Guidelines for the Community Physician

Adopted by the LACBA Board of Trustees on February 26, 2003.

I. Introduction

These Guidelines are for the community physician who is considering referring patients to, or participating in, a clinical drug or device trial. Principal investigators,¨ who are responsible for directing clinical trials, have additional obligations beyond those described in these Guidelines.

What are Clinical Trials?
Clinical trials use human subjects to gather information about the safety and efficacy of procedures, treatment modalities, drugs, and other interventions. It is essential to remember that, although there may be a reasonable expectation of benefits for some participants, clinical research trials are not intended to aid any particular patient.

By the time a clinical trial involves human subjects, it has passed through a series of other research steps, including animal testing. Clinical trials involving human subjects are divided into the following phases:

- Phase I clinical trials evaluate the safety of a new drug or device, how the drug should be administered or the device used, the frequency, and, in the case of drugs, dosage. Relatively few human subjects are enrolled in Phase I clinical trials.
- Phase II clinical trials provide preliminary information about how well a new drug or device works and generate additional information about the safety and benefits of the drug or device. Phase II clinical trials generally involve more human subjects than do Phase I clinical trials.
- Phase III clinical trials are designed to demonstrate whether a treatment is effective. Phase III clinical trials are frequently carried out through "double blind"[1] trials on large numbers of human subjects. These clinical trials compare the investigative drug or device to the standard of care, a placebo if ethically acceptable, or both. Human research clinical trials conducted in a community setting are usually Phase III clinical trials.
- Phase IV clinical trials provide for a continuing evaluation of a drug or device once it has been approved for marketing by the FDA and is available for general use.

Purpose of These Guidelines:
Both society and individuals can benefit from clinical trials on human subjects. The history of clinical trials, however, demonstrates the importance of proceeding in accordance with established ethical principles. Even very reputable institutions and investigators have conducted ethically questionable research. Researchers must ensure that ethical principles are closely followed and that the interests of human subjects are protected.

Responsibility for ensuring that research is ethical rests primarily with principal investigators and the Institutional Review Boards (IRBs) that approve research projects. However, practicing physicians can take steps to determine that clinical trials in which they or their patients participate meet ethical standards. These Guidelines were developed to assist community physicians in that process. Before a physician suggests or endorses participation to a patient, the physician should consider the associated risks and benefits, along with the patient's wants and needs.

II. Informed Consent

Informed consent to participate in clinical research, like informed consent to medical treatment, should be seen as a process of conversation rather than a document. The Informed Consent Form (ICF) provides documentation that the conversation has taken place, but is not a substitute for the conversation.
The ICF contains important information a physician needs to evaluate the clinical trial. Federal law requires that the investigator prepare an extensive written ICF for each clinical trial, which must be approved by the IRB. The required elements for all ICFs are listed in Appendix A.

If a physician decides to recommend participation in or to refer a patient to a particular clinical trial, the physician should review the ICF with the patient or the patient's surrogate decisionmaker[2]. Because the ICF must present all reasonably foreseeable risks as well as benefits, such review provides for a full discussion of the clinical trial between the referring physician and the patient. As part of the discussion, the physician should impress upon the patient that (a) the clinical trial involves an intervention of unproven efficacy, (b) if the study is a placebo control study, the patient may not receive the study intervention, and (c) the patient may even suffer harm. The physician should always make clear to the patient that participation in the trial means that the patient has no assurance of receiving the standard of care for his/her condition.

III. Checklist

Whether a physician is considering referring the patient or the patient has initiated the inquiry into a clinical trial, the following is a checklist that physicians may find helpful when they are evaluating such a clinical trial. Negative answers should alert the physician to potential problems with the study. The physician should discuss any concerns with the patient and, if appropriate, recommend against participation.

Threshold Question:

_____Has an IRB approved the proposed clinical trial?

Patient Care Issues:

_____Is there a possibility that the patient will benefit from the clinical trial?

_____Is the risk of harm to the patient within acceptable limits?

_____Does the information to be gained justify the risks to the patient?

_____Will the protocol allow the patient to remain on currently effective treatment?

_____Will the patient be informed of findings that, whether or not part of the clinical trial, could affect the patient?

Financial Impact:

_____Is participation in the clinical trial free of financial risk to the patient, such as the risk of loss of insurance benefits?
_____Is it clear who pays for medical care costs associated with the clinical trial?
_____If the clinical trial causes harm to the patient, is it clear who is financially responsible for the medical care necessary to remedy this harm?
_____Is there a clearly-defined process for settling clinical trial-related disputes?
_____Are reasonable travel and other out of pocket expenses to the patient reimbursed?

Incentives:
_____Is the financial or other remuneration to the physician for referring patients consistent with the effort expended[3]?
_____Does the clinical trial appear to be free of any improper patient inducement or pressure to coerce participation?

Additional Checklist Items In Cases Where the Treating Physician is also a Co-Investigator:
Increasingly, a patient's treating physician may also be a co-investigator for a clinical trial for which the patient may be a good candidate. A treating physician should recognize that his/her dual role could unduly affect the patient's decision to participate in the clinical trial. Therefore, the treating physician should consider the following additional questions:

_____Does the patient understand the difference between the physician's responsibilities as his/her treating physician and the physician's responsibilities as a researcher?

_____In obtaining informed consent, is the treating physician certain that he or she has not unduly influenced the patient?

_____Is the patient aware of any incentives for the physician to participate in or recruit patients to the study that might create a conflict of interest?

_____Can the treating physician protect the privacy of the patient as a subject in the clinical trial?

Note that according to the California Supreme Court, , "a physician who is seeking a patient's consent for a medical procedure . . . must disclose personal interests unrelated to the patient's health, whether research or economic, that may affect his medical judgment"[4]

Physicians are encouraged to review two AMA Ethics Opinions relating to clinical trials. One, entitled Managing Conflicts of Interest in the Conduct of Clinical Trials, is included as Appendix B. The other, The Use of Placebo Controls in Clinical Trials, can be found at Appendix C. To obtain more information about a particular clinical trial, a physician may request information on the clinical trial from the principal investigator. Appendix D is a model letter that a physician may use to make such a request for information. Appendix E provides a list of additional resources for information about clinical trials.

[1] A "double blind" clinical trial is one in which neither the subject nor the investigator knows whether the subject is receiving the experimental treatment or a placebo.
[2] The categories of individuals who may serve as surrogate decisionmakers for clinical trials differ significantly from the categories of individuals who are generally permitted to make decisions on behalf of incompetent patients. Recent California legislation created a hierarchy of family members (including domestic partners) who can consent to participation in research by a person who lacks decisionmaking capacity under specified circumstances. See Cal. Health & Safety Code § 24178 for details.
[3] The AMA has stated that it is unethical to accept payment solely for referring patients to research studies.
[4] Moore v. Regents of the Univ. of Calif., 51 Cal.3d 120, 129 (1990).

APPENDIX A
What You Should Know About The Informed Consent Form (ICF)

When investigators are doing research with human subjects, federal and state law specifically require that, at a minimum, certain topics be covered in the ICF. If these topics are not included, the researcher is not in compliance with the law. Further, state law expressly requires that all such oral and written information be given, "in nontechnical terms and in a language in which the subject or the subject's conservator or guardian or other representative.... is fluent." Finally, the subject should be provided with a copy of the signed and dated written consent form and a copy of the California Experimental Subject's Bill of Rights. The following are the things that must be included in the ICF:

1. The nature of the research.
   a. Its purpose.
   b. Duration.
   c. Procedures, including indication of which are experimental.
2. Risks and discomforts, including the possibility of receiving a placebo if the research includes one.
3. Benefits, both to the subject and to society.

4. Alternatives, including the standard of care for the subject's condition and if the study drug would be available outside the study.
5. Provisions made to maintain confidentiality.
6. Statement that participation is voluntary and refusal to participate will not lead to any penalty or loss of benefits.
7. Statement that subjects have a right to withdraw from participation at any time.
8. Whether there is compensation for injury sustained as a result of the research.
9. Whom to contact if the subject has questions in an emergency, or any other need to talk to an investigator.
10. The name, institutional affiliation, if any, and address of the person or persons actually performing and primarily responsible for the conduct of the clinical investigation.
11. The name of the sponsor or funding source, if any, or manufacturer, if the clinical investigation involves a drug or device, and the organization, if any, under whose general aegis the clinical investigation is being conducted.
12. The name, address, and phone number of an impartial third party not associated with the clinical investigation to whom the subject may address complaints about the clinical investigation.

In addition, the regulations list elements that should be included, if relevant. Some of these include:

1. Any additional costs the subjects may have resulting from clinical trial participation.
2. The number of subjects in the clinical investigation.
3. The possibility of risks that are currently unforeseeable.
4. If a placebo is to be administered or dispensed to a portion of the subjects involved in the clinical investigation, all subjects of such investigation must be informed of that fact. The subject need not be informed as to whether he/she will actually be administered or dispensed a placebo.
5. An estimate of the expected recovery time of the subject after the clinical investigation.

APPENDIX B
AMA Code of Ethics

Opinion 8.032
Managing Conflicts of Interest in the Conduct of Clinical Trials
As the biotechnology and pharmaceutical industries continue to expand research activities and funding of clinical trials, and as increasing numbers of physicians both within and outside academic health centers become involved in partnerships with industry to perform these activities, greater safeguards against conflicts of interest are needed to ensure the integrity of the research and to protect the welfare of human subjects. Physicians should be mindful of the conflicting roles of investigator and clinician and of the financial conflicts of interest that arise from incentives to conduct trials and to recruit subjects. In particular, physicians involved in clinical research should heed the following guidelines:

(1) Physicians should agree to participate as investigators in clinical trials only when it relates [sic] to their scope of practice and area of medical expertise. They should have adequate training in the conduct of research and should participate only in protocols which they are satisfied are scientifically sound.

(2) Physicians should be familiar with the ethics of research, and should agree to participate in trials only if they are satisfied that an Institutional Review Board has reviewed the protocol, that the research does not impose undue risks upon research subjects, and that the research conforms to government regulations.

(3) When a physician has treated or continues to treat a patient who is eligible to enroll as a subject in a clinical trial that the physician is conducting, the informed consent process must differentiate between the physician's roles as clinician and investigator. This is best achieved when someone other than the treating physician obtains the participant's informed consent to participate in the trial. This individual should be protected from the pressures of financial incentives, as described in the following section.

(4) Any financial compensation received from trial sponsors must be commensurate with the efforts of the

physician performing the research. Financial compensation should be at fair market value and the rate of compensation per patient should not vary according to the volume of subjects enrolled by the physician, and should meet other existing legal requirements. Furthermore, according to Opinion 6.03, *Fee Splitting: Referral to Health Care Facilities*,¨ it is unethical for physicians to accept payment solely for referring patients to research studies.

(5) Physicians should ensure that protocols include provisions for the funding of subjects' medical care in the event of complications associated with the research. Also, a physician should not bill a third-party payor when he or she has received funds from a sponsor to cover the additional expenses related to conducting the trial.

(6) The nature and source of funding and financial incentives offered to the investigators must be disclosed to a potential participant as part of the informed consent process. Disclosure to participants also should include information on uncertainties that may exist regarding funding of treatment for possible complications that may arise during the course of the trial. Physicians should ensure that such disclosure is included in any written informed consent.

(7) When entering into a contract to perform research, physicians should ensure themselves that the presentation or publication of results will not be unduly delayed or otherwise obstructed by the sponsoring company.(II, V).

Issued June 2001 based on the report *Managing Conflicts of Interest in the Conduct of Clinical Trials*,¨ adopted December 2000.

APPENDIX C
AMA Code of Ethics

Opinion E-2.075
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; however, physician-investigators should adhere to the following guidelines to ensure that the interests of patients who participate in clinical trials are protected.
(1) 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 institutional review board (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.

(2) 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.

(3) 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. (I, V)

Issued June 1997 based on the report *Ethical Use of Placebo Controls in Clinical Trials*,¨ adopted June 1996.

APPENDIX D
Sample Information Request Letter To Investigator

Clinical Investigator
Address
Address
Re: _____
[name of clinical trial]
Dear Clinical Investigator:
I am a community physician who is considering referring patients to the above clinical trial.
Please send me the following information regarding the clinical investigation:
1. The informed consent form and supporting documents, if any;
2. A summary of the clinical trial in non-technical language;
3. The source of funding of the clinical trial;
4. Financial incentives to the investigators; and
5. Any other important information.
This information may be sent to the following address:
_____
_____
_____
Sincerely,
_____

APPENDIX E
Clinical Trials Resources

Belmont Report:
In recognition of the concerns raised by the use of human subjects in clinical research, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued its Belmont Report in April 1979. The Report was intended as a ¡§statement of basic ethical principles and guidelines¡¨ to assist in resolving the ethical problems that surround the conduct of research with human subjects. The Commission sought to establish principles about clinical investigations on human subjects. Relying heavily on the Nuremberg Code, the guidelines emphasized rules for clinical research, informed consent for subjects, and establishment and function of Institutional Review Boards for oversight.

Articles:
Susan L. Coyle, American College of Phys.—American Soc'y of Internal Med., Position Paper: Physician-Industry Relations (pt. 1: Individual Physicians), 136 ANN. INTERN. MED. 396 (2002).

Catherine D. DeAngeles, Conflict of Interest and the Public Trust, 284 JAMA 2237 (2000).

S. A. Hutchins & R. Eckes, HIV Infection. Clinical Research. Consideration for Prospective Participants, 31 NURSING CLINICS N. AM. (Mar. 1996).

Steven Joffe et al., Quality of Informed Consent in Cancer Clinical Trials: A Cross-Sectional Survey, 358 LANCET 1772 (2001).

Robert Kelch, Maintaining the Public Trust in Clinical Research, 346 NEW ENG. J. MED. 285 (2002).

David Korn, Conflicts of Interest in Biomedical Research, 284 JAMA 2234 (2000).

Franklin G. Miller et al., Professional Integrity in Clinical Research, 280 JAMA 1449 (1998).

Franklin G. Miller & Andrew Schorr, Advertising for Clinical Research, 21 IRB (Sept.-Oct. 1999).

Karine Morin et al., Managing Conflicts of Interest in the Conduct of Clinical Trials, 287 JAMA 78 (2002).

Brian Pace, Participating in Medical Research Studies, 285 JAMA 686 (2001).