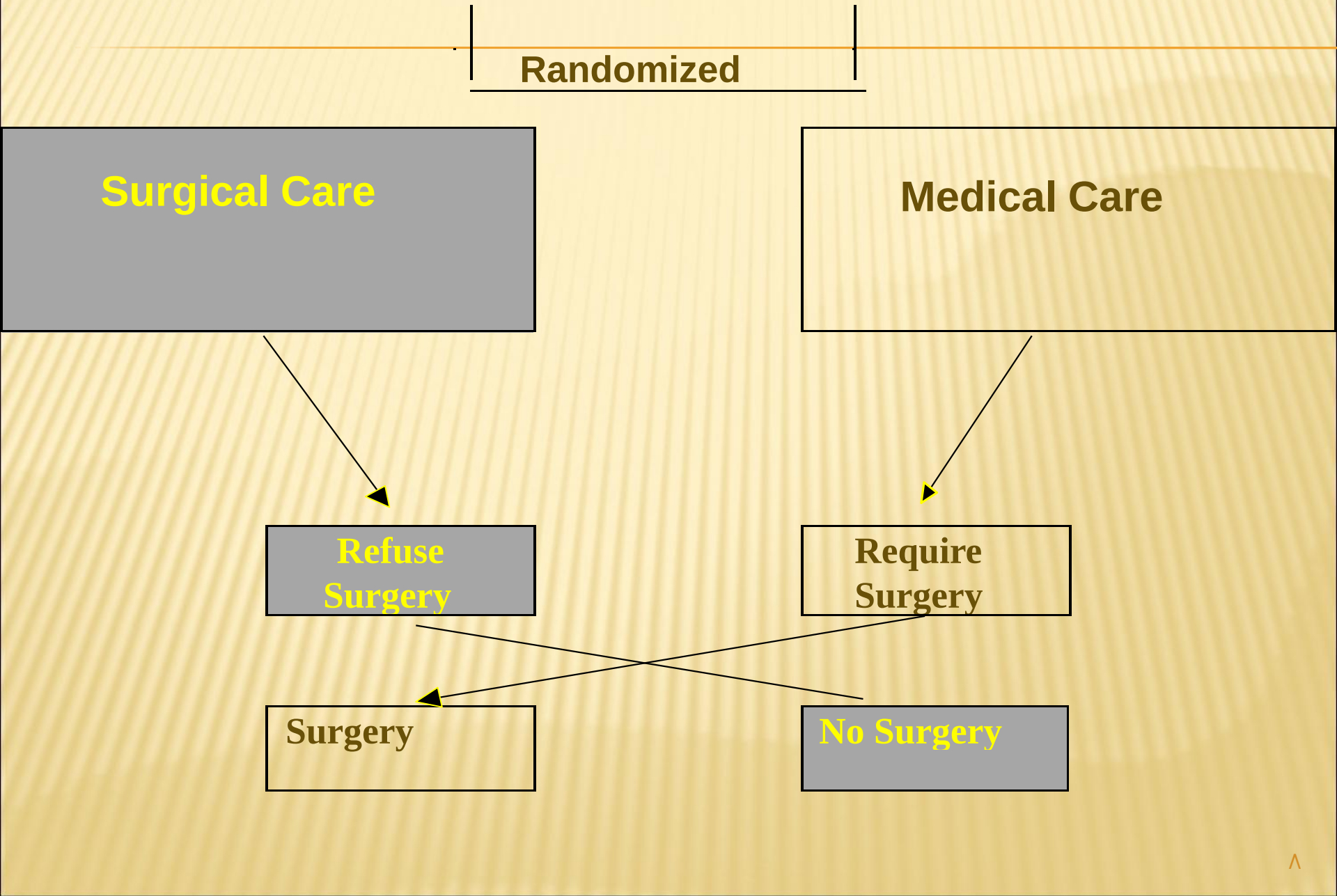
A: DESIGN OF A PLANNED CROSSOVER TRIAL



طراحی متقاطع:CROSS-OVER DESIGN



B: Design of a **UNPLANNED** Crossover Trial



CROSS-OVER DESIGN:طراحی متقاطع

- Advantage
  - Each patient their own control
  - Smaller sample size
- Disadvantage
  - Not useful for acute disease
  - Disease must be stable
  - Assumes no period carry over
  - If carryover, have a study half sized (Period I A vs. Period I B)

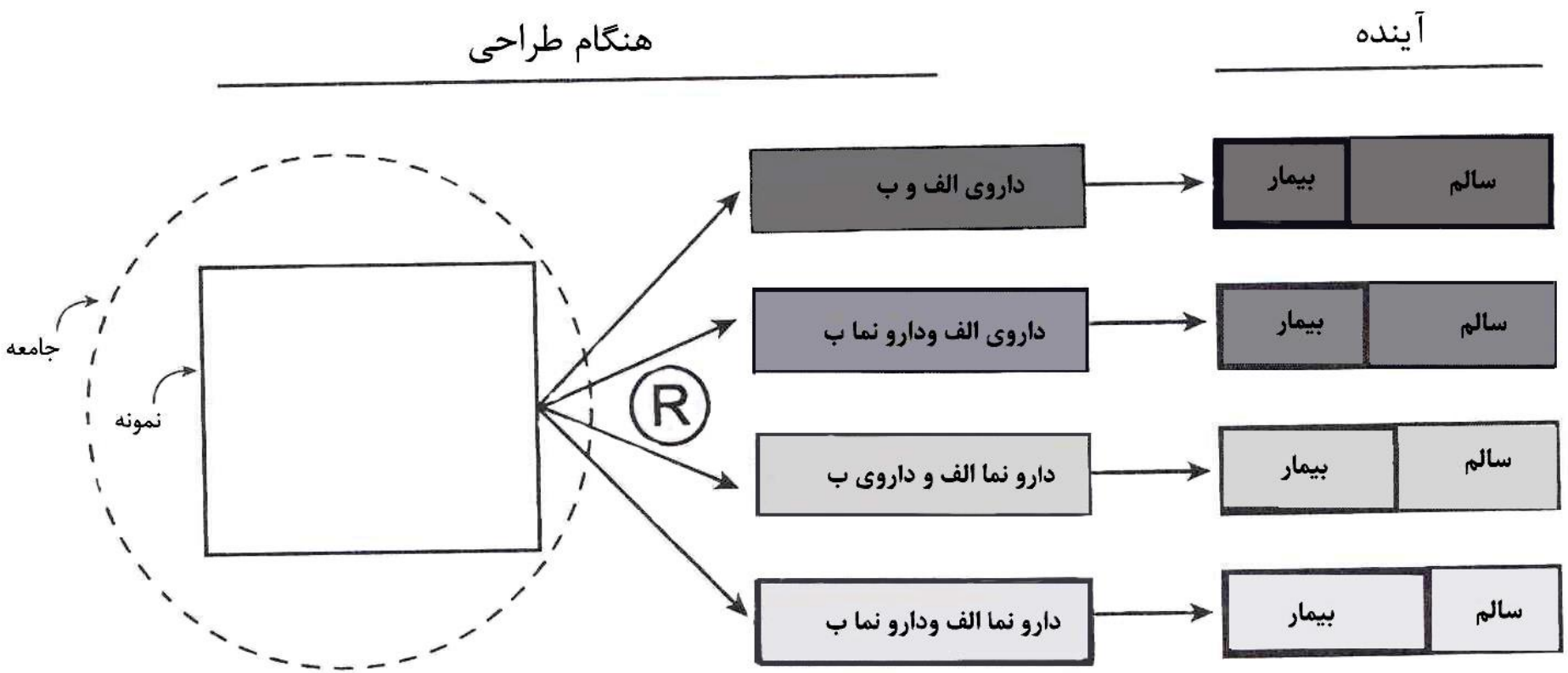
طراحی فاکتوریل: FACTORIAL DESIGN

- يك RCT با طراحي فاكتوريل به ارزشيابي مجزا و همچنين تركيبي از دو يا چند مداخله تجربي و در مقابل شاهد مي‌پردازد. اين طراحي امكان مقايسه مداخلات تجربي با شاهد، با يكديگر و تداخل احتمالي آنها را ارايه مي‌دهد.

Fractional Design

Treatment A	Treatment B: +	Treatment B: -
+	Both (A) and (B)	(A) only
-	(B) only	Neither (A) nor (B)

طراحی فاکتوریل: FACTORIAL DESIGN



FACTORIAL DESIGN

- Advantages
  - Two studies for one
  - Discover interactions
- Disadvantages
  - Test of main effect assumes no interaction
  - Often inadequate power to test for interaction
  - Compliance

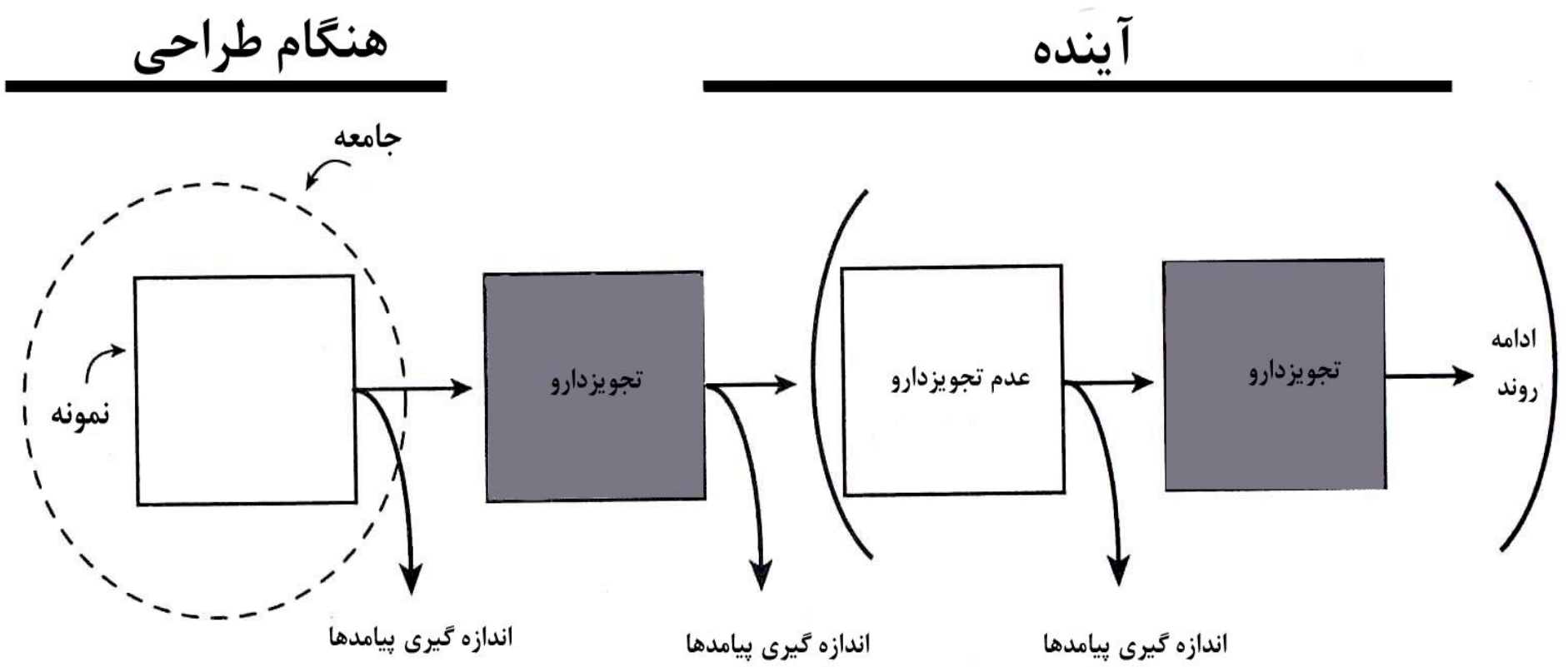
کارآزمایی مگا: MEGA DESIGN

- در اين كارآزمايي، مطالعه با شركت هزاران بيمار و جمع‌آوري اطلاعات محدود شده انجام مي‌شود. اين نوع كارآزمايي نياز به شركت كنندگان زياد (گاه صدها نفر) از چندين مركز يا چند كشور مختلف دارد.

کارآزمایی متوالی: SEQUENTIAL DESIGN

- مطالعه‌اي است با طراحي موازي كه در آن شركت كنندگان از قبل توسط بررسي كنندگان مشخص نمي‌شوند. در عوض بررسي كنندگان به نمونه‌گيري شركت‌كنندگان ادامه مي‌دهند تا سودمندي يكي از مداخلات مشاهده شد يا متقاعد شوند كه اختلاف مهمي در مداخلات وجود ندارد.

کارآزمایی متوالی: SEQUENTIAL DESIGN



SEQUENTIAL DESIGN

- Continue to randomize subjects until H_0 is either rejected or "accepted"
- A large statistical literature for classical sequential designs
- Developed for industrial setting
- Assumptions
  - Acute Response
  - Paired Subjects
  - Continuous Testing
- Not widely used

کارآزمایی با اندازه ثابت: FIXED SIZE DESIGN

- در این کارآزمایي بررسي کنندگان بطور استنباطي تعداد شرکت‌کنندگان را مشخص مي‌کنند. این تعداد بطور اختیاري یا با استفاده از روشهاي آماري تعیین مي‌شود. گاه این اندازه معادل ۳۰ نمونه در هر گروه مي‌باشد.

کارآزمایی باز: OPEN TRIAL

- کارآزمايي تصادفي شده‌اي است كه در آن كليه افراد درگير در كارآزمايي از مداخله‌اي كه هر يك از شركت‌كنندگان دريافت مي‌كنند آگاهند. اكثر كارآزمايي‌هاي مربوط به مداخلات جراحي از اين نوع هستند

ZELEN'S DESIGN :/ RANDOMIZED CONSENT DESIGN طراحی زلن

در اين كارآزمايي افراد واجد شرايط قبل از اعلام رضايت شركت در مطالعه براي دريافت درمان استاندارد يا مداخله تجربي، بطور تصادفي تخصيص داده مي‌شوند. گروهي كه جهت درمان استاندارد انتخاب مي‌شوند، به آنها گفته نمي‌شود كه در مطالعه (كارآزمايي) شركت دارند. حال آنكه به گروه منتخب جهت مداخله گفته مي‌شود كه در مطالعه شركت دارند.

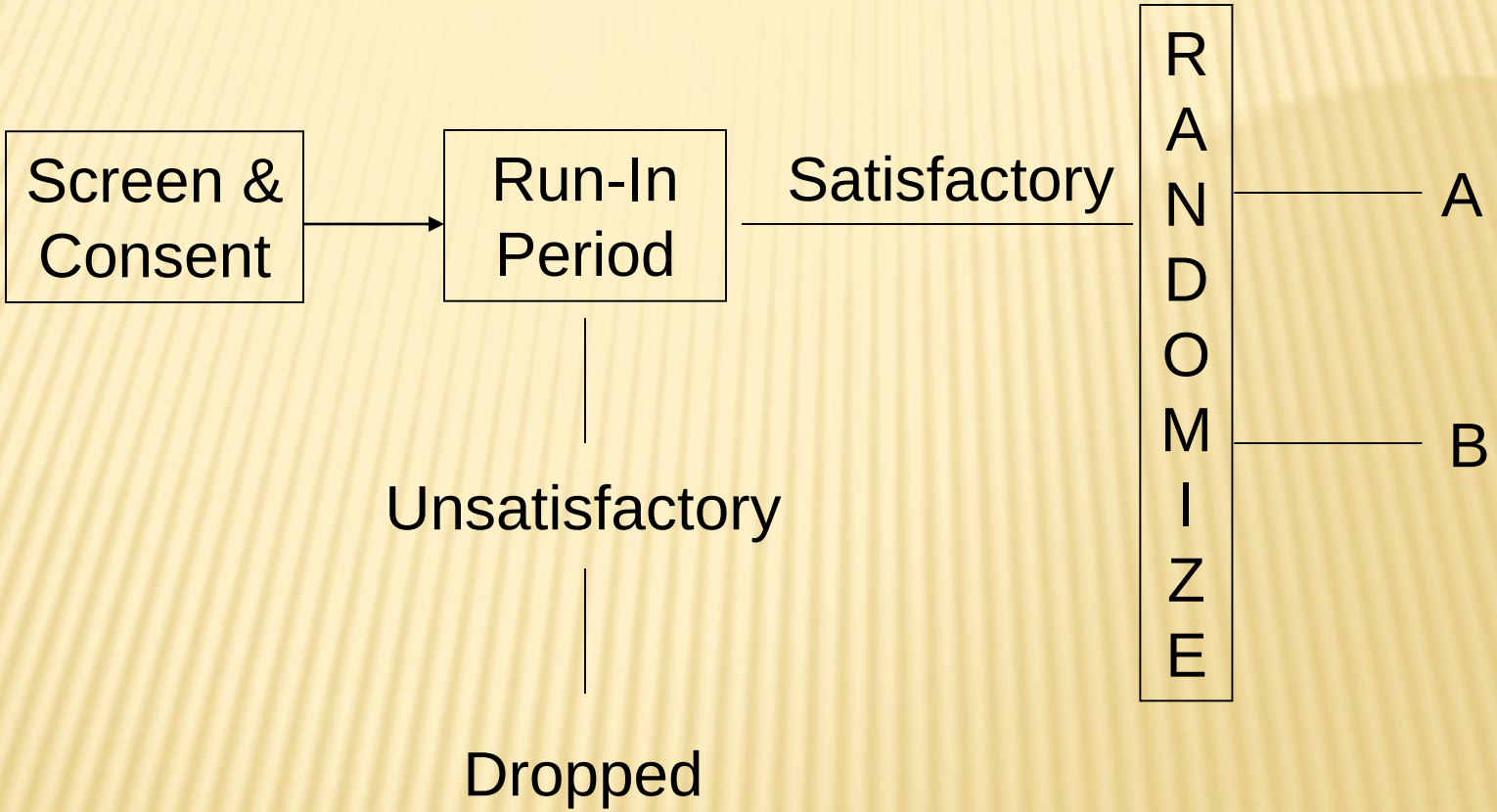
اگر شركت در مطالعه را رد كردند مداخله استاندارد را دريافت مي‌كنند (در اين طرح همه بيماران واجد شرايط در مطالعه در كارآزمايي شركت داده مي‌شوند اما ممكن است نسبت بالايي از شركت كنندگان درمان استاندارد و گروه كوچكي درمان مداخله را دريافت كنند).

- Advantages
  - Easier Recruitment
- Disadvantages
  - Need Low Refusal Rate
  - Control Must Be Standard
  - Unblinded
  - Ethical?
- Refusal Rate→ Dilution → Increase Sample Size

VENBERG'S DESIGN: طرحی ونبرگ

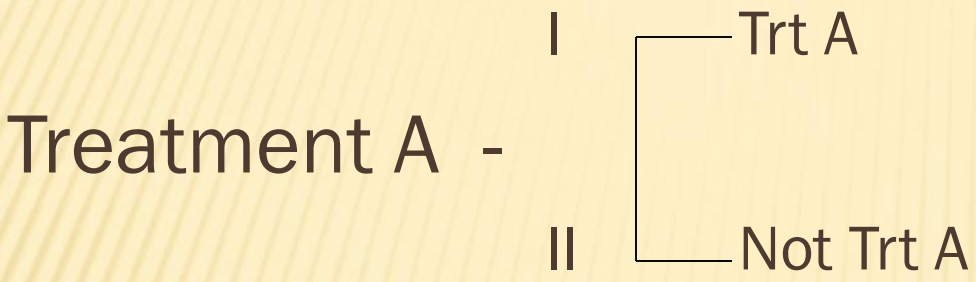
- در اين كارآزمايي افراد واجد شرايط به طور تصادفي به دو گروه تمايل (Preference) و RCTتخصيص داده مي‌شوند. به افراد گروه تمايل فرصت انتخاب مداخله‌اي كه دريافت مي‌كنند داده مي‌شود. حال آنكه افراد گروه RCT بطور تصادفي جهت دريافت هريك از مداخلات مطالعه بدون در نظر گرفتن علائق آنها تخصيص داده مي‌شوند. در پايان مطالعه پيامدهاي مربوط به هر يك از مداخلات در هر يك از گروهها مقايسه شده و جهت تخمين تاثير تمايل شركت كنندگان در پيامدها مورد استفاده قرار مي‌گيرند.

Run-In Design



Note: It is assumed that all patient entering the run-in period are eligible and have given consent

WITHDRAWAL STUDY



- H_0: How long should TRT A continue?
- Advantage
  - Easy Access to Subjects
  - Show continued treatment Beneficial
- Disadvantage
  - Selected Population
  - Different Disease Stage

PHASES OF CLINICAL TRIALS

- Phase Zero trials- Pre-human animal and laboratory testing
- Phase I trials
- Phase II trials
- Phase III trials
- Phase IV trials
  - Meta-analysis—phase 4
  - Retrospective cohort studies—phase 4
  - Case–control studies—phase 4

PHASE 0 - PRECLINICAL

- Pre-clinical (*in vitro)* animal studies
- Looking for dose-response

Phase 0 trials serves as a good tool for clinical researchers in testing the safety and efficacy of drugs **at micro level** before the onset of phase I trial.

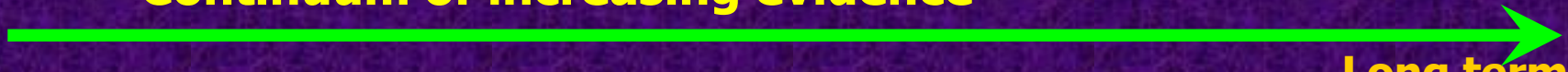
By design, phase 0 trials threaten lower risks to human subject than traditional phase I trials. As such, fewer preclinical supporting data are required prior to conducting a phase 0 trial.

The initial agent dose depends in part on the stated trial objectives, but should not be greater than **1/50th** of the no-observed-adverse-effect level (NOAEL) estimated from **animal** toxicology testing.

LIMITATIONS OF PRE-HUMAN ANIMAL AND LABORATORY TESTING

- High dose effects may not correlate with effects on humans
- Species differences may result in missing effects that later appear in human testing or after widespread clinical use

Continuum of increasing evidence



Long term implementation

Theory

Explore relevant theory to ensure best choice of intervention and hypothesis and to predict major confounders and strategic design issues

Preclinical

Modelling

Identify the components of the intervention and underlying mechanisms by which they will influence outcomes to provide evidence that you can predict they relate to and interact with each other

Phase I

Exploratory trial

Describe the constant and variable components of a replicable intervention and a feasible protocol for comparing the intervention with an appropriate alternative

Phase II

Definitive randomized controlled trial

Compare a fully defined intervention with an appropriate alternative using a protocol that is theoretically defensible, reproducible and adequately controlled in a study with appropriate statistical power

Phase III

Determine whether others can reliably replicate your intervention and results in uncontrolled setting over the long term

Phase IV

PHASE I TRIALS (FIRST IN HUMAN PHASE)

- First time testing on human
- In a small group of 20-80 cases
- Patients usually failed other alternatives
- Sometimes called dose-finding or dose-escalation studies
- Seeking maximum tolerated dose (MTD)

The earliest types of studies that are carried out in humans. They are typically done using small numbers of **healthy subjects** and are to investigate pharmacodynamics, pharmacokinetics and toxicity.

Purpose is:

- To assess tolerability
- To evaluate the safety
- To determine a safe dosage range
- Rectify side effects

PHASE I TRIAL DESIGN

More recently this phase is divided to two separated stages as:

- Phase Ia

Include the first dose in human with short term single dose studies to confirm safety before beginning a larger trial. The studies on average comprised of 6 cohorts with about 7 subjects per cohort.

- Phase Ib

The studies are more comprehensive repeated dose studies with the same goal being safety, tolerability and effective

LIMITATIONS OF PHASE I

- Small numbers mean many adverse events may be missed
- When includes patients not representative of those on whom the drug will be used, may not help predict adverse events

MINI-STUDY EXAMPLE 1

- A new drug completed phase 1 trials without evidence of important adverse events using healthy volunteers who reflect the age and ethnic distribution of outpatients in a major metropolitan area.
- When subsequently more widely used, it was found that patients on antidepressants had reduced effectiveness of their medication, that Vietnamese often had dangerously high blood levels, and that those on drugs for Alzheimer often reacted with rapid deterioration of their condition.

MINI-STUDY EXAMPLE 2

- A phase 1 trial of a new drug was conducted on 30 healthy, non-pregnant adults who were administered the drug at three different doses overa1-week period. The investigation monitored the absorption, metabolism, and excretion of the drug, as well as monitoring drug-sensitive organs and clinically observed adverse events. This phase 1 study did not find any clinically important adverse events and did not detect any damage to drug-sensitive organs. When the drug was used for longer periods in later studies, it was found that its effects on the kidneys were frequent and severe enough to preclude its approval for clinical use.

PHASE I TRIALS- EXAMPLE

Objective

To determine the maximum tolerated dose of a new therapy for advanced colorectal cancer

Outcome measure (endpoint)

The number of patients who suffer a dose-limiting toxicity

PHASE II TRIALS

Carried out in patients, usually to find the best dose of drug and to investigate safety.

- Tested in larger group of people. About 100 people
- Estimate of drug activity
- Decide if drug warrants further testing (Phase III)
- Estimate of serious toxicities
- There are various types from single-arm (one or two stage design) to randomized studies with several new interventions

Purpose is:

- To further evaluate
  - Safety
  - Effectiveness
- Screen for therapeutic activity
- If drug passes screen, test further

LIMITATIONS OF PHASE II

- Primary intent is assessment of efficacy.
- Small numbers and less than comprehensive assessment of harms often limit ability to draw conclusion about potential harms

PHASE II TRIALS- EXAMPLE

Objective

- To investigate Drug A in patients with Parkinson's disease.

Outcome measure (endpoint)

- The proportion of patents in whom the disorder progresses after 1 year.

Objective

- To examine the effect of therapy B for lung cancer

Outcome measure (endpoint)

- The proportion of patients who have a partial or complete outcome tumor response at the end of treatment

PHASE III TRIALS

Generally major trials aimed at conclusively demonstrating efficacy.

They are sometimes called confirmatory trials and, in the context

of pharmaceuticals, typically are the studies on which registration of a new product will be based.

- Still large group 1000-3000 people are tested
- Various designs
  - No control
  - Historical control
  - Concurrent
  - Randomized

Purpose:

- To confirm its effectiveness
- Monitor side effects
- Compare to commonly used treatments
- To gather information regarding safe use

COMMONLY USED PHASE III DESIGNS

- Parallel
- Withdrawal
- Group/Cluster
- Randomized Consent
- Cross Over
- Factorial
- Large Simple
- Equivalence/Non-inferiority
- Sequential

LIMITATIONS OF PHASE III

- Uniform characteristics of the participants may result in study and control groups with only one disease who are taking only one medication.
- Randomized controlled trials often too small, too short, and too simple to detect rare but serious adverse events.
- Randomized controlled trials often focus on one particular group of individuals, who are expected to be particularly responsive to the treatment.
- Randomized controlled trials often include individuals who have only one disease, are not on a spectrum of other treatments, and may not include especially vulnerable groups such as children, pregnant women, etc.
- Randomized controlled trials are designed to be conducted only as long as needed to establish efficacy.
- Randomized controlled trials are designed to establish efficacy for one particular indication.

MINI-STUDY EXAMPLE

- A randomized controlled trial of a new medication for treatment of Type 2 diabetes was used on newly diagnosed Type 2 diabetics without other diseases and who were not taking other medication. The treatment was very successful and no severe adverse events were found.
- When approved and used in practice, the treatment was quickly found to worsen kidney function among those being treated for hypertension with several anti-hypertensive medications.

PHASE III TRIALS-EXAMPLE

Objective

To evaluate the effectiveness of a Flu vaccine in the elderly

Outcome measure (endpoint)

The proportion of people who develop flu within 6 months (incidence)

Objective

To determine the effectiveness of Statin therapy in people without a history of heart disease

Outcome measure (endpoint)

Mean serum cholesterol level 12 months later

CLINICAL TRIAL PHASES

	Phase I	Phase II	Phase III
Question	Is the treatment safe?	Does the treatment works?	What are the long term results in lots of people?
Risk	Riskiest- First trial in Human. Use to determine doses	Moderate risk. Some safety information about the drug is known.	Lowest risk More information about safety and effectiveness is known
Length	Short-term. A few weeks to a few months	Medium Length. Usually about a year.	Longest May last for two to three years
NO. of Participants	Few participants	About one hundred participants	At least several hundred participants.

SUMMARY OF PHASES I-III

	# Subs.	Length	Purpose	% Drugs Successfully Tested
Phase I	20 – 100	Several months	Mainly Safety	70%
Phase II	Up to several 100	Several months- 2 yrs.	Short term safety; mainly effectiveness	33%
Phase III	100s – several 1000	1-4 yrs.	Safety, dosage & effectiveness	25-30%

PHASE IV TRIALS

Studies carried out after registration of a product. They are often for marketing purposes as well as to gain broader experience with using the new product.

- Post marketing studies
- Long term post Phase III follow-up
- To know about
  - Drug risks
  - Benefits
  - Optimal use

UNDERSTANDING THE POST MARKET PROCESS OF EVALUATING HARMS

- The drug may be advertised and marketed for a particular indication, the one for which it was studied and approved.
- Once the drug is approved, it may be used by prescribing clinicians for any patient. That is, the prescribing clinician has the authority to use the treatment for indications not specifically approved by the FDA.

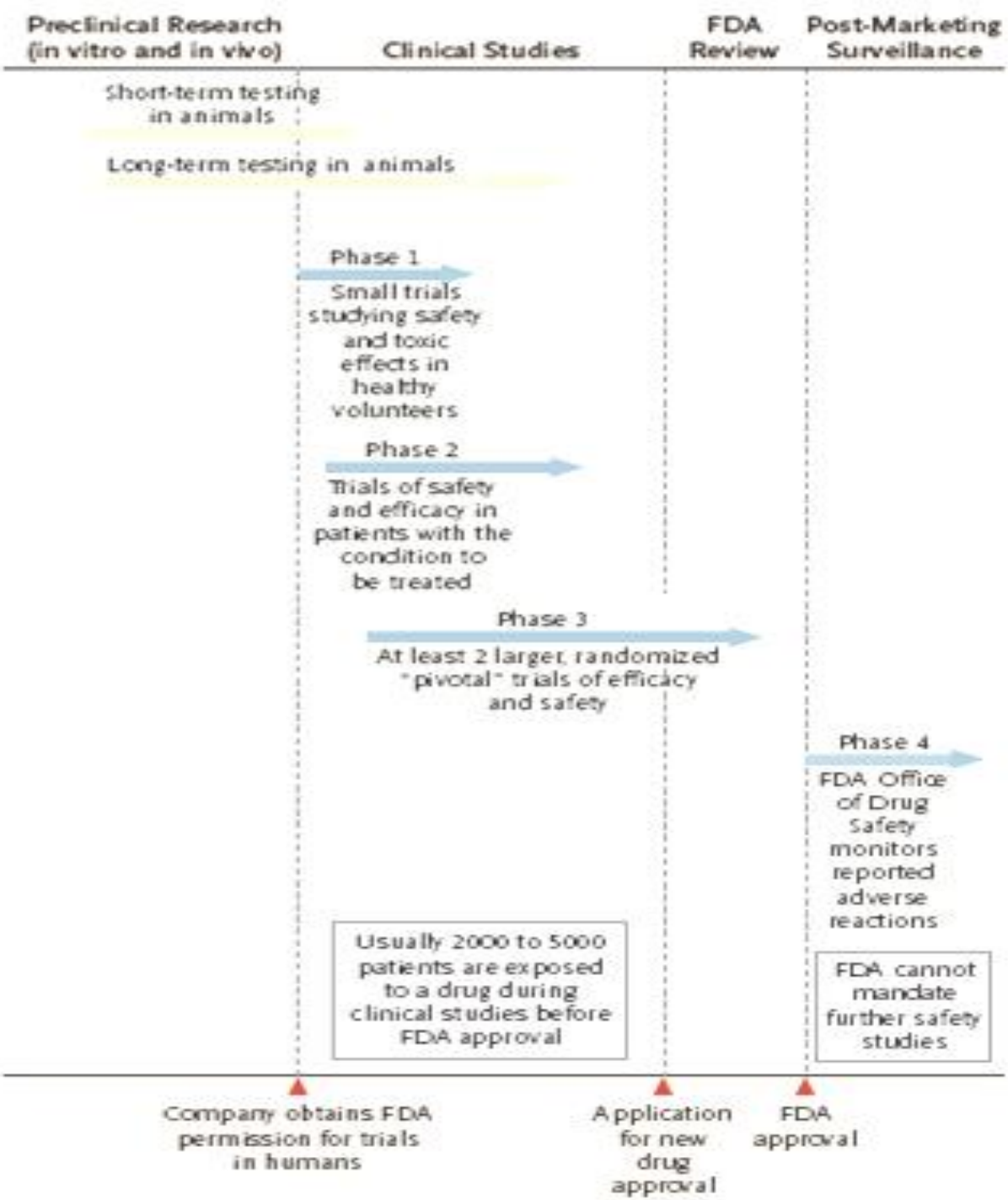
Use of treatments for indications not approved by the FDA is called off-label prescribing.

MINI-STUDY EXAMPLE

- A new β-blocker was first approved and marketed for treatment of angina. Clinicians observed that it also reduced blood pressure in many patients and began to use it off-label as a treatment for hypertension. The β-blocker was subsequently studied and approved by the FDA for treatment of hypertension. Clinicians continued to use it for off-label indications including migraine head-aches and tremors well before the FDA approved it for these indications.

LIMITATIONS OF PHASE IV

- Unplanned reporting system results may not detect adverse events especially if they are not dramatic, do not occur soon after the intervention, require special testing to detect their presence, are clinically unexpected, and/or are similar to the effects of the disease being treated.


Preclinical Research (in vitro and in vivo)
Clinical Studies
FDA Review
Post-Marketing Surveillance
Short-term testing in animals
Long-term testing in animals
Phase 1
Small trials studying safety and toxic effects in healthy volunteers
Phase 2
Trials of safety and efficacy in patients with the condition to be treated
Phase 3
At least 2 larger, randomized "pivotal" trials of efficacy and safety
Phase 4
FDA Office of Drug Safety monitors reported adverse reactions
Usually 2000 to 5000 patients are exposed to a drug during clinical studies before FDA approval
FDA cannot mandate further safety studies
Company obtains FDA permission for trials in humans
Application for new drug approval
FDA approval

PHASES OF CLINICAL TRIALS

Phase 0 - Preclinical

- Preclinical animal studies
- Looking for dose-response

Phase I

- Seeking maximum tolerated dose (MTD)
- Patients usually failed other alternatives

Phase II

- Estimate of drug activity
- Decide if drug warrants further testing (Phase III)
- Estimate of serious toxicities

PHASES OF CLINICAL TRIALS

Phase III

- Provide effectiveness of drug or therapy
- Various designs
  - No control
  - Historical control
  - Concurrent
  - Randomized
- Testing for treatment effect

Phase IV

- Long term post Phase III follow-up
- Concern for safety

PHASE V

- Phase V is a growing term used in the literature of translational research to refer to comparative effectiveness research and community-based research; it is used to signify the integration of a new clinical treatment into widespread public health practice.

CLUSTER RANDOMIZATION DESIGNS

- **Groups (clinics, communities) are randomized to treatment or control**
- **Examples:**
  - Community trials on fluoridization of water
  - Breast self examination programs in different clinic setting in USSR
  - Smoking cessation intervention trial in different school district in the state of Washington
- **Advantages**
  - Sometimes logistically more feasible
  - Avoid contamination
  - Allow mass intervention, thus “public health trial”
- **Disadvantages**
  - Effective sample size less than number of subjects
  - Many units must participate to overcome unit-to-unit variation, thus requires larger sample size
  - Need cluster sampling methods

سوالات کار گروهی

۱. دو کارآزمایی بالینی الف و ب برای ارزیابی یک دارو انجام شده است. در هر دو مطالعه، میزان مرگ بعد از درمان با داروی مورد مطالعه ۲۰% کمتر از گروه کنترل است. اما تنها یافته مطالعه الف با $P< 0.05$ از نظر آماری معنی دار است. محتمل ترین تفسیر کدام است؟

الف) مطالعه «الف» از دوز بالاتر دارو استفاده کرده است.

ب) مطالعه «الف» کمتر دچار اثر متغیرهای مخدوش کننده شده است.

ج). مطالعه «الف» از روش تصادفی سازی استفاده کرده است

د) مطالعه «الف» دارای حجم نمونه بیشتری از مطالعه «ب» است.

۱. مطالعات قبلي نشان داده‌اند که براي بيماران قلبي استفاده از قرص پلاويکس تأثير بهتري در مقايسه با والفارين دارد. شواهد و تجارب موجود موید چنین نتیجه گیري نيستند و مطالعه کارآزمايي دقیق‌تری را می‌خواهند طراحي کنند. به نظر شما تاکید محققان در طراحي مطالعه نسبت به مطالعات قبلي بايد بيشتر متوجه کدام عامل باشد؟

الف) خطاي نوع اول کوچک‌تر

ب) خطاي نوع دوم کوچک‌تر

ج) اندازه تأثير کوچک‌تر

د) کور سازی

۱. براي کاهش شيوع کم خوني ناشي از فقرآهن در جامعه و امکان غني سازي نان با آهن نياز به يك مطالعه مقدماتي براي تعيين اثربخشي- سطح ايمني و انجام پذيري اين اقدام داريم. مناسب ترين مطالعه اي را که پيشنهاد مي کنيد کدام است؟

الف- مقطعي مبتني بر جامعه

ب- کارآزمايي باليني شاهددار

ج- کارآزمايي در عرصه

د- کارآزمايي در جامعه

مطالعه زیر فاز چندم یک کارآزمایی بالینی است؟ چرا؟

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- **Efficacy of high-dose versus standard-dose influenza vaccine in older adults.**

BACKGROUND: As compared with a standard-dose vaccine, a high-dose, trivalent, inactivated influenza vaccine (IIV3-HD) improves antibody responses to influenza among adults 65 years of age or older. This study evaluated whether IIV3-HD also improves protection against laboratory-confirmed influenza illness.

METHODS: We conducted a phase ???, multicenter, randomized, double-blind, active-controlled trial to compare IIV3-HD (60 μg of hemagglutinin per strain) with standard-dose trivalent, inactivated influenza vaccine (IIV3-SD [15 μg of hemagglutinin per strain]) in adults 65 years of age or older. Assessments of relative efficacy, effectiveness, safety (serious adverse events), and immunogenicity (hemagglutination-inhibition [HAI] titers) were performed during the 2011-2012 (year 1) and the 2012-2013 (year 2) northern-hemisphere influenza seasons.

RESULTS: A total of 31,989 participants were enrolled from 126 research centers in the United States and Canada (15,991 were randomly assigned to receive IIV3-HD, and 15,998 to receive IIV3-SD). In the intention-to-treat analysis, 228 participants in the IIV3-HD group (1.4%) and 301 participants in the IIV3-SD group (1.9%) had laboratory-confirmed influenza caused by any viral type or subtype associated with a protocol-defined influenza-like illness (relative efficacy, 24.2%; 95% confidence interval [CI], 9.7 to 36.5). At least one serious adverse event during the safety surveillance period was reported by 1323 (8.3%) of the participants in the IIV3-HD group, as compared with 1442 (9.0%) of the participants in the IIV3-SD group (relative risk, 0.92; 95% CI, 0.85 to 0.99). After vaccination, HAI titers and seroprotection rates (the percentage of participants with HAI titers ≥ 1:40) were significantly higher in the IIV3-HD group.

Conclusions: Among persons 65 years of age or older, IIV3-HD induced significantly higher antibody responses and provided better protection against laboratory-confirmed influenza illness than did IIV3-SD.