an amiodarone -- this is a major consideration, and we want to make some suggestions about this.

And too few episodes -- I think maybe you've already addressed that. The current guidelines guidance say three episodes in the past six months, and now we're talking two. I think that's a very big improvement. That was one of the things we wanted to talk about.

But even some things like previous A.F. ablation -- because we get into the idea that we -- that was raised by Dr. Schoenfeld again just a moment ago about tools. We would suggest that the end point should be what works, because the techniques keep changing over time, and we'll address that in a moment as well.

So previous ablation -- if we can include those patients, we would really have a remarkably more -- a richer pool from which to select patients.

And there are other difficulties, too. You've heard a little about this already. The ACC/AHA/ESC guidelines for treatment, revised in 2006, elevated ablation of atrial fibrillation to a secondary treatment option, and so the -- out in community this is an expectation.

But the mechanisms of atrial fibrillation are incompletely understood, such that exquisite ablation targets well known for AVRT and AVNRT have not been identified. I mean, it's not unusual to have one burn and AVNRT is gone because you have a target, this little pathway. That's far from that with atrial fibrillation. Whether that will ever happen, we're not sure.

But this keeps evolving, and that's the point. Ablation techniques have continued to evolve, so that over the course of a clinical trial we should anticipate that further evolution will occur.

And right now, in fact, many other

outstanding laboratories that have contributed so much to our understanding such as we have now are suggesting a stepped approach. And this changes very often.

I mean, if you go past the past three years that this trial has been going on, the number of changes in -- advances in -- if you will, in the ablation technique have been very, very numerous. Every few months, in fact, sometimes they have changed.

And then the other thing is trying to find these patients -- Biosense Webster made a very, very strong effort to do that with recruitment outreach, patient-directed outreach with IDE approved direct-to-patient initiatives in newspaper ads, Internet ads, opt-in e-mail networks, clinical trial Web sites, et cetera, to thousands of patients.

Then there were physician-directed also to thousands of cardiologists and other physicians who were identified by the fact that they were treating atrial fibrillation

patients. Letters came from Dave Wilbur, the study's principal investigator, opt-in -- and this was also in the -- in the Chicago metropolitan area, largely, so -- where Dave is very well known -- he's well known anyway, but very well known.

It was opt-in mail networks. And even at the electrocardiology booth -- and the results -- Biosense Webster spent over a half million dollars to screen hundreds of resulting referrals. They enrolled a total of three patients from this effort, and all those patients came from the patient-directed approach. Not a one came from the physician-directed approach. So difficulties in enrollment.

So we want to start some -- provide some recommendations, and part of what we'd like to suggest is that perfect is the enemy of good. I read the guidance document from the FDA, and I must say that had I been on that guidance document writing group, I

would have written the same sort of thing. I think it's really very good.

But that's where we get to the notion that perfect or ideal is the enemy of good, and I think the Biosense Webster experience maybe speaks for others as well, shows how really, truly difficult it is to enroll.

So we would suggest greater flexibility is needed in the atrial fibrillation IDE study designs, inclusion-exclusion criteria should permit companies to tailor them to reflect better the current atrial fibrillation ablation patient populations.

So for instance -- well, we'll get to that, again, in a moment. But I'm talking about being on amiodarone, for instance, is a very big problem.

Recognize that catheters are tools. Don't use registration studies to try to answer questions comparing ablation lesion

patterns. I think accept the fact that many people use different approaches. The end point is the treatment of the patient.

So what are our suggestions for trial modification? Since the techniques of ablation continue to evolve and are very likely to continue to evolve, consider allowing the investigator to use a "whatever works" approach, the end point being apparent effective treatment of atrial fibrillation.

That is, this is a tool. This is not testing a single idea of how to treat atrial fibrillation. We don't have the target of an accessory connection to ART, AVRT or for atrial flutter or the slow pathway for AVNRT.

And since FDA guidance permits use of a previously ineffective anti-arrhythmic agent, consider modifying current restrictions on use of amiodarone.

For instance, if you read the guidance, it says for a -- or the current guidance says for a primary effectiveness end

point, the FDA recommends the relatively unambiguous end point of freedom from symptomatic atrial fibrillation of one year. This outcome should be in the absence of anti-arrhythmic drug therapy or, alternatively. using an anti-arrhythmic drug that was previously ineffective at a given dose.

Well, if you modify the restriction on amiodarone being six months -- so what if a little amiodarone is on board is the -- is -- we would suggest that that's an extrapolation of the idea that maybe ablation plus a drug is very effective.

There are data out there -- in fact, the first survey, worldwide survey, on atrial fibrillation demonstrated that 24 percent of the patients who were deemed effectively treated with atrial -- for atrial fibrillation by ablation had that success associated with the need for anti-arrhythmic drug therapy.

So again, trying to make

randomization possible -- not so difficult, and maybe reasonable -- that might be an idea.

So other alternatives to consider -- you've already seen some of that discussed this morning -- use a decreased burden of atrial fibrillation post-ablation as an acceptable end point.

Use a patient as their own control after obtaining appropriate baseline data. And use more liberal ways for patients to qualify with enough A.F. episodes per unit time.

I think maybe you've already done that by saying only two episodes, but I think the issue is not what's best. The issue is what works.

And especially I noticed all your -- the FDA presentation talked about a timely trial, one done in a reasonable period of time, because even in this current trial, when you finally reach the target sample size, you then have to follow them for a minimum period

of time, so it makes the trial get very long.

DR. YANCY: Thank you, Dr. Waldo. We appreciate your comments.

DR. WALDO: Thank you. That's my last line. Thank you.

DR. YANCY: I'd like to introduce Dr. Jean-Pierre Desmarais.

Let me remind the speakers that there is a monitor on the podium. When the light becomes yellow, you have two minutes, and it would be appropriate to start summing up. And when the light is red, please bring your comments to a conclusion.

Dr. Desmarais, if you'll indicate your affiliation, please?

DR. DESMARAIS: Good morning. My name is Jean-Pierre Desmarais. I am CryoCath Technologies Inc chief scientific officer.

CryoCath Technologies is a Canadian company with headquarters and manufacturing facilities in Montreal. We have approximately 220 employees worldwide. We

sell cardio ablation catheters into U.S., E.U. and selected other countries.

We have three PMA-approved products in USA -- Freezor for the treatment of AVNRT which we conducted an IDE, Freezor Xtra and Freezor Max for minimally invasive cardiac surgery, including treatment of cardiac arrhythmias.

Currently we're running an IDE trial for A.F. with the A.F. ablation tool box comprised of Arctic Front for electrical isolation pulmonary vein, Freezor Max for thermal triggers and a cryogenic console for delivery of cryogenic fluid.

The Arctic Front trial ablation catheter is a system for highest level of safety, multiple redundant system console, and the entire balloon surface freezes to allow rapid optimal cryo lesions and ease of positioning.

Our pivotal study design is randomized controlled trial 221 experimental

to control with two groups. The control group is atrial fibrillation drugs comprised of propafenone, flecainide and sotalol.

The experimental group is cryoablation plus atrial fibrillation drug, the same three drugs again.

Control failures can crossover six months and experimental subjects allow -- are allowed one to three instances in the ablating period.

Our conclusions are paroxysmal A.F. with patients that had failed one of the three drugs we mentioned prior for effectiveness at a minimum dose and two or more episodes of A.F. and two instances of ablation and atrium size of five centimeters or less.

Key exclusions criterias are persistent or permanent A.F., any prior ablation of the left atrium, amiodarone use in the last six months prior to ablation, presence of pacemaker or ICD, cardiac

pathology, valve prosthesis and ejection fraction of less than 40 percent.

The follow-up schedule and key assessment are at one month for safety, three, six and nine months -- nine months, a telephone call, and 12 months, weekly and symptom-driven monitoring with concurrent compliance monitoring and call-backs, 24-hour Holter monitoring of baseline, six and 12 months.

For safety purposes, we are doing MRI or C.T. for the pulmonary vein at baseline, six and 12 months, with additional assessment for phrenic nerve function, neurologic events, cognitive function, changes in quality of life impacts.

Key study outcome measures -- the effectiveness of primary is freedom from chronic treatment failure, defined as detectable A.F. after a 90-day blanking period, and the acute success is defined as a selection of three or more pulmonary vein for

the experimental group, obviously.

On the safety side, the primary end point is made for major atrial fibrillation events defined as cardiovascular deaths, key hospitalization, M.I. or stroke and procedural or CPEs or ablation procedure events are defined as key device and procedural status on experimental subject, again.

The trial progress in -- we enrolled our first patient in October '06 under conditional approval. In April '07, we had approval for a significant expansion. In August '07, we had unconditional approval.

We have two Canadian centers also enrolling in the study, and the status -- we're nearing halfway mark for enrollment, at a rate of enrollment of approximately one subject per site per month.

What are our enrollment issues as a company, the strain to enroll conversion rate is highly variable from center to center,

ranging from one to 20 percent. Subject resistance to controlled randomization occurs but another major difficulty is getting crossover option and desirability of cryoablation.

Some subjects lost to -- are lost to entrance refusal and most of our loss of enrollment are protocol-driven requirements such as whether they have documentation, intolerance to anti-arrhythmic drugs, and use of admiodarone within six months of ablation, obviously.

We'd like to bring to panel some consideration for discussion, and the first one is add the acceptance of a two-part safety assessment which separates out ablation procedural events, CPE, from long-term disease and drug events, MAFEs, is innovative and clinically relevant, we believe.

However, there are no concurrently monitored A.F. IDE studies, and therefore there are few reliable data on which to base

OPC estimates.

Existing publications are variable reporting and monitoring standards in referral practices and may have significant negative detection biases for aids.

On what should sponsor base their OPC or performance goals estimate is a question we have for panel.

Second, A.F. ablation studies are designed with rough estimates key study parameters which can lead to sample size and other design errors. Pre-specified interim analysis together with adaptive methods for sample size re-estimation allow -- would allow trials with results exceeding plan estimates to complete enrollment earlier and trials found to be underpowered to be expanded.

Can new guidance be offered which encourages and specifies acceptable forms of interim analysis and adaptive design for ablation trials?

Thirdly, currently conforming

study designs randomize against anti-arrhythmic drug treatment are complex, combining the difficulties of both drug and device studies. This leads to non-informative failures which obscure safety and effectiveness assessment.

Non-informative failures are bad for everyone. We strongly urge that any proposed study design changes lead to greater simplicity and flexibility.

Significant changes in guidance should not be retroactively applied to previously approved studies as well, as we feel we could be penalized.

Finally, in terms of effectiveness statistics, key outcome measure in the recurrence of A.F. is a time event measure exactly as in A.F. drug trials. The standard statistic is logarithmic tests or equivalent. FDA is requiring a test of immense proportions which is less efficient and less informative.

Close clinical follow-up backed by

weekly and symptom-driven TTMs with successful compliance programs give sufficiently detailed data to allow the use of time-to-event data for primary hypothesis. We urge the discussion and resolution of this key issue.

In conclusion, CryoCath is conducting an A.F. guidance conforming pivotal IDE trial and nearing the halfway mark for enrollment. Enrollment difficulties exist but are fairly typical of a randomized controlled trial device.

And these are being resolved by investigation -- investigator communication and site-specific intervention and support.

Clarity on safety of performance goals estimate, the use of interim analysis, simplification of trial design requirements and establishment of standard outcome statistical methods would help us complete further studies. Thank you.

DR. YANCY: Thank you very much.

Our next speaker is Helen Barold.

Please identify your affiliation.

DR. BAROLD: Sure. I'm Helen Barold. I'm the chief medical officer for CryoCor, and we're very happy to be here to present to you all, and we're very excited to say that we have completed enrollment in the impossible randomized controlled trial, and we're here to tell you a little bit about what that trial is and where we stand with it.

So we had our IDE approved on August 25th, 2004, and our first patient was enrolled on November 24th, 2004. We have actually finished enrollment in this randomized clinical trial. We finished over the summer. We have a one-year follow-up, so we expect to fully complete our trial some time in the summer of 2008.

Our study hypothesis is that cardiac cryoablation specifically with the CryoCor system can be as safe and effective as medical management for the treatment of symptomatic paroxysmal atrial fibrillation.

This is a multi-center study. It is conducted exclusively in the United States at 24 sites, both academic and private-practice sites across the country. It is a one-to-one randomization of cryoablation versus medical management.

The follow-up is for at least one year, and we do allow crossovers and retreatments, but that does restart the follow-up clock, so that if a medical management patient chooses to be crossed over into the ablation arm, they are then followed for an additional year.

In addition, if there is a retreatment on either one of those groups, they are also followed for a year. So these patients are in the study for quite a long time, potentially.

We have a three-month blanking period after the initiation of therapy, either medical therapy or ablation. The medical management is left up to the discretion of the

investigator. There are guidelines to optimize their medical therapy during the three-month blanking period.

The cryoablation protocol -- we look for primarily pulmonary vein isolation. We require at least isolation of three veins, although the investigators all -- are doing all the veins, and they can do additional lines if they feel necessary.

However, they must use the cryoablation device. If they use a second device, it's considered a failure of the device.

Our inclusion criteria is very similar to what the FDA has recommended -- the age between 18 and 75. You have to have at least three documented episodes of symptomatic paroxysmal atrial fibrillation within six months prior to randomization, and at least one of those have to be documented by ECG, although the majority of them have more than one documented.

You have to be refractory to at least one but not more than three anti-arrhythmic medications. We do allow amiodarone in our study. If you are on amiodarone at the time of enrollment, you need to stay on amiodarone. If you are not, you are not allowed to be placed on it. That is considered a failure.

Obviously, you have to be willing to participate in the study, and in addition to that, you have to have a therapeutic INR at least three weeks prior to randomization for those patients that meet the current guidelines.

Our major exclusion criteria are similar to the other studies -- no significant heart disease, no prior ablation for atrial fibrillation and/or any left atrial ablations, and also, no history of a stroke or TIA.

So in addition to the routine follow-up that's done on a -- you know, every three-month basis with the clinician, we also

weekly event recordings and symptomatic event recordings. And I can tell you to date that we have collected over 18,000 event recordings in our patients.

We do ask them if they feel anything to send it in, so we're having a -- you know, very good compliance and a lot of event recordings in these patients.

We also have a core lab that will over-read the event recordings and the core lab is blinded to the treatment arm.

In addition to that, all of the patients, medical management and the ablation patients, get C.T. scans. They all get C.T. scans at baseline.

The cryoablation therapy patients will get C.T. scans at three months and six months. If there's any evidence of pulmonary vein stenosis, they get additional C.T. scans. If not, they stop at six months.

The medical management patients get baseline and six months. In addition, we

have a core lab, again, blinded to the therapy, that reads the C.T. scans.

Our primary end points -- for safety, it is the percentage of patients in the cryoablation group presenting with a serious adverse event is not greater than 10 percent -- or is not 10 percent greater than the percentage of patients in the medical management group presenting with an SAE. We look at SAEs across the 12 months.

The effectiveness end point is the percentage of patients free from symptomatic PAF in the cryoablation group is higher than the percentage of patients free from atrial fibrillation in the medical management group, meaning those that got the ablation have less A.F. than those that have medical management.

This is our enrollment by site. You can see we have a number of sites that have enrolled across the country, variable types of sites and variable number of patients per site.

At this point, I'd like to just make one comment before I turn it over to Dr. Hugh Calkins to bring up some of the topics that we'd like to have you discuss for us.

Number one is that, you know, we're very excited to have completed enrollment in this trial. We feel that this is -- this is really a landmark trial in the role of atrial fibrillation therapy. I think for the first time we're going to understand a lot more about atrial fibrillation in general.

We're going to -- we have a control group that has weekly event recordings, and you know, to date nobody has had that. We definitely have studies on the medical management of atrial fibrillation but nobody's really monitored that closely.

So we're very excited to do this trial not only for our company but also for the field in general.

At this point, I'm going to turn

the discussion over to Dr. Hugh Calkins.

DR. CALKINS: Hi. I'm Hugh Calkins from Johns Hopkins. I'm a consultant to CryoCor.

DR. YANCY: Dr. Calkins, just --

DR. CALKINS: Yes.

DR. YANCY: -- a point of clarification. You also are scheduled to speak on behalf of ProRhythm?

DR. CALKINS: ProRhythm, yes.

DR. YANCY: And so these comments are in the context of CryoCor?

DR. CALKINS: Yes.

DR. YANCY: Thank you.

DR. CALKINS: There's three topics for discussion -- one, as pointed out earlier, the safety end point. We certainly agree with the concept that evaluation of device- and procedure-related major adverse events will be important.

And it also will be important -- it will be very challenging, as was pointed

out earlier, interpreting these complication rates in light of prior published studies where the data really has been collected in a very different fashion, as you have heard.

The next slide. Let's see. Go back here.

Another issue has to do with the effectiveness end point. We certainly agree with the guidelines for efficacy that have been proposed in the HRS consensus document, but we're also aware that when this data is considered that other secondary end points need to be considered in terms of on drug success, late success, decreased episodes.

I think all of us are aware of the fact that the published literature probably tremendously overestimates the true efficacy of catheter ablation when subjected to weekly event monitorings. So it's going to be most interesting and challenging when we try to interpret the results of these studies, several of which are, you know, done with

enrollment or nearing completion of enrollment.

And then the final, I think, challenge that we face and everyone in this field faces is how to deal with retreatments. The protocol is designed so that if a retreatment is within two months, it's considered not a treatment failure.

And yet clinical practice is typically to delay retreatments beyond two months because we all know about delayed healing, and there's certainly an inflammatory phase that can go on for three months or longer. So this, obviously, is a difference between how the study was designed and what is considered best clinical practice to date.

So we're, you know, delighted to have the study done, look forward to analyzing the results in a year, and it will certainly be an interesting panel meeting at that time. So those are just my comments on behalf of CryoCor.

And if I could move to my next presentation on behalf of ProRhythm, that I'm consulting for, and also the co-P.I. of their definitive trial -- and it's similar to prior trials.

This is a trial of high intensive focus ultrasound ablation, or HIFU is how it's referred to, and it's a balloon-based system that delivers ultrasound circumferentially around the pulmonary veins.

And like the other clinical trials, it's been designed for paroxysmal atrial fibrillation with a similar end point and a similar 12-month follow-up for success.

And as was suggested with Biosense, I want to share with you some data on the enrollment difficulties in these clinical trials. And I think as catheter ablation has moved along and off-label use has become more common, it's become increasingly common to enroll patients in randomized trials.

So to give you some data to think about, we looked at our experience between January and June of 2007 with the HIFU ablation system, and during this time at the enrolling centers, there were 1,300 subjects screened, 158 of whom were eligible, and 93 of whom refused randomization due to an anti-arrhythmic drug.

And I think one of the major problems with any drug trial is these patients come in wanting an ablation, and if they've already failed a drug, very few patients want to go on and try yet another drug.

And we all know that once you've failed your first anti-arrhythmic drug, that almost guarantees you you're going to fail your second or third anti-arrhythmic drug. So the current way drugs are mandated, I think, is very cumbersome.

And I think the entire field would benefit tremendously from saying if you failed a beta blocker or calcium blocker, you could

be randomized to ablation or an anti-arrhythmic agent, and that would give you a more effective comparator and, I think, help enrollment a great deal in all of these trials. But that's just one comment.

The top five reasons for screen failure were either a prior left atrial ablation -- we're all aware of the fairly high number of procedures being performed around the country and the world these days -- the presence of persistent or longstanding persistent chronic atrial fibrillation.

An important limitation, I think probably the most important one, is patients who've appeared, they're interested in the trial, but they haven't failed a prior anti-arrhythmic drug, and so that delays entry into the trial.

The fourth problem has been not willing to be randomized to anti-arrhythmic drugs, and once a patient's failed and they've been referred to a center for an ablation,

they pretty much want an ablation. And to tell them they have to go on another drug that also will almost for sure fail seems a huge burden to try to impose on our patients.

And finally, the fifth is the presence of a pacemaker or defibrillator.

So like Biosense, ProRhythm did the same thing and they developed some outreach screening where ads were placed, or radio ads or print ads were placed, in a number of markets around the country to try to get calls in to a screening center where a nurse would read a standardized script and try to get only appropriate candidates to the centers that were involved in the trial.

So here was the experience between June and September. Almost 1,700 patients were screened at these call-in centers, 181 subjects were referred to the enrollment sites because they appeared to meet criteria, and 83 patients were ultimately eligible for the study. Thirty-nine of the eligible subjects

were disqualified because they also had not been treated with a prior Class I or III anti-arrhythmic drug.

So that, I think, is going to be a repeated theme that you're going to hear throughout the morning.

This shows sort of how the pie chart looks. Again, like kind of Biosense's experience, you know, you've got to screen an awful lot of patients to get eligible patients' participation in these trials.

And then of the patients that were eligible, the 83 eligible patients, you know, you end up -- those end up sort of disappearing rapidly also, and so we ended up with 22 patients finally being reviewed actively to participate in this clinical trial.

So to sort of summarize the challenge that we're all facing is over 3,000 subjects were screened in the past eight months. The total enrolled were 41. The

percentage of screened patients to enrolled patients was 1.4 percent.

And so we estimate the number of subjects you need to screen to enroll 240 patients, which is the number needed for the study, is 17,600, and the estimated minimum duration of the study would be five years.

So as far as our proposal to the panel and to the distinguished members that are here today -- is we would certainly encourage a greater flexibility on the enrollment criteria, and we certainly would urge that we drop the need to fail a prior one Class I or III anti-arrhythmic drugs.

I think it's fine to say fail a beta blocker and calcium blockers to prove that rate control hasn't worked or you don't have simple afib, but to have them take flecainide and then fail that and then try to say we'll now put you on propafenone seems a little bit absurd and is a huge barrier for all of these trials. So I think that would be

my strongest recommendation.

Also, the limitations of amiodarone are a problem. And I think by doing this it will increase the number of eligible subjects significantly, and it will also broaden the range of indications for use.

So I thank you for your attention and congratulate you on this meeting.

DR. YANCY: I'd like to thank Drs. Waldo, Demarais, Barold and Calkins for very appropriate and time-sensitive presentations.

We have not yet heard from Burke Barrett, but we have -- we may have overlooked you.

If you are here -- yes. We don't have your presentation. Thank you.

MR. BARRETT: Thank you, Dr. Yancy. I don't have slides. I just have a very brief statement.

DR. YANCY: Will you be able to make a hard copy of that available today?

MR. BARRETT: Sure.

DR. YANCY: Thank you.

MR. BARRETT: Good morning, members of the advisory panel. My name is Burke Barett, and I'm the vice president of regulatory and clinical affairs for CardioFocus.

I'd like to thank the FDA both for the initiative made earlier this year to seek alternative clinical study designs for the evaluation of percutaneous A.F. devices and for the opportunity to speak briefly this morning.

CardioFocus is a small, 24-person medical device company developing a balloon-based catheter system intended to isolate the pulmonary veins in the treatment of A.F. We have no sales and only this one product, and so the clinical and regulatory environment for the evaluation of this product is the key factor we face as a company.

Let me describe our experiences to date. After a very straightforward FDA

review, our IDE was approved and we initiated our first clinical site in February of this year. Our study is an RCT with an anti-arrhythmic drug therapy as the control arm.

Our experiences with patient recruitment to date have been very challenging for a number of reasons, and details have been provided confidentiality to the FDA for the panel pack. Enrollment in clinical studies can in general be challenging, and so we looked at several factors in order to assess our enrollment experience.

We have recently made some protocol changes that may improve enrollment, but in general we believe our enrollment criteria are similar to most A.F. IDE studies ongoing as companies are working from the same FDA guidance as currently being implemented by the FDA.

We have a large number of study sites, currently 16, and we plan to expand and add more sites.

Our technology is investigational and that may cause some initial reluctance, but it seems to be interesting enough to the E.P. community and our clinical sites in particular to undertake this study.

Our clinical sites are all very active in A.F. ablation and have reasonably large A.F. ablation case volumes. Our clinical study sites report that patient reluctance to be randomized to drug after already having failed a drug and being referred to the ablation center is a primary reason for screen failures, even with the enticement of possible early crossover to ablation once a drug failure occurs.

To date our study sites have screened more than 60 candidates to enroll each patient.

The average of three ongoing studies based on data provided to AdvaMed, an industry trade association, shows that about 55 candidates need to be screened to enroll

one study patient. So in order to complete enrollment in a typically sized study of 200 to 250 patients may mean screening more than 10,000 patients.

This is a daunting task for the clinical study sites. If you extrapolate the screening experience onto a total of four to six ongoing plus soon-to-be launched percutaneous A.F. studies, the enormity of the patient screening effort in this field becomes obvious.

One company recently reported -- and we heard just a moment ago -- completing enrollment in an A.F. ablation study that took almost three years. Based again on data from the three companies that have ongoing A.F. studies and provided information to AdvaMed, we project a similar three-year enrollment period.

When the study initiation process of around a year post-feasibility study is added to one-year patient follow-up and one-

year post-study to gather data and prepare regulatory submissions, the current pivotal or Phase III process for percutaneous A.F. products is around six years.

This is for an acute procedure that typically lasts four to eight hours, non-implantable device, and we question if this meets the spirit of a least burdensome approach.

We evaluated the alternative clinical study design presented by Dr. Brockman in January of this year and we are very encouraged by this FDA effort to seek alternative regulatory paths to the current randomization-to-drug route.

However, at the time, given the unknowns of the design details that would ultimately be acceptable and the potential issues regarding powering that study, we decided to keep working on our ongoing trial as opposed to changing designs and restarting.

When we first designed our study,

we sought input from a significant number of E.P.s. We were told by many of them that a study comparing A.F. ablation and medication did not make for strong clinical science because patients that failed a drug are being randomized to additional drug therapy as the control.

Additionally, as we've already heard, the complications are not directly comparable between ablation and drug.

The publication of the HRS consensus statement on A.F. in May of this year was a significant event. It establishes, among other things, number one, that ablation strategies which target the P.V.s are the cornerstone of most A.F. ablation procedures; number two, definitions for follow-up and monitoring guidelines; and three, standards for reporting outcomes in clinical trials in Section 12 of the statement.

We believe that using the HRS consensus statement as a basis, reasonable

objective performance criteria or performance goals can be established for the evaluation of safety and effectiveness of percutaneous A.F. ablation devices.

Single procedure success rates using a 90-day blanking period and a strict criterion for failure over a one-year post-ablation follow-up could be established.

Likewise, ablation-related complication rates or performance goals could be established based on the literature and expert clinical opinion. We hope that you will consider this alternative OPC or performance-goal approach today.

Again, thank you for the opportunity to share the experiences of conducting our study today with the panel. Thank you.

DR. YANCY: Thank you again.

I'd like to thank all the speakers for your very thorough and pointed presentations.

We now have about 16 minutes for the panel to interact with each of the speakers, and I would ask you to direct your questions towards the given speaker, if that's possible, so that we can have a very efficient use of our time.

As I listened to the different speakers' presentations, I was struck that not all circumstances are associated with a failure of the ability to recruit. There's at least one trial that is fully recruited and results should be available soon.

There's another trial recently started that appeared to be 50 percent done. And I believe that in Dr. Waldo's presentation even the Biosense trial, despite the inertia, is accordingly close to completion as well.

We are sensitive to the most recent presentations that suggest that there are some major issues. And so these are things that we've heard.

We also heard intriguingly the

concept of adaptive trial designs, being able to adjust the trial size as we go, perhaps accounting for significant treatment effect.

Then we also heard some comments about being more flexible with enrollment criteria, and I think this is a circumstance where guidelines statements become terribly relevant; that is, having enrollment criteria that are in variance with those guideline statements.

So with that intro, let me yield to the panel to raise questions to the presenters.

Dr. Schoenfeld?

DR. SCHOENFELD: Just to reiterate Dr. Yancy's statement, I'm struck that Dr. Barold enthusiastically presented a nearly completed or a completed trial.

And looking at things, it struck me that one of the issues was -- and maybe there was a head start already happening in that three-year initiation, and then also the

issue of the amiodarone.

So a question to her I would ask is how would you distinguish your trial from other trials in terms of your ability to recruit?

I am separately struck by the other issues that have been raised by everyone -- Dr. Calkins exemplifies experience from a huge center that does a lot of trials. A lot of people are after him to get involved in more than one trial, as he also demonstrated by his two presentations.

And it harkens to a separate issue that I'm concerned about, which has to do with how you assure the two issues that FDA wants, which is safety and efficacy. If you want to recruit a lot of people, you then get a lot of centers, some of which may only do five ablations a year.

How do you standardize that? And I think that that's something else that I have as a concern for the FDA to address. In other

words, should there be centers of excellence that are doing this as part of the trials? How do you assure that type of concern?

But the first thing I would ask Dr. Barold is how she thinks that her recruitment is different from others that -- if she can provide some insight. Or do we eliminate the drug control entirely?

DR. YANCY: Mike on, please.

DR. BAROLD: Oh, sorry. I'm Helen Barold, and I'll answer your question. We strongly believe that a randomized clinical trial should be done, and we are proof that even a small company can complete this trial.

We are lucky that we have very good and motivated investigators. Our investigators believe in our product and they believe that this is a good trial, and they believe that the trial is important for the field.

And that's how we have sold it, if you will, to our investigators, and they -- so

they believe that this is something that should be done, and they convey that to their patients and are able to enroll.

It's been slow. It's been hard to enroll. But we've done it. We have used a number of sites. We have 24 U.S. sites. That is a lot of sites. We believe that it is important to have community sites, academic sites, high volume private-practice sites.

We do not have any small-volume afib ablators. They have to have met certain criteria in order to be part of the study.

But you have to remember that when the device is approved for an A.F. indication, it's going to be used throughout the community, and so we feel that it's important to give the -- whoever will be using the device an idea of how it's going to be used in all different types of hands, so -- you know, the very highly skilled academics and the very highly skilled private practice guys and girls.

So I think that the bottom line is -- is that we've got good investigators and they believe in the study, and that's how we finished enrollment.

DR. YANCY: This is just a generic comment, so please don't interpret it as being directed towards you, but one does wonder if there are inducements for the investigator to more avidly enroll based on reimbursement, because we certainly have to support our clinical enterprise.

Let's go to the next question. I think Dr. Blackstone had his hand up.

DR. BLACKSTONE: Dr. Waldo, you used two terms that I wish you would define for us. One is about inclusion criteria. The other is about assessment. Inclusion criteria is episodes of A.F. per time. Exactly what do you mean and how would you quantify that?

And what is your definition of A.F. burden and how would you monitor and obtain that?

DR. WALDO: Thanks, Gene. Well, actually, the per unit time is from the guidance. I mean, they talk about a six-month period. And the guidance originally said three episodes in six months, and now I hear that that's changed so that two is a very, very big difference.

And I'm not sure what the -- I mean, that as part of my theme, perfect the enemy of good. I mean, I think the ideal thing, the best thing, is clear, but it's been so very difficult to do, that to make enrollment a little easier and still have a rigorous, you know, valid trial is what our aim is.

Now, as far as burden, I'm not sure I'm -- I have a precise answer for you, but I mean, if you can -- I mean, there's a trial -- I had backup slides, actually, to show -- there was a recent trial just published this summer of only 14 patients, and -- but they had an A.T. 500 implant and this

is a Medtronic pacemaker that had terrific monitoring capabilities.

And so when they just looked at the -- at the efficacy of the trial on symptomatic recurrence, the efficacy -- it was 71 percent. But the harder they looked, the more they saw to the point where when they looked at just a Holter monitor at six runs -- weekly Holter, that sort of thing.

When they finally just looked at the A.T. 500, which looked at all the time, the efficacy rate was down to 43 percent. But striking as that is, when they looked at the burden, there was a dramatic decrease in the amount of atrial fibrillation that these patients had. Some had none. Three had none at all.

But of that burden, most of the patients had less than 30 minutes a day when they had something, but -- and not very often. So let me suppose that -- supposing a patient had three episodes a week of paroxysmal atrial

fibrillation before this, and even on drug therapy, and when you do the -- when you do the A.F. ablation, now they have X number of minutes, let's say 10, 15 minutes, once or twice a year, as an example, maybe that's a very good result.

So that defining what that burden is -- I think it would take a lot of heads to put it together, but I think a lot of us don't -- and that's in the guidelines -- want to talk about that, the HRS guidelines, that say that just the time to first recurrence is not the answer.

The total picture of how the patient feels -- and it's a lot easier if after ablation, for instance, not if the patient is symptomatic but the events are very infrequent. This is a very good treatment effect.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: Well, I was very encouraged by the information presented about

the positive movement to randomize clinical trials. And what I hear from the presenters was that there are three areas that might facilitate things even further.

And I wanted to ask the FDA, their clinical and statistical people, what they thought of, number one, relaxing the admiodarone requirement, especially in my mind if both arms of the study were -- had a randomization of amiodarone; relaxing from a -- the need to fail one drug to be randomized, because you would still have the randomization for -- and for one presentation that was 50 percent of their patient population that could have been in the study.

And the third thing is this little controversy of two episodes of A.F. versus three in the run-in period. Maybe we could just reiterate what is the current guidance on that.

But it seems to me a little tweaking of the system might facilitate things

and maintain the highest standard of evidence, which is the RTC.

DR. BROCKMAN: Let me take them in reverse order. The guidance documents are current thinking and the -- can you hear me? Okay. So guidance documents are our current thinking, and the catheter ablation A.F. guidance document was put out in 2004, largely written in 2003. That was four years ago.

Our thinking has evolved a little bit. I don't know -- I don't know that I view that as a huge change. Apparently some do. But going from three to two -- we recognize that companies have been having trouble enrolling, and that was one of the things we thought would help. So it's -- I don't think it's any more complicated than that.

In terms of allowing trials where patients are enrolled without having failed a prior drug, I think we've already discussed that. We have tried to follow the guidelines. And if you feel that we should be doing

differently, I'm certainly interested to hear those comments. But to this point, we haven't gone there.

And the first question was amiodarone. Actually, this is not something we've discussed internally. This has just occurred to me as we were talking about this this morning.

My reluctance to allow amiodarone use shortly before the ablation has been, in large part, because we wanted to capture effect off of drug after the ablation. And due to the long half-life, the long washout period, of amiodarone, I think it muddied the water in analyzing that data. And I still feel that way.

If, on the other hand, we were to look at whatever our end point is -- freedom from recurrent A.F. or freedom from recurrent symptomatic A.F. -- and the panel doesn't think it's important to differentiate whether or not patients are on anti-arrhythmic drugs,

then I think my reluctance to allow amiodarone shortly before the procedure would be less.

DR. YANCY: Certainly we have an extended period of time this afternoon to address the specific issues about amiodarone and about what constitutes failure of anti-arrhythmic therapy.

Let's continue the lines of questioning based on what the presenters gave us. I think Dr. Tracy was next to be recognized.

DR. TRACY: Just a quick question kind of reflecting the -- I'd like the FDA's reflection on what they consider burdensome. Some of these presentations -- it looks like there's three percent of the patients that are screened are enrolled, and the time for the studies is -- between inception and completion is six years-plus.

How does that stack up against other trials that have been done with ablation catheters, with other types of devices? Is

this a standard amount of time? Is this excessive? What is the feeling about this?

It seems excessive just on the surface, but maybe Dr. Zuckerman or somebody else could reflect on history here.

DR. ZUCKERMAN: Okay. I can't give you quantitative numbers, but I think everyone in the audience would agree that the system right now is not optimal. Hence our need to call this panel meeting, and to get all stakeholders in the room, and to analyze the situation.

But part and parcel -- and when I say analyze the situation, I do want to refer to the earlier comments where part of this problematic area right now has been fueled by off-label use, so there's a responsibility here for all stakeholders -- FDA, but also professional societies and industry, et cetera.

But we have what we have. I think we would all agree that we're looking for less

burdensome methodologies. But by the same token, we need to appreciate that our standard is at the time of a panel advisory meeting a reasonable assurance of safety and effectiveness.

And one only has to look at the panel meetings over the last year to understand how this panel has struggled when clinical trial tactics have been forgotten and we're just rushing to the goal line, or, better yet, I would again emphasize the comments made by Drs. Yancy and Blackstone at our panel meeting yesterday, where I think some of the same issues were raised.

So there's a delicate balance here, and there aren't going to be easy solutions. That's why we'd like you to do most of the heavy lifting.

(Laughter.)

DR. YANCY: So we'll let Dr. Page be the next lifter.

DR. PAGE: Just a brief question.

I'm concerned, when basically one or two out of 100 patients screened are actually enrolled, as to whether those -- that minority of patients represent the overall patients as a whole.

And along that line, we've heard five presentations. Are you keeping a registry of the patients who have been screened and not enrolled to make sure that when we do get an answer and a trial is complete whether those patients represent the patients that we as clinical cardiologists are seeing on a daily basis?

DR. YANCY: That's an excellent point.

Can someone from industry comment, please?

DR. BAROLD: We are not keeping a registry of the patients that are screened. We're, you know, up to here just taking care of the patients that are in the study. So no, we are not doing that.

DR. YANCY: Other questions from the panel? There are certain panel members that have not yet had a chance to -- please -- contribute.

Dr. Weinberger?

DR. WEINBERGER: As a non-electrophysiologist listening to this problem, I'm struck by the translation into practicalities. So burdensome translates into a particular enrollment size that you have to achieve in order to have the power to demonstrate effectiveness and safety.

So I'd like to pull back a minute and ask the FDA whether the safety end points are what's driving the -- the size -- the power necessary, or is it effectiveness end points and, if it's effectiveness end points, whether we could come up with surrogates that will reduce the burden on the sponsors.

DR. EWING: As a reminder, I'm Lesley Ewing, another electrophysiologist with the FDA. And that's a very long way to walk

over here.

The numbers are driven by safety assessment. It's a short answer.

DR. YANCY: Thank you.

Additional questions?

Dr. Neaton?

DR. NEATON: I just was going to ask the sponsors -- I mean, the suggestions which were made for expanding inclusion-exclusion criteria all made some sense to me, but they all, I think, would lead to a potential loss of power in terms of comparing the two treatment groups.

And so I presume that's been considered, and one feels that by relaxing them you could get a -- enroll a larger sample size in your study to preserve that power -- for example, concomitant use of amiodarone or reducing the number of prior episodes.

I think that would all kind of tend to potentially reduce expected treatment differences.

DR. YANCY: If there's no response to that, Dr. Slotwiner?

DR. SLOTWINER: Thanks.

I was struck listening to the sponsors' presentations at the progress that's actually been made with the clinical trials to date. As a practicing electrophysiologist who does these procedures, I'm very eager to have objective evidence demonstrating particularly the safety and efficacy. And I'm very aware of the difficulty in enrolling in these studies.

And I was quite willing to consider trial design B, the hybrid approach, but it sounds to me what I'm hearing from the sponsors is that there are small adjustments that we might be able to make that would change the enrollment sufficiently to continue with this more rigorous scientific approach.

And even if we were to look at trial design B more closely, I wonder if that would be taken up by the sponsors. And it's

my impression it might not be.

DR. YANCY: Interesting perspective.

Please, Dr. Calkins, feel free.

DR. CALKINS: I just want to make one comment about this alternate B which is coming up with the objective performance criteria. And I believe that that's impossible.

I mean, you heard the study that Al mentioned where, depending on how much you monitor, your success went from 80 percent to 20 percent or 30 percent. And you saw data presented earlier by Dr. Brockman showing the data from the -- from Germany where, you know, if you look for asymptomatic afib, your efficacy drops by about 20 percent or even further.

So we -- you know, there's a lot published on afib ablation, but if you look at how it was collected and how much monitoring was done for asymptomatic and afib, and if

they did it, none of the studies tell you what the compliance was to the monitoring protocol.

So I think you're just asking for trouble with this objective performance criteria, unless you pick 20 percent as your target efficacy or something like that. So I think that would be a very poor approach.

And the bigger challenge, which I think the group should comment on, which I think we struggle with is the issue of asymptomatic afib. And the guidance document now says that the goal should be elimination of symptomatic afib. So if you take the extreme patient, which we've seen in prior studies, they show up in paroxysmal afib.

You do an ablation procedure. They come back six months later in permanent afib but they're asymptomatic. And according to the current guidance document, that's successful. The patient's asymptomatic. They have no symptomatic afib. It's a success.

But hopefully everyone on the

panel would say if you went in with an intention of getting rid of afib and now you have permanent afib, it's hard to call that a success. And yet the primary end point of all these studies says that patient's a success. And we all know about placebo effect.

So I -- the consensus document which we struggled with for, you know, over a year -- you know, the -- our recommendation for a definition of success was freedom from afib, aflutter, acardia, symptomatic or asymptomatic off anti-arrhythmic drug therapy, which is the highest standard.

Now, when you have that high bar, the efficacy will obviously fall but, you know, it's the same thing if you go into a late afib and you end up with a left atrial flutter that's incessant, you could call that successful because afib's gone. Now you have an iatrogenic left atrial flutter. And prior studies that have been published have called that patient successful.

So this is why the published literature -- it was hard with -- we had a flutter panel meeting a while ago that was nearly impossible to come up with objective performance criteria. And this would be absolutely impossible.

So I strongly would discourage that alternative proposal and suggest you think more about, you know, the issue of how do we deal with asymptomatic afib and this issue about -- you know, all these studies are doing weekly event monitors.

And so either they have an event monitor showing afib -- they have no symptoms. When the panel meets to, you know, render an opinion, you're going to say well, that's -- that wasn't the primary end point, that's -- that's good, you know, we'll ignore that afib episode.

And I as an electrophysiologist say if I go in there to ablate afib, and a patient -- you know, and the afib's still

there, it's hard to call it a success, even if you caused it to be asymptomatic because of the natural history of afib.

And then the final comment, and I'll shut up, is -- has to do with this thing about afib burden which Al mentioned, which I think all of us who do this procedure see this quite commonly. You see a patient -- you know, five episodes of afib a day, or permanent -- you know, longstanding persistent afib. You do your ablation.

And six months later, they have a 10-minute episode of afib or two-hour episode of afib. The patient's tremendously pleased. They're off anti-arrhythmic drug therapy. They're happy as a clam. Yes, they had one recurrence.

And with all of these drug trials, we now would classify that patient as a failure, whereas the patient and the clinician performing the procedure would clearly call it a success and clearly would not recommend a

second procedure for that patient.

So I think that is really what I think the discussion, you know, should stretch to, is discussing the -- some of these tougher issues about when these studies, two of which are -- one's done, and one's almost done, and one's halfway done -- when they are done, you know, how you're going to try to interpret these results.

And I -- one final comment, if you will, is -- has to do with the question about the guidelines say to do an ablation you have to hit secondline therapy, you have to fail anti-arrhythmic drug therapy. And so that's really where this current study design came from.

And the reality is there's three randomized studies, small but randomized studies, looking at catheter ablation as first-line therapy. Each three -- each of the three has shown that catheter ablation is superior to anti-arrhythmic drug therapy.

So that's why patients are referred and come to us earlier on in the treatment modality. In the HRS/AHA/ACC consensus document we state that afib ablation should be performed, you know, after failure of a Class I or III drug, but we also say in certain circumstances it's reasonable to do as primary therapy.

And I think a very reasonable certain circumstance would be if this patient wants therapy sort of earlier on than you usually would apply it, and you have a randomized study where you're going to get incredibly important data in a careful way, and you have good preliminary data suggesting that might be the right answer, well, let these patients go on the study as first-line therapy after failing a beta blocker or calcium blocker. So thank you.

DR. YANCY: Dr. Calkins, let me just pose one question. I just wanted to be clear. From what I hear, you're suggesting

that as an electrophysiologist who is an investigator in these studies, you actually seem to be in favor of a traditional clinical trial design with the highest bar for resolution of atrial fibrillation, is that correct?

DR. CALKINS: Yes, that's correct.

DR. YANCY: And the comment you just made about the guideline statement -- I think the ACC/AHA statement says in rare occurrences R.F. ablation can be primary therapy. Is that correct, or can we get clarification of that?

DR. CALKINS: Well, the HRS -- the Heart Rhythm Society consensus document that was published this summer that was endorsed by the AHA, the ACC and the European organizations says that, you know, in certain circumstances it's appropriate to do catheter ablation as first-line therapy.

I'm not sure about the AHA document. I think maybe Rick was one of the

co-authors of that, or Al, or somebody. But I know in certainly the community of electrophysiologists and ablationists around the world, we consider, you know, certain patients -- they don't want drugs. They're young people. They come to you for an ablation. So we're doing it after appropriately doing this discussion.

But I'd much rather offer them a clinical trial where either they get a drug that has -- and by doing it that way, the drugs are more likely to work, because it's your first drug, you know, out of the block, as opposed to what we're doing now, which is sort of guaranteeing the drug arm's not going to work, you know, in virtually anyone.

DR. YANCY: All right. Thank you very much.

We've got a comment from Dr. Peters, who we've not yet heard from.

DR. PETERS: I agree with Dr. Calkins. I think before ablation gets too far

afield, we have one shot to do a randomized clinical trial comparing anti-arrhythmic drugs with ablation.

Hearing that recruitment is the biggest factor, I think, you know, as a -- somebody who deals with patients a lot, I could sit down with somebody and say okay, we have these two methods, we don't know which is better. I think I can convince a lot of them to go into a randomized clinical trial.

If we wait much longer, just like we did with angioplasty and bypass surgery, it will be too late. The ablation will have taken over, and we'll never get the information. So I would urge to use it as primary therapy and just offer it to people, and I think we'll get our sample size and do away with all the problems of bias and non-group comparability.

DR. YANCY: It's good to hear equipoise exists.

Dr. Schoenfeld?

DR. SCHOENFELD: I wouldn't -- I think I am inclined to agree with Dr. Peters and what he said as well. But I guess harkening back to what the issues are in terms of FDA, one of them is safety, and it's interesting to hear that that seems to be the primary concern of the two issues, the two mandates, safety and efficacy. And that seems to be easier, perhaps, to ascertain.

So then it goes, then, to the efficacy, which Dr. Calkins is addressing, and I guess what I would ask the various trialists or -- are you actually asking the patients why they're getting their procedures? What are they looking for? Why are we doing these procedures?

Because otherwise we're subjecting patients to a lot of intense investigation, a lot of potential risks, a lot of cost and expense. And so, really, what are the end points of what we're trying to achieve? And that will really, perhaps, drive who's

enthusiastic about going ahead with the studies.

And do you have that built into your trials in terms of what are the patients looking for, why are they coming for an atrial fibrillation ablation? Because it does strike me that, yes, you do have these patients that are now going to intractable left-sided atrial tachyarrhythmias or they're in chronic atrial fibrillation but feeling just fine, thank you.

So are they in there to feel better? Are they there to eliminate anticoagulation, which is another subject for discussion? Why are these people enrolling in the trials? Because that has a direct bearing on what we constitute or how we define efficacy.

DR. CALKINS: Let me address that. So I mean, the reason patients come to us is to feel better. And if you look at the consensus document, you know, the primary goal here, you know, is patients who failed one

drug or first-line but that have symptomatic afib. So clearly, that's the primary goal of what we're doing, is to make patients feel better.

We also make it crystal clear in this consensus document that anticoagulation should not be based on whether they had the procedure, not that that's not an appropriate indication of doing the procedure, but we need to follow the risk factors and anticoagulate them regardless of how you deem the procedure to be successful.

But you know, the argument for those that say that asymptomatic afib doesn't matter would be Mark's argument that if they came in to feel better and they're feeling better, even if they're in afib all the time, it's still success.

Well, that's an awfully risky sham procedure to do to get -- or -- because afib tends to get less asymptomatic as you go by, as you go from paroxysmal to sort of

persistent to chronic. There's a tendency to become less symptomatic. But fundamentally, if we're there to get rid of afib, you would think that afib should be done.

With the last comment being this thing about, you know -- you know, afib's almost gone, but not totally gone, you know, in the AHA afib document that was written last summer, in 2006, they make it very clear that a drug -- anti-arrhythmic drug can be considered effective even if you're still having afib provided the frequency or burden of the afib episodes is decreased enough where, you know, you continue a patient on flecainide if they're having two episodes a year lasting two hours.

And I think the same applies, you know, with atrial fibrillation ablation, that there are those patients that are dramatically improved. They aren't cured. I don't think we should use the term "cure," but that it is a beneficial therapy. But those are my

thoughts. But thank you.

DR. YANCY: Thank you very much.

We have time for two very brief comments, one from Dr. Morrison and then Dr. Zuckerman will have the last word.

DR. MORRISON: Well, I would just like to ask the other members of the panel if any of them are as shocked as I am to hear the FDA say we're designing trials where the sample size is based on safety rather than efficacy.

I can't think of a procedure in the history of medicine where we've gone to patients and say this is very expensive, it's very dangerous, we have no idea what good it does you, but we'd like to do it, and if we can talk you into a trial we're just going to see how many of you have serious adverse events.

If I'm the slow member of the class, please, one of you, enlighten me at the break. But it seems to me --

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DR. YANCY: So I think it's very appropriate --

DR. MORRISON: -- that efficacy is the issue.

DR. YANCY: Dr. Zuckerman, please?

DR. ZUCKERMAN: Thank you, Dr. Yancy, for giving me the last word, because this is --

(Laughter.)

DR. ZUCKERMAN: -- exactly the issue that I wanted to comment on to clarify certain things. And again, yesterday's panel session should be looked at -- upon as just a generic prototype of the common problem that we get into. I'm not specifically pointing out that manufacturer in any punitive way. It's a general problem that we see.

Our mandate is to be able to show at the end of the day -- conclude that we have a reasonable assurance of safety and effectiveness. So concurrent with Dr. Morrison's comments, certainly in a clinical

trial we have to see effectiveness and safety clearly demonstrated.

But the reality is that with this type of device treatment, as well as with many other device treatments, there are potentially devastating safety complications that occur with low frequency events, so that when you do a sample size calculation for safety and for effectiveness, the bigger sample size is the one that we want to see being offered in the trial, such that at the end of the day we've confidently concluded that the device is safe and effective.

Unfortunately, too often, we see the lower sample size estimate, and then at the end of the day this advisory panel sees an underpowered trial for safety, and they have real problems making a definitive conclusion.

Number two, the trial design that Dr. Peters and others suggested being a more broad, proof-of-principle trial is a very worthy suggestion and needs further discussion

this afternoon.

But again, I would underline that as opposed to second-line therapy, the offering of this technology as truly first-line therapy does bring into consideration some profound effectiveness and safety questions, from a sponsor's viewpoint might be a much larger sample size, and I hope that this panel will fully try to work that out this afternoon.

Finally, there's been mention of our most recent guidance document. I would like to clearly outline to investigators and the industry that guidance is guidance. Please always remember to read the first page, which is the preamble. Guidance is not regulations. It's not laws. It's only our suggestions at a particular point in time.

Certainly, we would encourage every sponsor to continue their enrollment logs. Certainly, after this panel meeting we're going to be very interested in meeting

with sponsors to see what can be done to perhaps revise appropriately trial designs in this challenging area. Thank you.

DR. YANCY: Thank you, Dr. Zuckerman.

We will take a 15-minute break. During the break, we would like for Drs. Packer, Prystowsky, Estes, McCarthy and Ad to ensure that your presentations have been uploaded so that we can move expeditiously once we reconvene.

We'll resume the meeting at 11:05. Thank you.

(Whereupon, the meeting went off the record at 10:54 a.m. and resumed at 11:10 a.m.)

DR. YANCY: Once again, if we could all gather and rejoin the meeting. Come to our seats so we can start on time, please.

Is A.V. ready to go?

We will now continue with the first open public hearing portion of the

meeting. Public attendees are given an opportunity to address the panel to present data, information or views relevant to the meeting agenda.

For the next hour, we have five speakers scheduled for this session. Each speaker has been allotted a maximum of 10 minutes to speak.

There is a monitor on the podium. When you see the yellow light, please begin to sum up. The red light is a prompt for you to bring your comments to close.

In the interest of time, we ask you to respect the time limits, be succinct, but please be thorough, as these are important issues.

The first scheduled speaker is Dr. Douglas Packer. Please inform us of your affiliation as you speak.

Eric, did you change anything?

DR. PRYSTOWSKY: We thought it would be best to start with this and let Doug

go second, if you don't mind.

DR. YANCY: That's totally fine. Thanks.

DR. PRYSTOWSKY: I'm not Dr. Packer, although I'd like to be at the Mayo Clinic. So --

(Laughter.)

DR. PRYSTOWSKY: -- I'm Eric Prystowsky. I'm from Indianapolis, electrophysiologist. As far as conflicts, I'm director of -- one of the board of directors at Stereotaxis, and I'm also a consultant for Bard, but I'm not -- I'm here really representing HRS.

And more importantly, I had a wee bit to do with this slide up here. I served on both guideline writing committees, and this is the updated maintenance of sinus rhythm algorithm that everyone's been sort of chit-chatting about today.

And let me just give you the background of it very quickly, and then I'm

going to really let Dr. Packer talk about our HRS statement, which I think is very important.

But to put in perspective why we have placed catheter ablation as a second-line treatment option, when we developed this back in '01 and then secondarily in '06, the concept was safety first. I don't think many people here would argue that probably, head to head, amiodarone typically wins in trials. That wasn't the issue.

Safety first was the issue. And at this time we wrote the guidelines in '06, we felt there were enough data actually in all four categories up there -- people with minimal to no heart disease, LVH, coronary disease and heart failure -- enough actually reported data to say that ablation could be absolutely available as a clinically relevant tool, okay, a treatment option for patients, not investigational, in all four of those categories.

And in fact, there was a lot of discussion in the left category of even bringing it up to first-line treatment along with the drugs. The only reason it wasn't is because we felt the worldwide safety data wasn't quite the same as the safety data from some of the best labs in the country, and so therefore we felt, with the data at hand, that we would list it as a second-line -- not investigational, mind you, approved, in our opinion, good clinical therapy.

So that's why it's there, and this -- in my opinion, some of the discussion that I listened to this morning is not really appropriately derived from the guidelines. This is the management currently of afib.

I would certainly, as a member of this committee, have never had a problem if you said in an investigational study, if you were happy using first-line treatment drug and first-line treatment ablation in an appropriate patient, I mean, that would never

bother me at all.

This doesn't mean we feel it's inferior to any anti-arrhythmic drugs out there. Not at all. That was never the intention. It was just meant as a worldwide guideline for safety. We quite feel it met first-line criteria. So I would, as a guideline member who had a lot to do with this particular slide, have had no problem with that, number one.

And number two, I'd like to remind everyone here that are so enamored with the idea that ablation is not approved, I was around in the early amiodarone days. I remember how amio got approved. I was in a meeting with the FDA in the Heart House in about 1984-ish.

And I think we all know it did not come through the approval process that is now rigorously imposed. It was basically given approval, and it's got a big black box. And unless on my flight from Indy this morning

between 7:00 and 7:30 someone approved it for afib, my understanding -- it's still not approved for afib.

So before you get overly carried away, do remember the most widely used drug, and the drug that's up there in four categories, is not FDA approved. So if you put amiodarone, Bram, up against ablation, then you have two investigational agents going against each other. So there's a conundrum.

(Laughter.)

DR. PRYSTOWSKY: Anyway, I just wanted to put a little into context this, and certainly be happy at a later point if there are questions to handle them.

I'd like to turn it over to Dr. Packer now. Thank you.

DR. ZUCKERMAN: The comedy aside, that is a relevant point, and that's why with trial design B from the FDA, again, we realize that sometimes standard of care is the most appropriate therapy, and that's how we'd like

this audience and panel to think about comparators. What is the most relevant standard of care? Forget the FDA approved indication for today.

DR. PRYSTOWSKY: Yes, and I appreciate that, because I would tend to support that.

DR. YANCY: Thank you again, Eric.

Dr. Packer?

DR. PACKER: I am Doug Packer from the Mayo Clinic. I am not Dr. Prystowsky. I am, however, representing the Heart Rhythm Society and was a member of the A.F. Ablation Consensus Task Force convened by the HRS for the purpose of providing a state-of-the-art review of A.F. ablation and then to report those findings, the findings of the consensus group.

The task force comprised 27 members. It was led by Hugh Calkins and was composed of members representing the ACC, AHA, European Cardiac Arrhythmia Society, European

Heart Rhythms Association, and the STS. You can see those that are listed there, and each one of those societies approved or endorsed this document.

My disclosure statement reflects substantial industry funding of my research activity and significant interaction with a variety of different research groups, and it's important to note that in the context of my comments.

So I think it's important to note that A.F. ablation has been practiced now for about 10 years. And each year there's someplace between 10,000 and 30,000 A.F. ablations performed in the United States. It's hard to get a good number or a good feeling for that number.

And despite that, there are no mortality data. There is nothing there that gives us any kind of indication as to what the long-term outcomes are. And I've listed here a variety of different questions that remain.

It's not my intent to review each and every one of those. Those are available in the HRS heart rhythm publication of the consensus statement.

You can see that they range in order from the impact of atrial -- ablation on atrial size to what's optimal ablative strategies for treatment of persistent and longstanding atrial fibrillation. Again, there are multiple questions that remain to be answered.

It is the consensus of the writing group that a writing of different clinical trials of different designs will be required to answer these questions. We believe that there will need to be sufficiently powered randomized mortality studies to get at some of the ultimate questions and answers.

CABANA is intended to do just that. That's a trial that needs to be held to a much higher standard in terms of randomization against available and best drug

therapy.

We believe that there should be multi-center clinical trials, that they're quite a bit more agile, can get at -- to -- get to answers of those vexing questions that I showed you rather quickly.

We also believe that there should be carefully constructed single- and multi-center registry studies. Now, the rationale for that is that these are the trials that tell us exactly how A.F. ablation is being performed, not necessarily what the consensus statement or the guidelines dictate.

It also gives us an opportunity to get at individual populations that might be significantly smaller -- hypertrophic cardiomyopathy, for example, or heart failure are a couple of examples.

And then finally, the industry-sponsored device approval studies that we're discussing today.

We came up with recommendations

from this consensus document, and the reason why we did is that if you look at the literature, if you were to try to come up with some kind of OPC criteria, if you were going to try to come up with some kind of performance guidelines, then you would find that the available literature have highly variable definitions and end points, substantial differences in treatment modalities.

The definitions of acute and long-term success are variable. There's variability of post-ablation blanking periods, follow-up, re-do and crossover treatments.

There's variability in accounting for asymptomatic A.F., as Hugh mentioned. And there's also incomplete accounting of adverse events, particularly the ones that occur after the first week.

And we look to long-term mortality trials to get us a very -- to give us the best notion of what to be -- is to be expected with

these kinds of therapies for that. But in the meantime, we basically have one week and perhaps as much as 30-day data.

We felt that if we were to make inroads with the consensus document that there should be a clinical trial section and that it should give a sense of minimum reporting. Now, this, again, is a consensus statement. It's not -- it's not a guideline statement.

Nevertheless, we felt that it would be advantageous to each one of us and for the better benefit of each of our patients to have minimum set of -- minimum set of criteria or requirements for reporting. Anyone could report whatever they want to, but they need to at least report this.

We believe that that should be dependent on the study designs. First, that the study's design should depend on the question to be answered.

Second, the trials assessing ablation outcome should not necessarily

require randomization against drug therapy, that there could be other randomization schemes.

Third, that randomization against an accepted standard of care ablation catheter may be sufficient for efficacy and safety assessment.

And we felt that sham procedures as a part of these studies are ill-advised.

So given that there may be differences in the approach or the design, at a minimum, reports from investigators, whether they're part of clinical trials or whether these are reports from individual single-site reports, there needs to be a clear description of baseline demographics, A.F. type and duration, and occurrence of cardioversion -- how long that last episode lasted before the cardioversion was performed.

There should be an adoption of the amended definitions of paroxysmal, persistent and longstanding persistent A.F. that are in

the consensus statement. The term of permanent atrial fibrillation does not seem to apply in the setting of atrial fibrillation ablation and surgical intervention.

The extent of the underlying heart disease, including atrial size and ventricular function, should be clear and the degree of non-cardiac disease needs to be specified.

We believe that there should be reporting of data based on a consistent initial post-ablation blanking period of three months. Now, it may well be that some trial or some group may prefer a different blanking period, but at a minimum, that information needs to be available such that trials can be compared or reports from single-centers can be compared across different boundaries and different studies.

And finally, additional reporting of occurrences or events during the post-ablation blanking period should be listed as early events, so while we tend now to ignore

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blanking period events, those would at least be recorded so that we would get some sense of what is being excluded.

We believe that there should be minimum requirements for monitoring follow-up. First, the requisite electrocardiogram documentation of recurrent A.F. in patients with persistent type symptoms -- these were intended to give us a means of identifying or differentiating between paroxysmal patients that have paroxysmal recurrence or persistent recurrences, and the intent was that there could be differences in monitoring intensity based on this.

Next event, monitor recordings in patients with intermittent symptoms thought to be arrhythmia-related. So event recorders of whatever type.

And then we felt that a search for asymptomatic A.F. at six-month intervals thereafter should be done using one of the following: Telephonic monitoring for four

weeks around the follow-up interval for symptom-prompted recording, and a minimum of weekly transmissions to detect asymptomatic events, again, with the emphasis being that we need to identify what events are asymptomatic and include them in our considerations of efficacy. Hugh mentioned that as well.

Twenty-four- to 72-hour Holter monitoring, or 30-day patient- or auto-triggered event monitoring, or some type of mobile cardiac outpatient telemetry would be acceptable.

We believe that the follow-up should be -- and that was the concurrence of the consensus group, that a minimum follow-up duration of 12 months would be advantageous, and that recurrences should include not just atrial fibrillation but also atrial flutter and the atrial tachycardias.

It's difficult to make a decision about exactly how long that episode should last. We came to the conclusion that any

episode lasting at least 30 seconds in duration that occurs after the blanking period should be classified as a recurrence.

One can then come up with different schemes and algorithms to decide whether or not that is complete or partial efficacy or whether it makes a difference from the standpoint of burden of the atrial fibrillation, but nevertheless, this would be a consistent guideline.

The primary efficacy end point of ablation should be freedom from A.F. and atrial flutter or tachycardia in the absence of anti-arrhythmic drug therapy, as Hugh mentioned.

And then follow-up should be reported. If we're talking about those off anti-arrhythmic drugs, they should be off a sufficiently long period of time that we can actually make some sense about the end point.

And finally, other end point considerations. The secondary end point of

freedom from A.F. and atrial flutter or tachycardia in the presence of previously ineffective anti-arrhythmic therapy is an important consideration that should also be included, and that A.F. burden should be considered separately from the primary efficacy end point.

Now some of the studies that have been reported merged that into overall primary efficacy end points. It's worth considering. It's difficult to document, but it should be considered separately.

We believe that the greater good is going to be fostered by standardization of some type of quality of life assessment and that all studies of A.F. ablation should include a complete reporting of major complications which is actually not done currently.

So again, this was intended to provide a state-of-the-art look at atrial fibrillation ablation. We as a consensus

group agreed to disagree on the final design of a clinical trial. We believe that these should be different, again, based on the questions being asked and answered.

But we do believe that those minimum criteria will allow us to make comparisons from one group to the next or one city to the next and perhaps come up with OPCs or performance guidelines. Thank you.

DR. YANCY: Thank you, Dr. Packer.

We will proceed next with Dr. Mark Estes.

DR. ESTES: Thank you very much, panel members, Dr. Yancy. I appreciate the opportunity to present on behalf of the American Heart Association who, as you've heard, has been involved with the guidelines and the consensus document. I have no relevant conflicts.

And I wanted to focus on, really, the documents that have been published, because I think that they serve to ground us,

look at clinical practice and can be useful in the discussions that ensue.

As has been referred to, this document was published in 2006 -- five different groups, 44 authors, 368 references -- a very scholarly document. And it really serves as the reference, I think, for answering the 11 questions which I received a day ago relative to the focus of this.

I'm going to try to make my comments, and as Dr. Prystowski has already indicated as a member of that panel that wrote the guidelines, for recurrent paroxysmal afib, A.F. ablation is appropriate if an anti-arrhythmic treatment fails. And that document in August of 2006 was quite clear that it was for second-line therapy in individuals who were symptomatic with afib.

And this becomes important because when we discuss anticoagulation, the AFFIRM trial, of course, enrolled patients who were candidates for either rate control and

anticoagulation or rhythm control, and it's an important distinction.

And then subsequently, for recurrent persistent afib, catheter ablation as second-line therapy for one anti-arrhythmic drug failure. But this is a group of symptomatic patients that were fundamentally different than those who were in the AFFIRM trial who were candidates for either group.

Subsequently, it's been referred to -- and as Dr. Packer presented as one of the authors, along with Dr. Calkins, on this -- a report came out which reflected, in fact, some of the evolution of the thinking.

This document, published in May of this year, stated that during the past decade catheter ablation of afib has evolved from a rapidly -- from a highly experimental, unproven procedure to current status of commonly performed ablations -- procedure in many hospitals throughout the world.

And during that time, actually,