In response to public concern over abuses in human medical experimentation, the dominant approach to the ethics of clinical research during the past 30 years has been regulation, particularly via institutional review board review and approval of scientific protocols and written consent forms. However, the effectiveness of regulatory mechanisms in ensuring the ethical conduct of clinical research is limited. Little attention has been devoted to the nature and role of professional integrity of physician investigators, a conscientious framework for guiding investigators in the socially important but morally complex activity of clinical research. Professional integrity is vital in forging an ethically sound relationship between investigators and patient volunteers, a relationship that differs in important ways from the patient-physician relationship in standard clinical practice. We examine critically 2 models of the moral identity of physician investigators, the investigator as clinician and the investigator as scientist; in neither of these 2 models can the physician investigator eliminate completely the moral conflicts posed by clinical research. The professional integrity of physician investigators depends on a coherent moral identity that is proper to the enterprise of clinical research. The roles of clinician and scientist must be integrated to manage conscientiously the ethical complexity, ambiguity, and tensions between the potentially competing loyalties of science and care of volunteer patients.

The predominant societal response to the ethical problems associated with clinical research during the past 30 years has been the implementation of regulatory mechanisms, including detailed federal regulations governing research involving human subjects and institutional review boards that examine and approve scientific protocols and written informed consent forms. The application of this regulatory structure has helped obviate “ethics disasters” and has improved protection of the rights and welfare of research subjects; however, there remain deficiencies that need to be addressed. Regulatory improvements, particularly the formulation of specific requirements for research involving subjects with impaired decision-making capacity, are currently under review by the National Bioethics Advisory Commission. Nonetheless, even under an ideal regulatory system, the ethics of clinical research will continue to depend significantly on the integrity of investigators. The actual process of disclosure and negotiation leading to informed consent and the ongoing relationship between physician investigators and patient volunteers can be expected to remain largely beyond the range of oversight by the institutional review board. Developing and maintaining professional integrity is a challenging task for physician investigators in view of the inherent ethical complexities of clinical research, coupled with the pressures to enroll patients, complete studies, and publish scientific articles. Of particular

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concern are financial incentives for investigators to recruit patients into clinical trials. Although clinical research is not unique in posing problems of professional integrity, scant attention has been devoted to understanding and promoting the internalized moral framework that ought to guide responsible investigators as they relate to patient volunteers. We suggest that the next step in the evolution of research ethics should be to address the integrity of physician investigators in their relationship with patient volunteers.

Professional integrity is intimately linked with the identity to which professionals subscribe. With respect to the complex role of the physician investigator, alternative identities may command allegiance. We examine critically 2 models of the professional integrity of physician investigators: (1) the investigator as clinician and (2) the investigator as scientist. We view the propensity to identify with one or the other of these roles as an effort to minimize the tensions between pursuing the welfare of patient volunteers and generating scientific knowledge. We contend, however, that these tensions are inherent in the enterprise of clinical research. Accordingly, we suggest the need to develop a conception of the professional integrity of clinical investigators that integrates the roles of the clinician and the scientist, guided by a straightforward recognition that moral conflict in clinical research can be managed but not eliminated.

Since clinical research is a team enterprise, professional integrity concerns all members of the research team, including investigators from various disciplines as well as research nurses, social workers, and any other professionals who interact with research subjects. In this exploratory article, however, we confine our attention to issues of professional integrity in the context of the relationship between physician investigators and patient volunteers. The moral tensions and conflicts between scientific rigor and patient care that arise in this relationship are likely to influence the interpersonal dynamics of the research team and the interactions of team members with patient volunteers. Clarification of professional integrity in the relationship between physician investigators and patient volunteers should pave the way for a comprehensive account encompassing the entire research team.

The Physician Investigator as Clinician: A Therapeutic Misconception

It is natural that physician investigators would gravitate toward an identity as a clinician. Becoming a physician involves an intensive and protracted process of professional socialization. Moreover, the environment of the academic medical center, in which medical students and residents are educated, operates in a way that blurs the differences between standard clinical practice and clinical research. Patient care and research are intermingled in this setting. Attending physicians who teach the practice of medicine are also engaged in and professionally committed to research. In view of the deep socialization of investigators as clinicians and the blurring of clinical medicine and clinical research in the academic medical center, investigators tend to rely on their moral self-understanding as healers to navigate the murky moral waters of clinical research.

Although perhaps functional to the enterprise of clinical research, it is ethically problematic if both investigators and patient volunteers see research from an exclusively therapeutic perspective. Appelbaum and colleagues have coined the phrase “the therapeutic misconception” in describing the tendency of patient volunteers to believe that the research procedures that they undergo were designed for their benefit, even when consent forms and conversations with investigators clearly identify some of these procedures as nontherapeutic measures that are being undertaken for purely scientific purposes.

We suggest that investigators themselves may be subject to a form of therapeutic misconception. Physician investigators typically view their guiding moral responsibility as the care of patient volunteers. Although this moral commitment should be paramount, clinical research uses procedures intended not for the benefit of patient volunteers but to generate scientific knowledge. These procedures carry risks to patient volunteers, often without compensating medical benefits. In the face of this potential divergence between pursuing patient-centered beneficence and scientific knowledge, the orientation of investigators as clinicians can promote a form of “cognitive dissonance” in which an effort is made to resolve the tensions between these aims and commitments by adopting a therapeutic orientation to clinical research in general and to the justification of research procedures that are, in fact, motivated principally by scientific aims.

To illustrate this tendency to conflature clinical research and clinical practice, we note the examples of phase 1 cancer trials and “washout” periods for psychiatric patients. In the first example, experimental compounds that appeared therapeutically promising in preclinical studies are initially tested on human subjects. Sometimes described under the rubric of “therapeutic intent,” these phase 1 trials are the last hope for desperate patients in whom standard therapy has failed. Yet these studies are explicitly designed for determining the maximum dose of experimental drugs that patients with cancer can tolerate. Freedman notes that these trials are often described as studies of safety and efficacy: “Calling it a study of efficacy, however, is simply false.” The second example, recently the subject of ethical controversy, is the common practice of testing psychotropic medications on volunteer patients who must first undergo a drug withdrawal (“washout”) period so that drug treatment trials can be conducted without the results being contaminated by the effects of medications that patient volunteers had been taking prior to entering research. An additional rationale for drug withdrawal is to permit nontherapeutic studies involving patient volunteers in an unmedicated state. In a recent article on the ethical rationale of drug withdrawal in schizophrenia research, 3 psychiatric investigators describe this practice as follows:

Potential benefits of drug withdrawal protocols include the ability to assess patients in a drug-free state and better characterize the nature of the illness, to have baseline assessment to more accurately assess treatment effects, to disentangle behavioral adverse effects of medication from manifestations of the disease, to identify early signs of tardive dyskinesia that may be masked by antipsychotic drugs, and to identify patients who may sustain remission without medication.

We do not dispute that genuine therapeutic benefits may accrue for some patient volunteers in phase 1 cancer clinical trials and in drug withdrawal schizophrenia research. Yet the comments about these types of studies by investigators sometimes gloss over the scientific considerations that motivate the design of cancer clinical trials and drug washouts in psychiatric research, as well as other forms of clinical research—considerations that may have nothing to do with therapeutic benefit for human research subjects.
We find the model of the “investigator as clinician” seriously flawed because it contributes to a distorted understanding of the nature of clinical research. A basic element of informed consent to research is that patient volunteers understand that they are being invited to participate in a study, which may or may not produce clinical benefits, as distinct from agreeing to undergo standard medical procedures that are clinically indicated for their condition. Patient volunteers need to recognize that physician investigators are not operating as physicians with sole concern for their patients’ medical best interests. Insofar as investigators conflate the context and language of medical care with that of research, they not only reinforce the therapeutic misconception for patient volunteers, they also fail prey themselves to the seduction of the therapeutic misconception. In so doing, they can undermine informed consent and contribute to the potential for patient volunteers to be exploited for the sake of science and the benefit of future patients and present researchers. Overcoming the therapeutic misconception is a primary ethical task for physician investigators, both in their self-understanding and the understanding of research that they strive to foster in patient volunteers. In addition to contributing to ethical problems in the relationship between physician investigators and patient volunteers, this clinical orientation has the potential to compromise scientific integrity by disposing investigators to circumvent random assignments or interfere with blind outcome assessments.20

The Physician Investigator as Scientist Only

Out of deep concern for the conflation of clinical research with clinical medicine, Katz offers a radical proposal for the moral self-understanding of physician investigators:

A morally valid consent in research settings requires a radically new personal and professional commitment to the patient-subjects and the informed consent process: Physician-investigators must see themselves as scientists only and not as doctors. In conflating clinical trials and therapy, as well as patients and subjects, as if both were one and the same, physician-investigators unwittingly become double agents with conflicting loyalties.21

We contend that this proposal, though it serves as a thought-provoking alternative to the prevailing model of the physician investigator as clinician, is also inadequate. First of all, it is impractical in that it presupposes that physician investigators are capable of shedding their identity as clinicians and adopting a wholly nontherapeutic identity as scientists. More significantly, we doubt that this transformation, if possible, would be desirable. The meager data available on the motivations of patients to volunteer for clinical research indicate that the chance of therapeutic benefit is paramount.22,23 It is probable, therefore, that the therapeutic misconception on the part of patient volunteers will continue to operate and need to be addressed regardless of whether investigators attempt to adopt an exclusively scientific role.

Clinical expertise as well as scientific knowledge attracts patients to participate in research. Clinical research generally depends on a more or less explicit quid pro quo between investigators and patient volunteers, namely that patients agree to participate in studies in exchange for the chance for therapeutic benefit. A complete purging of the therapeutic milieu of clinical research would likely undercut the motivations of patients to volunteer, and it is improbable that the altruism of contributing to scientific knowledge would sustain the enterprise. Many investigators might also find clinical research less attractive when divorced from any therapeutic concern for the well-being of patient volunteers.

The potential for harm to patient volunteers might be increased if investigators should shed their role as clinicians. The duty of nonmaleficence, enshrined in the maxim “first of all, do no harm,” carries over from medicine to clinical research. Investigators who adopted a purely scientific ethos might become less concerned about risks of physical harm to patient volunteers and rely on informed consent as sufficient justification of high-risk research. Katz21 has argued incisively and eloquently that the primary identification of physician investigators as clinicians complicates and impedes straightforward engagement with the ethical problems of clinical research. The solution, however, is not for investigators to surrender entirely a medical identity in exchange for a self-understanding as “scientists only.”

The model of physician investigator as scientist might seem more acceptable if all patient volunteers enrolled in clinical research are assigned a physician responsible for monitoring their well-being. In certain types of research, such as particularly high-risk studies or those involving especially vulnerable patients, the use of an independent clinician who is not associated with the research project or not institutionally affiliated with the investigators as a monitor may be desirable. Such a role is stipulated by a panel convened by the Maryland Attorney General to make legislative recommendations for research involving “decisionally incapacitated subjects.”24 Specifically, these recommendations would require a “medically responsible clinician” to monitor research subjects in studies that involve withdrawing standard medical treatment or present more than minimal risk. Experimentation with clinical monitors warrants evaluative research to assess its advantages and disadvantages. Ideally, such research should precede any regulatory requirement for clinical monitors in all or some subset of clinical research.

We doubt, however, that the use of clinical monitors can resolve the basic problem of tension between patient care and scientific rigor, which makes professional integrity so important in clinical research. Managing this inherent tension would need to be negotiated between investigators and clinical monitors; however, the presence, or periodic consultation, of “independent” monitors during clinical research offers no guarantee of protecting the rights and welfare of patient volunteers. The division of roles is likely to be workable only on the basis either of minimal interference by clinical monitors with the conduct of clinical research or of close cooperation between investigators and monitors. Accordingly, it remains to be demonstrated whether the addition of the clinical monitor would be effective or offer a genuine safeguard. Finally, the split between scientific and clinical roles may cause confusion in the minds of patient volunteers about who is responsible for what.

Integrating the Clinician and Scientist Roles

One possible approach to the hybrid identity of the physician investigator is to take the position that either the clinician’s or the scientist’s role should predominate depending on the nature of the study in question; that is, the physician investigator’s integrity is achieved by oscillating between the 2 roles. Thus, it might be argued that in therapeutic research, which tests experimental treatments holding a promise of medical benefit, physician investigators should adopt a clinician identity, whereas in nontherapeutic investigation, the
scientific identity should be adopted. This strategy suffers from the weakness that for many studies no sharp dichotomy can be drawn between therapeutic and nontherapeutic research.26 Any clinical study is likely to include some nontherapeutic procedures that depart from clinical practice, even though these may be merely minor or innocuous. Moreover, randomized clinical trials, recognized as the “gold standard” of treatment studies, introduce assignment of patient volunteers to study drugs, standard treatment, or to placebo by a selection process that is foreign to standard clinical practice, in which treatment decisions are made on the basis of judgments concerning what is in the patient’s best interests.

At the other pole of the dichotomy, in studies that hold little or no prospect of direct medical benefit, excellence in clinical management of patient volunteers is always required. Also, studies that are purely investigational, such as brain imaging protocols, may be linked to treatment studies. Often the research subject is invited to enter a research program that includes participation in therapeutic and nontherapeutic studies. Additionally, studies with a purely investigational purpose may, in fact, produce therapeutic benefits. Imaging studies to improve scientific understanding of pathophysiology may uncover undiagnosed disease or participation in nontherapeutic studies may contribute to patient volunteers’ capability of coping by promoting greater understanding of the conditions from which they suffer.26

The fact that the complexity of clinical research does not permit a clean cut between therapeutic and nontherapeutic studies suggests that alternating between a clinical or scientific orientation will not prove satisfactory. The root meaning of “integrity” is wholeness. The professional integrity of physician investigators depends on a coherent moral identity that is proper to the enterprise of clinical research, which is neither medicine nor laboratory science. We need to cultivate a conception of the moral identity of the physician investigator that integrates the roles of the clinician and the scientist without giving predominance to the one or the other.

The first step, we believe, is to acknowledge forthrightly that the moral problems associated with the conflicts of interest and loyalty between the role of the clinician and the role of the scientist are inherent to clinical research. Investigators must recognize and manage the moral tensions between the norms of patient care and the requirements of scientific investigation. The construction of such a conception of professional integrity is not a matter of creating a new identity but of bringing to light and cultivating the refined self-understanding and comportment of exemplary clinical researchers. A key element in accomplishing this task is to reflect on the relationship between the physician investigator and the patient volunteer.

Relationship Between Physician Investigators and Patient Volunteers

Just as physician investigators have an irreducibly hybrid moral identity, so do patient volunteers. To understand patient volunteers, who are human subjects of clinical research, as patients only distorts their role, just as much as does the understanding of physician investigators as clinicians only. Patient volunteers are patients whose suffering from their disease brings them to clinical research, but they participate as partners in the scientific enterprise. Whereas patients are compelled by need to seek medical care, patient volunteers are invited to participate in clinical research.21 This distinction, however, is often blurred in practice, particularly in treatment studies involving desperate patients or patients referred to research by their primary care physicians, who may also be desperate because of their inability to cure.

Equally inaccurate is the common characterization of clinical research as having an atmosphere in which investigators do not think of patient volunteers as individuals in need of care but only as members of a class sharing a diagnosis or mode of treatment.22 While this is true, by and large, of the aim and outcome of scientific inquiry, it fails to do justice to the process by which clinical research is conducted. The human subject is not a laboratory animal under the control and at the disposal of the investigator. Because investigators must recruit patient volunteers, solicit their participation, and maintain their cooperation with the requirements of the protocol, it behooves them to be interested in and attentive to patient volunteers as individuals. In addition to compassion for patient volunteers’ suffering, gratitude for their free choice to participate in research motivates investigators to take a genuine interest in their welfare. Furthermore, knowing that patient volunteers seek therapeutic benefits from research, investigators strive to produce benefit within the limits imposed by scientific investigation.

Shorter identifies “the benevolent expression of interest” as “one of the standard components of the patient-physician relationship.”23 Though different from the patient-physician relationship, the relationship between investigator and patient volunteer, which sustains clinical research, creates opportunities for “the benevolent expression of interest.” When the latter relationship works well, attentiveness by investigators is likely to promote in patient volunteers the satisfaction that an effort has been made to understand and help alleviate their suffering, which may have significant therapeutic potential. The strength of the placebo effect in clinical research may reflect, in part, the power of therapeutic attentiveness in the investigator–patient volunteer relationship.

Can a therapeutic alliance between physician investigators and patient volunteers be forged without obfuscating the nature of clinical research? The similarities and the morally relevant differences between the patient-physician relationship and the investigator–investigator relationship deserve recognition and study. In clinical research the relationship is less hierarchical and more collaborative and has greater potential for reciprocity. Patient volunteers, however, can obtain clarity about their own role only to the extent that they understand in general the difference between medical care and clinical research and specifically how any study to which they are invited to participate differs from standard clinical practice. To promote such a clear understanding in patient volunteers, investigators themselves must strive to be as clear as possible about what they are doing in the course of clinical research.

Clinical research relies on a quid pro quo between investigators and patient volunteers. In clinical research the patient volunteer trades his or her time, body fluids, inconvenience, and often discomfort mainly for the hope that research participation will produce therapeutic benefits. Investigators offer the possibility of benefit and the opportunity to contribute to the development of scientific knowledge that may lead to improved treatment of future patients. Therapeutic benefit connected with clinical research may derive from in-depth diagnostic testing, experimental treatment, education concerning the nature of the patient volunteers’ disease, referral
to appropriate treatment, and the therapeutic potential of the patient volunteer–investigator relationship.

The scope and limits of this exchange between investigators and patient volunteers must be openly acknowledged. The chance of therapeutic benefit for patient volunteers is part of the context but not the purpose of clinical research. Failure to clarify how clinical research differs from clinical care at the outset of research participation risks creating therapeutic misconceptions that may color the patient volunteer–investigator relationship throughout the course of clinical research. Devoting ethical attention to the quid pro quo that initiates and sustains clinical research should help make the negotiation of research participation more transparent, honest, and fair, with both parties reaching an accurate understanding of what is at stake in clinical research. With respect to the initial process of clarifying the reciprocal exchanges that are at the heart of clinical research, as well as the actual process of obtaining and maintaining informed consent, we endorse the words of Beecher that the only “reliable safeguard [is] provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator.”

Clinical Judgment in Clinical Research

Clinical research demands the exercise of clinical judgment by physician investigators—an ability that exemplifies the importance of professional integrity. Pellegrino and Thomasma conclude a detailed analysis of clinical judgments in medicine as follows: “In short, clinical judgments are both medical and inherently moral.” This is no less true for clinical judgments in clinical research.

Any clinical trial involving an experimental drug or procedure poses, for example, ethical questions about whether a particular patient volunteer should be discontinued from participation, or whether the trial as a whole should be stopped, owing to serious adverse effects. That regulations governing the reporting of toxicity of medications or other harmful complications exist and data safety and monitoring boards are involved in the oversight of large-scale multicenter trials does not lift the responsibility for clinical judgment from physician investigators. Physician investigators are always required to make clinical judgments regarding the seriousness of adverse events and whether a particular side effect is attributed causally to the experimental intervention and sufficiently threatening to the patient volunteer to warrant removing him or her from the study. These judgments must be made responsibly in a context in which the welfare of patient volunteers potentially competes with the pursuit of scientific knowledge.

A related example is the management of patient volunteers during drug withdrawal periods, regularly a part of studies of novel medications, such as psychiatric or antihypertensive drugs. To ensure washout of drugs taken before study entry as well as to conduct studies of patient volunteers while not taking medications, drug withdrawals lasting 4 to 6 weeks may be required. Yet even in inpatient settings with close monitoring and support, not all patient volunteers can tolerate stopping use of their medications for prolonged periods. The scientific results may be compromised by shortening the drug-free period for some patient volunteers; however, compassion and concern for patient volunteer safety constrain how far investigators and research staff can go in encouraging drug-free patient volunteers to stay the course necessary to meet protocol guidelines. Responsible investigators must exercise clinical judgment to determine if the drug-free period for particular patient volunteers should be cut short and treatment with appropriate medications be resumed.

To make such individualized clinical judgments, investigators must simultaneously evaluate patient welfare and scientific considerations. The potential conflict of interest in such situations is inescapable; it should be faced squarely and managed responsibly. Professional integrity requires that investigators, using clinical and ethical judgment, should be prepared to sacrifice scientific rigor when necessary to protect patient volunteers from exposure to severe suffering or disproportionate risks of harm. With informed consent of patient volunteers, minor risks and mild-to-moderate discomfort may be tolerated to conform to scientific protocols.

Education to Promote Professional Integrity

Professional integrity is developed in the context of professional education and practice. Accordingly, the foundations for professional integrity in clinical research should be laid in medical school. By being exposed to the scientific literature of medicine as well as observing patients enrolled in research protocols or assisting in the conduct of clinical studies, medical students and residents become acquainted with clinical research. The ethical dimensions of clinical research should receive attention in classroom and clinical education. The main priority for education in professional integrity at this stage should be to appreciate the ethically salient differences between clinical practice and clinical research. As medical trainees forge a professional identity as clinicians, they need to learn that the internal moral ethos associated with practicing medicine does not offer a fully adequate guide to the ethical conduct of clinical research. Awareness of the tensions and potential conflicts between loyalty to the standards of patient care and of scientific method constitutes a vital step in developing an internalized moral framework that can help investigators plan and conduct ethically valid clinical research. This understanding is important for all clinicians, regardless of whether they are engaged in research, since their patients may become enrolled in research protocols.

Physicians undertaking careers in clinical research learn about the design and conduct of research protocols primarily by apprenticeship—a practical education of learning by doing. Ethics education that grows out of this apprenticeship context is likely to be the most effective means of promoting professional integrity. Attention to ethics in the training of clinical researchers depends essentially on the stance of senior clinical investigators who function as supervisors, mentors, and role models. Their concern for and commitment to professional integrity must play a key role in promoting professional integrity among investigators in training. We suggest that senior investigators need to focus on the ethics of clinical research as an integral part of their educative role. Fostering ethical competence should be seen as being on a par with competence in research methods. This means that systematic and critical thinking with respect to ethical issues should be highly valued and cultivated, just as it is with respect to scientific methodology.

Collaborations between senior investigators and ethicists interested in clinical research (or clinical researchers with a specialized interest in ethics) can help in structuring more formal aspects of ethics education for investigators in training, including ethics rounds, case conferences, lectures, and semi-
nlar discussions. Journal clubs that discuss the latest scientific methods and results should also focus periodically on articles addressing ethical issues in human subjects research, such as placebo-controlled trials, withdrawal of standard medications during clinical studies, and the adequacy of informed consent.

The task of preparing protocol documents for institutional review board approval should be used as an educational opportunity to reflect on and apply ethical considerations relevant to clinical research. Investigators participating in this process, and in the conduct of research, must become familiar with the federal regulations governing human subjects’ research and relevant ethical principles, as outlined in the Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Anticipation and discussion of ethical concerns and deliberation about alternative ways to conduct scientifically and ethically valid research promote education in ethics, as well as aid in securing institutional review board approval for protocols.

As investigators in training develop insight into ethical issues inherent in clinical research, they will become better equipped to help patient volunteers understand what participation in research involves and how it differs from clinical practice. Ethically reflective investigators should help obviate and dispel therapeutic misconceptions that interfere with accurate understanding of clinical research and distort the relationship between investigators and patient volunteers.

**Conclusion**

The conduct of science within a therapeutic milieu makes clinical research ethically complex. In particular, this context can foster in both patient volunteers and physician investigators a morally perilous tendency to conflate research and clinical care in the form of “the therapeutic misconception.” It is natural for investigators to seek a moral self-understanding that simplifies the moral problems and eases the moral tensions posed by clinical research. Yet approaching the moral landscape of clinical research, and the relationship with patient volunteers, with the perspective that either the clinician or the scientist ought to predominate does not produce satisfactory ethical guidance. Professional integrity in clinical research demands facing squarely the principle that both roles must be integrated and managing conscientiously the inherent ethical complexity, ambiguity, and tensions between potentially competing loyalties to science and care of patient volunteers.

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**References**

19. Carpenter WT, Schoeler NE, Kane JM. The rationale and ethics of mediation-free research in schizophrenia. *Arch Gen Psychiatry.* 1997;54:401-407.