Ethics of Clinical Trials in Family Medicine

John L. Coulehan, MD, Kenneth F. Schaffner, PhD, and Marian Block, MD
Pittsburgh, Pennsylvania

In this paper several issues are examined that arise from conducting randomized clinical trials in a family practice setting. The distinctive research tradition in family practice involves a patient's primary care physician performing an experimental investigation that usually, though not invariably, is focused on common health problems. Representative clinical trials are presented as examples that illustrate two ethical difficulties evoked by such research: (1) a potential violation of the primary care physician's therapeutic imperative to provide the best possible treatment for his or her patient, and (2) the likelihood that the type of physician-patient relationship fostered in family practice significantly diminishes the capacity of the patient to give true informed consent. In an attempt to resolve these ethical difficulties, a model of moral reasoning is presented that is based on easily understood ethical principles and is applicable to actual clinical decision making. Using that model, a tentative set of rules or guidelines is offered for implementing clinical trials in family medicine.

Family medicine has become, in little more than 15 years, an established academic discipline throughout the United States. While there was a vigorous tradition of general practice research in Great Britain, family medicine in this country began its academic endeavor with but a trickle of isolated clinical observations and reports. Its pioneers, however, fostered intense discussion about the growth and direction of family medicine research and established investigative programs in most university-related departments. During the same 15-year period a vigorous debate also ensued about the ethics of biomedical research, particularly with regard to such issues as confidentiality, informed consent, and randomization.[1-3] Family medicine places a high priority on teaching clinical ethics,[4-7] but few commentators have addressed the specific ethical questions generated from family practice research.

This paper explores issues arising from the conduct of clinical trials in the family practice setting. First, clinical trials are placed within the context of a broader research tradition that has developed in family medicine. Then, using case examples derived from actual clinical trials, two particularly thorny issues for family physicians are sketched: Do randomized clinical trials violate the primary care physician's therapeutic imperative? Does the physician-patient relationship, fostered in family medicine, limit the patient's ability to give truly informed consent? Finally, some tentative suggestions about rules for clinical trials in family medicine are presented.

From the Departments of Community Medicine, and History and Philosophy of Science, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. Requests for reprints should be addressed to Dr. John L. Coulehan, Department of Community Medicine, M-200 Scaife Hall, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261.

Family Practice Research Tradition

The individual research projects undertaken by family medicine investigators are not unique to that discipline either in methodology or in content. Considered in the aggregate, however, these projects suggest a research tradition that has important characteristics, differentiating it from the traditions of other specialties. First, family physicians perform research projects more frequently in the context of ordinary medical practice than is the case with other specialties, and the investigator is more likely to be the patient's primary physician. Second, projects often deal with common medical problems, particuarly those of a self-limited or chronic nature. The end points (eg, pain relief, satisfaction, fewer days in bed) available for analysis in such projects are "soft" in comparison with such "hard" end points as mortality or objective progression of disease. Third, because of its commitment to patient care, family medicine research deals frequently with process components of the medical endeavor. Such investigations might explore, for example, aspects of physician-patient communication or specific arrangements for medical care, such as scheduling systems or flow charts. Fourth, as family medicine emphasizes a unitary or biopsychosocial account of illness rather than mind-body dualism, its research places heavy emphasis on the psychological and social features of somatic problems.

None of these features, of course, is specific to family practice research. In fact, the discipline borrows heavily from and often cooperates closely with investigators from other medical specialties, psychology, epidemiology, sociology, anthropology, health services research, and additional disciplines. This multidisciplinary approach, with its freedom to cut across traditional academic domains, is a fifth characteristic of the family medicine research tradition.

Two hundred twenty-seven main articles and 75 communications published in *The Journal of Family Practice* during a two-year period (1982 and 1983) were reviewed to determine which methodologies were commonly employed in family practice research. *The Journal of Family Practice* includes 25 percent of all papers published by family medicine faculty.[8] About 65 percent of the main articles and 43 percent of the shorter communications were reports of research projects. Most of the research could be placed in one of two methodological categories: clinical series of patients observed during a specified time period, either retrospectively or prospectively (26 percent); and cross-sectional surveys, by questionnaire or interview of patients, physicians, medical students, or other personnel (31 percent). About one third of the patient series-type investigations employed prospective protocols that required, for example, a specified array of studies at various defined times, rather than an observation of the "natural history" of patient care. Only four main articles and two communications reported controlled clinical trials (2 percent).

Randomized clinical trials and other protocol-based studies were likely underrepresented in *The Journal of Family Practice* because investigators could choose to publish them in other journals. A MEDLINE search revealed 25 additional randomized controlled clinical trials published by family physicians during the four-year period of 1980 through 1983. Though this type of family medicine research remains in its infancy, the specialty is actively encouraging clinical trials and multicenter collaborations in its attempt to build a sound tradition of research in primary care.

Family medicine clinical trials entail the same ethical questions as other biomedical research using human subjects. However, particular characteristics of site, content, and methodology common to the family practice tradition lead to questions of particular concern for family medicine investigators. On a first view, it would appear that this tradition presents fewer tough ethical questions than those of, for example, cardiology or oncology, since the methods tend not to be invasive and could usually be classified by institutional review boards as entailing minimal risk for the patient. These very characteristics—that the studies deal with ordinary medical problems in an ordinary patient care setting using low-risk modalities—do, in fact, suggest that family physicians must wrestle at least as carefully as other investigators with two issues: a conflict between the therapeutic imperative of medicine and the collective ethic of research; and the healer's power of persuasion, which might limit autonomy and informed consent. The two case examples below, drawn from the recent family medicine literature,

will serve as an introduction to an analysis of ethical problems in clinical trials.

Case 1. A multicenter, double-blind study was undertaken to compare the efficacy of a new salicylic acid derivative to that of placebo in treating pain. About 1,000 adult patients suffering from acute or chronic pain were enrolled in this seven-day trial conducted by over 200 family physicians. Patients with pain caused by rheumatic disease, trauma, surgery, or dental procedures were included in this study. There were several exclusion criteria, but none related to the severity of pain. Patients were randomly allocated to therapy, and efficacy was evaluated by both the experimenter and the patient, using a visual analog scale at the end of seven days. The new drug produced more good-to-excellent pain relief than placebo.[9]

Case 2. Once-daily antimicrobial therapy is effective in preventing recurrent urinary tract infections in women, but drugs used for this purpose may promote selection of resistant strains. Family practice researchers undertook a trial to compare a new antibiotic, which seemed less likely to promote resistant strains, with placebo as prophylaxis over a six-month period. All patients gave their written informed consent. About 60 women were randomly allocated either to the new drug or to placebo therapy. About two thirds of these patients completed the study. Only a few of the patients taking the antibiotic had recurrent infections during the six months, whereas almost one half of those taking placebo had recurrent infections.[10]

Overview of Moral Reasoning

These two cases illustrate a major dilemma that lies at the heart of clinical research. This dilemma results from the investigator assuming a dual role of physician (healer) and, at the same time, of scientist. As scientist the investigator's chief concern is to adhere closely to the scientific canons of valid experimental design, which may require that he or she sacrifice the goal of individualized best treatment to promote statistical efficiency. The duty is to acquire new knowledge so that future patients might benefit. It represents devotion to a *collective ethic* to use Clayton's term, rather than an *individual ethic*.[11] As physician, however, the investigator has a duty to apply existing knowledge to provide the best possible treatment for each individual patient. This individual ethnic is articulated by various professional codes and can be termed the *therapeutic imperative*. The dilemma, then, is between an individual patient's best interest and the best interest of all future patients.

One method of resolving the conflict between physician as therapist and physician as scientist is to insist upon the patient's free and valid informed consent about participating in a clinical trial. The patient autonomously, perhaps through motives of altruism, elects to become a subject in the trial, thereby allowing the physician to assign a protocol-dictated treatment rather than an individualized treatment. In one view the patient elects to become a co-adventurer in the search for new knowledge rather than a mere object of scrutiny.[12]

Beauchamp and Childress[13] present a schema of moral justification, modified here in Figure 1. They suggest that justification for any decision is by appeal to higher levels in the schema; that is, a particular judgment is justified by an appeal to a rule, and a principle is warranted by reference to an ethical theory. Beauchamp and Childress articulate four general principles that they believe are useful to adjudicate conflicts among cases and rules in biomedical ethics: autonomy, nonmaleficence, beneficence, and justice.[13] Informed consent has its basis in the principle of autonomy. The rule that physicians have a therapeutic imperative derives from beneficence, but sometimes the attempts to help dictate that beneficence must be limited by the principle, often considered more fundamental, of nonmaleficence ("First, do no harm."). Clinical trials create situations that may not satisfy the latter two principles, even though they are performed in an ostensibly therapeutic context.

Limits to Informed Consent

Limits for the Physician

The physician's therapeutic imperative derives primarily from the principle of beneficence. His or her respect for a person's autonomy requires the

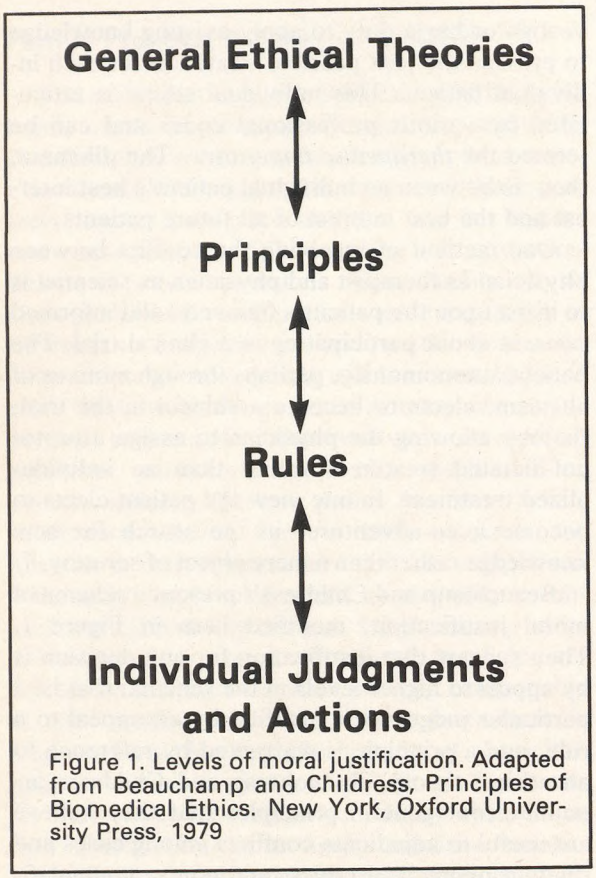

Figure 1. Levels of moral justification. Adapted from Beauchamp and Childress, Principles of Biomedical Ethics. New York, Oxford University Press, 1979

patient's informed consent be obtained prior to enrollment in a clinical trial. In a sense this informed consent yields a temporary, partial lifting of the duty to be beneficent in a particular situation. But does beneficence, or nonmaleficence, still place restraints upon a physician's participation in the investigation, even presupposing valid consent? Certainly, if the physician has a warranted belief that one treatment in a trial is more efficacious or more appropriate for that type of patient than another, it would be unethical for him to undertake the trial.

Clinical trials now normally compare a new treatment with the standard therapy for a condition, rather than compare the new treatment with placebo. Beneficence demands that a placebo-controlled trial be employed only when no standard treatment or preventive measure is known to be superior to placebo. Case 1 suggests a violation of this principle in that many adequate pain relievers are currently available, and it may have been unethical to compare the new salicylic acid derivative with placebo rather than comparing it, for example, to aspirin or acetaminophen. Case 2 presents a more striking example in which a significant clinical problem (ie, recurrent urinary tract infections) can be prevented by a medication, but the investigators elected to assign one half of the subjects randomly to an ineffective placebo treatment. The ethical issue here arises, not because the physician declines prophylactic treatment, which he might do in any case after considering the individual woman's situation, but because he declines his therapeutic choice through random assignment to placebo for one half the patients.

These two cases suggest that placebo-controlled trials are particularly problematic. It is also true, however, that many treatments for common primary care problems are currently unsupported by controlled studies. Often family physicians have an array of available treatments all of which are acceptable because little evidence supports one over another. This situation presents another dilemma to the physician who may, in ordinary practice, select treatment A over treatment B without solid, scientific grounds for doing so. Therapeutic decisions are always made in the context of uncertainty: uncertainty about the natural history of the disease, about idiosyncratic effects of a drug, or about other factors influencing illness in a given patient. Thus, therapeutic decisions, even if made with the best intentions, are frequently in error. Is the physician morally culpable for such error?

If the therapeutic actions are consistent with the standard of care for the patient's problem, the errors have no moral weight. The standard of care is based on existing biomedical knowledge, which, in turn, derives both from randomized controlled clinical trials and also from a consensus (eg, policy, common practice) among physicians of the given specialty. The therapeutic imperative must be based on a warranted belief, rather than an unwarranted or idiosyncratic belief, no matter how strongly held. It should be incumbent, then, upon a family physician to review carefully his beliefs about therapy before excluding a clinical trial, even a placebo-controlled one, as necessarily unethical. The family physician has a particular interest in finding interventions more powerful and

more predictable than those already available for the problems he treats. The physician who must respond, day after day, with great uncertainty to the therapeutic imperative must also come to grips with a scientific imperative to learn more and to better help his patients.

Limits for the Patient

The roles of healer and scientist may bear different weights depending upon patient care setting, the continuing physician-patient relationship, and the patient's expectations. In a complex protocol trial of cancer chemotherapy, the structure of relationships and expectations might be quite different from that which exists in a primary care setting. A patient in the former case will usually enter the trial only after referral from a primary physician to another physician, one who is strongly identified as an investigator. Numerous other research-related persons might be involved. Treatment is relatively invasive or risky, the stakes are high, and the situation is likely to be distinguished by patients and family as different from ordinary medical care. Family practice research, on the other hand, might take place in the patient's own physician's office, and might involve a relatively minor health problem, such as recurrent urinary tract infections or insomnia, over which the patient could be less inclined to weigh the issues. The investigator is likely to be a physician whom the patient knows and relies upon for other aspects of medical care. For all these reasons, the patient could defer to the physician's suggestion rather than making the autonomous decision envisioned by the doctrine of informed consent.

This situation raises the question of how much consent is influenced by the physician-patient relationship in family medicine. The physician-patient interaction is not a static contract, but rather it exerts an influence on the patient, the family, the illness manifestations, and on the disease itself. The relationship might be used to persuade the patient to take responsibility and become more autonomous, or to increase the likelihood of the patient's adherence to therapy. The mutual participation model of the physician-patient relationship enjoins mutual respect and negotiation, but does not imply a provider-consumer contract with both parties entirely autonomous.[14] The ethics of patient care are considerably more complex, as modeled recently to Thomasma in his 1983 account.[15]

In this context, then, the investigator-physician must tread carefully to avoid using his therapeutic relationship to persuade a patient to participate in his study. Family physicians might hesitate to explain studies in great detail because they feel the patient will not understand or does not really want to know all the details, or because the risks are too small to warrant such complete explanation. However small the risks, a clinical trial is not ordinary medical care and must be considered a temporary partial suspension of the therapeutic imperative. The issue of informed consent, therefore, is considerably different from consent for diagnostic procedures or surgery, for example. Investigators have found that the complete doctrine of informed consent, though espoused by most patients, is not so highly valued by them when faced with actual decisions about their own medical care.[16] Patients tend to rely on their physician's advice rather than think through all the alternatives. A randomized controlled clinical trial, however, partially removes the grounds upon which they base their reliance. Therefore, informed consent for such an investigation must be based on a more detailed, explicit risk-benefit analysis, one that the physician should not compromise by confusing it with the interests, desires, or behaviors of patients in ordinary medical care.

When these considerations are applied to cases 1 and 2, it is evident that a second ethical question must be raised. The first question was whether a placebo-controlled trial presented too great a suspension of the therapeutic imperative in these situations in which discomfort (pain) or acute illness (urinary tract infection) could be ameliorated by standard therapy. The second question is whether the consent obtained in these cases was truly informed by the standards of clinical investigation, as opposed to the standard of ordinary practice. Did the patients with pain from trauma or rheumatic disease truly understand that they were electing the possibility of placebo rather than an accepted analgesic? Did the women who had had recurrent urinary tract infection truly understand that they were turning down state-of-the-art

prophylaxis for random allocation to either a new drug or placebo?

Proposed Rules for Clinical Trials

The well-known Department of Health and Human Services and the Food and Drug Administration regulations about informed consent are examples of rules designed to help apply ethical principles in biomedical research.[17] The foregoing analysis suggests several supplemental guidelines that might be particularly helpful for clinical trials in family medicine.

With regard to the constraints that beneficence places upon the physician, placebo-controlled trials should not be employed if there is any efficacious standard of care available. Rather, a new treatment should be compared with the standard. Second, rules for trial termination, monitored by a third party, should be employed to stop a trial early if one treatment is shown to be more effective than the other prior to a scheduled completion time. Such statistical devices are now often employed in multicenter clinical trials to minimize the number of patients who must receive treatment by random allocation or to minimize the duration of such treatment. Third, patients should not be asked to purchase additional services or tests beyond the physician's normal office procedure just to participate in a clinical trial or protocol study. Such services should be provided at no charge.

With regard to the patient's informed consent itself, special emphasis and explanation should be given to the disclaimer that future medical care will not be affected by a patient decision whether to participate in the trial. This issue is of great concern in primary care. Second, the explanation should be given and consent obtained by someone other than the primary care physician. This technique will minimize the danger that the physician-patient relationship itself will influence the patient's desire or ability to weigh the study on its own merits. Third, the patient should neither be paid, nor should his ordinary medical care visits be paid for, as part of the trial. This rule, too, will help promote informed consent based only on the features of the protocol itself.

These suggestions are tentative and not supported by argument here. They are not, in fact, intended to apply only to primary care or family practice research. They are presented, however, as examples in the hope of initiating a discussion among family practice researchers about appropriate rules for clinical trials under their direction.

Acknowledgments

This work was supported, in part, by the A.V. Davis Foundation, the National Science Foundation's EVIST Program, and the National Endowment for the Humanities.

References

1. Fried C: Medical Experimentation: Personal Integrity and Social Policy. New York, Elsevier, 1974
2. Donagan A: Informed consent in therapy and experimentation. J Med Philos 1977; 2:307-329
3. Marquis D: Leaving therapy to chance. Hastings Cent Rep 1983; 13:40-47
4. Keller AH: Ethics/human values education in the family practice residency. J Med Educ 1977; 52:107-116
5. Bibace R, Comer R, Cotsonas CE: Ethical and legal issues in family practice. J Fam Pract 1978; 7:1029-1035
6. Dickman RL: Family medicine and medical ethics—A natural and necessary union. J Fam Pract 1980; 10:633-637
7. Christie RJ, Hoffmaster CB, McCracken EC: How family physicians approach ethical problems. J Fam Pract 1983; 16:1133-1138
8. Gjerde C, Clements W, Clements B: Publication characteristics of family practice faculty nominated for academic promotion. J Fam Pract 1982; 15:663-666
9. Ankri J, Ageorges P, Soubrie C, et al: Diflunisal versus placebo for treatment of pain in general practice. Clin Ther 1982; 5:85-92
10. Scheckler WE, Burt RAP, Paulson DF: Comparison of low-dose cinoacin therapy and placebo in the prevention of recurrent urinary tract infections. J Fam Pract 1982; 15:901-904
11. Clayton D: Ethically optimized designs. Br J Clin Pharmacol 1982; 13:469-480
12. Ramsey P: The Patient as Person: Exploration in Medical Ethics. New Haven, Yale University Press, 1970
13. Beauchamp TL, Childress JF: Principles of Biomedical Ethics. New York, Oxford University Press, 1979
14. Szasz TS, Hollender MH: The basic models of the doctor-patient relationship. Arch Intern Med 1956; 97:585-592
15. Thomasma DC: Beyond medical paternalism and patient autonomy: A model of physician conscience for the physician-patient relationship. Ann Intern Med 1983; 98:243-248
16. Lidz CW, Roth LH, Zerubavel E, et al: Informed Consent: A Study of Psychiatric Decision-Making. New York, Guilford Press, 1983
17. US Department of Health and Human Services rules and regulations. Federal Register 1981; 46:8366-8392