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Experimental study designs - Clinical trials

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Significance of clinical trials

- Clinical trials translate results of basic scientific research into better ways to prevent, diagnose, or treat disease
- Research studies involving people are designed to answer scientific questions and find better ways to prevent, diagnose, or treat disease

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Randomized controlled clinical trials

- A clinical trial is a planned experiment designed to assess the efficacy of prophylactic / diagnostic / therapeutic agents, devices, regimens, procedures etc. applied to human subjects
- It essentially involves comparing the outcomes in a group of patients treated with a test treatment with those observed in a comparable group of patients receiving a control treatment where patients in both groups are enrolled in a prospective study, treated or exposed to intervention and followed over the same period

The objectives of clinical trials

Clinical trials are normally conducted to evaluate new forms of therapy or prevention methods such as

- New drugs/ treatment
- New medical / health care technology
- New organization/ delivery system of health care
- New methods of primary prevention
- New programs of screening or early detection

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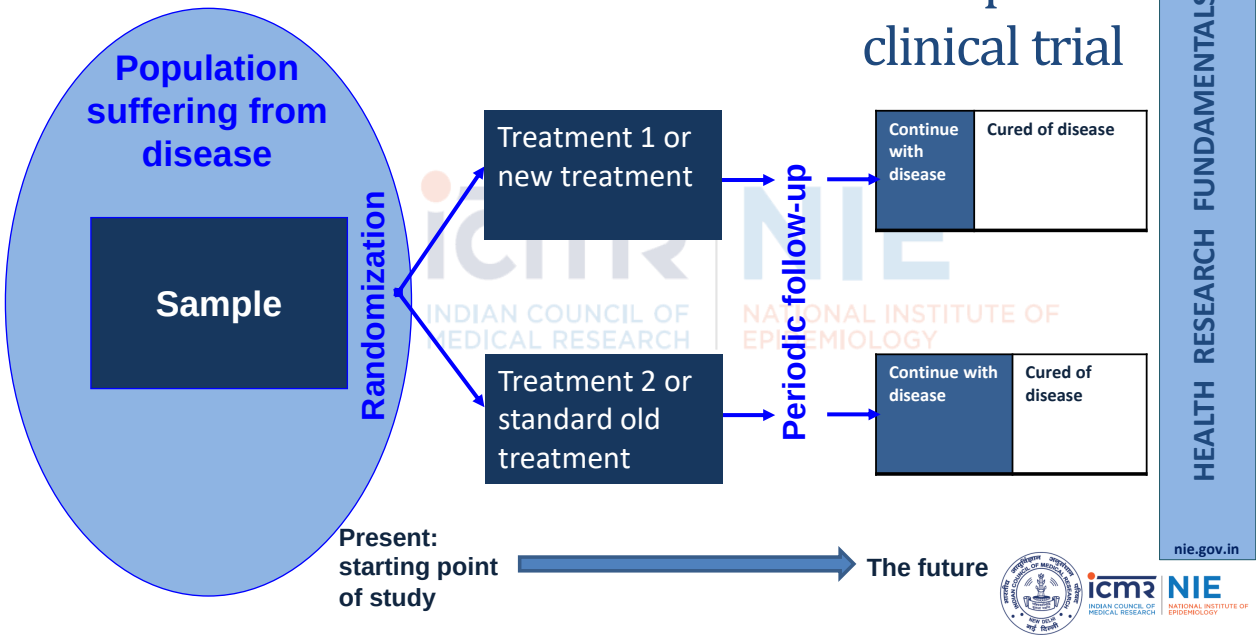
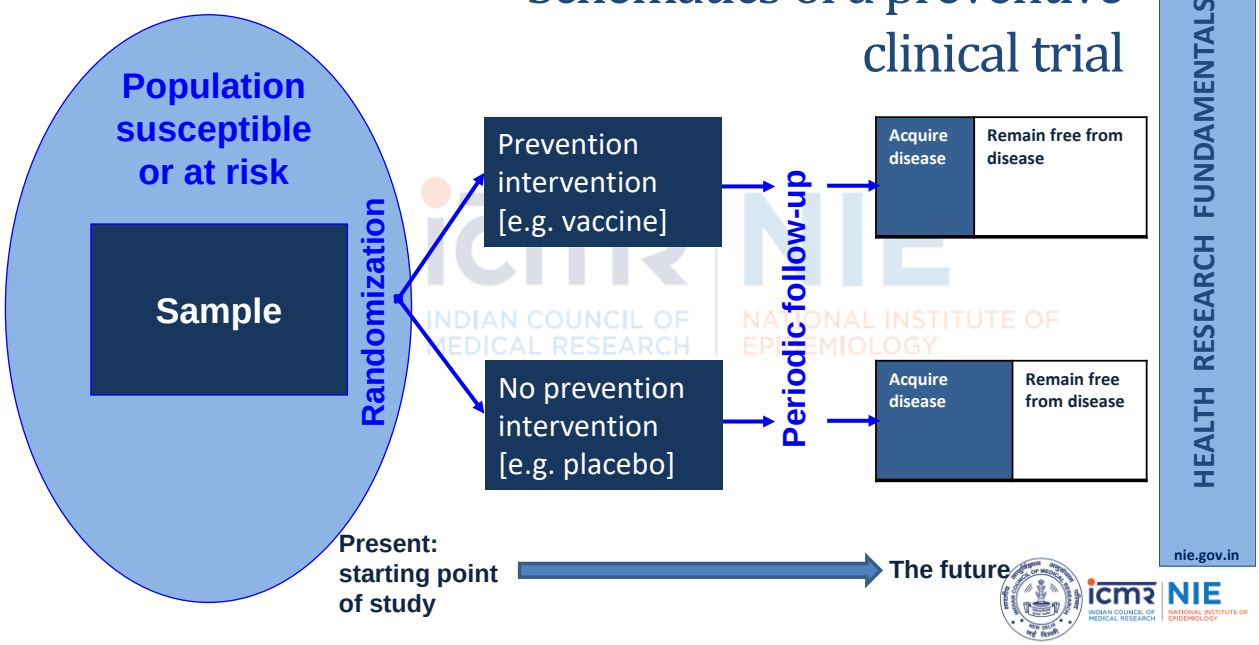
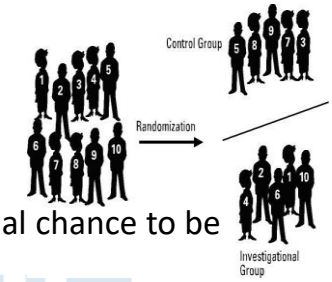
Schematics of a therapeutic clinical trial



Schematics of a preventive clinical trial



Randomization



Randomization ensures that participants have an equal chance to be assigned to one of two or more groups:

A. One group gets the most widely accepted treatment (standard treatment/ gold standard)

B. The other gets the new treatment being tested, which researchers hope and have reason to believe will be better than the standard treatment

Randomization provides the best way to prove the effectiveness of a new agent or intervention by ensuring that

A. All groups are as similar as possible

B. Confounding, co-interventions and bias in outcome ascertainment is minmized

Blinding in clinical trials helps in balancing groups during follow-up

- Blinding can be at the level of
  - participants [single blinding]
  - Participants and investigators [double blinding] and
  - Participants, investigators and analysts [triple blinding]
- Blinding helps to eliminate
  - Co-intervention: participants use other therapy or change behavior or study staff, medical providers, family or friends treat participants differently
  - Biased outcome ascertainment: participants may report symptoms or outcomes differently or physicians or investigators may elicit symptoms or outcomes differently

Phases in clinical trials and objectives

Trial phase	End-points/ objectives	Sample size and participants
Phase I	Safety Acceptability	Up to 50 Healthy volunteers
Phase II	Long-term safety Dose and schedule Early indications of efficacy	100 to 500 Low risk
Phase III	Effectiveness	1000 and more High risk
Phase IV	Post-marketing surveillance	1000 and more Community based

Example of a therapeutic trial

To study if a new drug regimen [NDR] effectively lowers viral load and improves CD4 counts in HIV infected persons compared to standard therapy [HAART]

1. Identify HIV infected persons, define inclusion and exclusion criteria
2. Randomize patients into 2 groups, one receives NDR, the other HAART
3. Follow-up periodically, estimate viral load and CD4 counts periodically
4. Use statistical methods to see if there are differences between viral load and CD4 counts in the two groups

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Example of a Prevention trial

A new vaccine candidate has been developed that has generated laboratory and animal data supporting its safety and ability to generate immune response. It is being considered a promising candidate for humans

1. **Decide at the national, regional and local level whether this vaccine is appropriate for the country and the population**
2. **Develop a Phase I trial design**
3. **Find healthy volunteers [adults/ children, men/ women]**
4. **Carry out screening followed by enrollment: Randomize patients into 2 groups, one receives vaccine, the other placebo**
5. **Follow-up the participants periodically, record safety and estimate immunogenicity periodically**
6. **Use statistical methods to establish safety and immunogenicity periodically**

Advantages & Disadvantages of RCTs

Advantages

- The only effective method known to control selection bias
- Controls confounding bias without adjustment
- Facilitates effective blinding in some trials
- Maintains advantages of cohort studies

Disadvantages

- May be complex and expensive
- Lack representativeness – volunteers differ from population of interest
- Ethical challenges are immense

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Thank you