

2. Steiner LA, Drop LJ, Castelli I, Alfille PH, Schouten R, Welch CA. Diagnosis of myocardial injury by real-time recording of ST segments of the electrocardiogram in a patient receiving general anesthesia for electroconvulsive therapy. *Anesthesiology* 1993; 79:383-8.
3. Castelli I, Steiner LA, Kaufman MA, et al. Comparative effects of esmolol and labetalol to attenuate hyperdynamic states after electroconvulsive therapy. *Anesth Analg* 1995;80:557-61.

**THE AUTHORS REPLY:** We thank Tavares and Volpe for sharing an interesting facet of their practice. However, we are unaware of studies that demonstrate the impact of routine screening with head CT on patient outcomes — even in areas where neurocysticercosis is endemic. The finding of only one case of active neurocysticercosis among 91 patients in their high-prevalence area lends support to the use of targeted neuroimaging. In areas where the prevalence of silent, space-occupying intracranial lesions is low, routine head CT before ECT is not justified given the low yield of actionable disease. We do agree that medical consultants should be aware of all settings where the risk of an intracranial lesion is increased. We thank our colleagues from Brazil for highlighting travel to or emigration from endemic areas as potentially important considerations.

We appreciate Welch's comment regarding the use of beta-blockers; this is a controversial area in the care of patients with ECT. In our article, we described the significant hemodynamic changes associated with ECT and the efficacy of beta-blocker therapy in blunting this response. However, despite Welch's description of a poor outcome, most patients tolerate these changes without

a major event. The vast majority of patients, including those in whom cardiac complications do develop, are able to complete a full course of treatment with no long-term cardiac sequelae (Table 2 of our article). The beneficial effect of the routine use of prophylactic beta-blockers in patients is therefore difficult to demonstrate overall. The potential risks of beta-blocker use are a shortened duration of seizures and reduced efficacy of ECT, though we acknowledge that these are not uniform findings in the literature.<sup>1-3</sup> We stand by our recommendation that prophylactic beta-blockers be used only for selected high-risk patients with either previous prolonged hypertension after ECT or a preexisting condition that requires tight hemodynamic control. If future data show no effect of beta-blockers on seizure duration and ECT efficacy, the risk-benefit calculation would change in favor of less selective use.

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1. Howie MB, Black HA, Zvara D, McSweeney TD, Martin DJ, Coffman JA. Esmolol reduces autonomic hypersensitivity and length of seizures induced by electroconvulsive therapy. *Anesth Analg* 1990;71:384-8.
2. van den Broek WW, Leentjens AF, Mulder PG, Kusuma A, Bruijn JA. Low-dose esmolol bolus reduces seizure duration during electroconvulsive therapy: a double-blind, placebo-controlled study. *Br J Anaesth* 1999;83:271-4.
3. Howie MB, Hiestand DC, Zvara DA, Kim PY, McSweeney TD, Coffman JA. Defining the dose range for esmolol used in electroconvulsive therapy hemodynamic attenuation. *Anesth Analg* 1992;75:805-10.

## Ethical and Scientific Implications of the Globalization of Clinical Research

**TO THE EDITOR:** In their article, Glickman et al. (Feb. 19 issue)<sup>1</sup> examine the growing phenomenon of clinical trials being conducted outside the regulatory framework of the developed world. They rightfully point out some of the ethical and scientific pitfalls of these investigations. However, they do not mention that the offshoring of clinical studies can also deprive critically ill patients in the developed world access to some of the latest drugs and devices, the underlying basic research for which was paid for through taxes by

these same persons. Perhaps this issue, as opposed to paternalistic concerns about inadequate regulation within the Third World, represents the biggest ethical dilemma we confront in this era of research globalization.

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1. Glickman SW, McHutchison JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med* 2009;360:816-23.

**TO THE EDITOR:** Glickman et al. imply that international outsourcing of clinical trials may compromise ethical and scientific integrity, but they fail to acknowledge an important safety net that does exist. The Food and Drug Administration (FDA) reviews results of studies regardless of their country of origin, and regulations require that the supporting clinical investigations performed under investigational-new-drug applications<sup>1</sup> be held to the same standards regardless of whether the clinical sites are located in the United States. The *FDA Guidance for Industry: Acceptance of Foreign Clinical Studies*<sup>2</sup> permits acceptance of data from a foreign clinical study “only if the study conforms to the ethical principles contained in the Declaration of Helsinki” or with laws and regulations of the country, whichever provide the greatest ethical protections. Aside from the ethical imperative, what is the economic advantage to the company of collecting poor-quality data that could compromise the final regulatory review? There is always room to improve regulatory capacity and training here and abroad, but this article dwells on potential insufficiencies rather than on the advantages of engaging international researchers to develop global products.

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1. 21 C.F.R. § 312.23(a)(6)(b).
2. Guidance for industry: acceptance of foreign clinical studies. Rockville, MD: Food and Drug Administration, March 2001.

**THE AUTHORS REPLY:** Adler points out the important implication that offshoring of clinical studies can deprive critically ill patients in high-income countries access to cutting-edge therapies. Research for these therapies, in particular, requires study designs that incorporate the complex environment of highly developed intensive and emergency care settings.<sup>1,2</sup> More broadly, the current emphasis on translational research is based on the concept of bench-to bedside research.<sup>3</sup> This type of research may warrant special consideration in the globalization of clinical trials.

We agree with Andrews on the important safety net that the FDA provides in clinical studies outside the United States. Yet, the FDA has been

challenged by “ever-expanding responsibilities in the face of a mostly flat annual budget.”<sup>4</sup> Thus, we cannot count on the FDA alone to ensure the ethical underpinnings of the global clinical research process.

Since the publication of our article, we have been made aware of independent investigations into the clinical research process in low- and middle-income countries that have validated many of the concerns we expressed.<sup>5</sup> At the same time, some of our colleagues in those countries have expressed concerns that our article calls into question the integrity of their work and our collaborations. This dichotomy underlies our basic concerns about the issues of ethical and research integrity in the globalization of clinical research. Currently, there is neither a global mechanism to identify investigators and institutions who strive to meet the highest ethical and scientific standards for clinical research nor a systematic means of tracking those who have violated these standards. We believe that implementing the recommendations in our article will help to remedy this situation.

Greater international cooperation among industry sponsors, contract research organizations, and interested governments could be used to further ensure the application of internationally established principles and policies in clinical research.

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1. Glickman SW, Anstrom K, Li L, et al. Challenges in enrollment of minority, pediatric, and geriatric patients in emergency and acute care clinical research. *Ann Emerg Med* 2008;51:775-80.
2. Cobb JP, Cairns CB, Bulger E, et al. The United States Critical Illness and Injury Trials Group: an introduction. *J Trauma* (in press).
3. Zerhouni EA. Translational and clinical science — time for a new vision. *N Engl J Med* 2005;353:1621-3.
4. Okie S. A to-do list for the new FDA commissioner. *N Engl J Med* 2009;360:1373-8.
5. Hundley K. Testing grounds: our medicine at what cost? *St. Petersburg Times*. December 2008. (Accessed June 4, 2009, at <http://www.tampabay.com/specials/2008/reports/india/>)