

the ethical dilemmas of clinical trials – long

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In Whose Best Interest?

Exposing the ethical dilemmas of clinical trials reveals a balance between researchers wanting to advance medicine, drug companies wanting to get their drug to market, and patients wanting to live.

By Heather L. Van Epps, PhD

Mark Origer almost didn't live to walk his daughter down the aisle. At 47, he was diagnosed with metastatic melanoma, one of the deadliest forms of cancer, and did not respond to any treatment. Origer was out of options. Without treatment, he was given six months to a year to live. But conversations with his oncologist and Internet searches with his wife led Origer to the National Cancer Institute, where Steven Rosenberg, MD, PhD, and his team were using an experimental gene therapy to treat patients with late-stage melanoma. Origer was enrolled in Dr. Rosenberg's trial, and the radical treatment—which involved removing tumor-fighting T cells from Origer, engineering them to be better killers, and re-infusing them back into his body—is working. Now 54, he has been disease-free for more than two years, and walked his daughter down the aisle in fall of 2005.

Most patients who participate in a clinical trial don't have such dramatic success stories. Rebecca Dinning's clinical trial experience began only after her breast cancer was successfully removed in a bilateral mastectomy. Dinning, who was diagnosed in July 2005 at age 31, is now participating in the ongoing TEXT (Tamoxifen and Exemestane Trial) study, aimed at determining which drug is better at preventing breast cancer from returning. But no matter the outcome, clinical trials like these are essential for the development of lifesaving cancer therapies.

Simply put, clinical trials are experiments, and thus the primary purpose of these trials is to learn whether a new drug or treatment is safe and effective—not primarily to benefit the patient. This fact raises many ethical questions. When, for example, is it appropriate to use patients as experimental subjects? And how are the rights of patients protected? These questions arose dramatically 60 years ago in Nazi Germany, when concentration camp prisoners were subjected to tortuous experiments without their consent. These atrocities prompted a set of ethical rules called the Nuremberg Code, which protects the rights of people who

participate in human research.

The Nuremberg Code and later guidelines, such as The Declaration of Helsinki (1964) and the Belmont Report (1979), require informed consent, meaning participants must volunteer with a full understanding that they are participating in research and understand why the research is being done and all the potential benefits and risks that go along with it. The patient can end participation in a trial at any time, for any reason, and a trial's design must be scientifically rigorous with every attempt to minimize harm and adequately monitor patients.

Even with built-in safeguards, there are many ethical issues for cancer patients to consider before deciding to enter a clinical trial. For Origer, the decision was easy. "My tumor was growing, and more tumors had shown up in my lungs. It was either try something radical or go home and die." Ethical issues, Origer says, never entered his mind.

Dinning also spent little time debating whether to enroll, as both tamoxifen and Aromasin® (exemestane) had already been shown to boost survival in breast cancer patients. Even though the chances were good that her cancer would not return, she was still anxious over which drug would be more effective.

But the decision is not always so easy, and it can also be hard for patients to decipher what they should and shouldn't worry about. The emotion that often surrounds a cancer diagnosis doesn't help, says Ezekiel Emanuel, MD, PhD, chair of clinical bioethics at the National Institutes of Health. "[Patients] are not the most level-headed at this time, and they cannot be expected to defend their own interests."

To Enroll Or Not to Enroll

Since patients may not be able to adequately uncover a trial's pros and cons, the responsibility falls largely to research physicians, who must educate patients about the scientific goals, potential risks, possible benefits of the study, and the alternatives to not participating as well as a reassurance that their refusal to participate will not affect their care. "You've got to be able to tell patients what is really important and what is likely [to happen]," says Dr. Emanuel. And this information varies depending on the type of clinical trial.

Phase I trials, for example, are designed to determine how high a dose of the experimental drug can be given and whether it has any side effects. Because phase I trials typically enroll patients whose tumors are resistant to available therapies and aren't designed to measure if the drug is effective, the response rate in phase I trials is generally low, meaning the chances are small that a patient's cancer will respond to the treatment.

Critics argue the unlikelihood of benefit makes early trials inherently unethical, even if the patient consents to participate. "My main concern

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with phase I trials is how well the patient understands the potential for benefit, says Steven Joffe, MD, pediatric oncologist at Dana–Farber Cancer Institute who conducts research on the ethics of clinical trials. It's the patient who says, "I'm probably going to get better" and then makes a decision based on that belief that worries me.

This type of misunderstanding, known as "the therapeutic misconception," is common, perhaps because the normal doctor–patient relationship is focused solely on improving the health of the patient, whereas the primary goal of a clinical trial is to answer a scientific question.

With such a low potential for benefit, figuring out why a patient would enter a phase I trial relates in part to the type of patients who are eligible. They have a life–threatening cancer and have typically not responded to conventional treatment. This feeling of desperation may lead patients to feel "their only other options are unproven therapies or palliative care," says Dr. Joffe.

Patients eligible for phase I trials may be reassured by a recent study published in the *New England Journal of Medicine* that reported a higher potential for benefit in phase I trials than previously thought—around 11 percent of patients benefited compared with earlier estimates of 4 to 6 percent. This is in part because phase I trials include not only traditional dose escalation studies of single drugs, but also new combinations or dosing schedules of FDA–approved drugs.

Rarely, phase I trials have astounding results, such as the 93 percent response rate in chronic myeloid leukemia patients treated with Gleevec® (imatinib). The drug was extremely effective because scientists identified the protein that caused CML, and the drug was designed to block that protein.

Phase II trials continue to test the safety of a therapy, but also begin to evaluate how well a new treatment works in a selected tumor type. Phase III trials, which are designed to compare the new drug with the best current treatment, raise their own set of tricky ethical issues.

Participants in phase III studies are randomly assigned to receive the conventional treatment, the investigational treatment, or, occasionally, a placebo if no standard exists. Some doctors argue randomization is unethical, as half the patients are denied a possibly more effective therapy. Randomized trials, currently the most accurate way to determine outcome of an experimental therapy, operate on the principle of clinical equipoise, a genuine uncertainty about which treatment will be more beneficial.

"I think the greatest difficulty comes up when patients are really hopeful that they will get the experimental therapy," says Dr. Joffe. "But randomization is essential to ensure we come away with a definitive answer as to which treatment is better." Indeed, many patients worry about being randomly assigned, and some opt out of trials because they want to be in

control of their treatment.

“I did wonder if I would prefer one [treatment arm] over the other,” says Dinning. “But I really couldn’t come to a decision over which one I hoped to be in.” Dinning was indecisive because she knew both drugs were already known to be effective. She also had altruistic motives. “If [the trial] helps progress our knowledge as a cancer community, then it is definitely worthwhile,” she says, adding with a laugh, “but I’m not so altruistic that I’ll hop on any clinical trial that comes along.” Dinning ultimately found out she had been assigned to the Aromasin arm.

Another important point for patients to understand about phase III studies is if they fall outside the research parameters for any reason during the study, they must leave the trial. “You have to stick to the protocol,” says Richard Klein, of the Human Subjects Protection Liaison Committee at the FDA. “The protocol sets the eligibility requirements to enter a trial so that participants share similar characteristics, such as type of cancer, stage of disease, and other existing medical conditions. This consistent patient profile is important when it comes to analyzing trial data to determine which treatment is more beneficial. The treatment of the individual is secondary to the research goals of the trial.”

Newer study designs may ease some of the fears and criticisms of randomization. Bayesian design, for example, allows for the design of trials to be evaluated and modified according to early data from a study. This may not change things for those who start a trial and are later excluded, but it might allow more patients to be randomized into the treatment arm that appears more beneficial as a trial progresses. Eligibility criteria can also be modified to favor patient groups that have responded better in an ongoing trial.

Regardless of the trial’s phase, “the small chance of a response provides important hope to patients,” says Martin Abeloff, MD, chair of the ethics committee for the American Society of Clinical Oncology and director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. “Patients also realize they are helping drugs be developed that will help other people.”

The Placebo Predicament

In some circumstances, a patient may be eligible for a placebo–controlled trial. The use of placebo raises the hackles of many critics, who don’t agree with the justification for withholding treatment from patients with a life–threatening illness like cancer.

Patricia Delaney, director of the FDA’s Cancer Liaison Program and herself a cancer survivor, is a staunch defender of placebo–controlled trials. She says placebos are only used when no proven effective treatment is available for a specific group of patients. The anti–placebo argument, says Delaney, is an overly emotional one.

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It gets characterized as, "How can you keep a potential cure from me?" This is a very emotional position that, so far, has not prevailed, mainly because there's no basis for comparison, no meaningful conclusion that can be reached about the benefits, if any, to be gained from a test therapy. Delaney emphasizes the experimental drug might shorten rather than extend survival or could negatively impact quality of life.

Placebo-controlled cancer treatment trials are only conducted in the United States in cases where no other treatment has proven effective, and in some prevention trials that test how well a drug or treatment prevents cancer from recurring. Two recent examples are the trials for Vectibix (panitumumab) for metastatic colon cancer and Nexavar® (sorafenib) for primary liver cancer. In both trials, patients receiving placebo were switched to the treatment arm of the study as soon as the drug was shown to be effective.

Dr. Abeloff appreciates the unique benefits of placebo-controlled trials. "There are some organizations that use placebo-controlled trials to demonize clinical research," he says. "This is totally unproductive." But he points out the number of placebo trials are decreasing as the number of proven, effective cancer treatments expand.

Considering Conflict

As if all of this wasn't enough for patients to think about, they should also be aware of potential conflicts of interest of those carrying out the trial.

The physician running the trial, for example, might own stock in or be a paid consultant for the company whose drug is being tested. Physicians are also motivated to publish their findings and advance their careers by enrolling a higher number of patients. Or the hospital conducting the study might receive payments from a drug company for each patient enrolled that covers or exceeds the costs of conducting the trial. These financial ties can create a motive for the physician to enroll as many patients as possible in the study or of greater concern, a vested interest in the trial's outcome.

Federal guidelines encourage but do not require disclosure of potential financial conflicts of interest to the patient. But some physicians feel "encouraged" disclosure is not enough. "No physician should ever be involved in making decisions in clinical trials if they have a financial interest in the outcome [of the study]," says Dr. Rosenberg. "When it comes to evaluating experimental treatments, this should be an inviolable rule."

Most clinical trials are run by academic research institutes or the government, which carefully monitor studies at every stage—from the study design to the treatment protocol to data collection and close examination of any conflicts of interest that exist with the physician and the drug company. Research conducted directly by a drug company falls under the

FDA's jurisdiction.

Drug companies may stack the deck in their favor when it comes to testing drugs they manufacture. A 2007 study of breast cancer trials published in *Cancer* found that pharmaceutical industry–funded trials have favorable results more often than non–industry funded trials. Authors of the study addressed possible reasons for the finding, including “the pharmaceutical industry may be more inclined to support or design smaller, single–arm studies for patients with advanced breast cancer [that] likely reflects their important role in the development of novel therapeutics” [and] in general, positive studies are more likely to be published than negative studies (publication bias).?

Investigators also clarified that cooperative group (non–industry) trials typically answer other crucial questions, such as optimal dose, toxicities, and duration of therapy?questions not necessarily at the top of the list for a drug company trying to get its drug approved.

Although many potential conflicts exist, they seem to be of little concern to patients. According to a study published last year in *NEJM*, most patients in cancer research trials are not worried about financial ties between doctors or research institutes and drug companies. For most of the patients, having that information would not have changed their minds about enrolling in the study. This indifference stemmed, in part, from the belief, which was indeed true, that oversight systems are in place to manage these types of conflicts and protect their interests as patients. Nevertheless, patients should check informed consent forms for disclosure of financial interests. If they don't see them, they should ask.

Communication Is Key

The many ethical issues surrounding a patient's decision to enter a clinical trial may seem overwhelming. Perhaps the most effective way for a patient and their family to grapple with these issues is by communicating with the doctors conducting the research trial. Dinning gives her oncologist glowing reviews. “As long as I had questions, I felt like he didn't have anywhere else to be,” she says.

And Origer praises Dr. Rosenberg's team at the NCI. “They did a good job of prepping me as far as what to expect [from the therapy],” he says. “They didn't raise my hopes unnecessarily and were very honest and upfront.”

“I've had a very positive experience,” says Dinning, “but all patients need to make their own decision on whether a trial is something they need to do.”

Origer certainly has no regrets. “It saved my life.”