

Published in final edited form as:

Stroke. 2009 June ; 40(6): e441–e442. doi:10.1161/STROKEAHA.108.531939.

## Clinical Trials, Devices, Unproven Treatments, and Clinical Equipose

**Warren W. Wasiewski, MD and Karen C. Johnston, MD, MSc**

Neurobiological Technologies, Inc (W.W.W.), Edgewater, NJ; and the Department of Neurology (K.C.J.), University of Virginia, Charlottesville, Va.

### Keywords

clinical trials; devices; equipose; stroke treatment

The importance of unbiased comparative research trials to answer clinical questions that guide best treatment practices is unquestionable. Large multicenter clinical trials are critical for answering important clinical questions that cannot be answered by observational data. These studies depend on adequate recruitment from unbiased samples of patients from the population of interest. Investigators participating in such trials must also have clinical equipose that the treatment under study may or may not be better than the standard treatments available. If such clinical equipose does not exist, then recruitment will be biased and potentially delayed. In recent years, stroke clinical trials have struggled to enroll patients to acute trials for a variety of reasons, including narrow eligibility time windows and, most recently, to the growing list of available, although not necessarily safe or efficacious, therapies.

In January 2008, the US Food and Drug Administration cleared the second device for removal of blood clots from the central nervous system vasculature, the Penumbra System.<sup>1</sup> The device was cleared based on demonstration of substantial equivalence to legally marketed predicate devices, in this case, the Merci Retriever models X5 and X6 in bench, in vitro, in vivo, and in clinical testing. The clinical data were presented as a late-breaking abstract at the International Stroke Conference 2008.<sup>2</sup> The Merci Retriever has been available since it received US Food and Drug Administration clearance in 2004.<sup>3</sup> These devices were both studied in a time window of 8 hours from stroke onset. Neither device has demonstrated safety or efficacy in a randomized, controlled comparative trial for acute ischemic stroke. The reported rates of symptomatic intracranial hemorrhage for both the Merci retriever and the Penumbra device exceed those reported in the National Institute of Neurological Diseases and Stroke rt-PA trial,<sup>2,4–6</sup> although without direct comparison of the implications of this are somewhat unclear. Additionally, both devices have been associated with device-related complications such as dissection and vessel rupture complicating further the estimates of risk–benefit ratio.

Recombinant tissue plasminogen activator administered intravenously within 3 hours of stroke onset received approval for treatment of acute ischemic stroke after demonstrating safety and efficacy in 2 National Institute of Neurological Diseases and Stroke randomized, controlled

© 2009 American Heart Association, Inc.

Correspondence to Warren W. Wasiewski, MD, Neurobiological Technologies, Inc, 2000 Powell St, Suite 800, Emeryville, CA 94608. runnerw3@yahoo.com.

#### Disclosures

W.W.W. was the Chief Medical Officer for Neurobiological Technologies Inc leading the clinical trial for the development of anecrod for treatment of acute ischemic stroke.

comparative trials with a total of 624 patients.<sup>6</sup> Over the last 12 years, the use of recombinant tissue plasminogen activator has remained relatively low due to numerous obstacles, but primarily due to the time to treatment limitation of 3 hours. Presumably based on the PRO-urokinase for Acute Cerebral Thrombosis (PROACT)-II trial data that demonstrated safety and marginal efficacy of prourokinase delivered intra-arterially to middle cerebral artery occlusions within 6 hours,<sup>7</sup> many centers now offer intra-arterial recombinant tissue plasminogen activator up to 6 hours from onset of stroke, although the dosing and specific protocols are not standardized. The use of intra-arterial recombinant tissue plasminogen activator has not been rigorously studied in randomized, controlled comparative trials and the assumption that the benefits demonstrated with prourokinase are the same as with recombinant tissue plasminogen activator may not be justified. Because intra-arterial recombinant tissue plasminogen activator has not been adequately studied to establish the risk and benefit in a specific population, it is unclear if the population being offered this treatment is the correct one and what the true risk-benefit ratio may be for this approach. There is substantial variability across the country because this non-US Food and Drug Administration-approved treatment is offered, and thus conclusions about the safety and efficacy from such observational data may be highly biased and confounded.

On this background of unproven and unapproved treatment approaches, well-designed clinical trials struggle to recruit patients to answer important clinical questions. Eligibility criteria for clinical trials are established to include only those patients in the population of interest, but it is important that all patients meeting those criteria be considered for the study to allow the results to be valid in representing that population. A significant bias can be introduced into the final study population if investigators assess patients for unapproved or unproven treatments and only enroll patients in clinical trials that they deem inappropriate for these unproven treatment interventions. In addition, evaluation of patients for these treatments before consideration of trial enrollment can substantially delay time to treatment for the investigational product. Ultimately, introduction of such bias into a trial risks dismissing potentially valuable treatments. Moreover, investigators clearly lack equipoise if they are diverting potentially eligible patients into unproven management options in preference to enrolling them into well-designed clinical studies.

Offering unproven or unapproved treatments by investigators threatens the very core value of randomized, controlled comparative trials and is significantly hampering our ability to answer important clinical questions. The availability of off-label therapies and the rapid approval mechanism for devices has flooded the acute stroke community with treatment options that compete with clinical trials. Investigators must bear in mind that anecdotal data and noncomparative observational data will never provide the level of scientific rigor supported by randomized, controlled comparative trials. Opportunities to help answer scientific questions may be lost every time we offer an unapproved or unproven therapy outside of a controlled clinical trial. Investigators who commit to participation in a clinical trial must agree to offer the study option in an unbiased manner. If they cannot comfortably do this due to true equipoise as to whether the trial options are better or worse than the otherwise available treatments (proven or not proven), then these investigators must decline participation in the clinical trial.

Acute stroke trial enrollment has always been difficult and continues to be a challenge. We encourage the stroke research community, and specifically the enrolling investigators, to prioritize the completion of acute stroke trials by inviting all potential candidates to participate in research trials and only offer off-label and unproven therapies if such clinical trials are not available to the patient. Rapid completion and analysis of clinical trial data will guide best clinical practice and improve stroke patient outcome and benefit all in the stroke community.

## Acknowledgments

We respectfully acknowledge the valuable insights of Dr David Levy in the preparation of the manuscript.

## References

1. Penumbra, Inc (San Leandro, CA). 501(k) Summary Letter: FDA. Sept 20;2007 Reference No K072718 (Penumbra System).
2. McDougall, C.; Clark, W.; Mayer, T.; Doerfler, A.; Grunwald, I.; Berkefeld, J.; Lopes, D.; Shownkeen, H.; Madison, M.; Budzik, R.; Heck, D.; Frei, D.; Zaidat, O.; Branca, V.; Ahktar, N.; Rai, A.; Chaloupka, J.; Hellinger, F.; Rasmussen, P.; Rudolph, S.; Spiegel, G. The penumbra stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in acute ischemic stroke.. Late-Breaking Science Abstracts presented at the International Stroke Conference; New Orleans, LA. Feb 20–22, 2008;
3. Concentric Medical Inc (Mountain View, CA). 501(k) Summary Letter FDA. Aug 3;2004 Reference No K033736 (Concentric Merci® Retriever).
4. Smith WS, Sung G, Starkman S, Saver JL, Kidwell CS, Gobin YP, Lutsep HL, Nesbit GM, Grobelny T, Rymer MM, Silverman IE, Higashida RT, Budzik RF, Marks MP for the MERCI Trial Investigators. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke* 2005;36:1432–1438. [PubMed: 15961709]
5. Smith WS, Sung G, Saver J, Budzik R, Duckwiler G, Liebeskind DS, Lutsep HL, Rymer MM, Higashida RT, Starkman S, Gobin YP, for the Multi MERCI Investigators. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke* 2008;39:1205–1212. [PubMed: 18309168]
6. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581–1587. [PubMed: 7477192]
7. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F, for the PROACT Investigators. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *JAMA* 1999;282:2003–2011. [PubMed: 10591382]