CLINICAL TRIALS

LEARNING OBJECTIVES

- Leaner should learn at the end of this lecture

1. What s a clinical trial
2. How many types f clinical trials are available
3. How to conduct a clinical trial

PERFORMANCE OBJECTIVES

- **Learner should be able to perform a clinical trial either in hospital or community setting whenever he faces a doubt regarding benefits of any intervention / drug safety or efficacy**

WHAT IS IT?

- It is an experimental epidemiological method.
- It is an interventional study on individuals, usually on patients.

WHAT IS IT?

A research study in human volunteers to answer a specific health question

(U.S National Library of Medicine)

WHY THEY ARE DONE?

1. As they provide better evidence of the effect or the outcome that cannot be obtained with any other observational method.

2. The variation is minimized and bias is controlled , hence more valid and their results speak truth.

WHY THEY ARE DONE?

3. Enjoying maximum confidence just like any other scientific laboratory experiment
4. Providing maximum amount of assurance
5. Fastest and safest way to find treatments that work in people and ways to improve health

WHAT ARE ITS OBJECTIVES?

- **Intervention trials determine whether experimental treatments or trials are safe and effective under controlled environments**
- **Observation trials address health issues in large groups of people in natural settings.**

WHEN THEY ARE DONE

- When the laboratory and animal studies yield the most promising results of the intervention, those results are tested by clinical trials

WHEN THEY ARE DONE

- **When the margin of the expected benefit or the outcome of an intervention is doubtful or very narrow (10to30%) only.**

- **When the margin is large, obvious and beyond doubt, it will be unnecessary to conduct clinical trials.**

WHAT ARE ITS TYPES?

- Treatment trials
- Prevention trials
- Diagnostic trials
- Screening trials
- Quality of life trials

TREATMENT TRIALS

They test

- New treatments
- New combination of drugs
- New approaches to Surgery
- New Radiation therapy

PREVENTION TRIALS

They try to find better ways to prevent disease in people and to prevent disease recurrence using

- Medicines
- Vaccines
- Vitamins
- Minerals
- Life style changes

DIAGNOSTIC TRIALS

- To find better tests for diagnosis of a disease
- To find better procedures for diagnosis of a disease

SCREENING TRIALS

- To find out the best way to detect certain diseases or conditions

LIFE STYLE TRIALS

- Also called Supportive care trials
- Often employed for the chronically ill patients
- They explore the ways to improve comfort and
- to improve the quality of life

PHASES OF CLINICAL TRIALS

- Phase -I trials
- Phase -II trials
- Phase -III trials
- Phase -IV trials

PHASE-I TRIALS

- FIRST TIME TESTING
- IN A SMALL GROUP OF 20-80

PURPOSE IS

1. TO EVALUATE SAFETY
2. TO DETERMINE A SAFE DOSAGE RANGE
3. RECTIFY SIDE EFFECTS

PHASE-II TRIALS

- TESTED IN LARGE GROUP OF 100-300 PEOPLE
- PUROSE IS TO FURTHER EVALUATE

1. SAFETY
2. EFFECTIVENESS

PHASE –III TRIALS

- STILL LARGE GROUP 1000-3000 PEOPLE ARE TESTED
- PURPOSE IS TO CONFIRM

1. ITS EFFECTIVENESS
2. MONITOR SIDE EFFECTS
3. COMPARE WITH COMMONLY USED TREATMENTS
4. TO GATHER INFORMATION REGARDING SAFE USE

PHASE-IV TRIALS

- POST MARKETTING STUDIES
- TO KNOW ABOUT

1. DRUG RISKS
2. BENEFITS
3. OPTIMAL USE

HOW IS IT DONE?

DESIGN OF CLINICAL TRIAL

Selecting the reference population

↓

Selecting the experimental population
(Exclude Non-participants)

↓

Selecting the study population
(Participants)

↓

Random allocation into

Intervention group — Comparison group

↓ — ↓

Apply intervention — No intervention

↓ — ↓

Uniform assessment of outcomes

PROTOCOL (STUDY PLAN)

- Study plan is carefully designed

1. to safeguard the health of the participants and
2. to answer the specific research question

PROTOCOL

- It describes

1. what types of people can participate,
2. the schedule of tests,procedures,medications, dosages
3. The length of study

PROTOCOL

- **It has to be explained in detail , to all the participants, particularly regarding benefits and risks.**
- **It should be submitted to the ethical committee for prior approval before commencing the study.**

EXPLAINING THE BENEFITS

- That they play active role in their own health care
- They gain access to the new treatments before they are widely available
- They obtain expert medical care
- Help others by contributing to research

EXPLAINING THE RISKS

- Unpleasant, serious or even life threatening side effects
- Failure of treatment
- Time waste for the participants

SELECTING REFERENCE POPULATION

- It is the population to which the results of the trial are applied and gets benefited from the trial.
- It can be the whole or part of the country
- It can be any specific population like school children, specific age groups, sex groups or disease groups

SELECTING EXPERIMENTAL POPULATION

CRITERIA

A sample selected from the reference population as per the feasibility and practicability.

1. Sufficiently large to neutralize confounding variables
2. Non-response restricted to <10%*
3. Sufficient number of end-points, preferably measurable and objective type.
4. Feasibility to inform the participants and to do the follow-up throughout and also after the trial

THE STUDY POPULATION

- **Actual participants on whom the trial will be conducted**
- **Drawn from the experimental population after excluding the non-participants**

REAL EXPERIMENT

- **The investigator has the choice to apply the intervention or the maneuver and manipulate in the study population**

INCLUSION /EXCLUSION CRITERIA

- Intention is to identify appropriate participants and keep them safe but not to reject personally.
- Help ensure that researchers will be able to answer the questions
- Based on such factors as age, gender, the type and stage of the disease, previous treatment history, other medical conditions.

INFORMED CONSENT

- **Informed consent document will be obtained from the participants in the study population after explaining them fully about**

1. **The purpose,**
2. **Duration,**
3. **Required procedures,**
4. **Expectations,**
5. **Risks and benefits,**
6. **Adverse effects of the trial if any,**
7. **Participants' rights**

INFORMED CONSENT

- It is a continuous process throughout the study of learning of key facts by participants about a clinical trial.
- It also explains the rights of the participant.
- It is not a contract and the participant can withdraw from the trial at any time.

ETHICAL ASPECTS

- Participants are human beings with a motive to help the researcher and society.
- Researcher should never be over-enthusiastic in his intervention to get his results while dealing with participants.
- Informed consent is not having a legal binding on the patients. It is a communication document.

BLOCKING

- This is done ,when the study population is heterogeneous consisting of men, women, patients with different levels of severity of illness and suspected to give results of varying frequency

BLOCKING

- This is done before random allocation.
- Sub –groups are stratified and blocked to make the trial more accurate.
- Participants are randomly allocated from these various blocks or groups so that the trial's internal validity will be increased.

RANDOM ALLOCATION

- **The participants in the study population are randomly allocated into two groups (Arms) using Random Number tables to avoid selection and confounding biases.**

WHY RANDOMIZATION?

- Allocation bias is minimized
- This elimination of allocation bias will greatly enhance the validity of the trial.

BLINDING

- The investigator, the participant and sometimes even the evaluator are all kept unaware (blinded) of the outcomes of the trial and secrecy is maintained to improve the validity.

PURPOSE OF BLINDING

- Blinding or Masking is done to eliminate

1. Investigator bias
2. Evaluation bias
3. Hawthorne effect

TYPES OF BLINDING

- SINGLE BLINDING
- DOUBLE BLINDING
- TRIPLE BLINDING

BLINDING TECHNIQUES

- **SINGLE BLINDING means the process wherein only the participant is unaware about what he is receiving.**

- **DOUBLE BLINDING means is where both the participant and the investigator are unaware about of the intervention. This eliminates observer bias to a large extent.**

- **TRIPLE BLINDING is a trial where even the evaluator is also not aware of the process.**

UNBLINDING

- In emergencies and life threatening situations for participants, unblinding can be done.

INTERVENTION

- After random allocation into arms,
- The intervention (new drug or new procedure) is applied to the one group and placebo or old procedure to the latter group.

FOLLOW-UP

- **Better compliance will lead to better validity which in turn enables for better generalizability**
- **Both the groups are similarly followed in all aspects like duration, type of follow-up**

MAINTENANCE OF COMPLIANCE

- Selecting high risk people as participants in study population*
- Frequent contacts with the participants through phone calls, home visits, clinic visits
- Providing calendar packs to the participants and asking them to stick on to calendar packs without fail.
- Giving incentives like free medical aid in future, giving some gifts.

NON-COMPLIANCE

- Non-compliance decreases the statistical power of the trial which speaks about the validity (truth of the results)
- Extent of non-compliance is directly proportional to the duration and complexity of the trial.
- Compliance is difficult when the end – points are time taking like incidence of cancers or death

ASSESSMENT CRITERIA

Whether the outcomes or end-points are single or multiple, subjective or objective, uniform & similar type of evaluation of end-points for both the groups is to be carried out.

ASSESSMENT CRITERIA

- Subjectivity of the outcome e.g. reduction of pain, may lead to observer error and poor assessment.
- Double blinding eliminates observer bias to a large extent.

INTENTION –TO –TREAT PRINCIPLE

Whole of the experimental population including non – participants ,once randomized, whether they are participating or not in the trial , have to considered for evaluation as our intention is to treat all the people randomized.

PLACEBO EFFECT

- Psychological relief of symptoms, not true biological relief, is often reported

HAWTHORNE EFFECT

- Sometimes the participants in comparison group may exaggerate the effects/outcomes to please the investigator or when they like the study or for some other reasons.
- This will affect the assessment unless controlled.

COMPARISON GROUP AND ASSESSMENT

- **Vital not only for improving the validity but also for proper assessment.**

CONCLUSION

- In this century, the clinical trials are not only very useful epidemiological experiments but also very scientific and when conducted properly and carefully helps to prove the safety and efficacy of a new drug or procedure for public usage.

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