What are some ethical concerns regarding the typical design of clinical trials in oncology?

The risk/benefit ratio is an important concern. When treating patients with an unproven intervention, it is essential to ensure that the risks and burdens are reasonably well-understood and that the prospect of benefit, either directly to the patient or through scientific advancement, is sufficient to redeem them. Patients who participate in clinical trials may need to undergo research procedures, such as tumor biopsies and extra imaging, as well as additional clinic visits. These are all burdensome, particularly for patients who are sick.

Another concern is fair subject selection. The population enrolled in a clinical trial should be consistent with the patients who will receive treatment with the drug, in terms of age, sex, ethnicity, and other factors. In particular, it is important to ensure that a disadvantaged population is not used to test a drug that will be available only to advantaged populations. For example, cancer drugs should not be tested in low- and middle-income countries if they will be available only in high-income countries.

Can ethical concerns be addressed within the design of a clinical trial?

There are several ways to address ethical issues within the design of a clinical trial. For example, although researchers might want to make organ biopsies mandatory to evaluate a secondary outcome, it might not be ethical to obligate patients to submit to this procedure. The trial design could be altered to make a biopsy optional, with a separate consent process. There are some intrinsically unethical trial designs, such as a trial that evaluates a treatment that has almost no prospect of benefiting patients or advancing medical care. Development of such a product would probably require more preclinical or basic science research to reach the risk/benefit balance that would justify a clinical trial.

What ethical concerns are raised by the funding sources?

Conflict of interest is an important concern. A private sponsor of a clinical trial has an interest in representing the product as favorably as possible. A sponsor that is heavily involved in the design and/or reporting could bias the clinical trial. For example, a randomized trial should have a comparator arm that is a standard of care. However, some standards of care are more effective than others. A sponsor could potentially bias the results of a trial by selecting a less-effective treatment for the comparator arm.

Sponsors sometimes use clinical trials not to answer a scientific question, but to promote a product. Drug companies are not permitted to market products off-label, but with a so-called seeding study, they can run a trial for an off-label treatment and publish the results in a journal, which effectively functions as an advertisement for the drug. Sponsors can also withhold publication of trial results.

It is common for pharmaceutical companies to pursue me-too drugs, which are minor modifications of existing agents. Although there is some value to having...
similar drugs on the market, a better investment—at least from society’s standpoint—would be to develop truly innovative therapies.

**H&O** What ethical issues should a physician consider when offering a patient enrollment in a clinical trial?

**JK** The first question to ask is whether the patient is likely to do as well or better by enrolling in the trial. In some cases, the new drug may not be sufficiently promising or it may be too toxic. Studies appear to show that new treatments outperform older treatments in a slight majority of cases. However, there are probably certain areas in cancer research where patients are more likely to benefit from receiving the older therapy rather than the experimental treatment in a clinical trial. For example, trials of combination therapy are sometimes conducted to discover synergistic or additive effects for different agents. Some data, however, appear to indicate that monotherapy tends to outperform combination therapy.

The next question is whether the patient has an adequate understanding of the risks and benefits of enrollment, as well as the alternatives to participation. Does the patient understand the likelihood of any benefit, and that he or she may be assigned to receive the control treatment? Does the patient appreciate any requirements for extra clinic visits and/or research biopsies, as well as any additional costs?

The patient should also recognize the differences and tensions between care and research. Clinical trials are performed primarily to answer a scientific question. It is hoped that the patient will receive good treatment as well. But the need to answer the scientific question requires elements not encountered in normal clinical care, such as randomization and blinding.

**H&O** What is the typical approach to obtaining informed consent?

**JK** It is essential to ensure that a patient has an adequate understanding of the risks and benefits of enrolling in a clinical trial. Typically, patients are given an informed consent document to read and sign. Most of the literature suggests that these documents are not the primary resource a patient uses to decide whether to enroll. The most effective way for a patient to understand the risks, benefits, and implications of participation is through a discussion with his or her physician. Patients—especially those with advanced disease—are often desperate; they may be distracted by their illness and willing to assume extraordinary levels of risk for a small prospect of benefit. Patients must understand what they are consenting to, especially for clinical trials evaluating cancer treatments, which may be associated with nontrivial toxicities. The physician should also explain the alternatives to participating in a trial—such as treatment with standard-of-care therapy outside the study or with palliative care.

Oftentimes, the discussion of a clinical trial takes place over 2 office visits. In the first, the physician broaches the prospect of participating in a clinical trial, which can lead to a preliminary discussion. The physician might offer a consent form at this first visit and suggest that the patient spend some time considering the pros and cons of enrollment. At the next visit, perhaps a week later, the physician will assess the patient’s interest.

There might be additional layers of informed consent in certain circumstances, such as trials in pediatric patients or those evaluating high-risk or novel agents. For example, if a treatment is associated with unusual risk, it may be helpful for the physician to explain the risk/benefit balance and then ask the patient questions to gauge how well he or she understand the implications of enrollment.

Some medical centers advertise themselves as places where patients can enroll into clinical trials and thereby receive state-of-the-art care. Many of the messages in these kinds of advertisements are potentially misleading and can frustrate the key goals of informed consent.

**H&O** Does it appear that patients who consent to enroll in clinical trials have different characteristics than those who decline?

**JK** Clinical trial populations tend to be younger, white, and slightly more educated. Trials may therefore provide biased information about the safety and efficacy of a drug. If clinical trials enroll relatively privileged patients, then information is lacking for the entire population. This bias can lead to problems in the delivery of equitable care. For example, we probably do not know as much as we should about the safety of cancer drugs in the elderly or in patients who are members of ethnic minorities.

**H&O** What types of ethical quandaries can arise for a physician who thinks that a clinical trial might be appropriate for a particular patient?

**JK** A physician might have concerns about how well a patient understands the risks and benefits of enrollment. Another important issue concerns eligibility. A physician might think that enrollment is a good option for a particular patient who does not meet a certain aspect of the eligibility criteria. For example, the patient might have a test result that just misses the level required for enrollment. This scenario can be a challenge for a physician who wants to adhere to the study rules to advance the science,
but may also believe that the patient will benefit from enrollment.

Many cancer trials, particularly phase 1 or 2 studies, limit enrollment to patients with advanced disease. In many cases, there is no standard of care for these patients. It is uncomfortable to discuss end-of-life care with a patient who has no further treatment options. It is tempting for a physician to offer these patients the option of participating in a clinical trial, rather than have a discussion about end-of-life care. Another important dilemma concerns phase 1 clinical trials. In order for trials to obtain reimbursement from Medicare, enrolled patients cannot receive hospice care, which might be the better course of action.

**H&O Are there different ethical issues in drug development for children and the elderly?**

**JK** Children cannot give a valid informed consent; surrogate consent must be provided by their guardians. There are strict limits on allowable risk for children in clinical trials. For example, invasive biopsies are not permitted unless they are a part of the clinical management plan.

Cancer largely occurs in older patients, but this population tends to be underrepresented in clinical trials. Elderly patients often metabolize drugs differently and can have distinct responses to treatment. It is important to include elderly patients in clinical trials.

**H&O Do newer cancer treatments pose any particular ethical challenges?**

**JK** Different therapies present unique challenges. For example, chimeric antigen receptor (CAR) T-cell therapy can have a narrow therapeutic index and the potential for life-threatening toxicities. It is important to obtain a careful informed consent to ensure that patients understand the substantial risk, as well as the prospect of benefit. In an area such as precision medicine, the therapy has been customized for the patient. This message can confuse patients by obfuscating the various ways that clinical trials limit the degree of customization, as their primary goal is to advance the science. Another concern with new therapeutic platforms is the limited information about risk and benefit. There can be uncertainty regarding the kinds of safety issues that might arise.

New therapeutic agents may be hyped in the lay press. Patients may read headlines suggesting that a new treatment has a dramatic impact and can even offer a cure. Patients might not appreciate that these outcomes might not be applicable to their particular circumstance. In addition, media reports of cutting-edge treatment often provide preliminary data from early-phase clinical trials. In many cases, drugs that appear promising in early-phase trials are not found to be safe or effective in large, randomized trials.

**H&O What concerns arise regarding the reporting of trial data?**

**JK** Trials can be reported in a way that obscures important information, such as safety data. In addition, many trials with negative results are never submitted for publication. A study from my group showed that only 35% to 40% of clinical trials for drugs that never receive approval are published with 5 years after trial completion. The failure to report trial results violates the compact between enrolled patients and researchers, and also frustrates the ability of healthcare systems and scientists to learn from the information.

**H&O What ethical issues can arise after a drug has been approved?**

**JK** Before a certain drug is approved, drug companies tend to test it only against cancers that are likely to respond, in order to obtain an approval as quickly as possible. Therefore, the company invests in the most promising kinds of trial designs at that point. After a drug is approved, researchers—both in industry and academia—may test it against many different malignancies, even if the supporting evidence is weak. In addition, researchers may conduct small, open-label, phase 2 studies of approved drugs, instead of larger, randomized trials. Clinical practice guidelines may then recommend these treatments based on the low level of evidence. Without definitive trials, there is uncertainty regarding whether a drug is truly useful in a given malignancy.

**H&O Does drug development raise any ethical issues from a societal standpoint?**

**JK** Most ethical challenges concern the protection of patients. As a society, it is also necessary to consider how to efficiently allocate scientific and medical expertise...
toward the most productive kinds of research. Government funding has subsidized the training of every clinician who performs research, even those who attended private schools. From a societal perspective, it is important to ensure that the scarce resource of scientific expertise is directed toward the testing of sound hypotheses.

**H&O** Are there ways in which Canada and the United States differ in their approaches to drug development?

**JK** Regulations and policies are similar between the United States and Canada. In Canada, with the public healthcare system, patients are covered for injuries that may occur during clinical trials. In the United States, patients have to hope that their insurance will cover any injuries. Fewer medical centers in Canada advertise clinical trials to patients. In Canada, there is a greater emphasis on public health–oriented interventions.

**Disclosure**

Dr Kimmelman serves in a remunerative capacity on a Data Safety Monitoring Board for Ultragenyx Pharmaceutical Inc.

**Suggested Readings**


