Cancer clinical trials are research studies that involve humans and are directly related to oncology care. Standards and legislation require that researchers submit study protocols to their institutional review boards for approval. This article reviews protections and FDA regulations for individuals who volunteer to participate in clinical research studies, as well as the role protective organizations play in the research field. This article also discusses the risks associated with participating in clinical trials and addresses why today’s cancer clinical trials are necessary to develop tomorrow’s standard of cancer care.

After completing this article, the reader should be able to:
- Describe the roles and responsibilities of the organizations involved in clinical research and protection of research participants.
- Explain how the rights and protections of research participants today have been influenced by historical clinical studies deemed unethical.
- Discuss the rules, regulations, and policies that protect the rights of human research participants.
- Describe the potential risks and benefits of participating in cancer clinical trials.
- Identify barriers that can keep cancer patients from participating in clinical trials.

In 1882, Dr William Stuart Halsted first performed the surgery that would subsequently be named after him. The radical mastectomy, or Halsted procedure, required extensive resection of the skin, fascia, and breast tissue, the underlying pectoralis major and minor muscles, and dissection of all axillary lymph nodes. Despite the fact this aggressive surgical procedure caused horrific disfigurement often accompanied by disabling adverse effects, it remained the standard treatment in the United States for all breast cancer, regardless of stage, for more than 70 years. Between 1891 and 1981, an estimated 500,000 women underwent the procedure.

Beginning in the 1920s some physicians began to question the necessity of such drastic surgery considering the physical and psychological consequences to patients, and many of them developed alternative treatment regimens; however, it was not until 1971 that a systematic scientific trial was proposed to compare the Halsted procedure against simple mastectomy and simple mastectomy combined with radiation therapy. The National Surgical Adjuvant Breast and Bowel Project published its study results in 1981 demonstrating that the rates of recurrence, relapse, metastasis, and death were statistically identical between the 3 treatment strategies. The study showed that women who underwent radical mastectomies received no additional benefits in survival, recurrence, or mortality despite the extreme morbidity of the procedure.

In 1973, the National Surgical Adjuvant Breast and Bowel Project initiated another study to evaluate the effectiveness of lumpectomy with or without radiation therapy compared with total mastectomy. The results of this study again demonstrated similar outcomes for women who had breast-conserving surgery instead of a radical mastectomy.
Today’s Cancer Clinical Trials Lead to Standards of Care Tomorrow

mastectomy. These 2 clinical trials changed the generally accepted standard of care for breast cancer. Now patients have treatment options based on the histology and stage of their cancer—and many times on personal preference. Just like with breast cancer, increased survival and decreased mortality and morbidity rates achieved today for many cancers can be linked directly to treatment information discovered through clinical trials. Almost all the standard treatments that cancer care providers use today, for almost every type of cancer, were developed as a result of past clinical trials.

Cancer Clinical Trials

Clinical trials are research studies that involve people, are performed to add to medical knowledge, and are usually the final step in a long research process that typically begins in a laboratory. The U.S. Food and Drug Administration (FDA) approves drugs, biological agents, and medical devices for human use after careful evaluation of clinical trial data. Cancer clinical trials—studies directly related to oncology care—drive the progress in the development of new drugs, devices, and techniques for the detection, monitoring, prevention, and treatment of cancer. Increased survival rates in patients with testicular cancer, breast cancer, lymphoma, and leukemia all have been achieved because of the treatment information gathered through cancer clinical trials. Morbidities related to cancer surgeries and other therapies also have decreased, and these studies have led to the development of new methods to minimize adverse effects of all types of cancer treatment.

Types of Clinical Trials

The National Cancer Institute (NCI) identifies 6 different types of cancer clinical trials: treatment, prevention, screening, diagnostic, genetics, and quality of life or supportive care. Treatment trials are conducted to evaluate the safety and efficacy of new treatments or to assess innovations to established treatment methods. They also evaluate the potential adverse effects of all treatments. Because of the nature of these studies, only people who have cancer are recruited to participate. These studies are instrumental in developing new cancer treatment methods, and comparing current standard therapies with new treatments determines the most effective approach for managing a particular cancer.

Special types of treatment trials include adjuvant and neoadjuvant studies. Adjuvant trials investigate additional therapies delivered after standard treatment to prevent the recurrence of cancer in patients who have no evidence of disease following treatment course completion. Neoadjuvant trials study additional therapies administered before standard treatment to reduce tumor size to a point at which it can be treated using standard therapy.

Prevention trials are conducted to identify interventions that might lower risks of particular types of cancer or cancer overall. Primary prevention trials involve healthy people who have not been diagnosed with cancer. Often these trials include only people who are at a higher risk of developing a particular type of cancer. Secondary prevention trials consist of people who have a history of cancer with the purpose of studying how to prevent recurrence or another primary cancer.

Prevention trials can further be classified as either action studies or agent studies. Action studies are used to determine activities or behaviors that inhibit cancer development. For example, an action study was published in 2005 by researchers affiliated with the American Cancer Society, which found that physical activity is not associated with overall prostate cancer risk, but might be associated with reduced risk of aggressive prostate cancer. Agent studies, sometimes called chemoprevention studies, evaluate substances such as medications or dietary supplements that could prevent or delay the development or recurrence of cancer. Agent prevention studies have led to FDA approval of tamoxifen and raloxifene for the reduction of breast cancer risk in certain postmenopausal women at increased risk.

Screening trials investigate methods to detect cancers earlier. The goal is to develop tests that can reduce cancer mortality by detecting the disease before patients show signs and symptoms, when treatment is easier and survival rates are higher. Screening trials also might be conducted to assess the merit of various tests based on accuracy, risks and benefits, ease of use, and cost effectiveness. Cancer screening trials typically involve individuals who have no signs or symptoms of cancer; however, the studies might limit enrollment to only those who are at higher-than-average cancer risk because of family history or history of exposure to carcinogens. For example, the recently concluded
National Lung Screening Trial compared low-dose helical computed tomography (CT) with standard chest radiography to detect lung cancer in current or former smokers. The results of this clinical trial demonstrated 20% fewer lung cancer deaths in participants screened with low-dose CT, and led the National Comprehensive Cancer Network to recommend that individuals at a high risk for lung cancer receive an annual low-dose CT for 2 years after a baseline low-dose CT with consideration for annual low-dose CT scans after the first 2 years.\textsuperscript{15,16}

Diagnostic trials evaluate new examinations or procedures to improve cancer diagnosis. Some trials compare 2 or more diagnostic techniques to evaluate whether one is more accurate in distinguishing between benign and malignant conditions. Other trials might attempt to measure the effect patient characteristics have on the accuracy of diagnostic techniques. Participants recruited for these types of studies include individuals who demonstrate signs and symptoms of cancer. This type of clinical trial includes research examining the ability of imaging modalities such as dynamic contrast-enhanced magnetic resonance imaging to differentiate between benign and malignant lesions.\textsuperscript{17,18}

Genetics trials are conducted to determine how an individual’s genetic makeup influences the risk of cancer, its detection, diagnosis, prognosis, and treatment.\textsuperscript{9} This type of research has identified genetic mutations associated with hereditary cancer syndromes.\textsuperscript{19} Genetics trials identified the mutations of the $BRCA1$ and $BRCA2$ genes associated with female breast and ovarian cancers. Current research in this area investigates genetically targeted therapy, in which the genetic features of malignant cells are used to design the most effective treatment.

Quality-of-life or supportive care trials focus on interventions that improve the quality of life for cancer patients and survivors, as well as their families.\textsuperscript{14} These studies include research on interventions to manage the following:\textsuperscript{9}

\begin{itemize}
  \item Treatment adverse effects.
  \item Psychological, spiritual, and emotional concerns related to cancer and treatment.
  \item End-of-life issues.
\end{itemize}

The effectiveness of supportive care can be measured either subjectively or objectively.\textsuperscript{9} Subjective data is obtained by surveying patients and their families regarding their feelings, beliefs, and needs. Objective data is gathered by reviewing diagnostic test results, physical examinations, or observing behaviors. This research is important because it often examines the needs and concerns of individuals, not only during treatment, but also throughout their cancer experience.

**Clinical Trial Settings**

Cancer clinical trials take place in the United States and in other countries. Trials are not conducted exclusively in large research institutions, but can take place in an individual physician’s office, local medical clinics, community hospitals, medical centers, and cancer centers. Individual hospitals or academic centers might sponsor trials conducted by their own researchers.\textsuperscript{20} Research is sponsored by private or for-profit businesses such as pharmaceutical and biotech companies, or by governments and nonprofit organizations.

The NCI, part of the National Institutes of Health of the U.S. Department of Health and Human Services (HHS), sponsors many clinical trials. NCI-sponsored programs include the Community Clinical Oncology Program and the Minority-Based Community Clinical Oncology Program, NCI Community Cancer Centers Program, the National Clinical Trials Network (formerly the Clinical Trials Cooperative Group Program), and the National Institutes of Health Clinical Center.\textsuperscript{14} The Community Clinical Oncology Programs allow community physicians to work with researchers conducting clinical trials supported by the NCI, and the Minority-Based Community Clinical Oncology Program provides ethnic and racial minority patients access to state-of-the-art cancer treatment, prevention, and control technology.\textsuperscript{21}

The Cancer Centers Program is made up of 68 NCI-designated cancer centers involved in research. To achieve this NCI designation, cancer centers must participate in laboratory, population-based, and clinical research, as well as provide patients the most current forms of treatment and access to clinical trials.\textsuperscript{22} In addition to conducting institutional research, these cancer centers also participate in at least one cooperative group.\textsuperscript{21}

Cooperative groups design and conduct clinical trials in networks that include hundreds of institutions and thousands of researchers.\textsuperscript{21} For example, SWOG (formerly the Southwest Oncology Group) is one of
the largest cancer clinical trial cooperative groups in the United States and consists of more than 4000 physicians conducting cancer research in more than 650 institutions.

Prior to March 2014, NCI sponsored 10 cooperative groups, 9 for adult oncology research and one for pediatric cancers. These groups have been consolidated into 4 adult groups and one childhood group under the National Clinical Trials Network.24

The National Institutes of Health Clinical Center in Bethesda, Maryland, is the nation’s largest hospital devoted entirely to clinical research.25 The center’s focus is on translational research, where laboratory studies are transformed into medical applications. Patients admitted to this center consent to participate in clinical research and are among the first to receive the “bench-to-bedside” treatment interventions developed through the interaction of scientists and clinicians.26

Benefits and Risks of Clinical Trial Participation

Cancer patients and their families might participate in clinical trials for a number of reasons.27 Because participants frequently have access to promising new interventions that would normally not be available outside a clinical trial, many study volunteers are patients who have already received all available treatments for their cancer with little or no positive results. If the intervention being studied is more effective than the standard therapy, these participants receive the first benefit.

Some cancer clinical trial participants volunteer for research because they feel they receive more attention and oversight of their care. Over the duration of a cancer clinical trial, study participants have regular contact with the medical professionals involved on the research team and are more frequently assessed compared to patients receiving standard treatment. For other cancer patients, participating in a research study makes them feel empowered because they are taking a more active role in their own health care. For many, the desire to be altruistic makes participation in clinical trials an attractive option. Participants can contribute vital scientific data about cancer and treatment that could benefit future cancer patients.

Although there are many benefits to participating in cancer clinical trials, there also are potential risks.28 For example, the study intervention might not provide a better outcome than the standard therapy, or it could produce unexpected reactions or more severe adverse effects. The additional testing and medical visits required as part of the clinical trial can be overly demanding on participants and their families. Finally, health care insurance might not cover some or all of the costs associated with investigational medications or procedures. The decision to participate in a clinical trial is not one to be taken casually, and cancer patients interested in clinical trials must carefully consider the risks and benefits before consenting to participate.

Design of Clinical Trials

There are 2 basic divisions of clinical studies: observational and interventional.27 In observational studies, researchers observe and collect data without interfering in the event taking place. In interventional studies—usually called treatment studies—the researchers evaluate the effects of a treatment on a selected group of participants. In addition, studies can be done prospectively or retrospectively. Prospective studies collect data from the beginning of the study. The research is planned and designed to answer specific questions. Participants are first enrolled in the study and then exposed to the study intervention. Data is collected during and after the participants receive the intervention.

Retrospective studies are not preplanned and examine preexisting data regarding past events. The outcomes of these studies have already occurred and researchers analyze data that was previously collected.

Retrospective studies for cancer clinical trials typically involve review of patient medical records and patient interviews. They are easier and less expensive to conduct than prospective studies. Retrospective studies also are useful when prospective clinical trials are not possible (eg, when exposing study volunteers to possible carcinogens would be unsafe and unethical). In a 1950 landmark paper, Ernst Wynder and Evarts Graham demonstrated a link between smoking and lung cancer based on retrospective information primarily gathered by interviewing 684 lung cancer patients about their smoking habits.29 If a prospective study had been conducted in an attempt to demonstrate this link, it would have taken several more years and would have exposed healthy volunteers to a suspected carcinogen.
The most notable disadvantages to retrospective trials is in patient selection. Volunteers cannot be screened or evaluated before they participate in the study, so the possibility of variation between volunteers is high and there are likely to be discrepancies in the types, amounts, and lengths of interventions and follow-up received.

**Phases of Clinical Trials**

Clinical trials conducted to develop new cancer therapies proceed in a stepwise manner. Each step represents a new phase in the clinical research process.\(^1\) Cancer treatment trials are designated as phase 0 through phase 4. Each phase requires a different number of research participants and is designed to address a distinct research question (see Table). Treatment trials always are assigned a phase whereas other types of trials, such as screening or quality-of-life studies, might not be.

Phase 0 trials involve approximately 10 to 15 participants. They are sometimes called microdosing studies, exploratory investigational new drug trials, or early phase 1 trials, because study participants might receive a subtherapeutic, but pharmacologically active, dose of a chemical or biologic agent.\(^2\)\(^,\)^\(^3\) Data on the safety and effectiveness of the agent cannot be assessed because of the low dose. However, preliminary data on pharmacokinetics (the action of a drug on the body over time) and pharmacodynamics (the effect of a drug on the body) can be collected.\(^2\) Participants who consent to participate in phase 0 trials must understand that although there is little risk in participating, there is no chance the test agent will provide therapeutic benefit.\(^3\)

The purpose of phase 0 trials is to increase the efficiency of drug development. New anticancer drug development is a lengthy and costly process with a more than 90% failure rate.\(^4\) Approximately 40% of all drugs fail in phase 1 clinical trials because of unsuitable pharmacokinetics.\(^4\) Evaluating the pharmacokinetics of a new drug in a phase 0 trial saves time and money by determining which medications or agents show enough promise to warrant further development and investigation.

Phase 1 clinical trials enroll approximately 15 to 30 participants and can take 9 to 18 months to complete.\(^5\)\(^,\)^\(^6\) They are conducted to evaluate the safety of chemical or biological agents, or other types of interventions such as new radiation therapy procedures.\(^4\) They establish the maximum tolerated dose and dose-limiting toxicities for both cytotoxic drugs and radiation therapy treatments. With respect to chemotherapeutic agents, phase 1 trials focus on the dosing, tolerability, and safety profile of the drug, as well as its pharmacokinetics and pharmacodynamics.\(^3\) Recent phase 1 clinical trials in radiation oncology have involved dose escalation in intensity-modulated radiation therapy and stereotactic body radiation therapy. Chemoradiation phase 1 studies investigate the maximum tolerated dose of a new chemotherapy agent combined with conventional radiation therapy. Because of the nature of this research, the patients most likely to volunteer for phase 1 trials typically have late-stage disease for which no standard treatment exists or for whom conventional therapies have been ineffective.

Once a dose or range of doses has been determined in a phase 1 study, phase 2 trials take place to evaluate the

| Table Phases of Treatment Trials\(^9\)\(^,\)^\(^2\)\(^7\) |
|-----------------|-----------------|-----------------|-----------------|
| **Study Phase** | **Objective** | **No. of Participants** | **Length of Phase** |
| Phase 0 | Gather preliminary pharmacokinetics and pharmacodynamics of chemical or biologic agents | 10-15 | < 6 mo |
| Phase 1 | Evaluate safety of intervention | 15-30 | 9-18 mo |
| Phase 2 | Evaluate effectiveness and safety | Usually < 100 but may include up to 300 | 1-3 yr |
| Phase 3 | Evaluate effectiveness against standard of care | 100 to several thousand | 2-5 yr |
| Phase 4 | Evaluate long-term safety and effectiveness | Several hundred to several thousand | Ongoing |
effectiveness of the intervention. They usually involve fewer than 100 research participants, but they can include as many as 300, and take 1 to 3 years to complete.14 They are measured against the known adverse effects of the current standard of care for a particular type of cancer or the innovative use of an existing intervention, with the purpose of comparing the effectiveness of a new intervention, typically involving anywhere from 100 to several thousand participants, are conducted to evaluate a therapeutic dose range and dose safety in selected patient populations. Phase 2b studies, sometimes referred to as pivotal trials, are well-controlled trials that continue to evaluate effectiveness at prescribed doses along with safety.27

Phase 2 trials are sometimes subdivided into phase 2a and 2b trials. Phase 2a trials are defined as pilot trials and are conducted to evaluate a therapeutic dose range and dose safety in selected patient populations. Phase 2b studies, sometimes referred to as pivotal trials, are well-controlled trials that continue to evaluate effectiveness at prescribed doses along with safety.27

At the midpoint of a phase 2 study in which half of the anticipated number of participants have been enrolled, researchers might suspend enrollment to perform an interim analysis and assess the progress of currently enrolled subjects receiving the treatment intervention.23 In studies that enroll smaller numbers of subjects, research data is monitored as it accumulates.35 Both of these data assessment methods allow trials to be terminated early if there are safety risks, concerns with the efficacy of the experimental therapy, or if there is enough early evidence of efficacy to move on to phase 3 testing.35 Many potential new interventions do not move beyond phase 2 testing. Between 2008 and 2009, the success rate for phase 2 trials for new drugs was only approximately 18%.36

The emphasis of phase 2 trials is on therapeutic effectiveness, but the safety of the treatment intervention continues to be assessed. Results of these trials are used to determine whether the intervention warrants further investigation in a phase 3 trial.27

Phase 2 trials might demonstrate a new intervention has benefits to the patient, but they do not establish whether the intervention is better than established treatments. Phase 3 clinical trials, involving anywhere from 100 to several thousand participants, are conducted to compare the effectiveness of a new intervention, or the innovative use of an existing intervention, with the current standard of care for a particular type of cancer.14 In addition, adverse effects of the new intervention are measured against the known adverse effects of the conventional treatment approach.

Phase 3 clinical trials often take 2 to 5 years to complete.27 Depending on the purpose of the study, participants might or might not have had previous treatment, and in many cases the type and quantity of previous treatment can affect a volunteer’s eligibility to participate in the study.

Phase 3 trials are conducted to evaluate the intervention in the target population with the test intervention administered exactly in the manner it will be used by health care practitioners in real-life patient care situations.27 These trials are randomized prospective controlled studies that use widely accepted scientific principles of good experimental design (ie, the study participants are randomly assigned to 1 of 2 treatment groups or “trial arms” before treatment begins).14,34 Participants assigned to the control group receive the current standard of care for their cancer, and participants assigned to the experimental group receive the investigational intervention. Because none of the treatment options is known to be superior over the other form of intervention at the beginning of the study, randomization is an ethical means for treatment arm assignment.27

Placebo medications or sham treatments are almost never used in cancer clinical trials.33 The administration of an inactive substance in place of an effective available drug or feigning an actual treatment or surgical procedure is blatantly unethical because patients would receive substandard care.11 To gain approval to conduct a clinical trial, researchers must demonstrate that the treatment interventions being studied meet the standard of care or can be potentially better. A placebo may be used when a clinical trial investigates a standard treatment combined with a new treatment. In that case, the control group might receive the standard treatment plus a placebo.32 A placebo also might be used in the rare circumstance that a new drug is tested and no effective treatment is available to the patient.31

Phase 3 study designs allow direct comparison of a new intervention with a standard treatment’s effectiveness, safety, and tolerability. For this reason, phase 3 studies frequently include a quality-of-life survey component.14 Following cancer clinical trials, a new intervention may be adopted if it demonstrates a positive qualitative effect on a patient’s life instead of a quantitative effect.

The key to a phase 3 trial is the random assignment of study participants to a trial arm. Randomization is
conducted to remove selection bias in the assignment process.\textsuperscript{11} Bias is defined as systematic error, as opposed to random error, introduced into a study that influences the results.\textsuperscript{39} A computer randomly assigns study participants to a trial arm without consideration of the wishes of either the patient or the study personnel (see Figure). Randomization ensures that each patient is as likely as any other patient to be assigned a particular treatment. Eliminating individual influences on trial arm assignment yields relatively comparable treatment groups and removes the possibility of systematic or preferential assignment of study participants to one treatment intervention over another based on patient characteristics, researcher preference, or subconscious opinion.\textsuperscript{39}

Clinical trials that use randomization to assign study volunteers to treatment arms are considered the most credible types of research when comparing different treatments to determine the superiority of one over others.\textsuperscript{39} However, there can be some disadvantages to random assignment of treatment, particularly related to enrolling study participants. For example, the randomization process might discourage patients from participating in cancer clinical trials. Some patients would prefer to have the treating physician select a treatment option based upon their individual situation and the physician’s opinion on what would be best for the patient, rather than having a treatment randomly assigned.\textsuperscript{39} Other patients initially consent to participate but withdraw from the study if they are not randomized to the new test intervention. Both these situations slow the enrollment process of the clinical trial, extend the length of time required to complete the study, and delay the development of potentially lifesaving cancer therapies.

Another technique used to avoid bias in clinical trials requires the participants, researchers, or both to be unaware of the treatment assignment.\textsuperscript{37} This procedure is called blinding or masking. In a single-blind study, only the researchers know which study volunteers have been assigned to each treatment arm. This
minimizes the risk of participants experiencing the placebo effect, which is likely to occur when a partici-
pant has the expectation of a benefit to the intervention, rather than receiving an actual benefit. In a double-
blind study, neither the volunteer nor the researcher knows the treatment assignment. In this case, the pos-
sibility of placebo effect is minimized and conscious or unconscious researcher bias can be eliminated. Blinding
cannot be applied in many types of treatment studies. For example, in radiation therapy, both patients and the
researchers know what type and amount of treatment is being delivered. In studies involving drugs or biologic
agents, blinding is more easily accomplished and is regularly done.

When an intervention has proven effective in a phase
3 study, it may undergo long-term study for effectiveness
and safety in a phase 4 trial involving several hundred
to several thousand participants. 4 Phase 4 trials, sometimes
called postmarketing studies, usually take place after a
new drug, intervention, or device has been approved by
the FDA for clinical use. Continuing evaluation is neces-
sary because procedures or devices might fail or have
adverse effects on patients after a few years. 27,40 Although
a phase 3 trial might evaluate an intervention for 2 to 5
years in a few thousand people, that evaluation is still
quite limited compared with the number of people who
use that intervention once it is approved and, in the case
of chronic diseases, for longer periods.

The FDA monitors events such as adverse reactions,
poisonings, and device malfunctions once a product has
been approved for market. In addition, once a product
has been approved by the FDA, the manufacturer must
continue to report product information, including new
findings and adverse events, to the FDA for the lifetime
of the product. These reports can be based on informa-
tion obtained in a phase 4 trial or may be completed by
health care providers or consumers reporting observa-
tions to the product manufacturer or the FDA. 27

A recent demonstration of the importance of phase
4 trials is evidenced in the removal from the market of
the COX-2 inhibitors rofecoxib (Vioxx) and valdecoxib
(Bextra). These nonsteroidal anti-inflammatory drugs
were used primarily to treat signs and symptoms related
to rheumatoid arthritis and osteoarthritis after initial
approval by the FDA for Vioxx in 1999 and Bextra in
2001. Further study of the 2 medications demonstrated
an increased risk of serious cardiovascular events in
patients using these drugs. Because of the unfavorable
overall risk vs benefit profile, the FDA asked the drugs’
manufacturers to withdraw the drugs voluntarily from
the market. Vioxx was withdrawn in 2004, and Bextra
was withdrawn in 2005. 41

Clinical trials are an integral part of the development
and approval of new drugs. The FDA is responsible for
reviewing the clinical trials results of new drugs to ensure
they are safe and effective for specific uses. 9 The FDA
not only approves new drugs, but also is responsible for
approving new medical devices, agents, and biologics.

Before a new drug or biologic agent can be tested
on people, the sponsor or developer must submit an
investigational new drug application to the FDA. This
is done only after the drug or biologic has undergone
initial laboratory studies and animal model testing for
efficacy and toxicity. After the application has been
approved, the sponsor can begin clinical trials. After
completion of phase 1, 2, and 3 trials, the sponsor can
file a new drug application or biologics license applica-
tion to the FDA. Only after FDA approval can the drug
or biologic be marketed to the public and typically only
for a specific purpose or use. The FDA requires the
drug or biologic to be labeled with information about
dosage, indication, safety, and adverse effects. 9

The Study Protocol

Before any clinical trial can begin, a master plan
must be developed. This written plan is called the
research or study protocol. The study protocol can be
considered a written agreement between the investiga-
tor, participants, and the scientific community. 50

The study protocol is not merely the “recipe” for the
study; it also is a description of its purpose and ratio-
 nale. 44 It usually is written by the principal investiga-
tor—the individual who has the ultimate responsibility
for the oversight of the research and management of the
clinical trial. Aside from providing the background and
outline for the planned study, the protocol defines how
the study will be carried out. 45 Individual researchers
involved in the study use the protocol to understand
the research goals and the procedures to be followed.
Depending on the amount of background information
provided, the complexity of the trial, and the required
procedures, protocols might be as short as 2 to 4 pages
or as long as more than 100 pages, with a typical length being 40 to 60 pages.\textsuperscript{37}

The protocol spells out every detail of the clinical trial, including\textsuperscript{44}:

- The trial objectives.
- Criteria for the inclusion and exclusion of participants.
- Screening and study procedures.
- Numerous appendices that define important information (eg, the schedule of events and activities, required laboratory tests, and toxicity criteria) (see Box 1).

Before beginning any study, the investigators must submit the protocol to the investigator’s institutional review board (IRB) for review. The IRB is responsible for determining the scientific validity of the study rationale and design. It also determines whether the study has an acceptable benefit-to-risk ratio for participants and that participant selection will be fair and equitable.\textsuperscript{37} IRB approval must be obtained before any clinical trial is initiated.

**Safeguards in Clinical Trials**

Research involving human participants is essential to the advancement of medicine.\textsuperscript{42} The increased cure rates of many types of cancer would not have been possible without the development of new and innovative treatments and the evaluation of the safety and effectiveness of these treatments. Researchers must follow ethical principles to protect the people who participate in these studies. In the past 100 years, however, there have been numerous instances of researchers failing to follow basic ethical standards to safeguard the rights of study participants.

One of the most infamous examples of unethical research came to light after World War II when the international community was made aware of the experiments performed by Nazi medical personnel on concentration camp prisoners.\textsuperscript{42} These experiments, which were brought to light during the Doctors Trial in 1946 in Nuremberg, Germany, were performed without consent from the participants and with no possible benefit to the individual participants. The experiments included exposing prisoners to mustard gas, freezing temperatures, burns, malaria, typhus, and poisons to investigate potential treatments. Other experiments forced prisoners to ingest nothing but saltwater to test methods for making seawater drinkable, and some prisoners were exposed to drugs, x-rays, and surgeries in studies conducted to develop rapid, large-scale sterilization procedures.\textsuperscript{44}

Twenty-three doctors were tried on charges of war crimes and crimes against humanity in the Doctors Trial. Many of these physicians, in their own defense, argued that the experiments were no different from other experiments that previously had been conducted in both the United States and Germany. They also argued that no international laws or even informal statements differentiated illegal from legal human experimentation.\textsuperscript{44} The verdict, which found 16 physicians guilty, established 10 points defining legitimate research. These points became known as the Nuremberg Code. The moral, ethical, and legal principles outlined in the code include the voluntary consent of subjects, the protection of participants from unnecessary physical and mental suffering and injury,

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**Box 1**

<table>
<thead>
<tr>
<th>Outline of Typical Study Protocol\textsuperscript{39}</th>
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<tbody>
<tr>
<td>A. Background of study</td>
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<td>B. Objectives</td>
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<tr>
<td>1. Primary question</td>
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<tr>
<td>2. Secondary question</td>
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<tr>
<td>3. Hypothesis(es)</td>
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<tr>
<td>4. Adverse effects</td>
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<tr>
<td>C. Study design</td>
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<tr>
<td>1. Study population</td>
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<td>2. Sample size</td>
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<tr>
<td>3. Enrollment of participants</td>
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<td>4. Interventions</td>
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<td>5. Follow-up visit</td>
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<tr>
<td>6. Data measurement</td>
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<tr>
<td>7. Safety assessment</td>
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<td>8. Data reporting</td>
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<tr>
<td>9. Termination policy</td>
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<tr>
<td>D. Organization</td>
</tr>
<tr>
<td>1. Participating investigators</td>
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<tr>
<td>2. Study administration</td>
</tr>
<tr>
<td>Appendices</td>
</tr>
<tr>
<td>References</td>
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<tr>
<td>Informed consent</td>
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</tbody>
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and the requirement that the risk to the participant does not exceed the benefit of the study (see Box 2).

Because the Nuremberg Code was so closely associated with Nazi war crimes, it had relatively little impact on biomedical research practices. Recognizing the need to establish recommendations to guide researchers worldwide, the World Medical Association adopted what has become one of the most influential documents in research ethics, the Declaration of Helsinki, in 1964. This document, which has its roots in the Nuremberg Code, sought to establish international guidelines for ethical research and addressed topics such as the need for human research to be based on laboratory or animal studies, the requirement of research protocols to be reviewed by an independent committee, the necessity for research to be conducted by qualified individuals, the obligation of informed consent, and the principle that the risks of research should not exceed the benefits.

Unlike the Nuremberg Code, the Declaration of Helsinki continues to evolve with advances in medical technology and changes in terminology. The seventh and most recent revision was completed in 2013. The Declaration of Helsinki does not have the force of law, yet it is still recognized as important authoritative guidance for conducting medical research on human subjects. The basic principles established by the Declaration of Helsinki, including respect for individuals, the right to make informed decisions, and recognition of vulnerable groups, often are incorporated into other important documents pertaining to research ethics.

Despite the Nuremberg Code and Declaration of Helsinki, unethical clinical research on humans continued with little notice from the general public or the medical community. There are hundreds of examples of unethical studies conducted by researchers—many of whom were sponsored by government agencies, medical and educational institutions, or sanctioned by state or federal governments.

The general public’s concern about unethical research practices was awakened in 1965 largely because of a speech given by Henry K Beecher, MD, a Harvard Medical School anesthesiologist. The presentation was made during a conference held by the Upjohn Pharmaceutical Company, and a number of journalists were present. Beecher reviewed 18 examples of clinical research that he considered to be unethical. After giving the speech, Dr Beecher revised it to include an additional 32 examples of unethical research, and submitted it for publication to the Journal of the American Medical Association. When the American Medical Association rejected the paper, Dr Beecher submitted it to the New England Journal of Medicine, which eventually published the manuscript after a few revisions in 1966. The article, which would later be considered the most influential single paper ever written on human subject experimentation, documented 22 examples of “unethical or questionably ethical studies,” all of which had been published in noted medical journals. Dr Beecher wrote that in almost all of the studies he reviewed, the researchers failed to mention consent of the study subjects. The names and institutions of researchers documented by Dr Beecher were withheld in his paper, as he did not wish to chastise individuals, but rather focus attention on widespread practices. The examples of unethical research presented included:

- Withholding of readily available effective treatment from study participants.
- Administering potentially unsafe therapies to subjects without diseases.
- Manipulating physiologic processes for no medical reason other than observation.
- Inducing diseases in otherwise healthy study participants.

Most notable in the research cited by Dr Beecher were the number of studies that involved children—particularly children living in institutions who were described as “mental defectives or juvenile delinquents.”

One of the studies presented in Dr Beecher’s paper—although unnamed at the time—has since come to be known as the Willowbrook Hepatitis Experiments. Willowbrook State School was an institution in Staten Island, New York, that housed and cared for children with mental disabilities in the late 1940s until 1987. Beginning in 1955, physicians there began conducting hepatitis studies that continued for more than 15 years. Hepatitis A was endemic at the institution, and the stated goal of the studies was to determine methods to protect children from the disease.

More than 700 children were involved in the studies—many of whom were deliberately infected with the hepatitis virus. Parents were asked to provide consent...
Box 2

The Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility that may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

for their children to participate in the studies, but it was questionable whether parents truly understood their children would be intentionally infected with the virus. The consent form was written so as to give the impression the injections were vaccines rather than live viruses. Later, as the main part of the school was closed to admissions because of overcrowding, parents were told there were openings in the hepatitis unit if their children would participate in the study. This action coerced parents into giving consent to receive care for their children. Eventually, the studies were discontinued as the truth came to light and there was pressure from the medical community to do so.

Another study highlighted in Dr Beecher’s paper took place in the early 1960s at Jewish Chronic Disease Hospital in Brooklyn, New York, and was cofunded by the U.S. Public Health Service and the American Cancer Society. Physicians, attempting to study the immune system’s role in defense against foreign malignant cells, injected live liver cancer cells beneath the skin of elderly debilitated patients. The patients were told they were receiving a skin test. Information that the injection contained live cancer cells, was part of a research study, or that the injection was not related to any course of treatment was withheld from the patients. The patients’ consent was never asked for nor received.

Dr Beecher concluded his paper by stating his opinion that ordinary people would not knowingly risk their health or their life for the sake of science and that, while it is difficult to obtain, it is absolutely essential that researchers strive to gain informed consent from
research participants for moral, sociologic, and legal reasons. In addition, because he was skeptical that fully informed consent could be obtained, Dr Beecher stated that an ethical approach to human research required an intelligent, informed, conscientious, compassionate, and responsible researcher as the most reliable safeguard of ethical research. He further stated that the editors of scientific journals should not publish research data that is improperly obtained. If scientists knew their results would not be published, they would not engage in improper and unethical research.85

Because the public attention from Dr Beecher’s works was focused on ethics in clinical research, in 1966 the Surgeon General of the U.S. Public Health Service announced that all researchers pursuing grants from the National Institutes of Health would need to provide evidence of documented informed consent of study subjects to receive funding, and that researchers’ institutional associates were to review and approve clinical research before it was initiated.11,54

Another study that brought public attention to unethical human research is now called the Tuskegee Syphilis Study. The study began in 1932, and was officially titled the “Tuskegee Study of Untreated Syphilis in the Negro Male.”97 Originally projected to last approximately 6 months, it continued for 40 years and was funded by the U.S. Public Health Service.11 The stated purpose of the study was to learn about the natural course of untreated syphilis.44 The study initially involved 600 African American men from poor rural areas around Tuskegee, Alabama. Nearly 400 men with syphilis and 201 men without the disease were told they were receiving treatment for “bad blood,” which was a local term used to describe a number of diseases including syphilis, anemia, and fatigue.57

In exchange for their participation, the men were given free medical examinations, free meals, and burial insurance. Instead of receiving any of the treatments for syphilis available at the time, the men were given vitamins and aspirin to lead them to believe that they were receiving treatment.44 Even after penicillin became widely available, and the drug of choice for syphilis treatment in 1947, the study continued with subjects being denied curative treatment. The wives of many of these men also became infected and their children were born with congenital syphilis. This study finally ended in 1972 after being exposed in a front-page article in the New York Times.77 The public outrage following this story led to the creation of an ad hoc advisory panel to examine the study. The panel was made up of members representing the fields of medicine, law, labor, education, administration, and public affairs.57

The panel determined the men had freely given permission to be examined and treated, but there was evidence that the researchers withheld information about the study’s true purpose and other facts necessary for these men to give informed consent. In addition, the men were never offered curative treatment when it became available, nor were they offered the option of withdrawing from the study. The panel concluded the Tuskegee Syphilis Study was “ethically unjustified” because very little knowledge was gained compared to the large risk to the health and safety of the participants.

Societal indignation increased when it became known that the study participants had been intentionally misled and denied effective treatment. A class-action lawsuit was filed on behalf of the men and their families in 1973, and in 1974 an out-of-court settlement of $10 million was reached. In addition, the U.S. government promised to provide lifetime medical benefits and burial services to all living participants, including wives, widows, and children. In 1997, President William Jefferson Clinton offered a public apology to the men and their families on behalf of the U.S. Government.

In 1973, the U.S. Congress held hearings about human subject research in response to the Tuskegee Syphilis Study and the number of other unethical trials that were uncovered.46 The consensus following the hearings was that federal oversight was needed to protect the rights and safety of research participants involved in biomedical and social science studies. In 1974, The National Research Act was signed into law.48 This law established regulations requiring local oversight committees to review human subject research.44 These oversight committees are the institutional review boards (IRBs) from which investigators obtain approval, and the IRBs are responsible for protecting the rights and safety of people participating in research studies and for guaranteeing research is conducted according to ethical standards.40

In addition to instituting the current IRB system, The National Research Act of 1974 created the National Commission for the Protection of Human
Subjects of Biomedical and Behavioral Research under the U.S. Department of Health, Education, and Welfare, now known as the HHS. The commission was charged with identifying ethical principles on which clinical research should be based and to establish guidelines for respecting these underlying principles. In 1979, the Commission issued a report titled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, more commonly known as the Belmont Report. This report is a statement of basic ethical principles and guidelines to help resolve the ethical problems surrounding research involving human subjects. Three basic principles were identified in the Belmont Report:

- **Respect for persons,** including respect for the decisions of autonomous individuals and protection of vulnerable persons with diminished autonomy.
- **Beneficence,** which requires researchers to maximize possible benefits and minimize potential harm.
- **Justice,** which requires the fair and equal distribution of the burdens and benefits of clinical research.

The methods used to uphold these principles are informed consent, the appropriate selection of study participants, and a carefully completed risk/benefit analysis prior to study initiation.

According to the Belmont Report, respect for persons requires research participants to be given the opportunity to choose what will or will not happen to them. Informed consent provides that opportunity when it contains 3 components: information, understanding, and voluntariness. To gain informed consent, information must be shared with a potential study participant, the participant must comprehend the information given, and the participant must voluntarily agree to participate in the research. The information given to the participant should include the research procedures; their purposes, risks, and anticipated benefits; alternative procedures; and a statement offering the study participant the chance to ask questions and withdraw from the study at any time. Comprehension can be assessed by the researcher but could require a written or oral test depending on the nature of the risk involved. Voluntariness is achieved when conditions are free of coercion and undue influence. Coercion involves an overt threat of harm to obtain compliance. Undue influence occurs when an excessive, gratuitous, or inappropriate reward is offered to gain cooperation, or when pressure from a position of power is used to gain consent, such as denial of appropriate medical treatment to those choosing not to participate in the trial.

Beneficence is promoted through an assessment of the risks and benefits of the study. Risk refers to the probability that harm will occur, and benefit refers to something of positive value related to health or welfare. Risks and benefits can affect the individual participant, families of the participant, or society at large. Because there is no perfect way to measure or balance anticipated and unexpected risks and benefits, the Belmont Report recommends performing a systematic, nonarbitrary analysis insofar as possible, verifying the necessity of using human subjects at all and taking only the risks necessary to achieve the experimental ends, while ensuring that no cruel or inhumane treatment is ever tolerated.

The principle of justice is exemplified in the selection of study participants. According to the Belmont Report, potentially beneficial research should not be offered only to some favored individuals while “undesirable” people are selected for risky research. Opportunities for participation must be equally offered. Also, certain groups of people, such as individuals in institutions, need to be protected against being used in research solely for administrative convenience.

After the Commission disbanded, the Office of Human Research Protections under HHS was charged with providing leadership in protecting the rights and well-being of participants participating in research conducted or supported by HHS. Using the Belmont Report, in the late 1970s and early 1980s HHS revised and expanded its regulations for the protection of human subjects, and eventually codified them in the 1981 Code of Federal Regulations (CFR), 45 CFR, part 46, subparts A-D. Subpart A is known as the Federal Policy and establishes the basic policy for human research subject protection; subpart B provides additional protections for pregnant women, fetuses, and neonates; subpart C is directed at biomedical and behavioral research on prisoners; and
subpart D addresses protections for children involved in research.61,64

In 1991, the Federal Policy for the Protection of Human Subjects, generally known as the Common Rule, was published and codified in separate regulations in 15 U.S. government agencies and departments (see Box 3).65 In each agency’s chapter of the section, numbers and language are identical to those of the HHS codification in 45 CFR, part 46, subpart A. The Common Rule outlines basic provisions for IRBs, informed consent, and assurances of compliance.65

In general, any research conducted by, for, or supported by any of the agencies mentioned above is governed by the Common Rule. Research that is not directly supported but regulated by these agencies also is subject to application of the Common Rule.61

The Common Rule states that IRBs are to comprise qualified members with the experience, expertise, and diversity to promote respect for its advice and counsel in protecting the rights and welfare of human subjects.64 IRB members must be able to determine the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and the standards of professional practice and conduct. Every IRB must have a minimum of 5 members representing diverse backgrounds, gender, race, cultures, and community attitudes, and include at least one member totally independent of the institution, one member primarily concerned with science, and one member primarily interested in nonscientific areas. The regulations require the IRB to meet regularly and have written procedures that are followed for the initial review of research projects, frequency of monitoring ongoing studies, and for reporting newly determined risks or harms not initially reviewed by the board.61

IRBs are charged with approving research in which risks to participants are minimized, primarily by using sound research design and procedures that do not unnecessarily put participants at risk, and using, whenever possible, procedures already being performed for diagnostic or treatment purposes of the participants. In addition, IRBs must evaluate the risk and benefit of the research on the participants, safeguard study participant confidentiality, and ensure the selection of research participants is equitable, being particularly cognizant of the rights and welfare of vulnerable populations such as children, pregnant women, prisoners, mentally disabled individuals, and those people who are economically or educationally disadvantaged.66 Perhaps the most important role of the IRB is to ensure there is documentation that potential study participants are fully informed about the research before giving consent to participate. The Common Rule established the elements for informed consent, which include a statement identifying the project as research and an explanation of its purpose, duration, reasonably foreseeable risks and benefits, and description of procedures to be followed (see Box 4).

The FDA regulates research involving products regulated by that agency, including research and marketing permits for drugs, biologic products, and medical devices for human use, whether or not the research is funded by HHS.64 Title 21 of the CFR is reserved for the rules of the FDA. The FDA must approve new drugs, biologics, and medical equipment before they can be used on patients. This authority was delegated to the FDA by The Federal Food, Drug, and Cosmetic Act of 1938.68 The act gave the FDA oversight over cosmetics and

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**Box 3**

**Federal Agencies and Departments Under 45 CFR, Part 46**

- Department of Agriculture
- Department of Energy
- National Aeronautics and Space Administration
- Department of Commerce
- Consumer Product Safety Commission
- Agency for International Development
- Department of Housing and Urban Development
- Department of Justice
- Department of Defense
- Department of Education
- Department of Veterans Affairs
- Environmental Protection Agency
- Department of Health and Human Services
- National Science Foundation
- Department of Transportation

The following agencies comply with all parts of 45 CFR, part 46:

- Central Intelligence Agency
- Department of Homeland Security
- Social Security Administration
medical devices and established a system that requires FDA approval of drug and device safety.

Specifically, the act required premarket approval of new drugs and gave the FDA the authority to review their safety before they could be sold. Additional authority was given to the FDA by the Kefauver-Harris Amendment to the Federal Food, Drug, and Cosmetic Act in 1962, which required manufacturers to provide proof of effectiveness and greater proof of safety before a new drug could be marketed. The Kefauver-Harris Amendment defines the nature of scientific evidence required for drug approval, and that the evidence be obtained through adequate and well-controlled investigations. 11 This amendment was passed in large part because of the discovery of severe birth defects caused by a drug called thalidomide. 27 Thalidomide was a sedative used in the late 1950s and early 1960s for the treatment of morning sickness in pregnant women. 34 Although the drug was commonly prescribed in Europe, it was never approved for use in the United States, primarily because there was insufficient safety data submitted by the manufacturer. By 1961, reports of significant numbers of infants being born with malformed limbs reached the United States. Many of the children had phocomelia, which is severe shortening of the arms or legs with potentially fused fingers or toes. 27 Shortly thereafter, the Kefauver-Harris Amendment became law, giving the FDA the authority to prevent similar tragedies from occurring in the United States. FDA human protection regulations are published as part of 21 CFR, parts 50, 56, 312, and 812. 67 Part 50 addresses protection of human subjects, part 56 addresses IRBs, part 312 addresses investigational drug applications, and part 812 addresses investigational devices. 67

The FDA adheres to principles of good clinical practices regarding the conduct of clinical trials. 71 Clinical practice guidelines are not legal requirements but recommendations for how clinical research should be

Box 4

The Common Rule 66

General requirements for informed consent:

- A statement that the study involves research, an explanation of the purpose of the research, expected duration of the participant’s involvement, a description of the procedures to be followed, and identification of any procedures that are experimental.
- A description of any reasonably foreseeable risks or discomforts to the participant.
- A description of any reasonably expected benefits to the participant or others.
- A disclosure of appropriate alternative procedures or courses of treatment that might benefit the participant.
- A statement regarding the extent to which confidentiality of the participant’s identity will be maintained.
- For research that may involve more than minimal risk, an explanation as to whether any compensation and medical treatment are available if injury occurs, and if so, the extent of compensation and treatment and how to obtain them.
- An explanation of whom to contact with questions about the research, participants’ rights, and whom to contact in the event of study participant injury.
- A statement that participation is voluntary, refusal to participate will not involve penalty or loss of benefits to which the participant is entitled, and the right of the participant to discontinue participation at any time without penalty.

When appropriate, additional elements of information will be given to the participant:

- A statement indicating that a particular procedure or treatment may involve risks to the participant (or the embryo or fetus, if the participant is or may become pregnant) that are currently unforeseeable.
- Anticipated circumstances in which the investigator may terminate the participant’s participation without the participant’s consent.
- Any additional costs that may be incurred by the participant from participation in the research.
- Consequences of a participant’s decision to withdraw from the study and the procedures to be followed to do so.
- A statement that the participant be provided with information regarding significant new findings occurring during the course of the study that may relate to the participant’s willingness to continue to participate.
- The approximate number of study participants.
conducted. The FDA has published several guidance documents addressing good clinical practices, and has collaborated on international good clinical practice documents such as those established by the International Conference on Harmonisation.

In 1990, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use was established. This committee, made up of regulatory agency and pharmaceutical company representatives from Europe, Japan, and the United States, was charged with developing international standards for quality, safety, and efficacy that would promote harmonization and coordination of technical guidelines between countries. The Guideline for Good Clinical Practice was published in 1996. The FDA has adopted the guideline for research sites, IRBs, and sponsors.

Further protections for human research subjects have been established by presidential executive orders. Since the mid-1990s, each of the past 3 presidents has established bioethics commissions to explore ethical issues in science, medicine, and technology. The National Bioethics Advisory Commission (1996-2001), created by President Clinton, examined topics including cloning, human stem-cell research, and research involving human subjects. President George W Bush established the President’s Council on Bioethics (2001-2009), which issued reports on stem-cell research, human enhancement, and reproductive technologies, among other subjects. The Bioethics Commission was created by President Barack Obama’s executive order in November 2009 and will terminate in September 2015 unless continued by the President.

These commissions have advised U.S. presidents on bioethical issues that arise from continued advancement in medicine, science, and technology. They also promote policies and practices to ensure research, health care delivery, and technological innovations are responsibly and ethically conducted.

Today, strong safeguards are in place to protect research participants from unethical practices and human rights abuses. Regulations enforced by the FDA and the Office of Human Research Protections ensure that clinical trials are reviewed and approved by IRBs before being initiated and that study volunteers have all the information needed to give informed consent.

**Barriers to Cancer Clinical Trial Participant Recruitment**

Clearly, cancer clinical trials are important in the battle against cancer. The results of these studies have made and continue to make a difference in the care that cancer patients receive. They provide the basis for the development of new drugs, biologic agents, medical devices, diagnostic studies, and treatment regimens that can benefit patients and their families now and in the future. Unfortunately, it often is difficult for researchers to recruit clinical trial participants. Only about 3% of adults with cancer participate in clinical trials. Reasons for this lack of participation include issues related to health care providers or patients themselves.

Physicians are not always aware of the types of clinical trials available for their patients, so they are unable to refer patients to a clinical trial. Many physicians might think that the standard cancer treatment is the best available and are uncomfortable referring patients to clinical trials in which their patients could be randomized to an investigational treatment. Lastly, some physicians might fear losing the relationships they have with their patients and the input into treatment decisions affecting them.

Because so many different sponsors conduct research, there is no complete list of clinical trials taking place at any given time. This is problematic for cancer patients seeking to participate in a clinical trial. The NCI maintains one of the most complete lists of ongoing cancer clinical trials, but potential volunteers must rely on information from their own health care providers or contact NCI-designated cancer centers, drug and biotechnology companies, and cancer advocacy groups on their own.

Research has consistently shown that many people are not aware that clinical trials exist and could be an option for treatment or prevention. Additional research has demonstrated that if a patient’s doctor does not recommend a clinical trial, the patient is unlikely to participate in one. Other reasons for lack of participation in clinical trials include not knowing where to find out about ongoing trials, the perception that there are no trials taking place in the local community, and concern about the potential costs associated with a clinical trial if health insurance does not cover participation.
Reference https://www.cancer.gov/..../clinicaltrials/types


Today’s Cancer Clinical Trials Lead to Standards of Care Tomorrow

To earn continuing education credit:
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Read the preceding Directed Reading and choose the answer that is most correct based on the article.

1. Agent studies in cancer prevention trials also are called _______ studies.
   a. chemoprevention
   b. pivotal
   c. adjuvant
   d. action

2. _______ trials investigate methods to detect cancers earlier.
   a. Prevention
   b. Diagnostic
   c. Treatment
   d. Screening

3. Genetics trials are conducted to determine how an individual’s genetic make-up influences all of the following except:
   a. detection.
   b. prognosis.
   c. treatment.
   d. quality of life.

4. Cancer patients might consider participating in a clinical trial to:
   1. access promising new interventions.
   2. reduce treatment costs.
   3. take an active role in their own health care.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

5. _______ studies typically involve review of patient medical records and patient interviews.
   a. Retrospective
   b. Interventional
   c. Prospective
   d. Action

6. Phase _______ clinical trials enroll about 15 to 30 study participants and evaluate the safety of an intervention.
   a. 1
   b. 2
   c. 3
   d. 4

continued on next page
7. Phase 2b studies are sometimes referred to as _______ trials.
   a. pilot
   b. pivotal
   c. action
   d. interventional

8. Between 2008 and 2009, the success rate for phase 2 trials for new drugs was about ______ %.
   a. 8
   b. 12
   c. 18
   d. 26

9. Phase _______ clinical trials use randomized prospective controlled studies to compare a new treatment intervention with the current standard of care.
   a. 1
   b. 2
   c. 3
   d. 4

10. To eliminate bias in clinical trials, researchers might:
    a. use randomization and blinding.
    b. let patients know whether they receive placebos.
    c. employ transparency and randomization.
    d. assign certain patients to a specific trial arm.

11. All of the following statements are true about study protocols except:
    a. They are written agreements between the investigator, participants, and the scientific community.
    b. They include a description of the study’s purpose and rationale.
    c. They define how the study will be carried out.
    d. They are kept confidential and shared only with researchers.

12. The _______ is responsible for determining the scientific validity of the study and ensuring there is an acceptable benefit-to-risk ratio for the participants before the study can begin.
    a. National Cancer Institute (NCI)
    b. institutional review board (IRB)
    c. American Cancer Society
    d. principal investigator

13. The principles of ethical research outlined in the Nuremberg Code include which of the following?
    1. voluntary consent of participants.
    2. protection of subjects from unnecessary suffering and injury.
    3. eliminating the need for human research.
    a. 1 and 2
    b. 1 and 3
    c. 2 and 3
    d. 1, 2, and 3

14. The _______ sought to establish international guidelines for ethical research and addressed topics such as the need for human research to be based on laboratory or animal studies, and the requirement of research protocols to be reviewed by an independent committee.
    a. Belmont Report
    b. Declaration of Helsinki
    c. Willowbrook Hepatitis Experiments
    d. Federal Food, Drug, and Cosmetic Act

15. Dr Henry Beecher’s paper on unethical research practices published in the New England Journal of Medicine documented _______ examples of “unethical or questionably ethical studies.”
    a. 10
    b. 18
    c. 22
    d. 32
16. Which of the following unethical practices took place during the Willowbrook Hepatitis Experiments?
   1. Study participants were intentionally infected with a disease.
   2. Parental consent was obtained through coercion.
   3. A newly discovered treatment was withheld.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

17. The ______ involved 600 African American men from poor rural areas.
   a. Willowbrook Hepatitis Experiments
   b. Belmont Report
   c. Nuremberg Code
   d. Tuskegee Syphilis Study

18. The federal law that established the IRB system is the ______ Act.
   a. Health and Scientific Affairs
   b. Belmont
   c. Biomedical and Behavioral Research
   d. National Research

19. The report titled Ethical Principles and Guidelines for the Protection of Human Subjects of Research is more commonly known as the:
   b. Declaration of Helsinki.
   c. Nuremberg Code.
   d. Common Rule.

20. The basic principles identified in the Belmont Report are:
   1. respect for persons.
   2. beneficence.
   3. justice.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

21. According to the article, one example of undue influence is when:
   a. a patient freely gives consent.
   b. a gratuitous reward is offered for cooperation.
   c. information is withheld to gain consent.
   d. misleading data is provided to get agreement.

22. ______ is the principle that ensures that cruel or inhumane treatment is not tolerated.
   a. Justice
   b. Autonomy
   c. Integrity
   d. Beneficence

23. The Belmont Report did not address protection of people in institutions.
   a. true
   b. false

24. The Office of Human Research Protections is under the umbrella of the:
   a. NCI.
   c. U.S. Food and Drug Administration.
25. The Federal Policy for the Protection of Human Subjects is generally known as the:
   b. Human Research Protection Regulations.
   c. Common Rule.

26. According to federal regulations, an IRB must have a minimum of ______ members.
   a. 5
   b. 6
   c. 9
   d. 12

27. The FDA’s authority to approve new drugs, biologics, and medical devices before they can be used on patients was established by:
   a. the Common Rule.
   b. presidential executive order.
   d. the Federal Policy for Protection of the Population.

28. The federal law that requires drug manufacturers to prove the effectiveness and safety of a new product to the FDA is called the:
   b. CFR Title 21.
   c. Kefauver-Harris Amendment.
   d. CFR Title 45, part 46.

29. Only about ______% of adults with cancer participate in clinical trials.
   a. 1
   b. 3
   c. 10
   d. 25

30. According to the article, which of the following does not contribute to the difficulty of recruiting patients to cancer clinical trials?
   a. There is not a complete list of clinical trials taking place at any given time.
   b. Physicians frequently are unaware of available clinical trials.
   c. Patients are concerned about the potential costs associated with a clinical trial.
   d. Patients are satisfied with the treatments they are receiving.
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