this could be potentially dangerous if you had too much bone porosity, and the answer in preclinicals and now in clinical studies is that no, it isn't, that bone porosity, while it's a great concern, is not a dangerous side effect.

So in summary, we've pretty much identified several different bone quality effects in a tissue. One is impairment of mineralization or osteomalacia. This is definitely a problem and this can be shown in preclinical studies, and it has been shown clinically to actually increase fracture rates.

The other histological findings that are associated with bone quality are increase in micro damage, increase in mineralization, which also occurs when you have decreased bone turnover, both of which do occur and they have been demonstrated but have not been shown to cause great detriments in the efficacy of the drugs, and then the increase in bone porosity which occurs with increased bone turnover.

So with many effective therapies we have combinations of positive effects and negative effects that go together, but other than the impairment of

mineralization, these effects tend only to blunt the efficacy of the drugs, not to cause actual detrimental side effects or increased fracture rates. So I'll stop there and we'll move on.

CHAIRMAN BRAUNSTEIN: Thank you for responding under very difficult circumstances. We'll take a few minutes to, again, have the Panel and guests free to ask questions for clarification from any of the initial six speakers. Yes, sir, Dr. Cummings.

DR. CUMMINGS: Charles, how long would it take in bone to see -- in the case of an antiresorptive in humans, how long would it take to see detrimental effects on bone strength if such were to occur as the result of an inhibition of resorption?

Would you see that in three or four years? Would it take longer, five, six, seven, eight? Do you know what the differences affect? Because most of these preclinical and other studies that you're talking about have been done over the course of a very short period of time.

DR. TURNER: That's an important question

and a difficult question to answer in the clinical setting because typically an antiresorptive therapy will cause a combination of an increase in the amount of bone tissue that's available for structural support.

So that's a positive effect, and maybe that bone tissue might have a little bit more mineralization, which tends to make it a little bit more brittle, or it may have some micro damage that accumulates because it doesn't repair as well.

Now the best we can say is that these two effects must balance each other to some extent because the outcomes at six, seven, eight, nine, ten years tend to still show fracture efficacy with antiresorptive treatment.

CHAIRMAN BRAUNSTEIN: Yes, Dr. Gelato.

DR. GELATO: I was going to ask Dr. Rodan, given the presentation that you made, or Dr. Rizzoli rather, or both, since you both talked about preclinical trials, whether the preclinical trials could be used as a screening mechanism.

In other words, if you find that there is

an agent that shows evidence of osteomalacia, which you so elegantly showed in both of your presentations for Etidronate and fluoride, and maybe that would say this is a drug that should not go on to development or, you know, if it is already in Phase I trials or whatever, that maybe it should be a drug that should be considered not to go further.

I mean, is that something that -- how these preclinical trials -- I guess it goes to the question that the other gentleman asked about, you know, how long does it take to see these effects in an animal because clearly they mirrored exactly what was seen in the clinical trials.

DR. RODAN: If the defect is in mineralization it can be readily detected relatively rapidly in animal studies based on the experience of decades now. And I think it would be wise not to proceed with such a drug into the clinic.

CHAIRMAN BRAUNSTEIN: Yes.

DR. ABADIE: It was exactly the sense of the role of the importance of the preclinical studies in the CPMP Guideline. I mean, that as far as the

registration is concerned, I would respond to that that we are not that, I would say, happy with considering the preclinical studies.

But to go into Phase II, exactly as you pointed out, we think that's important because if there is a defect in bone quality, it's clear that we will not encourage the company to go into Phase II.

CHAIRMAN BRAUNSTEIN: Okay. Yes.

DR. TAMBORLANE: I think I'm directing this at the Agency. But if you're looking at -- say you have an approved drug and you're looking at a new indication, say the use of a bisphosphonate for glucocorticoid-induced osteoporosis, do you ever go back and ask for preclinical studies if the mechanism might be different in a different indication?

CHAIRMAN BRAUNSTEIN: Dr. Orloff, do you want to --

DR. ORLOFF: Yes. We're consulting with our pharmacology colleagues.

DR. TAMBORLANE: I can make -- rephrase the question. Would there be a usefulness in doing such?

DR. ORLOFF: The answer with specific respect to the glucocorticoid-induced osteoporosis indication is no, we did not ask for specific preclinical studies in an animal model of glucocorticoid-induced osteoporosis, in that instance because the sense was that there was not a good animal model available.

Do you want to elaborate on the question?

DR. TAMBORLANE: Well, it just seems that, with the data they have presented, that these were good predictors. And Dr. Bone raised the issue that there may be different mechanisms with, you know, the effectiveness of the drug in glucocorticoid-induced osteoporosis might not -- might be different.

I'm just using that as an example, but you know, that's -- so it seemed to me that -- in the discussion that that might be -- useful information might be derived from that kind of approach.

DR. BONE: Could I respond to that? I actually didn't mean to imply what you inferred. What I was getting at is that -- I was suggesting that we probably only needed to look at fracture data if we

need fracture data to confirm that there is a consistent relationship between mass and strength.

We probably only need to do it in one indication, unless there is a particular reason to think it might be otherwise in a different indication. In other words, if preclinical testing or some good theoretical reason related to the drug's mechanism of action as it would relate to one of these other kinds of osteoporosis raised a serious question about whether the results might be different, then you would have more of a reason to look at fracture data.

But if there were no such reason, then what we're really asking is do we think there's a toxicity or not. Do we think that the drug in some way undermines its own benefit. And so that's what I was trying to get at.

I was sort of saying, if such a circumstance existed, then you might have to go and look at that as a completely separate entity, but that wouldn't necessarily be the case. I'm not suggesting that that should be the rule.

CHAIRMAN BRAUNSTEIN: Yes, Dr. Levitsky.

DR. LEVITSKY: Bill's question is actually a rather important one. It was my understanding that a number of the other disorders which have become peripheral beneficiaries of these drugs do have alterations in bone matrix, which is different from the osteoporosis associated with the loss of estrogen, and I wonder whether there shouldn't be a closer look before we sort of generalize.

CHAIRMAN BRAUNSTEIN: Which disorder is that?

DR. LEVITSKY: Well, I'm thinking, for instance, of glucocorticoid-induced. Aren't there changes -- don't the glucocorticoids change because they change protein turnover? Don't they have effects on bone matrix? Or for instance, in pediatrics, osteogenesis imperfecta, where there are some very excellent trials showing an effect of some of these drugs, which is wonderful. Obviously, the animal model is a little difficult, but nonetheless, it is a concern, perhaps.

DR. BONE: Gideon or Rene, in glucocorticoid steroid osteoporosis, do we know of any

reason to think that we would have a toxic effect with a drug in that model that wouldn't be apparent otherwise?

DR. RODAN: At the resolution at which we can evaluate it, there's no detected difference in bone as a material, in the composition or otherwise, in those disorders like glucocorticoid-induced osteoporosis. It is different in OI, osteogenesis imperfecta, where the collagen has a different structure.

However, it seems, especially based on the response to clinical intervention, that a major component of the fragility is increased bone turnover. That has been reported by Prokoff in OI 40 years ago. And this really is probably why there is response to antiresorptive therapy.

CHAIRMAN BRAUNSTEIN: Dr. Sampson.

DR. SAMPSON: It's a question, I guess, to Drs. Colman, Abadie and Rizzoli. It appears that in the FDA Guidance and the CPMP Guidance, in terms of fracture assessment, its incidence of fracture is the primary efficacy variable.

And I was wondering what would have led WHO to suggest that "time to fracture," to use their language, might possibly be a primary endpoint, for example, in studies of hip. The difference in choice of primary endpoints in the three documents, or maybe I'm just reading it -- I'd like to have further information on that, please.

CHAIRMAN BRAUNSTEIN: Dr. Abadie, do you want to start?

DR. ABADIE: The first endpoint is, for us, the patient as a sample unit. But the time, the time to event, which is the time to first fracture for one patient is extremely important, and obviously, we will ask for that for every submission.

DR. SAMPSON: But would that be considered secondary or is that considered a primary response variable in actually evaluating the primary efficacy?

DR. ABADIE: I think it will be a very important secondary.

CHAIRMAN BRAUNSTEIN: The major endpoint being fracture and secondary endpoint being how long it takes to develop a fracture?

DR. SAMPSON: Yes.

CHAIRMAN BRAUNSTEIN: Dr. Temple.

DR. TEMPLE: As a practical matter, if there are a lot of dropouts it's sometimes easier to do a hazard ratio based on time to first whatever it is. That's true whether it's cardiovascular endpoints or these.

I suspect that has something to do with the reason, too, although I must say it's much easier for people to understand fractures at six months, fractures at a year. That's more tangible than hazard ratios, I think, but I -- that may be the reason. It's an easier thing to calculate if not everybody stays in the study.

CHAIRMAN BRAUNSTEIN: Dr. Rizzoli, do you want to comment at all? No. Okay. Yes, Dr. Silverstein.

DR. SILVERSTEIN: Yes, thanks. Doctor -- I guess this is to you, Dr. Abadie. When you gave your presentation, you said that bone mineral density was not generally a good predictor of fracture risk, although it was good for bisphosphonates or better for

bisphosphonates.

And from a lot of the other presentations, it appears that if the preclinical studies show that the bone structure and strength in the preclinical trials are good, then bone mineral density appears to be a better predictor of how they're going to do in the clinical trials as far as fracture risk.

So if you are using drugs with good bone histology, good bone strength in the preclinical trials, can bone mineral density be used as a surrogate marker for fractures, do you think?

DR. ABADIE: Well, the point is well taken, but I'm afraid that in Europe we will not consider, as I told you before, the importance of the preclinical studies, and we will mainly focus on the fracture.

And the reason for that is, I think, sensible insofar as the BMD and the fracture may be qualitatively related in some sense, but probably not quantitatively related at least for most of the pharmaco class today.

I mean, if you take into account the

preclinical and the BMD, and if you say the preclinical is extremely important and the BMD is also important, therefore, you could go as the drug guidance of the Food and Drug Administration.

The problem is that we discard, more or less, in this reasoning the preclinical. And therefore, we are left with the BMD versus clinical fractures. As I told you, we are not absolutely sure that the relationship, and especially the quantitative relationship between BMD and fracture is sufficient to approve a drug based on BMD alone.

CHAIRMAN BRAUNSTEIN: Okay. Dr. Grady.

DR. GRADY: Yes. You know, I think we've had a couple of presentations that suggest that preclinical studies are pretty good at picking out agents that, even though they increase bone density, may not decrease fracture risk, and at least in retrospect have been pretty good at figuring out why that might be, at least for Etidronate and fluoride.

But I guess I'm -- that seems to me to be old history. That's not exactly what I'm worried about right now. I'm actually more worried about

estrogen, for example, and harmful effects that actually have nothing to do with bone. I mean, I guess you can't answer this, but that's my problem.

CHAIRMAN BRAUNSTEIN: Dr. Marcus.

DR. MARCUS: I'd like to address some -- now that this topic has been introduced of BMD, there have been some things that have --

CHAIRMAN BRAUNSTEIN: Well, we're going to have a discussion, a presentation on BMD and then there'll be ample time for elaboration on that afterwards. So why won't we wait until -- if it's a BMD question, why don't we wait until after we have the BMD discussion?

DR. MARCUS: That's fine.

CHAIRMAN BRAUNSTEIN: Okay. Yes, Dr. Bone.

DR. BONE: All right. Just a further comment about the question that was raised about time to first fracture. It's important to realize that the most of the fracture events that are counted in clinical trials are not clinically symptomatic.

These are -- what you'll hear about from

Dr. Faulkner are deformities of the vertebrae, and we're not doing an x-ray every day. We're only doing those at the specified event, or specified times, like annually or something like that.

So that kind of fracture, which constitutes a large percentage of the events that are counted in the trial, would be only detectable on sort of a per year basis, or something like that. You couldn't get the time-to-event comment.

One other thing I was just going to ask Dr. Rizzoli to comment about, because he has extensive experience with the category, the broad category, with many sort of the pleiotropic category, if we can call it that, of selective estrogen receptor modulators, is that, in the one marketed drug in this category -- and I'm sure that a lot of drugs have been washed out because of the testing that's been required -- but in the marketed drug we do have this discrepancy between the significant reduction in vertebral fracture and a relative risk of about one for the nonvertebral fracture, the hip fractures.

Can you give us a little discussion about

if we're seeing a disconnect there between the bone density effect and the fracture rate?

DR. RIZZOLI: I wish I could do it because this is an issue which has puzzled many, many people. I cannot give an answer why for the same decrease in fracture at the vertebral level and given an increase in bone mineral density, the peripheral fracture are not influenced in the same way.

So I cannot answer you. But you raised two other points. The first point is, within a category of compounds with probably exactly the same mechanism of action maybe the BMD is a relevant issue.

For instance, a new amino bisphosphonate having been shown in preclinical data that the relationship between BMD strength is the same, there is no mineralization impairment, the pharmacokinetics is the same, probably the effect on the fracture rate is likely to be similar.

On the contrary, with the SERMs, for which as you know the mechanism of action is probably very, very different from one compound to the other, it would be very difficult to draw a conclusion from one

compound to the other.

CHAIRMAN BRAUNSTEIN: Right. Yes, Dr. Watts.

DR. WATTS: In thinking about the preclinical studies I think it's important to separate where you're looking for safety or toxicity problems and where you're looking for efficacy problems.

In particular, the doses of Etidronate that were shown to impair mineralization in animal studies were much higher and the exposure much longer than the doses of Etidronate that were used in clinical trials.

And while I don't want to get into details on the Etidronate study, it was not powered to show an effect on fracture, but it did have extensive bone histomorphometry data available for at least seven years of treatment, and there were no problems with mineralization identified there.

So the dose that you study for toxicity certainly raises the possibility that there might be a problem with the lower dose used for efficacy, but it doesn't mean that a lower dose would be

ineffective.

Dr. Rodan, on the efficacy side, pointed out the strong relationship between increases in bone volume and increases in bone strength, and I asked him at the break and would appreciate a clarification: Since none of these agents have been shown to increase bone volume in iliac crest biopsies in humans, why should we extend the observation of this relationship in animals to the antifracture effect in humans.

DR. RODAN: You have the question. So I mentioned that in our three-year baboon study we did not see increases in volumetric bone amount in the ilium. We were very surprised about it, but we did see it in the spine, and this is what we published.

So the ilium has problems of sampling and it's a nonloading bone and so on. And the data are usually collected in the spine, so there are site differences which limit extrapolation from the ilium to the spine. So this is what I told Dr. Watts.

Now, I meant to answer some of the questions here. The very strong correlation one sees in amino bisphosphonates between bone density and a

reduction in fractures may have a quantitative component to it because amino bisphosphonates are the most efficacious inhibitors of resorption now used.

So the amount of change in bone whether due to mineralization or to increase bone, volumetric bone mass, is larger than for the other agents. And so we may not have the power to detect -- there may be a quantitative aspect to it.

We may not have the power to detect the fracture efficacy with agents that are not as robust in their antiresorptive effect, and there may not be a mechanistic difference between the action, all of them inhibiting resorption, but some less and some more.

So that's why the bisphosphonates came out to have such a strong correlation.

CHAIRMAN BRAUNSTEIN: All right. Thank you. I think we'll go ahead and move on to the next set of talks on measures that -- pardon?

DR. ORLOFF: I just want to make one comment, if I might, before you go on.

CHAIRMAN BRAUNSTEIN: Yes.

DR. ORLOFF: I wanted to make sure that Dr. Grady's question didn't get completely dropped, if indeed it was a question. And I think what it gets to, at least from my interpretation, is a concern that if certain drugs were approved based upon trials that didn't go as far as to assess fractures --so foreshortened, if you will, because of a requirement only to examine BMD -- there is no necessary reason why those trials have to be shorter or smaller, and that the safety concerns or the need for safety information will always drive the size and durations of trials, in this instance and for other, you know, parallel conditions, in a chronic asymptomatic disease in the vast majority of patients who are, you know, affected at any given time.

So there's always -- there will be opportunity to get safety information, both for the skeleton and at nonskeletal organ systems.

DR. GRADY: Well, that's true if estrogens are allowed to be approved based on only BMD studies. I mean, the average sample size there is a few hundred, compared to, you know, a few thousand in the

fracture studies.

DR. ORLOFF: That's a minimum sample size based upon considerations for efficacy. But I'm just saying that there's no reason why the trials have to be limited, and it's up to us to ask for more patients and longer duration to make sure that we're not overlooking some sinister effect that might accrue over the longer term.

CHAIRMAN BRAUNSTEIN: Thank you. We'll move onto the measures of clinical efficacy. The first speaker will be Dr. Faulkner, speaking about measurement of bone mineral density in vertebral fractures.

DR. FAULKNER: Thank you very much. I'm very pleased to be here today. I wish to acknowledge, by way of disclosure, that I am an employee of G.E. Medical Systems. We do manufacture densitometry and x-ray equipment. However, that's not the subject which I address today, differences in the equipment.

I am here to address the techniques in general. So I hope you'll find that acceptable; and acknowledge, also, the significant contributions of

Professor Harry Genant, actually one of my mentors in my early career. He is joining us by video conference and will be available if we have a question regarding the radiology, specifically in vertebral fracture assessment.

So I'd like to just start with the basics. My training is in biomechanical engineering, and one of the things which I have learned and has been confirmed to me repeatedly is that there is an exponential relationship between the density of bone tissue and the strength of that bone tissue. And this is done predominantly in excised specimens, but it has been well shown by decades of research.

So that we know that this exponential relationship is such that small declines in bone density correspond to large differences in strength, and in particular, fracture risk. I quote here a mets-analysis of Debbie Marshall which combined a lot of studies that had been done over the past several years showing this to be true.

But this also means that small increases in bone density, if we drive the curve the other way

a few percent, can reduce fractures by 30 to 90 percent. So, again, the nonexponential feature of the curve is that which I wish to stress.

It's not that if you wish to reduce fractures by 50 percent that you have to increase bone density by 50 percent. It's not even close to the case. It's very, very small changes leading to very dramatic changes in strength.

In fact, the conclusion of the Marshall review was that the predictability of bone mass was better than that of serum cholesterol for cardiovascular disease. You can see here that for bone density and fracture, as bone density increases the relative incidence of fracture decreases greatly.

There's about a tenfold gradient between those who have low BMD, lowest quartile, to those who have high levels of bone density. Wherefore, cholesterol in comparison, you can see that there is a similar type of relationship, but not nearly to the degree, about a fourfold change going from the lowest quartile -- or actually, the highest quartile of increasing cholesterol down to about, as you can see

here, much less of a steep gradient for cholesterol and heart disease.

There are a lot of different ways to measure bone density. I'm going to do a quick review of those here. They've been mentioned previously. It was possible, and still is indeed possible today to measure the peripheral skeleton using conventional x-ray techniques.

This is really unsuitable for a few reasons, though, for our discussion today. One, we'll talk a little bit about the utility of peripheral bone density measurements -- that is; nonspine, nonhip measurements, as I define them -- for monitoring changes in efficacy of drugs.

Also, conventional x-ray systems have limitations of using -- of requiring calibration phantoms, or they're not as well used, either clinically or in research today. There are other options, to use smaller peripheral-based x-ray units, as well. I show several here.

They are nice in that they're portable, but they have limited measurement sites, again. And

as you have been hearing, most of the time the requirements have been to measure spine and hip and these devices are not equipped to do that.

Ultrasound has been seen as a little more recent advance in the field of densitometry, though it has been around for some time. Ultrasound is speculated to maybe measure properties of bone which are beyond just bone density and might be related to some of the infamous quality issues, which we're discussing here.

But this really has remained to be determined, though. I think that this point, in particular, I believe that ultrasound is primarily an alternative measure of bone density.

It probably has some component due to other factors, as well, but at least your colleagues on the radiologic devices panel chose to approve it as an estimator of bone density, and I think for our purposes that's true, as well.

It's -- but not using x-rays, so that that does have some regulatory and safety considerations, though x-ray dose with all these techniques is

extremely low. Again, limitation here, even though some of these devices may have clearance from the radiologic devices panel of the FDA for monitoring, I think that we realize, as well, that it's by monitoring those sites in the peripheral skeleton, which don't change as rapidly, that you are -- they are not as efficacious for monitoring for the purpose of our discussion today.

Most of the Guidance, I think all of the Guidance documents that we've reviewed up to this point have concentrated on the use of central bone density measurements, that is, spine and hip measurements predominantly, using a technique, DXA.

It has the advantage of measuring not only the spine and hip, but can also measure forearm, total body measures. These can be of particular importance, for example, with some agents that may not have the same type of effects on the skeleton as antiabsorptive bisphosphonates.

For example, with a recent application with PTH, concerns over effects on cortical bone brought out the importance of doing total body and

forearm measurements. They are somewhat larger, their office space a little more expensive, but really considered the clinical standard.

In fact, all of the registration studies which have been done to this point have been based upon bone density information acquired using DXA. There are techniques using CT scanners that look at a slightly different property of bone.

A quantitative CT measures the volumetric density. The previous techniques use an area or a projection density, or grams per square centimeter. This is actually a volumetric technique, grams per cubic centimeter, are predominantly being done at the spine, has been done in some subsets of study populations, but has not been considered as a primary endpoint for the registration studies, possibly because of its limitation to the trabecular bone in the spine.

I'm showing a CT scan here. It really doesn't give you the full spectrum of both cortical and trabecular bone. But it has proved important for looking at some agents in a research setting, and

maybe in subsets of studies.

So it's often asked, I get the question quite frequently, well, you've got a lot of options for measuring bone density, and how well do the various bone density measurements correlate? And since I figured we'd have that question I would give you the numbers here.

It corresponds to -- I think my basic law of correlation is that anything in your body will correlate to anything else at about .6 to .7. And we see some variability around that number here.

But essentially, if you look at the different bones and the different skeletal sites using the various technologies, you do see modest correlations, not surprisingly, but not perfect correlations.

The bone density at say the spine will never really correlate -- will not correlate to a high degree of bone density at hip or other skeletal sites due to the fact that you've got completely different kinds of bone, cortical and trabecular ratios.

You've got a large variability in the

blood supply, surface to volume ratio, weight-bearing. So it really isn't -- would not be expected that they should be. And I think it's appropriate to evaluate several skeletal sites when looking at efficacy of bone density for therapeutic agents for these reasons.

But really, correlation in itself is not of that great of interest clinically, even though you may have a disagreement between the raw bone density values at different skeletal sites. What really is important is how these different skeletal sites and measures predict ultimately fracture.

And it has been reported in several trials, and again, showing the meta analysis from the Marshall paper, that hip fractures can be predicted by all BMD measurements, but that hip BMD itself is the best predictor of hip fracture.

I'm showing the age adjusted relative risk for fracture here as a function of the various bone density tests that are performed. And again, not surprisingly, you would think that a direct measurement of the hip would have the strongest relationship to eventual risk for hip fracture.

But it is also true that other skeletal sites, measurements at the spine and the heel and the forearm, can indeed predict fracture, but the relationship is not quite as strong as direct femoral measurements.

When looking at overall risk for fracture the measurements turn out to be very similar. You don't see one -- a preference for one skeletal site over another. In fact, all BMD measurements in the Marshall meta analysis were just about equally predictive of fracture risk.

So I think this has led to the conventional wisdom in the field that if you wish to predict fracture at a skeletal site, at least clinically, that you should try and measure that skeletal site directly.

But for overall risk of fracture of any osteoporotic fracture, then you can really measure any skeletal site and get similar types of results. but in our context of our discussion today, I think that we have to realize that the diagnosis or assessment of fracture risk is important at one level, but also, we

are interested in monitoring changes over time.

And these are very different challenges for bone densitometry. When we want to diagnose someone or assess fracture risk, we have to have an accurate bone density measurement. We have to make sure that the number is a true reflection of that patient's density.

We need to have valid reference ranges. We have to know what is normal in order to classify someone as outside of the normal range. And we've also, properly to assess risk, should -- need to include additional risk factors: age, prevalent fractures, family history and many other features must be incorporated, as well, in order to get an overall picture of fracture risk, because it is not just a feature of bone density alone, which you'll be hearing a lot from other speakers.

If we're looking at changes over time, though, if we're now looking at the ability to monitor, precision and instrument stability is really the most important feature here. We've got to have precision or reproduce-ability so that we know that

changes that we see over time are true changes in the patient, and not due to alterations in our technique, either alterations in our equipment or alterations in our measuring procedure.

And this needs to be carefully controlled in clinical trials. We've also got to measure response of skeletal site. If you choose a skeletal site that is maybe not as responsive, it may be difficult to see bone density changes, not due to any problems with the technology, but just due to the fact that you're measuring a site that is not changing very rapidly.

And also, appropriate follow-up time. If you wish to do a treatment study looking at change in BMD and confine it to a one-month duration, you will be disappointed because the changes, at least with the current therapies, don't occur nearly that quickly.

So you've got to have -- in most clinical situations it usually takes in individuals about two years to see clinically significant changes, maybe less for steroid-induced osteoporosis. I will point out, indeed, this is for individuals.

When you have group effects you can show changes much more quickly. So in monitoring responses, show data here from one of the postmenopausal registration studies, looking at this time at Alendronate and HRT compared to placebo.

In this case a slew of skeletal sites were measured. We had both the posterior and anterior spine, lateral spine measured, as well as the femoral neck, total hip, the forearm, both at the ultra distal region and the one-third region, and the total body.

And the -- percent BMD change at 24 months, shown here the largest changes indeed occurring at the spine in this early postmenopausal population with this metabolically active bone in the spine. And that was true both in the posterior, anterior and lateral view.

The lateral view looks at a little bit more trabecular bone than the PA view, but in this case they were fairly similar. And note that at least in the case of this particular study that you saw in some cases a loss of bone, or no change in bone density at some skeletal sites, when indeed, the

metabolically active site of the spine was showing a significant response.

So TROI's subskeletal site is indeed important. As I mentioned, though, 60 to 80 percent of -- when we take bone specimens of the bone specimen strength, this related to its bone density and it is both cortical and trabecular bone that are important.

If you look at the vertebral body here, for example, in a slide from Dr. Genant's lab, you can see trabecular bone components shown in red and the cortical components shown in blue. And at least at the vertebral body, the predominant weight-bearing site is in the vertebral body here, the posterior elements being used predominantly for muscle attachments and torsional stability.

So this is important to maintain this weight-bearing bone, but I think I point out in the spine it has been suggested by some that trabecular bone is of prime importance.

But I think you can see here from this picture that both cortical and trabecular bone are indeed present at the spine, and even to a larger

degree at such sites as the femoral neck, where cortical bone may represent as much as half of the bone density there.

Clinical studies have indeed confirmed that fracture risk is reduced by treatments that preserve bone quality, increase bone density and decrease bone resorption.

So at least as I've reviewed the information that we have, that those studies that have shown a positive effect on quality through various animal studies and bone density through both animal and clinical studies and decreased bone resorption, have by and large gone on to show some degree of efficacy for reducing fractures.

Though I agree with Dr. Rodan that to quantitate the exact relationship does require you to look at the fractures in detail, but by and large, that if you see this type of positive results here that you'll see a positive result in fracture studies, as well.

This is a meta analysis which was done by Richard Wasnich, looking at some 13 clinical trials

that were done and its potential -- the potential for a change in bone density to have an effect on vertebral fracture rates.

And it was noted here that those compounds which have a small change in bone density tend to have less of effect on reduction in vertebral fracture risk than those changes that have a large effect on bone density.

So this can be shown when you combine these multiple studies together into a meta analysis, though I will admit for individual studies it has been somewhat confusing as to why some compounds show an affect on bone density somewhat discrepant with their expected change on fracture risk.

I personally believe part of the difference is that we've got extremely disparate populations that we're studying. Some are early postmenopausal, some late postmenopausal, and it's not really fair for us to lump all of these together unless we do something like we've shown here, using a Poisson regression that accounts for differences in sample size.

But the general trend at least is that those compounds that show the greater increase in density, show the greatest reductions in risk. So we do have a lot of different methods for assessing bone density.

I breezed through a brief introduction of them all, but I think for our discussions here today we find that those that are monitoring response and predict fracture are the ones that we're trying to include in our investigations of these various therapeutic compounds.

DXA probably has the big advantage, which is why it's used, because of the fact it can measure the clinically relevant sites, both the spine and the hip. It has been well-documented. There are excellent procedures for performing quality control.

We understand the technology quite well and its ability to monitor has been shown, as well, in all these studies. So let me move on to a discussion of vertebral radiographs and the section that was predominantly prepared by Dr. Genant.

It's -- the idea with vertebral

radiographs are we need them as a detector of vertebral fractures, because not all fractures which happen in the spine, in fact a majority of them, are detected clinically.

Many of them pass by without being symptomatic to our patients, at least to the degree that they would present for some type of evaluation. And they have played a key role in establishing the efficacy of drugs in osteoporosis treatment and prevention.

And they have to be interpreted, though, very carefully, as it's not -- I'll show you some examples here -- it's not easy to do these without expert knowledge of anatomy and pathology and some experience looking at these films.

The challenge is really to look at shape recognition. I would sometimes go into Dr. Genant's office when I worked in San Francisco and watch while he read films, and he gave the example of the fact that you can look at a vertebral body and with a trained eye very readily determine whether or not it's fractured.

Whereas, sometimes with an untrained eye it's not easy to do that, and in some cases by using measurements of height, which we'll discuss later, have been proposed as a surrogate. But consider if you would a car that's been involved in an accident.

It would -- it's usually quite easy for us to tell visually if that car is a total loss. Whereas, if you were asked to put six points on that automobile and then based upon the placement of those six points determine if it was a total loss, I think you'd be quite frustrated.

So it's important to have I think at some point a visual assessment. Let's talk about the various deformity indices that we have. There are, as I mentioned, clinical or symptomatic vertebral fractures. This is sometimes used as a secondary endpoint.

That is, those patients who present with back pain or some symptom that would cause them to indicate that something might be wrong, would present and then upon verification with a spine film, that would be called a clinical vertebral fracture.

But many vertebral fractures are not clinically captured, and we've also determined that these nonclinical or morphometric types of fractures can be associated with an increased risk for subsequent fractures, as well. So they are indeed important to capture.

There are several methods to define fractures based upon spine films. There's a simple visual assessment, either a yes or no, based on a radiologist's read. Semi-quantitative visual assessment. That is a technique which divides vertebral bodies into a zero grade, being normal, then from a one being mild, two moderate, three severe.

This I'll explain in a little more detail in a moment. And then we have morphometry, which is a simply measure of heights of the vertebral body at various locations and looking at the ratios of those heights and comparisons within vertebrae or between vertebrae to determine if a fracture exists.

For vertebral radiographs, quality is first and foremost, as the same with bone densitometry. You need to have good quality

radiographs. As an excellent example, if you have garbage in, you will get garbage out.

So exposure is important to control. Patient positioning is extremely important because you can mimic the features of a fracture with poor positioning. A depiction of anatomy; ideally, you'd like to see T4 to L1 on the thoracic view and from T12 down to the sacrum on the lumbar view.

Having the overlap between the two views does allow us to accurately quantitate the vertebral levels. For visual assessment you of course need to have, as always, adequate film quality, but I think in this point the experience in trained observers is very important.

To distinguish fractures and other clinical conditions, technical and positional variations in the films requires a trained eye. I know that we've had the privilege of doing some studies comparing radiologists and it's surprising how frequently different radiologists will disagree upon whether or not a fracture exists in a film, just due to differences in their experience, but it has --

requiring the need for some kind of standardization in training.

These are probably going to be a little bit difficult to see with the lights up. I don't know if we can turn them down, but I wanted to provide for you just some of the challenges associated with vertebral fracture.

Is it possible maybe to dim the lights somewhat? Do we have someone that could do that? Thanks. You can see right here, one of the requirements is to have dim lighting while you want to read these, as you could see.

But here, we have an orthograde film, orthograde in that when we have the visualized vertebral bodies here that you do have a view where you're looking down the endplates in a way that allows you to accurately assess vertebral heights.

Whereas, you have here in this film if you can appreciate it, there are the endplates here seen slightly at an angle, which give them somewhat of an oval appearance; so it's very difficult to distinguish whether or not this is in fact maybe some kind of a

biconcave fracture, or whether it just has to do with differences in positioning.

And differences in x-ray technology, you can see an under-penetrated or over-penetrated film can be -- make it quite a challenge to assess whether or not someone has a vertebral fracture, as well. In this case, we've got two examples, though, of true osteoporotic fractures, at least according to Dr. Genant's eye, but I believe him.

You could see here deformities of the endplates that are shown here. This is a close-up view where you can see there's quite a decrease in vertebral height in these particular endplates. So these are examples of osteoporotic vertebral fractures.

But there are various different ways you can be tricked, such as here in osteomalacia, you can see that these vertebral bodies here are showing this bow tie or fish vertebrae appearance, in this case not due to osteoporosis, but due to osteomalacia. So it's important to be able to distinguish the differences.

Also, you've got examples here of

Cushing's disease, and also steroid-induced osteoporosis. I think it was questioned whether steroids caused differential effects on bone. At least a trained radiologist can appreciate some differences in the spine due to the presence of steroids.

Because of difficulties, though, and the qualitative nature involved with measuring the spine -- or visual assessment of vertebral deformities, there have been creation of semi-quantitative grading scores.

The most well known is that developed by Dr. Genant and his colleagues at the University of California, and have created this pictorial definition of the various grades of vertebral fracture for semi-quantitative grading.

And this is, as you can see, mild, which is approximately a 20 to 25 percent reduction in vertebral height; moderate, 25 to 40 percent, roughly, and severe, about 40 percent or greater reduction in vertebral heights, and this is for both wedge, biconcave and crush fractures, which examples are

shown here.

When doing a semi-quantitative assessment you need, of course, to have adequate film quality, as always, experienced and trained operator, but a well-defined fracture criteria and standardization to an atlas.

So when doing studies you'll find that the majority of them have provided some type of training and some type of an atlas so that those reading the films can indeed be brought into synchronization as to what's termed a fracture.

And very often, you have centralized analysis of these things so that you can have a consistent reading across studies. So there is an example of a grade one fracture, which is shown here, and a grade two fracture and a grade three, finally, a severe fracture based upon -- these are representative examples of the criterion which have been evaluated and proposed and used in the majority of the studies today.

You also have the ability now to look at incident, severe and moderate fractures. You see here

vertebral bodies. Here, this is a grade zero, which has become a grade two on subsequent follow-up, and also, a grade one fracture here, which has subsequently worsened to become a grade three fracture.

Actually, I think these are in -- may have gotten out of track here. But anyway, the progression of these is something that's difficult to appreciate sometimes in the films.

Vertebral morphometry, the final technique which I'll talk about, the measurement of vertebral heights themselves, requires highly standardized radiographic techniques and very careful patient positioning to evaluate the heights of these vertebral bodies.

It's important to have screening of experts, by experts for the appropriate vertebral levels and exclude vertebral bodies that aren't appropriate for measurement. You need to digitize the films, which has to be done in an appropriate way that allows them to be evaluated on computer analysis work stations using well-defined normative data and an

algorithm for fracture which is in line with consensus readings.

This is normally done and can be done straight off of the films, but I think in more recent studies this has been done off of digitized radiographs, using an electronic cursor, if right off the films, or using software tools specifically designed for this purpose.

And you can see here, quantitative morphometry with six-point placement. It's currently -- all the studies that have been done have usually looked at six points, evaluating the different heights of the posterior and the anterior, and then the mid-vertebrae.

But it becomes quite challenging in some cases. You can see here in this particular vertebral body where you've got an endplate deformity which has occurred. In this case it becomes quite difficult to know where to place the mid-vertebral point, as in you have two margins.

You have the margin here and then an inter-margin here, and the standard technique requires

you to split the difference and come halfway in between. Also, obliquity can cause some problems in these point placements.

So it is important, I think, to not rely exclusively on measures of vertebral height, but in the case of question to have a trained radiologist provide visual assessment, as well.

The morphometric deformities have been defined in most of the studies as having a three standard deviation or greater decrease in the AP or mid-vertebral height. This is one that's been used in -- for several of the studies.

For an incident deformity, that is, during the study, a 20 percent or greater decrease in either the anterior, posterior or mid-vertebral height has commonly been labeled as a morphometric incident, morphometric fracture.

Of the clinical trials, many of them which have come before this particular Committee, they have used a combination of the quantitative morphometry and the semi-quantitative visual reads of the films. That is, using the ability to measure the vertebral heights

and having that confirmed by a visual assessment using a semi-quantitative read.

Various permutations have been used, but I think these two techniques together have been virtually well-accepted as a good endpoint for vertebral fracture assessment.

It is possible to use some of the bone density equipment, as well, to assess whether or not someone might have a vertebral compression. This is an example here of a scan that was done with the bone density system.

The nice feature here is you have the equipment in many of the sites that are measuring bone density and it can measure the entire spine in one sweep, and you see here as a fracture which was identified, and a possibly important clinical tool, but it's not clear that this is going to replace spine films at this point.

There's the ability to measure patients both in the supine lateral view by laying them on their side. Other instruments use a decubitus position, and use dual energy techniques to equalize

soft tissue variations.

Here again, appreciate that there was a fracture at this point. But I present this as a potential for future technology and give the quote from Jackie Rea's article just a few years ago when she evaluated the ability of -- in this case she called it vertebral x-ray absorptiometry to assess vertebral fractures, and concluded it showed good sensitivity in identifying moderate and severe deformities and an excellent negative predictive value in distinguishing subjects without those -- without subjects from those with vertebral deformities on a per subject basis.

The part which I didn't show here, though, is I think for mild fractures, grade one type fractures, it does not perform nearly as well, missing potentially a third up to a half of these mild deformities.

And in addition, it becomes difficult to see vertebral fracture from about T6 and above using this particular technology. So at least at this point I don't think -- believe it as a replacement for

vertebral film technology.

So let me conclude that at least from a BMD standpoint we know it's strongly related to bone strength and fracture risk. That is something we know and I think agree on. Virtually all clinical studies have used DXA measures of spine and hip for determining efficacy of compounds, but they've been supported by bone quality, turnover markers and eventually fracture studies.

Vertebral fracture determination requires high quality radiographs and highly trained readers to be done properly, and a combination of visual that is semi-quantitative, and morphometric reads represents the current best practice, which we have. And I thank you for your attention.

CHAIRMAN BRAUNSTEIN: Thank you, Dr. Faulkner.

Our last speaker in this session is Dr. Hochberg, who's going to speak about relationship of drug associated change and bone mineral density to fracture risk.

DR. HOCHBERG: Well, while we I guess get

all set up I want to thank Dr. Braunstein and the Committee for the opportunity to be here today and to speak to you about a topic which has become one of my favorite areas of interest.

Now, I have to admit that I am not a card carrying endocrinologist or metabolism specialist. I am actually trained as a rheumatologist. So I come here from a different sub-specialty of internal medicine.

And specifically, my title is "The Relationship of Drug Associated Change in Bone Mineral Density to Fracture Risk." Now, a number of individuals this morning have commented on this issue of bone quality.

I'm not going to address bone quality, in particular, as it may be measured by bone turnover. But just to mention that the new definition of osteoporosis, which was proposed by a consensus conference from the National Institutes of Health and which was held about two years ago, suggested that measurement of bone mass with bone mineral density, as well as a measure of bone quality, possibly with bone

turnover, were integral components of the assessment of osteoporosis.

Now, I think the question that you want me to address and that I will try and address is, are changes in bone mineral density which occur with antiresorptive therapy, and I will also address it in terms of anabolic therapy, important in explaining the antifracture efficacy of approved agents for the treatment of osteoporosis.

And I'll address this in the context of both vertebral fractures, as well as nonvertebral fractures. Now, several people have commented on the laws of physics as applied to bone, and I just wanted to summarize the earlier comments from this morning in the slide that I made during the break.

So this is an "if and then" relationship. If the material properties of the structure remain normal, then an increase in mass of the structure will lead to an increase in strength of the structure. And this has been reviewed by Drs. Bone, Rodan and Rizzoli this morning.

It's been shown to be applicable to

antiresorptive agents of different classes demonstrated in preclinical studies. And the different classes are the nitrogen containing bisphosphonates and the selective estrogen receptor modulator, which may work by different mechanisms at the molecular level, although they all decrease bone resorption.

And it's also applicable to teriparatide, recombinant human PTH, which is not as yet approved. And I'll come back to this later on with some new analyses, but the concept would be that for antiresorptive agents, those that are currently approved for the treatment of osteoporosis in the United States, I noted that estrogen is not actually approved for treatment, although it is approved for prevention.

I'm not sure what the difference is between management and treatment, to be perfectly honest with you. I didn't look it up in Black's Law Dictionary. And then the anabolic agents, as well, neither of which are currently approved.

So let me start with vertebral fractures,

and you got an excellent review just now by Dr. Faulkner of the ways in which vertebral fractures can be defined and the ways in which they have been defined in some of these clinical studies.

Now, the analysis that I'll show you is really as a result of three meta analyses. So I'm not going to review the data from individual trials. I will say that earlier this morning Dr. Colman sort of reviewed the evolution of the relationship between BMD changes and vertebral fracture risk reduction from individual trials, and sort of went over the data for Etidronate and then the more recent bisphosphonates, as well as fluoride.

And then Dr. Abadie in his presentation showed one graph with the point estimates in the 95 percent confidence intervals for vertebral fracture reduction, plotted against the changes in bone mineral density compared to placebo for those agents, and I think suggested that there was not a sufficient or strong relationship between these.

Now, in the meta analysis that was done by Richard Wasnich and Paul Miller, which was briefly

referred to by Dr. Faulkner, they identified 13 placebo controlled trials of antiresorptive agents that reported both vertebral fracture incidents, as well as change in bone mineral density.

And they used the regression model to relate the change in bone mineral density to fracture risk reduction and they reported their best fit model. They did report sensitivity analyses where they eliminated individual trials, as well as all trials for individual agents and stated that this did not alter the results of the study.

But note that this analysis was performed and published prior to the publication of the data from the Risedronate vertebral fracture studies. And you've seen this graph just before, which is taken from their paper and shows the relationship between change in spine bone mineral density measured over the course of the study on the x-axis.

And this is the difference between the mean difference -- let me say the difference between the mean of the treatment group versus the mean of the placebo group, plotted against the relative risk

reduction for vertebral fractures.

Now, we have to remember that in this pooling we're pooling heterogeneous populations, because these are not all women with osteoporosis in these studies, and we're also pooling across different definitions of the outcome.

Dr. Faulkner showed you that there are different ways of defining vertebral fractures, and not all the studies defined a new vertebral fracture as a greater than 20 percent decrease and greater than four millimeter reduction in vertebral height.

Nonetheless, they did report a statistically significant relationship between change in spine bone mineral density and reduction in the risk of vertebral fracture. But what was also importantly reported in their study was that even that the model predicted for a drug which did not increase bone mineral density compared to placebo, that there was still a statistically significant reduction in the risk of new vertebral fractures.

It's also worth noting that they included studies of agents which are not approved for the

treatment of osteoporosis in the United States, such as tiludronate, and they also included some of the topical estrogen studies in terms of estrogen patch.

Now, Dr. Cummings, who's going to be speaking this afternoon in conjunction with Dr. Black and others, performed a separate meta analysis which was published earlier this year in the American Journal of Medicine.

They limited their analysis to randomized placebo controlled trails that lasted two or more years in duration, and had an ample number of fractures, five or more fractures per treatment group. They used a slightly different regression method, but again, examined the change in spine bone mineral density in relationship to the reduction in vertebral fracture risk.

And they reported a linear relationship, where the expected or estimated relative risk was equal to an aught .75 minus .03 times the increase in lumbar spine bone mineral density. So assuming a linear model, there was a significant reduction in relative risk of new vertebral fractures, independent

of any change in spine bone mineral density, but nonetheless, a small additive effect with changes in spine bone mineral density versus placebo.

Okay. And this table summarizes the two different models for a drug which would have no change in bone mineral density and a drug which would have an eight percent increase in bone mineral density.

Now, note that both of these looked at the change in bone mineral density occurring over the entire course of the study, not just within the first year of treatment. Okay.

Dr. Cummings and colleagues also recognized that the observed changes in lumbar spine bone mineral density explained only a small proportion of the actual reduction in the risk of vertebral fractures, and I think furthered this by coming up with another model where the observed relative risk in the study couldn't then be estimated from the expected relative risk, given the change in bone mineral density, and in fact, that the expected relative risk from the first model underestimated the true relative risk which was observed in the study.

Now, in preparation for today's meeting it was suggested to me that we go back and look at these studies and try and limit -- repeat an analysis, which was limited to agents which are currently approved for use for the treatment of osteoporosis in the United States.

So we went back and repeated the Wasnich and Miller analysis, excluded trials of nonapproved medications, specifically Tiludronate, and added the Risedronate birth studies, and this produced the total of 13 trials.

Now, the results were largely unchanged. Change in lumbar spine bone mineral density remained significantly associated with reduction in the risk of new vertebral fractures. And from the Poisson regression for every one percent increase in lumbar spine bone mineral density the relative risk of new vertebral fractures was .9, significantly different from one.

And there remained an independent effective treatment, even without any increase in lumbar spine bone mineral density, and here the

relative risk is .81, or about a 20 percent reduction in risk.

So there does appear to be a relationship between increase in lumbar spine bone mineral density and reduction in the risk of new vertebral fractures, although there is a residual effect which appears to be independent of the change in bone mineral density, and this is probably due to reductions in bone turnover, specifically bone resorption, which affect this indistinct and difficult to define concept of bone quality.

Now, Dr. Silverstein, in her question, highlighted this sort of conundrum which has been labeled the Raloxifene paradox by Dr. Riggs in an editorial earlier this year. And this is that some agents decrease vertebral fracture risk, but have not been shown to reduce the risk of nonvertebral fractures.

And these agents tend to have smaller increments in bone mineral density and bone turnover when compared to the amino bisphosphonates. So this actually prompted us to examine the relationship

between change in bone mineral density and reduction in the risk of nonvertebral fractures.

And we published earlier this year in the Journal of Clinical Endocrinology and Metabolism, along with Drs. Wasnich, Miller, Greenspan and Ross, an analysis which pooled randomized, double-blind, placebo controlled trials, which reported changes in bone mineral density and/or changes in biochemical markers of bone turnover, as well as incidence of nonvertebral fractures.

Now, we limited these trials to trials which were conducted in women with postmenopausal osteoporosis, defined either by the presence of a prevalent vertebral fracture with bone mineral density, or a T-score less than or equal to minus 2.0 measured at the lumbar spine or femoral neck, to try and get some homogeneity of the patient population.

There are, however, some differences in the outcome because some trials report all nonvertebral fractures. Some trials reported only a few nonvertebral fractures. So we're still -- we still have the problem of some heterogeneity with

regard to the outcome.

And this analysis focused on the change in bone mineral density which was seen within the first year of therapy, and then the overall reduction in the risk of nonspine fractures during the entire study.

So we identified 18 trials which had 30 active treatment groups, which had almost 70,000 women years of follow-up, 92 percent of which were present in the eight larger studies. And there were over 2,400 women who had an incident nonvertebral fracture.

Ninety percent of these fractures occurred in the eight largest studies. And this plot shows the relationship between the change in spine bone mineral density seen at one year in the treatment group as compared to the placebo group, and the relative risk for nonvertebral fractures.

This is a slightly curvilinear relationship where the intercept term, which is estimated from the model where there's no change in spine bone mineral density at one year actually goes through a relative risk of one or no risk reduction.

And the different trials are depicted by

different size circles, given the number of person years. But you can see that there's a lot of variability in the estimates from the individual trials.

A similar relationship, although slightly steeper, was noted when one plotted hip bone mineral density, either femoral neck or total hip, depending upon which was reported in the study, as compared to the relative risk of nonspine fractures.

And again, this so-called intercept term where there's no change in hip bone mineral density versus placebo was not significantly different from one. Now, I'm not going to show you the data for change in biochemical markers of bone turnover, because that's not the point of the discussion.

But this summarizes the results such that for every one percent increase in lumbar spine bone mineral density versus placebo there was an estimated eight percent reduction in the risk of nonvertebral fractures, and for every one percent increase in hip bone mineral density, this is within the first year of therapy, there was an estimated 27 percent reduction

in the risk of nonvertebral fractures.

Okay. The results were generally robust to removal of both individual trials as well as all trials of individual agents. Now, we also repeated this analysis, excluding trials of nonapproved medications, and this left us with a total of 15 trials.

Here again, the results were largely unchanged. Change in bone mineral density within one year remained significantly associated with reduction in the risk of nonvertebral fractures. The relationship was pretty much unchanged at the lumbar spine.

The amount of reduction was somewhat decreased with a change in hip bone mineral density. And again, there was no significant, apparent independent effective treatment without a change in bone mineral density.

So to summarize these results for antiresorptive agents for nonvertebral fractures, greatest and greater increases in bone mineral density within one year of therapy are associated with a

greater reduction in the risk of nonvertebral fractures.

So my conclusions from data on antiresorptive agents are that increases in bone mineral density are important indicators of antifracture efficacy of antiresorptive drugs, both for vertebral, as well as nonvertebral fractures, and increases in bone mineral density appear to be necessary to decrease the risk of nonvertebral fractures.

Now, another issue that was raised was, is there a threshold effect for vertebral fractures, and this does not appear to be the case in terms of changes bone mineral density or reductions in biochemical markers.

And we had stated in our paper that the results could not be extrapolated to anabolic agents. But for today's presentation we actually repeated these analyses again, and included the data from the pivotal Phase III trial of teriparatide, published in the New England Journal of Medicine, and found that the results were largely unchanged in the analyses,

both for vertebral fracture, as well as nonvertebral fracture.

Change in bone mineral density remained significantly associated with reduction in the risk of vertebral fracture, and change in bone mineral density at one year remained significantly associated with the reduction in the risk of nonvertebral fracture.

So when one incorporates the results from teriparatide, increases in bone mineral density remain an important indicator of antifracture efficacy for both antiresorptive and anabolic drugs. And I think the caveat here is based on the preclinical data, showing that one is making normal bone and that this is true for both vertebral as well as nonvertebral fractures.

So I want to thank you very much for your time and attention.

CHAIRMAN BRAUNSTEIN: Thank you, Dr. Hochberg.

We'll open both Dr. Faulkner's and Dr. Hochberg's presentations up for questions. I think Dr. Marcus will be first on the list.

DR. MARCUS: Yes. I have a question specifically related to Dr. Hochberg's presentation addressing the issue of heterogeneity among all the various trials that were put into your regressions.

It seems to me that one of the major sources of heterogeneity in those trials, various trials, was the initial bone mineral density of the patients on enrollment into the trial, and therefore, using as your outcome measure the percent change in BMD seems to me to be confounded by the fact that somebody who starts with a lower BMD might have, for the same increment in bone, a relatively higher percentage change, and I wonder if you've been able to look at those data, not looking at percent BMD changes but absolute BMD changes.

DR. HOCHBERG: We haven't looked at the data with regard to absolute BMD changes as opposed to percent. My -- I guess this a potential limitation in that you're right in that individuals who start out with a lower BMD will likely -- will have a greater percentage increase in bone mineral density with treatment.

One thing that we did was to restrict, at least, the BMD definition in the analysis of nonvertebral fractures to include studies just in women with postmenopausal osteoporosis. While there is a variability in BMD, it's not as great as in the studies which have looked at reductions in vertebral fractures. I think Dr. Cummings has a comment.

DR. CUMMINGS: We did it both ways and it didn't make a difference.

DR. MARCUS: Thanks a lot.

DR. HOCHBERG: Thank you, Steve.

DR. GELATO: This is for Dr. Hochberg. I guess the question I have is the drugs that don't show a change in BMD but do show a change in fracture risk, although it's only 20, 25 percent, if you use BMD as your primary outcome what would you do with those drugs? They would just be -- you know -- because clearly, as a clinician what I'm concerned about is, I mean, I see a number of patients who can't tolerate the bisphosphonates.

So you know, what do I do with them, you know? And so it becomes, if we're going to just look

at BMD --

DR. HOCHBERG: Well, I share your concerns as a clinician in terms of treating patients with osteoporosis who don't tolerate oral bisphosphonates. I think the issues are several and I'm certainly not proposing to the Committee that they decide to recommend changes in guidance and ignore let's say non-BMD effects of therapies, because clearly, all of these analyses have demonstrated that there is a relationship with reduction in vertebral fractures for drugs which do not have a robust effect on changes in bone mineral density as measured in the clinical trials.

What I do in clinical practice is obviously probably different from what other people do in clinical practice, but I tell my patients about the caveats of the results of the trials and what they can expect from -- what I feel they can expect from the individual drugs, and I base my choice of therapy on that.

CHAIRMAN BRAUNSTEIN: Let me follow up with a question to Dr. -- actually -- Rodan and Dr.

Turner about this. Are the antiresorptive agents also potentially decreasing the breakdown of the cross-struts in the vertebrae, or doing some other things that will maintain tensile strength, but you may not see a change in density because of the imprecision of the machines, or what?

DR. RODAN: Excellent question. Actually, they preserve the bone that is there, and on a very hypothetical basis it's possible that the bone that is added as part of the normal process of remodeling is added at places where it has the best mechanical function, because mechanical loads influence how bone is being built and remodeled.

So by giving the bone an opportunity to accumulate, the bone that is added may accumulate where it has the best mechanical function, and this is well established for 100 years now. So this may explain some of the discrepancy that you get increased fractures, resistance of fracture prevention, without actually seeing the cumulative bone. It's maybe where the bone has redistributed that is more favorable now.

CHAIRMAN BRAUNSTEIN: Dr. Turner, did you

want to comment?

DR. TURNER: Yes. I'd like to respond to your question and also make a comment about BMD. First, it's important to realize that bone resorption is a focal process. And if you could imagine a beam that supports a building, if you had somebody with a jackhammer trying to cut a little piece out of the middle it would greatly weaken the beam, and much more than what would be measured if you simply measured the overall amount of material that was in the beam.

So if you can produce a drug that inhibits bone resorption you can take away all of these little focal stress raisers or jackhammers from the trabecular bone. And this may well explain -- this hasn't -- this is somewhat hypothetical, but it makes sense and it may explain why some antiresorptive agents, particularly the example of the Raloxifene, was brought up.

That worked better in the spine than they do in the hip, because the hip fractures are more of a cortical bone, biomechanical problem, and they don't require -- the trabecular strut aren't as important.

And this, I think, is a very plausible hypothesis and it does link turnover with fracture reduction, and at a structural basis because, of course, turnover means nothing if it doesn't have a structural outcome.

And that's probably what's happening. Now, I do want to make one other comment and that has to do with, what is bone mineral density. This is a measurement that you get from a densitometer, but in the case of an antiresorptive agent you're actually decreasing bone turnover, which allows an extended period of secondary mineralization, and the amount of mineral in each strut of bone is actually higher.

So a bone mineral density that you measure with an antiresorptive agent will actually have more mineral for less volume. So it may mean something different than, say, an anabolic agent such as the parathyroid hormone fragment that's been reviewed by this body.

This increases bone turnover. So now, we actually have less time for mineralization. You have less mineral for each component and probably more bone volume. So you take an exact same bone marrow density

with the antiresorptive, and with a -- this type of anabolic agent you'll have a different bone volume, different amounts of actual bone tissue and different degrees of mineralization within the bone tissue.

So just lumping them together may -- it's nice to -- for certain purposes, but it doesn't explain everything. And we have to realize that this is somewhat of a -- is an imprecise measure of what's going on in the structure.

CHAIRMAN BRAUNSTEIN: Dr. Marcus.

DR. MARCUS: Thank you. I'd like to reemphasize what Charles Turner just said, because I agree with him fully. And in fact, there's been some ambiguity in some of the presentations that have been made.

For example, Dr. Colman first stated that BMD has now "risen to its proper place." I'd respectfully like to disagree with that. I think, actually, there's been more questions raised about BMD within the last few years than maybe we had before.

When you look at what happens when you raise BMD there are a multiplicity of ways in which

BMD can be raised. With antiresorptive drugs, certainly during the first period of several months when these little jackhammers, as Charles describes them, the resorption bays are being filled in, that does represent a true increase in the amount of bone tissue.

But subsequent to that, the secondary mineralization does mean that you gather more and more mineral over time just because the activation of new remodeling units to come and clean that up is much reduced.

Another way to increase BMD could be to increase the number of trabeculae without -- prior to anabolic therapy. That's something that has never been known to occur because the number of trabeculae are set in utero, actually before birth.

You could increase trabecular thickness with normally mineralized bone, and that would increase BMD, but that has not ever been observed to occur with antiresorptive therapy. Now, we have the advent of anabolic therapy.

And whereas, you might think it would be

a slam dunk that under all circumstances anabolic therapy with definition pari passu increase BMD, we have now learned that that actually is not always the case.

For example, there was presented this week at the Bone and Mineral Society a very interesting study of growth hormone, which showed that early on in growth hormone therapy there's actually an apparent reduction in BMD.

Now, we always used to think that was due to increasing the remodeling space by opening up new resorption bays, but in fact, this was a study from Denmark which was a very careful histological study, histomorphometric study, that showed that that actually didn't happen.

What was happening was that growth hormone was laying down new bone, but early on in that bone's life it is relatively undermineralized. Remember, BMD is an artifice. It is a compound number which represents the bone mineral content divided by the area.

So by expanding the area by increasing new

bone, but that bone not being as well mineralized as mature bone, there was actually the appearance of a reduction in BMD. And under certain circumstances it appears that a similar sort of thing happens early on in the treatment with Teriparatide.

Therefore, I think that depending on BMD is really fraught with a great deal of danger. The second point I want to make where there was ambiguity had to do with this term, "bone quality," which strikes me back to what I understood from my house officer days, is the meaning of the word idiopathic.

It's so vague as to be almost useless. And in fact, we had an awkward situation on this very panel when I was a member dealing with the presentation of the delayed release fluoride. Some of you were also on this panel at the same time, because measures of bone quality were used and introduced which really weren't highly validated and generally accepted as standards of measurement for the community.

Therefore, I think that what we have to do, and as a recommendation to this panel and to the

Agency, is to come up with specific validated parameters of bone quality, rather than just talking in sort of vague terms, such things on biopsy as cortical thickness, connectivity index, an index reflecting the percentage of plates versus rods.

Those are all validated, statistically robust measures that should be -- you should ask for listing up front for biopsy data. And furthermore, now that we have MRI and synchrotron, other noninvasive sorts of approaches to looking at structural parameters in studies, we should also encourage you to have specified a certain number of those parameters that are highly validated also to be called on, rather than just using the general term, we're going to look at bone quality. Thank you for indulging my mind.

CHAIRMAN BRAUNSTEIN: Thank you. Well, we'll be discussing more of these things this afternoon. Dr. Cummings is next, then Dr. Khosla and Dr. Watts.

DR. CUMMINGS: I have to agree with Bob that the changes in bone density and subsequent

changes in fracture risk have actually gotten to be much more interesting as one of the meta analyzers that Mark referred to.

We have looked closely at this data and one of the things that sort of magnifies this paradox is the fact that there have now been reported 60 to 65 percent reductions in risk in the first year, when the bone density changes are even less.

And the analyses that Mark and our group reported were for the aggregate of three years. If you try to do this for one year you would find that the discrepancy is much, much greater, but still, a gross underestimate.

Bone density increase is still -- it doesn't correlate very well, but it's just grossly underestimating the risk. And it's not clear how well it's predicting risk of fractures beyond that, you know, if you just look at second, third and fourth year because there, the reductions in risk of vertebral fractures are less.

Bone density is continuing to accrue. And so I think if we look at it more closely it is complex

and it's not straightforward that there is not the clear-cut statistical relationship that we reported between change in bone density and change in fracture risk when you take time into account.

And then things really seem to change -- this relationship seems to change a lot over time, and that was it.

CHAIRMAN BRAUNSTEIN: Thank you. And Dr. Khosla.

DR. KHOSLA: Well, I guess I agree with all of the comments that have been noted about the caveats with bone density, that you know, there are individual clinical situations where a patient, maybe on therapy, may not have a change in bone density but has still benefitted from the drug.

But I guess the -- you know -- just stepping back, it's pretty clear that if you use BMD as some sort of a surrogate, that it's actually a very conservative bias, because you're actually vastly underestimating the potential benefit from the antiresorptive drugs.

So it's not like you're going to go wrong

and overestimate the potential benefit. It's actually going to be a fairly significant underestimate of the benefit that you're going to -- you may get from that particular antiresorptive drug.

And actually, if I could just make -- because I wanted to ask Steve another question to follow up is that, have you or Mark actually combined, you know, looking at BMD changes and bone marker changes into a more global model to see if in a combination they may actually come closer to predicting the reduction in fracture risk with these drugs?

DR. HOCHBERG: Well, we tried to do that in the models to estimate reduction in nonvertebral fractures, and we couldn't get the regression models actually to work. And I think that was -- that's because of the of cross-studies there is a very, very high correlation between the reduction in bone turnover seen with the antiresorptive agent in that study compared to placebo and the increase in bone mineral density, which is seen in that study compared to placebo.

We actually found our square values of between .8 and .85, which are higher than the -- you know -- the sort of no expected correlations that Dr. Faulkner mentions of, you know, .6 to .7, for the reduction in bone turnover and the increase in bone mineral density.

So because of the very high correlation between the two, we couldn't force both into a single model.

CHAIRMAN BRAUNSTEIN: Dr. Watts.

DR. WATTS: I had notes on all of those points that I'd like to elaborate on just slightly. I think that it is more complex than bone density alone. The addition of anabolic agents makes it even murkier.

With teriparatide the increases in bone density were 50 percent or 100 percent larger than what was seen with antiresorptive drugs. Yet, the reduction in vertebral fractures was in the same order of magnitude.

We know that antiresorptive drugs have roughly a correlation between suppression of bone

turnover and increase in BMD. The suppression of bone turnover occurs early. The rise in BMD continues to accumulate over years.

And as Dr. Cummings has pointed out, the reduction in vertebral fracture, at least numerically, is greatest early rather than late. The turnover and density changes are so linked that it's probably impossible to separate those out.

Now, Dr. Faulkner showed us the measure of density with DXA, which is the standard for these trials, measures both cortical and trabecular bone, and therefore, might underestimate changes in the critical component of the skeleton, trabecular bone being more metabolically active and preservation or destruction there being more important for maintenance of bone strength.

So it may be that there are better ways that we could look at bone density, independent of turnover. But I don't think for a minute that bone density, at least for me, serves as an adequate surrogate, even for the antiresorptive drugs, much less for drugs that might have a way of laying down

new bone or changing the geometry of bone that would also have important structural implications.

CHAIRMAN BRAUNSTEIN: All right. Thank you. One last question, Dr. Grady.

DR. GRADY: Yes. I think these studies of the association of change in bone density and change in fracture risk are important for -- really, probably key for our consideration. So I hate to be dense, but I just want to ask -- I just want to understand how this was done.

So we have sample sizes of somewhere on the order of 13 to 18 or 19, right, and you looked at a predictor of univariate regressions, predictor variable of continuous outcome. And just in eyeballing those, they look pretty heterogeneous.

I wonder, number one, did you do -- you know -- did you do a formal test for heterogeneity, and -- they're homogeneous?

DR. CUMMINGS: Sufficiently that they could be pooled, the 13 of them.

DR. GRADY: Okay. So the sample sizes are rather small?

DR. CUMMINGS: They're -- yes, correct.

DR. GRADY: Okay. And secondly, I wonder, so those were --

DR. HOCHBERG: Can I -- you mean, the sample size in terms of the number of studies that are included?

DR. GRADY: Yes. That's the sample size when you're doing your regression analysis.

DR. HOCHBERG: Okay.

DR. GRADY: And secondly, did you look at any other variables in those models like, for example, age, you know, age since menopause, baseline BMD, lots of interesting sorts of additional --

DR. CUMMINGS: No. That information is often missing from the reports of trials. So it was just a heroic effort to be able to do -- just get the bone density that was sometimes variously reported. And the confidence, one thing you didn't mention is that there's a lot of variability around that.

The confidence limits around the relationships, mathematical relationships that Mark showed exclude no relationship, but you know, they're

pretty wide because of that heterogeneity. That's why I don't think you could use the equations to predict the reduction risk of vertebral fractures from these meta analyses without doing a trial.

CHAIRMAN BRAUNSTEIN: Dr. Marcus had one addition on that.

DR. MARCUS: I just had one tiny point. This shows you that you can pool some of the people some of the time.

(Laughter)

DR. MARCUS: That was not the point. The point was --

CHAIRMAN BRAUNSTEIN: Can I --

DR. MARCUS: -- addressing the issue -- just one tiny BMD issue. All of this presumes that the agent you are using is not itself changing the mineral structure of the bone. And I must point out that fluoride, which creates a larger molecule, introduces not just BMD as an artifice, but an artifact, as well as I saw one agent that has not yet been -- shown its head in this country that has apparently -- is on the books in Europe, and that is

strontium, because that will do the same thing.

You will see an artificially high BMD, which just represents a fact of the incorporation of a heavy metal into the bone, just like if it were lead.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Hochberg.

DR. HOCHBERG: Can I make a brief comment? Okay. First thing, in response to Dr. Grady, we did not adjust these models, as Steve said in his analyses, for age or baseline bone mineral density. We -- in our paper we actually reported the characteristics of the populations in the trials, but in the absence of having patient-based data from all the companies or the authors which sponsored the trials, we didn't do that, and that's a limitation, at least, of our analysis.

But recognizing that, you know, some agents in fact do artifactually change bone mineral density, none of these analyses include the more recent data for strontium ranelate, which was presented at the World Congress, I guess in May, or

the older data from fluoride.

CHAIRMAN BRAUNSTEIN: Okay. Great. We'll move onto the public -- open public hearing now, and we invite the individuals who are going to speak to please come up to the microphone in the center there. There's two written submissions that are available outside on the desk from GlaxoSmithKline and from Roche Pharmaceuticals.

Our first public speak is going to be Dr. Ginger Constantine, Vice-President Women's Health Research, Wyeth, and we ask all the speakers to please not only identify themselves, but identify if they have any conflicts of interest or potential conflicts of interest.

And if the speakers could speak from the middle, we'll show the slides up here. Thank you.

DR. CONSTANTINE: You're pointing in different directions, which is part of the conversation here, I guess. Hi. I'm Ginger Constantine.

I am a representative of Wyeth Pharmaceuticals and I would really like to thank the

Advisory Committee for allowing us to discuss some of the challenges from a pharmaceutical perspective company in developing these products, and also offer some suggestions for future development.

Now, I don't know how to flip the slide from back here. Thank you. On this slide is a list of eight different things which are predominantly the stumbling blocks to development for pharmaceutical companies, and these have predominantly been discussed this morning. So I won't bore you with all of them.

Obviously, the IRB and Ethics Committee -- obtaining approvals from IRBs and Ethics Committees have been a predominant issue. Country variability is -- has also been quite difficult in light of the global nature of trying to perform studies.

Trial size and cost are huge stumbling blocks. The complexity of the protocol for testing procedures, oftentimes depending on the compound that's being developed, may span several divisions within the FDA and concurrent sometimes on individual factors may be difficult.

Enrollment and retention of subjects,

especially with longer-term trials, has become quite difficult and it's obviously very difficult for the physician, as well as the patient. On the next slide you'll see the Wyeth position with regarding to these issues.

We do feel that placebo controlled trials are most efficient and reliable. We do feel that active reference drugs provide important therapeutic context and that protocol requirements and guidances need to be the same worldwide, if possible.

Patient testing requirements need to be practical and trials need to be short enough to allow for high patient retention. And this is a huge issue, especially when we go on to do analyses. Next slide, please.

So in light of this we have some suggestions for existing compounds -- of compounds which would include SERMs, estrogen and bisphosphonates. With a primary endpoint we would suggest statistically and clinically significant change in BMD for vertebral and nonvertebral fractures, and perhaps enroll subjects with a BMD of

minus 2 to allow for our placebo controlled trial.

A secondary endpoint would be reduction in the incidence of vertebral or nonvertebral fracture, with bone histomorphometry in a subset of patients demonstrating good bone quality. I'd like to just add the caveat that the first point certainly would be dependent on an adequate preclinical package showing good preclinical models for bone development and bone strength.

We would like to suggest a two-year trial for the durability of effect and to look at adverse events. And obviously, we would have to design an adequate safety database so that all of the safety issues that would come up could be adequately addressed.

I would like to thank the Advisory Committee for allowing us to present this position, as well as thank specifically the M&E division for their efforts in this and realize how difficult it is to address these challenges.

CHAIRMAN BRAUNSTEIN: Thank you. Dr. Orloff.

DR. ORLOFF: We need a -- before you go, we need a clarification on your primary endpoint. We don't understand -- you mean, to support an indication for the reduction in risk for vertebral and nonvertebral fractures, BMD alone?

DR. CONSTANTINE: Yes, with these other things.

DR. ORLOFF: With the secondary.

DR. CONSTANTINE: With all of these things.

DR. ORLOFF: Okay.

CHAIRMAN BRAUNSTEIN: Thank you. Our next speaker is Dr. Dere, Vice-President, Endocrinology, Lilly.

DR. DERE: Chairman Braunstein, Dr. Orloff and members of the Advisory Committee, Lilly commends the efforts of the Agency to provide a forum for discussion of this critical clinical topic. During the past years the FDA has approved a number of new agents for the prevention and treatment of osteoporosis.

The drugs were approved with heavy

emphasis on the existing 1994 draft FDA Guidelines for the development of osteoporosis therapies. These Guidelines were developed when there were few options available to the medical community to treat this potential debilitating disease.

It is now time to develop new guidelines which must take into account -- consideration advances in medicine and science and the current climate of drug development. These guidelines must take into account workable strategies for testing and registering osteoporosis therapies for women and men with osteoporosis of various etiologies.

We offer the following points for consideration as you continue your deliberations today. Number one, there is a need to define a common standard for demonstration of efficacy that can be applied to drugs of different classes.

Lilly believes that while BMD is a useful diagnostic to identify those at risk for osteoporosis, we maintain that the change in BMD and in biochemical markers of turnover are not suitable to replace fracture as an endpoint for evaluation of efficacy of

a new chemical entity.

The relationship between the change in BMD to that of a reduction in fracture risk is not the same for different classes of therapy and accounts for only a small part of the observed fracture risk reduction.

Lilly agrees with the current recommendation that a reduction in vertebral fracture risk is necessary to prove efficacy for osteoporosis compounds in order to obtain a treatment indication.

Using surrogates for vertebral fracture endpoints would make it difficult to establish the true antifracture efficacy of new drugs and would result in less informative and less competitive labeling for sponsors with new drug development programs.

However, we agree that treatment induced change in BMD remains an acceptable endpoint for new formulations and indications such as glucocorticoid induced osteoporosis and male osteoporosis for compounds whose fracture efficacy has previously been established.

Number two, while we recognize that a number of osteoporosis therapies are now available, Lilly maintains that a randomized controlled trial using calcium and Vitamin D for all patients should remain the standard for establishing efficacy and safety.

In the current environment there is a dilemma regarding the acceptability of these so-called placebo controlled studies for evaluation of compounds for treatment of a disease for which alternate treatments exist.

However, a relatively small placebo controlled study that clearly demonstrates superiority of a new drug over placebo may be more broadly useful and more ethical with respect to the number of patients exposed, than a larger study against an active comparator.

The European CPMP Guidance on osteoporosis drug development that was issued in 2001 states that: "Although active control trials are preferred, placebo controlled trials are still acceptable. Placebo controlled trials provide greater flexibility in study

designs, for example, the use of escape clauses and stopping rules to maximize patient safety and use of add-on therapies, and should be considered for drugs in development."

Number three, there are considerable challenges in conducting active comparator trials rather than placebo controlled studies. For example, these include: a lack of access to data other than that present in the public domain for the active comparator may hamper elucidation of statistical and sample size estimations for hypothesis testing.

Also, noninferiority trials would require exposing a larger number of patients in potentially longer clinical studies. Next, trials designed to establish either noninferiority or superiority of a drug compared to an established therapy might be compromised due to the difficulty in replicating the effectiveness of the comparator active therapy, depending on the population studied and the conditions of the trial design.

Without a placebo controlled group one could not know whether the active compound had worked

-- comparator had worked or not. Next, if an active comparator were required, how would a sponsor determine which therapy is best for comparison, given that different classes of osteoporosis therapies work by different mechanisms, have different pharmacokinetic profiles and even different target populations.

And finally, there may be a lack of understanding of the safety profile because the true adverse event rate for a new drug is best derived from placebo controlled studies. Number four, as I stated, Lilly maintains that the most appropriate study endpoint is the reduction in the incidence of osteoporotic vertebral fractures.

While demonstration of reduction of fractures at the hip is not required by current guidelines, guidance is needed for the purpose of label language on ways to be able to demonstrate efficacy at the hip.

It is not practical to limit studies specifically to hip fractures. For example, to demonstrate a 40 percent reduction in the incidence of

hip fracture assuming a three percent event rate, the number of patients required for a placebo controlled trial is 5,000.

And for an active controlled noninferiority study with a 20 percent margin of noninferiority, the number of patients required is 33,000. And for an active controlled superiority study the number of patients required would be 40,000.

Therefore, we propose that a reduction in combined nonvertebral osteoporotic fractures, an increase in hip BMD and improvements in bone structural measurements such as those describe by Thomas Beck and colleagues from DXA scans should be considered adequate to demonstrate substantial evidence for a hip fracture reduction claim.

Number five, guidelines should provide for the acceptability of shorter duration clinical trials, such as 12 months with a vertebral fracture endpoint for an antiresorptive, and possibly shorter for anabolic agents, provided preclinical studies clearly show no detrimental effect on bone quality and sufficient safety data will be accrued during follow-

ups such as in post-marketing surveillance programs.

While further guidance is needed on the number of years of follow-up required to assess clinical safety and durability of effect, we believe that a total exposure of three to four years should be considered appropriate for safety evaluation.

Number six, current guidelines do not consider histomorphometric parameters of bone biopsy as efficacy endpoints. Given the lack of treatment effect, i.e., fracture reduction predicted by changes in BMD alone, the Agency should consider accepting the use of advanced imaging and computer-based analytical techniques for demonstrating changes in bone micro architecture and quality.

For example, -3D analysis of bone structure using micro CT might provide efficacy measures of bone quality and structure, and could be used to define and distinguish true anatomical differences of different classes of osteoporosis therapies.

For the purpose of human studies, bone quality may be assessed by appropriate combinations of

bone mineral densitometry, specialized radiographic techniques in vivo and in vitro, such as micro CT, spiral CT and MRI, and histologic assessments of trabecular and cortical bone mass, cortical thickness, trabecular connectivity and bone remodeling.

Sponsors should be encouraged to consider new assessments for bone strength that could include bone quality and architecture during clinical development.

Number seven, with the availability of a variety of therapeutic options, drugs are likely to be used for the treatment of osteoporosis in a number of ways, alone or in combinations. Guidance is needed to support claims for sequential or combined use of osteoporosis agents with the same or different mechanisms of action.

And finally, there will be a critical need for harmonization of guidelines between the various regulatory agencies to provide for similar registration requirements across countries. Divergent guidelines will make registration of new osteoporosis therapies needlessly expensive and difficult.