

Questions for Discussion

Circulatory System Devices Panel, March 2, 2007

Trial Designs for Devices Intended to Close Patent Foramen Ovale for the Prevention of Recurrent Stroke

Both a practice parameter from the American Academy of Neurology (AAN) and guidelines from the American Heart Association/American Stroke Association Council on Stroke (AHA/ASA) concluded that there was insufficient evidence to evaluate the efficacy of percutaneous Patent Foramen Ovale (PFO) closure compared with medical therapy for the prevention of recurrent neuroembolic events (stroke/TIA). Recommendations were made for further study including stratified randomization to equally distribute subgroups based on age, PFO size, and other factors that may influence the risk of subsequent events.

Randomized trials are ongoing; however, enrollment has been extremely slow and FDA has been asked by some sponsors to reconsider the necessity of randomization.

1. Is randomization of device closure to medical therapy (in patients with cryptogenic stroke or transient ischemic attack (TIA) due to presumed paradoxical embolism through a patent foramen ovale (PFO)) essential to generate interpretable data for the evaluation of device safety and effectiveness to support approval of a Premarket Approval (PMA) Application?
2. If yes:
 - a. Please identify and discuss the barriers to enrollment in the current randomized trials.
 - b. Given your answer to the above, what (if any) changes do you suggest in order to facilitate enrollment? Please comment on the following:
 - i. investigational plan (patient selection criteria, statistical plan, follow-up, medical therapy arm)
 - ii. recruitment method (referral patterns, patient educational materials, direct patient incentives, advertising)
3. If no:
 - a. Please provide your recommendations for critical trial design elements such as:
 - i. overall design

- ii. control group
- iii. patient selection criteria
- iv. endpoints
- v. statistical methods
- vi. methods to reduce bias

4. Please provide any other recommendations you believe would facilitate enrollment and completion of these clinical trials.