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Ethical, Scientific, and Regulatory Perspectives Regarding the Use of Placebos in Cancer Clinical Trials

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ABSTRACT

Purpose
To examine the ethical, scientific, and regulatory issues in the design and conduct of placebo-controlled cancer clinical trials.

Methods
Several content experts contributed to this article.

Results
Specific criteria can be applied to determine the appropriate use of placebos in oncology drug development. Placebo controls may be justified to prove efficacy of a new treatment in diseases with high placebo response rates; in conditions that wax and wane in severity, have spontaneous remissions, or have an uncertain and unpredictable course; when existing therapies are minimally effective or have serious adverse effects; or in the absence of effective therapy. Use of placebos may also be justified to assure blinding of physicians and patients regarding treatment assignment so as to minimize bias in assessment of study end points. If a trial meets these methodologic criteria, it must then fulfill additional criteria to be considered ethical. These criteria include full disclosure to patients and an assurance that participants randomly assigned to placebo are not substantially more likely than those in active treatment group(s) to die; suffer irreversible morbidity, disability, or other substantial harms; suffer reversible but serious harm; or suffer severe discomfort.

Conclusion
We conclude that placebo-controlled oncology trials are scientifically feasible, ethically justifiable, and may be necessary or desirable to meet regulatory standards for drug approval. Using cross-over or randomized withdrawal trial designs, requiring inclusion of state-of-the-art palliative care, and developing valid and acceptable surrogates for survival are critical strategies to address some of the ethical dilemmas associated with placebo-controlled trials.

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INTRODUCTION

For nearly half a century, randomized, controlled clinical trials of anticancer therapies have been widely and successfully conducted to answer important clinical questions, resulting in substantial improvements in the care of patients with cancer. Until recently, these trials, almost without exception, did not use placebo controls, as use of placebos was considered to be either clinically unfeasible or ethically unacceptable. The recent development of several novel anticancer agents with distinct molecular targets has led researchers to begin to challenge the oncology community's long-accepted tradition of not conducting placebo-controlled trials.[1] Many targeted agents produce disease stabilization rather than tumor regression, and evaluation of their anticancer activity requires clinical trial designs that both control for the natural history of tumor growth and minimize investigator bias in assessing treatment outcomes. In addition, many new agents are administered orally and generally have reduced acute toxicities compared with more traditional cytotoxic drugs, as well as safety profiles that may mimic tumor-related symptoms, such as fatigue. Thus it may now be necessary and feasible to conduct placebo-controlled randomized clinical trials to adequately assess the safety and activity of molecularly targeted therapies used either alone or in combination with cytotoxic treatment. Indeed, a number of such trials have been performed recently to evaluate the effectiveness of several new agents (Table 1).

However, the successful accrual of cancer patients to these trials is not necessarily evidence for their ethical validity or clinical utility. Cancer physicians, investigators, ethicists, and patient advocacy groups continue to express concerns about the use

Table 1. Examples of Recently Reported Placebo-Controlled Cancer Treatment Trials

Agent	Disease	Setting	Design	Study
Letrozole	Breast cancer	Adjuvant	Monotherapy	Goss et al[2]
Sipuleucel T	Prostate	Asx, HRPC	Monotherapy	Small et al[3]
Celecoxib	Prostate	Increasing PSA	Monotherapy	Smith et al[4]
Sorafenib	Renal cell	Metastatic	Monotherapy-RDT	Ratain et al[5]
Sorafenib	Renal cell	Metastatic	Monotherapy	Escudier et al[6]
Sunitinib	GIST	Metastatic second line	Monotherapy	Demetri et al[7]
Marimastat	Breast cancer	Metastatic post first line	Monotherapy	Sparano et al[8]
R115777	Colon cancer	Metastatic/refractory	Monotherapy	Rao et al[9]
Oregovomab	Ovarian cancer	Remission consolidation	Monotherapy	Berek et al[10]
Atrasentan	Prostate	HRPC	Monotherapy-phase II	Carducci et al[11]
Marimastat	Small cell	Metastatic post first line	Monotherapy	Shepherd et al[12]
Erlotinib	Pancreas	Metastatic first line	Add on	Moore et al[13]
Erlotinib	Non–small-cell lung	Metastatic first line	Add on	Gatzemeier et al[14]
Gefitinib	Non–small-cell lung	Metastatic first line	Add on	Giaccone et al,[15] Herbst et al[16]
Calcitriol	Prostate	HRPC	Add on	Beer et al[17]
Isotretinoin	Melanoma	Adjuvant	Add on	Richtig et al[18]
Cetuximab	Head and neck	Metastatic	Add on	Burtness et al[19]
BMS 275291	Non–small-cell lung	Metastatic	Add on	Leighl et al[20]
Prinomastat	Non–small-cell lung	Metastatic	Add on	Bissett et al[21]
Tipifarnib	Pancreas	Metastatic	Add on	Van Cutsem et al[22]
Tamoxifen	Breast	Adjuvant	Add on	Fisher et al[23]

NOTE. This table was developed by conducting a literature search of studies published in the *Journal of Clinical Oncology* over the past 5 years that included use of a placebo. It is not meant to be inclusive of all placebo trials conducted in oncology.
Abbreviations: HRPC, hormone-refractory prostate cancer; PSA, prostate-specific antigen; RDT, randomized discontinuation trial; GIST, gastrointestinal stromal tumor.

of placebos in cancer clinical trials. In an online survey of nearly 6,000 cancer patients conducted by Harris Interactive in 2000, only 15% of those surveyed were aware of the option to participate in a clinical trial. Notably, of those who chose not to participate in a clinical trial, 31% reported the fear of receiving a placebo as a major factor in their decision.[24] Some patient groups consider placebo-controlled trials unethical once the safety of a promising new agent has been established and believe that marketing approval can be justifiably sought even if the new agent has only completed phase I trials. This issue has captured the attention of the United States Congress, resulting in proposed legislation to provide earlier access to investigational therapies and to limit the use of placebo controls in the evaluation of new drugs.[25] The United States Food and Drug Administration (FDA) also issued, in December 2006, new draft guidelines regarding access to promising new agents before marketing approval.[26]

Despite these concerns, placebo controls are increasingly being used in cancer treatment trials under specific circumstances. This is particularly the case when there is no effective standard treatment or when the standard of care has little effectiveness or is excessively toxic.

In an attempt to reduce the ethical concerns associated with placebo use, some trial designs permit patients whose disease progresses to become unblinded to the agent they are receiving and to receive the active agent if they had been receiving placebo. Some trials have incorporated designs and end points that might serve as surrogates for survival, thereby minimizing the time that patients are exposed to placebo.[27] However, these trial designs do not entirely resolve the significant ethical dilemmas related to giving placebos to patients with cancer. Also of concern is that such designs may ultimately fail to determine an agent's effects on important clinical outcomes, such as survival.

This article examines the use of placebos in cancer treatment trials from three perspectives, ethical, scientific and regulatory, and attempts to draw conclusions about their appropriate use in cancer drug development.

THE ETHICS OF RANDOMIZED CONTROLLED TRIALS

Randomized controlled trials are the gold standard of clinical research. They provide the best evidence for the safety and effectiveness of interventions. Clinical equipoise provides the most widely accepted ethical justification for randomized controlled trials.[28,29] Equipoise is a state of uncertainty about which of two or more therapies is most safe and effective. Theoretical or individual equipoise refers to the situation in which involved individuals (eg, physicians) are uncertain about the comparative safety and effectiveness of different interventions. Theoretical equipoise tends to be tremendously unstable. Any change in evidence, the success of one patient, or the adverse effects experienced by another can shift the views of individual physicians or even patients. In 1987, Freedman[28] argued that the proper ethical standard for randomized trials should not be theoretical equipoise, but rather clinical equipoise. He claimed that clinical research and medical practice are societal activities. The point of clinical research is to convince the community of physicians, not any individual physician, which therapy is the safest and most effective. Thus clinical equipoise requires genuine uncertainty or disagreement about the relative merits of two or more therapies within the expert medical community. A randomized controlled trial is conducted to resolve this uncertainty. Clinical equipoise entails two principles: there should be an honest null hypothesis and participants should not receive a treatment inferior to what is otherwise available in clinical practice. Although any

individual physician or patient may prefer one arm of the trial, the disagreement and uncertainty within the community of experts justifies the conduct of a randomized trial.

Clinical equipoise as the justification for randomized controlled trials has been strongly criticized. Hellman and Hellman[30] have argued against randomized controlled trials, claiming that individual physicians and patients have intuitions, feelings, and views about which intervention is best for each patient. They argue that for a physician to permit a patient to be randomly assigned to one or the other treatment, as if they were the same, is wrong; the physician is no longer the advocate of the individual patient's best interests. However, if there is true uncertainty about the merits of the interventions, then the patient's interests are served by any intervention specified in the research study, as there is no evidence to justify selecting one intervention over another as better for the patient.[31,32]

Miller et al[33] raise yet another objection to clinical equipoise, claiming it confuses the ethics of research with the ethics of clinical care. The goal of research, they argue, is not to provide optimal care to individual patients, but to generate generalizable knowledge to guide care for future patients. In this regard, a randomized controlled trial may be ethical if the knowledge gained is valuable, even if there are known effective therapies that are excluded from the trial. In Miller's view, there is no acceptance of the second principle entailed by clinical equipoise (ie, no inferior clinical treatment). In some circumstances, it may be acceptable to provide someone a study treatment that is not standard of care as long as the risk-benefit ratio is reasonable. Despite these objections, clinical equipoise remains the most widely accepted ethical justification for randomized controlled trials.

THE ETHICS OF PLACEBO CONTROLS

If it is sometimes ethical to conduct randomized controlled trials, when is it ethical to conduct randomized placebo-controlled trials? There is substantial disagreement about when placebos are ethical.[34,35] In general, it is argued that placebo controls are acceptable when certain methodologic and ethical criteria are both fulfilled.[36] That is, there must be a methodologic justification for placebos, and then the trial must fulfill ethical considerations regarding risk. Methodologically, placebo controls may be justified when they are necessary to prove that a new treatment has efficacy in a disease with a high placebo response rate; in a condition that waxes and wanes in severity, or has spontaneous remissions, or has an uncertain and unpredictable course; or when therapies exist that are only minimally effective or have serious adverse effects; or in the absence of any effective therapy. The use of placebos may also be justified to assure that physicians and patients are blinded to treatment assignment so as to minimize bias in assessment of study end points.

If none of these methodologic criteria are met, then there is no justification for conducting a placebo-controlled, randomized trial. Conversely, if any of these methodologic criteria are met, then a placebo-controlled trial must fulfill several additional criteria for it to be ethical. These criteria include that a patient randomly assigned to placebo should not be substantially more likely than those in active treatment group(s) to die; suffer irreversible morbidity, disability, or other substantial harms; suffer reversible but serious harm; or suffer severe discomfort. Importantly, these are comparative assessments. They compare the probable or potential experience of research participants who would receive active interventions with those who would receive placebo. In addition, the investigator and informed consent documents must fully disclose to potential participants the fact that the trial involves use of a placebo control.

This justification of placebo controls seemingly disagrees with the 2000 revision of the Declaration of Helsinki.[37] In Article 29, the World Medical Association stated,

"The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists."

Technically, whenever there exists any active treatment for a condition, the Declaration of Helsinki presumably prohibits use of a placebo control. It must be recognized that this view is not universally held. Indeed, almost all other ethical guidance regarding clinical research, such as that from the Council for International Organizations of Medical Sciences, the Nuffield Council on Bioethics, the National Bioethics Advisory Commission, and other commentators, disagree with the Declaration of Helsinki and permit placebo controls when the methodologic and ethical criteria delineated above are fulfilled.[38]

THE ETHICS OF RANDOMIZED PLACEBO-CONTROLLED TRIALS IN ONCOLOGY

In some cases, it is clearly unethical to conduct placebo-controlled, randomized trials in oncology. Either an appropriate methodologic justification does not exist, or the ethical criteria are not fulfilled. The placebo-controlled, randomized trials of ondansetron conducted in the late 1980s and early 1990s are a commonly cited example,[39-41] which raised an ethical dilemma.[42] There are good methodologic reasons to consider placebo-controlled randomized trials of antiemetics. The waxing and waning nature of the condition, the spontaneous remissions from nausea, and the high placebo response rate all provide some methodologic rationale for using placebo controls. Indeed, in 1981, the efficacy of metoclopramide for the treatment of chemotherapy-induced nausea was demonstrated in trials against placebo.[43] Thus in the ondansetron trials, there was no ethical justification for use of a placebo control because of the availability and proven effectiveness of metoclopramide. When the ondansetron trials were initiated, the use of a placebo control to manage nausea and vomiting from highly emetogenic chemotherapeutic agents would have inflicted substantial discomfort and even reversible but serious harm on patients and was not scientifically justified or ethically acceptable.

More recently, a phase III randomized, double-blind, placebo-controlled study of sunitinib was conducted in patients with gastrointestinal stromal tumors that had failed to respond or were refractory to imatinib therapy. Patients were randomly assigned in a 2:1 ratio to sunitinib or placebo, and patients randomly assigned to placebo were permitted to cross-over to active drug at the time of disease progression. Based on an interim analysis conducted during the study, sunitinib was approved by the Food and Drug Administration (US Food and Drug Administration) because it showed a significantly longer time to progression compared with placebo.[7] Despite the attempts made to minimize patient exposure to placebo and to provide active drug at disease progression, Joensuu[44] questioned whether the use of a placebo control was ethical in this study, as some patients

might have experienced slower tumor progression had they continued to receive imatinib instead of placebo.

In some cases, it is clearly ethical to conduct placebo-controlled, randomized trials of new anticancer agents. Methodologically, such trials can be justified if the patients have cancer, typically metastatic cancer, for which no approved, effective therapy exists, or the treatments that are available are only minimally effective and/or present serious, even potentially life-threatening adverse effects. In such cases, oncologists may decide to offer patients second-line, third-line, or even fourth-line treatments that have no proven efficacy. Indeed, physicians are frequently criticized for offering unproven treatments to such patients. There is no evidence, it is argued, that these treatments provide any tumor response, improvement in quality of life, or prolongation of survival. Yet such treatments are far from benign; they frequently have significant adverse effects and high financial costs. In these cases, providing optimal palliative care in the absence of additional attempts with anticancer therapy is not only reasonable, but usually ethically preferable.

Placebo controls have been resisted by many because they seem to entail doing nothing for patients who are dying. However, in oncology, placebo-controlled trials can be ethical if they fulfill all of the previously outlined criteria and do not simply involve the randomization between only a sugar pill and a potentially active anticancer agent. For the trial to be ethical, patients assigned to the placebo arm must also receive best supportive care. During the last decade, there has been tremendous progress in development of palliative care and expert consultative services for pain management. Thus clinical trials that include best supportive care should carefully delineate the elements of such care, including consultation with appropriate experts. The use of placebo in a randomized, controlled clinical trial that mandates implementation of truly the best supportive care possible would fulfill the ethical criteria and allow justification for the trial. Compared with the available alternatives for those with advanced cancer—unproven second-line, third-line, and fourth-line agents with serious adverse effects—optimal palliative and pain care clearly is a reasonable option in the care of these patients. It is ethically justifiable because, compared with using various unproven therapies, optimal palliative and pain care is not more likely to cause the patient to die, suffer serious, irreversible harm or disability, reversible but serious harms, or substantial discomfort. Indeed, compared with unproven treatments, palliative and pain care may provide patients less discomfort and prevent toxicity of ineffective therapies.

ISSUES IN CLINICAL TRIAL DESIGN

In therapeutic areas outside of oncology, placebos are viewed as a critical tool in drug development and are used routinely in phase II and III randomized, controlled trials. In oncology, placebos have been used far less frequently, particularly in patients with metastatic incurable malignancies, because of a perception that it is unethical to withhold active therapy from a patient. The challenge is in determining when an agent is sufficiently active in a particular disease that it becomes problematic for comparison to a placebo. As the purpose of phase II trials is to determine whether or not a drug is active, it can be argued that placebo controls are acceptable, particularly if used appropriately in this context.

Placebos have generally been viewed as unnecessary for phase II evaluation of cytotoxic drugs, as the activity of such agents can usually be determined by measuring the rate of partial and/or complete responses at the maximally tolerated dose. Tumor regression nearly always represents a drug effect, as spontaneous remissions of most cancers are exceptionally rare. However, molecularly targeted anticancer therapies, even though they may not produce tumor regression, may still have a major effect on the natural history of a disease. The randomized, placebo-controlled phase II trial of sorafenib in patients with advanced renal cell carcinoma revealed a confirmed objective response rate of only 4%—and an objective response rate of only 2% was observed in the subsequent phase III trial—but both studies demonstrated a marked improvement in progression-free survival.[5,6] Similarly, sunitinib produced an objective response rate of only 9% in a phase II study of patients with gastrointestinal stromal tumors[45] and a 7% response rate in a randomized, phase III placebo-controlled trial in such patients,[7] yet it significantly prolonged the progression-free survival of patients with imatinib-refractory disease. Both drugs received approval for marketing from the FDA based on statistically significant and clinically meaningful improvements in progression-free survival.

The phase II trial of sorafenib used a randomized discontinuation (withdrawal) design.[5] This trial design was first proposed in 1975 by Amery and Dony[46] as "a clinical trial design avoiding undue placebo treatment." In contrast with most phase II oncology trials (but consistent with phase II trials outside of oncology), the phase II sorafenib trial involved randomization, with the primary end point being the comparison of two treatment arms. In this trial design, patients are all initially treated with an active agent, followed by a reassessment of disease status (Fig 1). Those patients experiencing disease progression on treatment or who experience unacceptable toxicity are withdrawn from study. The remaining patients, who might potentially benefit from the drug, are then randomly assigned (double-blind) to continue on active therapy or on placebo. In the oncology trials where this design has been used, any patient with definite tumor regression after the initial treatment period has been allowed to continue on the agent in an open-label setting. After random assignment, patients are monitored closely for disease progression. Those patients whose disease worsens are unblinded and allowed to resume active therapy if they were randomly assigned to placebo.

At least two oncology trials have been recently completed using this design, one with sorafenib (a positive trial) and one with carboxyaminoimidazole (a negative trial).[5,47] The design has been used extensively in other therapeutic areas and has been highlighted by the FDA as an important tool in its Critical Path Initiative.[48]

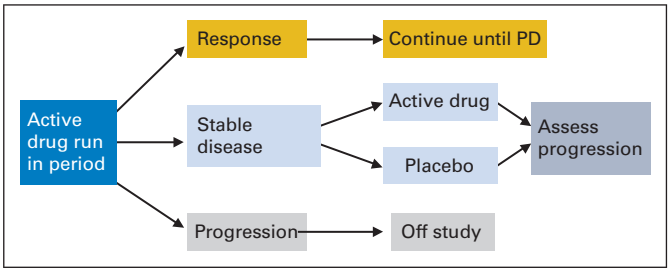

Fig 1. The randomized discontinuation trial design.[27] PD, progressive disease.

Many investigators responsible for the design and conduct of cancer clinical trials believe that this is an appropriate use of placebos in drug development, as placebos are used judiciously in the context of a drug of unknown benefit. At the same time, investigators are fully aware that the use of placebos for comparison with a drug with known activity is problematic. However, this dilemma can conceivably be managed with the use of cross-over designs, where patients on placebo are allowed to receive active therapy after the primary end point has been met. Such designs could be ethically and appropriately used in the phase II setting in lieu of the randomized discontinuation design, or even in phase III trials, as long as the primary end point is not survival. In registration-directed phase III trials, regulatory bodies would have to be willing to accept end points other than survival (ie, surrogates for survival or other meaningful clinical benefits) as evidence of clinical benefit.

Placebo controls may also be appropriate when used to minimize bias in the comparison of active therapies when survival is not the trial end point. In the Arimidex, Tamoxifen Alone or in Combination trial,[49] a randomized comparison of anastrozole with tamoxifen with the combination as adjuvant therapy in postmenopausal women with hormone-responsive breast cancer, the two active agents were compared in a double-blind, randomized clinical trial with two of the three arms including a placebo to mask the active agent so as to minimize physician and patient bias. The primary end point was disease-free survival. In this setting, no ethical concern exists because every patient receives active treatment.

REGULATORY ISSUES IN PLACEBO-CONTROLLED TRIALS

The FDA grants marketing approval for new oncology drugs and biologic agents either by a regular approval mechanism or by an accelerated approval mechanism. Regular approval is based on demonstrating that the agent under study has an effect on an end point of mortality or irreversible morbidity or on an established surrogate for mortality or irreversible morbidity. Accelerated approval regulations state that the FDA may grant marketing approval for a new drug or biologic agent for the treatment of serious or life-threatening diseases on the basis of adequate and well-controlled trials based on a surrogate end point that is reasonably likely to predict clinical benefit.[50,51] Clinical benefit is generally understood as an improvement in either quantity or quality of life. Approval under accelerated approval regulations requires that the sponsor continue to evaluate the agent to verify and describe its clinical benefit. In both situations, substantial evidence of effectiveness must be demonstrated.

A trial used for regulatory approval must be both ethically acceptable and scientifically informative. The International Conference on Harmonization has stated, "when a new treatment is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new treatment with placebo. Use of a placebo control may raise problems of ethics, acceptability, and feasibility, however, when an effective treatment is available for the condition under study in a proposed trial. In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control."[52] Thus the use of placebos or untreated controls is nearly always unethical when therapy exists that has been shown to improve survival or decrease serious morbidity.[35,53] Initial therapy of childhood lymphoblastic leukemia and testicular cancer are clear examples of when a placebo arm would be an unethical treatment.

TRIAL DESIGN OPTIONS AND CHOICE OF CONTROLS

In diseases where spontaneous remission and/or regression are not observed, single-arm trials may be useful. A response rate (tumor size reduction) is considered a direct effect of the treatment as it is not usually observed in the untreated natural history of the disease.[54] The interpretation of single-arm trials is often problematic because it relies on a comparison with historical data to draw inferences regarding the activity or effectiveness of the new treatment.[55] Differences in patient populations entered in trials, unrecognized prognostic factors, changes in supportive care, and introduction of alternative therapies over time can confound comparisons between trial results and historical data.[56] Single-arm trials seldom allow conclusions to be derived regarding time-to-event end points, such as survival, time-to-progression, or progression-free survival.

A randomized control design is the preferred design for demonstrating a drug's safety and effectiveness. The control arm could be either an active control or placebo, if ethically appropriate. The trial design can either be a superiority or noninferiority trial. Superiority trials demonstrate an improvement of an end point over the control agent. A noninferiority trial design demonstrates that a new drug is not worse by a defined amount (margin) than a known effective treatment on a specific clinical end point (usually survival).[57] Noninferiority trials require knowledge of the treatment effect of the control treatment. This treatment effect is derived from external information, usually multivariate analyses examining multiple trials. This external information is preferably based on data from past placebo-controlled trials that provided clear evidence of the effect of the control on a clinical end point.

One type of randomized control design is the add-on design. This design involves the addition of a new agent or placebo to be added to a standard drug treatment. Comparisons are subsequently made between the new drug and standard drug treatment to the placebo plus standard drug therapy. This design allows all study participants to receive treatment and has been used in registration trials.[58]

The selection of a trial's control group is critical because the choice affects "the inferences that can be drawn from the trial, the ethical acceptability of the trial, the degree to which bias in conducting and analyzing the study can be minimized, the types of subjects that can be recruited and the pace of recruitment, the kind of end points that can be studied, the public and scientific credibility of the results, the acceptability of the results by regulatory authorities, and many other features of the study, its conduct, and its interpretation."[52]

A concurrent control group is derived from the same population as the test population and evaluated in the same manner as the test population. Choices for concurrent control groups include placebo-treated, a different dose or schedule of the study treatment, a different active treatment, or a physician choice of control. Choosing the type of concurrent control needed for a trial can be complex, and open dialogue between investigators, sponsors, and regulatory agencies is often useful to facilitate the choice and develop the best possible trial design. Table 2 and Fig 2 are from the International Conference on Harmonization E10 guidelines Guidance for Industry: E10 Choice of Control

Table 2. Usefulness of Specific Concurrent Control Types in Various Situations

Trial Objective	Type of Control							
	Placebo	Active Noninferiority	Active Superiority	Dose Response	Placebo + Active	Placebo + Dose Response	Active + Dose Response	Placebo + Active + Dose Response
Measure absolute effect size	Y	N	N	N	Y	Y	N	Y
Show existence of effect	Y	P	Y	Y	Y	Y	Y	Y
Show dose-response relationship	N	N	N	Y	N	Y	Y	Y
Compare therapies	N	P	Y	N	Y	N	P	Y

NOTE. Reprinted with permission.[52]
Abbreviations: Y, yes; N, no; P, possible, depending on whether there is historical evidence of sensitivity to drug effects.

Group and Related Issues in Clinical Trials.[52] Table 2 lists the potential usefulness of each type of control based on the trial objective. Figure 2 provides a decision tree to help make the most appropriate choice of a control.

In conclusion, the need for well-designed randomized, controlled trials will continue with the development of an increasing number of agents with distinct molecular targets for which clinical benefits are likely to be disease stabilization rather than reduction of

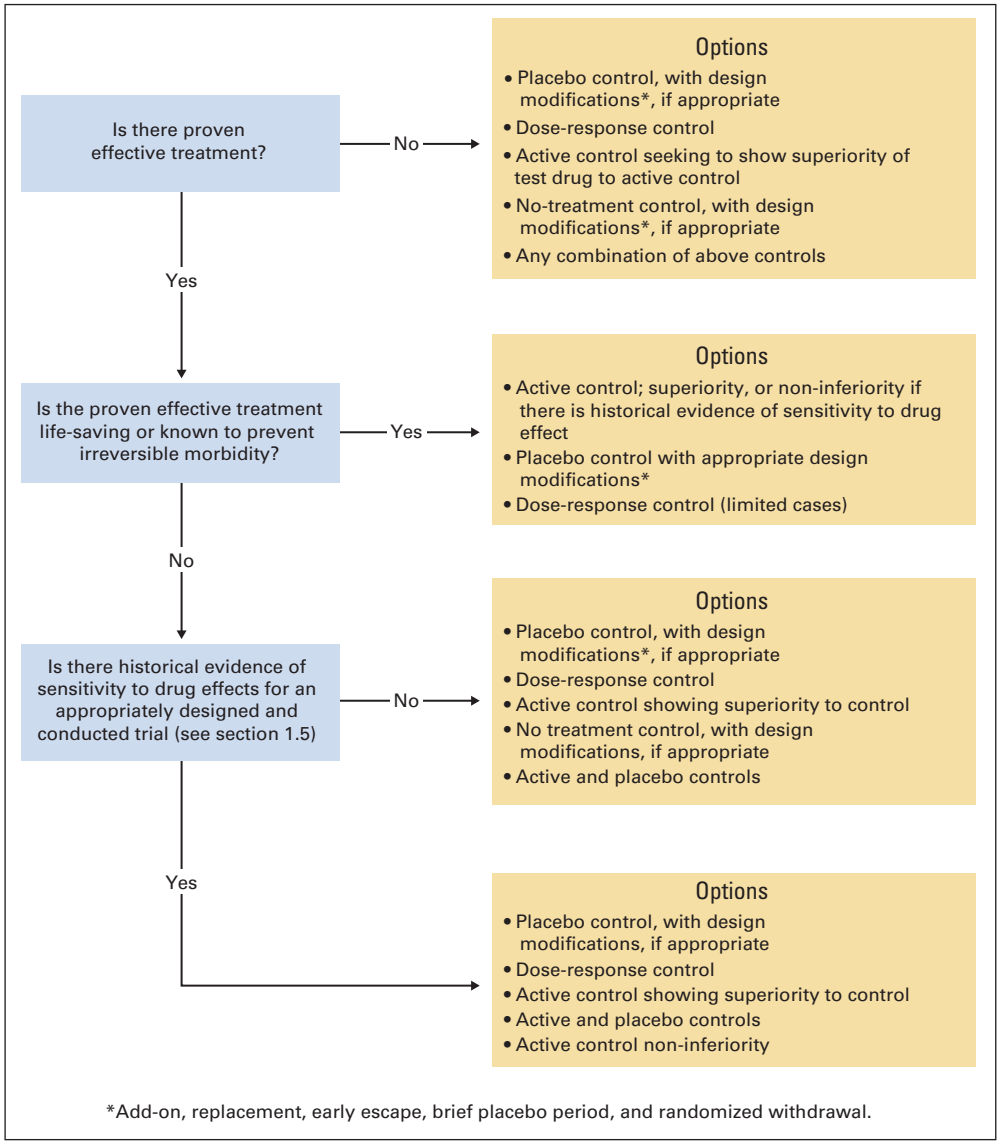

Fig 2. Choosing the concurrent control for demonstrating efficacy. This figure shows the basic logic for choosing the control group; the decision may depend on the available drugs or medical practices in the region.[52]

disease burden, and for which toxicities are relatively less severe than for traditional cytotoxic agents. The use of prospectively randomized control groups minimizes the significant risks associated with using data from uncontrolled trials, with time-to-event end points as a basis for drug access or approval. For example, a recent phase II trial of gemcitabine plus bevacizumab in patients with advanced pancreatic cancer concluded that the combination was quite promising on the basis of the observed progression-free survival and 1-year survival.[59] Yet a randomized, double-blind, placebo-controlled phase III trial of the identical regimen conducted by a cooperative group failed to demonstrate any benefit for bevacizumab in this setting.[60] Had bevacizumab been approved for use in pancreatic cancer based on the uncontrolled phase II data, patients would have been at risk for increased toxicity and cost without the potential to benefit. Virtually all parties would agree that effective new anticancer agents should become widely available as soon as their efficacy and safety are conclusively demonstrated. Perhaps the fastest way to improve access is the timely completion of well-designed, definitive clinical trials that provide evidence of the utility of a new drug and support marketing approval. In some circumstances, such trials may require the use of placebo controls to provide convincing evidence of drug safety and clinical benefit, and it is incumbent on the oncology community that such studies be conducted in an ethically appropriate manner so that patients are fully informed and protected from exposure to dangerous or ineffective treatments. We conclude that placebo-controlled oncology trials are scientifically feasible, ethically justifiable and may, in some cases, be necessary or desirable to meet regulatory standards for drug approval. The use of novel clinical trial designs such as cross-over designs or randomized withdrawal designs, the inclusion of state-of-the-art palliative care in clinical trials, and development of valid and acceptable surrogates for survival are critical strategies to address some of the ethical dilemmas associated with these trials.

This statement was developed to provide guidance to the scientific community on this important clinical trial design question. Significant questions and misperceptions about placebo use in oncology trials exist in the general public and among cancer patients. Providing clarity regarding the appropriate use of placebos may help assuage concerns and potentially contribute to increased enrollment in clinical trials. The American Society of Clinical Oncology intends to use these guidelines on placebo use to develop patient-focused materials that may be helpful to physicians in discussing this issue with potential trial participants. These materials may also be useful for the American Society of Clinical Oncology to present to the public and policymakers.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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