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 brain infarction due to acute M1 MCA occlusion from atrial fibrillation, a baseline NIHSS of 15, a clear mismatch on MR, no exclusion criteria and a baseline NIHSS of 15, a clear mismatch on MR, no exclusion criteria and an interventionalist readily available?” One could substitute “vascular neurologists” or “interventionalists” or any number of expert collectives for Stroke Centers.

Grotta and Barreto themselves suggest that the answer to this collective equipoise question is probably “yes” when they state: “we may have passed the ‘tipping point’ among stroke experts vis-a-vis IA thrombolysis beyond 3 hours. Our opinion in 2008 is that reperfusion can be effective within the 3- to 6-hour time window. This opinion is now so widely shared among stroke experts based on the data just described that we may well have passed the ‘tipping point’ at which the epidemic of treatment for these patients cannot be halted.” Is an ‘epidemic’ equipoise?

Kohrmann and Schwab, also vascular neurologists, suggest there is no collective equipoise on this issue in Germany. On the other hand, Donnan and Davis,3 vascular neurologists from Australia, state that “the uncertainty principle (aka equipoise) for the conduct of clinical trials is alive and well, and a sufficient number of clinicians worldwide would be prepared to randomize such patients.” Perhaps, but it is unclear that the “sufficient number” of clinicians represents >30% of stroke experts, certainly not interventionalists.

And what about patient equipoise? Patients often disagree with the trialists, which is why <30% of eligible patients are randomized and why we have informed consent. US Institutional Review Boards have required that the availability of stroke thrombectomy devices must be included in the informed consent which greatly complicates patient recruitment. Given this choice, would patients or families confronted with a devastating stroke and no absolute contraindications view “placebo” or intraarterial (IA) clot thrombolysis as equal choices? After all, the criteria for FDA approval of these devices were “safety and efficacy” and for Center for Medicare and Medicaid (CMS) reimbursement “reasonable and necessary.”5 Certainly a stroke device that is safe, effective, reasonable and necessary cannot be considered “unethical” (at least in the United States).

Equipoise is affected not only by the level of evidence available (and PROACT 2 was a phase 3 RCT) but by a host of other factors including accumulated experience, evidence from other organ systems (eg, cardiac) and physiological rationale. There can no longer be any question that in some stroke patients the risk/benefit ratio for IA (and possibly IV) thrombolysis is acceptable beyond 3 hours and that reperfusion is linked with better outcomes. However, as time increases so does the risk: benefit ratio, and clearly not every patient will benefit while some will be harmed. So a major challenge is to refine the selection factors by using new technology such as mismatch imaging. Unfortunately from industry’s perspective this reduces 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.6-7 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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