AMERICAN ACADEMY OF OPHTHALMOLOGY®

ADVISORY OPINION OF THE CODE OF ETHICS

Subject: Research and Innovation in Clinical Practice

Issues Raised: (1) How is it determined what differentiates "research" and "innovation in clinical practice" from "routine clinical practice"?

(2) What are adequate review mechanisms for research and innovative procedures?

(3) What constitutes appropriate informed consent for such procedures?

(4) When participating in research, what are the ophthalmologist's responsibilities?

Applicable Rules: Rule 2. Informed Consent
Rule 3. Research and Innovation
Rule 14. Interrelationships between Ophthalmologists
Rule 17. Confidentiality

Background

The purpose of Rule 3 of the Code of Ethics is to protect patients from being subjected to or potentially affected by inappropriate, or fraudulent research, and/or innovation in clinical practice. This rule advances Principle 2 of the Code of Ethics that "ophthalmological services must be provided with … respect for human dignity …" and Principle 7 that an ophthalmologist must "act in the best interest of the patient." Rule 3 defines research and innovation in clinical practice as activities that are undertaken in circumstances where "insufficient information exists," and therefore procedures are "conducted to provide information on which to base diagnostic, prognostic or therapeutic decisions and/or to improve understanding of pathogenesis …."

Ophthalmologists Dr. S, Dr. J, and Dr. M wish to know the applicability of the Code of Ethics to their conduct.

In the inquiries presented below, these doctors appear to be contemplating activities that may constitute research or innovation in clinical practice. Such activities are proper only when the potential risks to the patient are reasonable in relation to the potential benefits to the patient and the importance of the knowledge that reasonably may be gained.

First Inquiry

Facts — Dr. S, an ophthalmologist and Fellow of the Academy, proposes to perform nonemergency retinal surgery on a few patients using an innovative technique that, to the best of his knowledge, is a novel deviation from traditional techniques. Based on his review of peer-reviewed literature, Dr. S does not know of any clinical research by others on the proposed novel surgical technique or on similar techniques. He desires to perform the innovative procedure because he believes it might prove to be as effective as or more effective than conventional techniques for the type of patients he plans to select, and he hopes to publish his results. Dr. S intends to perform the surgery on a few adult inpatients in a hospital at which he has privileges and also on some patients at a freestanding ambulatory surgery center.

Resolution — Dr. S reasonably believes that the new technique may prove to be more effective for his patient as well as for other patients. Dr. S's desire to publish the results of his research does not vitiate this patient-oriented motivation, but it must not be the primary motivation for undertaking an innovative treatment.

A physician undertaking research or innovation in clinical practice involving human subjects also has an obligation to consider the research literature concerning the proposed procedures. In this case, Dr. S does not know of any reported research, but he should also ask colleagues or comprehensively search the peer reviewed literature for more information. His proposal is clearly for research or innovative clinical practice.

Dr. S is contemplating using a substantially novel procedure that has potentially significant consequences for his patient. Rule 3 may not apply to minor refinements or alterations of prevailing surgical techniques, especially when they pose little or no added risk to the patient. However, the new procedure that he proposes to perform is clearly research or innovation in clinical practice and must therefore be subject to adequate review mechanisms.

If the procedure or the drug is used in several cases or an attempt is made to determine the merits of the drug or procedure by conducting a research project, it is necessary to obtain approval from an Institutional Review Board (IRB) before proceeding. Some hospitals also have surgical review committees, and submission to such a committee may be necessary. Adequate review mechanisms should ensure that the research is competently designed and has some reasonable prospect of producing helpful results. Such mechanisms should also ensure that there is informed consent, that the rights of the research subjects are respected, and that research subjects are treated with the same concern and devotion as other patients. Dr. S intends to conduct some procedures in a hospital. If the new procedure is considered a modification of an earlier operation or a pilot procedure, in an individual case it is usually not necessary to obtain prior approval from the hospital's IRB. Further, in an individual case, if a drug is used for an indication or in a manner other than that for which it was approved and if it is being used in a compassionate sense, then it is also usually not necessary to have prior approval from the IRB.

Dr. S also proposes to perform certain of these procedures in a freestanding ambulatory surgery center. Before undertaking such surgery, his proposed research protocol should be reviewed by an appropriate professional review body, such as a hospital IRB or an independent IRB. Such a review mechanism should include professional surgical review and human-subject (ethical) review. If Dr. S cannot arrange for such review, or if his protocol is not approved by such reviewing bodies, he should not proceed. Repeated application to successive IRBs or similar bodies should be avoided unless the physician has a good faith basis for believing that a different decision will be made and is justified. If a professional review body has approved a course of research on certain types of patients as described above, the IRB is notified when the study is completed, and the IRB issues approval at certain intervals, usually annually.

After securing approval to proceed and after performing several procedures, Dr. S concludes that his innovation has merit. At this point, he may wish to share his findings with his colleagues either through publication or presentation at an appropriate forum (see Rule 14).

Second Inquiry

Facts — Dr. J is an ophthalmologist and a Fellow of the Academy. She has a patient with severe glaucoma who has not responded to conventional treatments, either with drugs or by means of surgery. Dr. J has reason to believe that the patient may respond favorably to a particular drug because she has observed some lessening of intraocular pressure in her patients who happen to be on the medication. However, the labeling and instructions for use of the drug do not include glaucoma, and the drug has possible moderate but not insignificant side effects. Dr. J has asked colleagues, and neither she nor they are aware of any research on use of the drug for glaucoma. In addition, an online computer search reveals no information about the use of the drug for glaucoma. Dr. J proposes to administer the drug to the patient initially in her office, then to prescribe it and periodically review the patient's condition. This is a case of off-label use of an approved medication.

Resolution — Dr. J's case also clearly qualifies as research or an innovation in clinical practice because she too lacks adequate information concerning the safety and therapeutic value of the proposed pharmacological agent.

Like Dr. S, Dr. J is contemplating using a substantially novel procedure, with potentially significant consequences for her patient, and it must therefore be subject to adequate review mechanisms.

Dr. J's case presents special problems, since her patient requires prompt treatment. Formal application to and review by an IRB may not be feasible. Research or innovative therapies should be applied in such an emergency only rarely and where the case has proven or is reasonably expected to be refractory to conventional treatments. However, in such a case, it may be appropriate to proceed with the new therapy after undertaking the degree of independent review by knowledgeable colleague(s) that is feasible under the circumstances (and that is later appropriately documented). If possible, Dr. J should obtain the opinion of a colleague concerning the possible benefits and risks of the therapy. It is significant that Dr. J has a reasoned clinical basis for trying the new drug and that she plans to monitor the patient's response carefully. The provision of Rule 3 requiring adequate review mechanisms is intended to advance, and not obstruct, patient care. It is intended to be flexible and not to mandate one type of review in all circumstances. Accordingly, varying levels of review may be appropriate in light of the seriousness, irreversibility, alternatives, side effects, risks, and other features of the proposed research or innovative therapy.

Rule 2 of the Code of Ethics establishes a general requirement that "the performance of medical or surgical procedures shall be preceded by appropriate informed consent." In addition, Rule 3 states that where research or innovation in clinical practice is contemplated, "appropriate informed consent for these procedures must recognize their special nature and ramifications." Informed consent for participation in research activities is a complex medical and legal concept, which has at least several basic elements.

First, the physician must inform the patient about the proposed treatment, its likely effects on the patient, and the purposes of the research. Legal decisions in the states are split as to how much information must be disclosed. Some require such information as most physicians in like circumstances would disclose, and others require all information that the patient would be likely to regard as significant in deciding whether to participate in the research and undergo the treatment. In addition, federal regulations may also govern informed consent for clinical trials and investigative procedures in certain contexts. Ophthalmologists should provide at least that degree of information required by applicable federal and state law (and they may wish to consult with their legal counsel to ensure that they do so). Apart from exceptional cases where the therapeutic privilege might apply, this will include data on the investigational character, purposes, effects, side effects, alternatives, and appreciable risks of the proposed therapy, including the possibility of no benefit from this treatment option. The method, purpose, and conditions of participation are also defined.

Second, the patient's consent must be based on comprehension; that is, the patient must understand the basic information and engage in a rational decision-making process concerning participation in the research.

Third, the patient must clearly indicate voluntary consent to the treatment proposed. An enthusiastic description of the project, patient reimbursement, and suggestions of major advantages to the patient are examples of incentives that encourage the patient to participate in a research project and that may unfairly influence the informed consent. The patient's consent should be reasonably free of undue or overbearing influences, such as the fear of loss of medical care or benefits if he or she declines to participate in the research. The patient has the right to withdraw from participation in the research activity at any time without consequence.

Substituted consent to treatment on behalf of a patient may be accepted by an ophthalmologist in conformity with law and good medical practice. For example, this may be permissible when the patient is unconscious or lacks the capacity to make an informed decision concerning treatment. In nonemergencies, ordinarily the informed consent of the patient (or a surrogate) for research or innovative clinical practice should be recorded in advance and in writing.

Based on the facts presented, both Dr. S and Dr. J should obtain appropriate informed consent from their patients. The procedure may be streamlined in Dr. J's case in light of the nature of the emergency facing the patient and related circumstances, as long as the patient's interests are always held paramount.

Third Inquiry

Facts: Dr. M sees a number of patients with inherited retinal disorders. He has consulted for a company developing a new gene therapy; based on what he has heard, he is excited about their new potential therapy and owns some of their stock. The company is preparing to initiate a clinical trial and has asked Dr. M to participate. His role will be to screen patients for eligibility, then refer them to the central study site where the surgical procedure will be performed, and follow-up will continue. At the current time, Dr. M has some familiarity with the proposed mechanism of action of the new treatment. Given his relatively limited role in the study, Dr. M would like to know his responsibilities.

Resolution: The proposed clinical trial is clearly research. Although Dr. M will not be performing the actual surgical procedure, his role in screening the patients puts him in an important position of ensuring appropriate informed consent and eligibility, and thus patient safety.

Dr. M should ensure that the study is "approved by appropriate review mechanisms (an Institutional Review Board [IRB]) and must comply with all requirements of the approved study protocol to protect patients from being subjected to or potentially affected by inappropriate or fraudulent research." Even though he may not personally be involved in obtaining IRB approval, he should be certain that the protocol is approved by an appropriate IRB and that the study is being conducted according to the approved protocol.

Rule 3 also states that "in emerging areas of ophthalmic treatment where recognized guidelines do not exist, the ophthalmologist should exercise careful judgment and take appropriate precautions to safeguard patient welfare. The ophthalmologist must demonstrate an understanding of the purpose and goals of the research … ." Therefore, Dr. M should have a clear understanding of the scientific basis of the research, the inclusion and exclusion criteria, and patient safety protections. He should take special care that patients who may have no other treatment options are not entering the study out of desperation and that they understand the possible risks of the study treatment, including further vision loss. As discussed more extensively in the case above, "appropriate informed consent for research and innovative procedures must recognize their special nature and ramifications."

Dr. M also has a responsibility to disclose his relevant financial interests in the company, both to the IRB and to potential study patients: "The ophthalmologist must … recognize and disclose financial and non-financial conflicts of interest." This disclosure ideally will be included in the informed consent form or as directed by the IRB. He should disclose recent and ongoing consulting for the company as well as his stock ownership, and he should fully comply with any IRB recommendations to manage his conflicts of interests. He should ensure that he puts the patients' interests above any actual or perceived conflicts of interest.

Finally, Rule 3 states that "commensurate with the level of his/her involvement, the investigator must accept personal accountability for patient safety and compliance with all legal and IRB-imposed requirements." In this case, Dr. M should personally ensure that the patients he is screening meet all the inclusion and exclusion criteria and that they fully understand the risks and benefits of the study before referring them for enrollment.

Applicable Rules

"*Rule 2. Informed Consent*. The performance of medical or surgical procedures shall be preceded by appropriate informed consent. When obtaining informed consent, pertinent medical facts and recommendations consistent with good medical practice must be presented in understandable terms to the patient or to the person responsible for the patient. Such information should include alternative modes of treatment, the objectives, risks, and possible complications of such a treatment, and the

consequences of no treatment. The operating ophthalmologist must personally confirm with the patient or patient surrogate their (his or her) comprehension of this information."

"*Rule 3.* Research is conducted to provide information on which to base diagnostic, prognostic therapeutic decisions and/or to improve understanding of pathogenesis in circumstances in which insufficient information exists. Research and innovation must be approved by appropriate review mechanisms (Institutional Review and must comply with all requirements of the approved study protocol to protect patients from being subjected to or potentially affected by inappropriate, or fraudulent research. In emerging areas of ophthalmic treatment where recognized guidelines do not exist, the ophthalmologist should exercise careful judgment and take appropriate precautions to safeguard patient welfare. Appropriate informed consent for research and innovative procedures must recognize their special nature and ramifications. The ophthalmologist must demonstrate an understanding of the purpose and goals of the research and recognize and disclose financial and non-financial conflicts of interest.

"*Rule 14. Interrelationships Between Ophthalmologists*. Interrelationships between ophthalmologists must be conducted in a manner that advances the best interests of the patient, including the sharing of relevant information."

"Rule 17. Confidentiality. An ophthalmologist shall respect the confidential physician-patient relationship and safeguard confidential information consistent with the law."

Other References

"*Principle 2. Providing Ophthalmological Services*. Ophthalmological services must be provided with compassion, respect for human dignity, honesty and integrity."

"*Principle 7. An Ophthalmologist's Responsibility*. It is the responsibility of an ophthalmologist to act in the best interest of the patient."

"Principle 8. Professional Integrity in Research. It is the responsibility of the ophthalmologist to maintain integrity in clinical and basic research. Professional relations with industry regarding research should advance the best interests of patients and the profession."

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P.O. Box 7424 / San Francisco, CA 94120 / 415.561.8500