

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CIRCULATORY SYSTEM DEVICES PANEL

Friday, October 24, 1997

12:40 p.m.

Salons C and D
Gaithersburg Marriott Washingtonian Center
Gaithersburg, Maryland

PANEL MEMBERS PRESENT:

Chairperson

Anne B. Curtis, M.D.
University of Florida

Executive Secretary

John E. Stuhlmuller, M.D.
Food and Drug Administration

Voting Members

Tony W. Simmons, M.D.
Bowman-Gray School of Medicine

Consultants

Kent R. Bailey, Ph.D.
Mayo Clinic

Jeffery A. Brinker, M.D.
Johns Hopkins University

Michael D. Crittendon, M.D.
Harvard University

L. Henry Edmunds, M.D.
University of Pennsylvania

Richard A. Hopkins, M.D.
Brown University

Richard E. Ringel, M.D.
University of Maryland

George W. Vetrovec, M.D.
Medical College of Virginia

Ronald M. Weintraub, M.D.
Harvard University

Kenneth G. Zahka, M.D.
Case Western University

Industry Representative

Gary Jarvis
Medtronics

Consumer Representative

David A. Gooray, M.D.

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1 P R O C E E D I N G S

2 DR. CURTIS: If everyone could please take their
3 seats, I'd like to call this meeting to order.

4 The first order of business will be a conflict of
5 interest statement to be read by Dr. Stuhlmuller.

6 DR. STUHLMULLER: The conflict-of-interest
7 statement. The following announcement addresses conflict-
8 of-interest issues associated with this meeting and is made
9 part of the record precluding even the appearance of
10 impropriety.

11 The conflict-of-interest statute prohibits special
12 government employees from participating in matters that
13 could affect their or their employer's financial interest.
14 To determine if any conflict existed, the agency reviewed
15 the submitted agenda and all financial interests reported by
16 the committee participants and has determined that there is
17 no conflict of interest to report.

18 In the event that the discussions involve any
19 other products or firms not already on the agenda for which
20 an FDA participant has a financial interest, the participant
21 should excuse him- or herself from such involvement, and the
22 exclusion will be noted for the record.

23 The agency would like to note for the record that
24 Dr. James Jagers, who is a guest speaker today, has

1 identified his institution, Duke University, as a clinical
2 site for one of the device investigations.

3 Dr. Jane Newburger, who is also a guest speaker
4 today, reports that her institution, Boston Children's
5 Hospital, has a sponsored investigator IDE and is a
6 participating clinical site in another trial. She has no
7 direct involvement in either study.

8 DR. CURTIS: There is no old business before the
9 panel today, we'll move right ahead to the new business.
10 The subject for discussion this afternoon is a clinical
11 trial design for transcatheter devices intended to treat
12 atrial septal defects, patent foramen ovale, and patent
13 ductus arteriosus.

14 We are going to start with an introduction by the
15 FDA. Donna Buckley?

16 [Slide.]

xx

17
18 MS. BUCKLEY: Good afternoon. My name is Donna
19 Buckley. I'm a reviewer in the Interventional Cardiology
20 Devices Branch, and I'm one of the primary reviewers for the
21 category of devices that will be discussed today.

22 [Slide.]

23 The purpose of this meeting is to obtain input
24 and, hopefully, a consensus from the Circulatory System

1 Devices Panel regarding appropriate study designs for the
2 evaluation of transcatheter closure devices, specifically
3 those devices intended to treat atrial septal defects,
4 patent ductus arteriosus, and patent foramen ovales.

5 [Slide.]

6 At present, there are no FDA-approved devices for
7 the treatment of ASDs, PDAs, or PFOs. Several ongoing
8 trials for these devices are currently under way.

9 FDA has worked interactively with sponsors during
10 protocol development. However, there are varying opinions
11 regarding the appropriate controls and endpoints needed to
12 demonstrate safety and effectiveness. Of particular concern
13 that has been debated is whether these devices should and
14 realistically can be randomized against surgery,
15 particularly with ASDs and PDAs.

16 [Slide.]

17 In order to facilitate the discussion on this
18 specific issue, FDA has invited two speakers: Dr. Jane
19 Newburger from Boston Children's Hospital and Dr. James
20 Jagers from Duke University Medical Center, who will both
21 be speaking shortly.

22 What I would like to do at this point is introduce
23 Gary Kamer, an FDA statistician, who will provide you with a
24 brief overview of statistical issues regarding the analysis

1 of randomized versus non-randomized clinical data, as well
2 as the effects of patient dropout in randomized trials.

3 Gary?

xx

4

5 MR. KAMER: Good afternoon.

6 [Slide.]

7 What I'm going to discuss first would be three--
8 and I'm called these controlled clinical studies, although
9 some people look at historical controlled studies and say,
10 Is there a control or not there? And I believe--or the
11 concurrent non-randomized studies the same way, but I
12 believe there is a control, but they are of different
13 quality, different type, than the randomized control. So
14 we're going to be looking at the relative advantages of
15 historical controlled studies to randomized clinical trials,
16 the relative advantages--

17 DR. CURTIS: Excuse me. Could you please speak
18 more clearly into the mike? And that's going to be true for
19 all of us here at the table. If you don't really speak
20 clearly into the microphone, they can't pick up what we're
21 saying.

22 MR. KAMER: Okay. And also the relative
23 advantages of concurrent non-randomized studies to
24 randomized clinical trials, and then, of course, randomized

1 clinical trials, we're going to have to look at the
2 advantages of those relative to the other two, primarily.

3 [Slide.]

4 We looked at the advantages of historical
5 controlled studies. Statistically, compared to our RCTs, I
6 really don't see where they have any great advantages
7 anywhere. Ethically--and this is important--they may be
8 used when clinical equipoise is questionable. You're not
9 treating patients when you use a historical control with a
10 treatment that you might consider not as good as or that has
11 been shown not to be as good as, as effective, as safe as an
12 experimental treatment.

13 Economically--and this is an area that the FDA
14 cannot consider, but I put it up here for completeness--
15 they're less expensive, usually, to run these studies, and
16 they're shorter in nature.

17 [Slide.]

18 The advantages of concurrent non-randomized
19 studies compared to RCTs: First of all, statistically you
20 have--sometimes you'll get an increased accrual rate by not
21 having a larger number of dropouts. You're decreasing that.
22 Ethically, I can't see any real reason for this or advantage
23 of this compared to an RCT. Economically, well, you're not
24 randomizing so there are some costs that are avoided with

1 this type of a study.

2 [Slide.]

3 The advantages of randomized clinical trials
4 compared to the other two methods or the other two
5 procedures would be, first of all, statistically--and this
6 is very important--it avoids patient selection bias,
7 intentional and non-intentional, population biases also.
8 The selection of different populations is something that
9 comes into play here. Also, it--and this is related--
10 improves the comparability of treatment groups so that
11 patients in both groups are similar in characteristics that
12 are both known and those which are not known but may affect
13 outcome. These first two are extremely important for the
14 clinical evaluation of the results of a clinical trial.

15 The third one is, quite often, the equity of
16 experimental environment. Under the other two non-
17 randomized situations, designs, you have at least one group
18 that may have a lesser or no experimental environment
19 nature. Basically, patients are different when they agree
20 to be in an experimental situation, and they also receive,
21 quite often, better or at least different treatment than
22 they would under a standard treatment without an
23 experimental environment.

24 Ethically--and this is important, and I think this

1 is the most likely--an RCT is most likely to yield a
2 correct, definitive result. That can be seen quite often
3 when you compare it with randomized--there have been studies
4 that have looked at randomized trials and the results of
5 studies when using historical controls in particular; and
6 they found out that they're different, they're really
7 different, sometimes in direction even, which means one
8 particular treatment arm is better, and then you look at it
9 with the randomized trial and you look at it with the non-
10 randomized trial, and it's not. And certainly the
11 differences in the size of that, treatment differences, can
12 vary.

13 Economically, the acceptance of study results are
14 more likely, and that means in the community, and that can
15 be an economic advantage.

16 [Slide.]

17 Now, going to the advantages of RCTs with
18 extensive patient dropout from the control arm, this is
19 where patients have been randomized. They said we do not
20 want to continue with the study because we do not get the
21 experimental treatment. This also could apply to the
22 experimental arm, but doesn't in most cases. I see none at
23 all. I see no advantages anywhere at all. It doesn't
24 clarify a situation. It makes it statistically difficult to

1 analyze. Economically, no real great advantage

2 [Slide.]

3 The possible analyses of the RCTs which has this
4 type of dropout from the control arm: Of course, you can
5 always just look at the patients that are proceeding with
6 the treatment. That's one of the possibilities. That's not
7 listed here, but that's the general one. But alternatives
8 are worst-case analysis, which would place the experimental
9 device at a disadvantage by saying anybody who would drop
10 out from the control arm would be considered a success. The
11 best-case analysis would do the opposite, and that would be
12 similar to an intention to treat, but it would obviously not
13 be a fair trial, I think, in any manner, shape, or form.

14 The analysis of compliant sites, there might be
15 some sites which have been much more compliant and have had
16 pretty good participation from both arms. Those could be
17 isolated. The other sites that were not so could be ignored
18 in the data. But in this case, all of these are either
19 subjective or destroy the advantages of randomization that
20 were mentioned earlier.

21 So what it really comes down to, I see a couple of
22 questions that need to be considered today. One is for this
23 set of devices, is an RCT, randomized clinical trial, both
24 feasible and ethical? And, secondly, if an RCT is both

1 feasible and ethical, are there acceptable reasons for not
2 requiring a properly conducted RCT given the relative
3 disadvantages of historical controls and non-randomized
4 concurrent studies?

5 Now Donna Buckley will continue.

6 MS. BUCKLEY: Thank you, Gary.

7 To conclude, FDA would like the panel to address
8 the following questions:

9 [Slide.]

10 One, should there be indications for shunt closure
11 in terms of dimensions and/or flow ratio as determined by
12 echocardiography?

13 Two, what is the appropriate control to which
14 transcatheter occlusion devices should be compared for the
15 treatment of: atrial septal defects, patent ductus
16 arteriosus, and patent foramen ovale?

17 [Slide.]

18 Three, for these devices, is a randomized control
19 trial both feasible and ethical?

20 If a randomized control trial is both feasible and
21 ethical, are there acceptable reasons for not requiring a
22 properly conducted randomized control trial, given the
23 relative disadvantages of historical controls and non-
24 randomized concurrent studies?

1 [Slide.]

2 What should the primary endpoints be for each
3 study? Should the primary endpoint be a composite one which
4 encompasses both safety and effectiveness measures?

5 What amount of residual shunting should
6 characterize the device as having "failed"? Does the
7 presence of shunts after device placement actually increase
8 the risk of endarteritis and/or endocarditis?

9 At what time period should the primary measures be
10 evaluated?

11 Thank you for your time and attention.

12 DR. CURTIS: Thank you.

13 From here we'll move on to the invited speakers.
14 The first speaker is Dr. Jane Newburger from Boston
15 Children's Hospital.

xx

16
17 DR. NEWBURGER: Thank you, ladies and gentlemen.
18 I'm going to spend about ten minutes addressing some of
19 those questions with an emphasis on device trials for ASD
20 secundum and patent ductus arteriosus.

21 [Slide.]

22 As Dr. Kamer has said, randomization or random
23 allocation allows equal distribution of baseline
24 characteristics that could confound an observed association,

1 and I think it's probably preaching to the converted to say
2 that when a randomized study is feasible and ethical, it's
3 inherently as valid, at least as valid as a non-randomized
4 study. And, occasionally, a non-randomized study on
5 efficacy can be plagued by confounding to the extent that
6 there really are insurmountable difficulties in reaching
7 valid inferences.

8 [Slide.]

9 So one has to ask the question: Is randomization
10 always necessary for assessment of efficacy? And I would
11 hold that randomization is not always necessary for control
12 of confounding by indication. For example, I don't think
13 anybody would say that one needs to have a randomized trial
14 for the efficacy of pericardiocentesis for tamponade or for
15 antibiotics in the treatment of staph aureus endocarditis
16 because those are instances where the efficacy is obvious in
17 the individual patient relative to the natural course of
18 things. On the other hand, I don't think any of us would
19 argue that randomization would be necessary to assess the
20 efficacy of primary prevention of myocardial infarction for
21 lipid-lowering agents. So the feasibility of control of
22 confounding in a non-randomized design is very much related
23 to the complexity and the subtlety of the indication.

24 [Slide.]

1 Randomization is the least necessary when the
2 efficacy of the intervention is obvious in an individual
3 patient and when the indication is of what I would call the
4 all-or-none type. For example, if you have a PDA, it should
5 be closed. Both criteria may be met in device trials for
6 ASDs and PDAs, but I think not for patent foramen ovale.

7 [Slide.]

8 How about assessment of safety? Is randomization
9 necessary for safety? Whereas one can have serious
10 confounding by indication in assessment of efficacy,
11 outcomes that reflect adverse effects do not have a tendency
12 to be associated with the indication for treatment.
13 Instead, contraindications tend to be predictive of side
14 effects, and the study can be restricted in principle to
15 patients who don't have contraindications to either
16 procedure.

17 In terms of rare adverse effects, such as
18 endocarditis, that we may worry about long term with
19 devices, the study of these is really not very efficiently
20 addressed in trials in any case.

21 [Slide.]

22 How do you facilitate comparability of study
23 groups without randomization? I do think it's essential to
24 have tight entry and exclusion criteria so that patients

1 should be studied in the same time period; they should be
2 from the same institution, if possible; they ought to be
3 equally eligible for device or surgical closure; and I think
4 it would be important in terms of studying adverse effects
5 to exclude patients who have comorbidities or relative
6 contraindications to one or the other technique.

7 Historical controls, I believe, are completely
8 inappropriate in these trials, in part because advances in
9 surgery continue to go along at a very fast clip. The
10 average patient who has had an atrial septal defect closed
11 has fewer inflammatory effects from bypass with use of
12 ultrafiltration, usually has, at least in our institution, a
13 very tiny sternotomy, and often is discharged on the second
14 post-operative day. That would not have been true five
15 years ago.

16 [Slide.]

17 Blinding is usually the cornerstone of assessment
18 of safety and efficacy, but in device trials, neither
19 patients nor their physicians can be blinded. Wherever
20 possible, therefore, outcomes ought to be objectively
21 measured, and when they are subjective, then interpretation,
22 if possible, should be done by independent readers as might
23 be achieved with a core lab.

24 [Slide.]

1 The ideal characteristics of the primary efficacy
2 measure would be that it would be easy to diagnose or
3 observe, free of measurement or ascertainment error, and
4 clinically relevant. In terms of clinical relevance, the
5 primary efficacy measure would need to vary with the device
6 indication.

7 [Slide.]

8 For atrial septal defect secundums, my goal as a
9 clinician is to obtain either complete closure or have only
10 a very trivial shunt with a $Q_p:Q_s$ less than 1.5. In terms
11 of assessment measures, echo and Doppler techniques are good
12 for seeing whether a residual shunt is present. If a shunt
13 is more than trivial, though, one will want to quantitate
14 it, and that may involve the use of other techniques, such
15 as MRI, catheterization, or radionuclide scanning, or
16 perhaps even a composite measure.

17 [Slide.]

18 For patent ductus arteriosus, again, as a
19 clinician, I would be completely dissatisfied if complete
20 closure were not obtained because the risk of endocarditis
21 would continue with even a small residual shunt. And I
22 think that one could effectively argue that a small residual
23 shunt with prosthetic material in a vessel could put you
24 even at greater risk. Here, echo and Doppler techniques are

1 really extremely good at detecting residual shunts.

2 [Slide.]

3 In terms of patent foramen ovale, which I'll only
4 touch upon--this is a much more complex measure, probably
5 not easily addressed without randomization--the goal would
6 be absence of recurrence of stroke and perhaps reduced need
7 for anticoagulation. And one's assessment measure would
8 need to be freedom from recurrent stroke.

9 [Slide.]

10 For adverse events, it's important to recognize
11 that the types of adverse events will differ for device
12 closure and surgical closure. I personally feel that
13 adverse events need to be recorded with equal rigor,
14 prospectively, in both treatment groups, with similar kind
15 of active surveillance by study personnel.

16 [Slide.]

17 Because you will have some apples and oranges in
18 device and surgery groups--for example, post-pericardiotomy
19 syndrome may happen in patients after surgery but not device
20 closure; device embolization certainly would never occur in
21 the surgical group--one needs to normalize, so to speak,
22 along a severity scale of adverse effects so that you can
23 compare the two groups.

24 A reasonable primary outcome measure might be the

1 number of moderately serious or serious adverse events that
2 are either possibly or definitely attributable to the
3 procedure within a specific time period.

4 Now, the classification of adverse events and
5 their attributability to a procedure can both be quite
6 subjective, and from that point of view, I think the posture
7 of the high-risk trial conducted at Children's where the
8 classification and attributability are overseen by a Safety
9 and Data Monitoring Committee that's impartial is probably
10 the cleanest way to assess or compare adverse events.

11 [Slide.]

12 In terms of timing of assessments, in concept one
13 would want to choose the time beyond which changes in
14 efficacy and safety would be uncommon. I think just from
15 clinical experience that a primary endpoint in efficacy at
16 about a year is a reasonable time, and, similarly, in
17 safety, primary endpoint of cumulative events by a year
18 seems like a reasonable cut point.

19 Whenever the end of these first trials--the end of
20 assessments occurs, there is no question in my mind that one
21 is going to have to do longer-term post-approval studies of
22 safety.

23 [Slide.]

24 I'd just like to make a couple of general points

1 in closing. Surgery is very highly effective for closure of
2 ASD secundum and patent ductus arteriosus. It really has to
3 be viewed as a gold standard for closure. Therefore,
4 there's interest in demonstrating that device closure is
5 equivalent in efficacy to surgical closure because other
6 aspects of device closure might be desirable relative to
7 surgery, and those include things such as cost or adverse
8 effects.

9 To test for equivalence in efficacy, the panel or
10 the trials committees will need to specify what is the
11 maximum difference in efficacy between devices and surgical
12 closure that's ethically acceptable.

13 I'm going to stop here. Thank you.

14 DR. CURTIS: I just want to ask one question. You
15 said that in your opinion historical controls were
16 completely inadequate, and you mentioned on one of your
17 slides that having a non-randomized but concurrent group,
18 preferably at the same institution, would be a good way to
19 go. I'm not sure how that wouldn't get you to a randomized
20 controlled trial right there.

21 DR. NEWBURGER: If you have patients who are being
22 monitored for adverse effects and efficacy by similar
23 methods concurrently, then you have at least avoided the
24 pitfall, particularly with regard to adverse effects, in

1 cost of using old surgical data.

2 DR. CURTIS: But if that's all being done at the
3 same institution, why not just randomize the patients?

4 DR. NEWBURGER: Oh, I think that there are a lot
5 of difficulties in randomizing patients. Patients often--I
6 mean, I think, as I said at the very beginning, if it wee
7 easy to do, if it were feasible, there's no question that
8 you couldn't lose doing that. It's inherently at least as
9 valid. But it seems unnecessary in ASD and PDA trials. And
10 patients often get sent to--at least at our institution and
11 at other institutions, they're referred specifically for
12 device closure, or patients sometimes have extremely strong
13 feelings of their own, and those feelings I think would not
14 influence in this particular instance your judgment of
15 efficacy.

16 DR. BRINKER: Who would get referred to surgery at
17 those institutions?

18 DR. NEWBURGER: Patients also do get referred for
19 surgery at those institutions, and I think when a patient--
20 when we as cardiologists at our institution first diagnose a
21 patient with atrial septal defect, those of us--really, I
22 think most of us would on that encounter talk about all the
23 pros and cons, what's known and what isn't known about
24 surgery and device closure.

1 DR. BAILEY: So are you saying that there wouldn't
2 be any bias, or that you could control for the bias by
3 measured parameters?

4 DR. NEWBURGER: I think just in the instance of
5 ASD secundum and patent ductus arteriosus, but not for
6 patent foramen ovale, you could control for confounding
7 because you can just the efficacy of the intervention in the
8 individual patient. And the indication for intervention is
9 very clean; it's an all-or-none indication.

10 DR. CURTIS: I just want to make a clarification
11 here. We have about five minutes to question each speaker
12 as they finish, but we have the opportunity later on to ask
13 them further questions.

14 Is there a question over here/

15 DR. RINGEL: Since we're in this vein, I just
16 wanted to ask--

17 DR. CURTIS: Please speak into a microphone.

18 DR. RINGEL: Why do you feel it has to be within
19 the same institution? Why can't surgeries be done
20 elsewhere?

21 DR. NEWBURGER: Well, this may be a practical
22 issue. The reason it would be wonderful if it could be in
23 the same institution is because the adverse effect
24 monitoring could be tighter. In fact, one could try to

1 build in the same kind of monitoring at outside
2 institutions, and it certainly would be, from a practical
3 standpoint, a lot easier to have referrals. I understand
4 that.

5 DR. WEINTRAUB: The one thing that this concurrent
6 trial in the same institution does not obviate would be, of
7 course, selection bias. At Children's Hospital, how does
8 this work? Why do some patients get referred to surgery and
9 others to a device? Because that really is--otherwise, the
10 comparisons are really not valid.

11 DR. NEWBURGER: Well, I'd just make two points. I
12 think what they choose--I would be naive if I didn't say it
13 probably depends on whom they speak to. I think all of us
14 who are physicians would understand that. But my point
15 here, Dr. Weintraub, is that I think selection bias isn't--
16 if you can make very tight entry and exclusion criteria, the
17 kinds of things that would--the biases that might be
18 physician or patient biases to lead them to one or the other
19 group are really not going to assess, are not going to
20 confound your evaluation, because the efficacy in the
21 individual patient is something that you can really in a
22 short term assess reliably.

23 DR. WEINTRAUB: The thing I'm concerned about
24 most, I think, is actually not even the efficacy, because if

1 you have a 90 percent success rate, for example, the default
2 position is always surgery, and it's been costly, perhaps,
3 to have two procedures. I think I certainly for one am more
4 concerned about significant complications.

5 DR. NEWBURGER: Right.

6 DR. WEINTRAUB: And I think it's hard to compare
7 them without pretty tightly comparable groups, and I'm not
8 sure you can get them this way.

9 DR. NEWBURGER: I am in total agreement with you.
10 I think that the only way to make adverse effects or side
11 effects comparable is to have extremely tight entry criteria
12 that really eliminate patients who have contraindications to
13 one type or the other type of procedure.

14 DR. CURTIS: In your opinion, what's the maximum
15 difference in efficacy between the two procedures that would
16 be ethically acceptable?

17 DR. NEWBURGER: I was hoping nobody would ask
18 that.

19 I think I would probably not like to see more than
20 a 5 to 10 percent difference in efficacy, and that assumes
21 that there are a lot of advantages to device closure that
22 are non-efficacy related. It's much easier if the patient
23 goes in and out, the fear of surgery, I suppose. But I
24 wouldn't like to see more than a 5 to 10 percent difference

1 in efficacy.

2 DR. CURTIS: Why not?

3 DR. NEWBURGER: I wouldn't think it was worth it,
4 personally.

5 DR. ZAHKA: Jane, what do you think can be done to
6 avoid the perception of families that they're being referred
7 for device closure in a randomized clinical trial as opposed
8 to being referred for a randomized clinical trial?

9 DR. NEWBURGER: Well, I think that the answer to
10 that will begin with the referring physicians, the referring
11 cardiologists, who need to understand that when they refer
12 their patient, they're referring their patient for
13 randomization.

14 Now, there's an additional complication, which is
15 that some patients and physicians might choose to wait under
16 those circumstances since an ASD closure might not be an
17 emergency, and that could lead to reduced referrals of any
18 kind.

19 DR. CURTIS: One last question now.

20 DR. HOPKINS: Actually, I have three. The first
21 question is: What is your justification for having
22 different efficacy outcome criteria for surgery and device
23 when both are basically indicated for prophylaxis primarily
24 of long-term medical problems?

1 DR. NEWBURGER: Can I answer them one by one?

2 DR. HOPKINS: Sure.

3 DR. NEWBURGER: I think that the criteria for
4 efficacy should be the same. Your outcome criteria for
5 efficacy and goals should be the same.

6 DR. HOPKINS: So the thing that you put on the
7 slide in which you reduced the shunt ratio to below surgical
8 criteria to 1.5 is not your outcome measure that you'd
9 recommend? In other words, the efficacy outcome criteria
10 for surgery, the gold standard, is complete closure, but the
11 criteria that you placed on the slide was to reduce the
12 patient shunt below the criteria needed for surgery, so the
13 outcome was the avoidance of surgery not the complete
14 closure of the ASD, if I understood the slide?

15 DR. NEWBURGER: Well, let me put it to you this
16 way: If I sent somebody to surgery and for some unusual
17 reason the surgeon didn't completely close the ASD, that
18 would still be my efficacy criteria, as long as the shunt
19 was very trivial.

20 DR. HOPKINS: But my question is: If there is a
21 residual ASD, the patient still has SBUS, still has embolic
22 risk, and still has the potential for enlargement of the
23 shunt over time. So why are the criteria different for the
24 intervention?

1 DR. NEWBURGER: Again, the criteria would be the
2 same, and ideally you would like them both completely
3 closed. But I think that in terms of endocarditis,
4 endocarditis is a risk for PDAs, but has not been known to
5 be a risk for ASDs. I don't know if that will be different
6 with a prosthetic, with a device in the atrial septum, and
7 that's something you may find out very, very long term.

8 DR. HOPKINS: I'll reserve my other questions for
9 later.

10 DR. CURTIS: Thank you.

11 We'll go on to the second invited speaker, Dr.
12 James Jagers from Duke University Medical Center.

xx

13
14 DR. JAGGERS: Thank you, members of the panel,
15 ladies and gentlemen, for inviting me to speak to this
16 timely problem.

17 [Slide.]

18 My comments today will be primarily related to the
19 need for prospective randomized trials and not necessarily
20 to the advantages of one particular therapy over the other.
21 I don't know which therapy is better. Certainly
22 transcatheter devices have merits, and they will continue to
23 have merits in the future. But I think we need prospective
24 randomized trials to show this, and in the next few minutes,

1 I hope that I can relay some of my thoughts and some of my
2 colleagues' thoughts concerning this.

3 [Slide.]

4 I was struck when I received the paperwork about
5 the mission of the DCRND, and I think it's very profound and
6 very specific. And I think these are the things we have to
7 address with any of our studies.

8 We promote, protect, and enhance the health of the
9 public by assuring that devices approved are safe and
10 effective, and that's what this is about, and how they can
11 enhance the health of the public.

12 We strive for excellence in regulation of devices
13 based upon comprehensive, timely, team-centered evaluation
14 of valid scientific evidence, and that's the question before
15 us: Which is valid scientific evidence?

16 Then, finally, we work in active partnership with
17 industry, medicine, and the scientific community. All
18 members of the partnership must agree upon this for the
19 benefit for the American public.

20 [Slide.]

21 The questions as I see before this panel, as I
22 understand it, are: First, is there enough experience with
23 these devices to warrant bypassing appropriate randomized
24 clinical trials? Secondly, has the safety and efficacy of

1 these devices been adequately demonstrated in non-randomized
2 trials to support their use for lesser types of trials?
3 And, thirdly, what is the best methodology to determine the
4 safety and efficacy of these devices? Should the
5 appropriate control group be and is the prospective
6 randomized trial just merely an overrated cumbersome design
7 that we should bypass in favor of quicker answers?

8 [Slide.]

9 As I mentioned, my job here today is not to
10 promote one or the other, but I would like to bring out what
11 the patient population is. This is not health hazard number
12 one, but this is a large group of patients that are
13 potential patients for this. Certainly atrial septal
14 defects are common. More common, though, is patent foramen
15 ovaes. Up to a third of the population has a patent
16 foramen ovale, and there is a lot of unexplained strokes in
17 this country that may be potential candidates for the device
18 closure.

19 Again, ductuses are quite common. There has been
20 transthoracic therapy for these already in place, and
21 there's certainly another group of patients that we as
22 congenital heart surgeons create and are very thankful to
23 have transcatheter devices when they come along. But their
24 efficacy for these things must also be established.

1 [Slide.]

2 So today what I'll talk about is what the current
3 results of atrial septal defect and patent ductus closure
4 are and why they are really the gold standard. We'll talk a
5 little bit about the report of results and complications of
6 occluder devices--I'm not going to spend a lot of time on
7 that--and then some of the misconceptions regarding surgical
8 closure, and then what is the optimal scientific study
9 design to evaluate this new technology.

10 [Slide.]

11 One of the arguments that prospective randomized
12 trials are not necessary is that the surgical outcomes are
13 so reproducible and so good that they are truly gold
14 standards. I present these two slides to show that there
15 are differences in reporting, there are differences in
16 results, and that perhaps maybe non-randomized trials may
17 not be the most appropriate.

18 Certainly the safety of the procedure is
19 outstanding, 100 percent, or as close to 100 percent
20 survival as any surgical procedure can be, and complication
21 rates are also quite small. The group from Columbus, Ohio,
22 presented in 1994 their results. I think that the
23 complications are low. Most importantly from the study, the
24 risk of residual defect was also low. It was about 7

1 percent, which goes along with other purported studies
2 between 2 and 8 percent.

3 Finally, their length of stay was lower, and this
4 represents something that we're seeing across the country.
5 Lengths of stay for atrial septal defect closures are really
6 decreasing. Their most current length of stay is reported
7 about four days.

8 The other study, Galal from Saudi Arabia, reported
9 another group of patients equally as effective at closing
10 atrial septal defects, but they reported that only about 20
11 percent of the patients got out of the hospital without a
12 significant complication.

13 So I think that the surgical results are not quite
14 as clear-cut as some of them may seem. The differences in
15 these two data don't mean that the group in Columbus does
16 better work than the other group. It just means that we
17 can't compare these apples and oranges.

18 [Slide.]

19 The ASD occluder devices are really actually quite
20 effective and quite safe. I'm not going to sit here and put
21 down the occluder devices, but they do have something that
22 is quite concerning: the 36 percent incomplete closure
23 defect. And I agree with some of the panel members'
24 comments that I don't think we can have two different

1 standards as far as closure of defects. Certainly as a
2 surgeon, if I have a residual atrial septal defect after a
3 closure, that is an unacceptable result. And I think that
4 probably we should hold the same standard towards any device
5 closure as well.

6 [Slide.]

7 Some of the complications of occlusion devices:
8 They actually are quite small, but most recently, the group
9 in Saudi Arabia, in Riyadh, had six devices, and three out
10 of the six had to be retrieved surgically because of
11 inability to retrieve with transcatheter devices and
12 embolization. This is a difficult problem, and I think
13 there's a lot of reasons for failure of this. And certainly
14 in some of the better groups--or in some of the better
15 results, these complications are decreasing.

16 [Slide.]

17 As Dr. Newburger mentioned, there are a lot of
18 misconceptions concerning surgery. Surgical sternotomies
19 and small thoracotomies are not disfiguring incisions, as
20 some may portray them to be. The incisions that we use now
21 are quite small. They are cosmetically better, although
22 they are still scars and they are still incisions. And we
23 as surgeons are trying to become more cosmetically aware and
24 more aware of pain management.

1 The long-term morbidity is something that we just
2 don't see with these incisions. Prolonged hospital stays
3 are very uncommon. The average hospital stay for an ASD
4 closure is now two to three days. Some groups are even
5 going to same-day surgery. The group in Loma Linda now is
6 discharging atrial septal defect closures on the same day.
7 Whether that's right or wrong, it's certainly a difference
8 from historical controls. And neurologic outcome from
9 cardiopulmonary bypass is an extremely rare event.

10 [Slide.]

11 I'll talk a little bit about some of the
12 advantages of prospective randomized trials. I think in the
13 modern era of randomized trials, which began in about 1950
14 with streptomycin and TB, some of these trials have been
15 constantly refined since then until their current state
16 today. Certainly medicine is replete with examples of
17 therapies that were supported but were not scientifically
18 founded. And without randomized trials, it would be very
19 difficult to repeal the opinions of some very well meaning
20 physicians concerning some of these therapies.

21 Randomization produces treatment and control
22 groups that are evenly balanced. They are able to pull in
23 not only known variables, but also unknown variables that
24 one cannot control for. The effects of treatment cannot

1 easily be extracted from variations in practice patterns
2 without randomized trials.

3 Multicenter studies would help to eliminate
4 differences in practice patterns. The way I close an atrial
5 septal defect is certainly going to be different than the
6 way somebody else closes it down the street. The incision
7 may be different. Multicenter studies with appropriate
8 criteria could help eliminate some of those differences.

9 Chance and bias can result in selection of
10 patients that are certainly not representative for each
11 group, and certainly if you use historical controls--ten
12 years ago we closed atrial septal defects when children were
13 older. They had worse RV dysfunction, perhaps a bigger
14 atrium, more prone to arrhythmias. The results in that
15 group may certainly be different than the children we close
16 at two years of age.

17 Eugene Pasami (ph) in the New England Journal of
18 Medicine in 1991 wrote, "The scientific importance of
19 randomized controlled trials is in safeguarding current and
20 future patients from our therapeutic passions." And I think
21 this is a real important statement.

22 [Slide.]

23 There are many disadvantages to non-randomized
24 studies. The study of historical controlled trials involved

1 selecting patient groups and matching them for variables
2 that you can think of, but you can't think of all the
3 variables. Strategy has important limitations. You can't
4 control for a large number of variables, and that would
5 require a prohibitively large sample size. Some of the
6 topics that Dr. Newburger mentioned with the differences in
7 outcomes and the differences in patient populations, it
8 would take a large sample size to control for those
9 compounding variables.

10 Type 1 errors, or the possibility of accepting a
11 hypothesis that may or may not--that may not be true are
12 relatively common with historical controlled trials.

13 [Slide.]

14 One example of this, I've taken a couple different
15 studies from the literature concerning patent foramen ovales
16 with strokes and TIAs. Dr. Bridges in Circulation in 1992
17 have reported on 34 patients that she placed the device in,
18 a group she placed the device in for patent foramen ovale.
19 Six out of those 34 has residual inter-atrial shunts, albeit
20 they were quite small. Four out of 34 had recurrent TIAs.
21 None of them had documented strokes, however.

22 Now, if I were to compare that with another group
23 of patients who were treated surgically but not randomized
24 and they were followed for two years, 2 out of 30 patients

1 had residual shunt; there was no post-operative strokes or
2 TIAs; and these were measured by symptoms or MRI.

3 Now, if I were to look at this in a non-randomized
4 fashion, there would be no question. But we all know that
5 we can't do that and that we need to have a randomized
6 prospective study to really tell the difference, especially
7 in this group.

8 [Slide.]

9 So, despite the perceived ethical dilemmas and the
10 difficulties in recruiting patients for such studies, the
11 randomized prospective study is still the optimal method for
12 evaluating devices and therapies. Some critics have charged
13 that randomized studies violate the physician's therapeutic
14 obligation to the patient. If a patient gets sent for a
15 device, then that patient should get a device and should not
16 go in the study. I don't think that that's really valid
17 since one therapy has definitely not been proven to be
18 better than the other. So that does not violate the
19 physician therapeutic obligation.

20 Before we release these kinds of devices for
21 general use, the therapeutic benefit must be very well
22 documented, because as we know from the past, therapies and
23 devices may be driven from a less than scientifically sound
24 manner, and we must protect the public from some of the

1 misinformation and unsubstantiated claims.

2 [Slide.]

3 What should be included in a study. I think that
4 any study, obviously, has to include morbidity and,
5 obviously, mortality. Importantly, I think that a year is
6 probably a good time to assess endpoints. Six weeks or a
7 month is also a good endpoint.

8 I think that we don't know what the long-term
9 outcome of a residual shunt is, and I'm not sure that even a
10 year is going to tell us that. Things like cost and length
11 of stay are probably not appropriate for this particular
12 discussion, although they should be evaluated, as they are
13 certainly different from any of our historical controls.

14 [Slide.]

15 So, in summary, surgical ASD and PDA repair are
16 very safe. We have continued to improve the surgical care,
17 incisions, and reduced hospital stay and costs. Any other
18 device or any other therapy must be measured against this
19 gold standard. There is no comparison to historical
20 controls. Certainly a non-randomized concurrent study would
21 allow some comparison, but I think it would be extremely
22 difficult to compare between centers and compare--and it
23 would take a huge number of patients, probably,
24 statistically to do this.

1 I'd like to thank the panel for the opportunity to
2 speak at this forum.

3 DR. CURTIS: You were talking about efficacy
4 before. You mentioned a study that had about a one-third
5 residual shunt. I think it was ASD repair. Is that really
6 a problem? If you could do a catheter procedure with
7 patients and two-thirds of the time you could get a good
8 result with no residual shunt and you were left with a
9 residual shunt, you can still operate on that kind of
10 patient, is that really a problem? As compared to surgery,
11 where no matter how you--I'm not going to say it; I was
12 going to say "no matter how you cut it." No matter how you
13 look at it, it is a major invasive procedure. And if you
14 have a residual shunt after surgery, that is a problem
15 because you don't want to have to go back in and reoperate
16 on somebody.

17 Is it the same thing if you do a catheter
18 procedure that doesn't get you an optimal result and then
19 you go ahead and do one time the major procedure?

20 DR. JAGGERS: I think it's important, I think we
21 have to really document the potential additive complication
22 risk with both a transcatheter device and the surgery. I
23 don't think we know whether or not--although it's been
24 successfully done, surgery after a device placement has been

1 done safely and does not appear to have any additive
2 detrimental effect, we don't know that for sure. That's why
3 it's important, I think, to compare randomized studies and
4 look at the crossover rate, look at that group separately,
5 and see if there is any additional risk.

6 I think the only way to do that is to actually
7 compare a randomized group.

8 DR. CURTIS: Go ahead.

9 DR. RINGEL: A comment and a question. The
10 comment is just a bit of irony. You're using a new or a
11 modification of a surgical technique to close ASDs, and I'm
12 going to guess you didn't randomize patients to do that.

13 The question is: What would be the problem with
14 concurrent non-randomized surgical trials where you get the
15 opportunity of speaking to parents, patients, describe your
16 technique, and if they want to go with you, fine; if they
17 want to go with a device closure, they go with a device
18 closure? You're more likely to get some equity in the
19 patients and also the patients feel that they have some
20 input into the decisionmaking rather than a toss of the dice
21 or whatever.

22 DR. JAGGERS: And that goes back to the basics of
23 randomization. If a patient comes to me and wants to have a
24 device closure--after I talk to him and he wants to have a

1 device closure, he gets a device closure, is he going to do
2 better with device closure? Is he going to get better
3 faster and that sort of thing versus surgery? I don't know.

4 If a patient comes to me and wants surgery--now,
5 this is looking at non-concrete variables like--not looking
6 at the closure device or survival, say. But if you look at
7 other things like how quick is he going to get back to work
8 or, you know, how long is he going to stay in the hospital,
9 if he comes to me and wants surgery and I tell him you can
10 have surgery and we'll get you out of here in three days,
11 he's going to do better.

12 Now, is that the question you're trying to ask, or
13 is that--

14 DR. RINGEL: Well, for the FDA, we're interested
15 in safety and efficacy, so time out of work and
16 psychological aspects are not what we're looking for, but
17 the opportunity for the patient to participate in the
18 decisionmaking process or to use other centers that are
19 doing the surgical technique that you're describing makes it
20 easier to accumulate numbers in a quick way so that if these
21 devices are proven to be efficacious, they can get out to
22 the public more quickly.

23 DR. JAGGERS: The only disadvantage that I see to
24 that is that there is potential difficulty with controlling

1 for specific variables. But that would be clearly the
2 second choice as far as studies, randomized control versus
3 this.

4 I think that that has some validity, and I don't
5 want to discount that, and that may be the most practical
6 way to do it. I think in the best of all situations, when
7 you're dealing with something that has straightforward
8 outcomes and very accepted outcome with surgery, then
9 randomized clinical trial is probably the best thing.

10 DR. RINGEL: Well, while I would say that it is
11 great that you can reduce the scar and make it more
12 cosmetically acceptable, my comment at the beginning was
13 meant to indicate that we do not know that that technique is
14 safe and efficacious.

15 DR. JAGGERS: Absolutely. That's--

16 DR. RINGEL: So it may be perfect timing to do
17 this study, but remember that if you're saying that that's
18 the gold standard, it isn't. The gold standard would be
19 then the traditional technique for the surgery.

20 DR. JAGGERS: That's true. I mean, I cannot say
21 that by doing a small incision I'm not increasing risk.
22 Certainly limited studies that we know about, it doesn't.
23 But that's why it's important also to look at multiple
24 centers and multiple different ways to look at it and see if

1 there's any specific difference in doing it. That would be
2 an important part of that study.

3 DR. CURTIS: Go ahead.

4 DR. EDMUNDS: Dr. Jagers, if we just concentrate
5 on the serious adverse events, stroke with residual and
6 death, would you estimate the power, a power calculation for
7 defining a difference between device and surgery for closure
8 of atrial septal defect? What do you think the "n" would be
9 in order to show--

10 DR. JAGGERS: The rates are so small that the "n"
11 would be very high.

12 DR. EDMUNDS: In the thousands?

13 DR. JAGGERS: I would think it would probably be
14 near thousands, yes; 1 percent risk of stroke, the "n" would
15 be extremely high.

16 DR. EDMUNDS: If we added residual defect, we can
17 get the "n" down considerably.

18 DR. JAGGERS: The "n" could be extremely small
19 with residual effect. Now, whether that's a fair estimate
20 of success, I don't know.

21 DR. EDMUNDS: That's another question. Then if we
22 say residual defect with greater than 1.5 to 1 shunt--

23 DR. JAGGERS: That's even smaller. I mean, I
24 don't know--the problem I have is what is defined as

1 efficacious. I mean, 1.5 to 1 or less shunt with the device
2 closure, is that what we should look for? Or should we look
3 for complete closure?

4 DR. EDMUNDS: Well, Dr. Newburger offered it for
5 us to shoot at.

6 DR. CURTIS: Okay. Thank you very much.

7 Before we move on to the sponsor presentations,
8 we'd like to go around the room and introduce everybody, if
9 you could tell your name and your institution and what you
10 do. I'm Anne Curtis. I'm a professor of medicine at the
11 University of Florida and director of Clinical Cardiac
12 Electrophysiology there.

13 DR. HOPKINS: Dr. Richard Hopkins. I'm chief of
14 cardiac surgery at Brown University. I'm both a pediatric
15 and adult cardiac surgeon.

16 DR. BRINKER: Jeff Brinker, professor of medicine
17 and radiology, Johns Hopkins.

18 DR. BAILEY: Kent Bailey, Mayo Clinic,
19 biostatistics specializing in cardiostatistics.

20 DR. VETROVEC: George Vetrovec, chairman of the
21 Division of Cardiology at Medical College of Virginia
22 Hospital's Virginia Commonwealth University in Richmond.

23 DR. EDMUNDS: I'm Hank Edmunds, professor of
24 cardiac-thoracic surgery at the University of Pennsylvania.

1 DR. SIMMONS: Tony Simmons, Wake Forest University
2 Medical School. I'm a cardiologist, electrophysiologist.

3 MR. JARVIS: Gary Jarvis. I'm the industry
4 representative to the panel.

5 DR. SAPIRSTEIN: My name is Wolf Sapirstein. I'm
6 the associate director of this division, and I'm sitting in
7 for Dr. Callahan, who had a commitment he couldn't escape.
8 His daughter's getting married.

9 DR. GOORAY: I'm David Gooray, an adult
10 cardiologist in Washington associated with Howard
11 University. I'm the consumer rep.

12 DR. RINGEL: Richard Ringel. I'm the director of
13 the pediatric cath lab at the University of Maryland in
14 Baltimore.

15 DR. WEINTRAUB: Ronald Weintraub. I'm a cardiac
16 surgeon at Beth Israel Deaconess Medical Center, Harvard, in
17 Boston.

18 DR. CRITTENDON: Michael Crittendon. I'm a
19 cardiac surgeon at the West Roxbury VA in Massachusetts and
20 Harvard University.

21 DR. ZAHKA: Ken Zahka. I'm the director of
22 pediatric cardiology at Rainbow Babies' and Children's
23 Hospital, Case Western Reserve University, in Cleveland.

24 Dr. STUHLMULLER: I'm John Stuhlmuller. I'm a

1 cardiologist with the Food and Drug Administration and
2 Executive Secretary for the panel.

xx

3

4 DR. CURTIS: Okay. The next order of business is
5 the sponsor presentations, and the first one will be by Dr.
6 John Moore, Children's Hospital in San Diego, California.

7 DR. MOORE: Thank you, Dr. Curtis.

8 DR. CURTIS: Excuse me. Each speaker who steps to
9 the microphone needs to tell us your financial affiliation
10 with the companies or the products that are involved.

11 DR. MOORE: Thank you, members of the panel,
12 ladies and gentlemen.

13 [Slide.]

14 I'm the sponsor for the U.S. clinical trials of
15 the Duct-Occlud device. I receive no direct financial
16 backing from them, simply subsidization to come to meetings
17 and to run the trial itself. We have four centers now which
18 are approved for a Phase I study in the United States. Most
19 of these centers are in Southern California.

20 DR. CURTIS: And that means they paid for your
21 travel here?

22 DR. MOORE: They paid for my travel here, yes.

23 I am grateful for the invitation to speak on
24 behalf of the Duct-Occlud device about issues involved in

1 clinical trials for percutaneous occlusion of patent ductus
2 arteriosus. One thing I would like the panel to consider
3 right at the outset--and I have not detected it in either of
4 the speakers to date--is to consider PDA, ASD, and PFO
5 separately. I think the issues in each of these lesions are
6 actually quite different, and I don't think it serves the
7 devices or the lesions or the patients well to consider them
8 as sort of a batched group.

9 Let me just give you a little background on ductus
10 to clarify what I'm talking about.

11 [Slide.]

12 First of all, a ductus is the persistence of a
13 fetal connection between the pulmonary artery and the aorta.
14 This is a structure which all people have and which normally
15 closes by constriction, thrombosis, et cetera, after birth.

16 Ductuses are different from septal defects or
17 fossa ovals. These are extra-cardiac. They are downstream
18 from significant circulations like the coronary circulation
19 and the cerebral circulation. These are vessels, not
20 defects per se.

21 [Slide.]

22 This introduces a lot of differences in terms of
23 transcatheter therapy. First of all, ductuses come in a
24 variety of types, sizes, and shapes, if you will. The size

1 of the ductus determines the flow characteristics, and they
2 have been classified as trivial, small, moderate, or large.

3 And the clinical differences in these different
4 types of ductuses are really rather dramatic. Let me walk
5 you through a series of slides. This is a trivial ductus.
6 As you can see, it's tiny, it's probably not audible, and it
7 has a non-significant hemodynamic shunt. This ductus is
8 believed to possibly cause an increased risk for SBE.

9 [Slide.]

10 This is a more typical small to moderate size
11 ductus. It is audible. The shunt may be in the range of
12 1.5. It may be slightly smaller; it may be slightly
13 greater. So, in a sense, this may be hemodynamically
14 significant, or it may not be.

15 [Slide.]

16 This is a large ductus. This is definitely
17 hemodynamically significant. It will cause pulmonary
18 vascular disease in the patient. Many devices are probably
19 not applicable to close this ductus. And what I'd like to
20 point out, then, is that there are a variety of ductuses.
21 Ductuses altogether are different from septal defects.

22 [Slide.]

23 And there are two basic reasons to close ductuses.
24 The first is hemodynamic, and certainly large ductuses,

1 moderate ones, and some that are called small probably have
2 hemodynamic reasons for closure. This is independent from
3 the second reason that is so widely touted and that I think
4 people are very preoccupied with, and that is to prevent
5 endocarditis. What is the risk of an unoperated patent
6 ductus arteriosus in terms of endocarditis? I truly don't
7 know. It's probably fairly small. The number you see on
8 the screen is one of them that appears in the literature.
9 But probably all ductuses, including trivial ones, cause an
10 increased risk of endocarditis in the patient.

11 [Slide.]

12 Now, the situation with ductuses is further
13 complicated by the fact that there are several widely
14 available--repeat, widely available--treatment modalities
15 for ductus arteriosus. These include nothing at all or
16 medical treatment, if you will.

17 Antibiotic prophylaxis: this is probably,
18 although this hasn't been proven either, sufficient for
19 trivial ductuses and some small ductuses to prevent
20 endocarditis. This is certainly something that is available
21 widely in the population and that is often recommended and
22 chosen by patients.

23 Secondly, surgery. In surgery, I'd like to point
24 out that the methodology for thoracotomy, et cetera, has not

1 benefited from recent advances in cardiopulmonary bypass, et
2 cetera. So that a lot of the things that have been said
3 about surgery don't apply to ductus closure. I think that's
4 important when you consider what the, quote, "gold standard"
5 is in this situation.

6 But there are also two widely available forms of
7 surgery that are used, and I think these are used
8 approximately equally around the country. I don't think we
9 can choose one as the gold standard over the other.
10 Certainly some institutions routinely ligate ductuses,
11 virtually all ductuses, and others routinely divide
12 virtually all ductuses.

13 And, finally, something that is maybe difficult
14 for the panel to deal with head on, there is a widely
15 available and widely utilized and in our literature called
16 standard treatment off-label use of an existing device, the
17 gianturco coil for ductus closure. I think it is pointless
18 and actually relatively absurd for the panel to ignore this
19 fact. This is the standard treatment for trivial, small,
20 and moderate ductuses at most institutions that have
21 interventional cardiology in the United States and worldwide
22 today.

23 [Slide.]

24 The Duct-Occlud device has advantages over the

1 other off-label device for percutaneous closure of ductus.
2 Those advantages are in the area of control and specific
3 design, and that's the effort that we're--that's the reason
4 why we're bothering to do this study, is because we believe
5 that we have a better device than the off-label device that
6 is in wide use.

7 We have complete control over this device. The
8 device has been specifically designed to close ductus in
9 terms of how it is configured and the material it is made
10 out of, et cetera. And, of course, it is less invasive than
11 the surgical options.

12 [Slide.]

13 This is what the device looks like. It's a
14 stainless steel coil with an hourglass configuration.

15 [Slide.]

16 And this is a ductus in which the device is being
17 deployed. One of the advantages is we can hold on to the
18 ductus. We can hold on to the device until we are
19 comfortable of its position--and we are in this particular
20 instance--and we can prove that the ductus is closed or
21 nearly closed before we let go of the device.

22 [Slide.]

23 And then the device fits in the ductus very
24 nicely, much better than the coil devices, and I won't show

1 you that.

2 [Slide.]

3 Now, the control issues in PDA trials need to be
4 considered separately from the control issues in ASD and PFO
5 trials. They're entirely different. First of all, the fact
6 that there are multiple available treatment modalities means
7 that the patients have multiple options. They can choose
8 surgery. They can choose to wait. They can choose a
9 gianturco coil. And I think for all practical purposes--and
10 this is purely on a feasibility basis, because I would agree
11 with all of the things that have been said about randomized
12 controlled trials, that, prospective, I think they're
13 better. But I think on a feasibility basis, this is not
14 possible to do today in this country. It is simply not
15 possible. Patients will not enter themselves into a
16 randomized trial because they will not accept surgical
17 therapy.

18 Now, prospective trials which are not randomized I
19 think is another issue and is one that the panel is being
20 asked to consider. But I think this is also a difficult
21 issue in the case of ductus, because there is more than one
22 surgical option. Both of these options are credible and in
23 wide use, and these tend to be used by different
24 institutions or different surgeons. They tend to rely on

1 one or the other.

2 Then, in addition to this, there is a widespread
3 use of the off-label device. Should that be considered the
4 standard against which the Duct-Occlud is compared.

5 I think that these issues, the fact that there are
6 multiple standards, if you will, or multiple practices in
7 the community also makes a non-randomized controlled trial
8 very difficult and possibly meaningless in the case of
9 ductus arteriosus.

10 [Slide.]

11 Now, the use of historical data I think is the way
12 to go with ductus. And I would suggest that the control
13 population be considered surgically treated patients, that
14 historical controls be used because surgery has been the
15 predominant treatment for nearly five decades, and there is
16 plenty of surgical data that is published and available to
17 use. Surgical population or the control group should
18 consist of both ligated and surgically divided patients,
19 because, after all, this is the practice in the community.
20 And if we look in the literature, particularly in some
21 reviews such as the Mavroudis article published in Annals of
22 1994, there are good summaries of much patient data that
23 could be utilized as historical controls.

24 [Slide.]

1 Safety measures for PDA trials need to consider,
2 of course, mortality, morbidity--and here I would agree with
3 Dr. Newburger that we need to have sort of major
4 complications and relatively minor complications, because
5 we're going to have an apples-and-oranges problem with
6 surgery and transcatheter treatment here--and I believe that
7 mortality/morbidity rates should be lower than historical
8 surgical controls. What I'm talking about essentially is 0
9 percent mortality for transcatheter closure of ductus and a
10 3 to 6 percent complication rate which should be
11 predominantly the minor complications. I think that those
12 numbers are in the literature, and those are fair standards
13 to use. I don't think we need to enroll patients in a
14 prospective study to rediscover those numbers.

15 [Slide.]

16 As far as efficacy goes, if you look in the
17 Mavroudis article, for example, he summarizes the
18 experience, the published experience in 2,600 patients who
19 were ligated and 2,200 patients that were divided. And I
20 think just those two numbers show you that the practice
21 historically and in the community today is approximately
22 even, division and ligation. The residual rate quoted in
23 his article, which was determined by examination, was 3.8
24 percent in the ligated patients, in aggregate, and, of

1 course, 0 in the divided patients.

2 There are certainly smaller studies, which I think
3 many of the panel members are familiar with and have
4 reviewed, that show a higher than 3.8 leak rate in certain
5 populations, small populations of surgically ligated
6 patients. So I believe that a reasonable expected residual
7 rate in the surgical historical control population should be
8 something on the order of 2 to 3 percent. I think that's
9 fair to say in the population as a whole.

10 [Slide.]

11 Now, efficacy measures for PDA trials need to
12 consider, first of all, that in the case of the Duct-Occlud
13 device, or any PDA-type device, that we are preselecting the
14 patients, that only patients who are non-neonates and who
15 have ductuses classified as trivial to moderate in size
16 would be candidates for the study. And I think the first
17 thing that needs to be considered in efficacy is how often,
18 when a patient is selected, can there be successful
19 placement of a device during a catheterization. And I think
20 here we have to acknowledge the fact that sometimes
21 selection is in error. Sometimes the ductus may be too
22 large for the device and, hence, the device was not placed,
23 or it may be too trivial and it's because it was so tiny the
24 device could not be placed in the ductus. And so we need to

1 have a small percentage--I would suggest 1 or 2 percent--of
2 unsuccessful treatments because the patients were not
3 selected adequately.

4 Secondly, I would suggest efficacy be divided in
5 the case of ductus between the trivial and small ductus in
6 which we would expect a much higher success rate, and
7 remember, these ductuses are only being closed to prevent
8 SBE prophylaxis. And so we're looking for 100 percent
9 closure. I agree with that. And I think the efficacy
10 measures here should be in the range of 98 to 99 percent
11 complete closure by one year, and there should also be an
12 arm of the protocol allowing us to perform a second
13 procedure, placement of a second device, in a small number
14 of the patients, the 1 to 2 percent that don't secure the
15 100 percent closure rate after six months. The goal of
16 these patients, then, should be 100 percent closure to
17 prevent SBE.

18 [Slide.]

19 In patients that have moderate size ductuses,
20 there are actually two goals here: One is elimination of
21 the hemodynamically important shunt; we should have a high
22 expectation that this occur in the 98 to 99 percent range.
23 And, secondly, elimination of the trivial shunt through the
24 device; this will probably be a little bit lower with

1 placement of one device, and I think it's fair here to give
2 a little bit more latitude, 94 to 95 percent by one year,
3 and then an arm of the protocol again allowing placement of
4 a second device in that 5 to 6 percent to secure 100 percent
5 closure.

6 I think these recommendations are consistent with
7 the fact that surgical residual rate can be expected to be
8 in the 2 to 3 percent range. I think in aggregate, if we
9 add the moderate to the small, then trivial ductuses, our
10 overall residual rate is going to be in the 2 to 3 percent
11 range if we consider the entire population.

12 [Slide.]

13 Now, timing of assessments, I would agree with
14 statements that have been made. I think that safety needs
15 to be monitored up to 12 months and efficacy needs to be
16 looked at at 6 and probably 12 months. These seem to be
17 good benchmarks, and I would agree with the comments that
18 were made earlier.

19 Thank you.

20 DR. CURTIS: Does anyone have any questions at
21 this time?

22 DR. BRINKER: The second procedure at 6 months for
23 both the very small and the maybe slightly larger are
24 presumably device procedures.

1 DR. MOORE: Yes.

2 DR. BRINKER: And can you remove this device
3 safely after 6 months, or are you thinking about putting in
4 a different device like a coil?

5 DR. MOORE: Yes. No, I would be thinking about
6 putting in a second device of the same type.

7 DR. BRINKER: Second device of the same type.

8 DR. MOORE: The Duct-Occlud device.

9 DR. BRINKER: What experience is there in that,
10 two of these--

11 DR. MOORE: Well, none in the United States.
12 There is experience in doing that in a European study that
13 has enrolled approximately 500 patients.

14 DR. BRINKER: What was the necessity of doing--

15 DR. MOORE: A residual leak rate.

16 DR. BRINKER: No, percentage-wise.

17 DR. MOORE: There were 20 placements of second
18 devices, and it was to close residual leaks, was the
19 indication.

20 DR. BRINKER: Twenty out of 500?

21 DR. MOORE: Of 500, yes.

22 DR. BRINKER: The only other question I have, you
23 said that the incidence of endocarditis pretty well--you
24 gave a number, 3 per 1,000 patient years. An average person

1 with a PDA lives 70 years. Is that 3 out of 15 risk of
2 endocarditis?

3 DR. MOORE: Over a lifetime.

4 DR. BRINKER: So that's not so low, is it?

5 DR. MOORE: No, it's not low. It's only low day
6 to day, but certainly if you have a PDA for your--

7 DR. BRINKER: Well, people usually live a whole
8 life.

9 DR. MOORE: --for your whole life, you probably
10 incur significant risk.

11 DR. BRINKER: Okay. Thanks.

12 DR. CRITTENDON: You were talking about a gold
13 standard of surgical care and thoracotomy is part and parcel
14 of doing a PDA closure, but there are some patients who are
15 getting video-assisted PDA closure. Do you have any
16 experience about that, know anything about that? Or maybe
17 Dr. Jagers could comment on that. I don't do that, but I'm
18 curious to know what the experience is of maybe a surgeon
19 who does it or whether you considered that.

20 DR. MOORE: Well, I personally have no experience,
21 but I would submit that that procedure needs to be subjected
22 to randomized clinical study if we're going to hold the
23 devices to the same pattern.

24 DR. ZAHKA: John, you defined trivial, small,

1 moderate. In your mind, is trivial the same as silent
2 ductus?

3 DR. MOORE: Yes.

4 DR. ZAHKA: And do you believe that those children
5 as well are at higher risk for bacterial endocarditis?

6 DR. MOORE: I think that's unknown. I put a
7 question mark on my slide, but I think certainly that there
8 are some members of the pediatric cardiology community who
9 believe that that puts the patient at risk and others who
10 don't. I don't think that there's good data there.

11 DR. ZAHKA: And would you anticipate that the
12 particular device you're discussing would be applicable to
13 the child with a trivial or silent ductus?

14 DR. MOORE: It can be used in those patients.
15 Whether it needs to be is another question.

16 DR. ZAHKA: And my final question is: Do you have
17 any reason to believe, by the design of this device, that it
18 would have a significant risk of left pulmonary artery
19 stenosis? And if so, what patient populations might that be
20 in?

21 DR. MOORE: This device--I only showed you one
22 size; actually, in your handout, you'll see there are
23 several sizes, some of which are quite small--has been
24 constructed so that it will not protrude significantly into

1 the aorta nor into the left pulmonary artery. And I think
2 those are design considerations that make this device
3 preferable to the gianturco coil.

4 DR. CURTIS: It sounds to me like if it's up in
5 the air how important it is to close a trivial PDA, that
6 that would be a patient group that would be very appropriate
7 for a randomized trial, and not necessarily as opposed to
8 surgery but as opposed to no interventional treatment.

9 DR. MOORE: I would agree.

10 DR. BAILEY: I think I heard you saying that
11 you're basically proposing an absolute standard here for
12 efficacy as opposed to a comparative one, which is sort of
13 the traditional one. But the criteria you mentioned seem to
14 be basically equality with surgery as the gold standard. Is
15 that true? Is that the goal of the strategy, or is that
16 actually a criterion by which you would define
17 acceptability?

18 DR. MOORE: Well, in terms of the safety, I think
19 that what I'm proposing is absolute equity or better by
20 device closure. In terms of the efficacy, what I'm
21 suggesting is that we look at historical controls of PDA
22 closures that have been published, the worst kind, if you
23 will, and consider both the divided and the ligated group,
24 and come up with the number such as that we can agree upon--

1 the number that Mavroudis puts forth is something on the
2 order of 3.8 percent residual leak rate in ligated patients-
3 -and basically hold the PDA device population to that number
4 or statistically equivalent number.

5 DR. EDMUNDS: There was a paper at the American
6 Association of Thoracic Surgery two years ago about video-
7 assisted ductus closure from Europe, and I think that they
8 had one hemorrhage necessitating emergency thoracotomy out
9 of something like 140 or 160 patients. Otherwise, they just
10 clipped the ductus, and I think the other things,
11 complications, were relatively trivial. I mean recurrent
12 nerve and so on.

13 I'd like to ask you what mortality and what
14 hemorrhage rate necessitating surgery you would tolerate
15 before you would say this is not as good as surgery.

16 DR. MOORE: First of all, the mortality rate I
17 think should be essentially zero. The hemorrhage rate also
18 should be--

19 DR. EDMUNDS: Be careful not to segue me. What
20 would you accept?

21 DR. MOORE: Well, I would accept 1 in 40,
22 certainly, anytime. I'd be happy to use that number.

23 DR. EDMUNDS: One in 40--

24 DR. MOORE: One in 140, sir. I'd be happy to use

1 that number as a comparative standard for mortality or
2 hemorrhage. I think that the devices can easily meet that
3 standard.

4 DR. HOPKINS: I'd like a follow-up question on
5 your sub-routine of the secondary procedure on a patient.
6 Given the necessity for an outcome of complete closure, are
7 you aware of any data that shows that a secondary cath-based
8 procedure following a residual leak following surgery has a
9 higher complication mortality rate than a secondary cath
10 procedure after a primary cath-based procedure? Do you
11 understand the question?

12 DR. MOORE: Is that a cath procedure after
13 surgery?

14 DR. HOPKINS: In other words, you showed data that
15 showed that the efficacy of primary surgery done by ligation
16 was essentially the same with about a 2 percent residual
17 leak rate as with a primary cath procedure. That group of
18 patients could enter the same sub-routine as your primary
19 failure patients in an interventional-based primary
20 procedure. Is there increased risk in placing a device in a
21 ductus which has been inadequately ligated as opposed to one
22 in which a previous device has been placed?

23 DR. MOORE: No, sir. In fact, many of the
24 patients that are in the series of gianturco coils are post-

1 surgical residual leaks.

2 DR. HOPKINS: So the sub-routine is equivalent.

3 DR. MOORE: Yes.

4 DR. RINGEL: I didn't really want to make a
5 comment, but I guess as long as we're being as forthright as
6 possible, you're going to have to include something about
7 radiation, which is something the surgical patients are not
8 exposed to, and some measure of acceptable radiation
9 exposure if--I don't know how long it takes you to do a
10 Duct-Occlud. A gianturco coil, you know, takes, whatever,
11 8, 10 minutes of radiation. I don't know what Duct-Occlud
12 takes. And then if you have to do it twice, you're going to
13 have to include some measure of radiation.

14 DR. MOORE: I'd be happy to do that.

15 DR. CURTIS: Thank you.

xx

16
17 The next presentation is actually a combined
18 presentation by Nitinol Medical Technologies, Microvena
19 Corporation, and AGA Medical Corporation, and they are
20 represented by Dr. Charles Mullins, Dr. Anirban Banerjee,
21 and Dr. Ziyad Hijazi.

22 DR. HIJAZI: Good afternoon. My name is Ziyad
23 Hijazi. I would like, first, Dr. Curtis, if you don't mind,
24 to talk about the PDA to follow up so that--

1 DR. CURTIS: You need to clarify your financial--

2 DR. HIJAZI: Yes, I will. Just to get it out of
3 the way, and then we will proceed to the ASD closure. I am
4 the chief of pediatric cardiology at the Hospital for
5 Children at New England Medical Center in Boston, and I have
6 no financial obligation to disclose with AGA aside from they
7 paid my trip coming here.

8 [Slide.]

9 This afternoon I would like to share with you
10 about a new device that has been already submitted to the
11 FDA as a pre-IDE protocol. As Dr. Moore has mentioned, for
12 the patent ductus arteriosus, clearly our patients, they
13 have many options available to them, and I would agree with
14 him not to have patients with PDA summed with the patients
15 with ASD or PFO because of the reasons that he mentioned.

16 [Slide.]

17 As we all know, management of PDA nowadays can be
18 done by both surgical closure or the catheter closure.

19 [Slide.]

20 The surgical closure, we are all aware of the
21 history, the technique, and the approach that is being used
22 nowadays, mainly the thoracotomy and the VATS, which is the
23 videoscopic-assisted thoracoscopic surgery.

24 [Slide.]

1 The results have been outstanding with a very low
2 mortality rate, less than 1 percent, and in many series, the
3 series that was published by Mavroudis was 0 percent.
4 However, we should not forget the morbidity of surgery,
5 whether it is the traditional approach or the VATS approach,
6 from bleeding, chylothorax, vocal cord paralysis, in those
7 patients who undergo the ligation and division of the
8 ductus, as well as the residual shunt which varies, as I
9 mentioned, from 0 in those patients who had their ductus
10 ligated and divided, up to 23 percent in smaller series in
11 those patients who had the ligation along.

12 [Slide.]

13 And, of course, there are other devices that are
14 off-label use, as Dr. Moore mentioned; however, they have
15 been used nowadays. Non-FDA-approved devices, the Rashkind,
16 the button, the plug, we are not going to talk about them.

17 [Slide.]

18 However, the off-label use, the gianturco coils
19 and the GGVOD, the gianturco-grifka (?) vascular occlusive
20 device, these two devices are being used across the United
21 States as well as worldwide to close most patients with
22 patent ductus arteriosus.

23 [Slide.]

24 Let me just talk briefly about the coil closure.

1 In 1995, there was a registry of coil patients which was
2 established at the University of Michigan, and within four
3 months, we collected 535 procedures from 38 centers, and the
4 patients' ages were anywhere from 15 days up to 71 years.
5 The PDA was moderate in size with a median of 2 mm.
6 However, we had also larger PDAs, up to 7 mm.

7 In that registry, the complete closure rate at the
8 end of the procedure was 75 percent; 20 percent of the
9 patients had residual shunt, and 5 percent failed the
10 procedure. And when I say failed, a coil could not be
11 implanted, so the procedure was terminated. And in those
12 535 procedures, there were 64 embolization rate. Obviously,
13 in the majority of them, the coils were retrieved in the
14 cath lab, and the ductus was either closed or left alone.

15 [Slide.]

16 These are just some slides to demonstrate to you
17 the multiple coil technique. This is obviously a large
18 ductus, and this is a small child, 5.7 mm, with a baby with
19 pulmonary hypertension, failure to thrive.

20 [Slide.]

21 And this ductus was completely closed using 6
22 gianturco coils. So we can do the procedure in any ductus
23 from 1 mm up to 7 mm without a problem. But, of course, it
24 takes a longer time, and the embolization rate is higher.

1 [Slide.]

2 The second device which is also off-label use--
3 however, it is being used for closure of the ductus--is the
4 grifka bag. In a recent abstract presented this March at
5 the ACC, 15 PDAs were reported on, and these are the
6 patients' ages, and there was 100 percent complete closure
7 rate of the ductus.

8 [Slide.]

9 So, clearly, our patients, they have an option.
10 This is an example of an angiogram in a patient that we had
11 with a large ductus. We crossed the ductus with a catheter.
12 We placed the grifka bag as you see here.

13 [Slide.]

14 And then we performed the angiogram with complete
15 closure of the ductus. The procedure was short. The
16 patient left on the same day without any incision.

17 [Slide.]

18 The purpose of my talk this afternoon is for the
19 panel members to consider this device for future registry or
20 trial, non-randomized, and the reason for that, the options
21 that are available to our patients, because we will not be
22 able to randomize against surgery, that's one; second,
23 because of the superb result that we have been achieving
24 with this device outside the United States. This is the

1 Amplatzer duct occlude. It is a mushroom shape or cone
2 shape. It has a retention disk here. And this is where we
3 will screw or attach the device to the cable delivery. So
4 this is a retrievable, repositionable device. You have
5 total control of the device until you release it. And
6 inside the material here, there is a polyester patch to
7 enhance thrombogenicity and the clotting to close the
8 ductus.

9 This device was invented by Kurt Amplatzer at the
10 University of Minnesota, and he demonstrated the efficacy
11 and safety of this device in a canine model of a [inaudible]
12 pulmonary graft.

13 [Slide.]

14 Now let me present and share with you our initial
15 clinical data outside the United States with this device.
16 Twenty-four patients underwent an attempt to close their
17 ductus using the Amplatzer duct occlude. Their median age
18 was 3.8, and their median weight was 15.5 kilograms. The
19 mean PDA size was the larger size, at 3.7 millimeter, and
20 the Qp:Qs, if you will believe this, because as you know,
21 measurement of Qp:Qs in patients with ASD or PDA is flawed
22 with errors, was 2.2.

23 [Slide.]

24 The protocol is very simple. Routine right and

1 left heart catheterization. No heparin administration. A
2 descending angiogram for the ductal and [inaudible] as they
3 are formed. Then we choose the proper size device to close
4 the ductus. Then we repeat the angiogram to assess our
5 results, and these are slides to show you the protocol.
6 Obviously, this is a large ductus. Again, this is a 5.7
7 millimeter in an 11-month-old baby. This is the [inaudible]
8 sheath crossing the ductus, then opening the retention disc.
9 And prior to the device release, similar to the duct
10 occlude, we performed a descending angiogram just to assist
11 the positioning of the device before we release. Up to this
12 second, the procedure is totally reversible. If we don't
13 like what we see, we can retract the device inside the
14 sheath and just start all over.

15 [Slide.]

16 Then you perform your angiogram, immediately after
17 the trace residual shunt at the end, through a forming
18 [phonetic] through the device itself. And within a few
19 minutes from the procedure, there was complete closure rate.
20 This baby was brought back for repeat cardiac cath to assist
21 his pulmonary artery hypertension because this baby had mean
22 [inaudible] of 46 millimeters, and at the one-month follow-
23 up, there was complete closure of the ductus, with
24 normalization of the PA [phonetic] pressure.

1 [Slide.]

2 This diagram summarizes our results. Twenty-four
3 patients were taken to the cath lab in an attempt to occlude
4 their ductus. One patient, the device was opened in the
5 correct position, but the prototype which was used in that
6 patient was 10 millimeters in length, and obviously, 10
7 millimeters in length when we performed the angiogram in the
8 aorta, the device was protruding. So before we released the
9 device, we took the device out, and we implanted a coil with
10 complete closure. So this patient, we did not implant the
11 device.

12 The other 23 patients, the device was successfully
13 implanted. In seven, there was immediate complete closure,
14 and in four, there was a trace residual shunt at the end,
15 and two patients with a small shunt. However, within 24
16 hours from the procedure, all 23 patients had complete
17 closure, all finished one-month follow-up, and all finished
18 a 3-month follow-up, and as a matter of fact, two of them
19 finished one-year follow-up still with complete closure of
20 the ductus.

21 There were no complications encountered during or
22 after the procedure.

23 [Slide.]

24 Fluoroscopy, as Dr. Ringel mentioned--the median

1 fluoroscopy was 13.5 minutes, and this is again to reflect
2 our learning curve, because this was our earlier experience
3 with it, with a range of 6.3 up to 47 minutes. However, the
4 impressive thing is the procedure time with a median of 60
5 minutes and again with a range from 36 to 185 minutes for
6 the learning curve.

7 [Slide.]

8 The follow-up now is more than one year, and so
9 far, no SBE, no delayed migration, and no thrombi-embolic
10 episodes and no wire fracture.

11 So 100 percent of the patients have complete
12 closure within 24 hours of the closure.

13 [Slide.]

14 Therefore, we can conclude that this device is at
15 least in the short term as effective and safe for closure of
16 the PDA, similar if not better than surgical closure.

17 Therefore, I would like to propose to the panel to consider
18 this device for future study, not in a randomized fashion,
19 but simply to have a registry. However, we have other
20 options that we can discuss if a registry is not possible.

21 But given the fact that we have at least two
22 option modalities available to the patients, the cords
23 [phonetic] and the [inaudible], it is very hard for us to
24 randomize against surgical closure at the same time.

1 Thank you for your attention.

2 DR. CURTIS: Thank you.

3 Why don't we just go ahead with the other
4 speakers, and then we can ask all the questions at the end.

5 MS. SMITH: Dr. Stuhlmuller, FDA representatives,
6 and members of the panel, my name is Ann Quinlan Smith, and
7 I am the Director of Regulatory Affairs and Quality
8 Assurance at Microvena Corporation, and I have the privilege
9 of introducing three physicians who have been chosen to
10 speak on behalf of an industry consortium consisting of
11 Microvena Corporation, AGA Medical, and Nitinol Medical
12 Technologies, Incorporated.

13 These speakers represent nearly 35 medical centers
14 participating in device clinical trials as well as patients
15 who are being treated for atrial septal defects.

16 The purpose of this presentation is to address the
17 key aspects of a study design for ASDs. The presenters will
18 represent the issues on a broad scale. Details of the study
19 design for each device will vary from company to company and
20 will need to be discussed with their individual FDA
21 reviewers.

22 Study designs for PFO indications will not
23 specifically be addressed by this group since the companies
24 are not far enough along in their research activities or

1 have not gathered enough information to comment in a
2 meaningful manner, and separate PDA interests have already
3 been discussed.

4 Our first speaker is Dr. Charles Mullins, from
5 Texas Children's Hospital. He will discuss issues of
6 randomization. Our second speaker is Dr. Ziyad Hijazi, from
7 the New England Medical Center. He will address control
8 group and endpoint options. Dr. Anir Banerjee, from
9 Children's Hospital Medical Center in Cincinnati will
10 discuss use of echocardiography to assess treatment success.

11 We are pleased to have such a distinguished trio
12 of medical experts representing our viewpoint, and I will
13 now turn it over to them.

14 DR. MULLINS: Good afternoon. Thank you very
15 much.

16 I am Dr. Mullins, professor of pediatrics at
17 Baylor College of Medicine. I have been in the clinical
18 practice of pediatric cardiology for 34 years, 28 of those
19 in an academic position with Baylor.

20 I am an investigator with CardioSeal device, but I
21 have no financial ties. I was provided my air fare and
22 housing here, but no other ties.

23 If I could have the first slide, please.

24 [Slide.]

1 As mentioned by previous speakers, we would like
2 to focus our attention on the secundum ASD indications for
3 this device. We also are in agreement certainly with Dr.
4 Newburger that probably the PFO is going to require a
5 randomization and is a completely separate issue.

6 DR. WEINTRAUB: Excuse me. Could we turn the
7 volume up on the speakers? I cannot hear very well.

8 DR. MULLINS: I won't tell you why I am hoarse,
9 because it might bias the panel.

10 [Slide.]

11 We would like to demonstrate the difficulties of a
12 randomized study with these patients. We propose an outline
13 for what we feel is a scientific, sound study, using
14 prospective and slight retrospective control elements. The
15 exact details of each study will be given by the companies
16 themselves.

17 [Slide.]

18 The whole subject of this panel, I gather, is
19 randomization, and I tried to look that up and find out
20 exactly why we are randomizing. Randomization, a
21 randomized, blinded, controlled study is the gold standard
22 of a pure scientific experiment. It is necessary to
23 determine the effects of unknown variables in two or more
24 arms of the study and to try to eliminate the bias in the

1 results.

2 [Slide.

3 There are some background facts that we would like
4 to present. The majority of the patients in the study are
5 children. They don't get to make the decision. Their
6 parents make the decision about the type of procedure or
7 type of repair or whatever they have. This puts a little
8 extra stress on the parents.

9 The patients and the parents are often very
10 sophisticated about their lesion. They know what an ASD is,
11 and also, they come in or are referred to us with an idea of
12 what type of repair they would like.

13 At the same time, they are very unsophisticated
14 about basic scientific studies--that is, it's hard for them
15 to understand the randomization and putting their child's
16 surgical or device procedure into the hands of pure chance.

17 We are going to grant that there are probably very
18 few unknowns about the standard surgical procedure for
19 closure of ASD. It has been performed, and I will go into
20 that a little bit later.

21 The study, of course, cannot be blinded either
22 prospectively or retrospectively, and there is a small
23 number of patients available for this study of any type.

24 [Slide.

1 There are some questionable issues in
2 randomization. Any intervention for an ASD for a patient
3 who qualifies for these studies is totally elective. It can
4 be delayed a year, 5 years, a decade, with no consequence to
5 the patient. And this is by the inclusion criteria of the
6 patients we are using.

7 As a consequence, there are now four choices for
8 therapy for an atrial septal defect. The patient can go to
9 surgery and have this closed in the standard form. The
10 patient can enter the randomized trial in the United States
11 and take a chance on getting a device versus surgery. The
12 patient can now get on an airplane or a boat, go to Canada
13 or go to Europe, and get one of these devices as a routine
14 procedure. This, of course, selects this out to the
15 affluent patients and does not provide it for the large
16 majority. And the fourth choice is to do nothing; they can
17 wait. And we have patients who fell out of the first trial
18 with the clamshell device which ended 7 years ago. They are
19 still waiting, and they are willing to wait even further.

20 The parents of these patients develop a great deal
21 more anxiety when you tell them, well, you may want the
22 device, or you may want surgery, but we're going to draw
23 straws, flip a coin, or pull something of the randomization
24 thing and take that choice away from you.

1 [Slide.

2 We are giving you the bias that surgery is a known
3 proven technique. We are proposing a device trial to test
4 the device, not to test surgery. Surgical correction is
5 accepted as a standard of care. It has now been performed
6 for slightly over 40 years, and really, in the last 20
7 years, until the new, noninvasive or minimally invasive
8 techniques, it has not been changed, and those minimally
9 invasive techniques have not been proven. So there is a
10 wealth of data in every institution on surgically repaired
11 patients, and there are still some ongoing surgical
12 patients.

13 [Slide.

14 Surgery as a "control" is not a benign
15 alternative. Dr. Yeager said the pain wasn't very
16 important. I doubt that he has tried it. It is very, very
17 important whether we can submit patients to this and say
18 that's not significant. I don't think that's true.

19 There is a scar. Maybe with the minimally
20 invasive, this will be a little more asymmetric scar. You
21 cannot guarantee which of these patients will get terrible
22 keloids and terrible scar formation. There seems to be no
23 scientific way of showing that. And 66 percent of these
24 patients are young ladies, so they are not going to be able

1 to grow hair over the scar as they get older and cover it
2 up.

3 Perfusion risks are real. They don't happen very
4 often, but there are real risks to cardiopulmonary
5 perfusion. There are still occasional episodes of
6 embolization, air or solid material. I heard a recent paper
7 from a neurophysiologist at NIH who pointblank started out
8 saying that going on cardiopulmonary bypass, you lose 10 to
9 15 percent of IQ points. That hasn't been documented too
10 well, but I'd had to think that I'd have to go back on
11 bypass.

12 Convalescence is not unimportant. I do not know
13 what the patients do who get the minimally invasive
14 surgery,k but certainly, when you get a vertical sternotomy,
15 you do not go back to full activity for at least 6 weeks.
16 You cannot even drive a car if you are an adult. If you are
17 a parent of a child, you have to stay home with that child,
18 because the day care centers don't take them with a fresh
19 scar and an oozing wound.

20 There are common adverse events in surgery. In
21 our previous device trials, we were told that giving blood
22 was an adverse event, so any surgical patient who receives
23 blood or blood products, it is an adverse event. Post
24 pericardiotomy syndrome is still fairly common in ASD

1 patients. Effusions are still quite common. Known
2 permanent risks, I'll grant you, are a very, very small
3 percentage, but I don't want to be in that one percent that
4 dies or has a stroke. I don't want to take a chance on
5 getting my other recurrent larynginal whacked on that
6 possibility, or diaphragm paralysis.

7 [Slide.

8 There are some favorable data available on the
9 devices. All three of the devices of the companies that we
10 are representing today have had trials in Europe and have
11 had European Community approval for years. These are on the
12 basis of favorable results on nonrandomized but concurrent
13 trials. There is a low incidence of permanent complications
14 from the device in the use in secundum ASDs.

15 All of these patients do have the crossover
16 possibility to surgery. That's actually a safety factor if
17 you're putting a device in which you can cross over to
18 surgery and have it removed. It's also one of the risks we
19 list in our informed consent of device closure, that yes,
20 we're going to try to close it with a device, but the down
21 side is you're going to have to go to surgery. So it's a
22 favorable anti-risk factor.

23 [Slide.]

24 The problems of ASD device studies. There is a

1 small number of patients available. I don't think it's one
2 in 1,500 live births; it's closer to one in 5,000 live
3 births, maybe 10,000. By the time we randomize these, we've
4 reduced it down to one in probably 20,000. Multiple studies
5 running concurrently, of course, divide up these available
6 patients for device implants.

7 [Slide.]

8 There is a marked pre-selection of the patient
9 population before and during a study that is randomized
10 against surgery. If a patient is offered surgery, there is
11 no randomization--they go to surgery, they are out of the
12 trial. Physicians will often not refer patients when they
13 call and ask if a device is available, and we say yes, but
14 when they get here, after they sign the informed consent, we
15 have to randomize them. Referred patients, once they get to
16 the study, once we talk to them, even if they came thinking
17 they were going to get a device, when we talk about
18 randomization, they drop out. Many patients continue to
19 wait. They just say, "Thank you, we'll come back when you
20 finish the study."

21 And the ultimate suitability or size of the defect
22 is determined after we have randomized the patient. It has
23 to be determined in the cath lab with the sizing of the defect.
24 So even after randomization, we lose patients from the

1 study.

2 [Slide.

3 I have this on sort of a flow sheet here. The
4 patient who sees the family practitioner or the pediatrician
5 is referred either to an adult cardiologist who is not aware
6 of the device, a pediatric cardiologist who is not aware of
7 the device, and they are referred to surgery.

8 There is the pediatric cardiologist who is aware
9 of the device and presents this to the patient. Some of
10 them drop out immediately. Some of them will accept
11 randomization.

12 You get down to the pediatric cardiologist who is
13 doing the procedure, and you ask them about randomization.
14 Some of those again drop out, some accept. You randomize.
15 You lose a few to surgery, or at least to waiting. You then
16 have a very small number of patients. In our experience,
17 it's starting with about five at this level and ending up
18 with one here.

19 [Slide.

20 I think this invalidates our statistical analysis.
21 A device patient can quit the study and switch to surgery at
22 any time. The surgical patient cannot do that. There is a
23 high number of dropout patients randomized to the surgery.
24 In one study, 50 percent have officially dropped out, not

1 scheduled surgery yet.

2 Patients randomized to surgery have actually been
3 known to switch to a different center to try to get re-
4 randomized or to a different device trial.

5 [Slide.

6 I think there is extreme emotional stress placed
7 on parents to put them into this type of an optional
8 therapy. Randomization to surgery results in a marked
9 filtering of the patients and delaying. Actually, we are
10 having a very hard time getting patients into the final
11 phase of the study, both from the referrals in the beginning
12 before the study, in the study, or the withdrawals in the
13 study. The statistical assumptions of the trial become
14 invalid. We think a randomized trial of invasive versus
15 minimally invasive procedures is not possible when the
16 therapy is totally elective.

17 Thank you.

18 I'd like to turn the podium back over to Dr.
19 Hijazi, who will talk about our proposal for a randomized
20 study.

21 DR. HIJAZI: Thank you, Dr. Mullins.

22 Again, I am Ziyad Hijazi, Associate Professor of
23 Pediatrics and Medicine at Tufts University School of
24 Medicine, full-time faculty. And as I mentioned, I have no

1 financial obligations to disclose with AGA, aside from
2 paying my accommodation and air fare coming here.

3 [Slide.

4 So, as we heard, there are two option modalities
5 for treatment of secundum ASD--the surgical closure, which
6 is the gold standard, and the catheter closure of ASD.

7 [Slide.

8 The surgical closure, we all know the history. It
9 has more than 40 years of extensive experience. The
10 approach is usually be a chest incision, and the defect can
11 be closed either primarily by a suture, if it is small, or
12 by a patch which can be from pericardium or dacron if the
13 defect is large.

14 [Slide.

15 The results also are very good, and although we do
16 not have very recent data, all of the data that has been
17 published in the literature indicates that the mortality is
18 very low. The mortality in the University of Alabama and
19 the [inaudible] Hospital combined was about one percent.
20 But mortality nowadays is even less than that, and when I am
21 going to propose for later on, we will use even more current
22 data to compare our results with.

23 The residual shunt rate we admit also is very low,
24 but it is not zero; it is in the range of less than 5

1 percent. This is a famous NIH study. Although, as I
2 mentioned, it is old, still there is incidence of residual
3 shunt, but we will not even compare our device data to such
4 old data. We will compare it to more recent data, and we
5 will talk about how we will do that.

6 [Slide.

7 Therefore, the surgical closure of ASD secundum
8 has little variability, and I would disagree with Dr.
9 Yeager--he showed two papers--one from Columbus, Ohio and
10 one from Saudi Arabia. I don't think that Saudi Arabia is
11 like Columbus, Ohio. The care in the intensive care unit
12 and the technique--and I have been in there, in that unit in
13 Saudi Arabia, for six weeks--is not the same. So we are
14 comparing out data in the United States.

15 Safety, therefore, is very high, with very low
16 mortality. The efficacy rate is very high, more than 95
17 percent complete closure rate.

18 Therefore, I think the panel should not feel
19 compelled to control variability through randomization. A
20 scientifically sound clinical trial is possible without the
21 need for a randomized control group.

22 So, how are we going to do that?

23 [Slide.

24 We would like to propose creating a surgical

1 registry as a control group. This registry could be a
2 collaborative effort from all the industry involved, or it
3 can be individualized to meet each company's individual
4 protocol.

5 [Slide.

6 We can design this registry with proper planning
7 so that we can minimize bias, provide objective outcome
8 measures--and this is very important; we are not talking
9 about subjective measures. We will set guidelines and
10 objective outcome measures, and we will ensure the
11 statistical soundness of the study, and we will allow for
12 meaningful prospective and retrospective safety and efficacy
13 assessments.

14 [Slide.

15 Now, we will propose to limit the surgical cohorts
16 to the clinical trial sites that are involved in the device.
17 But as Dr. Ringel has commented in the past, can that be
18 done outside the clinical trial site? The answer, of
19 course, is yes, as long as you assure that the guidelines
20 and the outcome measures are all the same, with strict
21 criteria.

22 By adhering to the clinical trial size, we can
23 ensure that at least the two treatment groups, the surgical
24 and the device group, will be similar in terms of physical

1 examination, imaging modalities in the same institutions as
2 they will be followed by the same physicians. And,
3 moreover, the data about the surgical cohorts should be
4 readily available in these clinical trial sites for review.

5 [Slide.

6 Now, certain key baseline characteristics can be
7 matched through inclusion as well as exclusion criteria.
8 Obviously, for the device group, certain criteria that
9 relate to stretch diameter and sizing is not applicable for
10 the surgical group.

11 [Slide.

12 Now, on the surgical cohort, we would propose that
13 these patients' defects be closed within 12 months of the
14 IRB approval of the clinical study. And I will explain this
15 in more detail so that we will be very clear on this point.

16 Therefore, by choosing this one-year period, our
17 data will reflect current surgical techniques--not even two
18 years--less than one year from now. And we will emphasize
19 that all of these patients have to have at least one echo
20 pre-closure of their secundum ASD.

21 So this diagram would explain and clarify my point
22 about how far we can go back, because when we talk about
23 historical control, the word itself is not as good, so we're
24 not talking about history, we're talking about current

1 patients. So if we assume that the panel and the FDA
2 approve our protocol for the registry now, by the time we
3 get our IRB, it will be at least December or January of next
4 year. From that time, from December of January, we can go
5 back one year and collect all patients who underwent
6 surgical closure in a sequential manner as long as they meet
7 all inclusion and exclusion criteria. Obviously, some of
8 them will be selected from patients who had surgery maybe
9 last week, so that some of these patients will also have
10 prospective evaluation as they enroll in this study.

11 [Slide.

12 The selection of all of these surgical cohorts
13 will be standardized. This will ensure capture of all
14 retrospective eligible patients in a sequential manner, and
15 thus we will eliminate the fear of selection bias that some
16 of the panel members raised.

17 [Slide.

18 The sample sizes will be determined to ensure the
19 statistical power is valid to analyze safety and efficacy
20 measures described in each company's protocol

21 [Slide.

22 And we will define guidelines for these measures.
23 Therefore, we will create standard guidelines for the data
24 capture, we will create objective outcome measures, and if

1 there is no interpretable echo in any of the patients post-
2 surgical closure after one month from closure--and the
3 reason we chose one month after surgical closure is because
4 we all know that in the immediate post-operative period, it
5 is very difficult to obtain a very good echo from the pain
6 and discomfort that these patients may have. Therefore, we
7 propose to bring them back after one month and obtain a good
8 echocardiogram to assess the results of the surgical
9 closure.

10 By doing this, we will allow for prospective as
11 well as retrospective elements of the trial. And again,
12 this will minimize the bias.

13 [Slide.

14 Now, there are certain outcome measures. Of
15 course, we have safety issues and efficacy issues to compare
16 the device to the surgical group. Let's talk first about
17 the safety issues.

18 Obviously, the major important thing is mortality
19 and major morbidity. We will accept the outcome measures,
20 anticipated and unanticipated, adverse events--for example,
21 mortality, stroke--in both groups, the device and the
22 surgical group element.

23 Also, in both groups, there are some observational
24 safety issues like device arm fracture or pericardial

1 effusion, that we will also have to ensure to include in the
2 study.

3 The assessment in the device group, since it is
4 going to be prospective, will be done by physical
5 examination as well as by radiographic modalities, whether
6 it is x-rays or echocardiograms. For the surgical group, if
7 it was in the retrospective manner, the chart review;
8 however, if the patient is recent, this will also be done in
9 a prospective fashion.

10 The timing of the assessment for safety will be
11 done according to the device protocol, and for the surgical,
12 usually, we will have one successful echo post-surgical
13 closure of the defect. So if you close the ASD now, we will
14 wait more than one month, and then obtain an echocardiogram.
15 If that echocardiogram is successful, we will consider that
16 patient a complete success.

17 [Slide.]

18 The efficacy issues--and here, mainly, we are
19 talking about residual shunt, and the residual shunt will be
20 assessed for both the groups, the device and the surgical
21 arms. Again, there are certain elements involved also with
22 safety. We would also be continuing to monitor the safety
23 issues.

24 Now, the assessment of the residual shunt for the

1 device group can be done by transthoracic echo and, on some
2 occasions, a transesophageal echo can be done if it is
3 included in the protocol; if not, of course, a transthoracic
4 echo will be sufficient in addition to physical examination.

5 However, for the surgical group, the chart review
6 will be performed, and also we will look at some prospective
7 elements in those patients who are recently enrolled in the
8 study by transthoracic echo.

9 On the timing, again, each device has its own
10 protocol, and for the surgical, as I mentioned, we will have
11 at least one post-operative echo after one month from the
12 surgical closure to meet our criteria.

13 [Slide.]

14 To continue on the efficacy assessment, success
15 and failure will be determined at the end of the trial for
16 the device arm. It will be according to each protocol. For
17 the surgical, we will take the last successful echo that
18 they had performed.

19 Now, if we look at some statistical assumptions,
20 doing this approach will clearly favor the surgical arm. We
21 will consider that any time the surgical patient has a
22 successful echo, we will take that as complete success, and
23 that's it, and there is no chance of that patient converting
24 into failure. However, the device group, you can start with

1 success and convert to failure, you can start from failure
2 and convert to success or from success to failure; and from
3 success to failure, let's say that you have a patient where
4 you close their defect completely, and then at [inaudible]
5 follow-up, you do an echocardiogram, and you see a clot or a
6 mass on the device. This will constitute failure.

7 For the surgical arm, as I mentioned, once it is
8 successful, it is successful throughout. There is no
9 converging to failure. And that clearly favors the surgical
10 approach.

11 [Slide.]

12 The current practice for surgery if the patient
13 has successful closure of their defect is that usually, we
14 follow these patients by physical examination and rarely do
15 we perform echocardiograms. However, if the surgical
16 closure was not successful, follow-up will be by physical
17 examination until they improve, or by echocardiogram until
18 they improve, or until they receive a second operation or
19 re-intervention.

20 [Slide.]

21 Again, this approach definitely favors the
22 surgical arm of the group, not the device arm, by using the
23 last available successful echo for the surgical group; also
24 use the last specific device protocol echo for these

1 patients.

2 [Slide.]

3 To minimize the echo bias--some people may raise a
4 question about how are you going to follow this by
5 echocardiography, and Dr. Banerjee will talk later on about
6 the echo. But we are going to create a core lab, an
7 independent core lab, to review all echo, surgical and
8 device patients. They will have standardized measurement
9 scale for the residual shunt, and if there is no
10 interpretable echo post-closure taken after one month for
11 the surgical arm, those patients will be brought back for
12 repeat echo. And in the event we cannot get these patients
13 back for repeat echo, we will grant them complete closure;
14 we will assume they have complete closure. Again, here, we
15 are favoring the surgical arm of the group.

16 [Slide.]

17 The success or failure of the procedure will be
18 determined at the end of the trial. The time for the
19 surgical arm is not important, so we will use the last
20 successful echo on them, irrespective of the time, and we
21 will review the surgical chart for major complications, the
22 need for re-intervention, physical examination for the
23 device, or also the need for re-intervention or major
24 complications.

1 Now let me turn the microphone to Dr. Banerjee,
2 who will talk about echo, and then I will come back to
3 conclude our talk.

4 DR. BANERJEE: Good afternoon, members of the
5 panel, ladies and gentlemen.

6 [Slide.]

7 My name is Ani Banerjee. I am a pediatric
8 echocardiographer with the faculty of Children's Hospital of
9 Cincinnati, and I have no financial interest in any of the
10 companies presenting at this meeting, except that my trip to
11 this meeting was paid for by the Microvena Corporation.

12 [Slide.]

13 Briefly, I will present to you the role of
14 echocardiography for evaluation of patients with atrial
15 septal defect before and after closure.

16 In the present day, echocardiography is the
17 imaging modality of choice of evaluating ASDs both before
18 and after closure. Two-dimensional echocardiography
19 provides adequate visualization of these defects, as shown
20 here.

21 Some of the other echo modalities, namely, color
22 Doppler and contrast echo if necessary, supplement the
23 images obtained by two-dimensional echocardiography and
24 allow us to quantify the degree of residual shunting and to

1 determine the direction of shunting.

2 The measure of shunt volume using Qp:Qs provides
3 suboptimal results by echocardiography due to technique
4 involved. In order to obtain accurate Qp:Qs measurements,
5 it involves very rigid techniques, namely, very linear
6 alignment of the Doppler signal and accurate measurements of
7 valve area. This is often not done routinely in most
8 hospitals because of the lack of optimal results from
9 echocardiography.

10 [Slide.]

11 The echocardiographic equipment that is used in
12 all centers involved in device deployment and surgery is
13 typically state-of-the-art equipment. In other words, the
14 equipment is so good nowadays that it does not lend to any
15 variability among centers.

16 All the echocardiographic studies on patients
17 going for both surgical and device closure is performed by
18 trained and experienced echocardiographers who are
19 accustomed to evaluating these defects before and after
20 closure.

21 They are all accustomed to obtaining standard
22 views of the atrial septum, and this should not impart
23 significant variability between centers.

24 Since these echos in participating centers are

1 performed using state-of-the-art equipment, and since they
2 are read by experienced echocardiographers, variations in
3 these echo procedure are not going to be significant. Due
4 to differences in image quality and patient stature, it will
5 be difficult, however, to use a standardized imaging
6 protocol in all centers.

7 For example, the gain settings that are applicable
8 to a 4-year-old child will definitely not be applicable to
9 an adult. Therefore, the imaging will be similar--
10 standardized protocols regarding gain settings and so on is
11 not a practical approach.

12 [Slide.]

13 The echocardiographic technique that is commonly
14 used to assess atrial septal defects is transthoracic
15 echocardiography. It is preferred both by patients and by
16 the referring physicians alike, namely because it is
17 noninvasive and much more comfortable. It produces
18 excellent images in children. Imaging in adults and
19 teenagers is also good, but occasionally may be less optimal
20 in teenagers and adults.

21 We propose that transthoracic echocardiography be
22 the imaging modality of choice during both surgical and
23 device deployment. However, transesophageal
24 echocardiography will need to be performed when clinically

1 indicated. It is physically uncomfortable. Children may
2 require general anesthesia, which itself has its own
3 complications and drawbacks.

4 However, excellent images are produced by
5 transesophageal echocardiography in most patients, and it
6 will be the technique of choice if the defect cannot be
7 adequately visualized by transthoracic echocardiography.

8 At this point, I would like to mention that you
9 heard Dr. Hijazi talking about the surgical cohort receiving
10 an echocardiogram done in the post-operative period. This
11 echocardiogram will be done by the transthoracic route, and
12 if this transthoracic echo is suboptimal, then the surgical
13 procedure will be considered a success, thereby giving the
14 complete benefit of the doubt to the surgical procedure.

15 [Slide.]

16 The potential for bias in interpreting pre- and
17 post-treatment echocardiograms will be further addressed in
18 two ways. Number one, a core lab will be used in which an
19 experienced echocardiographer who is not involved in any of
20 these device trials will be used. His or her expertise will
21 be used to review and confirm all the findings of others and
22 to provide a consistent interpretation of echocardiograms.

23 Moreover, standardized measurements using a
24 standard scale will be used to quantify any residual shunts

1 in a very consistent manner. For this, we propose the use
2 of the width of the color Doppler jet in millimeters. This
3 is based on the previously studied reports in the
4 literature.

5 Use of these tools to minimize bias provides a
6 controlled interpretation of all of these studies.

7 [Slide.]

8 Therefore, I would like to summarize the role of
9 echocardiography in ASD closure by stating that they
10 equipment in all centers is state-of-the-art, the
11 echocardiographers are all experienced and trained in
12 assessing the atrial septum very well, there are minimal
13 variations in technique involve, and the use of core lab
14 review and standardized measurement scales for residual
15 shunts will minimize the bias.

16 I would like to conclude by stating that the use
17 of standardized imaging, namely, setting actual gain
18 settings, does not offer any significant advantage.

19 Thank you very much, and I will now hand the
20 conclusion of this presentation over to Dr. Hijazi.

21 DR. HIJAZI: Members of the panel, obviously, we
22 are facing a significant problem as pediatric cardiologists
23 dealing with children with atrial septal defects.

24 Obviously, we would love to do a randomized procedure if

1 technically possible or if ethically possible. However, we
2 are facing many dilemmas.

3 First, the number of patients with atrial septal
4 defect is small. The majority of these patients if not all
5 are children, and they are asymptomatic. Therefore, they
6 can wait for many years, even decades, before we subject
7 them to any treatment. And oftentimes the decisionmakers
8 are their parents, so you can imagine the anxiety, the
9 emotional stress that is involved in this process.

10 And these parents know that they have the ability
11 to wait, they have the ability to withdraw consent after
12 they consent to surgery or the device, they have the ability
13 to travel if they have money to Europe to get the device,
14 and nowadays, we have also been seeing that in many centers,
15 if a patient goes to Center A for randomization and they
16 randomize to surgery, they will go to Center B and repeat
17 the same process. This has happened in at least a few
18 patients, so the statistical soundness of a randomized trial
19 is not possible.

20 Also, there are multiple companies vying for the
21 same number of patients. Therefore, our suggestion or
22 proposal for creation of a registry is a viable option and
23 solution to the surgical randomization process.

24 Thank you for your attention, and if you have any

1 questions, you are welcome.

2 DR. CURTIS: I do have one question about the
3 surgical registry that you just mentioned. I can see some
4 of the arguments for it, but clearly, the only thing that
5 puts a patient into the surgical group versus the device
6 group is not what the parents want the children to have. It
7 is not if they come and say "We want the device," they go
8 into that group, and--what--if they don't say anything, they
9 get surgery--I doubt it's like that.

10 There are so many variables in there that I really
11 wonder what kind of a comparison that's going to mean when
12 you get done. You're going to have different sizes of ASDs,
13 different ages of patients, different things that we can't
14 even conceive of right now, so what will it really mean,
15 because it's not just patient/parent preference that's going
16 to get them into one group or the other.

17 DR. HIJAZI: Yes, that's right. Obviously, there
18 will be patients who do not want even to have a device
19 because of the experimental nature of these devices, so
20 there will be some patients still nowadays even in device
21 centers who undergo surgical closure without being involved
22 in the randomization. And when we compare the two groups,
23 the device and the surgical arm, we will take all our
24 inclusion and exclusion criteria and match for all of them.

1 We may require 1,000 patients, we may require 3,000
2 patients, until we meet that end to ensure the statistical
3 soundness of the trial.

4 So we will set the inclusion/exclusion criteria,
5 and any patient who meets these criteria is involved in our
6 study. So it is a difficult issue to undertake, but that's
7 in our opinion the only option that we can at least tackle
8 the problem now with.

9 DR. CURTIS: If you were able to use the device in
10 any patient you wanted to, if there weren't this issue about
11 randomization, and you were able to offer it to everybody at
12 your hospital, how many patients would wind up having
13 surgery?

14 DR. HIJAZI: As you are probably aware, many of
15 the protocols specify size of the defect, and as Dr. Mullins
16 mentioned, the bottom line is the stretch diameter in the
17 cath lab. So even if I take a patient who looked eligible
18 to me by the transthoracic echo to the cath lab, if I go and
19 do the stretch diameter, this patient may not be eligible.

20 So to answer your question specifically, it's very
21 difficult to tell how many patients will be truly eligible
22 and truly will receive the device. So there will be
23 dropouts irrespective of what we do, because the criteria
24 that we have, the bottom line, the size, the stretch

1 diameter, is determined in the cath lab.

2 DR. CURTIS: So it sound like if the patient
3 seemed to meet your inclusion criteria by echo, you'd want
4 to do the device in all of them who agree to it--

5 DR. HIJAZI: That's right.

6 DR. CURTIS: --and the only ones who would drop
7 out would be the ones whom you got into the lab, and it
8 wasn't going to work.

9 DR. HIJAZI: Or those families who don't want the
10 device in their child.

11 DR. CURTIS: So it sounds like a small number.

12 DR. MULLINS: May I address that? I think, yes,
13 the investigators themselves have a bias. We believe in
14 these devices, and I think that's the better alternative.

15 Of all the devices I have put in, I don't think
16 two patients were mine primarily. They are sent to me by
17 another pediatric cardiologist, by an adult cardiologist,
18 most of them outside of our center. So they are sent
19 already prebiased or prescreened, if you will, when I talk
20 to them. There are still patients from within my own group
21 who go to surgery without talking to me or one of the other
22 investigators.

23 The other thing is that on our protocol, before a
24 patient can be included in a study, they have to read and

1 sign the informed consent; it is four pages of all the
2 possible problems you could have with the device as opposed
3 to the one-paragraph consent for surgery.

4 DR. RINGEL: I think this presentation opened up
5 many issues, not just randomization. Do we launch into
6 discussions of this now, or do you want to wait?

7 DR. CURTIS: Well, I think if you have a specific
8 question to ask any of the presenters.

9 DR. RINGEL: I'll start with the randomization
10 issue, then. I was concerned about the suggestion that
11 instead of randomizing patients, that you would then use
12 retrospective analysis of patients. I think you are much
13 more likely to get valid results if you do not limit
14 yourself to the investigating device institutions and do
15 everything prospectively but do nothing retrospectively.
16 Retrospective studies are really a problem, because you may
17 not be looking as carefully for minor side effects, you may
18 not be looking as carefully in the echo lab. There are a
19 lot of things they could miss retrospectively. So I would
20 urge you not to think if your own centers. You are taking
21 such efforts to use a core lab, but you are biasing by using
22 a retrospective study. I don't think I would do that.

23 DR. HIJAZI: Your point is valid. The reason we
24 included the retrospective element is simply for speed,

1 because there are many patients who have had the surgical
2 closure within the last year or so, so we can use other
3 centers, and as long as it is not randomized, we can use
4 other centers to enroll surgical patients who meet the
5 inclusion and exclusion criteria.

6 DR. WEINTRAUB: I think the one advantage of the
7 retrospective is that it does in a sense eliminate selection
8 bias for the future. I had never thought of it that way,
9 but it does.

10 You have obviously thought this out--or at least,
11 I presume. Have you looked at statistical power and have
12 you talked--how many centers are involved?

13 DR. MULLINS: For the CardioSeal, there are 14
14 now. And again, we are whittling down the patients to very
15 small numbers per center.

16 DR. WEINTRAUB: By defining the study group fairly
17 strictly.

18 DR. MULLINS: Yes.

19 DR. WEINTRAUB: Have you done any kind of
20 statistical work on how many retrospective surgical controls
21 there are among the study centers?

22 DR. MULLINS: We have not put that into exact
23 numbers, but that was one of the possible solutions, would
24 be to pool the surgical from--the three different industries

1 have semi-agreed to work together on that, at getting our
2 control for the surgery, to get enough numbers. But I don't
3 know--I'm not a statistician.

4 MS. GOLDSMITH: If I could help out with that, my
5 name is Sherry Goldsmith, and I'm with Nitinol Medical
6 Technologies, and I was involved in helping out with the
7 design issues.

8 In terms of the numbers that are needed, that's a
9 detail that is dependent on each company's protocol. We do
10 have statisticians who are advising us, and the number that
11 would be needed would be generated based on what is the
12 definition of either a difference or what is equivalence.

13 So to come up with an exact number right now, we
14 could not do that, but we could tell you that we could
15 ensure that we could come up with the right number of
16 patients to statistically answer that question.

17 DR. WEINTRAUB: And I guess one final question--
18 you sort of have to look at what the endpoints are--but if
19 you are constructing a control group, you have to construct
20 a null hypothesis, and in a sense, what would be the null
21 hypothesis--the null hypothesis that the device is different
22 from surgery in terms of a higher stroke rate, a higher
23 death rate? How would you look at it? What differences
24 would you look at?

1 MS. GOLDSMITH: We heard one of the speakers talk
2 about what would be acceptable equivalent, and we've heard
3 a rate of between 5 and 10 percent. So if you make an
4 assumption that the device group is equivalent to surgery
5 within that 5 or 10 percent, that does establish what the
6 "n" will be. I can't tell you what the "n" is right now,
7 but it would establish what that "n" is.

8 We have not talked about the 5 or 10 percent.
9 What is that made up of? Is it just residual leak? Is it a
10 combination of safety and efficacy? That's an issue that we
11 still need to discuss today.

12 DR. RINGEL: I saw a whole host of problems here,
13 one of which was that I believe each individual company has
14 a different study design. You're asking us to standardize
15 the comparison to surgery, but are you going to standardize
16 all of your study designs, because I saw that there is, for
17 instance, a difference in what's considered an acceptable
18 residual ASD amongst the groups. Some said 2 millimeters,
19 others said 3 millimeters.

20 Why are we going to standardize part of the
21 protocol, but not all of the protocol? How are we going to
22 analyze all of this?

23 Also, again, you use a core lab to give this
24 appearance of unbiased analysis of echos, but the echo

1 techniques you are going to be using, or the protocol for
2 echos, is going to be different between the surgical
3 patients and the device patients. In other words, you are
4 really stacking the deck against the devices by saying,
5 okay, we're going to accept anything from a surgery patient,
6 but yet one of the protocols has a transesophageal echo at
7 "x" months afterward--I can't remember how many months--but
8 you aren't going to require that for surgical patients.

9 We know you find a lot more residual defects on TE
10 echo than you do on transthoracic. Again, you may be
11 damning the devices by trying to make things easier now.

12 DR. HIJAZI: That's exactly our point. We are
13 giving the benefit of the doubt to the surgical patients.
14 We want to be comparable results with the surgical closure,
15 and this is the challenge. We are saying that any patient
16 who has surgical closure, and if they have had one
17 successful echo post-closure, they are always considered
18 successful. We are always biasing the--

19 DR. RINGEL: But be careful--you may be taking on
20 too hard a task if you now find by TE echo a lot of small
21 residual defects, and you didn't bother doing that in your
22 surgical patients, and if you had, you may have found they
23 also have 2 millimeter defects. Be careful.

24 DR. MULLINS: We've discussed this, and there is

1 another ethical problem of are we justified in doing a TE
2 echo on a post-op patient, particularly if it is a year ago,
3 and they think they are cured; the surgeon thinks and has
4 told them they are cured. You know, we can't hear an ASD
5 that's less than 1.5:1. That's when you start getting your
6 flow rumbles.

7 So the surgical criterion for correction is
8 usually it is closed in the operating room. If there is no
9 residual leak now on TE in the operating room, they're
10 closed. But not many of these people get even routine
11 transthoracic echos in the long-term post-operative, and I
12 don't think any of them get a routine TE in follow-up,
13 certainly not in our institution.

14 DR. BAILEY: If you made the device option
15 available without getting into the randomized trial, could
16 you still randomize a subset of patients? In other words,
17 could you do both things, a registry and a randomized trial?
18 I was thinking particularly if there is a subset of patients
19 who are not candidates for the procedure, it's hard to
20 conceive that you'd go abruptly from that situation to one
21 where everyone would rush out to use the device.

22 DR. HIJAZI: I think the problem that we may face
23 is the sample size because, as I mentioned, three devices
24 and a few centers that are involved, at least currently, and

1 if we want to take a sub-sample size and randomize, the
2 question is--and of course, I will leave it to the
3 statistician to determine that--what sample size we need,
4 and it may be prohibitive to do that simply because of the
5 total number of patients.

6 DR. EDMUNDS: I have to tell you that I think your
7 plan violates every statistical premise that I have ever
8 heard of, and I really don't think you can even seriously
9 talk about statistics with what you propose.

10 Number two, I have to question, if not reject,
11 your hypothesis that you are biasing the study in favor of
12 surgery. I think just the opposite. A patient with a
13 right-to-left shunt--are you going to do a device for that,
14 are you going to send him to surgery, or are you not going
15 to operate? How about in a patient with SPE and an ASD and
16 a regurgitant valve?

17 There a whole lot of patients who, because you are
18 both the gatekeeper and the provider of the devices, you
19 cannot be unbiased.

20 DR. HIJAZI: But the patients that you are talking
21 about--we are talking in our protocol about secundum ASD
22 with left-to-right shunt. No patient has right-to-left
23 shunt in this protocol. We are talking about left-to-right
24 shunt. And we are not talking about SPE with ASD; we're

1 simply straightforward--left-to-right shunt, ASD that meets
2 certain criteria.

3 DR. EDMUNDS: But Doctor, nevertheless, you are
4 both the provider and the triage officer. You determine
5 which limb the patient goes. That person is not independent
6 of the study, but if you really are going to do it your way,
7 he has to be.

8 DR. HIJAZI: But as Dr. Mullins mentioned, all of
9 these patients come referred to us, so we don't go out and
10 look for them and say we want to put devices in them. As a
11 matter of fact, we have a family here that is involved in
12 the randomization plan that we have, and they can speak to
13 that. So these patients come referred to us with the idea
14 of a device.

15 DR. EDMUNDS: I realize that, but I think we
16 should probably set aside the myth that you are doing
17 anything that has statistical inferences.

18 DR. HIJAZI: But the same thing--if you want to do
19 a truly randomized clinical trial, we have seen with the
20 flow chart that Dr. Mullins showed that there is a dropout
21 at every level of the trial. By the time you get to the
22 device, you have maximum one-fourth of the patients. So on
23 what basis can you--

24 DR. EDMUNDS: I understand that, sir. I just want

1 you to realize that you cannot have statistics when you have
2 such a problem.

3 DR. CURTIS: I don't want this to go back and
4 forth like that. I think you're making an excellent point.
5 There will always be some subtle reasons why a patient might
6 be referred to surgery, or you may not think you are going
7 to get the optimal outcome, even though they fit into your
8 criteria. So the fact that you're flipping a coin
9 invariably is going to introduce some bias there.

10 But rather than get into that, is there a common
11 over here?

12 DR. ZAHKA: Yes. Did you raise the question of
13 the ethics of this randomization trial?

14 DR. HIJAZI: No, we did not discuss the question
15 of ethics because we--

16 DR. ZAHKA: I thought you said you were concerned
17 that it was unethical.

18 DR. HIJAZI: We mentioned that we did not dwell on
19 that, but we would be happy to hear your opinion as a
20 panelist about the ethics of randomizing children who do not
21 make decisions for these trials.

22 DR. ZAHKA: My only concern is how the informed
23 consent is presented if, deep down, you believe that it's
24 not particularly ethical not to offer this to all children,

1 and that that may have impacted on your ability to keep
2 patients in the surgical arm.

3 And I might mention something that Chuck said, and
4 that is that he doesn't want to take the one percent risk of
5 having a stroke at the time of surgery. And I wondered
6 whether families would want to take the one percent risk, or
7 half-percent risk, of having a stroke as a result of a
8 device and how all of that is presented and why there aren't
9 more families, after you present them with the risks of
10 device closure, why they aren't, at least in part,
11 interested in surgery as an option.

12 DR. MULLINS: I think it is instinctive in every
13 parent and every patient to avoid acute trauma, and patients
14 know what surgery is. So I don't think--when you talk to
15 somebody--I mean, you see patients with ASD--they think the
16 child is normal, and all of a sudden, at 5 years, you say
17 he's got a hole in his heart, and it's going to have to be
18 fixed by heart surgery, and they are destroyed. You know,
19 they don't cope with that very well, and they know that
20 surgery is going to cut their child open. They know right
21 off that surgery carries a risk.

22 DR. ZAHKA: But many families don't cope with the
23 concept of the unknown equally well.

24 DR. MULLINS: That's exactly right--but i'll tell

1 you, they get a lot more detail about the risks of the
2 device than they do from the surgeon in terms of the risks
3 of the surgery. As I said, they have to read that and sign
4 it before we can even consider them for randomization.

5 DR. CURTIS: I think we need to move on because we
6 have one more sponsor presentation. We have Dr. Kathy
7 Jenkins from Boston Children's Hospital.

8 DR. JENKINS: Yes, and I have overheads. Thank
9 you for helping me with them.

10 [Slide.]

11 I am a pediatric cardiologist, not an
12 interventional cardiologist, at Children's Hospital in
13 Boston. My center is one of the centers in the low-risk ASD
14 trial sponsored by Nitinol Medical Technologies, but that is
15 actually not the reason why I was invited today.

16 The reason is that my institution also holds an
17 IDE for a different trial, which is using the CardioSeal
18 device in high-risk patients. It is not very similar at all
19 to the types of trials that are under discussion here.

20 I have no financial interest in Nitinol Medical
21 Technologies. Nitinol Medical Technologies is not the
22 sponsor of this trial and does not support it or provide
23 devices for it. And my way here was paid for by Children's
24 Hospital.

1 [Slide.]

2 At the risk of being redundant to some of the
3 earlier parts of the presentation, I'd like to talk about
4 the classical clinical trial design issues and specifically
5 about the role of the FDA in regard to them, and I will talk
6 more specifically about the trials under consideration here
7 at the end.

8 [Slide.]

9 It is fairly obvious that well-designed clinical
10 studies allow one to draw conclusions or make appropriate
11 inference based on data.

12 There are different types of errors in study
13 design which can threaten the validity of the findings of
14 many studies. There are two classic types of validity. One
15 is the internal validity of the study, which is the ability
16 of a study to determine truth within the context of the
17 study. The second type is external validity, or the
18 appropriateness of extrapolating the results of the study to
19 other non-study populations.

20 [Slide.]

21 The FDA finds itself under obligation to make
22 decisions about what products should reasonably be made
23 available to the public and typically does this by
24 interpreting results from clinical trials.

1 In order to facilitate this process, the FDA
2 places requirements on study design, and the primary purpose
3 of this is to assure the internal validity of the studies.

4 Based on the findings of the studies, the FDA then
5 makes a judgment about whether a treatment option should
6 reasonably be made available to the American public, usually
7 by comparing the alternative to other possible ones which
8 are available. In this regard, the FDA is functioning
9 similarly to many well-versed clinicians who guide their
10 families to make similar treatment decisions by comparison
11 various therapeutic options. And the FDA, similar to
12 clinicians like myself, is limited by our current state of
13 knowledge in our field.

14 Lastly, the FDA restricts the labeling of products
15 to prevent the public from generalizing the findings to
16 populations that were not study, and in this way, the FDA
17 controls the public's interpretation of the external
18 validity of the study.

19 [Slide.]

20 I think that this is the process that the FDA is
21 currently requesting some assistance with, and when I looked
22 at the questions that were presented in my panel pack that
23 were under consideration today, which I think everyone is
24 familiar with, I think the parts of the process that are

1 specifically under discussion here are how to protect the
2 internal validity of the particular trials under
3 consideration and in addition, to some extent, how to deal
4 with the current limitations of knowledge or state of
5 knowledge of this field in general.

6 I think the FDA has actually done a better job
7 even in those academic centers of understanding the issue of
8 external validity of studies because of limitations in
9 labeling.

10 [Slide.]

11 As we have heard many times today, the two major
12 threats to the validity of most trials are bias and
13 confounding. Bias occurs whenever the design or
14 implementation of a study makes it more likely that the
15 study will yield a particular result. There rare many types
16 of bias, and many of them have names, some do not--selection
17 bias, ascertainment bias, treatment assignment bias, outcome
18 assessment, and misclassification.

19 Confounding is more complex, but confounding
20 occurs within the context of a study when the effect of one
21 factor on an outcome is wrongly attributed to another
22 factor, typically, the treatment.

23 [Slide.]

24 The best way to protect a study from most forms of

1 bias and confounding is to conduct a randomized blinded
2 controlled clinical trial. It is important to understand
3 which aspects of protection are provided by each of these
4 features.

5 Randomization primarily protects a study from
6 confounding by assuring that the two groups are similar in
7 every way except for treatment.

8 Blinding primarily protects studies from bias,
9 particularly bias in outcome assessment.

10 And the presence of a control group assists
11 considerably with interpretation.

12 [Slide.]

13 Studies differ quite remarkably in their degree of
14 risk in terms of threats to their internal validity, and
15 study designers make decisions about how much protection to
16 provide within certain study designs based on what type of
17 threats they anticipate.

18 Studies can be protected from threats to their
19 validity in many ways. It is not necessary or even possible
20 to conduct a randomized blinded controlled clinical trial in
21 every case.

22 [Slide.]

23 In terms of the specific regulatory trials under
24 discussion here for ASDs, PDAs, and PFO closures, the major

1 problem with these trials is that the major threat to their
2 validity is bias, and blinding cannot be performed.

3 Also, in all cases, alternative reasonable
4 treatment strategies exist, although the field does not
5 possess complete information about their safety or
6 effectiveness.

7 I suppose I should include a third factor that
8 isn't on this slide, which is that there are fairly strong
9 patient preferences in regard to some of the treatment
10 options under consideration here.

11 [Slide.]

12 In thinking about these principles in terms of the
13 specific trials under consideration, I would make some
14 general recommendations to the panel when thinking about
15 trial design.

16 First of all, considerable effort should be made
17 to protect the validity of these studies from bias,
18 particularly in outcome assessment.

19 Comparison data or control data should be
20 collected because the results from these studies will be
21 difficult to interpret.

22 I think randomization should be required in
23 studies where the primary concern about confounding is high.

24 I also think that the regulatory trials may not be

1 the appropriate forum to advance the general knowledge of
2 the field regarding effectiveness of treatments.

3 [Slide.]

4 In terms of the specific recommendations that I
5 would make in regard to these three types of trials, in
6 terms of ASD trials, it is my opinion that confounding is
7 minimal if these trial designs are restricted to
8 particularly low-risk cases like the trial designs that I am
9 most familiar with.

10 I do believe that alternative reasonable
11 treatments exist for this condition and that the major
12 threat to the study is bias.

13 The design that I would propose would be a
14 nonrandomized design using concurrent surgical control data
15 with major protections against bias.

16 I believe the outcome assessments can be
17 descriptive in nature and that the panel will reasonably be
18 able to make a determination about whether these devices
19 should be made available as a treatment option for patients
20 and that clinicians will also be able to understand the
21 results from these studies, as they do from many studies, in
22 helping families choose options.

23 In terms of the PDA studies, I believe that
24 confounding by the size of the PDA itself is likely based on

1 the data from the original Rashkin trial.

2 I do not see any other major sources of
3 confounding if, once again, these studies are restricted in
4 entry criteria to particularly low-risk cases.

5 Clearly, multiple alternative reasonable
6 treatments exist, and once again, bias is the major threat.

7 I think that the proposed design could be either
8 randomized or nonrandomized. If the nonrandomized design is
9 chosen, then adjustment for size of PDA must be included in
10 the analysis phase.

11 I think that, once again, concurrent control data
12 using both coil embolization and surgical control data
13 should be used, and once again, the studies need to be
14 protected considerably against bias in outcome assessment.

15 In terms of PFOs, which has not been a major
16 discussion thus far today, I think that in this particular
17 study, confounding is a major threat since the risk for
18 stroke is complex and multifactorial.

19 I do think that alternative reasonable treatments
20 exist, and obviously, bias is still a threat.

21 For this particular group of trials, I think that
22 a randomized design would be necessary and essential, with a
23 comparison to anticoagulation. I would anticipate in these
24 studies that there will be treatment failure and would plan

1 on what should be done with them in the design phase.

2 And once again, as with all of these studies, I
3 think the major protection to the study needs to be in terms
4 of bias in outcome assessment.

5 Thank you very much.

6 DR. CURTIS: Thank you.

7 Questions?

8 DR. BRINKER: Yes. Your center is involved in the
9 study of the clamshell device, or the old barred device in
10 the high-risk group?

11 DR. JENKINS: CardioSeal--well, the high-risk
12 study was original done with original barred clamshell-2,
13 new design inventory, and is currently being conducted with
14 CardioSeal inventory--the high-risk trial.

15 DR. BRINKER: All right. Do you know when the
16 initial clamshell device was first placed in humans in this
17 country?

18 DR. JENKINS: I think it was 1985.

19 DR. BRINKER: Nineteen eighty-five. Do you know
20 why it has been 12 years, and we still don't have a device
21 for use? Do you have any idea why that is true in this
22 country?

23 DR. JENKINS: Do I have any idea why it is that
24 there is no device available on the market? Is that what

1 you're asking?

2 DR. BRINKER: Well, why a device initiated in
3 1985, 12 years ago--1989; I'm sorry--is still not available.

4 DR. JENKINS: I'm not very familiar with all of
5 the data on all of the devices. I am very familiar with the
6 clamshell-1 device.

7 DR. BRINKER: Right, and why is that not
8 available?

9 DR. JENKINS: I think the clamshell-1 device is
10 not available to the American public because the trials were
11 seized after the detection of device arm fractures.

12 DR. BRINKER: Right. And the second device?

13 DR. JENKINS: The second device--the CardioSeal
14 device?

15 DR. BRINKER: No, no--the modification of the
16 initial clamshell.

17 DR. JENKINS: The modification of the initial
18 clamshell, which is the clamshell-2 device, is the same
19 device as the CardioSeal device.

20 DR. BRINKER: And why is that not available yet--
21 well, I know there has been a change in company, but my
22 point is that this technology has been around for a long
23 time. Part of the problem is that there was never an
24 adequate study to determine its validity for years, and part

1 of the problem is also that this device was found to have a
2 defect in it, which may or may not be an important issue,
3 and part of the problem was that the information garnered
4 from the clinical study was not adequate to analyze for a
5 variety of reasons.

6 And what we're trying to do with some of these
7 discussions is to limit the opportunity to go through a
8 study and have at the end of that study a situation in which
9 we can't come to grips with whether the device is safe and
10 effective for use in the way it's being labeled.

11 DR. JENKINS: Well, I have an opinion about how it
12 was that that came to pass, which I can share with you--

13 DR. BRINKER: Okay.

14 DR. JENKINS: --which is that I think that the
15 original child designs included many non-low-risk patients;
16 that the problem with what to do for those patients really
17 was never adequately addressed in the studies, the way that
18 they were performed or the way they were conducted.

19 This predated any of my involvement in these
20 studies, but that is my opinion. And I believe that the
21 high-risk trial, which is a trial which is designed to
22 address these particularly unusual uses that clinicians find
23 valuable for these products has made it possible to have the
24 low-risk trial designs be much more tight in terms of their

1 selection criteria, and it's the basis of that tightness in
2 selection that leads me to believe that confounding is not
3 particularly high.

4 When compared with the very real patient
5 preferences, the question is given that we would all agree
6 that there are strong patient preferences, my particular
7 belief about that is from counseling families as a pediatric
8 cardiologist--there are strong patient preferences. The
9 question is whether the benefits to a randomized design in
10 terms of a protection against confounding factors which may
11 be unmeasurable and not adjustable in the post hoc analysis
12 warrants inclusion of a randomization.

13 DR. BRINKER: Well, do you believe if we had had a
14 randomized trial earlier on that this situation would have
15 been laid to rest, or is it--

16 DR. JENKINS: I don't, because I believe that one
17 of the major problems with those studies was that many of
18 the indications were not the indications that were the
19 purported indications for the trial. Approximately a third
20 of the data or more was not a purported indication for the
21 trial, and that third, I'm not sure--I suppose you could
22 have randomized that third, if that's what you're asking,
23 but I don't think that that was the problem. I think the
24 problem was that the entry criteria for the trial were not

1 the study group at the end of the trial.

2 DR. CURTIS: I'd really like to move ahead now
3 unless it's really pressing.

4 There is one letter we're going to have read into
5 the record.

6 DR. STUHMULLER: At this time, I need to
7 introduce a letter for the record from Dr. E.B. Sideris,
8 M.D., from Amarillo, Texas.

9 To summarize several points in this letter, Dr.
10 Sideris indicates that he has been a sponsor-investigator
11 for the buttoned device since 1991. Regarding atrial septal
12 defect closure, he feels that historical controls matched
13 for defect size and type, patient age, weight and several
14 other parameters should be used. He feels that randomized
15 studies are inappropriate for this purpose.

16 Regarding small PDA and occlusion of patent
17 foramen ovale, he agrees that prospective randomized trials
18 should be completed.

19 Regarding safety and efficacy measures, he feels
20 that his safety and efficacy measures are adequate. He
21 utilizes echocardiographic evaluation and feels that the
22 addition of data safety monitoring committees or core labs
23 would add minimal benefit to his study design.

24 DR. CURTIS: Thank you.

1 We are running behind schedule, so we are going to
2 move ahead to the open public hearing now.

3 I received a request from Dr. Mavroudis to go
4 ahead, because he has a commitment after this panel session.
5 He is representing the Society for Thoracic Surgery.

6 DR. MAVROUDIS: Thank you very much. That's nice
7 of you.

8 Getting to the point, I think the question we are
9 all looking at and trying to answer today is should the
10 prospective randomized controlled clinical trials be
11 required to compare the outcomes of surgical therapy versus
12 invasive catheter therapy regarding or relating to patient
13 ductus arteriosus closure and atrial septal defect closure.

14 As a practicing cardiac surgeon and a
15 representative of the Society of Thoracic Surgeons, the
16 short answer is yes, and may I use the next 7 or so minutes
17 to support that as best I can.

18 As a matter of analysis, there are, of course,
19 many ways to address this issue which include the use of
20 historical data, both favorable and unfavorable; the use of
21 uncontrolled concurrent data from different institutions--
22 that is to say, Institution A does surgery, and Institution
23 D does catheter devices--or the use of prospective
24 randomized controlled clinical trials at many participating

1 institutions, which of course is the question today.

2 First, I'd like to address PDA closure if I may.

3 Perhaps the most favorable risk-benefit ratio for all
4 congenital heart operations is ligation and division of
5 isolated patent ductus arteriosus. This relatively simple
6 operation with a limited complication rate frees the patient
7 from the lifelong potential of complications of pulmonary
8 hypertension, congestive heart failure, bacterial
9 endocarditis and ductile aneurysms, and we have all known
10 about that.

11 The introduction of percutaneous transcatheter
12 ductile closure devices and video-assisted thoracotomy
13 techniques have changed the scope of PDA closure, leading us
14 to this hearing.

15 In September of 1994, we published a paper, "46
16 Years of Patent Ductus Arteriosus Division," at Children's
17 Memorial Hospital in Chicago, which was quoted today a
18 couple of times, and we did this to set the historical
19 surgical standards for PDA closure. So from 1947 to 1993--
20 which was the designated time of the study--all patients,
21 1,108 patients, underwent PDA closure, and there were no
22 deaths, the complication rate was low, and it is a matter of
23 record.

24 The emerging alternatives have had variable and

1 improving results, and these are in contrast to what has
2 gone on today with ligation and division of patent ductus
3 arteriosus, which has a minimal amount of blood transfusion,
4 a very low complication rate, a 2-day hospital stay, and
5 with a mortality, of course, approaching zero.

6 The emerging alternatives, however, early on
7 showed a residual patency rate that was not insignificant,
8 not insignificant blood transfusion requirement, and notable
9 complication rates, sometimes requiring surgery, because of
10 device embolization, arterial thrombosis and sepsis.

11 The percutaneous transcatheter coil occlusion
12 device has had a better record, with more favorable
13 occlusion rates, fluoroscopy times and complication rates.
14 Important questions, however, still remain and remain
15 unanswered. What is the incidence of device-caused
16 endocarditis? There has been at least one case of
17 endocarditis that has been encountered. What will be the
18 natural history of a hemodynamically insignificant residual
19 shunt after coil occlusion? We do not know that.

20 What is the incidence of femoral vessel
21 complications due to transcatheter techniques? We don't
22 know that.

23 What is the incidence of distal clot embolization
24 when the tail of the coil protrudes into the aortic lumen?

1 We have some information on coil occlusion of collateral
2 vessels that show that there are minimal problems with that,
3 but we don't know that for ductus arteriosus.

4 To be sure, these questions can be answered
5 somewhat by historical controls which might compare the
6 results from different institutions, from different time
7 periods, with different procedural practices. It seems to
8 me that these are the kinds of problems and questions that a
9 prospective, randomized trial could answer.

10 Surgical therapy for PDA closure has been proven
11 to be highly effective. Historical controls, while
12 illuminating, do not reflect the modern technical and
13 anesthetic improvements. A well-designed two-armed study
14 involving traditional surgical ligation division and coil
15 occlusion ought to answer these kinds of questions that have
16 been raised.

17 Let me go to ASD now, if I may. Although the
18 issues are quite similar, I would like to address the
19 comparative therapeutic modalities of surgical ASD closure
20 and transcutaneous transcatheter ASD device closure.

21 There have been many historical surgical reports
22 showing the efficacy of ASD closure which document a minimal
23 recurrence rate--that's less than .6 percent--and a minimal
24 mortality rate--and that's less than .4 percent.

1 Our unpublished review of 212 consecutive cases at
2 Children's Memorial Hospital in Chicago who had an osseum
3 secundum ASD closure from 1985 to 1995 compares very
4 favorably to these reports. All of our patients had median
5 sternotomy bicable cannulation and aortic cross-clamping.
6 There were no deaths, no re-operations for bleeding, no
7 neurologic complications, and no patients with
8 mediastinitis. Four percent had minor complications which
9 included post-cardiotomy syndrome, pleural effusions, atrial
10 arrhythmias and pneumothorax. All patients had a post-op
11 echocardiogram--all of them--and none had residual atrial
12 shunts.

13 The ASD occluder devices have had variable success
14 rates with anecdotal reports of strut fracture, resultant
15 transient ischemic attacks, failure to endothelialize, and
16 device embolization. The 1993 report by Perry and
17 associates using the locked clamshell devices reported an 85
18 percent ASD closure rate and described strokes in two high-
19 risk patients out of a total of 150 patients. Latz
20 [phonetic] in 1996 reported excellent midterm results in 31
21 patients, although device arm fracture occurred in 85
22 percent of those.

23 Prewit [phonetic] in 1992 reported on a patient
24 who developed transient ischemic attacks after a clamshell

1 device placement and, on exploration, the device was found
2 to be poorly endothelialized and a cause of the TIAs. The
3 patient did not have TIAs after traditional ASD closure.

4 Agerwal [phonetic] in 1996 reviewed the published
5 reports of the various ASD closure devices and associated
6 complications and described a personal experience of three
7 failures with a DOS angel wings device, resulting in device
8 retrieval and surgical ASD closure.

9 It is quite clear that percutaneous transcatheter
10 ASD closure devices can be associated with significant
11 complications. It is also quite clear that technological
12 advances may result in better patient selection and improved
13 outcome. The best way to prove the comparative to efficacy
14 is with a randomized prospective clinical trial. The
15 important comparative discriminating factors include
16 incidence of complete closure rate over a defined time
17 period, incidence of transient ischemic attacks or stroke
18 over a one-year period, and complication rates referable to
19 surgery such as wound infection and so on, and complications
20 referable to catheterization such as device embolization and
21 femoral vessel complication.

22 Dr. Curtis, I wanted to mention two things that I
23 think went unanswered, and that is when you described if the
24 failure of the ASD occlusion device occurred, we can always

1 do surgery. Yes, I think that is right; one could always do
2 surgery. I want to point out, however, that this device is
3 a little larger than the ASD, that is does cause a reaction
4 there. And then one takes that out, one gets very close to
5 the conduction system and the atrial ventricular node there.
6 So although it hasn't happened, I have taken one out, and I
7 have seen the result of the intense fibrous reaction around
8 it, and I can see that if you do 50 of them, you will have
9 heart block in a certain significant number of them; I am
10 quite sure of that.

11 So I think that to say that it is a simple thing
12 to go back and do it, I think is not very simple, and ditto
13 for the patent ductus arteriosus. One would have to dissect
14 the entire aorta, arch of the aorta and the pulmonary artery
15 in order to clamp this, probably clamp it above and below
16 the ductus arteriosus, a period of ischemia for the kidneys
17 and so on, to have a safe outcome in that regard.

18 So I think that while the first operation is
19 relatively easy, the second operation is not.

20 I would like to thank the panel for allowing me to
21 speak to you. I can answer any question if you like. Thank
22 you very much for allowing me to be first.

23 DR. CURTIS: Go ahead.

24 DR. RINGEL: I just have one question. For the

1 things that you suggested need to be followed, and I would
2 agree--post-op infections and complications after the
3 patient leaves the hospital from surgery that you might not
4 be able to get by retrospective study, complications from
5 occluder devices and all that--I can understand you saying
6 you need a surgical control group, but I do not understand
7 why you say it has to be randomized.

8 DR. MAVROUDIS: Well, there are a couple of things
9 that you may want to accept or not. First, I think one of
10 you or somebody said that when there is a randomized study,
11 the repair and the therapy tends to get better. I think
12 that if one would pay close attention to the ASD closure and
13 using pericardium and some other things, my guess is that
14 instead of a 2 percent residual rate, there would be a zero
15 percent residual rate.

16 DR. RINGEL: You would do it even if the patient
17 came to you, and you knew you were in the study--

18 DR. MAVROUDIS: Yes.

19 DR. RINGEL: --but it wasn't a flip of a coin;
20 right?

21 DR. MAVROUDIS: So would you if you were treating
22 hypertension or something else.

23 DR. RINGEL: Right.

24 DR. MAVROUDIS: But if you were in a study, you

1 might--

2 DR. RINGEL: No, no--as part of a study, right.

3 DR. MAVROUDIS: --yes--you might--maybe you might
4 pay more attention to the diastolic blood pressure over
5 time. I don't know. I'm just saying--

6 DR. RINGEL: Well, no. I'm saying that's part of
7 the study. The question is randomization. Why does
8 randomization change that? Let's say the patient comes to
9 your hospital and gets to speak to you and gets to speak to
10 the interventional cardiologist, but then the patient makes
11 the choice as opposed to randomized.

12 DR. MAVROUDIS: Sure. I don't know that I can
13 speak very, very--and this is clearly a very difficult
14 problem, and I don't want to be rigid on this. I think the
15 best way to get this study over with and done is to try to
16 do the best we can and maybe even stretch things here and
17 there.

18 But remember--ASD sizes are different; some of
19 them are close to the conduction system, some of them are
20 not. I think that in order to get all these factors sort of
21 on the playing field, the linear playing field, it might be
22 the best way to do this and really get the answer is with a
23 randomized study.

24 I am not a statistician, and I don't know how many

1 would be needed to answer these questions. My guess is,
2 like Hank Edmunds thought, maybe 1,000 or more.

3 But I also would like to make a point that
4 patients get their information from doctors, and patients
5 get their skew on things from doctors and now, I suppose,
6 from the media. You know, I don't necessarily think that
7 coil occlusion is any safer than surgery. You could argue
8 that surgery is much safer than coil occlusion, depending on
9 what other things could be involved, and I think these kinds
10 of things can be told to the families in that kind of way
11 where they are able to make a decision in light of what is
12 true and what is not true, what is known and what is not
13 known.

14 So I think that while someone could be a zealot
15 for one thing and be a zealot for something else, I think
16 it's incumbent on us to try to go through that.

17 DR. RINGEL: But once again, if the parents or the
18 patient are allowed to speak to you and your interventional
19 cardiologist, why can they not then make the decision for
20 themselves? You, I assume, would present a very strong case
21 for why they should have surgery--

22 DR. MAVROUDIS: No. I wouldn't present a strong
23 case; I wouldn't. I can tell you that I wouldn't. I mean,
24 I'm giving you a strong case here of the point that I have

1 to make. It is somewhat a courtroom kind of thing that I am
2 the protagonist for surgery. But if a family comes into my
3 office, I would do what I think is the moral thing and tell
4 them that there are two ways of approaching this, and this
5 is the track record for this, and this is what I believe to
6 be the track record for this, and while the things are very
7 similar, you have got to be careful about this, this, and
8 this over there, and this, this and this over there. That's
9 it.

10 DR. CURTIS: I think the point has been made.

11 DR. MAVROUDIS: Thank you very much.

12 One question.

13 DR. EDMUNDS: I think less is better, but do you
14 really think, given the fact that patients don't like
15 surgery--I think we all can agree with that; I mean, surgery
16 is something that you have to have, not something you
17 particular go out and find--

18 DR. MAVROUDIS: I have 100 technology [phonetic]
19 patients who would--

20 DR. EDMUNDS: --we're not talking about
21 [inaudible]--

22 DR. MAVROUDIS: Fine.

23 DR. EDMUNDS: --okay--do you really think that
24 it's possible to randomize surgery versus an interventional

1 catheter, the fact being that so many patients from the
2 newspapers, the docs, the neighbors and so on, know that it
3 can be done with a coil or a device or something like that--
4 do you really think that we can randomize now between device
5 and surgery?

6 DR. MAVROUDIS: I don't know. I'm sorry. I wish
7 I could tell you, but I just don't know.

8 DR. EDMUNDS: Well, I think there are probably a
9 lot of people with you.

10 DR. MAVROUDIS: I don't know.

11 DR. EDMUNDS: I don't know, either, but I think
12 it's an open question.

13 DR. CURTIS: I think you're right. Thank you very
14 much.

15 DR. MAVROUDIS: Thank you very much.

16 DR. CURTIS: The next speaker is going to be Dr.
17 Marlene Tandy, from the Health Industry Manufacturers
18 Association.

19 DR. TANDY: Good afternoon. I am Marlene Tandy,
20 and I'm with the Health Industry Manufacturers Association.
21 HIMA is a Washington, D.C.-based trade association. We
22 represent medical device manufacturers. Many of our members
23 conduct clinical trials, and therefore they have a
24 significant interest in the methods that are used to design

1 clinical trials.

2 I think we would all agree--and that is what we
3 have discussed today--that the gold standard for any
4 clinical trial design is to have an active, concurrent,
5 randomized control. In this case, it would be open chest
6 surgery. And I think that that's exactly why these trials
7 were started that way, because that is the gold standard,
8 and I think that what's happened all along is that we've
9 wanted to be mindful of how is that actually working, and I
10 think that's why we're back here again to discuss this trial
11 design, because what might be the optimal method of choice
12 or treatment of choice or study design of choice
13 theoretically may not actually prove doable in practice.

14 We think that a good faith effort has been made to
15 conduct the trials with this type of randomized control, but
16 we have heard about some of the significant special problems
17 that have happened that make us at this point have to
18 reconsider how can we realistically move ahead.

19 When you have the dropouts that have occurred,
20 that have been discussed, and you have the patients moving on
21 to different centers, waiting until the child gets older,
22 you end up losing some of the advantages of randomization.
23 The active, concurrent randomization, its two biggest
24 advantages as we have discussed are to really minimize the

1 selection bias, and you maximize the comparability between
2 groups. But with all the dropouts and the shifting around,
3 what ends up happening, as we have said, is that the
4 comparability between groups starts declining, so you end up
5 in a situation where maybe you haven't really achieved one
6 of the advantages of the randomized design that we started
7 with.

8 Also, just the simple accrual of patients, the
9 lack of accrual, makes us think that if we stick with some
10 type of active, randomized, concurrent control, that we are
11 in reality never going to be able to complete these trials,
12 and what benefit would that serve in trying to figure out,
13 gee, are these devices safe and effective compared to some
14 type of surgery.

15 So we are sort of caught between a rock and a hard
16 place here. It's like people recognize that the randomized
17 method isn't necessarily achieving what we want. On the
18 other hand, historical controls have some serious
19 limitations. And I guess any trial design that would be
20 presented, that anybody could stand up here and argue for,
21 any trial design has limitations. Unfortunately, there is
22 no perfect design. So whatever we would come up with, there
23 would be pluses and minuses; it would be open to statistical
24 consideration.

1 I guess where we see the goal is to try to
2 maximize the positives and minimize the negatives of an
3 alternative method like historical controls. And probably
4 the most difficult thing about historical controls, the
5 thing that they are worst at, is the comparability, and that
6 is where we are really struggling is how can we design an
7 historical control method that is going to give enough
8 comparability to the trial, to the investigational
9 treatment, that we are going to feel comfortable with. That
10 is what we are struggling with and that is what we are
11 searching for.

12 I think the sponsors, with FDA and with the
13 panel's advice, are trying to come up with the next
14 generation trial where we would be comfortable enough with
15 the historical controls that are selected and to try to
16 tighten up their comparability and to try to give that a
17 place in this trial design so that we might ultimately be
18 able to collect the data we need to try to assess these
19 differences.

20 It is going to be difficult, but it is something
21 that at least we think is possible to do with everybody
22 working together to try to develop an appropriate historical
23 control model. We are concerned that if we stick with the
24 randomized, active, concurrent surgical model that we'll get

1 bogged down and will not be able to move forward.

2 Historical controls have been around for a long
3 time and have been used in device studies for a long time.
4 sometimes, that has been a good point, sometimes that's been
5 a bad point, and our argument basically is that you really
6 kind of need to tailor the historical controls to the
7 devices being considered and the plans being considered, and
8 that is basically what we're trying to do.

9 So we are hopeful that a method can be worked out
10 to permit historical controls in this case.

11 I want to add one more thing, which is that the
12 device law itself and the FDA's regulations do have some
13 flexibility in them to allow historical controls. That is
14 one reason why we are able to be here today and to even talk
15 about. In the drug world, as all of you who have worked
16 with drug trials have experienced, there is much less
17 flexibility in allowing methods other than the concurrent,
18 active, randomized control, but we think that you are on
19 solid ground to be able to recommend some alternative form
20 of control. And in a regulatory setting like this, which
21 this basically is, we are hopeful that that will offer some
22 comfort to everybody to know that it's possible to design
23 something in addition to what we have now and be on firm
24 regulatory as well as scientific ground.

1 We really appreciate the opportunity to be here.
2 I know we're running behind. I'd be happy to address any
3 questions.

4 Thanks.

5 DR. CURTIS: Thank you.

6 The next speaker is Dr. Thomas Hougen from the
7 American Heart Association.

8 DR. HOUGEN: Dr. Curtis, members of the panel, my
9 name is Thomas Hougen. I am a professor and chief of the
10 Division of Pediatric Cardiology at Georgetown University
11 Medical Center here in Washington. I come before you as an
12 invited speaker on behalf of the Council on Cardiovascular
13 Diseases in the Young of the American Heart Association.

14 I have no financial interest in the Heart
15 Association, and they paid nothing for me to be here today.

16 The committee should also know that I am the
17 chairman of the Efficacy and Safety in Data Monitoring
18 Committee of the CardioSeal clamshell device, from which I
19 receive no financial reimbursement for that. I am an
20 outside consultant for that Safety in Data Monitoring
21 Committee.

22 [Slide.]

23 I'd like to briefly show you some historical data
24 from a longstanding cooperative, multicenter group as listed

1 on this first overhead, which the Pediatric Cardiac Care--

2 DR. CURTIS: Excuse me. I need you to clarify--

3 DR. STUHLMULLER: You are involved with the
4 committee for which study? It just needs to be clarified
5 for the record.

6 DR. HOUGEN: The CardioSeal clamshell device.

7 DR. STUHLMULLER: You're involved with the sponsor
8 investigator study out of Boston Children's; is that
9 correct?

10 DR. HOUGEN: I am the chairman of the outside
11 Safety in Monitoring Data Committee.

12 DR. STUHLMULLER: Right. There are two studies.
13 One of them is the company study, and the other one is an
14 institutional study.

15 DR. HOUGEN: This is the institutional study.

16 DR. STUHLMULLER: That just needs to be clarified.
17 Okay.

18 DR. HOUGEN: This is the high-risk study. Thank
19 you.

20 About 20 years ago, a group of medical centers in
21 the Upper Midwest decided to collaborate to collect data on
22 the surgical outcome of congenital heart disease, and over
23 the last 18 years, they have done this. There are now 41
24 centers that cooperate in this multicenter database which is

1 the largest one in the country, and these centers are listed
2 here for your information. Most of these are small to
3 medium-sized medical centers. I don't think any of them are
4 centers for devices at this time, but they have collected
5 this data and soon will publish a book on some of the
6 outcome, and the next overhead will give you some historical
7 data on some of the lesions that were discussed today.

8 [Slide.]

9 Again, these are small to medium-sized medical
10 centers, and over the last 10 years, surgical outcomes for
11 secundum atrial septal defects in children and adults are
12 presented here. There were almost 2,000 operations
13 representing 7-1/2 percent of the 25,000 operations done in
14 this 10-year period. There were three deaths--one an adult
15 and two children--with a .16 mortality.

16 I bring this up because there may be an absolute
17 mortality that we are going to be faced with in closing
18 secundum atrial septal defects in children. It may reach
19 the anesthetic risk. Lengths of stay are listed there.

20 [Slide.]

21 Some the data that was already presented, I just
22 wanted to mention that the data that Dr. Yeager presented
23 from Columbus Children's Hospital, of these 58 cases at
24 follow-up by echo 4 months after surgical closure of the

1 atrial septal defect, this group found four, or 7.8 percent,
2 with a residual shunt.

3 [Slide.]

4 We have already talked about this study from Saudi
5 Arabia.

6 The next overhead, please.

7 [Slide.]

8 The American Heart Association Council on
9 Cardiovascular Diseases in the Young will publish in
10 December a supplement on interventional devices. In this
11 audience are at least two of the authors of that report. I
12 have copies if the panel would like them.

13 I am showing this because this group of authors
14 from the CBDY looked at indications for ASD devices. It is
15 shown here that there are some anatomic criteria, some of
16 which have been spoken to today. For instance, these are
17 all secundum atrial septal defects with a diameter of less
18 than 20 mm. There are certain other anatomic features that
19 make them favorable for ASD device closure.

20 The second point, conditions in which ASD devices
21 may be indicated--none. But importantly, number 3,
22 conditions in which there is general agreement that the
23 closure devices are inappropriate are listed, including
24 sinus venosus ASDs, primam ASDs, and ASDs that accompany

1 other heart disease requiring an operation.

2 Dr. Mullins indicated that in his flow chart, so
3 many patients are eliminated, and this just supports that,
4 that we are talking about a small group of secundum atrial
5 septal defects that may be amenable for device closure.

6 Next overhead, please.

7 [Slide.]

8 Again, from the Pediatric Cardiac Care Consortium
9 for PDA closures in infants, children and adults over the
10 last 10 years, there were, 1,635 operations in 1,619
11 patients. There were some re-operations. Infants had a
12 mortality of 2.8 percent. Most of those were in the first
13 few weeks of life. However, children, that is, over the age
14 of one year and less than 21 years, out of 1,000 or so
15 operations, one patient died--it was a 14-month-old with
16 complex heart disease. Length of stay is listed. A small
17 number of adults underwent surgical closure with no
18 mortality.

19 Again, there may be a minimal mortality with PDA
20 closure that we will have to accept, although I agree with
21 Dr. Mavroudis, many of the large series have no mortality,
22 and that obviously should be the goal.

23 Next overhead.

24 [Slide.]

1 This is a surgical series of 31 cases published in
2 1991 of ligation, not division, of the duct, and there was a
3 23 percent residual flow at follow-up by echo, and Dr.
4 Mavroudis and others spoke to his data of a 46-year series
5 with no residual flow and no mortality.

6 [Slide.]

7 The next overhead is the CBDY recommendations for
8 criteria for placing devices. These are not coils, these
9 are devices that are not available in the United States, and
10 they are listed. Some of these have been spoken to before--
11 symptomatic PDAs, asymptomatic with continuous murmur, and
12 then some silent ducts. The only indication that maybe we
13 shouldn't close is a silent duct that was incidentally found
14 on an echo for other reasons.

15 A condition in which there is general agreement
16 that closure is not appropriate is PDA with pulmonary artery
17 hypertension.

18 [Slide.]

19 The next overhead lists the indications for coil
20 occlusion, and they are listed here for the PDA that are
21 small. Conditions in which coil occlusion may be indicated
22 is the moderate size duct and so forth, and then there are
23 some other indications for coil closure and some
24 contraindications, that is, large PDAs. This is for the

1 coil.

2 I think those are all the overheads.

3 Very briefly, the benefits of controlled
4 randomized trials have been discussed today. The
5 establishment of safety and efficacy is important. I think
6 that trials that attempt to randomize will hasten approval
7 of these important devices, and I think they will also
8 improve the outcome for both arms of these studies.

9 The design of the trials is very difficult. The
10 designation of trial centers is difficult as is the
11 selection of patients. One assumes that the medical centers
12 are comparable for both device closure and surgery. There
13 has been some discussion about the problems of the parent or
14 patient expectation. The anatomic, physiologic and
15 noncardiac criteria exclude a number of patients, making the
16 trials again more difficult.

17 Patient and parent consent will be difficult, as
18 has been discussed, if travel to a distant medical center is
19 required for a treatment option that is available nearby.

20 Determination of endpoints of treatment most
21 likely should be complete closure of the defect, and should
22 be short, that is, one year, as has been mentioned. Since
23 historical data have shown that late closure of some small
24 residual shunts after surgery or device placement does

1 occur, a waiting period is justified. However, it is unfair
2 and unreasonable to have patients and families wait with
3 uncertainty for a distant endpoint.

4 I would like to summarize saying that the small
5 number of patients with suitable anatomy and physiology for
6 device closure of ASD or PDA poses interesting challenges
7 for the trial design. On one hand, the large body of
8 existing clinical data and physician experience with devices
9 encourages us to proceed as usual. However, treatment of
10 children with devices for a long lifetime requires careful
11 consideration, especially in situations where surgery
12 remains an acceptable choice of care.

13 The Cardiovascular Diseases in the Young Council
14 of the American Heart Association encourages this panel to
15 develop trials that foster the development, application and
16 approval of transcatheter-delivered devices to treat
17 congenital heart disease. I thank you for your time.

18 DR. CURTIS: Thank you.

19 The next speaker is David McCarthy, the parent of
20 a child with an ASD closed by an investigational device.

21 MR. McCARTHY: Good afternoon. My wife Cathleen
22 has joined me, as well as our 6-1/2-year-old daughter,
23 Kelley, who is a little shy to join us at this time.

24 Kelley received the device treatment just very

1 recently--

2 DR. CURTIS: I'm sorry. You have to tell us
3 whether or not you have a financial interest in any of the
4 companies.

5 MR. McCARTHY: Okay. Yes. We were invited down
6 here by AGA, the manufacturer.

7 DR. CURTIS: So they paid your expenses here?

8 MR. McCARTHY: Exactly.

9 DR. CURTIS: All right, thank you.

10 MR. McCARTHY: We'll basically be talking a little
11 bit about our feelings regarding the randomization process
12 in general as it applied to some of the trials and
13 tribulations that we went through from the time we first
14 found out about Kelley's situation.

15 Okay. In November of 1991, Kelley is diagnosed
16 with atrial septal defect. Since she was diagnosed at such
17 a young age, Dr. David Fulton, chief pediatric cardiologist
18 at Boston's New England Medical Center, suggested that we
19 want and see if the hole would close on its own provided no
20 other complications developed.

21 MRS. McCARTHY: It was very difficult for us to
22 hear that our baby had a heart defect and that she would
23 have to undergo open heart surgery if it didn't close on its
24 own. Chances of it closing were very slim, but we held onto

1 that hope for the first couple of years.

2 MR. McCARTHY: By November of 1993, during one of
3 Kelley's annual checkups, Dr. Fulton apprised us of a new
4 device being developed for those afflicted with ASD like our
5 daughter and a relatively new alternative to the traditional
6 surgical technique.

7 At that time, we did express some concern and
8 skepticism about placing something of a foreign nature into
9 our daughter's heart. However, knowing the many risks that
10 can be involved in open heart procedures, we elected to keep
11 an open mind and try to learn as much as we could about our
12 choices as we tried to decide what would be in our
13 daughter's best interest. This was a difficult process.

14 That brings us up to November of last year. We
15 were introduced to Dr. Ziyad Hijazi, the director of the
16 cardiac cath lab. By that time, it became apparent that
17 Kelley's condition would not heal on its own, and a decision
18 would have to be made on how to correct it.

19 During our appointment with the doctor, we were
20 given a visual demonstration of the septal occluder, known
21 to us as the "umbrella device."

22 MRS. McCARTHY: Actually being able to see this
23 device--we held it, we played with it; we put it inside a
24 piece of paper and pulled on it--we were amazed to see how

1 it wouldn't move. The paper did not rip; it just stayed in
2 place.

3 It gave us such an overwhelming feeling that this
4 was something that we could really think about doing for our
5 daughter rather than have to go through the regular surgery.

6 So at that time, Dr. Hijazi recommended that
7 Kelley go through the trans-esophageal echo to determine if
8 she would qualify for this device.

9 MR. McCARTHY: The next month, December of 1996,
10 Kelley underwent the TEE, which revealed that she had two
11 holes instead of just the one, as originally thought. But
12 she still qualified for the device, because the holes were
13 in a treatable area.

14 When we received the results of the tests, we were
15 happy that she qualified for the procedure and would not
16 have to undergo the open heart surgery. Then it was just a
17 matter of time before the procedure was scheduled.

18 Then, in May of 1997, of this year, Dr. Hijazi
19 phoned my wife and informed her of the randomization process
20 that was instituted by the FDA for treatment of ASD
21 closures. Seventy-five percent would have the device, and
22 25 percent would have the surgical closure. The process
23 would involve the choosing of sealed envelopes.

24 MRS. McCARTHY: I was devastated by this. I just

1 couldn't understand how anybody could make that decision for
2 us. We just felt that all decisions for her were being
3 taken away. So, being her parents, we felt it was our right
4 to make that decision and not anyone else's. But during the
5 phone conversation with Dr. Hijazi, we set up the
6 appointment for June 11th in Boston to go in there to choose
7 the envelope.

8 MR. McCARTHY: So on the 11th of June, the
9 randomization began at the cath clinic at New England
10 Medical Center in Boston. We met with Dr. Hijazi and his
11 nurse, Steve, and the envelopes. We were told that we were
12 the first ones to choose from the 20 envelopes, which
13 consisted of 15 device closures and 5 surgical closures.

14 And again, before choosing the envelope, we kind
15 of made known our feelings and our disgust at having to be
16 subjected to this method of determination. so, with
17 apprehension, we went ahead and chose the envelope, handed
18 it to Dr. Hijazi, and he went to open it, and upon opening
19 it, he announced that it read surgical closure. At this
20 point, Cathy didn't take it too well.

21 MRS. McCARTHY: Words could not describe how upset
22 we were at having such a major decision about our daughter
23 being taken away from us. We asked Dr. Hijazi at this point
24 what other options we may still have, and he replied that he

1 could not help us now because Kelley was now on record as
2 part of the randomization. We would have to have the
3 surgical procedure done, or wait for full approval of the
4 device, which would be at least 3 more years, maybe longer.

5 With that, we left, and we went home, very upset.

6 MR. McCARTHY: Upon returning home, I placed a
7 call to the FDA's New England regional office in Stoneham,
8 Massachusetts, just to go on record for what it was worth as
9 being against this policy regarding the randomization
10 process. At that time, I was told that the protocol was
11 generally established by the manufacturer of the device and
12 not the FDA, so any concerns that we had should be addressed
13 to the manufacturer and not to them.

14 MRS. McCARTHY: The next day, June 12th, I called
15 Dr. Fulton to thank him for everything he had done to help
16 us over the last few years and also to discuss with him our
17 unhappiness with the final outcome of everything.

18 I also mentioned the discussion that my husband
19 had had with the FDA the day before. Dr. Fulton replied
20 that it was the FDA that set the protocol and not the
21 manufacturer. We then provided Dr. Fulton with the FDA's
22 phone number so that some follow-up could be done on this
23 matter.

24 We also decided at that point to drop out of the

1 randomization study. By dropping out, we would be eligible
2 for other studies that came along.

3 MR. McCARTHY: However, things started to look up
4 a little bit after that, as in August of 1997, Dr. Hijazi
5 contacted us to see if we wanted Kelley to be part of a
6 special symposium study which would take place in September.
7 This symposium was scheduled to provide a forum in which the
8 doctor could perform the procedure via satellite uplink to
9 an audience of 200 cardiologists gathered at the Boston
10 Marriott. We obviously decided to be a big part of that and
11 elected to get involved.

12 MRS. McCARTHY: On September 10th, 1997, the
13 procedure was performed at Floting [phonetic] Hospital.
14 Everything went very smoothly, and Kelley was released the
15 next day, with no restrictions to her activities after the
16 first 24 hours. After that, Kelley was up and at it, with
17 no incision, no stitching, no pain and no scarring. She
18 acted like nothing had been done. She was playing for her
19 youth soccer team a week later, and here she is with us, six
20 weeks later. If she had had the open heart surgery, she
21 would probably still be recuperating now.

22 We, as Kelley's parents, feel blessed that the
23 opportunity to participate in this September symposium was
24 offered to us, but our hearts go out to the 25 percent that

1 have ASD but are not given the right to make their own
2 choice.

3 We hope that the FDA will reconsider their
4 decision about randomization by not just look at the numbers
5 but at the people that this really affects--our children.

6 Thank you.

7 DR. CURTIS: Thank you.

8 We appreciate everything you have gone through
9 with your daughter. I just wonder, though, from the way you
10 speak, whether or not--apparently, it sounds to me like you
11 felt so strongly about the use of the device and wanting to
12 get it for your daughter--

13 MRS. McCARTHY: At first, we weren't.

14 DR. CURTIS: --okay--but I just wonder--you agreed
15 to randomization, but did you really agree? I mean, did you
16 really intend to go through with it, because you had a 75
17 percent chance of getting the device--was it we'll do it,
18 but if not, we're going to drop out?

19 MRS. McCARTHY: I think we really looked
20 positively that we would get the device, and I don't think
21 we really kept it in our minds that we wouldn't get it. It
22 was just we will have it done. It will be done.

23 You know, you go into it thinking that, well,
24 it'll be somebody else that will get that, not us.

1 DR. BAILEY: Would you have gone into the trial if
2 the odds were 50-50?

3 MRS. McCARTHY: No, I don't think so; I honestly
4 don't. When it was first brought to us, we were very
5 hesitant about this, and for 6 years, it was like a
6 rollercoaster on what to do. And just the thought of the
7 surgical--we weighed both.

8 DR. CRITTENDON: Did you have a chance to speak
9 with the surgeon?

10 MRS. McCARTHY: Did we speak to the surgeon at one
11 time? We have spoken to so many of the different doctors at
12 the hospital that I am not absolutely positive if we spoke
13 to the surgeon himself. We did speak a lot with Dr. Fulton,
14 who is the chief cardiologist. He explained everything to
15 us both ways. He gave us the pros and cons of both.

16 DR. CRITTENDON: And was the process of
17 randomization and why randomization was needed for the study
18 explained to you?

19 MR. McCARTHY: Yes, and we have been educated
20 somewhat in the 2 or 3 hours that we've been here. You
21 know, we tried to educate as much as we could on the subject
22 of it, but we felt that there was a need on our part to try
23 to have our own control as to what we thought would be good.

24 This, almost going into the 21st century, and

1 after learning that much more about this device as time went
2 by, I think it's a real revolutionary type of procedure--and
3 nothing against surgery, but like was mentioned earlier, I
4 mean, if you don't have to have the surgery, why go through
5 it?

6 DR. WEINTRAUB: Do you think that the potential
7 complications were really explained to you in detail?

8 MRS. McCARTHY; Yes. We got pages to read about
9 it, to explain exactly what could happen. But there are
10 complications with everything that you have, and it's just
11 which is more than the other. She will be--which I did not
12 say--she will be watched closely. We do have follow-up
13 appointments. She's doing wonderful.

14 DR. WEINTRAUB: Just out of curiosity, because I
15 think part of our job is educational, how has this last 3
16 hours--or, do you understand the dilemma of the FDA?

17 MRS. McCARTHY: We do--or, I do--I do understand
18 that, but I also think that you also have to take into
19 effect, you know, look at it as a parent and--excuse me--

20 DR. BRINKER: Can I ask you one question? It seems
21 like part of your particular situation was that when you
22 were first introduced to the concept of having this kind of
23 procedure as an alternative to surgery, the issue of
24 randomization wasn't initially brought up.

1 MRS. McCARTHY: Oh, no. We knew nothing about
2 that at all.

3 MR. McCARTHY: No.

4 DR. BRINKER: And I guess you were sort of shocked
5 when you had to hear about this randomization thing.

6 MRS. McCARTHY: Oh, definitely, definitely.

7 DR. BRINKER: Do you think that if you were
8 introduced to this initially with the idea that we really
9 don't know whether one is safer than the other--that this is
10 a new technique, and in order to do this, randomization is
11 necessary from the very beginning--so that you didn't really
12 have your mindset that this is available, and I can choose
13 either one--I want to choose this, but all of a sudden, I
14 have to randomize. If randomization were part of the
15 original concept to you, do you think that that would have
16 made a difference?

17 MRS. McCARTHY: Yes, it probably would.

18 MR. McCARTHY: It would have, but when we were
19 first told about the process--I'm sorry, about the device
20 process--Kelley was only 2-1/2, 3 years old, and at that
21 time, Dr. Fulton made us aware that there were studies being
22 done, you know, that this was kind of like cutting-edge and
23 all that, so that's why we didn't rush into any rash
24 decisions. So we were trying to--and we knew that based on

1 her age, she did have some time, so there didn't have to be
2 any rash decisions.

3 MRS. McCARTHY: But he also told us at that time
4 that at any time, if we wanted to have the surgery, they
5 would do that. They never said to us: Do not have the
6 surgery. They completely left it up to us.

7 DR. CURTIS: Let me ask you--you said you had a
8 big, long consent form to look at about the complications.

9 MRS. McCARTHY: Oh, yes.

10 DR. CURTIS: When you got done, was it your
11 impression that the device had more of a potential for
12 complications than surgery, but it was less invasive, or did
13 you have the impression that surgery was going to be
14 riskier? I mean, how did it all weigh out or add up to you?

15 MRS. McCARTHY: I still felt that the surgery had
16 more risks involved in it.

17 DR. CURTIS: So your impression after hearing all
18 the risks was that surgery was riskier than having the
19 device?

20 MRS. McCARTHY: Yes.

21 MR. McCARTHY: Yes, because you talk about the
22 media that you are exposed to, and that's how people get
23 their information, and I kind of fall into that bracket, I
24 guess, to a degree, because if you watch the PBS specials or

1 some of those Discovery Channel things and so on, you see
2 the visual, graphic nature in which these open heart types
3 of operations are done, and it does get kind of emotional.

4 DR. RINGEL: May I ask, just out of curiosity,
5 were you told that there was a surgical option done across
6 town where the surgeon makes a 3-inch incision, and were you
7 aware that for surgery, two trans-esophageal echocardiograms
8 would not be needed without the additional risk of sedation
9 for the TE echos? Were you aware of those additional factors
10 outside of just the two procedures?

11 MR. McCARTHY: No. I would say if we were--when
12 the time came--okay--we weren't, but probably because we
13 hadn't really made a decision one way or the other as far as
14 which method we were going to go. We weren't given the
15 specifics, really, for the device closure, either, at the
16 very beginning.

17 DR. HOPKINS: Let me compliment you for coming
18 here. This is a pretty formidable group, so you are doing
19 terrifically.

20 MR. McCARTHY: Thank you.

21 DR. HOPKINS: You mentioned that your daughter now
22 is going to be followed closely for the rest of her life,
23 for the rest of her childhood.

24 MRS. McCARTHY: Yes, she will be.

1 DR. HOPKINS: What is your--

2 MRS. McCARTHY; I believe she will be seen in 2
3 months and then again in 6 months and then again in a year,
4 and I believe it will be a year after that--I'm not sure
5 exactly for how long.

6 DR. HOPKINS: And have you been told about the
7 need for antibiotic prophylaxis for dental procedures and
8 those kinds of things?

9 MRS. McCARTHY: No. I know right now, she is on
10 an aspirin a day for 6 months. Does that answer your
11 question?

12 DR. HOPKINS: Yes. Thank you.

13 DR. CURTIS: Okay. Thank you very much.

14 MR. McCARTHY: Thank you.

15 MRS. McCARTHY: Thank you.

16 DR. CURTIS: The last speaker at this part of the
17 session is Dr. Carlos Ruiz, from the Society for Cardiac
18 Angiography and Interventions.

19 DR. RUIZ: Thank you, Dr. Curtis, members of the
20 panel. I want to thank you in behalf of the Society for
21 Cardio Angiography and Interventions for having invited me
22 here.

23 I am a professor of pediatrics and medicine. I am
24 an interventional cardiologist at Loma Linda University. I

1 have no economic ties with any of the companies, and they
2 have not sponsored me coming here. The Society has
3 sponsored me coming here.

4 [Slide.]

5 One of the bad things about being the last speaker
6 of the day is that many of the things that I am going to be
7 saying are repetitive, and unfortunately, I had all my
8 slides made already, so there is nothing I can change at
9 this point, but I can probably add some insights into things
10 that you probably already know as far as the atrial septal
11 defects.

12 The natural history that we all know about the
13 ASD, classical from the paper of Campbell, shows that the
14 majority of patients up to the second decade are totally
15 asymptomatic and have a normal life expectancy up to that
16 point. Beyond that, there is a great incidence of attrition
17 that increases to close to 10 percent in the sixth decade.

18 Next slide, please.

19 [Slide.]

20 We have to understand that this natural history is
21 based on the analysis of predominantly if not all of them
22 symptomatic patients, and the conclusions drawn must be
23 guarded and are not applicable to isolated patients. No
24 data exists that I am aware of on the long-term prognosis of

1 asymptomatic children with ASD.

2 Next slide, please.

3 [Slide.]

4 The closing of ASDs--what are we pursuing with
5 that? Primarily, we must ensure that the patients become
6 symptomatic with advancing age, that the closure in
7 childhood prevents that, and that the closure in adults,
8 that the [inaudible] at that point can arrest the progress
9 of the symptoms and reverse the deterioration that this
10 congenital defect has caused.

11 Next slide, please.

12 [Slide.]

13 You have heard about the success of surgical
14 closure. The surgical closure restores life expectancy to
15 normal, and it is done before the age of 25. Also, there is
16 another paper that shows that if the patients are older than
17 45, that there is essentially no difference in whether they
18 are treated medically or surgically.

19 Now, this, I grant you, is very well-known data.
20 However, there are data contrary to that.

21 Next slide, please.

22 [Slide.]

23 We those two papers, by Sutton and Konstantinides,
24 that both show significant success in improving the quality

1 of life of these patients operated in ages older than 40.

2 Next slide, please.

3 [Slide.]

4 Traditionally, we know that the indications for
5 surgery for closing ASDs has been the presence of a Qp:Qs of
6 1.5:1 with a pulmonary vascular resistance of less than 15
7 units. However, I would probably find not much resistance
8 from any of our surgical colleagues in agreeing that any
9 size ASD today that shows evidence of volume overload is an
10 indication for closure regardless of what the Qp:Qs is for
11 whatever that is worth.

12 Next slide, please.

13 [Slide.]

14 Now, you have seen both studies showing the
15 incidences of complication from the surgery, and I am not
16 going to emphasize again that data. However, one of the
17 things that has not been mentioned by the previous
18 presenters that brought up this data from Galal and from
19 Helps is the fact that 16 percent of those patients do have
20 phrenic nerve damage. Granted, most of them are from
21 patients who have had right-sided thoracotomies and mostly
22 submammary incisions.

23 Next slide, please.

24 [Slide.]

1 Residual shunts have been well-established post-
2 surgery, and in different studies ranging anywhere from 2 to
3 7 percent, have been well-documented both from the clinical
4 standpoint as well as by the trans-thoracic echocardiography
5 studies.

6 However, a recent study presented in Circulation
7 in 1995 shows that when TEE is performed in those patients,
8 29 percent do have residual leaks.

9 Next slide, please.

10 [Slide.]

11 A rational approach to the management of ASDs in
12 adults, in particular those with symptoms, requires a
13 controlled assessment of the relative merits of medical and
14 surgical treatment.

15 Next slide.

16 [Slide.]

17 Therefore, the goal of using devices is primarily
18 to identify and justify the appropriateness of the type of
19 test and test methodologies, in essence to prove the safety
20 and efficacy of these devices, not necessarily to compare
21 with surgery or with any of the different types of
22 approaches there are by surgery.

23 Next slide, please.

24 [Slide.]

1 The testing strategies will need to identify the
2 safety and efficacy of issues, identify the relevant
3 parameters and variables, and identify and justify the study
4 populations that we are going to include in these studies.

5 Next slide.

6 [Slide.]

7 We also heard today what the randomization is, and
8 the purpose of randomizing primarily is to abolish any
9 biases toward any of the results. I agree with everything
10 that has been said today, that the gold standard is
11 randomized trials. However, we need to consider maybe more
12 than one gold standard, and I think that probably that is a
13 hard task that FDA is going to have to look into to come up
14 to similar standards as randomized studies.

15 Next slide, please.

16 [Slide.]

17 Randomization problems are definitely documented,
18 as has been shown by previous speakers today. Patients who
19 do not want the device, who want to go to surgery, will
20 bypass the randomization. Again, most patients will require
21 second party consent, i.e., the parents, and therefore, that
22 brings a component of significant emotional stress. But
23 most importantly, historically, we can document the
24 difficulty of randomized pediatric populations, and the

1 proof of that is the disproportionate percentage of drug and
2 device uses that are currently approved indications in the
3 pediatric population. I invite all of you to look through
4 the PDR as well as at any devices that are currently being
5 used.

6 Next slide, please.

7 [Slide.]

8 We have been using a lot of these devices,
9 actually if not the great majority, as off-label use, and
10 based on the assumption that children are small adults, and
11 I can assure you that there is nothing further than the
12 truth, that children are not small adults.

13 Next slide, please.

14 [Slide.]

15 Referring physicians is another problem. If I am
16 a general pediatrician, and from my reading of the
17 literature, I can look at the results from overseas in
18 European trials and see what sorts of complications and
19 success they have, and here, I have a patient that I have to
20 refer to be randomized, my feeling is that I'm going to hold
21 onto that patient until you finish the randomization, and
22 then I will refer the patient to you, because I do not have
23 any rush to refer that patient.

24 And as was brought up earlier, the fact that a

1 patient can be randomized in Center A does not mean he can
2 go to Center B or Center C to be randomized until they get
3 whatever they feel is what they want.

4 Next slide, please.

5 [Slide.]

6 Therefore, the real options for patients are not
7 only surgery versus device, as we expect to see
8 statistically from the randomized trials, but the reality is
9 that the patients do have the option to wait, and they do
10 have the option to go outside the United States to pursue
11 that device that is not available here.

12 Next slide.

13 [Slide.]

14 Surgical results for efficacy and safety are one
15 of the--I'm sorry. Randomization against surgery--
16 therefore, the surgical results for efficacy and safety are
17 well-established. The lack of significant variation between
18 different institutions as far as results from the surgery
19 and the fact that the long-term use of this approach to
20 close ASDs--all of those make randomization against surgery
21 perhaps not needed for this specific lesion.

22 Next slide, please.

23 [Slide.]

24 As Dr. Hijazi proposed, the study through a

1 registry that accounts for nonbiased, objective outcomes
2 measures and statistically sound design, with retrospective
3 and probably prospective elements of safety and efficacy
4 should probably be a viable alternative to study the
5 efficacy of this device.

6 Thank you very much.

7 DR. CURTIS: Thank you.

8 Is there any specific question from anybody?

9 [No response.]

10 DR. STUHLMULLER: For the public record, I need to
11 introduce a letter from the American College of Cardiology.
12 It is written by Dr. Arthur Garson, who is Vice President of
13 the American College of Cardiology.

14 The main points in his letter are the following.
15 First, he believes that the general premise in clinical
16 research in children should operate by the same principles
17 as clinical research in adults. Randomized clinical trials
18 are the current gold standard for clinical investigation and
19 should be pursued whenever and wherever possible and
20 practical.

21 Regarding the issue at hand today, they propose an
22 alternative study design because they have concerns, based
23 on what they have heard, as to whether it is practical to
24 conduct a randomized study. They feel that it should be a

1 prospective study comparing centers using catheter closure
2 with centers using surgical closure. It should be a case-
3 controlled methodology, with rigid criteria for entering
4 into the study, and that patients should be matched for
5 defect size, age, sex and several other parameters.

6 Regarding safety and efficacy, they feel that
7 standard safety and efficacy measures should be evaluated
8 and that, in addition, complications related to device
9 embolization should be factored into the safety and efficacy
10 analysis.

11 Regarding PDA, they feel that follow-up by
12 transthoracic echo at 6 months is adequate, and efficacy for
13 ASD and PFO closure would be comprised of a transesophageal
14 echo performed at 6 months after the procedure.

15 DR. CURTIS: We're going to take a break now, and
16 we'll reconvene at 4:45 for the open committee discussion.

17 [Recess.]

18 DR. CURTIS: We'll reconvene now. We are
19 obviously pressed for time here, because we have been told
20 that we need to conclude by 6 p.m.

21 Before of that, we have all had some chances to
22 ask questions of the sponsors, and even though I'm sure we
23 all have a few more we'd like to ask, we don't want to
24 short-change the discussion, which is already probably

1 shorter than it should be. So I think what we should do is
2 go around the room and have everybody make some comments and
3 really limit it to no more than 5 minutes--because if you
4 count that up, that's going to take an hour right there.

5 What we need to do before we leave here, if
6 nothing else--and if we get near the end, and we haven't
7 done this, I'll stop, and we'll address it--is we need to
8 give some opinions or guidance to the FDA about the answers
9 to some of the questions they have posed to us.

10 Let's just start to my left with Dr. Hopkins.
11 Please go right ahead.

12 DR. HOPKINS: Thank you.

13 There were just a couple of philosophical points
14 that became apparent to me as we looked at this over the
15 last few hours.

16 First of all, all of us are colleagues, and I
17 would just remind everybody out there that we put on a
18 different hat when we come into this room and join this
19 panel, and we're looking at these issues slightly
20 differently than when we get together at cardiac cath
21 conferences.

22 I think a couple of points became apparent to me.
23 First of all, the pediatric cardiologists and the
24 pediatricians, in effect the people who get to these

1 patients first, cannot be unbiased. It is absolutely
2 impossible. The point of everybody's discussion from the
3 very beginning was that you in effect said you could not be
4 unbiased.

5 That ups the ante a lot than for designing
6 appropriate research criteria to prove what we should be
7 recommending to the patient.

8 Don't forget that we don't need to panic here--
9 particularly in terms of the ASD closure, patients are doing
10 just fine.

11 We have a big, big bite to take out here. There
12 are really four different lesions that we're trying to talk
13 about in one day--the secundum ASD, the PDA, the PFO, and
14 the complex residual septal defect in complex congenital
15 heart disease. The issues, I think,, facing the FDA and the
16 researchers and the clinicians are different for each one of
17 those four, as was brought out today.

18 All of these need prospective trials. To me,
19 randomization is less likely to be feasible or important for
20 the PDA, the PFO, and the complex septal defect, since
21 indications are more driven by patient indicators in those
22 patient subgroups.

23 However, for the secundum atrial septal defect, I
24 think it is an extremely difficult problem. Clearly,

1 prospective studies need to be done. Historical controls
2 need only be condemned. The surgical results are different
3 today than they were 6 months ago, different than they were
4 12 months ago, and certainly different than over the 34
5 years of experience that some of the presenters had.

6 Patients in fact are getting different anesthesia
7 today, are eating dinner the night of surgery and going home
8 the next day. Many of the side effects of the so-called
9 stress of surgery are being ameliorated, and therefore it
10 truly is comparing apples to oranges when you look beyond
11 mortality, which everybody states is very, very low.

12 There are also confounding variables, as Dr.
13 Jenkins pointed out, and biases that are inherent to any
14 study in which indications are part of the randomization or
15 the allocation process. One, of course, is age matching.
16 The difficulty for undergoing the procedure in surgery is
17 different for a 3-year-old than it is for a 15-year-old and
18 certainly for a 50-year-old, and therefore any prospective
19 study must be age matched.

20 It was brought out by a number of the discussants
21 that the size and location of the defect needed to be
22 matched because a very small defect at surgery is sutured
23 shut, larger defects are patch-closed, and therefore, if you
24 are randomizing only large defects for surgery, you are de

1 facto randomizing a different kind of patient.

2 Finally, I am concerned about the patient
3 education in that it was brought out that there is a list of
4 complications that can occur from either device. However,
5 it was clear to me that the patient parents, if you will,
6 did not know exactly what they were trading off. And I
7 think that in fact that is important so that patient option
8 should be fairly presented to the parents. Some parents may
9 prefer to take the choice of a keloid scar formation as
10 opposed to a thermal artery occlusion. Some patients may
11 rather take the low risk of stroke with either procedure
12 versus embolization of the device.

13 It is also apparent, at least with the parents who
14 were in the room today, that they had no idea that they have
15 a device in their child's heart that requires lifelong SPE
16 prophylaxis and that there is a difference in the
17 recommendations by the American Heart Association between
18 having a device in the heart and having a patch closure of
19 an atrial septal defect in which no such prophylaxis is
20 needed after one year.

21 Therefore, in terms of the specific questions from
22 the panel, I would say clear there should be indications for
23 shunt closure that are determined by echocardiography and
24 are as similar as possible to the two arms of the study;

1 that the appropriate controls for trans-catheter occlusion
2 devices for ASD should in fact be surgical, and it should be
3 concurrent and prospectively developed. For patent ductus
4 arteriosus, it should be prospective, but perhaps not
5 randomized. For patent foramen ovale or for the complex
6 lesions, it becomes much more complicated. The patient size
7 of the cohorts is much smaller. But it needs to include
8 perhaps oral anticoagulation therapy.

9 It is not clear to me that true randomization is
10 in fact feasible, but prospective match studies need to be
11 done and, where feasible, I would recommend randomization.

12 The primary endpoint should be the same, and as we
13 brought out in the questioning earlier, the endpoint here is
14 to turn, at least in the ASD closure and in the PDA closure,
15 the child's heart into a normal heart. If you haven't done
16 that with one arm of the study, and you demand that of the
17 other arm of the study, it is clearly a flawed series of
18 presuppositions.

19 Any amount of residual shunting is failure, and
20 the assessment of the amount of shunting should be the same
21 for the multiple arms of the study.

22 The time period is very problematical. The
23 outcome of ASD closure is not known for 40 years, and
24 therefore the gold standard that one is trying to match with

1 the device is one that we won't know for 40 years. But
2 certainly, I think that for patients with the ASD closure,
3 there should be some ongoing registry for a much longer
4 period of time than one year to begin to assess the late
5 outcomes from the insertion of a device into a patient.

6 Thank you.

7 DR. CURTIS: Thank you.

8 Dr. Brinker?

9 DR. BRINKER: Well, I would hate to think that
10 we've lost a golden opportunity to prove one way or another
11 the validity of these devices by clinical trial. But
12 clearly, there is no clinical equipoise anymore on the part
13 of the investigators. I'm not sure there was at any point.
14 So the idea that we try to instill in these kinds of trials
15 is somewhat meaningless now. Investigators are convinced by
16 what they said that not only is an implantable device for
17 the indications listed--except for the PFO, we really
18 haven't heard yet--not only is it hands-down better, but it
19 might be unethical to randomize patients to what they also
20 consider is the gold standard.

21 And I think that is a real missed opportunity,
22 because at one time, there had to be one time in the 9 years
23 that these devices have been floating around where it was
24 reasonable to say that we really don't know whether one is

1 better than the other. And if we do the randomization
2 study, and we tell people that the only way they can get
3 this device is if they go into the study, and that we truly
4 don't know what the risks and obligations are, then this
5 whole thing would have been over. We would have known the
6 results, and we would have been able now to either refer our
7 patients to a device or to tell them that the devices just
8 aren't as good as surgery and that surgery is what they
9 should have.

10 We are going backward a bit in our way of
11 examining regulatory trials. Five or six years ago, we kept
12 seeing trials that were experiential. They were not based
13 on good scientific data. They were basically registries.
14 And many of these trials had trouble getting through panel
15 analysis. Then, we started concentrating more on getting a
16 kind of better clinical study from the get-go, and now we
17 are at a stage where it seems like it may be impossible to
18 get the right kind of clinical study.

19 So where does that leave us? It leaves us with
20 the possibility that 2 years or a year and a half from now
21 down the road, you may be submitting a PMA to the panel in
22 which there is an incidence of 15 percent residual shunt in
23 an ASD of greater than 1.5 percent with a device. We won't
24 have good concomitant data, perhaps, on surgery, but maybe

1 the surgery is zero percent or 5 percent residual shunt, and
2 it won't be a randomized study, and there will be a real
3 argument at the period where this comes to panel again as to
4 what the validity of the data is and how we can make a
5 decision based on the endpoints that were given in a study
6 that is not as tight as it should be.

7 Given that, I think that we don't want to be the
8 last country in the world to accept new technology, and we
9 need to come to some grips with what is feasible in the
10 current day. And I don't think we're going to do it today,
11 between now and 6 o'clock, but I think it is worthwhile to
12 air some of these thoughts, which is probably what is going
13 to happen.

14 I think I would like to get across one thing, and
15 that is that we need to be more adamant and design trials
16 better when newer devices come up so that we are not faced
17 with this again and again and again.

18 Thank you.

19 DR. CURTIS: Thank you, Dr. Brinker.

20 Dr. Bailey?

21 DR. BAILEY: One of the questions that has kept
22 coming up in my mind is the definition of "efficacy." If
23 you accept that surgeons can pretty much close the hole--if
24 you are limited to the interest in what the relative ability

1 of interventional cardiologists to close a hole with these
2 devices, or with each specific device--then I don't think
3 you would need a surgical control group at all. You could
4 just put everybody whom you could enroll into a registry,
5 and you could learn something about the rate of closure, and
6 perhaps the community could decide on a criterion for what
7 is an adequate rate of closure.

8 That's one sort of concept of efficacy.
9 Obviously, that does not get at side effects, complications,
10 and so on. But again, if one could decide on an acceptable
11 level of complications, one could get by without a control
12 group.

13 If you want to make comparative statements, and if
14 your concept of efficacy involves comparison with another
15 standard, a gold standard or whatever kind of standard, then
16 I think there is a quantum different, a qualitative
17 difference, between a randomized study and a prospective,
18 concurrent registry of surgery and devices. Although I
19 think that is a well-meaning idea and perhaps a useful idea,
20 and you can make these registries as large as you want,
21 you'll never really know what the bias is. It's not a
22 question of is there a bias; the question is how big it is.

23 So any inference has that lurking doubt, and I
24 think conscientious people coming from different backgrounds

1 can have very different and well-founded beliefs about how
2 big that bias is.

3 I am not convinced--and I agree that the data show
4 that randomized trials that were done ended up being
5 observational studies, and for whatever variety of intended
6 and unintended reasons, we are not able to convince patients
7 to stay in the trials. I think that that was an unfortunate
8 situation, and I am not sure to what extent that could have
9 been avoided by a different design, but it's not clear to me
10 that some of it, at least, or much of it, could not have
11 been avoided. And I speak as one who hasn't tried to do--I
12 am not demeaning or understating the difficulty of doing
13 such a trial. I can well appreciate the difficulty with the
14 emotional context.

15 In terms of ethics of a randomized study, it seems
16 to me that that is an educational problem to some extent.
17 One way you can look at it is if you are in a randomized
18 study with a 50-50 option, you are guaranteed at least a
19 minimum of or exactly a 50 percent chance of getting the
20 better treatment for you, and that applies no matter what
21 substratum of patient you are in. So if you are a very
22 conservative parent like I am, I might well opt for that as
23 the most ethical strategy for my child.

24 The other aspect of this that keeps lurking for me

1 is the issue that this is an equivalence trial versus a
2 demonstration of superiority, and I'm not sure exactly how,
3 but that does affect the relative merits of randomized
4 trials versus observational studies, and I think we need to
5 think about that and the fact that after all, you are not
6 expecting these devices necessarily to have equal operating
7 performance characteristics to surgery; you just want it to
8 be acceptably close. To me, that does have an impact on how
9 I feel between randomized trials and observational studies.
10 I am not exactly sure how much, but I know that it does.

11 I am not sure of the relative merits of concurrent
12 controls at the same centers in that I would be concerned
13 about selection factors being heightened in that context
14 versus other centers where the people are not competing for
15 the patient in the two arms. And I also really don't know
16 the relative merits of historical controls. I can conceive
17 of contexts where the historical control would be the best
18 comparison.

19 So I guess that where I end up is that I'm really
20 not sure, but I do think that if you want to make a
21 comparative statement about complication rates, a
22 comparative statement about efficacy, that at least you know
23 is unbiased, that you have to have a randomized trial in
24 which patients stay in the trial, and we don't have that,

1 unfortunately.

2 Depending on the context, I'm not sure a
3 comparative statement is necessarily necessary. There may
4 be contexts where it is fine to just make an absolute
5 statement of the prima facie efficacy of a particular
6 procedure as a route to approval, but that obviously has got
7 to be thought about.

8 One question that came up for me is if indeed you
9 allow a registry to be ongoing, could you not in addition
10 have a randomized component, and in that way, you would have
11 a situation where the patients would select themselves out
12 of the randomized trial if they really have their hearts
13 set on one treatment or another. I would much rather have a
14 third of the number of patients, but they all stay in their
15 assigned groups, than have three times the number of
16 patients where two-thirds of them drop out.

17 Thank you.

18 DR. CURTIS: Thank you, Dr. Bailey.

19 Dr. Vetrovec?

20 DR. VETROVEC: Well, I have been in a number of
21 multicenter randomized trials over the years, and I am a
22 believer that that is an excellent way to get at the science
23 that we are really trying to achieve. But from my
24 experience in those trials, I'm not sure that that is going

1 to be practical in this circumstance. I'm not sure there are
2 enough available patients given the numbers that will be
3 needed for a randomized trial to ever answer the question.

4 I would point out, for instance, the Barry
5 [phonetic] trial, which was the NIH-sponsored trial of
6 surgery versus angioplasty for multivessel disease, there
7 was a considerable amount of difficulty randomizing patients
8 in the trial, much of which related to patients' own bias
9 and some of which probably related to operator bias.

10 I remember a cardiac surgeon saying to me, you
11 know, Vetrovec, be real careful what you tell the referring
12 doctors because they will think we don't know what do to for
13 our patients, and that's why we're tossing a coin.

14 So I'm not sure, although a lot of thought has
15 been levelled at the interventionists on this side--I have
16 seen the surgeons be a little uncomfortable with randomized
17 trials also. And I think this is a practical issue.

18 The other pseudo-ethical issue I will bring up is
19 the education level of the patients who may agree to
20 randomization. I would point out in the Barry [phonetic]
21 trial that the patients who agreed to randomization had a
22 significantly lower education level than the patients who
23 did not agree to randomization in that trial.

24 So there are all kinds of peculiarities that come

1 into this, and given the additional emotional constraints of
2 parents in this, I don't thin it can be randomized,
3 particularly for the patients who are available.

4 I might also say that the issue that there was
5 some critical time in life when we could have done this
6 trial as a randomized trial is a bit difficult because the
7 fact is that you have to wait to a certain level of
8 experience so the device can be considered at a stable
9 enough state that you can compare it to a procedure that has
10 been done for 40 years.

11 So once you get to that level, usually the device
12 is pretty good, and the differences aren't too much, and
13 they are hard to fathom, and you're stuck. So that's a
14 problem, and while it's very nice to have a randomized trial
15 to quote, and we continue to live by them, including the
16 Cass [phonetic] study, which we still quote as the reason
17 for multiple-vessel bypass surgery in patients with
18 compromised ventricular function, the truth is that we don't
19 know that that still holds forth in the days of beta blocker
20 therapy, ace inhibitor therapy and so forth for patients
21 with heart failure.

22 So I think that we have probably overplayed all of
23 this. I would suggest, then, that this needs, at least for
24 the PDA and the ASD secundum types, some type of comparable

1 or reasonable parallel controls. I don't think they have to
2 be at the same centers, because I think there is some
3 advantage of getting perhaps a better population mix from
4 other centers. And I would think that the surgical patients
5 would need to have some relatively similar follow-up, if
6 nothing else but a transthoracic echo--something as best as
7 can be feasible to get comparable data.

8 On the PFOs, I did not get enough data today to
9 know the answer to that. I think that that is difficult.
10 Maybe that can be randomized. I think the whole issue of
11 whether anticoagulation alone is sufficient is another
12 potential arm. That, we probably haven't discussed enough.

13 And finally, for the complex patients, I
14 personally believe that they are so convoluted and difficult
15 and low in number that you just can't possibly randomize
16 those, and they have to remain in some type of registry.

17 Thank you.

18 DR. CURTIS: thank you, Mr. Vetovec.

19 Dr. Edmunds?

20 DR. EDMUNDS: I'm not going to compete for votes,
21 but I am going to tell you what I think. First of all, I
22 agree with Dr. Hopkins that there ought to be four groups
23 and you cannot put them all together. With the PFOs, we
24 have not discussed them at all. That is a potential shunt,

1 not an actual shunt, and I would hate to see any kind of
2 inference that if they need to be closed, then we do 30
3 percent of the population with the device. That's wrong.

4 Anticoagulation has its own morbidity, but we
5 didn't discuss that, and I don't think we can conclude on
6 that.

7 As far as the high-risk patients, which are
8 largely in our folder here, I would urge them to keep on
9 going exactly what they're doing up there, a very careful
10 selection of patients, very careful protocols, and
11 tabulating the results.

12 Now, as far as the ASDs and the PDAs, we need to
13 treat them separately. Medical technology is a moving
14 target, therefore, historical controls are of no value,
15 except for quantitative data--qualitative data, but not
16 quantitative.

17 Nonrandomized so-called controlled trials are just
18 observational studies. There is nothing you can do with
19 statistics there that really has any meaning.

20 Now, a randomized, prospective, double-blind
21 control trial is the late 1980's and 1990's gold standard,
22 but it's not feasible if surgery is one arm. There is no
23 way you can have a randomized prospective controlled trial,
24 let alone blinded trial, where surgery is one arm. You can

1 randomize between two surgical procedures or three or four,
2 and you can randomize between nonsurgical procedures, but
3 you cannot randomize a nonsurgical procedure with a surgical
4 procedure because our fellow citizens do not want to have
5 surgery if they can avoid it. That's a fact of life.
6 Surgeons don't want surgery if they can avoid it--they like
7 to do surgery, but they don't want surgery.

8 I don't think it is feasible, and I think we have
9 examples here, to carry out a randomized prospective
10 controlled trial over device versus surgery for ASD or PDA.
11 We're beyond that. We simply cannot enroll the patients.
12 It is just not feasible, and you cannot allow crossovers;
13 otherwise, you throw away your statistics.

14 The last thing is that to empower a study in which
15 the serious morbidity and mortality is so low, I think you
16 are really talking about big numbers. We are really talking
17 about hundreds and possibly even a thousand patients in each
18 group. That just makes the feasibility even that more
19 remote.

20 So, now I am against everything. I don't want to
21 end that way. I want to touch on endpoints. First of all,
22 I think we ought to concentrate on the serious endpoints,
23 and by that, I mean permanent endpoints--either death,
24 strike, infection, something that the patient doesn't

1 readily get over. The minor endpoints, we need to recover,
2 but if the patient gets over them, it's a nightmare rather
3 than a permanent deficit.

4 So if we concentrate on the permanent endpoints, I
5 think we'll be better off, not that we can discard the minor
6 endpoints--they're real--but I think we should try to keep
7 our focus.

8 What I recommend is probably going to have no
9 support in this room. I am going to recommend that the
10 devices have extensive bench testing to the point where they
11 reach the standards required of the aircraft industry for a
12 new jet engine or a new wing or a new anything on an
13 aircraft that is supposed to carry over 100 passengers.

14 Number two, I think the operators with these new
15 devices need to be trained on animals and have to pass stiff
16 competency tests much like a pilot would have to pass in
17 order to drive an airplane. We shouldn't have air embolism
18 happening to patients when it's clearly preventable and is
19 operative error.

20 Then, the third step in this process is that I
21 would grant IDEs and have the investigators go ahead with
22 the trial in patients who want the device, where they think
23 it is indicated, and to rigorously record what happens.
24 Now, before that happens, I would empanel a set of experts,

1 other interested and knowledgeable people, to set up
2 failsafe criteria. We heard one investigator say that he
3 would accept one death out of a ductus closure by
4 percutaneous criteria out of 40. I would not accept that.

5 DR. CURTIS: I think he corrected that to 100.

6 DR. EDMUNDS: One might accept or even consider
7 one in 400. Okay. Well, then, I'm pretty much at the end,
8 so I'll stop there.

9 DR. CURTIS: Thank you.

10 Dr. Simmons?

11 DR. SIMMONS: I guess I'm sort of looking at this
12 from almost an uneducated observer, being an electrician. I
13 certainly have to admit that congenital heart disease was my
14 lowest board score when I took the cardiology board.

15 However, in spite of that, looking at these data,
16 I am convinced--I'll tell you, there are low numbers and
17 high complications--and I guess I still think this is an
18 experiment. So, hearing these people come up and talk, each
19 one of them, I just got the impression that there was no
20 commitment among the investigators who were chosen by the
21 companies that this was still an experiment.

22 DR. CURTIS: Just be careful--we can't discuss
23 anything that was proprietary or any of the yellow
24 information in there.

1 DR. SIMMONS: Okay. So I guess I'm also
2 unconvinced that the patients are so unmoved. I also am
3 unconvinced that any one of these doctors, if they had been
4 impartial, couldn't have sat with that same family and
5 presented this whole thing in a different way so they
6 wouldn't have gone for the surgery, if they in their hearts
7 had felt that this was pretty equal.

8 So I guess what I'm saying is that I don't think a
9 randomized controlled trial can be done, because the people
10 don't want it to be done; so I think it's better that we do
11 a real study with concurrent controls and some very rigid
12 guidelines rather than trying to do a randomized study with
13 a lack of interest, and the participants end up with
14 something at the end that is not going to actually be
15 interpretable when you're done.

16 So I guess what I would suggest is concurrent
17 controls with multiple institutions. Open it up, since
18 you're going to need so many more patients, and let's
19 actually try to design a study with a lot of patients and
20 two groups that we can actually compare something at the
21 end, so the people who are doing the study will actually
22 have some commitment to.

23 And I think your suggestion about the independent
24 panel to evaluate these complex things is a good idea--the

1 characteristics of the patient, the complications, the
2 attention to detail. We need to be sure that in all the
3 groups if you are going to get that many institutions
4 involved, there is the same attention to detail as there is
5 in other groups.

6 That's all I really have to say.

7 DR. CURTIS: Thank you, Dr. Simmons.

8 Mr. Jarvis, any comments?

9 MR. JARVIS: I don't have any comments at this
10 time.

11 DR. CURTIS: Thank you.

12 Dr. Gooray?

13 DR. GOORAY: Thank you.

14 Just a brief comment on the concept of patient
15 education. I think the problem is the definition of
16 "choice." It seems to me that the concept of choice is very
17 essential in any democracy, and it seems to me it doesn't
18 matter what a patient's educational background is or what
19 their other background is--the minute you challenge their
20 concept of choice, they react in an opposite direction.
21 This was clearly brought out, and I think the point about
22 what is happening is that it would seem to me that what the
23 parents are doing--and the decision is made by the parents--
24 is they are making a decision for their child which commits

1 that child along a specific pathway.

2 If we take the analogy of cardiac transplant, once
3 we transplant somebody, we have defined their life
4 expectancy. So the point is that decision to transplant is
5 very important. We do not know what these devices are going
6 to show. They mentioned casually that the child takes an
7 aspirin for 6 months. Is that really adequate prophylaxis.
8 And if, God forbid, 10 years from now, an unforeseen
9 complication happens, how can they go back and say,
10 retrospectively, that they had the best data to make the
11 best decision, and who is the one to make that decision?

12 I think the problem goes beyond numbers and what
13 will happen to people. Sometimes, I think we in medicine
14 are asked to make decisions, and I think we make them in the
15 best light that we can, and most of the time, we are guided
16 by what patients are going to do 20 years from now, and I
17 think that that ought to be taken into consideration when we
18 come to decisions about things like this.

19 That's all.

20 DR. CURTIS: Thank you, Dr. Gooray.

21 Dr. Ringel?

22 DR. RINGEL: Thank you.

23 There were a number of things that came up that
24 disturbed me, and obviously, we don't have time to discuss

1 them all. There are a couple of issues that perhaps we
2 haven't focused on. One is the fact that we're trying to
3 make the surgical comparison end of this uniform amongst the
4 companies that are representing their devices here, yet
5 their protocols are not uniform, and I still have a problem
6 with that. The endpoints of acceptability are not uniform,
7 the size of residual shunts are not uniform with what's
8 going to be accepted, and even the way that it's going to be
9 evaluated, transthoracic, transesophageal, echocardiography.
10 I have concerns that even after we make a decision as to how
11 to compare the results, that we're going to be looking at
12 devices each one having a different protocol to use as a
13 basis for comparison to surgery. So I think that that is
14 regrettable.

15 I think that if we are going to compare surgery
16 and device closure for efficacy, it has got to be done with
17 the same technique. So I'm not saying that kids, after
18 having a device put in their heart, shouldn't have a
19 transesophageal echocardiogram, but if we're going to
20 compare the residual defect from surgery to a residual
21 defect with a device, then they should be by similar
22 techniques--in other words, transthoracic echocardiography.
23 So if there is no residual defect by transthoracic, and one
24 is found on transesophageal echocardiography in a child with

1 a device, is that considered a failure? How can it be
2 considered a failure if we haven't done the same thing in
3 the surgery patients?

4 So, if we've decided that it's unethical to do
5 transesophageal echocardiography on postoperative patients,
6 then we must use the same endpoint at least for efficacy.
7 Now, as far as safety is concerned, if the companies feel
8 that they need a transesophageal echocardiogram on the
9 device patients to make sure there aren't clots or arm
10 dislodgements, and so on, that's another issue. But for the
11 endpoint--because I know one of the things we have to talk
12 about is endpoint--it should be done the same way.

13 Another thing that was not brought up as far as
14 acceptability is that I think we have to consider what
15 percentage of patients go to the cath lab and then get
16 rejected for device placement as an unacceptable endpoint as
17 well. So there are certain unacceptable endpoints--the
18 number of strokes, the number of dislodgements, air emboli,
19 and so on--but how many patients is it acceptable to allow
20 to go to the cath lab to decide that the hole is too big to
21 put a device in. I think that that also has to be in the
22 endpoint discussion.

23 Then, finally, I think we shouldn't be randomizing
24 the patients. I think it has been said many times already

1 that this is no longer feasible. I think part of the reason
2 it is no longer feasible is the informed consent aspect. I
3 think that if we really want to do this right, then the
4 parents and the patients should be meeting the surgeons and
5 not just the cardiologists--they should meet with the
6 surgeons, who then describe from their own standpoint the
7 advantages of surgery. I think that if you do that, and you
8 do that in multiple centers, centers that do not have
9 devices, then I think that we will get a random survey
10 because we are not trying to randomize the emotional states
11 of the parents; we are trying to just randomize the patient.
12 And if you have case control, and you have an oversight body
13 that's looking to make sure we have the right age match, the
14 right weight match, the right ASD size match, I think there
15 should be no problem in accepting this data and being able
16 to make an informed decision.

17 As far as PDAs are concerned, I think it was
18 elegantly demonstrated multiple times that surgery is the
19 gold standard, that these things can be closed easily, and
20 historical controls I think are very adequate for PDAs, and
21 I think that that was nicely demonstrated in a very
22 thoughtful discussion by Dr. Jenkins about how to look at
23 the various problems. And even though we didn't discuss
24 PFOs, there are so many open questions as to whether PFOs

1 should be closed to prevent stroke and whether we are
2 preventing stroke or not, that clearly is going to have to
3 be randomized in some fashion.

4 DR. CURTIS: Thank you.

5 Dr. Weintraub?

6 DR. WEINTRAUB: I'm going to try not to repeat
7 things that other people have said.

8 With respect to comparisons, I think someone said
9 something to the effect that equivalence is not necessarily
10 comparative, and I think that that's very important. We are
11 looking at two different modalities. One is invasive and
12 causes pain and the sternotomy and all of that; the other
13 one is relatively simple, relatively painless, and much
14 easier on the patient.

15 So really, the question we are asking is not
16 whether one is better than the other, but rather, what's the
17 trade-off; what is the panel, what is the populace, what are
18 physicians willing to trade off in terms of safety and in
19 terms of efficacy.

20 The historical controls on ASD closure, for
21 instance, show low mortality and so on. Well, so far, so do
22 the IDEs show fairly low mortality, virtually none on the
23 devices. There are complications.

24 In answer to Jeff's question about if this had

1 been done as a randomized study 8 or 9 years ago, there
2 wouldn't be any more devices, because all of these things
3 are moving targets. Surgery is a moving target. So I think
4 you have to just accept that, and that's part of the game.
5 There has to be evolution of these devices.

6 So the question really is what are we looking at.
7 We are looking to find criteria for rejection. In other
8 words, we are trying to define criteria that say this device
9 is dangerous or this device is not acceptable even though it
10 may avoid an operation, but it is unacceptable because
11 either the recurrence rate is too high or the complication
12 embolization stroke rate is too high. That's what we really
13 have to define.

14 Now, the question is how to define it. I don't
15 think bench testing is going to define that. I mean, you
16 can check these things until the cows come home, but not
17 until you put it into animals and humans, or ultimately, the
18 animal, and maybe the best experimental animal is the
19 European--I don't know--but the question is how do we define
20 rejection. That's really what we're talking about.

21 In regard to the specifics, I think that PFO
22 closure for stroke is very interesting. I think that that
23 does really lend itself to randomization. Just off the top
24 of my head, if I would devise a study, it would be

1 anticoagulation versus surgery versus device, because long-
2 term anticoagulation is no picnic, and I think that that is
3 something that actually could be randomized, and I think the
4 device manufacturers and the physicians and the PIs would
5 all accept that as a possibility.

6 I have seen two patients in the last month with
7 exactly this problem. What do you do about it? The guy's
8 got a PFO, and he's had two strokes, and he's young. So I
9 think that that's really randomizable.

10 With respect to ASDs and PDAs, it seems to me that
11 you need a large IDE group. Now, should we call that a
12 registry? I suppose. Now we're sort of getting into what
13 we did with valves and looking for objective performance
14 criteria. Thou shalt not have more than one percent
15 embolization. Thou shalt not have more than--whatever.
16 Thou shalt not have more than 10 percent failure rate--
17 define "failure rate."

18 The only problem is how to establish those
19 criteria of rejection, and I don't really have a handle on
20 that at all. But I think that that is what we're really
21 looking for is to find those devices that aren't any good,
22 that are either dangerous or that don't work well enough to
23 be worthwhile using.

24 DR. CURTIS: Thank you, Dr. Weintraub.

1 Dr. Crittendon?

2 DR. CRITTENDON: I'm going to try not to be
3 repetitive as well, but there are some points that I want to
4 emphasize that I feel pretty strongly about.

5 One is that I think a major endpoint in terms of
6 efficacy ought to be that we ought to look for complete
7 closure of the ASD or PDA, that less than complete closure
8 is not adequate.

9 I think that these device companies should
10 probably get together and come up with a common protocol
11 instead of having different protocols, because I think the
12 studies will not be comparative otherwise.

13 And perhaps, looking at this 5 years from now, you
14 can come back and may have objective performance criteria
15 based on the things that the protocols that would be
16 standardized would find.

17 The other thing is patient education. I think it
18 was painfully evident--and I'm kind of happy that the
19 parents came, but I felt for them as well--that there ought
20 to be a lot more done, specifically about informed consent,
21 and I think the studies should include having a surgeon see
22 the patient as well as the cardiologist, because clearly, I
23 think the pediatric cardiologists are not unbiased.

24 That's all I have.

1 DR. CURTIS: Thank you, Dr. Crittendon.

2 Dr. Zahka?

3 DR. ZAHKA: I'd like to begin by thanking the FDA
4 for including individuals with pediatric experience on this
5 panel, because I do think that it is valuable to come to
6 this table with a body of experience about not only how we
7 take care of children, but also how we take care of their
8 families, and I think for those of us who have taken care of
9 families and children, the kinds of things that the
10 McCarthy's were so eloquent in saying actually came as no
11 surprise to those of us who have been dealing with children
12 for several decades.

13 And I think we can bring to the table a sense of
14 experience, and I think that we have got to have a lot of
15 gratitude as cardiologists to our surgical colleagues for
16 the wonderful things that they have done to help countless
17 children over the last four decades. I think that focusing
18 on the concept of helping children should be a pivotal part
19 of how we go about our decision process, because we do know
20 that we can help children, and while surgery does have the
21 opportunity to hurt children in some very palpable ways and
22 some psychological ways in the issue of the scar, I think
23 that as we come back to the premise of are we going to hurt
24 children doing what we're going to do as part of the FDA

1 process, if we don't sway from that mission and vision, then
2 I think that we'll make the right decision. If we look back
3 and say, oh, we found out about left pulmonary artery
4 stenosis with ductile devices, et cetera, and realize that
5 there were times when we weren't exactly right on the mark
6 first off, but we're going to make progress, and we're going
7 to help children, then I think the concept of helping
8 children with nonsurgical closure of the ductus in the ASD
9 is something that, as pediatric cardiologists, we all seek
10 to have and have available for all families that would like
11 to have it.

12 But I would like to come down on the side that
13 surgery is going to be tough to beat. I have heard from a
14 number of people the concept that if we can come to grips
15 with what we feel is an acceptable outcome, both in terms of
16 complications, residual shunts, AV valve regurgitation and
17 risk of stroke, and lay those benchmarks down at the very
18 beginning and agree with them, we will accept "x" number of
19 strokes out of 10,000 patients, or out of 1,000 patients, in
20 return for not having a scar, or we will accept this amount
21 of mitral regurgitation, or we will accept a 5-year risk of
22 endocarditis, or this or that. If we can set those
23 benchmarks down initially and go about that as the control
24 group and, if we waiver from those benchmarks, have the

1 courage to say we may be hurting children rather than
2 helping children, then I think we'll be on the right course.

3 And I do agree, I think it's going to be very
4 difficult at this point, because of many, many issues, to do
5 a classic randomization trial.

6 DR. CURTIS: Thank you.

7 I think one thing that there has been strong
8 consensus about this entire afternoon is that a randomized
9 clinical trial is not going to happen because it is not
10 feasible. I believe it is ethical, but it's just not going
11 to happen. The problem with it is--I wasn't happy with the
12 strong investigator bias. I mean, if you are presenting
13 somebody with an option for a randomized trial, and you
14 really come down heavy on one side and really don't
15 emphasize the other, that's not informed consent to the
16 patient.

17 But even if we had the perfect investigator who
18 fairly presented everything, or we had a surgeon and a
19 cardiologist sit down together, there will still be those
20 parents who say, "I don't want my child to have a scar; I'm
21 going to go to some other institution," or try to get it.
22 So I think that even in a perfect world, the families are
23 very strongly in favor of one or the other once they hear
24 the options. So I think we can lay that one to rest.

1 And also, even if there were a randomized clinical
2 trial, I think that what will be the outcome of all of this
3 and all the discussions about historical controls and
4 concurrent controls and all that--when all is said and done,
5 even if we have slight differences in complication rates
6 between the two procedures, I don't think it's going to
7 affect medical practice all that much. If you had a .5
8 percent stroke rate with surgery, and it was .7 or 1 percent
9 with the device, people are going to go with the device
10 because it's less invasive. I think that's what it's going
11 to come down to. So really precisely comparing the
12 complication rates of the two maybe isn't all that important
13 anyway.

14 But on the other hand, if we don't do a randomized
15 trial, I would like to be very careful that later on, no one
16 tries to make claims of superiority for the device over
17 surgery, because if you don't directly compare them, the
18 fact that over here, somebody's got this "x" percent
19 complication rate, whereas the device in this center does
20 this, it's apples and oranges, and you don't really know
21 that if you had randomized the patients, it would be the
22 same.

23 So with that as a background, I'm going to go
24 through these questions now and either give an opinion or

1 sum up where I think we are, or else try to get a few more
2 opinions before we close today.

3 The first question we were posed is: Should there
4 be indications for shunt closure in terms of dimensions
5 and/or flow ratio as determined by echocardiography?

6 I think in terms of the three lesions we are
7 talking about that the traditional indication for closing an
8 ASD is a shunt ratio of 1.5:1 and/or symptoms, but that kind
9 of a flow ratio. And I am not a pediatric cardiologist, so
10 if I'm misspeaking, I'll be happy to have somebody else say
11 something. But it sounds like since we're not really 100
12 percent sure what kind of complication rates we're going to
13 wind up with with these devices, that we shouldn't be
14 liberalizing the criteria to say, well, if you pick up any
15 kind of a hole on echo, go ahead and put the device in.

16 Is that not true?

17 DR. RINGEL: I don't think we've done that.

18 DR. CURTIS: You don't--

19 DR. RINGEL: I don't think we've done that for
20 about 15 years.

21 DR. CURTIS: But do we want that in this trial?

22 DR. RINGEL: No one gets flow ratios anymore.

23 DR. CURTIS: Nobody does that. So if you pick up-

24 -

1 DR. RINGEL: I mean, if you do an experimental
2 study, then--

3 DR. CURTIS: Are you talking about surgical
4 closure?

5 DR. RINGEL: Yes, for referral for closure of an
6 ASD, we're not doing flow ratios anymore.

7 DR. CURTIS: Okay. So if you're referred, and
8 there is one present, it gets closer--

9 DR. RINGEL: I think someone else said if you have
10 a sizeable ASD with volume overload, clinical criteria, they
11 get referred.

12 DR. CURTIS: Okay. Well, then, that would be an
13 acceptable indication, right?

14 DR. RINGEL: Yes.

15 DR. CURTIS: Okay.

16 DR. ZAHKA: You'd have to have a defect and
17 evidence for right ventricular volume load--and there are a
18 lot of other exclusions that you have to think about, but
19 that's the fundamental thing.

20 DR. CURTIS: Okay.

21 DR. BRINKER: We're interested in post-surgery--if
22 you have a patient post-surgery come back with a murmur, and
23 you do an echo, are there criteria for concern about--

24 DR. RINGEL: Are you saying for reclosure of an

1 ineffective--

2 DR. BRINKER: Well, this is the issue. It's not
3 who gets the procedure. This is the issue of--

4 DR. CURTIS: Well, actually, I am talking about
5 who gets it to start with, because that's what the first
6 question is, and we can go back to your point. But if
7 that's standard clinical practice, then if it's something
8 that should be closed, I think it could be closed under--

9 DR. RINGEL: Physical exam, EKG, echocardiography.

10 DR. CURTIS: Okay. So basically, you have a
11 defect that's picked up. Do you need RV--do you need right-
12 sided overload?

13 DR. ZAHKA: Yes, of the right ventricle, by
14 physical exam, ECG and echocardiography.

15 DR. CURTIS: Okay. So that sounds like that would
16 be a good criterion for who should be--

17 DR. EDMUNDS: But the operative word is right
18 ventricular overload.

19 DR. CURTIS: That's fine, and I think that's what
20 everybody needs to know.

21 DR. WEINTRAUB: Are you concerned that there's a
22 hole in the heart, and we've got this device, and hey, we
23 can just put the patient to sleep for a few minutes and no
24 problem--that's the danger--

1 DR. CURTIS: Yes, I agree.

2 DR. WEINTRAUB: --that this is so easy that
3 criteria that would be used to define surgery are now--it's
4 like the angioplasty--you have a lesion, we have a catheter.

5 DR. CURTIS: Well, in terms of a study, though, it
6 sounds like what you're all proposing would fit, so that
7 probably could be a general agreement.

8 For a PDA, would it be fair to say that you'd have
9 to have a murmur and an abnormal echo to fix it?

10 DR. RINGEL: For us, it is, where I practice. I
11 go to meetings, and there are polls and so forth, and there
12 are some pediatric cardiologists who recommend closure of
13 silent ductuses.

14 DR. CURTIS: Should that be part of a clinical
15 trial right now when we don't know what kinds of
16 complication rates and things there are?

17 DR. RINGEL: I personally would require a murmur.

18 DR. CURTIS: Okay.

19 DR. RINGEL: Ken, you're the other pediatric
20 cardiologist on the panel.

21 DR. HOPKINS: The importance is that the criteria
22 remain stable and the same for various arms--not the exact
23 specifics of the criteria. The shunt ratio is measured at
24 one point in time. Volume overload implies that there is a

1 significant shunt, even if at that one point in time, the
2 shunt was low.

3 So I think the point you're making is that they
4 should be consistent--

5 DR. CURTIS: Yes.

6 DR. HOPKINS: --not changed, not liberalized, and
7 not altered from one arm to the other.

8 DR. CURTIS: But I would also suggest that as of
9 right now, we wouldn't want to have a silent PDA included in
10 a clinical trial where we don't know what kind of
11 complication rates there are long-term, as was suggested.

12 DR. ZAHKA: I think that's correct.

13 DR. CURTIS: Okay. And finally, for a PFO, I
14 think you'd want to have somebody who had a PFO who had a
15 TIA or a stroke, right? I mean, we don't want to find a
16 third of the population as eligible for this. Okay.

17 DR. ZAHKA: But you may want to have the PFO in a
18 randomized trial.

19 DR. CURTIS: Yes. I'm just saying indications,
20 indications.

21 DR. ZAHKA: Are we going to talk about the age or
22 the size?

23 DR. CURTIS: The size of the PFO, do you mean?

24 DR. ZAHKA: No, the age of the child or the size

1 of the child, because it might depend on--depending on the
2 delivery devices--whether or not there should be a lower age
3 range or a lower size range.

4 DR. EDMUNDS: Madam Chairman, we did not discuss
5 PFO. I don't see how we can make any recommendations about
6 it.

7 DR. CURTIS: Well, it wasn't emphasized, but there
8 were some talks about it.

9 DR. EDMUNDS: Well, yes, but it was not discussed
10 thoroughly. What's the incidence of thrombal embolism with
11 PFO? What age groups are affected? What is the [inaudible]
12 of anticoagulation? We haven't discussed the issue.

13 DR. CURTIS: Well, that's true.

14 DR. SAPIRSTEIN: We would like your impressions,
15 though, even though you didn't discuss it.

16 DR. CURTIS: The problem is that if we don't--and
17 maybe your opinion is that you can make no comment at all--
18 but any opinions we have and any guidance--they will have to
19 go out and do something about this. I don't think we want
20 to bring this up at a subsequent meeting--or, maybe we do.

21 That would be my own opinion right now, is that
22 you'd want to have a TIA or a stroke having occurred and
23 then consider doing something about the PFO, because I think
24 that's standard clinical practice right now. We don't close

1 them because they exist.

2 DR. WEINTRAUB: There's not a lot of data on this,
3 I agree, but after a really good search of the literature
4 and so on, it might be a subject for a true randomized
5 study. We don't have the time to discuss it, but it's
6 something for the future.

7 DR. CURTIS: Okay.

8 If we could go to Number 2: What is the
9 appropriate control to which transcatheter occlusion devices
10 should be compared for the treatment of--if I could skip to
11 (c), the PFO--I have opinions, even if we didn't hear too
12 much. If there were to be a trial, that's the one area
13 where I think we should do a randomized clinical trial,
14 because I think you could randomize your device to
15 anticoagulation and/or surgery--three arms, two arms,
16 whatever--but I think since how to handle it is
17 controversial, and there is a nonsurgical option available,
18 there is anticoagulation, there isn't any reason why you
19 couldn't look at a study like that.

20 DR. WEINTRAUB: And the surgical option can be
21 minimally invasive.

22 DR. CURTIS: True, too.

23 DR. RINGEL: I know there are members who don't
24 want to discuss PFOs, but oral anticoagulation perhaps

1 versus device closure alone might be reasonable, because if
2 you look--I don't know if I'm allowed to say it--but there
3 are published results of PFO closure, virtual, complete
4 closure. I don't know that we need to know what surgery can
5 do. We know the surgeons can just put a stitch in a PFO and
6 close the chest and go on. I'm not sure you need three
7 arms. It would take a lot longer. And I think that if we
8 find something needs to be done, if we get an answer to this
9 very difficult problem, we shouldn't be stretching the study
10 out too long.

11 DR. EDMUNDS: I shouldn't have to remind a
12 pediatric cardiologist of the difficulty of anticoagulating
13 children.

14 DR. RINGEL: PFO and stroke is generally not a
15 child problem. I mean, I see one in 10 years.

16 DR. EDMUNDS: I've practiced cardiac surgery for
17 almost 40 years and haven't seen a thrombal embolic event
18 from a PFO. Ron has seen two in a month.

19 DR. WEINTRAUB: [Inaudible.]

20 DR. CURTIS: Bad luck.

21 DR. RINGEL: My Stroke Center tells me that they
22 see lots of them in patients age 40 to 60.

23 DR. BRINKER: But I think you don't see them
24 because they're usually referred to a trial of medicine

1 before--and that's what I think the comparative should be
2 initially. I think that a triple- or quadruple-arm study
3 with aspirin instead of anticoagulation would be too much to
4 ask of a sponsor.

5 DR. EDMUNDS: It might be very important to ask.

6 DR. BRINKER: Oh, it would be interesting.

7 DR. CURTIS: Okay. And then, the ASD and PDA.

8 There has been talk about--well, we have laid the randomized
9 clinicals to rest. The options are historical controls, a
10 surgical registry of some kind--those are the two primary
11 ones--and the other option could be, and we didn't really
12 talk about it today, although I think you were alluding it
13 to it--objective performance criteria. That was brought up
14 at the last panel meeting--although there really aren't
15 objective performance criteria for something that has never
16 been approved yet--we have nothing to compare it with--it's
17 not like the 16th heart valve that comes out.

18 So it might be that we could come up to some
19 consensus about what kinds of complication rates would be
20 acceptable. For instance, the mortality rate certainly
21 needs to be less than one percent and hopefully, close to
22 zero. But we have nothing to base that on--it would be
23 opinions here. That might be one way to go.

24 The only thing I would say about a registry is

1 that I think the worst thing we could do would be to have a
2 surgical registry where the patients who did not get the
3 device at that institution are the ones who are in the
4 registry.

5 I think if there is going to be some sort of
6 surgical registry, let it be another institution that isn't
7 studying it, and let them give it their best shot, because I
8 think we won't have any data that means anything from that.

9 I see a lot of heads shaking yes.

10 DR. BRINKER: There's another concern that I have,
11 and that is the ethics of that. Would you inform patients
12 at this other institution that they are part of a study that
13 is comparing surgery to a noninvasive form--and by the way,
14 you can't get the noninvasive form because you're here, or
15 we can't tell you about it?

16 DR. RINGEL: Well, you can, and you can offer to
17 send them to the closest center that does the procedure.

18 DR. BRINKER: And you think that that's going to
19 be different than patients going to Chuck's place--he said
20 he's already sending patients to surgery. Now, do you think
21 if you tell your patients we'll operate on you here, or you
22 can go there, or go to the next places that can do--

23 DR. RINGEL: I think I can answer that, because if
24 you are a pediatric cardiologist, not a surgeon, and you do

1 not have devices at your center, you have no bias. You do
2 not get the business, the dollars, the ego stimulation from
3 either the surgery or the device closure. So you can act as
4 that patient advocate, and you can tell them: This is
5 what's going on. Here, we can offer surgery. This is the
6 way the surgery is being done. The information will help to
7 determine whether surgery is the way to go in the future, or
8 device closure, and if you are unhappy, I will try to talk
9 to your insurance company and see if they can send you to
10 the closest device center.

11 DR. BRINKER: That's great, but based on what
12 you've heard, but based on what you've heard, do you think
13 that people will be saying, "Oh, give me surgery, since I'm
14 here"?

15 DR. RINGEL: I think that the surgeons have got to
16 be involved. I think you have got to pick centers that have
17 a surgeon who is enthusiastically willing to be part of the
18 study, meet with parents and patients, and talk to them
19 honestly about the alternatives.

20 DR. HOPKINS: I'd just like to leap in and support
21 the multicenter concept. It can play out in various ways,
22 and we can get the numbers, but I think the thing that is
23 important is that the patient characteristics be carefully
24 and prospectively watched, catalogued and matched when you

1 actually do the comparisons.

2 The other thing that was not pointed out by the
3 other discussants that I think is very important is another
4 confounding factor that I want to get into the record for
5 the staff. If you look at ASD and PDA closure by surgeons,
6 in most academic medical centers, that's the first operation
7 the senior resident does. Those are the operations being
8 done by the most inexperienced operators.

9 On the device deployment--you see, that's why
10 historical controls won't work--device deployment is being
11 done by the most experienced pediatric cath doctors. And
12 therefore, unless you prospectively define operator bias as
13 well, you're going to be introducing major confounding
14 variables--and don't kid yourselves--we're comparing two
15 procedures. We're not looking at just efficacy; we're
16 comparing--

17 DR. WEINTRAUB: Well, I have a bone to pick with
18 you on that, because I think we're not really comparing.
19 What we're doing is running two parallel registries, and
20 we're running the surgical registry to establish some sort
21 of baseline criteria of safety and efficacy.

22 Like Hank said, if you really want to compare
23 them, you're going to need 10,000 patients.

24 DR. HOPKINS: But it is a moving target. You

1 cannot compare 5 years ago--

2 DR. WEINTRAUB: No, no, I understand that. So
3 what you're saying is if we're going to have two registries,
4 run them contemporaneously--

5 DR. HOPKINS: With similar criteria.

6 DR. WEINTRAUB: --with closely-defined criteria,
7 and in a sense, use surgery to establish the gold standard,
8 again.

9 DR. HOPKINS: But similar criteria by patient
10 characteristics, operating maturity, all of those things.

11 DR. CURTIS: I think that's well-taken. So there
12 seems to be--

13 DR. EDMUNDS: You know, you use demographic
14 criteria to match, match controls. That's a long run for a
15 short slide.

16 DR. RINGEL: But I think that what we all want to
17 do is evaluate these devices in the fastest way possible so
18 that if they are good, we get them to the American public.
19 I think that's what we want to do. So what we have to do is
20 get together and figure out the fastest way we can do that
21 and make sure that we are evaluating safety and efficacy.

22 So most people here feel that historical trials
23 are not good. Randomized trials are going to take so long
24 that we're all going to be ancient by the time these devices

1 are available. So what do we have left?

2 The only question is whether it is within the
3 centers, or is it outside of centers, and I think the panel
4 feels that if we use external centers, we have a better
5 chance of getting unbiased results.

6 DR. CURTIS: Okay. I think we have a consensus on
7 that, and just to try to finish up the last three questions--
8 --appropriate primary endpoints for the study. I would think
9 it would be complete closure.

10 DR. RINGEL: You left out the control for PDA.
11 You did PFO and ASD.

12 DR. CURTIS: Well, the control is what we've been
13 talking about, this business about a prospective concurrent
14 registry; that would be your control.

15 DR. RINGEL: For PDA? You just did ASD.

16 DR. CURTIS: All right. What do you think?

17 DR. RINGEL: For PDA, for instance, I think
18 historical controls, because I think that you aren't going
19 to be able to find many places where you're going to get
20 surgery anymore, and it will take forever for this device
21 that's being proposed to come out, because unfortunately--or
22 fortunately, depending on which view you take--the
23 geonturcal coil is out there and being used, and it probably
24 would be inappropriate to compare the duct occlude to the

1 geonturcal coil.

2 DR. ZAHKA: Obviously, it's inappropriate, but if
3 we're going to be practical, would it be possible to compare
4 an off-label use to--

5 [Laughter.]

6 DR. RINGEL: So it's historical controls--

7 DR. EDMUNDS: But I think that you are going to
8 have to establish safety criteria. What mortality are you
9 going to accept with the new PDA closure device? What
10 serious complication rate are you going to accept? I think
11 this is--

12 DR. RINGEL: It's not only--

13 DR. EDMUNDS; May I finish? I don't think we can
14 establish this in 10 more minutes. I think it takes some
15 real thought and maybe some additional input to do this, but
16 this is the only way to go on this to my mind.

17 DR. RINGEL: The company represented by Dr. Moore
18 essentially said their mortality should be near zero, major
19 complications near zero, and minor complications, he gave us
20 a number that I thought was reasonable. I thought that was
21 laid out very nicely.

22 DR. CURTIS: Okay.

23 DR. SAPIRSTEIN: I was just going to say that as
24 long as you give us a direction, a path to follow,

1 historical, concurrent or randomized, we can get to the
2 endpoints, the definitive endpoints, later, with homework
3 assignments to you.

4 DR. CURTIS: I'm glad you pointed that out about
5 the PDA, because I think it's important to get that
6 distinction in there.

7 So we have a suggestion for a prospective surgical
8 registry for ASDs, historical controls that are deemed to be
9 adequate for the PDAs, and then we talked about a randomized
10 clinical trial for PFOs.

11 If I could move on to the primary endpoints for
12 the study, I think the primary endpoint is going to have to
13 be complete closure, if I could just throw that out; and
14 then the question is what would be good enough. Do we have
15 any consensus there? Do we need to have better than 90
16 percent complete closure, better than 80 percent?

17 DR. BRINKER: Is it only absolute percentage of
18 complete closure, or degree of--

19 DR. CURTIS: You could look at both. I mean, you
20 could say so much or complete closure. To me, if it's not
21 completely closed, there's going to be some residual shunt.
22 There may be some complete failures, but I think it's either
23 going to be--

24 DR. BRINKER: Well, I think the difference is the

1 PDA--I think an incomplete closure at least [inaudible]
2 leaves you with the risk of endocarditis.

3 DR. RINGEL: We don't know that.

4 DR. BRINKER: We don't know it, but it's not
5 unreasonable to think that.

6 DR. RINGEL: If it becomes inaudible, okay, and a
7 color flow echocardiogram, which was never in existence when
8 the first risks of having a PDA were written about--what
9 does a color flow echocardiogram mean, if there are a couple
10 of red cells that squeak by this thing, and you can't hear
11 the murmur anymore.

12 DR. HOPKINS: But you also have a foreign body
13 that wasn't there before. [Inaudible] physiology is
14 turbulent flow, and then you add a foreign body--you're
15 right--we don't have a prospective randomized trial from the
16 last 30 years, but the best evidence would suggest that is
17 an SBE risk. If that were my child, or that were me, I
18 would take penicillin every time I went to the dentist.

19 DR. RINGEL: Okay. Point well-taken.

20 DR. HOPKINS: So you must use the same criteria
21 for all arms of the studies.

22 DR. BRINKER: In fact, Moore has suggested that if
23 there is a residual defect, we might want to put in at 6
24 months, a second device, and that would be part of the

1 strategy for the protocol.

2 DR. CURTIS: There is always the possibility that
3 something that you couldn't hear, but pick up on echo, isn't
4 a problem when there is no hardware in there, but maybe is
5 if you have a device in there.

6 DR. RINGEL: I'll accept that.

7 DR. BRINKER: So I think Moore's outline of a PDA
8 approach--that is, put one in if there is residual shunt at
9 6 months, might try to put another one in--and that could
10 probably be a complete occlusion after [inaudible.]

11 DR. CURTIS: And then, at that point, would you
12 define a failure as a residual shunt?

13 DR. BRINKER: Yes.

14 DR. CURTIS: Okay.

15 DR. BRINKER: The ASD I think is probably a
16 different story, and that's why I was interested in the
17 1.5:1, even though nobody is happy with a shunt
18 determination. But somebody mentioned that that was the
19 cut-off for re-operation, and I was wondering what basis, if
20 any, exists.

21 DR. ZAHKA: That's very historical. I think that
22 most of us can probably figure out when the shunt is full
23 enough based on what the right ventricle does. I do believe
24 again that the money here, if you will, is going to be in

1 the morbidity, and if there is morbidity to device closure,
2 whether it's excessive embolization, mitral valve
3 regurgitation, pressure anywhere, arrhythmias, et cetera, et
4 cetera, if we set those benchmarks out ahead of time and say
5 the devices must meet these criteria for morbidity because
6 we know there is virtually no morbidity to surgery--I think
7 we know that--then I think we'll be safe.

8 DR. BRINKER: But Ken, what if there's 2.5:1
9 residual shunt, and there's no morbidity, but we know that
10 over a period of time--

11 DR. ZAHKA: No, but a failure would be persistent
12 right ventricular dilatation if there's a residual shunt.

13 DR. RINGEL: That's the same issue.

14 Dr. BRINKER: I'd be happy with you coming up with
15 specific criteria to say that the right ventricle doesn't
16 decrease in size to so-and-so, or something--I mean, there's
17 got to be something that will suggest that the shunt is too
18 much--

19 Dr. ZAHKA: I think we can come up with those.

20 DR. RINGEL: For study purpose, I think we could
21 come up with it.

22 DR. ZAHKA: Yes, we can come up with it.

23 DR. RINGEL: The problem I have is defining what--
24 let's say there's a small residual defect, let's say there's

1 a residual 3 millimeter defect or something like that. I
2 don't know, I really don't know what size is safe because of
3 the PFO data. We know that there are people having strokes
4 that have small holes, and I am uneasy in my lack of
5 knowledge in saying that it is okay for us to consider it a
6 successful closure if there's a 3 millimeter hole. I don't
7 know what to say.

8 DR. HOPKINS: I just have to agree completely with
9 that. There are multiple negatives outcomes from having an
10 ASD--bacterial endocarditis, embolization, stroke, as well
11 as volume overload congestive heart failure. And we are
12 focusing as an outcome on only one of those, and we would
13 not accept from surgery as acceptable reducing the size of
14 the ASD, and therefore, you must use--I mean, you can close
15 an ASD with virtually no mortality, extremely low morbidity.
16 Many centers are sending these patients home in 23 hours or
17 2 days after surgery. You cannot use different criteria.
18 It is either closed, or it is--

19 DR. BRINKER: Well, Chuck, when you looked at
20 shunts afterwards--I think part of the problem with these
21 occlusion devices is that most of them are porous for a
22 while--is it your feeling that most of the shunts that you
23 do see are due to the porosity or due to uncovered actual
24 holes in the septum?

1 DR. MULLINS: Usually, gaps at the edge of the
2 device [inaudible] closing off completely.

3 DR. BRINKER: Is there a time period where you
4 would say that it's long enough to see whether it's going to
5 cause--

6 DR. MULLINS: If it's still persistent in a year,
7 then there is much, much less chance that it's going to
8 [inaudible.] If we see a device where we have a 2
9 millimeter leak at the end of the procedure, then by one
10 month, it's gone.

11 DR. CURTIS: So if I could, it sounds like what
12 you're saying is that closed is good, and a failure is open,
13 and that you don't have to have anything else, because the
14 goal was to close it, and you had a reason to close it.

15 DR. HOPKINS: Exactly. I mean, you've converted
16 an ASD now into a prosthetic device over where there is
17 turbulent flow. It's exactly--there is nothing different
18 between that and having a micro valve prosthesis.

19 DR. EDMUNDS: Well, now, wait a minute. There
20 could be a lot of difference. We don't have any animal data
21 as to how these heal. We don't have a bit of data as to
22 whether you can put a second PDA device in and whether it
23 connects to the old one or whether they heal in solid. We
24 should have all of these data before--

1 [Simultaneous conversation.]

2 DR. CURTIS: Sorry, we can't--we don't have any
3 more time. We can't do that.

4 DR. RINGEL: That data is available.

5 DR. BRINKER: We do have data on the second
6 device. Moore said that 20 out of 500 people have had it in
7 Europe. I mean, there's stuff that we do have.

8 DR. CURTIS: There is some data.

9 DR. RINGEL: If you have a 1 or 2 millimeter hole,
10 I can't imagine that that's a problem.

11 DR. CURTIS: All right. We're going to have to
12 end up here. On the last question, I think I might suggest
13 that about a one-year follow-up would be acceptable to most
14 people. I don't think we need to go more than that, but
15 that some things change over the first few months, that
16 you'd like to see it go out that far.

17 DR. RINGEL: Yes.

18 DR. ZAHKA: Yes.

19 DR. CURTIS: We've made a lot of suggestions here.
20 Obviously, this will have to be really thought through, but
21 we have run out of time. There may be a homework assignment
22 to come out of this.

23 Is any member of the panel interested or willing
24 to look at the proposal, if there is one, about how to

1 redesign these clinical trials?

2 DR. RINGEL: Yes

3 DR. ZAHKA: Yes.

4 DR. CRITTENDON: Yes.

5 DR. CURTIS: Dr. Ringel, Dr. Zahka and Dr.

6 Crittendon. Okay. We've got some volunteers to look at it-

7 -and Dr. Hopkins.

8 DR. EDMUNDS: Well, Madam Chairman, is it safe to

9 say we have not reached a consensus?

10 DR. CURTIS: Well, I think it's safe to say we

11 have not reached a consensus on some of the issues here, and

12 unfortunately, we have run out of time. But what will

13 happen now is that the FDA will come up with a suggestion

14 for an outline for these clinical trials, and some members

15 of the panel will have an opportunity to look at it and make

16 further comments.

17 DR. SAPIRSTEIN: We'll nominate a few to volunteer

18 for further homework assignments.

19 DR. CURTIS: Okay.

20 Thank you, and we're going to need to adjourn the

21 meeting.

22 DR. STUHLMULLER: Two issues. One, will the panel

23 members leave all the panel information on the table; and

24 second, we need everybody to exit through the doors on my

1 right because of the reception out in the lobby.

2 [Whereupon, at 6:05 p.m., the proceedings were
3 concluded.]

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