Therapeutic Beneficence and Placebo Controls

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The obligation of therapeutic beneficence requires that all subjects in a randomized clinical trial receive the best available therapy (World Medical Association 2000). Best available therapy is provided when

a. the risks of each treatment are justified by the anticipated benefits for subjects; and
b. the risk-benefit ratio for each treatment is not known to be less favorable than any available alternative.

Recognizing that the use of placebo controls cannot meet this standard when there is a proven, effective therapy, Miller and Brody (2002) seek to dispense with the obligation of therapeutic beneficence.

They deploy two arguments to establish the irrelevance of therapeutic beneficence to the moral assessment of placebo-controlled trials. The first argument is that positing this obligation in the context of clinical trials confuses the ethics of clinical medicine with the ethics of clinical research. Because clinical investigators pursue purposes other than provision of clinical benefit to subjects and employ research procedures not tailored solely to the needs of particular subjects, it follows that the obligation of therapeutic beneficence is not relevant to the assessment of research practices. The second argument is that, even if this obligation is pertinent to the assessment of therapeutic procedures used in clinical trials, it does not apply to the evaluation of placebo controls. Placebo use constitutes a nontherapeutic intervention, and the risk associated with the latter must be assessed according to a standard other than therapeutic beneficence (Levine 1986). In light of these considerations, the moral evaluation of placebo use should be undertaken according to the standard of "absence of excessive risk."

The problems with this line of argument emerge when we attempt to explicate the meaning of "absence of excessive risk." Any increment of risk for placebo-control subjects results from the denial of best available therapy. This excess risk must be determined by comparing the risk-benefit ratio for placebo-control subjects to the risk-benefit ratio for persons receiving the best available therapy. Best available therapy is provided when conditions (a) and (b) (as specified above) are satisfied. Absence of excessive risk means that the risk-benefit ratio for placebo-control subjects is only slightly less favorable than the risk-benefit ratio for subjects whose active treatment satisfies these conditions. Thus, the requirements of therapeutic beneficence provide the standard of comparison for determining when the use of placebo controls does not pose excessive risk.

The same considerations elucidate the problem with the claim that the administration of placebo should be evaluated as a nontherapeutic intervention. Subjects receive placebo as a substitute for active treatment. The increment of risk associated with the use of placebo must be evaluated against the standard of best available therapy. By contrast, nontherapeutic procedures are not substituted for active treatment but rather for the condition of not being exposed to research interventions at all. The condition of not being exposed to research interventions is understood by reference to the daily life of normal, healthy individuals. The increment of risk associated with nontherapeutic procedures must be assessed by comparing the risks for subjects undergoing these procedures with the risks they encounter in daily life. The risks of daily life provide the standard against which absence of excessive risk is determined for nontherapeutic procedures. Thus, the assessment of placebo controls is governed by the risk-benefit standard governing therapeutic procedures, rather than nontherapeutic procedures.

Why are Miller and Brody so intent on undermining the relevance of therapeutic beneficence to the moral assessment of placebo-controlled clinical trials? The answer is that they assume that the obligation must have absolute priority (Freedman, Glass, and Weijer 1996a; 1996b). That is, the requirements of the obligation must be entirely satisfied by the interventions used in each arm of a clinical trial, including the placebo-control group. A more satisfactory approach involves recognizing that the obligation of therapeutic beneficence has only a general priority in the context of clinical research. This means that its requirements are considerably more important than promoting the welfare of society but may be modified somewhat when it is necessary to promote the welfare of society and when doing so involves only a modest cost to the interests of subjects. In some cases where there is a proven effective therapy for a serious medical disorder, the design features of a placebo-controlled trial can be configured so that there is no more than a minor increment of risk to placebo subjects compared to active-treatment subjects. These design features include entry criteria that exclude the sickest subjects, short duration of placebo use, stringent monitoring for adverse events, and early withdrawal of subjects who deteriorate. Similarly, in cases where treatment for a minor medical condition is being evaluated, the increment of risk associated with simply foregoing treatment may represent

only a modest cost to subjects. Thus, in the allergic rhinitis trial, placebo controls can be used because the risk-benefit ratio of no therapy is only slightly less favorable than the risk-benefit ratio of any available therapy, and the resulting knowledge may contribute to the welfare of those who suffer from allergies.

On this alternative view, therapeutic beneficence is maintained as the moral standard for determining whether participation in placebo-controlled trials may be offered to subjects. It cannot be dispensed with in any event, because it provides the standard against which placebo use must be assessed to determine that the increment of risk to subjects is not excessive. Once this determination is made, subjects may be invited to consider whether randomization is a matter of "approximate indifference" in the light of their own values and goals (Veatch 2002). However, given the vagaries of assuring adequately informed consent in the real world of clinical research, therapeutic beneficence should be maintained as an independent, threshold standard for determining whether placebo-controlled trials can be undertaken with proper regard for the welfare of subjects. On the other hand, therapeutic beneficence does not constitute an absolute priority. When placebo-controlled trials impose only a modest increment of risk compared to best available therapy, then subjects may be invited to participate if doing so is necessary to contribute to the welfare of patients as a group. Miller and Brody are right about this conclusion but wrong about the underlying rationale. ■

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Clarifying the Ethics of Clinical Research: A Path toward Avoiding the Therapeutic Misconception

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Much could be said about the analysis—with which I largely agree—offered by Miller and Brody (2002) of the justification for the use of placebos in at least some studies where partially effective treatments already exist. Here, however, I focus on one salutary implication of their argument, derived from their observation that physicians running clinical trials do not have a therapeutic obligation to offer optimal treatment. They note that the previous Helsinki approach appeared to confuse the obligations of researchers with those of clinicians in opposing the use of placebos when they are likely to be inferior to existing care. In fact, this confusion between the ethics of research and of ordinary clinical care appears rampant in the world of clinical trials. When it arises among subjects, which it often does, it is known as the "therapeutic misconception," a phenomenon that my colleagues and I described two decades ago (Appelbaum, Roth, and Lidz 1982; Appelbaum et al. 1987).

A therapeutic misconception occurs when a subject transfers to the research setting the presumption that obtains in ordinary clinical treatment: that the physician will always act only with the patient's interests in mind. In the research study, in contrast, the physician's actions—including the use of randomization, double-blind procedures, adherence to strict protocols, and administration of placebos—may be undertaken because they advance the scientific validity of the research study, rather than because they serve the subject. Such deviation from the principle of "personal care" (Fried 1974) cannot be justified in the absence of the subject's knowing consent to forego the usual advantages of the treatment setting. Altruism is the most obvious justification for a decision of this sort, though subjects may correctly perceive some self-interest at stake as well—for example, free medication, more careful follow-up, the chance that research advances will be of direct help in the future. But this kind of knowing consent is often absent.

Since our description of the therapeutic misconcep-