موضوعات مورد بحث

- انواع مطالعات اپیدمیولوژیک
- تعریف و تاریخچه کارآزمائی بالینی
- ضرورت انجام کارآزمائی بالینی
- نکات مهم در کارآزمائی بالینی
- نگاه اجمالی به کارآزمائی بالینی
- اصول طراحی کارآزمائی بالینی
- انواع کارآزمائی بالینی
- مراحل (فازهای) کارآزمائی بالینی

انواع مطالعات اپیدمیولوژیک

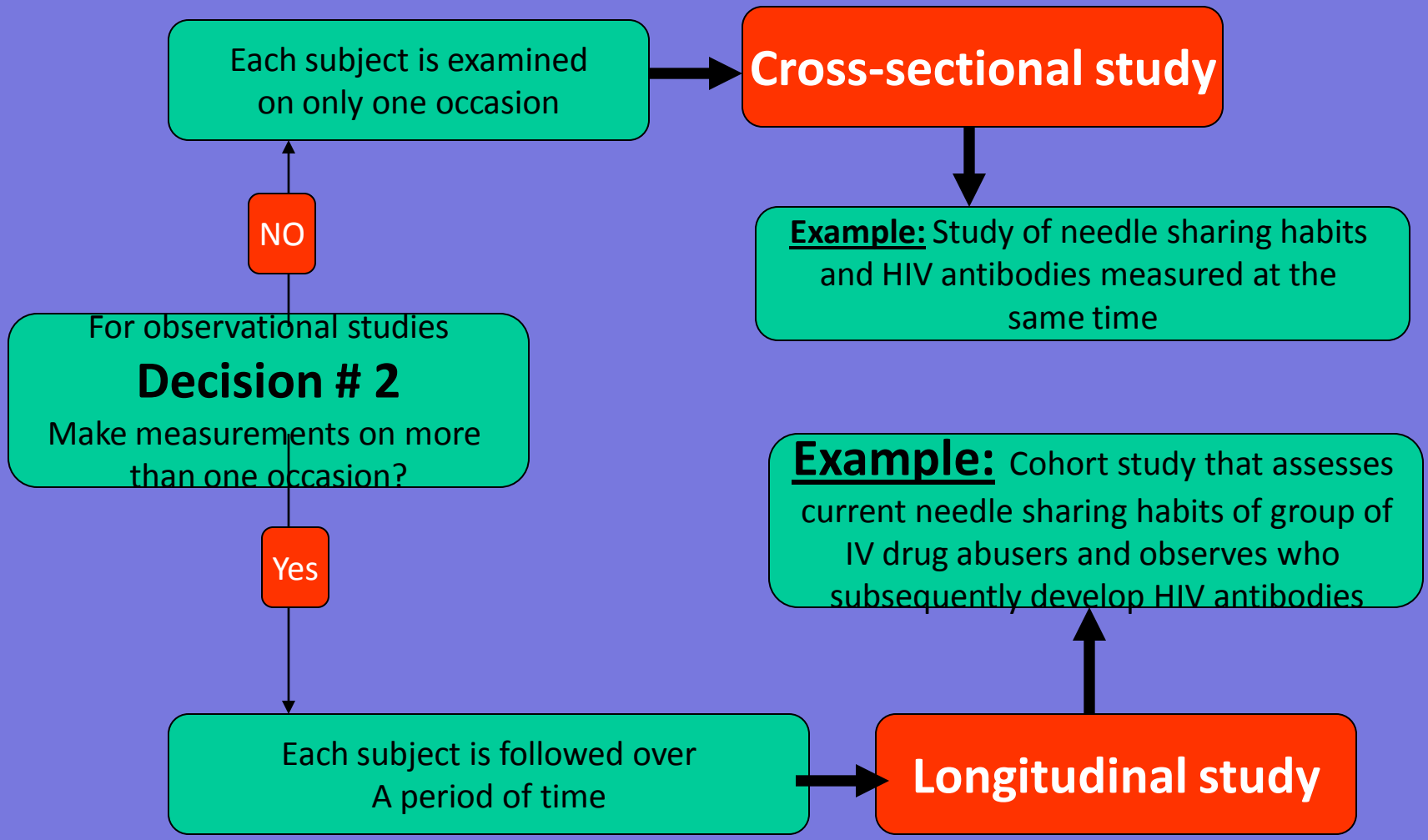
Why Do Research Studies?

- **To collect data on usual and unusual events, conditions, & population groups**
- **To test hypotheses formulated from observations and/or intuition**
- **To understand better one's world and make "sense of it"**

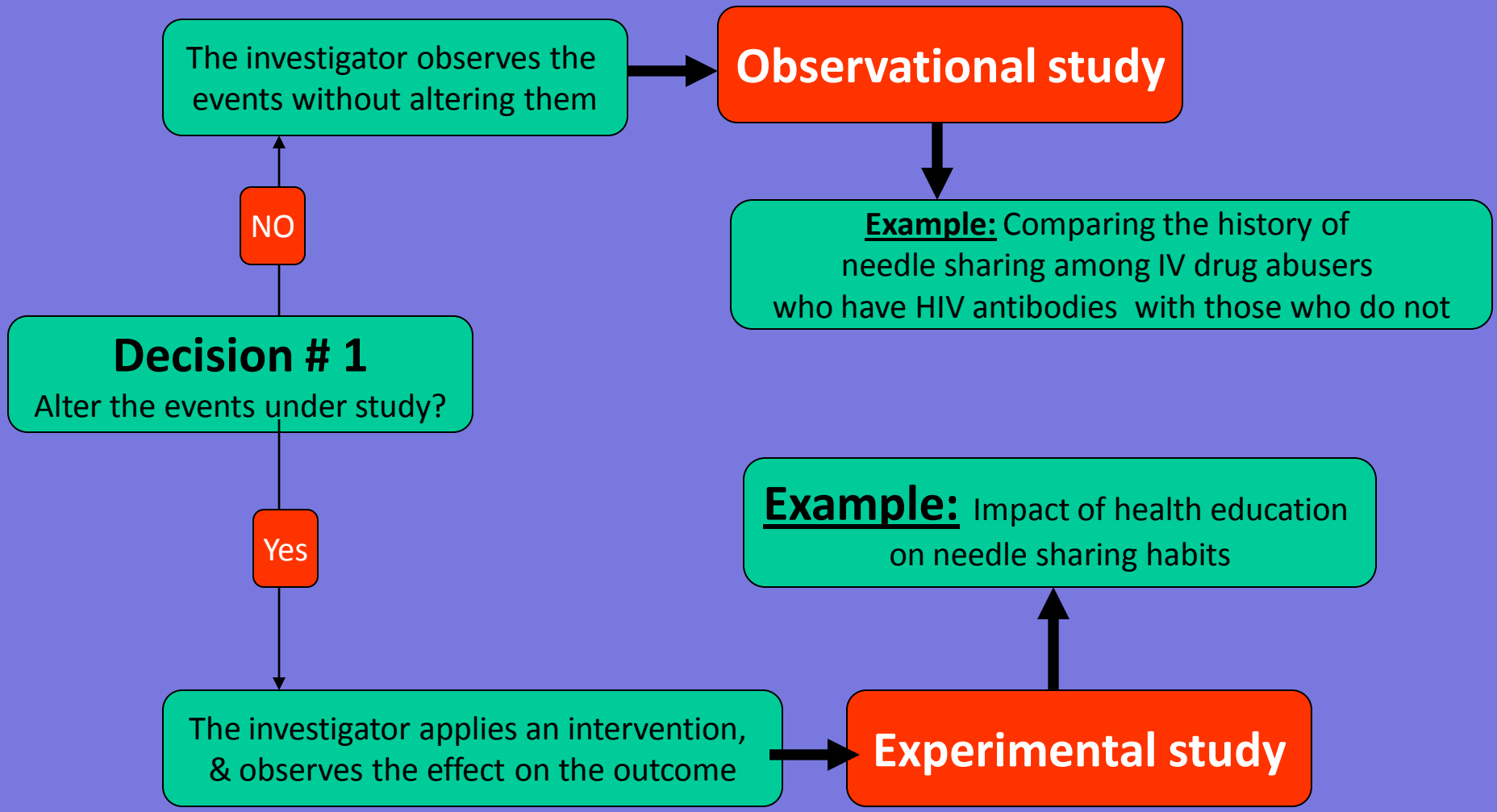
- **Various types of research studies**
- **Many classified as "Epidemiological Studies"**

Type of study	Alternate name	Unit of study
Observational studies		
Descriptive studies		
Analytical studies		
Ecological	Correlational	Populations
Cross-sectional	Prevalence	Individuals
Case-Control	Case-Reference	Individuals
Cohort	**Follow-up/ Longitudinal**	**Individuals**
Experimental/ intervention Studies		
Randomized Controlled Studies	Clinical Trial	Patients
Field Trial		Healthy person
Community Trial	Community intervention studies	Communities

Deciding which one to use



Deciding which one to use



Deciding which one to use

- Can you alter the events under the study?
- How strong is the hypothesis?
- How common is the disease or health event which is to be studied?
- How common is the exposure/ determinants of the health event?
- Do you want to study the different factors/ determinants of a health event or disease? Or; Do you want to see the multiple effect of an exposure?
- How much resources do you have?

تعریف و تاریخچه
کارآزمائی بالینی

Randomised Controlled Trial (RCT)

- Population is randomly allocated to two groups
- One group is given a specific treatment or intervention
- On average the groups are identical because they are randomised and therefore any difference in the measured outcome is due to the intervention
- Specified follow up period and specified outcomes
- e.g. drug better than placebo; surgical procedure compared with sham

Definition

All clinical trials are prospective studies in which individuals are exposed (or not) and followed for an outcome (or a few different outcomes). The outcomes must be clearly defined.

تعریف

کار آزمایی بالینی چیست؟

یک مطالعه همگروهی آینده نگر است که پژوهشگر در آن مداخله می نماید

Randomized Clinical Trials (RCT)
History

- The use of RCT in agricultural experiments was pioneered by R. A. Fisher in the 1920's.

- The Tuberculosis Trials evaluating the effectiveness of streptomycin, is generally accepted as the first RCT - Post World War II

- Randomization first used by RA Fisher in agriculture expts in 1920s
- First clinical trial using *randomization* in 1931 by Anderson on use of sanocrysin on TB patients. Also, first trial using *blinding*.
- *Placebo* first used in RCT in 1938 in cold vaccine trial.

East India Shipping Company 1600: General Lancaster's Ship

"And the reason why the General's men stood better in health then the men of other ships, was this: he brought to the sea with him certain Bottles of the Juice of Limmons, which he gave to each one . . . (Drummond and Wilbraham, 1940)

Lind 1747 on board the Salisbury

12 patients with *scurvy* taken on board

orange and lemon juice

These had sudden and visible effects
with one returning to duty after 6 days

Historical Minute
First "Clinical Trials"

- **Clinical Trials have a long history – even if not acknowledged as *Clinical trials***
- **Formal record of clinical trials dates back to the time of the *"Trialists":***
  - **Dr. Van Helmont's proposal for a therapeutic trial of bloodletting for fevers [1628]**
  - **Dr. Lind's, a ship surgeon, trial of oranges & limes for scurvy [1747]**

Historical Minute
First "Clinical Trials"

Historical Highlights of Drug Trials

- **1909: Paul Ehrlich - Arsphenamine**
- **1929: Alexander Fleming - Penicillin**
- **1935: Gerhard Domagk - Sulfonamide**
- **1944: Schatz/Bugie/Waksman – Streptomycin**
- **By 1950, the British Medical Res. Council developed a systematic methodology for studying & evaluating therapeutic interventions**

Fundamental Point:

A properly planned clinical trial is a powerful expt'l technique for assessing effectiveness of a drug or intervention.

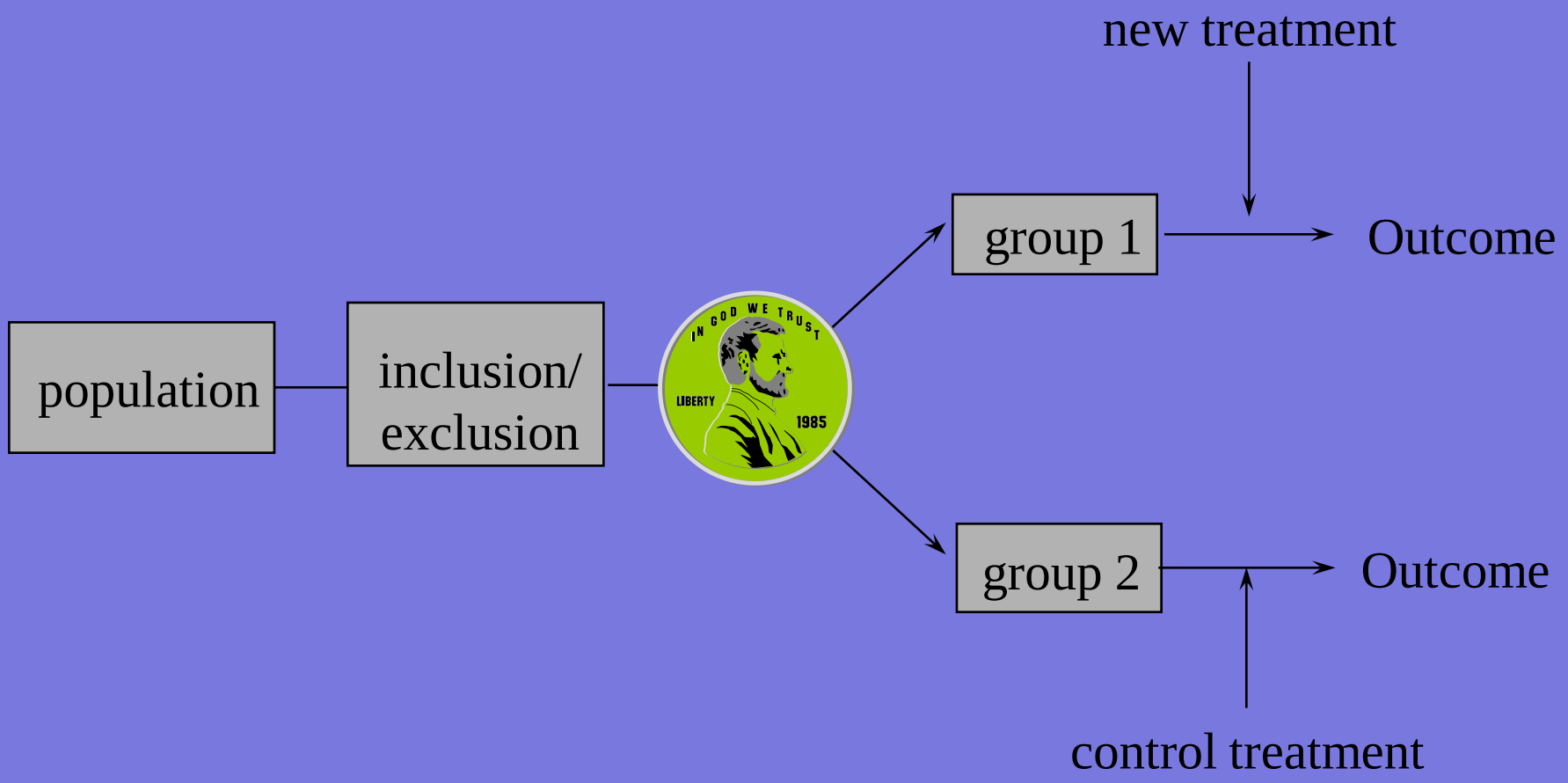
Defn: A clinical trial is a prospective study comparing the effect of intervention(s) against a control in humans.

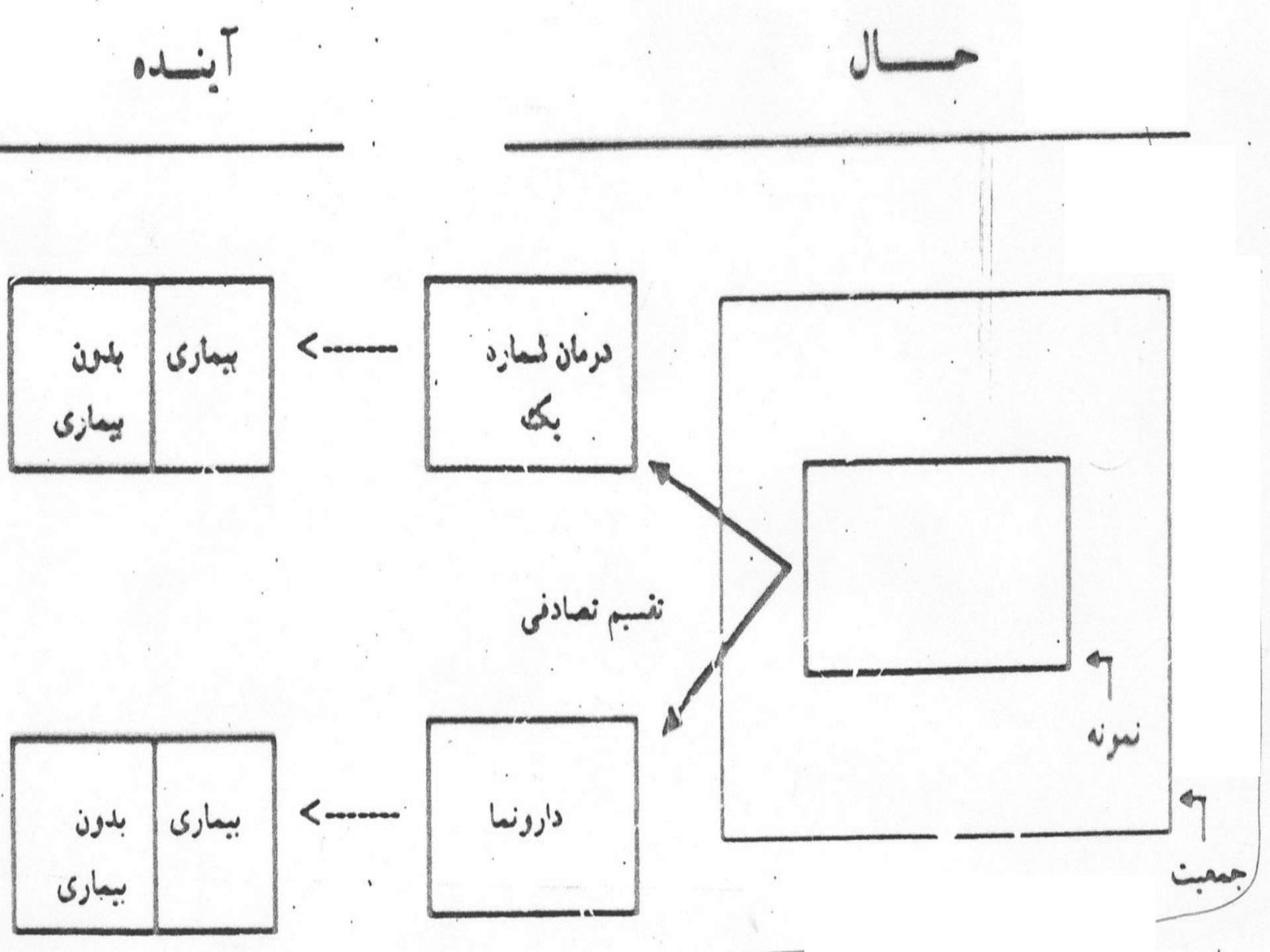
Terminology

Efficacy: How well an intervention works in an ideal setting.

Effectiveness: How well an intervention works in actual practice.

Randomised controlled trial

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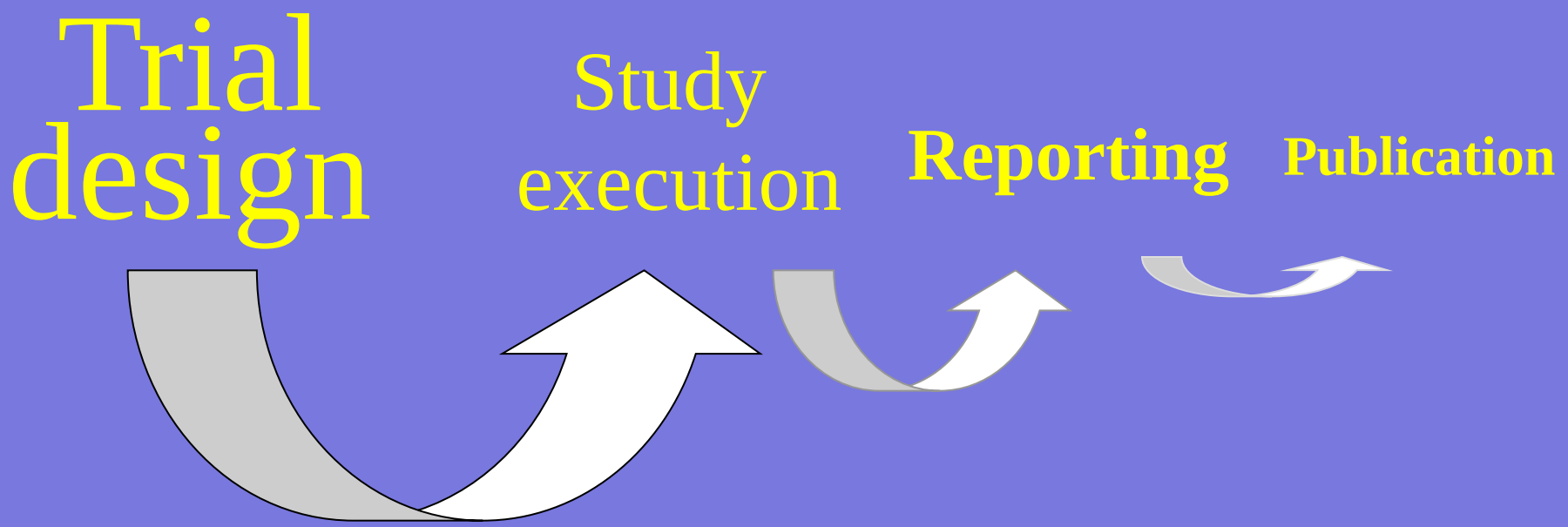

Trial design
Study execution
Reporting
Publication

ضرورت انجام کار آزمائی

بالینی

Rationale

- Why do a randomized blinded trial
  - minimize confounding
  - minimize co-interventions
  - minimize biased outcome ascertainment
- Why not do a randomized trial
  - major ethical issues
  - narrow research question
  - expensive
  - long time from idea to paper
- Generally reserved for mature questions

Why Use Randomized Clinical Trial?

"To make statements of cause and effect regarding an intervention"

- RCT is recognized as a sound scientific method
- By the 1960's RCT had established a track record as the most accepted methodology

All RCTs are controlled clinical trial

BUT

Not all controlled trials are RCTs

RCT IS NOT suitable for:

* ETIOLOGY AND CLINICAL COURSE

  smoking and cancer

* RARE & PROLONGED OUTCOME

نکات مهم در کار آزمائی بالینی

RCTs - a checklist

- Good randomisation procedures
- patients blind to treatment
- clinicians blind to treatment
- all participants followed up
- all participants analysed in the groups to which they were randomised (intention to treat)

Important Issues in RCT

- *Study population (participant)*

  treatment / control

- *Investigators*
- *Clinical intervention (medical surgical ,regimen ,hygiene)*
- *Outcome*

Requirements: Test and Control Groups

- Distinguishable.
- Medically justifiable
- Ethical base for each treatment
- Compatible with health care needs
- Either treatment acceptable
- Reasonable doubt about efficacy
- Benefits outweigh risks
- Similar to real-world use

Severity of Illness

- Difficult to measure
- Disease specific vs. general
- Use validated instruments
- Applicability to study population
- Acknowledge limitations

Allocation Scheme

- Masked to patients, MDs, others
- Cannot predict future assignments
- Allocation order is reproducible
- Allocation methods documented
- Allocation method has known mathematical properties
- Process provides a clear audit trail
- Departures from allocation can be detected

Other Considerations

- Test and control groups
- Outcome measure to evaluate study treatment
- A bias-free method for assigning patients to groups

Review of Steps for RCT Design

1. Select sample from population
2. Measure baseline variables
3. Randomize (RAS & etc)
4. Apply interventions & placebo or standard treatment or different dose or etc
5. Follow-up cohorts
6. Measure outcomes (primary & main outcome)

Measure Baseline Variables

- Define potential important variables
- Compare between study groups
- Account for differences in study design or analysis of results

Randomization

The allocation to study groups serves as the main predictor variable of the study. In the simplest design, one group receives the active treatment and the other remains as an untreated control.

Randomization

- Participants are assigned to treatment groups by chance with a known probability
- Random number table or computer
- Tamper-proof system
  - ordered, sealed envelopes
  - centralized system (phone, fax, web)

  Soft wares (RAS & etc)

  http://mahmoodsaghaei.tripod.com/Softwares/randalloc.html

Outcome Measures

- Easy to diagnose and observe
- Free of measurement or ascertainment errors
- Can be observed independent of treatment assignment
- Clinically relevant
- Chosen before the start of data collection

Why are clinical trials needed?

Because evaluating the effectiveness of a treatment using uncontrolled observations is very difficult, since other factors affecting treatment outcome may not be balanced in treatment groups.

Advantages of RCT:

- Groups more comparable b/c confounding variables are balanced
- Ability to detect small effects
- Most stat tests based on assumption of random allocation of pts to trt groups (validity)

Disadvantages of RCT:

- Expensive and time consuming
- Subject pool may not be representative
- Effective treatment may be withheld
- Expose pts to dangerous drugs

What is the question?

- Each clinical trial must have a primary question.
- The primary, as well as secondary questions, must be carefully selected, clearly defined, clinically relevant, and stated in advance.
- This includes the choice of response variable (ie., true clinical endpoint or surrogate endpoint).

Study population

- The study population is a subset of the population with the condition or characteristics of interest defined by the eligibility criteria.
- This population should be defined in advance, stating unambiguous inclusion (eligibility) criteria.
- The impact that the inclusion criteria will have on study design, ability to generalize, and participant recruitment must be considered.

Randomized control studies

- comparative studies with an intervention group and a control group
- the assignment of the participant to a group is determined by the formal process of randomization.

Randomized control studies . . .

- Sound scientific investigation almost always demands that a control group be used against which the new intervention can be compared.
- Randomization is the preferred way of assigning participants to control and intervention groups.

Randomization

- Randomization tends to produce study groups that are:

1. comparable with respect to known and unknown risk factors
2. Removes investigator bias in the allocation and treatment of patients
3. Guarantees statistical tests will have valid significance levels.

Randomization . . .

- Simple randomization is easiest to understand and use, but randomization can also be blocked, stratified, adaptive, etc.
- Randomization is best accomplished by an independent central statistical unit.

Blinding (Masking)

- Ideally, a clinical trial should use a double-blind design to avoid potential problems with bias during data collection and assessment.
- If using a double-blind design is not feasible, a single-blind design and other measures to reduce bias should be used.

Baseline Assessment

- Relevant baseline data should be measured in all study participants before the start of intervention.
- These baseline measurements can be used to determine eligibility (if obtained prior to assignment to treatment group).
- Can be also used to determine if the randomization produced identical groups (if not, can be used as covariates for adjustment of imbalance).

نگاه اجمالی به کارآزمائی بالینی

What Are Clinical Trials?

- Research studies involving ill people
- Try to answer scientific questions and find better ways to prevent, diagnose, or treat disease

Why Are Clinical Trials Important?

- Clinical trials translate results of basic scientific research into better ways to prevent, diagnose, or treat disease
- The more people take part, the faster we can:
  - Answer critical research questions
  - Find better treatments and ways to prevent disease

What Are the Different Types of Clinical Trials?

- Treatment
- Prevention
- Early detection/screening
- Diagnostic
- Quality of life/supportive care

Treatment Trials

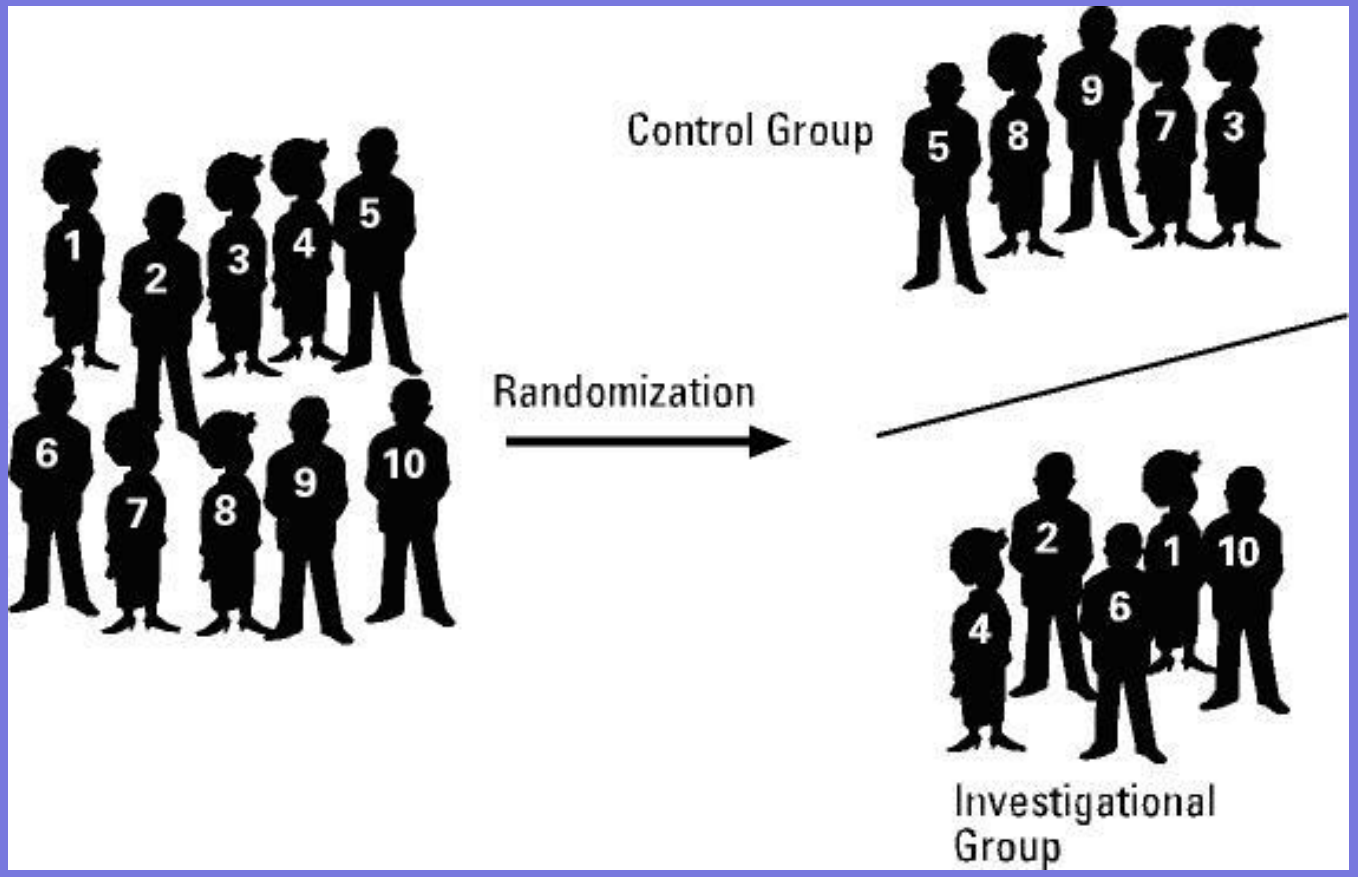
- What new treatments can help people with a particular disease?
- What is the most effective treatment for people with that disease?

Randomized Trials

Participants have an equal chance to be assigned to one of two or more groups:

- One gets the most widely accepted treatment (standard treatment)
- The other gets the new treatment being tested, which researchers hope and have reason to believe will be better than the standard treatment

Randomization



Why is Randomization Important?

- So all groups are as alike as possible
- Provides the best way to prove the effectiveness of a new agent or intervention

Treatment Trials

- What new treatments can help people with a particular disease?

- What is the most effective treatment for people with that disease?

Treatment Trials

Placebos are almost never used:

- Placebos are used only when no standard treatment exists
- Patients are told of this possibility before deciding to take part

Prevention Trials

- Evaluate the effectiveness of ways to reduce the risk of a particular disease
- Enroll healthy people at high risk for developing that disease

Prevention Trials

- **Action studies** (“doing something”)
- **Agent studies** (“taking something”)—also called “chemoprevention studies”

Clinical Trial Protocol

- Strict scientific guidelines:
  --Purpose of study
  --How many people will participate
  --Who is eligible to participate
  --How the study will be carried out
  --What information will be gathered about participants
  --Endpoints

Do Many People Take Part in Clinical Trials?

- Few people participate

Why participate in a clinical trial?

- Clinical trials provide opportunity to contribute to development of future therapies
- Opportunity to test new therapies before they are publicly available

Benefits of Participation

Possible benefits:

- Patients will receive, at a minimum, the best standard treatment (if one exists)
- If the new treatment or intervention is proven to work, patients may be among the first to benefit
- Patients have a chance to help others and improve patient care

Risks of Participation

Possible risks:

- New treatments or interventions under study are not always better than, or even as good as, standard care
- Even if a new treatment has benefits, it may not work for every patient
- Health insurance and managed care providers do not always cover clinical trials

Patient Protection

- There have, unfortunately, been past abuses in patient protection
- Federal regulations ensure that people are told about the benefits, risks, and purpose of research before they agree to participate

How Are Patients' Rights Protected?

- Informed consent
- Scientific review
- Institutional review boards (IRBs)
- Data safety and monitoring boards (DSMBs)

How Are Patients' Rights Protected?

Informed Consent:

- Purpose
- Procedures
- Potential risks and benefits
- Individual rights

How Are Patients' Rights Protected?

Data and safety monitoring boards:

- Ensure that risks are minimized
- Ensure data integrity
- Stop a trial if safety concerns arise or objectives have been met

Why Do So Few People Participate in Clinical Trials?

Sometimes patients:

- Don’t know about clinical trials
- Don’t have access to clinical trials
- May be afraid or suspicious of research
- Can’t afford to participate
- May not want to go against health care provider’s wishes

Why Do So Few People Participate in Clinical Trials?

Health care providers might:

- Lack awareness of appropriate clinical trials
- Be unwilling to “lose control” of a person’s care
- Believe that standard therapy is best
- Be concerned that clinical trials add administrative burdens

Core Components of Clinical Trials

- Involve human subjects
- Move forward in time
- Most have a comparison CONTROL group
- Must have method to measure intervention
- Focus on unknowns: effect of medication
- Must be done before medication is part of standard of care
- Conducted early in the development of therapies

Core Components of Clinical Trials

- Must review existing scientific data & build on that knowledge
- Test a certain hypothesis
- Study protocol must be built on sound & ethical science
- Control for any potential biases
- Study medications, procedures, and/or other interventions

Clinical trial phases

- Phase I – safety test in volunteers
- Phase II – small randomized, blinded study to test tolerability and efficacy on surrogate outcomes
- Phase III – large, randomized, blinded trial to test clinical outcome
- Phase IV – post-marketing study to assess side effects and/or additional uses

Table. Checklist of Items To Include When Reporting a Randomized Trial

Paper Section and Topic	Item Number	Descriptor
Title and abstract	1	How participants were allocated to interventions (e.g "randomized," or "randomly assigned").
Introduction		
Background	2	Scientific background and explanation of rationale.
Methods		
Participants	3	Eligibility criteria for participants and the settings and collected.
Interventions	4	Precise details of the interventions intended for each were actually administered.
Objectives	5	Specific objectives and hypotheses.
Outcomes	6	Clearly defined primary and secondary outcome mea methods used to enhance the quality of measurem training of assessors).
Sample size	7	How sample size was determined and, when applicat analyses and stopping rules.
Randomization		
Sequence generation	8	Method used to generate the random allocation sequ restriction (e.g., blocking, stratification)

		restriction (e.g., blocking, stratification).
Allocation concealment	9	Method used to implement the random allocation se or central telephone), clarifying whether the seque interventions were assigned.
Implementation	10	Who generated the allocation sequence, who enrolle participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the the outcomes were blinded to group assignment. I blinding was evaluated.
Statistical methods	12	Statistical methods used to compare groups for prima additional analyses, such as subgroup analyses anc
Results		
Participant flow	13	Flow of participants through each stage (a diagram is Specifically, for each group report the numbers of receiving intended treatment, completing the stud primary outcome. Describe protocol deviations fro reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-
Baseline data	15	Baseline demographic and clinical characteristics of ea
Numbers analyzed	16	Number of participants (denominator) in each group whether the analysis was by "intention to treat." numbers when feasible (e.g., 10 of 20, not 50%).
Outcomes and estimation	17	For each primary and secondary outcome, a summar estimated effect size and its precision (e.g., 95% c
Ancillary analyses	18	Address multiplicity by reporting any other analyses p

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Adverse events	19	All important adverse events or side effects in each in
Discussion		
Interpretation	20	Interpretation of the results, taking into account stud bias or imprecision, and the dangers associated wit outcomes.
Generalizability	21	Generalizability (external validity) of the trial findings
Overall evidence	22	General interpretation of the results in the context of

	Item number	Descriptor
Title and abstract	1	How participants were allocated to interventions (eg, "random allocation", "randomised", or "randomly assigned").
Introduction		
Background	2	Scientified background and explanation of rationale.
Methods		
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.
Objectives	5	Specific objectives and hypotheses.
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors, &c).
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.
Randomisation		
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were aware of group assignment. If not, how the success of masking was assessed.
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.
Results		
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-up.
Baseline data	15	Baseline demographic and clinical characteristics of each group.
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention to treat". State the results in absolute numbers when feasible (eg, 10/20, not 50%).
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (eg, 95% CI).
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.
Adverse events	19	All important adverse events or side-effects in each intervention group.
Discussion		
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.
Generalisability	21	Generalisability (external validity) of the trial findings.
Overall evidence	22	General interpretation of the results in the context of current evidence.

اصول طراحی کارآزمائی بالینی

مراحل

۱. نمونه اي از جمعيت انتخاب كنيد. (...).
۲. متغيرها را در آغاز مطالعه اندازه بگيريد. (...).
۳. تقسيم تصادفي كنيد. (...).
۴. مداخله ها را اعمال كنيد (...).
۵. گروه ها را پيگيري كنيد. (...).
۶. متغيرهاي وابسته را اندازه بگيريد (...).

Steps in conduct of RCT

1. The protocol
2. Selecting reference and experimental populations
3. Randomization
4. Intervention
5. Follow up
6. Assessment

Outcome variables

1. Clinical outcomes/endpoints (mortality, admissions, verified disease)
2. Surrogate outcomes

(risk factors, e.g. LDL chol, CRP, bone density) – leap of faith as changes in surrogate outcomes assumed to predict clinical outcomes.

Usually power and cost issues.

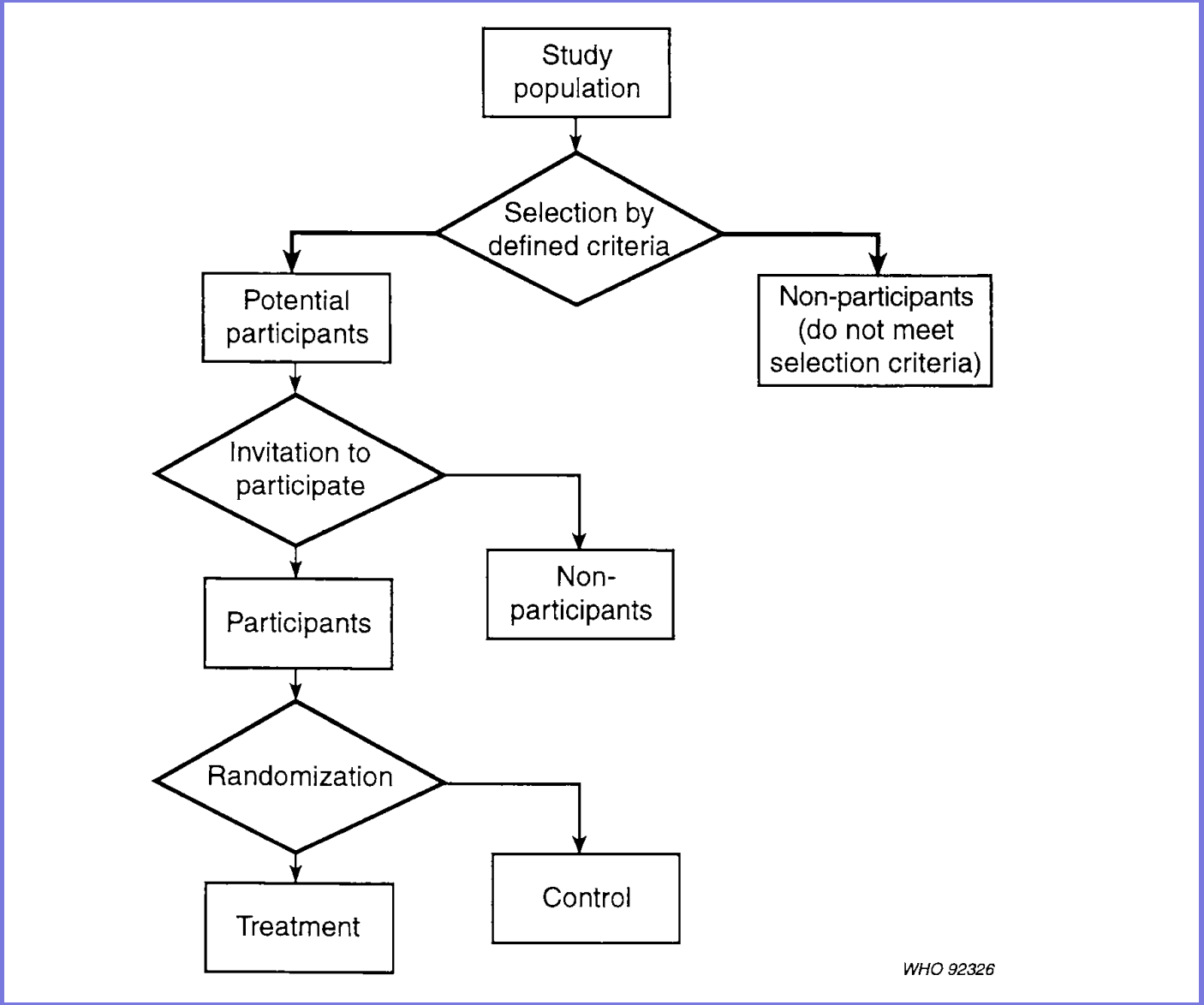
Endpoints

- Balance between being too ambitious or too conservative – a bit of common sense ("The O'Connor situation").
- Focus on a single or a limited number of pre-specified endpoints
- Just because you can measure 15 variables doesn't necessarily mean that a statistically significant finding in any of these is clinically meaningful
- Primary vs. Main endpoints

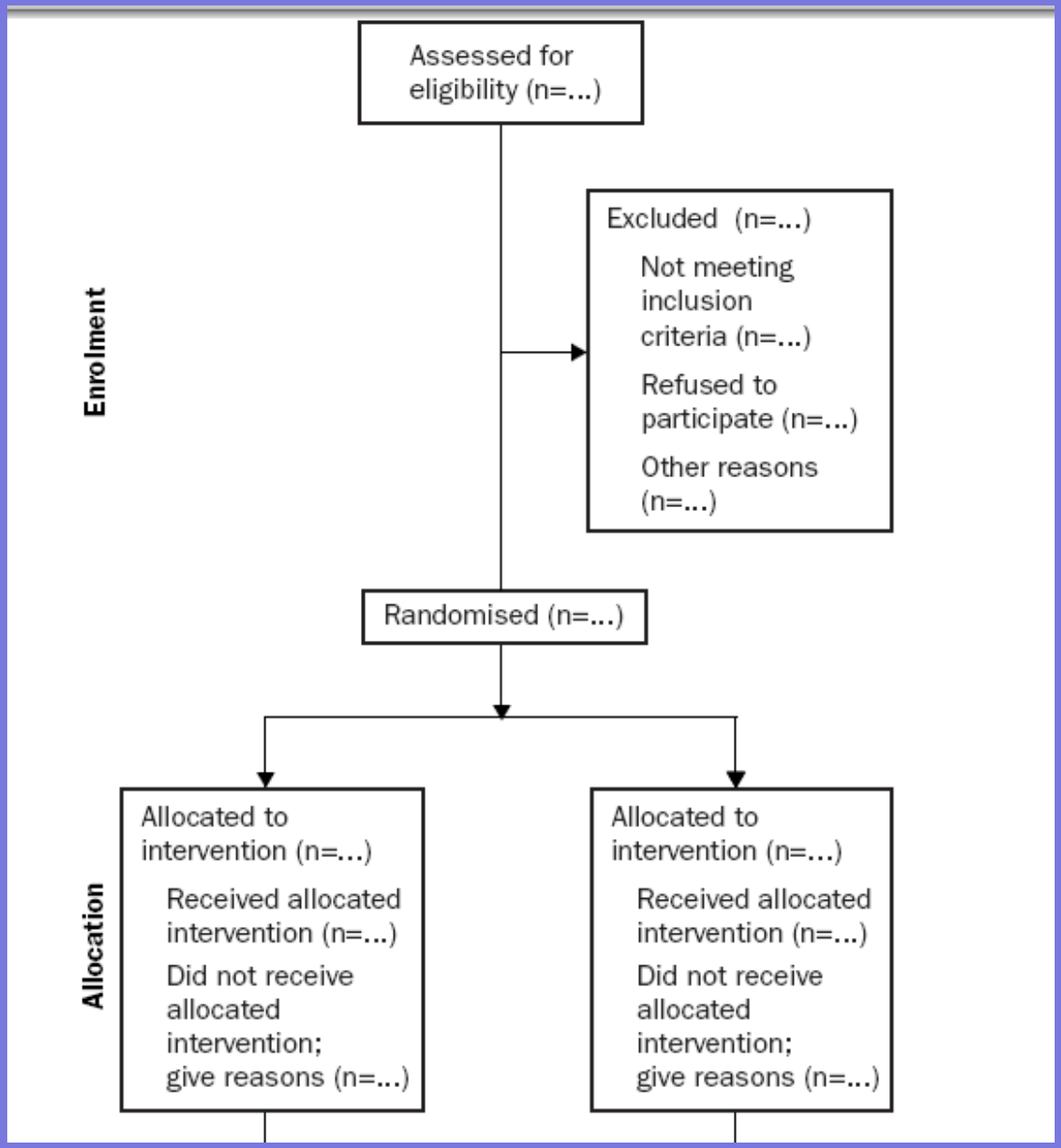
Monitoring

- Adverse events
- Safety concerns – grounds to stop a study?
- For small trials investigators monitor adverse events, large trials have Data and Safety Monitoring Boards (DSMB's)
- Every study needs a Data and Safety Monitoring Plan (DSMP)

Randomized Controlled Trials



Flow diagram of the progress through the phases of a randomized trial



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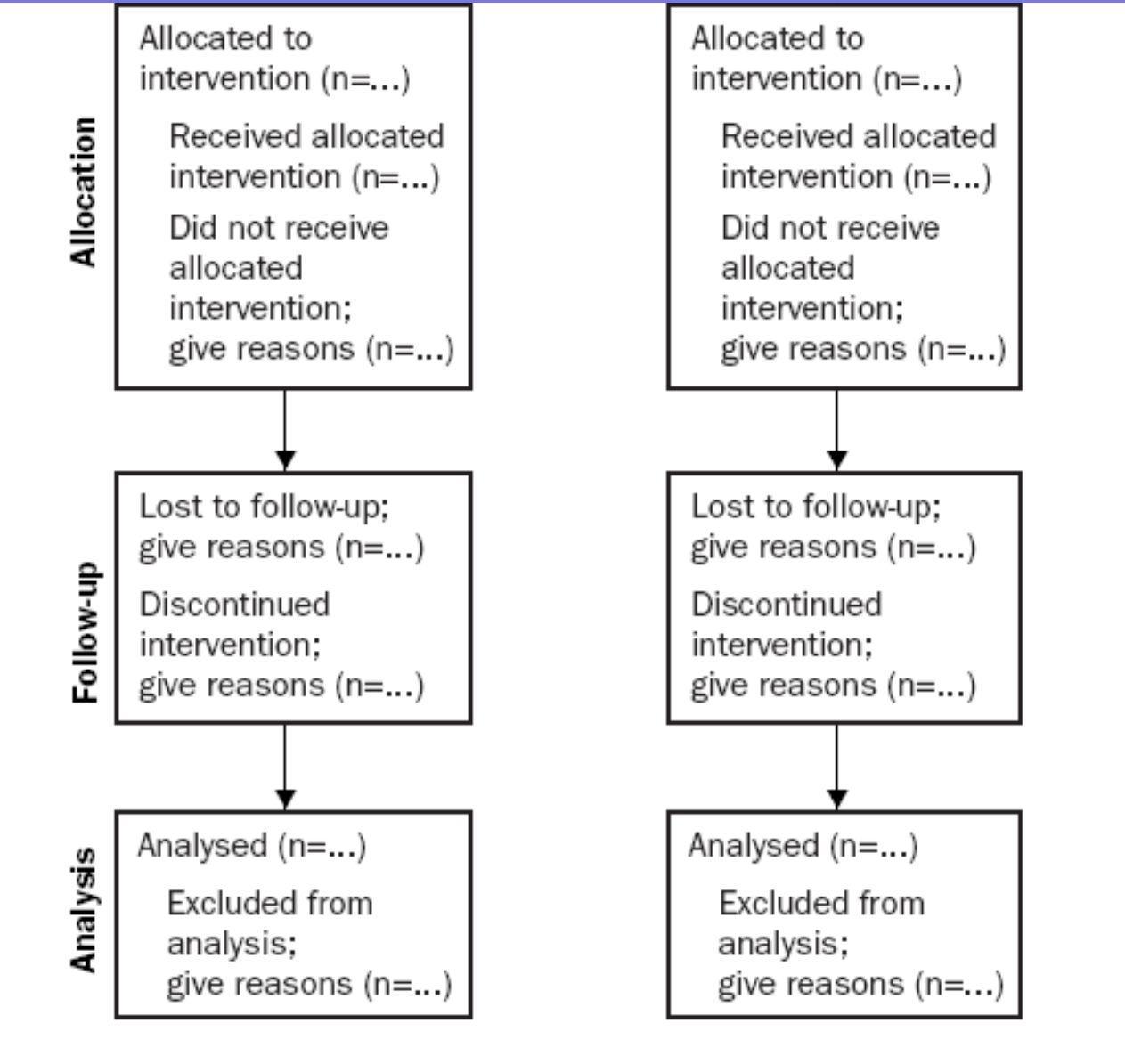
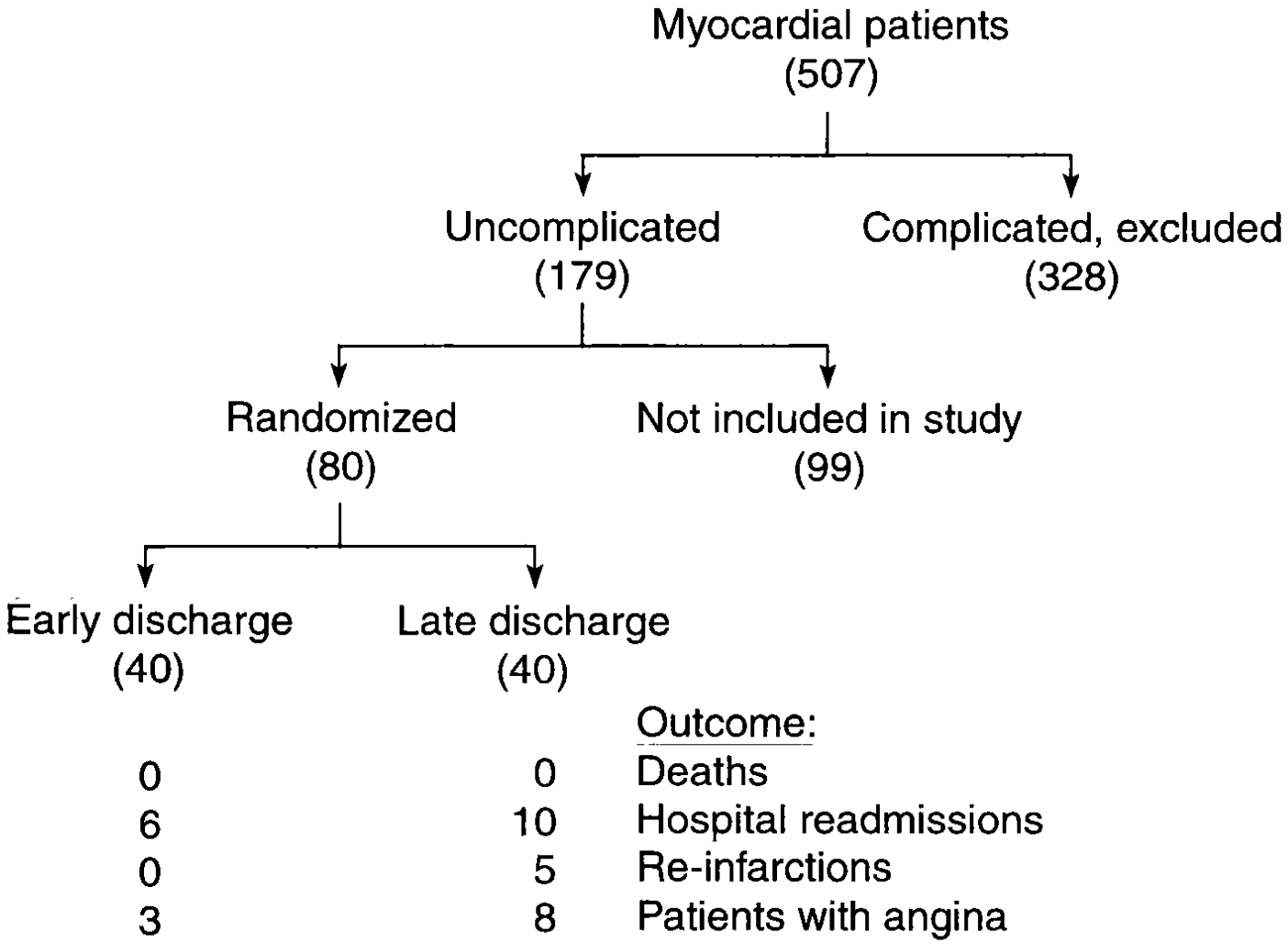


Example: Randomized Controlled Trials



WHO 92327

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انواع کارآزمائی بالینی

Types of Randomized Controlled Trials

1. Clinical Trial:

   Diagnostic, Therapeutic, Prophylactic, Devices, Procedures, Regimens, Protocols

2. Preventive Trial
3. Risk Factor Trial
4. Cessation experiments
5. Trial of etiologic agents
6. Evaluation of health system

Types of Randomized Controlled Trials:

1. Clinical Trial

- Concerned with evaluating therapeutic agent, mainly drugs

  eg. Evaluation of beta-blockers in reducing cardiovascular mortality

- Not all clinical trials are susceptible to being blinded

2. Preventive Trials:

- Trial of primary preventive measures eg. Vaccines

- Analysis of preventive trials must result in clear statement about benefits to community, risk involved and cost to health

3. Risk Factor Trials:

- Investigator intervenes to interrupt the usual sequence in the development of disease for those individuals who have risk factor for developing the disease

- Primary prevention of CHD using clofibrate to lower serum cholesterol

4. Cessation Experiment:

- An attempt is made to evaluate the termination of a habit which is considered to be causally related to disease
- Cigarette smoking and lung cancer

5. Trials of Etiological Agents:

- To confirm or refute an etiological hypothesis

6. Evaluation of Health Services:

- Domiciliary treatment of Disease X was as effective as more costlier hospital or sanatorium treatment

Types of Randomized Studies

- Parallel group
- Sequential trials
- Group sequential trials
- Cross-over
- Factorial designs
- Adaptive designs

Parallel Group

- Randomize patients to one of k treatments
- Response
  - Measure at end of study
  - Delta or % change from baseline
  - Repeated measures
  - Function of multiple measures

Sequential trials

- Not for a fixed sample size/ period
- Terminates when
  - One treatment shows a clear superiority or
  - It is highly unlikely any important difference will be seen
  - Special statistical design methods

Group Sequential Trials

- Popular
- Analyze data after certain proportions of results are available
- Early stopping
  - If one treatment clearly superior
  - Adverse events
- Careful planning and statistical design

Factorial design

- Each level of a factor (treatment or condition) occurs with every level of every other factor
- Vitamin A and Vitamin E for prevention of Hypertension:

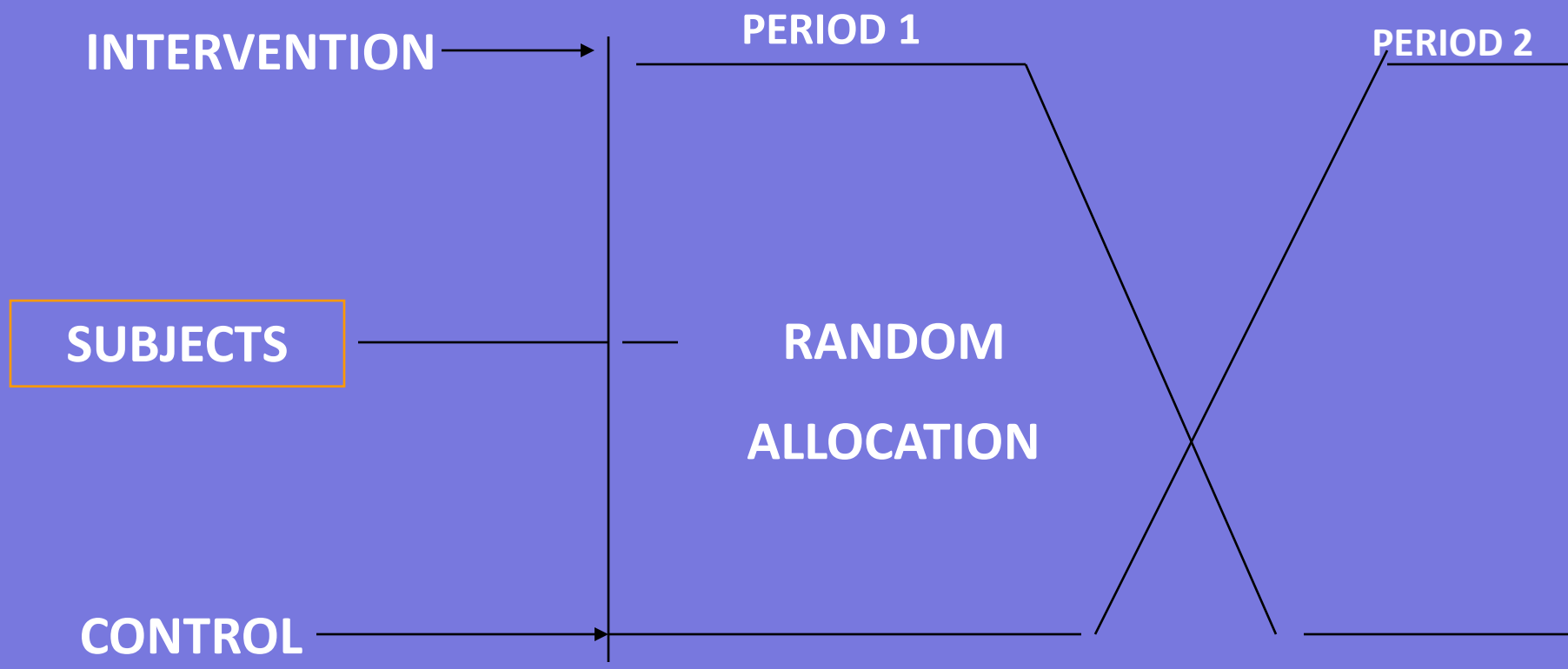
Vitamin A Placebo Vitamin E Placebo	**Vitamin A Vitamin E Placebo**
Vitamin A Placebo Vitamin E	Vitamin A Vitamin E

Incomplete/ Partial/ Fractional Factorial Trial

- Nutritional Intervention Trial
- 4X4 incomplete factorial
- Did not look at all possible interactions
  - Not of interest
  - Sample size Problem

Cross-over Trial

- Two treatments, two period cross-overs
- Use each patient as own control
- Must eliminate carryover effects
  - Need sufficient washout period



CROSS OVER DESIGN

Adaptive designs

- Smaller overall sample size (potential)
- Run-in; then analyze data continuously or fixed intervals
- Act like group sequential design
- Close an arm early
- Re-estimate sample size based on variance

مراحل (فازهای)
کارآزمائی بالینی

Stages of experimentation

- Phase I: Dose-finding (safety)
- Phase II: Preliminary evidence of efficacy
- Phase III: Comparisons to standard therapy
- Phase IV: Post-marketing surveillance

Phase I Trials:

- Initial studies to determine the metabolism and pharmacologic actions of drugs in either humans or ..., the side effects associated with increasing doses, and to gain early evidence of effectiveness; usually conducted on volunteers

Phase II Trials:

- Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with disease or condition under study and to determine the common short-term side effects and risks

Phase III Trials:

- Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug

Phase IV Trials:

- Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use