Chapter 1

History and Background of Oncology Clinical Trials

Karri Donahue, MSN, RN, CCRP, and Heather Benzel, BSN, RN, CCRP

Introduction

The field of oncology has been extremely fortunate to experience the advancement of treatment from preliminary cancer surgeries offering limited results to in-depth, targeted therapies increasing the overall survival and quality of life for many patients with cancer. Because less than 5% of new patients with cancer participate in clinical trials, many resources are being developed in an effort to increase trial participation as well as quality and patient safety (American Society of Clinical Oncology, n.d.).

Understanding the history of clinical trials, including successes, failures, and the risk for patient endangerment, is paramount in establishing and maintaining a quality environment for clinical trial patient care. Through an elaborate sequence of events, clinical trials have developed layers of federal and international policies and procedures to help safeguard the patient experience, encourage increased participation, and facilitate the trajectory of oncology research.

History

Experimental research studies on human subjects can be traced to ancient times. Early clinical trials often were comparative studies (see Chapter 3) that focused on the prevention of communicable diseases and on nutritional disorders, which were prevalent until the latter half of the 20th century (Lilienfeld, 1982). As early as 1863, Rudolf Virchow deduced cancer to its cellular origin by using a microscope (DeVita & Rosenberg, 2012). In an effort to promote public health in the United States, a one-room laboratory was created in 1887 within the Marine Hospital Service (predecessor to the U.S. Public Health Service). The Hygienic Laboratory was established to provide funding for research on the prevention, detection, and treatment of disease. The Ransdell Act of 1930 was enacted to legislate public funding of medical research and changed the name of the Hygienic Laboratory to the National Institute of Health (Harden, n.d.). The name was later changed to the National Institutes of Health (NIH) to reflect the addition of new institutes.

The first documented clinical trial in the United States using a matched control group, random assignment, and single-blinding (see Chapter 4) was reported in 1931 by J. Burns Amberson and colleagues. The trial evaluated the use of sanocrysin, a gold compound, in the treatment of patients with pulmonary tuberculosis treated at the W.H. Maybury Sanatorium in Northville, Michigan. Twenty-four patients were matched and then randomized to either group I (sanocrysin-treated) or group II (control). As a result of substandard and often absent informed consent processes, subjects were not aware of the differences in the treatment regimens between the groups (Lilienfeld, 1982).

In 1937, President Franklin D. Roosevelt signed the National Cancer Institute Act, which established the National Cancer Institute (NCI) as a division of NIH. NCI was the first disease-oriented institute of NIH, now totaling 27 institutes (DeVita & Rosenberg, 2012). The act mandated funding to support cancer research and training (Jenkins & Lake, 1988; White-Hershey & Nevidjon, 1990). The Federal Food, Drug, and Cosmetic Act was passed the following year to ensure that a drug demonstrated safety in humans before it could be marketed to the public (Swann, 1998).

The authors would like to acknowledge Sheila Breslin, RN, MS, for her contribution to this chapter that remains unchanged from the previous edition of this book.

In 1944, scientist Oswald Avery discovered that cellular information was not transmitted by proteins but rather by DNA (DeVita & Rosenberg, 2012). With this discovery, the door to biotechnology research and sequencing of the genome was opened. Later, it would lead to developing the bench-to-bedside therapies concept of translating what works in the laboratory and applying this to the patient treatment level.

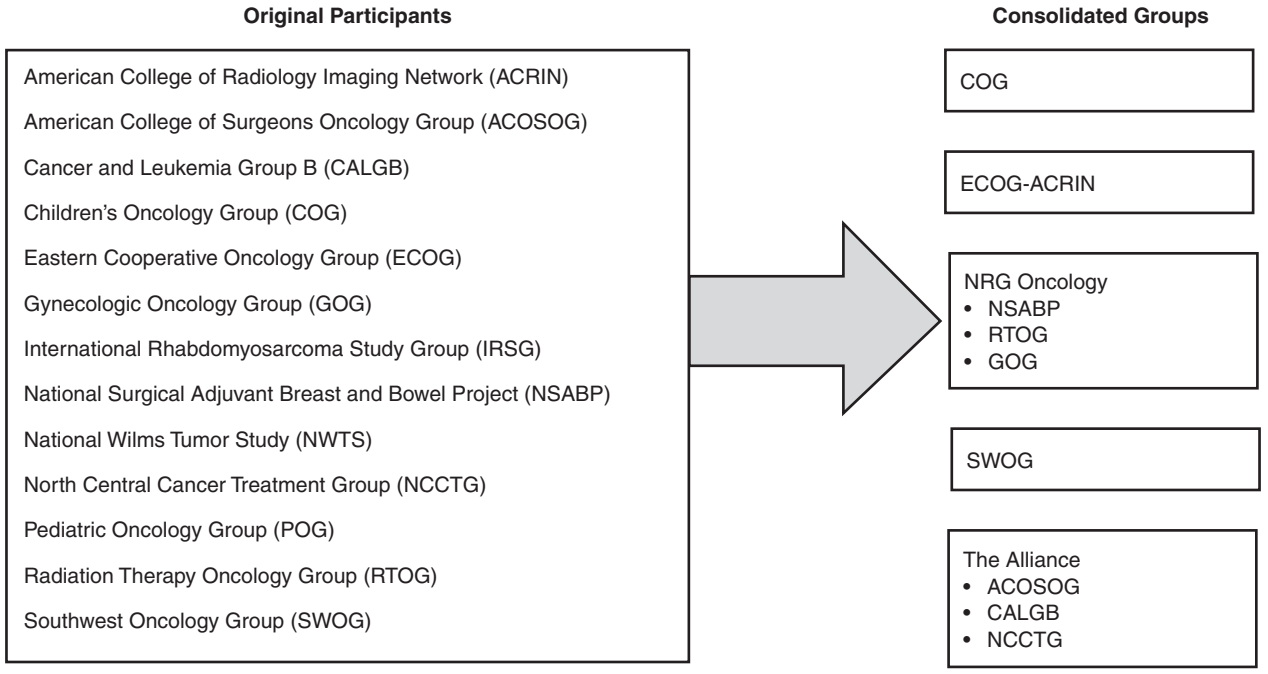
NCI began to fund cooperative oncology groups in an effort to expand enrollment in clinical trials in the mid-1950s. Cooperative oncology groups are composed of groups of physicians at institutions nationally who collaboratively design and implement clinical trials. The Clinical Trials Cooperative Group Program was originally composed of four pediatric and nine adult groups (Children's Oncology Group, n.d.; NCI, n.d., 2005) (see Figure 1-1). The initial consolidation occurred in 2000, when the four pediatric groups became one group, known as the Children's Oncology Group. The next consolidation occurred in 2014, when the nine adult groups were merged into four adult groups. The Cancer Therapy Evaluation Program, a branch of NCI's Division of Cancer Treatment, oversees the cooperative oncology groups (Cheson, 1991).

During the 1950s, there were great advancements in treatment with radiation and chemotherapy. Cobalt teletherapy was introduced to treat patients with radiation, along with the advancement in technology that allowed the beams to be delivered more accurately to the tumor and minimized exposure to normal tissue (DeVita & Rosenberg, 2012). In the mid-1970s, two breakthrough studies evaluated the use of single-agent and combination therapy in adjuvant breast cancer. Although NCI (2007) developed the combination regimen consisting of cyclophosphamide, methotrexate, and fluorouracil, the study was performed in conjunction with the Milan Cancer Institute in Italy because no major U.S. institution was willing to test combination therapy. Both studies had positive outcomes, and as a result of increased availability of treatments, including hormone and chemotherapeutic agents, as well as clinical trials and increasing diagnostic tools, the rate of cancer deaths began to decline by 1991. The war on cancer mandated the support of research as well as the reduction of incidence, morbidity, and mortality from cancer; these advancements assisted in fulfilling that directive (DeVita & Rosenberg, 2012).

The National Cancer Act of 1971 resulted in a large increase in NCI funding. NCI was charged with the responsibility of conducting basic scientific research in oncology and applying the results to clinical practice. The National Cancer Act also promoted the development of oncology training programs, facilities, and public education services (Jenkins & Hubbard, 1991; Jenkins & Lake, 1988).

By 1973, most oncology clinical trials were conducted at NCI-designated comprehensive cancer centers that received core grants from NCI to fund operations. Community oncologists, however, still were treating patients with cancer who might be eligible for enrollment in a clinical trial. In response, NCI developed outreach programs

Figure 1-1. U.S.-Based Clinical Trials Cooperative Group Program Members



Note. Based on information from Children's Oncology Group, n.d.; National Cancer Institute, n.d.

in an attempt to make clinical trials available to larger numbers of patients with cancer and to improve patient accrual into the trials. These programs provided funding for community physicians to participate in NCI-sponsored clinical trials (Cheson, 1991; Jenkins & Hubbard, 1991). Currently, approximately 85% of patients with cancer are seen and treated at community cancer centers or hospitals near their home communities with access to a wide array of clinical trial opportunities (NCI, 2014b).

The Cooperative Group Outreach Program, established in 1976 by the NCI Division of Cancer Treatment, allowed community physicians to affiliate with a cooperative group to offer their patients access to cooperative group trials. The Community Clinical Oncology Program, instituted in 1983, differed from the Cooperative Group Outreach Program in its funding source, research focus, accrual requirements, and affiliation policies. The NCI Division of Cancer Prevention and Control (DCPC) funded the Cooperative Group Outreach Program. Community physicians affiliated with cancer centers and cooperative groups to form a research base. In addition to cancer treatment, DCPC-sponsored clinical trials focused on prevention and early detection of cancer. The High-Priority Clinical Trials Program, established in 1988, targeted phase III cooperative group trials as high priority, thus increasing accrual (Cheson, 1991).

Transition took place among the cooperative groups, and NCI wanted to take the program a step further. NCI asked the Institute of Medicine (IOM) in 2009 to review the Clinical Trials Cooperative Group Program. In 2010, IOM recommended to consolidate the Clinical Trials Cooperative Group Program and fund no more than five groups (four adult groups and one pediatric group) (NCI, 2011) (see Figure 1-1). Grants were scheduled to be awarded to the five groups in spring 2014. The purpose of the consolidation was to (a) develop the competence of operations and data management centers so that more integration takes place, (b) enhance the ability to function together on a larger scale, and (c) prevent redundant studies that require large sample sizes to answer clinical questions among cooperative groups (NCI, 2012).

The NCI Board of Scientific Advisors approved the creation of the NCI Community Oncology Research Program (NCORP) on June 24, 2013. NCORP's purpose is to bring state-of-the-art cancer prevention, control, treatment, and imaging clinical trials; cancer care delivery research; and disparities studies to individuals in their own communities. NCORP is based at the Division of Cancer Prevention and replaced both the Community Clinical Oncology Program Network and the NCI Community Cancer Centers Program in 2014. To participate, institutions must apply within one of three NCORP components: research bases, community sites, and minority/underserved community sites. NCI aimed to provide an estimated $40.8 million and up to 40 awards for fiscal year 2014. Future amounts will be determined based on annual appropriations (NCI, 2013).

NIH released its NIH Roadmap in the early part of the 2000s, which enhanced the bench-to-bedside process by combining basic science and clinical medicine from clinical researchers to medical practitioner to patient (Kaitlin & DiMasi, 2011). With this came the push for bio-innovation. In 2004, the U.S. Food and Drug Administration (FDA) introduced the Critical Path Initiative with a goal of improving translation of basic research to safe and effective medicine and treatment options for patients (Kaitlin & DiMasi, 2011). This fostered identification of various biomarkers and other tools used to improve patient outcomes and survivorship rates and uncovered the potential to treat patients with targeted therapy, based on biomarkers and molecular abnormalities.

Growth of International Guidelines and U.S. Regulations

Fraudulent claims of safety and efficacy, as well as abuses in drug and device manufacturing, were rampant in the United States in the late 1800s, leading to untold numbers of serious injuries and deaths. As a result of these abuses, the 1906 Food and Drug Act was signed into law, establishing the first federal regulatory standards to ensure food and drug purity and truth in labeling. The Bureau of Chemistry, whose name was changed in 1930 to the U.S. Food and Drug Administration, implemented these laws. In 1938, a new, more stringent law was enacted that mandated drug safety testing and, for the first time, FDA approval prior to marketing. This legislation also brought the marketing of medical devices under the FDA's regulatory purview. The Kefauver-Harris Amendments to the Food and Drug Act were passed in 1962 after the discovery that thalidomide could cause fetal abnormalities. The amendment required preclinical testing of drugs, as well as proof of efficacy and safety, before use in humans. It also required that research subjects provide informed consent before participating in clinical trials (Swann, 1998) (see Chapter 14).

Research on vulnerable populations, such as slaves, prison inmates, people with mental illness and cognitive disabilities, the poor, children, and minority groups, was conducted in the United States from the mid-1800s to the mid-1900s without participants' informed consent (Allen, 1994; Merkatz & Junod, 1994). However, it was not until the exposure of medical atrocities performed on prisoners during World War II that a code of ethics for human experimentation was developed. The resulting Nuremberg Code of 1947 serves as the foundation for the ethical principles governing clinical research today (McCarthy, 1994; Merkatz & Junod, 1994; Nuremberg Code, 1949).

In 1964, the World Medical Association developed the Declaration of Helsinki, a set of international ethical guidelines for physicians involved in biomedical research.

These guidelines recommended preclinical studies before the implementation of human clinical trials, scientific justification for experimentation in humans, and a written protocol document with review by an independent committee. The declaration posited that research be conducted only by qualified medical personnel and offered guidelines for the provision of informed consent from human participants. The Declaration of Helsinki has been updated periodically since 1964, with the most recent update approved in 2013 (World Medical Association, n.d., 1996).

After the passage of the National Research Act (1974), the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created to develop written policies for the protection of human subjects. Published in 1979, the resulting Belmont Report led to the establishment of institutional review boards (IRBs), outlined protocol design criteria, and recommended that written informed consent be obtained from all research subjects (Jenkins & Hubbard, 1991; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). These policies were codified in 1981 in the *Code of Federal Regulations* (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979; Sparks, 2002).

One of the most important of these regulations, known as the "Common Rule" (Basic HHS Policy for Protection of Human Research Subjects, 2009), outlined specific measures that investigators and institutions must follow to protect subjects who participate in federally funded research. The Common Rule included criteria for the provision of informed consent, guidelines for the conduct of IRBs, and requirements for the protection of vulnerable populations, as well as other subject protections such as the mandate for data and safety monitoring boards, regulations regarding investigator conflict of interest, and training of clinical research personnel (NCI, 2005).

In 1996, members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) finalized a set of good clinical practice (GCP) standards for the conduct of clinical trials. Officially known as the *ICH Harmonised Tripartite Guideline for Good Clinical Practice* (ICH, 1996), its 13 principles (not regulations) were adopted by the United States, the European Union, Japan, Australia, Canada, and a number of other countries, as well as the World Health Organization. In addition to establishing consistent principles for the protection of human subjects, the goal of the ICH GCP guidelines is to streamline regulatory approvals of new drugs by developing consistent recommendations for the design, implementation, reporting, and interpretation of clinical trials worldwide (Dixon, 1999; U.S. FDA, 1996). (See Chapter 9: Good Clinical Practice for additional information.)

Passed by Congress in 1996 and implemented by the U.S. Department of Health and Human Services (DHHS) in 2003, the Health Insurance Portability and Accountability Act (HIPAA) influenced the conduct of clinical trials, mandating specific privacy protections for trial participants. For a detailed examination of the impact of HIPAA on clinical trials, the reader is referred to NIH Publication Number 04-5495 (U.S. DHHS, 2004).

Federalwide Assurance for the Protection of Human Subjects (FWA) (see Appendix 1) was passed in 2005 with the intent of enforcing that all research involving human study participants is subject to federal regulations and must be guided by ethical principles. The ethical principles specifically cited include the Belmont Report in addition to other appropriate ethical standards recognized by federal departments and agencies that have adopted the Common Rule (U.S. DHHS, 2014a).

The Office for Human Research Protections (OHRP) oversees the safety of participants in federally funded clinical trials. FWA is the only type of assurance of compliance currently accepted and approved by OHRP for institutions engaged in nonexempt human subject research conducted or supported by DHHS (U.S. DHHS, 2014b).

Treatment of Minorities and Women

Despite the increasing incidence of and mortality from cancer in the African American community, this group has been underrepresented in clinical trials (George, Duran, & Norris, 2014). Lack of participation by minorities in general and specifically African Americans largely had been attributed to fears of exploitation generated by the Tuskegee syphilis experiment conducted by the U.S. Public Health Service from the 1930s to the 1970s. This study allowed African American men with syphilis to go untreated, even after curative treatment was available, in order to study the natural progression of the disease. Therefore, there is a mistrust, feeling of fear, and lack of confidence regarding medical establishments and research among minorities, which continues to be a barrier for many researchers (Allen, 1994; George et al., 2014; McCarthy, 1994).

Lack of access to state-of-the-art health care; cultural or ethnic factors; economic status; language or literacy barriers; and long-standing fear, apprehension, and skepticism have been identified as obstacles to minority participation in clinical trials (George et al., 2014; NCI, 2005). However, because 40% of Community Clinical Oncology Program annual referrals are from minority populations, NCI provides funding to institutions that serve a high percentage of minority groups through its Minority-Based Community Clinical Oncology Program (MBCCOP), which was established in 1990 (NCI, 2005).

According to George and colleagues (2014), more than 30% of the U.S. population is of racial or ethnic minority; however, racial and ethnic minorities represent less than 18% of the participants in clinical trials. Causes of low participation in clinical trials by minority groups are complex. Reasons for low accrual may be due in part to a deficiency of available trials in communities with high disparate populations as well as the study design. Often disparate populations lack sufficient health care, resulting in an increase of disease processes. Clinical trial eligibility is often rigid and exclusionary of many of these comorbidities. MBCCOP accrued 10% of all ethnic minorities participating in NCI-approved clinical trials (NCI, 2005).

In 1977, women were excluded from participation in clinical trials because of concerns about the potential teratogenic effects of untested drugs on a developing fetus, partially as a result of severe birth defects caused by the drug thalidomide (effective in preventing nausea in pregnant women). This FDA-mandated exclusion applied to phase I clinical trials involving the use of untested drugs in pregnant women or women of childbearing potential. However, in practice, the exclusion was extended to all women in all phases of clinical trials (McCarthy, 1994).

These policies severely limited knowledge about gender- and race-related differences in drug safety and efficacy (Allen, 1994; McCarthy, 1994; Merkatz & Junod, 1994; Millon-Underwood et al., 1993). The AIDS epidemic highlighted the potentially discriminatory nature of these exclusionary practices (Kelly & Cordell, 1996; McCarthy, 1994). Between 1992 and 1993, 15% of all new AIDS cases reported were in women, and almost 75% of these women were either African American or Hispanic (Allen, 1994).

In 1986, NIH drafted its first policy promoting the inclusion of women in clinical trials (La Rosa, 1994). Since implementation of this policy, women of childbearing potential have been allowed to participate in phase I clinical trials as long as they are not pregnant. They must be advised of the potential for fetal damage if they become pregnant and must agree to use effective contraception while participating in a study (Merkatz & Junod, 1994). In 1990, NCI created the Office of Research on Women's Health to promote research on women's health issues and the participation of women in clinical trials (Pinn, 1994). The NIH Revitalization Act, passed by Congress in 1993, mandated the inclusion of women and minorities in all NIH-sponsored clinical trials (Pinn, 1994). As a result, participation of women in clinical trials is growing. Study data show women comprised 49% of NCI cooperative study enrollments between 1996 and 2002 for breast, colorectal, lung, and prostate therapeutic trials (Murthy, Krumholz, & Gross, 2004).

In 2010, the book *The Immortal Life of Henrietta Lacks,* written by Rebecca Skloot, was published. This story exposed the public to the struggle between ethics, race, and medicine. The book is based on the true story of Henrietta Lacks, better known as HeLa in the scientific world, who was diagnosed with cervical cancer in 1951. Cells were retrieved for the purpose of diagnosing her cancer; however, additional cells were taken without her knowledge or consent to contribute to research and are still being used in research today. The family was aware of the use of their mother's cells but was unaware of the full impact those cells have made in laboratories across the world until Skloot started communicating with them. With the use of Henrietta Lacks' cells and the publication of Skloot's book, bioethics began evolving, and the public became aware of the triumphs and tribulations of research today.

Treatment of Children and Older Adults

Historically, participation of children in cancer clinical trials has far exceeded adult participation. This is, in part, because childhood cancers are rare, and most children with cancer are treated at major academic institutions with access to clinical trials (Sateren et al., 2002). However, because children represent a vulnerable population, special protections have been implemented to safeguard their treatment. In 1983, laws to protect children in clinical trials were added to the *Code of Federal Regulations* (Burns, 2003; Hirtz & Fitzsimmons, 2002; Sparks, 2002).

Concerns have been raised that drugs used to treat adults were being administered without adequate testing in children (Hutchins et al., 1999; Sateren et al., 2002). In 1998, NIH issued a policy mandating the inclusion of children in clinical trials unless scientifically or ethically contraindicated (NIH, 1998). Then in 2002, the Best Pharmaceuticals for Children Act was passed, amending the Federal Food, Drug, and Cosmetic Act to improve drug safety and efficacy testing prior to use in children (Burns, 2003). Until recently, parental consent alone was sufficient for children younger than 18 years old to participate in clinical trials. Now, children younger than 18 years old are asked for their assent if they are mature enough to understand the trial and the expectations of the study. Although assent, unlike informed consent, is not required by law, many IRBs require it (NCI, 2014) (see Chapter 14: Informed Consent).

Underrepresentation of the older adult population has been another concern in clinical trials. In 1989, FDA published recommended guidelines for inclusion of older adults in clinical trials. However, they continue to be proportionally underrepresented in clinical trials, despite cancer incidence and mortality rates being highest in this population. Suggested reasons for underrepresentation include concerns about toxicities, the presence of comorbid conditions, perceived lack of benefit, advanced stage of disease at diagnosis, lack of awareness,

quality-of-life concerns, and a variety of socioeconomic barriers (Hutchins, Unger, Crowley, Coltman, & Albain, 1999; Lewis et al., 2003; Talarico, Chen, & Pazdur, 2004).

Older adults' lack of participation in clinical trials may not only limit the generalizability of results to older patients, but actually may result in less aggressive approaches to treatment because of misconceptions about tolerability, thereby compromising survival outcomes (Hutchins et al., 1999; Talarico et al., 2004). Excluding the older population is problematic because it is the greatest burden to healthcare costs in the United States (Herrera et al., 2010). Herrera and colleagues (2010) noted that 36% of personal healthcare dollars are spent on older adults, and older adults spend 42% of all prescription drug dollars. Increased representation of older adults in clinical trials, therefore, is critically important. Today, cooperative group trials, such as treatment (e.g., chemotherapy), quality-of-life trials, and registries, are designed specifically to include older adults.

Table 1-1 summarizes the significant events in the history of clinical trials development.

Evolution of National Healthcare Reform

In 2007, Medicare's Clinical Trial Policy (Centers for Medicare and Medicaid Services, 2007) revised the coverage for Medicare patients who participate in clinical trials. This revision helped to cover expenses accrued during participation in qualified clinical trials. While many states have adopted a variety of state-specific agreements to cover varying aspects of clinical trial participation, very little consistency exists among insurance carriers across the nation. In March 2010, the enactment of the Patient Protection and Affordable Care Act introduced requirements for insurance companies to provide coverage for routine costs associated with clinical trial participation (Phillips, 2010). With this in place, patients are able to choose the best option for treatment without worrying that certain tests or procedures will not be covered based on their participation in a clinical trial (Repucci, 2012). The new requirements went into full effect in 2014. The federal law will address coverage in all 50 states as well as the District of Columbia and includes Employee Retirement Income Security Act (known commonly as ERISA) plans, "self-insured" plans that are not mandated by state regulations (Phillips, 2010).

Summary

The evolution of clinical trials has resulted in dramatic improvements in the prevention and treatment of many diseases, including cancer. Advances in medicine, improved surgical techniques, the development of new drugs and devices, the application of statistical techniques to research studies, recognition of the need for regulation, and the development of ethical codes all have influenced how clinical trials are now conducted both in the United States and internationally. The focus today is not only the treatment and prevention of cancer, but also patients' symptom management and qual-

Table 1-1. Selected Events in the History of U.S. Oncology Clinical Trials Development

Year	Event
1747	Lind conducts the first documented comparative study on patients with scurvy.
1800s	Drugs and vaccines to treat smallpox, diphtheria, and cholera are developed and tested.
1887	The National Institutes of Health (NIH) is founded.
1900s	Research on prevention and treatment of infectious diseases begins.
1906	The Food and Drug Act, regulating drug purity, safety, and labeling, is signed into law.
1937	The National Cancer Institute Act establishes the National Cancer Institute (NCI).
1938	The Federal Food, Drug, and Cosmetic Act replaces the 1906 Food and Drug Act and requires that drugs be tested for safety before marketing.
1947	The Nuremberg Code establishes a basic code of ethics for experimentation on human subjects.
1962	The Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act mandate preclinical testing and the provision of informed consent.
1964	The Declaration of Helsinki establishes specific guidelines for physicians conducting human research.

(Continued on next page)

Table 1-1. Selected Events in the History of U.S. Oncology Clinical Trials Development *(Continued)*

Year	Event
1966	U.S. Surgeon General policy mandates independent review of all research on human subjects, proposing the establishment of institutional review boards.
1971	The National Cancer Act mandates NCI to conduct and apply basic cancer research.
1974	The National Research Act establishes the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.
1976	NCI initiates the Cooperative Group Outreach Program.
1979	The Belmont Report outlines ethical principles and guidelines for protection of human subjects.
1981	Laws governing the protection of human subjects in research funded by the U.S. Department of Health and Human Services (DHHS) are added to the *Code of Federal Regulations.*
1983	NCI funds Community Cancer Outreach Programs.
1986	NIH establishes policies for the inclusion of women in clinical trials.
1988	NCI establishes the High-Priority Clinical Trials Program.
1989	The U.S. Food and Drug Administration publishes guidelines for the inclusion of older adult patients in clinical trials.
1990	The Office of Research on Women's Health is created.
1991	Sixteen federal agencies adopt the federal policy for the protection of human subjects, known as the "Common Rule."
1993	The NIH Revitalization Act mandates the inclusion of women and minorities in NIH-sponsored clinical trials.
1996	The International Conference on Harmonisation establishes good clinical practice guidelines for human subject research. Congress passes the Health Insurance Portability and Accountability Act (HIPAA).
1997	The Food and Drug Modernization Act mandates establishment of a public resource for information on clinical trials.
1998	NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects mandates that children must be included in all NIH-sponsored research except under certain circumstances.
2000	The World Health Organization establishes international guidelines for ethics committees involved in the review of biomedical research.
2002	The Best Pharmaceuticals Act for Children amends the Federal Food, Drug, and Cosmetic Act to improve drug safety and efficacy testing for children.
2003	DHHS implements HIPAA.
2004	The International Committee of Medical Journal Editors issues a statement mandating public registration of clinical trials, including a description of informed consent and ethics committee approval as prerequisites for manuscript publication.
2005	Federalwide Assurance for the Protection of Human Subjects is required for all studies funded or conducted by DHHS that involve human subjects.
2006	NCI initiates phase 0 clinical trials to study the pharmacokinetics and pharmacodynamics of molecular-targeted drugs.
2007	Medicare's Clinical Trials Policy is revised with updated coverage rules for Medicare.
2007	Pilot program of NCI Community Cancer Centers Program (NCCCP) is launched and focuses efforts on cancer research, improving quality cancer care, and survivorship for patients who are treated at community hospitals.
2010	Enactment of the Patient Protection and Affordable Care Act requires insurers to cover routine costs of participation in clinical trials.
2012	Clinical Trials Cooperative Groups are consolidated from 13 groups to 5 (4 adult and 1 pediatric).
2013	NCI Community Oncology Research Program (NCORP) is created to bring state-of-the-art cancer prevention, control, treatment, and imaging clinical trials, cancer care delivery research, and disparities studies to individuals in their own communities. NCORP replaces the Community Clinical Oncology Program and the NCI Community Cancer Centers Program.
2014	Insurance coverage requirements for clinical trial participation go into effect as mandated by the Patient Protection and Affordable Care Act.

ity of life. Developments have been made to include more of the disparate populations and increase outreach activities within communities. Patients are more educated about their diagnosis and potential clinical trials and frequently seek out participation in research activities.

Key Points

- The progress made in clinical trials has positively affected the prevention and treatment of many diseases, including cancer.
- Factors that have influenced the way in which clinical trials are conducted include medical and surgical advances, development of new drugs and devices, application of statistical techniques to research studies, recognition of the need for regulation, and development of ethical codes.
- The focus today is not only the treatment and prevention of cancer but also symptom management and quality of life, genomics, personalized medicine, and biospecimens.

References

Allen, M. (1994). The dilemma for women of color in clinical trials. *Journal of the American Medical Women's Association, 49,* 105–109.

American Society of Clinical Oncology. (n.d.). About clinical trials. Retrieved from http://www.cancer.net/navigating-cancer-care/how-cancer-treated/clinical-trials/about-clinical-trials

Basic HHS Policy for Protection of Human Research Subjects, 45 C.F.R. 46 (2009). Retrieved from http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

Burns, J.P. (2003). Research in children. *Critical Care Medicine, 31,* S131–S136.

Centers for Medicare and Medicaid Services. (2007, October 9). National coverage determination (NCD) for routine costs in clinical trials. Retrieved from http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1&ncdver=2&bc

Cheson, B.D. (1991). Cancer clinical trials: Clinical trials programs. *Seminars in Oncology Nursing, 7,* 235–242.

Children's Oncology Group. (n.d.). Our history. Retrieved from https://childrensoncologygroup.org/index.php/history

DeVita, V.T., & Rosenberg, S.A. (2012). Two hundred years of cancer research. *New England Journal of Medicine, 366,* 2207–2214. doi:10.1056/NEJMra1204479

Dixon, J.R., Jr. (1999). The International Conference on Harmonization good clinical practice guideline. *Quality Assurance, 6,* 65–74.

George, S., Duran, N., & Norris, K. (2014). A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders. *American Journal of Public Health, 104,* e16–e28.

Harden, V.A. (n.d.). A short history of the National Institutes of Health. Retrieved from http://history.nih.gov/exhibits/history/index.html

Herrera, A.P., Snipes, S.A., King, D.W., Torres-Vigil, I., Goldberg, D.S., & Weinberg, A.D. (2010). Disparate inclusion of older adults in clinical trials: Priorities and opportunities for policy and practice changes. *American Journal of Public Health, 100*(Suppl. 1), S105–S112.

Hirtz, D.G., & Fitzsimmons, L.G. (2002). Regulatory and ethical issues in the conduct of clinical research involving children. *Current Opinion in Pediatrics, 14,* 669–675.

Hutchins, L.F., Unger, J.M., Crowley, J.J., Coltman, C.A., & Albain, K.S. (1999). Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *New England Journal of Medicine, 341,* 2061–2067.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. (1996, June 10). *ICH harmonised tripartite guideline: Guideline for good clinical practice, E6(R1).* Retrieved from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Jenkins, J., & Hubbard, S. (1991). History of clinical trials. *Seminars in Oncology Nursing, 7,* 228–234.

Jenkins, J.F., & Lake, P.C. (1988). Celebration of an era of public service at the National Institutes of Health and the National Cancer Institute. *Cancer Nursing, 11,* 58–64.

Kaitlin, K.I., & DiMasi, J.A. (2011). Pharmaceutical innovation in the 21st century: New drug approvals in the first decade, 2000–2009. *Clinical Pharmacology and Therapeutics, 89,* 183–188.

Kelly, P.J., & Cordell, J.R. (1996). Recruitment of women into research studies: A nursing perspective. *Clinical Nurse Specialist, 10,* 25–28.

La Rosa, J.H. (1994). Office of Research on Women's Health: National Institutes of Health and the women's health agenda. *Annals of the New York Academy of Sciences, 736,* 196–204.

Lewis, J.H., Kilgore, M.L., Goldman, D.P., Trimble, E.L., Kaplan, R., Montello, M.J., … Escarce, J.J. (2003). Participation of patients 65 years of age or older in cancer clinical trials. *Journal of Clinical Oncology, 21,* 1383–1389. doi:10.1200/JCO.2003.08.010

Lilienfeld, A.M. (1982). Ceteris paribus: The evolution of the clinical trial. *Bulletin of the History of Medicine, 56,* 1–18.

McCarthy, C.R. (1994). Historical background of clinical trials involving women and minorities. *Academic Medicine, 69,* 695–698.

Merkatz, R.B., & Junod, S.W. (1994). Historical background of changes in FDA policy on the study and evaluation of drugs in women. *Academic Medicine, 69,* 703–707.

Millon-Underwood, S., Sanders, E., & Davis, M. (1993). Determinants of participation in state-of-the-art cancer prevention, early detection/screening, and treatment trials among African-Americans. *Cancer Nursing, 16,* 25–33. Retrieved from http://journals.lww.com/cancernursingonline/Citation/1993/02000/Determinants_of_participation_in_state_of_the_art.2.aspx

Murthy, V.H., Krumholz, H.M., & Gross, C.P. (2004). Participation in cancer clinical trials: Race-, sex-, and age-based disparities. *JAMA, 291,* 2720–2726. doi:10.1001/jama.291.22.2720

National Cancer Institute. (n.d.). NCI's Clinical Trials Cooperative Group Program. Retrieved from http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group

National Cancer Institute. (2005). *Cancer clinical trials: The in-depth program* [NIH Publication No. 05-5051]. Bethesda, MD: Author.

National Cancer Institute. (2007, June 4). New approaches to cancer drug development and clinical trials: Questions and answers. Retrieved from http://www.cancer.gov/newscenter/pressreleases/PhaseZeroNExTQandA/print?page=&keyword

National Cancer Institute. (2011). A closer look: Cancer clinical trials system restructuring moves forward. *NCI Cancer Bulletin, 8*(24). Retrieved from http://cancer.gov/ncicancerbulletin/121311/page8/print

National Cancer Institute. (2012). *Cancer: Changing the conversation—The nation's investment in cancer research.* Retrieved from http://www.cancer.gov/aboutnci/budget_planningleg/plan-2012

National Cancer Institute. (2013). *Community Oncology Research Program guidelines.* Retrieved from http://prevention.cancer.gov/files/programs-resources/NCORPProgramGuidelines.pdf

National Cancer Institute. (2014a). Children's assent. Retrieved from http://www.cancer.gov/clinicaltrials/learningabout/patientsafety/childrensassent

National Cancer Institute. (2014b). NCI Community Cancer Centers program pilot: 2007–2010. Retrieved from http://ncccp.cancer.gov/Media/FactSheet.htm

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979, April 18). *The Belmont report: Ethical principles and guidelines for the protection of human subject of research.* Retrieved from http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

National Institutes of Health. (1998, March 6). NIH policy and guidelines on the inclusion of children as participants in research involving human subjects. Retrieved from http://grants.nih.gov/grants/guide/notice-files/not98-024.html

National Research Act, Pub. L. No. 93-348 (1974). Retrieved from http://history.nih.gov/research/downloads/PL93-348.pdf

Nuremberg Code. (1949). In *Trials of war criminals before the Nuremberg military tribunals under Control Council Law No. 10* (Vol. 2, pp. 181–182). Retrieved from http://www.hhs.gov/ohrp/archive/nurcode.html

Phillips, C. (2010). Insurance coverage expanding for cancer clinical trials. *NCI Cancer Bulletin, 7*(10). Retrieved from http://www.cancer.gov/ncicancerbulletin/051810/page5

Pinn, V.W. (1994). The role of the NIH's Office of Research on Women's Health. *Academic Medicine, 69,* 698–702. Retrieved from http://journals.lww.com/academicmedicine/pages/articleviewer.aspx?year=1994&issue=09000&article=00003&type=abstract

Repucci, N. (2012). A step-by-step checklist for conducting a clinical trial Medicare coverage analysis. *Medical Research Law and Policy Report,* pp. 1–9. Retrieved from http://www.dentons.com/en/insights/articles/2012/october/4/a-stepbystep-checklist-for-conducting-a-clinical-trial-medicare-coverage-analysis

Sateren, W.B., Trimble, E.L., Abrams, J., Brawley, O., Breen, N., Ford, L., … Christian, M.C. (2002). How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. *Journal of Clinical Oncology, 20,* 2109–2117.

Skloot, R. (2010). *The immortal life of Henrietta Lacks.* New York, NY: Broadway Paperbacks.

Sparks, J. (2002). Timeline of laws related to the protection of human subjects. Retrieved from http://history.nih.gov/about/timelines_laws_human.html

Swann, J.P. (1998). The Food and Drug Administration. In G.T. Kurian (Ed.), *A historical guide to the U.S. government* (pp. 248–254). New York, NY: Oxford University Press.

Talarico, L., Chen, G., & Pazdur, R. (2004). Enrollment of elderly patients in clinical trials for cancer drug registration: A 7-year experience by the U.S. Food and Drug Administration. *Journal of Clinical Oncology, 22,* 4626–4631. doi:10.1200/JCO.2004.02.175

U.S. Department of Health and Human Services. (2004). *Clinical research and the HIPAA Privacy Rule* [NIH Publication No. 04-5495]. Bethesda, MD: Author.

U.S. Department of Health and Human Services. (2014a). Federal policy for the protection of human subjects. Retrieved from http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html

U.S. Department of Health and Human Services. (2014b). Federalwide Assurances FWAs. Retrieved from http://www.hhs.gov/ohrp/assurances/assurances/index.html

U.S. Food and Drug Administration. (1996, April). *Guidance for industry E6 good clinical practice: Consolidated guidance.* Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

White-Hershey, D., & Nevidjon, B. (1990). Fundamentals for oncology nurse/data managers—Preparing for a new role. *Oncology Nursing Forum, 17,* 371–377.

World Medical Association. (n.d.). Declaration of Helsinki: Recommendations guiding physicians in biomedical research involving human subjects. Retrieved from http://www.wma.net/en/60about/70history/01declarationHelsinki

World Medical Association. (1996). Declaration of Helsinki. *BMJ, 313,* 1448–1449. doi:10.1136/bmj.313.7070.1448a