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Review Article

Professionally responsible experimentation in obstetrics and gynecology

Frank A Chervenak, Laurence B Mccullough

Department of Obstetrics and Gynecology, Weill Medical College of Cornell University, New York, USA

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Abstract: Professionally responsible experimentation is an essential component of the specialty of Obstetrics and Gynecology. In this paper we provide and ethical framework to guide such experimentation. We first define "experiment" and the two forms of experimentation in medicine, "innovation" and "research". We describe the checkered history of experimentation in medicine, to which professionally responsible experimentation in Obstetrics and Gynecology is designed as an antidote. We then set out an ethical framework based on three ethical principles (beneficence, respect for autonomy, and healthcare justice), the concept of medically reasonable, and the professional virtue of integrity. We then apply this framework to research and planned innovation in Obstetrics and Gynecology. Planned innovation should be prospectively reviewed and approved for its scientific, clinical, and ethical justification and for its informed consent process. It should be made clear to the patient that the proposed innovation has been peer-reviewed and approved and therefore should be considered an ethically permissible experiment. It should also be made clear that her refusal to authorize the innovation is not harmful to herself, the fetus, and future child. Research must be prospectively reviewed and approved by the obstetrician-gynecologist's Institutional Review Board for its scientific, clinical, and ethical justification and for its informed consent process. Professionally responsible innovation will bring innovation up to the standards of professionally responsible clinical research and ensure that the professionally responsible transition from innovation to clinical research.

Keywords: Ethics, experimentation, innovation, professionalism, research

Introduction

In the decades since the end of World War II in 1945, ethics has become an essential component of experimentation in the development of medicine and the specialty of Obstetrics and Gynecology. The choice of "has become" is deliberate, because the history of medical experimentation is replete with ethically unacceptable experimentation and ethically questionable experimentation, as well as ethically acceptable experimentation. Keeping this checkered history very much in mind, in this paper we provide an account of professionally responsible experimentation in Obstetrics and Gynecology. First, we define experimentation and its relationship to both innovation and research. We then provide a concise review of the checkered history of medical experimentation and the ethical challenges that this history has created. We next introduce an ethical framework, based on professional ethics in Obstetrics and Gynecology, for experimentation in Obstetrics and Gynecology and identify its implications for professionally responsible experimentation in Obstetrics and Gynecology.

Experiment, innovation, research

Clinical management is medically reasonable when in deliberative (evidence-based, rigorous, transparent, and accountable) clinical judgment it is technically feasible, the outcome of clinical management is expected to be clinically beneficial, and can be reliably predicted to occur [1]. For example, cesarean delivery for well-documented, intrapartum complete placenta previa is reliably predicted in deliberative clinical judgment to be life-saving for both the pregnant and fetal patients. Cesarean delivery for this intrapartum complication is therefore medically reasonable. Indeed, cesarean delivery is the only professionally responsible

way to manage this life-threatening complication.

Clinical management becomes an experiment when in deliberative clinical judgment it is technically feasible but its outcome cannot be reliably predicted to be clinically beneficial [1]. For example, the first time that fetal surgery was performed for sacrococcygeal teratoma to benefit a fetal patient, the procedure was an experiment. In general, the first time that a procedure is used or a medication given for a non-indicated use, clinical management becomes an experiment. An experiment can be undertaken with the goal of producing clinical benefit for an individual patient. This is called innovation [1]. The first surgery for sacrococcygeal teratoma was innovation. An experiment can also be undertaken with a group of patients with the goal of producing generalizable knowledge that can then be used to improve patient care in the future. This is called research [1]. A study in a series of patients of the toxicity and safety of a new anticancer drug that was promising in animal models would be research, Phase I research, to be precise.

It is very important not to equate experimentation with research. All research involves experimentation but not all experimentation involves research; some experimentation is innovation.

A brief account of the checkered history of experimentation

The history of experimentation in medicine is not one of uninterrupted scientific, ethical, and clinical excellence. Quite the contrary. Physicians have for centuries performed experiments on their patients, their family members, and themselves (autoexperimentation) that were poorly designed, executed, and interpreted and sometimes motivated by self-interest. For example, at the Royal Infirmary of Edinburgh in the eighteenth century young, ambitious physicians would declare patients incurable, sometimes without first providing the usual treatment for the patient's condition, in order to perform experiments with a medication that the physician had compounded in secret. This poorly designed and executed experimentation was motivated by self-interest in winning a name for oneself rapidly as a leading physician and thus build one's private practices [2].

This long and disturbing history culminated in the catastrophes of medical experimentation by physicians in Nazi Germany and Imperial Japan during World War II. Some of the Nazi physicians were tried and executed [3]. The Japanese physicians were allowed to return to academia and practice, even though they committed such acts as testing biological weapons on unsuspecting populations in occupied China [4].

The Nuremberg Medical War Crimes Tribunal of the Nazi physicians created the now-famous Nuremberg Code, which required scientifically valid experimentation and consent of subjects [3]. In the post-war period in the United States, these scientific and ethical standards, which had been promulgated by Americans at the Tribunal, were ignored. The result was preventable scientific and ethical catastrophes, such as the Tuskegee Syphilis experiment. This project, funded by the U.S. Public Health Service, had started in the 1930s but continued after the war and after penicillin was accepted as the treatment of choice in 1947. The study should have been stopped at that time, emphatically given the requirements of the Nuremberg Code. It was not. Indeed, many subjects were not informed about this new treatment. It was not until 1972 that the study was exposed in the lay press and Congressional hearings and finally stopped by the U.S. Public Health Service [5]. In a now-famous (but initially ignored) article published in the *New England Journal of Medicine*, Henry Beecher (1904-1976) described more than 20 studies that were conducted but were impermissible under the requirements of the Nuremberg Code [6]. The exposure of this scientifically and ethically unacceptable experimentation contributed to the current system of prospective review and approval of all human subjects research by an Institutional Review Board (IRBs) [7].

A definition of research appears in the section of the Code of Federal Regulations that governs human subjects research in the United States. In 45 CFR 46 (the new version of which takes effect January NN, 2018), sometimes also known as the "Common Rule", research is defined: "*Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge". (45

CFR 66.102(d)) 45 CFR 46 requires prospective review and approval of human subjects research for its scientific, clinical, and ethical quality, including the informed consent process. (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html, accessed October 16, 2017).

Innovation, by definition, is performed in a single patient, which, scientifically, does not permit creation of generalizable knowledge. This means that most IRBs do not consider the prospective review and approval of innovation to come under their jurisdiction. Some innovation is spontaneous, e.g., alteration of standard surgical approach for a hysterectomy because of unexpected abnormal anatomy that preoperative imaging did not detect. But much innovation is planned, such as in utero repair of fetal sacrococcygeal teratoma. Because IRBs did not have jurisdiction, both unplanned and planned innovation were self-regulated experimentation and this was accepted clinical practice for many years. This history changed in 2008, when the Society of University Surgeons adopted the position that all planned surgical innovation should be subject to prospective review and approval of its scientific, clinical, and ethical quality and for an informed consent process that makes it clear to the patient that the proposed innovation is an experiment and therefore not accepted clinical practice, i.e., is not medically reasonable clinical management. This review should be conducted by a departmental committee tasked by the chairman with such prospective review and approval, which will mean that the experiment is scientifically, clinically, and ethically justified [8].

Ethical framework: professional ethics in obstetrics and gynecology

Both 45 CFR 46 and the proposal from the Society of University Surgeons appeal to ethical concepts but these concepts are not stated explicitly, which would allow deployment of them in a framework that can be reliably applied to both innovation and research. We turn next to the task of clearly stating the components of the required ethical framework.

An ethical framework comprises clearly stated, clinically applicable concepts. The implications of these concepts are then used to make judgments about behavior, classifying it as either ethically obligatory (required to do), ethically impermissible (required not to do), or ethically permissible (may or may not do). The following ethical concepts are pertinent to ethical reasoning about innovation and research and are based on professional ethics in Obstetrics and Gynecology [1]. The ethical framework for innovation and research appeals to three ethical principles and one professional virtue.

Ethical principles provide general guides to behavior. These guides create what are known in ethical reasoning as *prima facie* ethical obligations: the obligation should be fulfilled unless in ethical reasoning it can be shown that another obligation should take precedence. The practical effect is that the implications of all pertinent ethical principles should be identified and their differences, if any, reconciled by giving reasons for their priority in specific clinical circumstances [1].

The ethical principle of beneficence creates the *prima facie* ethical obligation to provide clinical management that in deliberative clinical judgment is technically feasible and is reliably expected to result in net clinical benefit for the patient. The strength of beneficence-based ethical obligations is a direct function of the level of evidence that the expected outcome will occur. A rudimentary form of the ethical principle of beneficence appears in the Hippocratic Oath and other texts in the Hippocratic Corpus. However, what is probably the first use of “beneficence” with the meaning above comes much later, in Thomas Percival’s (1740-1804), *Medical Ethics* (1804) [9].

The concept of medically reasonable alternative is beneficence-based. This concept applies when two conditions are met: a form of clinical management is technically feasible and that form of clinical management is reliably expected to result in net clinical benefit for the patient. There is no ethical obligation to offer to a patient a form of clinical management that is not technically feasible, because there is no ethical obligation to attempt the impossible.

The ethical principle of respect for autonomy creates the *prima facie* ethical obligation to empower the patient with information that is sufficient to form the informational basis of the patient’s decision to either authorize or refuse to authorize clinical management that has been

offered or recommended [1]. The patient should be provided an amount of information adequate for her to understand the nature of her condition, its outcomes with and without clinical management, the medically reasonable alternatives for the clinical management of her condition, and the clinical benefits and risks of each medically reasonable alternative. It is ethically obligatory to recommend clinical management in two clinical circumstances: there is only one medically reasonable alternative or, of two or more medically reasonable alternatives, deliberative clinical judgment supports one as clinically superior. The patient's decision-making process should be voluntary, i.e., free from internal or external controlling influences. Making recommendations when justified is meant to influence the patient's decision making. However, such influence is not a *controlling* influence; the patient remains free to refuse to authorize what has been offered or recommended.

The ethical principle of justice creates the *prima facie* ethical obligation to treat a population of patients fairly. The key to the clinical application of this ethical principle is how to specify "fairly", so that the ethical principle of justice provides practical clinical guidance. The specification comes in the form of the concept of healthcare justice: every patient in a population defined by the patient's condition (e.g., stage I cervical cancer or premature delivery at 24 weeks) should receive clinical management that is medically reasonable [1].

The professional virtue of integrity creates the *prima facie* ethical obligation to provide clinical management that meets standards of intellectual and moral excellence [1]. Intellectual excellence is achieved by ensuring that deliberative clinical judgment is based on the best available evidence, especially as evidence relates to patient safety and quality. Moral excellence is achieved by putting the priority consistently on protecting and promoting the patient's health-related interests and keeping individual and group self-interest systematically secondary.

Clinical application of the ethical framework

General considerations

The ethical principle of respect for autonomy requires the Obstetrician-Gynecologist to make clear in the informed consent process that neither innovative clinical management nor investigational clinical management (research) is clinically acceptable practice, because neither has yet to be established as medically reasonable. To accomplish this goal, the Obstetrician-Gynecologist should explain that innovation or research (depending on which is being offered) is an experiment, because its outcomes cannot be reliably predicted. The obstetrician-gynecologist should take the time needed to ensure that the patient grasps two important points: the distinction between an experiment and clinically accepted practice; and the concept that a prospectively reviewed and approved experiment is ethically permissible.

In achieving this goal of the informed consent process, it is ethically impermissible to use words or phrases such as "treatment" or "therapy" alone or combined with "innovative" or "investigational", because doing so risks deceiving the patient by creating a false expectation that she can expect an outcome that is clinically beneficial. The ethical principle of respect for autonomy is incompatible with deception. Precision of thought and speech requires the Obstetrician-Gynecologist to be clear. This goal is achieved by using "innovation" or "research" combined with "clinical intervention". Achieving precision of thought and speech in the informed consent process is essential to ensure that the patient grasps the distinction between an experiment and clinically accepted practice.

Innovation

We endorse the proposal of the Society of University Surgeons that all planned innovation should undergo prospective review and approval in a peer-review process [8]. If the IRB declines jurisdiction, a departmental committee should be created to provide this oversight. The authors have elsewhere provided criteria for the initiation and evaluation of proposed innovation [1].

The following ethical considerations should guide the team proposing innovation in writing their protocol and informed consent form and the review committee in reaching a judgment that the proposed innovation is ethically permissible.

The ethical justification for innovation appeals first to the professional virtue of integrity, which requires that there be a scientific and clinical basis for the belief that the experiment is well designed, clinically significant, and has the possibility of succeeding. The ethical principle of beneficence requires that the estimated risk/benefit assessment supports the hypothesis that the clinical risks of the innovation will be outweighed by its clinical benefits. In obstetric innovation, this clinical ethical judgment must be based a thorough account of the clinical benefits and risks to the pregnant, fetal, and neonatal patients in the protocol and informed consent process.

The ethical principle respect for patient for patient autonomy requires that the informed consent process and the informed consent document describe the procedure in lay terms as well as known and possible clinical benefits and risks. The patient should be informed that the proposed innovation:

• Has been peer-reviewed and judged to be a scientifically and clinically justified experiment.

• Is an experiment and therefore not currently a medically reasonable alternative in the sense that its outcome cannot be reliably predicted to be clinically beneficial.

• Is an ethically permissible experiment.

The patient should also be informed that, because the innovation is an experiment, she is not required to authorize it. This is an especially important consideration in obstetric innovation because some pregnant women appear to be willing to authorize whatever is needed for fetal benefit. They need to understand that there should no expectation of fetal benefit. They also need to understand that refusing to authorize an innovative intervention does not harm the fetus and future child.

The ethical principle of healthcare justice requires that patient selection for offering an innovation should be not be based on such clinically irrelevant factors as race, religion, and, especially, source of payment. Selection should be based solely on clinical inclusion and exclusion criteria that are clearly stated in the approved protocol.

The requirement of the professional virtue of integrity that that planned innovation should be well designed is essential for making the transition from innovation to research [1]. Well-designed innovation should be understood as pre-research, which means that its outcomes can be reported as preliminary data in the research protocol.

Research

The professional virtue of integrity requires that all clinical investigators obtain approval for proposed research from their IRB. The protocol should be scientifically and clinically excellent and meet criteria for either early phase or randomized clinical trials [1]. (AJOB) The ethical principle of beneficence requires an evidence-based judgment that the risk/benefit ratio is favorable.

The ethical principle of respect for autonomy requires that the informed consent process and informed consent form meet all of the requirements of 45 CFR 46, especially stating clearly that the patient is being asked to participate in research and that she is not ethically obligated to consent, which is especially important in obstetric research. The ethical principle of healthcare justice requires that the recruitment process should not be biased by clinically irrelevant factors, especially race, socioeconomic status, and source of payment. This requirement also contributes to enrolling research population that is as representative as possible of the larger patient population that the research is designed to benefit in the future.

Conclusion

The current scientific, clinical, and ethical requirements for clinical research serve as a powerful corrective to the checkered history that preceded the creation and routine implementation of these requirements. Planned innovation in the absence of the requirements we have elucidated above offers no such protection to patients. The past practice of planned innovation without prospective review and approval should therefore be consigned to the past.

Obstetrician-gynecologists should no longer have confidence that planned innovation with-

out such review is scientifically, clinically, and ethically justified and is therefore an ethically permissible experiment. Nor should they have confidence that planned innovation without review is pre-research that supports a professionally responsible transition from innovation to clinical research. Prospective review and approval of planned innovation should therefore be considered the professionally responsible approach, to bring innovation up to the standards of professionally responsible clinical research and to ensure that the transition from innovation to clinical research is also professional responsible.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Frank A Chervenak, Department of Obstetrics and Gynecology, Weill Medical College of Cornell University, 525 East 68th St, Room J-130, New York 10065, USA. Tel: 212 746 3012; Fax: 212 746 8363; E-mail: fac2001@med.cornell.edu

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