that the Synergo system is effective. If not, what additional data or analyses are needed?

And what we're going to need is an official response to that question from each Panel member. So we'll go around from right to left for this first question, and pick a different direction for subsequent questions. So, Dr. Marcovich, your response to the question.

DR. MARCOVICH: Well, I certainly don't think this is perfect study, but I think as Dr. Connor pointed out, the magnitude of the effect was impressive enough that I think that in my opinion, the data are reasonable, or there's a reasonable assurance that the system is effective.

DR. TALAMINI: Thank you. Dr. Donatucci, your thoughts.

DR. DONATUCCI: I agree with it. It does appear to be effective, and I take a little bit of solace in the fact that I know that these patients by definition are going to be followed up. So it's not as if they'll be treated and then lost, and therefore if it's ineffective, we'll lose those patients. These patients will be carefully screened. So given the magnitude of the effect and the fact that they will be followed, I'm comfortable with that.

DR. TALAMINI: Thank you. Dr. Lippert.

DR. LIPPERT: Yes, I agree that it is effective despite the flaws.

DR. TALAMINI: Thank you. I can't see your name tag.

DR. BHUTANI: That's okay. Manoop Bhutani. What I feel is given Dr. Connor's comments that the design is not perfect, there are some statistical limitations but the magnitude of the effect was so large that considering the standard of care currently being BCG or MMC, that at least even if we discount some of these statistical considerations, it would be at least as effective as the current treatment but probably better and realizing that patients sometime may not respond to one therapy but may respond to the other, I think having more than one option, more than one effective treatment would make sense, and so that's what I feel at this point.

DR. TALAMINI: Thank you. Dr. Connor.

DR. CONNOR: I guess I agree with the Panel members who agree with me that the magnitude is large enough that it overcomes some of the biases that we understand exist. So I believe this is probably effective.

DR. TALAMINI: Okay. My answer to the

question, just going around the room, would be the same as well, that the effect is so great as to in my mind to overcome the statistical flaws. Dr. Dahm.

DR. DAHM: I also see that there are multiple issues with the study but the same way as we would, as we're willing to upgrade the quality of evidence that we assign to observational study of the effect size is large, and I suspect that this treatment is a lot less effective than it seems to be but it seems to be effective.

DR. TALAMINI: Thank you. Dr. Kalota.

DR. KALOTA: I think the treatment seems to be effective, and even if it was less effective than they're showing, it appears to be at least as effective as BCG and as a treating physician, there's many patients who can't tolerate it. So to have something else, even as effective as BCG, is worthwhile to me. So having potentially better is even better.

DR. TALAMINI: So just to clarify, you're saying that even if it was equivalent to BCG, there would still be an advantage in your mind as a clinician to have an additional therapeutic option.

DR. KALOTA: Correct. So there's that much margin in my mind if the statistics are off by quite

a bit.

DR. TALAMINI: Thank you. Dr. Redman.

DR. REDMAN: Yeah. Some of the concerns expressed, especially multiple sources of bias and the FDA questions, in my mind going back, I don't think there is that many biases in retrospect of look at the data. You can't collect pathology reports on patients who haven't had biopsies done. It appears from the data that cystoscopies were done. They were followed. The differences in mitomycin C, how it was administered, the control arm received mitomycin C as it's done in the office. So I don't think there's that many biases. In the two groups, when you look at them, even though weren't pre-stratified, they're similar. I don't see the bias there. The only one that can possibly exist is not having reviewed the pathology reports on entrance and see if they're complete pathology reports. So you can't assume that the inadequacies are the same in both arms. But the follow-up was done as stated and we have follow-up data and the treatment effect is substantial.

DR. TALAMINI: Thank you, Dr. Redman. Ms. Stokes.

MS. STOKES: Yes. I'll limit my response to the definition as presented to determine whether

or not Synergo is effective. And, in fact, when we defined it as providing reasonable assurance, I think that that is accomplished. I've gone through the definition clause by clause and I agree that as presented, it appears to be most effective, and the fact also that it is an alternative. Thank you.

DR. TALAMINI: Thank you, Ms. Stokes. Dr. Layton.

DR. LAYTON: Yes. I also believe reasonable assurance of effectiveness for the clinical study. I also feel that the device is doing what it's supposed to do.

DR. TALAMINI: Thank you, Dr. Layton.

So, Ms. Brogdon, in regards to Question 1, the Panel generally believes that the data is impressive enough as to overcome the clearly discussed and defined flaws in the statistical methods in the study, and that at least as an alternative therapy and more importantly as a better therapy, the Panel feels that this is effective. Is that adequate?

MS. BROGDON: That's adequate and clear. Thank you.

DR. TALAMINI: Thanks. So let's move onto Question Number 2.

Question Number 2 refers to Safety. Under 21 U.S.C. 860.7(d)(1), safety is defined as reasonable assurance based upon valid scientific evidence, that the probably benefits to health under conditions of the intended use, when accompanied by adequate directions for use and warnings against unsafe use, outweigh any probably risks.

As observed in pivotal Study 101.1 and the supporting clinical data sources, treatment with the Synergo system results in an increase rate of adverse rates, adverse incidences I think that should read, over mitomycin C alone, particularly posterior bladder wall tissue reaction, pain and bladder spasms. These events were generally mild, localized and transient. However, limitations in the design and conduct of the pivotal study potentially impair the ability to interpret the safety analysis including (a) the absence of concomitant medication information; (b) the retrospective completion of a portion of case reports forms; and (c) reliance on a small, limited study population to perform the risk/benefit analysis and generalize the study results to the general U.S. population.

Considering the design and conduct of Study 101.1 and the supporting clinical data sources,

please discuss whether the clinical data in the PMA provide reasonable assurance that the product is safe. If not, what additional data or analyses are needed.

And I think to keep things relatively random, why don't we start with Dr. Dahm and we'll go counterclockwise this time and come back around to me. So, Dr. Dahm.

DR. DAHM: So once again I think this was not the perfect study. I think the concerns that we have to review here are real. What is reassuring though is that the side effects or adverse events that were seen were mild in nature. So I think there's reasonable assurance that this device is safe in my opinion.

DR. TALAMINI: Thank you, Dr. Dahm. Dr. Connor.

DR. CONNOR: I basically agree and I would agree that even though we don't have as precise information as we want, the adverse events that seemed to be higher were short term and not terribly serious. So I would agree that the device is sufficiently safe.

DR. TALAMINI: Dr. Bhutani.

DR. BHUTANI: I agree that the device based

on the data thus far on studies and cumulative experience in Europe seems to be reasonable safe, and further assured by the fact that there are side effects that have been reported that have mostly been minor and self-limiting.

DR. TALAMINI: Thank you. Dr. Lippert.

DR. LIPPERT: I agree that the side effects, although higher incidence, are mild, this product is safe.

DR. TALAMINI: Thank you. Dr. Donatucci.

DR. DONATUCCI: I agree that when this product is used as indicated within the precautions, it appears safe.

DR. TALAMINI: Thank you, Dr. Donatucci. Dr. Marcovich.

DR. MARCOVICH: I agree also that it is reasonably safe.

DR. TALAMINI: Thank you. Dr. Layton.

DR. LAYTON: Yes, I also agree there's a reasonable assurance of safety. The adverse events I understand and I'll look at them and address them.

MS. STOKES: Yes, I find that the benefits to health clinically outweigh the adverse conditions that may exist, and I find the product reasonable assured that it is safe.

DR. TALAMINI: Thank you, Ms. Stokes. Dr. Redman.

DR. REDMAN: I agree that there's a reasonable assurance that the product is safe from the data that we were given.

DR. TALAMINI: Thank you. And I would share that opinion.

So, Ms. Brogdon, in regards to Question 2, the Panel was -- oh, I am so sorry. Dr. Kalota.

DR. KALOTA: I'm going to agree with the rest of the Panelists.

DR. TALAMINI: Okay. So, Ms. Brogdon, with regard to Question 2, the Panel sounds unanimous in their opinion that there's a reasonable assurance that the product is safe. Is that an adequate response?

MS. BROGDON: Yes, it is. Thank you.

DR. TALAMINI: Thank you. So moving on to Question 3, post-approval study, and I will read it as written although we sound as if we have information to the contrary.

The firm proposes to conduct a single-arm post-approval study, in which 211 subjects will be followed for 12 months to further evaluate the safety of this combination product. If the Synergo system

is recommended for approval, with or without conditions, please discuss whether the proposed design of this post-approval study is adequate to address all relevant remaining safety and effectiveness issues. If your deliberations, please discuss the following:

(a) The firm proposes to evaluate safety by comparing the frequencies of adverse events to those reported in Study 101.1. What would you suggest as the most appropriate comparator, and why?

(b) The proposed study does not include a plan to assess longer term post-market effectiveness in a larger, more diverse population. Should longer term effectiveness be studied post-market? If so, what endpoints should be evaluated?

(c) The current proposal includes one-year follow-up. Is one-year follow-up sufficient to assess the long-term performance of this combination product?

(d) The firm proposes non-inferiority tests for the 8 specified adverse events, using delta values of 10 percent and 5 percent for common, i.e. greater than or equal to 50 percent, and rare events, respectively. Please discuss the need for clarification of definitions of common versus rare

events, and the rationale for delta values and what might be appropriate in each case.

So I would ask the Panel members to do their best to answer these specific in the record questions with the knowledge that we've gained regarding the sponsor's plans as we've heard them. And I think each Panel member needs to address (a), (b), (c), and (d) separately to the extent possible.

Recognizing that this may be a slightly larger task than the other questions, Dr. Kalota, would you be willing to begin since I almost forgot you last time, and then we'll go clockwise.

DR. KALOTA: Okay. As I understand it, (a) is already going to be readdressed. I think the way that my understanding of what they're proposing now is more appropriate. As someone who is not in academics and doesn't write papers, it's much more useful for me to see absolute frequencies and numbers and not comparison to a previous study that the way it was previously suggested that they were going to do non-inferiority, I get lost on that. So the current way that it sounds like is proposed sounds much more effective to me.

DR. TALAMINI: So your suggestion as the most appropriate comparator would be what?

DR. KALOTA: Just delineating the safety issues rather than a non-inferiority.

DR. TALAMINI: Okay.

DR. KALOTA: I think in the long term, we need a longer-term study but for a specific post-market study, a year is probably appropriate. I don't see -- (b) and (c) to me sound very similar. One-year follow-up, I think there was a statistically significant difference in the results and so one year probably will show us what we need to see, but as a clinician, a minimum two-year follow-up would be appropriate. For FDA, one year I think is fine.

And (d), again we're getting into non-inferiority tests and I'm getting lost on the question of statistics there.

DR. TALAMINI: How about the issue of common versus rare events? Do you have an opinion there? If not, fine. We'll move on.

Ms. Brogdon, do you have a clarification for us?

MS. BROGDON: If they list all their side effects and all their events, then I think that's sufficient.

DR. TALAMINI: I think Ms. Brogdon is going to help us out here.

MS. BROGDON: I don't know if I'm helping here. I would just like to clarify what you said about one year versus two years.

DR. KALOTA: When I see my patients, I'm always having them -- for the first two years, I need to see them every three months. I think that's when the most common recurrences occur but as we saw in an early slide, the most common recurrences are in the first three to six months. So by one year, I think we do have sufficient information to make a determination on the results, but as a clinician, I'd like to see longer studies but it's purely a preference for my information. I don't think it's necessary for a FDA purpose. So one year would be sufficient in my mind.

MS. BROGDON: Thank you.

DR. TALAMINI: Dr. Redman, are you ready to tackle this one?

DR. REDMAN: Sure, (a), I think just reporting the incidence in numerical percentage points would be adequate at this point in time based on the toxicity profile, what we've seen with at least 101.1. So I think that answers (a).

(b), I might be a little confused on. My feeling is that if we have a problem with the

effectiveness of the agent, then we shouldn't be approving it, that we did already or recommended for approval. So I thought this applied to toxicity, and so I don't think there has to be a longer term for toxicity. My understanding is that as a urologist, this treatment is essentially six months, eight weeks and then monthly for four months, and that's six weeks and I'm assuming one-year follow-up for toxicity at least would be more than adequate for mitomycin therapy. So I'm not sure I'm answering that question. As far as toxicity, I think this study is proposed, post-marketing study for toxicity is fine.

DR. TALAMINI: For one year.

DR. REDMAN: For one year. I will, and I don't know if you can tell me this is off, can't do this, but I would suggest, not that I want to add another data point in, but one of the data points for toxicity be percentage of patients who are able to complete the full cycle of therapy and didn't stop because of recurrence but completed the full cycle therapy because a lot of times patients say I can't do this anymore and we as doctors don't really mark it down as a toxicity. So I think it would give some information of how this works out in the American

population which may not be as strict as the Italian population and say you need to do this and they just say, no, I'm not. So I think catching the data on how many complete the full cycle of therapy and don't stop because of recurrence, but stop for other reasons would be important to know.

DR. TALAMINI: So do you -- going back to (b), I think that the concept behind that is that the original studies were not done in a U.S. population. They were done in an overseas population.

DR. REDMAN: Right.

DR. TALAMINI: So I think one question is -- I think we need to answer that question with that in mind, and also the question of longer-term effectiveness. Do we need longer term effectiveness studies as part of a post-market study or not? It sounds like your answer was no.

DR. REDMAN: I'm assuming that we will have longer follow-up on the Study 101.2, the BCG, yeah, the study is going to be followed long term. I sort of look at this as if we think we need more effectiveness data, then we should be saying that there's not enough data to say it's effective now I guess. When I read the material, I didn't get the sense that the post-marketing study was for an

efficacy endpoint. It was for, lack of a better word, feasibility toxicity, can this -- is this safe when administered by American physicians to the American population.

DR. TALAMINI: Absolutely correct, that we can use the post-market plans to predicate our recommendations about approval or not, but say for instance, the device comes to America and for some reason, Americans respond very differently. Do we need to -- does the study, if it's going to occur, need to take that possibility into account?

DR. REDMAN: Well, if you're asking me as a medical oncologist, do we want efficacy data, I tell you all the time, yes.

DR. TALAMINI: Okay.

DR. REDMAN: The more, the better. But I guess the question is, is this study geared for us since it's not randomized, if it comes back and does not match the efficacy data exactly or close enough to 101.1 or the 101.2 arm with this methodology, and I apologize that I'm doing this from the drug perspective, I mean I'm looking at this as it's already approval, do you then pull it?

DR. TALAMINI: Separate question.

DR. REDMAN: Well, I guess what I'm asking

is if you're going to ask the sponsor to collect efficacy data, it's because you would act on that efficacy data. If you're not going to act on the efficacy data, then it's an extra, costs them more money, you know.

DR. TALAMINI: Yeah, I agree with you but with respect to this question, the assumption here is that there will be a study, and if so, what should it look at. That's great. Dr. Dahm, did you have clarification?

DR. DAHM: Yeah, I just had a comment. I mean we don't know whether we're going to get additional data from Study 102. It might get stopped early for benefit for instance. So if we want additional effectiveness data, I think we should decide that it should be part of the post-approval study.

DR. TALAMINI: Ms. Brogdon.

MS. BROGDON: I don't want you to feel that every Panel member has to commit themselves on all four parts of these questions.

DR. TALAMINI: Okay.

MS. BROGDON: We don't want to squelch the discussion that the committee needs to have. So what we need at the end is a consensus on the various

parts of this question, but I don't know that you discussed this enough to really come to a consensus.

Also, I wanted to ensure that you understand the purpose of our asking this question. If your recommendation in the end for is approval or approvable with conditions, then the question would be pertinent, whether there should be a post-approval study. So we're discussing this now as a contingency. So we would certainly like to hear all of your thoughts on the necessity of a study and what it should cover, what the purpose of it would be, and I would call your attention to slide 103. That was part of the FDA presentation about the various rationales for doing a post-approval study, and they would include longer term performance, community performance, that means outside investigational sites, effectiveness of training programs, subgroup performance, collecting data on rare adverse events and real-world experience. So these are some reasons for doing post-approval studies.

So again, I don't know that each member has to commit themselves on each part of this right now. We want to have a full discussion.

DR. TALAMINI: Got it. Dr. Donatucci.

DR. DONATUCCI: Yeah. I'd like to ask the

FDA a question that I had this morning but I was holding. In order to discuss post-market studies, one has to understand what would occur if there were no post-market study both in terms of tracking of adverse events and reporting of adverse events. Now, this is a combined product. I'm well aware of what happens in the drug realm, that there's a very strict mechanism. Any adverse event reported to a manufacturer has to be reported, codified and sent to FDA within a timeframe, et cetera, et cetera, and so you do signal analysis and you look for rare events.

With a device that's only been used in less than 200 people to date, rare is relative. And what happens to a device that is a combination that gets approved, goes to market, outside of this study, how are adverse events recorded prospectively?

MS. BROGDON: I'm looking for one of the statisticians who would have been involved in this, excuse me, epidemiologists who would have been involved in this. Dr. Wei, do you have a response to this, on how adverse events would be captured by CDRH versus CDER?

DR. LOYO-BERRIOS: My name is Dr. Nilsa Loyo-Berrios, the epidemiologist in the Office of Surveillance and Biometrics, and we do the post-

market surveillance for the devices. One of the post-market tools we have, it's called the MDR reporting system, and it's a passive surveillance. That means we receive voluntary reports from users, from facilities, and then the sponsors do have to have some requirements to submit deaths and injuries and malfunctions and all that. So through that system, we collect some of the adverse events that may happen outside of a control study.

DR. DONATUCCI: So I guess if you're going to do that, then the question is what, beyond the studies and the data that we've already seen, what do we require the manufacturer to provide that won't be captured through that mechanism?

DR. LOYO-BERRIOS: This mechanism is somehow limited because it depends on voluntary reports. This means we don't get all of them. By doing post-approval studies, if the Panel believes safety's a concern, then it should be addressed in a post-approval study, then there should be a hypothesis for the safety endpoint with power to study to test that hypothesis and then conduct the study.

DR. TALAMINI: Thank you. So since this question was written when there was a proposal on the

table that it sounds like is now up in the air, perhaps the Panel needs to think about this even though this is in the record at a higher level, a broader level of knowing, you know, having learned about this device and read all the data what issues there ought to be -- what issues should be considered if a post-market study is to be done. Perhaps that's a broader, easier question to address. Dr. Connor.

DR. CONNOR: So I think that's a good point and I'm glad you've brought the conversation back to here, and along that line, while you're here please. I guess so the -- ideally for clinicians it would be great to see a summary of adverse events, but from a regulatory standpoint and this gets out there and then there's a problem and maybe the device were recalled so to speak, is the post-approval study as currently proposed, is it of any benefit or is it doing anything other than getting clinicians data that they would want meaning it seems like -- there's nothing formal going on testing adverse event-wise in the current proposal, but you have a system in place that informally tracks adverse events if they happen that is self-report on the doctor's point of view which would then initiate some sort of action regulatory-wise if there's a problem. And it sounds

like that would happen anyway and that would be independent of the currently proposed post-approval study. So I wanted to make sure I understood that the current post-approval study isn't helping withdraw this product from market.

UNIDENTIFIED SPEAKER: Correct.

DR. TALAMINI: Dr. Redman.

DR. REDMAN: I'm sorry. To get back to this efficacy because I'm looking at the synopsis provided by the sponsor, but if you want to add efficacy on, you're going to have to collect in some reasonable fashion the initial stage and grade of all the patient's under -- such as the fact that if all of a sudden on this study post-marketing doesn't show the same result as 101.1, you'd have to go in and find out, well, is it because 90 percent of the patients were T1 grade 3 whereas in the initial studies they weren't that, or if it's highly superior, it may be -- you're going to have to accept the fact that it might be 90 percent of them are Ta grade 2 patients. So I don't -- I think that it puts a burden on, a further burden which you can do, you know, to the company saying if you want efficacy. As I read this, the main purpose, the only purpose was, and I guess we have the right to change this, but the

only purpose was to determine the toxicity, the side effects profile of the regimen.

DR. TALAMINI: Ms. Stokes, do you have thoughts on Question 3 and you don't need to go through the four points.

MS. STOKES: Thank you. As to (a), I think that the comparison to the frequency of adverse events, I think should be the comparator. I think we need some history. There is going to be a post-approval study, then with a new group of subjects, then we have some history upon which we can compare and look at the differences or the similarities as well. So I think that's a good comparable as stated in (a).

In terms of post-studies, long-term projects, long-term performance, I think the one year, I'm looking at (c) specifically, I think that the one-year follow-up appears to be sufficient. I think they needed to be tight controls over any new study group. And one concern I do have is, is there a long-term effect of heat upon the bladder? Are there any negative outcomes? I thought about the animal study, and the one thing I was concerned about is how long was this study conducted on the sheep? What was the data? We didn't hear about that. We

just have the conclusion that there were no adverse effects, but I assume that there had to be something but it wasn't disclosed in the information provided. My only concern to that, while the study group, here it's limited to 211 subjects, I'm not quite sure how you arrived at 211 when in the previous study it was difficult to even end up with 100 subjects, and I'm not sure why that occurred, but I think that hopefully we'll be able to get a sample that sort of represents what is actually happening in the community or the subjects that we look at altogether. Is 211 subjects representative of total number of patients that are out there with this particular condition, this particular bladder condition? Those are my comments.

DR. TALAMINI: Thank you. Does the Panel have a response to those comments or thoughts?

(No response.)

DR. TALAMINI: Dr. Layton, your thoughts on this question?

DR. LAYTON: Yeah, I have real short comments relative to what -- point (a), just reporting the incidence is adequate. (b) I'm not going to comment on. (c), a year is sufficient as far as I'm concerned. And then (d), common versus

rare events, I think a list of percentage, that type of thing is adequate.

DR. TALAMINI: Thank you. I'm having trouble getting, and maybe there isn't one, a consensus from the group about these -- certainly there seems to be developing consensus regarding absolute numbers and frequencies and perhaps the one-year length, but this question of the American population versus the European population, I haven't really heard anybody speak to. So perhaps that's not an issue or if it is, then the remainder of this discussion on the question, please bring it up. Dr. Marcovich, you're thoughts.

DR. MARCOVICH: Yeah, that was going to be an issue for me. I think, yeah, maybe they are the same population but we don't know that for sure, and I don't see why you would not want to track the efficacy of this in the U.S. population for some period of time. Maybe it does put more of a burden on the company but I'd rather have the burden on the company rather than on the patients that are submitting themselves to this.

DR. TALAMINI: What period of time?

DR. MARCOVICH: For the efficacy, I think one year would be a minimum, and that to go along

also with the safety.

DR. TALAMINI: What about the question of rare events versus common events? In a post-market study, should a post-market study attempt to detect rare events?

DR. MARCOVICH: I think every event that can be detected should be, you know, surveyed or it should be out there that, you know, one person has a catastrophic complication like a perforation, that should be noted. It can also be noted that it was an extremely rare event, but that should be noted. And I think the current method of, you know, voluntary recording is not adequate.

DR. TALAMINI: Okay. Dr. Donatucci.

DR. DONATUCCI: I'll try to be brief which is tough for me but I don't have an issue with the efficacy data. I'm more concerned about whether a post-market study of adverse events in a control population would be reflective of what will happen when the device is introduced into the general physician pool, and that's why I was concerned about what happens outside this study. Previous devices that were carefully studied, both pre and post-market, still had a significant number of adverse events that hadn't been anticipated due to improper

usage. So that's really -- in my mind, that's really where I would have some concern.

As far as the population, if anything, the European population tends to have more smokers today than the U.S. population. So I think the efficacy probably should be, if anything, better in the group in the U.S.

As far as duration, since you know that recurrences occur, by two years, that's going to be the maximum number of recurrences, and that's the endpoint. If you're going to look at it, then it would be two years. I'm not sure based upon our answers that it was safe and effective to start with, that it's necessary.

DR. TALAMINI: Thank you. Dr. Lippert, do you have thoughts?

DR. LIPPERT: I think he -- I was going to say what he said about the efficacy. If you're going to do it, it has to be two years, but I don't see the point on efficacy. To me, the point of this post-market -- post-approval would be safety and self-reporting is not appropriate. I've been in too many situations when something's not been right and everybody's just too busy to make the phone call to report it, and it doesn't get done. So I do think

that some safety is appropriate but not efficacy. And a year for safety's fine.

But I have the same concerns that he does about devices in a bigger population. I don't know how to deal with that with post-approval study. I wish there was a way to collect data that wasn't just voluntary.

DR. TALAMINI: Dr. Donatucci, I'm still struggling to hear a consensus, but we'll try and hear from everybody and see what we've got. Dr. Bhutani.

DR. BHUTANI: Well, regarding efficacy, I, as a clinician, I would like to see a two-year data in the U.S. population considering there are not U.S. studies on this device, but I think given the European data, it's not something that is necessarily a mandate to the company to bear the cost to do it but just it would be good to, since two year is the cutoff where all the other studies have looked at recurrence, it would be good to know that in the U.S. population but since most recurrence happens in one year, a one-year post-marketing study's planned anyway for safety, at least looking at the recurrence and the efficacy, at least at one year it would be I think appropriate.

And as far as safety is concerned, I think we should -- record all adverse events and it would be worthwhile to compare that with the frequency of adverse events in 101.1 in the European population to at least, since we know that we feel the adverse events in 101.1 were acceptable and minor and the frequency was low enough, we would like to know, I would like to know if that frequency is still low, and also if there are more adverse effects early on in the study during a period of training where physicians are being trained to do this, and I heard in the PAR presentation by the sponsor that there will be training of physicians during the PAR, and I think in my opinion, it would be very helpful for physicians involved in PAR who are getting trained and the ones who are training them, presumably they will be the physician in Europe or Israel who are doing this, to perhaps develop a threshold of minimum number of procedures required to be -- feel adequately competent which will be very useful for the general community as they venture into this device. And that's all I have to say.

DR. TALAMINI: So just one point I think of clarification. An initial post-market study has been talked about but what this Panel will have to decide

is whether the Panel feels they need to recommend that as part of our recommending approval or not. So, you know, that may or may not happen out there but for our job today, we need to figure out whether we think it's necessary or not. The discussion that we're having now is over what the study would look like if we did say it was necessary. So it's kind of convoluted, but -- Dr. Connor.

DR. CONNOR: Thank you. For (a), regarding a comparator, as I stated, I think the current idea of no formal comparator is the best comparator. They say all politics are local, but on a way, all medicine is local, too. So, you know, a clinician can see what the adverse event rate is published for, you know, all the Americans who receive this device, and they need to compare it to the alternative, and the alternative is probably their alternative in their practice in how they do whatever the particular alternative might be for that patient. So I think that's fair.

I also think it's fair though for those who want to see other data, maybe if this is published in a journal or somewhere else, that the European MMC data be replicated there just in the table. That way a clinician could. But I think no formal comparator

to me is the best comparator.

(b) regarding effectiveness, I think that we voted nine to nothing that we thought this was effective. So I think if (b) were concerned, we shouldn't have voted the way we did.

DR. TALAMINI: We didn't vote yet. You can't use that term.

DR. CONNOR: Nine of us indicated that we thought, yes, whatever we did back then.

(c), I think one year is enough information for adverse event data for me.

And (d). So I think to clarify something you said earlier, the question isn't I think whether we would or you would measure common versus rare events. Here it was whether common versus rare events had a different delta, and delta has gone away assuming we're not using a formal comparator. So you're still going to measure common versus rare events. So that's less relevant.

My question or the big thing that hasn't been brought up between the first proposed and your more recent proposed post-approval study was the sample size. I assume 211 was arrived at via power calculation using these non-inferiority studies, and the new proposal which I liked better, the sample

size is now 120, and I just wondered if there was any justification and you don't have to answer this because we haven't determined whether we even want to recommend a post-approval study. But if that happened, I would like to understand how that sample size came about and whether that will be enough to provide a precise estimate of adverse event rate since that's the goal.

DR. TALAMINI: Thank you. Dr. Dahm, further thoughts on this?

DR. DAHM: We need to focus on the things that are still under discussion. So I would agree with some of the other Panel members, that I would like to see effectiveness data from the United States. I think that would also be important for the clinicians that are going to use it. I think it would actually help the company with this, too, but that as an aside, I would ask for two-year data, and I would based that on the figure that would provide it with regards to the natural history of patients with bladder cancer that approximately 90 percent of them will recur at two years. So I would choose that as the timeframe.

To enter kind of a new thought, I think, I would love to see subgroup data on effectiveness for

the intermediate versus the high-risk group. I don't know whether that's something that we're interested in discussing but I think that might be an interesting focus of a post-approval study. We have so few patients that I don't think the current studies allow for that kind of analysis in an appropriate way. But I think since these two groups are prognostically different and the guidelines, you know, differ in the management, it would be nice to see how the device performs in each of those groups.

DR. TALAMINI: Thank you. So, Ms. Brogdon, with respect to Question 3, if there were to be a post-approval study recommended by the Panel, I don't think I could give you a clear -- I don't think there is a clear consensus and I therefore don't think I can express one to you regarding what that study should be with the exception that the Panel sounds like they agree on looking at absolute frequencies of events and that one year is adequate for adverse events but I think you do have on record a wide ranging discussion regarding the issue. Is that adequate?

MS. BROGDON: Let me just ask Dr. Nilsa Loyo-Berrios if the epidemiologists have any questions about the lack of comparator.

DR. LOYO-BERRIOS: Yes. We do believe that formal comparison is needed because it helps us put the study results into context and perspective. Say for example, the endpoint of interest is safety, is the safety of this device better in reference to what? Is it in reference to the standard of care or to any other treatment available to these patients. So we do believe a comparison is needed to help us put the study results into context.

DR. TALAMINI: Dr. Connor.

DR. CONNOR: So just a clarifying question for my own benefit. You and another FDA statistician has mentioned standard of care as the comparator here. That's usually a vague term. So if we recommended that the comparator be standard of care, is that something then that Medical Enterprises would have to discuss with FDA to identify for each adverse event how one estimates the standard of care rate because I'm just not sure I understand what that means.

DR. LOYO-BERRIOS: Well, whatever endpoint we decide would be the main endpoint of the study, then we will discuss with the company what would the best comparator be.

DR. CONNOR: Okay. And since you say main

endpoint, does that mean that the study would have one or two or just a few primary endpoints versus --

DR. LOYO-BERRIOS: Correct.

DR. CONNOR: -- I think what we were wanting to see is a list of adverse events that may have 15 or 20 but did provide information to clinicians.

DR. LOYO-BERRIOS: Correct, one or two or three endpoints, that would be the focus of the hypothesis test.

DR. CONNOR: Okay. Thank you.

MS. BROGDON: I'm feeling a little bit uncomfortable about this discussion because we are not pushing the Panel to recommend anything in particular, and I think it would -- I'd feel better if the Panel could understand this discussion that just happened as sort of a general discussion that applies to any post-approval study that FDA ends up requiring with a sponsor. We end up discussing protocols with them and what the comparators would be and so forth. So I don't want the Panel to take this discussion to mean we are pushing you to recommend a post-approval study.

DR. TALAMINI: Understood. Does any Panel member have a question about that, Ms. Brogdon? Yes.

DR. BHUTANI: So I'm trying to understand what this comparator means. You want to compare it to standard of care and does that put the onus on the sponsor to also conduct a trial with a standard of care delivery and compare adverse events? Otherwise -- well, I'll just stop here.

DR. LOYO-BERRIOS: That was just one example. The comparator, they can come up with a comparator. It could be historical controls. It could be -- I don't want to give any more examples because then you will think that I'm suggesting they do that but it doesn't have to be -- we are open to suggestions from the sponsor.

DR. BHUTANI: Okay. How about --

DR. TILLMAN: Hi, good afternoon. I'm Donna-Bea Tillman. I'm the Director of the Office of Device Evaluation, and I just wanted to, because the Panel seems to be sort of struggling with this issue. I just want to sort of put back into perspective why we ask companies to do post-approval studies and how that works. You've heard some conversations about hypotheses.

What's going to happen in not too much longer is you guys are going to make a vote, and you're going to vote about whether you want to

recommend approval, approval with conditions or not approval, and if you think you need a post-approval study, then you're going to vote approvable with conditions, and then we're going to ask you to tell us what that post-approval study needs to look like. So at some point in time, you're going to have to come to some kind of consensus about this, if you do end up going there.

When we ask you about post-approval studies, what we need to know is what is the question you're trying to answer with the post-approval study. The statisticians and the epidemiologists sometimes think of those as hypotheses but we do post-approval studies for a reason. And so what we need to hear from you is, if you determine that there is a reasonable assurance of safety and effectiveness, that's the first bar, and therefore the device can be approved, are there additional questions that remain regarding safety and effectiveness that you think can and should be answered in the post-approval setting? What are those questions? And then the statisticians and the epidemiologists can help us put those questions into more formal terms.

It sounds like from some of the discussion I've heard that what you're saying is that maybe the

question is what are -- you'd like more precise estimates of the adverse event rates to put in the labeling so physicians can make informed choices about how to treat their patients. So the question there would be what are more precise estimates of the adverse events rates in the U.S. population? That would be a question that you might say that you would like to see the post-approval study answer.

So what we'd like you to do instead of getting too sort of tied up in knots about some of these details is take a little bit of a step back and say, if you do think that the device can be approved, are there additional questions that you'd like to see answered. And I think if we could start with the questions and then get into the details, we'd be a little better off. Anybody have any questions for me about that?

DR. BHUTANI: Yes.

DR. TILLMAN: Yes.

DR. BHUTANI: So if I pose a question based on what you said --

DR. TILLMAN: Uh-huh.

DR. BHUTANI: -- based on our earlier discussions, based on the data from Europe, we feel the device is sufficiently effective to be

potentially approved.

DR. TILLMAN: Okay.

DR. BHUTANI: And we're accepting the European data, and we've also accepted at least in our discussions that there is sufficient evidence of the device being safe because of frequency of adverse effects was minor and low enough to be of acceptable risk/benefit ratio.

DR. TILLMAN: Okay.

DR. BHUTANI: So if I pose a question, I don't want to compare it to BCG or anything because right now safety profile appears to be, in relation to BCG, be acceptable, that it is introduced in the United States, and U.S. physicians perform it, does the safety profile of that stay low enough and safe enough? So my question would be after introduction in the United States, was the safety profile of this device similar to and not significantly worse than the European data?

DR. TILLMAN: So you want to use the previous study results as the comparator.

DR. BHUTANI: Because those were acceptable to us as being safe.

DR. TILLMAN: Right.

DR. BHUTANI: So my question is I'm

introducing it to U.S. population. I want to make sure we are not harming our patients.

DR. TILLMAN: So the question is, is it as safe in the U.S. population as it was in the original study?

DR. BHUTANI: Right.

DR. TILLMAN: I just think, and that's certainly -- if that's the question the Panel wants to ask, I think our statistical colleagues may say to you that sometimes when you try to do comparisons like that, you run into differences in patient populations. So if you end up with 90 percent of these patients being high-risk and 10 percent being moderate risk, can you compare those data to the data from the study? So that's a question that the Panel would sort of need to discuss. But, yeah, that is a question. The question is, is the adverse events profile in the U.S. comparable to what we saw in the study? If that's what the Panel thinks is a post-approval study, then we turn to our statistical colleagues to help us figure out how to answer that question. Okay.

DR. TALAMINI: Okay. Onto Question 4, unless there's more for Question 3. Ms. Brogdon?

MS. BROGDON: No, I think that's enough.

DR. TALAMINI: Okay. So Question 4, Labeling and Training. The firm provides physician and patient labeling for the Synergo system, as well as the approved package insert for mitomycin C. A physician training program is not proposed. If the Synergo system is recommended for approval, with or without conditions, please discuss whether the information provided is adequate to assure the safe and effective use of this combination product. If not, what additional information should be included in these labeling documents?

So let's see. Dr. Layton, would you like to give your thoughts on that question?

DR. LAYTON: Yes, I'll start out on it. First is we've received information relative to a physician instruction --

DR. TALAMINI: Closer to the mic. I'm sorry. They can't hear.

DR. LAYTON: I sat back too far. Sorry. We've received information on a physician instruction guide, a patient information guide, and the package insert. I did not see a user manual which would be the instructions for use for the physician. So I have not seen that.

What I have seen, yes, is very good. They

have the information. They have what they need. There was one instance brought up relative to shelf life, and that would be on the package label. We haven't seen the package label either relative to this particular product, but it would be on there, and because of the preclinical evaluation that was done and they saw no problems with the preclinical evaluation, I'm assuming they saw a proposed label. They saw a proposed user manual, and FDA signed off on it. So I see no issues with that, and I think they all are now proposing the training the program.

DR. TALAMINI: So perhaps we could get clarification on those two points. Is there a training program now proposed and is there a user manual? Did we have it and didn't find it or was it part of the packet? Could the sponsor or the FDA enlighten us on those two?

DR. O'DONNELL: There is a users manual, and it was submitted. And we are proposing a training program. There is one already used as a model in Europe and Israel to teach physicians whenever a new Synergo machine is brought online, and something very similar in nature would be utilized in the United States.

DR. TALAMINI: Thank you. So, Ms. Brogdon,

if I could ask an off line question, I believe that could be a potential condition of approval, could it not? If the Panel wanted to propose that, to have a physician training program?

MS. BROGDON: Yes, that's an appropriate condition of approval.

DR. TALAMINI: Ms. Stokes, do you have thoughts?

MS. STOKES: Yes, I just wanted to make sure that there was a training program to include the mentoring, the on-site training as well as the assessment of proficiency which I find to be very important.

DR. TALAMINI: Thank you, Ms. Stokes. Dr. Redman.

DR. REDMAN: Can the FDA mandate that a urologist cannot buy this machine or use it or be billed for the services without the certification that a training program has been gone through and passed?

DR. TALAMINI: Well, I would refer that to Ms. Brogdon, but certainly with past products I've been involved with, that was the case.

DR. TALAMINI: I'm not sure I have a complete answer to your question. We can require

that a training program be put into place. We can't require exactly what party offers that training. Can you tell me the rest of your question again?

DR. REDMAN: Well, if -- I guess I'm more of a market person. It behooves the sponsor to make sure that the individuals who are using their machine knows how to use it. Otherwise, they won't use it. I guess the other side of that is do you have the regulatory authority to say this is a new device, and before you can bill Medicare for its use, the physician has to be certified in its use? I mean is there a regulatory -- I come from the drug side. So I'm a medical oncologist. When FDA approves a drug, I'm board certified in medical oncology, I get to use that drug. Okay. I read about it and I learn how to use it but this is a device. So I'm a little bit different here. So can you require or do you require or is it just that we're asking industry to do this but it doesn't mean anything, I guess is --

MS. BROGDON: Let me ask some of my FDA colleagues how clear our requirements and sanctions are on this question.

DR. TILLMAN: This is a little bit of a gray area, but I do have -- part of your answer I can answer definitively. We don't get involved in

reimbursement. So we have no role to play in that. I think Nancy said it correctly. That is, as a condition of approval, we can require the company to have a training program and we can also make the device restricted which says that not only is it a prescription device but it's also a device for which people have to have been appropriately trained to use it but it's somewhat of a vague thing, and Jerry Predome (ph.) is knowledgeable about this. I don't know if you've got anything to add, but it's more of something that I think that we leave to the discretion of frankly the clinical community than we go out and rigorously enforce.

DR. REDMAN: If I could use an example, the da Vinci Robotic System which I was a part of that Panel, a training program was clearly mandated and it would be very difficult to do an operation in this country without having been trained on that device.

DR. TILLMAN: And so it's a company. The company controls who gets the device. So the company can say, come to our training program. If you don't come to our training program, we won't give you the device.

DR. REDMAN: That I understand. I'm from the drug world and I go back to Group C in approvals

and things, the restricted use. Okay.

DR. BHUTANI: If I may just answer the question a little bit that with devices, how things work, you know, each hospital grants privileges for particular procedures, and yearly like in gastroenterology, new procedures come in and every one or two years, there is sometime additions to the list of procedures and the hospital credentialing committee each sets their own standards about what is the minimum requirement, 180 days or 25 polypectomies, and that is one of the reasons I suggested that for physicians in the PAR study, if they actually record data of the minimum number of procedures required, and that gets published, then it becomes very easy for hospitals to put that as the minimum criteria for their physicians performing this and if there is nothing published, then somebody may have extensive training, but other guy may just go in and take a 2-day, 48-hour course and say I'm competent and the hospitals don't know any better because they don't have any standards to hang on. So it's up to the individual hospitals along with their physicians as to what minimum criteria they set up for granting privileges for a particular procedure.

DR. REDMAN: I understand now, and if the

question is addition to what they supply, do I recommend a training program, yeah, because I think industry would be nuts not to do a training program.

DR. TALAMINI: Thanks, Dr. Redman. Dr. Kalota.

DR. KALOTA: First of all, this would more than likely be done in the physician's office. So therefore hospital accreditation is going to have nothing whatsoever to do with it. In similar situations, companies offer the training and it's up to the urologist to do. What you do in your office is really up to you, and if you want to be safe or not. I believe they should have training. I don't see that we can attach it to reimbursement. It's up to the physician to take it but I do feel that there should be training available. Particularly as an individual, I hate computers. I hate anything technology. So you've got to teach me and you've got to teach me easily so I can follow it, and I'm not the only one out there. My concern is not what you've shown me on this data, but what an ignorant urologist in the community is going to do with this device, and a post-approval study is still going to be done by physicians who are competent in computers, who are used to doing research. What we need to know

is the individual urologist who is in Hicksville, wherever, doing this and to have the company come and teach them. At least that's a safer way of doing it.

DR. TALAMINI: Dr. Kalota, your opinion about the current labeling as submitted, is it adequate or does there need to be more?

DR. KALOTA: I think the labeling is fine, but I think there does need to be training for those who are willing to take advantage of it.

DR. TALAMINI: Thanks. Dr. Dahm?

DR. DAHM: I'm in agreement with everything that Dr. Kalota said. I don't really have anything to add.

DR. TALAMINI: So the information provided is adequate?

DR. DAHM: Yeah, but there should be training. We've heard that there is training proposed and --

DR. TALAMINI: I keep coming back to the information because that's the heart of the question. I want to make sure that we address that.

Dr. Connor.

DR. CONNOR: I have no major concerns or no concerns with labeling, and I think I'm most comfortable deferring to my clinician colleagues

regarding training.

DR. TALAMINI: Thank you. Sir.

DR. BHUTANI: I have one comment. There is something in the labeling regarding patients who are not able to give feedback about pain which is a safety mechanism, and I don't believe that it says about, you know, there are patients who may be on narcotics whose pain response may be blunted. I don't know if that's scientifically something that will decrease the safety of the device, but because feedback for pain is needed, perhaps, you know, patients may be on, you know, morphine or high dose narcotics and that, you know, whether they stop it for a week or something, so that they can have the procedure safely may be something to look at.

DR. TALAMINI: So do you have concerns that the current information doesn't address that adequately?

DR. BHUTANI: Yes.

DR. TALAMINI: Do you have an opinion regarding the training issue that's been discussed?

DR. BHUTANI: No, I think regarding the training, I am relieved to know that there is going to be a physician training program by the sponsor as I would like to have that happen.

DR. TALAMINI: Well, again, it will be up to us whether -- we will need to decide whether --

DR. BHUTANI: Sure.

DR. TALAMINI: -- that's a condition of our recommendation, you know, we recommend that as a condition or not.

DR. BHUTANI: Sure.

DR. TALAMINI: That's a line that we'll have to decide whether we want to cross as a committee.

DR. BHUTANI: Yeah, but at this point, I do feel that it's important.

DR. TALAMINI: Okay. Thanks. Dr. Lippert.

DR. LIPPERT: I've read in detail the patient information guide. It's excellent. I just would make sure condition that physicians who train on this do get a copy for patients because I work with other devices that the only way I can get information is go online and make copies of something. This is actually very good but it has to be available. Training should be required as part of the approval.

DR. TALAMINI: Thank you. Dr. Donatucci.

DR. DONATUCCI: Yes. I'd just make one suggested change in the black box. I would like to

see after the statement that Synergo and mitomycin C treatment is clinically indicated in patients of intermediate and high-risk, an additional comment that states patients with grade 1 Ta disease, less than three centimeters in size, which is low risk, should not be treated. My fear is, of course, that while we may know what intermediate risk is, not everybody does.

DR. TALAMINI: Do other Panel members have objections to that? Dr. Marcovich.

DR. MARCOVICH: I agree with what both of my colleagues here just said.

DR. TALAMINI: Ms. Brogdon.

MS. BROGDON: Could I just ask Dr. Donatucci, is your recommendation because of the risk profile to those patients?

DR. DONATUCCI: It's just not necessary basically, and my experience has been that when a product is introduced, the indications get stretched, and I think we know that that's a low risk population. They don't need to be treated with mitomycin C and this device.

MS. BROGDON: Thank you.

DR. TALAMINI: So, Ms. Brogdon, with respect to Question 4, the Panel generally believes

that the information provided is adequate with a few now well recorded issues that have been brought up. The Panel also feels on the related issue of training, that that is going to be an important aspect of the disbursement of this device if you will.

MS. BROGDON: Could I ask for a clarification on the training? I realize you haven't voted yet, but is the consensus that a training program should be offered or a training program should be in essence required by the company before a device is sold.

DR. TALAMINI: The consensus that I heard was required but again, we're not trying to avoid the appearance of voting here. So, Dr. Donatucci, comment?

DR. DONATUCCI: I didn't make a statement about that but I actually would argue against requiring it. From what I know so far, placing the Foley catheter and connecting the machine seems to be the extent of what you need to do here. So I don't know that we need formal training. That's much different than using a da Vinci.

DR. TALAMINI: Dr. Kalota, do you have an opposing point of view?

DR. KALOTA: No, I think it should be offered and for those who are comfortable. It may be that when it shows up in my office and all the details are there, I may feel comfortable but it should be available to me and that was how I worded it, that it should be available to those who want to use it, the training.

DR. TALAMINI: Let's try and clarify this a little bit. Do others have comments, and I don't want to weigh in, but the difference here I think is that this is a feedback loop mechanism with a computer between the doctor and the device. So I think that's what makes it a little different than just putting a Foley catheter in, but do others have opinions with respect to required versus offered? Because again, in a little bit, we're going to have to make some votes on this.

DR. BHUTANI: If I may say that if training was not an issue, why in the PAR the American urologists will be taking part in the PAR, proposed that we will have a training program? That makes me think that even the urologists who are interested in this device, working with the company, feel that some sort of training and orientation is required as they propose in their PAR. So if that's the case, then

why it is not necessary for physicians in practice to have, you know, initial training on the device and rather than saying they can do if they choose so? That's just how I feel about it.

DR. TALAMINI: Dr. Donatucci.

DR. DONATUCCI: Yeah. I just near a clarification. When we vote required, what does that mean for FDA? Because I recall a device that was approved 15 years ago that all of us literally had to get a certificate, and there was a lot of expense involved in terms of for the company and also just for our time. What happens when you require training? What does that actually entail?

MS. BROGDON: It would mean that there would be a written condition in the approval for the sponsor that they must require a training program in their distribution of the device. We wouldn't nail it down completely but I think we would see that as different from simply suggesting that a manufacturer offer a discretionary training program. For instance, a discretionary training program could be dropped at some later date but if it were required as a condition of approval, it couldn't be dropped without FDA's approval.

DR. DONATUCCI: To me, this device seems to

be on par with microwave thermal therapy in terms of the coupling, et cetera. And what are the standards now through FDA for microwave thermal therapy?

MS. BROGDON: I'll have to ask a representative from that branch. John Baxley.

DR. BAXLEY: There's training required for all microwave thermal therapy systems.

DR. DONATUCCI: But what that is just depends on -- you're not telling them what type of training. It's just training.

DR. BAXLEY: Well, it gets reviewed in the PMA, just to get a sense of the level of training. We see an outline of the training program.

DR. DONATUCCI: Okay. Fine. I guess in my own mind, because I was the one who objected to it. I don't object to education. I just don't want to make it burdensome because it's certainly something someone can learn through mentorship or -- but to go through formal -- when you say training, to me I have to go to something formal before I can do this, as opposed to having someone who's knowledgeable come in and mentor me in my operating room or office for that matter. So that's the part that I'm misunderstanding perhaps.

DR. TALAMINI: Well, no, I think you are

understanding it because that's exactly what this Panel will need to -- if we vote approval and we vote that training is a condition of approval, that's what will happen. I don't think it makes sense for the Committee to vote to say that the company needs to offer training because I don't know how you monitor, mandate or, you know, that doesn't make sense to me. So I think that's exactly the line that we're talking about. Ms. Brogdon, am I correct on that?

MS. BROGDON: Yes, I believe you are.

DR. TALAMINI: Further discussion on required versus --

DR. REDMAN: I still have a problem with this requirement. How do you regulate that requirement? I mean I agree with voluntary because I can probably guarantee you, at least the urologists I deal with, the vast majority of them that are going to use this, are going to voluntarily undergo some form of training, mentorship or other. So how do you -- if you require it, how are you going to oversee that requirement?

MS. BROGDON: We probably wouldn't oversee it very well.

DR. REDMAN: Then why are we requiring it? I mean are we going to make another statute that

can't be enforced?

DR. TALAMINI: Well -- Dr. Kalota.

DR. KALOTA: I don't think it should be required. I think that it should be offered but it's also very much a marketing item for the company. If I use it and screw up, I'm not going to use it again. If there's injury, I'm not going to use it again. If it's not effective, I'm not going to use it again.

UNIDENTIFIED SPEAKER: And you're going to tell everybody in your office.

DR. KALOTA: And I'm going to tell everybody and all my colleagues. So recommending it and making sure they have it available is to my advantage. Them doing it is really to your advantage. If I use technology once and it doesn't work, that's the end of it. I won't try it again.

DR. TALAMINI: So again for clarification from the FDA, I think you said that other microwave ablation devices -- I shouldn't say other, that microwave ablation devices do require training.

DR. BAXLEY: Well, the ones for BPH do. I'm not going to generalize that just because it's microwave, that it needs training but microwave devices that treat BPH do require training.

DR. TALAMINI: Okay. I think that exhausts

the discussion on Question 4.

DR. MARCOVICH: I'm confused. Because if you put a Foley catheter in front of me, I know what to do with it. If you put a machine with a bunch of buttons in front of me, maybe I can figure it out, but I don't want to figure it out on my patient. On the other hand, if the rep comes in to my first two or three, once I do these and says, here's how you do it, and then here's what you have to watch out for, that to me is considered training and that's adequate but as Dr. Donatucci says, I don't want to fly to San Diego to take a course on this.

DR. TALAMINI: Sure you do.

DR. MARCOVICH: Well, I want to fly to San Diego for another reason but the -- so I guess I want to know what training means before I say yes or no because I -- what's the -- it needs to be clarified in my mind what training means. Is it the rep coming into your office and telling you how to do it the first few times and answering questions, which is what's done for many other devices, or is it, you know, taking a course and having a certificate, et cetera.

DR. TALAMINI: Well, to me the difference is mandated, and I think that's the key line that

we're talking about. I mean the device can't be used without some kind of training if this is part of the approval. Ms. Brogdon.

MS. BROGDON: Training can encompass all the things you referred to. It can be mentoring in the operating room. It can be a classroom. It can be a wet lab. It can be animal studies. It can be all animal testing or treatments. It can be anything that you define it to be or anything the sponsor proposes.

DR. TALAMINI: Dr. Dahm.

DR. DAHM: Yeah. Could we not ask at this point what the sponsor is proposing? Maybe that will give some guidance to this discussion?

DR. TALAMINI: We could but we still will be left with the question of whether to mandate it or not but mandate some kind of training. We certainly could do that. Do the sponsors have a quick response regarding their plans for training?

DR. WITJES: Well, since I'm the only one who would have training, and I hate computers, it's very easy and I had to go to Milan unfortunately to have the training but it's an easy program.

DR. BHUTANI: So what I'm hearing is it's not as easy as putting a Foley catheter. Otherwise,

you wouldn't have gone from The Netherlands to Milan and personally saying it's as easy as a Foley catheter, it should be optional to a urologist to get training, and if there is injury, the urologist won't use it. I have an ethical problem from a patient perspective that if I have injury, then my urologist won't use it on others but I'm already injured. So from that standpoint, I think if we say training is required, why can't we create some sort of assurance from the company that before they put this device or sell it to any physician, they will have a minimum training program, orientation or as some of you suggested, the rep will be there for a certain number of procedures, for troubleshooting and so on, and I think that would be a small price to pay for safety of our patients and probably would insure that the safety data that looks good in Europe continues to be good for American patients.

DR. WITJES: Well, I think Dr. Kalota made a very good point. If you have some training, which it's not very difficult, but it's, of course, essential to work with the machine, the doctor will perform well, the patients will have good treatment and, of course, the company will support that.

DR. TALAMINI: Very quickly.

DR. KOREN: Yes, I would just like to comment, first of all, we do offer training programs, but there is a question, you know, once the machine is in the department, and you have a second generation of physicians who are also coming to use this device, and the question is whether they can learn this from their senior colleagues and they do not need the help of the company to come again and give them the guidance. So this may be the difference between required. We do offer it in Europe today.

DR. TALAMINI: Okay. Thank you. So the Panel members can think about all those issues, but not talk about them to anybody while we take a 10-minute break. It'll just have to be 10 minutes because we still have the voting to do. So we'll adjourn for 10 minutes.

(Off the record.)

(On the record.)

DR. TALAMINI: We will now resume with the meeting.

I want to remind the speakers to follow the disclosure recommendations as stated in the open public hearing disclosure statement that was read during the first open public hearing session. For

example, state your name, affiliation and indicate your financial interest, if any, in the device being discussed today or any other device.

Is there anyone in the audience who would like to address the Panel now? If so, please raise your hand and come forward.

(No response.)

DR. TALAMINI: Okay. Not seeing anyone, we'll not proceed to the FDA and sponsor summations.

Is there any further comment or clarification from the FDA?

MS. BROGDON: No, Dr. Talamini. Thank you.

DR. TALAMINI: Is there any further comment or clarification from the sponsors? Please be brief, if possible.

DR. GROSSMAN: The sponsor would like to thank the Panel for a careful review.

DR. TALAMINI: Thank you, sir. That was indeed brief.

We're now ready to vote on the Panel's recommendation to FDA for this PMA. Dr. Cooper will now read the Panel Recommendation Options for Pre-market Approval Applications and I would encourage all Panel members to listen very, very carefully. Dr. Cooper.

DR. COOPER: The Medical Device Amendments to the federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device pre-market approval applications, PMAs, that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. The definitions of safety, effectiveness and valid scientific evidence are as follows. Don't stop me if you've heard this before.

Safety as defined in 21 C.F.R. 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probably benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probably risks.

Effectiveness as defined in 21 C.F.R. 860.7(e)(1), there is reasonable assurance that a device is effective when it can be determined, based

upon valid scientific evidence, that in a sign portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid scientific evidence as defined in 21 C.F.R. 860.7(c)(2) is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of safety and effectiveness of the device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

Your recommendation options for the vote are as follows:

One, approval, if there are no conditions attached.

Two, approvable with conditions. The Panel may recommend that the PMA be found approvable subject to specified conditions such as physician or patient education, labeling changes or further analysis of existing data. Prior to voting, all of the conditions should be discussed by the Panel.

Third is not approvable. The Panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe, or the data do not provide a reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Following the voting, Dr. Talamini will ask each Panel member to present a brief statement outlining the reasons for his or her vote.

Dr. Talamini.

DR. TALAMINI: Are there clarification or questions from the Panel about these voting options before we look for a motion?

(No response.)

DR. TALAMINI: So it's clear, it's either approval and there aren't any conditions, it's disapproval, or it's approval and there are conditions. And if it's approval and there are

conditions, then we need to one by one go through those conditions. So it's sort of a three trees as up here.

So can we entertain a motion from a voting Panel member? Dr. Donatucci.

DR. DONATUCCI: I vote that we approve with conditions, the condition being that labeling change that I recommended and that training be required.

DR. TALAMINI: So as I understand it, and I'll have to be kept in line by the FDA, what we simply do is have -- we have a motion on the table for approvable with conditions. We'll need a second for that motion, and if we get that second, then we'll need to discuss what those possible conditions may be and amend the motion one by one with those conditions. So we would be looking for a second to Dr. Donatucci's motion of approvable with conditions. Dr. Kalota.

DR. KALOTA: I second that.

DR. TALAMINI: Okay. So we have a motion made and seconded for approval with conditions. Now, we need to entertain a discussion regarding the conditions or we need to have a motion regarding each condition. We need to second that, discuss it and then add that to the main motion. So if I could

entertain a motion for a condition. Dr. Donatucci.

DR. DONATUCCI: Okay. I move that we approve with the condition that the label include reference to non-treatment of Ta grade 1 tumors, that in addition to the labeling.

DR. TALAMINI: All right. Do I hear a second to a condition that the labeling be changed as stated by Dr. Donatucci?

DR. KALOTA: Not a second. I have a clarification. Single --

DR. TALAMINI: No, we just have to second that or not before we discuss it because if we don't like it we can do it again, but we need a second or not. Do I hear a second for Dr. Donatucci's stated --

DR. DAHM: I second that.

DR. TALAMINI: Okay. Dr. Dahm. So Dr. Dahm second's that motion. So that's now on the table for discussion. Dr. Kalota.

DR. KALOTA: Is that a single site, multiple site?

DR. DONATUCCI: It's the definition of low risk that was presented earlier today which I believe was defined as Ta grade 1, less than 3 centimeters.

DR. TALAMINI: Further discussion.

DR. DONATUCCI: Single.

DR. KALOTA: Okay. That was my question.

DR. DONATUCCI: Single.

DR. KALOTA: Single. Okay.

DR. TALAMINI: Further discussion for that condition from the Panel?

(No response.)

DR. TALAMINI: Okay. So that's been made and seconded and discussed. Is there another motion for a condition, and again you need to help me make sure this is right, Ms. Brogdon.

MS. BROGDON: I believe you need to vote on this condition and whether it should be added to the motion or not.

DR. TALAMINI: Okay. That -- we don't have that on our yellow tree but okay. Now, do we have to also -- per each vote, do each Panel member need to explain their vote for each condition or not? No. Just for the main motion.

MS. BROGDON: Correct.

DR. TALAMINI: Okay. So does somebody have the official language of Dr. Donatucci's condition or can you state it precisely again, Dr. Donatucci.

DR. DONATUCCI: My motion is that we add a clause after -- at the end of the black box, instead

of a period, after intermediate and high-risk, there will be a semicolon that says, patients with low risk disease defined as Ta grade 1, single focus, less than 3 centimeters not be treated.

DR. TALAMINI: All right. So we will need the voting Panel members to vote on that motion. It's been discussed. All those who vote in the affirmative, please raise their hands.

DR. CONNOR: Can we --

DR. TALAMINI: We already discussed it.

DR. CONNOR: It's a procedural matter.

DR. TALAMINI: Let's do the vote then.

DR. CONNOR: That's what it's about.

DR. TALAMINI: Okay. What's the question? Procedural question.

DR. CONNOR: My procedural question is something that I perceive as strictly clinical or maybe my opinion. I know less about it. Is there a present or --

DR. TALAMINI: You may abstain.

DR. CONNOR: Okay.

DR. TALAMINI: You main abstain, yes. Those not in favor? Abstentions? Okay. So I need to state the names. Will the yeses raise their hands again please? Dr. Marcovich is a yes. Dr. Donatucci

is a yes. Dr. Lippert is a yes. Dr. Dahm is a yes. Dr. Kalota is a yes. Dr. Redman is a yes.

And those not in favor?

(No response.)

DR. TALAMINI: Those abstaining, if you could raise your hands? So that would be Dr. Connor and Dr. Bhutani.

Okay. So that condition then gets added to the main approval with conditions motion that's on the floor. Other conditions?

DR. BHUTANI: I'd like to introduce a motion that in the labeling in the contraindications which is number 3 in the labeling, and I'm going to read it, because the patient's ability to detect pain is an essential safety mechanism, Synergo treatment is contraindicated in patients whose pain response has been significant decreased by any means (previous surgery or ionizing radiation therapy, general anesthetic or other condition) and between anesthetic and other condition, use a narcotic pain medications be added, as that would blunt a patient's ability to detect pain.

DR. TALAMINI: Do I hear a second?

(No response.)

DR. TALAMINI: Not hearing a second, is

there a further -- so that motion would go down in defeat for not having a second. Is there a new motion related to that. Dr. Donatucci.

DR. DONATUCCI: I would just add that --

DR. TALAMINI: Are you making a motion?

DR. DONATUCCI: Yeah, I would add basically the word narcotics -- how did you state it please?

DR. BHUTANI: Or general anesthetic or narcotic pain --

DR. TALAMINI: I guess my recommendation would be to watch the specificity and stick with the theme. I'm not -- I can't make the motion but in making these motions, I probably need to think carefully about the specificity issues.

DR. DONATUCCI: I move we further qualify it by saying chronic narcotic therapy.

DR. BHUTANI: I second that.

DR. TALAMINI: Discussion regarding that condition?

DR. DONATUCCI: We're open for discussion now. The reason I say that, of course, is that not knowing what the -- not having treated a patient, not knowing what the pain threshold in the office would be for treatment with heat, you're going to need to provide some sort of sedation/analgesia I believe and

therefore if we preclude all narcotics, we've just essentially eliminated our ability to do that in the patients.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: I actually disagree completely. Someone who is on chronic narcotic is still going to be able to sense pain. If you're going to treat them at the time, to cover up their pain, then that's different but people who are on chronic narcotic actually usually have a lower pain threshold and are more likely to complain.

DR. TALAMINI: Might I suggest that, and again we have a motion on the table that we're going to vote on, that we consider -- the problem with this is the specificity. It may be better to ask that the labeling refer to this issue of narcotic pain during treatment rather than specifically mandate or contraindicate it. Does that make sense? Other discussion on this motion?

(No response.)

DR. TALAMINI: Okay. So that specific motion is on the table. Dr. Donatucci, you want to state it again for us?

DR. DONATUCCI: The word was we were going to add chronic narcotic --

DR. TALAMINI: Okay.

DR. DONATUCCI: -- as to the precaution.

DR. TALAMINI: Okay. So a motion's been made and seconded and discussed. All those in favor of that motion as the additional condition, raise your hand? Those opposed. We have Dr. Redman opposed, Dr. Kalota opposed, Dr. Lippert opposed, Dr. Donatucci opposed, Dr. Marcovich opposed. Do we have abstentions? Dr. Connor abstained. Dr. Dahm abstained. So I believe that goes down to defeat. Am I correct, Ms. Brogdon? I believe that goes down --

MS. BROGDON: Yes, I believe so.

DR. TALAMINI: Okay. So do we have a new motion to be entertained? Dr. Donatucci.

DR. DONATUCCI: My move is that we -- well, I'm not sure how to handle as you just suggested in a motion. I'm looking at you, Mark, because you're the one that made the suggestion.

DR. TALAMINI: I can't make a motion.

DR. DONATUCCI: We'll just need an explanation frankly.

DR. TALAMINI: Well, my suggestion was that the real issue is this device being used in patients that are narcotized, and that if we simply -- that we

just have the labeling refer to that as an issue, that might be adequate for the Panel, but again, I'm not making a motion.

DR. DONATUCCI: I'll make the motion. I move that the labeling refer in precautions to a narcotized patient who may not be able to sense pain appropriately.

DR. TALAMINI: Do we have a second? Dr. Kalota. Discussion of that condition? Discussion, Dr. Redman.

DR. REDMAN: I don't think there's any medical definition of a narcotized patient.

DR. TALAMINI: Well, this motion isn't mandating that in the language. It's merely saying that it be the topic. Is that right?

DR. DONATUCCI: The motion as I think I suggested it was that in the precautions, consideration would be given to the state -- let me rephrase that.

DR. KALOTA: Medically induced decreased pain sensation.

DR. TALAMINI: So we've got a motion on the table. It's been discussed. Further discussion?

(No response.)

DR. TALAMINI: So let's ask -- yeah,

Dr. Lippert.

DR. LIPPERT: So this is already in the labeling a contraindication. So what is it that we're doing?

DR. BHUTANI: It's not in the contraindications. It says in the contraindications, because a patient's ability to detect pain is an essential safety mechanism and it gives -- it's contraindications for pain response has been significantly decreased by any means.

DR. LIPPERT: But isn't that enough?

DR. BHUTANI: Previous surgery, ionized radiation, generalized anesthetic or other condition.

DR. LIPPERT: Which says it all.

DR. BHUTANI: But I think -- yeah. I think Dr. Donatucci's motion is instead of putting it as a contraindication in the precaution section, we just list that in patients who are on narcotic pain medicine, care should be -- some sort of wording about taking that into consideration. Is that correct?

DR. DONATUCCI: That's correct.

DR. BHUTANI: It's not a contraindication but it's a precaution to the physician to be aware of this issue when he or she decides to stop chronic

medicine or whatever their judgment is regarding that.

DR. TALAMINI: Okay. So the motion on the table again, Dr. Donatucci, is --

DR. DONATUCCI: That reference be made in the precautions to the possibility that narcotics decrease the sensation and therefore may impact the ability -- the safety issues.

DR. TALAMINI: Okay.

DR. DONATUCCI: I'm not a writer. So I'm not going to give you the exact wording.

DR. TALAMINI: All right. Those in favor of adding that requirement to the labeling?
Ms. Brogdon, you're uncomfortable.

MS. BROGDON: Sometime we're going to ask you to put that into words. You don't have to do it at this moment, but I think we're going to want some fairly clear direction on that.

DR. TALAMINI: Okay. Fair enough.

DR. DONATUCCI: Chair?

DR. TALAMINI: Yes, sir.

DR. DONATUCCI: Can I withdraw my motion?

DR. TALAMINI: I think once it's been made and seconded, it has to be voted upon.

DR. DONATUCCI: Okay.

DR. TALAMINI: You certainly can vote against it. All right. Those in favor of the motion? Those opposed? I'm sorry. We had one in favor. Dr. Bhutani. Those opposed? We have Dr. Marcovich, Dr. Donatucci, Dr. Lippert, Dr. Connor, Dr. Dahm, Dr. Kalota, Dr. Redman. So the motion goes down to defeat.

So now that we've practiced with Robert's Rules of Order, it's time for somebody to think about a motion for some of these bigger issues that are lurking in your minds. Dr. Kalota.

DR. KALOTA: I propose that there is training by the company.

DR. TALAMINI: Can you put that into motion language for us? And I think specifically as we've discussed, we have to have a motion that either mandates or doesn't mandate training.

DR. KALOTA: My motion would be that the company offers training. Or if we mandate training, then we're back to what does that mean? I don't think we should have to be sent to San Diego even if we want to but the rep coming in is fine with me. So --

DR. MARCOVICH: My understand is --

DR. KALOTA: Or colleague training is fine.

DR. MARCOVICH: -- if we mandate the training, we don't necessarily mandate what the training is.

DR. TALAMINI: So actually procedurally again I can't make a motion but I believe the cleanest way to approach this would be if somebody could make a motion that proposed mandated training. That would allow us to fully discuss it and either approve it that way or not, and if not, then think about something else. Again, I can't make the motion but I think that's the cleanest way to deal with it.

DR. KALOTA: Then the motion is to mandate training.

DR. TALAMINI: Okay. So we have a motion on the table that the sponsor mandate training for this device.

DR. MARCOVICH: I second that motion.

DR. TALAMINI: Okay. Discussion other than that which we've already had? I guess my question for discussion would be how the details of that training would be worked out?

DR. CONNOR: So can I ask a question?

DR. TALAMINI: Yes.

DR. CONNOR: I wanted to clarify that this mandate is mandating that training is offered but not

requiring a clinician receive training.

DR. TALAMINI: I believe the motion on the table is that it be required. Mandated to me means that that's a condition of approval that physicians be trained on the device. Dr. Lippert.

DR. LIPPERT: As was pointed out to us that training could be a mentor in your group who already knows how to do it. So that training could take any form but it's mandated. So I have a senior partner who knows how to do it, has been doing it, that person can teach me. (Trouble with mic.)

DR. TALAMINI: Did everybody hear that, first of all? Tap on it and make sure it's working. Just give it a tap. We have too many mics on. Everybody else turn --

DR. LIPPERT: Can you hear me now? My understanding is that training can be my senior partner who has been doing this for sometime could teach me, a mentor or it could be that I'm trained by the company personnel. We're mandating training but my understanding was it could be any form.

DR. TALAMINI: So not included in the motion was how that training could be worked out but potentially it could be that the details of the training be determined by the FDA with the sponsor.

DR. BHUTANI: What I would suggest is that, yes, a mentor, a physician performing this could teach his or her partner but when a new device is introduced, the initial physicians who are going to be using it will need -- preferably should have some sort of training. So perhaps we could mandate a requirement to the company that when they install a new device in an office or a hospital, where that device doesn't exist, that whoever at the time intends to use it, they will provide some sort of orientation and training, not necessarily that any physician ever in that facility who is going to use it be required, whenever they install or sell a new device, that presumably whoever is there hasn't used it. They don't have it, and at the time of initial installation or --

DR. TALAMINI: So I guess I'll take the privilege of the Chair to say that whereas this Panel is expert on issues of urology and GI, we probably are not experts on issues of competency and training. So I think it's probably up to us to figure out whether we believe training should be mandated or not but to have the details be worked out by experts who do understand those issues. I say that humbly and carefully, but I think that's probably true.

Dr. Donatucci.

DR. DONATUCCI: Since I originally brought up the fact that I was against it, I'm not for it, and I'll tell you why. Once I was told that actually FDA does require training for microwave thermal therapy, I'm comfortable, since I went through that, that the training is not overly intrusive, and I think contrary to a prior experience, I think I believe that FDA has the good sense and the common sense and the expertise to make it, require it, to do it right, not make it burdensome. So I'm comfortable with the requirement and leaving it to them to figure out how.

DR. TALAMINI: Further discussion? Ms. Brogdon, did you have a comment?

MS. BROGDON: I just want to make sure that I understand that this condition would be that the sponsor design and set up a training program, and that would be the condition of approval, and then we would work off line with the sponsor to work out the details of that. Is that correct?

DR. TALAMINI: That wasn't specifically stated in the motion but I certainly comfortable with that. I don't think we probably need to go back and redo the motion for that detail. Other discussion?

Dr. Dahm.

DR. DAHM: No.

DR. TALAMINI: Further discussion on this condition? If not, we'll go ahead and call the question, those in favor of adding this condition to the main motion, please raise your hand.

DR. REDMAN: Can you read the motion? I'm still not sure what it is?

DR. TALAMINI: To the best of my recollection, as it now stands, it's that as a condition of approval, the company be required to provide a training program, a mandated training program.

DR. REDMAN: Required to provide.

DR. TALAMINI: No, that it be required for use with -- I mean we didn't redo the motion. I supposed we could if we wanted to be completely clean, but what Ms. Brogdon clarified was that this was a training program to be developed by the company in conjunction with the FDA.

DR. REDMAN: And that what is being required is not only the development of that program but that that program be utilized before a physician -- so both. There's two mandates. One, the development of a program, and one that it be

required to be administered --

DR. TALAMINI: Correct.

DR. REDMAN: -- for lack of a better word.

DR. TALAMINI: Correct. Okay. Those in favor? We have Dr. Marcovich in favor, Dr. Donatucci in favor, Dr. Lippert in favor, Dr. Bhutani in favor, Dr. Dahm in favor, and Dr. Kalota in favor.

Those opposed? Dr. Redman is opposed. Dr. Connor is opposed.

Do we have any abstentions?

(No response.)

DR. TALAMINI: So that motion carries. Further conditions? Dr. Redman.

DR. REDMAN: I'll bite the bullet. That there be a post-approval study as currently outlined --

DR. TALAMINI: I know you're going to be very careful with this motion.

DR. REDMAN: -- by the sponsor -- I lost my page -- as currently proposed by the sponsor in their presentation, which I don't have exactly, to assess the safety profile of -- only the safety profile and that for one-year follow-up which is what they're proposing to do. That didn't come out very clean.

DR. TALAMINI: Want to give it another shot

before we put it in stone?

DR. REDMAN: Yeah. That the -- I guess the easiest thing would be the post-approval study as outlined by the sponsor in their presentation, that's not what they initially recommended, but what they presented in their presentation today, be part of the approval process. I don't think I need to go through bit by bit their proposal.

DR. TALAMINI: Do we have a second?

DR. KALOTA: Second.

DR. TALAMINI: Dr. Kalota seconds the motion. Discussion? Dr. Dahm.

DR. DAHM: I think the timeframe to look at it should be two years rather than one year.

DR. TALAMINI: So the motion doesn't state specifically other than as proposed by the sponsor. But your recommendation, your discussion point is that you believe it should be two years?

DR. DAHM: I think the sponsor's proposing the one-year time horizon but I was thinking maybe somebody could --

DR. TALAMINI: There are heads nodding but I think it would be best if you gave -- are they allowed to give a formal answer at this point to a question?

MS. BROGDON: I believe so.

DR. TALAMINI: Okay. If you could formally tell us.

DR. DAHM: So the objective of the PAS was to provide data on safety, and on that basis, we propose a one-year program follow-up specifically for the safety elements, realizing we would also be collecting data on the effectiveness but it was not the primary objective of the PAS.

DR. TALAMINI: Okay. Dr. Connor.

DR. CONNOR: May I ask, Doctor, that given the motion was for, to better understand the safety profile, your rationale for asking that that be extended to two years?

DR. DAHM: I guess my next discussion point would have been that I also would like to get additional data on effectiveness and the issue I had mentioned before that I'd be concerned of is the performance of the agent in the intermediate versus the high-risk group. So I don't think the study should only look at safety. It should also look at effectiveness.

DR. TALAMINI: So you're actually speaking -- you're not speaking in favor of the motion as stated?

DR. DAHM: I guess not.

DR. TALAMINI: Okay. Other discussion? Dr. Connor.

DR. CONNOR: The easiest way for us to handle this, there was a motion regarding adverse event data and the safety profile. Should we be considering that and then we should separately consider efficacy. That way we're not trying to build one huge thing that we all have differing opinions of or identifying individual components that we think are important.

DR. TALAMINI: That sounds like a great strategy. Other discussion regarding this motion on the table for this post-market study?

DR. REDMAN: Will we be requiring two studies then if we get two different --

DR. TALAMINI: We might be requiring two studies but the second motion, if it arises, could propose that they actually be one study with a second element. Further discussion? Dr. Connor.

DR. CONNOR: My only comment is I guess I would leave open -- I think that the motion would entail the 120 sample size and I would recommend that the sample size be left open such that the FDA with input from the sponsor could arrive at the sample

size that answers the scientific question. I think we should be recommending what our scientific question is and let the experts at FDA identify the sample size necessary. We're saying one year is enough. The one year goes to the scientific question but sample size is implicit in the motion. We have no idea if that answers the scientific question or not. So I think we should leave that to FDA to work out with the sponsor.

DR. TALAMINI: Well, thankfully, Dr. Connor, all of what we do here today are officially recommendations. So the FDA can take our recommendations or not.

Further discussion?

DR. DAHM: Let's say one year. Does that mean one year from the day of approval that that clock starts ticking and 365 days later we stop looking? Because that doesn't make sense.

DR. REDMAN: It's an additional -- well, my interpretation, it's an additional study that the one year is from -- they start treatment, each patient is followed for a year as outlined here.

DR. TALAMINI: Ms. Brogdon, did you have a comment?

MS. BROGDON: No, Dr. Redman's description

is correct.

DR. TALAMINI: Further discussion on this condition?

DR. REDMAN: So the current motion is that there be a safety study and that the safety study have a timeframe, a time horizon of one year of follow-up. Is that --

DR. TALAMINI: Right. That would be and again, this is all framed within this Panel's recommendation.

DR. REDMAN: Right.

DR. TALAMINI: Okay. So let's call that question, those in favor of the study motion that Dr. Redman proposed, those affirmative, please raise your hand? Dr. Marcovich is affirmative. Dr. Donatucci is affirmative. Dr. Lippert is affirmative. Dr. Bhutani is affirmative. Dr. Connor is affirmative. Dr. Dahm is affirmative. Dr. Kalota is affirmative, and Dr. Redman is affirmative. So that motion carries.

Do we have another condition motion to be entertained? Dr. Dahm.

DR. DAHM: So I make the motion that there be a study that provide additional information on the effectiveness that has a two-year time horizon and

that looks at the -- let me leave it at that.

DR. TALAMINI: And not to mess with your motion, but would that necessarily need to be a separate study or could it be part of this study or an extension of this study?

DR. DAHM: It could be an extension of the study.

DR. TALAMINI: Okay. Do we have a second for that motion? Looking for a second.

DR. DONATUCCI: Second.

DR. TALAMINI: Dr. Donatucci seconds the question so it's open for discussion. Further discussion on this extension of the study.

DR. DONATUCCI: Since I seconded it, I'll just quality that. We have previously stated that we're comfortable, despite the issues with the pivotal trial, that the efficacy data was satisfactory, that the change was between therapy and -- was satisfactory to make it approvable. In a post-market study, I just need some clarification, Phillip on your thoughts, what you want to see between the intermediate and high-risk group differentially. Can you expand upon that?

DR. DAHM: I guess I'm concerned -- this is a delicate balancing act because as you say, we've

kind of decided that we have reasonable assurance of efficacy but when you look into the individual subgroups and I'm particularly worried about the high-risk patients, I think we have less -- it would be fair to say that we have less assurance of efficacy. So -- and there we have -- and also current guidelines recommend for the high-risk patients recommends BCG and cystostomy as the "standard" of care. And in our study, we compared in the pivotal trial that we reviewed here, the comparator was mitomycin which is not what is primarily recommended for these patients. So as I think about this further, I think I would -- so this post-marketing study should specifically look at those patients in my opinion.

DR. TALAMINI: I think a further potential argument for an ongoing effectiveness study is this European versus American issue. I don't know how important that is but certainly there would be those who would say it's important to look again in the American population.

Further discussion? Dr. Kalota.

DR. KALOTA: If we request this, how specific do we have to be? I refer to the questions brought up by Dr. Redman, and are you going to

mandate how many people of a certain type of cancer in it to get the answers that you want?

DR. DAHM: So what -- similarly to what Dr. Connor brought up for the previous discussion, I don't think we'll be able to arrive at the details of this study here at this Panel meeting. So I think things like sample size and those kind of things would have to be discussed separately. So I don't think we can provide those details.

DR. TALAMINI: But your motion is that it be an effectiveness study. Am I correct?

DR. DAHM: Yes.

DR. TALAMINI: Further discussion on the motion?

DR. BHUTANI: Let me understand this correctly. The sponsor has already stated that in their PAS proposed, even though their one-year study is based to look at safety, they will be looking at efficacy. So that's at least as proposed a minimum on the table, one-year safety and efficacy and what you are proposing is those same group of patients be followed for up to another year so that efficacy of two year be then determined. Is that what your motion is?

DR. DAHM: I guess that deserves specific

considerations in the trial design if we're going to look at effectiveness. So it can be the same trial, can be the same study, but we'd have to plan it accordingly if that is information we'd like to derive from the study.

DR. LIPPERT: If your concern is only the high-risk group, why are you including high and intermediate?

DR. DAHM: I follow that. That sounds -- so my real concern is the high-risk group.

DR. BHUTANI: Could you then suggest perhaps, perhaps so that we don't -- since your concern is high-risk, could that be just the high-risk group patients be followed for two years and not the low risk group or the intermediate risk group, excuse me.

DR. DAHM: That sounds good. That sounds like a --

DR. TALAMINI: Dr. Connor.

DR. CONNOR: That's what I was going to recommend and point out. I guess again I think the motion, we should be motioning that we have scientific questions that we'd like to see answered and let the experts at FDA answer those questions and it sounds like we want to know more about efficacy in

the high right American group, and that may be achievable by taking a subset of patients that would be in the study that Dr. Redman proposed and we voted on. So I think that by doing a subset in that population, if that's what FDA thinks is best, then we could achieve our goal that way.

DR. TALAMINI: Well, and I think that is the sense of the motion. I'm not sure we need to defeat it and have a new motion. That's the sense of the motion. Further discussion?

(No response.)

DR. TALAMINI: Okay. So let's call the question on an extension study for looking at effectiveness. Those in favor, please raise your hand. I see Dr. Donatucci, Dr. Dahm. Those opposed, please raise your hand. Dr. Marcovich, Dr. Connor, Dr. Redman. Those abstaining. Dr. Kalota and Dr. Bhutani. Dr. Lippert, you're opposed.

DR. LIPPERT: Yes.

DR. TALAMINI: Dr. Lippert is opposed. So, Dr. Cooper, where do we stand on that motion?

DR. COOPER: Two to five opposed.

UNIDENTIFIED SPEAKER: So it's defeated.

DR. TALAMINI: So that condition is defeated. So we're standing by at three conditions

to the main motion. Are there any further motions for conditions? Dr. Lippert?

DR. LIPPERT: I motion that they provide the patient information guide to all purchasers so that the user can provide that to patients. I can think of purchases of equipment we've made that came with no patient information guide.

DR. TALAMINI: Do we have a second for that motion?

DR. CONNOR: I second.

DR. TALAMINI: Second. Discussion?

(No response.)

DR. TALAMINI: Was the company planning on doing that? Perhaps could the company tell us whether that is already planned or not as part of our data input for our discussion?

DR. O'DONNELL: Yes, it's already planned.

DR. TALAMINI: Further discussion on that condition?

(No response.)

DR. TALAMINI: Okay. Let's call the question on that condition. Those in favor of adding that as a condition for approval, raise your hands. Dr. Marcovich, affirmative. Dr. Lippert, affirmative. Dr. Bhutani, affirmative. Dr. Connor,

affirmative. Dr. Redman, affirmative. Those opposed? I see no opposed. Those abstaining? Dr. Kalota abstains. Dr. Dahm abstains and Dr. Donatucci abstains. So I believe that motion carries.

Further conditions?

(No response.)

DR. TALAMINI: Okay. So I think we are ready for our main motion vote, and we are standing by with four conditions. Ms. Brogdon.

MS. BROGDON: Yes. Before you go any farther, I'm just looking at my notes on the condition about the post-approval study to assess safety, the one-year study, and I wonder if I could just ask our epidemiologist whether there is any clarification they need about the question that this study would answer. So could I ask if the staff has any comment on that? Dr. Wei, come to the microphone please.

DR. WEI: Yeah, I only have one more question about the comparison group, Study 101 and the comparison group or use other.

DR. TALAMINI: The comparative group or use other -- use a different comparative group or -- perhaps you could state the question again for us.

I'm sorry.

DR. WEI: Yeah, the Panel want to use Study 101 and the comparison group, I wanted to hear your comment, and do you think that a comparison group is okay or you have another recommendation for the comparison group?

DR. TALAMINI: Panel members? Dr. Redman.

DR. REDMAN: I didn't imply any comparative group. It's reporting incidents.

DR. BHUTANI: But I believe the sponsor is planning to compare the adverse effects in the United States -- with the results that were reported in 101. Is that correct?

DR. TALAMINI: So it looks like there's some confusion regarding the data in 101, I guess. Ms. Brogdon, would this be -- would it be appropriate to have the sponsor answer that question or not?

MS. BROGDON: I think, Dr. Wei, we've asked our question enough. If the Panel wants to ask the sponsor to clarify what their proposal is, I think that's appropriate.

DR. TALAMINI: Does the Panel feel they need that clarification?

DR. DAHM: No.

DR. TALAMINI: No. Okay. Dr. Connor, comments?

DR. CONNOR: I think the motion was that we want information about the adverse event profile in Americans, that we were not asking for a comparator group, and I think that's our recommendation to FDA and our vote and they can take that under guidance.

DR. TALAMINI: Okay. Ms. Brogdon, are you okay with that?

MS. BROGDON: Yes. Thank you.

DR. TALAMINI: Thank you. Okay. So I think we're ready for our main motion vote. Dr. Cooper, have you been keeping track of conditions? You might be more reliable than I in reviewing them and stating them for the Panel.

DR. COOPER: The first treatment of condition was to add to the labeling, not treating the low risk tumors. I think that was the Ta grade 1, less than 3 centimeters, single, definition of low risk tumors.

The second condition of approval was to have training mandated for the use of the device.

The third condition was to have a post-market, one-year study as outlined by the sponsor on safety, and I believe that extended to the high-risk

group. Is that correct?

UNIDENTIFIED SPEAKER: No.

DR. COOPER: No. We did not go there. Okay. And the fourth condition was the patient information guide being provided to all users.

DR. TALAMINI: Correct. So it's been moved and seconded that PMA P010045 for the Synergo SB-TS 101.1 Device and mitomycin C from Medical Enterprises, Ltd. be approved with those conditions. With a show of hands, please indicate if you concur with the recommendation that the Synergo SB-TS 101.1 Device and mitomycin C be found approvable. Hands please. With the conditions. Excuse me. So Dr. Marcovich is affirmative. Dr. Donatucci, affirmative. Dr. Lippert, affirmative. Dr. Bhutani, affirmative. Dr. Connor, affirmative. Dr. Dahm, affirmative. Dr. Kalota, affirmative. And, Dr. Redman, affirmative. So a unanimous Panel vote.

So there are no disapproving votes and there are no abstentions, I believe we now need to -- well, it's the recommendation of this Panel to FDA that the Medical Enterprise, Ltd. PMA Apparently P010045 for the Synergo SB-TS 101.1 Device and mitomycin C be approved with the conditions as stated. The motion was unanimous with how many in

favor?

MR. COOPER: Eight.

DR. TALAMINI: Eight in favor, none opposed and no abstentions.

I will now ask each Panel member to state the reason for his or her vote starting with Dr. Marcovich.

DR. MARCOVICH: I voted that way because I believe the data provided a reasonable assurance that the device is effective and safe as per the discussion today.

DR. TALAMINI: Dr. Donatucci.

DR. DONATUCCI: I agree that I believe the data as presented led to my decision to vote affirmatively for safety and efficacy for this device.

DR. TALAMINI: Dr. Lippert.

DR. LIPPERT: It works. I voted to approve the device because it is effective and safe based on the data.

DR. TALAMINI: Dr. Bhutani.

DR. BHUTANI: I voted for approval with conditions because I believe there is reasonable scientific evidence regarding its efficacy and safety with potential health benefits to American patients.

DR. TALAMINI: Dr. Connor.

DR. CONNOR: I voted for approval because I have reasonable assurance of efficacy and safety.

DR. TALAMINI: Dr. Dahm.

DR. DAHM: Based on the evidence that was presented here today, I have reasonable assurance that the product is effective and safe.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: Likewise, I voted in the affirmative because I believe the data supported efficacy and safety.

DR. TALAMINI: Dr. Redman.

DR. REDMAN: I voted approval because I have a reasonable assurance that it's effective and safe.

DR. TALAMINI: Terrific. Well, I want to thank the Panel -- if we could ask for comments from Ms. Stokes and Dr. Layton.

MS. STOKES: I would just like to comment that I agree with the Panel, that indeed the product appears to be reasonably -- there's a reasonable assurance that it is safe and is effective.

DR. LAYTON: I agree with the recommendations and the conditions.

DR. TALAMINI: Thank you very much. So I