Designs of Clinical Trials

Factors to consider in selecting a clinical trial design

- Study population and indication
- Treatment duration
- Carry over effects
- Cost and logistics
- Patient convenience
- Statistical considerations

Role of Placebo in Clinical trials

- No standard treatment exists.
- Standard treatment is ineffective.
- Standard treatment is inappropriate for the particular clinical trials.
- The placebo is reportedly effective in treating the disease.
- The disease is mild and lack of treatment is not considered to be medically important.

Role of Placebo in Clinical trials

- The placebo is given as an add-on treatment to an already existing regimen that is not sufficient to treat patients.
- The disease process is characterized by frequent spontaneous exacerbations and remission(e.g., peptic ulcer).
- "Escape clauses" or points are

Run in period

Before randomization of patients a run-in (or lead-in) period of placebo, no active treatment, dietary control, or active maintenance therapy is usually employed.

Advantages:

1. It acts as a washout period to remove effects of previous therapy.
2. It can be used to obtain baseline data and to evaluate if patient fulfills study entry criteria.
3. It can be used as a training period for patients, investigators, and their staff.
4. It helps in identifying placebo responders.
5. It provides useful information regarding patient compliance.
6. It can be used to estimate and compare the magnitude of possible placebo effects between groups.

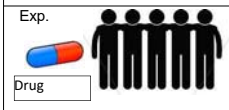
Parallel Group Design

- It is of two types:

1. Group comparison parallel design: In this method, efficacy of treatment is using two groups (Treatment vs Control group).

2. Matched pair parallel design: In this method, pairs of subjects are formed possessing the same characteristics and who might be expected to respond similarly to the treatments.

Group comparison Parallel Design

Treatment Group/ Arm	Control Group/ Arm
Exp. Drug 	

•Most common clinical design.

•Complete randomized design in which each patient receives one and only one treatment in a randomized fashion.

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Group comparison Parallel Design

Advantages:

a) It's simple and easy to implement.
b) It is universally acceptable.
c) It is applicable to acute conditions.
d) Analysis is less complicated and interpretation is straight forward.

Disadvantages:

a) It does not into account the inter-individual variability.

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Matched Pair Parallel Design

Pair A	Pair B	Pair C	Pair D
			

•In this method, pairs of subjects are formed possessing the same characteristics and who might be expected to respond similarly to the treatments.

• Matching of patients is done before randomization

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Matched Pair Parallel Design...

Advantages:

a) Requires small study population.
b) Can reduce variability from treatment comparison (compared with parallel froup designs).

Disadvantages:

a) The prognostic characteristics are not easily defined.
b) Patient recruitment is slow.
c) When the number of co-variates is large, this design is difficult to implement.

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Cross over design

- A crossover design is a modified randomized block design in which each block receives >1 treatment at different dosing periods.
- A block can be a patient or a group of patients. Patients in each block receive different sequences of treatments.
- A crossover design is called a complete crossover design if each sequence

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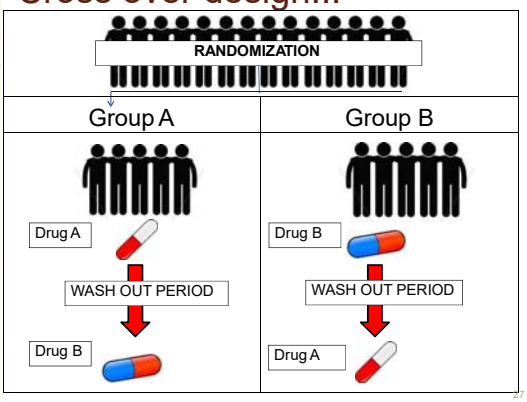
Cross over design...



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Cross over design...

Crossover designs may be used in clinical trials in the following situations where

1. Objective measures and interpretable data for both efficacy and safety are obtained.
2. Chronic (relatively stable) disease are under study.
3. Prophylactic drugs with relatively short half-life are being investigated.
4. Relatively short treatment periods are considered.
5. Baseline and washout periods are

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Cross over design...

Advantages:

1. It allows a within-patient comparison between treatments, since each patient serves as his or her own control.
2. It removes the interpatient variability from the comparison between treatments.
3. With a proper randomization of patients to the treatment sequences, it provides the best unbiased estimates for the differences between treatments.

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Cross over design...

Disadvantages:

1. Carry- over effects: The residual influence of treatments on subsequent treatment periods. Avoided by wash out period.
2. Order effects: Order in which the tt are administered affects the outcome.
3. Period effects: The diff. between the study periods.
4. Drop-outs can be higher.

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Concept of Wash-out effects

AKA carry over / residual effects.

It is the rest period between 2 treatment periods.

- It permits the effect of previous treatment to wane off.
- It should be long enough for the treatment effect to wear off so that there is no carryover effect of previous treatment to next.
- It depends upon the nature of the drug.

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Williams design

When there are more than two treatments to be compared, a complete crossover design is called William's design.

I. William's design with three treatments

ACB	BAC	CBA
BCA	CAB	ABC

II. William's design with four treatments

ADBC BACD CBDA DCAB

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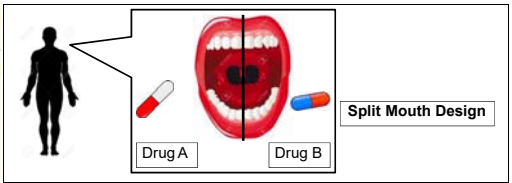
Split person design



•Occasionally, it is possible to administer the two interventions at the same time.

•Very similar to that of the cross-over trial, except there is no equivalent to the **periods** or to the **wash-out** although a carry-over (now termed **carry-across**) effect is likely to be present.

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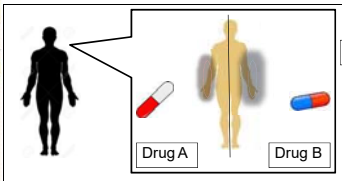
Split person design...



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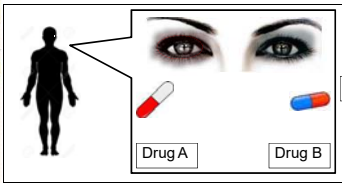

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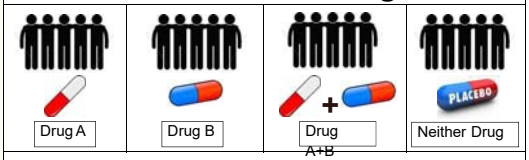
Factorial designs

2× 2 Factorial design



•Used when it is desired to study the influence of a number of factors on the treatments compared as well as their interaction with different treatments.

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Factorial designs...

- Uses:

1. Make efficient use of clinical trial subjects by evaluating two treatments with same no. of individuals.
2. Influence of a number of factors can be studied together which might require many trials if done individually.
3. Establish dose-response characteristics of the combination of A and B when efficacy of each has been previously established.

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Factorial designs...

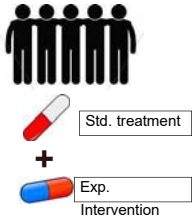
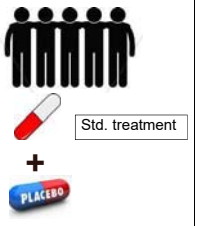
- Advantages:

1. A greater precision can be obtained in estimating the overall main factor effects.
2. Interaction between different factors can be explored.
3. Additional factors can help to extend validity of conclusions derived.

- Disadvantages:

1. Difficult to analyse.
2. Large designs require large no of subjects.
3. Between subjects design lacks statistical

Add- on Design

Group A	Group B
	

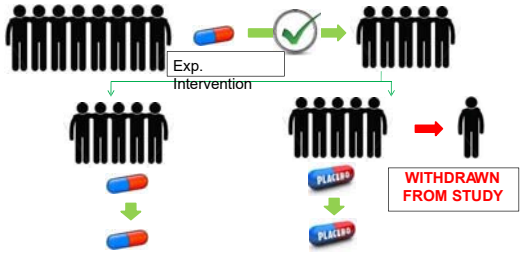
•A placebo-controlled trial of an experimental intervention is tested with people already receiving an established, effective treatment.

Add- on Design...

- Uses:

1. Add on design is especially useful for testing of an experimental interventions that have mechanism of action different from that of established effective treatment.
2. It can be used for long term studies of treatments of conditions like heart failure since established treatment is life saving and is not being denied.

Randomized Withdrawal Design

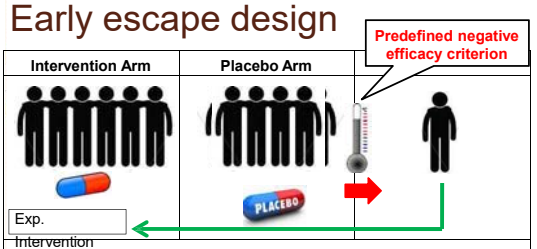


•Here, individuals who respond (+)ly to an experimental intervention are randomized to continue receiving that intervention or to receive a placebo.
•Return of symptoms in placebo group causes withdrawal of subject from that group.

Randomized Withdrawal Design

- Advantage: This trial design minimizes the amount of time that individuals receive a placebo.
- Disadvantages:
  1. Carry over effects.
  2. Difficulties in assessing whether the underlying disease process is still active.
  3. Long lag times to adverse events if the disease is in remission.

Early escape design



•Participants are removed from the study if symptoms reached a defined level or they fail to respond to a defined extent.
•The patient could then be switched over to another
therapy, including the test treatment if appropriate.

Early escape design...

- Advantages:

1. It minimizes an individual's duration of exposure to a placebo.
2. Ethically justifiable.

- Disadvantages:

1. Complex statistical analysis.
2. Difficulties in assessing whether underlying disease is active or not (like Randomised withdrawal design).

Study designs for Small Populations

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Study designs for small populations

- Defined as <50 possible patients recruited in 5years with multicentre/ multinational recruitment.

1. Rare diseases
2. Unique study populations (e.g. Astronauts)
3. Individually tailored therapies
4. Environments that are isolated
5. Emergency situations
6. Public health urgency
7. Restricted resources coupled with an important need

N- of- 1 Design

- They are cross over trials in which one participant receives the experimental and the control interventions.
- Typically the number of pair of interventions varies from two to seven.
- The number of interventions is not pre specified so that the clinician and the patient can decide to stop at will.

N- of- 1 Design...

- Indications:

1. If an RCT has shown that some patients are unresponsive to treatment.
2. If there is doubt about whether a treatment is really providing benefit to the patient.

Decision Analysis based Design

Outcome	Intervention A	Intervention B
		
Beneficial outcome	1. Utility (0-1) 2. Probability	1. Utility (0-1) 2. Probability
Adverse Outcome	1. Utility (0-1) 2. Probability	1. Utility (0-1) 2. Probability

•Utility are numeric values assigned to each outcome which reflects the "desirability of the event".
• Probability are the "chances of event to occur".
•Decision analysis combines the probability with utility to calculate an "expected utility".

Decision Analysis based Design…..

- Thus decision analysis is used during the planning phase to structure the question.
- One obtains best estimates of for each probability and utility.
- Sensitivity analysis is done where potential important values (utility and probability) are changed over a likely range to create a model structure.
- This design is dependent upon on the assumptions made about parameter values and model structure.

Adaptive design

- These designs are used when an RCT clearly begin to favour one intervention over another.
- Advantage: Over time more patients will be assigned to the more successful treatment.

- Disadvantages:

1. In most trials, patients are heterogeneous with respect to important prognostic factors.

Adaptive design

2. It does not protect against bias introduced by changes in the types of patients entering into trial overtime.

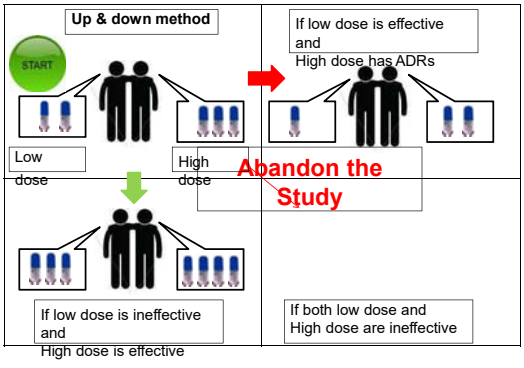
Adaptive designs can be of two types:

1. Sequential designs
2. Rolling designs

Sequential Design

- Here the participants are sequentially enrolled in the study and are assigned a treatment (usually at random).
- The efficiency, safety and efficacy of the experiment is improved by changing the rules as the study progresses.
- Various for sequential designs are:
  1. Up & down methods (Most Common)
  2. Stochastic approximation methods
  3. Maximum likelihood methods
  4. Bayesian methods

Sequential Design...



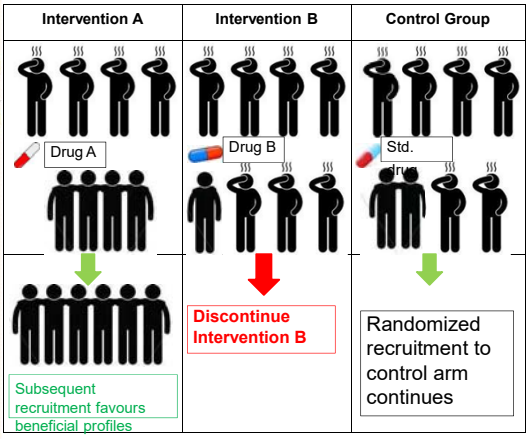
Sequential Design...

- Problems with sequential designs:

1) Uncertainty of sample size.
2) Duration of trial cannot be stipulated in advance.
3) Resources (funding).

Rolling design

- Design that can **roll on continually** by **introducing new treatment options** from the evidence accumulated, dropping those of either proven efficacy or if found not to be effective.
- Make use of **intermediate endpoints** (in contrast to the traditionally used endpoints that require longer patient follow-up).



Risk based Allocation Design

Individuals with higher risk or greater disease severity

Individuals with lesser risk or lesser disease severity

Potentially superior Experimental treatment

Relatively inferior Experimental treatment

- This design allows individuals at higher risk or with greater disease severity to benefit from a potentially superior experimental treatment.
- Advantages: Ethically more justifiable.
- Disadvantage: It is a non-randomized design.

Miscellaneous Study designs

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Cluster Randomized Design

Cluster/ Group A	Cluster/ Group B	Cluster/ Group C
 Intervention A		

- For assessment of non-therapeutic interventions such as lifestyle intervention or new educational programs for smoking cessation.
- Randomization can be performed on intact social units- family, school, worksites, athletic teams, etc.

Cluster Randomized Design...

- Although the trials adopt a cluster randomization, the analysis of data completely ignores this fact and uses subject as the unit of analysis.
- Thus, the unit of analysis may not be necessarily the same as the unit of randomization.

Enrichment Design

Enrichment phase	
Randomization phase	

•Phase of manipulation of dose levels of a therapeutic agent for identification of patients with drug efficacy is Enrichment phase.
• The patients with drug efficacy identified at enrichment phase are randomized to receive either efficacious dose of drug or matching placebo.

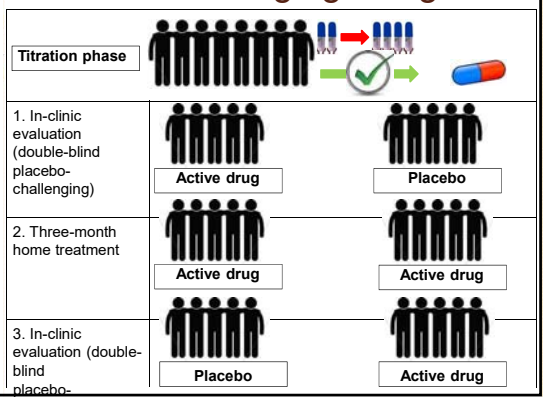
Placebo Challenging design

- For treatment of erection dysfunction, a design that consists of a :-

1. "Titration phase" for achieving optimal dose and
2. "Crossover active treatment phase" with two placebo challenges (i.e., pre- and post-treatment) is often considered.

- Design of this kind is a placebo-challenging design.

Placebo Challenging design..



Blinded reader designs

- A clinical trial for evaluation of medical imaging products with blinded imaging evaluation is said to have a blinded reader design.
- It is not feasible to blind the investigators who administer the investigational medical imaging agents.
- So effectiveness of medical imaging drug products should be evaluated based on the images by *readers (usually trained radiologists)* obtained with the investigational agents or controls under different conditions

Trial with Zelen's design

- Here, the patients are randomised before they give consent to participate in the trial.
- Those who are allocated to standard treatment group are not told that they are part of the trial.
- Those who are allocated to the experimental intervention group are told that they are part of the trial. If they refuse to participate in the trial, they are given the standard treatment but analysed as if they had received the experimental intervention.

Trial with Zelen's design...

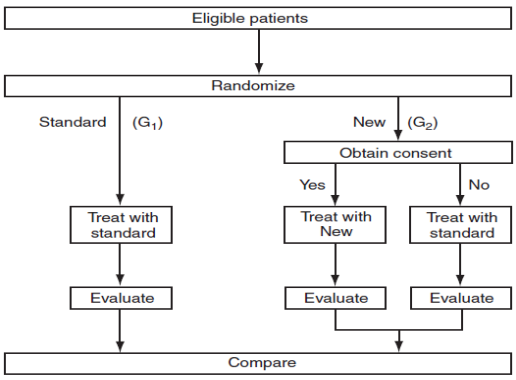
- Advantages:

1. Almost all eligible individuals are included in the trial.
2. Allows the evaluation of true effect of experimental intervention in patients.

- Disadvantages:

1. Open trials.
2. The statistical power of the study gets compromised if large no of patients choose the standard treatment.

Trial with Zelen's design...



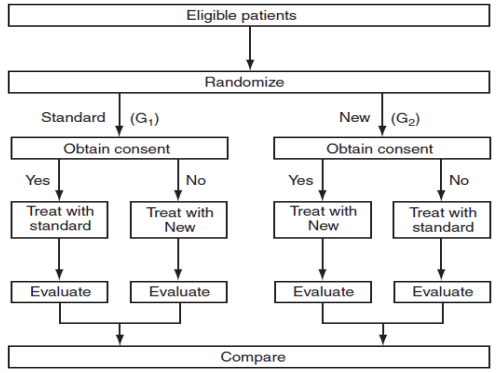
Trial with Zelen's design...

- There is ethical concerns of not telling patients that they have been randomised to receive the standard treatment.
- So, the original Zelen's design can be modified by informing participants of the group to which they have been allocated and by offering them opportunity to switch the group.

- Disadvantages:

1. Lack of blinding

Trial with Zelen's design...



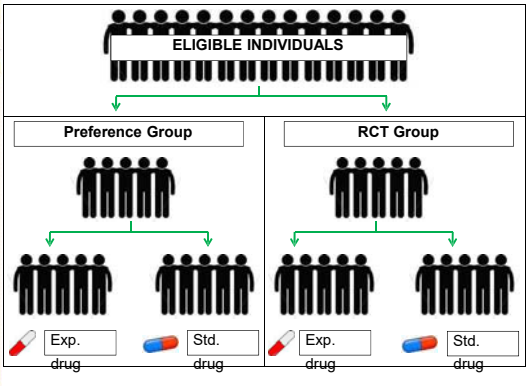
Trial with Wennberg's design

- In this design, eligible individuals are randomised to:

1. "Preference group" where patients can choose between exp. or std. treatment at will.
2. "RCT group" where patients are randomised between both arms.

- Rarely used.
- They are likely to be more frequently used as consumer participation in healthcare decisions and research is increasing.

Trial with Wennberg's design...



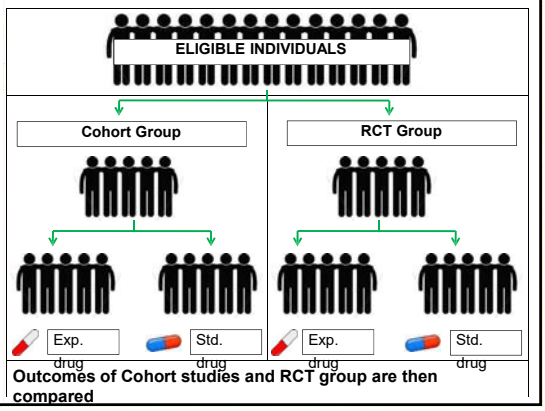
Trial with comprehensive cohort design

•A comprehensive cohort trial is a study in which all participants are followed up, regardless of their randomisation status.

1. If a person agrees for RCT, he is randomised to one of the study interventions.
2. If a person does not agree for RCT, he is given his intervention of choice and followed up as if he were a part of a cohort study.

•At the end, the outcomes of RCT and cohort study are compared to assess their similarities

Trial with comprehensive cohort design



Designs using historical controls

- Very rarely, a new treatment is given to all patients and result are compared with the past (historical controls).
- It is almost always unacceptable even for disease like leukaemia because:

1. Standards of diagnosis and treatment change with time
2. Severity of some diseases fluctuates

- An exception to this rule is the case-control study

Factors in choosing clinical trials designs

1. Chronology of events: Chronological effects may be very important in any trial design, but particularly in cross over design.
2. Subject convenience: Lengthy trials requiring multiple visits and involving washout periods may compromise patient compliance.
3. Trial cost: Very lengthy trials may not be routinely feasible due to prohibitive costs

Trial designs phase wise

- Phase I CT: All patients receive the drug, thus an unblinded, open label trial is suitable.
- Phase II through III CT: Parallel designs, Cross over, Factorial designs are most commonly used.
- Phase IV CT: Non experimental (observational) designs- These include epidemiologic designs such as case control or cohort studies