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Ethics and Clinical Research

Ruth Macklin



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INTRODUCTION

We often forget that one of the factors which led to the development of bioethics was the need and the desire to prevent abuse in medical research with humans. Apart from experiments conducted on Jewish prisoners by the Nazis, which obviously lie outside the realm of any ethical considerations, during the second half of the 20th century there have been a number of episodes involving research with humans which have gone down in history as examples of practices which did not comply with the most basic ethical requirements. As an initial response to such problems, the Nuremberg Code and the Helsinki Declaration established a set of principles and guidelines designed to set out the basic obligations of researchers with regard to the subjects used in the performance of the research. As a result of these declarations of principles and the establishment of ethics committees to evaluate clinical research protocols, research involving human subjects is no longer a free for all.

Despite this, many questions remain, and in the face of growing scientific and technical complexity, the existing ethical criteria are just that: criteria which cannot be applied automatically. It was to address these questions and concerns, faced by all responsible researchers, that the philosopher Ruth Mack-lin, one of the world's leading experts on bioethics, visited Barcelona. She was invited to deliver the third cycle of the "Josep Egozcue Lectures" organized each year by the Víctor Grífols i Lucas Foundation. The text of her lectures is reproduced on the pages which follow.

In her introductory lecture, Ruth Macklin raised a question which may seem superfluous at this stage: Why is ethics important in research? It may seem superfluous until we remember that researchers confront a series of complex challenges to maintain the integrity and coherence of the three principles of bioethics set out in the prestigious Belmont Report: respect for people's autonomy, beneficence and justice. In the light of these principles, there are certain issues for which a fully satisfactory answer has yet to be found in practice. To start with, the controversial notion of "informed consent" demands an ongoing evaluation to assess whether the information provided to the patient really is comprehensive and adapted to the patient's needs and interests, and whether the voluntary nature of subjects' participation in clinical trials is really ensured. We also need to ask what benefit the patient does and should receive from inclusion in the trial, and whether this potential benefit complies with the basic principles of distributive justice which state that nobody should be excluded from the right to health protection. The fact that the researcher who proposes the trial and the doctor caring for the patient are almost always the same person may confuse the patient, leading him to believe that he will benefit directly from inclusion in the trial, or limiting his freedom to act without pressure of any sort. Macklin placed great emphasis on this issue, which is not usually questioned or even discussed when considering the ethics of research with human beings.

Her second lecture tackled the question of ethics in multinational research. It is well known that multinational clinical trials are becoming increasingly common, that they are performed in countries with different cultural traditions and ethical criteria, and also that the pharmaceutical industry and trial sponsors in industrial countries often perform some or all of their research in developing countries. The particular vulnerability of subjects in these countries means that they may fall victim to exploitation. Limited education, poverty, ancestral customs and prejudice may all open the door to unscrupulous behaviour and double standards in applying ethical guidelines in other countries. At the same time, we need to give serious consideration to what benefits are due to subjects who participate in trials, both during the course of research and once the trial has finished, and to the question of where responsibility for enforcing and complying with this obligation lies. Under the pretext of ethical relativism, or in the name of cultural diversity, ethical requirements are sometimes relaxed when trials take place in countries whose traditions are different to our own. But Macklin argued forcefully against using the excuse of "ethical imperialism" to circumvent standards which should be applied universally.

In her final lecture, Macklin discussed what she calls the "grey areas" of research. The fact is that more and more research is conducted, and that those

studying public health issues, such as epidemics, are interested not just in treating and controlling the epidemic itself, but also in researching various aspects of it. If this sort of activity is research, then what ethical requirements should apply to it? The same question can also be raised with respect to "model treatments": who determines whether these constitute research, and how should this be done? Or programmes designed to improve the quality of hospital care. How should these be conducted without jeopardizing people's privacy and the respect they are due? Is it always necessary to submit the "research" proposal for the approval of an ethics committee? Although this issue has received little attention in bioethics, it is one which concerns health professionals.

With the publication of these lectures, the Foundation aims to provide the basis for an open-ended debate, because both the development of medical research and discussion of the meaning and scope of ethical principles and human rights raise challenges which can no longer be ignored. As Ruth Macklin has argued, health professionals must demonstrate their commitment to ethical principles, because only if they do this can they generate the trust between patients, doctors and researchers which is so essential.

Victoria Camps President

Research Ethics Today: What issues confront researchers and ethics committees? The answer to the question, "Why is ethics important in research?" may be obvious, but it is worth elaborating a little. First of all, human subjects of research may be harmed. Since most medical research involving humans is carried out by medical doctors, we may recall the ancient mandate to physicians to "do no harm". In the research setting, not all risks can be predicted in advance, precisely because the activity itself involves novel aspects. And because of the novelty, the harms of a research study may end up outweighing any potential benefits. In order to minimize the possibility of harm to subjects, various protections and safeguards must be put in place.

But harm is not the only ethical category relevant to research. Human subjects may be *wronged*, even if they are not harmed. To treat people as a "mere means" or "instrument" to benefit others wrongs them by violating a cardinal ethical principle¹. An obvious example in the context of research is experimenting on people without their knowledge or consent. Other examples of wrongs to persons that may not actually cause harm is lying to them, even when the lie is not discovered; failure to keep promises made in good faith; and deception even if not known or discovered by the person who is deceived.

Past abuses in human subjects research

Research involving human beings has a long history, some of it honorable, and some distinctly less so. One of the darkest episodes in all of human history was the era in Nazi Germany, where otherwise highly reputable doctors conducted cruel experiments on captive populations, including young children.² But the Nazi experiments are off the scale of any measure that would

seek to determine ethical acceptability of research. For one thing, the intended outcome of very many experiments was death of the victims. With the exception of the cruelly harmful experiments on twins and other children with deformities of some type, conducted by Josef Mengele, most studies on adults were aimed at learning something that might help the German war effort. Experimental subjects were exposed to freezing water to see how long they could survive in these conditions, and whether they could be revived after long exposure. The aim was to see whether German military personnel could survive and if so, for how long, if they landed in the frigid North Sea in the midst of combat. Other victims were subjected to low atmospheric pressure to simulate the high-altitude conditions German pilots would experience in case pressurized cabins failed to operate correctly. In these and other horrific experiments, the subjects either died as a direct result, and those that did not were killed afterwards. Following the war, at the Nuremberg Doctors' Trial, sixteen German physicians were found guilty of war crimes or crimes against humanity, and several were executed.

A positive outcome of the Nuremberg Trial was the Nuremberg Code, issued in 1947, the first international document that dealt with ethics in the conduct of research³. The first item in the code states: "The voluntary consent of the human subject is absolutely essential". Curiously, however, the Nuremberg Code had little or no influence on physicians conducting research. For anyone who even knew it existed, the Code was seen as irrelevant to what physicians in Europe and North America would do if they conducted research on human beings. It was viewed, plain and simple, as something that pertained to Nazi doctors.

The Japanese government also conducted experiments related to the war effort in World War II. Their experiments, on Chinese and Russian prisoners of war in Manchuria, were mostly on chemical and biological agents designed to serve as weapons. In germ warfare experiments carried out by the Japa-

^{1.} The classic statement of this principle is the "categorical imperative" formulated by the German philosopher, Immanuel Kant, in his main work on ethics, *The Groundwork of the Metaphysics of Morals* (published in 1785): "So act as to treat humanity, whether in your own person or in another, always as an end, and never merely as a means."

^{2.} References describing the experiments conducted by the Nazis are too numerous to cite. For two books that address the Nazi experiments from the perspective of bioethics, see George J.

Annas and Michael A. Grodin (eds.), *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation* (New York: Oxford University Press, 1992), and Arthur L. Caplan (ed.), *When Medicine Went Mad* (Totowa, NJ: Humana Press, 1992.

^{3.} See Annas and Grodin, ibid.

nese, thousands died from anthrax, bubonic plague, cholera, and other diseases. After the war, a deal was struck between authorities in the United States and the Japanese doctor in charge of the experiments. The deal was for the germ warfare data in exchange for immunity from war-crimes prosecution. The United States apparently believed that having those data was more important than conducting a war crimes trial against the Japanese experimenters⁴.

The United States also conducted war-related research, but it was during the Cold War era and the experiments were all related to human radiation in one form or another⁵. Cold war activities included mining uranium, manufacturing atomic bombs, using nuclear powered submarines, and other activities using radioactive materials. In one experiment on humans, cancer patients were subjected to total body irradiation. The justification was that there were no effective anti-cancer treatments and the cancer in these patients would worsen until they died. So it was seen as ethically justifiable to do high-risk research on patients who would die soon anyway.

Another experiment injected small doses of plutonium into hospitalized patients to study biodistribution of radioactive material in the human body. Interestingly, the patients were told it was a medical experiment and asked to give their consent. However, they were not informed that what was being injected was a radioactive substance. Researchers maintained that the doses were too small to do any harm. Later, when a government investigation was conducted, the researchers tried to cover up their experiments. Perhaps surprisingly, the cover-up got them into more trouble than the experiments themselves. That was because they lied to government officials, which can lead to a worse punishments than what might have been imposed for the initial wrongdoing. In still another study, conducted at a school for mentally handicapped boys, the children were invited to join a "science club," and were fed cereal with tracer doses of radioactive isotopes. The purpose was to track the body's absorption of calcium and iron. Neither the children nor their parents were asked to provide informed consent for these studies. Researchers maintained that in both the plutonium and radioactive isotope studies, the doses were too small to cause harm to the subjects. An journalistic exposé of these and other radiation experiments led to President Bill Clinton's appointment in the mid-1990s of a special commission, the Advisory Committee on Human Radiation Experiments, charged with investigating those experiments conducted decades earlier, and making recommendations about any remedies owed to the subjects or their families, as well as steps to prevent any such occurrences in the future.

Three episodes that occurred in the United States in the mid-twentieth century are well known examples of unethical conduct in research. The most infamous of these was the Tuskegee syphilis study⁶. This was an observational study, not one in which any substances were injected into people. However, it shows that even an observational study can be seriously unethical if it fails to provide beneficial treatment that exists outside the study. The subjects were poor black men in the southern part of the United States. Most were illiterate, none were told they were subjects in research or why they were being given medical examinations. All of the men had been diagnosed with syphilis, and none were given treatment even after penicillin was discovered to be an effective therapy for the disease. The purpose was to study closely the natural history of untreated syphilis. When the study began in 1932, there was no effective treatment for syphilis. But the study continued until 1972, long after penicillin was widely available. The study was carried out by the US public health service. It wasn't until 1997 that President Bill Clinton issued an apology on behalf of the people of the United States to eight surviving men and the families of those who had died during and after the syphilis study.

Sheldon H. Harris, Japanese Medical Atrocities in World War II. A paper read at the international citizens forum on war crimes & redress, Tokyo, Japan, December 11, 1999. Available at http://www.vcn.bc.ca/alpha/speech/Harris.htm. Accessed 2 November 2009.

^{5.} For a complete account of the US radiation experiments, see: Advisory Committee on Human Radiation Experiments, *The Human Radiation Experiments* (New York: Oxford University Press, 1996).

Research Ethics: The Tuskegee Syphilis study. Available at http://www.tuskegee.edu/global/ story.asp?s=1207598, Accessed 2 November 2009.

Another grim tale was the Willowbrook hepatitis study⁷. In that episode, researchers studying viral hepatitis deliberately injected mentally retarded children residing in a state institution with a strain of hepatitis. The disease was rampant in the institution, which was overcrowded and unsanitary. Almost all the children who lived there contracted hepatitis from other children. The researchers argued that the children to whom they deliberately gave the disease would have gotten it anyway. But as subjects in the research, they were isolated from the other children, placed in a cleaner environment, and were given better treatment because they were being studied. Interestingly, the parents of these children gave their consent for the children to be injected with the hepatitis virus. There was a long waiting list to enter the institution, and those parents who agreed to place their children in the research were able to jump the queue and gain earlier admission. The researchers argued that because the children in the study were in a better environment than the other children in the institution, they were benefited by having been deliberately injected with hepatitis.

These researchers learned a lot from the study and their research was instrumental in the development of an effective preventive vaccine against viral hepatitis. From an ethical point of view, does the end justify the means?

A third unethical experiment was conducted on elderly patients in the Jewish Chronic Disease Hospital in New York City⁸. Most of these patients had some degree of dementia, and had varying illnesses for which they were hospitalized. The experiment consisted of injections of live cancer cells into their bodies. The researchers were studying the immune system, and were certain the injections would not cause cancer in the patients. They made some effort to obtain consent from the subjects, whose ability

to give consent was impaired. However, they withheld the information that what they were injecting were live cancer cells. They claimed that since people have a great fear of cancer, the patients would refuse, despite being told that there was no chance they would actually get cancer. This rationale was similar to that of the physicians who injected plutonium into patients, withholding the information that the substance was radioactive. When the Jewish Chronic Disease Hospital experiments were eventually discovered and revealed, the physicians who conducted them were charged with "unprofessional conduct, and fraud and deceit in the practice of medicine."

Biomedical research today is a far cry from these and other abuses of the past. The Nazi and Japanese experiments were, even at the time they were carried out, off the scale by any measure of ethics in the conduct of research on human beings. They could appropriately be likened to torture. The three US experiments just described were unethical for different reasons than the Nazi experiments. However, the US examples had something in common. All three involved subjects who were vulnerable in some way. The subjects in the hepatitis study were children, they were mentally retarded, and they were institutionalized. The patients in the Jewish Chronic Disease hospital were sick and demented, and therefore could not give properly informed consent even if they had been told about the live cancer cells. And the poor black men in the syphilis study were uneducated and uninformed about what was being done to them, as well as having effective medication for their condition withheld.

Wherever in the world research is carried out today, it must adhere to internationally recognized ethical standards. These universal standards are embodied in various guidance documents, including the Declaration of Helsinki, issued by the World Medical Association⁹; the ethical guidelines published by the Council for International Organizations of Medical Sciences

David J. Rothman and Sheila M. Rothman, The Willowbrook Hepatitis Studies, in (eds.) Bonnie Steinbock, John D. Arras, & Alex John London, *Ethical Issues in Modern Medicine*, 6th Edition. (McGraw Hill, 2003).

^{8.} John D. Arras, "The Jewish Chronic Disease Hospital Case," in Steinbock, Arras, & London, supra n. 7.

^{9.} World Medical Association, *Declaration of Helsinki* 2008. Available at http://www.wma.net/ en/30publications/10policies/b3/index.html.

(CIOMS);¹⁰ the UNESCO Universal Declaration on Bioethics and Human Rights¹¹; national laws and regulations that exist in every industrialized country and in a growing number of developing countries, as well as numerous directives related to ethics in research from the European Commission. With all these laws, regulations, and guidelines, one would think that most ethical problems in research involving humans have been resolved. Unfortunately, however, that is not the case. But it is not that these laws and ethical guidelines are being ignored by researchers or the sponsors of research. Rather, the problem lies in the complexity of research in today's world, and the fact that ethical principles exist in a very general form, requiring interpretation when applied to specific cases.

Nor is it the case that there is lack of systematic review of proposed research or oversight of research while it is ongoing or completed. One of the procedures required by all laws and guidelines governing research is that proposals to conduct research undergo prospective review by an independent, properly constituted ethical review committee. This is a procedural safeguard that seeks to ensure that risks of research are not unacceptably high, that the research is scientifically and technically sound so that some benefit may result, at least in the form of contributions to knowledge. Committees are also charged with ensuring that informed consent documents disclose pertinent information to potential subjects, and that the consent forms are written in a language that ordinary people can understand. What, then, are the problems confronting researchers and the research ethics committees established to ensure that research on humans is carried out in an ethical manner? The remainder of this article identifies an array of challenges that arise in interpreting universal ethical guidance and applying those guidelines in the actual conduct of research.

Challenges confronting researchers and ethics review committees

Some ethical challenges that researchers and ethics committees face have been present for a long time, others have gained attention only recently, and still others are the results of new scientific and technical advances that have created ethical questions and problems for the first time. The ones discussed in the remainder of this article are: ensuring properly informed consent from research subjects; making risk-benefit assessments; recognizing and avoiding the "therapeutic misconception;" interpreting what is required by justice in research; determining when an incentive offered to potential subjects constitutes an "undue inducement" to participate in research; when do researchers have a conflict of interest; what special challenges are raised by human genetics research, gene transfer research, and stem cell research.

Respect for persons

But first, a reminder of the fundamental ethical principles governing research involving humans. The principle known as *respect for persons*¹² is usually interpreted to mean respect for individual autonomy. In that meaning, the principle mandates obtaining informed consent from each individual to be enrolled in a research study. In addition to informed consent, the principle requires protecting the confidentiality of research data, as well as in the conduct of the research itself; and it requires ensuring privacy in the recruitment of research subjects and activities such as interviews and household surveys.

Consent must not only be *informed*, it must also be *voluntary*. The question arises whether patients can easily refuse to participate in research when their own physician is also the researcher. And in resource-poor settings (which exist even in wealthy countries) if patients do not have access to state-of-the-

Council for International Organizations of Medical Sciences, *International Ethical Guidelines* for Biomedical Research Involving Human Subjects. (Geneva: CIOMS, 2002); International Ethical Guidelines for Epidemiological Studies (CIOMS, 2009).

^{11.} Available in Spanish and English at http://portal.unesco.org/shs/en/ev.php-URL_ ID=1883&URL_DO=DO_TOPIC&URL_SECTION=201.html. Accessed 2 November 2009.

^{12.} One of the first statements of this principle as applied to research appeared in: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidance for Research Involving Human Subjects* (US Department of Health, Education, and Welfare, April 18, 1979).

art medical care outside a trial, it is questionable whether their consent to participate in a research study testing a medication they need can be fully voluntary. A different aspect of voluntariness is the freedom that participants must have to withdraw from a study at will, whatever may be their reason for doing so. However, subjects may be reluctant to withdraw if they think it will displease their doctor (who is the researcher).

Another factor that can influence individuals' voluntariness to consent in research is incentives offered for participation. All international guidelines and national regulations prohibit anything that would constitute a coercive offer or "undue influence" to participate in research. However, these guidelines cannot be more specific in determining what constitutes undue inducement, and research ethics committees have a difficult time determining which incentives are appropriate, and what is likely to compromise voluntariness. The biggest worry is usually the offer of money, which is relatively rare when the research subjects are patients but that does occur in certain studies where there is no prospect of direct benefit to the patients. However, in situations where the pool of potential subjects is from a population with few financial resources, the concern is heightened even for low-risk research. In most resource-poor settings the chief worry is medical care and treatment provided during the research study. Can the provision of diagnostic or therapeutic measures that patients would not otherwise obtain constitute an undue inducement to participate in research? This question is not likely to be faced by research ethics committees in Western Europe, where government health systems provide adequate care for all citizens. It does arise, however, in most resource-poor countries in the developing world, as well as in the United States, which does not have universal health care for its population.

Nevertheless, the most prominent ethical challenge in the area of informed consent is not that of voluntariness, but rather, the potential subjects' understanding of the information provided in consent documents or in the process of obtaining consent. This is an old issue in research ethics, and has been getting worse as research has become more complex. Consent documents are overly long, impossibly complicated, and typically written in technical language that the ordinary moderately educated person cannot fathom. It is not unusual to see sixteen-page, single-spaced consent forms riddled with medical terminology embedded in lengthy sentences. This is partly because industrial sponsors prepare consent forms aimed at minimizing potential liability and not at promoting understanding by subjects. It also occurs when most of the consent document is lifted verbatim from a grant proposal intended to be read by medical scientists reviewing the proposal for a funding agency. The electronic ease of cutting and pasting text enables busy researchers to take this short cut rather than compose an understandable consent form.

Another flaw in the process is that forms often overstate the anticipated benefits of the research and omit or understate some of the risks. When all is said and done, however, the informed consent document is less important than the actual *process* of informing and gaining consent. Researchers are busy people and generally do not want to spend time in this activity. They either short-circuit the process, or else they send a medical resident or even a medical student to a patient's bedside to obtain consent. That maneuver is ethically unacceptable, since the person obtaining consent for the research must be able to answer any and all questions a prospective subject may have. Medical students are surely unqualified for that task, and a medical resident unconnected with the research is also inappropriate.

Beneficence

The second well-known ethical principle in research is *beneficence*¹³. Simply put, this principle mandates that proposed research seek to maximize expected benefits and minimize potential harms, including psychological and social harms. It is an application of the more general utilitarian ethical principle: right actions are those that have a favorable balance of beneficial consequences over harmful ones. This principle is relatively easy to apply retrospectively, but is obviously problematic when applied to future actions or states of affairs. The challenge is heightened in research, where in the nature of the case something new is being tried, possibly for the first time. One of the tasks of a review committee is to ensure that research design is

^{13.} Belmont Report, supra n. 12.

adequate to derive benefits from results. This requires prospective review by experts in scientific methodology, as well as by an ethical review committee. Another responsibility of the committee in seeking to minimize risks of harm is to ensure that vulnerable subjects are protected. This requires both a determination of which subjects are vulnerable in research and how they can best be protected. It is obvious that children, demented individuals and others with cognitive impairment are vulnerable, but who else? Some have contended that women are vulnerable, but that makes sense only in those countries or cultures where women are oppressed and not permitted to make decisions for themselves. Some also say that pregnant women are vulnerable, but that confuses concern for protection of the woman herself and concern for the fetus. When research is proposed or conducted in resourcepoor settings, it is often held that the majority of the population is vulnerable by virtue of their poverty. While that is certainly possible, it is important not to be overly paternalistic in seeking to protect mentally capable adults from the risks of research they may wish to join.

The principle of beneficence requires researchers and committees that review research to ensure a favorable balance of potential benefits over risks of harm. But making risk-benefit assessments is notoriously difficult. First of all, the idea of "balancing risks against potential benefits" in research is at best, a metaphor. Secondly, it is the research subjects who bear the risks; the potential benefits can accrue to many, and that could be far in the future. Furthermore, benefits may be largely unknown, especially in early phases of drug trials. And finally, research that provides no direct benefits to subjects is permissible, as long as it holds the prospect of benefits to future patients or contributions to scientific knowledge.

If we think back to the abuses that occurred in research in the United States in past decades, we recall that none of the worst cases held out any promise of direct benefit to the subjects. What was unethical about the Tuskegee study was the total absence of consent and withholding penicillin for treatment of the men once it became available. What was unethical about the Willowbrook hepatitis study was deliberately infecting a vulnerable population, unable to consent on their own behalf and with parents who were desperate to get the children into the overcrowded facility. What was unethical about the Jewish Chronic Disease Hospital case was, once again, failure to inform the elderly, demented patients about the nature of the substance they allegedly agreed to have injected into them. The same flaw existed in the case of the plutonium injections into hospitalized patients. Even if no direct harm was deliberately inflicted on these subject populations, they nevertheless were wronged in a process of recruitment and conduct of studies that were unethical.

Principles of justice

The most difficult principle to apply to the context of research is that of justice¹⁴. This is, in part, because there is more than one principle of justice. The most relevant conception here is that if distributive justice, which calls for a fair distribution of benefits and burdens. Subjects should not be selected for recruitment in research based on convenience or their ability to be manipulated, conditions that pertain to institutions (e.g., mental hospitals or prisons) in which potential subjects reside. Another application of distributive justice pertains to who undergoes the risks and who is likely to receive the eventual benefits of research. If the population for a drug study consists of poor people, because they are the patients in public hospitals where the research is being proposed, but the beneficiaries are the wealthier population who can afford the drugs or who have insurance to pay for them, that would appear to be a violation of the principle of distributive justice. A different principle of justice is *compensatory* justice, which deals with what people are owed. For example, subjects who are injured as a result of participation in research should certainly receive care and treatment, and possibly also monetary compensation. However, it is rare that provision is automatically available for monetary payments to injured subjects, and in the US, at least, consent forms promise only "immediate, short-term" treatment to subjects who may be injured in the course of research. If a lifelong disability results from a research injury, subjects have only the recourse to pursue the matter through the courts.

^{14.} Belmont Report, supra n. 12.

An interesting reversal of presumption has occurred in determining what distributive justice requires in research. The original presumption, when ethical principles were first being applied to this context, focused on research risks. The predominant view was that biomedical research is a risky enterprise, and the key aim was to protect subjects from harm. The concern was that vulnerable groups can be exploited by being "overstudied" in research, and therefore disproportionately exposed to harm. Although protecting potential research subjects from harm is, of course, still a paramount ethical concern, a paradigm shift occurred with onset of the HIV/AIDS epidemic and the first clinical trials. The focus then shifted to the potential benefits of enrolling in research. No treatment existed for this fatal disease, and the first eligible subjects were clamoring to get into clinical trials. This gave rise to the idea that there exists a "right" to be a research subject, a view that persists especially for diseases or conditions that have no cure or effective treatment. In such cases, participation in research may provide therapeutic benefits not available outside clinical trials. Examples are conditions like multiple sclerosis, motor-neuron disease, quadriplegia, and Alzheimer's disease. Of course, the clinical trials may conclude that the experimental treatment did not, in fact, provide any benefit to the subjects. But the anticipation of possible benefit is what drives some patients with these and other diseases to seek to enroll in clinical trials.

The therapeutic misconception

The paradigm shift that resulted in a new emphasis on potential benefits of participation in research has reinforced a problem that has long existed when patients are enrolled in research. This is the so-called "therapeutic misconception," the belief that the *purpose* of research is to provide therapeutic benefit to subjects rather than to contribute to generalizable scientific knowl-edge¹⁵. As already noted, many clinical trials do have the prospect of conferring direct benefit on research subjects. However, the misconception is the

subjects' belief that the physician-researchers are like their personal physicians, making decisions in their individual medical interest. But this cannot be the case, since physicians conducting research in which even their own patients are enrolled may not alter the dosage of the study drug, change to another medication, or deviate from the written protocol. The only recourse a researcher may have is to remove individuals from the study if they experience undesirable side effects. Adding to the potential confusion, consent forms typically refer to the researcher as "your study doctor," possibly reinforcing the belief that the person conducting research is "your doctor." Empirical studies in which current or former research subjects were queried about their participation have revealed that the therapeutic misconception is, indeed, widespread.

The therapeutic misconception is probably hardest to dispel when the person conducting the research is at the same time the subject's physician. Physicians themselves may unintentionally contribute to the problem. This can occur when researchers overstate the benefits of research, or implying that the benefits are already known when, in fact, the very purpose of the investigation is to determine whether those potential benefits are actual benefits. In another way, sometimes the language used in advertisements or announcements to recruit research subjects is misleading, as in the claim: "We have frontier treatments at our medical center." Honesty in the presentation of what is offered is the first step at seeking to avoid the therapeutic misconception. In addition, it bears repeating at various points in the conduct of research, beyond making it clear in the informed consent process and document.

Conflicts of interest

The three prominent principles of ethics discussed in this article cover many aspects of research with human subjects. A different issue arises under the heading "conflict of interest." Typically thought of as a financial matter, conflict of interest can take many forms¹⁶. Perhaps the most fundamental conflict

Henderson GE, Churchill LR, Davis AM, Easter MM, Grady C, et al. (2007) Clinical Trials and Medical Care: Defining the Therapeutic Misconception. *PLoS Med* 4(11): e324.

See, for example, AAMC website: Financial Conflicts of Interest in Academic Medicine. Available at http://www.aamc.org/research/coi/. Accessed 2 November 2009.

is when a physician has dual roles as healer and researcher. Often called a "conflict of commitment", this involves tension between physicians obligation to act in their patients' best interest and their obligation to achieve accurate results by adhering strictly to the research protocol. In caring for patients, physicians may alter the dose of a medication or switch to a different medicine. But as just noted in discussing the therapeutic misconception, following a prepared protocol precludes these options for the physician conducting research.

The more common form of conflict of interest —a financial conflict — occurs when researchers have large investments in companies that support their research. The usual remedy for such conflicts of interest is "full disclosure", as if disclosing the conflict makes it disappear. A variation on this has become common in the biotechnology arena, where researchers who make significant discoveries spin off a new company, in which they become a major shareholder. If the new company then sponsors subsequent studies in which the researcher is involved, the result is a clear conflict of interest. As much as reputable investigators may sincerely believe they are not influenced by ties to a particular pharmaceutical or biotechnology company in conducting or analyzing their research, evidence exists in the published literature that researchers whose studies are supported by one pharmaceutical company often obtain results biased in favor of the sponsor when compared with nonindustry supported research on the same topic.

To whom must a researcher disclose a financial conflict of interest? Normally, any financial conflict of interest related to research in which the researcher is either the principal investigator (head of the research) or a collaborator must be disclosed to the research ethics committee. The committee then has to determine whether the conflict is sufficiently serious to require a remedy of some sort. It is rare, however, for the informed consent documents that research subjects read and sign to disclose anything about a researchers financial conflicts of interest. When people have been asked whether they would like to have such information about the researchers in charge of studies in which they participate, some individuals said they would want to know about researchers' potential conflicts of interest while others did not care. Consent forms normally identify the sponsor of the research but do not say anything about financial arrangements between the sponsor and the researchers. One common arrangement is direct payment by the company to the researcher for each patient enrolled in the study. These payments can go higher than USD 5000 per patient, which is clearly an incentive for physicians to enroll as many patients as they can in the research they are conducting. One wonders, therefore, whether a temptation may exist for the researcher to promote the study by overstating its potential benefits to patients. Behavior that would clearly be unethical is for a physician to "shade" the inclusion or exclusion criteria for entry into the study, for example, by enrolling patients with a blood pressure reading that exceeds what the research protocol allows. Yet when physicians are offered so much money for each patient enrolled especially by a target date set by an industrial sponsor—the temptation may propel the researcher to cross that ethical line.

Increasing technical complexity of research

A final challenge in research with human subjects today is the introduction of new scientific areas, often involving increased technical complexity. For example, the explosion of research in different aspects of human genetics poses an array of special problems. The science of genetics and the meaning of genetic findings may be poorly understood or misunderstood by subjects. Some genetic research focuses on genetic diseases that patients already have. That is one of the easier matters to understand. However, new genetic findings in a patient population often have implications for relatives of subjects. When informed that the condition is one that relatives are also likely to have, subjects may refuse to contact and inform relatives themselves and deny permission for the researcher to get in touch with relatives. This can pose a dilemma for a physician who is also conducting research, especially if the relatives are also patients of the physician. What then is the researchers' obligation?

A different scenario occurs in the increasingly common practice of doing a genetic add-on study to the primary research being conducted. A bit of blood is taken to be stored and studied for genetic possibilities. Subjects in the pri-

mary study must provide their consent for future studies using their stored biological samples. But the nature of that future research cannot be known at the time the sample is taken. Some people have argued that informed consent is impossible in that situation, since if the nature of the future study is unknown, how can consent possibly be informed? Others argue that if subjects are clearly informed that the future studies are unknown at the present time, and the subjects are still willing to provide blood or other samples for future use, then they are consenting voluntarily to the unknown future research.

Two areas of research that have given rise to ethical controversy are gene transfer research, commonly known as "gene therapy," and human embryonic stem cell research. In the first of these, the promise of gene transfer research remains unfulfilled now almost twenty years after the first trials were initiated in humans. When gene transfer research was introduced as potential therapy, there was much hype in the media. There have been few, if any benefits in these two decades of trials in humans, and some cases that actually did appear to confer benefits were later found to have unacceptable side effects. This was the case in a trial for children who suffered from Severe Combined Immunodeficiency (SCID), a primary immune deficiency that renders the individual susceptible to death from infections that normal people's immune systems can easily combat. SCID is often called "bubble boy disease". SCID became widely known during the 1970's and 80's, when the world learned of David Vetter, a boy with X-linked SCID, who lived for 12 years in a plastic, germ-free bubble. When gene transfer research first appeared promising in this patient population, the results were dramatic. Later, however, some children who had received the experimental gene therapy developed leukemia and later died, which changed the initial promise into a question about the widespread use of this mode of treatment¹⁷. Still other unknown risks remain today, including harm that may not become evident for many years.

Another worry is the possible inadvertent insertion of genes used in such research into the individuals' germ line. That would enable transmission to offspring and future generations, with unknown consequences, some of which could cause harm to future generations. Scientists and regulatory agencies have been extremely cautious, generally prohibiting any deliberate genetic research that seeks to alter the germ line. Yet the possibility does exist of unintentional insertion of genes into the germ line, so gene therapy research remains an area that deserves continued ethical scrutiny.

Finally, we come to one of the most recent controversies: embryonic stem cell research. When researchers succeeded in deriving the first embryonic stem cells in animal models in the late 1990s, it was viewed as scientific breakthrough. As occurred with gene transfer research, much hype surrounded the potential for cures of very many diseases and other conditions. While scientists cautioned that progress would be very slow, the hope for success and financial support of stem cell research continued. However, from the outset and still for many people today, this area of research remains controversial because of the views of some religious groups regarding status of human embryos. The research requires the destruction of human embryos from which the cells are derived. The least controversial source of embryonic stem cells is that of cryopreserved embryos left over from IVF (in vitro fertilization) in infertility clinics. The embryos are "left over" from infertility treatments, and the couples whose gametes were used to create the embryos no longer want them for treatment and are unwilling to pay for their continued storage in freezers. These embryos would otherwise simply be destroyed. Yet opponents of any destruction of embryos continue to argue against their use for potentially valuable scientific research. More controversial, however, is the creation of human embryos specifically for the purpose of research, whether stem cell or other types of research. Some countries allow the creation of embryos specifically for research, other countries prohibit it, and many countries have no laws one way or the other¹⁸.

Science News, Why Gene Therapy Caused Leukemia In Some 'Boy In The Bubble Syndrome' Patients, *ScienceDaily (Aug. 10, 2008)*. Available at http://www.sciencedaily.com/releases/2008/08/080807175438.htm. Accessed 2 November 2009.

For detailed information and references on human embryonic stem cell research see http:// www.mbbnet.umn.edu/scmap.html. Accessed 2 November 2009.

Conclusions

Research involving human beings as subjects is critically important for the progress of medical science. However, the unfortunate history of past abuses has shown that ethics must be an integral part of the research enterprise. To assist in that enterprise, ethical principles are important yet they do not provide precise guidance in specific situations. Ethical principles do not tell us exactly what to do; rather, they require interpretation and serve as benchmarks in evaluating the ethics of past and potential future actions. It is impossible for guidelines or regulations to specify every detail and circumstance that can arise in the design and conduct of research.

For research to be ethical, it requires a sustained commitment by well-trained investigators. Trust in the physicians and others who conduct research is necessary in order for patients and healthy volunteers to enroll in research. People should be able to trust medical researchers, much as they trust their own physicians. At the same time, it is important for patients to be aware that when their own physicians seek to recruit them in a clinical trial, the obligation of their physician is no longer directed solely at the patient's best interest. Maintaining the integrity of the research process and following the scientific requirements of the protocol is necessary for research to attain any benefits that may be forthcoming.

Beyond the requirement for voluntary, informed consent of every individual (or a person's surrogate) for entry into research, an important procedural mechanism is prospective review of the research protocol by a properly constituted ethics committee. The committee is charged with ensuring that the written information provided to the prospective subjects is accurate, that the recruitment process protects potential subjects privacy and confidentiality, and that any risks of the research are justified by the anticipated benefits to the subjects or others. Special challenges exist when research is highly technical, as in genetic research, when the techniques are novel, as in gene transfer research, and when the research that requires the destruction of human embryos.

Ethics in Multinational Research "Multinational research" refers to biomedical, epidemiological, or social science research that involves investigators and subjects from more than one nation. The type of multinational research that has raised the most ethical concerns is that in which the investigators or sponsors are from an industrialized country and the research is conducted in a developing country. The chief ethical concern that has dominated this type of research is a worry about exploitation. Individuals who are recruited for research subjects in the host country might be vulnerable by virtue of their low educational level, lack of familiarity with modern scientific concepts, and poor or nonexistent access to medical treatments in their own community. These considerations may make many residents of resource-poor countries open to exploitation in some manner.

Most traditional ethical concerns have focused on problems associated with informed consent. Several related factors are a cause for such concerns. The first is the relatively low educational level of the majority of people in African and many Asian countries. This shortcoming is not only related to basic literacy, but also to health literacy and more particularly, with what is currently referred to as "research literacy." In some cultures, there may even be a total lack of familiarity with modern scientific concepts. In societies or cultures where many people believe in spiritual causes of disease and treatment or cure at the hands of a shaman, it is hard to imagine that they can provide properly informed consent to research, given their basic lack of understanding of the causal mechanisms of disease. But even among the better educated people in developing countries, it is likely that they are unacquainted with the concept of informed consent. It remains true that in such places physicians constitute an educated elite and medicine is still practiced in a paternalistic fashion. Patients are accustomed to trust their doctors to make decisions for them, and many physicians expect to do so.

Equally problematic is the degree to which voluntariness may be compromised when people generally lack medical treatment. In this circumstance, the prospect of obtaining medical attention in the context of research becomes inviting. Whether agreement to enroll in research stems from the "therapeutic misconception" (the belief that research subjects are patients receiving individualized medical treatment¹), or from an accurate understanding that the activity in question involves uncertain benefits, the prospect of some medical treatment may serve as an inducement to participate. In and of itself, this does not constitute exploitation. Nevertheless, it poses the ethical question of whether agreement to participate in research is fully voluntary on the part of people who otherwise lack access to medical treatment.

The greater the differences in culture and customs between the sponsoring country and the host country in multinational research, the greater the likelihood that questions of cultural and ethical relativism will arise². An overarching question is whether the ethical principles so firmly entrenched in research should apply—or apply in the same way—in some countries. Different positions have been staked out in the bioethics literature on this point. Some people contend that it is a form of "ethical imperialism" to seek to impose ethical values from one culture or society on another, rather different culture or society. Consider, for example, the following two views on informed consent.

"It is ethical imperialism at its worst to assume that the informed consent requirement, which does indeed serve one (only one) moral principle in the Western setting, is in itself such a universal ethical standard³."

And:

"Appeals to cultural sensitivity are no substitute for careful moral analysis. We see no convincing arguments for a general policy of dispensing with, or substantially modifying, the researcher's obligation to obtain first-person consent in biomedical research conducted in Africa⁴."

Henderson GE, Churchill LR, Davis AM, Easter MM, Grady C, et al. (2007) Clinical Trials and Medical Care: Defining the Therapeutic Misconception. *PLoS Med* 4(11): e324.

^{2.} For a thorough discussion of cultural and ethical relativism in medicine and research, see Ruth Macklin *Against Relativism: Cultural Diversity and the Search for Ethical Universals in Medicine*. New York: Oxford University Press, 1999.

^{3.} Lisa H. Newton, Ethical imperialism and informed consent, *IRB: A Review of Human Subjects Research*, Vol. 12 (May-June 1990).

^{4.} Carel B. IJsselmuiden and Ruth R. Faden, Images in clinical medicine, *NEJM*, Vol. 326 (1992).

Two situations have sometimes been defended by relativists even though they depart from the widely accepted ethical standard for informed consent. The first is the perceived need to withhold key information from potential research subjects; and the second is the cultural custom of requiring husbands to sign consent forms for research in which their wives are participants.

The first situation arose in a breast cancer study carried out by US researchers in Vietnam⁵. The US researcher said to the research ethics committee at his institution: "American standards would not be acceptable to Vietnamese physicians, political leaders in Vietnam, or the vast majority of Vietnamese patients". The reasons given were that patients do not participate in medical decision making in Vietnam, so it would be very odd to ask them to do so in a research study. In addition, it would be necessary to withhold from potential subjects any elements that would convey uncertainty, as patients normally trust their physicians and believe in their competency. Further, the researchers contended that they could not provide the explanation that the proposed treatment in the study would be determined by randomization. And finally, they resisted the need to reveal to potential subjects the existence of alternative therapies, that is, what they would receive if they chose not to enroll in the breast cancer study. This discussion between the researchers and the institutional ethics committee was limited to the debate over the contents of the consent document. It did not include an ethical issue we shall examine a bit later: whether any beneficial results of the breast cancer study would ever be available to women in Vietnam.

The issue of spousal permission for entry into research is even more divergent from European and North American practices. Some cultures maintain the custom of requiring husbands to sign consent forms for their wives to participate in research. This practice not a law, but is an accepted requirement for medical treatment as well as for research. Researchers in those countries have traditionally accepted the requirement, as customary practice, and the informed consent documents have had a line for the signature of a woman's husband. The question is whether that practice violates the principle, *respect for persons*, as it limits a woman's autonomy to decide for herself.

An assumption that must be questioned is whether the ethical principles governing research should be considered "Western" principles or rather, universal principles that should be applied everywhere. It is true that the principles had their origins in European philosophy and political theory. But just because the origins of an idea emanated from Europe or North America does not mean the idea cannot be considered universally applicable.

A major worry about research sponsored by industry or wealthy countries and carried out in developing countries is that exploitation of the poorer country might occur. In order to determine whether research in a developing country is exploitative, consider the following definition of 'exploitation': "Exploitation occurs when wealthy or powerful individuals or agencies take advantage of the poverty, or powerlessness, or dependency of others by using the latter to serve their own ends (those of the wealthy or powerful), without adequate compensating benefit for the less advantaged individuals or group⁶." To test any situation in which a suspicion exists of exploitation, we would have to determine whether research subjects serve the interest of the sponsors of research and enter the arrangement without adequate compensating benefit to themselves. It may be difficult to apply this test, but exploitation is a serious ethical wrong, and therefore careful scrutiny is required before that charge may be leveled against a sponsor of research.

An array of ethical concerns regarding international research has arisen over the years, but those concerns have rarely been cast in the language of justice. Upon examination, however, it is evident that these concerns can be expressed in terms of justice⁷." One often-heard objection is that researchers should not embark on studies in developing countries when for ethical reasons that research could not be carried out in a developed country.

R.R. Love and N.C. Fost, 'Ethical and Regulatory Challenges in a Randomized Control Trial of Adjuvant Treatment for Breast Cancer in Vietnam,' *Journal of Investigative Medicine*, 45 (1997), 423-431.

^{6.} Ruth Macklin, Chapter 4, "Avoiding Exploitation," *Double Standards in Medical Research in Developing Countries.* Cambridge, U.K.: Cambridge University Press, 2004.

^{7.} See Macklin, supra n. 6, Chapter 3, "Striving for Justice in Research."

A prominent concern in the international research arena has been that disadvantaged people in developing countries suffer a disproportionate burden of bearing the risks of research without the opportunity to enjoy any benefits that may accrue. Residents of developing countries may lack access to the products of research carried out in their countries if the medications are too expensive for individuals or the ministries of health to afford. This results in an unjust distribution of benefits and burdens of research.

This global imbalance gives rise to questions regarding what is owed to research subjects and to others in the community or country when multinational research is conducted in resource-poor countries. Two leading questions are: What are the obligations of sponsors and researchers to research participants during a clinical trial? And what is owed to research participants and others in the community or country when the trial is over? One prominent episode in the late 1990s galvanized attention to these questions and led eventually to the revision of leading international declarations and ethical guidelines for research with human subjects⁸.

In several countries with a high disease burden of HIV/AIDS, clinical trials were proposed and conducted with the aim of reducing mother-to-child transmission (MTCT) of the AIDS virus. These trials used a new experimen-

tal regiment in one arm and a placebo (inactive substance) in the other arm. The purpose of these trials was to test a preventive treatment that would be affordable and feasible to administer in resource-poor countries. At the time, a proven method existed and was available to HIV-positive pregnant women in North America and Western Europe. But that method was so expensive it was out of reach for women in Thailand and Africa, as well as for the Ministries of Health in poor countries. The developed country method also required a well-developed infrastructure to administer the drug, and many poor countries lack that infrastructure, especially in rural areas. Although the research was designed to benefit the population in the countries where it was being carried out, a controversy erupted over the research design, specifically the use of placebo in the control arm of the study. Critics argued that a placebo control was unethical because a proven, effective treatment existed in industrialized countries, and that should be the comparator in the study. Defenders of the research design argued that the studies were ethical since the placebo group received the current "standard of care" in those countries, and therefore they were not being made worse off than if they had not been enrolled in research at all.

There thus emerged two opposing views. One view held that it is ethically acceptable to use a placebo control in that situation. In order to develop affordable medications for use in poor countries, the only appropriate research design is one that tests the experimental drug against a placebo. We may call this the "double standards" view. The opposing view maintained that the same standards adhered to when research is conducted in the sponsoring, industrialized country should be used in the resource-poor country. This is the "single standards" view regarding multinational research. Although the particular episode that gave rise to the controversy occurred more than a decade ago, the debate persists today and has taken on some different forms as new research goes forward.

One such form has emerged in a different type of prevention trial. The MTCT trials sought to prevent HIV transmission from an HIV-infected woman to her offspring. Other prevention trials begin with uninfected individuals. Here the purpose is to test a method that would prevent individuals from becom-

^{8.} Among the many journal articles that addressed this controversy are the following: Marcia Angell, 'The Ethics of Clinical Research in the Third World,' NEJM, 337 (1997), 847-849; Peter Lurie and Sidney Wolfe, 'Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries,' NEJM, 337 (1997), 853-856; George J. Annas, and Michael A. Grodin, 'Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa,' American Journal of Public Health, 88:4 (1998), 560-63; Robert A. Crouch and John D. Arras, 'AZT Trials and Tribulations', Hastings Center Report, (1998), 28:6, 26-34; Christine Grady, 'Science in the Service of Healing,' Hastings Center Report, 28: 6, (1998), 34-38; Leonard H. Glantz, George J. Annas, Michael A. Grodin, and Wendy K. Mariner, 'Research in Developing Countries: Taking "Benefit" Seriously,' Hastings Center Report, 28:6 (1998), 38-42; Robert J. Levine, 'The "Best Proven Therapeutic Method" Standard in Clinical Trials in Technologically Developing Countries, IRB: A Review of Human Subjects Research, 20:1 (1998), 5-9; David B. Resnik, 'The Ethics of HIV Research in Developing Nations,' Bioethics, 12:4 (1998), 286-306; Reidar K. Lie, 'Ethics of Placebo-controlled Trials in Developing Nations,' Bioethics, 12:4 (1998), 307-311; Carlos Del Río, 'Is Ethical Research Feasible in Developed and Developing Countries?'

ing infected or at least to keep an HIV infection at such a low level that the individual would not develop the symptoms of AIDS disease. Examples of methods currently undergoing clinical trials are microbicides, vaccines, and drugs that are used as part of the AIDS treatment cocktail. An ethical question posed at conferences and in published articles is: What level of care and treatment should be provided to participants in an HIV prevention trial (e.g., vaccine, microbicide) who become HIV-infected during the trial? This and other questions that lacked satisfactory answers led to the halting of prevention trials already begun, and prevented other proposed trials from starting.

Those episodes involved an investigation of whether antiretroviral pills of a medication known as Tenofovir could be used prevent infection among sex workers, drug injectors and other people at high risk of becoming infected. Early trials in Cambodia and Cameroon got off to a bad start and were halted because of poor communication between researchers and potential participants. Among other requests, participants in the trial demanded care and treatment during the trial and any successful products that would result from the trial. Arrangements had not been made in advance to the satisfaction of the subjects in the trial, and their protests led to stopping the trial.

What do international ethical guidelines say about providing care and treatment to participants during a clinical trial? The answer depends on which guidelines are consulted. Let us look first at the International Ethical Guidelines for Biomedical Research Involving Human Subjects, issued by the Council for International Organizations of Medical Sciences (CIOMS) in 2002⁹.

Guideline 21 is entitled "Ethical obligation of external sponsors to provide health-care services," and it says:

External sponsors are ethically obliged to ensure the availability of: health-care services that are essential to the safe conduct of the research; treatment for subjects who suffer injury as a consequence of research interventions; and services that are a necessary part of the commitment of a sponsor to make a beneficial

intervention or product developed as a result of the research reasonably available to the population or community concerned.

In an explanatory column that follows the guideline itself, it says: "Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praise-worthy to do so... It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study."

This commentary makes it clear that any such decision rests on an *agreement*, and not an *obligation* of the sponsor.

A much stronger statement of obligation appears in an ethical guidance document issued jointly by UNAIDS (the joint United Nations Programme on HIV/AIDS) and the World Health Organization (WHO) in 2007, entitled *Ethical Considerations in Biomedical HIV Prevention Trials*¹⁰. Guidance Point 13 states:

Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counseling and access to all state of the art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial.

When this guidance point was introduced at conferences and workshops sponsored by these two international organizations, a series of objections arose. Some participants in these conferences responded incredulously. "Would that include a partially effective vaccine or microbicide when such methods become available?" If so, this will make it difficult, if not impossible, to analyze the results of HIV prevention trials; "Researchers may not be able to provide *all* state of the art HIV risk reduction methods, for financial reasons as well on account of feasibility"; "This requirement would make prevention research grind to a halt."

^{9.} Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: CIOMS, 2002).

^{10.} UNAIDS/WHO, Ethical Considerations in Biomedical HIV Prevention Trials (Geneva, 2007).

What ethical principle could arguably be used to justify such a strong requirement? The most plausible principle is that of *beneficence*¹¹, which imposes an obligation to maximize benefits and minimize harms in medical research and treatment. Providing treatment for participants in clinical trials is one way of maximizing health-related benefits, so it can be argued that therefore, an obligation exists to provide treatment to such individuals.

Opponents of this position argue on several different grounds that no obligation exists to provide care and treatment to research subjects who acquire the target disease during a prevention trial. Their argument begins with the premise that research is not therapy. It follows, then, that the obligations of researchers are not those of clinicians treating patients. Although it is true that research and treatment are two different activities, with different goals, it does not automatically follow that researchers do not have some of the same obligations as clinicians. The obligation to provide treatment in a prevention trial may stem from the concept of *reciprocity*. Volunteers in a prevention trial have subjected themselves to discomfort and inconvenience, if not also some physical risks, and therefore may deserve medical treatment if they require the very disease the study intervention is designed to prevent. One problem with this argument is that the other volunteers in a prevention trial would similarly deserve something in return for their participation. But if the trial does not yield a successful product, the volunteers who remain uninfected will receive no benefit. This may appear to be unfair. Yet individuals who are uninfected during a prevention trial remain healthy, so there is no benefit they could receive that would be analogous to the treatment provided to the volunteers who became sick during the trial.

A second argument opponents make is simply to claim that treatment would not be financially affordable. What this means, in effect, is that "double standards" are ethically acceptable based on economic considerations. However, this is not an ethical argument in response to the claim that an obligation exists to provide medical treatment to trial participants who become infected. At least in the context of HIV treatment, huge investments by international governmental donors and philanthropic organizations such as the Gates Foundation have now succeeded in making HIV treatment available to very many people in resource poor countries. Moreover, no one who becomes HIV infected during a prevention trial will need treatment immediately, and it may be as long as ten years before most people would be medically eligible for antiretroviral treatment. As treatment for AIDS continues to scale up in many developing countries, what was once deemed unaffordable has been demonstrated to be entirely possible.

Still another controversial question about medical treatment for research participants relates to post-trial obligations. What is owed to subjects in any type of biomedical research when their participation ends, and what, if anything, is owed to the community from which the subjects were recruited? Here again, two starkly opposed positions exist¹². On one view, no obligation exists on anyone's part to provide for research subjects once the trial is concluded. For one thing, to provide successful products of research is certainly beyond the ability of researchers themselves. What about an industrial sponsor of research? In this case, the argument is that to require companies to provide products is unreasonable, as they are businesses that must realize a profit. What, then, about the Ministry of Health in the developing country where the research is carried out? The response is that most developing countries lack the necessary resources to provide the products because the cost of pharmaceutical or biotechnology products is out of reach. Based on these considerations, opponents of any further obligation once a trial is completed conclude that if providing successful products were made a requirement for embarking on research, much important research could not be done in developing countries and the population would lack the benefits of such research.

An opposing view maintains that an obligation does exist to make successful products of research "reasonably available" to the research participants who still need them after the trial is over, and to the community or even the coun-

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidance for Research Involving Human Subjects* (US Department of Health, Education, and Welfare, April 18, 1979).

^{12.} These opposing positions are discussed in Macklin, supra n. 6, Chapter 3, "Striving for Justice in Research."

try where the research is conducted. This position is stated in three major international guidelines for ethics in research. The Declaration of Helsinki is an influential document that has undergone two major revisions since the version issued by the World Medical Association in 1996. The latest revision of the Declaration in 2008 has this to say:

Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research¹³.

This latest version represents a step back from the version that existed before the 2008 revision. The 2000 Declaration of Helsinki did not limit the requirement to disadvantaged or vulnerable populations. That earlier version said: "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research." One can only speculate why the World Medical Association introduced this restriction only a few short years after undertaking a major revision of its well-known Declaration.

The CIOMS International Ethical Guidelines¹⁴ reiterates the position first articulated in an earlier version of the document:

Before undertaking research in a population or community with limited resources, the sponsor and the researcher must make every effort to ensure that:

-the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and

-any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community (Guideline 10).

As generous as this guideline appears to be, it has some problems of interpretation. How to interpret the requirement that research must be "responsive to the health needs and priorities" of the population? Is research 'responsive' to the health needs of the population just so long as it addresses a health problem that is prominent in the country or region? Or must some steps be taken before the research is initiated to seek to ensure that successful products are made available to the population at the conclusion of the research? And how are the "priorities" of the population to be determined? By the prevalence of certain diseases in that population? Are the priorities what the Ministry of Health says they are, even if the population would disagree, if asked? There is much concern today about so-called "neglected diseases", ones that are considerably less prevalent than AIDS, malaria, and tuberculosis yet seriously affect significant numbers of people. A commentary in CIOMS that appears following the guideline provides a partial answer to these questions:

... It is not sufficient simply to determine that a disease or condition is prevalent in the population concerned and that new or further research is needed. If successful interventions or other benefits result from such research, the ethical requirement of "responsiveness" can be fulfilled only if they are made available to the population.

By far the strongest statement of obligation appears in the UNAIDS/WHO Guidance for HIV biomedical prevention research¹⁵. Guidance point 19 says:

Researchers should inform trial participants and their communities of the trial results. During the initial stages of development of a biomedical HIV prevention trial, trial sponsors and countries should agree on responsibilities and plans to make available as soon as possible any biomedical HIV preventive intervention demonstrated to be safe and effective...to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country.

At the time of this writing, there have been no genuinely successful products resulting from HIV prevention trials. Hopes remain for developing a successful microbicide, and the results of an HIV preventive vaccine trial in Thai-

World Medical Association, *Declaration of Helsinki*, 2008. Available at http://www.wma.net/ en/30publications/10policies/b3/index.htmlparagraph 17).

^{14.} Council for International Organizations of Medical Sciences, (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS, 2002.

^{15.} Supra, n. 10.

land, released at the end of September 2009 showed some promise¹⁶. However, the degree of protection the vaccine appeared to afford was relatively modest, probably too low for a regulatory agency to license. The public health benefits of a successful prevention of HIV infection would be so enormous, there is little doubt that a collaborative effort to make successful products widely available will occur.

Nevertheless, the overarching question remains: If an obligation does exist to provide successful products of biomedical research, on whom does that obligation fall? The only reasonable answer is that no one country, industrial sponsor, or agency will or should bear the entire burden of providing treatment or successful products of research. A changing picture in recent years has shown progress in making products affordable and accessible to resource-poor countries. Among these are pharmaceutical manufacturers' free donations or reductions in price of drugs, grants made to developing countries by the Global Fund to fight AIDS, tuberculosis, and malaria, the manufacture of generic medications in some developing countries, the huge US PEPFAR program for HIV/AIDS, which also has funds to combat TB and malaria, as well as the Gates Foundation and other large private philanthropic organizations.

No one of these efforts by itself can or should assume a disproportionate responsibility for making the successful products of research available in developing countries. However, in seeking to ensure global justice, we must entertain novel and untested approaches to narrowing the gap between the developed and the developing worlds. Prior arrangements among all stake-holders can help to bring it about that proven interventions will be made widely available to developing countries in which they are tested and thereby prevent the exploitation of disadvantaged populations in poor countries.

^{16.} Results of the trial are summarized at http://www.hivresearch.org/phase3/factsheet.html. Accessed 2 November 2009.

Grey Areas: Drawing the Line Between Research and Non-research

Uncertainties and dilemmas

Many unresolved difficulties remain in the domain of human subjects research. These include, among others: how to improve the process and documents for obtaining informed consent; how to determine when risks to research subjects are "reasonable"; which research subjects are vulnerable and in what ways; what constitutes an "undue inducement" to participate in research. These are among many traditional, ongoing concerns in research ethics.

However, more fundamental issues pertain to the distinction between research and non-research. This distinction has typically focused on the distinction between therapeutic, prophylactic, or diagnostic measures for the care and treatment of patients, and interventions that are part of a research project designed to contribute to new knowledge. Less well-studied are some "grey areas" that address the question: When is an activity research and when is it something else that resembles research, but is not (or need not be) subjected to the usual ethical requirements for research. A different, yet related question is how to determine when a medical practice has become the "standard of care" in the field or specialty area. The answer has implications for the design and review of research, aside from the more familiar question of when a deviation from the standard of care constitutes medical malpractice.

Activities that resemble research

Two activities that blur the line between research and non-research are public health practice and quality improvement (QI) in clinical settings. The methodology may be identical in activities that are considered to be non-research and those typically considered research, and publication of results may follow the conclusion of the activity in both situations. Moreover, informed consent may be needed for both types of activities –but is often not undertaken in those cases treated as non-research.

Given these uncertainties, the question arises: Why is it necessary or important to make a distinction? Several ethical requirements obtain when an activity is considered research: a full written protocol must be submitted to a research ethics committee (REC); informed consent from human beings is normally required (but may be waived under certain conditions); research subjects have the right to refuse to participate and to withdraw from the activity at any time; and most research is subjected to some type of governmental oversight. However, these ethical requirements are often absent in public health practice and QI.

One might think that the uncertainty can be resolved by referring the definition of 'research'. A widely accepted definition of 'research' is the following: "*Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge!." As we shall see, a key element in this definition is "designed to contribute to knowledge that is generalizable." Also important to note is that the definition does not mention the publication of results of the activity as a feature that qualifies it as being research. Yet some have maintained that publication is a *de facto* determinant of research.

Public health practice and research

Three main activities are routinely carried out as part of public health practice. The first of these is surveillance, defined as "the ongoing, systematic collection, analysis, and interpretation of outcome-specific data, closely integrated with the timely dissemination of these data to those responsible for preventing and controlling disease or injury."² This activity is typically conducted by governmental agencies with the authority to carry out investigations. But surveillance can also be conducted by academic researchers who

This definition appears in the United States Code of Federal Regulations, 45 CFR 46.102. Available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102. Accessed 2 November 2009.

^{2.} US Centers for Disease Control and Prevention, *Guidelines for Defining Public Health Research and Public Health Non-Research*, Revised October 4, 1999. Available at http://www.cdc.gov/OD/science/regs/hrpp/researchDefinition.htm. Accessed 2 November 2009.

have grants or contracts with a government to carry out the activity. In some cases (perhaps an increasing number) surveillance may involve taking blood or other biological samples from people. In that case, even if the activity is not considered research, individuals' consent would be necessary because the intervention involves invasion of the body. This may be as innocuous a procedure as obtaining a cheek swab, but it would still require the individual's permission.

A second common activity in public health practice is response to emergencies. The US Centers for Disease Control and Prevention, the nation's preeminent governmental public health agency, defines this activity as follows: "A public health activity undertaken in an urgent or emergency situation, usually because of an identified or suspected imminent health threat to the population, but sometimes because the public and/or government authorities perceive an imminent threat that demands immediate action³." This is typically done under governmental authority, but exceptions include humanitarian organizations like Médecins Sans Frontières (MSF) or the International Red Cross. Examples include outbreaks of infectious disease; floods, earthquakes, and other natural catastrophes; an epidemic of food-borne illness, and other situations. The purpose of the response is to document the existence and magnitude of a public health problem in a community or region and implement appropriate measures to deal with the problem. The problem that arises for the ability to distinguish between public health response to emergencies and public health research is that what is learned in the course of the investigation may lead to generalizable knowledge, even if that was not the initial intent of the activity.

A different ethical problem arises when an emergency response is designed as a research study in the first place. It may be an urgent response to the emergency with the usual public health purpose, and at the same time be an opportunity to conduct research that could lead to knowledge applicable to future similar situations. An example might be a questionnaire accompanied by drawing blood from people who become sick and those who remain well during a disease outbreak. At the same time that public health authorities take steps to slow the spread of the disease and protect uninfected people from becoming infected, they may seek to determine whether any biological or life style factors caused some people to get sick while others did not. The effort to make such a determination qualifies as an intention to contribute to generalizable knowledge, and therefore as research.

The ethical problem that now arises is that the intention to conduct research would require preparation of a detailed research protocol. This would have to be submitted to the relevant REC for review and clearance, and the committee might request revision and resubmission of the protocol. This would delay the initiation of the response to the emergency, possibly resulting in greater harm to the population. In addition, conducting the activity as research could require obtaining informed consent from individuals for an activity as simple as a survey or short interview. This additional activity could take time and resources away from dealing directly with the emergency situation. If blood samples are sought from individuals, it is interesting to consider whether greater pressure can be exerted on them to allow their blood to be taken when the intervention is considered an emergency response than when it is clearly a research maneuver. In the latter case, the ethical requirement of the right of individuals to refuse to participate and not to be pressured or subjected to "undue influence" should govern.

Regardless of whether the distinction can be made between data gathered for emergency response and data gathered for research, RECs could establish a policy for disease outbreak investigations⁴. One possible element of the policy might be that investigators need not submit a full, detailed protocol to the committee at the outset of the study. A short statement of purpose and procedures of the investigation can be prepared and submitted for expedited, or quick review by the committee chair or other designated member. Even if the emergency response includes elements that unquestionably appear to be research, a duly constituted ethics oversight body could decide to waive the

^{3.} Ibid.

Ruth Macklin and Ethan Cowan, Conducting Research in Disease Outbreaks, *PLoS Neglected Tropical Diseases*, Vol. 3, Issue 4; April 2009: 1-3.

requirement for signed consent forms in favor of oral consent or even no consent from participants for interviews or surveys. This waiver could only be granted when individuals cannot be identified and, as already noted, their consent must be obtained for collection of blood samples or other biological specimens.

The third common public health practice is program evaluation. This typically involves a systematic evaluation, using scientific and statistical procedures, to arrive at the conceptualization, design, implementation, and usefulness of public health programs. It is evident that identical methods are used in research. If public health officials seek to compare a newly proposed program with an existing program, does the comparison automatically render the study research? If the new program were instituted and evaluated without a comparison with the existing one, would it then qualify as innovation but not research? Another way of putting the question is whether "operations research" is "research" or rather, program evaluation.

The debate

One argument maintains that a narrow definition of public health research is needed for any of these situations. The reasoning is that if it were necessary to submit all proposals to a research ethics committee, long delays would occur before a public health project could be carried out. In particular, if it were necessary to obtain informed consent from each individual before gathering personal information for surveillance, some people would refuse and therefore, the results would not be valid.

An opposing argument holds that a broad definition of public health research is preferable. The reasons are that research ethics committees could better ensure that individuals' privacy and confidentiality will be protected, and those who are investigated would be given the right to decide what should happen to their personal information.

A third position is that it is impossible to make a clear distinction between public health research and practice because there is an irreducible overlap in the activities in both situations. Therefore, efforts to make the distinction should cease. The opposite position is that it is necessary to clarify the distinction because the current situation is very confusing, and different groups and agencies accept different definitions of when an activity is research and when it is public health practice.

A clear example of this confusion is the different viewpoints of the Centers for Disease Control and Prevention (CDC) and the health departments of the individual states. The CDC distinction between public health research and practice is based on the intention of the activity: If the primary intent is to prevent or control disease or injury or to improve a public health program, and no research is intended at the present time, the project is non-research. If the primary intent changes to generating generalizable knowledge, then the project becomes research⁵.

Officials in state governments in the US made strong objections to this definition as published in the CDC's guide in 1999: "We don't consider these activity to be research when the state carries them out. However, if another entity carries out the same activities, that would be research and would require review by a research ethics committee⁶." According to this position, it is not the intent that determines whether an activity is research, it is the organization or sponsor of the activity.

One possibility is to decide that public health surveillance is at the same time research and practice, although an emphasis can be on one or the other, perhaps differing at various times in the course of the investigation. What is required in either case is the articulation of ethical principles that justify and possibly limit the collection of data. Another step would be to develop a mechanism to oversee ethical aspects of public health practice that currently have no ethical oversight. Reform of the current systems could serve to appropriately situate the regulation of human subjects protections relative to public health more broadly.

^{5.} CDC Guidelines, supra n. 2.

^{6.} Amy Fairchild, Dealing with Humpty Dumpty: Research, Practice, and the Ethics of Public Health, *J of Law, Medicine, and Ethics*, 2003; 31 (4): 615-23.

Quality improvement in clinical settings

To demonstrate the uncertainties in this area, let us consider two case examples. In the first, a quality improvement project in a US hospital aimed to improve the dialysis measures of adequate blood cleaning through better compliance with dialysis prescriptions⁷. The proposed project was not submitted for review by the Research Ethical Committee (REC) in the institution. Following completion of the project, two scholarly papers were published in journals. In compliance with the REC's rules, a faculty member involved in the project reported the publications to the REC. The committee determined, after the fact, that the project was research and should have been submitted to it for review. The faculty involved in the project appealed to two federal agencies for clarification of the matter. The two federal agencies consulted disagreed with each other about whether the project was research⁸. The US federal agency that oversees research eventually ruled that the activity was research and should have had review by an REC⁹.

In the second case, a leading US medical school developed a Quality Improvement (QI) program with a checklist designed to prevent hospital infections. The checklist was initiated in 108 intensive care units, and the study found that rates of infection were lowered in the units, and lives and money were saved¹⁰. The authors of the study published their results in the *New England Journal of Medicine*. When the published findings became known to the US Federal agency that has the responsibility for overseeing ethical aspects of research, the agency wrote to the medical school that designed and sponsored the project, claiming that these activities were human subjects research and were done without proper REC approval. The agency ordered the activities using the checklists in the intensive care units to halt immediately. The medical school replied that they considered the activity exempt from review by the research ethics committee, but admitted that the REC should have made that decision rather than deciding on their own. The hospitals, for their part, replied that their involvement in the project was QI, and not human subjects research. When journalists learned about the episode, they reported it in the popular press. The case caused a furor and public outcry, with many people condemning the federal oversight agency for shutting down what was obviously a beneficial project. A program that succeeded in reducing infections and saving lives and money, was shut down arbitrarily by an agency on what appeared to be a mere technicality. In an interesting turn of events, following the negative publicity, the federal oversight agency reversed its decision¹¹.

How should we understand the ethical requirements when quality improvement projects are initiated in clinical settings? The requirements for protection of human subjects of research appear to apply, as well, in many quality improvement projects. Privacy concerns exist in QI as well as in research; trying a new mode of treatment in a hospital may place patients at risk or make them worse than the current mode of treatment. Typically, QI studies make no attempt to obtain informed consent from patients. Interestingly, it is usually the behavior of physicians or other health professionals that is being studied, with the aim to improve some aspect of patient care. When QI projects are treated as research, it is the health workers who must grant consent to be studied, not the patients. One study design for QI projects is to compare a new mode of care with an existing one in two different clinical settings or in different units of the same hospital. With that design, a QI project becomes indistinguishable from a study using a "control group", just like research.

Similarly to the situation regarding public health practice and research, it is

Joanne Lynn, When Does Quality Improvement Count as Research? Human Subject Protection and Theories of Knowledge. Qual Saf Health Care 2004; 13:67-70.

^{8.} Jeffrey Brainard, Government and Politics section, *The Chronicle of Higher Education* (November 26, 2004): 21.

^{9.} Joanne Lynn, supra n. 7.

Mary Ann Baily. Harming through Protection? *New England Journal of Medicine*, Volume 358:768-769, February 21, 2008. Available at http://content.nejm.org/cgi/content/full/358/8/768. Accessed 2 November 2008.

^{11.} Linda Carroll, A Boost for QI Research, *The Hospitalist*, September 2008. Available at http://www.the-hospitalist.org/details/article/187749/A_Boost_for_QI_Research.html. Accessed 2 November 2009.

argued that if all QI projects were treated as research, then QI projects would be much slower to get started because proposed projects would have to undergo prospective review by a research ethics committee. That, in turn, would increase the work load of existing committees and would place additional burdens on those doing the QI by requiring detailed reports. Moreover, if it were deemed necessary to obtain individual informed consent from patients, that would make projects logistically impossible to carry out. But exactly the same problem arises in the type of research known as cluster randomization. It is not individual patients or research subjects who are randomized but rather, institutions or units in a health care facility. Arguably, patients in a hospital or other clinical facility where such studies are undertaken should be notified. But it would be impossible to carry out the research or QI project if patients were given the opportunity to opt out.

In general, those conducting studies that might qualify either as research or as QI prefer to classify them as QI. As already noted, QI does not require preparation of a detailed protocol or review and approval of the protocol by a committee. Therefore, QI activities can be designed and implemented without the need for changes that may be required by an REC. Nevertheless, there are other points investigators consider to be in favor of treating a proposed project as research rather than QI even when the project clearly seems to be QI and not research. Practitioners may wish to present it as research if they think the results may warrant eventual publication. Many people hold the belief that if publication is intended, it must therefore be research. This is because journal editors will question whether research ethics committee approval has been obtained. In addition, as the examples cited above indicate, past experience demonstrates the trouble that may ensue from an REC or governmental oversight agencies when studies are considered QI rather than research and not submitted for REC review. As in the case of seeking to distinguish public health practice from public health research, the attempt to draw a sharp line may simply be futile¹². Those designing and implementing a project should consider the options carefully and choose what they take to

12. David Doezema and Mark Hauswald, Quality Improvement or Research: A Distinction Without a Difference? *IRB: Ethics & Human Research* 24 No. 4 (2002): 9-12.

be the ethically right course of action, with an adequate justification for whatever choice they make.

Determining what is "standard of care"

Identifying the "standard of care" in medical practice can have implications for the design of research and review and approval of a research protocol by an REC. The line demarcating research from medical practice is typically clear in the case of experimental drugs and devices. New drugs and devices must be approved by a regulatory agency before crossing the line between research and accepted medical practice. However, other medical interventions lack the "bright line" provided by regulatory agency approval. These include new surgical procedures, new routines introduced into an intensive care unit (ICU) or other unit of a hospital, and newly developed procedures for treatment that do not involve new drugs or devices. The following example illustrates the problems involved in this "grey area."

The example is a protocol for a procedures known as "early goal directed therapy" (EGDT) to deal with sepsis in the emergency room, a serious medical problem that physicians deal with frequently¹³. An intensive care protocol that was tested by a prominent researcher demonstrated a dramatic benefit in reduced mortality of patients admitted to the emergency room. This benefit was reported in one paper published in a leading medical journal. Because this medical procedure did not undergo the type of rigorous research typical of investigations on new drugs, a degree of uncertainty remained about the efficacy, and in some cases the appropriateness, of this highly intensive medical journal led to the adoption of this intervention by some emergency departments. However, the question arises: at what point could it be considered "standard of care"?

^{13.} This example was provided to me in personal communication by a student, who requested that details not be included in any published commentaries on the situation described herein.

How is the standard of care for a medical procedure normally determined? The answer is not entirely clear. This is at least partly because the term "standard of care" began as a medico-legal concept in the practice of medicine. As one expert in health law has noted: "Standard of care' is a legal term denoting the level of conduct a physician or health care provider must meet in treating a patient so as not to be guilty of negligence, usually called malpractice... This is a profession-centered standard, and encompasses a wide range of practices¹⁴." It is evident that this medico-legal definition is of limited value in determining what is the standard of care in particular circumstances where a lawsuit or a charge of medical malpractice is not at issue.

The relevance of this issue in the context of research takes us back to the distinction (or lack) between QI and research. If a particular medical intervention can be considered the standard of care, then studying its implementation in a new setting may be considered QI rather than research. However, if the intervention is not considered the standard of care in that setting, a proposal must be prepared for submission to the REC and evaluated according to the ethical requirements for review of research.

How much evidence is needed before a new medical or surgical procedure can be considered the standard of care in that branch of medical practice? Does evidence always have to be a result of randomized, controlled clinical trials, as is true for experimental drugs? Does endorsement of a treatment protocol by a professional medical or surgical society determine that it has become standard of care? How many papers validating the procedure must be published in reputable journals in the field? There are no clear answers to these questions.

However, in situations where it appears clear that a medical intervention has become the standard of care, a variety of reasons exist for studying the implementation of that intervention in a clinical setting. A study may look at the time it takes to implement a new procedure in the hospital or unit; the skill of practitioners in implementing a complex new routine may be the object of study; and often, it is the monetary cost of the implementation that is under investigation. Thus the questions posed in studying the implementation of a procedure may differ sharply from studying the safety and efficacy of the procedure itself, which is the typical focus of initial research on the procedure.

An implementation plan appears to resemble a QI study rather than research. Nevertheless, it remains unclear. A full protocol may not (or need not) be submitted to the REC for review. It may -or need not- be compared with the existing intervention in that hospital or unit. Interestingly, however, even if such investigations do undergo REC review, the risks would be assessed differently from a typical research study in which the outcomes include the safety of the procedure in patients. Finally, the intervention would not require informed consent from seriously ill patients or their representatives if it is introduced as a newly developed hospital procedure. But if it is considered research, then the individuals whose behavior is being studied would be the physicians and other health care personnel, and their informed consent would be necessary since they would be the research subjects.

Some (tentative) conclusions

It should be clear from the foregoing discussion that attempts to make a sharp distinction between research and public health practice or quality improvement may be an exercise in futility. When genuine uncertainty or overlap exists, it is arbitrary to seek a definition that makes a clear distinction. Instead, what is needed is ethical oversight of such activities whether they are determined to be research or non-research: human beings may be placed at risk, their privacy may be intruded, and psychological or social harm may result from the inquiry itself or from a breach of confidentiality.

As others have noted, the rules and procedures for prospective review of research by an REC are probably ill-suited to ethical review of many public health and QI activities. Participation in research is optional, whereas arguably, patients and health care providers have a responsibility to participate in

^{14.} George J. Annas, *Standard of Care: The Law of American Bioethics* (New York: Oxford University Press, 1993): 4.

QI to ensure that appropriate measures are in place for the safety and well being of patients¹⁵. A mechanism should be established for ethical oversight for public health practice and QI, but that mechanism should not be the existing REC that reviews research in that institution or setting. And finally, ethical guidance is necessary as well as a mechanism for review. The elaborate international guidance and the national laws and regulations that exist for research with human subjects should be supplemented by ethical guidance that addresses public health practice and quality improvement in clinical settings.

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- Double Standards in Medical Research in Developing Countries (Cambridge: Cambridge University Press, 2004).
- Against Relativism: Cultural Diversity and the Search for Ethical Universals in Medicine (New York, Oxford University Press, 1999).
- Surrogates and Other Mothers: The Debates over Assisted Reproduction (Philadelphia: Temple University Press, 1994).
- Enemies of Patients: How Doctors are Losing Their Power and Patients Are Losing Their Rights (New York, Oxford University, 1993).

^{15.} Joanne Lynn, supra n. 7.

Publications

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