Ethics and Feasibility of Placebo-Controlled Interventional Acute Stroke Trials

To the Editor:

The ethics of performing a randomized controlled trial (RCT) of thrombolytic therapy in the 3- to 6-hour window with a placebo arm were recently debated in *Stroke* and during the recent International Stroke Conference. The key ethical principle involved is equipoise.

Grotta and Barreto,1 both vascular neurologists, address equipoise as follows: “So, is it “ethical” to have placebo-controlled trials given the data? This can best be answered by posing the following question. Would I be willing to be randomized into such a trial at a center capable of expert intravenous or endovascular therapy if I myself had an M1 middle cerebral artery occlusion and NIHSS score of 15 at 4 hours after the onset of symptoms? The answer would be a hesitant “yes,” but I surely hope that we hurry and obtain an answer before I have to make such a decision.”

This tepid response represents only individual equipoise. However, because individuals rarely agree, the most widely used definition of equipoise is “collective” equipoise. Johnson et al2 conducted an ethometric study to find out how much collective equipoise can be disturbed before the potential subjects in a trial think that it is unethical. “Half of our subjects perceived a trial as unethical when equipoise was disturbed beyond 70:30. In other words, when 70% of experts favor one treatment, 50% of subjects would prefer that treatment to be administered rather than subjected to critical assessment. When equipoise is disturbed beyond 80:20, less than 3% of subjects would consider human trials morally justifiable.”

So the question might be rephrased as: “Would >70% of Stroke Centers favor endovascular therapy over medical therapy only in a 60-year-old man with a 4.5-hour bland infarction due to acute M1 MCA occlusion from atrial fibrillation, a baseline NIHSS of 15, a clear mismatch on MR, no exclusion criteria and stroke thrombectomy devices.6,7 It seems Washington at least is not so concerned about the potential market and increases the cost of the RCT. Nonetheless, in my view and the placebo issue aside, a >3-hour RCT that does not adequately account for stroke heterogeneity will either require a huge (and likely not feasible) sample size or will be doomed to failure.

Complicating ethics is the issue of feasibility. Are there enough interventionalists who agree that IA thrombolysis versus a placebo control is ethical to randomize >400 relatively homogeneous patients in a reasonable timeframe? The painfully slow recruitment in MR RESCUE and IMS3 (no placebo arm) suggests not. In the United States, ethics are further conflated by CMS hospital reimbursement policies for IA stroke thrombolysis and the availability of 2 FDA approved thrombus removal devices.5-7 It seems Washington at least is not so concerned about the ethical need for a placebo-controlled RCT. The subtleties of thrombus removal versus an improved modified Rankin Scale score at 90 days are likely to be lost on patients and families in the throes of an acute stroke.

I do not pretend to be a bioethicist. However, I do suggest that performing a sufficiently powered “placebo”-controlled RCT of IA stroke thrombolysis in the >3-hour window, while ethical in some collectives, may not be feasible in most. Novel approaches give hope for trials like EXTEND but will perhaps require a worldwide effort. In my view, alternatives to the traditional RCT that reduce sample size, improve homogeneity and eliminate or
reduce the “placebo” arm will be needed for the next ethical, feasible and hopefully successful RCT in acute stroke.

Disclosures
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4. Donnan GA, Davis SM. The ethics of thrombolytic trials beyond 3 (or 4.5) hours: randomized controlled trials are required to change clinical practice. *Stroke.* 2009;40:1545.
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