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by D. Woods

SUMMARY

For the third time, an FDA advisory committee told manufacturers that there is no substitute for a randomized clinical trial of PFO closure for stroke patients, and they expect the ongoing trials to be completed. ♦ The panel said minor protocol changes – in randomization schemes, enrollment criteria, and enrollment time frame – might be acceptable, but only with a statistical penalty. ♦ Reducing the total number of patients in the trials would not be acceptable. ♦ Slow enrollment in the ongoing trials has been due to off-label device use and patient and physician preferences, and the panel suggested medical societies help boost enrollment by educating patients and physicians.

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA Panel Unanimous: Randomized Trials Required for PFO Closure Devices

The FDA's Circulatory Systems Devices panel of the Medical Devices Advisory Committee unanimously agreed that PFO (patent foramen ovale) closure devices for prevention of stroke require randomized controlled trials (RCTs). Device manufacturers had asked the FDA to re-evaluate whether randomized trials are necessary since enrollment has been extremely slow. The panel disappointed manufacturers – especially NMT Medical and AGA Medical – by remaining immovable on randomized trials as the gold standard.

PFO is a common congenital cardiac anomaly in as much as 25% of the general population, most prevalent in patients 50 years old and older, especially those with cryptogenic stroke. No studies have been completed on PFO closure for strokes and transient ischemic attacks (TIAs), and closure's safety and efficacy are still unknown. Until last fall, PFO closure devices were available under a humanitarian device exemption (HDE), but currently they are only available for patients enrolled in a clinical trial, enrolled in a registry, or receiving a device off-label.

The 14-member panel was made up of two cardiac surgeons, two pediatric cardiologists, four cardiologists, three neurologists, a statistician, an industry representative, and a patient advocate. The panel chair, Dr. William Maisel, a cardiologist from Beth Israel Medical Center, summed up the panel's view: "For patients with PFO and first cryptogenic stroke, randomization is necessary. For a subset of patients who fit former HDE criteria, (an option) might be enrollment in a registry." As for the ongoing trials, he said, "For patients with a first cryptogenic stroke and a PFO, the data on closure are unclear. We'd like to see these trials completed, and, hopefully, they'll be completed in a timely fashion."

At the Cardiovascular Revascularization Therapies (CRT) meeting in Washington DC a few days later (March 7, 2007), Dr. Maisel reviewed the panel's findings:

- Randomized clinical trials are necessary. He predicted the ongoing trials could be completed in two or three years.
- The slow enrollment in ongoing clinical trials has been due to off-label device use and patient/physician bias.
- Medical therapy is the standard of care for first cryptogenic stroke; PFO closure is ***not*** the standard of care.
- For patients with a first cryptogenic stroke:
  - A longer enrollment window is acceptable.
  - Broadening enrollment criteria is acceptable (age, TIA, etc.).

- RCTs are necessary, but other randomization schemes are all right (e.g., 2:1).
- Pooling of control data is acceptable as long as patients are relatively comparable in the different trials.

➢ Professional medical societies should conduct physician and patient education campaigns to get physicians to enroll patients in ongoing trials.

➢ The FDA made the right decision to allow patients at perceived higher risk, who fell under the previous HDE definition, to be entered into a registry that collects data on those patients but which may not lead to device approval.

Background

At the FDA's request, both NMT and AGA voluntarily withdrew their HDE in October 2006. An HDE is limited to a target population of 4,000 or fewer individuals annually, and usage was higher than that. The FDA found in a recent review that: "The patient population described by the approved indication (patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who have failed conventional drug therapy) is significantly in excess of 4,000 patients in the U.S. per year. This finding means that these devices are no longer eligible for HUD (humanitarian use device) designation and therefore, no longer eligible for marketing under an HDE. Given the larger number of patients eligible for the device, FDA believes that the devices should be subject to the same requirement that applies to all Class III (highest risk) devices that do not meet the narrow criteria for the HDE, namely, a demonstration of reasonable assurance of both safety and effectiveness, not just safety and probable benefit." However, NMT's CardioSeal and AGA's Amplatzer are approved for other indications, so they are available for off-label use for PFO closure.

Five companies have devices in trial or in development for PFO closure of stroke: NMT, AGA, Cardia, St. Jude, and W.L. Gore. Among the ongoing PFO closure for stroke trials underway are:

➢ **CLOSURE I.** NMT's 1,600-patient, prospective, multicenter, randomized trial evaluating the effectiveness of PFO closure for stroke and TIA with StarFlex vs. best medical therapy. CardioSeal, the NMT closure device which was used under the HDE, is FDA-approved for ventricular septal defect closure in the U.S. Both StarFlex and CardioSeal have a C.E. Mark and are commercially available in Europe.

➢ **CARS.** NMT's trial for PFO closure with StarFlex after recurrent stroke, which was initiated after the HDE withdrawal. Although patients in the CLOSURE I trial received the implant at no cost, patients in the CARS trial can be charged for the device.

➢ **RESPECT.** AGA Medical's 600-patient, prospective, multicenter, randomized trial, to evaluate PFO closure with Amplatzer PFO Occluder vs. medical management in the recurrence of cryptogenic stroke.

➢ **CARDIA PFO trial.** This is a trial comparing Cardia's PFO closure device to warfarin. This device does not yet have FDA approval or a C.E. Mark.

FDA Presentation: The Case for Randomized Trials

In the FDA's briefing documents in preparation for the meeting, the agency reiterated its expectation that the ongoing trials would be completed. The FDA does not require RCTs for all new technologies, but randomization becomes increasingly important, the agency noted, when:

1. The method of diagnosis is variable, and the disease state is poorly understood.
2. There is no single agreed upon standard of care.
3. There are likely covariates that may impact data interpretation.
4. There are reasons to believe that bias may be a significant problem.

Cryptogenic stroke, the FDA concluded, fits this category, saying, "Unfortunately, the treatment of patients with cryptogenic stroke who have a PFO appears to have these limitations, making this condition an ideal and necessary candidate for study under a randomized controlled trial."

At the panel meeting, FDA officials reiterated past guidance: that RCTs are essential. They also emphasized that PFO closure effectiveness has not been established compared to medical therapy.

An FDA official said that in two prior meetings the Circulatory System Devices advisory committee had stressed that randomized controlled trials are essential. During the second meeting (in 2002), the panel also recommended that the primary endpoint should be stroke and death at two years and agreed that the patient population should be limited to patients with permanent neurological deficit (i.e., stroke). The staffer also explained why the HDE approvals were voluntarily withdrawn by the companies: The patient population getting them was more than the 4,000 patients per year permitted in the U.S. under an HDE.

Despite previous panel recommendations, enrollment in RCTs has been very slow. Multiple reasons were cited, including:

- Patient bias (they want the hole closed).
- Medical therapy (warfarin) is incompatible with the active lifestyle of younger patients.
- Physician bias.
- Off-label use of other septal occluders.

Dr. Billy Dunn, a stroke neurologist with the FDA's Center for Drug Evaluation and Research (CDER), described the pathophysiology of PFO, concluding that the literature is conflicting, and the relationship between stroke and PFO is unclear, "What do we know? One thing is clear, the data are definitely uncertain. Existing data are wide-ranging, confusing, and often contradictory…Obviously, additional data are needed in this area."

He reviewed current therapies:

- Medical therapy – e.g., antiplatelet therapy (preferred for most patients) or anticoagulation (e.g., warfarin) therapy.
- Surgical closure. Surgery has high defect closure rates and debatable efficacy in reducing recurrent stroke and TIAs, given their variable recurrence rates (~0%-20% in 5-24 months of follow-up).
- Percutaneous device closure.
  - Effectiveness has not been established vs. medical therapy.
  - A systematic review of 10 non-randomized unblended studies of device closure showed recurrence at one year was ~0%-4.9% and major complications (death, transfusion, cardiac tamponade, surgical intervention, and pulmonary embolism) occurred in ~1.5%.

Dr. Julie Swain, a cardiothoracic surgeon with the FDA, then discussed the FDA's current trial design recommendations. She said, "We recommend that there be prospective, multicenter, randomized controlled trials. It should be 'best medical therapy' vs. 'device + best medical therapy'…We recommend a superiority hypothesis…The sample size calculations are going to be very sensitive to the initial assumptions. That's why we recommend the sponsor use an adaptive sample size design…To date, FDA has recommended that RCTs comparing device closure to medical therapy are necessary:

- To establish proof-of-principle (i.e., closure of a PFO reduces the risk for recurrent embolic events).
- To establish a reasonable assurance of safety and effectiveness to support a PMA (premarket approval) application."

Another FDA presenter concluded, "Enrollment in RCTs continues to be slow despite trial modifications and sponsor efforts, which have included:

- Inclusion of TIA patients.
- A longer enrollment window from initial event.
- Novel trial designs (e.g., sequential designs, unequal randomization).
- Allowance for multiple control medical therapies.
- Sponsor education and marketing campaigns.
- An increased role of neurologists as investigators.

PUBLIC WITNESSES

Dr. Larry Latson, director of the pediatric and congenital cardiac catheterization lab at the Cleveland Clinic and a consultant for several PFO trials, described problems with doing PFO/stroke trials when there are very different methods of treatment. He said patients are frightened when they realize that they are vulnerable to stroke, and they don't want to give up control, "Closing the hole makes a lot of sense to the majority (of these patients) if they feel that the procedure is not too bad…Catheter procedures take a few hours, and to many patients that meets the 'not too bad' criterion, and they are 'reasonably safe.'" He suggested looking at nuances and variations to RCTs, such as allowing a large percentage of trial patients from outside the U.S., where PFO closure may not be as widely utilized and where there may be some different economic incentives than in the U.S., "This is against the usual trial design, but we might be able to leverage geographical variations in practice, such as allowing sites to enroll only in one arm, device, or medicine." He concluded that the ultimate proof-of-principle will not come from single device trials and that additional trials by the National Institutes of Health (NIH) will be needed, "Medicines and devices are like shooting with a shotgun. We need to refine the patient selection."

Three medical associations favor RCTs

Officials representing the American Heart Association (AHA) and the American College of Cardiology (ACC) agreed that RCTs are important in determining the value of PFO closure for stroke.

1. American Academy of Neurology. Dr. Steven Kittner, a stroke neurologist and an investigator in an ongoing PFO closure trial, told the panel that non-randomized designs are not valid, "It is highly plausible that patients choosing or guided towards device closure could be a lower risk group, making the statistical adjustment inadequate." He said that the possibility of a pooled randomized control group "would not be valid," adding, "Cryptogenic stroke is very heterogeneous with respect to stroke recurrence risk…The concept of maintaining a stratified analysis within a randomized design is preferable." He said that the gorilla in the room is off-label PFO device closure and suggested that restricting Medicare reimbursement to RCTs and recurrent stroke when on medical management might aid trial completion. He endorsed the idea of pooling data from various trials to determine proof-of-principle, though noting that the obstacle to that would be using an ineffective device in such trials.

2. American Heart Association (AHA)/American Stroke Association (ASA). Dr. John Ring said that the AHA's opinion is simple: There is no substitute for randomized control trials when it comes to filling the knowledge gap about PFO closure and stroke. He said there are questions that need answers, "Does treatment in fact improve outcomes? If so, which outcomes and what treatment? What are the indications for surgical closure? These questions deserve answers

that are based on fact, not opinion or good intentions…The current literature – which lacks prospective, randomized controlled trials – is flawed and incomplete…The longer we delay…the more difficult the issue will be to study." He said that while the devices can be implanted with low risk, the long-term risks remain undefined, making it impossible for patients and doctors to make informed decisions.

3. American College of Cardiology. The ACC submitted a statement saying that randomized trials are necessary.

PANEL DISCUSSION

The key issues for the panel were PFO closure for stroke in general, RCTs, trial design, pooling of trial data, transient ischemic attacks, trial endpoints, and trial enrollment issues. The FDA wanted the panel to discuss whether randomization of device closure to medical therapy is essential for PMA approval, and if so, what ideas the panel had on how to facilitate enrollment.

The panel agreed that RCTs are necessary, and members agreed there are few effective ways to limit off-label use of PFO closure devices. There was considerable discussion about what to do about patients with more than one stroke, but the panel generally agreed that those patients who formerly fit into the HDE category – and there was discussion on whether those patients should be called "high risk" – should be enrolled in registries. The panel agreed that little is known about the pathogenesis of stroke, and no one knows if PFO closure works in stroke patients.

PFO closure for stroke in general

Many panel members pointed out that PFO closure has not been proven effective for stroke, and a relationship between PFO closure and stroke has not even been established. After the discussion, the panel chair asked the members if anyone disagreed that PFO closure for first cryptogenic stroke is ***not*** the standard of care. No one really disagreed.

Panel member comments included:

- *Dr. John Somberg, professor of pharmacology at Rush University:* "The standard of care currently is that we do not know the definitive therapy, and medical therapy is what people are doing. When you hear the ACC, the academic world, neurology, the AHA…Any judge would say (medical therapy) is the standard of care. And that is critical."
- *Dr. Clyde Yancy, a cardiologist at Baylor University:* "If you listen to the AHA, percutaneous closure of a PFO is a Class IIb recommendation, with Level of evidence a C. That's one step away from a III, which is: Don't do it…A very august body that took its time…has adjudicated it, and those are the findings."
- *Dr. Norman Kato, cardiothoracic surgeon from Encino CA:* The American Academy of Neurology has said there is insufficient evidence (for PFO closure) in the case of cryptogenic stroke. The AHA has essentially said the same thing. When we can say that this is no longer a cryptogenic stroke but a 'PFO event stroke' will be the day that I can conclusively say, 'Let's go ahead and close that PFO.' This is a device trying to make the anatomical defect a part of the disease process; and, in fact, it should be the reverse. The science should be there that conclusively shows the relation link between the anatomical defect and the outcome. Then and only then can you create devices/therapy to test whether that is safe and effective."
- *Dr. Richard Ringel, pediatric cardiologist from Johns Hopkins:* "The reason I'm on this panel is because I believe it is absolutely essential that we get to the bottom of the question or answer what needs to be done about PFO and stroke, what the relationship is, and whether closure is adequate. Before people too robustly condemn off-label use of devices, keep in mind that there are many fields, including my own field of pediatric cardiology, where the patient populations are too small – or there are other reasons (RCTs can't be completed). There are patients out there who do not qualify for trials or for reasons of their own refuse to be in a trial. Physicians are faced with these patients and have to decide if they are going to deny the existence of reports that seem to indicate that this is an effective therapy. So, I urge you to keep that in mind."

RCTs

The panel agreed that randomized trials are essential, but not until after discussion as to whether there might be alternatives. The panel also agreed that for a first cryptogenic stroke, the standard-of-care is medical therapy. The panel chair asked the members, "Does anyone here think that we do not need randomized trials?" There were not any negative answers to that question. A neurologist on the panel added, "I think that's the consensus of the panel – randomized controlled trials are the only way to get the good answer, the good information." A cardiothoracic surgeon on the panel agreed, "After hearing all the comments, it's difficult to condone a relaxation of the traditional randomized study that we've all placed confidence in, in terms of trying to get a device to market, and we don't know whether PFO closure works or doesn't work. We have to be cautious in the precedent, saying it'll take 10 years to get the trials done, and maybe that's what we're going to have to do in order to maintain the rigor of the process."

Other panel member comments included:

- *Pharmacologist:* "The panel has to be realistic. People with economic incentive have tried for more than a decade. Panels have contributed from 1997 to 2007. And we have a major public health issue that is unanswered. We have to be creative. For example, maybe a pooled

study looking at proof-of-concept and then finding a way to evaluate each device is the way to go. (If we) stay rigid …we will never reach a conclusion here. A lot of people are throwing their hands up, and it could never be answered. I think, if possible, the best (option) is a randomized control trial. If that doesn't work, maybe a meta-analysis is appropriate down the line."

- *Cardiothoracic surgeon:* He summed up many other members' frustration, saying, "We're allowing the device to drive the pathology of the disease. It's like creating a test. We don't know if it's related to a biomarker. So, I think we have to be very cautious about proceeding forward. Maybe it has taken 10 years because we don't know enough about the disease's process to know how to treat it, and doing a device trial is really ahead of itself, perhaps."
- *Dr. Richard Jonas, a pediatric cardiologist at Children's National Medical Center in Washington DC:* "I think we should insist on randomized trials."
- *Dr. David Good, a neurologist at Penn State College of Medicine:* "We're looking at disease we don't know the cause of and devices that we're not sure do what job…Cryptogenic stroke is common…Anatomical differences are critical. On top of that, there is an emotional issue, and to make things worse, we have relative equipoise between closure and medical management. It seems the only way you can answer the question is through some form of randomized clinical trial. That's my opinion."

Trial design

In addition to agreeing on the need for RCTs, the panel also agreed that a superiority was preferable to a non-superiority trial design. A panel member said, "It's very difficult to get away from the randomized control trial…If we can move forward, perhaps we can take whatever data are acquired and then, going forward with new device applications, you can use a single-arm study in a non-inferiority construct. But for the initial trials, I think you need to demonstrate that it works."

Asked if there is a target enrollment that the FDA thinks would be necessary to reach a meaningful endpoint, an FDA presenter said, "The (issue)…is trying to develop a reasonable estimate – both in the control population and the device (group). The literature, whether for medical therapy or for the non-randomized studies, have a wide range of reported breaks of recurrent events, and there are some differences across trial designs, but largely the sample sizes are driven by the estimated rates and how conservative you want to be in wanting to make sure that you have sufficient power at the end of the day when the trial is done."

Pooling of trial data

In the morning, there was a lot of discussion on the possibility of sponsors pooling their data, and panel members appeared to think that would be both a good idea and a solution to slow trial enrollment. Both the panel statistician and another panel member spent some time making the case for some type of pooling of data by the companies.

The panel's statistician, Sharon-Lise Normand Ph.D. of the Harvard School of Public Health, repeatedly made the case for what she termed a "meta-analysis," although she later amended her definition of that to a kind of "stratified analysis." She said, "I may have misled when I used the word meta-analysis…With a meta-analysis, you think of published studies. That's not what we're talking about…I wouldn't necessarily categorize this (pooling idea) as a meta-analysis. Think of it as a big stratified analysis – different devices with slightly different operating characteristics…conducted approximately within the same time frame…I think using the control groups is an enormously good idea to move forward, and one would worry a little about the exchangeability of the devices in and of themselves. You may worry about those in terms of safety and maybe effectiveness as well. Pooling the control group would be useful."

A panel member asked if there is precedent for sponsors to join forces and pool data. Dr. Bram Zuckerman, Director of the FDA's Division of Cardiovascular Devices in the Center for Devices and Radiological Health (CDRH), responded that there are regulatory barriers to pooling, as well as company reluctance in general to share information, but it was a possibility and had been discussed in the past, but that the sponsors were unable to agree on how to do it, "There would not be any regulatory criteria to prevent it. However, it has been done very infrequently, and the reason has been the reluctance of sponsors to pool resources…The essential requirements that the Agency would be looking for are…proof-of-principle and proof-of-device. The most successful application of this process was in one of the largest trials that CDRH has been involved with. The trial was, I believe, a breast imaging randomized trial where four companies participated. They effectively…combined control data, so that, at the end of the day, there was a positive result for the overall trial, and the individual sponsors were able to benefit from labeling changes."

However, later in the day – after a closed session with sponsors and more panel discussion – members concluded that, although pooling might be a good idea, it would not be practical in this case for a number of reasons, including:

- Company reticence to share information. Outside the meeting, a Cardia official said his company would be happy to share its limited data, but he doubted that bigger companies, such as NMT Medical, would ever share their information.
- Regulatory problems.
- Device differences, leading to potential safety issues.

Other panel comments and questions on pooling included:

- "I'd love to see a way to more simply get these studies to completion, so we have some answers. I'm afraid that we're going to have to do these trials one by one, get the results, and then we can look at an overview analysis of all the data. I have a lot of trouble with taking the information and then start to smash it together and come up with a guideline or recommendation that has substance to it. I think the tail may be wagging the dog here. We need to build the foundation and ***then*** talk about combining the data."
- "I agree with the suggestion that the medical control groups could be pooled, but I strongly disagree with pooling the device patients. Having removed several of these devices surgically, it's clear that some of them have a risk of thrombogenicity. And the different designs are likely to have different thrombolic risks. We should not recommend pooling device data."
- "I would be reluctant to accept a meta-analysis for proof-of-concept. There many be other concomitant disease situations concurrent with PFO that drive the disease process, and (PFO) closure may not have any bearing here."
- "Really, there only needs to be pooling of the control data. There doesn't have to be collaboration of the companies…It's obvious that the companies have read the existing data in very different ways, resulting in trials that propose a range of 600 to 1,600 patients total for both arms…Has (the FDA) done the number crunching with an unbiased eye and come up with what you think is a (number)? I'm thinking about the concept of pooling controls. We need to know how many controls are required. Has the FDA looked at the question in an unbiased way as possible?...How can two studies be accepted – one with 600 patients and one with 1,600?... I'm trying to figure out what the control rate would be, to help companies establish a reasonable research plan."
- "There still should be, one would hope, an absolute baseline rate, regardless of the size of the effect. There should be some consensus to figure out or agree upon a baseline rate in a control group."
- "As I understand it, there is no regulatory obstacle to proving the concept that closing the hole will benefit. Would it also be possible then…if there was adequate exposure or the FDA requested an additional registry, to determine the effectiveness (of these devices)?"
- "It would be difficult to pool devices because there's the conceptual possibility that some (devices) might have a higher occurrence rate for provoking clot formation on the device itself."
- "If each company gave their open device data, there would be a tremendous penalty to pay. But we're looking to see whether closing the PFO makes a difference or not. If a PFO is closed, I don't want to know what device was used, I want to know if it works...(Otherwise), we may be discussing this until 2010 or 2014. There are tangential issues and all are solvable at some point…But right now let's look at the pooled control data…and get an idea of what we're doing. Maybe there's a deleterious effect, and maybe the approaches are wrong."

The FDA's Dr. Zuckerman made several points in response, including:

- "There are always safety issues…During a trial of this type, where there would be individual device types, the data safety monitoring board as well as the Agency would need to follow trial progress to make sure that one device, perhaps, was not an outlier, but that is all part and parcel of good trial design."
- "Unfortunately, I don't believe, even with our third party unbiased eyes, we can determine estimates that are more or less valid than what the sponsors have provided…If you believe your device would provide a 50% treatment effect – 50% reduction in the number of strokes and death in two years – depending on where you placed your estimates…the sample size will be different than if you think the rate will be 8% in two years. So, even with the same 50% reduction rate, you can still have different sample sizes."
- "From the Agency's perspective there is no one trial design that we will necessarily agree (on). There are multiple clinical trials ongoing with different assumptions that we believe have been supportable enough so that sponsors can take the risk of trying to develop adequate clinical data…The discussion of what is the real baseline control rate is a very difficult one that merits a lot of review."
- "There's a regulatory problem that's not well appreciated here. When a sponsor has an ongoing IDE trial, the data belongs to the sponsor, not to the FDA. Hence, the aggregate meta-analysis of control data…could not legally be performed by the Agency without the concurrence of the sponsors…That's a fundamental issue here."
- "This has been a fascinating discussion on one potential pathway for getting these trials completed, which is for companies to be able to work together, and I appreciate why this discussion has gone down this road because we have a challenging and extremely important public health problem. However, it has been the rare exception rather than the rule that this is the pathway that the industry usually takes, and I hope that people on this panel will consider some other options…I really think the devil is in the details…It would need considerable effort by industry and the Agency, and I think the agency would be extremely willing. But at the end of the day, where would it lead the Agency?...If we do see a signal or proof-of-principle, would it be okay to reduce requirements for each device manufacturer in terms of what they individually need to show?"

- "The problem is known or unknown covariants in different populations. The idea that we can agree on the baseline rate and essentially develop performance criteria, that's why we're here. There are so many covariants that affect this that you won't know what the baseline is."

Transient ischemic attacks (TIAs)

The panel chair asked if stroke prevention, stroke, and TIA prevention all were appropriate endpoints and if anything else had to be considered. Several members said they were worried about TIA as an endpoint, saying that it just adds to "the noise" and "muddies the waters." Comments included:

- *Dr. Gary Abrams, a neurologist at the University of California, San Francisco:* "I think that TIAs are another messy issue in this whole mix. To me, stroke is logical, but I think TIA would make this that much more messy. I wouldn't favor TIA."
- *Pharmacologist:* "I see patients with PFO on advanced medical therapies, and what do you do with them? Close it or not. TIAs can be very scary and devastating, and I think they may answer an important clinical question. I'm asking people to think about it. You may have the power to look at both (stroke and TIA)…That may be the advantage of a pooled study…To answer a very important clinical question – whether people with a PFO and a TIA need this closure as well."
- *Neurologist:* "But as we all know, not everything that looks like a TIA is a TIA, and it can create noise. Sometimes it can look like TIA and be stroke. So maybe building something in – having an MRI indicator after a transient event – might be a reasonable way of looking at this."
- *FDA's Dr. Zuckerman:* "However you approach it, the key is making sure that your definitions provide you with a target population of interest. If you use the classical definition of TIA, you have the risk of having patients that don't represent that population."

Enrollment problems

A panel member asked why enrollment was so slow when the HDEs were pulled due to use in more than 4,000 patients. Dr. Zuckerman answered, "We know how many devices were distributed but (not what) the indications were – whether it was at least two strokes or off-label use under HDE access."

Asked if off-label use has prevented trial enrollment, an FDA official said, "Our thoughts would be that (there is) bias in terms of patients showing up, knowing what they want. They come in (to the doctor) having been educated by the Internet, are scared to death, and they've seen on someone's website that someone who had a stroke had a hole. That's a significant factor, and the off-label use is available for the patient who says, 'I absolutely want the device.' There are physicians out there who will use the device off-label to close the PFO."

Panel comments included:

- "Once again, off-label use is really condemning the whole paradigm, and without being able to control that, it compromises the science."
- "I am frustrated because I hear about off-label use, but I don't hear the numbers. This seems to be the argument as to why there's trouble enrolling patients. I just really urge the panel and my colleagues outside of the panel to provide some solid numbers about it, and I don't mean sales. That doesn't take a lot of effort. I'm uncomfortable right now believing – because no one has been able to provide it to me – that there is solid evidence that this is happening in the community."
- "If off-label use were stopped and the only access was through the trials, the trials would begin promptly. It might be constructive to talk about the possibility of that strategy."
- "I hate to be crass, but the financial pressures are tremendous. I know we're not supposed to talk about cost, but if this plan is to go forward, we've seen that all the king's horses and all the king's men are not able to get everybody to agree to use the clinical trial as the vehicle to find the answer…People want to do the procedures."
- *Dr. Philip Gorelick, a neurologist at the University of Illinois at Chicago:* "I wake up every morning and go to work, and it's being done. We all know it's being done. It's accepted without having the hard data."
- *Panel chair:* "We don't know how much off-label use there is. We're hypothesizing that it's a major effect, but we certainly haven't seen a lot of data…I agree that it's being done. I don't agree that it's the sole impediment to enrollment. I don't think eliminating it will cause a huge spike in trials."
- "Be careful what you ask for. If you ask for regulated medicine, it can be a pox. Off-label use can be useful. While I'm not encouraging off-label use, the other extreme would be a highly regulated health industry where someone would be controlling your practice of medicine. If you had a proof-of-concept, the panel should just consider whether the standard would then change for devices and whether there would be more performance standards and registries."

There was some discussion on who is – and should be – driving the PFO closure for stroke trials: cardiologists or neurologists. A neurologist on the panel asked, "I'm trying to get a sense about who's driving these trials. There was a comment that neurologists were getting more involved in these trials. (Are these studies) being predominantly driven by cardiologists in terms of site investigators and then neurologists are being added on over time?" An FDA official responded, "These trials have been ongoing for more than a decade. When they originally started, it was primarily cardiologists and cardiology treatment…We were dealing with

a population of stroke patients…That was acknowledged by sponsors, and neurologists were included as co-investigators in trials. Enrollment was slow…Neurologists are in the best position to talk about treatment options for stroke."

Although some panel members said they thought all patients could be included in trials, the majority agreed that certain high risk patients should be placed in a special registry, not an RCT. Comments on this topic included:

- *Panel chair:* "There are clearly patients that physicians do not feel comfortable randomizing…There are populations of people who cannot be randomized and will not be randomized. Maybe there should be an IDE registry for them, and physicians can decide. I don't see any other way to get that information."
- "We don't know if the closure works. Why would we let it happen in elderly people?"
- "I think there is ***no*** subset that should not be randomized. I don't think the first thing to do is take the sickest of the sick and randomize them, but nobody knows if surgery is better or either is better than medicine. And which medical therapy? So, I don't think there's a group you can exclude from a randomized control trial, but there may be some you initially don't put into those studies."
- *FDA's Dr. Zuckerman:* "I think you're getting to an important problem. Realistically, there's always tension between getting a tight patient population and widening it out and having heterogeneity. There will also be patients who fall outside the first randomized trial protocol. The practical problem the industry and FDA have is that usually the industry will concurrently develop both a randomized trial and sidebar registries. Sometimes there's the hidden assumption in the industry that the sidebar registries, if completed earlier (than the RCT), would have enough data to provide reasonable assurance of safety and effectiveness. In this sort of situation, however, where we don't have proof-of-principle… registries would have to be complementary to the randomized trial and not be able to stand on their own legs."
- "Registries would not stand on their own."
- "We need to be clear on what the focus is. If the focus is to identify patients not appropriate for trial, then a concurrent registry would be good for that. If, on the other hand, the registry would be universal – looking outside the clinical trial – the patients who don't get to the clinical trial are by definition different."
- "I think it should be proven effective for the lower risk population before being used for the high risk population. It needs to be tested rigorously in the kinds of trials currently devised, excluding the high risk patients."
- *Industry representative, Marcia Yaross Ph.D. of Biosense Webster:* "Each individual sponsor has the right to identify the patient population. It's not the job to necessarily identify whether this device works in all segments of the disease population."

FDA Questions for the Panel

1. Is randomization of device closure to medical therapy (in patients with cryptogenic stroke or TIA due to presumed paradoxical embolism through a PFO essential to generate interpretable data for the evaluation of device safety and effectiveness to support approval of a PMA?

YES, unanimously.

2. Please identify and discuss the barriers to enrollment in the current randomized trials.

The chair summarized the panel's thoughts on these issues: "We recognize issues about patient selection. That's the company's risk. Any change (in an ongoing trial) could water down the data, and you risk losing everything. So, we suggest (sponsors) working with the FDA. Follow-up has already been extended a lot longer than originally intended. We didn't talk about referral methods, besides involving neurologists more. Education materials – certainly we can do a lot better in that regard."

3a. Please comment on the investigational plan (patient selection criteria, statistical plan, follow-up, medical therapy arm).

Panel members suggested that education efforts and getting neurologists involved in the trials are most important at this point.

Panel comments included:

- *Panel chair:* "Do people have issues with changing randomization schemes midway through a trial? Maybe going from 1:1 to 2:1? Maybe changing sample sizes midway through a trial?...If an interim analysis showed an indication, and someone says you need 500 instead of 1,000 patients to complete the trial, is that acceptable?"
- *Statistician:* "There are (statistical) methods that will penalize you for looking at the data and upping the enrollment or downsizing…I can't see the allocation or size going down. But I think that with changing the design *de novo* from the beginning, with more innovative schemes – in other words, selecting designs that are addressing the realities – that you can't get enough patients. You can do an interim analysis, reduction of sample size, but all of those (things) have to be incorporated in the design at the beginning, and they have to be agreed upon. In this type of framework you can't make the design so complicated that when it comes to a panel they're not going to understand it. I'd recommend doing something at the beginning."

- *Industry rep:* "I agree with setting up an analysis plan at the beginning and sticking with it. But if a company starts a trial and partway through there are barriers, that's where I would hope that the panel and the FDA will be realistic about coming up with alternative means of addressing some kind of interim analysis and adjustment."
- *Pharmacologist:* "There were discussions in the closed panel session about specific protocols, but I thought the consensus was that things that would facilitate reaching the proof-of-concept that closing a hole is beneficial would be a good idea. And if that could be done without destruction of all study integrity, go for it. So, I would urge the FDA to be facilitory, and I think they have been supportive of that activity."
- *Dr. John Hirshfeld, an interventional cardiologist at the Hospital of the University of Pennsylvania:* "We should be very circumspect about trying to relax criteria or endpoint criteria. I'm concerned that that may reduce the likelihood that a trial would be positive. It would conceivably allow more noise into the dataset."

3b. What (if any) changes do you suggest in order to facilitate enrollment? Please comment on recruitment methods (referral patterns, patient educational materials, direct patient incentives, advertising).

The panel agreed that medical association websites describing post-stroke therapy, including PFO closure, in a neutral way, would help patients and doctors make more informed decisions.

Panel comments included:

- "There are certain basic incentives that are important. There are people socially isolated, and they need things like money to get there (to the study site), flexible hours, and those kinds of things. This isn't talking about incentivizing people with dollars to get into the study."
- "The companies could improve recruitment re: insurance issues. Some people can get these off-label, but some can't because of finances."
- "I agree that a patient shouldn't have to pay for the procedure in a trial. Many of these patients fall below the Medicare age…Certainly industry could help participate in advertising…Sponsors should look at their referrals and weed out sites that aren't referring."
- "I like the idea of a campaign…with industry and professional societies. I personally am not a big fan of patient incentives for enrollment in trials."
- *Pharmacologist:* "I'd hope the associations would perhaps have a website…Patients want something, but it might be useful to have an authoritative society on the Internet where people could go for non-financially (influenced information) that maybe the answer is not out there, and maybe they should become part of a randomized clinical trial…There's need for more guidance out there. Maybe there could be a place where people could get a body of information that they trust."
- *FDA's Dr. Zuckerman:* "There's an unprecedented opportunity here…I want to emphasize that while this is a panel meeting, the agency will see this as a continuous process, and somehow we need to figure out how to get the right information to patients in an unbiased fashion. I don't know if we need a separate Internet site in addition to using the current professional association sites as a true message."
- *Neurologist:* "Once they get to the websites, if they go to them, they'll be just as confused as the physicians who don't know what to do, which is a good thing, and I believe that the physicians have to be well-educated…I'd hope that the trialists involved in these studies, companies, and societies might go on a year or two marketing campaign to get this information out so we can help get these trials completed and the randomization done."
- *Statistician:* "I wonder if there are patient advocacy groups. Targeting them would be pretty useful."
- *Neurologist:* "One idea would be to get neurologists more involved through the process."

4. For alternative trial designs, please provide your recommendations for critical trial design elements such as: overall design, control group, patient selection criteria, endpoints, statistical methods, and methods to reduce bias.

Panel chair summary: "The panel consensus at this moment is that patients at higher risk – they've had their second stroke and have already been treated on medical therapy – can't be enrolled in a trial, and we're not offering any treatment. That doesn't seem satisfactory. Do you want to enroll them in a randomized trial? Because physicians won't want to risk a third stroke."

Panel comments included:

- *Pharmacologist:* "We have to answer the question: Is closing the hole the important thing? So, I think the registries can come at a later date, and I'd rather see the randomized trials off and running first."
- *Panel chair:* "The bottom line is that there are going to be patients and physicians who want to close off a PFO. Right now, their choice is an FDA IDE (investigational device exemption), which some people here say shouldn't exist, or they get a device that's not designed for PFO closure. That's not satisfactory. So putting a box around the patients and doing the best to separate the two groups is the way to go."
- *Statistician:* "We need to answer the first question, and then work on registries later."

- *FDA's Dr. Zuckerman:* "I want people to recognize reality. Although there are ways to game the system because every protocol has its gray areas, adjunctive registries can be designed, they can have numerical limits such that there's no infinite possibility of gaming the system relative to a randomized trial. The question is can we obtain this data concurrently and efficiently so that we can get a fuller evaluation of the landscape here using that type of design?...This is the central question to the whole meeting. The HDEs were removed because the FDA concluded we were dealing with a substantially larger population than 4,000 patients. As a corollary, IRBs, when the HDEs were in effect, were not doing their due diligence. Those are issues for a different discussion."
- *Pediatric cardiologist:* "There was not strong oversight of IRBs, and IRBs were giving their physicians blank checks, saying, 'You can do what you like.'"
- *Pharmacologist:* "If we're asking societies and groups to get involved here, we also must make it clear we don't know how to treat people with two strokes! I've heard people today saying, 'Gee, whiz! Two strokes doesn't necessarily make a third stroke that likely.' So, it's not 'three strokes and you're out' in this ballgame…I would try to pool the interventionalists to see if I had a proof-of-concept. I'd also initiate a randomized controlled study of those patients. If we say we will establish a registry of hopeless cases and we will never find the answer, then we will never find the answer."

The chair asked panel members if they are willing to randomize the **former HDE indication** patients to medical therapy. Responses included:

- "I'm not a neurologist, but I never saw a reason why they couldn't be included in the trials. We don't know any more about those patients than patients who had their first event."
- "I disagree. If we have a precedent with HDE for high risk, I'd hate to backtrack on that. It just seems schizophrenic."
- "I don't think the two issues are that tightly linked…I think that we've heard a lot about the psychological trauma of being a recurrent stroke patient, so I don't have a problem saying, 'This group has had two events. We don't know if it works, but rather than subject them to a third event by a protocol, then it's reasonable to go with registry enrollment.'"
- *Neurologist #1:* "We don't know the answer, but the reality is that on the street they won't get into the study."
- *Neurologist #2:* "I'm a little conflicted, but the reality is such that probably these people won't get into a study."
- *Neurologist #3:* "I say two strokes, throw the kitchen sink at them, and put them in the registry."
- *Statistician:* "I don't think they should go into the registry."
- *Cardiothoracic surgeon:* "I'm really torn. Nothing I've seen says the HDE group was a high risk group. High risk for what? I don't know what that means. I don't know what putting them in a registry is going to mean either."
- *Pharmacologist:* "I think these patients should go in a randomized trial. It doesn't have to be the same randomized trial, but they should go into a trial. The data are useful."
- *Pediatric cardiologist:* "First choice should be a randomized trial, and failing that, a registry."
- *Another pediatric cardiologist:* "I have a problem that may make me change what I said. If I remember correctly, some protocols allow some patients randomized to medical therapy to cross over to device closure if they have an event on medical therapy. If that's the case, I'd have to feel differently about what I said before. Is that correct about the protocols?...There's no way I can't support getting a place in the registry."

On endpoints, the chair summarized the panel thinking: "We agree on stroke, but we're unclear on TIAs. Recognizing that, it (TIA) is going to create some noise."

Other panel comments on endpoints included:

- *Statistician:* "I wonder if we should question whether the main endpoint should be two years...It sounds like a two-year endpoint matters."
- *Neurologist:* "The stroke risk after TIA is relatively high early on. In the first seven days it may be as high as 10%. If you look at the long-term projection, however, what you end up finding out is that, depending on the datasets, there may be a 40%+ risk over four years of having a stroke. We're in a bit of uncharted territory because the subset of stroke may vary. This whole thing of cryptogenic ischemic stroke in younger people is fairly uncharted territory, so we extrapolated…from other clinical trials. They usually run around two years. They rarely go to three years. So, I don't think we really know. The early time period is a high risk period after TIA and high risk stroke, but that does not stop there… If you have a stroke, then you get in the trial. Then, you have another stroke, and everyone gets excited. One of the challenges is that the investigators try to find the mechanism of that stroke. I suggest the investigators get as comprehensive a workup as possible."
- *Panel chair:* "Randomizing patients early may be a way of increasing the event rate. We have to recognize the safety of the implant may not be the same the day after the implant."

- *FDA's Dr. Zuckerman:* "(Whether the main endpoint should be two years) is a key question. The reason the Agency suggested two years initially is that we really do need to see sustained duration in the frequency of events over time because we just don't know. The usual statistical analysis proposed is that we just evaluate everyone once they reach two years and make a simple comparison…One of the practicalities of running trials is that the patient has to be identified as having the first event, the kind of stroke (has to be determined), a PFO identified, and then the patient enrolled in trial. So, there may be some time between the first event and when the trial begins…We found that trying to keep that period of time to 90 days is an enrollment barrier…so we've allowed the window to extend to 180 days, and in some cases beyond that."

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

The panel was split on how to define high risk patients and whether those patients should be in a randomized trial or a registry. The panel also rejected the idea of a non-inferiority trial of PFO closure for stroke.

The FDA's Dr. Zuckerman proposed a hypothetical trial design, but the panel balked at the idea of a non-inferiority trial. He said, "A randomized control superiority trial would be the easiest way for a sponsor to show safety and effectiveness. However, I'd like the panel to comment on an alternative design that would consist of two trials. The first would be designed as an equivalence trial vs. medical therapy. If the sponsor is able to show non-inferiority, it would be quickly followed by a second trial – a single-arm registry of device use. The control would be prior control data from the randomized trial. With this design we could never definitively show that device closure is superior to medical treatment because the whole trial construct is not randomized. Could we get a reasonable ballpark estimate that the two treatment therapies are equivalent, and would that be good enough for a sponsor?" The panel's statistician responded, "The first study would be a randomized study. I think it's equivalence, and we agreed that non-inferiority would not fly. Equivalence could be quite large. I'm not sure how much it's going to buy you in terms of population size. The rate of equivalence would be much debated. If you showed equivalence – that medical therapy and PFO closure were equivalent – then, if you had a well-designed observational study, I would be comfortable with using that information to go on to learn more about the device in terms of superiority, which is not cheap." Another panel member added, "You can't skirt the issue of whether medical therapy works, and we don't know if it works. And what kind of medical therapy? The sense of the panel is that we need a randomized controlled trial to see whether closing the hole works. But until we get over that hurdle, that's a very slippery slope to try to scale." A third panel member said, "If you showed comparability to anticoagulant therapy, that would be helpful because that's a challenge to the physician. If you showed the same outcomes with the device as opposed to single or combination antiplatelet therapy, that wouldn't be a resounding reason to use the device because staying on antiplatelet therapy is not a big deal. You need to show superiority to antiplatelet therapy." The panel chair added, "What's being discussed is new trials, not ongoing trials."

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