7.1.2 Informed Consent in Research

Informed consent is an essential safeguard in research. The obligation to obtain informed consent arises out of respect for persons and a desire to respect the autonomy of the individual deciding whether to volunteer to participate in biomedical or health research. For these reasons, no person may be used as a subject in research against his or her will.

Physicians must ensure that the participant (or legally authorized representative) has given voluntary, informed consent before enrolling a prospective participant in a research protocol. With certain exceptions, to be valid, informed consent requires that the individual have the capacity to provide consent and have sufficient understanding of the subject matter involved to form a decision. The individual's consent must also be voluntary.

A valid consent process includes:

(a) Ascertaining that the individual has decision-making capacity.

(b) Reviewing the process and any materials to ensure that it is understandable to the study population.

(c) Disclosing:

  (i) the nature of the experimental drug(s), device(s), or procedure(s) to be used in the research;

  (ii) any conflicts of interest relating to the research, in keeping with ethics guidance;

  (iii) any known risks or foreseeable hazards, including pain or discomfort that the participant might experience;

  (iv) the likelihood of therapeutic or other direct benefit for the participant;

  (v) that there are alternative courses of action open to the participant, including choosing standard or no treatment instead of participating in the study;

  (vi) the nature of the research plan and implications for the participant;

  (vii) the differences between the physician's responsibilities as a researcher and as the patient's treating physician.

(d) Answering questions the prospective participant has.

(e) Refraining from persuading the individual to enroll.

(f) Avoiding encouraging unrealistic expectations.

(g) Documenting the individual's voluntary consent to participate.

Participation in research by minors or other individuals who lack decision-making capacity is permissible in limited circumstances when:

(h) Consent is given by the individual's legally authorized representative, under circumstances in which informed and prudent adults would reasonably be expected to volunteer themselves or their children in research.

(i) The participant gives his or her assent to participation, where possible. Physicians should respect the refusal of an individual who lacks decision-making capacity.

(j) There is potential for the individual to benefit from the study.

In certain situations, with special safeguards in keeping with ethics guidance, the obligation to obtain informed consent may be waived in research on emergency interventions.

AMA Principles of Medical Ethics: I,III,V

Opinion 7.1.2, Informed Consent in Research, re-organizes content from several previous opinions and associated background reports:

CEJA Report 3-A-16 Modernized *Code of Medical Ethics*

CEJA Report E-I-98 Conflicts of interest—biomedical research

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

Report of the Judicial Council A-A-66 Declaration of Helsinki

7.1.2 Informed Consent in Research

Informed consent is an essential safeguard in research. The obligation to obtain informed consent arises out of respect for persons and a desire to respect the autonomy of the individual deciding whether to volunteer to participate in biomedical or health research. For these reasons, no person may be used as a subject in research against his or her will. *[New content sets out key ethical values and concerns explicitly.]*

Physicians must ensure that the participant (or legally authorized representative) has given voluntary, informed consent before enrolling a prospective participant in a research protocol. *With certain exceptions, to be valid, informed consent requires that the individual have the capacity to provide consent and have sufficient understanding of the subject matter involved to form a decision.* The individual's consent must also be voluntary. *[New content addresses gap in current guidance.]*

A valid consent process includes:

(a) Ascertaining that the individual has decision-making capacity.

(b) Reviewing the process and any materials to ensure that it is understandable to the study population. [New content highlights importance of consent process*.]*

(c) Disclosing:

(i) the nature of the experimental drug(s), device(s), or procedure(s) to be used in the research;

(ii) any conflicts of interest relating to the research, in keeping with ethics guidance;

(iii) any known risks or foreseeable hazards, including pain or discomfort that the participant might experience;

(iv) the likelihood of therapeutic or other direct benefit for the participant;

(v) that there are alternative courses of action open to the participant, including choosing standard or no treatment instead of participating in the study;

(vi) the nature of the research plan and implications for the participant; [New content addresses gap in current guidance.]

(vii) the differences between the physician's responsibilities as a researcher and as the patient's treating physician.

(d) Answering questions the prospective participant has.

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AMA Principles of Medical Ethics: I,III,V

CEJA Report 3 – I-98
Conflicts of Interest: Biomedical Research

INTRODUCTION

In December 1989 the Council on Scientific Affairs and the Council on Ethical and Judicial Affairs issued their joint report "Conflicts of Interest in Medical Center/Industry Research Relationships." In regards to disclosure, the guidelines state

> (c) clinical investigators should disclose any material ties to companies whose products they are investigating. They should disclose their financial ties, participation in educational activities supported by the companies, participation in other research projects funded by the companies, consulting arrangements, and any other ties. The disclosure should be made to the medical center where the research is conducted, organizations that are funding the research, and journals that publish the results of the research.[1]

Revitalized discussions about full disclosure of any financial interest by those who conduct biomedical research have encouraged the Council to reconsider these minimum requirements.

DISCUSSION

It is difficult to deny that research-related gifts, either financial or material, play an important role in supporting research and increasing productivity. A study which examined academic scientists' experience with research-related gifts from industries revealed that 75% of those who received biomaterials, 66% of those who received discretionary funds, and 67% of those who received research equipment rated these gifts as "essential," "very important," or "important" to the progress of their research. Correspondingly, the data suggested that such gifts were associated with a variety of restrictions and expectations of returns, including the expectation of prepublication review of articles or reports.[2] The debate over calcium-channel antagonists has exemplified the need for complete disclosure of relationships with pharmaceutical companies for researchers who publish articles examining pharmaceutical products. A recent study of physicians' financial relationships with the pharmaceutical industry demonstrated that supportive authors were much more likely than critical authors to have financial associations with manufacturers of calcium-channel antagonists, as well as with manufacturers of other products.[3] In addition, it has been reported that the tobacco industry paid several scientists over $156,000 to write letters to the editors of health and industry related journals, as well as newspapers such as the Wall Street Journal, discrediting a 1993 Environmental Protection Agency report that linked secondhand smoke to lung cancer.[4] For example, one biostatistician received $10,000 to write a letter to the Journal of the American Medical Association.[5] Letter campaigns such as this may mislead the public and the medical profession by presenting biased opinions that distort serious health-related controversies.

Conflicts of interest vary and can be interpreted differently. Many researchers and authors may feel that they can remain objective in areas of their expertise regardless of financial associations or research-related gifts. Critics view this claim skeptically. The integrity of the medical community and the research done within depends on the avoidance of real or perceived conflicts of interests and the accompanying biases. Of utmost concern is protecting the public from a researcher's or author's opinion that is tilted due to personal interests.

RECOMMENDATION

Many medical journals have adopted policies that require conflicts of interest to be disclosed to readers.[6, 7] For the following reasons, the Council on Ethical and Judicial Affairs recommends that the following statement be adopted and that the remainder of this report be filed:

1. An explanatory statement that discloses conflicts of interest to readers should accompany published research. Other types of publications, such as a letters to the editor, should also include an explanatory statement that discloses any potential conflict of interest.

REFERENCES

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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
Presented by:	Charles W. Plows, MD, Chair
Referred to:	Reference Committee on Amendments to Constitution and Bylaws (Betty P. Stephenson, MD, Chair)

Introduction*

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

Clinical Research

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

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

Placebo-controlled Trials

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

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* 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.

allowing investigators to discern the effects of the drug under investigation. One of the best means to fulfill this requirement is to compare an experimental therapy with placebo.[4,5]

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

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

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

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

Ethical Questions Raised by the Availability of Accepted Therapies

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

The trials of ondansetron as a medication to control post-chemotherapy emesis are cited as an example of the certain discomfort suffered by the control group despite the availability of other effective drugs.[8,9] Critics find it difficult if not impossible to justify this type of suffering as it requires the physician-investigator to intentionally deprive patients of care that could provide relief. They contend that such behavior violates the physician's ultimate obligation to individual patient advocacy by willfully placing the interests of the control patients behind those of future patients or society at large. This reasoning can lead to an inappropriate image of investigators as physicians who rely upon an "ends justify the means" approach to research and consequently demands careful scrutiny and educated discourse.

Effective and Accepted Therapies

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

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

Alternative Trial Designs

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

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

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

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

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

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

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

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

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

Additional Alternatives

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

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

Declaration of Helsinki

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

Informed Consent

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

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

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

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

Considerations for the Ethical Use of Placebo Controls

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

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

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

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

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

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

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

Conclusion

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

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

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

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

3. Informed consent cannot be invoked to justify an inappropriate trial design. IRBs as well as investigators have an obligation to evaluate each study protocol to determine whether a placebo control is necessary and whether an alternative study design with another type of control would be sufficient for the purposes of research. Protocols that involve conditions causing death or irreversible damage cannot ethically employ a placebo control if alternative treatment would prevent or slow the illness progression. When studying illnesses characterized by severe or painful symptoms, investigators should thoroughly explore alternatives to the use of placebo controls. In general, the more severe the consequences and 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 be justified. Similarly, the use of a placebo control will more easily be justified as the severity and number of negative side-effects of standard therapy increase.

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

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

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REPORTS OF STANDING COMMITTEES OF THE HOUSE OF DELEGATES

JUDICIAL COUNCIL

The following reports (A, C, D) were presented by Dr. E. G. Shelley, *Vice Chairman*. Report B, "Eulogy for James H. Berge, MD," appears on page 12. Report E, "Nominations for Affiliate Membership in the American Medical Association" appears on page 163.

A. Declaration of Helsinki

During the past several years, the American Medical Association has given much attention to the subject of ethical guidelines for clinical medical investigation. A number of meetings have been held at which representatives of the Association and other organizations such as the American Federation for Clinical Research, the American Society for Clinical Investigation, the Central Society for Clinical Research, and the American College of Physicians, have discussed the desirability of adopting guidelines or standards or rules for clinical medical investigation. It is the consensus of knowledgeable individuals in this field that guidelines for medical clinical investigation should be developed and promulgated. It is the further thinking of these individuals, and the Judicial Council concurs in this thinking, that the Declaration of Helsinki adopted by the World Medical Association in 1954 is the expression of basic principles to which all honorable physicians and investigators can subscribe and may be accepted as guides to ethical conduct in medical investigation.

The Judicial Council has reviewed the Declaration of Helsinki and is of the opinion that it is in accord with the *Principles of Medical Ethics* of the American Medical Association. The Judicial Council, therefore, submits this Declaration to the House of Delegates with the recommendation that the House of Delegates endorse the Declaration of Helsinki as a guide to those who are engaged in clinical medical investigation.

DECLARATION OF HELSINKI
RECOMMENDATIONS GUIDING DOCTORS IN CLINICAL RESEARCH

It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the doctor with the words: "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest." Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to suffering humanity, the World Medical Association has prepared the following recommendations as a guide to each doctor in clinical research. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and the clinical research, the essential object of which is purely scientific and without therapeutic value to the person subjected to the research.

I. *Basic Principles*

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.
2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.
3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.
5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

II. *Clinical Research Combined with Professional Care*

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, re-establishing health, or alleviating suffering. If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.
2. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

III. *Non-Therapeutic Clinical Research*

1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out.
2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.
3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.
3b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice.
3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.
4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.
4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued. The investigator or the investigating team should discontinue the research if, in his or their judgment, it may, if continued, be harmful to the individual.

REPORT OF REFERENCE COMMITTEE ON AMENDMENTS TO CONSTITUTION AND BYLAWS: On recommendation of the Reference Committee, the House voted to adopt Report A of the Judicial Council and Report M (p. 51) of the Board of Trustees and urged publication of the Declaration of Helsinki in state and local journals for the information of all physicians.

The following report was presented by Dr. Philip H. Jones, *Chairman:*

Report A of the Judicial Council and Report M (p. 51) of the Board of Trustees urge that the Declaration of Helsinki, already adopted by the World Medical Association, be endorsed by the House of Delegates as a guide to those who are engaged in clinical medical investigation. The Judicial Council report further indicates that the Declaration of Helsinki is in accord with the *Principles of Medical Ethics* of the American Medical Association.

C. Special Report Concerning Unethical Hospital Assessments

At the Clinical Convention of the AMA House of Delegates in November 1965, the Pennsylvania delegation introduced resolution no. 13. The resolution reads as follows:

WHEREAS, A 'bed tax' has been imposed on doctors serving on the medical staffs of hospitals under the guise of voluntary contributions to intern and resident educational programs; and

WHEREAS, Physicians have lost their hospital privileges as a result of refusing to pay such 'contributions'; and

WHEREAS, Such taxes have been declared in violation of the *Principles of Medical Ethics* of the American Medical Association; Section 7, paragraph 9, which reads as follows;

> "Compulsory Assessments, that is, assessments which, if not paid, would automatically cause doctors to lose staff membership, are not in the best traditions of ethical practice. It is not proper to condition medical staff membership on compulsory assessments for any purpose." (Judicial Council, 1962);

therefore be it

Resolved, That it is hereby declared to be a violation of the *Principles of Medical Ethics* of the American Medical Association for a physician, group or organization of physicians to take any action that imposes payment by physicians to a hospital for any purpose when such payment or nonpayment will, in any way, affect the granting or retention of hospital privileges to any physician.

The Reference Committee on Insurance and Medical Service, believing that the *Resolved* clause of resolution no. 13 broadens the area of previous Judicial Council opinions, recommended that resolution no. 13 be referred to the Judicial Council for consideration and such action as it deems necessary.

In 1952 the Judicial Council called attention to proposals whereby some hospitals suggested that physicians who utilize the hospital facilities pay to the hospital a percentage of the fees which they receive from their patients while being cared for in the hospital. The Council expressed its opinion that this was a form of fee splitting or sharing of professional fees with a lay organization which should not render professional services in the first place, but which in addition, has already levied its regular bill for the services which it legitimately rendered.

At the June 1958 Annual Convention of the Association, resolution no. 55 asked that the House of Delegates reiterate its position with regard to condemning compulsory assessments of members of medical staffs for building funds and the practice of required audits of staff members' financial records as a requisite for continued staff appointment. The Reference Committee on Medical Education and Hospitals recommended