reality is, they are getting to be impractical, if not impossible, simply because of IRBs, unless there's a clear statement and a consensus, which there does not appear to be around this table.

It's a simple fact. You're going to have to do positive comparator trials in the more severe cases, I think.

And the other point I would emphasize is the add-on model is probably only not very complicated to interpret, but as I understand it, the data that are emerging are, that in fact adding on anabolics with non-resorptives, are not at all additive. I think that was mentioned earlier by somebody.

DR. BONE: There are some preliminary data about that. That isn't final by any means.

CHAIRMAN BRAUNSTEIN: Dr. Levitsky?

DR. CUMMINGS: Could I?

CHAIRMAN BRAUNSTEIN: Did you want to comment?

DR. CUMMINGS: I need to tell Bob or respond to Bob in one sense. The gradient of risk at which something becomes acceptable to test is a really

slippery slope, and it's hard to define. But it's not so much -- the principle that seems to get lost is that it's not so much when a trial is ethical but when a decision about that trial being worthwhile or ethical switches from the patient who makes that decision to us.

And so, I think that there's a certain small level of risk where it's acceptable from my point of view that I could recommend therapy to the patient, but it's okay if she refuses on the basis of information about her absolute risk and joins a trial.

And I think it's not so much that we, as a community, wouldn't recommend treatment to someone whose bone density is below a -2.5. I would recommend it, but I would accept her refusal, an informed refusal to say to me "that's fine, but I'd rather be in a trial" because I don't think the risk is sufficient for me to overcome her right to make an informed decision. And that's different --

DR. TEMPLE: Then the consent form would tell her right now we've got serious people in this condition.

DR. CUMMINGS: Yes. But see --

DR. TEMPLE: It should be urged that treatment should be used in people like you.

DR. CUMMINGS: Absolutely, Bob. But right now the consent forms, unfortunately they create problems for the IRBs that the FDA could help with.

Now, I'll say that drugs reduce the risk of fracture by 50 percent, and your risk of dying from fractures is 10 to 20 percent, and they do not put things in terms of the absolute risk and benefit for an individual patient who's looking at the trial. Those absolute risks of transient disability are modest to small for the patients we've been talking about. And for permanent irreversible disabilities -- I haven't calculated those, but those are really tiny for the class of patients that we're talking about.

And informed consent needs to be much clearer about absolute risks rather than the relative risks that we have used to promote the importance of the disease.

DR. TEMPLE: That's obviously clear, but it also needs to be clear on what the standard

recommendation is, that there are therapies that will ultimately work in this, and other things that I imagine would have an effect on --

DR. CUMMINGS: Yes, they need to see their physician and hear that too. But I think the FDA could help out with the problem of IRBs who really only understand the relative risks -- and I think if the FDA said that this is an acceptable class of patients in which to design trials, I mean that would help clarify things a lot for people who are confused about absolute and relative risk.

DR. TEMPLE: You probably don't want us to make the uniform determination on it. You probably want to leave it local. I'm just guessing, but --

CHAIRMAN BRAUNSTEIN: Dr. Levitsky?

DR. LEVITSKY: I will ask a question, rather than stating an opinion, for those of you who know more about the pharmacology of these compounds. In these very low-risk people who would be entered into a placebo trial, is there a way to do a time-to-fracture study so that you decrease the exposure of these patients, rather than --?

DR. MARCUS: The answer is "yes". There are many designs one could use. You could say that statistically you'd need to get a total of 75 fracture, let's say, in order to have the power to distinguish one group from the other, and then you'd just continue your trial until that 75th fracture is achieved. And then "wham", you'd cut it off. There are other models too, but you're quite right. You don't have to stick to a three-year model.

DR. LEVITSKY: That would diminish the risk for any individual person --

DR. MARCUS: Of course.

DR. LEVITSKY: -- if that was your approach.

CHAIRMAN BRAUNSTEIN: Dr. Temple?

DR. TEMPLE: I'm sorry I didn't think of this before. We have urged in settings where controlled trials are difficult -- such as seizure studies and recurrence of atrial fibrillation -- just what you suggested, because in a certain sense everybody gets one event, and not more than one event. That's a little -- it's truer if it's something like

seizures where everybody is going to have one in the first month.

But, it does reduce the burden on the people who aren't treated. They at least don't get multiple fractures or stay on it a very long time and accumulate the risk. So that does seem worth thinking about, time to first event.

CHAIRMAN BRAUNSTEIN: Okay. Dr. Sampson?

DR. SAMPSON: I'm not prepared to address in terms of patient populations that would be suitable for placebo, but I was thinking back again to Dr. Cummings' excellent presentation this morning in terms of fracture incidents and non-inferiority.

And he and his colleagues used a certain -- left a sample size impression, a very large sample size. And they used a delta, to me about 25 to 33 percent of the difference between placebo and active. And they also assumed that the test compound was equal in efficacy to the active -- and I'm just talking about efficacy. And those are rather stringent assumptions, I think, in some ways.

Dr. Temple alluded to the fact that larger

deltas might be acceptable -- in the range of 50 percent, maybe even larger. And if you were to use one of the less efficacious comparators and assume that you were more efficacious in that comparator in powering the study, that would in effect further reduce the sample size.

So at least when people have the choice of using an active comparator, I think there might be less severe sample size considerations than maybe the presentation left this morning.

CHAIRMAN BRAUNSTEIN: Dr. Lukert?

DR. LUKERT: I think I already stated what my parameters would be for placebo-controlled trials, a person without a recent fracture. And with the safety net, which sort of addresses what you say, they wouldn't be allowed to have more than one fracture. Even if their bone density starting falling more than your predetermined amount, they would be removed from the study.

As far as the active controls, I think the only place I would consider it practical would be combinations. I think eventually those are going to

have to be studied, the combinations of anabolic and antiresorptive agents.

CHAIRMAN BRAUNSTEIN: Dr. Aoki?

DR. AOKI: I basically concur with Dr. Watts and Dr. Bone's opinions regarding the placebo and the comparator studies.

CHAIRMAN BRAUNSTEIN: Yes, so do I. That low-risk groups -- all groups should get vitamin D and calcium and exercise. In low-risk groups, I see no major ethical problems with carrying out a placebo trial to either a fracture endpoint or BMD, depending on the class of drugs.

As far as the individuals who are at high-risk with multiple fractures or recent fractures, I think an active control study is reasonable and that a placebo-controlled study in that setting is not.

Dr. Gelato?

DR. GELATO: I agree with pretty much everything that's been said, except that I think in the high-risk group they should not be given a therapy until it has been proven to be efficacious. I agree with Dr. Bone, Watson, and McClung. I think that

until you know it works, they're not a group that you should really take a chance on, because the risk is too great for them. There's not a good risk-benefit ratio there.

CHAIRMAN BRAUNSTEIN: Dr. Grady?

DR. GRADY: I find this a very difficult issue. I mean, I think you can pick out specific language from the Declaration of Helsinki, but the sort of intent of it is generally to say that the risk to participants in a trial should definitely not outweigh the potential benefit of what we're going to learn scientifically, or the public health benefit.

And I think in this case that that's how we justify it. I think that there is some risk for people in the placebo group, but that it's small. And hopefully we stand to learn something that outweighs that small risk.

That said, I still think we should think harder about non-inferiority trials. I mean, I think what continuing to do placebo trials leads to -- or is going to lead to -- is eight or ten bisphosphonates on the market, with clinicians not really having a good

idea of which one is better than any of the others. That really doesn't do a service to science or society either.

And I think the main reason we don't do equivalence trials is because they have such practical problems, and it is also problematic to interpret them. So if you don't really learn anything from them then you haven't met the requirements of the Declaration either.

CHAIRMAN BRAUNSTEIN: Dr. Abadie?

DR. ABADIE: I think placebo may be ethical in patients who are usually not treated, where the drugs are not seen as widely available medications. And that's the case in Europe, at least in certain countries, as in my country, in patients with low risk, that is, without any pre-evident fractures at the beginning.

And I would probably strongly echo the time-to-event statistical analyses. In fact, we have already thought about that for the multiple sclerosis, where in fact we have exactly the same problem of active control trials. Before, we'd think that the

placebo in these particular populations may be also acceptable with the time-to-event approach.

With respect to the active control trial, certainly not pivotal unless it's a superiority trial -- because we would like to see superiority on fracture either versus active control but it will be probably difficult -- or versus placebo.

For the rest, I would say, such as a new dose, new formulation, I would probably go along with the active control trial in a non-inferiority setting with BMD as a first endpoint, but only -- only I would say -- in case of new dose, new formulation, new pharmaceutical formulation.

CHAIRMAN BRAUNSTEIN: Dr. Silverstein?

DR. SILVERSTEIN: I agree with everything you said. As a clinician, one of the difficult things -- as Dr. Grady said -- is, why should I choose one drug over the other? And in the absence of active control trials, we really don't know. And so, I think that there is a role for them, in this particular instance and in many others as well.

CHAIRMAN BRAUNSTEIN: Dr. Rodan?

DR. RODAN: I agree with the Chair regarding low-risk patients. The proviso that patients who fracture -- for example, it was shown in clinical trial that Alendronate reduced by 100 percent the occurrence of more than two vertebral fractures. So there is a way to prevent really significant deleterious outcomes in patients involved in the trials, based on existing therapy.

CHAIRMAN BRAUNSTEIN: Okay. Dr. Rizzoli?

DR. RIZZOLI: Yes. Calcium and vitamin D we all agree -- it's more than a placebo, particularly if it's a full dose given, which is not always the case in several trials, in which was given just the minimal dose.

Second, the risk should be defined on the absolute risk base, not only on BMD but other risk factors in the presence of multiple fractures. And finally, I'm not sure that the high-risk patient should not enter a placebo, calcium, vitamin D controlled trial if, for instance, he or she is in a class of age in which there is no well-established treatment, or if we ever design a little bit less

stringent, like a time-to-fracture or shortened study, with the possibility after one year to be switched to the active drug.

CHAIRMAN BRAUNSTEIN: Dr. Hochberg?

DR. HOCHBERG: I guess I agree with a lot of what's been said before, both by the Chair and by my colleagues to the right and by my colleagues across the wide gap between the table.

I comment on a little bit of this question about add-on studies.

One of such designs is the issue of taking so-called partial responders, or non-responders, to therapy and then randomizing them to either continue on their therapy if they're a partial responder, or add on a therapy. We know that patients who get active drug in this situation have fractures. They just have fractures at a lower rate than the group that receives the placebo -- everybody getting calcium and vitamin D.

So, one question would be: Could you design an add-on trial where you would continue patients on active drug and then add on something, as

compared to adding on placebo in that situation? That obviously might be a possibility for this so-called high-risk population.

I think the other comments people have made are all very reasonable. I don't want to trivialize things. I think often times we consider when we enroll patients in trials whether the so-called "mother test" -- this is relevant to osteoporosis -- as to whether you would enroll your mother in the trial. I think, given the low-risk in the overall group for serious outcomes and looking at absolute risk as suggested by Dr. McClung at the beginning of this discussion -- is a reasonable way of making those decisions.

CHAIRMAN BRAUNSTEIN: Dr. Cummings?

DR. CUMMINGS: Nelson Watts said it beautifully. I couldn't add anything to what he said. So Nelson, if you wouldn't mind restating it. That would be my comment.

(Laughter.)DR. CUMMINGS: I also agree with everything that Bob Marcus is about to say.

(Laughter.)DR. CUMMINGS: And Bob, the

most serious comment is actually about the international scope of the trials. I think that Bob's -- I actually support not only the ethicalness but I think the desirability of doing trials in places where people are not getting adequate access to -- it's a small -- we should talk more about that. In large part, because the trials that you have approved, or you've let go -- not right now -- for registration at the FDA, are almost all being recruited outside of the United States.

And so we may believe that we shouldn't include patients who have multiple fractures or severe or recent fractures in trials like this, and may decide that for the United States. But in fact, 90 to 95 of the patients that are being recruited right now to fracture prevention trials are being recruited outside the U.S., many of them outside of Europe, mostly in places where there isn't any alternative for treatment of osteoporosis.

I don't know how you consider that when you are considering the design of these trials. But regardless of what we're saying about what's

applicable in the United States, the numbers of fractures -- most of the fractures in these trials are going to come from areas where there isn't adequate medical care, and they're being assigned to a placebo or the active drug.

DR. TEMPLE: I basically think that's okay.

DR. CUMMINGS: So do I, but --

DR. TEMPLE: But CEOMs, the National Bioethics Advisory Committee, and damn near everybody else does not.

Just so you know, there's a great international debate about such things. My own view is that if it's not available, you're doing good for all the people in the trial, because at least some of them are getting the good stuff. But I can tell you, that's highly controversial.

DR. CUMMINGS: I'm just wondering -- it needs to be thought through clearly. Whatever -- if there's a revision of the Guidelines here and you put in some suggestions about or limits as to who should be in the trials, how does that influence or affect

the design of trials that are then done in a unified protocol around the world?

DR. TEMPLE: Other countries determine who can be in trials. We don't tell them what to do.

DR. CUMMINGS: You don't tell them, but there is one unified protocol that is usually based on discussions with the FDA, not with -- It's a counter-party issue.

DR. TEMPLE: As a general matter subject to debate, if another country decides that something is ethical, they're a country. It means you get to decide if you're a country. It's one of things countries can do.

There's controversy about that, too. But, I think that has generally been our position, unless there is something really just obviously awful.

CHAIRMAN BRAUNSTEIN: We'll let Dr. Watts make a brief comment, and then we'll go on to Dr. Marcus.

DR. WATTS: Very brief. I think the ethical objection to doing a trial in a country where these drugs are not available is that the population

of that country does not stand to benefit from the results of that trial. And therefore, it's not ethical to take the trial there.

CHAIRMAN BRAUNSTEIN: Dr. Marcus?

DR. MARCUS: I have often looked up to the opinions stated by my three gray eminent friends over there ever since I was young and in training.

(Laughter.)DR. MARCUS: And I'm prepared to be persuaded to some degree by them today -- as well as by Dr. Lukert, who isn't so gray -- that there may be a problem with people who have multiple fractures and recent fractures.

The interesting thing is -- and this is a new twist that I haven't heard before or seen before in print -- the concept of new fracture. The Helsinki Declaration, the European -- I've forgotten what the acronym is, but the European position paper on placebo-controlled trials and osteoporosis -- just talk about prevalent fractures and they, to my knowledge, they don't address the recency.

But I'm persuaded by you, Nelson, and Henry, and Michael, and Barbara, that the recency may

actually provoke an additional risk which is not justifiably undertaken.

That being said, I want to make a strong plea for placebo-controlled trials. And if we have an education problem among our colleagues and IRBs and in universities, well so be it. We need to educate them.

I think it is unconscionable to subject a person to the risks of a trial where you are not going to get the accurate estimate of efficacy or safety. End of story.

I think the Amoxicillin story with *Otitis Media,* where people got into recognizing the efficacy of that drug for so much for so long that that became the standard comparator. Everything fell apart when a new placebo-controlled trial showed that efficacy wasn't there. That's how it was presented to me in the *New York Times*.

Bob Temple may want to correct that, but the concept is still, I think, an important one when you don't really know the efficacy or the safety of a drug in absolute terms. You're exposing people to an unmerited risk, and so I think there is still a strong

role for placebo-controlled trials.

CHAIRMAN BRAUNSTEIN: Yes, Dr. Bone?

DR. BONE: I'd like to add one comment which -- I think it's obvious, but it probably needs to be stated for the record.

And that is, I think everyone would accept enrolling a patient who was at comparatively high-risk, if that patient either had contraindications or categorical refusal to take any of the drugs that had established any fracture efficacy -- I just wanted to have that in the transcript.

CHAIRMAN BRAUNSTEIN: Great. Okay --

DR. LEVITSKY: Can I?

CHAIRMAN BRAUNSTEIN: Yes, Dr. Levitsky.

DR. LEVITSKY: I asked you a question before, and the reason I asked it is because I've been sitting here applying the "mother test" while you all talked.

If a placebo-controlled trial can be conducted in women where the outcome will be measured only radiologically, and that is by small micro fractures at the vertebrae that will not involve any

disability. That is probably a time-to-fracture trial. I think it is acceptable.

If people who enter this trial have three days of disability because of their fracture -- when there is a drug out there which is perfectly appropriate this disorder and which they should be receiving treatment with -- I think any argument about availability in the community, any argument about what is available in the country, is not an ethical argument.

CHAIRMAN BRAUNSTEIN: Yes, Dr. Watts?

DR. WATTS: I want to clarify that. I think what Dr. Cummings said about disability was that the average disability for the patient who fractured was measured in days.

And so, if we're looking at a relatively lower risk population and the fracture rate is two percent in the treated group and one percent in the placebo group, then the difference is one percent of people in that trial might have a day or two of disability, not that everyone in the trial would have days of disability.

DR. CUMMINGS: Can I clarify that? There are some people who have the average fracture that occurs, carries with it in our data so far of approximately 100 days of disability. This is three months.

The reason it's an average -- and this goes back to what David pointed out -- is that when you average things like this, you're really not taking account of the fact that for an occasional patient there is a more prolonged -- and the average is about three months of disability. It's because that happens infrequently -- to one to two percent of the people per year -- that you end up with that average of three. It's not spread out over everybody.

And it's really interesting that, in most of medicine, we have bent over backwards to allow our patients to make informed decisions about treatments -- even if we believe they are beneficial to them. It's in the world of clinical trials where that trend seems to be going just in the opposite way, where we are taking on the decision-making about what's acceptable to our patients.

And I think that the right threshold for the discussion is: At what point do we continue to allow patients to make informed decisions about this? And I that there is a degree of modest disability where that is allowable, where I wouldn't allow my mother -- I would allow my mother into the trial, but would I allow her to make her own decision? Damn well right, because she makes her own decisions. She doesn't ever call me.

So, where is that point where you allow informed decision-making to be made on the part of the patients? And I'm not sure about that. But I think that that's the issue, not where we think personally that line is drawn.

CHAIRMAN BRAUNSTEIN: Dr. Silverstein?

DR. SILVERSTEIN: I think Dr. Bone made a very reasonable suggestion, which is that drugs of unknown efficacy should first be tried in a low-risk population, in placebo-controlled trials to demonstrate efficacy. And then for the high-risk people, be in comparative studies, superiority.

You didn't say that, but that's my --

DR. BONE: Yes. My additional comment to that was, I thought that it should come after some initial evidence of efficacy in a lower-risk patient population.

DR. SILVERSTEIN: Right, then the higher risk.

DR. BONE: Bear in mind here, as Dr. Abadie pointed out, in places where there are -- let's say, social consensus -- about what medications are provided by social health schemes in, say in Europe and actually in Canada, the patient with a low bone density and no fracture is not considered a patient for whom treatment will be provided -- if one of these active agents would be provided, beyond calcium and vitamin D.

So there's -- we're not talking about something where there's a compelling consensus that active pharmacological intervention beyond that kind of support is compelling.

CHAIRMAN BRAUNSTEIN: Dr. Levitsky?

DR. LEVITSKY: Well, I think that the issue of social consensus is a real one. But the

social consensus in this country is probably somewhat different right now. And if we can define an appropriate social consensus that would allow us to study a low-risk group that would not otherwise be treated, that's one thing.

But if we have a relatively low-risk group for whom the medical consensus presently is that they should be receiving Alendronate once a week, or something like that, then it's very hard to see not offering them that, unless they are among that group who cannot take this drug or who are very much aware that that drug is available and do not wish to take it and wish to join that trial. That is a very difficult road to walk when you're consenting patients.

CHAIRMAN BRAUNSTEIN: Dr. Zerbe?

DR. ZERBE: I just want clarify one practical issue related to informed consent.

I think it's fair to say that companies would be very reluctant to in any way to put together or approve informed consent, which viewed in retrospect, could be considered as inadequately informing. So I think there's a lot of care in

presenting for protection, if nothing else, a very conservative description of the risks that are associated with that.

CHAIRMAN BRAUNSTEIN: Dr. Temple?

DR. TEMPLE: I think some of the discussion of what the consensus is is very important to this. I must say, I think that's the argument that works.

The distinction between Amoxicillin and this is perfectly clear. There was no evidence in fact that Amoxicillin was useful for a middle ear infection. So, it's obviously perfectly reasonable to use placebo-controlled trials. Also, nothing much happens to you if you don't get treated right away.

In this case, everybody believes that at least certain drugs, not the one that's in the study or the placebo, actually work. That's a different situation. You're denying someone therapy that you all believe works.

But, if that's not really the ordinary practice -- there have been ethical discussions about this by Benjamin Freedman and others, who was not a

fan of placebos, that said if there's real data in the community or uncertainty about whether it's worth even on economic grounds, then that's a legitimate area to continue to carry out studies.

I just think it's very important to make those parts of the arguments, because I'm worried about this.

CHAIRMAN BRAUNSTEIN: Dr. Lukert?

DR. LUKERT: Well, I just want to second what Dr. Cummings was saying about taking about away patient autonomy. I've been astounded at the discussions that we've had in several different venues on this subject -- of how the patient's decision to enter a trial is just totally disregarded. I mean, it's as if they shouldn't make that choice because we know that treatment is better for them.

And, there are a lot of people who will make the decision to enter a trial, even with knowing these are your risks for fracture, the pros and cons of entering this trial. A lot of people are still -- there must be some altruism still present in the world, and I think we should not take away the

autonomy of an individual to make those decisions.

CHAIRMAN BRAUNSTEIN: We'll give Dr. Marcus the last word.

DR. MARCUS: First of all, I think that it's not really accurate to say that we're denying treatment. Any patient, who has ever been in a clinical trial that I've been involved with who said that they would like to drop out of the trial and be on drug "X", went with my blessings and with my goodwill and agreed to be part of the follow up studies.

So, we are not denying anybody therapy.

I was a trial investigator for Merck's FIT trial for the NIH PEPI trial, as well as for a Lilly's MORE trial, so I have personally consented well more than 1,000 patients in osteoporosis clinical trials over a span of 12 years. I have been overwhelmed by the number of women who say they want to participate in the trial because they want to do something which will ultimately help their daughters and help other people.

The altruism gene is very strong, and the

ethics community in this field seems to disregard it entirely. And I think that's a very bad precedent.

CHAIRMAN BRAUNSTEIN: We'll give Dr. Orloff the chance to make some final comments.

DR. ORLOFF: I want to thank everybody for an incredibly thoughtful morning and afternoon, and a lot of hard work. I think it's quite remarkable that we were so successful in convening this group on relatively short notice.

As I said earlier, Henry Bone deserves a lot of credit for his input, as does Eric Colman, of course, who headed up the FDA side of things. Kathleen Reedy did the organization, and Dr. Braunstein clearly isn't particularly rusty after all these years out of the game.

I also wanted to say that if you move, make sure we have your phone number. But even if we don't, we will find you, because this is not the end of this discussion.

We've got a good group. I'm sure we'll call on you again. It'll take us quite a while to go through the transcripts and decide where to proceed

next. But, we've got a good start, so thank you all very, very much.

CHAIRMAN BRAUNSTEIN: Thank you.

(Applause.)

(Whereupon, the above-entitled meeting was concluded at 5:31 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Before: FDA-CDER

Date: September 25, 2002

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represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.