The Ethics of Clinical Research in Developing Countries

by Joseph Brunet-Jailly

In a paper published recently in a prominent medical journal, the authors directly contested the ethics of the use of placebo controls in research on mother-to-infant HIV transmission carried out in developing countries.[1] However, a group of experts meeting at the World Health Organization in Geneva in June 1994 considered this type of research design as offering "the best option for a rapid and scientifically valid assessment of alternative drug regimens to prevent perinatal transmission of HIV."[2] Even the National Institutes of Health (NIH) strongly recommends this research design. When a research team from Harvard requested financing from the NIH for a study in Thailand to compare the reference regimen (set up by the ACTG 076 study) with three shorter-term treatments using zidovudine, the NIH suggested, instead, a placebo-controlled design rather than the originally proposed comparative design.[3]

According to the Declaration of Helsinki, "every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method."[4] Some people argue that this ethical principle will be respected if the patients in the control group are provided with the standard medical care prevailing in their country.[5] As pointed out by critics of the placebo-controlled design, this means no zidovudine for pregnant HIV-positive women in all poor countries. To these critics, this double standard—that is, one standard for those in the "north," who have ready access to medical care, and another standard for those in the "south," who do not have nearly the same access to medical care—is unacceptable. It is unacceptable, they argue, to treat a patient involved in a research protocol differently, depending solely on whether he is from the north or from the south. And it is unacceptable to give a placebo to the patients in the control group when an efficient treatment exists. They believe there should be but one standard for all and that treatment of the control group with the best existing therapeutic method in the world is, thus, an absolute and incontrovertible ethical principle. As one critic noted,

> One reason why ethical codes are unequivocal about investigators' primary obligation to care primarily for the human subjects of their research is the strong temptation to subordinate the subjects' welfare to the objectives of the study. . . . It is sometimes argued explicitly that obtaining a rapid, unambiguous answer to the research question is the primary ethical obligation. With the most altruistic of motives, then, researchers may find themselves slipping across a line that prohibits treating human subjects as means to an end.[6]

In what follows, I argue that the "best therapeutic method" principle, when applied solely to the subjects of the research, largely neglects the requirements for justice inherent in ethics, as well as the real meaning of informed consent.

Justice

Is there a justification for treating patients who become subjects in research protocols differently from patients who do not? By defining their own ethical criteria, ethicists and the research codes they promote, and the researchers who comply with such codes, are naturally protected from criticisms; from this point of view, the more rigid the criteria, the better. One can write without hesitation that the standard of care is "a normative standard of effective medical treatment, whether or not it is provided to a particular community."[7] But research intervenes within a society; in effect it defines three communities: those who participate in the experimental arm; those who participate in the control group; and, inevitably, the "others" in society, who suffer the same health condition but who do not participate in the trial at all. Research agrees on the treatment of the community of cases in a way that is consistent with ethical principles; it agrees on the treatment of the community of controls in a way that is also consistent with ethical principles; but it does not concern itself with the situation of the particular community comprised of the "others." Where is the justification here?

This issue has been somewhat addressed in the context of developed countries with regard to placebo-controlled clinical trials involving new drugs to fight AIDS. It frequently happened that the patient-subjects enrolled in these trials abandoned them *en masse* or totally altered them by suppressing randomization and/or by sharing drug doses between cases and controls. With such behavior, the requirements for true voluntary enrollment in the clinical trials had to be more clearly specified. One of those requirements was that all patients should have effective access to the investigational drugs without any obligation to participate in a clinical trial[8]—in direct opposition to the current standard in most Western countries, where only those in the experimental arm of a trial are provided the investigational drugs and the community comprised of the "others" is ignored.

Giving everybody effective access to the investigational drug ends up suppressing the three-way distinction among communities. Doing so makes the research design much more difficult to implement. But when all have access to

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does not prevent subpoenas seeking its production from being issued. A researcher who fails to respond to a subpoena may face serious consequences. The subpoenaing lawyer may seek to compel production in accordance with the subpoena if a response is not made within the time set out in the subpoena. Failure to comply with a court order to produce the requested information could subject the researcher to contempt of court proceedings and corresponding penalties. Accordingly, a researcher faced with a subpoena for confidential research data should respond to the subpoena by taking appropriate legal steps (in consultation with an attorney for the health care institution conducting the research) to prevent disclosure of the data. In practice, informing the lawyer who issued the subpoena of the legal protections applicable to the data may be all that is required. Once she understands that the law prevents her accessing the information, she may be willing to withdraw the subpoena. If the subpoenaing lawyer refuses to withdraw the subpoena, the next step would be to ask the court to quash or dismiss the subpoena. This would entail submitting legal documentation to the court explaining why the subpoenaing lawyer should not get access to the data.

Protective Orders. If other protections are not available, the researcher may still be able to protect the confidentiality of research data that is sought by subpoena by seeking a protective order from the court. Under discovery rules, judges have broad discretion to craft appropriate protective orders.[22] Judges should balance the need for evidence in the legal proceedings against the need to maintain confidentiality of research data. If production of research data will take place, it may be possible to minimize the impact.[23] For example, a judge might order that the underlying data be produced, but without identifying information. This was the approach taken in *Farnsworth v. Procter & Gamble Co.*,[24] which affirmed the issuance of a protective order permitting the Centers for Disease Control to withhold the names and addresses of women who participated in research on toxic shock syndrome when producing the research data. In that case, the CDC contacted the participating women and some of them agreed to speak with Procter & Gamble. Alternatively, a judge might require production of confidential data, but limit disclosure of the data only to parties to the lawsuit and their attorneys and require that those people agree to keep the data confidential.[25] Another approach could be to order disclosure of confidential material to a neutral third party.[26] This approach would allow the requesting party the ability to have independent analysis conducted on the data without compromising the identify of research subjects. Creative approaches may protect sensitive information, while allowing some disclosure.

CALENDAR

NOVEMBER 11-12 Arizona State University and Samaritan Health System in Phoenix will cosponsor an NIH/FDA Human Subjects Protection Workshop, **Contemporary Issues in Behavioral Research**, to be held in Tempe, Ariz. For information: Darlene Marie Ross, Office for Protection from Research Risks, National Institutes of Health, 6100 Executive Blvd., Suite 3B01, MSC-7507, Rockville, MD 20892-7507; (301) 435-5648; (301) 402-0527 fax; dr20a@nih.gov.

DECEMBER 5-7 Public Responsibility in Medicine and Research (PRIM&R) and Applied Research Ethics National Association (ARENA) will hold their annual **IRB conferences and 25th Anniversary Gala** in Boston, Mass. For information: PRIM&R/ARENA, 132 Boylston St., 4th Floor, Boston, MA 02116; (617) 423-4112; (617) 423-1185 fax; prmr@aol.com; www.aamc.org/research/prmr.

Conclusions

Legal protections are available to protect the highly sensitive and private information AIDS researchers gather from their research subjects. Researchers may be unaware of these protections and may leave their data vulnerable to compelled disclosure. Several available protections will allow researchers to fulfill their obligations to their research subjects to protect confidential information from disclosure as completely as possible.

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20. S.D. Codified Laws, §34-14-1 (1998).
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22. Federal Rule of Civil Procedure 26.
23. Deitchman v. Squibb & Sons, Inc., 740 F.2d 556 (7th Cir. 1984).
24. See note 1, Farnsworth v. Proctor & Gamble Co. 1985.
25. See note 2, Application of American Tobacco Co. 1989.
26. See note 23, Deitchman v. Squibb & Sons, Inc. 1984.

The Office for Protection from Research Risks lists contact people for additional information on certificates of confidentiality on its web page.[13] Researchers should consult this list and contact the appropriate person to obtain an application and if they have questions about obtaining a confidentiality certificate. If research is federally funded, the confidentiality certificate may be available directly from the funding agency.

To date, no court cases have been reported regarding confidentiality certificates in expanded research contexts. Accordingly, it is uncertain whether the extensive protections against disclosure will stand up in actual practice. One case, *People v. Newman,* was decided under the previous statute. In that case, a witness to a murder "told police that she believed she had previously seen the killer in the waiting room of a methadone maintenance treatment clinic . . . where she was also a patient."[14] The director of the clinic was served with a grand jury subpoena requesting that he produce photographs of patients who met certain criteria. (The clinic maintained the photographs to ensure that only eligible patients received methadone.) The director refused to obey the subpoena and was found in contempt of court. On appeal, the court reversed, holding that the confidentiality certificates the director received from the Secretary of Health, Education and Welfare and the Attorney General protected the records and that the director could not be compelled to produce the photographs in the criminal proceeding.[15] Because this case was decided under the older statute by a New York state court, a court deciding a case involving the scope of a federal confidentiality certificate under the new statute would not be required to follow its ruling. Nevertheless, the strong protection of confidential data may be persuasive to other courts.

State Research Protections. States laws may provide other protections for confidential research records. California, for example, has enacted legislation that provides broad protections to AIDS-related research records against disclosure in California legal proceedings.[16] Under this legislation, personally identifiable research records from AIDS-related research are confidential and disclosure of them may not be compelled. There are some exceptions to the prohibition on disclosure of confidential AIDS-related research records, including: (1) where the research subject consents in writing; (2) for audit purposes; (3) "to meet a bona fide medical emergency of a research subject" and (4) for public health department special investigation. In addition, production of confidential research records may be compelled in criminal proceedings or investigations against the research subject, but only if the court "finds there is reasonable likelihood that the records in question will disclose material information or evidence of substantial value in connection with the criminal charge or charges or investigation, and there is no other practicable way of obtaining the information or evidence." The burden is on the person seeking disclosure to show good cause to produce the documents and the court must "weigh the public interest and need for disclosure against the injury to the research subject and the harm to the research being undertaken." If the court orders disclosure, it should impose limits on that disclosure as necessary.

The California statute requires that participants in an AIDS-related research study be informed of the protections under the confidentiality statute. It also provides for civil and criminal penalties for disclosures in violation of the statute. "Confidential research record or records" is defined as "any data in a personally identifying form, including name, social security number, address, employer, or other information that could, directly or indirectly, in part or in sum, lead to the identification of the individual research subject, developed or acquired by any person in the course of conducting research or a research study relating to AIDS."[17] The statute applies to any research "relating to Acquired Immune Deficiency Syndrome (AIDS)." Accordingly, although the statute does not use the term HIV, HIV-related research should be covered by the statute because HIV is the causative agent of AIDS.

While the California statute protecting AIDS research records appears to be unique, other states offer protection to research records where that research is conducted by or with the state agency responsible for public health. For example, Massachusetts, North Dakota, and South Dakota have laws that restrict the use of the confidential research data for research purposes and provide that the information is not admissible in any legal action.[18-20]

Medical Records Protections. Depending on the context of the research, state laws protecting the confidentiality of medical records may also provide protection for research data. If the research information is collected within the context of providing medical treatment and the data is maintained within medical records, then medical records legislation will afford some protection for the data. However, this protection likely will be less extensive than that provided by the research-specific protections described above. Many medical records statutes include exceptions to the general rule that medical records must be kept confidential. They permit, for example, disclosure of medical records when the patient initiates legal proceedings in which her medical condition is at issue (e.g., in a medical malpractice suit or disability claim). In addition, California, for example, permits disclosure of medical records in a criminal action against the patient. Unlike the statute protecting AIDS research records, there is no requirement to show good cause to obtain disclosure of medical records for use in a criminal action.[21] Thus information obtained through a research project about a subject's drug use and included in the subject's medical record could be used against the subject in a criminal action.

Responding to Subpoenas. The fact that legal protections exist for confidential research data

may be invoked. Because the availability of these protections may vary depending on the research context and on state law, researchers will need to consider which protections apply to a given research project.

Why Worry About Confidentiality?

In obtaining consent to participate in a research study, researchers typically assure subjects that they will take steps to protect the confidentiality of the information the subjects provide. Researchers have an obligation to their subjects to protect the confidentiality of the information. This obligation stems from two separate ethical principles. Under the principle of beneficence researchers have an obligation to minimize harms to subjects that might arise from their participation in the research study. Confidentiality is required to minimize the risks of discrimination and other social harms. In addition, under the principle of respect for persons researchers have an obligation to respect the privacy of the research subjects. As a practical matter, researchers must provide assurances that the information they collect will be treated confidentially if they want research subjects to provide sensitive, private information.

What Protections Are Available?

At least four different types of legal protections may be available to a researcher for protecting identifiable research data: federal confidentiality certificates, state research protections, state medical records protections, and protective orders from the court.

Federal Confidentiality Certificates. A federal confidentiality certificate may be issued to qualified research projects that permits a researcher to withhold "the names or other identifying characteristics" of the subjects from people not connected with the research project, even if faced with a subpoena or a court order.[4] Although confidentiality certificates previously were available only to those engaged in research involving mental health or drug use,[5] in 1988 the protections were extended to "persons engaged in biomedical, behavioral, clinical, or other research" (42 USC 241(d)). The research project does *not* have to be federally funded to qualify for a confidentiality certificate.[6] The certificate protects confidentiality in *any* legal proceeding, whether it is federal, state, or local (42 USC 241(d)).

The Public Health Service issued an Interim Policy Statement (dated 22 May 1989) outlining the PHS's policy on granting confidentiality certificates.[7] The policies outlined by the PHS track the regulations issued when confidentiality certificates were limited to mental health or drug use research[8] and the PHS Interim Policy Statement indicates that it will look to those regulations for guidance.[9] These regulations are being rewritten and the revised regulations are expected to cover the broader scope of confidentiality certificates.

A researcher must apply for a confidentiality certificate. The justification for requiring a confidentiality certificate should be carefully spelled out because, according to the PHS Interim Policy Statement, the protection will be granted "sparingly." To qualify for a certificate, the research must be "of a sensitive nature" and protection must be "necessary to achieve the research objectives." The PHS lists the following research categories as "sensitive":

> a) Information relating to sexual attitudes, preferences, or practices; b) Information relating to the use of alcohol, drugs, or other addictive products; c) Information pertaining to illegal conduct; d) Information that if released could reasonably be damaging to an individual's financial standing, employability, or reputation within the community; e) Information that would normally be recorded in a patient's medical record, and the disclosure of which could reasonably lead to social stigmatization or discrimination; [and] f) Information pertaining to an individual's psychological well-being or mental health.[10]

Most HIV research will fall within one if not more of these categories. Projects that fall within the stated criteria, specifically including a showing of special need for confidentiality, typically will be granted the requested certificate; however, if there are other means of protecting the confidentiality of the data, such as not using identifiers, those methods are preferred.

Under the previous regulations, the effective date of the certificate is the *later* of the date of issuance or the commencement of the research (42 CFR 2a.6). The sample confidentiality certificate attached to the Interim Policy Statement uses this same effective date.[11] Accordingly, to provide the most protection for eligible projects, researchers need to obtain a confidentiality certificate at the earliest opportunity before research commences.

Certificates are issued to discrete research projects only. Significant changes in the research project may require reauthorization of the certificate (42 CFR2a.6). Researchers should allow up to three months for the application process, although it may take longer if special problems arise.

The PHS requests that the proposed confidentiality certificate be submitted with the application. The proposed confidentiality certificate must include certain features, including: (a) any exceptions to the protection afforded by the certificate, including disclosure of identifying information where the subject has consented in writing, review of records for DHHS audit purposes and under FDA legislation, and any circumstances in which the researcher would voluntarily disclose information (e.g., infectious disease reporting); (b) the researcher's obligation to use the certificate to avoid compulsory disclosure and to inform the research subjects of the protections—and the limits of those protections—provided by the certificate.[12]

Does the advertisement disclose important features of the study design that may influence enrollment: e.g., the use of placebos or the requirement for prior medication withdrawal?

Does the advertisement mention that risks will be disclosed prior to study enrollment?

IRBs should carefully review the inducements offered by advertisements to ensure that they are not "undue." To obviate the risk of undue inducement, we suggest that IRBs recommend that investigators prepare recruitment advertisements that appeal to altruistic motivations, rather than appealing exclusively to individual benefits for sick patients.

Conclusion

Recruitment of research subjects is the first stage of the informed consent process. Advertisements are a common tool for subject recruitment and therefore should be evaluated in light of their potential impact on the informed consent process. We have analyzed advertisements as posing the related risks of contributing to the therapeutic misconception that confuses clinical research with clinical care and of creating undue inducements for research participation. Ethical evaluation of advertisements by IRBs calls for balancing the goal of promoting access to clinical research with protecting vulnerable patients from exploitation.

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Practicing Safer Research

Using the Law to Protect the Confidentiality of Sensitive Research Data

by Leslie E. Wolf and Bernard Lo

Introduction

In research on HIV, investigators often collect highly sensitive and private information, such as data on sexual behaviors and drug use. Disclosure of this information could subject the research participants to embarrassment, discrimination, stigma, or even criminal prosecution.

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Researchers generally take steps to protect the confidentiality of their subjects and the information they have provided. For example, researchers commonly use codes to identify individual participants. They may store the key to the code in a safe or locked drawer which may be accessed by only a few members of the research team. In some projects, data may be collected anonymously or stripped of all personal identifiers.

While these steps to protect research subjects' confidentiality are important, they may not be enough. Researchers also need to take steps to protect their research data from compelled disclosure pursuant to a subpoena or court order. For example, research records for a specific research subject could be subpoenaed by a prosecutor for use in a criminal case against the subject involving possession of drugs. Records could also be sought in civil cases, such as custody disputes. Although unlikely, a prosecutor could subpoena the entire data set to assist in prosecution of known prostitutes. Scientists conducting research on topics such as toxic shock syndrome and asbestos have had their data subpoenaed for use in product liability lawsuits.[1,2] Unfortunately, researchers may be unaware of the available legal protections and, therefore, their data may be vulnerable to disclosure. Theoretical analyses of legal protections for confidentiality have been published.[3] This article takes a more practical approach: to describe and analyze the types of legal protections for confidentiality of research data and how those protections

of charge is a standard feature of clinical research, which advertisements typically highlight. Without this provision, research participation would not be a financially reasonable proposition for most patients and recruitment into clinical research would be seriously impaired, if not impossible. The offer of free examinations and treatment is morally problematic only if it induces people to volunteer for clinical research because they lack access to needed medical treatment. With 43.4 million Americans lacking health insurance in 1997 and approximately 71.5 million without insurance for at least part of the year, the offer of free treatment takes on the potential for inducement that might be considered undue.[11] Moreover, many persons with health insurance lack coverage for prescription drugs, which may make the offer of free medication attractive.

Some recently collected data help to elucidate this issue. In connection with the President's Advisory Committee on Human Radiation Experiments, 1,882 patients in outpatient clinics at 16 hospitals across the country (including major academic medical centers, VA medical centers, and large community hospitals) were interviewed concerning their participation in clinical research.[12] Twelve percent of the patients had no health insurance, which is roughly comparable to the general population. Of the 380 patients who reported that they had participated in treatment studies, 28% stated that a reason which "contributed a lot" to their decision to participate in research was the fact that this was "the only way to get specific treatment," and 11% stated that this was the "best way to pay for treatment." With respect to this latter finding the authors of the interview study observe, "This finding is morally troublesome since decisions regarding participation in research should not be influenced by constraints on access to health care."[13] No less morally troublesome would be to exclude from clinical trials those without health insurance or the ability to pay for needed treatment, for this would infringe equitable access to research and subject selection.

Is the offer of free treatment in exchange for research participation an unfair bargain in view of our current health care system? We contend that the offer of medical examinations and study medications at no cost is an important informational component of advertisements for clinical research. Since the problem of potentially undue economic inducements for research participation stems from the lack of universal access to health care in our society, an equitable solution does not lie within the purview or power of institutions that conduct clinical research. Nevertheless, advertisements should balance inducements aimed at recruiting subjects with adequacy of disclosure about research participation.

A subtler, but more pervasive, aspect of inducement concerns the tendency of advertisements for clinical research to appeal to the neediness of persons who are suffering from diseases. By targeting the negative symptoms of illness, advertisements play on the vulnerability of patients. In some cases, advertisements suggesting that research participation provides medical benefits to suffering patients may offer undue inducement, as well as contribute to a conflation between research and clinical care.

The Focus of Advertising

Patient volunteers have a hybrid status.[14] They are suffering persons in need of medical treatment, and they are individuals who choose to participate in scientific research. Advertisements reflect the tendency of clinical research to focus on patient volunteers as patients. The problems of fostering the therapeutic misconception and undue inducement might be diminished if advertisements for clinical research stressed the invitation and opportunity to volunteer for participation in research.

In the study of research participation cited above, [15] it was found that altruistic motivations were no less often reported than self-interested motivations. Of those patients in treatment studies, 76% indicated a "way to help others" and 69% "advance medical science" as major reasons for research participation; 69% indicated "gave hope" and 67% "chance to get better treatment." These data suggest that advertising appealing to altruistic motivations to contribute to scientific research and to help future patients might prove as effective as the prevailing appeal to individual benefit.

Recommendations

The regulations of the Department of Health and Human Services concerning Protection of Human Subjects—the Common Rule—do not mention advertisements for clinical research as within the purview of IRBs. The FDA, however, requires that IRBs review and approve advertisements to recruit human subjects. The extent of compliance with this guideline is questionable: in a 1988 survey of 74 medical school IRBs, less than 40% reported that they required prior approval of advertisements for recruiting human subjects.[16] Since advertisements may set the stage for interactions between patient volunteers and investigators and influence the quality of informed consent, they should be subject to IRB scrutiny and approval.

IRB oversight should aim at ensuring that advertisements strike a reasonable balance between the legitimate goal of recruitment and the adequacy of disclosure about the nature of clinical research. We recommend that IRBs review proposed advertisements in the light of the following questions:

Does the advertisement make clear that subjects are being recruited for research?

Does the message of the advertisement have the potential to contribute to confusion between research participation and standard clinical care?

Are the suggested benefits of research participation commensurate with the scientific protocol and consent forms?

consent. Patients who confuse participation in a clinical trial with medical treatment lack adequate understanding of what research participation involves. Undue inducement impairs the voluntariness of the decision to participate in research. This focus on advertisements in the light of informed consent is consistent with FDA guidelines: "Direct recruiting advertisements are seen as part of the informed consent and subject selection processes."[6] Ethical evaluation of advertising for clinical research needs to balance the legitimate recruitment function with fidelity to the standard of informed consent.

The Risk of Contributing to the Therapeutic Misconception

Given that advertisements may function as the initial step in the informed consent process, at the very least all advertisements for clinical research should mention that volunteers are being recruited for a study or for research. Nearly all the advertisements that we observed conformed to this minimal requirement; however, they frequently downplay the fact that research is involved. Two notable exceptions are the following. An advertisement placed by the National Institute of Alcohol Abuse and Alcoholism reads: "Is alcoholism destroying your family? If you are eligible we provide: free evaluation; a 5-week in-patient alcohol treatment program at no charge to you."[7] The reader may infer from the offer of free treatment that research is involved, but there is no explicit mention of this critical fact. Another advertisement states: "If you are African American & experience sudden intense rushes of anxiety that may include heart racing, dizziness, sweating, trembling, and numbness and tingling, you may be eligible for psychological treatment."[8] The only hint that this is an advertisement for research is its location in a column headed "Volunteers."

More significant than the bare fact of disclosing that volunteers are being recruited for research is the overall tenor of the message of the advertisement and the motivations to which it is directed. In most cases, advertisements for patient volunteers begin with bold type referring to a disease and/or symptoms. In the case of psychiatric research, these advertisements sometimes include pictures of people showing signs of psychic distress. The advertisements typically note that study medications and medical examinations or evaluations will be provided free of charge. It appears that the predominant intent is to gain the attention of persons who are suffering (or their family) and to offer personal benefit. The appeal to suffering patients risks creating unrealistic expectations for medical benefit, since there is no guarantee that patients will benefit from research participation. On the other hand, none of the advertisements that we observed appeal to altruistic motivations to contribute to scientific knowledge that might benefit future patients.

Even though advertisements almost always disclose that persons are being recruited for research, they typically appeal to prospective research subjects as patients seeking needed treatment rather than as volunteers invited to join investigators as partners in research. A major difficulty in this appeal to personal suffering and benefit is that it fosters the expectation that clinical research has the same individualized, patient-centered orientation that clinical care has, whereas in fact clinical research is designed primarily to produce generalizable knowledge about a class of patients. Accordingly, the prevailing focus of advertisements may contribute to the "therapeutic misconception," confusing clinical research and standard clinical care. Some commentators see the therapeutic misconception as a pervasive characteristic of clinical research that compromises informed consent.[9,10]

What Advertisements Do Not Communicate

Advertisements for clinical research also should be evaluated with respect to what they fail to communicate. None of the observed advertisements mentioned any risks of study participation. Detailed disclosure of risks is a matter for conversations between investigators and potential research subjects and for consent forms. However, advertisements at least should mention that risks of study participation will be disclosed and discussed before enrollment begins. Indeed, the fact that advertisements mention potential benefits suggests that they should not omit any mention of risks. Such omission may skew the perception of what is involved in research participation.

Another significant omission in observed advertisements is any reference to the use of placebos. There is no way of knowing the nature of the study design from most observed advertisements. It would be surprising, however, if none of them involved placebo controls, given the frequency of placebo arms in clinical trials. Investigators may fear that mention of placebos might dissuade some potential subjects from inquiring about research participation. On the other hand, advertisements that create the expectation of benefit and offer free treatment might incline patients to decide in favor of research participation without careful thought about the meaning of enrolling in a placebo-controlled trial. Unrealistic initial expectations may be fostered that are not dispelled by the subsequent informed consent process, even when the use of placebos and how this makes a clinical trial different from standard clinical care are adequately disclosed.

Clinical trials often require that patient volunteers stop prior treatment for a period of time before they receive medications under investigation. A few of the advertisements mentioned that patients must be free of medications as a condition of enrollment. It is not clear, however, whether this requirement was disclosed for all studies involving a drug washout.

The Risk of Undue Inducement

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Advertising for Clinical Research

by Franklin G. Miller and Andrew F. Shorr

The dramatic growth in funding of the National Institutes of Health and private sector efforts in drug development will increase the demand for research subjects in clinical trials.[1,2] Advertising is an established mechanism to recruit human subjects for research. This practice, however, has received scant ethical attention. In this article we examine ethical issues and make policy recommendations concerning advertising for clinical research. We focus specifically on newspaper advertisements directed at recruiting patient volunteers. The points raised are relevant to other forms of marketing for clinical research in broadcast media as well as on the Internet.

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There are important similarities and differences between advertising for health care and for clinical research. Nelson et al. argue that health care advertising should conform to higher standards than commercial advertising, since patients differ from consumers in significant respects.[3] Because the ill and injured in need of health care are vulnerable and dependent, health care operates in the context of an expectation of trust. Accordingly, they advocate evaluating health care marketing in terms of a fiduciary relationship between health care providers and patients: "Specifically, the means used in promoting health care services should be consistent with the ethical standards that bind providers."[4] (3) A fiduciary model of advertising for clinical research is appropriate for the very same reasons. In view of the history of abuses of trust in clinical research, stringent standards for advertising are appropriate. These standards, furthermore, should reflect the distinctive nature of clinical research. Unlike the individualized, patient-centered focus of clinical care, clinical research is aimed at producing generalizable knowledge via studies governed by scientific protocols.

Methods

We examined weekly issues of *Washington Post* health section from 1 December 1998 through 16 February 1999. A total of 111 advertisements addressed to persons suffering from particular diseases or specific symptoms were identified. The number of distinctive advertisements is considerably less, since many of them appeared in more than one issue. Sponsors of the advertisements included institutes of the National Institutes of Health, academic medical centers, for-profit research firms, physician practice groups, and individual investigators.

Ethical Framework

For many research participants, initial interest may be stimulated by advertisements. This first, anonymous communication between researchers and patient volunteers may tap motivations, foster beliefs, and create expectations that influence research participation in ethically significant ways. Commentators on the ethics of clinical research have noted the need to balance the traditional normative framework of protecting the rights and welfare of research subjects with the more recent goal of promoting access to clinical trials.[5] Advertising to recruit research subjects serves the latter goal; however, the accuracy of advertisements about clinical research and the nature of the inducements they offer raise ethical issues pertaining to subject protection.

Our review of print advertisements for clinical research is animated by two related ethical concerns: (1) Do they promote a realistic understanding of what is involved in research participation, or do they obfuscate the important differences between clinical research and standard medical care? (2) Do the inducements offered to participate in research unfairly take advantage of the neediness of potential research subjects? Both of these concerns are relevant to the basic standard of informed

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ANNOTATIONS

American College of Obstetricians and Gynecologists. "Ethical Considerations in Research Involving Pregnant Women." *Women's Health Issues* 9 (1999): 194-8.

The ACOG Committee on Ethics has developed a "Committee Opinion" statement addressing informed consent, the role of primary caregivers in consent, and risk-benefit balancing for women and fetuses involved in clinical research. Commentaries by Virginia Sharpe, Patricia Roche and Michael Grodin, Frank Chervenak and Laurence McCullough, and Elena Gates follow this article. These commentaries look at the new guidelines in comparison to the existing federal regulations, paying special attention to balancing maternal-fetal harms, paternal consent, and innovative therapies.

Edwards, Sarah J. L., et al. "Ethical issues in the design and conduct of cluster randomised controlled trials." *British Medical Journal* 318 (1999): 1407-9.

Randomization by cluster can be especially useful for trials involving public health education and intervention, and evaluation of health services delivery and policy. However, clustering gives rise to unique ethical issues with respect to informed consent and utility. The authors outline the ethical concerns of cluster trials, distinguishing interventions targeted at groups from those targeted at individuals but affect groups. To ensure the best interests of the group and group members, "guardians" should give informed consent before volunteering groups as subjects. In addition, the authors call for group-targeted interventions to have procedural safeguards, and individual-targeted interventions should involve individual informed consent.

Margurite Strobel
Research Assistant

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Well, economists are now measuring our lives, and their costs, and the exact benefit of each medical intervention! Engineers also pretend to solve complex problems with simple calculations, but the solutions they propose have often proved impracticable. But are the rights and interests of the patients concerned?

Yes, they are! The right of patients is certainly to obtain complete information about the medical care they receive as well as about the possible alternatives; their right is certainly to evaluate those alternatives; their right is certainly to refuse to participate in a study if they wish; and their right lies undoubtedly in the possibility to choose for themselves their own ends (provided that the latter also respect human dignity). Is dignity not entirely present in the decision to participate in a protocol of public interest? The personal evaluation of one's interests, which is what each patient will do if he is effectively granted the right to express himself, will necessarily involve subjective aspects, but this individual expression and subjectivity must be respected. This is the expression of human dignity! In addition, one has to consider the cultural context specific to the subject's community, which must also be respected as long as it is itself respectful of human dignity. Wouldn't it be better to allow the parties concerned to define for themselves their own interests? Wouldn't it be the best way to respect their dignity, their rights as well as their interests?

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conditional requirement in itself does not tell us how to respect dignity in particular and concrete situations. As Roviello notes, "in a plural world, the tolerance principle according to which we acknowledge each individual has an equal right to think and to act by himself, and through which we indirectly acknowledge the necessity and the relevance of a negotiation about 'values,' is the main guideline for introducing into the real world the nonnegotiable requirement to respect human dignity, which essentially requires autonomy as a power to judge and act by oneself."[19] In other words, "this is precisely when I want for someone else the same as what I would want for me: I want that person to be treated as an autonomous individual and as an equal in dignity."[20] This is very far from the attitude of those ethicists who claim to be the best defenders of the "residents in impoverished, postcolonial countries, the majority of whom are people of color!" It is indeed true that the refutation of the paradigm of medical paternalism has just begun.[21]

Without ignoring the asymmetries of power or information, it seems that the self-declared ethical authority of the "north" is not compatible with respect for dignity. The issue of consent must be addressed much more carefully than it has been to date. It makes no sense to claim that the problem is simply solved by meeting "the requirements for informed consent which would have been prevailing if the work had been done in the United States."[22] Those requirements must be assessed in their specific anthropological context, which is, of course, difficult to do. But one cannot profess in the north to know "whether patients are justified in violating trial protocols for the sake of an individual advantage they might gain"[23] and distrust any consent provided by those in the south. Of course one cannot ascertain whether collective interest has a large influence on individual consent, but northerners do not have to decide on this point in place of the southerners concerned. Informed consent necessarily relates to the following crucial question: is the possibility of a personally guaranteed advantage or a possible future benefit for the community worth the constraints and possible risks entailed in the given research protocol?

We should not be afraid of being carried far away from the rules dictated by our northern ethicists. Remember that when taken seriously, informed consent must be obtained "even if a refusal might be considered as conflicting with the best interest of the patient."[24] There is but one very specific situation in which substituting the judgment of a third party for the subject's own judgment is justified: "The only purpose for which power can be rightfully exercised over any member of a civilized community against his will is to prevent harm to others; for his own good, either physical or moral, is not a sufficient warrant; he cannot rightfully be compelled to do, or forbear because it will be better for him to do so, because it will make him happier, because, in the opinion of others, to do so would be wise or even right," wrote J. S. Mill.[25]

Nor should we fear falling into the sort of relativism in which everything resulting from freedom is consistent with ethics. No, one must not confuse "the negotiation which compromises values by undermining the principle which is a constituent of their ethical consistency, with the one which is not only justified but also imperatively required because it originates in the principle of equal distribution in the respect" of human dignity.[26]

Procedures and conditions relative to informed consent have to be specified, enforced, controlled and evaluated,[27,28] but there are absolutely no grounds for claiming that such procedures and conditions should be those prevailing in the north. Unquestionably, public authorities are already trained to negotiate consent contracts (research approvals, decisions by ethics committees), but no one knows whether the dignity or, more simply, the rights and interests of patients are really taken into account. All research takes place in such a context of uncertainty. Therefore, any ethical reflection on research should refer not to those so-called universal rules based on principles that are abstract and applicable in any context, but rather to the practical conditions under which, in a particular place and at a particular time, the decisions will only be influenced by the unconditional obligation to respect the dignity of human beings, preferably through educational and democratic procedures.

But we must also look beyond the principle of case-by-case negotiation on the conditions of each research project, whether with governments or with individual subjects. We argue for an ethical perspective that is not limited to research alone. Therefore we must ask whether there exist, in the society, other decisions or negotiations where the rights and interests of all patients (not just of those involved in research protocols) as well as of individuals who are in good health are engaged and are to be respected.

Just one example: how can one be sure that a particular intervention is more beneficial than another intervention if the latter could have been implemented with the same amount of resources? Can one rely on cost-effectiveness or cost-benefit analysis of the various interventions in the health sector? It seems increasingly clear that we can, as the global disease burden is assessed more and more precisely, disease by disease, continent by continent, age group by age group, measured by the number of years spent in good health (more precisely, disability-adjusted life-years).[29] The anticipated benefits from many well-proven medical interventions are also being assessed more and more precisely. It is already possible to draw some implications of this new knowledge to define priorities in the field of public health.[30] The benefits that can be expected from interventions that are not yet fully designed are also becoming quantifiable—in some cases, it is already possible to estimate the order of magnitude of the benefits that would result from a particular research direction.

the drug, patient-subjects in the experimental arm would deliberately submit themselves to the research protocol, controls would deliberately renounce the investigational drug(s), and the "others" could do what they deem good for themselves. This remains perfectly in line with the ethics of research as defined by the Declaration of Helsinki: "In research on man, the interests of science and society should never take precedence over considerations related to the well-being of the subject."[9] This is also in line with the principle of justice inherent in all classical presentations of medical ethics, i.e., "an act is not ethical unless it is equitable, that is, unless it is available to all who need it."[10]

Moreover, discussing effective access to investigational drugs shows that it is unfair to focus narrowly on the small group of subjects—the cases and controls—while ignoring the condition of the community of "others." It seems difficult to dispute that narrowly conceiving ethics as relevant only to *participants* in clinical trials, a conception typified by the Declaration of Helsinki, actually encourages research oriented toward the problems of rich countries rather than toward the problems that oppress the poorest countries. Such is the consequence of individualistically centered research ethics—in other words, of shortsighted ethics. If we believe the ethical principles of research are established and formulated in order to protect human rights, it is nonsense to apply them only and exclusively to a small group of subjects while ignoring the fact that these principles should be applied to all patients. Such pretense merely assuages one's conscience and leaves the issue unresolved.

This narrow conception also ignores the fact that the ethical ground for publicly funded research lies exclusively in the improvements in *collective* welfare that may stem from new knowledge. One can hardly suggest that a research effort supported by the community is of interest only to a single individual or that the focus of such efforts be limited to a minor problem in a minority. There does seem to be agreement that less attention should be paid to the minor problems of patients in the minority as long as the problems affecting the majority remain unsolved. Many research projects, simply because they use resources, deprive some patients of proven treatments to which they would or should normally be entitled: this is true in rich countries and even more so in poor countries. In both contexts, the poorest patients are also the ones who bear most of the costs of the decisions that stem from a narrow conception of ethics. Ethical reflection cannot focus exclusively on the rights and interests of the individual patients enrolled in research projects. The ethics of clinical research must be able to affirm that research will have an advantage for the community.

This issue of the legitimacy of research cannot be addressed, without hypocrisy, by considering only the effects on the patient-subjects involved in the protocols. The legitimacy of research involves an evaluation: one should be able to anticipate the cost of an expected benefit, which is essentially collective, at a price that will be charged to some particular individuals. Most of the time, the patients who suffer today will bear the cost for those who will benefit in the future. The ethical aspect of efficiently allocating scarce resources is obvious:[11,12] resources placed at researchers' disposal are ineluctably removed from other possible uses; for instance, they are diverted away from patients who might have been treated had those sums been invested in their direct care instead. Neither researchers nor ethicists bear the cost of research. The payers are the citizens; especially the sick.

These considerations lead us to examine the procedures that are preferentially used or proposed by ethicists to protect the rights and the interests of research subjects, primarily the requirement for informed consent.

Consent

In criticizing placebo-controlled trials Marcia Angell goes so far as to dispute the validity of the principle of informed consent: "informed consent, important though it is, is not protection enough, because of the asymmetry in knowledge and authority between researchers and their subjects."[13] Lurie and Wolfe reinforce this paternalistic position: "residents of impoverished, post-colonial countries, the majority of whom are people of color, must be protected from potential exploitation in research."[14]

This position seems quite comfortable for the researcher, but quite hypocritical for the citizen and quite contemptuous of the patient. Ethicists largely agree that no one is able to make a decision on an "entirely autonomous" basis[15] and that what is actually attainable consists of "substantially autonomous" decisions.[16] To conclude from this that ethicists or the state should put themselves in the place of the subjects actually giving consent is a step that should not be taken. When bargaining on the protocol conditions by ethics committees takes precedence over one-on-one discussion with each potential subject, the unassailable right of the patient to decide for himself in matters that concern him is withdrawn. This right to decide for oneself must be preserved for all, in all circumstances, in all countries.

Therefore, a further criticism of this shortsighted conception of ethics is in order: it has no memory of its origins. It has forgotten its roots in Anglo-American philosophy, which attaches greatest importance to the individual, to his or her autonomy of decision, and to the protection of his or her private life.[17]

Let's come back then to those foundations with an overview that is quite rough but, I believe, adequate. Dignity is an intangible dimension of each human being, a dimension that each human being faces as an "unconditional" requirement. That is, "a requirement which is also its own end and which cannot be a means to reach an end different from itself," a requirement "which makes sense in itself and by itself and not through something else than itself."[18] But to know that dignity is such an un-