I Need a Placebo Like I Need a Hole in the Head

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In this issue of the *Journal of Law, Medicine & Ethics*, Peter Clark provides a comprehensive and sound ethical analysis of clinical trials examining the treatment of advanced Parkinson's disease with fetal tissue transplantation.[1] These studies raise profound questions about how clinical trials of surgical interventions ought to be conducted. At stake is not only the ethical basis of such trials, but differing views as to the proper role of science in medicine and its limitations.

Experience with the broader debate on the ethical permissibility of placebo controls has taught us that the choice of control treatment is an aspect of trial design in which ethical and scientific issues overlap. Accordingly, I will highlight, and perhaps expand upon, three issues raised by Clark: What scientific questions ought clinical trials of surgical interventions ask? How should the ethical analysis of risk for such trials be conceived? And, are surgical patients a vulnerable population?

Explanatory and Pragmatic Scientific Questions

Beecher was perhaps the first to recognize that surgical interventions might have a placebo effect.[2] This is viewed by some as necessitating placebo-controlled trials for novel surgical interventions. According to a recent article by Emanuel and Miller, placebo-controlled trials are required from a scientific standpoint when one of the following conditions obtain:

- there is a high placebo response rate;
- the condition is typically characterized by a waxing and waning course, frequent spontaneous remissions, or both;
- existing therapies are only partly effective or have very serious side-effects; or
- the low frequency of the condition means that an equivalence trial would have to be so large that it would reasonably prevent adequate enrollment and completion of the study.[3]

In truth, only the last condition provides a scientific argument for conducting a placebo-controlled trial.

The randomized controlled trial is rightly viewed as the gold standard in the evaluation of novel medical and surgical interventions. The fact that many conditions wax and wane or spontaneously improve calls for the inclusion of a control group, in which the novel intervention is compared with standard treatment or, if none exists, placebo.[4] The efficacy or side-effects of current treatment do not argue for the use of a placebo control, as the scientifically relevant question is whether the new treatment is more effective and safer than standard treatment, if any. Patient and physician factors in choosing one treatment arm or another, however, pose a serious source of bias. Accordingly, patients must be allocated randomly to one treatment arm or another. Finally, patient and physician reporting of outcome measures may be influenced by knowledge of treatment allocation. Where possible, then, patients and physicians are blinded as to the treatment administered. Importantly, none of these methodological strengths of the randomized controlled trial require the inclusion of a placebo control.

In the absence of a standard surgical approach against which a novel intervention, such as fetal cell transplantation, might be compared, a placebo control is required. This is, I take it, not contentious. The controversy surrounds what the placebo control ought to be. In it simplest form, the placebo control may be a no surgery arm, in which patients continue to receive medical treatments, as indicated. The trial in question, however, involves a range of further interventions,

Journal of Law, Medicine & Ethics, 30 (2002): 69–72.

including placement of stereotactic equipment, scalp incisions, partial burr holes, general anesthesia, intravenous antibiotics, and low-dose cyclosporin. Two reasons motivate the addition of these procedures to the placebo arm. First, if blinding is to be preserved, patients in the placebo arm must undergo similar procedures to the patients in the experimental arm. Second, the trial aims to dissect out the effect of the fetal tissue transplant per se from the other interventions provided. Both of these scientific rationales are open to criticism.

While blinding is a desirable feature of a randomized controlled trial, it is not indispensable. Trials with disparate treatment arms often cannot reasonably preserve blinding. For instance, trials comparing chemotherapy and radiation therapy for cancer treatment commonly proceed without blinding because sham procedures to preserve the blind would be unduly burdensome on patients. Until recently, trials involving a surgical and non-surgical arm would have been viewed by many as the most obvious case in which a blind could not be preserved, since sham surgical procedures were largely viewed as paradigmatically unethical.

The motivation to conduct surgery trials with a sham surgical control must, therefore, come from the second rationale. But can a placebo-controlled trial, so designed, answer the question, what is the contribution of fetal cell transplantation per se to the overall observed effect? There is good reason to doubt whether it can.

As Clark points out, the current design fails to control for the effect of stereotactic needle insertion on brain tissue. In order to answer the question posed, therefore, one would need a very much more complex trial — one in which at least the effect of stereotactic needle insertion is controlled for with a sham needle insertion treatment arm. Ascertaining the contribution of the various components of treatment would require a trial with many arms: the experimental arm; a sham needle insertion arm; a sham surgical arm with no needle insertion; an arm with anesthesia and no sham surgery; and a no treatment arm. This challenges the supposed simplicity of the placebo-controlled study design.

It should be further recognized that even this more complex, multi-arm trial rests on questionable assumptions. Whether a placebo-controlled trial can assess the contribution of various treatment components rests on the assumption that each treatment component has an additive effect. Only on this additive model can the observed effect be thought to be constructed from a series of components, each adding a discrete proportion of the observed efficacy. Treatment components may, however, have a more complex relationship. For instance, psychological and physical effects may interact with one another. An optimistic outlook may enhance the efficacy of a physical effect, and a physical effect may buoy a patient's optimism that a treatment is in fact working. This multiplicative relationship between treatment components would tend to undercut the ability of a trial to focus on particular components in isolation.

Recognizing the scientific limitations of placebo-controlled trials, I have argued elsewhere that trials ought to focus on pragmatic rather than explanatory scientific questions.[5] Thus, in the face of no available treatment for certain patients with advanced Parkinson's disease, a trial of a novel therapeutic intervention ought to ask: Is fetal cell transplantation preferable to no surgery? This question requires a no surgery control, not a control with sham surgical interventions.

Risk Analysis

Sham surgery trials raise an interesting challenge for the ethical analysis of research risk. Typically, placebos in drug trials are viewed as a therapeutic intervention. Should sham surgery be analyzed in the same way? I think not.

Previously in the pages of the *Journal of Law, Medicine & Ethics*, I argued for a component analysis approach to research risk.[6] This approach was recently endorsed in the final report of the U.S. National Bioethics Advisory Commission.[7] The approach to risk analysis flows from the recognition that procedures in a study may be administered with different intent and, hence, require differing moral calculi. Therapeutic procedures, be they drug, surgery, or psychological intervention, are administered with therapeutic warrant and with the hope of providing direct benefit to the research subject. Non-therapeutic procedures, including added blood tests, x-rays, and questionnaires, are not administered with therapeutic warrant and serve merely to help answer the scientific question at hand.

Therapeutic procedures must pass the test of clinical equipoise.[8] That is, at the start of the trial, there must exist a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment. When there is no effective treatment available for a medical condition, novel treatments ought to be compared with placebo. Once effective treatment exists, however, novel interventions should usually be tested against best available standard treatment. Thus, the ethical analysis of therapeutic procedures is a harm-benefit analysis.

Non-therapeutic procedures, by definition, offer no prospect of benefit to individual subjects and, accordingly, a harm-benefit analysis is inappropriate.[9] Two separate moral tests are applied to such procedures. First, the risks of non-therapeutic procedures must be minimized consistent with good scientific design. Second, the risks must be reasonable in relation to the knowledge to be gained. Thus, the ethical analysis of non-therapeutic procedures is a harm-knowledge calculus. Importantly, moral tests for both therapeutic and non-therapeutic procedures must be passed in order for a study to proceed.[10]

The simplest design for a trial of fetal cell transplantation, in which the intervention is compared to a no surgery

control, fits this model easily. Fetal cell transplantation and no surgery are therapeutic interventions. In order for the trial to proceed, there must exist disagreement as to the preferred treatment. Given the promise shown by early trials of fetal cell transplantation and remaining uncertainties regarding long-term outcome, this test is likely fulfilled. The study will certainly involve non-therapeutic interventions, such as questionnaires and PET scans. The institutional review board (IRB) must ensure that the risks associated with these procedures are minimized and reasonable in relation to the knowledge to be gained. Again, these requirements can probably be fulfilled unproblematically. Thus, a trial of fetal cell transplantation with a no surgery control can fulfill the various ethical tests contained within the component analysis approach to risk analysis.

Sham surgery trials are controversial precisely because procedures are added above and beyond those present in a no surgery design. Research subjects in the control arm have a stereotactic frame fitted, undergo anesthesia, skin incisions, and have partial burr holes made in their skull. Each of these added procedures is administered without therapeutic warrant and solely to answer the scientific question at hand. Thus, sham surgical procedures must be analyzed as non-therapeutic interventions. Whether risks can be minimized consistent with sound scientific design is, of course, the pivotal moral question. As I have argued above, sham surgical designs have significant scientific disadvantages and, accordingly, a no surgery control likely represents a superior scientific design. Furthermore, given the gravity of the risks associated with anesthesia and surgery, whatever knowledge is likely to be gained from such procedures likely fails to outweigh the risks posed. Therefore, I agree with Clark when he concludes that sham surgery designs "fail the test of beneficence."[11]

Vulnerable Populations

A note of caution needs to be introduced, however, when answering the question of whether subjects for surgical trials in Parkinson's disease are a vulnerable population. Vulnerability is a complex notion. Research subjects may be vulnerable for three reasons: (1) they are incapable of making decisions regarding research participation; (2) they are so situated as to call into question the voluntariness of such decisions; or, (3) they are likely to experience undue harms as a result of study participation.[12] Patients with advanced Parkinson's disease may be vulnerable of one or more of these three reasons. But the IRB must exercise discretion in its determination that a study population is vulnerable. As Levine rightly observes:

> It should be understood that each person, when measured against the highest standards of capability, is relatively vulnerable. We are all dependent on someone or something and susceptible to temptation by what we consider very large sums of money.... It is easy to identify too many persons as vulnerable and to apply procedures designed to protect the interests of vulnerable persons too extensively. Some judgment is required. In each case it is worthwhile to reflect on the implications of labeling persons as vulnerable. Are we being disrespectful of persons by repudiating their authority to live according to their considered judgments?[13]

Labeling persons with advanced Parkinson's disease as vulnerable runs the risk of inflicting upon them the final indignity in a life of restricted autonomy.

Ignoring the Complexity of Clinical Medicine

As morally unsettling as sham surgery trials are, they are but part of a larger problem in the conduct of clinical research. Medical science in North America suffers from a strong scientistic bias, according to which it is thought that clinical trials ought to mirror laboratory experiments in which variables are manipulated one at a time. But the clinician's office is not a laboratory anymore than a research subject is a lab rat. Clinical care and human response to disease are simply too complex to be captured by such a simplistic model. This erroneous approach to science has caused us to believe that greater scientific ends are being served when we deprive a patient with schizophrenia of needed treatment in a placebo-controlled trial or expose a patient with Parkinson's disease to the risks of sham surgery. Fully embracing the complexities of clinical medicine not only causes us to see these studies as unethical, but it reveals that the scientific goals pursued by them are illusory.

Acknowledgments

Professor Weijer's research is funded by a Canadian Institutes of Health Research Operating Grant and New Investigator Award, as well as a Dalhousie University Clinical Research Scholar Award.

References

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2. See H.K. Beecher, "Surgery as Placebo," *JAMA*, 176 (1961): 1102–07.

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4. B. Freedman, C. Weijer, and K.C. Glass, "Placebo Orthodoxy in Clinical Research I: Empirical and Methodological Myths," *Journal of Law, Medicine & Ethics*, 24 (1996): 243–51.

5. See *id.*

6. C. Weijer, "The Ethical Analysis of Risk," *Journal of Law, Medicine & Ethics*, 28, no. 4 (2000): 344–61.

7. U.S. National Bioethics Advisory Commission, "Report and Recommendations of the National Advisory Bioethics Commission," *Ethical and Policy Issues in Research Involving Human Participants*, vol. 1 (Bethesda: NBAC, 2001).

8. See Weijer, *supra* note 6.

9. See *id.*

10. See *id.*

11. See Clark, *supra* note 1.

12. C. Weijer, "Research Involving the Vulnerable Sick," *Accountability in Research*, 7 (1999): 21–36.

13. See R.J. Levine, *Ethics and Regulation of Clinical Research*, 2d ed. (New Haven: Yale University Press, 1988): at 73.