populations, just densinometric osteoporosis, I believe that that applies to everyone. But I think that's the only one I could buy.

CHAIRMAN BRAUNSTEIN: Dr. Watts, then Dr. Marcus.

DR. WATTS: I want to agree with Dr. Grady's conclusions but clarify some of the terminology.

The way the current labels read for agents on the market prevention is a drug that prevents bone loss in people who are normal to start with. So that's preventing someone's bone density from dropping below an arbitrary line, and that's not related to prevention of fracture. When I treat patients, I'm interested in preventing fracture and those are drugs that are currently labeled for treatment of osteoporosis.

DR. GRADY: But what's the reason we should be interested in preventing loss of bone mass?

DR. WATTS: That's a different question.

DR. GRADY: No, it isn't. It's to prevent fractures, isn't it?

DR. WATTS: But there's actually no data to show that the agents -- that the populations that have been treated for prevention of bone loss are actually protected from fracture later on. I think the discussion today is for agents that are being considered for treatment of osteoporosis, which means reduction in fracture, not just prevention of bone loss.

A second minor point -- or it may seem minor -- but I think it's unethical and impractical to do a study of osteoporosis in a low-risk population. This is relative. It needs to be a lower risk or a higher risk population. But if it's a low-risk population and they have essentially no risk of osteoporotic fractures, then it doesn't make sense.

DR. BONE: I meant minus two and a half.

DR. WATTS: I understand, but I just wanted to clarify it.

And finally, my bottom line is I'm not comfortable with BMD as the only marker. If we have a drug in class that has been shown to reduce fractures and we can show that a different regimen of

the same drug or perhaps another drug in class has the same effect on density and turnover markers, I would be much more comfortable and I would be willing to extrapolate then antifracture efficacy and postmenopausal osteoporosis to antifracture efficacy and glucocorticoid-induced bone loss or in male osteoporosis provided those same surrogate endpoints, both density and turnover markers, showed a similar response.

CHAIRMAN BRAUNSTEIN: Dr. Marcus was next.

DR. MARCUS: I would like to introduce just a little bit of a commercial reality testing here.

I think there's a stakeholder in this field -- and I congratulate the agency on having representatives from all the stakeholders in the osteoporosis field. For the first time to my knowledge since my association with the panel, there have been representatives from industry invited to sit at the table, and I think that's terrific. However, there is one stakeholder that isn't here, and I think that that actually lets one point of view not be

expressed. That is the third-party payors.

I'd just like to point out from my experience when Fosamax first came on the market that I spent hours on the telephone trying to convince third-party payors to allow patients to receive this drug. The resistance towards receiving that drug was astonishing, particularly in the state of California where managed-care elements were extremely potent.

I think that the tendency on the part of payors has been to define the narrowest possible group of people for reimbursement of pharmaceutical interventions for osteoporosis. If you were to define a treatment effect based on a very low-risk population, I don't think there's a snowball's chance in hell of it ever being reimbursed by third-party payors. And, furthermore, this just gives them exactly the opening they want to turn down high-risk patients because they would say "Well, you haven't shown it for high-risk patients."Therefore, I see the prospect of investing in a large-scale study in a so-called lower-risk population to be extremely unattractive to industry and something which is

basically a non-starter.

CHAIRMAN BRAUNSTEIN: Dr. Rodan.

DR. ORLOFF: Dr. Marcus, first of all we appreciate your recognition of our recognition of all the stakeholders. We actually had not realized you had gone over to industry.

I'm kidding. That's why we asked you here today.

(Laughter.)DR. MARCUS: Yes, you did.

DR. ORLOFF: Could you please move to the back.

(Laughter.)DR. ORLOFF: No. I wanted to make sure that we understood you that -- are you actually saying that even evidence of fracture risk reduction in a low-risk population might not be extrapolated as proof of principle to a higher risk population as far as a third-party payor is concerned?

DR. MARCUS: As far as I can trust the insurance industry, that's exactly what I'm saying.

DR. BONE: Can I just clarify one point, and Nelson corrected me on this. When I said "low", I should have said "patients who just meet diagnostic

criteria for osteoporosis". I didn't mean to imply the osteopenia population or somebody like that. I meant to refer to patients who would meet diagnostic criteria for osteoporosis but did not have a recent fracture or multiple fractures. And we could talk about whether one remote, not very bad fracture put them on one side of the line or the other, but the lower-risk or moderate-risk population.

DR. MARCUS: I think I said "lower". And it's a continuum. I think the closer you get to people who are truly in need of a drug, from above average to a very high-risk, the more likely you are to have a meaningful experiment that will result in a viable product.

CHAIRMAN BRAUNSTEIN: Let's hear from Dr. Rodan and then I'm going to try to focus some of the questions a little bit more if we can.

Dr. Rodan.

DR. RODAN: Going back to BMD, when I start a lecture on osteoporosis, I say that "science starts when you can measure something." Frances Bacon, 1700.

For osteoporosis, this started when people were able to measure bone density. A lot of data -- and Dr. Cummings contributed quite a bit to it -- showed a very close epidemiologic link between BMD and fracture risk, not only cross-sectionally but prospectively as well. And this is why before '94 this was an acceptable standard. The correlation broke down when etidronate and fluoride didn't follow this paradigm. We know very well today why this was the case.

Again, for agents that changed BMD, the tight correlation which was shown epidemiologically, was not the same. Actually, it went in the opposite direction. A smaller increase in BMD produced a larger fracture protection, as pointed out by Dr. Khosla. So there is enough science there, and physics supports that, to relate BMD to fracture risk.

Now the Ibandronate example doesn't fit this paradigm. My understanding is that Ibandronate is now submitted for approval at some agencies. It has fracture risk when given with a different regimen. So this modification, which Mike McClung suggested,

that we should take into account the ways the drug was given and maybe include the suggestion by Dr. Lukert of biochemical markers as an additional criterion, may correct this problem.

Again, if you go to preclinical studies, they can indicate if the bone is normal. And if the bone is normal, then the BMD increases regardless of the weaknesses of BMD because it looks at the cross-sectional picture rather than at the structural picture. The bone risk is not going to increase. The quantity by which this will reduce fracture risk cannot be predicted from preclinical studies. This maybe can be taken care of in the label. And so this is sort of to put this in together somehow.

CHAIRMAN BRAUNSTEIN: Let me make a stab of trying to focus the discussion a little bit more. Let's make the assumption that every drug, whether it's of an existing class that's been shown or a new class of drugs coming through, will have adequate preclinical studies that will show that the type of bone that's produced is normal bone, it's got good tensile strength, and all those things that are done

that are absolutely required before a Phase III study is done for the European regulatory agency.

So all that's done. Let's just make the assumption of good bone quality to start with. And then let's break down these four different classes here to two classes. One being the existing class of drugs that are on the market. For instance, the bisphosphonates or the SERMS. And the others are new classes of drugs that are not yet on the market such as new mechanistic action and a new bone anabolic agent. So those are the unknowns at the present time.

And then we have three groups of patients: those who have a low bone mineral density, two and a half standard deviations below the young adult mean on bone mineral density but no fractures; a second group of individuals who have a single fracture, age undetermined; and a third group who has either had recent fractures or multiple fractures.

So those are the three groups because those are almost three different populations, although they may be along a continuum in addressing what type of evidence we would want to see.

And then we have two other variables: the acceptance of bone mineral density as a surrogate for those groups, or acceptance of fracture as a surrogate. I would stick in with the bone mineral density "with evidence of" -- if it was an antiresorptive agent -- "depression of antiresorptive markers." And if it was an anabolic agent, simulation of anabolic markers. So that will make it even tighter.

So with those type of variables and assumptions, what I'd like to do is sort of go around the room and ask you to express your opinions on this having heard what you've heard. And if you have no opinion, just pass. This way I'd sort of like to get a feel of the group of what people think, given the state of the knowledge, would be the best way to approach the endpoints, the primary endpoints.

Sundeep, we'll start with you.

DR. KHOSLA: Well, I guess I kind of mentioned some of my views on this to begin with. But I think for new compounds in established classes, like a new bisphosphonate or a new estrogen or SERM where

we understand now very well the molecular mechanisms by which these drugs act -- and you've already alluded to the fact that there's adequate preclinical data on all of these --

I think you can make a case that, provided you see the expected increase in bone density and the expected reduction in bone turnover markers, that, in fact, may be a reasonable surrogate for many situations.

CHAIRMAN BRAUNSTEIN: For all three situations, those with multiple fractures, and those with no fractures below bone density?

DR. KHOSLA: Scientifically, I don't see a fundamental difference in terms of how these drugs are going to act on bone in those three circumstances, so I don't feel uncomfortable feeling that that combination is probably adequate.

I think when you started talking about classes "C" and "D", where you've got unknown or new molecular actions or an anabolic agent where we have much less experience -- I mean the two anabolic agents that we've studied has been fluoride, where we know

the bone quality was abnormal, and PTH which seems to follow the BMD fracture relationship. But I think there I'm a little less comfortable because we don't have the body of data that we do with the other two classes, and, there, we may obviously want to exercise more caution and get more reliable fracture data.

CHAIRMAN BRAUNSTEIN: So would you accept a bone density for approval but then require continuation to fracture endpoint, or just fracture endpoint for approval?

DR. KHOSLA: For classes "C" and "D"?

CHAIRMAN BRAUNSTEIN: Yes.

DR. KHOSLA: I guess I would. Provided all the preclinical data is there, you could make the case that you would accept bone density with the fracture data pending.

CHAIRMAN BRAUNSTEIN: Okay. Mike.

DR. MCCLUNG: I would alter my opinion about that a little bit. Again, I think I agree with Sundeep that the three classes of patients or the categories of patients don't influence my thought very much other than the ethical questions about which

patients ought to be included in trials.

The clinical impact of an additional vertebral fracture is a function of the number of vertebral fractures the patients have at baseline. And so for patients who haven't had a vertebral fracture or have had a small or remote vertebral fracture, the clinical impact that is measured in a variety of studies is very small; whereas, if the patients had multiple fractures, an additional fracture is a substantial thing. And doing a placebo-controlled trial among patients with very severe pre-existing fractures under any circumstances in my personal view is not attractive.

CHAIRMAN BRAUNSTEIN: I set these three up in anticipation of getting to the placebo trial issue.

DR. MCCLUNG: Right. So back to the specific question about whether BMD would be an acceptable endpoint, again I think that in classes of drugs where we're confident about the relationship already between BMD and fracture risk, as long as the bone density -- and not only the magnitude but especially the pattern of change in bone markers is

evident. The pattern may be at least as important as the intensity. And that accepting a bone density endpoint for registration of the drug, with the presumption that that would translate into fracture reduction, I think is adequate.

With regard to the new drugs where we don't know that relationship in clinical studies -- the relationship between changes in BMD and/or turnover and the relationship to fracture reduction -- I believe that we still need to have fracture endpoint as the primary determinant for approval for the drug. And then after we've established that in a set of trials with however many drugs Dr. Grady is happy with, then we can begin to amplify that data.

CHAIRMAN BRAUNSTEIN: Great. Thank you. Dr. Watts.

DR. WATTS: The wording of the Declaration of Helsinki was raised earlier, and I think there's one thing that's not really considered there that's relevant to the ethics of placebo-controlled trials. And that is what some call a diagnosis gap or a therapy gap, that there are many people out there who

have osteoporosis who aren't identified and aren't treated. It's getting progressively more difficult to find patients who are suitable for these trials as Dr. Cummings points out.

And I think one of the reasons is that the low-hanging fruit have already been identified and are already on treatment. It's not as though we are taking patients from our clinics and putting them into these trials. I have never done that. We identify people for these trials from advertisements in the newspaper and targeted mailings and radio ads. These are often people who have not been tested for osteoporosis and probably wouldn't be tested and wouldn't be treated, were they not brought into a trial.

Having said that, I still have considerable difficulty on ethical grounds taking someone with multiple fractures or recent fractures and putting them into a clinical trial. But I feel quite comfortable in having patients with low bone mass alone or with a minor or remote clinical fracture receiving active drug versus vitamin D -- calcium and

vitamin D.

It's my feeling that the only time I would be comfortable with surrogates -- and it's a combination of bone density and turnover markers -- would be in other dosing regimens or other clinical applications of drugs that have already been shown to reduce fractures. And let me quickly explain why I feel very strongly about that.

We're talking about class effects. How many amino bisphosphonates do we have on the market where this relationship is proved? Two. How many have been studied where this relationship wasn't proved? One, maybe two. How many selective estrogen receptor modulators do we have on the market where this relationship is proved? One. How many anabolic agents do we have on the market where this relationship is proved? Zero.

So I would be very happy if a drug that's been shown to reduce the risk of vertebral fractures in a lower- to moderate-risk population of postmenopausal women with osteoporosis is tested in men or glucocorticoid-treated patients and shows the

same effect on bone density and the same effect on turnover markers. I would accept that in my clinic as adequate proof of fracture reduction.

I'd also like to highlight very briefly another nuance of this that has come out from Dr. Bone and others. And that is, once we've shown a reduction in vertebral fracture, we should probably be less stringent in our requirement to show reduction of non-vertebral fractures. Use a one-sided test instead of two. Use a more liberal statistical level and so on.

I think once it's out there that it's reducing fractures, as long as we see the trends for other fractures, we should be happy.

CHAIRMAN BRAUNSTEIN: Dr. Bone.

DR. BONE: Thank you. I just want to touch on a point that I touched on earlier to remind people that when we speak about placebo-controlled trials for osteoporosis, there are several things that should be born in mind.

First of all, we are really using a placebo injection as a mask for the active treatment. But there is background treatment for all the patients

in all the trials. And this is a background treatment that has been shown to be efficacious in reducing fracture risk in a number of studies.

The other point is that we never withdraw patients -- essentially, in any trial that I've ever been involved in -- withdraw patients from active treatment in the way that patients are withdrawn, for example, in some other indications and replaced with a test drug. Patients who've had efficacious drugs in the past are just simply excluded from the trial unless they've been off them for years.

I am I think impressed by the consistency of the relative risk reduction for fractures, comparing vertebral versus vertebral and non-vertebral versus non-vertebral, that the high- and low-risk groups are consistent for the same drug. So I'm pretty well satisfied that in the patient who has bone density in the osteoporotic range with or without a remote, single, not very bad fracture, the information that we get about the effect on bone fragility is generalizable to patients treated with the same drug at higher risk. There is no good scientific reason to

think otherwise in any case I'm aware of.

The other point I remind us all of is that in part what we're doing here is just confirming that the animals got it right, that there wasn't something that was distorting the relationship between mass and strength.

I think for initial assessment of any fracture efficacy, probably the lower-risk, placebo-controlled trial model is still very well within the boundary of ethical acceptability. And I think there is a consensus about this amongst people who take care of patients with osteoporosis as their main occupation (or very nearly so, within one standard deviation anyway, give or take), exactly who would be included for example.

But I think there is equally a consensus that the patients who are at particularly high-risk, such as those who have had recent or multiple fractures, are not in the category that we would include in such a trial.

I also think that they are probably not in the category in which we ought to initially evaluate

antifracture efficacy. I think you can make a case that we ought to have at least some evidence of antifracture efficacy in the first kind of trial I was discussing before we take on the problem of the very high-risk patient.

And so I think that comparative evidence of efficacy can be obtained in an active control trial in high-risk patients in a later stage of development, and that would be my preference. There might be exceptions to this. I certainly could imagine that that wouldn't universally be my position, but sort of the first crack.

I think that what evidence we would require for initial registration is inexplicably linked to what evidence doctors need in order to make good, intelligent, clinical decisions. So we might very well distinguish between the minimum level of evidence that the agency might require to conclude that a drug is safe and efficacious and the level of information that a doctor might require in order to practice medicine in his or her clinic and make a decision about whether to use drug "A", drug "B", or

drug "C" in a particular patient's case.

So I think that we will want to have evidence of antifracture efficacy for clinical decision-making even if we don't, strictly speaking, require it in every case for the initial registration. I think this is in part addressed by the current guidance, which isn't so bad after all when you read it.

In the current guidance, the U.S. provides for the ability to register the drug on the basis of clinical trials where BMD is the primary endpoint provided the fracture data is showing a favorable trend in a fully enrolled, ongoing trial. And I think this helps us with the drugs where we're not quite comfortable enough to say, okay, BMD is all we need, but where we really want to be able to move along and we're not so worried after all about those.

So it was a belts-and-braces approach when it was undertaken, and it still has some utility.

CHAIRMAN BRAUNSTEIN: So on a new bisphosphonate, you would want not only the BMD but you'd also want fracture data?

DR. BONE: I think that the fracture data will be essential, and the agency is going to have to rule on whether that is a registerable claim, whether it's the initial registration criterion or not. I'm saying it may not be as big a distinction as it sounds like in the first place in that category.

CHAIRMAN BRAUNSTEIN: And the same with SERM?

DR. BONE: With respect to SERMs, we have a more pleiotropic category of drugs here with hundreds of actions, potentially, on every single organ system practically. This is a more complicated situation. We have a pretty specific idea now about how amino bisphosphonates act primarily. Although as Graham Russell has recently pointed out, local intraskeletal pharmacokinetic differences may actually make a fairly big difference between, in certain respects, between drugs within the class.

But for SERMs, I think what is required here for us to make a good intelligent decision is how specifically characterized the mechanisms of action of the SERM would be. In other words, are all of the

skeletal effects exactly those that are mediated in the way that we think they are by an estrogen-like action?

Now this something that Dr. Rizzoli has talked about, how there are some changes that may be individually drug-specific and not be entirely class-characteristic. I think this is particularly important because, of all the drugs we're talking about, this as a class has the greatest potential for use in the prevention of postmenopausal bone loss, as opposed to intervention after that has occurred.

I think that the characterization specifically here could lead to the decision that the initial indication could be, in some instances, for prevention of bone loss -- much as was the case for the registration for Raloxifene -- and that would be have to be purely on a bone density basis with no adverse safety profiling on fracture; whereas, the use of such a drug as a second-line drug for treatment of established osteoporosis, that might not be the main intervention with a particular drug in the so-called SERM category, depending on how it profiled out.

CHAIRMAN BRAUNSTEIN: Let me see if I have this straight. For bisphosphonate, you'd want bone mineral density and fracture follow-up. For a SERM, you want just bone mineral density?

DR. BONE: Well, no. What I'm saying is if we think we're going to use -- if we have characterized the SERM very precisely as having an estrogen-like action and we're proposing it to be used, not so much initially for treatment of established osteoporosis but for prevention of bone loss, then it becomes a different question. There, the only endpoint you can use is bone density.

But this depends entirely upon the preclinical characterization being bullet-proof. Otherwise, you're back to a bigger problem.

CHAIRMAN BRAUNSTEIN: If it's going to used as treatment for osteoporosis --

DR. BONE: For the indication treatment of osteoporosis, you have a bigger problem because we've had this discrepancy between vertebral and hip fracture. And I think, there, you're forced to rely on fracture rate.

CHAIRMAN BRAUNSTEIN: Okay. So you'd want both bone density and fracture?

DR. BONE: Yes.

CHAIRMAN BRAUNSTEIN: Thank you. And what about the other two classes?

DR. BONE: Yes, I'm sorry for going on quite so long.

I think that in the case of an anabolic agent, it's practically inconceivable that an anabolic agent, given at several times the intended therapeutic dose, will produce no disturbances in the histology or mineralization and so forth of bone. So I think this absolutely falls in the category where we'll learn more about these drugs, and we may eventually change our mind about bone density, but for now, that has to be a fracture endpoint.

For the new mechanistic class of antiresorptive drugs -- in other words, something totally novel unlike any of the ones we have on the market -- I think that the current guidance is a reasonable starting point, which is what I just described a few minutes ago.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Worcester.

DR. WORCESTER: As the Consumer Rep, I'm going to try and look a little bit more at the bigger picture and particularly draw the point that, speaking on behalf of women, what women want to know is what's going to actually reduce fracture.

The idea that just because you can measure something and manipulate it, doesn't mean a whole lot to women who want to know what difference it's going to make in their lives. And, certainly, the kind of information that those of us who teach and work with consumers find out is that a lot of people are very confused with the information out there and really want the safest kinds of products.

So what I've heard today has really fit in with where I came to the meeting, with thinking that at this particular moment in history, probably we have never known better what we don't know, both in terms of what we're intrigued about in terms of the relationship of bone mass measurements related to osteoporosis, fractures, and other things, but also

the whole set of products that we're talking about today, particularly how this particular issue fits in with other things.

I'm here representing not just people who may want and need treatment but also the masses of healthy women who are very confused about what to take. So I want to just comment that a lot of other organizations -- now we've heard how NIH and both the British Columbia Office of Health have in the last couple of years come out with pretty strong statements about needing a lot more information on the relationship of bone mass density to osteoporosis.

And so I think we might be before our time if we were jumping in and saying we knew more about what it meant in terms of fracture reduction. But also in terms of the Women's Health Initiative this summer, I think what it is a reminder of is even when we think we know quite a bit about products, we want to know the next step.

So I would come down to saying a couple of points. Long-term safety, looking at fracture reduction is what's going to mean a lot to the people

who are going to use this. And then I want to come back to what I've heard several other members of the committee and our presenters talking about today.

I feel much less comfortable than other people grouping all the people who are going to use these products together. I think we've heard several times in a very persuasive way that the differences between different women make a huge difference.

Dr. Faulkner this morning in movingly telling us how important bone mass measurements are said, "It's not fair to be lumping all those groups together." I, in some ways, feel the same. We need to be looking at the difference between prevention and treatment.

And Dr. Watts said, "There's no evidence that bone mass density serves as an endpoint for the prevention of osteoporosis." So I think we keep hearing in different ways, we don't want to combine everything together right now.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Zerbe.

DR. ZERBE: Yes. At this point I mean

it's hard to say anything new.

CHAIRMAN BRAUNSTEIN: Then you don't have to say very much.

(Laughter.)DR. ZERBE: I'll just make a general comment that, of course, we've been working for a decade looking for surrogate markers. And looking at it from the outside, this is actually one of the better documented surrogate markers for efficacy. As we look to try to simplify clinical research and bring therapies more rapidly to patients, this looks like an opportunity.

Nevertheless having said that, as the very learned people here have analyzed, I think there's really not a consensus at this point that you can accept, in any simple way, bone mineral density to replace fractures. I think the exception is in the area of bisphosphonates perhaps. I would draw the parallel to the lipid area.

As I sit down and look at it -- and Dr. Orloff made the point very well -- if you look at statins, a class of drugs approved, the approval has been based not on endpoint but on surrogate markers,

cholesterol. And as you go through parallels, what was known when these additional agents were approval, what subsequently has been required, whether this explains all of cardiovascular disease, there are many parallels.

It's hard for me to distinguish why one would accept lipids, the parameters for lipid approval being cholesterol and not accept bone mineral density in a class of drugs that were understood and you had the preclinical bone mineral density data and preclinical morphology and strength to support the point.

So I guess if someone could provide clarity on that and explain the difference, it might help me understand the resistance to that.

CHAIRMAN BRAUNSTEIN: David.

DR. ORLOFF: Indeed, I might offer that we actually talked a little bit about this at lunchtime. With regard to the comparisons between the statins and let's say the amino bisphosphonates, there is actually, with regard to the mechanic of antifracture efficacy, there is probably a lot more known and

there's a lot more bits of information to be garnered in any individual case under investigation in order to permit comparisons of a new drug to a drug that has established itself as an antifracture therapy than exists for possible comparison between statins.

For example, we don't have arterial biopsies for patients treated with Lipitor to compare the effect of Lipitor on the potential to reduce cardiovascular outcomes to Zocor. And yet, not that we've allowed it, but people are using Lipitor like it's -- you know. I don't want to say "water". I got in trouble for that one time.

(Laughter.)DR. ORLOFF: I think it is fair to say that the extension of that to the SERMs is not as clear-cut for many reasons that were put forward. The SERMs were designed to have differential tissue effects. So the whole idea of translating from one to another doesn't seem as solid. But with regard to the bisphosphonates, it seems that there's a pretty good case that bone mineral density could be the basis for that.

I'm a little bit less comfortable,

frankly, with some of the things proposed about bone mineral density being used for formulation or indication extensions. Because the one example that was cited, as I understood it, was a formulation difference where there was dissociation between bone mineral density --

PARTICIPANT: Different drug.

DR. ZERBE: I thought subsequently they had filed for that drug, I thought somebody said.

DR. BONE: There was a very different treatment strategy. It was not a formulation difference. It was a difference between giving a dose every three months and giving continuous dosing. So there was a majority difference in the strategy.

DR. ZERBE: So it may still hold the formulation. You can still raise the question about other indications like steroid- induced osteoporosis versus postmenopausal, just to highlight that point.

CHAIRMAN BRAUNSTEIN: Dr. Temple, you had a question or comment.

DR. TEMPLE: Well, some people have certainly said that if you wanted to go from a once-a-

week treatment to a once-every-three-month treatment and you had fracture data on the once a week, it might be reasonable to use bone mineral density to go to the change.

So that means for every change like that, you've got to redo the fracture data.

DR. MCCLUNG: No. But it's not bone density by itself.

DR. TEMPLE: No, no. I understand.

DR. MCCLUNG: It's bone density and markers --

DR. TEMPLE: -- and turnovers and markers. Right. But you would have to redo the fracture data.

DR. WATTS: Let me try to clarify the issue that I raised. The two amino bisphosphonates that are approved are Alendronate and Risedronate. They've both been shown to reduce fracture risk with daily oral dosing. And within the last two years, both have been approved with once-a-week dosing on the basis of equivalent changes in BMD and bone turnover markers. I think the latter is the key to my acceptance of this.

Ibandronate is another amino bisphosphonate that is not currently on the market in this country. In the initial trial, it was powered to be fracture study with every-third-month intravenous injections that showed a significant gain in bone density. And if you looked only at the samples drawn pre-dosing, there was a reduction in turnover, and it didn't reduce fracture risk.

Almost simultaneous with that, there was an oral dosing trial that appears to show a fracture reduction and is going forward. In retrospect, the IV dosing is said to be maybe not the right dose. Maybe it should've been a higher dose, or maybe every third month was not often enough.

And there's some data from Phase II and Phase III studies to suggest that the suppression in turnover was not sustained. And so if you're dosing every third month, not only would I want to see equivalent BMD changes, but I would want to see probably at least monthly turnover markers to show that suppression is sustained to the same degree that it sustained with the regimen that has been shown to

reduce fracture.

DR. TEMPLE: So that's still a surrogate. It's obviously not fractures but a more sophisticated version.

DR. WATTS: It's two surrogates in combination.

DR. TEMPLE: Just for analogies with blood pressure, we usually ask that there be evidence that blood pressure is held down throughout the day, not just at peak. So there are similar kinds of --

CHAIRMAN BRAUNSTEIN: Let me just introduce a time check here. We have an hour and 45 minutes and still a lot of questions, so I'd like everybody to keep their comments brief. We're continuing to go around the room.

DR. HOCHBERG: Can I briefly make a comment?

CHAIRMAN BRAUNSTEIN: Sure.

DR. HOCHBERG: First of all, I want to apologize for being out of the room, but I was on a conference call for an NIH project.

But this morning I didn't talk about the

relationship between changes in biochemical markers and bone turnover because I was asked to focus specifically on bone density. I agree with Dr. Watts that you need to really satisfy both of these surrogates in order to say that a new amino bisphosphonate, which looks like a duck and quacks like a duck, behaves the same way probably with regard to fracture risk reduction, that you need to see sustained suppression of bone turnover and comparable increases in bone mineral density.

And then, if you have an antifracture trial, you would anticipate that you would see similar degrees of fracture risk reduction.

CHAIRMAN BRAUNSTEIN: Okay. Dr. Levitsky.

DR. LEVITSKY: I have very little to add. I think everyone's opinions mirror mine.

I believe that in classes "C" and "D", the newer agents, that one must have fracture risk as an outcome. For the bisphosphonates, I would feel more or less comfortable if they were approved with just increasing bone density and the bone marker changes. But as a prescriber, I would find it very difficult to

prescribe a drug that I could not say to a patient caused a decrease in fracture rate. Therefore, I suspect that drug companies will be driven by that as much as anything else to get the additional data.

The SERMs trouble me because I don't know what the new ones will do in other tissue. So I think maybe we need more data for that.

The only new thought is I was toying with whether the most severely affected people who are already on an accepted drug for osteoporosis, whether that group might be candidates for add-on trials with a newer drug with a different action.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Sampson.

DR. SAMPSON: As a statistician, I'm always concerned about using a surrogate. I always argue that one needs strong, scientific, and statistical evidence. The question here is whether bone mineral density can stand as a surrogate for fracture rates or fracture incidents.

I think one has to be very cautious in establishing surrogacy in this regard. I think that

the issues that have been identified here in terms of whether or not the compound is in the same class in which there's been a previously established -- and it's been well-shown -- relationship between bone mineral density and fracture incidents, the animal data has to be supported for the particular compound of interest.

I hear dosing regimen is of particular concern, that it not be strongly or dramatically different. I hear also that to establish surrogacy or to support the surrogacy argument, one needs to look at, in addition, marker data. I hear that using fracture data as safety, but I would still look at fracture data even if I'm looking at bone mineral density.

In summary, I think that one just needs to be very, very cautious in this regard.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Lukert.

DR. LUKERT: First, who I would enter into the study. I would be comfortable entering a woman who, by bone density definition, has osteoporosis and

has one remote fracture. But I wouldn't be willing to enter someone into a placebo-controlled trial that had a recent or multiple compression fractures or serious non-vertebral fractures.

With a proviso on the ones that I would enter that there would be the safety net that you would be measuring their bone densities periodically, and if you saw a threshold fall in their bone density, they would be removed from the study. Then I would feel comfortable with that.

I pretty much agree with what has been said about the Class 1 and 2. The new mechanistic drugs, like if we're getting into the osteoprotegeran group or the bone morphometric protein to things that really are new and we don't have a lot of understanding of what those are doing in humans, I think that not only would I want fractures, but I would want histology on a subgroup of those patients to make sure we know what's going on in human bone.

In those, I don't think we can be sure that happens in the animal could be applied to the human, although I certainly feel comfortable with that

with the bisphosphonates. I don't think I have anything else to add to that.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Aoki.

DR. AOKI: Well, I'm pretty much in agreement with Dr. Bone and colleagues. I'd just like to emphasize the importance of the animal studies because in this presentation so far today, I have not heard a major dichotomy that bone strength in itself is not the best predictor of decreased fractures in humans.

So if bone strength and bone volume in animals correlate so strongly with a positive clinical outcome in terms of vertebral fractures and hip fractures, then the question is: What's the relationship to bone mineral density?

It seems to me it's very important to do those studies in animals with any of these drugs that we talking about to see if, in fact, bone strength is increased, especially in ovariectomized animals that are treated with any one of these four classes; and then also to see whether the bone mineral density can

serve as a surrogate by doing the appropriate bone mineral density studies at varying doses. Then I think once you enter Phase I, Phase II in clinical trials, I think that if you have any surprises, the animal studies should be looked at again to see if an explanation can be obtained.

And then, finally, I think in addition to what we've all talked about in terms of the studies themselves, I think that all of these agents should be followed at least in the Phase IV fashion, that after approval has been given, that the companies be required to continue to look at the fracture data to see if in fact it plateaus like in like five years or actually increases.

CHAIRMAN BRAUNSTEIN: Thank you. I actually ultimately want to see fracture data on any drug that comes out that's going to be used for preventing or treating osteoporosis. Although I think from a regulatory standpoint, some may be approved based on surrogate markers.

With the bisphosphonate group, there are certainly a lot of patients who are being treated with

permidronate intravenously on a monthly basis for which we don't have a lot of data, good data. There have been reports of Zometa being used on a once a year basis to increase bone density, but we don't know if that's going to result in decreased fracture rates.

So even with the bisphosphonates that are coming out, I would like to see ultimate fracture data. Although I would accept bone mineral density as a surrogate for getting initial approval but would require ultimately fracture data showing efficacy.

In regards to the SERMs, I also would like to see, ultimately, fracture data. I would be inclined to accept bone mineral density for a prevention type of indication. But certainly if it's going to be used for treatment, I would like to see the fracture data for efficacy.

And for the other new classes of drugs, I would like to see fracture data, and I wouldn't accept bone mineral density as a surrogate.

Dr. Gelato.

DR. GELATO: Okay. I'd like to see

fracture data for all new drugs that come to the market because I agree that it would be a hard sell to tell a patient that, yes, the bone mineral density may increase, but I have no idea whether you're going to have a fracture or not. So that's important.

For the bisphosphonates, I feel the same way. I think if it's a new drug, even though it's in that class, we should have fracture data. I would accept bone mineral density and bone markers for dosing changes within a class. I think that that's perfectly acceptable because we've already established that it does alter or impact on fracture reduction.

I would not add patients who have multiple fractures into studies. I think they need to be treated, and I think that, in my mind, it's unethical to do that.

In terms of the SERMs, I feel the same way. We need fracture data in that class in particular because there are so many different effects that they have on various tissues. We really need to know what the safety margin is in these drugs if and when they come to market.

Obviously, we need to continue to collect long-term safety data on all of these drugs. Because as we've seen with the estrogens, several years were needed before we actually were able to say one way or the other what effects they had on coronary artery disease, stroke, and so on.

And for drugs that are truly new agents with new mechanisms of action, I agree with Dr. Lukert. I think we need to have bone biopsies and look at the histology of the bone and make sure that the bone that we are increasing is the bone that we want.

CHAIRMAN BRAUNSTEIN: Dr. Tamborlane?

DR. TAMBORLANE: I basically agree with that. I think that fracture data, except for an extension of an indication for an established antifracture drug and/or dosing changes and so forth.

CHAIRMAN BRAUNSTEIN: Okay. Dr. Grady.

DR. GRADY: I also agree with also everything Dr. Gelato said. I guess I would just make two more points.

I think I might also be willing to accept

BMD and other markers for new classes of patients, particularly if it would be very difficult to get fracture information in those patients such as steroid-treated patients.

And the final thing I'd like to say is that I agree with what everybody has been saying about SERMs, and I'm assuming that we're including estrogen in that category, which makes me also point out that right now, FDA's guidance makes a special exception for estrogen which I think needs to be reconsidered.

CHAIRMAN BRAUNSTEIN: Dr. Abadie.

DR. ABADIE: My recommendation will be extremely close to colleagues.

I think for all types of drugs, new molecular entities and others, for us the fracture will be monitored in the initial registration for new molecular entities probably because, as has been said, we don't know the drug, we don't know the efficacy and safety, we don't know the relation between the BMD and risk factors, so it's clear that we'd like to see fracture.

For the old entities, we could potentially

accept BMD for bisphosphonate. But as far as we're concerned in Europe, there would be an impact on the labeling. And we'll end up with a magnificent paper with a marketing utilization, but the drug will not penetrate the marketplace so it will be totally worthless.

For the placebo and the low risk, the data that I show seems to go along with the fact that there is some consistency between the low-risk and the high-risk patients. I think there is a possibility to extrapolate from the low-risk to the high-risk patients with the vertebrae or with respect to the vertebrae. Although the database is relatively small, I think we can extrapolate.

The potential to use placebo in low-risk patients for me is something, which as far as the EU is concerned, these are probably acceptable from an ethical viewpoint.

And finally the problem which is the most difficult and where I don't have any clear idea, I must admit, is the problem of the hip. I think that we have to be innovative. I'm not absolutely sure

that the study of hip fracture in a high-risk patient is ethical with the placebo even if we put the calcium and vitamin D in and maybe some -- I don't design, but the ways, the potential impacts on the labeling could be appropriate.

CHAIRMAN BRAUNSTEIN: Dr. Silverstein.

DR. SILVERSTEIN: Okay. I'm really going to echo a lot of what's been said.

I have difficulty putting into placebo-controlled trials people I think need treatment. So, therefore, I think anybody who is a high-risk that I would treat needs to either go into an active control or an add-on study. I couldn't justify in my own mind putting them in placebo-controlled. The low-risk, intermediate- risk I could.

As far as bone mineral density, I think I feel fairly comfortable with bisphosphonates, new classes of bisphosphonates and new indications for those drugs that have already been tested using bone mineral density and turnover markers. But for all new drugs, I think fracture data is going to be important. But even in those drugs that use bone mineral density,

I would think it would be a good idea to have something similar to what the growth hormone registries are, to have long-term follow up of fracture risk.

So you don't need the fracture risk for registration but you still have that data. You'll continue to follow those patients and get those results later on. I guess that's all I have to say.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Rodan.

DR. RODAN: Yes. I agree with things which were said around the table.

I think that for agents that have a known mechanism of action and act selectively on bone and inhibit bone resorption, bone mineral density reduction in markers could be used for initial registration, with fractures being done subsequently. Osteoporosis is a continuum of risk. And so proving efficacy in low-risk patients should probably be extrapolatable to high-risk patients, as already stated by Dr. Abadie and others.

For other indications, I think this can be

extended if one agent has been shown to be effective for a particular indication and other indications, like glucocorticoid-induced osteoporosis which is similar to postmenopausal osteoporosis in many respects.

That's basically it.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Rizzoli.

DR. RIZZOLI: Yes. Regarding a new molecule with a new mechanism of action to have the fracture is mandatory now. Regarding the bisphosphonate and with the long history of the assessments, the relationship between strengths and BMD and bone turnover, this particularly offers a benefit for the patient because for instance, if you had a beautiful bisphosphonate with a 50 percent bioavailability, I would find it a little bit surprising to wait three years to have the fracture data and not to benefit the patient, provided the relationship between strengths, BMD and markers is as the other compound have been demonstrated as efficacious in fracture incidents.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Turner.

DR. TURNER: I'm going to focus my comments on the preclinical issues, which I have a bit more experience with.

I think that we've seen that the animal studies have predicted pretty well the safety issues that we face with these drugs. We haven't had a lot of surprises. In the case of ovariectomized rats in particular, we maybe overestimate the efficacy in some cases, but they've generally been predictive.

But they seemed to have missed in many cases on extraskeletal effects. This is a concern that is very important and is becoming more important, it seems, as we're learning more about estrogen. But we certainly missed on predicting extraskeletal pathologies in at least one SERM, if not a couple. There are the issues with estrogen. There are the extraskeletal effects of parathyroid hormone, which in fact were picked up by the animal studies.

So this I think needs to be considered very carefully in the clinical design as well. In

fact, with some drugs, particularly SERMs and anabolic hormones like parathyroid hormone, trials may be designed with special attention to extraskeletal effects and the power calculations.

I want to hit on a couple of nuances when it comes to the very specific, potentially new molecular targets or mechanistic classes brought up here -- not necessarily just for antiresorptive agents but also for new anabolics that may follow parathyroid hormone -- and that is that if a target is very specific molecularly, it may be targeted to the human, and there may not be sufficient crossover with many animal species.

Currently, FDA guidelines require two analyses in two species. It may be in some cases that only primates or maybe only a select number of species actually respond to the treatment. So there may be some need for rethinking some of the preclinical guidelines when it comes to some of these new, very targeted compounds.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Hochberg.

DR. HOCHBERG: Well, thank you for allowing me as a guest to make some comments. Basically, I think it's difficult at the end of a U-shaped table, but I pretty much agree with the Chair. But I would like to bring up maybe a couple of small issues.

I think Dr. Rodan makes a strong point that one could generalize amino bisphosphonates into a "class effect" with adequate preclinical data and data from clinical trials that demonstrate similar changes in bone mineral density and similar reductions with continuous suppression of biochemical markers of bone turnover.

I think this is what was done with the statins for approval for the treatment of hypercholesterolemia, which is a risk factor just like osteoporosis is. And companies did not do pivotal trials showing reduction in myocardial infarctions to get approval of statin for the treatment of hypercholesterolemia.

I think you can really compare osteoporosis to hypercholesterolemia. You can also

compare osteoporosis to hypertension. I'm not aware that drugs other than thiazides and maybe one or two others have been shown to reduce stroke incidence in clinical trials that have approved drugs for the treatment of hypertension.

So I think you could apply this class effect to amino bisphosphonates. I agree with you with regard to other agents.

This issue of prevention of bone loss, which is a separate indication, gets to this question of -- there's not a similar indication for prevention of hypertension in people who have intermediate blood pressure levels of, let's say, between 120 and 135 systolic and 80 to 89 diastolic. But we know that those individuals are at greater risk of having bad cardiovascular events as compared to people with low/normal hypertension from data published from Framingham, just like we know that people with intermediate levels of bone density are at greater risk of fracture than people with normal bone density in multiple variable-adjusted models from various epidemiologic studies.

So the prevention here is to maybe prevent further bone loss, like one considers preventing an increase in blood pressure or preventing the development of diabetes in people with impaired glucose tolerance or preventing hyperlipidemia in somebody with a mildly elevated cholesterol.

Obviously, we don't want to medicalize something, which is a laboratory test where a large proportion of otherwise healthy individuals fall into that group. But it seems to me that if one was going to allow approval for a prevention indication then it should be focused on the laboratory test, which is being treated, and not on a fracture outcome which requires a magnitude larger sample size in order to demonstrate antifracture efficacy for something which would need to be established first in people with osteoporosis. I agree with the comments about placebo-controlled studies in terms of enrollment of low-risk patients. The question about doing the studies to demonstrate efficacy for hip fracture reduction. We know that calcium and vitamin D are efficacious at least in residents of long-term care

facilities for reducing hip fracture versus placebo. So we really have an active comparator study if we can compare to calcium and vitamin D in the appropriate population. And we haven't really established hip fracture risk reduction in the very elderly with osteoporosis yet. So that's actually a population that could be studied.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Cummings.

DR. CUMMINGS: Thank you. I join the consensus that new bisphosphonates with the same patterns and same magnitudes should be, I think, allowed to be registered and develop new indications on the basis of that. But I don't think that's going to solve our problem. I think that that generates a lot of new me-too drugs. Unfortunately, I don't know that many sponsors are that enthusiastic about following that path.

I think that the field really needs a way to encourage the development and permit the development of new classes of agents. I think that's where the real issue is, not in the fifth and sixth

bisphosphonate.

It's tough to figure out how to do that, but I think that the model of using moderate-risk patients, excluding high-risk patients, and encouraging placebo-controlled trials for those new classes -- and I would include in that new SERMs because I don't think we know enough about that class. But some ways that the agency might consider trying to make this easier might be simplifying or encouraging companies to simplify the nature of these complex expensive trials that are going on because I think that some of the costs could be dramatically reduced.

Then let's see. Anabolics. I think that that's a class where we have a unique opportunity to encourage the development of anabolics in testing as add-ons or comparison to usual care or current practice. I think we may be able to design adequately trials in the anabolic arena as add-on trials.

But my major concern is that the current guidelines really don't address the most important issue to me, looking long term. And that's that we really don't -- if this is a chronic disease that

requires 10, 20, 30, 40 years of care and therapy, I think that we need to think carefully of strategies and require that, after registration, there be long-term adequately powered strategies to test the continued efficacy and safety of these drugs beyond two to three years.

Give sponsors the opportunity to get an initial registration for a year- to two-year studies, but make sure that the plan is built in and incentives are built in to make sure that we know how well patients are faring after five and ten years after use of this drug in otherwise asymptomatic, healthy people.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Marcus.

DR. MARCUS: I think it's simplistic to use the term that has been used many times around the table of "amino bisphosphonates". The fact of the matter is the two drugs which are currently approved are in fact amino bisphosphonates. The drug Ibandronate that was mentioned before is not strictly speaking an amino bisphosphonate, although it is a

nitrogen-containing bisphosphonate.

There are bisphosphonates which are currently on the dock which are being shown as posters, which actually are very different in terms of their molecular structures although they do maintain the bisphosphonate linkage between the two pyrophosphate groups. I believe on is called Apomine, a bisphosphonate ester.

In other words, the heterogeneity of the compounds is going to be growing, and I would predict that the agency is going to be faced by compounds, which are not really amino bisphosphonates. For all of those, I'm afraid that I would have to support fracture trials because I can't rely on identity and mechanism of actions with currently available drugs.

I think that extension from drugs of known efficacy to different classes of patients such as glucocorticoid-associated osteoporosis, males in a drug where the efficacy has been established in women, and some other examples like that are perfectly appropriate to have a BMD surrogate endpoint.

I think that Dr. Lukert, Dr. Braunstein,

and Dr. Gelato made compelling cases, though, based on moral, clinical, and other grounds that it is really more desirable to have fracture endpoint trials. Certainly for other drugs which are in the antiresorptive sphere, such as the integrin disruptors or other osteoprotegerin or cathepsin inhibitors, things which are coming along that line, it's a totally new ballgame and these have to be treated as brand new entities and have fracture-related trials.

Finally, with respect to the non-vertebral fracture, I would strong urge the Agency to permit lumping of non-vertebral fractures. I think that the nightmarish aspects of trying to do a hip fracture study have already been pointed out. In the interest of time, I won't go much more into it. But, I think it's perfectly appropriate to treat non-vertebral fractures as a class.

Thank you.

CHAIRMAN BRAUNSTEIN: Great, thank you. I'm actually going to combine three questions into the next set, and then there's going to be one final question at the end. So let me explain this and

please feel free any of you who have to stretch, get up and stretch, and then come on back.

The next question is going to have to do with what duration of study is appropriate for the assessment of effectiveness, what duration of study is appropriate for assessment of safety, and what other specific safety monitoring should be conducted for those four classes of drugs that were described. So, that's one question that I'm going to ask everybody just to briefly answer.

And then the last question will have to do with the use of placebo versus active control. What types of groups of patients do the members of the panel, as well as the guests, feel would be appropriate to apply a placebo to or active control to or neither.

So let's go to the first question. Dr. McClung, what duration of study is appropriate for assessment of effectiveness, of safety, and what other safety monitoring should be conducted?

DR. MCCLUNG: Well, I think the duration for efficacy and safety are very different. Efficacy,

at least with the classes of drugs that we know about, can probably be assessed in a year's time. Again, we've already made the caveat that the preclinical data are clean.

But for safety circumstances, both skeletal safety and extraskeletal safety effects may not show up nearly in that time, and there needs to, even if approval is granted, a plan to have long-term surveillance about safety type issues.

CHAIRMAN BRAUNSTEIN: So "long-term" is open-ended?

DR. MCCLUNG: I would say five years at a minimum that we need to have that duration because that's the duration of therapy that we are going to aim, with the exception of anabolic agents perhaps. At least for antiresorptive agents, long-term therapy seems to be necessary.

And then the other important piece of that is that once therapy is discontinued, we actually need to know what happens upon withdrawal to help clinicians and all of us understand how best to use the drugs. It may be that five years of therapy may

protect the patient during the five years of therapy, but if the effect wanes very quickly, we need to know that because it makes a difference in whether we decide to continue therapy beyond that five years or not.

CHAIRMAN BRAUNSTEIN: Any specific safety issues, measurements outside of the usual?

DR. MCCLUNG: I think that the safety issues in terms of skeletal safety are already well put together. Obviously, the extraskeletal safety issues depend entirely upon the nature of the compound, what we learn from its mechanism of action, and what are suspicions are about what the side effects might be.

CHAIRMAN BRAUNSTEIN: Terrific. Dr. Watts.

DR. WATTS: Although vertebral fracture efficacy can probably accepted on the basis of a one-year trial, I think it's more difficult to establish the non-vertebral fracture efficacy.

I think one of the convenient things about a three-year trial of agent versus placebo is that it

gives you an adequate opportunity to pursue safety, both skeletal safety and non-vertebral safety with the appropriate trap doors as Dr. Lukert mentioned. So patients with declining BMD, they leave the trial. They have an endpoint, a fracture, whether it's a vertebral fracture or non-vertebral fracture. They go on active treatment.

With the lessons of the recent Women's Health Initiative Study ringing in our ears, I'm not sure that we can really say that there's no lower limit of time to establish safety. We may never see a trial of that same magnitude that will give us the same detail of information.

But, I agree with Dr. McClung that it depends -- the length of safety for non-skeletal issues depends on your concerns about non-skeletal effects.

CHAIRMAN BRAUNSTEIN: Okay. Dr. Bone.

DR. BONE: Thanks. I think, first of all, that the observation period is likely to be somewhat influenced by the way the drug works and its pharmacokinetic characteristics and so forth. In

other words, something that stays in the skeleton for a long period of time might be different, or it accumulates or it has cumulative biological effects, and might be looked at in a different way from something that acted very differently.

But with that having been said, I think, generally speaking, I'd like to have three years of information prior to registration. I think there may be instances in which that isn't the period of active therapy, and it might not be the period of blinded therapy. But that should be as a first cut the observation period.

I would certainly support the idea of extending the observation period for two more years past registration to look for changes. I think the even longer-term suggestion that Dr. Cummings has a lot of merit, but somewhere between five and ten years there may be a practical tradeoff. One of the things that can be done in that situation is a cross-over study between the placebo-controlled group and the active control, active arm, say, after three years so that everyone is treated after five years and you can

look at a resolution of effect, a cumulative dosing for five years and so on, and get a lot of information in a very rigorous way from that kind of observation. I think generally speaking, that's how I would approach that.

I think the kind of data that we're collecting now in terms of density, morphometric fractures, clinical fractures, and markers of bone resorption and formation are the only ones I know about that would be appropriate. But, somebody will probably think of something else to add as we go along. For example, some of these ideas that are intended to look at structure.

The last question would be: How late in the game would you look at biopsies? You might want to consider looking at biopsies relatively late in the game if you have people who have been on a drug for five years, for example. That would be a nice opportunity to do what's being done in the continuation of the FIT trial.

CHAIRMAN BRAUNSTEIN: Dr. Worcester.

DR. WORCESTER: I think the shorter answer

would be longer rather than short. In terms of finding out the safety issues, I think we may want to separate out what I will call "younger women". In anyone under about the age of 65, there might be different lengths of time that we would want to do prevention trials versus treatment.

And I also think Dr. Cummings idea of maybe tying in the approval to how long a drug has been studied and keeping it open-ended so that we can keep track of longer things but get good products on the market.

CHAIRMAN BRAUNSTEIN: Dr. Zerbe.

DR. ZERBE: It sounds like in a year to 18 months, one should be able to demonstrate efficacy, although there were some data presented that suggested the longer-term efficacy is something that does need to be considered, and therefore a controlled period extending up to three, to even longer, years probably is worth considering for the right classes of drugs. Obviously, open-label extensions are important and would have to be geared to the class of drugs.

One issue that hasn't been addressed that

I think is worth pointing out is that we need to be careful that we're not too dogmatic. I think that there's a very good argument for the anabolic agents, for example, that continuous therapy for long periods of time may not be the optimal treatment, and that there needs to be enough flexibility in the guidelines to ensure that appropriate therapy, perhaps a rest period if you've got an anabolic agent would be a more appropriate and safer therapy. That needs to be also considered in the guidelines.

CHAIRMAN BRAUNSTEIN: Great. Dr. Levitsky.

DR. LEVITSKY: I agree with all and have nothing to add.

CHAIRMAN BRAUNSTEIN: Okay, great. Dr. Sampson.

DR. SAMPSON: With regard to efficacy, it sounds like the current two- to three-year duration for fracture incidents is reasonably appropriate. I would also like to agree with Dr. Cummings that, for intended long-term usage, designs or schemes be developed to monitor long-term efficacy and safety.

I'm certainly not prepared to say how many years one would want to do each of efficacy and safety. That would depend on the scheme and the plan.

CHAIRMAN BRAUNSTEIN: Dr. Lukert?

DR. LUKERT: Well, I would be in favor of two years to prove efficacy by bone density measurements just because I think you need four measurements to make sure that you have an accurate assessment of where the bone density is going.

As far as safety is concerned, I think with a drug like a bisphosphonate that's stored in the skeleton, I think there need to be monitors as long as the drug is used because we really don't know much about what those long-term exposures do to either the hematopoietic system or bone.

CHAIRMAN BRAUNSTEIN: Okay. Dr. Aoki.

DR. AOKI: I agree with Dr. Lukert.

CHAIRMAN BRAUNSTEIN: Thank you.

For BMD endpoints -- although my comments about fractures still hold -- but for BMD endpoints, I would want a minimum of a year, probably about 18 months to show an increase; for fracture endpoints, a

minimum of three years; for safety endpoints, a minimum of five years, especially considering the wide distribution of these agents to a large number of the population who are also taking other medications.

I think the more information for the longest period of time, the better. I would encourage the companies to follow what was suggested about keeping at least a large cohort and keeping information on the large cohort for as long as the drugs are out in order to obtain continuous safety information and provide that. Again, I think that's very reassuring to both the doctors and most especially to the patients.

DR. GELATO: I don't really have anything to say different about the duration for safety and efficacy. I think two to three years for fracture is appropriate.

I would just like to make two points that I think were already said. But to reemphasize them, I think we need data on, when we stop the drug, what happens to the patient, what happens to the bone mineral density. Does it stay sustained? Do they

lose? That data I think is very important.

And I really like Dr. Silverstein's idea about having a registry like there is for growth hormone where these patients, who as long as their on drugs, they're continued to be monitored and information gets put into a database that is accessible to people about efficacy as well as safety issues and adverse events and so on.

CHAIRMAN BRAUNSTEIN: Okay. Dr. Tamborlane.

DR. TAMBORLANE: Yes. I'd just like to follow up on that because I know that we've talked on this side of the room about how it's not so easy. You know, how would you interpret the long-term efficacy/safety data. I think it would take some good thinking to try to design it in a systematic way without a control group per se.

You're then talking about some substantial investment of time and effort if this is going to be done in a conscientious way, and it raises the question of: Are there ways that industry could be incentivized to really go after this in an effective

way?

CHAIRMAN BRAUNSTEIN: Well, I think patients often are drawn to drugs that appear to be the safest of the class, and that information gets out and gets disseminated fairly rapidly.

Dr. Grady.

DR. GRADY: I'm in favor, I think, for fracture outcomes of three-year randomized trials. So a continuation of the randomized, blinded comparisons for three years perhaps for registration but then follow up for an additional two years, still with randomized, blinded design, for safety issues and then again some follow-up beyond that.

I think the idea of having a registry is a good one. But it's very problematic to make comparisons to a registry, so I think there should be some effort put into to trying to develop models perhaps using the placebo rates in the individual trials or coming up with some sort of decay rate based on multiple placebo groups and multiple trials to try to get a handle on this. I think Dr. Watts brought this up and, of course, so did Steve.

Finally, I think that companies should be required to make available major outcome data, and this would vary a little bit by the class of drug. But for SERMs, for example, there should be available numbers and annual rates of coronary events, stroke, venous thrombolytic events, et cetera to allow people to do systemic reviews and meta-analyses, which I think could be very helpful but are almost impossible to do with industry-sponsored trials because the data are not made available.

CHAIRMAN BRAUNSTEIN: Dr. Abadie?

DR. ABADIE: I think, although we can have efficacy data in probably a shorter duration than three years, I would probably vote for a three-year's data because I think that, apart of efficacy, safety is also important. Probably in three year's time we will have more data on safety and potentially also on efficacy, although I'm not sure.

With respect to the registration or to the post-marketing commitments, I have mixed feelings about the registry because I have already some examples of that in Europe. I think if we set up a

registry, it raises for us a certain number of problems. We need to know exactly what we are looking for.

And the examples of registry that we have so far show us that if it is a fishing expedition, it's not that cost-effective, I would say. It's okay for something which goes beyond the marketing authorization with respect to efficacy and safety, but, please, let's know before what we are going to look for.

CHAIRMAN BRAUNSTEIN: Very good. Dr. Silverstein.

DR. SILVERSTEIN: I agree with duration of two to three years. I'd like to just touch on the registry issue.

I agree that you need to have certain adverse events, fracture incidence, et cetera, that you'd want to put into the registry. But, in addition, other adverse events could be added and then if people noted that they were seeing a lot of patients with pancreatitis or something like that, they could then query the registry to see how many

other adverse events were in the registry.

I think that's really an invaluable thing for drugs that require long-term use, as these will. So I still want to make a plug for that.

I would also like to agree with whoever it was who said that certainly with the anabolic agents and possibly some of the newer agents, there should be a cohort perhaps five years down the road that had bone biopsy studies to see what they were doing.

CHAIRMAN BRAUNSTEIN: Okay. Dr. Rodan.

DR. RODAN: I agree with bone biopsies.

(Laughter.)

DR. RODAN: -- for agents that act selectively on the skeleton by known mechanisms and inhibit bone resorption. It's acceptable to register such agents initially based on bone mineral density. Probably two years would be sufficient with a proviso that fracture data would be collected over the next two years or three years, which means four years all together.

Now the two-year data could, as now in the guidelines, already show a trend for prevention of

fractures, depending on the group that you selected for study. This will be very similar to the current guidelines but would reduce from three years to two years. Just remember that the three years is there because of etidronate problems.

I fully support what Dr. Cummings suggested, a long-term follow-up of patients, dependent on the agents, the agents that thin bone. We really have a responsibility to find out what's happening over time, and if mechanisms are different as well.

Now extraskeletal pathology, every agent has to be, by law, evaluated for its toxicity on all organs. This should be part of the package with this. However, for agents that we know based on mechanisms that act on other organs -- SERMs, estrogens, and so on -- there could be this additional burden of proof, which we now added on bone agents, to have additional toxicology for bone, which is basically what we're discussing.

It could be expanded for other target tissues or for agents known to have effects other

tissues. For example, sex steroids and derivatives, maybe in reproductive tissues and so on.

CHAIRMAN BRAUNSTEIN: Dr. Rizzoli?

DR. RIZZOLI: The duration of the study might take into consideration the capacity of the drug to restore the strengths. And maybe with a very strong anabolic, duration of 18 months would be enough, as compared with something working more slowly. But in terms of safety, certainly, the observation should last far beyond the time of treatment.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Turner?

DR. TURNER: I think there's considerable evidence that a year or 18 months is enough to see efficacy. But there's very little information, at least to my mind, of how long you have to wait to really understand safety.

One issue that's of great interest to me is this waning effect of the bisphosphonate treatment that Dr. Cummings brought up. I should point out that we don't know what the long-term consequences are of

reducing bone remodeling repair for 10 or 15, 20 years. Certainly at our institution, we're spending a lot of NIH's money to try to better understand this. I don't think anybody really knows how much you can reduce remodeling safely and how long you can reduce it without causing some potential adverse effects.

So, there are some mechanistic issues in the long-term that I don't think we fully understand. There are probably other perils that apply to anabolic agents, other agents as well. I don't mean to pick on bisphosphonates. But I think there are some major unknown mechanistic issues there.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Hochberg?

DR. HOCHBERG: I was just telling Dr. Cummings that I don't have a lot to add.

I think the data showed that you can demonstrate antifracture efficacy for vertebral fractures within 12 months. But if you're looking for non-vertebral fractures, it depends on how many people you want to study. That's the trade-off, as opposed to how long you want to study them because these are

time-to-event studies. So, you just have to accrue enough fractures to be able to show that your reduction is statistically significant.

I think, as everybody has said, the longer you follow patients, the more safety data that you accrue. But even in the trials -- which are an order of magnitude larger than those that I see my colleagues do in rheumatology in patients with rheumatoid arthritis -- we still may miss some rare adverse events, which is why it's important to collect data post-marketing.

In my experience with various companies who have done trials in rheumatoid arthritis, they generally have not followed through on the Phase IV commitments to monitor patients long-term. There are mechanisms set up to do this, through patient self-report and observational studies, in order to collect these kinds of data.

CHAIRMAN BRAUNSTEIN: Dr. Cummings?

DR. CUMMINGS: I would flip things around. I would start with -- Where the Guidelines I think right now are weakest is in the planning of long-term

observations, long-term trial -- long-term data about safety.

If there were a solid plan that had a biologically relevant duration of follow-up, five or ten years, then I think that in that context I would be happier about seeing a drug approved after one year of fracture data. I'm not sure whether it's one year or two years or three years -- Gideon and others have pointed out that that depends on the biology of the drug.

I would really resist the notion that you would set up a single three-year, four-year, or two-year arbitrary time point. I would say that that's where flexibility is warranted; it's at one, two, or three years, depending on the biology of the drug. And in the context -- the most important thing is that you establish a context for a biologically relevant long-term period of observation compared to the initial control experience.

When it comes to registries, the best registry is the treatment cohort within the randomized trials that you've got. Just registries of people on

drugs are not -- they are really problematic to analyze. So I think that that long-term plan is best established as very long-term, biologically relevant long-term follow-up of the treated groups within the randomized trials, with whatever is necessary.

And one last thing, what's the incentive for industry in doing this long-term? I mean, there are precedents. But I mean, with Tamoxifen, you've got a five-year indication. You can use Tamoxifen for five- years, right?

DR. TEMPLE: Yes, but do you know how they got that?

(No response.)

DR. TEMPLE: They randomized people with -- they continued therapy versus stopping therapy --

DR. CUMMINGS: That's right.

DR. TEMPLE: -- a randomized, controlled trial, not a registry.

DR. CUMMINGS: Okay.

DR. TEMPLE: Not a registry, but an adequate plan. Needless to say, to link the approval to the duration of evidence that's in front of you.

In other words, approve it for -- where in the label this is approved for two or three or five years or ten years use or indefinite use. I think it depends on the nature of the evidence you've been provided, and I would link those two in some fashion.

CHAIRMAN BRAUNSTEIN: Dr. Marcus?

DR. MARCUS: With respect to safety, I agree with Steve and Marc Hochberg that really for a vertebral fracture, if that's what you want your indication to be, you can have a good endpoint within 12 months.

That being said, I also agree that to get non-vertebral fracture data is probably going to take a longer period of time. Furthermore, I agree completely with Dr. Gelato with respect to the off rates.

There are some drugs whose effects are lost relatively quickly, such as estrogens. There are other drugs in which bone mineral density as well as antifracture efficacy appear to be enduring. They're robust even after a period off drug. Teriparatide is one that appears to be like that. Therefore, it would

be sensible to have in a trial a period of -- maintained on the trial after termination of the drug. So, I can imagine that somebody might be on drug therapy for two years, with then a third year of follow-up, of continued examination of efficacy.

With respect to safety, there are free safeties and strong safeties, as you all know. The strong safety is what you get within the course of your randomized-controlled trial. You get all the up-front safety events related to the treatment.

The more distant safety events are very hard to get. And with all due respect to Dr. Grady's idea of keeping people on randomized drugs out to five years, I think that that's a non-starter. It's a non-starter because number one, it would be unethical after you showed efficacy of a drug out, say one or two years, to keep somebody on the alternative treatment, out yet another three years.

Number two, I think that it doesn't really get to the safety issues that you'd really want to get, which are those events which are relatively rare and don't just emerge right during your first pass

during the controlled trial.

I'm a neophyte in the pharmaceutical industry, and I've heard of this "rule of three". That is, if you have something like a rare event, something that occurs 1 out of 10,000 times, that you really need to have 30,000 people to make it possible even to see. You'll never see those kinds of events within a controlled clinical trial, no matter how long you sustain that trial.

So, I think that out to three years for a planned safety event within the trial is appropriate. And then, I certainly agree with the sentiment of the community here, which has expressed its desire to see longer-term assessment of safety, and long-term meaning at least five or more years. Thank you.

CHAIRMAN BRAUNSTEIN: Thank you. Okay, we'll try to tackle the last question now.

DR. TEMPLE: Can I just make one comment before?

CHAIRMAN BRAUNSTEIN: Yes, sure.

DR. TEMPLE: I want to join Eric Abadie's skepticism about registries.

If you're looking for very rare events, too rare to show up in your trials, and if they're conspicuous, pancreatitis or something, the spontaneous reporting system is rather good at that. If what you're looking for is an increased risk of something that is otherwise existing -- heart attacks, strokes, things like that -- finding those in registries is not very likely.

After all, why did we think estrogens reduced the risks of heart attacks? Because data from registries -- Framingham and things like that -- said it did. So, anything but randomized trials is not very good at these small subtle and yet potentially important risks, and the sort of obvious stuff usually comes out.

Maybe there are exceptions to that, but it's very hard to have a registry that's big enough to do what you really want it to and that finds the subtle things, because there's no really good control group.

You're in epidemiology, and small risks are not easily detected, epidemiologically. I mean,

what did the WHI show? It showed very small increases, but they were considered very important. So if one really wants these things, I think long-term active controlled trials are extraordinarily difficult but are at least possible. Registries doesn't seem like the very likely way out to me.

CHAIRMAN BRAUNSTEIN: Well, the other issue also is that the incentive for doing a long-term active controlled trial goes away once something is out of the strong regulatory environment. So if it's going to be done in the long-term, it's probably set up best at the beginning, before it's marketed.

DR. TEMPLE: I guess I wanted to make one exception. If there's some particular thing you're worried about, a tumor of some kind or something like that, that may be suitable for registries. Where there's something very focused, that can be done.

DR. GRADY: Could I make one more point?

CHAIRMAN BRAUNSTEIN: Yes.

DR. GRADY: I think the Tamoxifen example is a really good one. I think right now, not only is there no incentive for companies to continue some sort

of structured evaluation after getting their drug registered -- because if they do, they stand to prove that it's only good for five years. That's what happened with Tamoxifen.

Tamoxifen probably would've been used lifelong, had the NCI not done a study in which they randomized women to stop or continue after five years. So it was that study that got the drug limited to five years. So I think the whole idea that we might approve drugs for the duration of use that they've been proven to be beneficial in randomized trials could be an incentive for extending the length of those trials. Right now the incentive is to do a short trial and don't do anything after that.

CHAIRMAN BRAUNSTEIN: Thank you. Okay, for the final question -- this will concern the use of placebo versus active control, when is placebo appropriate, when is active control appropriate, both for efficacy and safety. And if you could define the populations, if you think that there's a difference. That is, women or individuals whose T-scores are less than two and a half standard deviations below the

young adult mean, without fractures, those with one fracture, those with multiple fractures, new fractures.

DR. MCCLUNG: Well, with that opening, let me say that we actually know how to stratify patients in the gradients of risks based on bone density and other risk factors. Using strictly a BMD T-score cutoff actually is too naive.

We could factor in age and the presence or absence of fractures, and there are ways to assess absolute fracture risk. Perhaps rather than choosing T-scores, we can choose levels of absolute risk to categorize patients into a very low-, medium-, or high-risk.

For very low-risk patients, patients with normal bone density values, there's no ethical concern about the safety of a placebo-controlled trial, but there -- in my view -- is a real question about why one would do it. Because it's less clear to me as time goes on about the need for pharmacologic intervention in very low-risk patients.

For intermediate risk patients, we've

talked about bone density values and age and absence of vertebral fractures that put them in a modest risk category. I am perfectly comfortable with those being patients involved in placebo-controlled trials and think that that's the right group in which to do the studies.

The group again which I think we've all agreed shouldn't be involved in placebo-controlled trials are the patients whose individual risk over the short run of the study is so high that there is ethical concern, patients with recent or multiple vertebral fractures.

The active controls studies, I think, would fall into two categories. One would be to document superiority of one drug over another. I'm not a big fan of equivalence or non-inferiority studies, particularly with bone density as an outcome. Because while bone density is a very strong predictor of fracture risk among untreated patients, the relationship between changes in bone density in response to treatment and subsequent -- and its relationship to fracture risk is less strong.

So, demonstrating superiority would be a reason to do it. Or more practically and more interestingly, to look at the effect of combined therapies when the mechanisms of actions of the two drugs are clearly different. I think there isn't justification for combining sets of antiresorptive agents, but there is strong interest and rationale for combining anabolic and antiresorptive agents.

And they are high-risk patients, those with vertebral fractures could be the subjects in the study, both of them receiving our current best regimen, and then one group receiving the additional drug, and the other to compare with our standard best therapy. Thank you.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Watts?

DR. WATTS: I don't think it's ethical to do placebo-controlled trials in osteoporosis. I want to be clear that when we say "placebo", and Henry has mentioned it several times, we really mean everybody gets calcium and vitamin D, and one group gets an agent that masks the fact that they're not getting the

active agent.

I think those trials are perfectly appropriate for patients who are at lower risk of fracture, that is with low bone density -- and I don't know whether it's -2 or -2.5 -- and age gets factored in there. I think it's appropriate for patients who have one vertebral deformity of indeterminate age. I think it's not appropriate for patients with clinical fractures or multiple fractures.

I think the active control trials are best suited, as Dr. McClung says, for superiority or a unique situation of add-on. I think that equivalence or non-inferiority trials are almost worthless, either with a BMD endpoint or fracture endpoint. I think there's a danger in looking at BMD as a good surrogate, particularly when it comes to these novel agents or combinations of antiresorptive and anabolic agents, because I can give you scenarios in which a combination might produce less of a gain in BMD than one of the agents that has the most effect on BMD. Yet, the combination might have a better effect on bone strength and reduce the risk of fracture.

I'm not sure if the agency is ever going to get into that issue, but it's already a thorny one in the bone field and we don't have the anabolic agents on the market yet.

CHAIRMAN BRAUNSTEIN: Dr. Bone?

DR. BONE: Thank you. I concur with my colleagues that in patients where the background, in trials where the background therapy is calcium and vitamin D and we're comparing an additional agent versus a masking placebo tablet or other injection of whatever, that that kind of trial can appropriately be carried out in the patient who meets the criteria for osteoporosis diagnosis but does not have higher risk characteristics.

This would be the -2 or the -2.5 standard deviation patient. It would be the patient who has no more than one remote fracture. That patient might take into account other risk factors, as Dr. McClung has added, that might bump that patient out of the trial. But certainly, recent or multiple fractures would put the patient out of the placebo-controlled trial category.

I think that we have to think about taking the higher risk patient into an active comparator trial at an early stage of development. If we don't have established efficacy for the test agent, I'd rather get that in low-risk patients than go into high-risk patients with an unproven drug. So, I would reluctant to consider an active comparator trial of the non-inferiority type until I had some evidence of antifracture efficacy with the novel drug in a low-risk background situation.

I think we have to be a little careful when we talk about add-on trials. It sounds very attractive. But we've never done one, except for the calcium and vitamin D background therapy in which we've demonstrated additional efficacy, that I can think of.

And I think we should be pretty careful about making regulatory policies out of something that we've only imagined and never tried. There was some evidence presented based on bone density data at the recent meetings of an add-on trial with an anabolic agent and a antiresorptive agent. It looks to me like

you might well have missed the effect, based on the evidence that was presented at the meeting. I may have wrongly concluded -- drawn a wrong inference, if that were the only evidence.

So, I think we should be very cautious about depending on that as the primary test of efficacy. I think it's certainly a reasonable thing to find out more about drugs with, and to determine whether adding the two drugs together would effect -- The latest combination therapy is actually better than mono-therapy with one or the other. But I don't think we can rely upon that as our primary evidence of antifracture efficacy.

If you did see antifracture efficacy in that situation, it might help you to conclude that you had an antifracture effect, but then you would still be plagued in many cases by the question of whether it was specific to that combination, and could be generalized to mono-therapy. So, I think there are some problems with that. There might not be fatal problems in every case, but we shouldn't regard that as so easy as it might have first sound.

So I think our best and really arguably the most ethical approach is to get our primary evidence of antifracture efficacy in the comparatively low-risk osteoporotic patient in a placebo-controlled trial with background therapy of calcium and vitamin D.

CHAIRMAN BRAUNSTEIN: Dr. Zerbe?

DR. ZERBE: Did Dr. Temple want to add something?

DR. TEMPLE: I know you're going around the table, but I have to ask this question, because it has to do with the things before.

I just want to mention what my credentials are for asking this question. For the agency, I have been on the attack on the Declaration of Helsinki, arguing the importance of continuing to do placebo-controlled trials when there is no irreversible risk to the patient. I've even been abused slightly for that. I feel very strongly about it, and I'm well aware --

CHAIRMAN BRAUNSTEIN: But you got some very nice articles in the Annals out of it.

DR. TEMPLE: -- and I'm very well aware of the difficulties with active control trials. However, the ICH E10 document and others uniformly agree that where available therapy -- and one might add available widely-accepted therapy -- produce a death or some irreversible morbidity, you really can't continue to do those trials.

So what I can't figure out is why it's okay to treat people whose irreversible morbidity you are depending on -- otherwise you won't succeed in this trial; there has to be more fractures in the untreated group or the trial doesn't show what you want it to -- why that's okay.

DR. BONE: Because that doesn't constitute irreversible morbidity, Bob.

DR. TEMPLE: Well, not in everybody.

DR. BONE: Not generally. When we're talking about vertebral deformities measured by millimeters in these patients, we are not talking about irreversible morbidity or mortality.

DR. TEMPLE: Okay, I still have one more question.

It seems to me what the standard of care is is very important to this. And I think Dr. Silverstein said this before. If the consensus among experts like you guys is that people with a certain condition ought to be treated to prevent those things, I think it's very difficult to say leaving them untreated is easy.

For what it's worth, in the international arena, I've argued -- but with no support from anybody -- that it's okay to go to a country that can't afford a drug and do trials there against placebo, even though you wouldn't do that in your own country. Believe me, that is not a welcome position. Nobody buys that.

So I still -- that raises the question here. If you all believe that a certain thing is a standard -- now maybe you don't, in which case I understand the position -- how does this add up?

CHAIRMAN BRAUNSTEIN: Dr. Watts?

DR. WATTS: I was sorry that I hadn't mentioned, when it was my turn, that if we have a consensus about placebo-controlled trials two to three

years duration in lower to intermediate risk patients, that someone with authority needs to clarify this for IRBs.

And the two points that I would make -- Henry has made one, and I'll make it again -- that the likelihood of a permanent and serious harm is low in the population groups that we talked about, and there are ways to minimize that. I mean, there has to be a difference in fracture number.

But the second point --

DR. TEMPLE: Low but real? Or low?

DR. WATTS: It is measurable. But the second point that I think is not accounted for in the Declaration of Helsinki is the fact that I mentioned earlier. That is, we are not taking these people out of our clinics. We are not taking people off of effective therapy. We are going out and looking harder and harder and harder for people who haven't been tested, haven't been diagnosed, and are very unlikely to receive treatment during the course of these trials.

Now I realize the ethicists would say,

well, that's a healthcare delivery problem and you can't use that as an ethical justification for including these people in trials. But I think that's short-sighted. I think if we're not doing these trials, those people are not going to be identified and they're not going to be treated.

So, the likelihood that a huge number of people will suffer harm if we don't do these trials is greater than the likelihood of patients in the trial getting placebo suffering.

DR. TEMPLE: I think it's very important to develop that part of the argument. We had a case where someone wanted to leave a 2B3A inhibitor out of the treatment of someone was undergoing -- who I guess had acute coronary syndrome. And we initially said, you can't do that trial. We have data that shows it prevents heart attacks.

And what they were able to show was that the serious cardiovascular community was worried about the bleeding, was worried about the cost, and were not using it. And we though "okay". But it seems to me, those arguments are very critical here to explain why,

when the fractures -- I mean after all, the difference in fractures is the endpoint. They're going to get more fractures, or you lose.

Why is that okay? And also, what do you tell them as they enter? The second part of it. That seems very important. Just saying the risk is low doesn't really make it.

CHAIRMAN BRAUNSTEIN: One could also argue that it's unethical to let a drug go on the market that hasn't been unequivocally proven to be efficacious.

DR. TEMPLE: I totally agree with that, but that's not usual. The desire and need for a study is not usually considered sufficient reason to allow patients to come to harm. You know, these are all delicate and difficult matters. But the dogma is, you're supposed to think about the people in the study, not the benefit to the community primarily.

DR. ZERBE: The individual versus the population.

DR. TEMPLE: That's correct. That's the usual standard. I mean, all these things can be

debated.

CHAIRMAN BRAUNSTEIN: Dr. Zerbe?

DR. ZERBE: I yielded my time, I guess. It was worthwhile.

It sounds like there's a consensus around placebo-controlled trials, and the more modest would be the exception. I think the issue is the more severe. And just to underscore the point that -- I think it's going to become more and more difficult, if not impossible, to do those trials unless there is a pretty active and unified argument that says that they should be done as placebo-controlled trials rather than -- if that's the view. And I don't think it is even around this table. So it's effectively ruled out. A placebo-controlled trial in severe cases --

CHAIRMAN BRAUNSTEIN: Severe. I think we're actually keying in on the less severe.

DR. ZERBE: Yes. I understand that, but I'm just stressing the two categories that there is consensus around. You can argue about the ethics for a long time about the severe. And there are population issues with regard to ethics, but the