PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH

SECOND EDITION

EDITED BY

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Preface

The positive reception of the first edition of *Principles and Practice of Clinical Research* prompted the second edition, which was written in the context of continued growth and scope of clinical research as a discipline since the publication of the first edition in 2002. The course at the National Institutes of Health (NIH) Clinical Center, which led to the production of the first edition, has been in existence for ten years and is now taught to nearly 1,000 students annually at the NIH Clinical Center and at multiple long-distance learning sites, including both domestic and international partners.

This second edition includes new chapters on clinical research from a patient's perspective, managing conflicts of interest in clinical research, the clinical researcher and the media, clinical research from an industry perspective, data management in clinical research, how to evaluate a protocol budget, and the role of the human genome project and genomics in clinical research. All other chapters have been updated with extensive changes in the chapters on technology transfer and how to successfully navigate the NIH peer review process for grants.

We hope that this book provides the reader with an expanded awareness of the broad scope of clinical research and the tools to conduct such research safely and effectively. Our goals as investigators should be to strive to improve the well being of patients in general while ensuring the safety of our research subjects enrolled in investigational protocols.

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CHAPTER

1

A Historical Perspective on Clinical Research

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If I have seen a little further it is by standing on the shoulders of giants. —Sir Isaac Newton, 1676

The successful translation of a basic or clinical observation into a new treatment of disease is rare in an investigator's professional life, but when it occurs, the personal thrill is exhilarating and the impact on society may be substantial. The following historical highlights provide a perspective of the continuum of the clinical research endeavor. These events also emphasize the contribution that clinical research has made to advances in medicine and public health.

In this chapter, and throughout this book, a broad definition of clinical research of the Association of American Medical Colleges Task Force on Clinical Research is used.[1] That task force defined clinical research as

> a component of medical and health research intended to produce knowledge essential for understanding human disease, preventing and treating illness, and promoting health. Clinical research embraces a continuum of studies involving interaction with patients, diagnostic clinical materials or data, or populations, in any of these categories: disease mechanisms; translational research; clinical knowledge; detection; diagnosis and natural history of disease; therapeutic interventions including clinical trials; prevention and health promotion; behavioral research; health services research; epidemiology; and community-based and managed care-based research.

1. THE EARLIEST CLINICAL RESEARCH

Medical practice and clinical research are grounded in the beginnings of civilization. Egyptian medicine was dominant from approximately 2850 BC to 525 BC. The Egyptian Imhotep, whose name means "he who gives contentment," lived slightly after 3000 BC and was the first physician figure to rise out of antiquity.[2] Imhotep was a known scribe, priest, architect, astronomer, and magician (medicine and magic were used together), and he performed surgery, practiced some dentistry,[1] extracted medicine from plants, and knew the position and function of the vital organs.

There is also evidence that ancient Chinese medicine included clinical studies. For example, in 2737 BC Shen Nung, the putative father of Chinese medicine, experimented with poisons and classified medical plants,[3] and I. Yin (1176–1123 BC), a famous prime minister of the Shang dynasty, described the extraction of medicines from boiling plants.[4]

Documents from early Judeo-Christian and Eastern civilizations provide examples of a scientific approach to medicine and the origin of clinical research. In the Old Testament, written from the 15th century BC to approximately the 4th century BC,[5] a passage in the first chapter of the Book of Daniel describes a comparative "protocol" of diet and health. Daniel demonstrated the preferred diet of legumes and water made

for healthier youths than the king's rich food and wine:

> Then Daniel said to the steward . . .
> "Test your servants for ten days; let us be given vegetables to eat and water to drink. Then let your appearance and the appearance of the youths who eat the king's rich food be observed by you, and according to what you see deal with your servants:
> So he harkened to them in this matter; and tested them for ten days.
> At the end of ten days it was seen that they were better in appearance and fatter in flesh than all the youths who ate the king's rich food. So the steward took away their rich food and the wine they were to drink, and gave them vegetables."
> Daniel 1:11–16

The ancient Hindus also excelled in early medicine, especially in surgery, and there is evidence of Indian hospitals in Ceylon in 437 and 137 BC.[4]

2. THE GREEK AND ROMAN INFLUENCE

Although early examples of clinical research predate the Greeks, Hippocrates (460–370 BC) is considered the father of modern medicine, and he exhibited the strict discipline required of a clinical investigator.

His emphasis on the art of clinical inspection, observation, and documentation established the science of medicine. In addition, as graduating physicians are reminded when they take the Hippocratic oath, he provided physicians with high moral standards. Hippocrates' meticulous clinical records were maintained in 42 case records representing the first known recorded clinical observations of disease.[6] These case studies describe, among other maladies, malarial fevers, diarrhea, dysentery, melancholia, mania, and pulmonary edema with remarkable clinical acumen.

On pulmonary edema, he wrote the following:

> Water accumulates; the patient has fever and cough; the respiration is fast; the feet become edematous; the nails appear curved and the patient suffers as if he has pus inside, only less severe and more protracted. One can recognize that it is not pus but water . . . if you put your ear against the chest you can hear it seethe inside like sour wine.[7]

Hippocrates also described the importance of cleanliness in the management of wounds. He wrote, "If water was used for irrigation, it had to be very pure or boiled, and the hands and nails of the operator were to be cleansed."[8] Hippocrates' teachings remained dominant and unchallenged until Galen of Pergamum (ca. 130–200 AD), the physician to the Roman Emperor Marcus Aurelius.[9] Galen was one of the first individuals to utilize animal studies to understand human disease. By experimenting on animals, he was able to describe the effects of transection of the spinal cord at different levels. According to Galen, health and disease were the balance of four humors (blood, phlegm, black bile, and yellow bile), and veins contained blood and the humors, together with some spirit.[9]

3. MIDDLE AGES AND RENAISSANCE

In the Middle Ages, improvements in medicine became evident, and the infrastructure for clinical research began to develop. Hospitals and nursing, with origins in the teachings of Christ,[10] became defined institutions (although the forerunner of hospitals can be traced to the ancient Babylonian custom of bringing the sick into the marketplace for consultation, and the Greeks and Romans had military hospitals). By the 1100s and 1200s, hospitals were being built in England, Scotland, France, and Germany.

Early progress in pharmacology can be linked to the Crusades and the development of commerce. Drug trade became enormously profitable during the Middle Ages. Drugs were recognized as the lightest, most compact, and most lucrative of all cargoes. The influences of Arabic pharmacy and the contact of the Crusaders with their Moslem foes spread the knowledge of Arabic pharmaceuticals and greatly enhanced the value of drugs from the Far East. The records of the customhouse at the port of Acre (1191–1291) show a lively traffic in aloes, benzoin, camphor, nutmegs, and opium.[11]

Documentation through case records is an essential feature of clinical research. Pre-Renaissance medicine of the 14th and 15th centuries saw the birth of "Consilia" or medical-case books, consisting of clinical records from the practice of well-known physicians.[12] Hippocrates' approach of case studies developed 1700 years earlier was reborn, particularly in the Bolognese and Paduan regions of Italy. Universities became important places of medicine in Paris, Bologna, and Padua.

Clinical research remained mostly descriptive, resembling today's natural history and disease pathogenesis protocols. In 1348, Gentile da Foligno, a Paduan professor, described gallstones.[12] Bartolommeo Montagnana (1470), an anatomist, described strangulated hernia, operated on lachrymal fistula, and extracted decayed teeth.[12] There was also evidence of the beginning of a statistical approach to medical issues during this period. For example, a 14th-century letter from Petrach to Boccaccio states that

> I once heard a physician of great renown among us express himself in the following terms: . . . I solemnly affirm and believe, if a hundred or a thousand of men of the same age, same temperament and habits, together with the same

surroundings, were attacked at the same time by the same disease, that if the one half followed the prescriptions of the doctors of the variety of those practicing at the present day, and that the other half took no medicine but relied on Nature's instincts, I have no doubt as to which half would escape.[13]

The Renaissance (1453–1600) represented the revival of learning and transition from medieval to modern conditions; many great clinicians and scientists prospered. At this time, many of the ancient Greek dictums of medicine, such as Galen's four humors, were discarded. Perhaps the most important anatomist of this period was Leonardo da Vinci (1453–1519) (Fig. 1-1).[14] Da Vinci created more than 750 detailed anatomic drawings (Fig. 1-2).

4. SEVENTEENTH CENTURY

Studies of blood began in the 17th century. William Harvey (1578–1657) convincingly described the circulation of blood from the heart through the lungs and back to the heart and then into the arteries and back through the veins.[16] Harvey emphasized that the arteries and veins carried only one substance, the blood, ending Galen's proposal that veins carried a blend of multiple humors. (Of course, today we know that blood contains multiple cellular and humoral elements, so to some extent Galen was correct.) The famous architect Sir Christopher Wren (1632–1723), originally known as an astronomer and anatomist (Fig. 1-3), in 1656 assembled quills and silver tubes as cannulas and used animal bladders to inject opium into the veins of dogs.[17] The first well-documented transfusions of blood into humans were done in 1667 by Richard Lower and Edmund King in London[18] and mentioned in Pepys' diary.[19]

The 17th century also brought the first vital statistics, which were presented in Graunt's book, *Natural and Political Observations Mentioned in a Following Index, and Made Upon the Bills of Mortality*.[20] In this book of comparative statistics, populations and mortality sta-

FIGURE 1-1 Leonardo da Vinci self-portrait (red chalk); Turin, Royal Library. From reference 14, Figure 1.

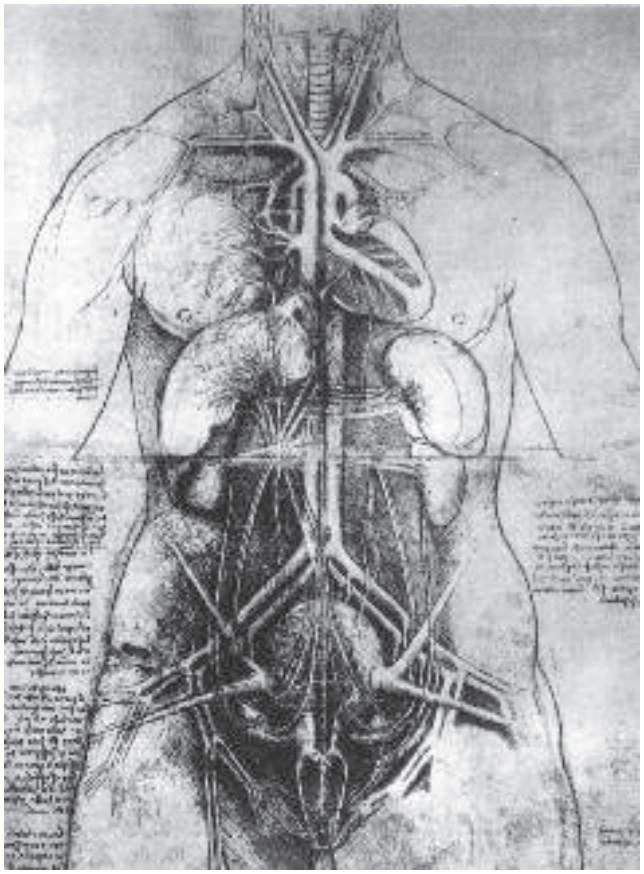


FIGURE 1-2 Example of anatomic drawing by Leonardo da Vinci. Trunk of female human body, with internal organs seen as though ventral side were transparent. From reference 14, p. 369.

tistics were compared for different countries, ages, and sex for rural and urban areas. The importance of using mortality among groups would have major importance in future clinical studies.

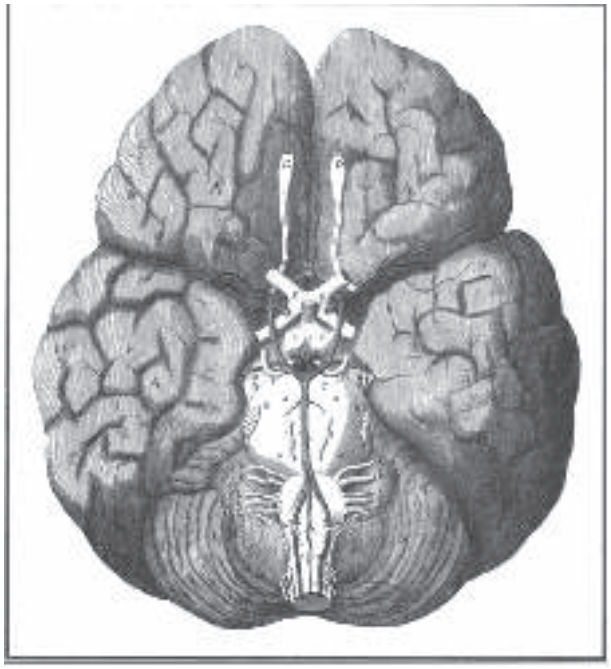


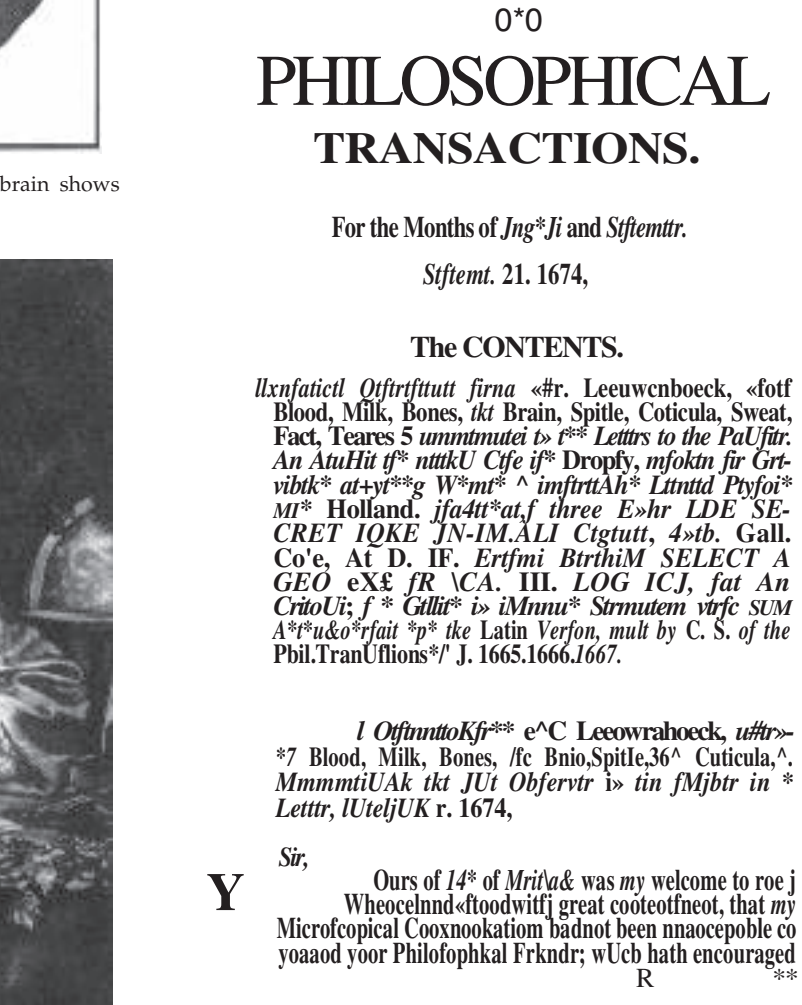
FIGURE 1-3 Christopher Wren's drawing of the brain shows blood vessels discovered by Thomas Willis.[15]

FIGURE 1-4 Antony van Leeuwenhoek. From reference 21.

5. EIGHTEENTH CENTURY

The 18th century brought extraordinary advances in the biological sciences and medicine. At the end of the 17th century, Antony van Leeuwenhoek of Delft (1632–1723) invented the microscope. Although he is best known for using his microscope to provide the first descriptions of protozoa and bacteria, Leeuwenhoek also provided the first description of striated voluntary muscle, the crystalline structure of the lens, red blood cells, and spermatozoa (Figs. 1-4 and 1-5).[21]

Modern clinical trials can be recognized in the 1700s. Scurvy was a major health problem for the British Navy. William Harvey earlier had recommended lemons to treat scurvy but argued that the therapeutic effect was a result of the acid in the fruit. James Lind (Fig. 1-6), a native of Scotland and a Royal Navy surgeon, conducted a clinical trial in 1747 to assess this hypothesis comparing three therapies for scurvy (Table 1-1).[22] Twelve sailors with classic scurvy were divided



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PHILOSOPHICAL

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FIGURE 1-5 Title page from Leeuwenhoeck's paper on *Microscopical Observations.* From reference 16.

FIGURE 1-6 James Lind.

TABLE 1-1 Treatment of Scurvy by James Lind

Treatment Arm	Cured	*p* Value[a]
Sulfuric acid	0/2	>0.05
Vinegar	0/2	>0.05
Seawater	0/2	>0.05
Cider	0/2	>0.05
Physicians	0/2	>0.05
Citrus fruit	2/2	>0.05

[a]Compared to patients in the five areas of the trial; no placebo group.

into six groups of two each, all given identical diets, and the various groups supplemented with vinegar, dilute sulfuric acid, cider, seawater, a nutmeg, garlic, and horseradish mixture, and with two oranges and one lemon daily.

Sulfuric acid, vinegar, seawater, cider, and physician's remedy had no benefit. Two sailors receiving citrus fruit avoided scurvy. Although not significant because of sample size, this early clinical study formed the basis for successfully avoiding scurvy with citrus fruit. The studies with sulfuric acid, vinegar, and cider excluded acid as a likely explanation for the beneficial effect of citrus fruit.

The 18th century saw great progress in the area of surgery. A remarkable succession of teachers and their students led these studies. Percival Pott of St. Bartholomew's Hospital described tuberculosis of the spine or "Pott's disease."[23] John Hunter, Pott's pupil, was the founder of experimental and surgical pathology as well as a pioneer in comparative physiology and experimental morphology. Hunter described shock, phlebitis, pyremia, and intussusception and made major findings of inflammation, gunshot wounds, and the surgical diseases of the vascular system.[23] Hunter's student, Edward Jenner (1749–1823),[23] introduced vaccination as a tool to prevent infectious diseases (Fig. 1-7).[24] Jenner was aware that dairymaids who had contacted cowpox through milking did not get smallpox. In 1798, Jenner conceived of applying the observation on a grand scale to prevent smallpox.[25]

Jenner was not the first to conceive of the idea of inoculation for smallpox. For example, the Chinese had thought of this earlier and Sir Hans Sloane had done small studies in 1717 using variolation (inoculating healthy people with pus from blisters obtained from patients with smallpox).[26] In addition, James Jurin published several articles between 1723 and 1727 comparing death from natural smallpox in people who had not been inoculated with those who had been inoculated. Jurin showed that death occurred in 5 of 6 subjects in the first group compared to 1 in 60 in the latter,[27] providing one of the first studies using mortality as a critical clinical end point. In 1734, Voltaire wrote, "The Cirassians [a Middle Eastern people] perceived that of a thousand persons hardly one was attacked twice by full blown smallpox; that in truth one sees three or four mild cases but never two that are serious and dangerous; that in a word one never truly has that illness twice in life."[28] Thus, Voltaire recognized natural immunity to smallpox, which was an important concept for future vaccinology. In 1721, Cotton Mather demonstrated that variolation protected citizens of the American colonies in Massachusettes,[29] and in 1777 George Washington used variolation against smallpox to inoculate the Continental Army, the first massive immunization of a military.[30] Jenner was the first to try vaccination on a large scale using scabs from cow pox to protect against human smallpox and the first to use experimental approaches to establish the scientific basis for vaccination. Jenner transformed a local country tradition into a viable prophylactic principle. Jenner's vaccine was adopted quickly in Germany and then in Holland, Denmark, the rest of Europe, and the United States.

FIGURE 1-7 Edward Jenner (painting by Sir Thomas Lawrence). From reference 3, p. 373.

The 1700s were also when the first known blinded clinical studies were performed. In 1784, a commission of inquiry was appointed by King Louis XVI of France to investigate medical claims of "animal magnetism" or "mesmerism." The commission, headed by Benjamin Franklin and consisting of such distinguished members as Antoine Lavoisier, Jean-Sylvain Bailly, and Joseph-Ignace Guillotin, had as a goal to assess whether the reported effects of this new healing method were due to "real" force or due to "illness of the mind." Among the many tests performed, blindfolded people were told that they were either receiving or not receiving magnetism when in fact, at times, the reverse was happening. The results showed that study subjects felt effects of magnetism only when they were told they received magnetism and felt no effects when they were not told, whether or not they were receiving the treatment.[31] This was the beginning of the use of blinded studies in clinical research.

The 18th century also provided the first legal example that physicians must obtain informed consent from patients before a procedure. In an English lawsuit, *Slater v. Baker & Stapleton*, two surgeons were found liable for disuniting a partially healed fracture without the patient's consent.[32] This case set the important precedent described by the court: "Indeed it is reasonable that a patient should be told what is about to be done to him that he may take courage and put himself in such a situation as to enable him to undergo the operation."

6. NINETEENTH CENTURY

In the first days of the 19th century, Benjamin Waterhouse, a Harvard professor of medicine, brought Jenner's vaccine to the United States, and by 1802 the first vaccine institute was established by James Smith in Baltimore, Maryland. This led to a national vaccine agency, which was established by the Congress of the United States under the direction of James Smith in 1813.[33]

Jenner's vaccination for smallpox was followed by other historic studies in the pathogenesis of infectious diseases. The French physician Pierre Charles Alexandre Louis (1787–1872) realized that clinical observations on large numbers of patients were essential for meaningful clinical research. He published classical studies on typhoid fever and tuberculosis, and his research in 1835 on the effects of bloodletting demonstrated that the benefits claimed for this popular mode of treatment were unsubstantiated.[34] On February 13, 1843, one of Louis' students, Oliver Wendell Holmes (1809–1894), the father of the great Justice Holmes, read his article, *On the Contagiousness of Puerperal Fever*,[35] to the Boston Society for Medical Improvement (Fig. 1-8). Holmes stated that women in childbed should never be attended by physicians who have been conducting postmortem sections on cases of puerperal fever; that the disease may be conveyed in this manner from patient to patient, even from a case of erysipelas; and that washing the hands in calcium chloride and changing the clothes after leaving a puerperal fever case was likely to be a preventive measure. Holmes' essay stirred up violent opposition by obstetricians. However, he continued to reiterate his views, and in 1855 in a monograph, *Puerperal Fever as a Private Pestilence*, Holmes noted that Semmelweis, working in Vienna and Budapest, had lessened the mortality of puerperal fever by disinfecting the hands with chloride of lime and the nail brush.[36]

Ignaz Philipp Semmelweis (1818–1865) performed the most sophisticated preventive clinical trial of the 19th century that established the importance of hand washing to prevent the spread of infection (Fig. 1-9).[37] Semmelweis, a Hungarian pupil, became an assistant in the first obstetric ward of the Allgemeines Kranken-

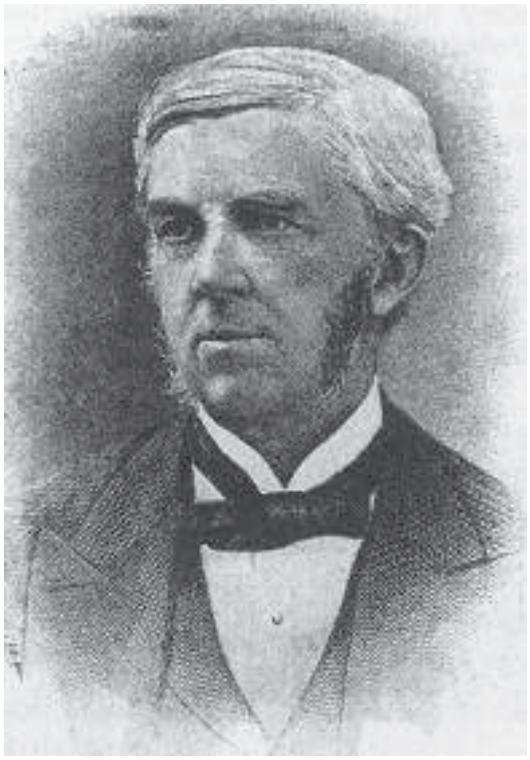

FIGURE 1-8 Oliver Wendell Holmes. From reference 3, p. 435.

haus in Vienna in 1846. Semmelweis was troubled by the death rate associated with puerperal or "childbed" fever. From 1841 to 1846, the maternal death rate from puerperal sepsis averaged approximately 10%, and in some periods as high as 50%, in the First Maternity Division of the Vienna General Hospital. In contrast, the rate was only 2 or 3% in the Second Division, which was attended by midwives rather than physicians. The public knew the disparity, and women feared being assigned to the First Division. Semmelweis became frustrated by this mystery and began to study cadavers of fever victims. In 1847, his friend and fellow physician, Jakob Kolletschka, died after receiving a small cut on the finger during an autopsy. The risk of minor cuts during autopsies was well-known, but Semmelweis made the further observation that Kolletschka's death was characteristic of death from puerperal fever. He reasoned that puerperal fever was "caused by conveyance to the pregnant women of putrid particles derived from living organisms, through the agency of the examining fingers." In particular, he identified the cadaveric matter from the autopsy room, with which the midwives had no contact, as the source of the infection.

In 1847, Semmelweis insisted that all students and physicians scrub their hands with chlorinated lime before entering the maternity ward, and during 1848 the mortality rate on his division dropped from 9.92%

FIGURE 1-9 Ignaz Philipp Semmelweis. From reference 4, p. 436.

to 1.27%. Despite his convincing data, his colleagues rejected his findings and accused him of insubordination. The dominant medical thinking at the time was that the high mortality in the charity hospital related to the poor health of the impoverished women, despite the difference between the control (no chlorinated lime hand washing) and experimental (washing with chlorinated lime) divisions. Without any opportunity for advancement in Vienna, Semmelweis returned to his home in Budapest and repeated his studies with the same results. In 1861, he finally published *The Etiology, Concept, and Prophylaxis of Childhood Fever*.[37] Although Holmes' work antedated Semmelweis by 5 years, the superiority of Semmelweis' observation lies not only in his experimental data but also in his recognition that puerperal fever was a blood poisoning. The observations of Holmes and Semmelweis were a critical step for medicine and surgery.

In addition to discovering the importance of hand washing, the first well-documented use of ether for surgery (1846) by William Thomas Green Morton with

Dr. John Collins Warren as the surgeon at the Massachusetts General Hospital also occurred during the 19th century.[38] Oliver Wendell Holmes is credited with proposing the words *anesthetic* and *anesthesia*.[38] Recognition of the importance of hand washing and the discovery of anesthetics were essential findings of the 19th century that were critical for the development of modern surgery.

The work of Holmes and Semmelweis on the importance of hand washing also opened the door for Pasteur's work on the germ basis of infectious diseases. Louis Pasteur (1822–1895) was perhaps the most outstanding clinical investigator of the 19th century (Fig. 1-10). He was trained in chemistry. His fundamental work in chemistry led to the discovery of levo and dextro isomers. He then studied the ferments of microorganisms, which eventually led him to study the detrimental causes of three major industries in France: wine, silk, and wool. Pasteur discovered the germ basis of fermentation, which formed the basis of the germ theory of disease.[39] He discovered *Staphylococcus pyogenes* as a cause of boils and the role of *Streptococcus pyogenes* in puerperal septicemia. In other studies, he carried forward Jenner's work on vaccination and developed approaches to vaccine development using attenuation of a virus for hydrophobia (rabies) and inactivation of a bacterium for anthrax.

The work of Pasteur was complemented by the studies of Robert Koch (1843–1910), who made critical technical advances in bacteriology. Koch was the first to use agar as a culture media and he introduced the petri dish, pour plates, and blood agar to make bacterial culture and identification easy and widely available. Koch cultured the tubercle bacillus and identified the etiologic agent for anthrax, which was later used by Pasteur to develop a vaccine, and he established "Koch's postulates" to prove that an infectious agent causes disease (Fig. 1-11).[39]

FIGURE 1-10 Louis Pasteur. One of the remarkable facts about Pasteur was his triumph over a great physical handicap. In 1868 at age 46, just after completing his studies on wine, he had a cerebral hemorrhage. Although his mind was not affected, he was left with partial paralysis of his left side, which persisted for the remainder of his life. This photograph, taken after he was awarded the Grand Cross of the Legion of Honor in 1881, gives no hint of his infirmity. From reference 23, p. 116.

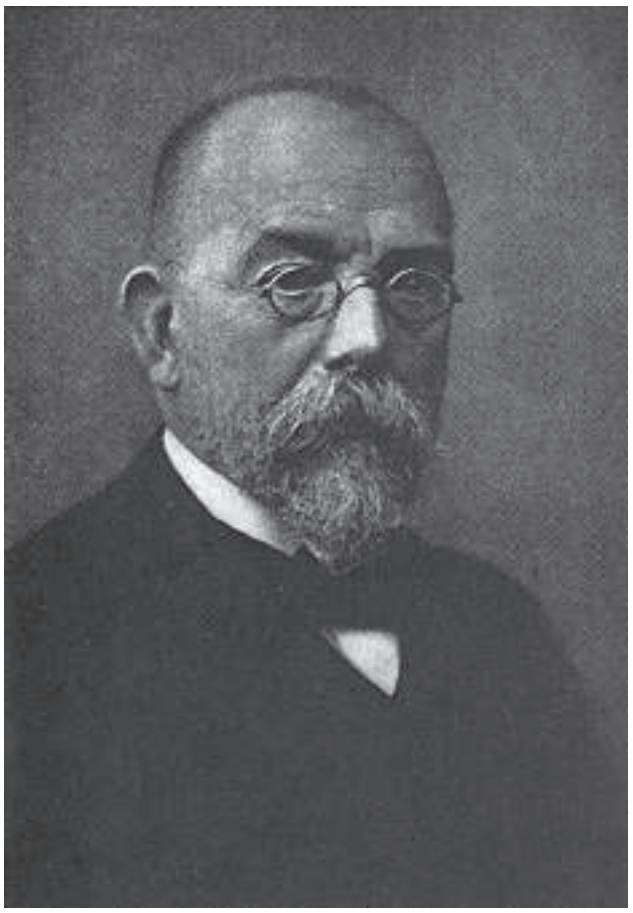

FIGURE 1-11 Robert Koch. His career in research began in 1872 when his wife gave him a microscope as a birthday present. He was then 28 years old, performing general practice in a small town in Silesia. This was an agricultural region where anthrax was common among sheep and cattle, and it was in the microscopic study of this disease in rabbits that Koch made his first great discovery of the role of anthrax bacilli in disease. From reference 23, p. 132.

The studies of Pasteur and Koch were performed during the same period as the work of the Norwegian Gerhard Armauer Hansen (1841–1912). In 1874, based on epidemiological studies in Norway, Hansen concluded that *Mycobacterium leprae* was the microorganism responsible for leprosy. Hansen's claim was not well received, and in 1880, in an attempt to prove his point, he inoculated live leprosy bacilli into humans, including nurses and patients, without first obtaining permission. One of the patients brought legal action against Hansen. The court, in one of the early cases demonstrating the importance of informed consent in clinical research, removed Hansen from his position as director of Leprosarium No. 1, where the experiments had taken place. However, Hansen retained his position as chief medical officer for leprosy[40] and later in his life received worldwide recognition for his life's work on leprosy.

In the same era, Emil von Behring (1854–1917) demonstrated in 1890 that inoculation with attenuated diphtheria toxins in one animal resulted in production of a therapeutic serum factor (antitoxin) that could be delivered to another, thus discovering antibodies and establishing a role for passive immunization. On Christmas eve of 1891, the first successful clinical use of diphtheria antitoxin occurred.[39] By 1894, diphtheria antiserum became commercially available as a result of Paul Ehrlich's work establishing methods for producing high-titer antisera. Behring's discovery of antitoxin was the beginning of humoral immunity, and in 1901 Behring received the first Nobel prize. Koch received the prize in 1905 (Fig. 1-12).

The Russian scientist Elie Metchnikoff (1845–1916) discovered the importance of phagocytosis in host defense against infection and emphasized the importance of the cellular components of host defense against infection.[41] Paul Ehrlich (1854–1915) discovered the complement system and asserted the importance of the humoral components of host defense. In 1908, Metchnikoff and Ehrlich shared the Nobel prize (Figs. 1-13 and 1-14).

At the end of the 19th century, studies of yellow fever increased the awareness of the importance of the informed consent process in clinical research. In 1897, Italian bacteriologist Giuseppe Sanarelli announced that he had discovered the bacillus for yellow fever by

FIGURE 1-12 Emil von Behring. From reference 39, p. 7.

FIGURE 1-13 Elie Metchnikoff in his forties. Reprinted frontispiece of E. Metchnikoff, *The Nature of Man: Studies in Optimistic Philosophy*. New York, Putnam, 1903. From reference 40, Figure 5.

FIGURE 1-14 Paul Ehrlich. From Reference 39, p. 9.

FIGURE 1-15 Marie Curie (1867–1934).

injecting the organism into five people. William Osler was present at an 1898 meeting at which the work by Sanarelli was discussed, and Osler said, "To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction . . . is criminal."[42] This commentary by Osler had substantial influence on Walter Reed, who demonstrated in human volunteers that the mosquito is the vector for yellow fever. Reed adopted written agreements (contracts) with all his yellow fever subjects. In addition to obtaining signed permission from all his volunteers, Reed made certain that all published reports of yellow fever cases included the phrase "with his full consent."[42]

Toward the end of the 19th century, women began to play important roles in clinical research. Marie Curie (1867–1934) and her husband, Pierre, won the Nobel prize in physics in 1903 for their work on spontaneous radiation, and in 1911 Marie Curie won a second Nobel prize (in chemistry) for her studies in the separation of radium and description of its therapeutic properties. Marie Curie and her daughter, Irene, promoted the therapeutic use of radium during World War I (Fig. 1-15).[43]

Florence Nightingale (1820–1910), in addition to her famous work in nursing, was an accomplished mathematician who applied her mathematical expertise to dramatize the needless deaths caused by unsanitary conditions in hospitals and the need for reform (Fig. 1-16).[44]

FIGURE 1-16 Florence Nightingale (1820–1910).

7. TWENTIETH CENTURY AND BEYOND

The spectacular advances in medicine during the 20th century would never have happened without the centuries of earlier progress. In the 20th century, medical colleges became well established in Europe

and the United States. The great contributions of the United States to medicine in the 20th century are linked to the early commitment to strong medical education. The importance of clinical research as a component of the teaching of medicine was recognized in 1925 by the American medical educator Abraham Flexner, who wrote, "Research can no more be divorced from medical education than can medical education be divorced from research."[45]

Two other dominant drivers of the progress in medicine through clinical research were government investment in biomedical research and private investment in the pharmaceutical industry. These investments, closely linked with academia, resulted in enhanced translation of basic observations to the bedside. Sir Alexander Fleming's discovery of penicillin in 1928 in Scotland spawned expansion of the pharmaceutical industry with the development of antibiotics, antiviral agents, and new vaccines. Banting and Best's discovery of insulin in 1921 in Canada was followed by the discovery of multiple hormones to save lives.

In the 1920s and 1930s, Sir Ronald Aylner Fisher (1890–1962), from the United Kingdom, introduced the application of statistics and experimental design.[46] Fisher worked with farming and plant fertility to introduce the concept of randomization and analysis of variance—procedures used today throughout the world. In 1930, Torald Sollman emphasized the importance of controlled experiments with placebo and blind limbs to a study—a rebirth of the "blinded" or "masked" studies originated by Benjamin Franklin in 1784. Sollman wrote, "Apparent results must be checked by the 'blind test,' i.e., another remedy or a placebo, without the knowledge of the observer, if possible." (Fig. 1-17)[47]

With these approaches many new drugs for treatment of hypertension, cardiovascular disease, manic depression, and epilepsy, to name a few, were developed.

The spectacular advances in the 20th century were associated with troubling events in clinical research that heightened public attention and formalized the field of clinical bioethics. The Nazi's human experimentation led to the "Nuremberg Code" in 1947 that was designed to protect human subjects by ensuring voluntary consent of the human subject and that the anticipated result of the research must justify the performance of the research. The Tuskegee syphilis experiments initiated in the 1930s and continued until 1972 in African American men and the Willowbrook hepatitis studies in the mid-1950s in children with Down syndrome highlighted the need to establish strict rules to protect research patients.

FIGURE 1-17 Testing puddings and gelatins at Consumers Union. Copyright 1945 by Consumers Union of U.S., Inc., Yonkers, NY. Reprinted with permission from the April 1945 issue of *Consumer Reports*.

In 1953, the U.S. National Institutes of Health (NIH) issued "Guiding Principles in Medical Research Involving Humans" that required prior review by medical committee of all human research to be conducted at the newly opened NIH Clinical Center. In 1962, the Kefauver-Harris amendments to the Food and Drug Act stipulated subjects be told if a drug is being used for investigational purposes, and subject consent must be obtained. In 1964, the World Medical Assembly adopted the "Declaration of Helsinki" stressing the importance of assessing risks and determining that the risks are outweighed by the potential benefits of research. In 1966, Henry Beecher pointed out major ethical issues in clinical research.[48] During the same year, the U.S. Surgeon General issued a memo to the heads of institutions conducting research with Public Health Service grants requiring prior review of all clinical research. The purpose was to ensure protection of research subjects, assess the appropriateness of the methods employed, obtain informed consent, and review the risks and benefits of the research; thus institutional review boards were established. In 1967, the Food and Drug Administration added the requirement that all new drug sponsors obtain informed consent for use of investigational drugs in humans.

In the past 50 years, clinical research has become big business. The pharmaceutical industry and the biotechnology industries have engaged university-based clinical investigators in the business of clinical research. Interaction between federal investigators and industry, encouraged by the U.S. Congress when it passed the

Federal Technology Transfer Act in 1986, successfully increased the translation of basic research to the bedside by government scientists. At the same time, however, the relationship between industry and academia grew closer and new ethical, legal, and social issues evolved. Clinical investigators became increasingly associated with real and perceived conflicts. Examples of these issues included promoting an investigator's financial or career goals while protecting the patient, protecting "unborn children" while pursuing the potential use of embryonic stem cells to rebuild damaged organs, and protecting patient confidentiality as a result of gene sequencing. As a result of these issues, the public engaged in debate about the safety of current and future generations of patients who volunteer to partner with the clinical investigator on protocols.

The opportunities for doing clinical research in the 21st century are greater than ever. Today, understanding and meeting public concern are as important for the clinical investigator as performing the clinical study. Principles for conducting clinical research have evolved from centuries of experience. As the science moves forward, ethical, legal, and social issues pose special challenges for the clinical investigator. These challenges are the focus of the following chapters of this book.

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CHAPTER

2

Ethical Principles in Clinical Research

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Clinical research has resulted in significant benefits for society, yet continues to pose profound ethical questions. This chapter describes ethical principles that guide clinical research and briefly considers the history of clinical research ethics and particular ethical challenges in randomized controlled trials.

1. DISTINGUISHING CLINICAL RESEARCH FROM CLINICAL PRACTICE

Clinical research involves the study of human beings in a systematic investigation of human biology, health, or illness, designed to develop or contribute to generalizable knowledge. Clinical research includes a set of activities meant to test a hypothesis, permit conclusions to be drawn, and thereby contribute to generalizable knowledge useful to others. The goal of clinical research is to generate knowledge useful to improving medical care or the public health and thus serve the common or collective good. The individual subject participating in clinical research may or may not benefit from participation.

Clinical research is distinct from clinical practice in that the purpose and goals of each, although not mutually exclusive, are quite different. The purpose of clinical practice is to diagnose, prevent, treat, or care for an illness or condition in a particular individual or group of individuals with the goal of meeting the needs of and benefiting that individual(s). Clinical practice is a set of activities designed to enhance the patient's well-being and has a reasonable expectation of success. In some cases, participation in clinical research does meet the health needs of, and benefit, individual patient-participants. In fact, through participation in good clinical research, an individual may receive a very high quality of patient care and treatment, yet that is not the goal of research, and much research does not directly benefit individual participants.

2. WHAT DOES ETHICS HAVE TO DO WITH CLINICAL RESEARCH?

Broadly, ethics is a systematic method of inquiry that helps us answer questions about how we ought to live and behave and why. With respect to clinical research, there are two fundamental ethical questions: (1) Should we do research with human subjects? Why or why not? and (2) If yes, how should it be done? In addressing the first question, two competing considerations are recognized. On the one hand, clinical research is valuable in generating practical knowledge useful for advancing or improving medical care and health. On the other hand, respect for the inviolability, safety, dignity, and freedom of choice of each individual is indispensable. Advancing or improving medical care and/or the public health is desirable as a public good—good for society. Such knowledge is knowledge in "the service of action, [because] health professionals seek knowledge in order to know how to best serve."[1] The pursuit of knowledge through research should be rigorous because false knowledge applied in practice can be harmful. Rigorous clinical research is an important means to the end of progress in medical and health care—progress that would not be possible without research. It has been claimed that conducting clinical research designed to understand human health and illness may be more than a social good; it may be a social imperative.[2] In contrast, it also has been asserted

that although progress in medical care and health is good, it is an optional good[3] and that other considerations, such as the primacy of the individual, should take precedence. Even if one accepts that improvement in medical care or health is a social good, and that clinical research is an essential means to that end, limits are necessary as progress is achieved through research with human beings. Human subjects who participate in research are the means to securing practical knowledge. Because human beings should never be used "merely as means to an end, but always as ends in themselves,"[4] the need to respect and protect human participants in research is paramount.

The primary ethical tension in clinical research, therefore, is that a few individuals are asked to accept some burden or risk as research subjects in order to benefit others and society. The beneficiaries of research may sometimes include the subjects themselves but also will include others with similar disorders or risk profiles, as well as future persons and society. Asking human subjects to bear any risk of harm or burden for the good of others creates a potential for exploitation. Ethical requirements for clinical research aim to minimize the possibility of exploitation by ensuring that research subjects are not "merely used" but are treated with respect while they contribute to the social good, and their rights and welfare are protected throughout the process of research. Through history, the perception and acceptance of the methods, goals, and scope of clinical research have shifted significantly along with attention to and appreciation of what respecting and protecting research subjects entails. A brief detour through the history of clinical research illustrates these changing perspectives.

3. HISTORY OF ETHICAL ATTENTION TO CLINICAL RESEARCH

3.1. Benefit to the Individual

For hundreds of years, research was done sporadically. There was little basis for a distinction between experimentation and therapy because most therapy was experimental. Systematic evidence of the effectiveness of medical interventions was rare. Experimental therapy was often used to try to benefit ill patients, but such "therapy" frequently contributed to or caused morbidity or mortality. Most researchers were medical practitioners, motivated to do what they thought best for their patients, and trusted to do the right thing. Fraud and abuse were minimized through peer censorship because there were no specific codes of ethics, laws, or regulations governing the conduct of research. Early regulations, such as the Pure Food and Drug Act of 1906 in the United States, prohibited unsubstantiated claims on medicine labels. Yet, research began to grow as an enterprise only after the development of penicillin and other early antibiotics and the passage of the Food, Drug, and Cosmetic Act in 1938 that required evidence of safety before a product was marketed.

3.2. Benefit to Society

Around World War II, there was a dramatic shift in clinical research with tremendous growth in research as an enterprise. Pharmaceutical companies were established; large amounts of both public and private money were devoted to research; and research became increasingly centralized, coordinated, standardized in method, and valued. Human subjects research entered what has since been described as an "unashamedly utilitarian phase."[5] During this period, individuals were often included as research subjects because they were available, captive, and possibly considered unimportant, but they were seen as making a contribution to society. Infectious diseases were a significant problem for the armed services. The federal government and the pharmaceutical industry supported intensive research efforts to develop vaccines and antibiotics for infectious diseases to help the soldiers.

A large part of this effort was accomplished through research conducted in prisons, orphanages, homes for the emotionally or developmentally disturbed, and with other institutionalized groups. There was a fairly clear distinction between research and therapy; subjects not necessarily in need of therapy were accepting a personal burden to make a contribution to society. A utilitarian justification was the basis of claims that some individuals could be used for the greater common good. Revelations of the Nazi medical experiments and war crimes raised concerns about research with human subjects.

3.3. Protection of Research Subjects

In the late 1960s and early 1970s in the United States, shock and horror at stories of abuse of human subjects led to intense scientific and public scrutiny and reflection, as well as debate about the scope and limitations of research involving human subjects. A renowned Harvard anesthesiologist, Henry Beecher, published a landmark article in the *New England Journal of Medicine* in 1966[6] questioning the ethics of 22 research studies conducted in reputable U.S. institutions. Accounts of and debate about the hepatitis B studies at Willow-

brook, the U.S. Public Health Service Tuskegee syphilis studies, and others all generated intense public attention and concern. Congressional hearings and action led to the passage in 1974 of the National Research Act (EL. 93-348) and the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This extremely influential body authored multiple reports and recommendations about clinical research, including reports on research with children and institutional review boards (IRBs). Included in their legacy is the Belmont Report, in which ethical principles underlying the conduct of human subjects research and their application are explicated.[7] The emphasis of the commission's work was the need to protect individuals participating in research from potential exploitation and harm. The commission's work provided the basis for subsequent federal regulations codified in 1981 in Title 45 U.S. Code of Federal Regulations, Part 46, titled "Protection of Human Subjects." These regulations in 1991 became the currently operative Common Rule (45CFR46).[8] The Common Rule governs the conduct of human subjects research funded through any one of 17 U.S. federal agencies. The major thrust of these federal regulations and many of the existing codes of research ethics is protection of subjects from the burdens and harms of research and the possibility of exploitation.

3.4. Research as a Benefit

Events in the late 1980s and 1990s altered some public perspectives on clinical research. Certain very articulate and vocal activists claimed that participation in research can be a benefit that individuals should not be denied rather than a harm to be protected from.[9] According to this perspective, espoused by activists for individuals with the human immunodeficiency virus and breast cancer, among others, participation in research is a benefit, protectionism is discrimination, and exclusion from research can be unjust. Empirical studies have demonstrated that oncology patients, for example, who participate in clinical trials benefit through improved survival.[10,11] Activism and changes in public attitudes about research led to substantive changes in the way research is done and drugs are approved.

In addition to the possible benefits of participation, it was also claimed that certain groups of people traditionally underrepresented in research were being denied the benefits of the application of knowledge gained through research.[12] Since 1994, the U.S. National Institutes of Health requires those who receive research funding to include certain groups of traditionally underrepresented subjects, such as women and ethnic minorities.[13] Since 1998, NIH guidelines emphasize the importance of including children in research.[14]

3.5. Community Involvement in Research

In recent years, the growth of genetics research and of international collaborative research, in particular, has highlighted an ethical need for more community involvement in research. Clinical research does not occur in a vacuum but is a collaborative social activity that requires the support and investment of involved communities, and it comes with inherent risks and potential benefits for communities. As such, involvement of the community in helping to set research priorities, planning and approving research, evaluating risks and benefits during and after a trial, and influencing particular aspects of recruitment, informed consent, and the form of community benefits demonstrates respect for the community and is likely to promote successful research.

4. CODES OF RESEARCH ETHICS AND REGULATIONS

Throughout this history several influential documents have helped to shape our sense of the contours of ethical research (Table 2-1). Most were written in response to specific crises or historical events, yet all have accepted an underlying assumption that research as a means to progress in medical care or health is good. The Nuremberg Code, a 10-point code on the ethics of human experimentation, was written as the concluding part of the judgment at the Nuremberg Trials (1949).[15] Established in response to Nazi experimentation, the Nuremberg Code recognized the potential value of research knowledge to society but emphasized the absolute necessity of the voluntary consent of the subject. The Nuremberg Code established that to be ethical, the conduct of research must

TABLE 2-1 Selected Codes and U.S. Regulations Guiding Research with Human Subjects

- The Nuremberg Code (1949)
- The Declaration of Helsinki (2000)
- The Belmont Report (1979)
- CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002)
- International Conference on Harmonization Guidelines for Good Clinical Practice (1996)
- Title 45 US CFR, Part 46–The Common Rule
- Title 21 US CFR, Parts 50 and 56

have the rights and welfare of the subject as its utmost priority. Most subsequent codes and guidelines for the ethical conduct of research have maintained this emphasis and incorporated the necessity of informed consent. The Declaration of Helsinki was developed by the World Medical Assembly in 1964 as a guide to the world's physicians involved in human subjects research.[16] The Declaration of Helsinki recognizes that some, but not all, medical research is combined with clinical care and emphasizes that patients' participation in research should not put them at a disadvantage with respect to medical care. The Declaration of Helsinki also recognized as legitimate research with people who cannot give their own informed consent but for whom informed permission would be obtained from a legal guardian. Recognized as "the fundamental document in the field of ethics in biomedical research,"[17] the Declaration of Helsinki has had considerable influence on the formulation of international, regional, and national legislation and regulations. The Declaration of Helsinki has been revised several times (1975, 1983, 1989, 1996), and most recently in 2000. Additions to the 2000 version of the declaration, especially those related to the use of placebo controls and obligations to assure post-trial access to tested interventions, have been the subject of continued debate among international researchers.

The Belmont Report, published by the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, described three broad ethical principles that guide the conduct of research and form the "basis on which specific rules could be formulated, criticized, and interpreted."[7] The three principles are respect for persons, beneficence, and justice. Respect for persons requires respect for the autonomous decision making of capable individuals and protection of those with diminished autonomy. Informed consent is the application of this principle in clinical research. Beneficence requires not deliberately harming others, as well as maximizing benefits and minimizing harms. This principle is applied to clinical research through careful risk–benefit evaluation. Justice requires a fair distribution of the benefits and burdens of research. The application of justice described in the Belmont Report is to the selection of research subjects.

The Council of International Organizations of Medical Sciences (CIOMS) in conjunction with the World Health Organization (WHO) issued *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, first in 1982 and revised in 1993 and 2002,[17] that explored the application of the Helsinki principles to the "special circumstances of many technologically developing countries." The CIOMS guidelines, noting an increase in international research, acknowledge differing circumstances in developing and non-Western countries, where there is generally less of a focus on the individual. CIOMS adopts the three ethical principles spelled out in the U.S. National Commission's Belmont Report and maintains most of the tenets of Nuremberg and Helsinki but provides additional and valuable guidance and commentary on externally sponsored research and research with vulnerable populations.

United States federal regulations found in Title 45 of the U.S. Code of Federal Regulations, Part 46 (45CFR46)[8] were first promulgated in 1981 for research funded by the Department of Health and Human Services (formerly the Department of Health, Education, and Welfare). These regulations were extended in 1991 as the Federal Common Rule, applicable to research funded by any of 17 U.S. federal agencies. Based on the recommendations of the National Commission, the Common Rule stipulates both the membership and the function of IRBs and specifies the criteria an IRB should employ when reviewing a research protocol and determining whether to approve it. The Common Rule also delineates the types of information that should be included in an informed consent document and how consent should be documented. Subparts B, C, and D of 45CFR46 describe additional protections for DHHS-funded research with fetuses and pregnant women, prisoners, and children, respectively.

The U.S. Food and Drug Administration (FDA) regulations[18] found in Title 21, USCFR, Part 50, "Protection of Human Subjects," and Part 56, "Institutional Review Boards," contain regulations that are similar, but not identical, to those found in the Common Rule. Compliance with FDA regulations is required for research that is testing a drug, biologic, or medical device for which FDA approval will ultimately be sought.

5. ETHICAL FRAMEWORK FOR CLINICAL RESEARCH

Based on a synthesis of guidance found in the various ethical codes, guidelines, and literature, a systematic framework of principles that apply sequentially to all clinical research was proposed.[19] According to this framework, clinical research must satisfy the following requirements to be ethical: social or scientific value, validity, fair subject selection, favorable risk–benefit ratio, independent review, informed consent, and respect for the enrolled subject[19] (Table 2-2).

TABLE 2-2 Ethical Framework for Clinical Research

Principles of Ethical Clinical Research	Description
Value	Research poses a clinically, scientifically, or socially valuable question that will contribute to generalizable knowledge about health or be useful to improving health. Research is responsive to health needs and priorities.
Validity	Study has an appropriate and feasible design and end points, rigorous methods, and feasible strategy to ensure valid and interpretable data.
Fair subject selection	The process and outcomes of subject and site selection are fair and based on scientific appropriateness, minimization of vulnerability and risk, and maximization of benefits.
Favorable risk–benefit ratio	Study risks are justified by potential benefits and value of the knowledge. Risks are minimized and benefits are enhanced to the extent possible.
Independent review	Independent evaluation of adherence to ethical guidelines in the design, conduct, and analysis of research.
Informed consent	Clear processes for providing adequate information to and promoting the voluntary enrollment of subjects.
Respect for enrolled participants	Study attends to and shows respect for the rights and welfare of participants both during and at the conclusion of research.

5.1. Value and Validity

The first requirement of ethical research is that the research question be worth asking—that is, have potential social, scientific, or clinical value. Research has value when the answers to the research question might offer practical or useful knowledge to understand or improve health. Critical to value is the usefulness of the knowledge gained, not whether the study results are positive or negative. Value is a requirement because it is unethical to expend resources or to ask individuals to assume risk or inconvenience for no socially valuable purpose.[20] A valuable research question then ethically requires validity and rigor in research design and implementation in order to produce valid, reliable, interpretable, and generalizable results. Poorly designed research—for example, studies with inadequate power, insufficient data, or inappropriate or unfeasible methods—is harmful because human and material resources are wasted and exposed to risk for no benefit.[19]

5.2. Fair Subject Selection

Fair subject selection requires that subjects be chosen for participation in clinical research based first on the scientific question, balanced by considerations of risk, benefit, and vulnerability. As described by the National Commission in the Belmont Report, fairness in both the processes and the outcomes of subject selection prevents exploitation of vulnerable individuals and populations and promotes equitable distribution of research burdens and benefits. Fair procedures means that investigators should select subjects for scientific reasons—that is, related to the problem being studied and justified by the design and the particular questions being asked—and not because of their easy availability or manipulability, or because subjects are favored or disfavored.[7] Extra care should be taken to justify the inclusion in research of vulnerable subjects, as well as to justify excluding those who stand to benefit from participation. Since exclusion without adequate justification can also be unfair, eligibility criteria should be as broad as possible, consistent with the scientific objectives and the anticipated risks of the research. Since distributive justice is concerned with a fair distribution of benefits and burdens, the degree of benefit and burden in a particular study is an important consideration. Scientifically appropriate individuals or groups may be fairly selected consistent with attention to equitably distributing benefits and burdens as well as minimizing risk and maximizing benefit.

Persons are considered vulnerable if their ability to protect or promote their own interests is compromised or they are unable to provide informed consent. Although there remains some disagreement about the meaning of vulnerability in research and who is actually vulnerable,[21] there is support for the idea that among scientifically appropriate subjects, the less vulnerable should be selected first. So, for example, an early drug safety study should be conducted with adults before children, and with consenting adults before including those who cannot consent.

Certain groups, such as pregnant women, fetuses, prisoners, and children, are protected by specific regulations requiring additional safeguards in research. According to U.S. regulations governing research with children, a determination of the permissibility of research with children depends on the level of research risk and the anticipated benefits. Accordingly, research that poses minimal risk to children is acceptable, research with more than minimal risk must either be counterbalanced by a prospect of direct therapeutic benefit for the children in the study, or by the importance of the question in children with the disorder

under study, or be approved by a special panel convened by the U.S. Secretary of DHHS.[22] Permission for the research participation of children is sought from their parents or legal guardians, and the child's assent is also sought whenever possible.

Fair subject selection also requires considering the outcomes of subject selection. For example, if women, minorities, or children are not included in studies of a particular intervention, then the results of the study may be difficult to apply to these groups and could actually be harmful. Therefore, study populations recruited for research should be representative of the populations likely to use the interventions tested in the research.[23]

Similarly, it has been argued that justice requires subjects to be among the beneficiaries of research. This means that subjects should be selected as participants in research from which they or others like them can benefit and not be asked to bear the burdens of research for which they can reap no benefits. This understanding of justice has raised important and challenging questions in the conduct of collaborative international research. Some have argued that if a drug or vaccine is tested and found effective in a certain population, there should be prior assurance that that population will have access to the drug or vaccine.[24] Alternatively, subjects or communities should be assured of and involved in negotiation about fair benefits from research that are not necessarily limited to the benefit of available products of research.[25]

5.3. Favorable Risk–Benefit Ratio

The ratio of risks to benefits in research is favorable when risks are justified by benefits to participants or society and research is designed in a way that minimizes risks and maximizes benefits to individual subjects. The ethical principle of beneficence obligates us to (1) do no harm and (2) maximize possible benefits and minimize possible harms. It is a widely accepted principle that one should not deliberately harm another individual regardless of the benefits that might be made available to others. However, as the Belmont Report reminds us, offering benefit to people and avoiding harm requires learning what is of benefit and what is harmful, even if in the process some people may be exposed to some risk of harm. To a great extent, this is what clinical research is about (i.e., learning about the benefits and harms of unproven methods of diagnosing, preventing, treating, and caring for human beings). The challenge for investigators and review groups in clinical research is to decide in advance when it is justifiable to seek certain benefits in research despite the risks, and when it is better to forego the possible benefits because of the risks. This is called a risk–benefit assessment.

The actual calculation and weighing of risks and benefits in research is complicated. Investigators in designing a study consider whether the inherent risks are justified by the expected value of the information and benefit to the participants. Studies should be designed in a way that risks to participants are minimized and benefits are maximized. When reviewing a study, an IRB must first identify the possible risks and benefits and then weigh them to determine if the relationship of risks to benefits is favorable enough that the proposed study should go forward or should instead be modified or rejected. When reviewing studies with little or no expected benefit for individual subjects, the IRB has the sometimes formidable task of deciding whether the risks or burdens to the subjects in the study are justified only by the potential value of the knowledge to be gained, sometimes a particularly difficult risk–benefit assessment. Prospective subjects do their own risk–benefit assessment to decide whether the risks of participating in a given study are acceptable to them and worth their participation.

Many kinds of risks and benefits may be considered in a risk–benefit assessment, including physical, psychological, social, economic, and legal. For example, in a genetics study, the physical risks may be limited to a blood draw or buccal swab, and assessment of the potential psychological and social risks may be more important. Investigators, reviewers, and potential subjects may not only have dissimilar perspectives about research but also are likely to assign different weights to risks and benefits. For example, IRBs consider only health-related benefits of the research in justifying risks, whereas subjects are likely to consider access to care or financial compensation as important benefits that may tip the balance for them in favor of participation. Acknowledging that risk–benefit assessment is not a straightforward or easy process does not in any way diminish its importance. Careful attention to the potential benefits to individuals or society of a particular study in relation to its risks, as well as consideration of the risks of not conducting the research, is one of the most important steps in evaluating the ethics of clinical research.

5.4. Independent Review

Independent review allows evaluation of the research for adherence to established ethical guidelines by individuals with varied expertise and no personal or business interests in the research. For most clinical research, this independent review is carried