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on the Medical Uses of Isotopes

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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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TELECONFERENCE

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TUESDAY, JUNE 18, 2013

The meeting convened telephonically at 2:00 p.m., Milton Guiberteau, M.D., ACMUI Vice Chairman, presiding.

MEMBERS PRESENT:

MILTON J. GUIBERTEAU, M.D., Vice Chairman

SUSAN M. LANGHORST, Ph.D., Radiation Safety Officer

STEVEN MATTMULLER, Nuclear Pharmacist

CHRISTOPHER J. PALESTRO, M.D., Nuclear Medicine Physician

ORHAN H.SULEIMAN, Ph.D., FDA Representative

WILLIAM A. VAN DECKER, M.D., Nuclear Cardiologist

LAURA M. WEIL, Patients' Rights Advocate

JAMES S. WELSH, M.D., Radiation Oncologist

PAT B. ZANZONICO, Ph.D., Nuclear Medicine

Physicist

JARED THOMPSON, Stand-in Agreement State Representative (non-voting)

MEMBERS NOT PRESENT:

JOHN H. SUH, M.D., Radiation Oncologist

BRUCE R. THOMADSEN, Ph.D., Chairman

NRC HEADQUARTERS STAFF PRESENT:

BRIAN MCDERMOTT, Director, Division of Materials Safety and State Agreements

PAMELA HENDERSON, Deputy Director, Division of Materials Safety and State Agreements

CHRISTIAN EINBERG, Designated Federal Officer

ASHLEY COCKERHAM, Alternate DFO

SOPHIE HOLIDAY, ACMUI Coordinator

SANDRA GABRIEL, Ph.D., FSME/DMSSA/RMSB

DONNA-BETH HOWE, Ph.D, FSME/DMSSA/RMSB

GRETCHEN RIVERA-CAPELLA, FSME/DMSSA/RMSB

NRC REGIONAL STAFF PRESENT:

JENNIFER BISHOP, R-III/DNMS/MLB

JACKIE COOK, R-IV/DNMS/NMSB-B

SARA FORSTER, R-III/DNMS/MLB

CASSANDRA FRAZIER, R-III/DNMS/MLB

BOB GALLAGHER, R-I/DNMS/MB

MICHELLE HAMMOND, R-IV/DNMS/NMSB-B

LATISCHA HANSON, R-IV/DNMS/NMSB-A

DENNIS O'DOWD, R-III/DNMS/MLB

RANDY RAGLAND, R-I/DNMS/MSIB

LESTER TRIPP, R-I/DNMS/MB

MEMBERS OF THE PUBLIC PRESENT:

MAXWELL AMURAO, Columbia University

AMANDA BARRIAGE, Nordion, Incorporated

JANET BUKOVCAN, Nordion, Incorporated

ROBERT DANSEREAU, New York State Department of Health

SUSAN EFLER, Nordion, Incorporated

ANDREW KANG, US Food and Drug Administration

KAREN LANGLEY, University of Utah

RALPH LIETO, St. Joseph Mercy Hospital

STEVEN MARSH, Baystate Health

SCOTT MCGHEE, Nordion, Incorporated

ANDY MCKINLEY, American Society of Nuclear Cardiology

DARREN PERRERO, Illinois Emergency Management Agency

MIKE PETERS, American College of Radiology

GLORIA ROMANELLI, American College of Radiology

DANIEL SAMSON, New York State Department of Health

KAREN SHEEHAN, Fox Chase Cancer Center

MICHAEL SHEETZ, University of Pittsburgh

DANIEL SNYDER, Geisinger Health System

NANCY STANLEY, New Jersey Department of Health

CINDY TOMLINSON, American Society of Radiation Oncology

ED TRUSKOWSKI, New Jersey Department of Health

GARY WILLIAMS, Department of Veterans Affairs, National Health Physics Program

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P R O C E E D I N G S

2:06 p.m.

MR. EINBERG: As the Designated Federal Officer for this meeting, I am pleased to welcome you to this public meeting of the Advisory Committee on the Medical Uses of Isotopes.

My name is Chris Einberg. I am Chief of the Radioactive Materials Safety Branch, and I have been designated as the federal officer for this Advisory Committee in accordance with 10 CFR Part 7.11. Present today as the alternate Designated Federal Officer is Ashley Cockerham.

This is an announced meeting of the committee. It is being held in accordance with the rules and regulations of the Federal Advisory Committee Act and the Nuclear Regulatory Commission.

This meeting is being transcribed by the NRC, and it may also be transcribed or recorded by others.

This meeting was announced in the April 30, 2013 edition of the Federal Register, Volume 78, page 25320.

The function of the committee is to advise the staff on issues and questions that arise on the medical use of byproduct material. The committee provides counsel to the staff, but does not determine or

direct the actual decisions of the staff or the Commission. The NRC solicits the views of the committee and values their opinions.

I request that whenever possible we try to reach a consensus on the procedural issues that we will discuss today, but I also recognize there may be minority or dissenting opinions. If you have such opinions, please allow them to be read into the record.

Dr. Bruce Thomadsen, ACMUI chairman, is unable to attend today. Dr. Mickey Guiberteau will be serving as the acting chairman of this meeting.

At this point, I would like to perform a roll call of the ACMUI members participating today.

Dr. Mickey Guiberteau, Vice Chairman, Diagnostic Radiologist.

VICE CHAIRMAN GUIBERTEAU: Present.

MR. EINBERG: Dr. Sue Langhorst, Radiation Safety Officer.

MEMBER LANGHORST: Present.

MR. EINBERG: Mr. Steve Mattmuller, Nuclear Pharmacist.

MEMBER MATTMULLER: Present.

MR. EINBERG: Dr. Christopher Palestro, Nuclear Medicine Physician.

MEMBER PALESTRO: Present.

MR. EINBERG: Dr. John Suh, Radiation Oncologist.

Dr. Orhan Suleiman, FDA Representative.

MEMBER SULEIMAN: Present.

MR. EINBERG: Dr. William Van Decker, Nuclear Cardiologist.

MEMBER VAN DECKER: Present.

MR. EINBERG: Laura Weil, Patients' Rights Advocate.

MEMBER WEIL: Present.

MR. EINBERG: Dr. James Welsh, Radiation Oncologist.

MEMBER WELSH: Present.

MR. EINBERG: Dr. Pat Zanzonico, Nuclear Medicine Physicist.

MEMBER ZANZONICO: Present.

MR. EINBERG: And then Jared Thompson who is standing in for the Agreement State Representative.

MR. THOMPSON: Present.

MR. EINBERG: Mr. Thompson is standing in. He is not a full member of the committee, so he does not have the voting authority.

I now ask that the NRC staff members who are present to identify themselves. I'll start with the individuals in the room here. And we have Dr. Gabriel,

Gretchen Rivera-Capella, Sophie Holiday, Pam Henderson, and myself, Chris Einberg.

Now we will go to the NRC employees on the phone.

MR. RAGLAND: Randy Ragland, Region 1.

MR. GALLAGHER: Bob Gallagher and Lester, in Region 1.

MR. TRIPP: Lester Tripp, Region 1.

MR. EINBERG: Okay, thank you, Region 1. Anybody from the headquarters? Headquarters staff on the phone?

MS. COCKERHAM: Ashley Cockerham.

MR. EINBERG: Region III, do we have anybody on the phone?

MS. FRAZIER: Sandy Frazier.

MS. BISHOP: Jennifer Bishop.

MS. FORSTER: Sara Forster.

MR. O'DOWD: Dennis O'Dowd.

MR. EINBERG: Okay, thank you. Now Region IV.

MS. HAMMOND: Michelle Hammond.

MS. HANSON: Latischa Hanson.

MR. EINBERG: Okay. Are there any other NRC staff that I missed?

Next we will identify members of the public

who notified us that they will be participating on the teleconference. When I call your name, please answer.

Maxwell Amurao, Columbia University.

DR. AMURAO: Present.

MR. EINBERG: Amanda Barriage, Nordion, Inc.

MS. BARRIAGE: Present.

MR. EINBERG: Jane Bukovcan, Nordion, Incorporated.

MS. BUKOVCAN: Present.

MR. EINBERG: Sue Bunning, Society of Nuclear Medicine and Molecular Imaging.

Frank Costello, Pennsylvania Department of Environmental Protection.

Robert Dansereau, New York State Department of Health.

MR. DANSEREARU: Present.

MR. EINBERG: Casey Deitrich, CQ Transcription.

Susan Efler, Nordion, Incorporated.

MS. EFLER: Present.

MR. EINBERG: Andrew Kang, U.S. Food and Drug Administration.

DR. KANG: Present.

MR. EINBERG: Thank you. Karen Langley,

University of Utah.

MS. LANGLEY: Present.

MR. EINBERG: Ralph Lieto, The St. Joseph's Mercy Hospital.

MR. LIETO: Present.

MR. EINBERG: Steven Marsh, Bay State Health.

Scott McGhee, Nordion, Incorporated.

MR. McGHEE: Present.

MR. EINBERG: Roger McGregor, Nordion, Incorporated.

MS. BARRIAGE: He's not on this call.

MR. EINBERG: Thank you. Andy McKinley, American Society of Nuclear Cardiology.

MR. McKINLEY: Present.

MR. EINBERG: Darren Perrero, Illinois Emergency Management Agency.

MR. PERRERO: Present.

MR. EINBERG: Mike Peters, American College of Radiology.

MR. PETERS: Present.

MR. EINBERG: Gloria Romanelli, American College of Radiology.

MS. ROMANELLI: Present.

MR. EINBERG: Daniel Samson, New York State

Department of Health?

MR. SAMSON: Present.

MR. EINBERG: Michael Sheetz, University of Pittsburgh.

MR. SHEETZ: Present.

MR. EINBERG: Karen Sheehan, Fox Chase Cancer Center.

MS. SHEEHAN: Present.

MR. EINBERG: Daniel Snyder, Geisinger Health Systems.

MR. SNYDER: Present.

MR. EINBERG: Cindy Tomlinson, American Society for Radiation Oncology, ASTRO.

MS. TOMLINSON: Present.

MR. EINBERG: Gary Williams, Department of Veterans Affairs, National Health Physics Program.

MR. WILLIAMS: Present.

MR. EINBERG: Okay, is there anybody else on the line that has not identified themselves yet?

MS. COOK: Jackie Cook, Region IV.

MR. TRUSKOWSKI: Ed Truskowski and Nancy Stanley, State of New Jersey.

MR. EINBERG: Okay, thank you. I would also point out that this meeting is also using the GoToMeeting application to view the presentation

handouts in real time. You can access this by going to www.GoToMeeting.com and searching for meeting ID 157043040. Once again, 157043040.

MS. COOK: Excuse me. I just got a message saying the session is full on GoToMeeting.

MS. HOLIDAY: Hi, Jackie. This is Sophie. I'm aware of that. So what we're asking is that people that are calling in from the same office, whether that be from the regions or from the same professional office, that you use only one line because there are a limited number of lines available.

MS. COOK: Okay.

MR. EINBERG: Thank you.

MS. HOLIDAY: But the GoToMeeting is used so that you can see the report that's also available online on the ACMUI handout page. It's the same exact report.

MR. EINBERG: At this time, I ask that everybody on the call who is not speaking to place their phones on mute. If you do not have the capability to mute your phone, please press *6 to utilize the conference line mute and unmute functions. I would ask everyone to exercise extreme care to ensure that the background noise is kept to a minimum as any stray background sounds can be very disruptive on a conference call this large.

At this point, I'd like to turn the meeting over to Dr. Guiberteau.

VICE CHAIRMAN GUIBERTEAU: Thank you, Mr. Einberg.

I'd like to first of all welcome the members of the committee: Jared Thompson, who is standing in for Darice Bailey, who has recently left the committee as a representative from the Agreement States; the NRC Headquarters and regional staff, other Agreement State participants, and members of the public.

As you know, the purpose of this call is to discuss the draft Yttrium-90 microsphere brachytherapy medical events analysis performed by a subcommittee of ACMUI, the members of which are listed on the draft, which if you're at GoToMeeting should be on your screen.

And I'd like to ask Dr. Welsh, who has chaired this subcommittee to give us his report.

MEMBER WELSH: Thank you, Dr. Guiberteau. I'm using the speaker phone, so can people hear me?

MR. EINBERG: Yes, we can hear you here at the NRC.

MEMBER LANGHORST: You sound good, Jim.

MEMBER WELSH: Okay, so the report is relatively short and what I thought I would do is go through the whole thing, of course, not verbatim, but at

least conceptually and deliver the presentation that way. But before I do so, I am reminded that some of the material is highly sensitive and Sophie Holiday provided an email reminder to us all about the sensitive nature of this.

And perhaps before I go into my official presentation, I'd like to ask Sophie to reiterate what she said in that email about the sensitivity so that we're all very careful.

Sophie, if you're here, could you remind us exactly what the issues were?

MR. EINBERG: Dr. Welsh, this is Chris Einberg. Sophie just stepped away. However, let me just say that the sensitive aspect of this information or this data is the raw numbers that were provided to the committee should be handled as proprietary information and that should not be discussed in a phone call.

Additionally, the number of medical events associated with incidence rates per manufacturer should also be avoided, that the raw data is considered to be sensitive.

MEMBER WELSH: Thanks. So for those reasons I'm going to speak in generalities throughout here and just allude to percentages rather than quote specific number of incidences and especially avoid any

allusion to the number of cases with either of the two microsphere -- micro-brachytherapy option.

Earlier this year at our meeting, the subcommittee was formed and was charged with investigating the apparent increase in medical events over the past several years and also exploring why there appears to be a greater incidence of medical events of one type over the other, specifically glass microspheres over the resin microspheres.

So NRC has provided us with a table that goes back five years, six years, from 2007 through 2012 inclusive. The percentage of medical events is tabulated here. Regarding this table, one can glean that aside from 2007 which appears to be an anomaly, there was never a year where there was more than 0.36 percent medical event rate. And that 0.36 medical event of incidence was in the most recent year 2012 and specifically using the TheraSphere glass microspheres.

So one comment that I would like to make right off the start is that if that is the highest, we're still dealing with -- that is the highest from 2007 which appears to be an anomalous year, we're still talking about a medical event rate that is quite low. How low should it be is open to speculation. I know Dr. Zanzonico asked the question about how these figures

compare with other brachytherapy and they are higher, but we're talking about 0.2 versus 0.05, something of that sort. So even though it may seem like a tenfold greater incidence, we're talking about very, very low numbers in reality.

DR. KANG: Hello, can I ask a question?

MEMBER WELSH: Sure.

DR. KANG: This is Andy Kang from the CDLH FDA. Could you give the chronology of what the percent of incidence is? Is that percent reported today at NRC or is the percent of incidence United States or percent incidence are you talking about?

MEMBER WELSH: I believe these are the percentages of cases using the Yttrium-90 microspheres that wound up as medical events and were eventually reported to the NRC.

DR. KANG: That means a percent incidence related to the number of those number of patients?

MEMBER WELSH: Well, it does get a little bit complicated in that with the SIR-Spheres, it usually is a one-to-one ratio between doses and patients. With TheraSphere, it is not exactly a one-to-one ratio because on occasion there can be more than one vial shipped per patient.

VICE CHAIRMAN GUIBERTEAU: This is Dr.

Guiberteau. Could we hold our questions until Dr. Welsh has had a chance to present his entire report?

DR. KANG: Sure.

VICE CHAIRMAN GUIBERTEAU: Thank you. Go ahead.

MEMBER WELSH: I just wanted to point out that the numbers are relatively low with 0.36 being the highest in any given year aside from the Year 2007. In the past three years, medical events rates for TheraSphere have apparently increased from .1 to .29 to .36. And for SIR-Spheres, the rate has also increased in the past three years from .08 to .13 to .18. And for that reason, superficially, one would detect a trend. And that was perhaps what prompted this investigation in the first place. But when we look more carefully at that chart, the trend becomes kind of questionable. And 2007, which probably should be thrown out because it is the anomaly year, was the highest year on record for medical events rates of the whole table.

Also, however, for 2009, there was for TheraSphere, .30 which is the same as 2011. And for SIR-Spheres, it was .17 percent in 2009 which was the same as 2012. And therefore, when you look at this table you start to wonder if there really is a trend or not. And one of the points that we bring up in the report is that

it may be impossible to state with any kind of certainty that there truly is a statistically-significant increase of medical events over the past several years.

So with that as the introduction, based on the data that's been presented, we had a few general observations. In the past couple of years, there might have been an increase in the past two years --

VICE CHAIRMAN GUIBERTEAU: Excuse me, Jim. Someone needs to mute their phone, please. We're getting some background interference.

Sorry, please go ahead.

MEMBER WELSH: In the past couple of years at least, there does appear to be an apparent increase in medical events. When we look at the specifics, it seems that the major cause of these medical events were flow problems. However, there was no specific cause that could be singled out as the most frequent or most obvious explanation for all of this. And one of the conclusions of this observation is that there is a lack of a specific and consistent root cause. One of the conclusions of that observation is that it points to a general process that is complicated and perhaps not robust. We looked at this in further depth and we concluded that perhaps saying that it's not robust is too strong terminology. I prefer to say this was a complex

procedure that is delicate and somewhat susceptible to error because of the nature of the procedure, the complexity, and the large number of steps.

We did find out that both of these Y-90 microsphere approaches, the TheraSphere glass microspheres and the SIR-Spheres resin microspheres are complicated procedures and we could not say that one was more complex and more susceptible to error because of increased complexity. Both of them are multi-step procedures and somewhat challenging.

In relationship to a question that was posed by Dr. Zanzonico, I'll go into this more in depth later, but I would say that this procedure is a bit more complicated than most brachytherapy procedures. I know Dr. Thomadsen does not fully agree with that, but I'd like the opinion of anybody else on the subcommittee or the committee who actually does this to put in their two cents about the relative level of difficulty between Y-90 microsphere brachytherapy versus HDR/LDR brachytherapy.

My opinion is this is more challenging because of the number of steps and number of other reasons that I'll go into.

As far as the specific observations, we came to the conclusion that both of them are complicated procedures using complex delivery apparatus and that the

complexity is inherent with both manufacturers' devices because they are designed to specifically prevent problems during the delivery. But we did come up with a number of reported reasons for why there was this frequent under-dosing phenomenon in the past couple of years.

The under-doses were mostly due to low flow rates. And the low flow rates could be caused by low flow rate due to pausing, due to clumping, due to in one case leaking of the priming line reduced pressure. In another instance, there was reported low flow rate because the needles might have been inserted at an improper angle or that there was a defective catheter or that the hemostats caused crimping or deformation of the tube and that subsequently limited flow. In one instance, there was a slow flush due to small arteries which I would suggest, perhaps, should not be listed here as one of the medical events.

Another incidence had the "dose seemed harder to push." Another one was low flow rate, not otherwise specified. In another instance, there was a piece of the septum within the vial that seemed to be blocking the flow. Another example was the clamp not being fully opened and that's an obvious example of human error. And then there was another case of status due to

vascular spasm, or small and fragile vessels that slowed delivery which, of course, should not be medical event or perhaps it was a malfunction of the delivery system. The users were unable to explicitly state which of the two.

So whenever these were reported, the question of training was raised as a possible explanation for these medical events, but we've seen over the past several years that whenever there is not something that is very specific, whenever there is something that just seems to happen randomly, the licensees will often throw out the possibility that training -- there's a question about the training. We did not find any evidence that lack of training or insufficient training could really explain what's been going on in the past few years.

One of the subcommittee members has pointed out that the Nordion training program appears to be excellent, the SIRTex training program. So it doesn't appear that lack of training is the clear, obvious explanation for all events.

For some of the examples of licensees' explanations for medical events, they are referring to TheraSphere. For the SIR-Spheres, there were a couple of explanations offered as well. One was occlusion of the catheter because the catheter was too small.

Another one was the procedure was halted because of patient pain which we point out should not be listed as a medical event. It's patient-related. Another example was slow delivery that eventually led to settling and inability to deliver the required dose. Another example was the microspheres getting stuck to the septum because the bottle was shipped upside down.

There were a number of examples of human error such as wrong patient, wrong lobe, or misread prescriptions. That really don't help us in any way. They were not enlightening.

Regarding the microspheres sticking to the septum, when the bottle was shipped in an inverted fashion, the vendor was made aware of that problem and agreed never to ship them in a fashion that microspheres settle on the septum of the vial any more.

One member of the subcommittee has reviewed all of this and said that compared with a permanent implant prostate brachytherapy or high-dose-rate gynecological brachytherapy that he did not feel that Y-90 microsphere brachytherapy is more complex or more patient dependent. Another subcommittee member has pointed out, however, that there is a gross difference in the precision between HDR brachytherapy, prostate seed implant brachytherapy, and other forms of what I

call macro-brachytherapy versus this microsphere brachytherapy.

Dosimetry in microsphere brachytherapy is quite limited and suffers from gross imprecision and so to compare external beam to compare conventional brachytherapy to compare radio immunotherapy with microsphere therapy in any form or fashion is probably a meaningless comparison.

Although it doesn't state it explicitly in the report, however, I'm saying now that I think that there is a very, very big difference between technical aspects of conventional brachytherapy like prostate seed implants and gynecologic HDR brachytherapy, breast brachytherapy in that -- in those things that I'm calling macro-brachytherapy, you do get some type of a visual. And you do get some kind of direct feedback that allows you to operate, if not real time, very relatively quickly.

You just don't have the same sense when you're doing the microspheres because you're pushing a liquid with a hydraulic system. And sure there is some cloudiness within that liquid that you know the microspheres are in that cloudy region, but really is nothing like doing a cervical implant, for example. It's a hydraulic system that may be similar to the old

Beta-Cath that we used to use for coronary artery brachytherapy, but again with Beta-Cath and the other forms of intracoronary brachytherapy, even though they were hydraulic like the Y-90 microspheres, you still could see something very clearly on the angiograms. You don't see anything quite as cleanly, crisply, and clearly using Y-90 microspheres. And therefore, I think that there is a much greater technical challenge when using Y-90 microsphere brachytherapy than there is for the other types of brachytherapy.

We point out that Y-90 micro-brachytherapy is manual brachytherapy in 10 CFR 35.1000. That really doesn't have anything to do with this. One other thing that was brought up during our numerous discussions was that in 2011, interventional radiologists were eligible to become authorized users if they have the appropriate training, education, and experience. We came across no evidence to suggest that that had anything to do with the apparent increase in medical events.

So in conclusion, the subcommittee was not able to identify an obvious root cause for this apparent trend towards increased medical events. And in fact, the question remains about whether this apparent trend is a genuine trend or not statistically significant at all, given what I said at the introduction about some of

the years being higher than the most recent years and maybe the past three years just being an artificial trend that doesn't mean anything.

So rather than come up with recommendations, specific recommendations such as different clamps and different syringes that many of us have thought about and maybe even suggested to the vendors, one on one, over the past several years, none of us on the subcommittee felt that our analysis here justifies going forth with any such formal recommendations. And we are aware that if we were to put forth some recommendations that are based on shaky ground in the first place, we could inadvertently possibly increase the complexity of the overall procedure and introduce additional failures rather than an improvement. And so therefore such recommendations were not considered warranted at this point. Again, we point out that maybe this is not really a statistically-significant deviation from the background in a procedure that has had a low baseline medical event rate to begin with.

Finally, at least one of us felt that although these were under-doses and therefore classifies as medical events by the definition, that they were not of major clinical significance in most cases. They were

simply the medical event type that I would call of a regulatory nature and serve the purpose of alerting NRC of a possible trend that someday could become clinically significant rather than being a true clinical significance today.

One of the subcommittee members pointed out that an under-dosed patient might not live as long, but I would submit and I can -- I think we can support this statement that in cases where under-doses were identified, sometimes patients could go back and get the repeat treatment, and therefore, the full dose was administered. I don't think that these medical events were truly a great clinical significance to the patients.

In conclusion the subcommittee felt that it's important to continue to monitor these reported events and if the trend -- at that point we could pass on some recommendations, but to do so beforehand would be premature. That's pretty much it. Thank you, Dr. Guiberteau.

VICE CHAIRMAN GUIBERTEAU: Thank you, Dr. Welsh. That was an excellent, excellent summary of what seems to be a very thorough investigation into the issue. If I may, I would like to add one other thing to your excellent summary just to make certain that I understand this is that one of the questions was the apparent

discrepancy between numbers of medical events between the two different types of microspheres. And my understanding here is that there was not only no one root cause or more than one root cause for the medical events, in general, but none that could be applied to discriminate as to why one should have more events than the other. Is that correct?

MEMBER WELSH: That is my personal interpretation. I think that is the general consensus of the subcommittee. I would invite other subcommittee members or anybody on the ACMUI to offer their perspective, but upon our analysis, I personally was not able to clearly identify any explicit reason why there appears to be more medical events with one than the other.

VICE CHAIRMAN GUIBERTEAU: Thank you. And with that, I would like to open the call to questions from the committee members, the ACMUI members, and specifically from any different opinions or supportive opinions of the subcommittee members.

MEMBER LANGHORST: Mickey, this is Sue Langhorst.

VICE CHAIRMAN GUIBERTEAU: Yes, Sue.

MEMBER LANGHORST: I am fully supportive with the summary that we have in this draft report. There really are just too few numbers to say one way or

another. And I think it's wise just to keep an eye on it and see what trends show up in the future years.

VICE CHAIRMAN GUIBERTEAU: Thank you. Are there any other comments?

MEMBER ZANZONICO: Yes, this is Pat Zanzonico. Thanks, Dr. Welsh and the subcommittee. It really was a very thorough job and clear presentation.

I would tend to agree. I think the numbers are very small at this point in terms of the ME incidence and it would really be premature and counter productive as Dr. Welsh pointed out to suggest operational changes. And I just tend to think and this is just a perception, I don't have any data to base this on, that the reported numbers of MEs are likely an over estimate. I suspect they include a number of cases of stasis that are reported as MEs. And as Dr. Welsh pointed out in most, if not in all cases of stasis. I think they're just largely patient specific, unavoidable, biological events that don't represent a failure or a deficiency of the procedure of the product, but of the nature of what's being done. So I would agree completely that it's -- while, of course, it should continue to be monitored, it would be premature to suggest any changes in procedure, etcetera at this point.

VICE CHAIRMAN GUIBERTEAU: Thank you, Pat.

Any other comments?

MEMBER WELSH: Dr. Guiberteau, it's Jim Welsh again.

VICE CHAIRMAN GUIBERTEAU: Yes, Jim.

MEMBER WELSH: One thing that I don't know if I mentioned when I was giving my summary is that TheraSphere and SIR-Spheres went through slightly different FDA pathways. The net results was that at the start TheraSphere is used frequently for -- or used for hepatocellular carcinoma and SIR-Spheres were used for colorectal liver metastases. I have no reason to believe that one disease entity is more likely to provoke a medical event than the other. And I don't have any data to say whether or not the initial distinction between TheraSphere being the HCC hepatocellular carcinoma microsphere of choice and SIR-Spheres being the colorectal metastases microsphere of choice, I don't have any data to suggest that that's still going on. But I can say that a number of years back there was this very clear distinction where TheraSphere was primarily HCC and SIR-Spheres was for liver metastases.

Just speculating out loud that if one disease entity was more likely to provoke a medical event than the other, it could explain things. However, that speculation is unjustified. It's unscientific. I have

no data to back it up, but it's simply an observation that one microsphere did go through a different FDA pathway than the other leading to disease entity treatments that are slightly different. I'm not sure if that has anything to do with this at all.

VICE CHAIRMAN GUIBERTEAU: Thank you, Dr. Welsh, for that explanation of the differences between FDA approvals.

Any other comments from the subcommittee members or members of ACMUI?

MEMBER MATTMULLER: Yes, Dr. Guiberteau, this is Steve Mattmuller.

VICE CHAIRMAN GUIBERTEAU: Yes, Steve.

MEMBER MATTMULLER: I'm in complete agreement with all previous comments. My only extra thought I'd like to add as we keep an eye on this in the future is that perhaps it would be more appropriate to compare the Y-90 microspheres to other therapies that an interventional radiologist administers in a similar fashion, through a catheter, through the femoral artery, through the hepatic artery rather than trying to compare it to other brachytherapy procedures.

In the past I've had -- and I don't expect an answer today, but do interventional radiologists record medical events or whatever they may call them?

VICE CHAIRMAN GUIBERTEAU: Someone needs to mute their phone, please. We're getting a lot of background. There we go.

MEMBER MATTMULLER: I'll try again. Do interventional radiologists record medical events or whatever they may call them, events, adverse occurrences, etcetera, for the other therapies they administer in a similar method? And if so, how do those rates compare to microspheres' medical event rate?

And the one therapy that comes to mind is chemoembolization of hepatic tumors which is administered in a very, very similar method as the Y-90 microspheres.

And then the final thought would be even if we do have these different error rates or event rates or whatever we call these, there is still the unique characteristics of Y-90 microspheres that I would suggest that it's possible to measure their error rate much more accurately than any other type of interventional radiological therapy.

VICE CHAIRMAN GUIBERTEAU: That's a very interesting point, Steve. And yes, they do keep track of complications of those types of procedures. On the other hand, the localization procedures are similar, but in this case you have -- most of those are embolization

procedures are using macro amounts of occlusive material as opposed to microspheres which are much more susceptible to flow differences based on multiple factors including how the patient is constructed, the patency of the vascular system as well as the catheter and the delivery of the microspheres. I mean it would be probably disingenuous to try to compare those one on one, but it wouldn't hurt to look at some of the complication rates in general, as you point out. This is my opinion, but just from the diagnostic radiology perspective. Other comments?

MEMBER WELSH: Yes, Dr. Guiberteau. Dr. Welsh here. I would just point out what Steve just said is -- I think it's an excellent point. We, working with NRC here, are obliged to compare Y-90 microsphere brachytherapy with conventional brachytherapy because the treatments that are regulated by NRC. I suggest recently that maybe it would be wonderful if NRC had a broader purview or another entity that had the ability to regulate all of ionizing radiation, but I think that Steve's point is right on the money, that Y-90 micro-brachytherapy, despite its name, is in many ways more similar to chemoembolization case than it is to prostate seed implant or HDR breast brachytherapy. Yet, they are obliged to make that comparison because NRC

doesn't have the ability to look at the other interventional radiology procedures.

I would love to see that data maybe from the side of interventional radiology or some place that does have that to see if Y-90 microsphere brachytherapy truly is in any way different from other interventional radiology procedures or if it's right down the middle as far as complexity and event rates. It could be that we're comparing apples and oranges here by trying to compare Y-90 micro-brachytherapy with microspheres to other brachytherapy that you're accustomed to. Maybe the appropriate comparison, as Steve said, is other IR procedures.

VICE CHAIRMAN GUIBERTEAU: Thank you, Dr. Welsh.

Other comments from subcommittee or ACMUI members?

MEMBER ZANZONICO: This is Pat Zanzonico again. I would like to make one caveat. I think that is an excellent suggestion in terms of comparison of medical event rates. But I think we should bear in mind that one of the advantages and disadvantages of radiation radioactivity that it can be detected to sensitively and measured so accurately. So I think inherently we can identify what might be considered a misadministration,

or a medical event I should say, with a radionuclide-based procedure like Yttrium-90 than we might be able to do with nonradioactively-labeled material in conventional chemoembolization. So in other words, there may be a bias to a higher ME rate with Yttrium-90 microsphere than we might see with nonradionuclide-based procedures just because of the ability to so sensitively detect and measure the dose and lack of delivery of the complete dose, etcetera, etcetera. That's just a caveat I wanted to raise in connection with what is otherwise a very good suggestion.

VICE CHAIRMAN GUIBERTEAU: Thank you, Dr. Zanzonico.

Further comments?

MEMBER LANGHORST: This is Sue Langhorst. I'd like to follow on with what Pat just said. It's really frustrating that we get perhaps punished because we are able to make these precise, much more precise measurements with radioactive materials and thus potentially do harm with not having that treatment available. And so that's a frustration from my point of view in that just because we can measure it, doesn't mean that it's going to be a worse outcome than other types of interventional procedures.

VICE CHAIRMAN GUIBERTEAU: Thank you, Dr.

Langhorst.

Additional comments from the Committee?

MEMBER PALESTRO: Mickey, excuse me, Chris Palestro. In terms of comparing this sort of therapy to chemoembolization or other interventional therapies, I think you potentially can compare parts of it, of the technique, but not all of it. And I don't know that you're going to get necessarily valid comparisons. For example, if the radioactive microspheres leak out of the catheter for whatever reason, a clamp wasn't done properly, well, the procedure is over for that day.

On the other hand, with chemotherapeutic interventions, it may be possible if there's chemotherapy available that they just go ahead and find another vial or two or three or whatever it takes. So I'm not quite sure what kind of information or how valid those sorts of comparisons are going to be.

VICE CHAIRMAN GUIBERTEAU: Thank you, Dr. Palestro.

Any additional comments? If none from the committee or subcommittee, then from NRC staff or members of the public?

Hearing no one with an additional comment or question, I would like to ask Dr. Welsh if he is seeking the approval of the ACMUI for this report, if it is your

final report analysis on these event rates?

MEMBER WELSH: Yes, Dr. Guiberteau. I suppose before I pose that I would just respond to Dr. Palestro's final point that it is true that perhaps such a comparison would be of questionable meaning and value. However, I still think it's better than what we are currently doing which is comparing Y-90 microsphere versus other types of brachytherapy. Now that's a comparison that really seems to be meaningless in my opinion as somebody who has done both of these. But that's just a comment of questionable relevance and value.

Getting back to your point, yes, I think that with the exception of a couple of minor typos that have been identified by myself, by Sophie Holiday, and recently by Dr. Zanzonico, the subcommittee report that you have available is essentially is, in essence, the report that we would like to submit and seek approval from the entire ACMUI.

VICE CHAIRMAN GUIBERTEAU: I will accept that as a motion from you. Is there a second?

MEMBER LANGHORST: This is Sue Langhorst. I second that.

VICE CHAIRMAN GUIBERTEAU: Thank you, Sue. Any other discussion on the report before the committee

votes? Hearing none, I'll call the motion. All those in favor of approving this medical event analysis of Yttrium-90 microsphere brachytherapy say aye.

(Chorus of ayes.)

Any opposed? Any abstentions?

The report is unanimously approved by those on this call. And I believe that concludes our business.

I want to thank the members of the subcommittee especially for this very excellent analysis of these medical events and their conclusions and their willingness to continue to monitor these numbers in the future, and of course, your interest in how to further place these medical events in the proper setting of medical practice as well as safety of patients, although the medical practice part is probably best undertaken by the specialty societies as was pointed out by Dr. Welsh.

If there is no other business before us, then I would accept a motion to adjourn this call.

MEMBER MATTMULLER: Motion to adjourn.

VICE CHAIRMAN GUIBERTEAU: Is there a second?

MEMBER LANGHORST: This is Sue Langhorst. I'll second that.

VICE CHAIRMAN GUIBERTEAU: Well, since our business is complete, we are adjourned.

Mr. Einberg, is there anything else we need from you?

MR. EINBERG: Nothing else from the NRC. And on behalf of the NRC, we thank the subcommittee and the full committee for their excellent work in this area. And we'll continue to monitor trends in this area and we'll see if any other actions are necessary in the future. So with that, I concur that we should adjourn.

VICE CHAIRMAN GUIBERTEAU: Thank you very much.

(Whereupon, at 3:03 p.m., the teleconference was concluded.)