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Effective Trial Design Need Not Conflict with Good Patient Care[1]

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Miller and Brody (2002) assume that placebo-controlled trials offer scientific and methodological rigor, and they ignore well established ethical and legal standards of care defining the duty of physicians toward their patients.

Some argue that placebo-controlled trials (PCTs), and not trials with an active control (ACTs), are required to demonstrate whether an unproven treatment is effective (Temple 1982; Temple 1996; Temple and Ellenberg 2001). Little supporting evidence has been offered for the superiority of PCTs. Most of the evidence consists of underpowered trials or poorly designed equivalency studies, thus undermining the argument that scientific and methodological rigor can only be provided by PCTs. Miller and Brody fail to come to grips with the methodological limitations of PCTs, assuming, without demonstrating, their "superior rigor."

Freedman, Weijer, and Glass (1996a) and others (Greenberg et al. 1992; Shapiro and Shapiro 1997) have pointed out numerous methodological difficulties with PCTs, the most serious of which concerns blinding. Any argument that PCTs are superior to ACTs requires that trialists and research subjects cannot determine who is receiving active treatment and who is on placebo. Yet Miller and Brody ignore the many difficulties with blinding, difficulties that undermine arguments for the superiority of the placebo-controlled design. The importance of blinding is recognized in the CONSORT Statement adopted by key medical journals and editorial groups (Moher, Schultz, and Altman 2001). It requires that reports of trial results include "how the success of blinding was evaluated." Unfortunately, many trials provide no commentary on blinding in their published results.

Furthermore, the argument that PCTs are required for scientific rigor leads inescapably to the conclusion that ACT trials of new therapies in areas such as infection control or oncology may result in approval of inferior treatments precisely because in these areas withholding available active treatment is clearly recognized as unethical.

Even if PCTs *are* the only scientifically valid methodology to evaluate new therapies, this alone does not make their use ethically acceptable. Neither does is fulfill legal obligations to patients seeking care. Miller and Brody ignore the weight of ethical and legal commentary holding that an investigator's chief concern should be the health and well-being of subjects (Freedman, Glass, and Weijer 1996b; Giesen 1995; Picard and Robertson 1996). The Declaration of Helsinki (World Medical Association 2000) states that "considerations related to the well-being of the human subject should take precedence over the interests of science and society." Hence the duty of physician-investigators to "protect the life, health, privacy, and dignity of the human subject." This duty is not lessened by the subject's consent (Articles 3, 5, 10, 15). Physicians' codes of ethics require them to consider first their patients' well-being (Canadian Medical Association 1996). No exception is made for patients who are research subjects.

Investigators who are physicians cannot withdraw from their ethical obligations merely because they are attempting to answer a legitimate, even important, research question. They must assure themselves that a state of clinical equipoise exists prior to mounting a trial in order to assure that patients seeking care will not be disadvantaged by their random assignment to any trial arm. Even though trials deal with "groups of patients," as Miller and Brody point out, ethical trial design requires that each prospective patient-subject receive an "individualized assessment" of the suitability of participation in the trial. With clinical equipoise, the choice between standard treatment A and experimental treatment B is indifferent. With sufficient evidence from pretrial investigations supporting the proposition that B is at least as good as A, they can be randomly offered as equivalent, and physician-investigators can maintain their duty to provide subjects with effective treatment. Substituting placebo for standard treatment clearly does not maintain this duty.

Conducting a trial is not an invitation to practice substandard medicine. If research subjects seeking treatment are owed less than patients, then subject health and comfort is expendable. Miller and Brody ignore the fact that research ethics has argued to the contrary for the past thirty years. They further ignore the protection afforded patients by law. The principles of general medical law establish standards of care for treatment offered to patients. The legal standard for care provided in the context of research is not lower than for care outside a research protocol. In fact, some courts have set the standard higher, rather than lower, in cases of medical research (Giesen 1995; Picard and Robertson 1996).

Miller and Brody argue that PCTs can be smaller by

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design than ACTs, thus sparing a certain number of individuals the exposure to unknown risks of the intervention being tested. No ethical theory or principle of law recognizes a duty to nontrial participants (those "spared" exposure by using a PCT), or even to future patients, that trumps the physician-investigator's duty to patients recruited to the current trial.

Consent alone is an insufficient defense when a physician fails to act according to the established standard. Prospective research subjects should not be invited to consent to what by law would constitute negligence in the practice of medicine. Physician researchers who fail to provide available effective treatment, or what has been judged to be the equivalent by pretrial clinical evidence, can be held to the same, or higher standards than the practitioner who is not involved in research.

Freedman, Glass, and Weijer (1996b) argue that issues of consent and of risk/benefit must each be resolved in a satisfactory manner before a trial can be approved. They do not argue that PCTS are never an appropriate design. Freedman listed a number of circumstances in which PCTs are ethically acceptable based on allowable risk (Freedman 1990). Some competent patients might be altruistic enough to refuse treatment for a minor condition to participate in research "when withholding such therapy will not lead to undue suffering or the possibility of irreversible harm of any magnitude" (Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada 1998). Such patients may not compromise their right to treatment if they enter a PCT of a new treatment for allergic rhinitis, depending upon how debilitating the condition is for them.

Miller and Brody believe that "the obligations of physician-investigators are not the same as the obligations of physicians in routine clinical practice." We disagree. Patients seeking treatment should not be disadvantaged by enrolling in a clinical trial. Clinical equipoise allows good trial design to coexist with good patient care when active treatment is the comparator for new clinical interventions. ■

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