

## SOUNDING BOARD

## The Therapeutic Orientation to Clinical Trials

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Traditionally, clinical trials have been understood as continuous with clinical medicine.<sup>1</sup> In providing medical care for patients, the physician makes observations, investigates, tests hypotheses, and experiments with different treatments. Moreover, the exemplary physician is always learning how to improve treatment for future patients on the basis of clinical experience with current patients and familiarity with the medical literature. Chalmers summarized this view as follows: "The practice of medicine is in effect the conduct of clinical research. . . . Every practicing physician conducts clinical trials daily as he is seeing patients. The research discipline known as the 'clinical trial' is the formalization of this daily process."<sup>2</sup> From this perspective, both clinical trials and medical care are conceived as scientifically guided, therapeutically oriented activities conducted within the context of the physician–patient relationship.

We contend that a therapeutic orientation to clinical trials obscures the ethically significant differences between clinical research and medical care. As a result, it interferes with informed consent and with the development of a concept of professional integrity that is appropriate to clinical research.

DIFFERENTIATING CLINICAL TRIALS  
FROM MEDICAL CARE

Clinical medicine aims to provide individual patients with optimal care. The risks of diagnostic tests and treatments are justified by the prospect of compensatory medical benefits for the patient. By contrast, clinical research is devoted to answering scientific questions in order to produce generalizable knowledge. Physician-investigators conduct clinical trials to evaluate experimental treatments in groups of patient-subjects, with the ultimate goal of benefiting future patients by improving medical care. To be sure, the contrast between the group focus of clinical trials and the individual focus of medical care should not be overstated. Physicians are obligated to practice medicine in the context of a profession-

al standard of care, and not according to idiosyncratic judgments about what is best for a specific patient. Nonetheless, they are expected to make competent treatment recommendations tailored to the characteristics of individual patients.

Many patients receive therapeutic benefits from participating in clinical trials — benefits that may even surpass those of standard medical care.<sup>3</sup> However, randomized clinical trials differ fundamentally from standard care in their purpose, characteristic methods, and justification of risks. Interventions evaluated in randomized trials are allocated according to chance. Double-blind conditions and, often, placebo controls are used. For scientific reasons, protocols governing clinical trials typically restrict flexibility in the dosing of study drugs and the use of concomitant medications. Trials often require drug washouts before randomization to establish a drug-free base line from which to assess the efficacy of treatment. Research interventions such as blood sampling, imaging procedures, and biopsies are often performed to measure trial outcomes. These strictly research-based interventions pose risks to participants that are not compensated for by medical benefits but that are justified by the potential value of the knowledge to be gained from the trial.

Although these differences between clinical trials and standard medical care have frequently been noted,<sup>4-6</sup> their ethical significance has not been sufficiently appreciated. Accordingly, clinical trials continue to be conceived from a therapeutic perspective oriented around the physician–patient relationship. After discussing the therapeutic orientation to clinical trials, we will describe the ethical problems associated with this perspective and offer suggestions for overcoming it.

CLINICAL TRIALS AND THE  
PHYSICIAN–PATIENT RELATIONSHIP

Clinical research is conducted in settings where standard patient care is also provided. These settings include academic medical centers and physi-

cians' offices, which are increasingly being used as sites for industry-sponsored clinical trials.<sup>7,8</sup> Wearing white coats, investigators perform research procedures with the same medical instruments that are used in standard care. This therapeutic ambiance may make it especially difficult to appreciate how clinical trials differ from personalized medical care.

The language describing research with patient-subjects illustrates the conflation of clinical research and medical care. Patient-subjects are typically described simply as "patients," which obscures the important differences between being a research subject and being a patient who is receiving personalized care. Research institutions display this therapeutic orientation on their Web sites.<sup>9</sup> For example, the Web site of the M.D. Anderson Cancer Center, a leading center for cancer research and care, asserts that "a clinical trial is just one of many treatment options at M.D. Anderson,"<sup>10</sup> suggesting that the scientific experimentation of clinical trials is a form of medical therapy. Advertisements aimed at recruiting research subjects typically appeal to patients who are suffering from disease and seeking therapy.<sup>11</sup> They rarely appeal to the altruistic motivation to contribute to a scientific investigation that may help improve medical care for future patients.

The prevailing ethical thinking about clinical trials, which invokes the principle of "clinical equipoise," has endeavored to justify these scientific experiments in the context of the therapeutic physician-patient relationship. According to this principle, a clinical trial is ethical only if the expert medical community is uncertain about the relative therapeutic merits of the experimental and control treatments that will be evaluated in the trial.<sup>12</sup> When a state of clinical equipoise exists, no patient is randomly assigned to a treatment known to be inferior, thus making clinical trials compatible with the therapeutic obligation of physicians to treat patients according to a scientifically validated standard of care. Freedman and colleagues assert that "as a normative matter, it [clinical equipoise] defines ethical trial design as prohibiting any compromise of a patient's right to medical treatment by enrolling in a study."<sup>13</sup>

Ethical randomized trials require "an honest null hypothesis."<sup>14</sup> However, it is erroneous to presume that these studies should be governed by the ethics of the physician-patient relationship. Though intuitively appealing, this presumption conflates the ethics of clinical research with the ethics of medical care.<sup>15</sup> The principles of beneficence

and nonmaleficence governing medical care direct the physician to help individual patients and to avoid subjecting them to disproportionate risks.<sup>16</sup> In clinical research, beneficence is primarily concerned with promoting the well-being of future patients, and nonmaleficence places limits on the risks to which research participants are exposed for the benefit of future patients and society.

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ETHICAL PROBLEMS  
WITH THE THERAPEUTIC ORIENTATION  
TO CLINICAL TRIALS

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The therapeutic orientation to clinical trials contributes to ethical problems. First, it obstructs the full realization of informed consent to participate in research. The tendency of patient-subjects to confuse their participation in clinical trials with personalized medical care has been called "the therapeutic misconception."<sup>4</sup> A variety of evidence suggests that the therapeutic misconception is widespread, although no systematic data on its prevalence are available.<sup>17</sup> There is reason to be concerned that insofar as patient-subjects confuse research with therapy, they do not accurately comprehend what they are doing and thus may be vulnerable to exploitation. Investigators also may be subject to therapeutic misconceptions about clinical research,<sup>6,18,19</sup> although this possibility has not been studied systematically. It is likely that a therapeutic orientation to research on the part of investigators fosters the therapeutic misconception among patients who volunteer to participate in trials.

Second, the blurring of clinical trials and patient care in the minds of investigators diverts attention from inherent conflicts between the pursuit of science and the protection of research participants.<sup>6</sup> Medical care is characterized by a convergence of the doctor's interests and the patient's interests. The patient desires to regain or maintain health; the physician is dedicated to providing the medical help that the patient needs. By contrast, in clinical trials, the principal interests of the investigator and the participating patient may diverge. Patient-subjects typically seek therapeutic benefit from research participation, although they also may be motivated by altruism.<sup>20</sup> Investigators are primarily interested in answering scientific questions about groups of patients, although they also have an interest in providing patients with benefits from their participation. If investigators conceive of clinical trials as a form of medical care, they may erroneously presume

that trials are designed to promote the best interests of participants. By viewing clinical trials in the context of the therapeutic physician-patient relationship, investigators may lose sight of the ways in which the interests of investigators and subjects diverge and thus may find it easy to tolerate or rationalize research activities that may compromise the subjects' well-being.

Third, the therapeutic orientation to research involving patients interferes with investigators' development of a sense of professional integrity.<sup>6</sup> Integrity involves a coherence of beliefs and conduct.<sup>21</sup> Unlike standard medical care, clinical trials typically include procedures that are designed to generate valid scientific data and that are known to subject patients to risks that are not offset by potential benefits; for example, the protocol of a trial may include a biopsy that is performed solely to measure a study outcome. If physician-investigators see patient-subjects in the guise of a therapeutic physician-patient relationship while they conduct research activities that depart significantly from the ethical framework of medical care, then their professional self-understanding lacks integrity.

Professionals with integrity take care to avoid exploiting their clients. The therapeutic orientation to clinical trials eases the recruitment and retention of patient-subjects by fostering trust that their well-being will be promoted.<sup>22</sup> However, trust associated with a distorted concept of the relationship between physician-investigators and patient-subjects is ethically suspect because it contributes subtly to the potential for exploitation. To avoid exploitation and misplaced trust, an investigator approaching a patient about enrollment in a study should describe his or her own role as primarily that of a scientist in pursuit of knowledge aimed at improving medical care for future patients, rather than as that of a personal physician dedicated to promoting the individual patient's health.<sup>23</sup> Making the relationship with patient-subjects a partnership in pursuit of science will require positive efforts on the part of physician-investigators to counteract therapeutic misconceptions about clinical trials.

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OVERCOMING THE  
THERAPEUTIC ORIENTATION

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How, then, should we conceive of the relationship between physician-investigators and patient-subjects? A potentially promising line of inquiry is to examine whether the relationship between investi-

gators and healthy volunteers can inform the development of a model of research with patient-subjects. In most research with healthy volunteers, the purpose of the relationship, from the vantage point of the investigators, is solely scientific. With the exception of those in prevention studies, healthy volunteers are seen neither by the investigators nor by themselves as patients in need of treatment. Because there is no therapeutic motivation to volunteer and because treatment is not provided, investigators often offer healthy volunteers payment as an incentive for participation.<sup>24</sup>

Paying patients who volunteer to participate in a study is less common, for two reasons. In clinical trials, the prospect of a benefit from an experimental treatment and the provision of free ancillary medical care are viewed as compensation for participation. Furthermore, paying patients is believed to be inappropriate. It goes against the grain of the physician-patient relationship, in which patients or their insurance providers pay physicians. Nevertheless, consideration should be given to making payment of volunteer patient-subjects a routine feature of clinical research, because it would symbolize that this activity is different from clinical care. Although there may be concern about coercion or undue inducement, moderate payment would probably be less of an incentive than free treatment. Dickert and Grady suggest that paying patient-subjects might help dispel the therapeutic misconception.<sup>24</sup>

Just as it is inaccurate to conceive of clinical trials as a form of medical care, it is unrealistic to think of research involving patients as the same as research involving healthy volunteers. Unlike healthy volunteers, patient-subjects do need treatment and care. Patients receive experimental treatments in clinical trials, and they may shuttle between clinical care and research participation under the supervision of a single physician or single group of physicians. Research observations and interventions often accompany treatment given according to the standard of care. Especially in the context of research with severely ill patients, physician-investigators have a responsibility to provide appropriate medical attention and care at the same time that they engage in scientific investigation. Nevertheless, investigators' professional integrity requires them to assess each intervention with a patient-subject in order to discern whether it is aimed at patient care or at research. To view clinical trials as therapeutic and as falling under the physician-patient relationship because some aspects of research are associated with

care constitutes an ethical distortion that ought to be scrupulously resisted. Achieving ethical clarity in the relationship with patient-subjects is a formidable challenge in view of the clinical settings and psychosocial forces that foster an ethically inappropriate therapeutic orientation. But ethical clarity is what professional integrity in clinical research demands.

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## The Integral Role of Clinical Research in Clinical Care

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The ethical justification for clinical research as currently conducted has been questioned on the grounds that physicians do not make a strict and unequivocal distinction for their patients between clinical research and clinical care, and their patients may therefore participate in clinical studies with the false impression that they are being cared for to the best of their physicians' ability.<sup>1</sup> This issue raises difficult and controversial questions about the intentions, goals, and responsibilities of clinical researchers, as evidenced by the numerous editorials and articles on the subject that have appeared in the *Journal* in recent decades.<sup>2-6</sup> These are certainly timely questions in view of the widely publicized deaths of several patients during clinical trials in recent years<sup>7</sup> and the fear among laypeople that patients may be

used as "guinea pigs."<sup>8</sup> These questions are also valid in view of the observation that physicians engaged in clinical research may paradoxically see such research as both interfering with the individualization of patient care and providing superior care.<sup>9</sup>

The performance of clinical research has always been acknowledged to entail an essential conflict between the individualization of patient care and the standardization of the scientific method.<sup>2</sup> This conflict is most obvious in the performance of randomized clinical trials, in which the selection of certain aspects of the treatment regimen is taken out of the hands of the treating physician. The basic ethical justification for such trials is the principle of equipoise, which suggests that it is ethically acceptable to choose a treatment plan by random assign-