

1 That was kind of the hypothesis at that point, and
2 that's what we did for the SCRIPPS trial, and that
3 kind of basically picked up into the GAMMA trial.

4 When variation sources are used to
5 basically -- that go around a bend, you do have a
6 little bit more dose on the inner side of the bend, a
7 little bit more, and I think there are actually one or
8 two studies that are published. But I don't think
9 it's going to be any significantly more to any
10 particular point if you look at the two millimeter
11 radius or two and a half or three millimeter radius.

12 Once again, typically, in the coronary
13 arteries you don't have it bent to that gentle bends.

14 DR. HOLMES: And the vessel straightens
15 out with the device in place. So going around a
16 significant curve, it sort of gives it more gentle lay
17 of the land with that.

18 DR. PARISI: So you have no data or do
19 have data on whether the instrument and procedure is
20 more efficacious in one or another location. It's the
21 same throughout, as best you know?

22 DR. HOLMES: Correct.

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1 DR. PARISI: I'm also concerned still
2 about this late term or very long term problem in
3 younger individuals. As I see patients who get
4 stented, they tend to be across the whole spectrum,
5 but there are several special populations.

6 One is the older patient who the surgeon
7 really doesn't want to take to the operating room.
8 Maybe they have had one or two bypass procedures
9 before, and you're trying to do everything you can to
10 keep them minimally symptomatic.

11 Then there's the young patient, because
12 they are early on and you want to save them for
13 surgery later. So they're in their forties, and they
14 have an isolated single lesion such as the lawyer you
15 presented, and we're going to see a number of those
16 who will be irradiated. What happens to them a decade
17 or two later? I don't think we know the answer to
18 that.

19 We're hopeful it won't be anything bad,
20 and that the coronary artery or the area of the heart
21 around it doesn't become a little fibrotic strand.
22 But having seen a number of patients who have suffered

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1 the effects of mediastinal radiation, not only for
2 Hodgkin's but earlier on when they had enlarged thymus
3 glands where they didn't even have chemotherapy then,
4 and seen the devastating results, I still think that
5 that's something that we ought to at least have our
6 eyes fixed on.

7 DR. HOLMES: I agree entirely with that.
8 We need to continue to have long term surveillance of
9 these patients. I think we also need to keep in mind
10 and remember that atherosclerosis is a progressive
11 disease and, just because they have a single
12 angiographic thing in the proximal, they probably have
13 it all over the place. And the surgeon can attest to
14 that.

15 I suspect it's unlikely when they go in
16 and feel the artery that there is -- everything else
17 is incredibly clean. So oftentimes it's a progressive
18 disease, and they will have more problems related
19 later on.

20 DR. HARTZ: That just reminded me of
21 something. That 45 millimeter length -- that's about
22 the distance from the proximal to the distal LAD.

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1 That's about the distance from the AB group to the
2 cross of the heart to the right coronary. That's
3 about the distance from the left main ostium, way past
4 the bifurcation of the circ.

5 Once you get past those distances, the
6 vessel is so small, does it really work? Are you
7 going to continue to include that 45 millimeter seed
8 length? That seems extraordinarily long.

9 DR. HOLMES: I think that's a great
10 question. I think there are a couple of things.
11 There are a number of issues in terms of stent
12 implantation in general that are beyond the purview of
13 this where we as interventional cardiologists need to
14 make sure we never trap the distal vessel, so that if
15 you need to go in, you don't have to cut out metal.
16 That's the first thing.

17 The second thing is the patients that got
18 the very, very long seeds were often those patients
19 that had already had a LIMA and then had something to
20 the circumflex and had something go wrong with the
21 right coronary artery, and the right coronary artery
22 was stenosed from top to bottom. So you had a whole

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1 length of something that needed to be treated, and the
2 patient had already had a couple of other options in
3 terms of surgery explored.

4 So that would be the typical thing that
5 you would see that in. We certainly don't want to be
6 faced with radiating around the apex or anything like
7 that.

8 DR. HARTZ: It's important that you
9 understand that when we read this, some of these
10 issues that you're bringing up were not made clear to
11 us.

12 DR. PARISI: One final question. It may
13 be a detail, maybe not. But back on the same table,
14 since we've been talking about myocardial infarction,
15 I think most of the focus has been on comparing the
16 group that received the irradiation versus the control
17 group, and there seem to be twice the rate and, from
18 what I interpreted, most of that was due to late
19 thrombosis.

20 If we go to the acute line of myocardial
21 infarction in the three trials and come across it, in
22 the WRIST trial there was a very high incidence in

1 both groups, which I think is for elective
2 angioplasty, 10.8 percent and 7.7 percent.

3 I didn't quite understand why in this very
4 experienced center there would be such a high
5 incidence in both groups when none of the other
6 centers had that. Could you explain that?

7 DR. DONOHOE: Sure. And I would ask Dr.
8 Waxman to respond.

9 DR. WAXMAN: We did a very aggressive
10 ablation therapy in both groups using rotational
11 atherectomy, which is associated with usually high
12 risk CK -- Also our definition was more sensitive to
13 the TEK dose, because we were very cautious about it.
14 So I think that explains.

15 I'd like to stress that this is true for
16 both groups, for the placebo and for the radiation
17 arm.

18 DR. PARISI: But it's not specific then
19 that using this device with a long dwell time. It's
20 more that you did more rotobladers and that type
21 thing.

22 DR. WAXMAN: Correct. Almost all native

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1 arteries, and substantial amount of them -- It's in
2 the package -- underwent rotational atherectomy.

3 DR. DONOHOE: I'd like to -- Your comment
4 earlier about fibrosis -- There was some discussion
5 earlier. Just to follow up on that, I just wonder if
6 I could ask Dr. Amols again to respond to that.

7 DR. AMOLS: Thank you. I think, actually,
8 a number of panel members have asked questions about
9 dose to the heart and to surrounding tissues. It's
10 important to realize that the dose from this source
11 drops off extremely rapidly as a function of distance.

12 Just to give you an example, by the time
13 you are, say, one centimeter away from the source, the
14 dose is down by almost a factor of 20 from what the
15 prescription dose would be. Two centimeters away,
16 it's down by a factor of over 100.

17 The reason for this, it's a geometry
18 effect, and it's an attenuation effect of the
19 radiation. So the actual volume of tissue that gets
20 a large dose is a few cubic millimeters.

21 Again, by the time you get a centimeter
22 away, the dose in many cases that the patients receive

1 from fluoroscopy and angiography is comparable and, in
2 some cases, even more than the dose that they are
3 getting from the brachytherapy procedure, and the
4 volume of tissue irradiated in the fluoroscopy is
5 significantly larger.

6 The other issue I'll point out, and I
7 think Dr. Simmons asked it: The uniformity of dose
8 within the lesion itself will never be uniform even
9 under the best of conditions. It never has been, and
10 it never will be, again because even over the
11 thickness of a vessel wall, which is a few millimeters
12 at most, the change in dose over that volume could be
13 factors of two or three or four, in some cases more.

14 All of the clinical trials that have been
15 conducted so far have this basic physics limitation,
16 and as Dr. Tripuraneni said, in the SCRIPPS trial and
17 in other trials the dose prescription literally
18 accepted doses between 800 Centigrade and 3,000
19 Centigrade. You can't do better than that, and the
20 clinical results -- Well, I wouldn't argue about
21 efficacy, but that's what we believe the dose window
22 is.

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1 CHAIRPERSON CURTIS: Thank you. We want
2 to wrap up these questions pretty soon so that we can
3 get on to the questions for the panel. So, Dr. Mehta,
4 if you have anything specific you want to ask?

5 DR. MEHTA: Yes, I do have actually five
6 questions. Some of them are very short.

7 I'll start with a blinding question first.
8 We are told that essentially everybody involved in the
9 trial was blinded, including the patient. The nature
10 of these studies is such that at least one person
11 needs to remain unblinded, and that's either the
12 physicist or the radiation safety officer where they
13 are specifically kept away from clinical evaluation of
14 patients in every instance.

15 DR. HOLMES: Specifically, they were.

16 DR. MEHTA: Second question I have is
17 regarding the edge effect. Has there been any effort
18 to actually decrease the length of the Iridium seed?
19 In other words, not to treat two to three millimeters
20 beyond the stent, but to actually treat within the
21 stent to see if the edge effect can be diminished?

22 DR. DONOHOE: Actually, in responding to

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1 that question, it kind of leaves open the starting
2 question, I guess, as to what extent do we have edge
3 effect in the study, and then what can be done about
4 that, to the extent that it presents an issue.

5 I'd like to ask Dr. Lansky to respond to
6 the question about edge effect and what we understand
7 about that.

8 DR. LANSKY: Sure. My name is Alexandra
9 Lansky. I'm the Director of the Angiographic Core
10 Laboratory, and we performed the angiographic
11 analysis, actually, of all three trials, the SCRIPPS,
12 the WRIST, and the GAMMA I trial.

13 I just wanted to show the methodology so
14 that this was clear, I think, to everybody to
15 understand exactly what we did and how to interpret
16 the data. Next slide, please.

17 First of all, just an example of what edge
18 restenosis looks like. This is a typical patient with
19 a mid-LAD lesion with diffuse in-stent restenosis
20 treated with, in the GAMMA trial, radiation therapy.

21 What you see here at follow-up is that
22 there's a focal restenosis occurring just distal to

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1 this radiation ribbon. So this effect is presumed to
2 be due to a proliferative effect in a zone of dose
3 falloff. If I could have the next slide, please.

4 Now the important question is did we
5 include in our analysis a segment that was long enough
6 in order to detect and measure this entity? I just
7 want to go through this.

8 What we did was --

9 CHAIRPERSON CURTIS: If you could be
10 brief, please.

11 DR. LANSKY: Sure. What we did was we
12 prospectively analyzed three segments, the stent
13 segment which was mentioned earlier, the radiated
14 segment, and the lesion segment. I just want to
15 really focus on the lesion segment.

16 This was a segment where we identified the
17 minimal lumen diameter that extended 5 millimeters
18 proximal and distal to the radiated or injured region.
19 So it really was inclusive of the radiation edge plus
20 five millimeters and/or any zone of injury. If you
21 can go to the next slide.

22 Graphically or schematically, this is what

1 it looked like. We identified the stent, any zone of
2 injury, the radiation wire, and then a zone of 5
3 millimeters on each end of this. Next slide.

4 Then focusing specifically on the GAMMA I
5 trial, how can we interpret these data? I think the
6 main and the most important way to interpret this is
7 that, when we look at the lesion restenosis rates, you
8 have to keep in mind that this is inclusive of any
9 kind of restenosis occurring at the edges.

10 What we have seen is a significant
11 reduction, from 55.3 to 33.4 percent, irrespective of
12 the precise location or the physical location of the
13 minimal lumen dimension, whether it was within the
14 stent or at its edges.

15 What we did see in the GAMMA I trial, as
16 was referred to initially, was this isolated stent
17 edge restenosis, ten percent -- just over ten percent
18 -- in the Iridium versus 4.3 percent in the placebo
19 group.

20 I think it's important to understand the
21 limitations of the methodology, and that is there is
22 a certain component of those patients who have in-

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1 stent restenosis that is diffuse, and Dr. Holmes
2 shared that data with you where the patients assigned
3 to the placebo group actually had more diffuse
4 disease, and you would expect then that patients with
5 an MLD, a minimal lumen dimension, identified within
6 the stent would extend to involve the edges.

7 So when we define the entity of edge
8 effect, I think it should not be limited exclusively
9 to those patients that have isolated stent edge
10 restenosis, but should also include that portion of
11 the patients who have diffuse disease and would extend
12 to the edges.

13 Now to answer the question, the strategy
14 so far has been to use longer seeds to cover any zone
15 of injury in an attempt to reduce the edge effect, and
16 we have not gone to a shorter source train to try and
17 see if that had any impact.

18 CHAIRPERSON CURTIS: Could you state your
19 financial interest?

20 DR. LANSKY: I'm sorry. I have no
21 financial interest in Cordis. I am here on behalf of
22 Cordis, and they are paying for my travel expense and

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1 an honorarium.

2 CHAIRPERSON CURTIS: And if there are any
3 remaining questions from the panel members to the
4 company, I would ask that whoever is representing
5 Cordis, please limit your answers to the question
6 asked and not be giving us additional information at
7 this point. Dr. Mehta?

8 DR. MEHTA: The next question I have is
9 specifically regarding the issue of what dose are we
10 getting to the target tissue relative to external
11 situations? Can you give us some examples of
12 Hodgkin's lymphoma, for example?

13 Whereas it's true that there are
14 significant differences in the volumes that are
15 irradiated, and in the end that's exactly what might
16 drive the late complication rates, it's perhaps
17 important to try and understand from a biological
18 perspective whether 8 to 30 Gy given in 20 minutes is
19 more or less than 45 or 50 Gy given over four, five or
20 six weeks.

21 Have you done ^{**}any biological modeling, as
22 limited as the models are, to try and understand this

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1 impact?

2 DR. PARIKH: I don't think we have done
3 any biological modeling. The only model that's
4 available is the model using the biological equivalent
5 dose, and that model has well known limitations in the
6 fact that, while it's a model that one can use over
7 the range of conventional fractionated radiation
8 therapy, it's difficult to come up with a single
9 fraction dose into a biologically equivalent dose and
10 try to compare that with fractionated radiation
11 therapy.

12 The key thing probably is the limitation
13 of the volume. When you compare the Hodgkin's
14 patients with the patients in the vascular radiation,
15 we are limiting the dose to an extremely short segment
16 of the artery. Less than six percent of the heart
17 receives a dose of 180 Centigrade or more. So we are
18 limiting the dose to a very, very small volume.

19 The other pieces of information are that
20 when these patients do fail in that patients that have
21 actually had restenosis, despite radiation, the
22 restenosis phenomenon is much more focal, and the

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1 length of the restenotic lesion is statistically
2 shorter than the failures that happen in the placebos.

3 So they are actually, if anything,
4 converting the natural history of these patients to a
5 more favorable lesion group, and all the patients that
6 have failed have been mostly amenable to either a
7 percutaneous intervention or bypass surgery.

8 So we aren't creating any lesions that are
9 more complex than lesions that are more difficult.

10 DR. MEHTA: The final question I have is
11 that there was a slide that was presented early this
12 morning which was a composite data summary of patients
13 with no stent placements. These were pooled data, and
14 three endpoints were demonstrated, in-stent
15 restenosis, in-lesion restenosis, and MACE, and all
16 three were statistically significant.

17 These were presented separate from the
18 patients who received new stents, because, obviously,
19 we've heard so much about the impact of the stent. My
20 question to you is specifically regarding this cohort
21 of patients.

22 I calculated this out to be 84 patients,

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1 I believe, in the radiation arm and 72 in the placebo
2 arm. Have you done a subgroup analysis to see whether
3 diabetes is what's driving this difference, whether
4 it's the LAD that is driving this difference, whether
5 it's one or more of the trials that's driving this
6 difference? What's driving this difference in the
7 pooled data of 84 versus 72 patients?

8 DR. KUNTZ: Which difference are you
9 referring to?

10 DR. MEHTA: In the in-stent restenosis and
11 the in-lesion restenosis and MACE, it's your slide
12 number 77 on page 26.

13 DR. KUNTZ: Yes, I understand that. Are
14 you asking is there a diabetic interaction of
15 radiation therapy?

16 DR. MEHTA: Right. There's a significant
17 difference, and we've heard that there are some
18 factors that predict for differences. For example,
19 diabetics in one of your studies did much better.

20 The question I have is have you done a
21 subset analysis on this group --

22 DR. KUNTZ: Oh. Was a tendency for the

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1 non-new-stent to have a higher or lower incidence of
2 diabetics, for example?

3 DR. MEHTA: Or any of the prognostic
4 variables.

5 DR. KUNTZ: Right. We did a saturated
6 multi-variable model looking at the main effects of
7 diabetes, lesion length, LAD location, reference
8 vessel size, presence of new stents in both acute and
9 late term complications, and we found that there was
10 no significant independent effect between diabetes, in
11 and of itself, and the results of efficacy of
12 radiation therapy or placebo, nor was there a diabetic
13 interaction between the use of new stents.

14 DR. MEHTA: So if I understand that
15 correctly, does that mean that the effect of diabetes
16 resulting to improved clinical outcomes is limited to
17 patients with new stents?

18 DR. KUNTZ; No, not at all. Let's just
19 review the diabetic issue. Patients with or without
20 diabetes have a benefit from radiation therapy.
21 There's probably a tendency for diabetic patients to
22 have a more relative benefit, because of the fact that

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1 the placebo size has such a larger event rate.

2 So the relative treatment effect is
3 slightly larger. We tried to understand whether that
4 was a special significant difference. The way to test
5 that is by looking at the interaction between diabetes
6 and radiation therapy, and that was not significant.

7 So diabetics and non-diabetics benefit
8 from this therapy. Clearly, the subset of diabetics
9 do well, which is always a question: Is this limited
10 to diabetics or non-diabetics?

11 With respect to whether patients with new
12 stents or non-new-stents still have effective therapy,
13 we've shown that, in fact, there is effective therapy
14 whether you use a stent or without a stent. If we
15 look at the interaction between use of a new stent and
16 radiation therapy, there is no special interaction.
17 This works for both groups.

18 Now whether there's a clustering of
19 diabetics in the new stents that explains the
20 difference per se would require the diabetic
21 interaction to be positive or the new stent to be
22 positive, and there wasn't. And the multi-variable

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1 model would, therefore, rule out the probability that
2 diabetes explains the difference we see here with no
3 new stents.

4 So I think I'm answering your question.

5 DR. MEHTA: Yes. Thanks.

6 CHAIRPERSON CURTIS: Dr. Domanski, did you
7 have anything else you wanted to ask?

8 DR. DOMANSKI: No. I don't think so.

9 CHAIRPERSON CURTIS: Okay. Dr. Griem?

10 DR. GRIEM: Yes. I'd like to get back to
11 the question of the dose. That comes up first. It
12 comes out of the proceedings of the Radiation Research
13 Society seven weeks ago in which Brenner from Columbia
14 discusses the radiobiology of radiation for restenosis
15 and comes up with a fact in paragraph 2 that over 20
16 Gy delivered in a period of less than one hour results
17 in unacceptable complications.

18 I think the 30 Gy and the variability
19 between 8 Gy and 30 Gy is so wide and that here is
20 some hard data that would suggest that there is maybe
21 a tolerance level. **

22 Now where else do you see this question in

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1 single treatments? When Kinsella treated patients in
2 this city intraoperatively for tumors in the abdomen,
3 he got into trouble over 22 Gy, and when Gillette did
4 it at Colorado State on dogs he got into trouble
5 around 20 Gy.

6 Now when you look at the late radiation
7 studies by Archimbeau and Fajardo on skin in the
8 depth, again they're getting in trouble with blood
9 vessels at these sort of dose rates. Then I suppose
10 one can put in the Stewart and Fajardo data on heart
11 from the Hodgkin's, but that is not single fractions.

12 So it would seem to me that the physics of
13 the dose here is very critical. When you look at the
14 exponential data on page 5-033, you see that I think
15 you have to get some help from AAPM and a group to
16 define this dose very accurately. This is
17 exponential. It's given with millimeters, and that
18 concerns me.

19 Now finally, the business of the metal:
20 I'm an orthovoltage radiotherapist. I learned on 250
21 KEV, which is very close^{**} to this energy. When we
22 treated lip cancer and didn't coat the lead spatula to

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1 prevent radiation of the teeth and so forth -- and if
2 we didn't coat that, we got a terrible reaction on the
3 lip. All you needed to do was coat that either with
4 a finger cop or some wax, and you didn't get this
5 reaction.

6 So anything scattering off of metal, and
7 the back-scatter will give you an additional dose. I
8 think that, again, microdosimetry on your stents may
9 give you some answer to the problems. So that's
10 related to question Number 9.

11 I think that late effects of radiation
12 occur beyond six months, and more like two and three
13 years later. That's again from my orthovoltage
14 experience.

15 CHAIRPERSON CURTIS: Mr. Jarvis, did you
16 have anything you wanted to say?

17 MR. JARVIS: Just a couple of things. I
18 think when we look at like six-month angiograms -- I
19 know I've worked with the core lab here, and it's been
20 a definitive -- I think all -- if not all, the
21 majority have used that ^{**}core lab for stent studies.
22 I think we need to look at that and rely on that type

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1 of data.

2 I think another thing we need to look at
3 is there was a data safety monitoring board, and it
4 was the same people reviewing the data, and the same
5 adjudication committees were also reviewing the data.
6 So I think that's an important part, because we had
7 uniformity throughout the study.

8 When we talk about this 100,000 patients
9 that we're getting each year that pop up, you know,
10 the problem of throwing out numbers like that is, as
11 these things go on and on and trials take longer and
12 longer, and we've seen this between Europe and the
13 U.S., practices change, and it's difficult to, shall
14 we say, hold investigators in line; because a lot of
15 them will say, well, before in the U.S. we couldn't
16 use Tyclid in clinical studies, but yet there was
17 investigators that gave it. So there was deviations
18 off that type of thing.

19 So I think we need to be aware that, if
20 you look at long term studies, practices change, and
21 it makes it difficult to roll all these numbers in.

22 The animal model: I've worked extensively

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1 with the Mayo Clinic in the past on animal models, and
2 Rob Schwartz there is considered an expert in the
3 field of animal models. The hard part for us
4 manufacturers is that, when we come to FDA, there's
5 really not much guidance on what kind of animal model
6 we use. We have to come and propose that.

7 So in a way, we're a moving target when we
8 come to these advisory panel meetings why we didn't do
9 something. It's difficult. So I think we need to
10 look at this -- When you have human data, especially
11 some stuff coming out of Europe and even here, we
12 almost have to reverse engineer things to go back for
13 an animal model. Not to say it shouldn't be done, but
14 I think you should look at human data versus animal
15 data as its priority, because there are certain things
16 that will not happen in animal models but will happen
17 in human models, and vice versa. It's been proven out
18 in other studies.

19 One other thing is, whenever you have six-
20 month angiographic follow-up -- I've addressed this
21 personally with other things -- that, in a way, you're
22 getting worse case, because if you didn't do that

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1 angio and they were asymptomatic, you wouldn't know
2 it. So in a way, we're biasing ourselves by doing an
3 angiographic follow-up.

4 No matter what agreement you have between
5 investigators that you won't treat a patient or you'll
6 treat a patient within certain parameters, that's
7 really at the discretion of the physician that's
8 treating that patient at that time, and we as sponsors
9 cannot -- It's hard to dictate that and get them to
10 follow that, because they need to do what's in the
11 best interest of the patient.

12 That's all I have.

13 CHAIRPERSON CURTIS: All right. Dr.
14 Ayres, did you want to make any comments?

15 DR. AYRES: I don't have too much to say,
16 not being a clinician. I would note I have one small
17 labeling issue that I understand may have been worked
18 out, that we have a new protocol being proposed, and
19 they're back in the dark ages with milligram radium
20 equivalence for specifying the activity.

21 The other: It does bother me that this
22 study incorporates a dose range over a factor of four.

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1 One wonders how much clinical effects, both positive
2 and negative, might be masked in that dose range, and
3 it does seem that the corresponding animal and
4 radiobiology studies seem a little thin in
5 establishing what some of these effects may or may not
6 be. It seems that -- I think there's ongoing work,
7 and that may help, but at this point I'm not sure all
8 the radiobiology is that well understood.

9 I am interested, but it hasn't come up in
10 discussion -- Question 8 in the FDA's questions here
11 about the elements that should be contained in the
12 physician's training program, which is, of course,
13 clearly of interest to us.

14 CHAIRPERSON CURTIS: Well, we will get
15 into that in a little bit. Mr. Dacey?

16 MR. DACEY: There's just a very
17 generalized consumer perspective that I'd like to
18 present. Our complex and rapidly changing
19 demographics are producing and creating more
20 information seekers and more qualified information
21 seekers.

22 Now in the community where I live, 90

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1 percent of the households have Internet access, and it
2 being a university community, there's quite a few
3 scientists, atmospheric scientists, and then down the
4 road there's a general population.

5 Now the scientists in the community are
6 going to appreciate all the science that I'm hearing
7 today. When it comes to the general population who is
8 -- just now they are having classes at the library on
9 how to use the Internet to get medical information.
10 For some of them, it's a leap of faith, and they have
11 to trust the science.

12 In both cases, but probably more with the
13 scientists in my community, they are going to be
14 asking tough questions of their providers, of the
15 sponsors, and you have to be prepared for that. I
16 know, just because I know the populations that I deal
17 with and the many, many patients that I've dealt with,
18 that their focus is going to be on the safety and
19 especially on the long term issues.

20 So I guess I'm just -- In the whole scheme
21 of things and looking at your application and your
22 conclusions, the label warning, the physician training

1 program, the provided updated information, the post-
2 market issues certainly, and the informed
3 physician/patient decision -- There's a population of
4 patients that are getting a lot smarter, and I think
5 you must be prepared for that.

6 CHAIRPERSON CURTIS: Thank you. I think
7 this would be an appropriate time for us to take a
8 break. When we come back, we'll have a discussion
9 among the panel here. If the people representing
10 Cordis could step back at that point -- Thank you.
11 We'll be back at 3:15.

12 (Whereupon, the foregoing matter went off
13 the record at 3:00 p.m. and went back on the record at
14 3:18 p.m.)

15 CHAIRPERSON CURTIS: The first thing I'd
16 like to do now is that we are required to have a
17 second open public hearing. So if there is any member
18 of the public who didn't have a chance to speak
19 earlier this morning who wants to make any comments at
20 this time, please make yourself known. If not, we'll
21 close that.

22 What we're going to move on to now are the

1 questions that were posed to the panel. We are going
2 to go through these, and in many cases we're hoping
3 that there is going to be a fairly easy consensus to
4 this, because we'd like to move to a motion as
5 expeditiously as possible.

6 We'll take question Number 1 first. The
7 actual question was: The definitions for myocardial
8 infarction and target lesion revascularization in the
9 GAMMA I trial are provided on pages 0005-0298 and 005-
10 0299. Please discuss whether you believe these
11 definitions are adequate to assess the clinical
12 performance of the device.

13 Anybody can pop in here.

14 DR. DOMANSKI: Well, I basically asked
15 them this question for that reason, and thought the
16 answer was pretty satisfactory. I think they did a
17 good job, actually, on trying to ascertain a difficult
18 endpoint. I thought the thing was pretty well
19 conceived.

20 CHAIRPERSON CURTIS: Has everybody had a
21 chance to look at those two pages and see if --
22 Remember the myocardial infarction for a Q-wave MI was

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1 developed and have new pathological Q-waves with CPK
2 or CPK-MB levels elevated above normal, and the non-Q-
3 wave MI is defined in there as well.

4 DR. HARTZ: I just have the question --

5 CHAIRPERSON CURTIS: Let's all make sure
6 we speak clearly into the microphones.

7 DR. HARTZ: Are we going to stick to this
8 old-fashioned definition of infarcts forever on all of
9 these protocols having to do with revascularization or
10 are we going to go with troponins? I mean, a lot of
11 hospitals --

12 DR. DOMANSKI: Well, they don't have --
13 But they don't have troponin is the thing, and they
14 weren't doing them probably at that time. So the
15 troponin is a sensitive way of doing it. It's not
16 available. CPK is an effective way of doing --

17 DR. HARTZ: But in most hospitals now you
18 can't get a CPK.

19 DR. DOMANSKI: We can in ours.

20 DR. HARTZ: We can't in ours.

21 DR. DOMANSKI: I don't think this is a bad
22 way of doing it, as a matter of fact. I mean, I think

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1 troponin is more sensitive.

2 DR. HARTZ: Well, what if you can't get a
3 CPK in your institution is what I'm saying. That's
4 very common now.

5 DR. DOMANSKI: Then you need troponins.
6 Unusual, but --

7 CHAIRPERSON CURTIS: The question being
8 posed is whether or not you can assess the clinical
9 performance of the device based on the definition
10 given there, and I think the answer is yes. Whether
11 or not a troponin might be a better way to go with the
12 next clinical trial design is a good question and can
13 be, I think, addressed at that time. Kent?

14 DR. BAILEY: I guess the only qualm I have
15 about the idea that this is clinically driven
16 revascularization. It's a dead horse which is still
17 kicking, but the point is that we can't necessarily
18 use this as a reflection of what would have happened
19 in a non-angiographic study.

20 So in a sense, it's very closely related
21 to an angiographic endpoint^{**}, sort of a composite of an
22 angiographic endpoint and a clinical one; because you

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1 have the opportunity to look at -- You know, I think
2 one can accept that the radiation changes the lumen
3 diameter. And if that's enough for clinical efficacy,
4 fine. But if you then say, well, what about the
5 clinical impact, well, we're measuring the clinical
6 impact with a definition that's very closely related
7 to the luminal diameter or the percent stenosis.

8 So it's really more of a -- It's not pure
9 clinical endpoint, in my point of view. That's why I
10 would like to know what -- You know, what was the
11 proportion of patients in the two groups that had
12 positive exercise tests?

13 It would be nice to know. I would feel
14 differently about the need for revascularization if
15 indeed the amount of exercise positivity was greater
16 in the placebo group and the rate of rest angina was
17 greater in the placebo group. But once you factor in
18 the percent stenosis, then you're back to --
19 Potentially, it could be simply the fact that you get
20 a smaller stenosis at six months or whenever with the
21 radiation.

22 CHAIRPERSON CURTIS: I think, if you say

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1 somebody has resting angina and it's restenosis and
2 you've got to do something about it, that's target
3 lesion revascularization. It's reasonable. Or if
4 you've got a positive stress test of whatever kind and
5 you're demonstrating ischemia and it's stenosis and
6 you have to do something about it, I don't think any
7 of us would argue with that, that that's a good reason
8 for having to reapproach a vessel.

9 The question is the asymptomatic ones.
10 You posed that question before. The impression I got,
11 although we didn't get specific numbers, was that it
12 was a small percentage of the total where it was, you
13 know, the occluso-stenotic reflex where you were taking
14 a lesion and saying I've got to fix that.

15 We don't know what the answer to that is.

16 DR. BAILEY: My impression is you could --
17 Could you not also have a positive exercise response
18 without a 50 percent stenosis?

19 CHAIRPERSON CURTIS: I think that would be
20 unusual, and I think by -- I forget what the
21 definition said about that**.

22 DR. HARTZ: The definitions simply give

1 the traditional literature characterization of an
2 infarct, but they are really not relevant to what
3 we're talking about in this study; because these are
4 infarct definitions. They don't necessarily say they
5 are in the target vessel region.

6 The patient may have infarcted, but in a
7 remote territory. So if the only question is are
8 these adequate definitions of an infarct, yes, they
9 are. They are the traditional literature definitions
10 of myocardial infarction. Whether they will be
11 pertinent to this trial, I guess, is another issue, if
12 we want to address that at all.

13 CHAIRPERSON CURTIS: I mean, their
14 definition of target lesion revascularization said you
15 would have to have a positive stress test with more
16 than a 50 percent stenosis there. So under that it
17 was nonclinically driven.

18 DR. TRACY: I think on page 0733 they
19 reference to Table 12 in Section 8B which provided a
20 breakdown of the presence of ischemic symptoms and
21 science in patients who underwent repeat TLR, and
22 their estimate was only four percent or ten of 252

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1 patients underwent nonclinically driven TLR, and there
2 was no significant differences between the treatment
3 groups.

4 So I read that as the rate of occulo-
5 stenotic dilatation, which is relatively low. But I
6 think that is a little bit different from the question
7 number 1, which is just looking at is this definition
8 of MI okay to work with.

9 I think, from the perspective of answering
10 question 1, yes, it's a definition. It may not be the
11 definition we would set up in the year 2000, but it's
12 a definition, and I think the data are interpretable
13 in light of this definition.

14 CHAIRPERSON CURTIS: So you're satisfied
15 with the definition of MI as posed. Is the definition
16 of target lesion revascularization as written out
17 adequate to assess performance? I think the answer is
18 yes to that, particularly since the business about the
19 asymptomatic stenosis is a small percentage.

20 You know, one way to -- I suppose the only
21 other alternative here that we would really have to
22 consider is should those be thrown out? You know,

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1 would you have to have had symptoms and/or positive
2 stress test with a stenosis in order to have that be
3 clinically driven?

4 I think the implication I was getting
5 before was that many of those patients are going to
6 wind up getting symptoms. That's, you know, maybe
7 some supposition. It may be some experience that
8 intervention was sound.

9 I don't have a problem leaving the
10 definition as is. Does anybody else?

11 DR. PARISI: These investigators and the
12 patients are blinded. So I think it's really sort of
13 moot in my mind, completely moot. I mean, it's not
14 that the investigators knew that this person had
15 radiation. There's no way they could have known
16 unless they broke the blind, and I don't see why they
17 would have.

18 CHAIRPERSON CURTIS: So the definitions
19 for both MI and TLR are adequate as written, and we
20 can leave them be.

21 Question Number 2: This relates to the
22 six and nine-month follow-up. I think -- In the GAMMA

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1 I study, patients were scheduled to complete
2 angiographic follow-up at six months and clinical
3 follow-up at nine months. FDA infers from information
4 provided by the sponsor on page 5-733 that all
5 patients completed clinical follow-up preceding
6 angiographic follow-up at nine months.

7 Please discuss whether you believe any
8 conclusions can be drawn.

9 I asked the company representatives that
10 question specifically, and they said that there was
11 follow-up after nine months. So I think that answers
12 that question.

13 Let's move on to Number 3: Late total
14 occlusion was observed at a higher rate in the
15 treatment arm of the GAMMA I trial.

16 I think some of the problems we have here
17 with these definitions are just you have to finally
18 understand what's being said by late thrombosis versus
19 late occlusion and what total occlusions refer to.
20 But they are referring here to pages 5-94 through 96
21 for definitions of thrombosis and occlusion.

22 Questions that are being posed are, first:

1 Please discuss which definitions of late thrombosis
2 and occlusion are adequate to assess the clinical
3 performance of the device.

4 Secondly: Discuss whether the definitions
5 employed by the sponsor are clinically meaningful and
6 whether they adequately differentiate late stent
7 thrombosis from late total occlusion.

8 Anybody want to make a comment?

9 DR. DOMANSKI: That sends us back
10 specifically to those pages. I thought the discussion
11 of that was nicely handled, actually, by the
12 investigators in terms of trying to clinically
13 separate it out. Of course, you can't be perfect in
14 doing that, but typically when something suddenly
15 thromboses, you have a clinical -- you have an acute
16 coronary syndrome generated in something that's
17 gradually hyper -- I don't know what the right past
18 tense of this is -- they are in the process of
19 undergoing hyperplasia and closing off, and
20 collaterals are developing.

21 You know, it can be a silent event. I
22 don't know that you could handle it any better than

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1 they did. Now we can go back to the specific verbiage
2 on those particular pages, but I thought it was pretty
3 well handled.

4 CHAIRPERSON CURTIS: Well, I think, too,
5 that -- Could you ever have a thrombosis that's
6 clinically silent? I don't see why not, even though
7 that's not usually what you think of. But short of
8 getting in there and actually looking at the
9 pathology--

10 DR. DOMANSKI: And who knows what the last
11 -- You know, if something gradually closes down, is
12 there sometimes a thrombotic event with collaterals?
13 I mean, I think -- You know, actually, I think
14 probably again it's probably adequately handled.

15 CHAIRPERSON CURTIS: Yes. I think in most
16 cases of thrombosis, it probably would be associated
17 with an MI, in most cases the total occlusions, might
18 not. If there's going to be some overlap, is it so
19 important to know the difference? It's not, and you
20 can't go any -- There's really no further way to
21 differentiate that anyway,** as far as I can see.

22 DR. HARTZ: This is the issue about which

1 I felt most strongly. I think that -- Like I said, I
2 think it's irrelevant to a patient or to me if a
3 vessel closes, if nothing happens to the myocardium.

4 There's nothing in these definitions or
5 anything else that tells us what really happens to the
6 myocardium, and that's why I'm not even sure those
7 definitions are meaningful or why they have been
8 broken down like this.

9 I think that, if the investigators can
10 show us whether the patients had an event by using a
11 wall motion test, I would be much happier than seeing
12 these definitions.

13 I mean, basically, the final common
14 denominator in an infarct is a thrombosis -- or in a
15 leg loss or a stroke is a thrombosis. So even if
16 these are hypertrophic lesions at the site of the
17 stent, so what? Eventually, they're going to clog.
18 If there's plenty of collateral, it's not going to
19 cause any problem.

20 So can the investigators give us at some
21 point, a year or something, some measure whether -- I
22 don't think these are very meaningful definitions at

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1 all.

2 DR. DOMANSKI: Well, I must say, though,
3 I think they do have a meaningful definition of
4 whether they had an event, because they were looking
5 for MI. The trouble with the wall motion abnormality,
6 at least in isolation, is that there are things other
7 than an acute MI that can cause it.

8 I think they do, actually, have a marker.
9 I'm not sure that -- Of course, it adds information of
10 a sort, but I'm not impressed that it's either better
11 or really necessary to add that to what they've done.

12 DR. HARTZ; I feel strongly about it,
13 because they already told us about infarcts. We know
14 about infarcts. Dr. Holmes said very emphatically, if
15 they close acutely, we're going to see it. They're
16 going to bump their enzymes. They're going to be in
17 trouble.

18 DR. DOMANSKI: Well, that's the point.
19 You know whether they had an infarct, and you know
20 whether they died. Now they haven't given you a
21 quantitation of the wall motion, but I guess I'm
22 unimpressed that adds a lot to this particular

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1 discussion.

2 CHAIRPERSON CURTIS: Okay. Question
3 Number 4 --

4 MR. DILLARD: Dr. Curtis, if I could just
5 ask for a little more clarification perhaps on the
6 second part of that, whether or not they can
7 adequately differentiate late stent thrombosis from
8 late total occlusion. Could I get maybe just a brief
9 discussion on that particular point? I mean, do you
10 think it differentiates them adequately?

11 CHAIRPERSON CURTIS: Well, I thought I had
12 answered that.

13 MR. DILLARD: Sorry. I apologize.

14 CHAIRPERSON CURTIS: What we're saying is
15 that, you know, unless you're actually in there
16 looking at the pathology, you're never going to know,
17 and to some extent, it's a clinical judgment.

18 I think it's a reasonable attempt they've
19 made to differentiate the two, and there is no better
20 way that I know of. I guess that's really the bottom
21 line is can you do better than that? I don't think
22 so.

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1 Are you sometimes making an assumption
2 that something is an occlusion when it's really a
3 thrombosis? Probably. But I don't think you can
4 tease it out better than that.

5 MR. DILLARD: Okay. So the answer is
6 that, yes, they've adequately --

7 CHAIRPERSON CURTIS: Yes.

8 MR. DILLARD: Great. Thank you.

9 DR. TRACY: A question would be, in a way,
10 what difference does it make. If there is occlusion,
11 there is occlusion. We've hung a lot on thinking that
12 the occlusion is related to thrombosis, but if there
13 is some other mechanism that's involved late on in
14 occlusion on these vessels, we don't know it. We
15 don't know how to know it at this point in time.

16 I think that the only thing we can say in
17 terms of is the definition adequate, yes, it's
18 adequate, but there is a little bit of a question in
19 my mind exactly what's going on, and I think part of
20 long term surveillance might be at trying to -- I
21 don't know how to define it, but to be vigilant if
22 there is something else that comes up in any future

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1 information on follow-up on these patients.

2 I'm not sure how we would ever know it
3 any better, because we're not going to recommend that
4 IVUS or something else be done at some point later
5 down the road. So I'm not sure how we could more
6 concretely get at it, but it is a little
7 disconcerting.

8 CHAIRPERSON CURTIS: Question Number 4:
9 Intracoronary radiation may stimulate neointimal
10 hyperplasia at the lesion edge. That's the edge
11 effect. We have here in the GAMMA I report, edge
12 effect is defined as the in-lesion restenosis rate
13 minus the in-stent restenosis rate.

14 The question being posed is: Please
15 discuss the adequacy of the sponsor's definition and
16 methodology used to quantify edge effect. That's on
17 pages 5-732 through -- Oh, it's 773 through 822.

18 DR. BAILEY: One question I have about
19 this: It sounds from the definition that you're
20 looking at the percent of patients in whom the lesion
21 outside the stent area restenosis but not the stent.
22 I'm wondering, would it make more sense to look at

1 just all those cases in which the nearby lesion
2 restenosis as opposed to the difference, if you're
3 trying to look at the total impact on the surrounding
4 tissue.

5 CHAIRPERSON CURTIS: I'm not sure I
6 understand how you would --

7 DR. BAILEY; In other words, these two
8 rates, the ten percent is the difference between the
9 overall lesion restenosis rate and the in-stent
10 restenosis rate, which is the proportion of cases
11 where the lesion restenosis but not the stent.

12 CHAIRPERSON CURTIS: I'm going to have to
13 look at these pages, if anybody else wants to make any
14 comments.

15 DR. BAILEY: And I mean, that's not
16 directly looking at the rate at which the surrounding
17 tissue restenosis.

18 DR. DOMANSKI: Let's think about that for
19 a minute. If the whole thing is restenosed and you
20 get one number, and then you subtract from that the
21 ones where the stuff in the stent isn't restenosed,
22 then you get the fraction where it's restenosed at the

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1 edges, don't you?

2 DR. BAILEY: Well, you get a restenosis at
3 the edges and the stent also. This just looks at the
4 cases where only the surrounding -- the lesion outside
5 the stent restenosis.

6 DR. DOMANSKI: But that's --

7 DR. BAILEY: Well, it doesn't account for
8 the edge plus stent restenosing.

9 CHAIRPERSON CURTIS: I guess, if you know
10 the answer to this, maybe you could tell me, but I
11 don't understand the question about the restenosis
12 rate, because you've got the in-stent and you can have
13 a certain percentage of restenosis, and you can have
14 the lesion at a certain percentage of restenosis. I
15 don't know how you subtract out one from the other and
16 make any comments about the edge there.

17 Are we talking about a percent stenosis or
18 percentage of patients who had the problem develop?

19 DR. BAILEY: Well, as I understand it, the
20 one number that's being -- The larger number is the
21 percent of patients in whom there's a restenosis
22 somewhere in the target lesion. The smaller number is

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1 the number of -- percent of patients in whom there is
2 a restenosis in the stent.

3 So the difference, to me, would be the
4 number of patients in whom there is not a restenosis
5 in the stent but there -- you know, there is one
6 outside the stent.

7 CHAIRPERSON CURTIS: Does this account for
8 patients who have got them in both places?

9 DR. BAILEY; Well, that's what I'm saying,
10 that patients who have it in both places are
11 subtracted out.

12 CHAIRPERSON CURTIS: Do you have any page
13 number where this is?

14 DR. TRACY: I think that 0727 through -29
15 there's several -- Again, there's a whole bunch of
16 different definitions that make it a little bit hard,
17 but I wonder what the fundamental question is.

18 Is the fundamental question is something
19 evil happening at the edges because of the radiation
20 leaking out? Is that the question? I'm not sure what
21 the question is here. **

22 DR. DOMANSKI: Well, I guess the question

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1 is one of definition. I mean, there are a lot of
2 concerns about the edge, like maybe subtherapeutic
3 levels of radiation producing stimulation and so
4 forth, not that I necessarily am an absolute expert on
5 that. But I think the question that they are asking
6 is a very mechanical one.

7 That is, what about this definition?
8 That's what's being addressed. I don't think it's
9 anything more subtle than just correctly getting the
10 definition.

11 DR. TRACY: Well, which definition? If
12 you look at page 0729, I see a whole bunch of
13 different definitions in Volume 2 of 2, page 0729.

14 MR. DILLARD: Can I clarify maybe in
15 general here while we're all looking for the
16 information.

17 You're hitting on the issue we're
18 struggling with, and I think there's a couple of
19 reasons why we're struggling with it. Number one is
20 one of the data interpretation in terms of how
21 important the edge effect^{**} is and what the number is
22 perhaps, and how to define it; and whether you come up

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1 with ten percent or whether you come up with eight
2 percent, the definition will probably drive what the
3 percentage will be.

4 Given that -- I mean, given that the
5 definition of the edge effect in this case maybe isn't
6 completely clear, one of the other pieces that I think
7 we struggle with is how do we adequately give that
8 information to you as the clinician based on this
9 particular trial and have a clean definition?

10 So that, if it comes around to a labeling
11 situation, how do we define edge effect? What's the
12 most clinically meaningful way to define it so that we
13 can get that particular information based on the trial
14 data to the clinician?

15 We're struggling with that, just like you
16 are, too. I don't know that there is a clean answer,
17 whether or not when we look at these definitions which
18 Chris is now trying to find for me here -- Hang on a
19 second.

20 DR. WILSON: Madam Chairwoman, our
21 inability to find the definition in the documents
22 specifically aside, I personally thought that the

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1 sponsors made a very clear explanation of how this
2 would be defined in their verbal presentation, and I
3 was satisfied with it.

4 I thought it was important to retain that
5 definition to understand the use of this device and
6 also to evaluate downstream results with regard to the
7 possible proliferative stimulation by low doses of
8 radiation at the tips of the radioactive source.

9 So personally, I was satisfied with what
10 they explained.

11 CHAIRPERSON CURTIS: Do you understand it
12 to be the way it's stated in the question, though,
13 that it's in-lesion restenosis rate minus the in-stent
14 restenosis rate?

15 DR. WILSON: Yes, I do, and I was
16 satisfied with that.

17 CHAIRPERSON CURTIS: Okay. I think what
18 we've been struggling with a little bit here is that,
19 if you had somebody who had in-stent and edge stenosis
20 and you're subtracting that out, you're going to lose
21 those patients. **

22 MR. DILLARD: Well, and that's -- Maybe I

1 might turn it back to you to perhaps get the sponsor
2 to clarify it, too, what they believe their definition
3 is, because perhaps what we have is a terminology
4 situation here.

5 DR. LANSKY: I appreciate the opportunity
6 to clarify this issue. I think it's been very, very
7 confusing not only to you but, I think, to many
8 clinicians. We have struggled over the last couple of
9 years, three or four years, actually, in trying to
10 define this whole entity. It's taken us actually
11 probably until a year ago to really define --
12 precisely define this entity.

13 I think one of the important points that
14 I'll make again is the fact that, when we defined the
15 lesion analysis, that lesion does incorporate the
16 whole problem of the whole entity or the whole issue
17 of edge restenosis. So that's issue number one.

18 I think, when we define edge effect, what
19 we need to do, and we have now learned, is to
20 systematically analyze the edges, both proximal and
21 distal, in every single** one of the patients and
22 compare those between placebo and active group.

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1 This is not something that we did at the
2 beginning of the GAMMA trials, because we simply
3 didn't know about this whole issue.

4 I think the closest definition that we can
5 come to in the context of these studies and in terms
6 of the methodology is to look at either the restenosis
7 that is isolated to the edge of the stent, which is
8 the definition that Dr. Stuhlmuller defines, or to
9 look at the restenosis that occurs at the edge of the
10 radiation source.

11 If that's the case, then if we could -- if
12 you remember the numbers, there is actually no
13 difference between the placebo group and the active
14 group. So again, I think this is an entity that we
15 have more precisely defined.

16 Unfortunately, the methodology that we did
17 it by initially did not specifically and
18 systematically analyze it in every single one of the
19 patients. However, I would say that, irrespective of
20 the amount of edge restenosis, the overall restenosis
21 rate, even including the ^{**}edge, is significantly
22 reduced with gamma radiation. Does that help?

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1 CHAIRPERSON CURTIS: I think it does. It
2 sounds -- I mean, you have all the angiograms. Right?

3 DR. LANSKY: Correct.

4 CHAIRPERSON CURTIS: So if you want to
5 know how much stenosis there is at the edge, you can
6 look at the edges of the lesions. That's actually
7 exactly what it is you're looking for. So I'm not
8 sure I see the point of some surrogate calculation for
9 restenosis here, based on, you know, one minus the
10 other. It would take some work, I guess, to actually
11 make those measurements, but if you want to know edge
12 effect, I think you should measure edge effect.

13 DR. LANSKY: That's exactly right. If we
14 wanted to precisely quantify this, then we would have
15 to go retrospectively and reanalyze that specific zone
16 in every single one of the patients, and that's
17 something we could do. I'm not even convinced, if we
18 did that, that there would be a difference between the
19 two groups, actually.

20 CHAIRPERSON CURTIS: That may be true, but
21 I think the definition as "given here does not really
22 answer that particular question.

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1 DR. LANSKY: You're right. The definition
2 that is there relates to isolated stent edge
3 restenosis, and I think we need to be very precise
4 about that, and not confuse edge effect with isolated
5 stent edge restenosis. I do believe that they are
6 separate entities.

7 DR. HARTZ: Could I ask a question?

8 CHAIRPERSON CURTIS: Yes.

9 DR. HARTZ: Have these all been read with
10 edge detection and stored?

11 DR. LANSKY: What we do have are actual
12 printouts, thermal printouts of all the analyses. So
13 we could go back and, based on caliper measures, we
14 could reanalyze them.

15 DR. HARTZ: I mean, if the data is already
16 available, I don't see what would be so difficult
17 doing what you said, actually measuring the edge
18 effect.

19 DR. LANSKY: No, it's possible to do it.

20 CHAIRPERSON CURTIS: Thank you. So then
21 for question Number 4, I think what we're saying here
22 is that the definition as given in the materials we

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1 have is not adequate, and that actually measuring edge
2 effect would give you an answer as to what the edge
3 effect is.

4 MR. DILLARD: Thank you.

5 CHAIRPERSON CURTIS: Okay. Number 5:

6 The sponsor provided a retrospective analysis that
7 contained pooled data about native coronary artery in-
8 stent restenosis in patients who did not receive an
9 additional stent. We heard all the discussions about
10 this.

11 There's a proposed warning for the
12 labeling about the fact that placement of a new stent
13 during the radiation procedure has been associated
14 with a higher rate of late thrombosis in comparison to
15 the placebo arm. You should avoid putting in a stent,
16 but if you do need one, it is recommended that the
17 patient be placed on antiplatelet therapy for 12
18 months.

19 So the two questions here are: Discuss
20 whether the study data and analyses provided support
21 the information contained in this warning; and comment
22 on whether any other information should be included in

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1 the labeling regarding late thrombosis.

2 DR. PARISI: I think the data does support
3 the first question. The second issue, though, is what
4 information should be included regarding maybe
5 prevention of late thrombosis is what is meant there.

6 I think that the raw data should be there
7 from further trials like SCRIPPS III and WRIST Plus,
8 so at least whoever is using this would know the raw
9 data on what the likelihood is of extending treatment
10 with antiplatelet agents.

11 CHAIRPERSON CURTIS: Other comments?

12 DR. BAILEY: In that regard, I guess we
13 looked at some of the preliminary data, but I did not
14 see the analysis of just the stented -- the newly
15 stented patients, which were about 25 percent of these
16 patients. So that was a much smaller number cohort
17 that are being followed than the overall group, and we
18 saw the rate of -- I mean, sure, the rate of
19 thrombosis was zero, but zero out of 100 or 200 or
20 whatever is different than zero out of 50.

21 So we should look at confidence intervals
22 based on the ones that are actually stented.

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1 DR. HARTZ: Since these are blinded, that
2 means that 50 percent of the patients with a new
3 stent, those that don't get radiation, will also be
4 maintained on the antiplatelet therapy for a year.

5 DR. BAILEY: These are registries,
6 nonrandomized.

7 CHAIRPERSON CURTIS: This is a warning
8 that would be in the clinical labeling. I certainly
9 think there is enough information in what we were
10 given to warrant a caution or a warning specifically
11 about those patients, because the events did happen in
12 most patients.

13 So that should be clearly made -- It
14 should be clear to clinicians taking care of patients
15 that you don't want to do that, if at all possible.
16 So I think we have enough data to support the
17 information.

18 Whether that ultimately basically
19 eliminates the problem of late thrombosis, that, I
20 think, we don't know. But we know to be cautious
21 about those patients.

22 The problem about the antiplatelet therapy

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1 -- I think it's a guess whether 12 months is adequate.

2 DR. DOMANSKI: You know, one way of
3 handling that is to drop the "for 12 months,"
4 recommend that the patient be placed on antiplatelet
5 therapy. I mean, I'm not sure when to take them off
6 in that setting.

7 DR. MEHTA: I would agree that I would
8 have a similar concern. If we put in something that
9 says keep a patient on something for 12 months, it
10 implies we know that keeping them on only for 12
11 months has value. We have no data to base that
12 statement on.

13 CHAIRPERSON CURTIS: All right. So I
14 agree thoroughly, we don't know whether 12 months is
15 the right recommendation. Do we put any number in
16 there in terms of time and say we don't have the
17 information or leave it totally --

18 DR. PARISI; I think you ought to put
19 what's being done, but with the caveat showing the
20 data so that people can make a decision whether they
21 want to go longer or perhaps not. I suspect, by the
22 time this is out in general use, there will be more

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1 data, and this would keep people into getting that
2 data to find out how long.

3 So I wouldn't want to use nothing there,
4 because I think patients will get into trouble.

5 CHAIRPERSON CURTIS: Right. So it sounds
6 then that the warning probably should be revised to
7 include some of the information that's available about
8 the raw numbers about late thrombosis and that at this
9 point we don't know what the optimal length of
10 antiplatelet therapy is, but that we know it has to be
11 some minimal length of time; because otherwise we know
12 that patients do get into trouble.

13 DR. TRACY: Can we really ask them to
14 refer to data that's not contained in this packet,
15 though? I mean, that's data that's from trials that
16 are not included here or follow-up that's not really
17 included in this data.

18 Maybe we don't really need them to
19 specifically include data, but just to say that
20 further studies are -- whatever -- warranted or
21 ongoing. But I don't think you can ask them to refer
22 to information that is not available to us as we're

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1 making this decision. I think the answer is we don't
2 have the information, but we think it's a more
3 extended period of time, but we don't know exactly
4 what that is.

5 CHAIRPERSON CURTIS: Well, I think what we
6 know from the data we have here is that eight weeks
7 wasn't enough.

8 DR. TRACY: Right.

9 CHAIRPERSON CURTIS: That you've got in
10 the data in front of us. So I think that could be
11 stated clearly, and that -- and I don't know what we
12 can say about developing endothelialization of new
13 stents. If we know anything there at that point, it's
14 just -- I mean, that's what we're trying to do, is
15 cover the period of time until there is endothelium
16 covering the stent and we think we're safe. So it's
17 about all, I think, we could say. But we know eight
18 weeks is too short. It's got to be longer than that.

19 DR. HARTZ: How do we know that?

20 CHAIRPERSON CURTIS: Because in -- I can't
21 remember which one it was now. Was it GAMMA I had the
22 eight weeks?

1 DR. HARTZ: But that infers that we know
2 the mechanism. If something is not endothelialized in
3 six weeks, it's not going to ever endothelialize
4 probably. Right? There's no other branch of vascular
5 medicine or intervention where something isn't
6 endothelialized in six weeks.

7 I mean, I understand your point that maybe
8 there are still closures, but we can't say that they
9 are due to non-endothelialization.

10 DR. PARISI: On page 563B, Section 5, I
11 think you do have the late thrombosis for 374
12 patients. The way I read this table is at least at
13 three months you've got an effective sample size of
14 close to 200 patients treated --or 195 treated in
15 accordance with the recommendations, and there is no
16 late thrombosis.

17 So something positive is happening.
18 Whether it's through investigator behavior and not
19 using stents or whether it's through use of
20 antiplatelet agents, I think something positive is
21 happening in this table. "

22 CHAIRPERSON CURTIS: Any other comments on

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1 this point? Yes?

2 MR. DILLARD: Jim Dillard. One just real
3 quick question, which is: It's on the part of every
4 attempt should be made to avoid new stent placement in
5 the irradiated area. One of the things we struggle
6 with is the difference between a warning and a
7 contraindication.

8 I know you've had extensive discussion
9 about that particular area of the data, but I was just
10 curious whether or not you would touch on whether or
11 not you think the data is strong enough to be a
12 contraindication at this point or should it remain a
13 warning?

14 DR. DOMANSKI: I think it may depend on
15 the results you're having, though, in the cath lab is
16 the problem. I mean, if you really thought you have
17 a lousy result and you really wanted to stent the
18 thing, you know, I hate to saddle somebody with
19 something that's a contraindication. I mean, one's
20 enthusiasm would have to be fairly low for stenting
21 it, but if you got into trouble, you have a decent
22 result.

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1 CHAIRPERSON CURTIS: Plus, think there's
2 an incidence of thrombosis, but it's not, you know, 90
3 percent. It's not something that's -- You know, it's
4 low. So you're just increasing the risk that that's
5 going to happen. So I would agree with keeping it as
6 a warning.

7 MR. DILLARD: Thank you.

8 CHAIRPERSON CURTIS: Number 6: I'll just
9 read the question and see if I can get through it with
10 that: Please discuss whether you believe the probable
11 clinical benefit of the radiation treatment (that is,
12 reduction in TLR) outweighs the probable risks of
13 death, MI, late total occlusion, late stent
14 thrombosis, and edge effect posed by the device in the
15 intended patient population.

16 I think this gets really heavily into the
17 discussions we were having this morning about risk
18 versus benefit and how much, you know, death plus MI
19 balances out against target lesion revascularization.
20 This is risk versus benefit and gets to the heart of
21 safety and efficacy. So if anybody wants to make any
22 comments. Jim?

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1 MR. DILLARD: I might clarify one thing.
2 Jim Dillard.

3 If nobody noticed this, this is the safety
4 question disguised in your particular situation. So
5 just so that everybody knows what they are trying to
6 talk about here, that this is what we think of as
7 safety, as the half of the equation of safety and
8 effectiveness. So everybody think about answering
9 that question there.

10 DR. DOMANSKI: Well, the reason that I was
11 going to -- and I don't know that I'm going to be here
12 because of the way time is going, but the reason that
13 I was ultimately going to move to approve this PMA is
14 because I think that this question is answered as well
15 as it's going to be answered in the near term.

16 You have an entity that is significant
17 clinically for which there is no other treatment, for
18 which this treatment is indeed effective, and solid
19 evidence with a mechanism at least that's reasonable
20 postulated that gets around the particular
21 complication that worries us.

22 Whether there's a mine waiting in a

1 pathway in this forest somewhere down the pike, I
2 don't know, but the time necessary to find that would
3 be very long, and it would keep this thing off the
4 market.

5 Secondly, I think we're going to find that
6 in the post-market surveillance anyway. So I think
7 that the answer to this question is clear.

8 CHAIRPERSON CURTIS: Other comments? It
9 just seems too easy. I think we've had a good
10 discussion about a lot of this. You know, the problem
11 of death is that you would have to have thousands of
12 patients to really know clearly a difference.

13 MACE is a commonly looked at endpoint in
14 these trials. There was a clear difference there. I
15 think the thing that probably bothers everybody at
16 least a little bit -- I mean, the deaths are so small,
17 and the details -- I don't think you can make much of
18 them. But it's just a little bit bothersome to me
19 that you would have more MIs, yet less restenosis and
20 target lesion problems in the radiation group, but yet
21 again the number of MIs was ^{**}small and the number of --
22 the TLRs was much greater.

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1 So I think overall, when you put the whole
2 thing together, I think the probable clinical benefit
3 does go toward the radiation therapy, and I agree with
4 you.

5 All right, product labeling, question 7:
6 Please comment on the INDICATIONS FOR USE section as
7 to whether they identify the appropriate patient
8 population for treatment with the device.

9 Can anybody quickly tell me where that is
10 in this packet for us to look at?

11 MR. DILLARD: Part 2(a) and 2(b) under the
12 Labeling. Should be in Volume I, page 5 and Section
13 Two. Should be the second page under instructions for
14 use. Looks like Section 2, page 005, at the bottom.

15 CHAIRPERSON CURTIS: If everybody has read
16 that, does anybody have any comments on the proposed
17 indications? It's for native coronary arteries only,
18 which I think we would all agree with.

19 DR. TRACY: You know, that's -- I am
20 curious what happened to the stents in the saphenous
21 vein grafts. They just disappeared as the data got
22 pooled. I mean, I think, based on the data that we

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1 have, I agree that this is an appropriate indication,
2 but somewhere a bunch of people got lost that we
3 really didn't talk about today. It's just curious.

4 CHAIRPERSON CURTIS: I think the reading
5 of the indications is a little bit unclear to me,
6 because it says the system is for use in the treatment
7 of native coronary arteries -- that's fine -- with in-
8 stent restenosis -- that's fine -- following
9 percutaneous revascularization using current
10 interventional techniques and/or coronary stenting
11 with approved stents.

12 So I guess what's trying to be said is
13 that the patient already had a stent, and now they
14 either get balloon angioplasty or rotational
15 atherectomy or whatever to try to open that up again
16 and/or another stent. And you're using this radiation
17 therapy to prevent restenosis.

18 DR. TRACY: Does that mean -- That is a
19 little confusing. Does that mean that they can put in
20 a stent in the place where they're irradiating?

21 CHAIRPERSON CURTIS: Yes.

22 DR. TRACY: Then that's different from

1 what the warning indicated, and that should be, I
2 would think, reworded somehow or another.

3 DR. PARISI: You would just try to avoid
4 that, if you can, but if you think in the end it's the
5 only way to bail a patient out, you're going to go for
6 it. I think it's pretty clear.

7 CHAIRPERSON CURTIS: So you're happy with
8 that?

9 DR. PARISI: I'm happy with that, the way
10 it is. As long as it's native vessels and -- You
11 know, the next section has the warning.

12 DR. TRACY: I don't like the idea of
13 having it stated as a warning in one place and having
14 it stated glibly as part of the indication. I read
15 right through that and thought that that meant that
16 that had previously been done. But as you pointed out
17 to me, that is an indication, which we then
18 subsequently warn against doing. That's kind of
19 illogical, to me.

20 CHAIRPERSON CURTIS: What about if that
21 sentence just ends after "following percutaneous
22 revascularization using current interventional

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1 techniques" period? It doesn't say you can't stent,
2 but it doesn't include that in there. I think it
3 would be a little bit less confusing. So I would
4 suggest doing that.

5 Next question: Please comment on the
6 CONTRAINDICATIONS section as to whether it identifies
7 all conditions under which the device should not be
8 used because the risk of use clearly outweighs any
9 possible benefit.

10 That starts right at the bottom of that
11 page.

12 MR. DILLARD: And ends there.

13 CHAIRPERSON CURTIS: And ends there, yes.
14 So the only contraindication currently is patients in
15 whom antiplatelet and/or anticoagulate therapy is
16 contraindicated. Are we missing anything that's
17 important?

18 DR. MEHTA: I have a question about
19 radiation and use to vaso-occlusive cardiac disease.
20 Should that be a contraindication? Suppose somebody
21 has had strong radiation to the heart. Is that a
22 specific contraindication?

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1 DR. GRIEM: I think there are some
2 contraindications here. Do not use in a patient who
3 is pregnant. Okay? Do not use in ataxia T-line
4 jactitation, because it's very sensitive to radiation.

5 CHAIRPERSON CURTIS: Well, should any of
6 those be contraindications instead of warnings? I
7 guess that's the real question.

8 DR. MEHTA: Take the same story he was
9 talking about, the Hodgkin's lymphoma adolescent who
10 at age 35 gets an MI, now has a stent. Should we be
11 giving them intracoronary radiation?

12 DR. HARTZ: Not used in patients who
13 underwent previous radiation in the immediate vicinity
14 of the thorax.

15 DR. GRIEM: Yes, that's the one up above
16 that which is also stated.

17 DR. MEHTA: My question is should that be
18 a specific contraindication rather than a warning?

19 CHAIRPERSON CURTIS: Because what you're
20 saying is slightly different. You're saying the
21 patient has radiation induced cardiac disease. This
22 warning says anybody who has had radiation to the

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1 thorax.

2 DR. WILSON: But I disagree with that,
3 Madam Chairwoman, because thorax is too general.
4 Immediate vicinity is fine, but thorax -- The patient
5 could have had radiation therapy to the thorax for a
6 mesothelioma far out on the pleura, which would have
7 no implications for this therapy whatsoever.

8 So I think this sentence could stop at the
9 word "vicinity" or "previous radiation treatment in
10 the immediate vicinity" period, or "immediate vicinity
11 of the intravascular brachytherapy target." But
12 radiation of the thorax -- The thorax is a pretty big
13 part of the anatomy, and most of it is well away from
14 this area of interest.

15 CHAIRPERSON CURTIS: All right. So I see
16 what you're saying. So you're saying that the warning
17 does not need to be as broad as radiation of the
18 thorax. It just should be radiation in the immediate
19 vicinity of the target vessel.

20 DR. WILSON: Right.

21 CHAIRPERSON CURTIS: But the other comment
22 about radiation induced cardiac disease -- I think

1 that's true. I don't think you would want to do --

2 DR. MEHTA: That could be handled by this
3 definition, though.

4 CHAIRPERSON CURTIS: It would be?

5 DR. MEHTA: Yes.

6 DR. TRACY: Just out of curiosity, why are
7 some of these "do not use" is in the warnings as
8 opposed to in the contraindications?

9 CHAIRPERSON CURTIS: Well, if they should
10 be contraindications, we need to say so.

11 DR. TRACY: They seem more logical as
12 contraindications, and the other things, the warnings
13 like verify source of location seems more like an
14 appropriate thing to warn people about. I don't know
15 if it's maybe a problem of semantics, but I would
16 shift the things like "do not use in patients who
17 underwent previous intravascular brachytherapy,"
18 pregnant patients and so on -- I would move that over
19 to the contraindication section, just have the
20 warnings as the more --

21 CHAIRPERSON CURTIS: Well, to me, a
22 contraindication means you never do it, that there's

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1 an absolute reason not to do it. I mean, if you can't
2 give somebody antiplatelet therapy and we know that
3 there's a problem with late thrombosis, that's not
4 going to make any sense. It's not going to help them.

5 Would you never, ever use this in a
6 pregnant patient? You wouldn't want to, but what if
7 you had a pregnant diabetic who had had, you know,
8 previous stent and is having rest angina and, you
9 know, has got a few months to go? I mean, you
10 wouldn't want to do it, but if you got really pushed,
11 you could do it.

12 DR. BAILEY: Shouldn't it be reworded then
13 so that it's not -- It sounds like an absolute, the
14 way it's worded: Do not use.

15 CHAIRPERSON CURTIS: Yes. It's just that
16 that's what warnings are. That's what warnings are.
17 It's you shouldn't do it, but it's not exactly
18 contraindicated. There is a difference there.

19 I think contraindications do have to be
20 limited to things where, you know, it's absolutely
21 wrong to do it in all cases^{**}.

22 MR. DILLARD: Yes. Dr. Curtis, thank you.

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1 One of the things maybe that will just help streamline
2 this section is that perhaps focusing on those major
3 issues that you see might not be in a particular
4 section, which might be helpful more so than having a
5 lengthy discussion about whether or not it should or
6 shouldn't be a contraindication or a warning.

7 Some of those are semantics. Some of them
8 we have definitions on. I think it would be most
9 important to focus on any issue that you think is
10 glaringly not in a section or is in a section and
11 shouldn't be, and you might give us some
12 recommendations. But I wouldn't spend anymore time on
13 it than that.

14 CHAIRPERSON CURTIS: Okay. Well, and
15 given that, we've been looking at the warnings. The
16 precautions are also being asked if we could just
17 review those and see are we missing anything
18 important. I can't think of anything else. Does
19 anyone else have any?

20 DR. WILSON: Not to editorialize, Madam
21 Chairwoman, but in the third bullet under
22 contraindications genetic radiation sensitivity

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1 disorders, I think that should say known genetic
2 radiation sensitivity disorders; because these are
3 exceedingly rare and difficult to identify. In fact,
4 they are seldom detected.

5 This might suggest that patients should be
6 tested in advance for these disorders, and it would
7 create a devil of a problem if people start to think
8 they had to do that.

9 CHAIRPERSON CURTIS: Point well taken.
10 Another one of the questions in this same section
11 here: Please comment on the remainder of the product
12 labeling as to whether it adequately describes how the
13 product should be used to maximize benefits and
14 minimize adverse events.

15 Do we have any other recommendations
16 regarding the labeling of the device?

17 So are there any other comments about
18 that? Is there any specific area here the FDA has a
19 concern about, if you could raise it?

20 MR. DILLARD: No, not at this time.s

21 DR. TRACY: ^{**}Dr. Curtis, the team that is
22 described in the presentation involves physicists --

1 A whole slew of people are involved in doing a lot of
2 calculations, etcetera.

3 This is -- and including IVUS. This
4 limits this to a fairly small number of centers, I
5 would think, that would have a physicist or, you know,
6 radiation oncologist, interventionalist, somebody with
7 an IVUS. That is really -- Maybe it will come up
8 under the appropriate training for the physicians, and
9 probably we may discuss it at that area. But I don't
10 know whether we should mention it somewhere in the
11 general precautions.

12 I'm not sure. I'm not sure that all of
13 these people are needed, since we haven't really
14 established what the appropriate dose of radiation is
15 and how critical it is to make all these various
16 calculations that have been made in this protocol.
17 I'm not sure that it's mandatory, but there is an
18 absence of any mention of it in the precautions here.
19 I don't know what to do about that, but it's notable.

20 CHAIRPERSON CURTIS: Okay. Well, we
21 obviously do have to have ^{**}adequate training for this.
22 I think there was some comments made by them. Maybe

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1 it may need to be strengthened.

2 Let's move on to the training program
3 aspect of it: Please discuss what important elements
4 should be contained in the physicians' training
5 program for this product.

6 Talking about the need for collaboration
7 between a cardiologist, radiation oncologist and
8 radiation physicist -- I mean, I do have a real
9 concern, too. The numbers we got about doses and what
10 happens if you don't do the IVUS properly, what
11 happens if you miscalculate the dose you need, what
12 happens if you get a real outlier in terms of too
13 much/too little, and if people don't know what they're
14 doing here, there is a real potential for harm.

15 DR. DOMANSKI: But isn't -- Obviously,
16 training is critically important, but isn't this
17 question sort of vanilla? I mean, clearly, they need
18 to understand the -- people need to understand the
19 indications. They need to understand the technique.
20 They need to understand the likely complications and
21 how to handle them, and that should be handled in some
22 sort of a training course, much like the ones that

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1 have been generated over the years for many of these
2 devices.

3 I mean, I'm not sure what the FDA is
4 specifically asking that's really different here.

5 MR. DILLARD: Jim Dillard. One of the
6 questions and one of the things we, obviously, have a
7 regulatory authority over in terms of pre-market
8 approval applications are labeling and training. One
9 of the issues that concerns us is when a clinical
10 protocol necessitates quite a bit of high level and
11 differentiated involvement in terms of the clinicians.

12 What message do we send to the company in
13 terms of a training program about who needs to be
14 trained and how much of the training that we might
15 have learned from the clinical study do we need to
16 pass on to those people who are then going to utilize
17 it, I think, in regular clinical practice?

18 I think sometimes it's an uncomfortable
19 position to be in to say how much of what we learned
20 from the clinical study actually needs to be passed on
21 to the day to day clinical situation, and what's
22 important from that study to pass on.

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1 So I think it's a generic comment. And
2 while I think there are some vanilla issues that go
3 along with it, which I agree with you on, we are
4 looking for some potential specifics here about how
5 much of that knowledge that we have from the
6 individual physicians here needs to be passed on for
7 successful clinical usage.

8 DR. WILSON: I would like to respond to
9 that. I think that from the radiological standpoint,
10 once the intervention by the cardiologist is
11 performed, what you're actually dealing with is an
12 intraoperative temporary, interstitial or interluminal
13 brachytherapy implant using a high dose rate source.

14 I think that that requires the involvement
15 of a qualified source handler as defined in our C-
16 Code, Part 35. So I think that that should be the
17 training requirement for some elements of the multi-
18 disciplinary team.

19 If I could continue, I think that the
20 steps in this multi-step treatment delivery process
21 that's been defined -- As I said, first of all,
22 there's t he intervention to open the vessel. Then

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1 there is the phase of the radiation dose planning.
2 That's a joint responsibility between the
3 cardiologist, the medical physicist, and the radiation
4 oncologist.

5 Then there is the actual dose computation.
6 That's done by the medical physicist, supervised by
7 the radiation oncologist. Then there's the actual
8 radiation administration procedure. That, as I've
9 heard it, is to be done by the radiation oncologist,
10 assisted by the medical physicist.

11 Then, of course, you have the safety, the
12 radiation safety issues that control the source
13 handling and the monitoring for radioactivity in the
14 area once the procedure is completed, and then there
15 is the long term need for surveillance and
16 interpretation of the long term results that come out
17 of the procedure, which largely are going to fall into
18 the precinct of the radiation oncologist, I would
19 submit.

20 It seems to me that what the sponsors have
21 said repeatedly is that this procedure in the
22 experience that is recorded in these books to date has

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1 been provided by that multi-disciplinary team that I
2 just outlined.

3 In fact, I think that where this has being
4 done throughout the country at this time, there is
5 such a multi-disciplinary team that is actively
6 providing it. I don't know of any other context in
7 which this kind of methodology is being provided.

8 I think there is no difference here
9 between the use and provision of interstitial
10 temporary brachytherapy compared to the way the team
11 works with regard to gynecological implants for cervix
12 cancer, for prostate cancer with urologists and
13 others, for brain tumors with neurosurgeons, and so
14 on. So I would see no reason to depart from that
15 particular multi-disciplinary framework.

16 I thought it was remarkable that they
17 mentioned -- The number varied. It was either 630 or
18 1,000 cases to date that have been treated with this
19 methodology, and there wasn't a single misadventure or
20 misadministration reported to the NRC. I think that's
21 an outstanding record and a tribute to the multi-
22 disciplinary context in which this has been provided

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1 here to date.

2 There was no technical failure, and I
3 think that is also a consequence of the multi-
4 disciplinary expertise being brought to bear in the
5 operation of the device in almost 1,000 cases.

6 CHAIRPERSON CURTIS: Over here?

7 DR. MEHTA: I think I would like to echo
8 what Dr. Wilson is saying, because he's clearly
9 pointed out that we have had some dramatically
10 successful application of this product without any
11 hazardous events.

12 We need to recognize that this is
13 hazardous material, and that's why this morning we
14 asked for the definition of safety. Is safety limited
15 to patients? And we believe it's not. It expands
16 beyond the patient.

17 It expands to the physicians, the people
18 in the interventional cardiologist suite, the hospital
19 personnel, the rooms where this source is going to be
20 traveling in the hospital, and therefore, it needs to
21 be addressed according to the NRC regulations for
22 which there are many other successful models.

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1 DR. AYRES: Yes. I guess if I could make
2 a comment -- I agree, this trial worked out very well,
3 but there have been misadventures, just not in this
4 one.

5 I guess to really properly answer this
6 question kind of depends on where we end up, because
7 we do determine who is authorized and who is not to
8 handle these sources. Right now we're working very
9 well with FDA, and it is the team that you see here.
10 We, in fact, specify that the radiation oncologist and
11 the radiation physicist be part of this during the
12 human trials phase.

13 I can only speculate and say I think that
14 is going to continue, but I can't say for certain at
15 this point.

16 DR. HARTZ: Just a generic question: Do
17 all cardiology fellowships include a didactic physics
18 portion? So there may be some cardiologists who come
19 out who don't know anything about the physics of this?

20 CHAIRPERSON CURTIS: That's true. And I
21 would presume that, in terms of handling these types
22 of radioisotopes, you would have to have somebody who

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1 is licensed.

2 DR. WILSON: Currently, it's inexorably
3 linked to having completed an ACGME approved training
4 program in radiation oncology to be a qualified source
5 handler.

6 CHAIRPERSON CURTIS: So that would mean to
7 us that we don't have to be concerned in the future
8 that a cardiologist will say I've done 100 of these,
9 and I don't have to worry about it anymore; I can do
10 it myself.

11 DR. WILSON: Well, as our colleagues say
12 that the matter is under review is my understanding,
13 and the ACMUI has, in fact, voted -- but it's only an
14 advisory body -- has voted to advise the NRC that,
15 with regard to high dose rate brachytherapy
16 procedures, which this is, that that training and
17 experience framework not change.

18 I think it was suggested that that may not
19 be where the NRC will end up, and I wouldn't want to
20 speculate.

21 DR. AYRES: I believe -- We haven't made
22 the final call. So I can't give an official position

1 on it, but as the one who takes the first cut at it,
2 that's the direction I intend to go.

3 There are other issues, though, such as
4 perhaps the ion implanted stents where the radiation
5 safety issues are a lot less. We might go a different
6 direction, but that's not before this panel, and I'm
7 not sure it will be, and we'll deal with that when it
8 comes. But high dose rate is certainly a significant
9 safety concern to NRC, and the controls of the
10 training and experience requirements will probably be
11 maintained at a pretty high level, and it is board
12 certification or training and experience that is
13 essentially equivalent in radiation oncology to get
14 that authorization.

15 CHAIRPERSON CURTIS: I would also presume
16 that not every interventional cardiologist is an
17 expert at IVUS. Right? And if you don't know how to
18 do intravascular ultrasound very well or you're not
19 experienced at it, and you don't make the measurements
20 correctly, there are going to be incorrect
21 calculations there, too. **

22 So I think in any kind of a training

1 program, you've got to address that issue. It's just
2 not enough to have a radiation oncologist or physicist
3 available who can help deliver the materials, but you
4 have to be able to do that.

5 So if you have some centers who want to
6 get into this and are not familiar with IVUS, there
7 has to be some training or some experience with that.

8 DR. TRACY: Not every study that was
9 involved in this had IVUS as part of the defining
10 mechanism for determining the dose. There was at
11 least one segment of patients that simply got a dose.

12 Now I think that -- That was the SCRIPPS,
13 yes. I think that -- WRIST, I'm sorry. I think,
14 though, that we certainly need somebody certified in
15 handling the materials, but I still have questions,
16 because we don't know what the appropriate dose is,
17 how much we can prescribe to any given center, that
18 you must have IVUS, you must measure, you must have
19 the physicist calculate this. Then you have to have
20 the radiation oncologist come in. Then you have to
21 have the cardiologist delivering this thing.

22 I just don't know that that's practical

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1 nor that the entire data that we've seen here really
2 supports that complicated scenario that we're talking
3 about here. I don't know.

4 I personally don't think that it does
5 support that, because it seems to be a tremendous
6 degree of overlap in the dosages. I'm not sure
7 exactly what the dosing indication is going to be, or
8 the recommending dosage is going to be in this thing.
9 But there's a tremendous overlap.

10 CHAIRPERSON CURTIS: GAMMA I was tailored.
11 Right?

12 DR. TRACY: Yes, GAMMA I was tailored, but
13 is that necessary?

14 CHAIRPERSON CURTIS: That was, as the
15 sponsor said, the pivotal study. So I think, you
16 know, that point is very well taken. I think it would
17 be hard at this point to say, well, the IVUS really --
18 it's very complicated, don't need to do it. I mean,
19 I think that's what -- The main study that was done
20 used IVUS and calculated the dose on that basis.

21 I think, if you're going to say that's not
22 necessary, there are simpler ways to do it, that will

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1 have to be demonstrated, I would think, at this point.

2 DR. MEHTA: I think one other issue that's
3 important is that, as the use of radiation sources
4 stands currently, especially high dosage brachytherapy
5 sources, the NRC rules require that you have a
6 prescription, which means you have to have an a priori
7 dose, which means you need to be able to calculate it,
8 which means you need to be able to verify that you
9 delivered it.

10 So it doesn't matter what dose you choose,
11 you need to be able to calculate it, and you need to
12 be able to deliver it. So we can't escape from that
13 reality.

14 CHAIRPERSON CURTIS: All right. Let's
15 move on to Number 9, post-market evaluation.

16 Based on the literature, do you believe
17 that additional clinical follow-up is necessary to
18 evaluate the chronic effects of intravascular
19 radiation administration? If so, how long should
20 patients be followed, and what endpoints and adverse
21 events should be measured?

22 DR. WILSON: My bias is that patients will

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1 have to be followed for a long period of time. We
2 heard a lot about the cardiac consequences of
3 mediastinal radiation for lymphoma and Hodgkin's
4 disease, but I thought a better example to consider
5 was the example of post-mastectomy radiation therapy
6 to the left side of the chest where a strip about six
7 centimeters wide along the parasternal area was
8 irradiated in many prospective randomized trials.

9 Actually, in those studies, particularly
10 the one from Scandinavia that is frequently cited with
11 Rutchrist and is still being studied, at five years
12 post-treatment there was actually survival advantage
13 from the post-mastectomy radiotherapy in patients
14 treated in that manner, but by ten years there was
15 emerging a late cardiac mortality related to the
16 irradiation, mostly consequential to vascular effects
17 which are still being seen and unfolding two decades
18 later.

19 So my bias is that it's going to take a
20 long period of time when you're using -- and that's
21 with fractionated radiotherapy 60 Gy in a month or six
22 weeks compared to 30 Gy given in one fraction over 20

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1 minutes, which is biologically a very large dose.

2 I think it's going to take years, perhaps
3 decades -- hopefully, the patients will live that long
4 -- to be able to manifest that, given their severe
5 state of illness. But I think it will take a long
6 time that, I would say, has to be measured in years.

7 CHAIRPERSON CURTIS: Other comments? And
8 if we're going to measure it in years, what endpoints?
9 What are we looking at? Do the patients need to have
10 repeat angiography at certain defined points in time?

11 DR. WILSON: I think there could be
12 clinical endpoints, but I'd say five years at a
13 minimum would be --

14 DR. MEHTA: I would add to that to say
15 that maybe an angiographic endpoint should also be
16 included, because these are patients that have cardiac
17 events that may or may not be related directly to the
18 particular lesion that was irradiated.

19 So if somebody just has an MI, did they
20 have an MI because it is that particular arterial
21 segment that was involved or was it some other
22 arterial segment? So I think it should be a

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1 combination of angiographic and clinical endpoints.

2 DR. HARTZ: I want to know what you are
3 all referring to as clinical events, because I want to
4 know if there's ischemia, where it is and what
5 function it is. Do we really need an angiogram except
6 maybe one long term for completion of this study to
7 exit the study, when we can get all this information
8 in other ways?

9 I did not -- I keep seeing this illusion
10 to three-year follow-up. What is a three-year follow-
11 up? What are the clinical endpoints? They're not
12 discussed. So are they Echoes? Are they stress
13 tests? What are they?

14 I think it's very, very important that we
15 have something built into this study that tells us
16 what myocardial function and ischemic burden are, and
17 yearly, at least yearly.

18 DR. GRIEM: What is the most benign tests
19 that you might look at the heart with, and it's
20 probably ultrasound.

21 DR. HARTZ: Yes, plain old ultrasound will
22 give you just function. Stress echo would give you

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1 function and ischemia.

2 DR. GRIEM: But I think that's less of a
3 problem, say, than doing an MRI or a spiral CT. You
4 know, you can get up into megabucks of tests and so
5 forth, and what is the cost effective way of
6 evaluating the heart? This isn't my field.

7 DR. HARTZ: Since these patients all have
8 coronary disease anyway, they should be having these
9 tests on a routine basis, and that's why I'm wondering
10 how often one really needs to do angiography in these
11 patients, if all these tests come up fine. This is a
12 part of the routine follow-up of this group of
13 patients.

14 DR. GRIEM: And can MRI and the case base
15 do this sort of information without angiogram?

16 DR. HARTZ: I don't know. I have to ask
17 Dr. Curtis and the other cardiologists, because I
18 don't know much about cardiac MRI.

19 CHAIRPERSON CURTIS: It's not going to
20 give you functional information. So I wouldn't think
21 we would normally be looking at that.

22 DR. SIMMONS: You could do a dibutamine

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1 MRI which costs about the same amount money as a
2 stress echo, and you get function. You might get some
3 added information. Certainly, the recent stuff has
4 shown that you can actually see proximal coronary
5 arteries. So you might actually get some information
6 on calcium, things like that.

7 I mean, you could do -- With the stent,
8 you could do a dibutamine MRI, couldn't you?

9 CHAIRPERSON CURTIS: Sure. One of the
10 problems is the further you get out -- You know, these
11 patients usually don't have single vessel disease. If
12 you're looking at what's the rate of MIs five years
13 out, I mean, it could be a different vessel, and
14 that's not necessarily going to tell you anything.

15 Same thing, they've got coronary artery
16 disease. The death rates far out may not be that
17 meaningful. What do we really -- You know, if you're
18 talking about long term follow-up, what do you really
19 want to know? You want to know if anything bad is
20 happening to that vessel that got worked on and/or the
21 muscle that that supplies. I think that's really what
22 it gets down to.

1 So possibly a stress echo, you know, some
2 sort of a stress evaluation where it also gives you
3 the wall motion in that distribution laid out might be
4 the most important information.

5 DR. TRACY: But the problem is that what
6 are you comparing it against. You have a group of
7 people who are in the -- currently in the non-treated
8 group who also have the same type of risks for future
9 events, such as progressive coronary disease, future
10 infarction, depressed ejection fraction and so on and
11 so forth.

12 I'm not sure that in isolation you're
13 going to be able to analyze any information that
14 you're collecting on people. I think you should be
15 collecting clinical information, but to go on a hunt,
16 you know, saying let's get a bunch of tests that
17 probably are clinically indicated in the future but to
18 sort of mandate that they be done without having
19 something to compare it against doesn't seem
20 particularly useful to me.

21 Either we're going to say follow everybody
22 who's been enrolled for the next ten years and see

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1 what happens or we're going to say follow these people
2 on a clinical basis and do studies as indicated
3 clinically, which will probably, hopefully, pick up
4 anything that we're not thinking about at this point
5 in time.

6 I just don't know what to compare it
7 against.

8 CHAIRPERSON CURTIS: Well, and certainly,
9 the placebo group -- I mean, if this comes on the
10 market and you've got people that have got stenosis,
11 they're going to go right in and get radiation therapy
12 themselves. You can lose the comparison group that
13 you had originally.

14 DR. TRACY: Right.

15 CHAIRPERSON CURTIS: Did you have a
16 comment?

17 DR. WILSON: I was only going to say that
18 I agree with the comments made by both of you. As was
19 pointed out, the dose drops off dramatically away from
20 the source itself. So that one would expect few, if
21 any, detectable biological consequences beyond the
22 adventitia of the vessel.

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1 So my thoughts were, if there are to be
2 late radiation consequences, it is pertinent just to
3 the irradiated segment of that vessel, and I was
4 thinking about the structural integrity of that
5 vessel, possibility of aneurysms, loss of -- rupture,
6 something at that immediate site.

7 I would agree that clinical follow-up with
8 investigation as needed will uncover those biological
9 -- late biological consequences, if they are there.

10 CHAIRPERSON CURTIS: Would there be any
11 value to, say, trying to get angiograms in a group of
12 patients three years out, something like that?

13 DR. WILSON: I'd have to punt that back to
14 the cardiologists to answer that. I don't know.

15 DR. PARISI: I think these patients don't
16 go away. They come back for particularly coronary
17 angiograms, because there are other events that occur.
18 This is a part of a process that we only palliate, and
19 they will be back for another angiogram.

20 I bet you, 80 percent of these patients
21 will be back for another angiogram in five to ten
22 years, and I think we should focus on the segment

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1 that's been treated and see what happens in that area.

2 I guess the other issue I would raise,
3 though, is what about lung cancer or other kinds of
4 tumors that might arise in the chest? Those, I think,
5 should be logged and whether they are out of
6 proportion to what you might expect. That would,
7 obviously, occur on a clinical basis.

8 CHAIRPERSON CURTIS: Then it sounds like
9 you're proposing some sort of clinical follow-up of
10 the patients who have been in the trial, and not
11 asking for a routine angiogram at a point in time, but
12 that any patient who has an angiogram that the data be
13 reviewed at that segment.

14 DR. BAILEY: Another consideration is
15 whether, if you tried to undergo a routine angiogram,
16 how many you would actually be able to get back. I'm
17 also questioning the value of the routine angiogram,
18 just because how many are you going to actually get,
19 and who is going to be missing.

20 These patients will have all sorts of
21 different treatments. You know, you have
22 revascularization occurring. So you know, I think

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1 other than following them up clinically, I'm not sure
2 that you would be able to interpret the angiographic
3 data. You know, maybe a subset, a sample, to look at
4 something specific, but I think if it doesn't show up
5 clinically, I'm not sure you're going to get any other
6 insight from an angiographic -- routine angiographic
7 follow-up.

8 CHAIRPERSON CURTIS: Well, the only other
9 problem I see with an approach that says, if you get
10 an angiogram, would you please send me a copy -- it's
11 not very formalized, and you may not get a lot back.

12 DR. HARTZ: Using the reasoning that's
13 been used several times today about the fact that
14 practice patterns have changed, in 1995 had stress
15 echo been more commonly used, most likely it would
16 have been included as a baseline for this study, and
17 most patients probably now get that or some good form
18 of stress testing.

19 I would think that all patients entering
20 now, that should be mandated, that there's some form
21 of good measure of structure and function going into
22 this study that can be repeated when there's a

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1 suspicion of ischemia.

2 CHAIRPERSON CURTIS: I don't know if
3 that's always true. I mean, there are plenty of times
4 where we have people who have classic symptoms, and we
5 don't get functional tests on everybody. If you've
6 got a good pre-test probability of coronary disease,
7 we go and do an angiogram.

8 DR. HARTZ: I don't -- So you are thinking
9 that these patients can be followed -- I mean, I think
10 it's a wonderful baseline. It's a wonderful baseline,
11 especially because they are going to be registered
12 patients, and frequently we have false negatives.

13 CHAIRPERSON CURTIS: Even on angio.

14 DR. HARTZ: But that's just an opinion.

15 CHAIRPERSON CURTIS: Well, I think I'd
16 like to leave with some consensus here as to what we
17 think would be appropriate as a post-market
18 evaluation. Does anybody want to sum it up or just
19 kind of lay something out on the table that would be
20 appropriate? Any of our interventionalists?

21 DR. PARISI: Well, I think if there is an
22 angiogram, we ought to have a specific evaluation of

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1 the area previously irradiated.

2 CHAIRPERSON CURTIS: Would you take, say,
3 the GAMMA I patients who have already been studied,
4 that group, a new study?

5 DR. SIMMONS: Well, they already proposed
6 something. I guess we weren't supposed to see it or
7 not. I mean, they actually had a 650 patient database
8 that they were going to be willing to follow for five
9 to ten years, and then collect all the data, including
10 any angiograms. So that would include the patients
11 from the SCRIPPS and the GAMMA I, II, III, IV, V and--

12 CHAIRPERSON CURTIS: I think, if those
13 patients were followed clinically and you knew what
14 the angiographic appearance was of the vessels that
15 were targeted when angiograms were done, that would
16 probably give you the information that was important.

17 DR. SIMMONS: But 650 patients followed
18 for five or ten years --

19 CHAIRPERSON CURTIS: That should be
20 adequate.

21 MR. DILLARD: ^{**} Jim Dillard. Can I ask for
22 one clarification, which is: While I think it was a

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