CHAPTER I

INTRODUCTION

1.1 CLINICAL TRIALS

In health care a clinical trial is a comparison test of medication or other medical treatment such as a machine versus placebo (the standard medical treatment for a patient’s condition). Clinical trials vary greatly in size from a single researcher in one hospital to a multi-centered international study funded by a pharmaceutical company with over 100 participating hospitals on several continents. The number of patients to be tested can range from less than 50-1000’s. During the clinical trial the researcher recruit patients with the predetermined characteristics to participate, administer the treatment, and collect data on the patient’s health for a defined time period. The data include things like science, amount of study drug in the blood and whether the patient’s health gets better or not. The researchers sent the data to the trial sponsor, who then analyses the pooled data using statistical tests.

A clinical trial may be designed to

Assess the safety and effectiveness of a new medication or device on a specific kind of patient.

Assess the safety and effectiveness of a different dose of a medication than is commonly used.

Assess the safety and effectiveness of an approved medication or device on a new kind of patient.
Assess whether the new medication or device is more effective for the patient’s condition than the already used standard medication or device.

Compare the effectiveness in patients with a specific disease of two or more already approved interventions for that disease.

Types of studies

Clinical trials can be divided into observational and interventional studies.

Observational studies

Individuals are observed and the investigators measure their outcomes. The researchers do not actively manage the experiment and they merely observe the effects of preexisting factors on the individuals.

Interventional studies

The research subjects are given a particular medicine or other intervention and the researchers measure how their health changes. The US-NIH organizes trials into five different types. They are treatment trial, prevention trial, diagnostic trial, screening trial and quality of life.

1.2 PHASES OF TRAILS

For pharmaceuticals clinical trials are commonly classified into four phases. For new drugs, the drug development process will normally proceed through all four stages over many years. If the drug successfully passes through the phase I, II and III, it will usually be approved for use in general population. Phase IV are post approval?
studies. Before pharmaceutical companies start clinical trials on a drug they conduct extensive pre-clinical studies.

Phase 0

This is a recent designation for exploratory first in human trials conducted in accordance with US FDA 2006 guidance on exploratory investigational new drug studies.

Phase I

These are first stage of testing in human subjects and normally a small (20-100) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of a medication.

Phase II

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (200-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients.

Phase III

These studies are randomized controlled trials on a large patients groups (300-3000 or more depending upon the disease, medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current gold standard? treatment. Once a drug has proven satisfactory after Phase III trials the trial results are usually combined into a large document containing a comprehensive description of the methods and
results of human and animal studies, manufacturing processes, formulation details and shelf life. This collection of information makes up the regulatory submission that is provided for review to various regulatory authorities in different countries so they may then grant the sponsor approval to market the drug.

**Phase IV**

It involves the post launch surveillance and ongoing technical support of a drug which is designed to detect any rare or long-term adverse effects over a larger patient population and time scale than possible during the initial clinical trial and such adverse effects are detected by Phase IV trials.

### 1.3 RANDOMIZED CONTROLLED CLINICAL TRIAL

An important advance in clinical research is the acceptance of the Randomized Clinical Trial (RCT) as the optimal study design. The RCT is a type of research design for comparing different treatments, in which the assignment of treatments to patients is done by some random mechanism. The process of assigning treatments to patients is called randomization. Randomization means the type of patients assigned to different treatment modalities will be similar if the sample sizes are large. The purpose of this section is to describe the place of RCTs within the practice of Evidence-based Medicine (EBM) summarizes the methods by which such trials were located. It is generally accepted that results from well-designed RCTs are the gold-standard for directing clinical decision making. The RCTs are
the most appropriate trial methodology for the investigation of causal relationships between therapy and clinical effects because of a low potential for systematic bias. Randomization is properly concealed and blinded methodology it also eliminates systematic bias by removing all factors other than vagaries of chance in determining the arm of a study of any individual subject will be allocated. Avoiding the misinterpretation of random events to clinically meaningful interpretation is the realm of statistical analysis and appropriate empowerment of well-designed trials.

The aim of Randomized Controlled Trial (RCT) is to evaluate the safety and efficacy of a new intervention such as new drops, new surgical procedures or new healthcare delivery method the intervention must be conducted randomly. Randomization is defined as a selection or assignment process in which there is any relation with every legitimate outcome of a known probability?. This will prevent the patient passing on his task to the next patient thus provide a baseline comparison with the study groups. The intervention should be standardized and stabilized throughout the trial, the side effects should be minimized, the route of administration should be easy and it has the real-life practicality. Group assignment is very important. Trial group should receive the new medication or intervention, the control group should be granted standard medication, placebo or no treatment as according to the nature of the trial. Standard procedure or no procedure should be considered in the control group if your choice for trial is intervention.
In RCT you need to look out for bias which is a systematic error and it has four types namely selection, performance, attrition and detection. Bias can be prevented by randomization, allocational concealment, and centralization, forming your own number for each patient, blinding-preferably double a good staff communication and establishing a new protocol with everyone’s full compliance.

Block randomization is defined as a clinical trial paring two treatments (Treatment A and B). Block size of $2n$ is determined in advance where for every $2n$ patients entering the study, $n$ patients are randomly assigned to treatment B. A similar approach can be used in clinical trials with more than 2 treatment groups. For example if there are $k$ treatment groups then the block size might be $kn$ where for every $kn$ patients, $n$ patients are randomly assigned to the first treatment, $n$ patients are randomly assigned to the second treatment and so on and $n^{th}$ patients are randomly assigned to the $k^{th}$ treatment.

In some clinical studies patients are subdivided into bgroups or strata according to characteristics thought important for patient outcome. Separate randomization lists are maintained for each stratum and this procedure is called stratification. Either random selection (ordinary randomization) or random assignment (Block randomization) might be used for each stratum. Typical characteristics used to define strata are age, sex, or overall clinical condition of the patient. A clinical trial is called double blind if neither the physician nor the patient knows what treatment he or she is getting. A clinical trial is called single blind if the patient is blinded
as to treatment assignment but the physician is not. A clinical trial is unblended if both the physician and patient are aware the treatment assignment.

1.4 TUBERCULOSIS

Of all the infectious diseases that have plagued man, tuberculosis has probably been responsible for the greatest morbidity and mortality. It has apparently plagued man ever since human beings emerged as a species on this planet. Its depredations, especially over the last several 100 yrs have earned it the epithet, ?The captain of all the men of death?.

Tuberculosis (TB) is an infectious disease caused by bacillus called *Mycobacterium tuberculosis* that most commonly affects the lungs but also can involve almost any organ of the body. Many years ago, this disease used to be called ?consumption? because without effective treatment, these patients often would waste away. Today, of course tuberculosis usually can be treated successfully with antibiotics.

TB, one of the major public health problems in the developing countries of the world today, has made its impact felt throughout the ages. No other disease has so much sociological, economic and health significance as TB has. From the various skulls and bones, which have been recovered from different parts of the worlds, TB was found to be evident in Neolithic man. Images of hunchbacks had been left by ancient civilizations. The Egyptians of antiquity made engravings and paintings on stone and recorded some descriptions of c...
Their mummified bodies have given definite evidence of TB of bones and joints. In a mummy of 21st dynasty of Egypt, Potts’ disease was established. TB was evident in mummies indicated that s early as 5000BC, man suffered from it. Babylonian scriptures also described TB’s evidence. In Chinese literature ?La oping?, a disease of lung that fits in with TB conditions in its symptoms was mentioned.

In Rig-Veda, which is dated as about 2000BC, a hymn is consecrated to the cure of ?Yakshma? which very much conforms to the present descriptions of consumption or TB? Susrutha described the disease and observed that it was difficult to cure. In ancient Greece and Macedonia TB was referred in some books. Hi (460-377BC) also devoted part of his attention to TB. the famous library of ?Leipzig? there is a fold, which contains information that Jesus suffered from this condition.

When the inhaled tuberculosis bacteria enter the lungs, they can multiply and cause a local lung infection (pneumonia). The local lymph nodes associated with the lungs may also become involved with the infection and usually become enlarge. The hilar lymph nodes (the lymph nodes adjacent to the heart in the central part of the chest) are often involved.

In addition, TB can spread to other parts of the body. The body’s immune (defense) system, however, can fight off the infection and stop the bacteria from spreading. The immune system does so ultimately by forming scar tissue around the TB bacteria and isolating it from the rest of the body. Tuberculosis that occurs after initial exposure to
the bacteria is often referred to as primary TB. If the body is able to form scar tissue (fibrosis) around the TB bacteria, then the infection is contained in an inactive state. Such an individual typically has no symptoms and cannot spread TB to other people. The scar tissue and lymph nodes may eventually harden, like stone, due to the process of calcification of the scars (deposition of calcium from the bloodstream in the scar tissue). These scars often appear on X-rays and imaging studies like round marbles and are referred to as a granuloma. If these scars do not show any evidence of calcium on -ray, they can be difficult to distinguish from cancer.

Sometimes, however, the body's immune system becomes weakened, and the TB bacteria break through the scar tissue and can cause active disease, referred to as reactivation tuberculosis or secondary TB. For example, the immune system can be weakened by old age, the development of another infection or a cancer or certain medications such as cortisone, anticancer drugs, or certain medications used to treat arthritis or inflammatory bowel disease. The breakthrough of bacteria can result in a recurrence of the pneumonia and a spread of TB to other locations in the body. The kidneys, bone, and lining of the brain and spinal (meninges) are the most common sites affected by the spread of TB beyond the lungs.

Over eight million new cases of TB occur each year worldwide. In the United States, it is estimated that 10-15 million people are
infected with the TB bacteria and 22,000 new cases of occur each year.

Anyone can get TB, but certain people are at higher risk, including

people who live with individuals who have an active TB infection

poor or homeless people

foreign-born people from countries that have a high prevalence of TB, nursing-home residents and prison inmates

alcoholics and intravenous drug users

people with diabetes, certain cancers, and HIV infection (the AIDS virus)

Health-care workers

There is no strong evidence for a genetically determined (inherited) susceptibility for TB.

**Symptoms of Tuberculosis**

As previously mentioned, TB infection usually occurs initially in the upper part (lobe) of the lungs. The body's immune system, however, can stop the bacteria from continuing to reproduce. Thus, the immune system can make the lung infection inactive (dormant). On the other hand, if the body's immune system cannot contain the TB bacteria, the bacteria will reproduce (reactivate) in the lungs and spread elsewhere in the body.

TB can be diagnosed in several different ways, including chest X-rays, analysis of sputum, and skin tests. Sometimes, the chest
X-rays can reveal evidence of active tuberculosis pneumonia. Other times, the X-rays may show scarring (fibrosis) or hardening (calcification) in the lungs, suggesting that the TB is contained and inactive. Examination of the sputum on a slide (smear) under the microscope can show the presence of the tuberculosis-like bacteria. Bacteria of the *Mycobacterium* family, including a typical mycobacteria, stain positive with special dyes and are referred to as Acid-Fast Bacteria (AFB). A sample of the sputum also is usually taken and grown (cultured) in special incubators so that the tuberculosis bacteria can subsequently be identified as tuberculosis or atypical tuberculosis.

Several types of skin tests are used to screen for TB infection. These so-called tuberculin skin tests include the Tine test and the Mantoux test, also known as the PPD (Purified Protein derivative) test. In each of these tests, a small amount of purified extract from dead tuberculosis bacteria is injected under the skin. If a person is not infected with TB, then no reaction will occur at the site of the injection (a negative skin test). If a person is infected with tuberculosis, however, a raised and reddened area will occur around the site of the test injection. This reaction, a positive skin test, occurs about 48-72 hours after the injection. When only the skin test is positive, or evidence of prior TB is present on chest X-rays, the disease is referred to as "latent tuberculosis." This contrasts with active TB as described above, under symptoms.
Vaccine against Tuberculosis

Bacille Calmette Guerin, also known as BCG, is a vaccine given throughout many parts of the world. It is derived from a typical *Mycobacterium* but offers some protection from developing active tuberculosis, especially in infants and children. This vaccination is believed to be important in parts of the world where TB is quite common. This is not the case in the United States. When BCG has been administered, future PPD and Tine skin tests remain positive and can cause some confusion when trying to diagnose TB. It is also important to realize that even with a BCG vaccine in childhood, tuberculosis can still occur in an adult exposed to the tuberculosis bacteria, which calls into question the real utility and effectiveness of this vaccination.

A new blood test is now available that can help distinguish between a prior BCG vaccine and a positive PPD due to B infection. This test involves mixing the patient’s blood with substances that produce a TB-like immune response. After a period of time, the immune cells, if infected with TB, produce interferon-gamma, a protein produced by the body to defend against an infection. This test, like most, is not perfect, but with the proper clinical information can help distinguish a real TB infection from a positive reaction on the test due to a prior BCG vaccine.

Treatment against Tuberculosis

A person with a positive skin test, a normal chest X ray, and no symptoms most likely has only a few TB germs in an inactive state
and is not contagious. Nevertheless, treatment with an antibiotic may be recommended for this person to prevent the TB from turning into an active infection. The antibiotic used for this purpose is called isoniazid (INH). If taken for six to 12 months, it will prevent the TB from becoming active in the future. In fact, if a person with a positive skin test does not take INH, there is a 5%-10% lifelong risk that the TB will become active.

Taking isoniazid can be inadvisable (contraindicated) for those suffering from alcoholism or liver disease. Also, isoniazid can have side effects. The side effect occur infrequently, but a rash can develop, and the individual can feel tired or irritable. Liver damage from isoniazid is a rare occurrence and typically reverses once the drug is stopped. Very rarely, however, especially in older people, the liver damage (INH hepatitis) can even be fatal. It is important therefore, for the doctor to monitor a patient's liver by periodically ordering blood tests called "liver function tests" during the course of INH therapy. Another side effect of INH is a decreased sensation in the extremities referred to as peripheral neuropathy. This can be avoided by taking vitamin B6 (pyridoxine), and this is often prescribed along with INH.

A person with a positive skin test along with an abnormal chest X-ray and sputum evidencing TB bacteria has active TB and is contagious. As already mentioned, active TB usually is accompanied by symptoms, such as a cough, fever, weight loss, and
Active TB is treated with a combination of medications along with Isoniazid. Rifampin (Rifadin), Ethambutol (Myambutol) and Pyrazinamide are the drugs commonly used to treat active TB in conjunction with Isoniazid (INH). Four drugs are often taken for the first two months of therapy to help kill any potentially resistant strains of bacteria. Then the number is usually reduced to two drugs for the remainder of the treatment based on drug sensitivity testing that is usually available by this time in the course. Reptomycin, a drug that is given by injection, may be used as well, particularly when the disease is extensive and/or the patients do not take their oral medications reliably (termed "poor compliance"). Treatment usually lasts for many months and sometimes for years. Success of treatment of TB is dependent largely on the compliance of the patient. Indeed, the failure of a patient to take the medications as prescribed is the most important cause of failure to cure the TB infection. In some locations, the health department demands direct monitoring of patient compliance with therapy. Surgery on the lungs may be indicated to help cure TB when medication has failed, but in this day and age, surgery for TB is unusual. Treatment with appropriate antibiotics will usually cure the TB. Without treatment, however, tuberculosis can be a lethal infection. Therefore, early diagnosis is important. Those individuals who have been exposed to a person with TB, or suspect that they have been, should be examined by a doctor for signs of TB and screened with a TB skin test.
Drug-resistant TB

Drug-resistant TB (TB that does not respond to drug treatment) has become a very serious problem in recent years in certain populations. For example, INH-resistant TB is seen among patients from Southeast Asia. The presence of INH-like substances in the cough syrups in that part of the world may play a role in causing the INH resistance. Drug-resistant cases are also often seen in prison populations. However, the major reason for the development of resistance is poorly managed TB care. This can result in poor patient compliance, inappropriate dosing or prescribin of medication, poorly formulated medications, and/or an inadequate supply of medication. Multidrug-Resistant Tuberculosis (MDR-TB) has emerged. More recently, Extensively (extremely) Drug Resistant Tuberculosis (XDR-TB) has emerged. These bacteria are resistant to three or more of the second-line treatment drugs.

XDR-TB is seen throughout the world but is most frequently seen in the countries of the former Soviet Union and Africa. Preventing XDR-TB from spreading is essential. The World Health Organization (WHO) recommends improving basic TB care to prevent emergence of resistance and the development of proper laboratories for detection of resistant cases. When drug-resistant cases are found, appropriate treatment is required. This will prevent further transmission. Collaboration of HIV and TB care will help limit the spread of tuberculosis, both sensitive and resistant strains.
Conceivably, TB could have been eliminated by effective
treatment, vaccinations, and public-health measures by the year
2000. However, the emergence of HIV changed the whole
Because of HIV, a tremendous increase in the frequency (incidence) of
TB occurred in the '80s and throughout the '90s. This increase in TB
happened because suppression of the body's immune (defense) system
by HIV allowed TB to occur as a so-called opportunistic
With the increasing HIV epidemic in Africa, serious concerns are being
raised about the development of MDR-TB and XDR-TB in this
population. Hopefully, control of HIV in the future will check this
resurgence of tuberculosis.

1.5 SURVIVAL ANALYSIS

Enormous progress has been achieved in the development of the
science of clinical trials during the 20th century. In this progress,
methods have been developed, implemented, and refined that enable
the reliable, efficient, and ethical evaluation of the benefits and risks
of interventions that target the treatment and prevention of human
diseases. One of the most important components of this development
has been the formulation of censored data survival analysis methods.
The primary outcome measure in a clinical trial design to provide a
reliable assessment of benefit and risk often is defined to be the time
to occurrence of a clinically important event, such as death, detection
or progression of a disease, or occurrence of a clinically significant
morbid event such as a serious infection, stroke, or major organ
failure. The methodological developments in this field were largely
achieved in the latter half of the 20th century and in turn have had an enormous impact on the science of clinical trials. The field of survival analysis is very rich.

Survival data is a term used for describing data that measure the time to a certain event. In survival analysis, the event may be death, occurrence of disease, time it takes for a patient to respond to a therapy, or time from response until disease relapse (i.e., disease returns). It is necessary to define the starting time, say 0, from which times are measured. The problem of analyzing time to event data arises in a number of applied fields, such as medicine, biology, public health, epidemiology, engineering, economics, and demography. Although the statistical tools applicable to all these disciplines, our focus is on applying the statistical tools to biology and medicine.

Censoring distinguishes survival analysis from other classical statistical methods. In medical research, the event of interest is usually the time to death of a patient after the diagnosis but it might be the time to recovery or remission as well. Depending on the direction of the censoring, censored data can be classified into right observed when the survival time exceeds the observed one, and left censored when the survival time is less than the observed one. Left censoring is particularly important in studies on infectious diseases such as hepatitis or HIV. In the realm of right censored data, a distinction can be made among three different types of censoring.
Type I Censoring: (Fixed Time)

Let $T_1, T_2, \ldots, T_n$ are $n$ independent and identically distributed life times and $t_c$ the fixed censoring time. As an alternative of observing $T_1, T_2, \ldots, T_n$ the random variables of interest to observe that

$$T_i = \begin{cases} T_i & \text{if } T_i < t_c \\ t_c & \text{if } T_i \geq t_c \end{cases}$$

Type II Censoring: (Fixed number Censoring)

Let $r < n$ are fixed, observe $t_1, t_2, \ldots, t_r$, where $r$ is specified in advance. The test ends at time $T=t_r$ and $(n-r)$ units have survived. Again it is possible to observe the exact time of failure for failed units and $T_1, T_2, \ldots, T_n$ are iid observations. Type II censoring has the significant advantage that you know in advance how many failure times your test will yield—this helps enormously when adequate tests. However, an open-ended random test time is generally impractical from a management point of view and this type of testing is rarely seen. It is a useful technique for economical use of first in industrial life testing.

Random Censoring

The subjects enter the study at different times and different time points. Some individuals fail and some individual lost-to-follow-up, some individual still alive at the end of the study and their exact survival times are unknown.

Right and Left Censoring

Right censoring which is more common form occurs when the exact survival time is not known. All that is known when the exact
survival time exceeds the recorded value. This occurs there is a
defined time (t=0) where the observation of time is st d for all
subjects involved in the study. A right censored subject?s time would
be terminated before the outcome of interest is observed.

Left censoring is not common in clinical trial and an observation
is left censored if the event of interest has already occurred when
observation of time begins. In other terminology left censored data can
occur when a subject?s survival time is incomplete at the beginning of
the follow-up period.

Interval Censoring

An observation is said to be interval censored if it is known only
that the observation is in the interval (C_i, C_j). Interval censoring is still
another type of censoring for which life time is known only to fall into
an interval.

Truncation

Truncation objects can be detected only if their value is greater
than some number and the value is completely known in the case of
detection or only part of the population is observed. The observable
subset is defined by the value of X and the fraction unobserved is
unknown.

Survival Function

The object of primary interest is the survival function
conventionally denoted S, which is defined as

\[ S(t) = \Pr(T > t) \]
where \( t \) is some time, \( T \) is a random variable denoting time of death, and "Pr" stands for probability. That is, the survival function is the probability that the time of death is later than some specified time \( t \). The survival function is also called as survivor function or survivorship function in problems of biological survival and the reliability function in mechanical survival problems. In the latter case, the reliability function is denoted \( R(t) \).

Usually one assumes \( S(0) = 1 \), although it could be less than 1 if there is the possibility of immediate death or failure.

The survival function must be non-increasing: \( S(u) \geq S(t) \) if \( u \geq t \). This property follows directly from \( F(t) = 1 - S(t) \) being the integral of a non-negative function. This reflects the notion that survival to a later age is only possible if all younger ages are attained. Given this property, the lifetime distribution function and event density (\( F \) and \( f \) below) are well defined.

The survival function is usually assumed to approach zero as age increases without bound, i.e., \( S(t) \to 0 \) as \( t \to \infty \), although the limit could be greater than zero if eternal life is possible. For instance, we could apply survival analysis to a mixture of stable and unstable carbon isotopes; unstable isotopes would decay sooner and later, but the stable isotopes would last indefinitely.

1.6 DATA BASE

The National Institute for Research in Tuberculosis, a permanent establishment under the Indian Council of Medical Research (ICMR), is an internationally recognized institution in
Tuberculosis (TB) research. It is a Supranational Reference Laboratory and WHO Collaborating Centre for TB Research and Training. It is also an Internationally Certified Institute for Excellence in Research (ICER). The Tuberculosis Chemotherapy Centre (now designated as the Tuberculosis Research Centre) was established at Madras in 1956 as a 5-year project, under the joint auspices of the Indian Council of Medical Research (ICMR), the Government of Tamil Nadu, the World Health Organization (WHO) and the British Medical Research Council (BMRC). The purpose of the centre was to advise on studies designed to provide information on the mass domiciliary application of chemotherapy in the treatment of pulmonary tuberculosis.

In the last 50 years at NIRT, more than 1,00,000 TB patients have been screened and 15,000 patients have been enrolled to various ongoing clinical trials. The first controlled clinical trial, which established unequivocally the value of out-patient treatment for pulmonary tuberculosis, has received world-wide acclaim as the classic “Madras Study”. Later, the Centre evolved supervised intermittent chemotherapy as an alternative system of treatment, especially for urban areas and large cities. Recently, treatment for approximately 6-months with powerful drugs has been shown to be equally effective. The Centre is undertaking a series of trials to evaluate the efficacy of such short course regimens under Indian conditions.

So far, 35 Randomized Controlled Clinical Trials for treatment of both Pulmonary and Extra-pulmonary TB (including TB spine, TB
meningitis, TB lymphadenitis) have been done at NIRT in collaboration with various medical college hospitals and non-profitable organizations in Madras city. These studies are broad-based and go beyond the confines of chemotherapy to include epidemiological, bacteriological, biochemical and immunological investigations.