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Innovative Practice: Ethical Guidelines

ABSTRACT: Innovations in medical practice are critical to the advancement of medicine. Good clinicians constantly adapt and modify their clinical approaches in ways they believe will benefit patients. Innovative practice frequently is approached very differently from formal research, which is governed by distinct ethical and regulatory frameworks. Although opinions differ on the distinction between research and innovative practice, the production of generalizable knowledge is one defining characteristic of research. Physicians considering innovative practice must disclose to patients the purpose, benefits, and risks of the proposed treatment, including risks not quantified but plausible. They should attempt an innovative procedure only when familiar with and skilled in its basic components. A clinician should share results, positive or negative, with colleagues and, when feasible, teach successful techniques and procedures to other physicians. Practitioners should be wary of adopting innovative procedures or diagnostic tests on the basis of promotions and marketing when the value of the procedures or tests has not been proved. A practitioner should move an innovative practice into formal research if the innovation represents a significant departure from standard practice, if the innovation carries unknown or potentially significant risks, or if the practitioner's goal is to use data from the innovation to produce generalizable knowledge. If there is any question whether innovative practices should be formalized as research, clinicians should seek advice from the relevant institutional review board.

Overview

In 21st-century medicine, the pace at which innovations are introduced into clinical practice continues to increase. Many innovations differ considerably from previous practices and may or may not have been subjected to formal research protocols. In this context, the boundary between innovative practice and medical research becomes blurred, making it difficult for physicians to distinguish between them and to recognize the ethical issues that are involved.

When innovative practices are introduced, they may become widely accepted based on anecdotal reports of success. As a result, formal research

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may never be done that might show 1) that the innovative practice carries higher risk than other treatments or 2) that it is no more effective than standard treatment. An inappropriate introduction of an innovative practice, circumventing the formal study of the new technique, leaves patients and practitioners without the necessary data for appropriately assessing an innovation's risks and benefits, as well as its long-term effects on health.

In this Committee Opinion, the Committee on Ethics will review efforts to distinguish innovative practice from research, identify ethical concerns raised by innovative practice, and note current obstacles to the conduct of formal research. Recommendations will focus on two questions: 1) When does the clinician have an obligation to subject an innovative practice to formal research? 2) In situations where innovative practice is not regulated as research, what special ethical obligations might the clinician have—to patients, to the community of medical professionals, and to society at large?

Distinguishing Innovative Practice From Research

In clinical practice, physicians aim to benefit their patients by providing the best possible procedures and treatments. The desire to improve currently available practices has given an important impetus to the development of new medical knowledge. The notion of what is best or most appropriate evolves with time, ongoing research, and changing individual and societal values. Good clinicians constantly adapt and modify their clinical approaches in ways they believe will benefit patients. The introduction of such innovative interventions is guided primarily by the judgment of the individual physician, although professional organizations often advise and monitor.

Formal research, however, is highly regulated in the United States. Research protocols involving human participants must be described in detail and submitted to an institutional review board (IRB) for approval. Federal regulations mandate that IRBs approve research protocols in order to ensure adequate disclosure to potential participants, informed consent from participants, appropriate risk–benefit ratio, protection of participants' privacy, and freedom of participants to withdraw from the study at any time.

Innovative practice has elements in common with research including, for example, the desire to

learn and to improve treatment. Yet, innovation in practice frequently is approached very differently from formal research, which is governed by distinct ethical and regulatory frameworks. The federal research regulations as expressed in the “Common Rule” draw a sharp distinction between research, which is regulated, and innovation, which is not, stressing the production of generalizable knowledge—knowledge that can be applied beyond the particular individuals studied—as the defining characteristic of research (1). However, the distinction is somewhat artificial and is not always clearly delineated.

An innovative practice may later become the subject of a formal research protocol, with the results of this research then applied to guide evidence-based practice. In some cases, however, innovative practice that appears to be safe and effective may become accepted practice, even if it has never been subjected to formal research and an evidence base has never been developed to support efficacy and safety. When this happens, patients and practitioners are left without the data they need to make adequately informed decisions.

Background: History and Evolution of Terminology

It often is difficult to draw a clear line between innovative practice and research. The history of research regulation illuminates the effort to clarify the distinction.

The National Commission for the Protection of Human Subjects, established by federal statute in 1975, developed the *Belmont Report* in 1978 to identify the basic ethical principles governing human research (2). In defining *research*, the National Commission first distinguished it from “the practice of accepted therapy.” However, examples proposed to the National Commission led it to recognize that much practice is *experimental* (a term the American College of Obstetricians and Gynecologists' Committee on Ethics interprets as congruent with the term *innovative*), even though it is not formalized as research. Should all such experimental practice be treated as research and governed by the ethical and regulatory guidelines for research? The National Commission decided against taking this position and adopted a narrower definition of research, concluding that research occurs when the clinician or investigator intends the work to result in generalizable knowledge (2).

According to the National Commission, “‘Research’ designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to contribute to generalizable knowledge” rather than being “designed solely to enhance the well-being of an individual patient or client” (2). The fact that activities designed to enhance patient well-being may depart significantly from standard or accepted practice does not of itself make them research. However, the National Commission strongly urged that “radically new procedures” be tested by formal research at an early stage and that medical practice committees insist that new techniques and treatments be submitted to formal hypothesis testing. The National Commission did not, however, define “radically new,” leaving its definition to the judgment of practitioners.

Federal research regulations in effect since 1981 incorporate these concepts to a limited degree, defining *research* as follows: “Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge” (3). The preamble to the regulations as finalized in 1981 explicitly states that the definition is restricted to “generalizable knowledge” because the regulations were not intended to encompass “innovative therapy” (4).

In March 2003, the Lasker Foundation, a charitable trust established to promote advances in medicine, sponsored the invitational “Lasker Forum on Ethical Challenges in Biomedical Research and Practice.” The forum focused on the intersection of research and practice and questioned the artificial separation between “what is called research and therefore requires more regulatory oversight, and what is called ‘care’ and requires little or none” (5). The report on the Lasker Forum proposed that clinical innovation involving a significant departure from standard of care imposes particular moral duties on the practitioner. In the view expressed at the forum, a practitioner who attempts through innovation to benefit an individual patient also is morally obligated to facilitate the development of knowledge useful to other physicians and patients, thus suggesting an obligation to conduct research on the innovative practice.

The Lasker Forum report proposed criteria for identifying the ethical threshold that mandates moving from innovative practice to formal research. In this view, the most important criterion is the degree of departure from standard practice, followed by the

potential for harm to the patient from the innovative practice. Other criteria proposed for consideration are the goal of the clinician investigator, the availability of organizational structures supportive of research, and the presence of commercial interests or conflict of interest (5). These considerations will be discussed more fully after examination of specific ethical concerns related to the introduction of innovative practices.

Ethical Concerns Regarding Innovative Practice

A variety of problems may arise when innovative practices are inappropriately introduced apart from formal research protocols. These problems often have ethical implications related to patient safety, patient autonomy, and the patient’s right to effective therapy:

- Premature adoption of innovative practices without adequate supporting evidence may promote wide acceptance of therapies that are ineffective. Examples of procedures that have been proved ineffective include:
 - Bed rest or home uterine activity monitoring for prevention of prematurity (6, 7)
 - Bone marrow transplant for breast cancer (8)
 - Diethylstilbestrol or paternal antigen sensitization for the prevention of recurrent miscarriage

From an ethical perspective, recommending procedures that are not effective for the intended purpose is misleading to patients, incurs increased unnecessary costs both financial and personal, and violates the patient’s autonomy-based right to consent to therapy after accurate disclosure. In addition, an unproven innovative treatment may carry additional risks or morbidity in comparison with standard treatment, as in the case of bone marrow transplant for breast cancer.

- Premature adoption of innovative practices without formal scientific testing may compromise the ability to determine effectiveness, weigh risk against benefit, compare the practice with other procedures, or develop alternative approaches. When results of an innovative practice are publicized without adequate testing, it may become increasingly difficult to recruit participants for a clinical trial, particularly one that

involves randomization. Such may have been the case when techniques for maternal–fetal surgery, electronic fetal monitoring, and laparoscopic hysterectomy were first introduced as innovative and only later systematically studied.

When innovative practices are widely adopted without formal research testing, an incremental risk over standard practice may not be recognized, and relative effectiveness, safety, and risk–benefit ratio may never be determined. Such a situation may make it difficult or impossible for physicians to know if they are fulfilling their obligation to provide safe and efficacious treatment to patients (9).

- Long-term safety concerns may result when innovative practices are widely adopted as standard practice without adequate scientific testing. Examples in which careful, continued study after a technique’s introduction demonstrated small but potentially important risks include:
 - Limb reductions associated with early chorionic villus sampling (10, 11)
 - Sex chromosome abnormalities associated with intracytoplasmic sperm injection used in assisted reproductive technology (ART) (12, 13)

Although innovations in obstetrics and ART offer important benefits to prospective parents, they also may carry long-term risks that are not recognized unless formal research is carried out. Because of their eagerness to become parents, infertile couples may be willing to overlook risks involved in the use of ART. It is the responsibility of practitioners to carry out the studies that are needed to ensure that patients are offered effective and safe procedures. Appropriately, many ART centers and practitioners have participated in the ongoing registries and collaborations needed for this research.

Research Barriers to Be Overcome

Medicine cannot advance without innovation. Recent examples of highly valuable innovations include new efficient laparoscopic components that may improve visualization and new laparoscopic procedures, such as laparoscopic retroperitoneal lymph node dissection, that may speed or otherwise facilitate closed surgical procedures. This could

reduce the need for open procedures that may be associated with longer or more complicated post-operative recovery. At times, it may be appropriate to introduce an innovative technique apart from a formal research protocol. However, both the National Commission for the Protection of Human Subjects and the National Bioethics Advisory Commission stipulate that innovations in clinical practice should be studied under a research protocol as soon as it is appropriate to study them systematically (2, 14).

A number of barriers to the conduct of formal research exist, with some of them specific to particular subspecialties:

1. *Lack of supportive structures.* In many clinical situations, the structures to facilitate research, such as administrative support and an IRB, may be lacking. Even if a particular innovation is ripe for formalization as research, research may be difficult to accomplish without the necessary supportive structures. Bureaucratic obstacles may be cited as an excuse for not conducting research; however, such obstacles do not provide valid reasons for failure to conduct appropriate research under ethical guidelines. Rather, clinicians ought to advocate changes in policy and collaborative efforts that will provide necessary support for research.
2. *Absence of financial reimbursement.* In addition to the lack of supportive structures, financial pressures may inhibit the pursuit of appropriate research. Insurance coverage may be available for treatment that is described as innovative therapy, but not for formal research. This reimbursement situation played a role in the promotion of the untested procedure of bone marrow transplant for breast cancer, for example (15).
3. *Lack of oversight for surgical innovation and research.* The absence of regulations that specifically govern surgical innovation and research has frequently been noted. Proposals have been suggested to ensure oversight of surgical innovation when formal research is not planned, for example, submission of a written plan to the department head for referral to an ad hoc committee. This committee would provide peer review of “medical and scientific plausibility, the adequacy of patient safeguards, and the legitimacy of [the] clinical rationale” (16).
4. *Prohibition of federal funding for ART and embryo research.* Because of the statutory pro-

hibition of federal funding for in vitro fertilization and early embryo research, most research on ART is privately funded and is conducted within the practice of clinical infertility treatment. Hence, it may be difficult to obtain funding for some types of research on ART, particularly basic research.

Clinical Decisions on Moving From Innovation to Research

The field of medicine could neither progress nor be practiced without innovative therapy. Given the importance of formal research for evidence-based medicine, however, the medical community must determine when an innovative practice should be subjected to formal research. If there is any question whether an innovation should be formalized as research, it is advisable that the protocol be submitted to an IRB for review. From an ethical standpoint, the following considerations offer guidance and criteria to the clinician for a decision to move from innovation to formal research (5):

- *The degree of departure from standard practice.* As recommended by the Lasker Forum, if innovation constitutes a significant departure from standard practice, the innovative procedure should quickly be subjected to a formal research protocol. Significant departure from standard practice occurs, for example, in most maternal–fetal surgery and many new ART techniques. However, minor modifications, such as a change in a step during surgery, a different kind of suture, or a new instrument similar to an old one, clearly do not require formalization as research.
- *The potential for harm to the patient.* When an innovation carries risks that are unknown or that may be significant in proportion to expected benefits, its safety should be assessed through a formal research protocol with the oversight of an IRB, one of whose primary purposes is to protect the welfare of participants. In addition, formal research is essential in order to identify long-term risks that may affect the safety of large numbers of patients in the future.
- *The intent of the physician.* The original intent in an innovation may be solely the welfare of the individual patient. If the physician intends, however, to eventually use results of a trial of the

innovation to produce generalizable knowledge, the trial should be formalized in a research protocol. Valid generalizable knowledge ordinarily requires randomized clinical trials rather than reliance on case series and unplanned observations (17).

Special Ethical Requirements for Innovative Practice

Duties to Patients

When patients become participants in a formal research project, they become protected by the federal regulations for research involving human participants. Even when a particular project does not strictly fall under federal regulations because it does not involve federal funding or oversight by the U.S. Food and Drug Administration, most institutions still comply with federal standards. Also, reputable journals require compliance with ethical guidelines as a condition for publication. Access to results of clinical trials, even trials with negative outcomes, is protected by the clinical trials registration process (18–20). Many journals now require evidence that trials were previously registered before accepting reports for consideration for publication.

The same protections do not hold for a patient who is offered innovative therapy. Although the intent of such innovation is to provide the most beneficial treatment possible for the patient, the patient may not realize that a therapy is new or experimental. The practitioner has the obligation to disclose information that would be material to the patient's decision, and in many cases, a patient would want to know that a proposed therapy is innovative. As with all therapies, the practitioner has the obligation to disclose the purpose, benefits, and risks of the proposed innovative treatment, including not quantified but plausible risks. In addition, the practitioner has a particular obligation to protect the patient from potential harms that are not proportionate to expected benefits, a role that the IRB assumes with respect to formal research protocols. To minimize risk, physicians also need to consider their own knowledge and skill levels and should attempt an innovative procedure only when familiar with and skilled in its basic components.

Patient protection requires transparent communication. In the words of the Lasker Forum report, “Where innovation is clearly present, the require-

ments for disclosure are likely to become more pressing” (5). It may be important to the patient to know how often this procedure has been done, what this particular physician’s experience with the procedure is, and what is known and unknown about possible adverse events and long-term sequelae. Care should be taken that a patient is not unduly influenced to consent to an innovative procedure solely out of deference to her physician. When the advantages and disadvantages of a truly new approach are explained to the patient, the assistance of an experienced third-party communicator, such as a patient representative or social worker, may be helpful (5). Particular care is needed when discussing proposed treatments with vulnerable or possibly desperate patients because they may be eager to pursue innovative but unproven procedures or treatments.

Duties to the Profession and to Society

Innovative practice, unlike research, is not directed specifically toward the production of generalized knowledge. Yet, it is expected that innovation would lead to the improvement of practice in general, not just the practice of an individual physician. This expectation imposes two duties on the physician: 1) to structure the process of innovation so as to learn from it, even if it is not as successful as hoped, and 2) to share what is learned with the medical community as a whole and, where appropriate, with society. A clinician should share results, positive or negative, with colleagues and, when feasible, cooperate in teaching successful techniques and procedures to other physicians.

Current focus on clinical trials, especially randomized clinical trials, suggests that they ordinarily provide the best opportunity for unbiased learning within the practice of medicine. Consequently, innovative practice should move toward clinical trials whenever possible in order to provide evidence-based knowledge to the medical community for the welfare of patients.

Practitioners need to be careful not to adopt innovative procedures or diagnostic tests on the basis of promotional and marketing campaigns when the value of such procedures and tests has not yet been proved. For example, serum-based screening tests for ovarian cancer have been promoted even though more research is needed to determine whether they are effective (21, 22). Similar cautions apply to off-label and unproven uses of pharmaceuticals that may be suggested to physicians. In all

cases, physicians should rely on documented evidence to guide clinical practice.

Summary

The introduction of innovative practices and techniques is essential to medical progress. Ordinarily, however, innovations should be subjected to systematic formal research as soon as feasible:

- In the absence of formal research, innovative practices may become widely accepted without adequate data for assessing risks and benefits.
- Without an adequate evidence base, practitioners cannot determine whether an innovative technique is the most safe and effective method for treating a patient.
- Without adequate data on the risks and benefits of new treatments, patients are unable to provide a true informed consent.

A practitioner should move an innovative practice into formal research when one of these criteria is satisfied:

- The innovation represents a significant departure from standard practice.
- The innovation carries risks that are unknown or that may be significant in proportion to expected benefits.
- The introduction of the innovation is expected to result in generalizable knowledge, which depends on results of formal clinical trials.

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