

8

Contemporary Bioethical Issues in Pharmacology and Pharmaceutical Research

Janet Fleetwood

BIOMEDICAL ETHICS IN PHARMACOLOGY: AN INTRODUCTION AND FRAMEWORK

The relationship between physicians, scientists, and the pharmaceutical industry is a mutually advantageous one that is fraught with ethical complexity. Seemingly straightforward questions, such as whether a physician ought to enroll patients in a drug trial, which drug to prescribe when any one of several may be effective, and how to stay abreast of new drugs while remaining objective, become difficult when examined closely. This chapter provides a conceptual framework for bioethical analysis, presents some cases that illustrate ethical problems, and delineates some guidelines for consideration.

Bioethics is the study of ethical issues associated with providing health care or pursuing biomedical research. Most approaches to bioethics in the United States are secular in nature and presuppose no particular religious or theological perspective. While one's religious beliefs may play an important role in determining personal morality, the broader endeavor of bioethical analysis attempts to be devoid of any particular religious perspective. Similarly, bioethical analysis stands independent of legal analysis. Although the law is often a consideration in bioethical decision making, laws in themselves do not determine the morality of an action. Laws are supposed to reflect a societal consensus on issues and are established to set a minimum standard of behavior.

Thus, while religion and law provide guidelines for acceptable actions, religious beliefs, and knowledge of the law are frequently insufficient to guide moral action, in the realm of health care. Solving problems that arise in the scientific and clinical contexts requires knowledge of ethical principles and the methodology for applying them. While bioethical analysis is multifactorial, four moral principles play key roles in establish-

ing a basic framework. These principles were developed from a pluralistic, albeit North American, framework. Although not every problem will involve all four principles of bioethics, an understanding of the principles of autonomy, beneficence, nonmaleficence, and justice will build a solid framework for critical analysis.

The *principle of autonomy* entails that persons should be treated as inherently valuable individuals with the moral right to make decisions about their own lives. To the extent that one's actions and choices do not negatively affect others, individuals with the capacity to make their own decisions should be free to do as they wish, even if their choices are risky or harmful to themselves. The principle also entails that persons with diminished autonomy, such as those who are illiterate or retarded, deserve to have their interests protected. Many moral obligations for professionals engaged in scientific research or health care are derived from the principle of autonomy, such as the physician-researcher's obligation to fully inform potential research subjects and respect the individual's informed consent or informed refusal. This obligation is founded on the principle that individuals are the appropriate decision makers for choices that do not harm others.

The *principle of beneficence* entails helping people to further their interests. As the primary moral principle quoted in medical codes and oaths, the principle of beneficence is fundamental to the practice of medicine and clinical research. For example, concerns about beneficence motivate physicians, pharmacologists, pharmacists, and clinical investigators, all of whom share the goal of conducting studies that will ultimately benefit society by producing or refining effective treatments.

The *principle of nonmaleficence* asserts that professionals have an obligation to prevent harm or if harm is unavoidable, minimize that harm. This principle plays an

important role in clinical research, as it entails an obligation to minimize risks to each participant. Moreover, drug approval procedures, such as those implemented by the Food and Drug Administration (FDA), are designed to protect patients from harm while ultimately facilitating the marketing of drugs that have maximal therapeutic benefits. Thus the principles of beneficence and non-maleficence dictate that the overall goal of scientific advancement cannot trump the duty to protect human subjects of clinical research from harm.

The *principle of justice* states that individuals should be given what they deserve, be that benefit or burden. Cases that are alike should be treated similarly, and relevant distinctions should be drawn consistently. The principle of justice does not specifically state what distinctions are fair or which criteria are reasonable; it simply requires that, once criteria are determined, they be applied fairly. Justice is important in many areas, such as recruitment of research subjects for pharmaceutical studies. For example, researchers must guard against distributing the burdens of participation disproportionately among populations that are poorly equipped to give informed consent, such as children or the mentally incompetent.

The principles of autonomy, beneficence, nonmaleficence, and justice form a foundation for analysis of ethical quandaries. In addition, a comprehensive ethical analysis will include considerations of cultural and religious diversity of patient–subjects, health care providers and interpersonal relationships; an assessment of the profession-based duties and obligations of the health care professionals, including an examination of relevant professional oaths and codes; and an analysis of relevantly similar previous bioethical dilemmas.

BIOMEDICAL ETHICS AND CLINICAL RESEARCH

For more than 50 years, scientists, physicians, bioethicists, and the media have focused on a variety of issues in research with human subjects, or clinical research. In 1948, in response to the atrocities perpetrated by Nazi experimentation, the Nuremberg Code was developed to set forth guidelines for the acceptable conduct of scientific research. In 1964 the World Medical Association adopted the Declaration of Helsinki, which specifically guides physicians in biomedical research. These documents specify basic moral guidelines ultimately founded on concerns for autonomy, beneficence, and justice. The guidelines require the following:

- Subjects must give voluntary consent before being enrolled in any study after being fully advised of the study's aims, methods, benefits, risks, and discomforts.

- Proposed studies must have sufficient scientific merit to warrant their risks.
- Studies must be designed to avoid all unnecessary physical and mental suffering.
- Potential benefits to subjects must outweigh risks to subjects.
- Researchers must ensure subjects' privacy and confidentiality.
- Subjects must have the right to withdraw from the study at any time.
- Researchers are obligated to stop the study if continuation is likely to result in injury to subjects.

The guidelines further require that research on human subjects be conducted by qualified individuals and that most clinical research be reviewed by an independent committee, which is generally an institutional review board.

In addition to the Nuremberg Code and Declaration of Helsinki, The International Ethical Guidelines for Biomedical Research Involving Human Subjects was issued in 1982 and revised in 1993 by the Council for the International Organization of Medical Sciences (CIOMS). Those guidelines define national policies for biomedical research, apply ethical standards to the circumstances often present in research in economically developing nations, and define mechanisms for ethical review of human subjects research.

In drug studies, specific ethical concerns focus on balancing benefits and burdens to subjects, on the need for investigators to use noninvasive and minimally painful means of determining drug disposition, on minimizing the frequency of bodily fluid sampling, and on choosing study subjects who are representative of the target population whenever possible rather than exposing healthy volunteer subjects. Placebo-controlled studies create special obligations pertaining to the potential deception of subjects and raise difficult questions about subjects' informed consent.

Recently, attention has focused on the issue of international medical research, especially that done with patients in economically developing nations. For example, one controversy focused on a highly publicized placebo-controlled study in Africa examining the prevention of perinatal transmission of HIV using zidovudine (AZT). Since such a study in an economically developed nation would probably not have a placebo arm, critics argue that this reflects a double standard for research. They assert that one standard for ethical research should prevail, regardless of the social and economic conditions of the subjects. Bioethicists and those directly involved in research are reconsidering whether subjects who are already suffering under impoverished conditions might suffer further exploitation at the hands of medical researchers.

Those who designed the study point out that placebo-controlled studies are the most rigorous available and that AZT would not otherwise be available to this population. Enrollment in the study offered a benefit over and above the status quo, they assert, and did not deprive subjects of anything they could otherwise obtain. Yet such “studies in nature” pose complex ethical issues. If the research relies on the continuation of undesirable social conditions, such as the general lack of prenatal care, critics assert that there is a fundamental obligation to improve those background conditions rather than take advantage of access to the perfect “laboratory.” While the clinical study has certainly not made the underlying conditions worse, the study has done little to correct the underlying deprivations. Even so, is that the role of pharmaceutical research or a broader social role that goes beyond what researchers should have to provide? While it would be foolhardy to insist that the only ethically acceptable research is done on patients with full access to comprehensive health care, we do not want to make those who are already deprived and in poverty into “lab rats” who participate in research that ultimately benefits primarily those in the developed world.

Clinical research can target the needs of those in economically developing nations and those who are medically underserved in the United States. Yet we must be cautious in the design and implementation of research studies to ensure that those who are the most vulnerable, whether locally or abroad, are offered the most protections and stand to gain proportionately from the studies in which they participate. Research must satisfy the needs of the population in which it is undertaken, and the products developed during the course of the research must subsequently be made reasonably available.

CONFLICTS OF INTEREST AND THE PHARMACEUTICAL INDUSTRY

A *conflict of interest* occurs when an individual’s private goals are inconsistent with that person’s official responsibilities. The interrelationship between scientists, physicians, and researchers and the pharmaceutical industry has given rise to a variety of well-publicized cases raising concerns about conflicts of interest.

Researchers and drug companies are interdependent. The pharmaceutical industry depends on scientists and clinicians for research, development, and marketing. Conversely, the medical profession depends on research that is largely financed by the pharmaceutical industry. While this interdependence often benefits industry, research, and patient care, conflicts of interest may arise in two main areas: (1) drug research and development and (2) clinical education and product marketing.

Drug Research and Development

Pharmacology, unlike some other basic science disciplines, has a unique status when it comes to potential conflicts of interest. The pharmaceutical industry combines a desire for discovery and development with profit-motivated marketing and sales goals. Although scientists and physicians share the desire for drug discovery and development and are motivated by the desire to contribute to scientific advancement and improved patient care, pharmaceutical companies are simultaneously under strong commercial pressures. Pharmaceutical companies are therefore willing to offer financial incentives to physician–researchers who conduct studies, recruit patients, or are helpful in product development and testing. In some cases, this financial support may compromise professional judgment in conducting, analyzing, or reporting research.

For example, often a pharmaceutical company will contract with a private physician to recruit patients into a drug study. While this arrangement frequently offers patients access to treatment that might otherwise be unavailable, the potential conflict may ultimately result in lack of objectivity in study design, data interpretation, and dissemination of research results. For example, a 1986 study in the *Journal of General Internal Medicine* found a statistically significant relationship between drug company funding and outcomes favoring a new therapy.

In addition, this kind of arrangement places the physician in a dual role as a clinician–researcher, with sometimes competing obligations to the drug company and the patient. The doctor assumes a position of responsibility to the company while simultaneously maintaining the usual duties to protect and benefit his or her patients. The physician’s role as patient advocate can easily be compromised, since physicians also have a potentially competing interest in enrolling patients in the trial. In fact, patients may mistakenly believe that when their personal family physician suggests they enroll as a subject in a study, the doctor is suggesting enrollment because it is in that specific patient’s interest to participate. However, the enrollment offer probably has little to do with that particular patient’s care and more to do with the physician’s desire to enroll subjects.

At minimum, the principles of autonomy and beneficence require that patients be told the source of funding for sponsored studies in which they are invited to enroll and advised of any potential conflicts between the physician’s research interests and treatment recommendations.

Although disclosure to patients is important, patients are generally ill suited to assess how a potential conflict of interest actually affects their treatment. In addition to disclosure to patients, we need rigorous reporting requirements for those engaged in drug studies.

Institutions should implement clear policies, and professional guidelines should be developed, to prohibit relationships that place patient care secondary to financial gain.

Clinical Education and Product Marketing

The second area for ethical concern is clinical education and product marketing. The line between “education” and marketing is frequently a blurry one, and it is often difficult to separate a company’s desire to educate physicians about products that may genuinely enhance patient care from the company’s desire to increase profits. As the gatekeepers for all prescription drugs, physicians have the power to determine which drugs will compete successfully in the marketplace, making doctors the logical targets for marketing efforts by pharmaceutical firms. In fact, pharmaceutical companies spend more than \$11 billion each year on promotion and marketing. Between \$8,000 and \$13,000 is spent annually on each physician. However, many company-sponsored arrangements may conflict with the physician’s responsibility to act in the best interest of the patient. A voluntary code has recently been adopted by the Pharmaceutical Research and Manufacturers of America which establishes guidelines for relationships between the pharmaceutical industry and health care professionals.

Ultimately, prescribing practices are the main source of concern, as physicians may be induced to prescribe some products rather than others based on factors other than therapeutic effectiveness or cost. Many drug companies have generous programs for providing their products free of charge to those who cannot afford them. However, free samples provided by drug companies directly to physicians’ offices should be used cautiously, and the choice of drugs should be made on the basis of medical indications, not sample availability. While samples supplied to physicians’ offices to be given to patients may enable a patient to try a drug for a few weeks to be sure it is tolerated, they also serve to get patients started on a particular product which presumably will have to be continued and paid for by the patient or a third-party payer. The patient, as a health care consumer, is not in a position to assess the need for a certain drug or decide whether it is prescribed appropriately and sometimes cannot accurately determine whether it is therapeutically effective. Thus, the patient is entitled to be protected by the physician, whose primary role is that of patient advocate as dictated by the principles of beneficence and nonmaleficence.

Product marketing presents other ethical issues as well. In addition to direct product advertising in medical journals and direct to consumer advertising in the popular media, pharmaceutical company sales representatives frequently visit physicians. Although the

salesperson’s goal is clearly to promote sales, often these visits take the form of “education” for busy clinicians. Company representatives present “educational” information, provide meals, and may give gifts or incentives to the doctor. Although such visits may keep clinicians informed about current products, they may also precipitate conflicts of interest. Gifts of more than token value, trips to resort areas for “educational” programs with little scientific merit, and cash incentives for prescribing a drug or having it added to a hospital formulary all are cause for concern. The line between a gift and a bribe is not a sharp one, and clinicians and drug company employees should strive to avoid any impropriety. The American Medical Association has stated in its Current Opinions that gifts should primarily benefit patients and should not be of substantial value. While textbooks, modest meals, and educational or work-related gifts, such as notepads or textbooks, may be appropriate, cash payments are not appropriate. Physicians should not accept gifts from companies if the gift might compromise or appear to compromise the physician’s objectivity. A helpful criterion suggested by the American College of Physicians when considering the ethical appropriateness of a particular interaction between a physician and drug company is to ask whether one would be willing to have the arrangement generally known. If not, the action falls outside the realm of ethical acceptability and should be avoided.

Medical students and residents are not exempt from the influence of drug companies. Many students and residents are offered gifts of educational books or equipment or are invited to attend company-sponsored events. Young professionals need to be extremely careful to avoid impropriety and should receive specific instruction about the ethically appropriate scope and limits of interactions with drug company representatives.

The area of continuing medical education is similarly mired with controversy, as “educational” meetings may be simply soft sells at company expense to encourage physicians to prescribe one company’s product over a competitor’s. While some industry-sponsored education provides a good opportunity for unbiased scientific exchange, such as when a drug company underwrites the cost of an educational program but places no restrictions on topics discussed or speakers chosen, too often “education” is a euphemism for marketing. To be considered legitimate, a conference or meeting must be primarily dedicated to scientific and educational activities, and the main incentive for bringing attendees together must be to further broad knowledge.

In addition, physicians may be invited to serve as a drug company “consultant.” These “consultants” are invited to a company-sponsored symposium, which is sometimes nothing more than a sales pitch for that company’s products with little real interaction or consultation. While consultants who provide genuine services

may receive reasonable compensation and accept reimbursement for travel expenses, token consulting or advisory arrangements cannot be used to justify compensating physicians.

Speakers at company-sponsored events who are drawn from the professional community should subject their presentation to the same level of scientific rigor as they would apply to a presentation at a professional meeting. In particular, they should refrain from allowing the pharmaceutical company to influence the data they present, the means of presenting it, or the outcomes drawn. When companies financially support conferences or lectures other than their own, the organizers of the conference should maintain control over the topics and speakers selected. If a speaker wishes to mention a specific product, he or she should be sure to avoid any appearance of impropriety by comparing it fairly and completely with competing products. Researchers and clinicians who are invited to conduct studies supported by drug companies and present their data at company-sponsored educational events should take special care to conduct the study meticulously, analyze the data rigorously, and present the data as objectively as possible. Speakers should avoid accepting lecture invitations to events at which the drug company pays the audience to attend and should object if the company's marketing representatives conduct sales activities, such as distributing samples or brochures about a specific product, when an event has been promoted as educational. In addition, industry sponsorship should be noted in any publication reporting study results. Finally, both attendees and speakers should demand that financial sponsorship be revealed before registration and that financial relationships between speakers and the promoter be plainly stated. In short, to ensure objectivity and eliminate any appearance of conflict of interest, doctors should get their information primarily from

professional peer-reviewed journals and not rely solely on material provided by drug companies.

In addition to these general guidelines, three questions are useful to assess the ethics of an arrangement between pharmaceutical company and researcher-clinician. First, would it be embarrassing for the clinician if the public knew about the financial arrangement? Arrangements that would cause embarrassment or lead others to suspect a conflict of interest should be avoided. Second, can the physician reveal the financial arrangements to patients whom the clinician invites to participate in the study? If the physician feels uncomfortable discussing the remuneration with patient recruits because of the appearance of a conflict of interest, the physician should not participate. Third, would the clinician pursue the same treatment strategy if there were no financial incentive? If the physician would likely choose another treatment were it not for the financial rewards from the drug company, the physician should reconsider offering enrollment for the patient. Finally, do any professional codes, institutional policies, or other guidelines preclude participation?

FINAL CONSIDERATIONS

The principles of autonomy, beneficence, nonmaleficence, and justice provide a conceptual framework for analyzing issues pertaining to clinical research and the complex relationship between science, industry, and patient care. To develop a broad understanding of these issues, that basic framework should be filled in with an understanding of cultural considerations, profession-based duties and obligations, and an analysis of previous bioethical issues. Continual scrutiny of bioethical issues in pharmacology is warranted as we develop better insight into the moral dilemmas of the field.

Study QUESTIONS

1. Joel Martin, a pediatrician at a residential facility for mentally retarded children, has been approached by the Modern Pharmaceutical Company. The company would like Dr. Martin to enroll children aged 4 to 7 in one of their clinical trials for a new drug to treat conjunctivitis (pinkeye). Dr. Martin recognizes that the children's parents would be able to give informed consent or refusal on behalf of their children, that risks have been minimized, and that overall, the study drug is likely to help the participants. He is concerned, however, about the drug companies' decision to enroll retarded children before

healthy children in the community. Modern's representative points out that the incidence of conjunctivitis in the facility is very high and so provides an excellent setting for the study to be completed quickly. Dr. Martin considers the population of the facility extremely vulnerable. The ethical principle that underlies Dr. Martin's concerns is:

- (A) Autonomy
- (B) Beneficence
- (C) Nonmaleficence
- (D) Justice
- (E) Medical neediness

2. The main ethical problem with medical research in economically developing nations in which subjects are medically underserved is that:
- (A) Subjects are frequently not compliant, as they do not understand the importance of the study, raising ethical issues about risks and benefits for the subjects that complete the study.
 - (B) Researchers cannot generalize from the outcome with a medically underserved population to draw conclusions that would be applicable in the United States because of the numerous other variables that affect the outcome of the study.
 - (C) Subjects are not asked to give informed consent, as they cannot understand the complexities of a research study.
 - (D) Subjects are included in studies of treatments that are not available in underserved countries but are available in the United States, raising issues of equity and fairness toward disadvantaged populations.
 - (E) Subjects are deprived access to medical treatments that would be available in their country were they not part of a randomized, placebo-controlled study.
3. When does a conflict of interest occur?
- (A) When an individual's private goals are inconsistent with that person's official responsibilities
 - (B) When an individual's research interests are in conflict with the research of an individual in another institution or corporation
 - (C) When two researchers want to do research in the same area but there is only enough available funding for one researcher to do the research adequately
 - (D) When an individual has a conflict between his or her research interests and the requirements set forth by the Nuremberg Code
4. Susan Brown, a community-based internist in Little Town, U. S. A., has received a letter inviting her to become a consultant to the Modern Pharmaceutical Company. Modern would like Dr. Brown to attend a medical consultants' meeting at the Golden Sunset Resort, an elegant resort about an hour away from Little Town. The agenda includes a Saturday morning presentation by representatives from Modern, with time over lunch for the medical consultants to give feedback to the company representative about the company's products. The rest of the weekend is unscheduled time for Dr. Brown to enjoy the resort. Dr. Brown will be paid \$1000 for her consulting services. When considering whether or not to attend Dr. Brown should:
- (A) Decide whether she thinks she would be biased toward Modern products by the company's generosity; if she believes she can remain objective, it is acceptable to attend.
 - (B) Determine whether she feels favorably toward Modern's product line; if she already prescribes Modern products and prefers them to the competition's, she cannot be biased by their presentations, so there is no ethical issue in attending.
 - (C) Consider how important it is for drug companies to be able to get feedback on their products from physicians and attend to ensure that the company gets accurate information.
 - (D) Consider that her time is valuable, so she deserves to be compensated by Modern.
 - (E) Consider the guidelines by the American Medical Association and choose not to attend under the stated conditions.
5. A helpful criterion suggested by the American College of Physicians when considering the ethical appropriateness of a particular interaction between a physician and industry is to:
- (A) Determine whether the interaction violates any laws or statutes; if not, the action is acceptable.
 - (B) Determine whether one would be willing to have the arrangement generally known; if not, the action should be avoided.
 - (C) Determine whether the action compromises the profit margin of the pharmaceutical company and therefore is not in the interest of the shareholders; if so, the action should be avoided.
 - (D) Determine whether patient care is negatively affected; if not, the action is ethically acceptable.

ANSWERS

1. **D.** The principle of justice is a relevant consideration when subjects are selected for clinical research. It requires that members of a vulnerable population, such as institutionalized patients with mental retardation, not be exploited. The principle of autonomy would be most relevant to the parents' ability to consent or refuse on the child's behalf, something Dr. Martin thinks is handled satisfactorily. Dr. Martin believes risks have been minimized and the overall study drug is likely to help the participants, so the study has satisfied the principles of nonmaleficence and beneficence. The principle of medical priority is not mentioned in the chapter and pertains to treating the most medically needy patients first, which is not at issue here.
2. **D.** An ethical issue arises when one includes medically underserved patients in a study without providing them with the level of care available to others. Problems with noncompliance, while potentially damaging to a study, do not pose ethical problems in medically underserved populations not encountered elsewhere. Effective study design can overcome problems with generalizing from one population to the next. Subjects everywhere should be

provided with information at a level the subject can comprehend and asked to give informed consent. Subjects in medically underserved populations are not deprived of access to medical treatments that are available in their own country, only those that are available only elsewhere.

3. **A.** A conflict of interest occurs when an individual's personal interests conflict with official responsibilities, such as those required by one's profession. So, for example, a physician who owns shares in a drug company that is sponsoring a clinical trial in which the doctor enrolls patients may have a conflict of interest. Conflicts of interest do not generally pertain to conflicts between researchers or the requirements set forth by the Nuremberg Code.
4. **E.** The American Medical Association guidelines suggest that Dr. Brown should not attend. Clearly, the educational nature of the meeting is dubious. Even if we consider it a consultancy rather than an educational meeting, Dr. Brown's role as a "consultant" is not well specified, and the compensation for her consultancy may be seen as excessive. Although she may believe that she can remain objective despite the company's generosity, numerous studies show that prescribing patterns change in response to pharmaceutical company largesse. Similarly, the fact that she often prescribes their products does not mean that her objectivity cannot be compromised. For example, she may not consider new products from other companies as carefully because of her preference to keep prescribing Modern's products. While admittedly her time is valuable, the amount this company will spend on her expenses and honoraria far exceed what is reasonable.
5. **B.** Considering whether one would be willing to have an arrangement generally known is a quick test of the ethical appropriateness of an action. While some individuals may have a relatively low standard for what they would be willing to have publicly known, for most people this test can provide a useful guideline. The simple fact that an action falls within the law does not make it morally acceptable. Considerations of the profit margin for the pharmaceutical company shareholders is impor-

tant for company employees but bears little relevance on physician-pharmaceutical company interactions, in which the physician is supposed to be primarily a patient advocate. Finally, although patient care may not be directly affected by an action, the action may be ethically problematic if it gives the impression that the physician is under undue influence of the pharmaceutical company and thereby willing to put patient care behind company profit.

SUPPLEMENTAL READING

- Council on Ethical and Judicial Affairs, American Medical Association. Gifts to physicians from industry. *JAMA* 1991;265:501. Updated June 1996 and June 1998. Available online at <http://www.ama-assn.org> (E-8.061 Gifts to Physicians from Industry.)
- Davidson R. Source of funding and outcome of clinical trials. *J Gen Intern Med* 1986;1:155–158.
- Emanuel E, Wendler D, and Grady C. What Makes Clinical Research Ethical? *JAMA* 2000;283(20):2701–2711.
- Executive Committee of the Pharmaceutical Research and Manufacturers of American (PhRMA), PhRMA Code on Interactions with Healthcare Professionals, July 1, 2002. Available online at <http://www.phrma.org>
- Fletcher J et al. *Introduction to Clinical Ethics* (2nd ed.). Frederick, MD: University Publishing, 1997.
- Kessler DA. Drug promotion and scientific exchanges: The role of the clinical investigator. *N Engl J Med* 1991;325:201–203.
- Levine RJ. Some recent developments in the international guidelines on the ethics of research involving human subjects. *Annu N Y Acad Sci* 2000;918:10–8.
- Svensson C. Ethical considerations in the conduct of clinical pharmacokinetic studies. *Clin Pharmacokinet* 1989;17:217–222.
- Wazana A. Physicians and the Pharmaceutical Industry: Is A Gift Ever Just a Gift? *JAMA* 2000;283(3):373–380.
- Wolfe SM. Why do American drug companies spend more than \$12 billion a year pushing drugs? *J Gen Intern Med* 1996;11:637–639.

CASE Study Dr. Drew and the Hypertension Drug Trial

Lee Drew, MD, has been invited by Modern Pharmaceutical Company to participate in a new drug trial for hypertension. For every patient Dr. Drew recruits through his small private practice, he will receive \$1,000 to help defray the costs of quarterly blood draws and the additional paperwork required by the study. In addition, Modern Pharmaceuticals will replace Dr. Drew's computer system to enable better patient tracking. Given the declining reimbursement rates from third-party payers, Dr. Drew could really use the financial support but wonders what benefits this drug offers to patients. Is it simply a me-too or copycat drug, designed primarily to make money for the drug company? And, if so, can Dr. Drew be justified in asking patients to enroll in the study? Still, Dr. Drew finds the financial incentives tempting and knows the risk to patients is low. How should Dr. Drew resolve the ethical dilemma?

ANSWER: Dr. Drew faces many ethical questions in deciding whether or not to participate in the drug trial for hypertension sponsored by the Modern Pharmaceutical Company. In analyzing whether to participate, Dr. Drew should focus on the primacy of the role of *physician*, with the attendant duty to protect patients from harm, and recognize that the role of *investigator* must remain secondary. Having established the priority of Dr. Drew's obligations to provide good patient care and protect patients from harm, Dr. Drew should assess the study's value. Assessing value entails analyzing whether the data generated will change the course of patient care or otherwise provide a valuable scientific benefit, over and above profit for the pharmaceutical company.

Further, Dr. Drew should examine the scientific validity of the study and assess whether the study is well designed and positioned to answer the question at hand while minimizing risks and maximizing benefits to subjects. Dr. Drew should consider whether subjects will be selected fairly, and whether subjects will be well informed. Dr. Drew should consider the quality of the ethical and scientific review that the protocol has undergone by the Institutional Review Board, and see if the protocol raises ethical issues that have not been addressed. Finally, Dr. Drew should consider whether the payment offered is commensurate with the time, effort, and actual expenditures to enroll patients and implement the trial. The offer of a computer system to enable better patient tracking is especially troubling, since it is debatable whether such a system really serves the needs of patients or primarily serves the needs of the drug company. In any case, PhRMA guidelines recommend that physicians not accept gifts over \$100 in value even if they offer benefit to patients, so Dr. Drew should not accept the computer system even if its absence makes it impossible to participate in the study. Finally, if Dr. Drew feels that the study is valuable, well designed, and meets ethical standards, before enrolling any patient Dr. Drew should consider whether that patient is doing well on current therapy. Enrollment is most easily justifiable for a patient who is not doing well on standard therapy and most ethically problematic for patients whose current therapy is effective. These issues, although complex, must be considered and resolved before Dr. Drew can determine the ethical justifiability of participating.