Research Methodology

Designs for RCTs

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Study Design

- *Observational*
  - Descriptive
  - **Analytic**
    - **Cross-Sectional**
    - **Case-Control**
    - **Cohort**
- *Experimental* *(Randomized Control Trial – RCT)*

DESIGN FOR CLINICAL TRIALS

The first step in selecting an appropriate design is to determine the *objective(s).*

- To clarify the study objectives we should ask:
  - What aspects are being studied?
  - Is it important to investigate other issues that may have an impact on the study drug?
  - Which control(s) might be used?

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- **Clinical Trial (on patients)**

  - Field Trial (on healthy people) 

  - Community Trial (on communities)

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- The design of the trial can be very simple as the single-arm trial with no control group, or it can be very complicated as a 12-group factorial design for the evaluation of the dose responses of combination drugs.

SINGLE ARM TRIALS

- Mostly in phase II clinical trials

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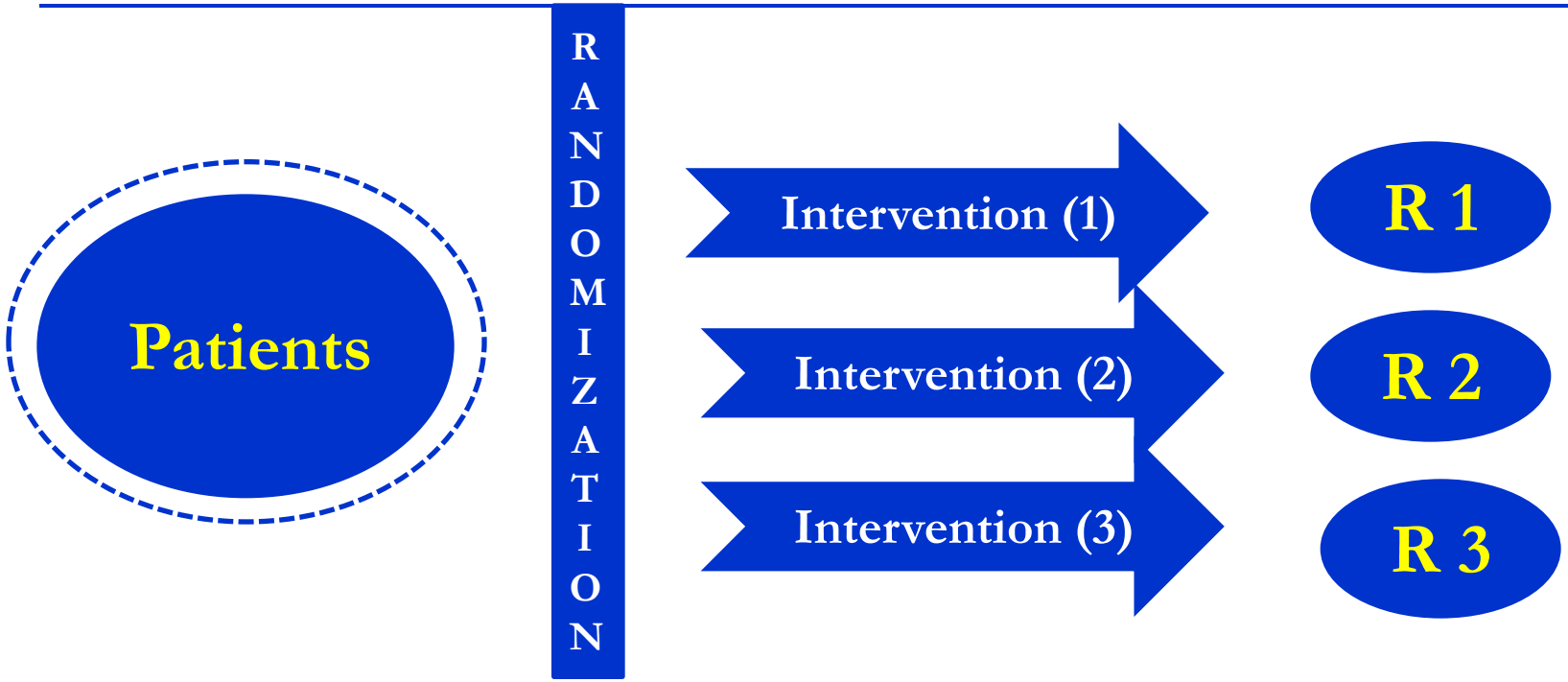
Single Arm Trials (Cont.)

- **Advantages:**
  - All resources, i.e. subjects and financial costs, are concentrated on one group
  - Specify how many subjects should respond to the new treatment in order to justify further investigation
  - Useful for serious diseases such as cancers

- **Disadvantages:**
  - By not conducting a randomized comparison, we are left with all the difficulties of interpretation the results

PARALLEL GROUP DESIGNS

"gold-standard" of clinical research.



- There are as many groups as study treatments under comparison.
- Each patient is assigned to only one of the treatment groups through randomization.
- All treatment groups are treated and evaluated simultaneously

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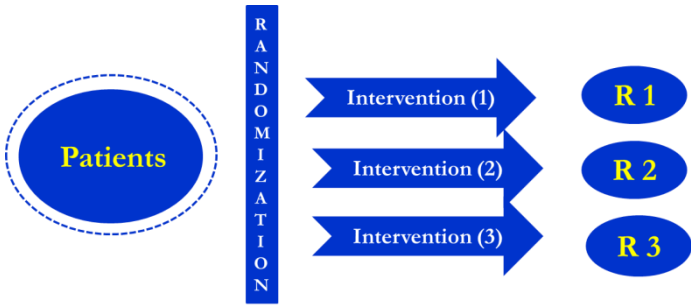
Parallel Group Design(Cont.)

- **Advantages:**
  - The duration of the study is shorter and the visits fewer.
  - The statistical analysis requires fewer assumptions and straightforward.
  - It is simpler and makes bias-free comparisons easier to obtain.
  - It is applicable to acute conditions.
  - For ethical consideration with the control, we can allocate patients unequally to treatment groups (in a random fashion) to allow more patients to receive the treatment (e.g., in a 2 to 1 or 3 to 1 ratio).

- **Disadvantages:**
  - It requires a larger sample size.
  - In some few situations, it cannot be applied.

Parallel Group Design(Cont.)
(Completely randomized)

- with a simple randomization and balanced (the treatment groups have equal/approximately equal) or unbalanced size.



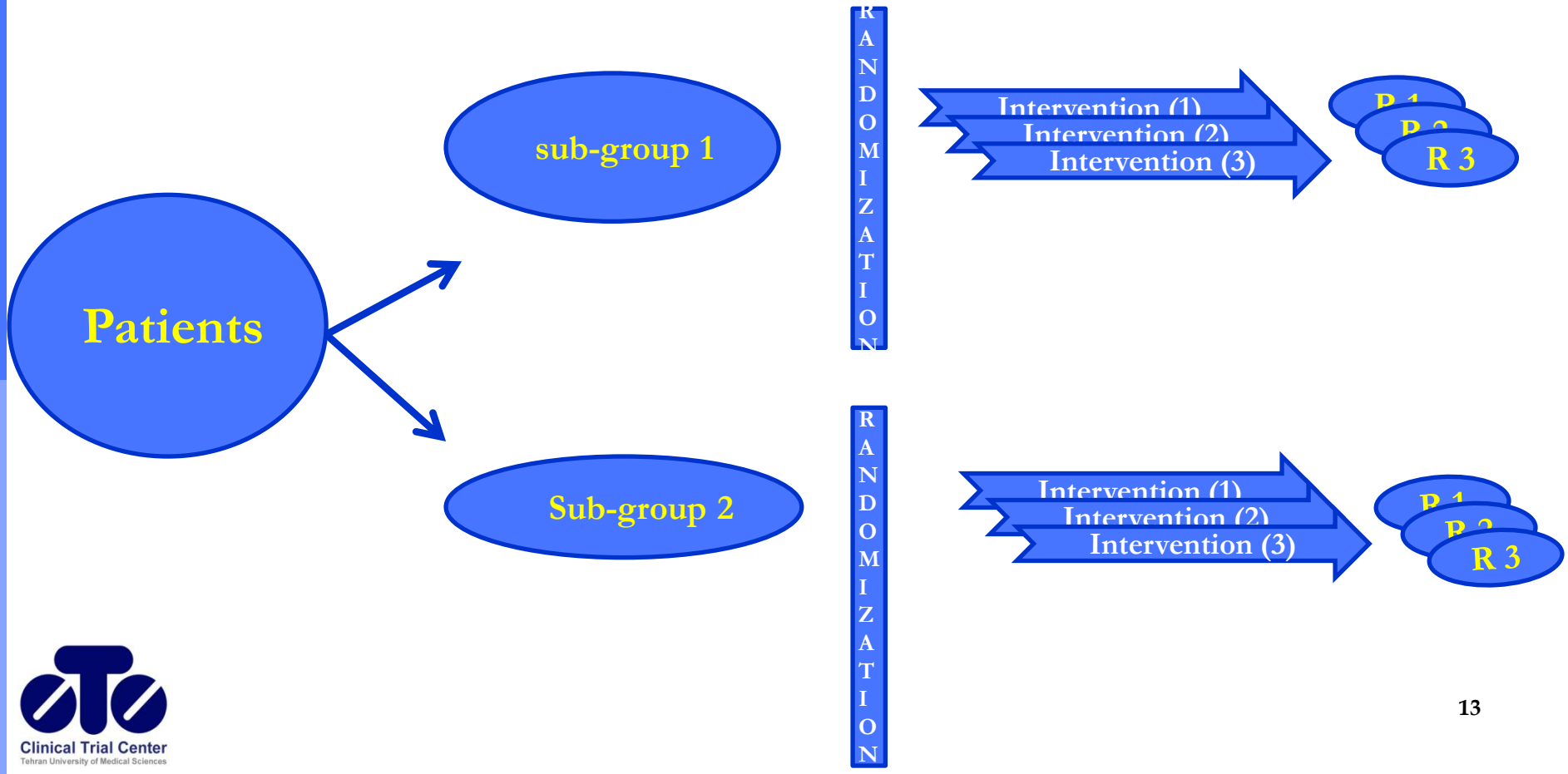
- **Advantages:**
  - It is simple and easy to implement.
  - It is universally accepted.
  - Analysis is less complicated, and interpretation of the results is straightforward.

Parallel Group Design(Cont.)
(Completely randomized)

- **Disadvantages:**
  - it usually requires more patients than other comparative designs.
  - by chance, the distribution of important baseline features may not be homogeneous across the treatment groups.
  - The smaller the sample size, the more likely it is that a meaningful imbalance will occur.

Parallel Group Design(Cont.)
(Stratified Design)

- with a stratified randomization considering some prognostic factors as sub-experimental factors.



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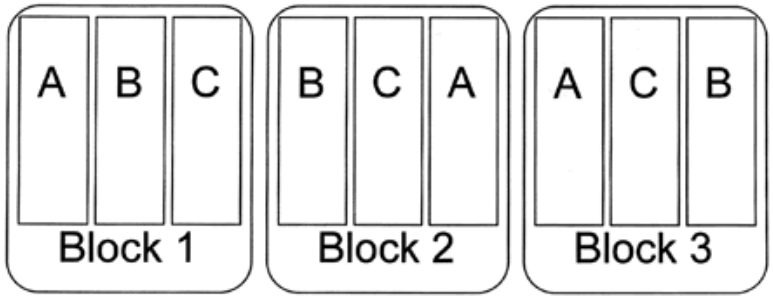
Parallel Group Design(Cont.)
(Stratified Design)

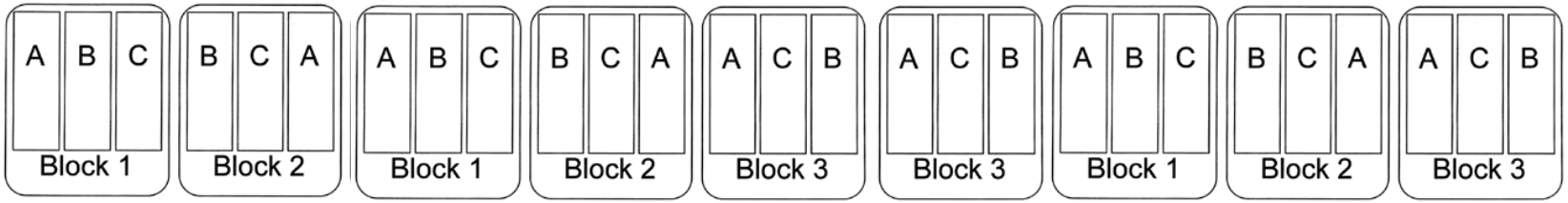
- **Advantages:**
  - it is more efficient than the completely randomized design.
  - requiring fewer patients.
  - comparing the responses to the treatment in the different strata. These are called interaction studies, which needs more sample size.

- **Disadvantages:**
  - What is the most important prognostic factors?
  - How many prognostic factors can be controlled?
  - If the covariates are imprecisely assessed, then may introduce error.

Parallel Group Design(Cont.)
(Randomized Block Design)

- This design is primarily used to reduce time-related imbalances between the treatment groups.
- Time can be a sub-experimental factor but not a prognostic one.
- Time can be a prognostic factor.

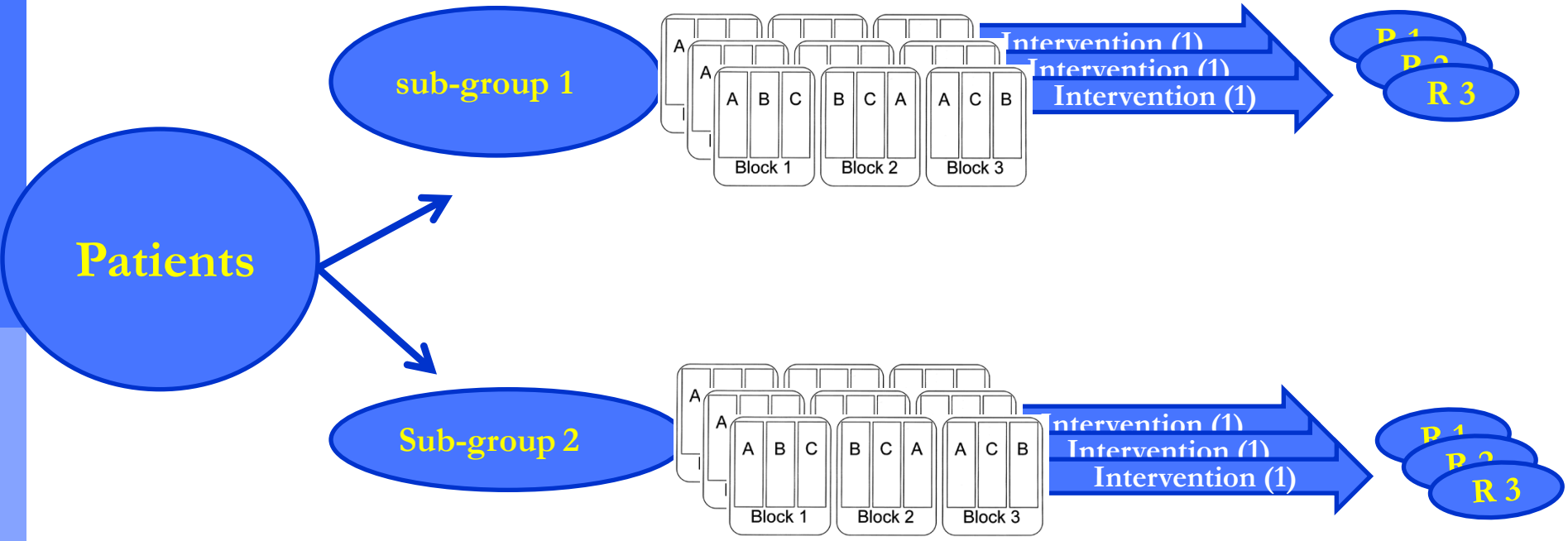




Random

Parallel Group Design(Cont.)
(Randomized Block Design)

"Matched" PARALLEL GROUP DESIGN



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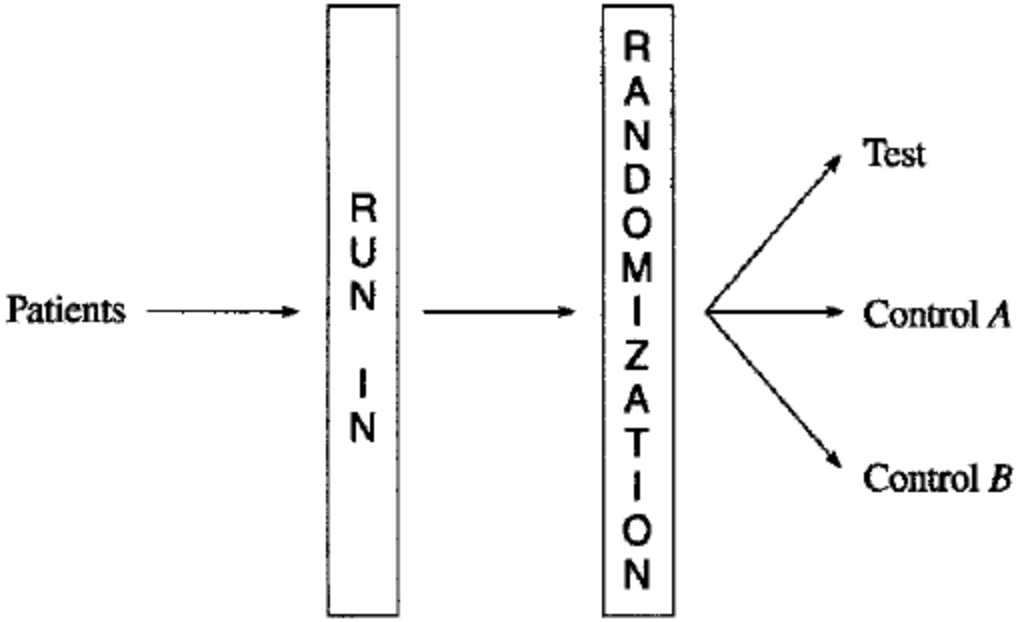
Parallel Group Design(Cont.)
(Randomized Block Design)

- **Advantages:**
  - It controls for the factor "time of enrolment".
  - It is a completely balanced scheme of assignment to the treatments

- **Disadvantages:**
  - A little complex statistical analysis.
  - Very difficult to use if many factors must be considered in "matching" the units.

Run-in Period



- Before patients enter a clinical trial, a run-in-period of placebo, no active treatment, dietary control, or active maintenance therapy is usually employed prior to randomization.
- A run-in period is usually employed based on a single-blind fashion.

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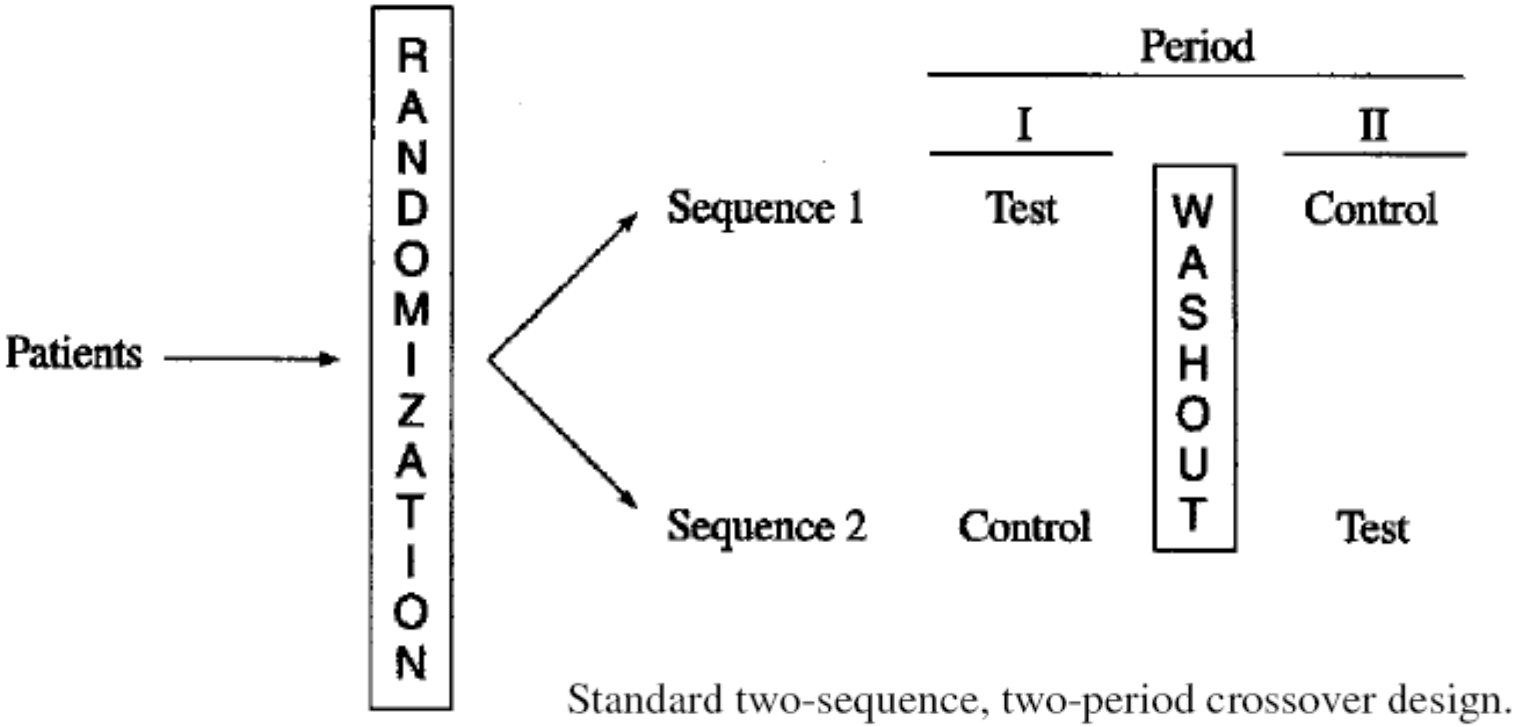
Run-in Period

- **Advantages:**
  - It acts as a washout period to remove effects of previous therapy.
  - It can be used to obtain baseline data and to evaluate if patient fulfills study entry criteria.
  - It can be used as a training period for patients, investigators, and their staff.
  - It helps in identifying placebo responders.
  - It provides useful information regarding patient compliance.
- **Disadvantages:**
  - may not be suitable for patients whose conditions are acute requiring immediate treatment.
  - it increases the length of a study and requires extra study visits.
  - It increases the cost.
  - It decreases enthusiasm by patients and investigators.

CROSSOVER DESIGNS



Standard two-sequence, two-period crossover design.

- **Sequence (Period) Effect?**
- **Carryover Effect?**

Conditions?

Using before phase 3?

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CROSSOVER DESIGNS

- **Advantages:**

  - Allows within-patients comparisons of treatments
  - Removes interpatient variability
  - Provides the best unbiased estimates for the differences between treatments
  - Decreases number of patients needed

CROSSOVER DESIGNS

- **Limitations:**
- It is applicable where:
  - Objective measures for efficacy and safety are obtained
  - Chronic and relatively stable disease
  - Prophylactic drugs with relatively short half life
  - Relatively short treatment periods
  - Baseline and washout periods are feasible
- It increases the duration of the study
- Its analysis is not straightforward:
  - The paired design
  - The period and carry-over effects
- The effect of loss to follow-up

Factorial Design

Panel A: A Full 2 × 2 Factorial Design for Combination Therapy of Two Components Each at Two Dose Levels

Group	Drug *A*	Drug *B*
1	Placebo	Placebo
2	Placebo	Fixed active dose
3	Fixed active dose	Placebo
4	Fixed active dose	Fixed active dose

Two applications:

1. **Quantifying the interaction between the two treatments**
2. **Opportunistic situations**

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More complex designs

Group	Drug *A*	Drug *B*	Drug *C*
1	Placebo	Placebo	Placebo
2	Placebo	Placebo	Fixed active dose
3	Placebo	Fixed active dose	Placebo
4	Placebo	Fixed active dose	Fixed active dose
5	Fixed active dose	Placebo	Placebo
6	Fixed active dose	Placebo	Fixed active dose
7	Fixed active dose	Fixed active dose	Placebo
8	Fixed active dose	Fixed active dose	Fixed active dose

Group	Drug *A*	Drug *B*
1	Placebo	Placebo
2	Placebo	Active dose 1
⋮	⋮	⋮
$b + 1$	Placebo	Active dose b
$b + 2$	Active dose 1	Placebo
$b + 3$	Active dose 1	Active dose 1
⋮	⋮	⋮
$2(b + 1)$	Active dose 1	Active dose b
$a(b + 1)$	Active dose a	Placebo
$a(b + 2)$	Active dose a	Active dose 1
⋮	⋮	⋮
$(a + 1)(b + 1)$	Active dose a	Active dose b

A Full (*a+1) * (b+1) Factorial Design for* Combination Therapy of Two Components at *a and b Dose Levels*

Designs for Ethical Considerations

- Adaptive Randomization
- Preference trials
  - Zelen's design
  - Comprehensive cohort design
  - Wennberg's design
- Variations of placebo-controlled trials:
  - Add-on design
  - Replacement design
  - Randomized Withdrawal design
- Sequential analysis

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Equivalence/Non-inferiority

vs. Superiority

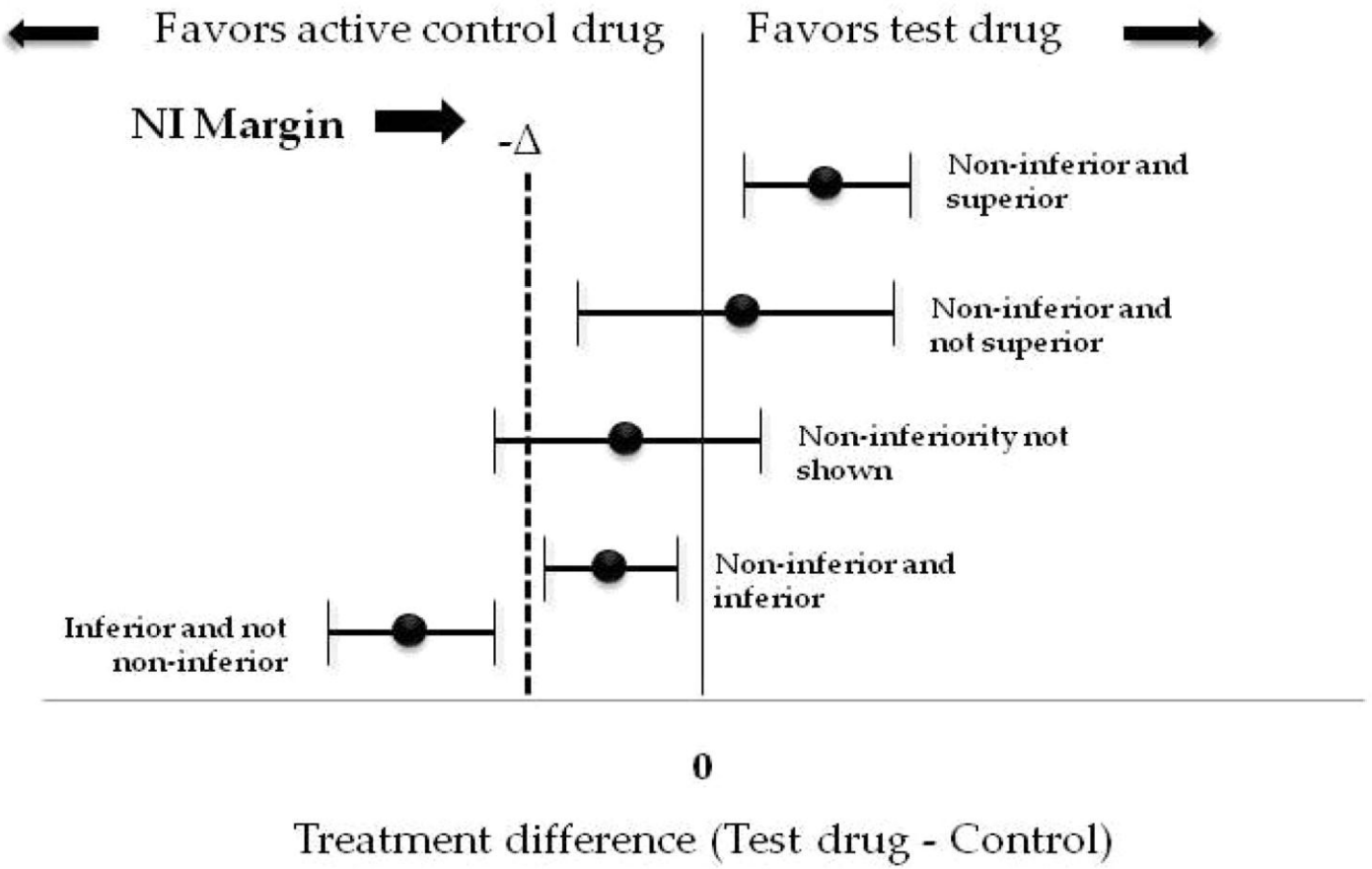
Equivalence/Non-inferiority Vs. Superiority

- Sometimes, the goal is not to show that the new treatment is better, but that the new treatment is 'equivalent' to the control.

- If the CI lies strictly within [-Δ, +Δ] the two treatments are called 'equivalent.' But the amount of Δ is more important in equivalency/non-inferiority than superiority.

- Non-inferiority is different from equivalence. In an equivalence trial, the desired conclusion is that two products are the same or 'not unacceptably different' from each other. In a non-inferiority trial, by contrast, the aim is to show that a new product is not unacceptably worse than an older one.

Equivalence/Non-inferiority Vs. Superiority



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CLUSTER RANDOMIZED DESIGNS

- For assessment of nontherapeutic interventions such as lifestyle intervention or new educational program for smoking cessation.
- Randomization is performed at the cluster level (such as family, school, worksites, athletic teams, hospitals, or communities) rather than at the subject level.
- The unit of analysis may not be necessarily the same as the unit of randomization.
- The standard methods for sample size calculation and data analysis considering subject as analysis unit are not appropriate here.