Ethical Issues of Chemoprevention Clinical Trials
Victor G. Vogel, MD, MHS, and Lisa S. Parker, PhD

Ethical issues associated with clinical research in cancer chemoprevention trials are multiple and varied.

Background: Chemoprevention of malignancy is a new concept in clinical medicine, and little is written about the ethics of identifying and enrolling eligible subjects in chemoprevention clinical trials.

Methods: The authors identify the ethical issues raised in the conduct of clinical chemoprevention trials and review the ethical considerations that should guide clinical researchers in the design and conduct of this new type of clinical trial.

Results: The ethics of chemoprevention clinical trials are complicated because (1) chemoprevention lies at the intersection of disease management and health promotion, (2) there are conflicting interests competing in these trials, and (3) multiple values play a role in determining the nature and magnitude of the risks and benefits of chemoprevention of cancer. Ethical questions related to these trials concern the enrollment of healthy individuals rather than cancer patients, confidentiality in recruitment, the enrollment of "high-risk" subjects, randomization, informed consent, trial monitoring, and competing outcomes and toxicities.

Conclusions: These issues will be resolved with the accumulating clinical experience and ethical deliberations that accompany ongoing clinical chemoprevention research studies.

Introduction

Chemoprevention can be defined as the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenic progression to invasive cancer.\(^1\)\(^-\)\(^3\) Epithelial carcinogenesis proceeds through multiple discernible stages of molecular and cellular alterations and provides the scientific rationale for cancer chemoprevention. Before an agent identified in the laboratory as having potential efficacy as a chemopreventive drug can be tested in human beings, a suitable "target population" must be identified along with an obtainable endpoint for a clinical trial. This endpoint could be the emergence of incident cancer cases or an intermediate (ie, "surrogate") endpoint.\(^4\)\(^,\)\(^5\)

A number of chemoprevention trials in various stages are currently being conducted in the United States and Europe.\(^2\) Chemoprevention of malignancy is a new concept in clinical medicine, and little is written about the ethics of identifying and enrolling eligible subjects in chemoprevention clinical trials. In the sections below, we identify the ethical issues raised in the conduct of clinical chemoprevention trials and review the ethical considerations that should guide clinical researchers in the design and conduct of this new type of clinical trial.

Ethical Background and Issues in Chemoprevention

Bioethics was born in the late 1960s at a time of general concern for individual rights, including patients' rights,\(^6\) and as a result of the frustration and confusion that medical professionals experienced as they faced new but often scarce technologies (eg, dialysis). Bioethics, therefore, also emerged as a professional ethic for health care providers and continued implicitly to give more weight to the values and goals of medicine and science than to the cultural norms, and sometimes idiosyncratic values, of patients.

Recently, the Food and Drug Administration displayed favoritism toward medical values when it determined that silicone implants should remain available for reconstructive purposes following mastectomy but should be severely restricted for use in breast augmentation. The connection between cosmetic reconstruction and life-saving, curative treatment, a quintessential medical value, was cited as the relevant difference between the two uses.\(^7\)\(^,\)\(^8\)

In resolving questions of justice and the equitable allocation of potentially beneficial interventions, bioethics asserted that the medical establishment could not engage in God-like reasoning and make value judgments about the relative worth of different ways of living. However, in selecting candidates for organ transplantation, values, qualities, or lifestyles that fall outside accepted norms are deemed contraindications for transplantation.\(^9\) Because some ethical problems and conflicts have been identified as arising rather predictably in various medical contexts, bioethics now advocates taking a "preventive ethics stance" toward them.\(^10\)

Anticipating and implementing structural solutions to (or ways of resolving) ethical problems may provide the best hope of promoting patient autonomy, protecting and
promoting patient welfare, and allocating scarce resources equitably. The design of chemoprevention trials and the eventual delivery of chemopreventive agents as standard care constitute an especially rich arena in which to identify and attempt to resolve ethical conflicts and to examine the normative assumptions of experimental preventive medicine and their interaction with patients' values. As a preventative medical intervention, chemoprevention reflects an anticipatory stance, anticipating and preventing disease development based on state-of-the-art knowledge about disease etiology and course as well as therapeutic agents. Similarly, based on current understanding of ethical concerns in clinical trial design, health belief models, and psychologic and social risks attending preventive interventions, it is possible to pursue a preventive ethics approach in designing chemoprevention trials and to anticipate the particular complicating factors in chemoprevention that raise ethical concern.

Chemoprevention Clinical Trials

The ethics of chemoprevention are complicated for three fundamental reasons. First, chemoprevention lies at the intersection of different approaches to the management of disease and health promotion. Second, and relatedly, several conflicting perspectives or interests are at play in chemoprevention trials, as in all clinical research. Third, as in all areas of medicine but especially in this context, values play an important role in determining the nature and magnitude of the risks and benefits of chemoprevention. We review these sources of ethical concern and propose suggestions to sort out conflicting interests and to assure that appropriate normative goals are pursued.

First, the ethics of chemoprevention clinical trials reflect ethical considerations of experimental interventions (as opposed to standard care), of prevention (as opposed to cure or treatment), and of public health strategies as well as individualized approaches to disease management. Thus, those participating in chemoprevention trials are not typical patients in two senses—they are research subjects and they are likely to be healthy.

Second, although cancer patients might be assumed to have the treatment or cure of their disease as a primary interest, those seeking to prevent disease generally view this as one goal among many. If the risks or burdens are too high or if other conflicting pursuits are valued more highly, potential trial participants may prefer to forgo chemoprevention entirely. (This is, of course, equally true of ill patients, but the seriousness of their condition may make treatment a prerequisite for pursuit of other goals.) In addition, physician-researchers who want to accrue patients to their randomized trials have professional interests that may conflict with the interests of both their eligible and enrolled subjects. Thus, the experimental and preventive nature of chemoprevention introduces a variety of interests on the part of those offering it, which can also conflict with the multitude of possibly conflicting interests that subjects have with respect to the intervention.

Because the benefits of chemoprevention are demonstrated in the aggregate but are unlikely to be evidenced in every subject, it is difficult (and currently impossible) for individuals to predict how the potential benefits of chemoprevention affect one's own interests and interact with one's personal priorities. In this regard, chemoprevention resembles a classic public health intervention rather than individualized therapy. A potential subject might highly value avoiding cancer, which argues in favor of choosing chemoprevention at least once its benefit is demonstrated, and yet the individual may develop cancer anyway or might have avoided cancer without the chemoprevention intervention. From the individual perspective, the risks and burdens associated with chemoprevention will be incurred, but the benefits may accrue to others. However, from the perspective of an entire population at risk, chemoprevention would be a valuable means of disease reduction. (Moreover, our highly cancer-averse subject may be randomized to a nonchemopreventive control arm. Also, all research subjects may be said to incur risks and burdens for the primary benefit of future generations.)

Finally, it is tempting to assess the risks and potential benefits of chemoprevention trials through the lens of medical science. Such examination would tend to emphasize eventual aggregated outcomes as well as risks, side effects, and benefits that fit medical models of deleterious or beneficial consequences. Nevertheless, it is crucial to give adequate weight to nonmedical values, to be cognizant of extra-scientific factors that affect subject accrual and interpretation of risks, and to take seriously the values and concerns of patients when balancing conflicting interests, assessing the appropriateness of a proposed clinical trial, determining what information must be disclosed to subjects during informed consent, or identifying proper stopping points. It is important to ensure that stopping rules, for example, are not only pertinent to medico-scientific values (eg, statistical significance) but also relevant to the actual concerns of subjects. Moreover, although medico-scientific and patient perspectives may often differ, these differences may be more dramatic when no disease condition exists than when patient and professional unite their interests and efforts. In preventive interventions, medical professionals are more likely than members of the public to give overriding weight to concern about the disease under study.

Healthy Individuals vs Cancer Patients

Individuals who are ill typically enter the health care system willingly and request diagnosis and treatment. In contrast, those who are at risk of developing a disease seldom present to the system requesting initiation of primary preventive interventions. However, healthy individuals may seek screening and early detection of cancer. Clinical trials extract a price from those who participate, even healthy individuals. The costs of participation involve lost time, the expenses of clinic visits and laboratory testing not provided by the trial, the costs of additional tests and procedures resulting from close observation, the administration of daily medications, and the possibility of toxicity due to the agent under investigation. In addition, the social and economic risks of stigma and discrimination in employment or health and life insurance may accompany participation in clinical trials of screening and prevention strategies, because participation in them implies that subjects may be at increased risk for expensive or stigmatizing diseases. Patients with cancer or other severe, life-threatening illnesses are likely to endure significant hardship and treatment-related toxicity in the hope of receiving curative therapy. Indeed, many will enroll in trials of experimental therapies in this sometimes mistaken hope.

Despite its severity, however, cancer is a rare disease even among individuals who are at increased risk. Identification of conditions that increase the risk of developing malignancy is not difficult. These include a family history of the disease, the presence of epidemiologic risk factors (eg, age at first live birth), or biopsy-documented premalignant histologic change (eg, proliferative benign breast disease with or without atypia, oral leukoplakia, colon polyps). Relative risks associated with these conditions range from modest levels of 2 to 4 to very high levels of 10 or greater. Nevertheless, most individuals with these conditions will not develop malignancy. We have not yet defined the lifetime probability of developing disease that justifies enrollment of such individuals in a clinical trial, and it is not apparent how the chance of developing malignancy should be compared to the risk of toxicity related to the agent under study or resulting from the monitoring procedures to be used during the trial.

Individuals frequently differ in the priority they give to avoiding particular disease conditions or the disability they attribute to being ill; the personal nature of this normative assessment complicates the establishment of a standard of care or a standardized protocol for trial enrollment. In situations where the likelihood of disease development is uncertain, standardization is even more complicated, because individuals differ in their degree of risk aversion and have difficulty appreciating probabilistic information. Generally, where there is lack of consensus about how individuals will value health intervention opportunities, it is best to inform them of the intervention and allow them to decide. This rule of thumb, however, is tempered by concern about protecting them from psychosocial and economic risks, such as insurance discrimination. Appropriate preventive ethics strategies include informing prospective subjects in stages of increasingly detailed information, not recording initial offers of participation in medical records (to avoid insurance discrimination), and early "mirandizing" prospective participants about psychosocial and economic risks as well as health-related risks of participation.

Moreover, it is unclear whether the individuals enrolled in a clinical chemoprevention trial should be considered "patients," "subjects," or "participants." Labeling healthy individuals as patients carries the potentially negative connotations of illness and all of the behavioral metaphors associated with illness. The creation of new classes of the asymptomatic sick (eg, considering gene carriers as ill), which attends various screening strategies, and the medicalization of conditions for which there may be a...
While designating those enrolled in chemoprevention trials as "subjects" is important to reflect the experimental nature of the enterprise and the dual roles of their physician-researchers, this designation may make some individuals feel more vulnerable, as though they are human guinea pigs. Steps must be taken to inform them honestly of the conflicting obligations that physician-researchers face and to ensure that such conflicts are resolved in favor of protecting each of them. A subject must realize the physician-researcher relationship differs from the personal physician relationship due to its role in more global goals, but steps must be taken to ensure that it is still a well-justified, trusting relationship.15 Candor about the existence of possible conflicts empowers patients; it is often not the existence of conflicting professional interests and obligations that concerns patients, but their initial unawareness of them. When such conflicts are discovered -- often following a negative outcome -- a sense of betrayal and mistrust ensues. Preventively disclosing potential and uneliminable conflicts allows patients to consent explicitly to these background risks of participation.

Confidentiality in Recruitment

Among patients who have established relationships with a particular physician, it is common for the physician to offer participation in various treatment clinical trials to those patients with medical conditions lacking defined treatment or for whom the trial would offer therapy not otherwise available because of issues such as access or cost. Where the researcher is also the patient's personal physician, special care must be taken to ensure that neither appearance nor reality of conflict affects the interests of the patient. Access to potential subjects for a cancer chemoprevention clinical trial is problematic, however, because the subjects of interest often have no established therapeutic relationship with the responsible clinical investigator. They may be relatives of cancer patients under treatment, or they may be individuals listed in a pathology database because of a prior biopsy showing the presence of a premalignant histologic condition. Some ongoing chemoprevention clinical trials have used tumor registry data to identify relatives of cancer patients who may be acceptable and willing candidates for trial participation.10 Pathology databases have been similarly employed, but uniform mechanisms or guidelines for using these resources have not been established.

Issues of privacy and confidentiality and concerns about introducing psychosocial and economic risks arise with respect to recruiting subjects from populations. These must be balanced with both the potential desire of subjects who are at increased risk for malignancy to know about potentially beneficial interventions and the potential benefit to larger populations of completing chemoprevention trials. Recruitment strategies that seek to enroll the relatives of cancer patients in chemoprevention clinical research risk violating principles of confidentiality designed to protect patients. Moreover, unless such relatives already know that they are at increased risk of cancer, their introduction to this information may create anxiety and disrupt their life plans, self-concepts, or familial relationships (eg, if they blame their relatives for not informing them). Those found not to be at increased risk may experience a sense of "survivor guilt" and disrupted family relationships. Most importantly, although we live in an era of increasing medicalization and rapid increases in medical knowledge, the exercise of autonomy entails that people still have a right not to know about their health status.

In some studies of genetically determined disease, use of a proband to identify and make the initial contact with other family members has proved to be a useful recruitment strategy that might be employed in this context.13 A conversation with a family member (eg, a cancer patient) does not introduce the same degree of risk to employment and insurability as might contact by a researcher. Even becoming aware of a family history of disease may, however, introduce such risks because of requirements by insurance companies of honest self-reporting. Nevertheless, a family member may make an initial, suitably general contact of relatives, who in turn may be asked to contact researchers if they are interested in further information about trial participation.

Recruitment by family members also raises concern about the degree to which participation is voluntary. Would pressure by family members be likely, and would this pressure be impossible for researchers to monitor and prevent? Generally, the degree of familial pressure that accompanies positive ties of affection, respect, and interdependency is deemed acceptable. However, researchers should inquire whether prospective enrollees felt pressured to participate, and they should take steps to minimize this pressure, regardless of its source.17

Because enrollment in a clinical prevention trial also may jeopardize either employment or insurance, especially if a criterion for entry in the trial is being a member of a "high-risk group," special care must be taken to warn prospective enrollees of this risk and to protect their confidentiality.18,19 These measures might include applying for a federal certificate of confidentiality whenever possible and maintaining records concerning research participation separate from personal medical records. Maintaining separate records will be difficult, if not impossible, in the case of chemoprevention, however, because of the nature of side effects and the importance of receiving informed and comprehensive medical care while participating in the trial. If subjects are healthy and have not yet experienced the outcome event(s) in a prevention trial, it is not clear whether the records of their participation in the trial should or must be considered a part of their medical record.

It is ironic that undertaking steps to prevent disease jeopardizes insurability. However, given the severity of some of the risks of chemoprevention and the current uncertainty of benefit, the perspective of some insurers is comprehensible, if not admirable.20,21 Developments in genetics and preventive medicine are likely to prompt health care and health insurance reform measures, but these measures are likely to lag behind more widespread problems of discrimination. Researchers would be advised to advocate such reform as they are well equipped to describe the medico-scientific benefits of such social reform.

"High-Risk" Subjects

Individuals who are at increased risk of malignancy do a poor job at accurately estimating their risk,22 and this is true even among individuals who are identified as "numerate." Also, such subjects may overestimate the personal benefit they will experience if they participate in a clinical trial. Because all clinical trials involve some risk, even if the adverse events are not causally related to either the interventions or the observations associated with the trial, clinical investigators are obligated to present both the risks and benefits of a clinical trial to potential subjects. We have very little data, however, regarding the ability of potentially anxious, high-risk subjects to understand accurately either the risks or the benefits of trial participation in quantitative terms. It is important to collect data concerning the abilities of subjects to appreciate risks and benefits of trial participation and the effect of this information on their health beliefs and behaviors. These data may improve the process of informed consent.

Randomization

Randomization is one method of enhancing the scientific merit of a study by reducing bias and increasing the ability to generalize study results. However, randomization also complicates the processes of enrolling subjects and obtaining informed consent, and it introduces some specific psychologic and social risks to trial participation. Can we randomize high-risk subjects to a placebo? Placebos are selected because of their presumed lack of effect on the outcome of interest, but their use denies individuals assigned to them the potential benefit of effective prevention. Subjects considering participation in a prevention clinical trial cite the possibility of being assigned to placebo therapy as a reason for nonparticipation.23 Their reluctance often can be balanced by the promise of close surveillance for the development of early malignancy. Nevertheless, individuals who are newly identified as being at increased risk for developing cancer and who are subsequently randomized to a placebo arm...
of a trial incur the psychologic distress of knowing of their risk without the possibility of the hoped-for benefit.

In addition, anyone participating in such a trial, particularly those at increased risk of disease, incurs the risks of discrimination. Those randomized to a placebo group incur such risks without concomitant potential benefit. It must be remembered, however, that the benefits of chemoprevention are not established. Those in the control group do not incur the side effects and possible risks of the chemopreventive agent itself.

Clinical experimentation is surrounded by emotionally and normatively charged rhetoric. Experimental interventions are of proven benefit, yet they hold promise of benefit. The conflicting discourses of caution and promise must be clarified for potential trial subjects in order to assure that they are not inordinately swayed by either perspective.

An additional issue concerns prophylactic surgery. For example, some women who are at increased risk of breast cancer elect prophylactic mastectomy. Can we ask subjects to forgo prophylactic surgery to enroll in a chemoprevention trial? If we do, can we randomize subjects to prophylactic surgery v/s a chemoprevention agent?

What about placebo assignments? If a woman would choose prophylactic mastectomy to prevent breast cancer, can we assign her to placebo treatment as part of a prospective intervention trial? According to a preventive ethics approach, it is important that researchers anticipate these questions and outline solutions that do not undermine the scientific integrity of the study while preserving the rights of subjects to seek other treatment or to withdraw from a trial. These proposed means of handling both potential subjects who desire alternative treatment and study subjects whose desires change in light of new developments should form an integral part of research protocols submitted to Institutional Review Boards and discussed with prospective subjects.

**Informed Consent Process**

Informed consent is required of subjects and patients in all research and therapeutic contexts to promote their autonomy and protect their welfare. Medically unsophisticated individuals are not, however, the sole monitors of their own welfare; Institutional Review Boards must assure that a proposed clinical trial is of sufficient merit and presents an appropriate risk-benefit ratio before prospective subjects may be asked to give informed consent to participate. (Standard of care serves a similar role in therapeutic contexts.) The doctrine of informed consent requires that patients or research subjects be competent, that the risks and benefits of the proposed intervention be disclosed to them, that they appreciate the risks and benefits and weigh them in accordance with their own value systems in order to reach a decision to consent or refuse the proposed intervention, and that their decisions be voluntary.

The disclosure component of informed consent in a chemoprevention trial may differ substantially from that required by a treatment trial consent. In a trial that involves treatment of a gravely seriously disease, any benefit will be welcomed if it accepted and efficacious standard therapy is available. Also, benefit will likely be welcomed at considerable cost in terms of toxicity if the disease carries a high risk of morbidity or mortality. The analogous risk-benefit equations have been neither defined nor clarified for prevention trials. Assessing benefit will be especially problematic because successful prevention results in "non-events" (ie, disease does not occur). Moreover, although a non-event may be appreciated by an individual who does not develop the disease during the trial, the significance of the efficacy of the preventive strategy can be seen only in group data. Therefore, it is particularly important for researchers to admit explicitly that some recipients of chemopreventive agents will not experience any benefits, although it is hoped that as a group chemoprevention recipients will fare better than controls. Patients involved in preventive strategies are frequently confused on this point.

Nevertheless, following the guidelines established for treatment trials, it is evident that the informed consent process should include a description of the research including sample sizes, research design, length of treatment, tests required, expected outcomes, the known risks and benefits of the agents to be studied and the associated clinical and opportunity costs. Known drug toxicities should be described, and a clear description should be provided of who will pay for management of toxicity and any anticipated and unanticipated outcomes. In addition, informed consent, like a preventive ethics approach, requires disclosure of many of the design considerations, the confidentiality precautions, and the social and economic risks discussed above. Supplied information should be relevant to the experience and values of the subjects. For example, subjects may be more interested in the likelihood, nature, and magnitude of side effects to be expected than the precise probability of cancer risk reduction (eg, <5% vs <40%) or the scientific processes thought to explain malignancy suppression. Rather than merely making disclosure and leaving prospective subjects to make a decision, physician-researchers should encourage subjects to disclose their values, priorities, and details of their particular life situations and then help them to understand and weigh the complex and often probabilistic information in light of those values.

**Weighing Outcomes and Toxicities**

In clinical situations where toxic therapy is employed, the possibility for injury exists. The statutory and case law relating to medical torts defines when a compensable injury has occurred. These injuries are usually defined as occurring as a direct consequence of a practitioner's negligence and deviation from community standard of practice. Given this context, it is difficult to argue that malignancies defined as outcomes of primary interest that occur among subjects voluntarily consenting to participate in a cancer chemoprevention trial constitute compensable injury. This view appears defensible if the observed outcome would have occurred whether or not the subject participated in the trial and subjects were told at trial enrollment that they would not be compensated for expected events. Here, although not in all cases, ethical and legal obligations seem to coincide.

It cannot be similarly argued that no ethical responsibility or potential legal liability arises if participation in the trial may have contributed to the risk of a life-threatening event. In that situation, more complex arguments pertaining to relative benefits and risks will be invoked, but the bounds of those arguments are not yet well defined. It is possible that a research participant in a prevention trial might perceive the occurrence of a malignancy or other serious illness to be a consequence of the study drug, but it seems reasonable to ascribe causal injury, and hence ethical responsibility and potential legal liability, only if the study investigators knew of a potential risk and failed to inform the participants.

This latter possibility raises another known challenge of prevention clinical trials. During the course of the trial, which may extend as long as a decade or more, there will be developments that affect the willingness of subjects to enter or remain in the trial. These can include new screening methods, new therapies for either the primary or secondary outcomes, and general lifestyle trends that may have an overall impact on the outcome of the trial (eg, widespread changes in levels of exercise, intake of dietary fat, or general disapproval of smoking and other adverse behaviors). In a clinical trial of extended duration, it is likely that participants will desire to be informed about therapy that is of potential benefit. This may create an ethical dilemma for the investigator who seeks to provide all possible benefits to the trial participants while also seeking to preserve the scientific integrity of the trial.

**Interim Strategies**

Adopting a preventive ethics approach helps to address these questions. Even if researchers cannot anticipate the precise nature of future developments in advance, they can anticipate their occurrence, develop a policy governing interim disclosure, and inform prospective participants of it during the process of informed consent. The policy should at least address whether subjects will be kept abreast of relevant new developments by researchers and what effect new developments and resulting
Possible egress from the study will have on trial design. Researchers may decide to require that subjects "re-consent" to participate at specified intervals during long-term trials, thus affording subjects an opportunity to learn of new developments, while providing more orderly intervals of participation for purposes of data analysis. Agreements by subjects to participate in a trial generally are not considered promises that subjects are morally bound to fulfill, nor are they legally enforceable contracts. With rare exceptions, a subject retains the right to withdraw from a clinical trial in order to protect his or her welfare if the burdens of trial participation prove greater than anticipated or if the subject's situation changes.

**Trial Monitoring**

Clinical trials of cancer prevention strategies require years to complete, and subject recruitment and enrollment can be a lengthy process. Ongoing monitoring of both outcomes and toxicity is required in all clinical trials. Monitoring of the data accrued in the trial should be performed by an independent group of reviewers reporting to the trial organizers. These provisions are motivated by a desire to ensure subject welfare and the scientific merit of clinical trials during their progress. Members of the data monitoring board of a prevention trial must have full access to all of the data relevant to the trial. Also, they must be empowered to make a recommendation to terminate a trial early or to close accrual to one arm of a multiple treatment trial if toxicity is severe or greater than anticipated (ie, greater than participants agreed to risk), if the drop-out rate due to toxicity or other considerations becomes unacceptable, or if there is overwhelming benefit from the intervention while the placebo group is experiencing the outcome to be prevented at the design rate.

Discussion of the statistical rules used for making decisions about stopping a prevention trial early are beyond the scope of this review, but both sound ethics and sound science argue that stopping rules for a trial must be defined before the trial commences. Also, it is necessary to define the relative weights of each of the trial's outcomes if there are multiple disease endpoints in a prevention trial (eg, breast cancer, heart disease, or osteoporosis, as in the Breast Cancer Prevention Trial). Large clinical trials are expensive to design and conduct, and high-risk subjects, carefully defined and selected to have increased rates of disease, are difficult to accrue. An agent being studied may be found early in a clinical trial to be effective in preventing one endpoint of interest, but other endpoints may not have achieved significance. If a monitoring committee stops a trial when one endpoint reaches significance, we may never have adequate opportunity to assess other endpoints. Also, it is possible that endpoints reaching significance late in the trial may have a larger effect size than a different endpoint reached earlier in the trial.

It is challenging to determine which of multiple endpoints is the most important (ie, how do we assign weights to outcomes?), and few accepted guidelines have been published. It would seem evident that death is a more important event than disease incidence, but it is not clear how much more significant it is or how stopping rules should be defined. Such questions cannot be answered on scientific grounds alone. The relative weighting of various endpoints -- indeed, the identification of an event as an endpoint worth studying -- involves complex normative decisions with political, cultural, and economic dimensions, as well as scientific considerations. Therefore, it is crucial not only to define stopping points at the outset of a study, but also to recognize the normative dimensions of such aspects of trial design.

**Conclusions**

The ethical issues associated with clinical research in cancer chemoprevention are multiple and varied, and additional work is required to accrue relevant data and to more clearly define the ethical issues raised by this type of research. Continuing dialog among clinicians, ethicists, scientists, chemoprevention trial participants, and potentially eligible subjects form the general population will lead to both clarification of and consensus about these issues while permitting ongoing research in clinical cancer prevention. Further resolution of these issues will derive from both the accumulating clinical experience and the ethical deliberations that accompany chemoprevention trials currently being conducted in the United States and around the world.

**References**

From the University of Pittsburgh Cancer Institute, Pittsburgh, Pa (VGV) and the Department of Human Genetics at the University of Pittsburgh (LSP)

Address reprint requests to Dr Vogel at the University of Pittsburgh Cancer Institute, 3471 Fifth Ave, Suite 802 Kaufmann Bldg, Pittsburgh, PA 15213-3221.