Chapter 1
Clinical Trials: Historical Aspects and Importance and New Drug Developments

1.1 Introduction

A clinical study is conducted for researches in human volunteers (also called participants) to achieve medical knowledge. Clinical studies can be done as clinical trials (interventional studies) or observational studies [1].

1.2 Clinical Trials

Clinical trials are performed for specific interventions according to the research plan. These trials are continued for 'medical products, such as drugs or devices; procedures; or changes to participants' behavior, such as dietary changes'. They compare medically the standard methods with placebo. Safety and efficacy are also investigated [1].

In an observational study, investigators can reach health data of the participants. Investigators may observe different groups of subjects [1].

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Who Conducts Clinical Studies?

Clinical studies are conducted by a principal investigator who is mainly a medical physician. A research team of 'physicians, nurses, social workers, and other health care professionals' are also worked for these studies [1].

Clinical studies can be sponsored, or funded, by 'pharmaceutical companies, academic medical centers, voluntary groups, and other organizations in addition to Federal agencies such as the National Institutes of Health, the U.S. Department of Defense, and the U.S. Department of Veterans Affairs'. Physicians and other individuals can also sponsor clinical research [1].

Clinical studies may be conducted in 'hospitals, universities, physicians' offices, and community clinics' [1]. The length of the study varies and participants should be given information for the study duration [1].

1.2.1 Why Are Clinical Studies Conducted?

- 'Evaluating one or more interventions (i.e., drugs, medical devices, approaches to surgery or radiation therapy) for treating a disease, syndrome, or condition'
- 'Finding ways to prevent the initial development or recurrence of a disease or condition including medicines, vaccines, or lifestyle changes, among other approaches'
- 'Evaluating one or more interventions aimed at identifying or diagnosing a particular disease or condition'
- 'Examining methods for identifying a condition or the risk factors for that condition'
- 'Exploring and measuring ways to improve the comfort and quality of life through supportive care for people with a chronic illness' [1]

1.2.2 Participating in Clinical Studies

There is a protocol of the research and it contains the information below:

- 'The reason for conducting the study'
- 'Who may participate in the study (the eligibility criteria)'
- 'The number of participants needed'
- 'The schedule of tests, procedures, or drugs and their dosages'
- 'The length of the study'
- 'The data related to the participants' [1]

For participation to the clinical studies, there are criteria called as eligibility.

Clinical studies have standards outlining who can participate, called eligibility criteria or inclusion criteria [1]. These are 'age, sex, the type and stage of a disease, previous treatment history, and other medical conditions' [1].

1.2.3 How Are Participants Protected?

An informed consent is signed by the participants. It gives information to the potential and enrolled participants. Signing this, the participants accept to enrol the study. It gives information for the risks and for potential benefits of the study [1].

Institutional review boards

Each clinical study and biological product or medical device must be 'reviewed, approved, and monitored by an institutional review board (IRB)'. An IRB is formed by 'physicians, researchers, and members of the community'. Its role is 'to ensure that the study is conducted ethically and that the rights and welfare of participants are preserved' [1].

Considerations for Participation

To participate the clinical study, medical knowledge should be given for 'the benefits and risks of therapeutic, preventative, or diagnostic products or interventions' [1].

Clinical trials are conducted for 'development and marketing of novel drugs, biological products, and medical devices' [1].

1.3 Historical Aspects of Clinical Trials

'The evolution of clinical research has a long and fascinating journey. The recorded history of clinical trials goes back to the biblical descriptions in 500 BC. It moves from dietary therapy – legumes and lemons – to drugs. After basic approach of clinical trial was described in 18th century, the efforts were made to refine the design and statistical aspects. These were followed by changes in regulatory and ethics milieu. This article highlights the major milestones in the evolution of clinical trials [2]'.

The first reference to a clinical trial can be found in the Bible. King Nebuchadnezzar II (605–562 BCE) ordered that a group of children be given meat and wine diet for three years. Another group of children were given pulses (e.g. beans, peas, lentils) and water. After 10 days, the king observed that 'pulses and water' group were fitter than 'meat and wine' group. The trial was stopped then.

Around the tenth century, the Persian scientist Ibn Sina (Avicenna) wrote 'Al-Quanun fi al-Tibb or the Canon of Medicine, a book that represented a comprehensive collection of all existing medical knowledge, incorporating Arabic medical lore and personal experience into the writings of Hippocrates, Galen, Dioscorides, and others'. He recommended that [3]:

- 'The drug must be pure'.
- 'The drug must be used on a "simple" disease'.

- 'The drug must be tested on at least 2 different types of disease'.
- 'The quality of the drug must correspond with the strength of the disease'.
- 'The timing of observations should be measured to rule out the effects of natural healing'.
- 'The drug must show consistency over several trials'.
- 'A drug should be tested in animals first, thereafter in humans, as the effects in animals and humans may not be the same'.

The Canon was 'the medical authority for centuries and set the standards for the practice of medicine in Europe, as well as the Middle East' [3].

1.3.1 562 BC–1537: Pre-James Lind Era

The world's first clinical trial is recorded in the 'Book of Daniel' in the Bible [4]. This experiment resembling 'a clinical trial was not conducted by a medical, but by King Nebuchadnezzar a resourceful military leader' [4]. During his rule in Babylon, Nebuchadnezzar's people ate only meat and drank only wine [4]. However, several young men of royal blood ate vegetables. The vegetarians were better nourished than the meat-eaters [4]. This was an open uncontrolled human experiment [2].

Avicenna (1025 AD) in his encyclopedic "Canon of Medicine" describes some interesting rules for the testing of drugs [5]. He suggests that "in the clinical trial a remedy should be used in its natural state in disease without complications". He also recommends that two cases of contrary types be studied and that study be made of the time of action and of the reproducibility of the effects [5]. These rules were related for contemporary approach in clinical trials. However, there seems to be no record of the application of these principles in practice.

"The first clinical trial of a novel therapy" was conducted accidentally by the famous surgeon Ambroise Pare in 1537 [4, 6]. In 1537 while serving with the Mareschal de Motegni, he was responsible for the treatment of the battlefield wounded soldiers. As the number of wounded was high and the supply of conventional treatment – oil – was not adequate to treat all the wounded, he resorted to unconventional treatments. He describes, "At length my oil lacked and I was constrained to apply in its place a digestive made of yolks of eggs, oil of roses and turpentine. That night I could not sleep at any ease, fearing that by lack of cauterization I would find the wounded upon which I had not used the said oil dead from the poison. I raised myself early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses" [5]. 'However, it would take another 200 years before a planned controlled trial would be organized'.

1.3.2 1747: James Lind and Scurvy Trial

James Lind is considered the first physician to conduct a controlled clinical trial of the modern era [4–7]. As a surgeon working in a ship, Dr Lind (1716–94) was appalled by the high mortality of scurvy among the sailors. He planned a comparative trial of the most promising cure for scurvy [4–7]. His vivid description of the trial covers the essential elements of a controlled trial.

Lind's Treatise of 1953, which was written while he was a resident in Edinburgh and a fellow of the Royal College of Physicians, contains not only his well-known description of a

controlled trial showing which oranges and lemons were dramatically better than the other treatments for the disease but also a systematic review of previous literature on scurvy [8].

1.3.3 1800: Arrival of Placebo

The word of placebo was used in medical literature in the early 1800s [4]. Hooper's Medical Dictionary of 1811 defined it as 'an epithet given to any medicine more to please than benefit the patient'. However, in 1863, physician Austin Flint (USA) planned the first clinical study. He compared a dummy remedy with an active treatment in 13 patients with rheumatism. He applied herbal extract instead of an established remedy. In 1886, Flint described the study in his book *A Treatise on the Principles and Practice of Medicine*. 'This was given regularly, and became well-known in my wards as the placeboic remedy for rheumatism. The favorable progress of the cases was such as to secure for the remedy generally the entire confidence of the patients' [2].

1.3.4 1943: The First Double-Blind Controlled Trial (Patulin for Common Cold)

'The Medical Research Council (MRC) UK carried out a trial in 1943–4 to investigate patulin treatment for (an extract of Penicillium patulum) the common cold [6]. This was the first double-blind comparative trial with concurrent controls in the general population in recent times [9]. It was one of the last trial with non-randomized or quasi-randomized allocation of subjects [9]. The MRC Patulin Clinical Trials Committee (1943) was chaired by Sir Harold Himsworth and its statisticians were M Greenwood and W J Martin. This nationwide study included

over a thousand British office and factory workers suffering from colds. This was quite a challenging endeavor in the wartime'.

'The study was rigorously controlled by keeping the physician and the patient blinded to the treatment. The treatment allocation was done using an alternation procedure. A nurse allocated the treatment in strict rotation in a separate room. The nurse filled the record counterfoil separately and detached the code label for the appropriate bottle before asking the patient to visit the physician [9]. The statisticians considered this an effective random concurrent allocation. However, the outcome of the trial was disappointing as the analysis of trial data did not show any protective effect of patulin [9]'.

1.3.5 1946: The First Randomised Curative Trial (The Randomised Controlled Trial of Streptomycin)

The randomisation idea appeared in 1923. The first randomised control trial was conducted in pulmonary tuberculosis with streptomycin in 1946 (UK) [9, 10]. According to Dr Hill's randomisation scheme, alternation procedure of 'allocation concealment' was applied at the time patients were enrolled in the trial. In this trial, objective measures were used such as X-rays, and they were evaluated by experts who were blinded in the treatment of the patients [11].

'Sir Bradford Hill compelled his allocation ideas over several years with randomisation replacing alternation to better conceal the allocation schedule; however, he had only used them in disease prevention. Dr. Hill instituted randomization – a new statistical process which has been described in detail in the landmark BMJ paper of 1948 [10]'.

'Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case)

was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill. The details of the series were unknown to any of the investigators or to the coordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the panel, and before admission to the streptomycin centre, the appropriate numbered envelope was opened at the central office; the card inside told if the patient was to be an S or a C case, and this information was, then, given to the medical officer of the centre. Patients were not told before admission that they were to receive special treatment. C patients did not know throughout their stay in hospital that they were control patients in a specific study; they were, indeed, treated as they would have been in the past, the sole difference being that they were admitted to the centre more rapidly than was normal. Usually, they were not in the same wards as S patients, whereas the same regime was maintained [2]'.

'Sir Bradford Hill was anxious that physicians would be unwilling to give up the doctrine of anecdotal experience. However, the trial quickly became a model of design and implementation and support Dr Hill's views and subsequent teaching, and resulted, after some years, in the present virtually universal use of randomised allocation in clinical trials [9]. The greatest influence of this trial lay in its methods affecting virtually every area of clinical medicine [11]. Over the years, as the discipline of controlled trials has grown in sophistication and influence, the streptomycin trial continues to be referred to as ground-breaking [11]'.

1.3.6 Evolution of Ethical and Regulatory Framework

'The ethical framework for human subject protection has its origins in the ancient Hippocratic Oath, which specified a prime

duty of a physician – to avoid harming the patient. However, this oath was not much respected in human experimentation and most advances in protection for human subjects have been a response to human abuses (e.g. World War II experiments)'.

'The first International Guidance on the ethics of medical research involving subjects – the Nuremberg Code was formulated in 1947. Although an informed consent for participation in research was described in 1900, the Nuremberg Code highlighted the essentiality of voluntariness of this consent [12]'.

'In 1948, Universal Declaration of Human Rights (adopted by the General Assembly of the United Nations) expressed concern about rights of human beings being subjected to involuntary maltreatment [12]. The brush with thalidomide tragedy helped the U.S. pass the 1962 Kefauver-Harris amendments, which strengthened federal oversight of drug testing and included a requirement for informed consent [13]'.

'In 1964 at Helsinki, the World Medical Association articulated general principles and specific guidelines on use of human subjects in medical research, known as the Declaration of Helsinki. The Declaration of Helsinki has been undergoing changes every few years, the last one being in 2008. However, the use of placebo and post-trial access continue to be debatable issues [2]'.

'In 1966, the International Covenant on Civil and Political Rights specifically stated, 'No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his consent to medical or scientific treatment' [12]. In 1966, Dr. Henry Beecher's study of abuses and the discovery of human exploitation of Tuskegee study in the 1970s reinforced the call for a tighter regulation of government funded human research [13]. The US National Research Act of 1974 and Belmont Report of 1979 were major efforts in shaping ethics of human experimentation. In 1996, International Conference on Harmonization published Good Clinical Practice, which has

become the universal standard for ethical conduct of clinical trials [2]'.

'In parallel to ethical guidelines, clinical trials began to become embodied in regulation as government authorities recognized a need for controlling medical therapies in the early 20th century. The FDA was founded in 1862 as a scientific institution and became a law enforcement organization after the US Congress passed the Food and Drugs Act in 1906. Afterwards, the legislation progressively demanded a greater accountability for marketing food and drugs and the need for testing drugs in clinical trials increased. The regulatory and ethical milieu will further continue to evolve as new scientific disciplines and technologies will become part of the drug development [2]'.

1.3.7 The Food and Drug Administration (FDA) in the USA

'In the 19th century, what little control over food and medications existed was the responsibility of the individual states and was inconsistent from state to state. The adulteration and misbranding of foods and drugs was commonplace, with snake oil salesmen increasing as the century progressed. Furthermore, many medicinal products were compounded in individual pharmacies, making oversight difficult. The first federal law which addressed the protection of the consumer with regard to therapeutic substances was the Vaccine Act of 1813, which established a national source for uncontaminated smallpox vaccine. However, the Vaccine Act was repealed after only 9 years due to a fatal accident and public scandal of a contaminated vaccine'.

'In 1862, the President Lincoln created the Division of Chemistry, the predecessor of the FDA, as part of the new Department of Agriculture. Starting in 1867, the Division of

Chemistry began investigating the corruption of agricultural commodities. Harvey Washington Wiley in his role as chief chemist expanded the investigative role of the Division of Chemistry in 1883. He was instrumental in the enactment of the Biologics Act of 1902 in response to the deaths of several children caused by contaminated smallpox vaccines and diphtheria antitoxins. This Act granted the federal government premarket approval for every biological drug and approval over the process and facility producing such drugs. He also compiled Foods and Food Adulterants, a 10-part study published from 1887 to 1902. In this study, he administered varying amounts of the questionable food additives which were in use to healthy volunteers to determine their affects on health. Based on these results and the filthy conditions described in Upton Sinclair's book, The Jungle, he unified a diverse group that included state chemists, food and drug inspectors, the General Federation of Women's Clubs, and national associations of physicians and pharmacists behind the Pure Food and Drugs Act (also known as the Wiley Act), which was signed into law by President Theodore Roosevelt on June 30, 1906'.

'The 1906 law recognized the privately produced US Pharmacopoeia (USP, originated in 1820) and the National Formulary as the official standards' for 'the strength, quality, and purity of drugs, and defined adulterated drugs as those that were listed in the USP', but failed USP specifications [3].

'In 1927, the Bureau of Chemistry was re-organized into the Food, Drug, and Insecticide Administration to oversee regulatory functions, and the Bureau of Chemistry and Soils to conduct non-regulatory research. In 1930, under an agricultural appropriation act, the name of the Food, Drug, and Insecticide Administration was shorted to the Food and Drug Administration (FDA)'.

The Durham-Humphrey Amendment of 1951 resolved 'the debate about what constituted a prescription medication and what could be considered over-the-counter'. The Food Additives Amendment of 1958 allowed the 'FDA to regulate dietary supplements'. In 1976, the Congress prohibited the FDA from

'controlling these products in response to pressure from supplement manufacturers'. Also in the same year, the Medical Device Amendments were passed, which divided devices into three categories [3]:

- 'Class I (eg, tongue depressors, gauze) are subject to reporting requirements and Good Manufacturing Practices'
- 'Class II (eg, blood pressure cuffs, sutures) are subject to the same controls as Class I plus product-specific performance standards developed by the FDA'
- 'Class III (eg, angioplasty catheters, artificial hearts) must pass an FDA approval process similar to novel drugs'.

All new devices are categorised as 'Class III, unless it can be shown to be substantially equivalent to a previously approved device' [3].

1.3.8 European Medicines Agency (EMEA)

'Although the EMEA was not established until 1995, numerous events paved the way for its creation. The European Union (EU) was first conceptualized in 1951, when six countries (Belgium, France, West Germany, Italy, Luxembourg, and the Netherlands) created the European Coal and Steel Community by pooling their resources into a common market. In 1957, the European Economic Community, the predecessor to the EU, expanded the common market beyond just coal and steel to all financial sectors of the member countries through the Rome Treaties. In 1973, the United Kingdom, Ireland, and Denmark joined the EU; Greece joined in 1981, Portugal and Spain in 1986, and Austria, Finland, and Sweden joined in 1995. In 2004, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, the Republic of Cyprus, the Slovak Republic, and Slovenia joined the EU, and, in 2007, Bulgaria and Romania joined for a total of 27 countries or member states. As in the

United States, disasters often prompted change in the EU. Thalidomide was introduced in Europe in 1957 to alleviate morning sickness in pregnant women. By 1960, thalidomide was available in more than 20 countries in Europe and Africa (it was never granted approval in the United States) [3]'.

'In 1965, the First European Directive, known as 65/65/EEC, was enacted by the Council of the European Economic Community and stated that no medicinal product could be placed on the market in a member state, unless the authorization was issued by the competent authority in that member state. Thus, pharmaceutical manufacturers had to seek an approval from each individual country before marketing was commenced in that country. The Second European Directive (75/319/EEC) in 1975 hoped to alleviate some of the multiplicity involved in seeking approval across Europe by introducing mutual recognition, so that authorization in one member country would allow marketing in other member countries without having to repeat the entire approval process. 75/319/EEC also established the Committee for Proprietary Medicinal Products (CPMP), which consisted of representatives of the member states to provide an opinion, if there was a dispute about any particular product in the various member states' [3].

1.3.9 Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

'In 1943, Japan passed the first Pharmaceutical Affairs Law, with revisions in 1948, 1960, and 1979. The Pharmaceutical Affairs Law, enacted by the Ministry of Health, Labor, and Welfare, regulated the quality, effectiveness, and safety of medical drugs and equipment'. In 2004, the 'Pharmaceuticals and Medical Devices Agency (PMDA)' was established as an 'independent, non-governmental agency separate from the Ministry of Health, Labor, and Welfare' [3].

1.4 Evolution of the Drugs

'The modern U.S. drug regulatory system has its roots in amendments to the 1938 FD&C Act that Congress passed a generation later, partly in response to the grim effects of thalidomide [14]. The 1938 act made major changes in the FDA's regulation of drugs. Manufacturers more commonly consulted with the agency before marketing a new product and the agency became increasingly involved in overseeing the design and conduct of clinical trials of experimental drugs [15]. Although the 1962 drug amendments purported simply to elaborate the new-drug approval system, they, indeed, transformed it [14]'.

Emergence of the New Drug System

- Expansion of jurisdiction: The premarket approval is required for 'novel drugs' [14].
- Oversight of clinical investigations: 'The act prohibits the interstate shipment of any novel drug for which the FDA has not approved an NDA' [14]. The FDA has supplemented this requirement with 'a mandate for review by a local institutional review board (IRB) and, to facilitate monitoring of compliance with both requirements', the agency has established detailed specifications for IRB operations and record keeping [14].

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