

7.3.1 Ethical Use of Placebo Controls in Research

A fundamental requirement of biomedical and health research is that it must provide scientifically valid data. In some research, this can best be achieved by comparing an intervention against a control to identify the effects of the intervention. Used appropriately, a placebo control can provide valuable data, particularly when there is no accepted therapy for the condition under study.

The existence of an accepted therapy does not necessarily preclude use of placebo controls, but because use of a placebo deprives participants in the control arm of access to accepted therapy for some period of time, it requires thoughtful ethical justification. In general, the use of a placebo control will more easily be justified as the severity and number of negative side effects of standard therapy increase.

To ensure that the interests of human participants are protected, physician-researchers and those who serve on oversight bodies should give careful attention to issues of methodological rigor, informed consent, characteristics of the medical condition under study, and safety and monitoring, in keeping with the following guidelines:

- (a) Evaluate each study protocol to determine whether a placebo control is scientifically necessary or an alternative study design using a different type of control would be sufficient for the purposes of the research. Placebo controls are ethically justifiable when no other research design will yield the requisite data.
- (b) Assess the use of placebo controls in relation to the characteristics of the condition under study in keeping with the following considerations:
 - (i) Studies that involve conditions likely to cause death or irreversible damage cannot ethically employ placebo controls if an alternative therapy would prevent or slow the progression of illness;
 - (ii) Studies that involve illnesses characterized by severe or painful symptoms require a thorough exploration of alternatives to the use of a placebo control;
 - (iii) In general, the more severe the consequences or symptoms of the illness under study, the more difficult it will be to justify the use of a placebo control when alternative therapy exists. Consequently, there will almost certainly be conditions for which placebo controls cannot ethically be justified.
- (c) Design studies to minimize the amount of time participants are on placebo without compromising the scientific integrity of the study or the value of study data.
- (d) Pay particular attention to the informed consent process when enrolling participants in research that uses a placebo control. In addition to general guidelines for informed consent in research, physician-researchers (or other health care professionals) who obtain informed consent from prospective subjects should:
 - (i) describe the differences among the research arms, emphasizing the essential intervention(s) that will or will not be performed in each;
 - (ii) be sensitive to the possible need for additional safeguards in the consent process, such as having a neutral third party obtain consent or using a consent monitor to oversee the consent process.

- (e) Ensure that interim data analysis and monitoring are in place to allow researchers to terminate a study because of either positive or negative results, thus protecting participants from remaining on placebo longer than needed to ensure the scientific integrity of the study.
- (f) Avoid using surgical placebo controls—i.e., a control arm in which participants undergo surgical procedures that have the appearance of therapeutic interventions but during which the essential therapeutic maneuver is not performed—when there is a standard treatment that is efficacious and acceptable to the patient and forgoing standard treatment would result in significant injury. In these situations, physician-researchers must offer standard treatment as part of the study design. Use of surgical placebo controls may be justified when:
 - (i) an existing, accepted surgical procedure is being tested for efficacy. Use of a placebo control is not justified to test the effectiveness of an innovative surgical technique that represents only a minor modification of an existing, accepted surgical procedure;
 - (ii) a new surgical procedure is developed with the prospect of treating a condition for which there is no known surgical therapy. In such cases, the use of placebo must be evaluated in light of whether the current standard of care includes a nonsurgical treatment and the risks, benefits, and side effects of that treatment;
 - (iii) the standard (nonsurgical) treatment is not efficacious or not acceptable to the patient;
 - (iv) Additional safeguards are in place in the informed consent process.

AMA Principles of Medical Ethics: I,V

Opinion 7.3.1 Ethical Use of Placebo Controls in Research re-organizes content from previous guidance and associated background reports:

CEJA Report 3-A-00 Surgical “placebo” controls

CEJA Report 2-A-96 Ethical use of placebo controls in clinical trials

REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS*

CEJA Report 3-A-00

Subject: Surgical “Placebo” Controls¹

Presented by: Herbert Rakatansky, MD, Chair

Presented to: Reference Committee on Amendments to Constitution and Bylaws
(Jimmie A. Gleason , MD, Chair)

1 Introduction

2

3 Before new drugs, devices or procedures are used in the clinical setting, it is important that they
4 be validated.² This can be accomplished through clinical trials, which help gather information on
5 their safety and efficacy. Retrospective or historical trials occasionally permit investigators to
6 compare the experimental intervention to a standard treatment from data previously gathered.
7 Prospective trials are relied upon primarily to establish causal relationships between a variable
8 and an outcome.³ This design makes it particularly easy to compare the outcomes in two groups
9 that receive different interventions, where one arm of the study undergoes a standard procedure
10 and the other undergoes an experimental procedure. The reliability of the data derived from such
11 trials is further improved when subjects are randomly assigned to either arm, and when subjects
12 and investigators are not informed of the assignment. This design, the randomized, double-blind
13 study, is considered the gold standard of clinical research because it minimizes random errors,
14 eliminates bias and, thereby limits the risk of reaching an incorrect conclusion.⁴ In some of these
15 studies a placebo is used in the control arm as a substitute for an active intervention.^{5,6} Use of a
16 placebo enables investigators to measure absolute efficacy of the experimental intervention,
17 whereas other types of controls support judgments about comparative efficacy.

18

19 Recently, renewed concern about the use of placebos has resulted from reports in the media and
20 the medical literature of surgical trials that included “sham” surgery.^{7,8,9,10} Although investigators
21 conducting such trials have referred to them as placebo surgery,⁹ this Report generally uses the
22 term surgical “placebo” control to refer to the control arm of studies where subjects undergo
23 surgical procedures that have the appearance of therapeutic interventions, but during which the
24 essential therapeutic maneuver is omitted. The Council on Ethical and Judicial Affairs believes
25 that this recent trend in surgical research requires careful ethical exploration. This analysis
26 begins with a brief review of the current standards that are used to evaluate the ethical soundness
27 of research designs and then proceed to a more detailed examination of placebos and their use in
28 surgical research.

29

30 Clinical Research: General Considerations

31

32 The National Commission for the Protection of Human Subjects of Biomedical and Behavioral
33 Research has defined research as “activities designed to develop or contribute to generalizable
34 knowledge.”¹¹ It is widely accepted that such activities are necessary to foster treatment advances
35 that will benefit future patients. However, it is equally acknowledged that almost all clinical
36 research involves a certain degree of risk and, therefore, that safeguards must be applied to

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1 protect subjects.¹² To that effect, the federal regulations (“Common Rule”) require that
2 Institutional Review Boards (IRBs) review protocols to ensure that:

- 3
4 (1) Risks to subjects are minimized (i) by using procedures which are consistent with
5 sound research design and which do not unnecessarily expose subjects to risk,
6 and (ii) and whenever appropriate, by using procedures already being performed
7 on the subjects for diagnostic or treatment purposes.
8
9 (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to
10 subjects and the importance of the knowledge that may reasonably be expected to
11 result.¹³
12

13 The Council has previously discussed safeguards in the context of clinical investigation. In
14 particular, it stated that a physician-investigator is responsible for assuring that a study is
15 “competently designed, under accepted standards of scientific research, to produce data which are
16 scientifically valid and significant.”¹⁴
17

18 However, the methodological design of clinical trials can raise complex scientific and ethical
19 issues. One such issue is the requirement that a trial should be undertaken when there is genuine
20 uncertainty regarding the comparative merits of two treatments.¹⁵ Furthermore, it has been
21 argued that randomizing subjects to either the experimental or the standard treatment is ethically
22 acceptable only when there is “ equipoise ” or a belief within the general medical community that
23 the experimental intervention will provide at least equal or greater benefit than the standard
24 therapy.^{16,17} Most studies that meet this requirement compare two active treatments. But there
25 are instances when equipoise may exist between a placebo and a new intervention. For example,
26 there may be no proven effective therapies to treat a particular condition, or an otherwise
27 effective therapy may not be appropriate for a particular patient population. The use of placebos
28 also may be justified when the standard treatment poses risks to the subjects, or when the
29 condition being studied is relatively minor.
30

31 Placebo controls

32

33 The precise meaning of the term placebo has varied over time,¹⁸ but generally it is understood as
34 “a medicine given merely to please the patient.”¹⁹ Much of the controversy surrounding placebos
35 stems from the element of deception that is present when a physician provides a placebo instead
36 of an active treatment without informing the patient. Yet, in a number of cases, even though a
37 presumably inert treatment is provided to patients in lieu of an active treatment, a therapeutic
38 response has been observed—referred to as the “placebo effect.”²⁰
39

40 Although there continues to be disagreement regarding the use of placebos in treatment, this
41 Report focuses on the use of a placebo in the context of surgical control trials. Unlike the
42 therapeutic setting, in a control trial the subject is informed about the possibility of receiving a
43 placebo. As one leading ethicist has observed, the use of a placebo in the context of clinical trials
44 when subjects are informed of the possibility does not include the same element of deception that
45 the use of placebos in the clinical context does.²¹
46

47 The use of a placebo as a control usually is intended to present few physical risks to subjects,
48 although it is acknowledged that subjects who receive a placebo may experience some negative
49 “placebo side-effects”. Other risks involved in the use of a placebo are that subjects may be
50 required to delay or may forego receiving a beneficial treatment. Alternatively, the placebo effect
51 may result in some benefit to the subjects

“Placebo” Controls in Surgical Clinical Trials

Starting in the 1950s, placebo use in clinical trials evolved into a common methodology as interest in the placebo effect and the double-blind procedure grew.¹⁸ With the recent development of “sham” surgery, new questions have been raised about the use of placebo in clinical trials. In the case of the transplantation of fetal tissue into subjects with Parkinson’s Disease, the active arm of the study received an experimental intervention. The subjects in the control arm underwent most elements of the surgery but did not receive an injection of fetal tissue intended to produce therapeutic effects. Subjects were prepped for surgery, received anesthesia, had incisions made at the surgical site, received antibiotics, etc. Unlike trials of medications in which the placebo control generally involves a sugar pill or other inert substance, subjects in the control arm of these surgical trials were exposed to many of the risks and discomforts generally associated with invasive surgical procedures. Indeed, the investigators in these trials admitted that the risks involved were greater than those incurred by subjects who receive a placebo in pharmacological studies. They further recognized that the use of a procedure that could cause harm without offering a compensating benefit poses ethical problems and might violate the principle of non-maleficence.⁹ This led one commentator to conclude that “performing surgery in research subjects that has no potential of therapeutic benefit fails to minimize the risk of harm,”¹⁰ in violation of applicable ethical guidelines.

Nonetheless, there are strong arguments in favor of using clinical trials to evaluate the therapeutic value of surgical procedures. Particularly, if a trial comparing a novel surgical procedure and a surgical “placebo” control reveals no benefit for subjects in the active arm, then presumably ineffective operations will be prevented from taking place in the future. In the early 1960s Henry Beecher argued that scientists should investigate the extent of the placebo effect so that dangerous operations that were no more effective than placebos would not be performed.²² This recommendation followed the report that internal mammary artery ligation, a popular procedure used in patients with myocardial ischaemia during the 1950s, produced no greater therapeutic benefit than an incision without ligation.²³

Ethical Discussion

How should surgical “placebo” controls be evaluated in light of the above considerations? The first question is to determine whether such surgery should be considered analogous to a placebo. Like a placebo, this variant of a surgical procedure enables investigators to factor out confounding variables and make judgments about absolute efficacy. A study design involving a surgical “placebo” control may yield data of superior scientific validity but, as stated above, placebos generally are understood to present few risks. In the case of a surgical “placebo” control, however, the control arm is subjected to risks associated with surgery, such as infection and anesthesia reactions. Consequently, the ethical use of a surgical “placebo” control may require that the informed consent process be adapted to emphasize the risks involved in both arms of the trial, along with a description of the difference between each arm of the trial in terms of the essential procedure that will or will not be performed.

The use of “placebo” controls in surgery, should be carefully delineated. First, they should be used only when no other trial design will yield the requisite data. This determination should be guided by the Common Rule, which requires that risks be minimized and that those remaining risks be reasonable in relation to the importance of the knowledge to be derived and in relation to the benefits, if any, that subjects may realize.¹³ In many instances, it will in fact be preferable to compare a new surgical procedure to an existing standard, using a randomized trial.⁴ This will

1 typically be the case when a surgical technique is developed as an innovative modification of an
2 existing surgical procedure. However, when a new surgical procedure is developed with the
3 prospect of treating a condition for which no known surgical therapy exists, using surgical
4 “placebo” controls may be justified, but must be evaluated in light of whether the current standard
5 of care includes a non-surgical treatment that offers some benefit and the limitations of that
6 treatment. The risk assessment of the surgical “placebo” control should be weighed against the
7 benefits and side-effects of the existing standard treatment. If foregoing a treatment that is
8 efficacious and acceptable to the patients (in terms of side effects, personal beliefs, etc.) would
9 result in significant injury, it would be ethically impermissible to forego it in order to conduct a
10 trial that uses a surgical “placebo” control. The standard treatment would have to be maintained.
11 However, if the standard treatment was not fully efficacious, or was not acceptable to the patient,
12 a surgical “placebo” control could be used and the standard treatment foregone.

13 14 Conclusion

15
16 The use of placebos in randomized, double-blind clinical trials is widely held to be a gold
17 standard of research design. Recently, similar methodology has been used in the context of
18 surgical trials. Surgical “placebo” controls as described here raise ethical issues generally
19 associated with the use of placebos, such as deception and informed consent. The use of surgical
20 “placebo” controls also requires a careful assessment of the specific scientific benefits as well as
21 surgical risks.

22 23 Recommendations

24
25 The Council recommends that the following be adopted and the remainder of the report be filed:

26
27 The term surgical “placebo” controls refers to the control arm of a research study where
28 subjects undergo surgical procedures that have the appearance of therapeutic
29 interventions, but during which the essential therapeutic maneuver is omitted.

30
31 The appropriateness of a surgical “placebo” control should be evaluated on the basis of
32 guidelines provided in Opinions 2.07, “Clinical Investigation,” as well as the following
33 requirements:

- 34
35 (1) Surgical “placebo” controls should be used only when no other trial design will yield the
36 requisite data.
37
- 38 (2) Particular attention must be paid to the informed consent process when enrolling subjects
39 in trials that use surgical “placebo” controls. Careful explanation of the risks of the
40 operations must be disclosed, along with a description of the differences between the trial
41 arms emphasizing the essential procedure that will or will not be performed. Additional
42 safeguards around the informed consent process may be appropriate such as using a
43 neutral third party to provide information and get consent, or using consent monitors to
44 oversee the consent process.
45
- 46 (3) The use of surgical “placebo” controls is not justified when testing the effectiveness of an
47 innovative surgical technique that represents a minor modification of an existing surgical
48 procedure.
49
- 50 (4) When a new surgical procedure is developed with the prospect of treating a condition for
51 which no known surgical therapy exists, using surgical “placebo” controls may be

1 justified, but must be evaluated in light of whether the current standard of care includes a
2 non-surgical treatment and the benefits, risks and side-effects of that treatment.

3

4 (a) If foregoing standard treatment would result in significant injury and the standard
5 treatment is efficacious and acceptable to the patient (in terms of side-effects,
6 personal beliefs, etc.), then it must be offered as part of the study design.

7

8 (b) When the standard treatment is not fully efficacious, or not acceptable to the patient,
9 surgical “placebo” controls may be used and the standard treatment foregone, but
10 additional safeguards must be put in place around the informed consent process.

11

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REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS

CEJA Report 2-A-96

Subject: Ethical Use of Placebo Controls in Clinical Trials

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Referred to: Reference Committee on Amendments to Constitution and Bylaws
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1 Introduction*

2

3 The House of Delegates adopted Resolution 1, Ethical Use of Placebo Controls, at the Annual
4 Meeting in 1995. That resolution, sponsored by the Young Physician's Section, called upon the
5 American Medical Association to "study the ethical use of placebo controls in studies evaluating
6 drug therapies in those conditions for which effective treatment exists." In response to this charge,
7 the Council on Ethical and Judicial Affairs presents the following examination of the use of placebo
8 controls in circumstances where an accepted therapy is available.

9

10 Clinical Research

11

12 The advancement of scientific knowledge within the medical community is one of the fundamental
13 duties of all physicians.¹ Scientific research has provided physicians with the means to satisfy their
14 enduring commitment both to individual patient health and the collective health of society.
15 However, clinical investigation relies upon participants who are willing to accept a certain level of
16 risk to facilitate the improvement of medical practice. While the risks involved are generally
17 limited, there are cases where negative outcomes have been severe,² thus forcing the scientific
18 community to address concerns that the needs of future patients could take priority over the needs of
19 the patient participants in clinical research.

20

21 The Council has examined this issue in previous work and has provided ethical guidelines that
22 protect patients participating in research protocols from undue risk and exploitation in the name of
23 some greater benefit to society.³ Competent study design, careful implementation, and
24 conscientious supervision help to ensure that clinical research satisfies its dual obligation to provide
25 verifiable scientific data and to safeguard the rights of participants.

26

27 Placebo-controlled Trials

28

29 One fundamental requirement of clinical investigation is that it must provide scientifically valid
30 data. In the development of new drugs, trials must therefore be designed with a control capable of

* In accordance with the Joint Report of the Council on Ethical and Judicial Affairs and the Council on Constitution and Bylaws (I-91), this report may be adopted, not adopted, or referred. It may be amended, with the concurrence of the Council, to clarify its meaning.

1 allowing investigators to discern the effects of the drug under investigation. One of the best means
2 to fulfill this requirement is to compare an experimental therapy with placebo.^{4,5}

3
4 Despite the general support of placebo controls within the scientific community, opponents of this
5 research model have voiced objections. A particularly heated debate erupted when, in 1977, the
6 National Institute of Allergy and Infectious Diseases organized a 22-institution study to determine
7 the efficacy of adenine arabinoside (ara-A) in the treatment of herpes simplex encephalitis, a disease
8 then characterized by a mortality rate of 70 percent. Despite the nature of the disease and some very
9 preliminary research which indicated a potential for benefit, a placebo control was used in 10 of the
10 28 patients who met all the criteria for inclusion. As predicted by the history of the disease, 7 of the
11 10 control patients died. Mortality in the experimental group, however, was a vastly improved 28
12 percent.⁶

13
14 Objections to this trial centered in part on the insistence of experimenters to adhere to the rigors of
15 statistics and to subsequently include a placebo group despite the historical data which could verify
16 a mortality rate similar to that demonstrated by the control. In essence, some critics felt that the
17 interests of the control group had been given insufficient weight in considerations of trial design
18 because the investigators refused to undertake a more complicated analysis based upon an historical
19 control group.⁷

20
21 This critique of the Ara-A study is not fair to the investigators involved. Many factors may
22 contribute to the inability of past cases to provide an effective control and as a result, historically
23 controlled trials can be difficult to interpret and often yield optimistic but inaccurate results. For
24 instance, in 32 uncontrolled trials of portocaval shunt operations for portal hypertension, 24 reported
25 positive results for survival. However, in six randomized studies of the same treatment, the
26 operation was never shown to be effective.⁴ There are a number of possible explanations for this
27 and similar discrepancies. Patients formerly receiving treatment may have been evaluated using
28 different criteria or they may have experienced a different medical environment affecting their
29 response to treatment. Additionally, it may be difficult to find an equivalent patient sample as past
30 studies may have relied upon markedly different inclusion criteria. While it may not be possible to
31 identify all the factors contributing to the poor performance of many historically controlled studies,
32 the results are well documented. Researchers who compared 56 historically controlled clinical
33 studies with 50 randomized controlled studies for the same condition discovered that the
34 experimental therapy was shown to be effective in 44 of the historically controlled trials. Those
35 trials employing more rigorous controls achieved a far more modest success rate finding positive
36 results in only 10 of 50 trials.⁴

37
38 Despite the indicated difficulties associated with the alternative controls proposed by critics, the ara-
39 A study was useful in providing a forum for discourse on the ethical use of placebo controls.
40 However, the existence of federal guidelines that accommodate different study designs in the case
41 of fatal or serious disease render many of the aforementioned objections to the majority of placebo
42 controls difficult to sustain. In most cases the clinical research community recognizes the value of
43 well-designed placebo controlled trials in determining the efficacy of an experimental therapy.⁵

1 Ethical Questions Raised by the Availability of Accepted Therapies

2
3 Many observers can justify the risks borne by patients in a placebo group by arguing that the
4 absence of effective treatment for a given condition warrants if not demands the rigorous study of
5 experimental drugs. Additionally, because no adequate therapy exists, the control group may not be
6 any worse off than non-participants. However, when a therapy does exist, support for placebo
7 controls often dissipates in the face of what some perceive to be ideals which emphasize the
8 potential benefits gleaned by future patients without giving sufficient weight to the interests of
9 research participants. Under these conditions, the possibility is raised that the risks associated with
10 receiving a placebo will include the fact that participation in the control group will often deprive
11 patients of standard medication. An argument can be made that this substantially elevates the level
12 of commitment demanded of enrollees by potentially requiring the tolerance of discomforts that
13 could otherwise be avoided.

14
15 The trials of ondansetron as a medication to control post-chemotherapy emesis are cited as an
16 example of the certain discomfort suffered by the control group despite the availability of other
17 effective drugs.^{8,9} Critics find it difficult if not impossible to justify this type of suffering as it
18 requires the physician-investigator to intentionally deprive patients of care that could provide relief.

19 They contend that such behavior violates the physician's ultimate obligation to individual patient
20 advocacy by willfully placing the interests of the control patients behind those of future patients or
21 society at large. This reasoning can lead to an inappropriate image of investigators as physicians
22 who rely upon an "ends justify the means" approach to research and consequently demands careful
23 scrutiny and educated discourse.

24
25 Effective and Accepted Therapies

26
27 Before the objections to placebo-controlled studies that deny participants access to accepted
28 therapies can be addressed, it is important to appreciate the complexity of the issue by establishing
29 the limitations of the terms "accepted" and "effective." Accepted therapies that constitute standard
30 practice or that provide physicians with a treatment option do not always demonstrate statistically
31 significant benefit when tested against controls. Similarly, those drugs that have been labeled
32 "effective" through research cannot offer an unconditional guarantee of full benefit when applied
33 clinically. Many drugs are only partially effective at alleviating the conditions they are designed to
34 treat and even drugs that may be considered more fully effective rarely confer total benefit across all
35 patients. Additionally, the use of many drugs is accompanied by adverse effects which may prevent
36 their application to certain patients. These issues of uncertainty inherent in drug therapy
37 significantly complicate any discussion of ethical positions and proposed alternatives that hinge
38 upon the presence of established treatments.

39
40 The ability of placebos to confer benefit in some circumstances adds a further element of
41 complexity. Although the mechanism is unclear, there is evidence to suggest that treatment with a
42 placebo can have a measurable effect.¹⁰ Additionally, patients often improve spontaneously or as a
43 result of the increased attention characteristic of many clinical trials. When the possible benefits of
44 participation in a placebo group are coupled with the uncertain nature of drug therapy and the often
45 inconsistent behavior of a particular disease under study, it becomes clear that deciding whether or
46 not to include a placebo control is not as simple as choosing between providing and denying
47 effective treatment.

1 Alternative Trial Designs
2

3 The importance of conducting well designed and well controlled clinical trials is underscored by the
4 fact that ineffective medications are financially burdensome to society and potentially dangerous to
5 patients. Consequently, well controlled clinical trials are a necessary extension of the physician's
6 obligation to safeguard the health interests of all patients. It is therefore imperative that any
7 discussion concerning the potential drawbacks of placebo-controlled trials be accompanied by an
8 evaluation of viable alternative trial designs that may be able to ensure the safety and efficacy of
9 experimental or unproved medications.

10
11 In circumstances where an accepted therapy exists, one of the most frequently used alternative study
12 designs employs an active control. This type of protocol allows the investigator to compare directly
13 the effects of the experimental drug with the effects of a standard therapy without denying any
14 patients in the control group access to accepted medications. Aside from its apparent advantages in
15 patient protection, it has been argued that the true goal of medical research when one therapy has
16 already been established is to compare the experimental drug with existing drugs.⁸ In other words,
17 some observers maintain that what is important to researchers and practicing physicians is how well
18 the new drug measures up to standard treatments and not how well it performs against placebo.

19
20 It is important to recognize the shortcomings of the assumption that clinical trials are conducted
21 only to establish the comparative efficacy of a new drug. Relative efficacy is not the sole
22 characteristic upon which the value of a drug is measured and in fact a physician may very well
23 prize an effective drug even if it cannot match the performance in research trials of an accepted
24 therapy.^{11,12} Not all patients or diseases behave according to the statistical mean of clinical
25 research trials and consequently many patients may not respond to standard therapy. Others may
26 have adverse reactions which preclude its use or may have cost concerns that can be alleviated by
27 the introduction of an alternative. If drugs are compared exclusively to existing treatments, those
28 that are less effective might be discarded despite the potential advantages they could confer to
29 patients with varied needs. In short, a process that requires an experimental drug to demonstrate
30 efficacy comparable to that of existing medications could reduce the variety of clinical options
31 available to physicians. It seems clear that there are ultimately many aims of clinical research
32 besides a need to establish the efficacy of an experimental drug as compared to that of an existing
33 therapy.

34
35 Even if one doesn't recognize the variety of motivations for clinical research and assumes that
36 establishing comparative value between drugs is the primary aim of clinical research for conditions
37 treated with an existing therapy, several other potential problems still exist and must be addressed.
38 For instance, the abandonment of placebo controls could often result in statistical complications. In
39 trials that attempt to evaluate the effectiveness of an experimental drug in relation to an active drug,
40 establishing equivalence between the unknown and the control will often be the goal. However,
41 unlike trials designed to prove a difference, there is no agreed upon standard to establish a
42 statistically significant similarity.^{4,13} As a result, conclusively demonstrating that two drugs have an
43 equal effect is extremely difficult.

44
45 Even if equivalence could be demonstrated conclusively, many accepted therapies have not
46 consistently shown a level of response that provides a useful comparison. For instance, in the 14
47 efficacy studies conducted on Prozac before it was granted FDA approval, it was demonstrated to be

1 significantly more effective than placebo only 5 times.¹⁴ If an experimental drug is compared only
2 to an accepted therapy with similarly inconsistent research results, demonstrating an equivalent
3 effect between the drugs is not an inherently useful result. Under these circumstances, there would
4 be no means to determine if both drugs were effective, if neither was effective, or if the study was
5 simply incapable of distinguishing an effective agent from one that is ineffective. This problem is
6 clearly illustrated by the trials of one antidepressant considered by FDA in the early eighties.¹⁵ The
7 new drug was compared both to the standard antidepressant, imipramine, and to placebo in six
8 separate trials. When the experimental drug was compared with imipramine alone, both drugs
9 appeared to confer substantial and equal benefit in all trials. However, when the data from the
10 placebo group was examined, the active drugs were shown to be more effective than placebo in only
11 one of the six trials. In fact, based on the data it would be difficult to assert that the five remaining
12 trials even suggested the superiority of the active drugs much less a significant or demonstrable
13 positive effect.¹⁵

14
15 One final concern about trials designed to establish equivalence is the inherent incentive structure.
16 Studies designed to establish a difference between a control and an experimental drug provide an
17 incentive to conduct careful research since poor technique tends to obscure differences rather than
18 create them.^{4,13,16} When studies are geared toward demonstrating equivalence between two
19 therapies however, there is less pressure on investigators to ensure that the high standards of clinical
20 research are met. Flaws in equipment, errors in measurement and even insufficiently controlled
21 external factors may support the conclusion rather than defeat the trial.^{13,16} This raises the
22 possibility that in some cases apparently favorable results may not in fact be meaningful.

23
24 The concerns surrounding the use of active controls do not necessarily preclude their use in
25 comparative research. The benefits of providing control group patients with standard treatments
26 cannot be denied. Consequently, the past performance of the standard drug should be considered by
27 study designers to determine if it could provide a sufficient point of comparison for the conditions
28 and populations involved in a research protocol. If the standard treatment is consistently effective,
29 as in the case of certain antibiotics, it may be more difficult to justify the use of placebo. However,
30 the uncertainty of benefit that characterizes most medications may make them unsuitable as
31 controls. In these cases, the use of placebo will be more easily justified.

32
33 One possible solution to many of the difficulties associated with actively-controlled clinical trials is
34 to combine the use of active and placebo controls.^{13,15} The active control may allow comparisons to
35 be made that will prove helpful in clinical practice. The placebo, meanwhile, will standardize the
36 entire trial. If the active control is characterized by inconsistent results, the placebo will provide the
37 necessary baseline to test the experimental drug. If the active control is well established and
38 consistently effective, the placebo control will verify the usefulness of the study itself.¹⁷ In this
39 case, if the active control proves to be no more useful than placebo, there may be problems with the
40 selected patient population, study design, or research technique. It is important to note that the
41 placebo group can be relatively small and still satisfy the demands of clinical research. While this
42 design confers substantial statistical advantages, it still requires a placebo group and may not meet
43 the demands of critics who contend that the use of placebo is unacceptable in cases where an active
44 control is available.

1 Additional Alternatives

2
3 The problems associated with active control trials require the further analysis of other alternatives
4 that may be effective at minimizing the risk to patients while still providing adequate data.
5 Modifications to placebo-controlled trials can often satisfy these requirements. For instance, fail-
6 safe protocols prevent seriously ill patients from being kept on placebo by implementing frequent
7 clinical examinations and incorporating fixed criteria for determining when patients should no
8 longer participate.^{4,18} Patients who show any decline at the time of their first examination are
9 removed from the trial. Likewise, those who show no improvement by the second or third
10 evaluation are also removed. Alternatively, it is possible to monitor patients and shift those non-
11 responders in the placebo arm of a clinical study to the active medication.^{13,18} This simultaneously
12 prevents patient attrition from the study and ensures that patients who require active medication are
13 treated accordingly. Other escape clauses and rescue treatments can also be included in a trial
14 design to prevent participants from being exposed to undue risk.⁴

15
16 Some conditions may allow for the use of alternative study designs that do not require placebo. For
17 instance, some experimental treatments can be tested with dose-response and concentration-
18 response designs.¹⁸ Whenever possible, these and other models should be considered by researchers
19 as an alternative to placebo-controlled protocols.

20
21 Declaration of Helsinki

22
23 Regardless of safeguards designed to protect patients, opponents of placebo-controlled trials that
24 would deny participants access to accepted therapies suggest that requiring such a control clearly
25 violates the ethical considerations outlined in the Declaration of Helsinki.^{8,19} Originally written in
26 1964, the Declaration was augmented in 1975 to read in part, "In every medical study, every patient
27 -- including those of a control group, if any -- should be assured of the best proven diagnostic and
28 therapeutic method."²⁰ While this statement does appear to proscribe the use of placebo controls in
29 circumstances where a proven therapy exists, it seems equally to preclude all clinical research as
30 subjects in the experimental arm of any trial are guaranteed to receive an unproved therapy. A more
31 complete reading demonstrates that the intent of the Declaration of Helsinki is not to provide unduly
32 restrictive mandates but to protect the interests of patients who are willing to accept some risk for
33 potential but undetermined benefit or for the benefit of others. This obligation to protect the
34 altruistic participants was also elaborated in the Belmont Report authored in 1979 by the National
35 Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.²¹ These
36 documents share the sentiment that, while eradicating all risks inherent in human research is not
37 realistic, researchers must attempt to minimize the potential dangers involved in their respective
38 studies.

39
40 Informed Consent

41
42 Ensuring rigorous adherence to the principle of informed consent is perhaps the best possible
43 solution to the ethical difficulties associated with using a placebo control rather than an accepted
44 therapy control. The right of patients to control their course of medical care is one of the
45 fundamental tenets underlying standards of informed consent. A result of this freedom is that
46 patients cannot be expected to conform to one response when presented with information that
47 requires analysis of the risks and benefits involved.²² As with other areas of medicine, patients who

1 are considering involvement in clinical research should be allowed to weigh the risks of being
2 denied access to the standard treatment against the benefits of facilitating a more efficacious study.
3 To assume that patients would not volunteer to suffer minor symptoms for the benefit of future
4 generations could be construed as paternalistic. Furthermore, such an assumption may undermine
5 the patient's legitimate, altruistic motivations and deny him or her the opportunity to contribute to
6 medical progress.

7
8 Informed consent, however, cannot be relied upon to justify all research proposals.²³ There may be
9 research designs that would subject participants to unnecessary or extreme levels of risk and
10 patients must be protected from these trials. Institutional Review Boards (IRB) and Ethics
11 Committees should continue to screen research designs to evaluate the threat of possible harm to
12 patients in an effort to minimize the risks of clinical research and to preserve the integrity of
13 medical investigation.

14
15 Institutional review of research proposals must be accompanied by rigorous adherence to the
16 requirements of informed consent during the trial. This need is reinforced by studies which have
17 shown that participants in clinical research have difficulty understanding the process and
18 implications of controlled trials.²⁴ One such study indicated that 40 percent of patients in
19 psychopharmacologic trials failed to recognize that some participants would be given a placebo
20 rather than an effective treatment.²⁵ This failure to comprehend the risks involved or even the
21 procedure itself has been attributed in part to patients' adherence to the assumption that their
22 physician would only act in their best individual interests.²⁵ Whatever the cause of this
23 misunderstanding, it must be addressed through the provision of comprehensive information by
24 physicians and careful adherence to the guidelines governing informed consent. Consent forms
25 should be reviewed by IRBs prior to a protocol's initiation to ensure that they contain all the
26 necessary material including but not limited to study design, use of placebo controls and the
27 subsequent implications, possible side-effects, and mechanisms for the protection of patient welfare.
28 If the risks of a particular trial warrant additional caution, an objective third party can be included
29 in the consent procedure to verify understanding and assent.⁴ Finally, the standards of informed
30 consent should never be lowered for any reason including a belief that full disclosure would deter
31 patients from enrolling in a study thus adversely impacting the viability of that initiative.

32 Considerations for the Ethical Use of Placebo Controls

34
35 The advantages of using placebo controls in clinical research are clear and the use of these controls
36 is generally accepted in the scientific community, although exceptions have been made on ethical
37 grounds for conditions involving predictable and irreversible consequences.²⁶ However, as
38 previously discussed, circumstances in which the experimental drug is applied to a condition with a
39 standard treatment raise some legitimate ethical concerns that need to be addressed in the research
40 process. Clinical investigators studying a drug under these circumstances cannot simply assume
41 that the use of a placebo control is justified because of its capacity to provide superior data. While
42 statistical results that can be verified in experimentation are important to ensuring the safety and
43 efficacy of prescription drugs, the individual needs of the research subjects must be given priority in
44 the protocol design. When an accepted therapy exists, several factors must be considered to ensure
45 that study proposals meet equally the demands of science and ethics.

1 Perhaps the most significant factor to consider is the condition for which treatment is being tested.
2 Diseases that would cause irreversible damage over the course of study preclude the use of placebo
3 controls if including them would deny patients access to medications capable of preventing or
4 slowing illness progression.^{13,15,18,27,28} Additionally, conditions that are characterized by severe or
5 painful symptoms require researchers to carefully consider alternative designs and may render
6 inappropriate the use of placebo controls. For conditions that typically cause mild symptoms, the
7 use of placebo controls is justified if patients give their consent to participate after being adequately
8 informed about the nature of the trial and alternatives to enrollment.

9 Another significant factor to consider is the drug against which an experimental therapy may be
10 tested. As noted earlier, most medications are not effective across all populations. The conditions
11 for those who are not helped by otherwise effective medications demand the continued development
12 of competing or alternative drugs. Furthermore, those groups that are not responsive to existing
13 medications could serve in a placebo-controlled trial with no subsequent denial of benefit.¹⁸
14

15 The side-effects of known therapies also warrant consideration in the process of formulating a study
16 design.^{27,28} Some commonly used therapies can cause severe adverse effects and secondary
17 consequences that may allow researchers ethically to conduct placebo-controlled trials even though
18 existing therapies are effective. Following the necessary assumptions that underlie the ethical
19 requirement of informed consent, researchers must recognize that patients cannot be expected to
20 behave uniformly, even in identical situations. Some patients may be willing to forgo standard
21 treatment and accept the possibility of receiving a placebo if they can avoid suffering the adverse
22 effects of the accepted course of therapy. Within the confines of ethical practice, it is not the
23 position of the researcher or physician to deny patients the opportunity to make that decision. If the
24 adverse effects of a standard drug are so mild and the benefits so great as to call into question the
25 competence of a patient who would choose to forgo that treatment, offering patients the option of
26 entering a placebo-controlled trial would be unethical.
27

28 The cost of existing medication might also encourage some patients to seek enrollment in a placebo-
29 controlled trial. However, this characteristic of standard therapy must not be relied upon to attract
30 patients in low socioeconomic groups. While cost may motivate the development of new therapies,
31 the inability of a patient to pay for standard medication cannot be used to justify enrolling that
32 patient in a clinical trial. Furthermore, it is unacceptable to argue that those patients who do not
33 normally have access to standard therapies would not be deprived of treatment by entering a placebo
34 arm and can therefore provide a control group. Such enrollment capitalizes on their misfortune and
35 relies upon the coercive force of monetary constraints to satisfy the statistical demands that require
36 a sufficiently large control population. It would also be unacceptable, however, to exclude them
37 from such research solely on the basis of their monetary resources.
38

39 Another consideration is the length of the study. It is easier to justify denying a patient standard
40 therapies for a brief period of time than it is to support the long-term exclusion from accepted
41 treatment. If a researcher adequately justifies a placebo-controlled study and the IRB approves the
42 design, the obligation remains to minimize the time patients are denied access to standard treatment.
43 Interim data review by objective observers currently allows investigators to terminate studies if
44 they prove ineffective or dangerous. Likewise, if a drug demonstrates its efficacy and safety prior to
45 scheduled trial termination, participants receiving a placebo are switched to the active treatment.
46 These practices, as well as the implementation of alternative study designs that minimize the

1 exposure to placebo, should continue in order to prevent patients from being denied accepted
2 treatment unnecessarily. Additionally, the ability of patients to end their participation in the trial
3 must be made explicit to prevent any subjects from feeling trapped by their initial consent.

4
5 Conclusion
6

7 The controversy that surrounds the use of placebo controls in research is particularly intense when
8 the experimental drug is designed to treat conditions for which known effective therapies already
9 exist. Critics contend that their use conflicts irreconcilably with the physician's primary duty to
10 treat the individual patient. There is little doubt that presenting a patient with a placebo in place of a
11 more effective medicine does introduce a level of conflict with the physician-investigator's
12 obligation to exercise every available option for each individual patient. It should be noted,
13 however, that this conflict is similar to that involved in most clinical research that requires the
14 physician to present the patient with a certain level of risk in return for uncertain benefit.
15 Furthermore, the expense of abandoning placebo controls altogether would be paid by future
16 generations of patients who might be exposed to drugs of unknown efficacy or denied a sufficient
17 number of options to meet individual needs. This ultimately introduces a conflict with medicine's
18 enduring commitment to providing safe and effective treatments.

19
20 Recognizing the need to balance two distinct obligations on the part of the physician, the Council
21 proposes the following guidelines to safeguard the interests of the individual patient in light of the
22 need to provide adequate data for the advancement of medicine.

23
24 1. Placebo controls are an important part of medicine's commitment to ensuring that the safety
25 and efficacy of new drugs are sufficiently established. Used appropriately, placebo controls can
26 safely provide valuable data and should continue to be considered in the design of clinical trials.
27 The existence of an accepted therapy does not necessarily preclude the use of such controls.

28
29 2. Investigators must be extremely thorough in obtaining informed consent from patients. To
30 the extent that research is dependent upon the willingness of patients to accept a level of risk, their
31 understanding of the potential harms involved must be a top priority of any clinical investigation.
32 The possibility presented in some studies that patients often do not fully understand the research
33 protocol and therefore truly can not give informed consent demonstrates a need to heighten the
34 efforts of researchers to impress upon their subjects the nature of clinical research and the risks
35 involved. Patients are capable of making decisions when presented with sufficient information and
36 it is the responsibility of the IRB and the individual investigators involved to ensure that each
37 subject has been adequately informed and has given voluntary consent. Each patient must also be
38 made aware that they can terminate their participation in a study at any time.

39
40 3. Informed consent cannot be invoked to justify an inappropriate trial design. IRBs as well as
41 investigators have an obligation to evaluate each study protocol to determine whether a placebo
42 control is necessary and whether an alternative study design with another type of control would be
43 sufficient for the purposes of research. Protocols that involve conditions causing death or
44 irreversible damage cannot ethically employ a placebo control if alternative treatment would
45 prevent or slow the illness progression. When studying illnesses characterized by severe or painful
46 symptoms, investigators should thoroughly explore alternatives to the use of placebo controls. In
47 general, the more severe the consequences and symptoms of the illness under study, the more

1 difficult it will be to justify the use of a placebo control when alternative therapy exists.
2 Consequently, there will almost certainly be conditions for which placebo controls cannot be
3 justified. Similarly, the use of a placebo control will more easily be justified as the severity and
4 number of negative side-effects of standard therapy increase.

5
6 4. Researchers and IRBs should continue to minimize the amount of time patients are given
7 placebo. The rationale provided by investigators for the length of study will give IRBs the
8 opportunity to ensure that patients are given placebo therapy for as short a time as possible to
9 provide verifiable results. Additionally, the interim data analysis and monitoring currently in
10 practice will allow researchers to terminate the study because of either positive or negative results,
11 thus protecting patients from remaining on placebo unnecessarily.

12
13 5. Science should continue to pursue alternative study designs that will allow investigators to
14 test new drugs effectively without exposing patients to a withdrawal from standard treatments.

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