UNIT 13 INTRODUCTION TO CLINICAL TRIALS

Structure

13.1 Introduction

Objectives

13.2 Regimen, Efficacy and Safety

13.3 Types of Clinical Trials

13.4 Need of a Clinical Trial

13.5 Control Group in a Clinical Trial

13.5.1 Concurrent and Historical Parallel Controls

13.5.2 Placebo

13.5.3 Self-Control

13.6 Ethics in Clinical Trials

13.7 Clinical Trial Registration

13.8 Statistical Ethics in a Clinical Trial

13.8.1 Random Selection of Subjects

13.8.2 Randomisation and Matching

13.8.3 Blinding and Masking

13.8.4 Equipoise and Sample Size

13.9 Phases of a Clinical Trial

13.9.1 Phase I

13.9.2 Phase II

13.9.3 Phase III

13.9.4 Phase IV

13.10 Random Error and Bias in a Clinical Trial

13.10.1 Random Error

13.10.2 Biases

13.10.3 Steps for Minimising Bias

13.11 Summary

13.12 Solutions/Answers

13.13 Suggested Further Reading

13.1 INTRODUCTION

In Sec. 11.3 of Unit 11 of previous block of this course we have discussed the difference between experimental and non-experimental studies with examples. Recall that one of the examples of experimental studies was clinical trials. And we promised there that clinical trials will be discussed in Block 4 of this course in details. So, it is time to keep our promise. An experiment is something that we intentionally do to see what its effect is. You may have conducted experiments in your schools and colleges. You know that experiments are performed under controlled conditions in laboratories to test hypotheses. Clinical trials are experiments on human beings conducted in a scientific way. The objective is to find out whether, when we do something to a group of people, it gives you the desired result in many of them or not? Some newly devised or modified regimen is intentionally applied on people with or without disease to find out the efficacy and safety of this regimen. Therefore, we define

clinical trials as the scientific investigations that examine and evaluate safety and efficacy of drug therapies in human subjects in which individuals or subjects are randomly allocated to two groups, known as the "**experimental**" and the "**control**" groups. The experimental group is given the drug being tested and the control group is given the drug in current use; if no such drug exists, then a **placebo**, an inert substance such as a sugar pill or a saline injection, is used. Randomisation is the basic difference between clinical trials and other experiments. Need of control group will be discussed in Sec. 13.5. The controlled clinical trial is now a well-accepted method of measuring the relative efficacies of different therapeutic regimens for many diseases.

Regimen, efficacy and safety are very important terms and so the next section, i.e., Sec. 13.2 is devoted to explanation of these terms. We will be using these terms frequently in this course and you should be absolutely clear about the meaning of these terms. You will soon learn in this unit why a group without disease is also needed in most clinical trials.

Various types of clinical trials are discussed in Sec. 13.3. That will give you an idea of the wide variety of clinical trials. Specific objectives of this unit are listed below this paragraph. You must continuously evaluate your learning against these objectives. After this basic information, we come to the real subject matter of this unit. Why should a trial on human beings be done at all? This is explained in Sec. 13.4. All trials require a control group for comparison. Various types of controls are discussed in Sec. 13.5. Ethical aspects and clinical trial registration which is altogether a new concept in clinical trials are discussed in Secs. 13.6 and 13.7 respectively. Sec. 13.8 is on statistical ethics such as randomisation and blinding. Since they are done on human beings, one special precaution taken is that clinical trials are done in phases. These phases are explained in Sec 13.9. Data from clinical trials can be biased if additional precautions are not undertaken. Some commonly occurring biases are listed in Sec 13.10. This section also gives details of random error that happens because the trial is conducted on a sample of subjects. Methods to control various biases and random error are also given in this section. Those of you who are keen to learn more may like to read some books and other material so that you are more clear about these concepts. Books for further reading are suggested in Sec 13.13.

Objectives

After studying this unit, you should be able to:

- identify situations where clinical trials are essential, desirable, not needed, and cannot be conducted;
- appreciate why clinical trials are conducted in phases, and what the objectives of different phases are;
- state the importance of statistical ethics in conducting clinical trials, and
- explain the meaning of randomisation and blinding.

13.2 REGIMEN, EFFICACY AND SAFETY

As already stated regimen, efficacy and safety are very important and frequently used terms, so let us define these terms one by one:

Regimen

Regimen could be a substance (such as a medicine or a combination of drugs), a procedure (such as ECG), a diagnostic test or medical device, a behaviour

(such as exercise, eating garlic, reduced intake of oil or ghee), etc. This regimen is expected to change the status of the disease. It may cure the disease or reduce its severity, or even be more convenient or less costly alternative to the existing treatment. Regimen may also mean replacing injection by tablet, replacing toast-butter by fruits, changing one exercise to another, etc. Regimen includes the dose, duration, etc. You must have seen doctors prescribing that a medicine (say, a tablet of 100 mg) be taken three times a day for seven days. All this is part of the regimen. You will see many examples in this unit of different types of regimens. Sometimes regimen may also be termed as treatment.

Efficacy

Some regimens are expected to reduce the severity of disease such as drugs to reduce pain, some are expected to provide complete relief such as medicines to bring down the fever to healthy level, some are expected to speed up recovery such as exercise for pain in joints, some help in reducing the chance of early death such as chemotherapy for cancer, some are expected to increase your health such as nutritious diet, etc. All these are **outcomes** of the regimen. Some persons or patients respond to the regimen and some do not. The percentage of patients or persons who respond to the regimen as per expectations is called efficacy. If 72% patients of a disease recover after the prescribed regimen, the efficacy of that regimen is 72%.

Safety

Most regimens cause some discomfort. For example, a drug may upset your stomach. A surgery can mean loss of wages and heavy expenditure. Cancer treatment may prevent death but the person is not able to perform heavy work. Head surgery after injury helps to avoid death in many patients, but some die. All these come under safety. Thus it is a broad term to include all adverse effects. Adverse effects are not restricted to health but also include economic factors such as money spent, duration of disease that could mean taking leave from job, cost of doctors and hospital that you may not bear but the government bears, etc. Regimens should not only have high efficacy but should also be sufficiently safe for the patients and the society.

It should be clear that clinical trials are conducted on **human beings**. Persons are the **subjects** of experiment in clinical trials. Experiments done on animals or in the laboratory do not come under clinical trials. Since human beings are involved, a lot of care and precautions are required in clinical trials so that the subjects cooperate, are not unduly harmed, and produce unbiased results. In India prior approval for conducting the clinical trials on human beings is required, usually on the basis of detailed submissions or protocols from Ethics committee. In addition, in case of new molecule development, protocol is required to be approved from Drug Controller of General (India), DCGI Details are given in Sec.13.6 . Registration of clinical trials which is now mandatory in our country is discussed in Sec. 13.7.

Now, you can try the following exercise.

E 1) A trial is conducted in which some people with high blood pressure were randomly allocated into two groups. First group was advised to do some yoga and take simple diet each day and second group was given one 50 mg tablet once a day to control blood pressure. This drug can cause vomiting in some cases. At the end of four weeks, 60% of group I and 70% of group II had normal blood pressure.

i) What are the regimens for group I and group II in this trial?

ii) What are the efficacies in group I and group II?

iii) What are the safety issues in group I and group II in this trial?

13.3 TYPES OF CLINICAL TRIALS

There are a wide variety of clinical trials. The clinical trials that are commonly used are explained here.

Therapeutic Trials

Most popular are trials for drugs and other regimens that could reverse the disease and improve health. These are called therapeutic trials. For example, a trial for a new drug for treating diabetes is a therapeutic trial.

Intervention Trials

The trials, in which the investigator intervenes before a disease has developed in individuals with characteristics that increase their risk of developing the disease, are known as intervention trials.

Diagnostic Trial

The intervention in a diagnostic trial is not a therapeutic regimen but a procedure that can change the diagnosis and thus the course of the treatment. Thus they have the potential to improve decision-making and patient management. For example, typhoid can be diagnosed either by a laboratory (Vidal) test or by signs and symptoms. Comparison of the two would be called a diagnostic trial. This requires a **gold standard** that gives nearly a perfect diagnosis in all suspected cases. Note the definition of a gold standard in this case.

Prophylactic Trial

Prophylaxis is a procedure that promotes health or controls factors that adversely affect health. A prophylactic trial is generally conducted in the field where a community is involved. But it can be conducted in a clinical setup also. These are also called **preventive trials**. An example is a trial on a prophylactic drug such as aspirin to reduce heart ailments in people of age 50 years or more. These people do not actually have disease but are prone to disease in future if such preventive action is not taken.

A prophylactic trial in the field could be for a strategy such as lifestyle changes for coronary disease or could be for vitamin intake—even drugs that can prevent occurrence or recurrence of adverse events. Giving vitamin A supplements to infants and young children to improve their retinol level is an example of such intervention. Such trials have tremendous value in policy formulation, in saving lives, and in improving health, but they do not receive that kind of attention.

You can see that a prophylactic trial is not necessarily conducted in a general population. Vitamin A trial cited in the preceding paragraph is for children. A trial on educational campaign for responsible sexual behavior to prevent HIV and other sexually transmitted diseases may target adolescents. Another trial on iron supplementation (that increases hemoglobin level in blood) may target poor pregnant women so that they bear healthy children.

Field Trials

Field trials are done in community residing in an area. For example, the

intervention could be training to the block health workers on how to take Pap smear in women. This can improve the cancer detection rate. This can be compared with an area where no such training was given. Pap smear helps to detect cervical cancer in women of middle and old age.

Screening is done to find if anyone has the likelihood of disease. Whether he or she actually has the disease is found later by more investigations. Screening is only for likelihood. You have already studied about screening in Unit 12 of this course. For example, obese people of age 40 years or more can be screened for possible diabetes by random blood sugar test. If their blood sugar level is high, they can be further examined later for fasting level. For this they will be asked to come in the morning without eating anything. Screening trial can be small or huge. The prostate, lung, colorectal, and ovarian cancer **screening trial** initiated in 1992 in the United States has enrolled more than 150,000 participants.

Vaccine Trials

Vaccine trials are for evaluating efficacy of vaccines in preventing or slowing the progress of a disease. In the case of HIV, for example, there could be a vaccine that stops HIV infection, and there could be another vaccine that slows down development of disease—AIDS—in those already infected. In 2021 lot of vaccine trials for COVID-19 were conducted in different counties.

Now, you can try the following exercise.

E 2) Talk to your family and friends and prepare one example each of a regimen that can be tested for curing the disease (therapeutic), one for preventing a disease (prophylaxis), one for screening a disease, and one for a disease that requires vaccine.

13.4 NEED OF A CLINICAL TRIAL

Sometimes mere observation is not enough. You may have tried twisting the tail of a dog to see how he reacts. There is always a curiosity to explore the consequence of our actions. The first basic feature of any experiment is manipulation—called the regimen. This is the human intervention. The natural course of events is sought to be changed by such human intervention. Although an experiment can be carried out for an intervention whose mechanism of action is still unknown, we cannot say that the effect is due to the intervention unless we also have a suitable explanation of why that effect has appeared. For example, if you give a drug to reduce high blood pressure, not only should the drug reduce it but also we should be able to say that the drug has such and such property that acted on the level of blood pressure and reduced it. This kind of explanation is called biological explanation. Sometimes, a regimen is devised on the basis of already known biological properties and then tried on actual patients to see if it really works.

Whenever a new regimen is developed, you would like to see practically how much it works in the target group of people for which it is meant. For example, if there is a new treatment for kidney diseases, it is necessary to find if it really works in kidney patients, or in what percentage of patients it is effective, or in what kind of patients it is effective. Is it sufficiently effective in old age patients or not, or is it effective in severe cases or not. This is done even if you are sure of its excellent biological properties. No regimen is put into practice unless it is actually demonstrated to be effective in a group of people. For this

it is necessary to conduct a trial. Without a successful trial, no new drug can be introduced into the market.

Beside efficacy, clinical trials also tell us about the safety of the regimen – what types of side-effects appear and whether people really accept that kind of regimen or not.

For what kind of interventions is a trial essential? Clinical trial is essential for almost all new regimens. Without the trial, nobody knows if it is really effective. For drugs that can have serious side-effects, a trial is a must. You will soon learn about phases in which a trial is conducted. These phases give us an idea of what kind of side-effects can appear. For a treatment that requires a surgery or that requires inserting something in the body (such as a colour or an instrument), a trial is necessary since these can have serious adverse effects. Most drugs also have one side-effect or the other. Some drugs cause loose motions, some will cause itching, some can damage the liver, some can increase blood pressure level, etc. A clinical trial is necessary for all such new regimens.

There are other regimens that are not harmful but gains from them are doubtful. Dietary changes and physical exercise kind of regimens come into this group. For such regimens, trials are desirable but not necessary. Trials give confidence since then people know that this was tried and found to be effective. If the objective is to compare the efficacy of one such regimen with another such as comparison of exercise/diet changes with a drug for high blood pressure, a trial is necessary because only the trial can reveal that one is better than the other or not.

Opposed to this, there are 'regimens' which can be harmful. Pollution is harmful and we cannot intentionally expose some people to pollution to see the kind of harm it does. Dirty water can cause cholera but we cannot conduct an experiment on this since we cannot ask people to drink dirty water. Similarly, we cannot ask people to smoke for 10 years to see if it really causes lung cancer. Some of these substances can be tried on animals such as rats but certainly not on human beings. Thus no clinical trial can be done for regimens for which we already know that they can harm us.

Now, you try the following exercise.

E 3) Name two types of regimens for which a clinical trial is essential, and one regimen for which a clinical trial is desirable but not essential. Also, name two regimens for which clinical trial cannot be conducted. Also give one line reason for each.

We have already said that clinical trials are conducted on human beings, so several precautions are taken in conducting clinical trials. These are:

(i) trial on a control group also;

(ii) use statistical tools such as randomisation, matching, blinding, good sample size;

(iii) conduct trials in phases, and

(iv) control random error and biases.

Next four sections of this unit are devoted to discuss these issues.

13.5 CONTROL GROUP IN A CLINICAL TRIAL

All experiments on human beings become more valid when these have at least

two groups. One group gets the regimen under trial and the other group gets either the existing regimen or almost nothing at all. The first is called the **test arm** and the second is called **control arm** of the trial.

13.5.1 Concurrent and Historical Parallel Controls

When the control group is a separate group of patients, this is called **parallel control.** This is different from self-control. Self-control is explained later in this section. Parallel controls are of two kinds: concurrent and historical.

Whereas it is clear that a group of patients will get the test regimen to see if it really works without causing much discomfort, the role of control needs to be understood. If we want to establish that our new regimen is better or at least as good as the existing regimen, our control group gets the existing regimen. For example, if we have a new drug that may be quicker in relieving pain, one group of patients with pain will get this new regimen and another group of patients with similar pain will get the existing drug. The control group that gets the existing drug must be similar in all respects such as they must be of nearly same age, must have similar pain, must be of same health, etc., so that these factors do not affect our findings. Nobody should be able to say later on that our regimen was found effective because the test group was more healthy who could tolerate the pain, or that they had less pain to begin with than the control group, or any such factor.

The control group is called **parallel** when it is a separate group and is similar to the test group at the start of the trial. Generally, you will also have another group of subjects together with the test group. Both are selected from currently available patients. Such another group is called **concurrent control**. In some special cases, the existing regimen may have been already tried earlier on a similar group of patients. This is called **historical control**. If results of a good historical control group are available, you do not need to study it again now with the test regimen. In this case, there is no need of a concurrent control.

13.5.2 Placebo

In some situations, when the drug is for a condition for which no therapy exists, control group is not given any therapy. But they are still given something. You might have heard a story of how your uncle felt better in a sickness when he was given coloured water, which he was told was a medicine. It is an established scientific fact that some people get better because of psychological effect. If you are given a harmless chalk tablet in the name of a drug, you may show improvement because you thought that you are being treated. Some people improve due to mantra-tantra due to psychological effect. This psychological improvement has been seen in as many as 30% of the people in some situations.

Such inactive substance is called **placebo**. The improvement due to psychological effect of placebo is called **placebo effect**. Placebo must be harmless and should not contain anything that can cure the disease. We tell you later on why this should look like the drug. Difference in efficacy between the test arm and control arm gives us the real efficacy of the regimen. Now nobody can say that this difference was due to **psychological effect**.

There is always a question about using a placebo on patients who are known to have the disease because they need an active treatment to cure their ailment. However, placebos can be easily used in the following situations.

1. No standard treatment is available, i.e., the existing treatment has doubtful results—perhaps no better than a placebo.

2. New evidence has emerged regarding the doubtful efficacy of the existing therapy.
3. Existing regimen is too costly, or is rarely available to the population at large.
4. On patients who have already been given existing treatment and have not benefited, and no second line of treatment is available for them.
5. Test regimen is an add-on to the existing regimen. This means that all patients in the trial, including those on placebo, would receive the normally prescribed therapy anyway.
6. Patients refuse to accept existing therapy, and are willing to be part of a trial where they know that they can receive a placebo.

In situations where these conditions are not met, a group on existing therapy can serve as control. But control is now widely considered a scientific necessity.

13.5.3 Self-Control

Sometimes disease status in patients is assessed before the treatment and after the treatment. For example, you can measure blood sugar level of diabetes patients and ask them to do special yoga for 15 days. Then measure their blood sugar again. Such trials are called **before-after trials or self-control trials**. These are also called **uncontrolled trials**, although in this kind of trial, patients serve as their own control. If there is a statistically significant decline in average blood sugar level, can you say that this decline is due to yoga? The answer is no because some of these people may have shown decline due to psychological effect which may not be due to yoga. Despite this deficiency, self-control trials are done whenever it is difficult to find equivalent controls. However, generally, parallel controls should be used. Yoga trial mentioned above will give more scientifically valid results when a group is kept on yoga for 15 days and another group is observed without yoga for 15 days. Both the groups can be measured before and after. Difference between improvement seen in yoga group and any improvement seen in non-yoga group will tell us whether yoga was helpful or not, and in what percentage of cases. There are other types of self-control such as cross-over and we will discuss these in Unit 15 of this course.

One disadvantage of self-control is that placebo effect is mixed with the drug effect – thus actual drug effect cannot be assessed. Second is that actual level before the treatment can affect the level of improvement after the treatment. For example, if haemoglobin level is low at 7 g/dl, an improvement is easy but if it is 13 g /dl, further improvement is difficult. Even when the difference of after-values with before-values is taken, the analysis will give biased results in this situation. The advantage of self-control is that it requires half the cases since no separate control group is required. If control is existing regimen, self-control works well. This means that the control is an existing treatment and test regimen is add-on that can be given along with the existing treatment. For example, existing treatment may be a drug to control blood sugar level and the subjects are also asked to take less oil and do exercise. In this case, less fat and exercise is the regimen under test. Blood sugar level with the use of drug is the level before the test regimen and this can be measured after a month of less oil and exercise to see if it really helped.

Sometimes the same subject is observed repeatedly to see what the effect of the regimen is at different times. In our yoga example, you can go on for 60 days

and record blood sugar level at 15 days, 30days, 45 days and 60 days. This will give an idea of what duration is good enough to bring about a change.

Now, you can try the following exercises.

E4) Select the best statement for the role of control group in clinical trials.

A. To control the size of the trial.
B. To control the uncertainties in the conclusion.
C. To control sampling error.
D. To control the placebo group.

E5) Placebos are useful in clinical trials because

A. they help in comparing active treatment to no treatment.
B. they help in blinding.
C. they help in comparability in non-randomised trials.
D. they help in comparing two similarly active treatments.

E6) A control must be a

A. placebo. B. treatment.
C. no treatment. D. any of the above.

E7) True or false. Give your reason for each in one line.

A. An active control is the one that works in a large percentage of cases.
B. A control must involve a placebo.

13.6 ETHICS IN CLINICAL TRIALS

A clinical trial can only be conducted in India after the protocol (which is a detailed document for conducting the clinical trials and will be discussed in the next unit.) is approved by an appropriately constituted and competent Ethics Committee. This has been implemented with the specific purpose of safeguarding the rights and wellbeing of the volunteers participating in a trial. All clinical trials being conducted in India must follow in letter and spirit the Ethical Guidelines for Biomedical research on Human participants (2006) developed by the Indian Council of Medical Research (ICMR), New Delhi (http://icmr.nic.in/ethical_guidelines.pdf).

Ethics committees may be Institutional Ethics Committees or Independent Ethics Committees (IEC) which function outside institutions, for those researchers who have no institutional attachments or work in institutions with no ethics committee. In addition to developing new drug, the Schedule Y of the Drugs and Cosmetics Act, 1940, as amended from time to time, details out the rules and regulations applicable to clinical trial requirements for import, manufacture and obtaining marketing approval for a new drug in India. (http://cdsco.nic.in/Drugs&CosmeticAct.pdf). The details are beyond the scope of the course. This gives you an idea that every clinical trial has to obtain approval from ethics committee who is responsible for any type of loss to participants recruited in a clinical trial. This gives an idea that clinical trials could be conducted only after the approval of the Ethics committee.

13.7 CLINICAL TRIAL REGISTRATION

To increase the accountability and transparency in the conduct of the clinical

trial, the World Health Organisation (WHO) has made a statement that all interventional clinical trials are expected to be registered in any publicly available system. Keeping this mandate, Indian Council of Medical Research (ICMR) took the lead in India and an online system (www.ctri.nic.in) for registration of all clinical trials being conducted in India has been established by National Institute of Medical research which is one of the institutes of ICMR and launched on 20th July 2007. This system (www.nic.in) is known as Clinical Trials Registry – India (CTRI). You can see the details on the (website www.nic.in). This section only gives you an idea about the accountability of trials conducted in our country.

13.8 STATISTICAL ETHICS IN A CLINICAL TRIAL

Clinical trials are done with great precautions. We have discussed about requirements of social ethics in Sec. 13.6 such as providing complete information to the patients regarding good and bad points of the regimen, taking informed consent, etc. In this section we will discuss about statistical ethics.

13.8.1 Random Selection of Subjects

One of the primary objectives of a clinical trial is to provide an accurate and reliable clinical evaluation of a study drug for an intended patient population with certain diseases. In practice, statistical and clinical inference are usually drawn based on a representative sample (a group of patients to be enrolled in the trial) selected from the intended patient population of the clinical trial. A representative sample provides the clinician with the ability to generalise the findings of the study. Therefore, selecting patients for a clinical trial plays an important role in best answering the scientific and/or medical questions of interest regarding the study drug. Basically selecting patients for a clinical trial involves two steps. First, we need to define the intended patient population. Patients are then selected from the intended patient population for the clinical trial. For a given disease, the intended patient population is often rather heterogeneous with respect to patient characteristic and the severity of the disease. The heterogeneity of the intended patient population can certainly decrease the accuracy, reliability, and the generalisation of the findings of the study. In clinical trials the intended patient population usually involves various sources of expected and unexpected biases and variabilities. For example, bias and variability due to differences in patient demographic characteristics such as age, sex, height, weight, and functional status are expected. Bias and variability caused by changes in disease status and concomitant therapies are unexpected. For good clinical practice it is therefore desirable to define the intended patient population in such a way that it is as homogeneous as possible with respect to these patient characteristics in order to reduce bias and variability. In addition for selection of patients, eligibility criteria should be defined clearly for the intended patient population and the process of selection of patients. In a similar way controls could also be selected in random manner.

For example, if we have 150 patients of heart disease for a trial, these 150 should have broadly the same features as generally seen in patients of heart disease in that area. This means that they should be of similar age, must have similar sex ratio, must have same socio-economic status, etc. This representativeness is easily achieved when we select our subjects by some kind

of random method. For example, all consecutive patients coming to a clinic from January to December could be a good random sample as there is no bias. This holds when the number of subjects in the trial is large. A small sample selected in this way may not be representative.

13.8.2 Randomisation and Matching

The subjects in test arm and control arm should be similar to begin with. Only then can any difference found at the end be attributed to the regimen. For this equivalence, one of the two possible strategies is adopted. One is that if we have a total of 150 patients who provided consent, 75 are randomly allocated to the test arm and the other 75 to the control arm. R**andomisation** means each subject has equal chance to be in either group. The purpose of randomisation is to reduce the bias in subject selection. This is the same as random allocation. Elaborate procedures are followed for this but we won't discuss them here. These days random allocation can be easily done with the help of computer generated numbers. This strategy is followed when the number of subjects is large. In case of large samples, randomisation works well and is very likely to give equivalent groups. Randomisation also provides a basis to use statistical methods since statistical methods require that there is some kind of randomness in the data.

Randomisation may not work for small samples. For small sample, another strategy, called **matching** is followed to ensure that the subjects in the test arm are similar to the subjects in the control arm. In this, one subject in control arm is intentionally selected such that it matches with one subject in the test arm. Matching could be for age, sex, obesity, etc. For example, if you have one male patient of age 55 years in the test arm, a male patient of nearly the same age is included in the control group. Ideally, you should have two matching subjects among those who have agreed to be in the trial, and you should randomly decide who would receive test regimen and who control regimen.

In some situations it is possible to simultaneously give a different treatment to known pairs such as two eyes or two legs of the same persons. Twin studies also come under this category. Randomisation can be done within each pair to determine which one will receive test regimen and which control regimen – whether right eye will receive test regimen or the left eye. Thus randomisation and matching can go on simultaneously. If the trial is on comparison of methods such as two instruments for measuring blood-pressure, many pair of arms would be easily available. If the trial is for treatment regimen, it would be extremely difficult to find matched pairs, such as the same severity of glaucoma in the two eyes, or both limbs with same degree of paralysis.

It may not be possible to find a control of age 62 years for matching with a case of 62 years. In most situations, matching within ±2 years for adults is considered adequate. Such relaxation can be possibly allowed for other factors as well. In tough situations, **group matching** is done instead of **one-to-one matching**. This means that if 30% of cases are females, 30% of controls are also females; if 60% cases are obese, a similar percentage is in the controls. This is also called **frequency matching**. There is no one-to-one matching in this case. Fig. 13.1 shows a typical illustration of one-to-one matching of participants with respect to age, sex and obesity.

In most cases, one matched control is included in the study for each case, but when controls are easy to find and are less expensive you can include two or more controls for each case. This increases the sample size and helps to

increase the reliability of the conclusion.

You can see that matching may mean incurring extra cost due to baseline investigation on a large number of subjects many of which may be discarded as unmatchable. Generalisability suffers as the control group is somewhat distorted. Because of this reason, evidence from such experiments is not considered as strong as from randomised trials.

Matching of the Study Participants in Test Arm and Control Arm for Age, Sex and Obesity

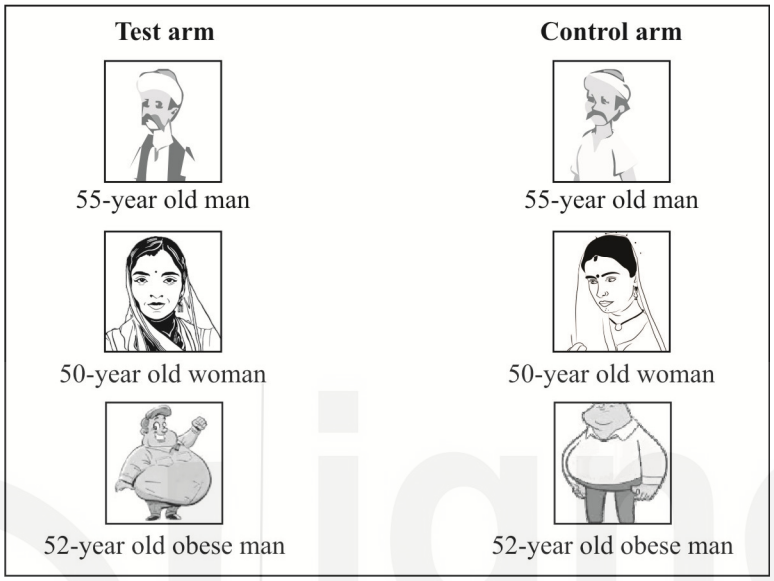

Fig. 13.1: One-to-one matching with respect to age, sex and obesity.

13.8.3 Blinding and Masking

If everybody knows who is receiving test regimen and who is receiving control regimen, this is called an **open trial**. This introduces the possibility of patients psychologically changing their response when they know that they are in the control group. They may feel discriminated against if the allocation is open. Also, patients who know that they are receiving a new regimen may either show increased anxiety or may have favourable expectations. In addition, patients are more likely to seek another treatment in an open trial, and more likely to dropout.

Another statistical ethics followed in clinical trials is that the **patients** are not told that they are receiving the test regimen or the control regimen. This is called **blinding**. Many patients, if they know that they are receiving placebo or existing therapy, will show different improvement or no improvement. To avoid this bias, blinding is adopted. Many times the **doctors or nurses** who assess the progress of patients also show bias if they know that the patient is on placebo. Thus they are also not told who is in which group. This makes the trial **double-blind**, one blinding for the patient and the other for the nurse or doctor. They will not know that the patient has received test regimen or control regimen. Sometimes even the statistician who analyses the data also becomes interested in showing that the test regimen is better and does the analysis accordingly. In that case, the **statistician** is also not told which group is test and which group is control. He or she is only told that one is group A and the other is group B. This makes the trial **triple-blind**. Codes of this remain secure with a third person who keeps them secret. These codes are revealed only when the final results are available. In open, single-blind, double-blind and triple-blind trials who is/are **blind** () and who is/are **not blind** () is shown

in Table 13.1.

Trials that use parallel concurrent controls with randomisation and double blinding are called **double blind randomised controlled trials** (RCT). Such trials are the industry standards and most preferred.

Table 13.1 Blinding Status of Patients, Doctors or Nurses and Statistician in Open, Single-blind, Double-blind and Triple-blind Trials

Trial	Patients	Doctors or nurses	Statistician
Open			
Single-blind			
Double-blind			
Triple-blind			

Morality issues are attached to blinding because the information is withheld from the participants on the one hand who would be keen to know what they are getting in case an unusual side effect appears or unusual recovery occurs. If the doctor does not know, he may not be able to take remedial measures if anything wrong happens to the participant. In this last case, this code is broken for that patient but remains secret for other patients.

Blinding is not easy to implement. There are situations where blinding is not feasible. For assessing the outcomes such as quality of life, readmissions, and falls after hip surgery, blinding is just not possible if one regimen is keeping the patients in hospital for a specified number of days, and the other is early discharge and home care. In most surgical interventions control has to be another kind of surgery, and not a placebo. A sham surgery may be unethical many times because it exposes a patient to surgical risks. In either case, it is extremely difficult to enforce blinding in a surgical trial. The patient can be kept blind after proper consent but the surgeon or nurse definitely knows. However, a mechanism can possibly be developed wherein all assessments subsequent to the operations are done by another surgeon who does not know and cannot find whether the patient belongs to the test surgery or the control surgery.

It is also necessary to make the test regimen and control regimen similar so that nobody knows what is what. If your test regimen is a tablet and control is coloured water, everybody would immediately know what is what. For blinding to remain in effect until the end, it is necessary that both the regimens must look alike, must taste alike, must have similar packaging, etc. This procedure is called **masking**. This includes that the patients in the two groups should have similar diet and should be transferred from one ward to the other in a similar way. They must be administered in an undifferentiated fashion. If one regimen is once-a-day (OD) and the other twice-a-day (BD), the OD group should be given a placebo second dose to give an identical look.

Masking is the arrangement made to ensure that the identity of groups is not revealed till the trial is over. In fact, this can improve compliance and retention of the subjects by clearly demonstrating that groups are being treated equally. Sometimes complaints of the patients can reveal that his or her regimen is a test or the control. A very careful strategy may have to be devised in some situations so that the bias is minimised if not eliminated.

Now you know why clinical trials are so difficult to conduct and manage. These are very expensive also. But there are other precautions too as per the following details.

13.8.4 Equipoise and Sample Size

There are other aspects of statistical ethics. One is that the doctors should be really uncertain that the regimen is effective or not and safe or not, or that it is better than existing regimen or not. This is called **clinical equipoise**. If many doctors already know that the regimen is good or many know that it is bad, there is no need to conduct the trial. Also the patients also should be uncertain about the outcome. Then only they will give correct results. This is called **patient equipoise**. Both equipoises are important so that no bias creeps into the results.

Next is that the trial must be conducted on adequate number of subjects, particularly in third phase as shortly will be explained. If a trial is conducted on small number of subjects, the results are not reliable, and it can mean wastage of time and efforts. If you conduct a trial on 5 patients and all of them show improvement, you cannot say that the efficacy is 100%. This can happen by chance in these 5 patients. In next batch of 5 patients, only 3 may show improvement. This reduces efficacy to 60%. Such big difference cannot happen in large samples. If one sample of 300 patients tells you that efficacy is 85%, another trial on 300 patients can only make a difference of 1 or 2%. Statistical formulas are used to calculate the sample size. We will discuss this aspect in the next unit.

Now, you can try the following exercises.

E 8) A) What is the purpose of randomisation?

B) When would you use randomisation and when matching in a clinical trial?

C) Who is blinded in a double blind trial? What are the advantages of blinding?

D) What is the difference between blinding and masking?

E) What is equipoise? Why is this important?

E 9) What is the most common purpose of randomisation?

A. To obviate the need of a placebo group.

B. To guard against ethical considerations.

C. To bypass blinding.

D. To achieve initial equivalence of the groups.

E10) In a double blind trial

A. the patients do not know that they are receiving active treatment or placebo.

B. the assessors do not know which patient has received active treatment and which placebo.

C. both the above.

D. the patients and the statistician do not know the allocation.

E11) A clinical trial must involve

A. randomisation. B. control group.

C. blinding. D. none of the above.

E12) Difference between blinding and masking is

A. no difference.

B. blinding is similar looking regimens.

C. masking is concealment of allocation.

D. none of the above.

E13) True or False. Give your reason for each in one line.

A. A double-blind trial eliminates all chance of bias.

B. All trials are randomised and controlled.

C. Matched controls reduce the cost of the trial.

13.9 PHASES OF A CLINICAL TRIAL

As stated earlier, since clinical trial is an experiment on human beings, great caution is used. Many are listed above. Among the others, these trials are done in phases – first on small number of special subjects and then a higher number and then a full trial on large scale. But before trying on human beings, properties of the regimen are studied in the laboratory by biochemical reactions.

In the context of drug development, an experiment in the laboratory is performed first to develop a compound that has desirable biochemical properties—this is likely to be beneficial in either promotion of health, prevention of sickness, or treatment of disease; and second to establish that these properties are indeed present. This exercise requires enormous inputs of theoretical knowledge about various compositions. Once such a compound is obtained, its properties are investigated. The compound is modified as needed and the drug development starts. A formulation is prepared that could ultimately take the shape of a drug. This formulation is first tried on animals that could somewhat simulate human conditions. Trying a new drug on human subjects without establishing its efficacy and safety in laboratory and animal setups is considered unethical, and is almost never allowed.

The above consists of two stages. At the first stage the molecule is tested in cell lines in the laboratory to see the biochemical reactions. This is also called in vitro viz. outside the living organism. Then at the second stage molecule is tested in animals in the laboratory. Both are called **pre-clinical phases** since they do not involve experiment on human beings. When these phases give successful results, trials on human beings start, again in phases discussed below:

13.9.1 Phase I

The first objective is to see if that regimen can really be given to human beings – that they tolerate this substance and their health does not become bad due to the regimen. In this phase, 10 to 20 volunteers who are willing to try that regimen are included. Some are given low dose and some are given high dose. When this is done, the total number may become 40 or even more. The trial goes on only for a short time. These volunteers may be healthy people. This does not matter since we are not interested to know the efficacy of the regimen in this phase. Sick people, who volunteer, can also be included. This phase tells us whether the regimen is harmful or not, and gives some idea of what range of dose is tolerable. There is no control group in this phase. This phase is not done on a large group since the regimen may turn out to be harmful to human beings.

13.9.2 Phase II

When phase I is successful, we are now prepared to try it on a larger group. Now the subjects are the patients for whom it is meant. If the regimen is for heart patients, this phase is done on heart patients. Somewhere near 100 subjects are given each dose and different types of patients such as children, women and serious cases are also included. The total number of patients can be 300 – 400. Some patients are not given that regimen but are given an inactive substance, called placebo, or some can be given existing therapy. This is called control group as explained earlier. This group gives us a comparison of the drug group with placebo or existing drug. Phase II gives us some idea of the efficacy of the regimen in the target patients and also gives us an idea of more side effects as this phase goes on for a longer time. It goes on for a longer time because some side effects may take time to appear. This is the crucial phase that really establishes that the regimen is useful in human patients. Pharmacological properties of the regimen are also studied in this phase. These properties relate to where the drug goes in the body, how the drug works, how much is retained and how much goes out of the body through urine, etc.

Phase II of a trial is done on patients for whom the test regimen may be eventually indicated. The objectives of this phase are to (a) get initial idea of potential clinical efficacy, (b) assess short-term incidence of side effects, (c) identify a dose schedule for various kinds of cases (such as for mild, moderate, severe, or for children and adults), (d) interaction with other drugs or effect of comorbidities (comorbidities are other simultaneous sicknesses, for example, some drugs for control of blood pressure do not work when kidney is also affected), and (e) collect further pharmacologic data. Phase II also establishes or refutes that the new regimen is likely to meet at least the minimum level of efficacy. If this level is not met, there is no use pursuing the regimen any further. Sometimes it is a randomised trial with a control group on the pattern of a phase III trial.

Phase II can help in learning more about the treatment regimen, and about the type of patients and kind of symptoms for which the treatment is beneficial. An appropriate dose and the appropriate subjects are identified for the phase III trial. Phase II may have to be stopped early if the regimen is found beyond tolerance in patients. Failure of phase II may help to identify the problems with the regimen, which may indicate the need to go back to the basics for improving the formulation.

When interpreting results of a phase II trial, note that the efficacy and toxicity might be interdependent. This means that if you give higher dose, the efficacy would be high since improvement can occur in larger number of subjects but, at the same time, will also cause more harm by increased side-effects. In this phase, comorbidities are generally not excluded because applicability would suffer. Comparison of efficacy and side effects in patients with and without comorbidities will help define the exclusion criteria for phase III trial.

13.9.3 Phase III

After achieving success in phase II, a big trial is done by randomly allocating patients to the regimen and control. Nearly 300 patients in each group are included. Each group could mean 300 children, 300 adults, etc. or it could mean 300 males and 300 females, or it could mean 300 of mild disease, 300 of severe diseases, etc. Generally same number of controls is also included. These are not standard numbers. Phase III studies can involve from several hundred to several thousand subjects because these are performed after preliminary

evidence regarding the effectiveness of the drug has been demonstrated. Phase III is generally a double-blind RCT which has been mentioned earlier. This trial (i) confirms the efficacy obtained earlier in phase II, (ii) gives more information on side effects as some side effects are rare that may not have shown up in phase II where the number of subjects is not so large, (iii) provides the evidence for the regulatory authorities to approve the drug for marketing. Drug regulators do not approve any new drug without successful phase III trial.

You can see that phase III is a large-scale trial with generally 300–1000 subjects recruited for each arm. The follow-up must be sufficiently long for efficacy and side effects to emerge, and to rule out that any relief is transient. Sometimes safety is a major issue, particularly when efficacy is already exceeding 80%. For side effects, a larger sample may be needed than to evaluate efficacy. This phase is expected to provide a full picture of the clinical performance of the treatment under test. Specifically, this can include (a) exact identification of the diagnostic group that responds reasonably well, and comparison of the beneficial and adverse effects with those of the existing treatment, if any; (b) an increase in patient exposure in terms of both the number of patients and the length of follow-up so that less common and late side effects can also be identified; (c) more evidence on possibility of adverse interaction with other treatment regimens with which the new treatment is likely to be prescribed; (d) the ideal dose regimen for different types of patients with regard to age, body weight, severity of disease, etc.; (e) further pharmacological studies; and (f) receptivity to the treatment regimen of communities with different medical cultures. The last objective can be achieved by conducting a multicentric trial. A trial is called **multicentric** when it is done in several centres.

Those patients who may be harmed are excluded from phase III of the trial. For example, a regimen may not be good for pregnant women. This is identified from phase II trial.

13.9.4 Phase IV

These are carried out after a drug has been licensed. In this phase information is collected about side effects, safety and the long term risks and benefits of the drug. Thus the story does not end here. Despite successful results in third phase, some regimens are found useless or harmful when actually used over a long period on large number of patients after it is marketed. Thus vigilance is kept even after the drug is in the market. This is called **post-marketing surveillance** and is considered phase IV of a trial. You may have heard that a particular drug is banned or withdrawn after it is used for several years. This is done on the basis of post-marketing surveillance.

Under post-marketing surveillance, all adverse reactions and other events attributable to regimen are monitored. The effectiveness is also evaluated. Patient preferences are studied.

Comments: Note how these phases help us in keeping the cost and side effects low. If a regimen fails in the early phase, there is no need to spend any more time and money. Drug companies spend millions of rupees to develop a regimen that could help some specific kind of patients.

In some special cases, some of these phases may be skipped. If a drug is already approved and is in the market for a particular disease, it can be tried for another related disease without going through all the phases. Note that this drug has already passed phase I, that is how it is in the market. Since it is already in the market, its safety is also known and efficacy is known for

another disease. **Thus in this case, only phase III trial is needed**. This also need not be as large as is needed for an entirely new regimen.

A brief overview of the key points of different phases of clinical trials is given in Table 13.1.

Table 13.1 Brief Overview of Phases I, II, III, IV of a Clinical Trial

Phase	Key Points
Phase I	• Trial goes on only for a short time and in a small group of people. • To determine a safe dosage range and to identify side effects. • To evaluate safety of the regimen. • Here volunteers (subject) may be healthy people. Sick people, who volunteer, can also be included. • In this phase there is no control group. • Here we are not interested to know the efficacy of the regimen.
Phase II	• Trial goes on for a longer time and in a larger group of people. • To identify a dose schedule for various kinds of cases (such as for mild, moderate, severe, or for children and adults) and to assess short-term incidence of side effects. • Here subjects are patients for whom it is meant. This phase gives us some idea of the efficacy of the regimen in the target patients. • To further evaluate safety of the regimen. • Pharmacological properties of the regimen are also studied.
Phase III	• Drug is given to large groups of people to monitor side effects. • To confirm the efficacy obtained earlier in phase II. • To get more information on side effects as some side effects are rare that may not have shown up in phase II where the number of subjects is not so large. • In this phase we compare the new regimen with the existing drug to see whether the new regimen is more effective than the existing one or not. So here we need a control group. • To provide the evidence for the regulatory authorities to approve the drug for marketing. Drug regulators do not approve any new drug without successful phase III trial.
Phase IV	• Phase IV trials are carried out after a drug has been licensed. In this phase information is collected about side effects, safety and the long term risks and benefits of the drug after it is marketed. • Phase IV trials refer to keep vigilance to monitor for effectiveness and safety even after the drug is in the market and so called **post-marketing surveillance.**

Now, you can try the following exercises.

E14) In this phase we determine a safe dosage range and identify side effects:

A. Phase I B. Phase II C. Phase III D. Phase IV

E15) In this phase of clinical trial we identify a dose schedule for various kinds of cases (such as for mild, moderate, severe, or for children and adults) and assess short-term incidence of side effects.

A. Phase I B. Phase II C. Phase III D. Phase IV

E16) In this phase of clinical trial we confirm the efficacy obtained in earlier phase, and compare the new regimen with the existing drug to see whether the new regimen is more effective than the existing one or not.

A. Phase I B. Phase II C. Phase III D. Phase IV

E17) This phase of clinical trial is carried out after a drug has been licensed. In this phase information is collected about side effects, safety and the long term risks and benefits of the drug after it is marketed.

A. Phase I B. Phase II C. Phase III D. Phase IV

13.10 RANDOM ERROR AND BIAS IN A CLINICAL TRIAL

You have already learnt in Block 1 of MST-005 that samples vary from one another and thus results also vary. If you take a random sample of 12 students and measure their weight, the mean would be different from the mean of another sample of 12 students. Variation is an essential feature of human beings.

13.10.1 Random Error

In case of clinical trials, when you conduct this on 200 subjects and then again another random sample of 200 subjects, the results would vary. One sample can give you efficacy of 74% and another sample can give you efficacy of 77%. This variation would occur even when both trials are done under the same conditions. This is called **random error** as it arises because of the chance that random samples differ from one-another. This variation would occur even when you repeat the trial in same subjects. Trial involves so many steps and variation can occur in each of them. Even for a simple measurement such as weight, when you measure the same person again, the weight may differ because of machine error or because the pressure exerted on the machine is not the same. This may be small but it would most likely be there. This occurs due to chance but remember that chance is the name of those factors which are either unknown or beyond human control. This is the most important lesson from statistics, and do not forget this in your life.

The magnitude of random error depends mostly on the size of the sample included in the trial. As explained earlier, large samples tend to give same result when repeated but small samples do not. Thus random error can be minimised by conducting a large sized trial. It cannot be avoided altogether.

13.10.2 Biases

The results from the clinical trials must be accurate and reliable in order to provide a valid and unbiased assessment of true efficacy and safety of the medication or drug under study. The accuracy and reliability are usually referred to as closeness and the degree of the closeness respectively of the clinical results to the true value regarding the target population. These could be assessed by bias and variability of the primary clinical endpoints or outcome used for clinical assessment of the study drug.

Now, what is bias? Bias occurs due to the known factors which can be avoided.

If your sample happens to have more patients of younger age, the regimen might work well on them but you would not know if it is equally effective in older patients. This bias has occurred because your sample was not fully representative. You can avoid this by choosing a stratified sample so that all age groups are adequately present in the sample. Statistically we measure any deviation from true value known as bias. There are a large number of such factors that can cause bias. Only the important ones are described below. The entire list will be too long for you to remember.

Nonresponse: The inability to get full or partial information from the subject after inclusion in a study is termed nonresponse. This can happen due to the subject becoming uncooperative, change address, become injured so that they no longer wish to be a part of the study, die, or any such reason. The opportunity for nonresponse is particularly present in follow-up studies but even in the case of one-time evaluation, the subject may refuse to answer certain questions or may not agree to submit to a particular investigation or examination even when prior consent has been obtained. Sometimes nonresponse can be as much as 50%.

Nonresponse has two types of adverse impacts on the results. The first is that the ultimate sample size available to draw conclusions reduces, and this affects the reliability of the results. This deficiency can be remedied by increasing the sample size corresponding to the anticipated nonresponse. The second is more serious. Suppose you select a sample of 3000 out of one million. But if only 250 respond out of 3000, your survey could be severely biased. These responders could be those who are favourable or those with strong views. If not biased, a sample of 250 is not too bad to provide a valid estimate or to test a hypothesis in most situations. Mostly the nonresponding subjects are not random segment but are of specific type such as seriously ill cases who do not want to continue in the study, or very mild cases who opt out after feeling better, or some such segment. Their exclusion can severely bias the results. A way out is to take a subsample of the nonrespondents, and undertake intensive efforts for their full participation. Assess how these subsample subjects are different from the regular respondents and adjust the results accordingly. A provision for such extra efforts to get responses from some nonrespondents should be made at the time of planning the study.

Experience suggests that some researchers fail to distinguish between nonresponse and zero value or absence of characteristic. For example, if you ask how many times you were sick during the last one year, zero means no sickness. This is not nonresponse. If the person says he does not remember, this is nonresponse. Take care that this distinction is maintained in the data you are dealing with.

Although there are statistical methods such as imputation for missing values and intention-to-treat analysis that can partially address the problem arising from nonresponse, but no analysis, howsoever immaculate, can replace the actual observation. Thus all efforts should be made to ensure that nonresponse is minimal if not altogether absent. Strategies for this should be devised at the time of planning the study, and all necessary steps should be taken.

Variety of Biases to Guard Against: Medical study results often become questionable because some bias is detected after the results are available. Therefore, it is important that all sources of bias are considered at the

time of planning a study, and all efforts are made to control them.

Various sources of bias are as follows. Some of the biases in this list in fact are collection of many biases of similar type. If all these are stated separately, the list may become unmanageable. These are described in brief here just to give you an idea.

1. **Definition Bias:** The study subjects should be sharply defined so that there is no room for ambiguity. For example, if the cases are of tuberculosis, specify that these would be sputum positive, Mantoux test positive, established by x-ray, or some combination. An unclear definition gives a chance to the assessor to use his own interpretation that can affect the validity of the study.

2. **Bias in Design:** This bias occurs when the case group and control group are not equivalent at baseline, and differentials in factors affecting the results are not properly accounted for at the time of analysis.

3. **Bias in Selection of Subjects:** The subjects included in the study may not truly represent the target population. This can happen either because the sampling was not random, or because the sample size is too small to represent the entire spectrum of subjects in the target population. Studies on volunteers always have this kind of bias. Selection bias can also occur because the serious cases have already died and are not available with the same frequency as the mild cases (**survival bias**).

4. **Bias due to Concomitant Medication or Concurrent Disease:** Selected patients may suffer from other apparently unrelated conditions but their response might differ either because of the condition itself or because of medication given concurrently for that condition.

5. **Bias in Detection of Cases:** Error can occur in diagnostic or screening criteria. For example, a laboratory investigation done properly in a hospital setting is less error prone compared to one carried out in a field setting where the study is actually done. In a prostate cancer detection study, if prostate biopsies are not performed in men with normal results after screening, true sensitivity and specificity of the test cannot be determined.

6. **Lead-Time Bias:** All cases are not detected at the same stage of the disease. With regard to cancers, some may be detected at the time of screening, for example by pap smear, and some may be detected when the patients start complaining. But the follow-up is generally from the time of detection. This difference in “lead time” can cause systematic error in the results.

7. **Bias due to Epistemic Factors:** Efforts can be made to control only those factors that are known. But there may be many factors unknown that can affect the results. These epistemic factors can bias the results in very unpredictable ways.

8. **Contamination in Controls:** Control subjects are generally those that receive placebo or existing therapy. If these subjects are in their homes, it is difficult to know if they have received some other therapy that can affect their status as controls.

9. **Interviewer Bias or Observer Bias:** Interviewer bias occurs when one is able to get better responses from one group of patients (say, those who are educated) relative to the other kind (such as illiterates). Observer bias occurs when the observer unwittingly (or even intentionally) exercises more care about one type of responses or measurements such as those supporting a particular hypothesis than those opposing the hypothesis.

10. **Instrument Bias:** This occurs when the measuring instrument is not properly calibrated. A scale may be biased to give a higher reading than the actual or lower than the actual such as a mercury column of a blood pressure instrument not being empty in the resting position. The other possibility is inadequacy of an instrument to provide a complete picture, for example an endoscope not reaching the site of interest, thereby giving false information.

11. **Hawthorne Effect:** If subjects know that they are being observed or being investigated, their behaviour and response can change. In fact, this is the basis for including a placebo group in a trial. Usual responses of subjects are not the same as when under a scanner.

12. **Recall Bias:** There are two types of recall bias. One such bias arises from better recall of recent events than those that occurred a long time ago. Also, serious illnesses are easier to recall than mild illnesses. The second type of bias arises when cases suffering from a disease are able to recall events much more easily than the controls if they are apparently healthy subjects.

13. **Mid-Course Bias:** Sometimes the subjects after enrollment have to be excluded if they develop an unrelated condition such as an injury, or become so serious that their continuation in the trial is no longer in the interest of the patient. If a new facility such as a health center is started or closed for the population being observed for a study, the response may alter. If two independent trials are going on in the same population, one may contaminate the other. An unexpected intervention such as a disease outbreak can alter the response of those who are not affected.

14. **Self-Improvement Effect:** Many diseases are self-limiting. Improvement over time occurs irrespective of the intervention, and it may be partially or fully unnecessarily ascribed to the intervention. Diseases such as arthritis and asthma have natural periods of remission that may look like the effect of therapy.

15. **Digit Preference:** It is well known that almost all of us have a special love for digits zero and five. Measurements are more frequently recorded ending with these digits. A person aged 69 or 71 is very likely to report one's age as 70 years. Another manifestation of digit preference is in forming intervals for quantitative data. Blood glucose level categories would be 70–79, 80–89, 90–99, etc., and not 64–71, 72–79, etc. If digit zero is preferred, 88, 89, 90, 91, and 92 can be recorded as 90. Thus intervals such as 88–92, 93–97, and 98–102, are better to ameliorate the effect of digit preference, and not the conventional 85–89, 90–94, 95–99, etc.

16. **Bias due to Nonresponse:** As already discussed in detail, some subjects refuse to cooperate, some may suffer an injury, some may die, or become

untraceable. In a prospective study, there might be some dropouts for various reasons. Nonrespondents make two types of effects on the responses. First, they are generally different from those who respond, and their exclusion can lead to biased results. Second, nonresponse reduces the sample size that can decrease the power of the study to detect differences or associations.

17. **Attrition Bias:** The pattern of nonresponse can differ from one group to the other in the sense that in one group more severe cases drop out, whereas in another group mostly mild cases drop out.

18. **Bias in Handling Outliers:** No objective rule is available to label a value as outlier except a guideline that the value must be far away from the mainstream values. If the duration of hospital stay after a particular surgery is mostly between 6 and 10 days, some researchers would call 18 days as outlier and exclude it on the suspicion of being a wrong recording, and some would consider it right and include it in their calculation. Some would not exclude any outlier, however different it might be. Thus the results would vary.

19. **Recording Bias:** Two types of errors can occur in recording. The first arises due to the inability to properly decipher the writing on case sheets. Physicians are notorious for illegible writing. This can happen particularly with similar looking digits such as 1 and 7, and 3 and 5. Thus the entry of data may be in error. The second arises due to the carelessness of the investigator. A diastolic level of 87 can be wrongly recorded as 78, or a code 4 entered as 6 when memory is relied upon, which can fail to recall the correct code. Wrongly pressing adjacent keys on the computer keyboard is not uncommon either.

20. **Bias in Analysis:** This again can be of two types. The first occurs when gearing the analysis to support a particular hypothesis. For example, while comparing pre- and post-values, for example, hemoglobin (Hb) levels before and after weekly supplementation of iron, the increase may be small that will not be detected by comparison of means. But it may be detected when evaluated as a proportion of subjects with levels <10 mg/dl before and after iron supplementation. The second can arise due to differential interpretation of p-values. When $p = 0.055$, one researcher may refuse to say that it is significant at 0.05 level and the other may say that it is marginally significant. Some researchers may change the level of significance from 5% to 10% if the result is to their liking.

21. **Interpretation Bias:** This arises from the tendency among some research workers to interpret the results in favour of a particular hypothesis ignoring the opposite evidence. This can be intentional or unintentional.

22. **Bias in Presentation of Results:** Scales in graphs can be chosen such that a small change looks like a big change or vice versa. The second is that the researcher may merely state the inconvenient findings that contradict the main conclusion but does not highlight them in the same way as the favourable findings are done.

23. **Publication Bias:** Many journals are much too keen to publish reports that give a positive result regarding efficacy of a new regimen compared with the negative trials that did not find any difference. If a vote count is

done on the basis of the published reports, positive results would hugely outnumber than negative results, although the fact may be just the reverse.

13.10.3 Steps for Minimising Bias

The purpose of describing various types of biases in so much detail is to create awareness to avoid or at least minimise them. Everything possible should be done to keep them under control. The following steps can be suggested to minimise bias in the results in a research setup. All steps do not apply to all the situations. Adopt the ones that apply to your setup. Details of some of these steps are in subsequent units.

1. Develop an unbiased scientific temperament by realising that you really want to search for the truth.
2. Specify the trial in full detail.
3. Assess the validity of the identified target population, and the groups to be included in the study in the context of objectives and the methodology.
4. Assess the validity of pre-existing factors and outcomes for providing correct answer to your questions. In addition, there might be other factors at work about which nobody knows. Medical science is still very incomplete and we do not know about many factors that affect health and disease.
5. Carry out a pilot study and pretest the tools such as questionnaire and laboratory kits. Make changes as needed.
6. Choose a representative sample, preferably by a random method.
7. Choose an adequate size of sample in each group.
8. Researchers and coworkers should be trained in making correct assessments.
9. Use matching, blinding, masking, and random allocation as needed.
10. Monitor each stage of research, including periodic checking of data.
11. Make determined efforts to minimise nonresponse and partial response.
12. Double check the data and rectify errors in recording, entries, etc.
13. Analyse the data with proper statistical methods. Use standardised or adjusted rates where needed, perform the stratified analysis, or use mathematical models such as regression to take care of those confounders that could not be ruled out by design.
14. Interpret the results in an objective manner based on evidence.
15. Report only the evidence-based results, enthusiastically but dispassionately.

16. Exercise extreme care in drafting the report and keep comments or opinions separate from evidence-based results.

Now, you can try the following exercise.

E 18) List three biases of your choice and state what you would do to avoid those biases.

13.11 SUMMARY

Let us summarise the main points discussed in this unit.

1) **Clinical trials** are experiments on human beings conducted in a scientific manner where a potential beneficial regimen is assessed for its efficacy and safety by actually using it in a group of people.

2) **Randomisation** means that all available eligible subjects are randomly allocated into two groups – one group receives test regimen and the other control regimen. In **single-blinding**, patients are not told that they are receiving test regimen or control regimen so that they do not change their response. In **double-blinding**, the doctor or the nurse who is assessing the patient is also not told so that they do not give biased assessment. In **triple-blind**, the statistician is also not told.

3) Clinical trials are done in phases. **Phase I** is on volunteers just to check that humans can tolerate the regimen. Tolerable dose is identified. **Phase II** is done on patients on whom the drug is supposed to be effective. This phase also gives an idea of efficacy. If efficacy is lower than anticipated, the trial is discontinued. **Phase III** is mostly double blind Randomised Controlled Trials popularly known as RCT on a big sample. This establishes efficacy and safety of the regimen, and steps can be taken to get approval for selling the drug in the market.

4) **Random error** can be large in trials of small size that is the results would not be reliable. Bias can occur due to nonresponse and a large number of other factors. All these must be taken care of for the trial to provide believable results.

13.12 SOLUTIONS/ANSWERS

E 1) (i) Regimen for group I – Yoga and simple diet, regimen for group II – 50 mg tablet once a day.

(ii) Efficacy in group I – 60%, efficacy in Group II – 70%.

(iii) Group I – no safety issue, group II – vomiting in some cases.

E 2) Answer is not unique it may vary family to family and friend to friend. One sample answer is given as follows:

Example of a regimen that can be tested for curing the disease is a trial for a new drug for treating diabetes.

One example for preventing a disease may be a trial on a prophylactic drug such as aspirin to reduce heart ailments in people of age 50 years or more. These people do not actually have disease but are prone to disease in future if such preventive action is not taken.

RT-PCR test for COVID-19 is one example of a regimen for screening a disease (infection of COVID-19).

Finally, the vaccine Covishield is an example of a regimen for the disease (Infection of COVID-19) that requires vaccine.

E 3) There are many regimens for which a clinical trial is essential. Two of them are listed below:

(i) A clinical trial is essential for putting a new drug, say for 'inducing sleep' into practice because there are many issues related to a new drug about which one has to take care of such as:

- Is it effective on the subjects of target group?
- What are its side-effects?
- What is the percentage of patients on which it is effective?, etc.

(ii) A clinical trial is essential for a new treatment, say for kidney diseases, because before putting a new treatment into practice, it is necessary to find:

- Does it really work in kidney patients?
- Is it effective in severe cases or not?
- What are its side-effects?, etc.

One regimen for which a clinical trial is desirable but not essential is given below:

Those types of regimens that are not harmful but gains from them are doubtful comes under this category such as: dietary changes or physical exercise.

Two regimens for which clinical trials cannot be conducted are given below:

(i) We should not intentionally expose some people to pollution to see the kind of harm it does, because our subjects are human beings and we know in advance that pollution is harmful to health.

(ii) We should not conduct an experiment such as "give dirty water to drink to the human being" to see the adverse effect on human being because we know in advance that it is harmful to one's health.

E4) Answer is B. Because control group helps to ascribe the outcome differentials to the test regimen – thus helps in controlling the uncertainties in the result. Other options are not valid for control group.

E5) Answer is A. As placebo is no treatment and simulates equivalent psychological conditions that help in proper comparison.

E6) Answer is D. Since control can be any of the first three depending upon the objective of the trial.

E7) a) False. An active control is generally an existing treatment but it may or may not be sufficiently effective.

b) False. A control can be an existing active treatment.

E8) **A)** The primary purpose of randomisation is to divide the subjects in to two equivalent groups before the trial is started. This may not work well when the group sizes are small. Randomisation tends to equalize not only the known factors but also unknown factors. The other purpose of randomisation is to provide statistical basis for using statistical methods because statistical methods require some element of randomness.

B) Randomisation is preferred when the group sizes are large. Matching serves better when the group sizes are small. However matching can be done only for small number of factors.

C) In a double blinded trial, firstly, the subjects (participants) are blinded so that they do not know that they are receiving the new regimen or the control regimen. This helps in eliminating the biased response from the participants. If the subjects know that they are receiving the control such as placebo, they may react differently than if they do not know what they are getting.

Secondly, the persons who are assessing the participants are blinded so that their assessment is fair. If they know that the subjects they are assessing have received new regimen than their assessment can be different than if they know that the subject has received placebo or existing regimen.

D) Blinding applies to the persons, namely the subjects and the assessors. They are not told who is receiving which regimen. Masking applies to the regimen itself – to the drug or procedure or whatever is under trial. The test and the control regimen must be indistinguishable – they must look alike, packaged alike, taste alike, etc. Also at the same time, things like diet, transfer from one ward to the other, laboratory investigations should also be alike so that nobody can figure out who is getting test regimen and who is getting control regimen.

E) **Clinical Equipoise:** If doctors are really uncertain that the regimen is effective or not and safe or not, or that it is better than existing regimen or not. This is called clinical equipoise.

Patient Equipoise: If patients are uncertain about the outcome only then they will give correct results. This is called patient equipoise.

E9) Answer is D. Randomisation increases the likelihood of equivalence of groups at the time of start of the trial so that any effect can be properly ascribed.

E10) Answer is C. 'Double' blind means that neither the patient nor the assessor knows the allocation. If statistician is also to be blind, this becomes triple blind.

E11) Answer is D. Randomisation, control group and blinding are desirable but not necessary.

E12) Answer is D. Blinding is for allocation of the subjects and masking is for apparent similarity of the regimens. Without masking, blinding is not effective.

E13) a) False. Double-blinding reduces specific biases in assessment but other biases such as in allocation can still creep in.

b) False. Nonrandomised and uncontrolled trials are also done.

c) False. Finding matched control means looking for the right person and this can increase the cost because many persons will be investigated to find the right matching.

E14) Correct answer is A refer the key points listed out in Table 13.1.

E15) Correct answer is B refer the key points listed out in Table 13.1.

E16) Correct answer is C refer the key points listed out in Table 13.1.

E17) Correct answer is D refer the key points listed out in Table 13.1.

E18) The list of three common bias while conducting the clinical trials are given below:

1. Bias in selection of patients
2. Bias in definition of cases
3. Instrument Bias

The selection bias could be removed by randomisation and blinding. Clear cut definition may be set in the protocol to avoid bias in definition. All the exclusion and inclusion criteria may be defined according to the type of cases required in the trial. One should validate the instrument prior to the actual recruitment of subject by conducted pretesting of the instrument on normal subjects. If needed corrections may be made.

13.13 SUGGESTED FURTHER READING

If you have understood all that is explained above, there is no need to study any other book. This material is enough to give you enough learning of this Unit. If something is not clear, or if you want to know more, you may consult the following:

Indrayan A., Basic Methods of Medical Research, Publisher AITBS, Delhi. Third Edition, (2012).

Chow Shein-Chung and Liu Jen-pei, Design and Analysis of Clinical Trials-Concepts and Methodologies, Publisher John Wiley & Sons, Inc., (1998).