

The ethics of placebo-controlled trials: The case of asthma

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Some have argued that placebo-controlled trials (PCTs) are unnecessary and unethical in conditions such as asthma for which there is standard therapy. This article, by using asthma clinical trials as an example, examines the ethics of PCTs. There remain several scientifically sound reasons to conduct PCTs: (1) ensuring scientific validity of the trial, (2) evaluating new therapies less effective than the gold standard, (3) minimizing the number of patients exposed to potentially inefficacious or dangerous therapy, (4) studying clinical situations in which withdrawal of therapy might be considered, and (5) determining the true incidence of side effects. Opponents of PCTs err by conflating clinical research with clinical practice and ignoring the fact that all clinical research involves some sacrifice on the part of the subject for the ends of the research and the good of future patients. PCTs do not per se violate major ethical codes. Properly conducted, PCTs remain a valuable and ethical tool in the armamentarium of modern scientific medicine. (*J Allergy Clin Immunol* 2005;115:1228-34.)

Key words: Placebo-controlled trial, research ethics, asthma, validity, assay sensitivity

Placebo-controlled trials (PCTs) have been the subject of vigorous debate in recent years. This debate was occasioned at least in part by the 2000 revision of the Declaration of Helsinki, which at first impression would appear to prohibit most placebos in clinical research.¹ Debate has concerned both whether such trials are ethical^{2,4} and whether they are scientifically necessary.⁵ It is difficult, however, to examine the ethics of PCTs in the abstract, without regard to the disease and subjects being studied.

Physicians and ethicists tend to agree that placebos in some contexts would clearly be unethical—for example, when the patients in question have a disease capable of imminently producing serious permanent disability or death, for which clearly effective treatment exists. In such

Abbreviations used

ACET: Active-control equivalency trial
ICH: International Conference of Harmonization
ICS: Inhaled corticosteroid
IRB: Institutional Review Board
LTRA: Leukotriene receptor antagonist
PCT: Placebo-controlled trial
RCT: Randomized controlled trial

cases, treatment should not be withheld by giving some subjects placebo.^{6,7} Examples here include many cancers and infectious diseases and some cardiovascular conditions.⁸ On the other end of the spectrum, some conditions may cause discomfort, but that discomfort is mild enough that many patients forego therapy for the condition.^{6,7} Examples here include mild to moderate allergic rhinitis, alopecia, and mild heartburn. The more ethically challenging cases concern diseases for which an effective treatment exists for a potentially serious condition, but for scientific reasons a placebo arm might be desirable. Examples of such conditions include depression, hypertension, some other cardiovascular conditions, and asthma.^{6,7} These conditions have in common the fact that they are potentially serious, but chronic, and many researchers believe that PCTs may be conducted in such a way as to minimize risk to study participants. The purpose of this article is to examine the ethics of PCTs for one such middle ground condition: bronchial asthma. The availability of standard therapy, particularly inhaled corticosteroids (ICSs), for this condition has resulted in vigorous debate over the propriety of PCTs.⁸⁻¹⁰ It is the thesis of this article that there remain good scientific reasons for conducting PCTs for asthma medications, and that with proper selection of patients, intensive monitoring, and informed consent, such trials may be ethically conducted. This analysis of asthma trials has wide applicability to other middle ground conditions in which the existence of effective therapy gives rise to debate over the propriety of placebo controls.

PCTS: AN ETHICAL ANALYSIS

Why PCTS? Scientific value and validity

Ultimately, the scientific value of each study must be determined on a case-by-case basis, and there may be

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disagreement in a given case. The goal of this section is to examine some of the scientific reasons for using a placebo arm in a clinical research study and to demonstrate that these reasons often remain despite the existence of standard therapy.

Much of the criticism of placebo controls in clinical research, including asthma research, has centered on the contention that placebo controls are not scientifically necessary. If true, this is a powerful criticism, because any clinical research trial without a sound scientific rationale, whether or not it included a placebo control, would be unethical. As the Council for International Organizations of Medical Sciences guidelines state, "Scientifically unsound research on human subjects is *ipso facto* unethical in that it may expose subjects to risks or inconvenience to no purpose."¹¹ There are, however, at least 5 sound scientific reasons a placebo arm might be used, and these are relevant to controlled trials of asthma medications. They are (1) ensuring the scientific validity of the clinical trial (assay sensitivity), (2) evaluating new therapies that are promising but less potent than the gold standard, (3) minimizing the number of patients exposed to potentially inefficacious or toxic therapy, (4) studying common clinical situations in which withdrawal of therapy might be considered, and (5) determining the true incidence of adverse events (side effects) associated with therapy. These considerations are discussed in the context of asthma trials.

Ensuring the scientific validity of the clinical trial

It has been suggested that once standard therapy exists for a given condition, PCTs are unnecessary because active control equivalency trials may be performed comparing new treatments with standard therapy. This view reflects a fundamental misunderstanding. In clinical research trials, it is important that the scientific validity of the trial can be confirmed. Scientifically valid research must distinguish between active and inactive treatments. This ability of a study to distinguish between active and inactive treatments is known as *assay sensitivity*.⁶ One can show that the new therapy is superior to a control treatment, or one can show that the new therapy is equivalent to or not worse by some defined amount than a known effective treatment.⁶ A well-designed study that shows superiority of a treatment to a control (whether placebo or an active therapy) provides strong evidence of the effectiveness of the new treatment, limited only by the statistical uncertainty of the result, and no information external to the trial is needed to support the conclusion that the treatment is effective.⁶ On the other hand, an active-control equivalency trial (ACET) that shows equivalence between the new and standard therapy, does not in itself show that the new treatment is effective. One must rely on the untested assumption that the active treatment had an effect in this particular patient population in this particular trial. Support for this assumption could, of course, come from a series of previous studies in which the active

treatment had consistently outperformed placebo. Temple and Ellenberg⁶ observe, "In this respect, an ACET is similar to a historically controlled trial."

With the ACET, there is no internal check on the assay sensitivity of the trial. Although it seems reasonable to assume that a standard therapy would perform in a manner superior to placebo, in practice, there are many conditions for which assay sensitivity cannot be assumed, ie, that apparently well-designed trials fail to demonstrate superiority of accepted active therapy over placebo. These include antidepressants, anxiolytics, antihypertensives, antianginal agents, angiotensin-converting enzymes inhibitors for heart failure, postinfarction β -blockers, antihistamines, nonsteroidal asthma prophylaxis, and motility-modifying drugs for gastroesophageal reflux disease.⁶ If assay sensitivity cannot be assumed, an ACET showing equivalence cannot be thought to have demonstrated the effectiveness of the new drug. Likewise, in an active control trial designed to show superiority of the study drug, a subset of refractory patients may be studied, and equivalence with standard therapy could result in a type II error.

In addition, PCTs create a strong incentive for clinical investigators to minimize errors in the design and conduct of the trial, whereas ACETs may create the opposite incentive. Most imperfections in a clinical trial, such as patient noncompliance with treatment, use of concomitant medications that might have an effect on the disease being studied, or inclusion of inappropriate patients, tend to reduce the observable differences between treatment groups, promoting the conclusion that the 2 treatments are indistinguishable. Investigators seeking to demonstrate a difference between treatments have a strong incentive to minimize such imperfections. This incentive is absent when the intent is to demonstrate lack of difference.⁶ This is not to suggest that investigators designing ACETs do not endeavor to ensure trial quality or that they purposefully design sloppiness into their trials so as to show equivalence. On the other hand, it is "important...to recognize the possible influence of the desired outcome on the conduct of the clinical trial."⁶

This observation has relevance to asthma trials. It has been objected that because the placebo response rate (ie, the percentage of patients on placebo that show improvement) in these trials is low, placebo controls are unnecessary.⁹ Part of the reason for this low placebo response rate in asthma trials, however, is the extreme rigor with which subjects are selected. Patients in such trials generally must meet precisely defined criteria regarding symptom scores, spirometry, and freedom from possibly confounding conditions, medications, and smoking. Consequently, most asthma investigators find that only a small percentage of patients with asthma are appropriate evaluable subjects for asthma trials.¹² In trials designed to show equivalence, the incentive to conduct trials with such rigor would be reduced, making recruitment for the trial easier, but potentially compromising the validity of the trial.

Evaluating new therapies that are less potent than the gold standard

Frequently, new medications are introduced that are no more effective than existing therapies but have other potential therapeutic advantages. Examples of such medications include the newer antidepressants and antipsychotics (fewer side effects than older drugs), second-generation antihistamines (lack of sedation), and COX-2-selective anti-inflammatories (less gastrointestinal bleeding). In some cases, however, a new class of medications is developed that is less potent than the older medication, but still has other important advantages. The leukotriene receptor antagonists (LTRAs) provide an excellent example of such a class of medications. LTRAs (eg, montelukast and zafirlukast) are now known to be less potent than ICSs in the treatment of asthma.¹³ LTRAs do, however, have some important advantages over inhaled steroids. First, these medications are pills or chewable tablets rather than inhalers, which may improve adherence to the treatment regimen, as may once-daily dosing.¹⁴ Second, LTRAs are anti-inflammatory medications that are not steroids, therefore eliminating any concerns about possible steroid side effects. If, however, LTRAs were evaluated only by active control equivalency trials, comparing them with ICSs, they would have proven less effective than ICSs, and they would never have come to market. Placebo-controlled studies, on the other hand, proved LTRAs to be superior to placebo, and 2 LTRAs obtained Food and Drug Administration approval.

Minimizing the number of patients exposed to potentially inefficacious or dangerous therapy

Physicians and patients have a serious interest in avoiding the approval and marketing of inefficacious treatments. If an inefficacious medication were to obtain regulatory approval and come to market, millions of patients could incur the cost of the medication and have any side effects without benefit. This is not a merely theoretical consideration. For many years, patients with frequent ventricular premature complexes were treated with antiarrhythmia drugs with the goal of decreasing mortality from abnormal heart rhythms. Although these drugs were effective in making the electrocardiogram look better, they actually increased mortality from arrhythmias.¹⁵ Likewise, postmenopausal women were encouraged to take hormone replacement therapy to reduce risk of cardiovascular disease. Recent placebo-controlled studies demonstrated that hormone replacement therapy did not have this benefit and may in fact increase coronary heart disease.¹⁶ Medical practice has changed, we think for the better, because of studies in which controls were not given what was then standard therapy.

Investigators also have a duty to minimize the number of experimental subjects exposed to drugs in the course of clinical trials, again, both to reduce the number of subjects who are exposed to inefficacious treatment and to minimize those exposed to any toxicity of the study

medication. Leon¹⁷ demonstrates statistically how placebo controls can reduce the number of subjects needed for clinical trials compared with active-control superiority trials. A larger between-group size effect is expected in PCTs than in trials with an active comparator. If, for example, a placebo with an assumed 10% response rate were compared with an investigational drug with a 70% response rate, 24 subjects would be needed to detect a statistical difference between the drug and placebo.¹⁷ On the other hand, if an investigational drug with a 70% response rate were compared with a standard therapy with a 60% response rate, 752 subjects would be required to demonstrate superiority. In an active control superiority trial, a dramatically higher number of patients would be exposed to potentially ineffective or toxic therapy than in a PCT.

Studying clinical situations in which withdrawal of therapy might be considered

A study by Lararus et al¹⁸ published in *JAMA* prompted a response criticizing it for its inclusion of a placebo arm.¹⁹ This National Institutes of Health-sponsored study was conducted to investigate whether low-dose ICS therapy can be eliminated and replaced by a nonsteroid controller medication, the long-acting β -agonist salmeterol. Initially subjects were randomized to triamcinolone, an ICS, or salmeterol. At the end of the study, there was a placebo run-out phase in which some of the patients had their triamcinolone reduced by 50%, then discontinued. In their letter, Botkin et al¹⁹ criticized this placebo run-out phase as not essential and because "placebo conferred greater risk than 'available alternative approaches.'" Lazarus²⁰ replied that the study design "mirrored a common clinical scenario" in which "patients with well-controlled asthma often stop using their IC, or request a medication that is 'not a steroid.'" He points out that in this case "recognition of the potential for corticosteroid adverse effects has led experts to recommend reduction or discontinuation of ICs when asthma is well controlled 'after several weeks or months of therapy.'"²¹ Studying such clinical situations in which a reduction or elimination of standard therapy might be considered is another situation in which placebo controls may be valuable.

Determining the true incidence of side effects (adverse events)

Clinical studies of new medications, particularly phase II and III studies conducted to gain regulatory approval of these medications, are designed to evaluate the safety and efficacy of the new treatment. Consequently, data on adverse events during a clinical trial are often as important as data on the efficacy of the medication. Physicians and patients will want to know what side effects the medication in question might cause, so as to weigh better the benefits and burdens of prescribing or taking the medication. However, some medical illnesses and symptoms are common, and many people have them whether or not they are taking medication. In the course of a clinical trial,

therefore, some subjects will have headaches, respiratory infections, backaches, menstrual cramps, and so forth. A placebo arm study can help distinguish whether the study medication is truly causing these symptoms, in which case the incidence of these will exceed that of placebo, or whether these symptoms are occurring in the study population independent of the study drug.

DOES A REQUIREMENT OF CLINICAL EQUIPOISE BAR PLACEBO CONTROLS?

The principle of clinical equipoise was proposed by Freedman²² in an influential article in the *New England Journal of Medicine* in 1987. Freedman²² argued that the ethics of clinical research required a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. This uncertainty would generally be the consequence of a “present or imminent controversy in the clinical community over the preferred treatment.” Freedman et al² subsequently used the principle of equipoise to attack PCTs in conditions for which accepted treatment exists. PCTs are unethical, they argue, because they “involve compromise of a patient’s right to medical treatment” and involve “medical attention that is known to be inferior to current medical practice.” Clinical equipoise allows a trial to go forward only when “the treatment arms in a randomized controlled trial [are] consistent with the standard of care to which physicians are held...²³ and therefore, PCTs would be unethical.

There are several problems with attacking PCTs by invoking the concept of clinical equipoise. The first problem is with the concept itself. There are numerous examples of nontherapeutic research involving human subjects. Researchers studying asthma have performed lung biopsies and bronchoalveolar lavage for studies of airway inflammation. These studies, because they offer no therapeutic benefit to the subject with asthma, would clearly lack therapeutic equipoise, because no asthma specialist would recommend bronchoscopy as therapy for asthma. Likewise, phase I clinical trials, pharmacokinetic and toxicity studies of new medications performed in health volunteers would be unethical, because the volunteers undertake the risk of exposure to the new medication, as well as the discomfort of repetitive phlebotomies and other studies, without any expectation of therapeutic benefit. Miller and Brody²⁴ ask, “If physician-investigators are subject to a therapeutic obligation in the case of clinical trials, which makes [randomized controlled trials] ethical only when they conform to clinical equipoise, it is puzzling that physician-investigators can perform any research procedures that pose risks but no compensating therapeutic benefits to the patient volunteers; for example, studies of pathophysiology that administer biopsies or lumbar punctures, or imaging procedures that use ionizing radiation. In other words, why should therapeutic beneficence govern clinical trials but not the whole of clinical research?”

Weijer,²³ an opponent of PCTs, answers that only therapeutic procedures are held to the standard of clinical equipoise because “it would make no sense to speak of nontherapeutic procedures such as questionnaires, extra blood draws, or X rays, in the context of the standard of care.” He distinguishes nontherapeutic procedures that “are justified by moral tests that rely on minimizing risks and ensuring commensurate gains in knowledge...in precisely the same way as nontherapeutic procedures in RCTs.”²³ This appears to be a distinction without a difference. All randomized controlled trials (RCTs), whether or not they include a placebo, have nontherapeutic aspects. Clearly a RCT is not the same as clinical practice, not only in that nontherapeutic procedures are performed, but also in that “personalized attention characteristic of medical therapy is lacking in clinical trials that provide treatment according to a scientific protocol.”²³ Defenders of PCTs merely argue that the use of a placebo arm in a RCT be judged by the same standard Weijer²³ uses for nontherapeutic research: whether risk to the patient-volunteer is minimized and whether there are sound scientific reasons to use a placebo. Miller and Brody²⁴ summarize this point: “Placebo controls are ethically justifiable when they are supported by sound methodological considerations and their use does not expose research participants to excessive risks of harm.”

A RCT, even in the absence of a placebo arm, differs from clinical practice in another way. All clinical research involves in some way temporarily abandoning or doing something different than the “best current diagnostic or therapeutic method.” Even in an active equivalency trial, in which the investigational drug is compared with a standard therapy, subjects receiving the investigational drug are clearly not getting the best proven treatment.²⁵ Even if the investigator believes the investigational and standard therapies to be in equipoise, any uncertainty involved in the trial constitutes a nontherapeutic aspect of the trial. Further, even in an add-on trial, in which both arms of the study receive the standard therapy and one group receives the investigational drug as an add-on, the add-on group takes additional risks of toxicity of the new therapy. Again, the add-on group is receiving something different than the best proven therapeutic method. This, too, is a nontherapeutic aspect of the trial in question.

The problem is that the concept of equipoise ignores the ethically relevant distinction between research and clinical practice, a distinction recognized in the Nuremberg Code²⁷ and subsequently in the Belmont Report.²⁸ Recognizing that research and practice are fundamentally different, how then can human subjects research be justified? It appears that the only way to justify entering and randomizing a volunteer in a clinical trial is the willingness of the volunteer, after proper informed consent, to sacrifice for the good of the research and hence for the good of future patients. This willingness to sacrifice is an act of charity or altruism on the part of the volunteer. To some ethicists, the idea that an individual might be willing to sacrifice for the good of others (particularly in a medical context) might seem foreign. On the contrary, it is not

uncommon at all. The fact that tens of thousands of people serve as blood and plasma donors, and thousands serve as living donors of a kidney or a lobe of a liver, some to unrelated recipients, demonstrates that modern medicine very much depends on charity or altruism. As discussed, there are of course limits to how much sacrifice an investigator might ethically ask of study subjects. The Institutional Review Board (IRB) plays a critical role in reviewing proposed research projects, ensuring proper procedures for informed consent, and monitoring conduct of the trial. In this way the IRB, as well as the investigator, is responsible for making sure that the research does not ask the subject to undertake too much risk. It appears reasonable, however, that a subject with asthma may consent to incur a low amount of risk by foregoing standard treatment, usually ICS, for a short, closely monitored period in the context of a PCT.

The need for protection of the research subject is particularly relevant in the case of vulnerable subjects such as children. The Food and Drug Administration Center for Drug Evaluation and Research Pediatrics Working Group Consensus Statement in 2000 addressed the question of when placebo controls might ethically be used in pediatric research. The Center for Drug Evaluation and Research statement allows placebos under the following circumstances: (1) placebo controls are allowed for serious or life-threatening conditions when there are no approved or adequately studied therapies; (2) add-on trials are generally acceptable; and (3) PCTs of minor illnesses or symptomatic conditions are generally acceptable. In all 3 cases, discontinuation criteria should be established for subject safety or to minimize patient discomfort. Data monitoring committees should be used if necessary to ensure subject safety.²⁹

SAFETY OF PLACEBO IN ASTHMA TRIALS

This article contends that asthma is a middle ground condition, for which effective therapy exists for a potentially severe condition, but for which carefully designed and monitored clinical trials might be ethically conducted. The scientific reasons for conducting an ethical clinical trial are considered. Also integral to conducting a clinical trial ethically is minimization of risk. Is risk adequately controlled in PCTs of asthma?

One way that risk can be minimized in a PCT of asthma or other chronic disease is by careful monitoring. The study by Lazarus et al¹⁸ provides an example of the intensive monitoring typical of asthma studies. Subjects in this study recorded asthma symptom scores (for shortness of breath, chest tightness, wheezing, cough, and mucus production), daytime and nighttime peak flow meter readings, use of rescue albuterol, and other illnesses twice daily throughout the study. Patients were evaluated at the study site every 2 to 4 weeks, at which time interval history, physical examination, diary review, and spirometry were performed. An asthma-specific quality of life questionnaire was administered 3 times during the course

of the study.¹⁸ Subjects were immediately withdrawn from the study if they met criteria for treatment failure or asthma exacerbation, both of which were precisely defined by the protocol, or for physician judgment for safety. In addition, all subjects were supplied with albuterol inhalers and encouraged to use this medication as a rescue inhaler for symptomatic relief. There were no severe adverse respiratory events in this PCT.

More empiric data on the outcomes of those randomized to placebo in PCTs would be helpful, but what data we do have are encouraging. Kellerman et al³⁰ have presented data evaluating outcomes of the placebo group in asthma studies. In a report of more than 1500 subjects in 6 clinical trials, 442 subjects received placebo. Approximately 60% of these patients were discontinued from the study for lack of efficacy, but there was only 1 asthma exacerbation, which did not require hospitalization, and there were no deaths. Gallant³¹ also cites 4 clinical trials of an ICS, representing more than 1000 subjects, in which 272 subjects received placebo. There were 4 asthma exacerbations with 2 resulting in hospitalization, and no deaths. Gallant³¹ concludes, "These data suggest that subjects who fit criteria for moderately severe asthma, provided they are given a 'safety net' for physician notification and study discontinuation, can safely be evaluated in clinical trials and are exposed to minimal risk under these conditions." It appears that risk can be minimized for subjects receiving placebo in clinical trials of asthma.

DO ETHICAL CODES BAR THE USE OF PLACEBO CONTROLS?

The recent debate over the ethics of placebo controls was occasioned in part by the fifth revision of the Helsinki Declaration in 2000. Specifically, the declaration appeared to rule out the use of placebo controls in clinical trials of conditions for which effective treatment exists. Paragraph 29 states, "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."¹

This language proved controversial, particularly because a literal interpretation appeared to exclude most placebo controls in clinical research.^{32,33} In 2002, however, the World Medical Association issued a "Note of Clarification of Paragraph 29" that, although reaffirming "its position that extreme care must be taken in making use of a PCT and that in general this methodology should only be used in the absence of existing proven therapy," explicitly allowed placebo in several circumstances.³⁴ These include the following:

- Where for compelling and scientifically sound methodological reasons, its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic, or therapeutic method

- Where a prophylactic, diagnostic, or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm³⁵

Although the terms *compelling and sound reasons* and *additional risk* need to be conscientiously interpreted by the investigator and the IRB in the context of a given proposed study, the World Medical Association has clearly backed away from an absolute prohibition on the use of placebo in studies of diseases for which standard treatment exists.

Nor do other important ethical codes concerning human experimentation explicitly reject PCTs. The Belmont Report, promulgated in 1979 by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research and revised in 1991, guided clinical research in the United States for decades.²⁸ The Belmont Report endorses a set of “basic ethical principles”: respect for persons, beneficence, and justice. Placebo controls are not specifically mentioned. The report recognizes that in research “risk can never be entirely eliminated,” but encourages “systematic, non-arbitrary analysis of risks and benefits.”²⁸ Similarly, the 1991 Department of Health and Human Services Regulations for the Protection of Human Subjects, also known as the *Common Rule*, require that institutional review boards approve research only if “risks to subjects are minimized” and “risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result.”³⁴ The *Common Rule* also includes other ethical requirements such as equitable selection of subjects, confidentiality, and informed consent. Placebos are not explicitly mentioned.

The International Conference of Harmonization (ICH) represents an effort to harmonize pharmaceutical regulation in the United States, Europe, and Japan. In its document “Statistical Principles for Clinical Trials,” the ICH acknowledges, “Scientifically, efficacy is most convincingly established by demonstrating superiority to placebo in a PCT, by showing superiority to an active control treatment, or by demonstrating a dose-response relationship...”³⁶ The ICH recognizes ethical concerns with placebo controls “when effective therapy that is known to prevent death or irreversible morbidity exists.”³⁷ In other circumstances, “The appropriateness of placebo control v. active control should be considered on a trial by trial basis.”

DISCUSSION

Despite the existence of standard therapies for many conditions, including asthma, there remain valid scientific and practical reasons to conduct PCTs. If the physician investigator has sound scientific reasons for the use of a placebo, obtains proper informed consent, and ensures that risks are minimized and that subjects are properly

monitored and the trial is approved and overseen by a vigilant IRB, the use of placebo is ethical. The investigator and study personnel must endeavor to ensure that subjects act after consideration of all of the risks and benefits of the trial, and out of altruism and a wish to advance medical science. When these conditions are met, PCTs remain a valuable, and ethical, part of the armamentarium of modern scientific medicine.

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