



FROM BIRTH TO DEATH AND BENCH TO CLINIC

THE HASTINGS CENTER BIOETHICS BRIEFING BOOK

for Journalists, Policymakers, and Campaigns

CHAPTER 5

Clinical Trials

Christine Grady, "Clinical Trials," in *From Birth to Death and Bench to Clinic: The Hastings Center Bioethics Briefing Book for Journalists, Policymakers, and Campaigns*, ed. Mary Crowley (Garrison, NY: The Hastings Center, 2008), 21-24.

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clinical trials

by Christine Grady

Framing the Issue

Clinical research with human participants utilizes a systematic approach to help understand human health and illness in order to find safe and effective ways to prevent, diagnose, and treat disease. Most clinical research in the United States is sponsored by pharmaceutical or biotechnology companies, which spent more than \$10 billion on it in 2002; the U.S. National Institutes of Health is the second largest sponsor. Clinical research has a long history and has resulted in significant benefits for society, yet it continues to pose profound ethical questions.

Clinical research involves clinical trials, which are designed to test the safety and efficacy of interventions in humans. Carefully conducted clinical trials of treatments, prevention modalities, medical devices, and other interventions are considered the fastest, safest, and best way to determine whether they work for cancer, HIV/AIDS, asthma, and many other diseases. Treatment trials test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy. Prevention trials test medicines, vaccines, vitamins, or lifestyle changes to see if they can prevent disease or disease recurrence. There are ethical concerns about clinical trials because some individuals are asked to accept a burden or risk in order for researchers to develop knowledge that will benefit others.

Steps in Clinical Research

Clinical research follows a standard trajectory of different steps. These include:

■ Preclinical research.

- **Laboratory.** Preclinical research begins in the laboratory, where researchers identify promising human interventions. Scientists often evaluate hundreds of thousands of molecules in order to find a few that have the potential to become a safe and effective treatment.

- **Animal studies.** The few promising therapies discovered in laboratory research are then tested in animal models to evaluate safety and desired therapeutic effect. Animal testing, although somewhat controversial, is a critical step in the process. However, the way a potential treatment works in animals may not mimic what will happen in humans. According to CenterWatch, only about

Christine Grady, RN, PhD, a Hastings Center Fellow, heads the Section on Human Subjects, Department of Bioethics, at the Clinical Center of the National Institutes of Health.

HIGHLIGHTS

- Clinical trials are specifically designed to test the safety and efficacy of interventions in humans and are preceded by laboratory and animal research.
- Only about one out of every five new drugs that enters clinical testing receives Food and Drug Administration approval.
- A randomized controlled trial is a type of clinical trial comparing two or more interventions. RCTs are the principal method for demonstrating the safety and efficacy of new interventions.
- There are ethical concerns about clinical trials because some individuals are asked to accept risk in order to develop knowledge that may not directly benefit them.
- According to U.S. regulations, clinical trials must be approved by an institutional review board to determine whether they are ethical and participants' rights are protected.
- Federal regulations also usually require that the participants give informed consent—a goal often imperfectly realized.

EXPERTS TO CONTACT

Christine Grady, RN, PhD, Head, Section on Human Subjects, Department of Bioethics, Clinical Center, National Institutes of Health • cgrady@nih.gov, 301-496-2429

Karen J. Maschke, PhD, Research Scholar, The Hastings Center • maschkek@thehastingscenter.org, 845-424-4040, x223

CLINICAL TRIAL PHASES

Phase	Participants	Purpose	Special Features
Phase 1	Small number (20–80) of participants, usually healthy volunteers, in some cases patients with advanced disease (e.g., cancer)	To evaluate safety, identify side effects, determine a safe dose range, and learn how the agent is absorbed and handled by the body (pharmacokinetics/dynamics).	Often first time tested in humans
Phase 2	Larger number (hundreds) of patients with the condition under study	To further evaluate safety and to determine if the agent has the intended effect in humans.	Sometimes randomized controlled trials
Phase 3	Larger still (thousands) of people with the condition under study	To confirm or further evaluate an agent's effectiveness, monitor side effects, compare it to commonly used treatments, and collect other information that will be used to determine whether the agent should be approved and marketed.	Usually randomized, controlled trials
Phase 4 (postmarketing study)	Various populations	To collect additional information after an agent is approved and marketed regarding its risks, benefits, and use in various populations over a longer period of time.	

one out of every 50 drugs tested in animals is determined to be safe and effective enough to test in humans.

■ **Clinical trials.** Researchers send an Investigational New Drug (IND) application to the Food and Drug Administration for permission to begin clinical trials in humans. Experimental drugs, biologics, devices, and other interventions are tested in human clinical trials to determine if they are safe and effective; what dosage is best; what the side effects are; and whether the experimental intervention is as effective as or more effective than other available interventions. A clinical trial follows a careful plan described in a written protocol that usually includes the background and purpose of the study; inclusion and exclusion criteria for participants; the schedule of tests, procedures, and other activities; the length of the study; the primary and secondary outcomes and how they will be measured; statistical methods; anticipated risks and benefits; and other details. Clinical trials are conducted in a series of stepwise phases, usually leading to a randomized controlled trial, or “RCT.” RCTs are considered by many to be the gold standard for clinical research in humans (see box, “Clinical Trial

Phases”) Approximately one out of every five new drugs that enters clinical trials ultimately receives FDA approval. It can take as long as 20 years and an estimated \$800 million to bring a single new drug treatment from its initial discovery through to the market.

Special Features and Challenges of Randomized Controlled Trials

A randomized controlled trial is the principal method for demonstrating the safety and efficacy of new interventions in humans. The ethical justification to begin an RCT is a lack of convincing evidence that one of two or more interventions is superior in its therapeutic efficacy, safety, or clinical usefulness. This situation is often referred to as “clinical equipoise.” An RCT aims to disturb equipoise by comparing two or more interventions to determine whether one is equivalent or superior to the others. For example, an RCT might show that individuals with cancer receiving one chemotherapy regimen live longer than those receiving a different regimen; an RCT of an HIV vaccine might aim to determine if the group of individuals receiving the vaccine have lower rates of infection than those receiving a placebo.

An RCT has several distinct features that aim to

REQUIREMENTS OF ETHICAL CLINICAL RESEARCH

Value	Ethical research should aim to answer a clinically, scientifically, or socially valuable question that will contribute to generalizable knowledge about health or be useful to improving health.
Validity	Ethical research should have an appropriate, rigorous, and feasible design, end points, methods, and implementation plans to ensure valid and interpretable data.
Fair subject selection	The process and outcomes of subject and site selection should be fair and based on scientific appropriateness, minimization of vulnerability and risk, and maximization of benefits.
Favorable risk-benefit ratio	Research risks should be minimized and justified by potential benefits to participants and/or to society (the value of the knowledge).
Independent review	Independent review should evaluate adherence to ethical guidelines in the design, conduct, and analysis of research.
Informed consent	Research should include clear processes for providing adequate information to and promoting the voluntary enrollment of research participants.
Respect for enrolled participants	Both during and at the conclusion of research, actions should demonstrate respect for the rights and welfare of participants.

ensure scientific rigor. These include:

- **Randomization.** Participants do not choose, but are assigned—or randomized—by chance to either the “experimental” or “control” intervention in order to keep the two groups similar in relevant and otherwise uncontrollable aspects.
- **Control.** The control group is given either a standard intervention for the disease under study or a placebo.
- **Blinding or masking.** To reduce potential

bias, RCTs are often blinded or masked. This means that neither the participant (single blind) nor the research team (double blind) knows which intervention the participant is receiving.

- **Statistical evidence.** Concluding that the experimental agent is better than or equal to the control agent is based on a predetermined statistical algorithm showing that the results are significant and highly unlikely to be due to chance. The commonly accepted level for statistical significance in RCTs is $p \leq 0.05$. This is

INFORMED CONSENT

Elements of Informed Consent	Description	Challenges
Disclosure of information	Study information should include purpose, research procedures, risks, benefits, alternatives, and other pertinent information. Disclosure should take into account participants' language, education, familiarity with research, and cultural values. Both written information and opportunities for discussion are usually provided.	There is a need to balance the goal of being comprehensive with the amount and complexity of information in order to give participants the information they need to understand the study details and make an informed decision.
Understanding	Participants understand the purpose, risks, benefits, alternatives, and requirements of the research.	Empirical data show that participants often do not have a good understanding of the details of the research.
Voluntary decision-making	Participants must be free from coercion and undue influence, as well as free to choose not to enroll.	Many possible influences can affect decisions about research participation.
Authorization	Participants usually sign a written consent document.	For some individuals or communities, requiring a signature reflects lack of appreciation for their culture or literacy level, and may even put them at risk.


understood to mean that the probability that the relationship of variables is due to chance is less than or equal to 5%.

Ethical Considerations in Clinical Trials

Clinical trials are necessary to find out what is safe and what works so that health professionals know how to prevent and treat illness effectively. Nonetheless, there are ethical concerns about clinical trials because human research participants are a means to developing knowledge that will benefit others. Although participants may be among the beneficiaries of research knowledge, they do not necessarily benefit directly from participation in research—and, more importantly, their benefit is not the goal. The ethical principle of respect for persons requires that individuals be treated with respect for their dignity and not used merely as means for others' ends.

Ethical codes and guidance help delimit when and how research should be conducted with human participants. The Nuremberg Code, the Declaration of Helsinki, the *Belmont Report*, and the U.S. Code of Federal Regulations (45 CFR 46 and 21 CFR 50, 56, and others) provide guidance for researchers to respect and protect the rights and welfare of human research participants. Most of these codes and regulations were formulated in response to historical examples of abuse, such as experimentation by Nazi doctors, the Public Health Service Tuskegee syphilis study, and others. A synthesis of this guidance and the literature suggests that to be ethical, clinical research should satisfy several criteria (see box, "Requirements of Ethical Clinical Research").

According to U.S. federal regulations, clinical trials must be reviewed and approved by an institutional review board, or IRB, before they begin and then periodically throughout the study. An IRB is a committee of physician-investigators, statisticians, community advocates, and others that determines whether a clinical trial is ethically acceptable and whether the rights of participants are adequately protected. Federal regulations also require that the participants give their informed consent, except in particular cases allowed by the regulations and deemed acceptable by an IRB—for example, for certain kinds of minimal risk research (45 CFR 46.116(d)), and some cases of emergency research (21 CFR 50.24). Informed consent is a process that involves disclosing study information to the partici-

pant so that he or she has sufficient knowledge to make an informed and voluntary decision to participate or continue to participate in the research. Although widely accepted as an integral part of ethical clinical research, the goal of well-informed individuals making voluntary choices about research participation is often imperfectly realized (see box, "Informed Consent"). 

RESOURCES

Web sites

- www.hhs.gov/ohrp – Office for Human Research Protections. Includes policy guidance, educational and public outreach material, news, and a FAQ.
- <http://clinicaltrials.gov> – Maintained by the National Institutes of Health. A registry of federally and privately supported clinical trials conducted in the United States and around the world that also includes resources, news, and a glossary.

Recent news

- Reed Abelson, "Financial Ties Cites as Issue in Spine Study," *New York Times*, January 30, 2008.
- Andrew Pollack, "Gene Therapy Study to Resume after Woman's Death," *New York Times*, November 26, 2007.
- Gardiner Harris, "Report Assails FDA Oversight of Clinical Trials," *New York Times*, September 28, 2007.
- Ricardo Alonso-Zaldivar, "Opening Up the Findings of Drug Trials," *Los Angeles Times*, September 17, 2007.
- Ivan Oransky, "Transparency Needed in Drug Researchers Finances," *Boston Globe*, October 7, 2006.

Further reading

- Steven Joffe and Franklin G. Miller, "Bench to Bedside: Mapping the Moral Terrain of Clinical Research," *Hastings Center Report*, March-April 2008.
- Susan Gilbert, "Trials and Tribulations," *Hastings Center Report*, March-April 2008.
- Karen J. Maschke, "Human Research Protections: Time for Regulatory Reform?" *Hastings Center Report*, March-April 2008.
- Timothy Caulfield, "Legal and Ethical Issues Associated with Patient Recruitment in Clinical Trials: The Case of Competitive Enrollment," *Health Law Review*, issue nos. 2-3, 2005.
- Trudo Lemmens, "Piercing the Veil of Corporate Secrecy about Clinical Trials," *Hastings Center Report*, September-October 2004.



See legislation appendix.