DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE OF THE

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

Wednesday, February 4, 2004

8:00 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

P. Joan Chesney, M.D., Chair
Thomas H. Perez, MPH, Executive Secretary

SGE CONSULTANTS (VOTING):

Mark Hudak, M.D.
David Danford, M.D.
Richard Gorman, M.D., FAAP
Robert Nelson, M.D., Ph.D.
Susan Fuchs, M.D.
Robert Fink, M.D.
Victor Santana, M.D.
Norman Fost, M.D., MPH
Judith O'Fallon, Ph.D.
Ralph D'Agostino, Ph.D.
Mark Fogel, M.D.
Tal Geva, M.D.
Craig Sable, M.D.
Vasken Dilsizian, M.D.
Marilyn Siegel, M.D.
Phillip Moore, M.D.

MEMBERS (VOTING):

Mary Glode, M.D.
Steven Ebert, Pharm.D. (Consumer Representative)

FEDERAL EMPLOYEE (VOTING):

Mario Stylianou, Ph.D.

INDUSTRY REPRESENTATIVE:

Samuel Maldonado, M.D.

FDA:

Julie Beitz, M.D.
Sally Loewke, M.D.
Susan Cummins, M.D.
Diane Murphy, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. CHESNEY: Welcome back, everybody. Dr. Loewke is going to give us an overview of the questions again but, first, the folk at the FDA had asked for one of us to do a recap of what we covered yesterday and Dr. David Danford, our resident cardiologist, has offered, under duress, to do that.

[Laughter]

So, why don't you go ahead?

Recap of Day 1

DR. DANFORD: Thank you, Dr. Chesney. The subcommittee had quite a full day yesterday of excellent, very informative presentations on pediatric cardiac imaging and the agents currently in use to enhance that imaging.

FDA began by identifying four classes of these injectables, including gadolinium agents for cardiac MRI, radiopharmaceuticals for evaluation of myocardial function and perfusion, microsphere contrast for echocardiographic image enhancement, and iodinated contrast for angiography and CT.

With the exception of the iodinated contrast, which is labeled for angiographic use in

children as young as one year of age, all pediatric cardiac use of these agents is currently off-label. Desiring to obtain information about these agents that would allow labeling for pediatric use, FDA assembled speakers to address, one, what pediatric subpopulations receive these agents; two, what diagnostic purposes are being served; three, how the imaging data affects patient management; and, four, what additional labeling is needed.

From this, it was hoped that we could determine what, if any, pediatric labeling information could be extrapolated from the adult experience and what research studies should be designed to obtain the data required for responsible pediatric labeling.

Dr. Geva introduced the concept that there are huge numbers of patients living with congenital heart disease in the United States that are surviving longer, and frequently they have residual anatomic and functional cardiovascular impairments and may have a lifelong need for medical surveillance that includes cardiac imaging.

We repeatedly heard from multiple presenters that unenhanced standard, regular old echocardiography was the imaging modality of first

choice for most of these patients. It accounts for more procedures than MRI, cath, CT and nuclear studies combined. Its shortcomings are poor diagnostic quality in certain subgroups of patients, like older and bigger patients, those with chest wall deformities or prior cardiac surgeries, those with pulmonary disease and those in whom the primary focus of diagnostic interest is outside the heart, for example, aortic arch, pulmonary artery branches, systemic or pulmonary veins. Unenhanced echo is also suboptimal when the diagnostic question is one of coronary perfusion.

So, when standard echo fails to provide the diagnostic information required for management of heart disease one of the other imaging modalities is selected. MRI is one of those modalities, and we heard from Dr. Fogel that gadolinium contrast is injected in the large majority of pediatric cardiac MRI examinations. MRI often provides images superior to echo for aortic arch and its branches, pulmonary arteries and veins and the systemic veins, and it can also provide information on myocardial perfusion and tissue characterization.

The anatomic MRI data is suitable for

processing into 3D reconstructions that are aesthetically impressive and highly clinically relevant for the guidance of surgeons and interventional cardiologists as they plan treatment. MRIs applications are limited by artifact when objects made of certain metals are in the field of interest.

There was support in our discussions for investigations to define the appropriate pediatric gadolinium dose, its safety in children with heart disease and the diagnostic accuracy in pediatric cardiac applications.

Like MRI, cardiac CT is also superior to standard echo for imaging of extracardiac large vessel abnormalities like aortic aneurysm, double aortic arch and other vascular rings, pulmonary artery sling, pulmonary branch stenosis, aortic coarctation and pulmonary systemic venous anomalies.

Nonionic iodinated contrast is used in essentially all pediatric cardiac CT exams. It has a long record of safe use in children and is approved for angiography in patients as young as one year old. The subcommittee heard concern, however, about radiation exposure from CT imaging

and struggled with the issue of separating the risks of the contrast agent from the risks of X-ray exposure.

Like CT, cardiac catheterization with angiography utilizes nonionic iodinated contrast material and X-rays. It has broad diagnostic applicability in a wide range of conditions, including both intracardiac and extracardiac anomalies, and is increasingly performed as a means to treat the condition by means of balloon valvuloplasty or angioplasty, stent placement, the creation of holes where they are physiologically advantageous and the closing of holes where they are not.

The diagnostic information obtained with angiocardiography is, therefore, often with immediate application to therapeutic intervention. Even in the shrinking minority of such procedures now done for purely diagnostic purposes the anatomic details provided angiographically often guide surgical treatment.

One speaker suggested that there were few, if any, pediatric labeling issues remaining about the use of iodinated contrast material in the cardiac cath lab, but another suggested that we

actually lack information about the true maximum safe dose and in some complex cases in the cath lab we enforce an artificial maximum, resulting in deferred angiography and return to the cath lab for second procedures that might not be in the patient's interest if it were established that greater volumes of contrast could safely be administered in a single sitting.

We heard that nuclear cardiac imaging differs from the modalities we have discussed so far, and its focus is not on anatomy but on function, blood flow and myocardial perfusion. Not surprisingly, its applications in the cardiomyopathic processes and abnormalities of pulmonary blood flow and coronary arterial perfusion were emphasized. The use of radioactive pharmaceuticals to obtain this information is associated with radiation exposure to the patient.

While there was support for studies to determine the pediatric safety and appropriate pediatric dosing, concerns were raised that NIH guidelines for radiation exposure in pediatric research subjects may be an impediment.

Contrast echocardiography employs encapsulated air or other gas bubbles to enhance

endocardial edge detection by harmonic ultrasound imaging. This adds information on myocardial function and perfusion to the cardiac anatomic and Doppler blood flow diagnostic information that is generally available on standard echo.

The potential for pediatric application or contrast echocardiography is currently largely unrealized as most pediatric centers do not provide routine contrast echo services. Nevertheless, there was interest in obtaining pediatric safety and efficacy data for these contrast agents as some experts would estimate that as many as five percent of all patients having pediatric echocardiography would benefit from the clinical information about myocardial perfusion and ventricular function that contrast provides.

Finally, representatives of a number of national professional organizations, including the American Academy of Pediatrics, the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Nuclear Medicine and a representative of one pharmaceutical company all spoke in strong support of FDA's initiatives to promote responsible pediatric use of these agents through labeling.

DR. CHESNEY: Thank you very much. That was excellent. We should have asked you for copies last night.

DR. DANFORD: I wasn't ready last night.

DR. CHESNEY: Thank you. I did have one announcement to make. Dr. Hari Sachs had asked me to tell you that on March 29-30 the FDA and NIH are jointly sponsoring a neonatal workshop, in Baltimore, which will cover pain, pulmonary, neurologic and cardiac issues, and there is more information available on the web site for anybody who is interested--and ethics.

Dr. Loewke, would you like to get us started on the job at hand?

Discussion of Questions to the Committee

DR. LOEWKE: Good morning. I just wanted to clarify a couple of points and maybe run through an example that might help the discussion for later, so bear with me here. Let me find my slides.

[Slide]

I wanted to talk a little bit about extrapolation. The agency has commented that when there is potential to use adult efficacy data and extrapolate that to the pediatric population--I

just wanted to clarify that we would fully intend to do PK parameters, PK studies and safety studies in the pediatric population. So, the question that is posed to the panel today is whether or not there is any case in which we can extrapolate efficacy data to children so we wouldn't have to do large efficacy trials in the pediatric population.

[Slide]

I don't want to beat a horse to death but I wanted to just throw these back up so we can see what really is approved in the pediatric population, and reiterate that everything that really was talked about yesterday, most of it is being used off-label in the pediatric population.

What I really wanted to focus our discussion on is what products are currently being used in a large enough population that additional drug labeling would make a considerable health benefit and make efficacy trials feasible.

I just wanted to walk through an example. I hope it might help. Dr. Fogel talked about gadolinium yesterday and he had identified that MR angiography is performed in patients with congenital heart disease to look at vascular anatomy. So, I am thinking that obviously there is

benefit in this particular area to study the gadolinium product. The question is that first we need to identify which patient populations. I assume you are looking at things such as anomalous vessels, aneurysms, coarctations, etc. that you pointed out. So, what are the relevant populations? We just need to identify what specific groups of patients we want to look at anatomy for.

Within that population, are all the abnormalities considered equal? I don't mean from a clinical standpoint but I mean from an imaging standpoint. Could you do a general angiography exam with gadolinium and see all of these different types of abnormalities, or would you have to change your procedure or modify your procedure for any particular one? If that is the case, we would tend to probably exclude that. We want to try to get a homogeneous group of patients in which all those types of anomalies or abnormalities of vasculature you want to look at would be captured in a standard MRI angiography. I don't know if it is possible; I am just throwing it out there.

Then, we would need to identify whether just knowing vascular abnormality--do you find that

clinically useful? Do we have to prove that that is clinically useful? If we have to prove that, how would we go about proving that as part of the clinical trial?

Then, how do we validate the findings on the MR angiography? I was thinking last night maybe many of these patients go on to interventional angiography. Maybe we could use the findings of that procedure to confirm the abnormality seen on MR. Maybe many of these patients go on to surgery and we could use surgical findings to confirm the abnormalities picked up by MR.

That is just sort of an example of how we are trying to work through these and the types of information we are trying to get so we can try to figure out where to go.

DR. CHESNEY: Just before you sit down, could I ask the committee and our consultants whether you have questions for Dr. Loewke as to exactly what they are looking for? Yes, Dr. D'Agostino and then Dr. Fogel.

DR. D'AGOSTINO: If you break down every possibility we could go on forever. Are you looking for some sort of general type of indication

so that then there is sort of a guideline or response to these questions that sort of gives some input on how one would go about putting the trial together? I am just concerned that the specifications, you know, can get very, very detailed. When you were saying can you lump these together, there were some people on this side of the table shaking their heads, no, you can't. So, does that mean that for each possible condition there is another trial, or are you just looking for some sort of generalities in terms of how you could give guidance to industry and the FDA and some sense from the advisory committee?

DR. LOEWKE: We are trying to capture what information and what populations are large enough that we can pursue efficacy trials that would give benefit to the pediatric population. If we can't lump patients, then we have a problem.

DR. D'AGOSTINO: Right.

DR. LOEWKE: But I needed to hear from the panel what they think we can or cannot do, given their experience.

DR. D'AGOSTINO: I went through this with the FDA in terms of pain models and we ended up, in terms of analgesics, laying out a tremendous number

of pain models, and what-have-you. In the end we just said we can't fill page upon page upon page but there are some general principles, and I am gathering that that is where you are heading, that there are specifics but there are still general principles that would lead from one condition to another so that we could give you decent input to putting trials together.

DR. LOEWKE: From the talks yesterday, generally a role that I was seeing is that we are largely doing these studies to do anatomy. CT does that; MR does that. There are reasons to do perfusion studies in kids. So, knowing those global areas, now I just want to get a little more to what specific populations shall we be looking at because why are you doing these studies? Then, how we should at least design the endpoints that would have clinical value to the community? Then we can go from there.

DR. D'AGOSTINO: We do a lot these--the Framingham study, and we find oftentimes that you find calcium or something like that and you get all upset about it. To produce a better image of that that we don't know what to do with, or anything like that, isn't very helpful. So, when you say is

it clinically useful, then does that mean that we have to be able to identify in the protocol that it actually has a clinically meaningful condition that is tied into it? Or, is it just an enhancement of the image that we may not know anything about?

DR. LOEWKE: Well, that is what we are trying to get at.

DR. D'AGOSTINO: Right.

DR. LOEWKE: We don't just want enhancement. If it doesn't mean anything and isn't useful to the practicing community, then that is not the endpoint--

DR. D'AGOSTINO: So, we need a standard beyond just the image.

DR. LOEWKE: Right.

DR. D'AGOSTINO: Thank you.

DR. CHESNEY: I have Dr. Fogel, Dr. Geva, Dr. Fink and Dr. Fost.

DR. FOGEL: I wanted to step back for just a minute. Yesterday we got a lot of speakers together and we heard all sorts of wonderful talks about how we use contrast agents and how we might eventually design efficacy and safety trials in children to prove that that, indeed, is efficacious and safe in children and adds clinical benefit and

value to their medical care.

I guess I want to step back for one second. I guess this was bothering me last night and this morning, that is, a number of people brought up the notion that a number of these agents are off-patent. We could sit here all morning and talk about what wonderful trials we would design and how we would do it but, from a practical standpoint, how will the FDA approach, once we do give recommendations--how will the FDA approach getting the trials done? I mean, is there some sort of carrot that you guys think you are going to stick in front of the pharmaceutical industry, as you did with the pediatric exclusivity rule, that would be able to accomplish this? Or, is this really more an academic discussion?

DR. CUMMINS: This is not just an academic discussion. I want to reassure all of you of that. I spent most of my time yesterday talking about the on-patent process. There is an off-patent process as well. That off-patent process is done in collaboration with the National Institutes of Health. It is specified in the Best Pharmaceuticals for Children Act. Annually--actually it has been a couple of times a

year, the NIH lists in the Federal Register drugs that are high priority for study and the FDA develops a written request for those high priority drugs and issues them to industry. If industry does not want to conduct the studies, then those off-patent written requests are referred to the NIH and the NIH then translates them into request for proposals and they are awarded for study.

We have been doing this now for about 18 months. We have a process in place. A couple of contracts have actually been awarded. There is a coordinating center that is coordinating all these studies and there is definitely a mechanism for translating the recommendations that we get from you all into studies for off-patent products.

DR. FOGEL: That is great. I must have missed that yesterday. Thank you.

DR. CUMMINS: Well, I don't think I explained it enough so rest assured.

DR. CHESNEY: Could we ask you--we were discussing this in the van this morning--does the NIH have money to do these studies, or do they go in a list and maybe the top one is funded and the other hundred aren't?

DR. CUMMINS: Without being responsible

for spelling out the NIH process in detail, yes, they have funding to do these studies. These studies are not funded through the NIH Foundation; they are funded through the NIH budget.

DR. D. MURPHY: They have some funding, yes. You know, Congress suggested that they have 200 million dollars for this and then appropriated none. So, the issue is that the institutes are now each having to find this money, and they have. But, you are right, there clearly are limitations and you will have to march through the priority list.

DR. CHESNEY: Thank you, Dr. Murphy. Dr. Geva, Dr. Fink, Dr. Fost and Dr. Nelson.

DR. GEVA: I wanted to ask a question. What are the advantages or what is the incentive to, let's say, get gadolinium for pediatric cardiology applications approved by the FDA?

DR. CUMMINS: The approval would allow for labeling of a product in the pediatric population so it would give us data on efficacy, on dosing and on safety that we could then put into the label. Currently, as you all acknowledged, we don't have that information in the label. The products are all being used off-label.

DR. GEVA: Perhaps if I may, to just answer some of the questions that were asked earlier about the patient populations and specific diagnoses--to answer your specific question, I would think that what you are looking at is essentially the entire population of patients with congenital heart disease as far as designing these studies. I don't think that it makes a lot of sense, at least early in the process, to break it down to very specific diagnoses.

I can tell you that of the patients who come for an MRI examination, as Dr. Fogel mentioned yesterday and that is the experience in our center as well, the majority get gadolinium MRI studies. So, to start breaking it down into specific diagnoses you would probably be doing yourself a disservice. Now, there are a number of ways by which you can address the issue of efficacy and that would be a fascinating academic discussion.

DR. CHESNEY: Thank you. Before we get down to that issue, I think Dr. Fink had a question and Dr. Nelson had a question.

DR. FINK: I guess mine actually coincides with what Dr. Geva was saying. I don't really think that you can measure efficacy for these

agents and what we really need is safety and PK/PD data for their usage in children because what I heard yesterday is that there are differences in technology, and which agent is most effective may depend on how many tesla your MRI scanner has; the experience of the operator; whether the cardiologist prefers MRI or CT after they have done the echo. And, the effectiveness we are really looking at may depend on the thoracic surgeon or the skill of the interventional cardiologist and these are really agents for helping to just do the image. So, I think efficacy for these agents really is the imaging and what we primarily want in pediatrics is safety and PK/PD data.

DR. LOEWKE: We need to give the user information about the performance of these agents, and we look at the image and we compare it to a standard of truth to show them how it performs to what may be currently used. It gives them a sense of how this performs; do they want to use this in place of something else. So, there is value and it is very important to look at the efficacy of these products.

DR. FINK: I didn't hear a whole lot of discussion yesterday about different agents that

are used or what we are comparing it to. It seemed like for MR it was pretty much gadolinium and that there wasn't a lot of variation in agents.

DR. LOEWKE: I am not sure I understand your question.

DR. FINK: For efficacy are you looking at the various efficacies of the different gadolinium agents or variation between, let's say MR versus CT?

DR. LOEWKE: No, you are looking at the particular MR agent and you are comparing it to what--depending on what we define as a standard of truth, whether it be a comparator agent that is already approved for the indication or whether it is a standard of truth such as conventional angiography that is currently a gold standard for use in the cardiac population today. So, it gives the user a sense of where this falls into their arsenal, and how to use it, and how to rely on the information that they get from it.

DR. FINK: But it would seem that that is primarily machine driven. A 3 tesla coil is better than a 1.5 tesla coil, or a 16 detector CT is better than a 4 detector CT. It would seem like the technology available has a far greater impact

than potentially these agents.

DR. LOEWKE: I think we heard yesterday that it is a combination of both the agent, the drug and the user too. It is a combination. We try to put factors in place to accommodate for some of those issues when we design a trial.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: I guess I have a question and a comment. I just want to make sure I know which are on-patent and off-patent so as we are discussing the issue I have a sense of the public health impact for the feasibility of doing the trials. I guess since Bristol-Myers Squibb likely is the one who put in those two, I am inferring from the fact that they presented on nuclear imaging that, in fact, the nuclear imaging products are on-patent. I am assuming most of the gadolinium products, unless there is some fancy one in the wings, are off-patent. The nonionic contrast is probably off-patent but the fancy echocardiography bubbles are likely on-patent because that is new. Have I gotten that right? I am just trying to understand which are on- and off-patent as we are discussing these different modalities.

DR. CUMMINS: Whether or not a drug is on patent is actually more complicated than one might imagine, and I would encourage you to put aside the patent status of any product and focus on the product. We really need your scientific advice. Then we can think about how that fits into the whole on-patent/off-patent process.

DR. NELSON: So be it. Let me then continue. I am still unclear about the issue of extrapolation and trying to separate out in terms of properties of the agent and the resolution of the imaging versus application to the population. Part of this, in my mind, then translates to how you would try to design a trial. For example, when I listened to the echocardiography presentation and looked at the slides, it sounds like that one of the issues is the ability to differentiate a tissue-liquid interface and the relationship between the resonance of the bubbles and the harmonics of the machine in relationship to the harmonics of the tissue and the harmonics of the liquid--so, a very complex interaction. If you said that what you need to see a good image is a resolution better than--I think you mentioned 1 mm or 2 mm, 1-2 mm, the question then is under what

circumstances can you demonstrate that you have a product that gives you that 1-2 mm resolution assuming all other factors remain constant as far as tissue harmonics and liquid harmonics.

So, if I was looking at a protocol and asking do you need to do that in a neonate to answer that question, you know, can you demonstrate a 1 mm resolution, my question would then be are all other factors equal apart from the properties of the agent itself? That would be the question and then you would have to tell me what are the harmonics of the adult tissue of the heart. I would then say, well okay, if it is the same use adults; if it is not use kids. So, that is the kind of technical question I would ask in evaluating a protocol.

If then you said, okay, we have an agent that has demonstrated 1-2 mm resolution, do we then take it to a pediatric population and try and show that we can find clinically useful information? That then goes to the next step and I think it goes to trying to sort out what is the nature of the kinds of questions that we need to ask.

I must confess, you know, I understand an image. If anybody in the audience is in art

history or art appreciation, I mean imaging is--but it is unclear to me--if you took the gadolinium MRI scans, if you see a double arch you are going to see a double arch and I am not sure you need to know 1 mm resolution to see a double arch. So, some of the questions are going to vary depending upon the modality. It sounds to me, from what I saw, I confess it looked like most of the complex questions are in the nuclear and the echo where there are still a lot of unanswered questions, whereas in the CT and the MRI it was more a question of extracardiac use of it for imaging of vessels that you can't see in the other modalities, putting function aside.

So, I think, you know, as we go through these--I mean, all the questions break down each particular imaging modality so it is not only population but it is what do we really need to see via CT, via MRI versus imaging and the like. So, I think separating out those questions is important and that is why when I think about PK and safety data I also consider the basic properties of the agent, independent of whether or not you are using it to find clinically useful information.

I don't know if that helps. You know, can

you extrapolate? If all you need to do is see a 1 mm vessel, find a 1 mm vessel in an adult basically, if that is all you need to see. You don't use kids until you have to use kids.

DR. CHESNEY: Lots of hands and lots of lists here but, Dr. Siegel, do you have a specific response to his comment?

DR. SIEGEL: To three of the comments. First on the patient population for each examination, I think the patient population is really more than complex heart disease. There are several things that have been brought up here. One, the extracardiac or the vascular lesions; two, valvular lesions; three, simple septal lesions; and, four, complex heart disease. So, if we are looking at that, and that does bring up the point of, as you said, if we see a vascular lesions how sophisticated do we need to get? We have seen it and that is the end of the imaging. So, looking at the patient population we need to sort of deal with those areas, where each of these exams fits in and do we need more to confirm it or do we stop at a certain point.

I think the other confusion in my mind--there are two things. There is endpoint and

gold standard. I think maybe we are overlapping them. The endpoint would be a clinical outcome. If we were doing antibiotics, you know, does the patient get better? An endpoint here is a little bit more difficult to define. But if you look at it clinically, there are I think at least two endpoints. If somebody has a widened mediastinum, whether it is on a CT or MR to look at the arch, and we find something and we can say what is the clinical usefulness? The clinical usefulness there terminates further imaging studies. We are not going to have a correlate on that. So, in some cases the clinical usefulness is that it terminates additional imaging studies or diagnostic workup. In other instances it is going to lead to further evaluation or treatment. So, if we do a study and you see a septal lesion, it is perhaps going to lead to echo or catheterization.

So, to me, the two clinical endpoints, at least in a simplistic world, would be termination of additional studies and end of the workup or if we need further workup. That is a clinical outcome.

Gold standard then is if we wanted to confirm a lesion that needed further workup, how do

we do it? Again, it is going to depend on the modality. If I am doing CT, you know, probably echo is going to have to be my god standard if I wanted to do a study. If this is an incidental pickup, it probably would go to echo but somebody might say do an MR. I mean, that is going to be a little tougher. If you design a study you could probably get very specific on what you wanted to do clinically after you find a lesion and it is up to us perhaps to suggest or up to a clinician to decide what they want. But I think we are dealing with, you know, gold standard and endpoint here, and gold standard might vary for each study.

DR. CHESNEY: Thank you. I have Dr. Dilsizian, Dr. Gorman, Dr. Geva and Dr. Fogel.

DR. DILSIZIAN: I guess I wanted to respond to Dr. Loewke's request. There are two questions you asked. One is extrapolation from adults to kids. I think yesterday we all said adults and kids are different. But, at the same time, I would like to emphasize that a lot of the things we use, let's say, in nuclear medicine perfusion imaging and function--the concept of flow and function can be extrapolated from adults to kids but what we need to do then is that at the end

it would be wise to test these in adults because the dosimetry is much more favorable. Once you have shown your efficacy and the accuracy in adults, now you can, in essence, apply this in kids but with the caveat that it has to be retested because their vessels may be small; the organs are smaller; the radiation exposure is now different. But I think that it is perfectly safe or wise, at least in my mind, to have it approved in adults at first and then accept it in kids but then repeat it in kids to see whether a difference exists or not.

The reason I say that is because, for example in nuclear, as you know, perfusion and function has been approved by the FDA. It is one of the few indications that has been done. But we now are extrapolating use in kids but we haven't really tested in kids. So, I think it would be wise, again, for echo bubbles or DTPA to do the same thing. I think we have to first show efficacy in adults and then apply it in kids. I know they are different but, given the safety issues, I think it is always wiser to test it in adults first.

DR. CHESNEY: Can I ask you how do you define efficacy?

DR. DILSIZIAN: There are two approaches.

For perfusion imaging one would say, in adults for example, I would like to detect coronary artery lesions so I can angioplasty that lesion or send the patient to surgery. Therefore, we use traditionally coronary angiography as the gold standard and say can I non-invasively predict a perfusion defect which will then guide cath and angioplasty or surgery?

We have learned, however, since then that there could be perfusion defects that are not necessarily anatomical. There could be vasoconstriction or other physiological parameters of hypertrophic cardiomyopathy where we have no coronaries but the demand is different. So, physiological information is not necessarily equivalent to anatomical information.

So, the next question is how do I judge those patients? I hope I made the case that in those patients you look at outcome--syncope, sudden cardiac arrest--to see whether identifying those patients and treating them or not treating them changes the outcome of that patient's symptoms. So, those are the two endpoints. One is an anatomical correlate as a gold standard and the other one would be outcomes--syncope, sudden

cardiac arrest or some other adverse events.

DR. CHESNEY: I think Dr. Siegel mentioned yesterday that accuracy is efficacy here, efficacy of diagnosis. Next, Dr. Gorman and then Dr. Geva and Dr. Fogel.

DR. GORMAN: The question of gold standard is one that we didn't discuss much yesterday but the clinical definition I think has already started to be expressed and expounded here, which is that the clinical definition of a gold standard is if you stop intervening at that time and your clinical predictions come true, then you made a clinical diagnosis that was appropriate. If you continued to intervene after you do a procedure of any of these sorts and the next procedure confirms your diagnosis, then it was again an efficacious procedure. So, you then begin to have a moving gold standard target which is that for each of these many lesions that we could discuss there is a series of modalities that would help diagnose them.

Clinically, there is a pediatric population that is enriched for cardiac lesions and everyone undergoes cardiac imaging and I would suggest them as a potential first place to start study design. Every single one of those undergoes

a cardiac imaging procedure I think in the United States for whether they have clinical findings or not. They also have potential benefit.

DR. CHESNEY: Dr. Geva, Dr. Fogel and Dr. Sable.

DR. GEVA: To go back to the efficacy issue, I would like to expand on Dr. Siegel's comment and that is that there are at least two ways of defining efficacy in the context of this discussion. One is diagnostic accuracy and it depends on the specific trial and the specific lesion or group of lesions that are being investigated. One can choose an appropriate "gold standard" and that may be something that has been around for decades, such as angiography which is commonly accepted as the best that is currently available; surgical observations; a compilation of all available imaging tests--there are several ways of going about putting together a reference standard. Not all of these are true gold standards but they have been around long enough and that is what is being used most commonly so if a new agent or a new technique is being proposed it is a common thing to test it against those.

Then, a different approach to efficacy is

to look at an outcome, clinical outcome with the use of a new diagnostic technique. To give a specific example, currently all patients, let's say, who are candidates for a certain surgical procedure, let's say the Fontan operation, routinely undergo cardiac catheterization and one can design a study whereby instead of routine cardiac catheterization selected patients undergo non-invasive preoperative testing and that is an arm in a clinical trial. Patients are randomized to standard invasive testing versus non-invasive testing. Then one can look at set clinical outcomes--freedom from intervention, length of stay and so on and so forth.

So, studies like that can certainly be designed. Although you don't directly test the diagnostic accuracy of, let's say, gadolinium MRI, you are testing whether the use of gadolinium MRI can be used in order to achieve equivalent clinical outcome but with less cost, less risk for the patients, less radiation and so on.

DR. CHESNEY: Dr. Fogel, Dr. Sable and Dr. D'Agostino.

DR. FOGEL: Yes, I have a number of comments. First going to the efficacy issue, I

just wanted to say that I strongly support the notion that efficacy is a very important part of this entire discussion. It goes towards the whole notion of, because we have seen a potpourri of diagnostic imaging modalities, obviously, if you have efficacy on the various imaging modalities in a given patient population or a given category of a patient population you can then compare the various diagnostic imaging modalities and say, well, imaging modality X is more efficacious than imaging modality Y in this particular instance and that would actually improve patient management and patient care in the sense that you would then have some real data to say, well, if this patient comes along with a certain likelihood the best clinical pathway for one to follow would be to get imaging modality X and then Y and then go on to intervention Z because we have shown that X is more efficacious than Y in this patient population.

So, I think that that would be very useful. It would improve patient safety because you wouldn't have to do sedation for an echocardiogram and then do sedation for an MRI; you could just do it once and then move on to the next diagnostic imaging modality or therapy. So, I

think that would be very important to do and I voice strong support for efficacy.

In terms of efficacy being a clinical outcome, which I have heard a number of speakers talk about, we all have to recognize that imaging in an of itself, to use the clinical trial terminology, is really a surrogate, and it is a surrogate for something that is really true, which would be holding the heart in your hand and being able to see the whole heart, being able to miniaturize yourself down to a teeny little person and see that little coronary artery and walk through it. But apart from that, it really is a surrogate.

As such, with clinical outcome there is so much that--let me step back for one second. The imaging itself is just one component of a multi-faceted thing that is going to happen to the patient. There are all sorts of other imaging modalities that might occur, as well as interventions and postoperative care.

So, although I guess you could design trials that would have imaging modalities and look at the clinical outcome, I would imagine you would need a lot of patients and it would be very noisy

because there are so many other factors that go into a patient's clinical outcome other than the diagnostic imaging modality. I think it would be very, very difficult in terms of being able to show efficacy in that particular way. Now, if you want to do it against a gold standard, that would be surgical observation, unfortunately, sometimes pathologic observation. That is totally different. But clinical outcome sounds like it would be pretty noisy data.

Finally, the last thing I wanted to mention is the extrapolation issue of Dr. Nelson. I have to say that I don't really think you can extrapolate from adults to kids, as we all mentioned yesterday. I don't think that if you have a 3 mm or 4 mm aorta in a child you can then say, well, can I see a 3 mm coronary artery in an adult? Well, if I can see a 3 mm coronary artery in an adult, then I can certainly see a 3 mm aorta in a child. That doesn't really work. There are a lot of technical issues that go on in there--tissue attenuation, the size of the patient, how big a field of view you need to see the various structures--a lot of technical things go into the fact that I don't think you can really do a good

extrapolation from adults into children and I would be very wary of doing that.

DR. CHESNEY: Dr. Sable and Dr. D'Agostino, and then I would be very interested in polling all our experts to see if they agree with you. Let's do that right now, if you don't mind. Would you all agree that you can't extrapolate from adult data to children? I think that was one of the big issues.

DR. MOORE: I would not agree. I would say, just to focus on what I think the issue here of this subcommittee, whether additional labeling is required for some of these agents and labeling specific for pediatrics to make sure that these agents are safe and effective, I would argue a little bit along Dr. Nelson's lines that gadolinium and certainly iodinated contrast have a lot of data that is available both in adults and children in terms of their safety and efficacy in other areas in the body and in other modalities which can be translated over to cardiac imaging. I would argue that the focus really needs to be on some of the newer agents and perhaps some of the radiopharmaceuticals and some of the echo contrast agents in terms of the specific issues with safety

and efficacy.

Just to speak to that point, you know the gold standard in many institutions nowadays for some of these cardiac lesions is no longer angiography; it is already considered gadolinium MRI or iodinated contrast CT. So, to then go back and say we are going to evaluate efficacy in these agents that are already clinically being used in many areas of the country as the gold standard in these applications doesn't make a whole lot of sense to me, and I think we can extrapolate from a lot of the data that is already out there for some of these very experienced agents.

DR. SIEGEL: Well, I am going to go the opposite way.

DR. CHESNEY: Dr. Siegel?

DR. SIEGEL: I don't think we can extrapolate because of the various varying factors in children, which would be the smaller size; the faster heart rate; the inability to hold their breath; the motion. I think that is going to make it harder to see or more difficult to see these smaller lesions.

As far as just following up on another comment, I do agree that safety issues have been

proven in the iodinated contrast media, but I am not sure about the efficacy because that has really not been shown in children. I think we still have to prove that.

DR. DILSIZIAN: I actually go somewhere in between.

[Laughter]

And the answer is, as I said before, yes, you can extrapolate but do test again in the kids. The reason I disagree with the comments is that everything we have talked about, whether it is gadolinium, micro bubbles or perfusion, we tested in adults first and then we are testing it in kids. The knowledge base came from adults. We extrapolate to the kids but we haven't really checked the efficacy in the kids, which has to be tested. Yes, there is extrapolation but test again in the kids.

DR. SABLE: I think, as everyone seems to be agreeing, it is not a simple answer. First of all, we can't come up with a blanket answer for our different modalities. Just to use echo as an example, I think if you divide patients by weight or size above a certain age and weight there is probably reasonable utility to extrapolating for a

given patient population. For example, a 14-year old who had Kawasaki disease with a structurally normal heart would be a very reasonable population to study, very much based on extrapolating from adult data, although I think it should be done in children also. Conversely, a 3-year old who had a transposition repair in whom we want to try to assess regional wall motion I think has a lot more unanswered questions.

Just to kind of cover one other thing about gold standards versus other ways to design tests, I think a lot of us feel that MRI or contrast-enhanced CT may be a gold standard for some things, but the reality is that in most adult studies that I would pattern my pediatric studies after they are not using gold standards because it is much more difficult to design tests using a very subjective standard which is widely accepted as having a physician or a group of physicians look at different segments of the heart and saying I can see it well; a little bit; not at all, and asking the question does this modality improve my ability to see what I am trying to see. Most tests are much more easily designed but clearly not as elegant as having a gold standard such as MRI or CT

or the ultimate gold standard which would be surgical or pathology which we rarely have.

DR. CHESNEY: Dr. Geva, can we extrapolate from adults to children?

DR. GEVA: I agree with Craig that this is complex. There is no blanket answer. I would say with regard to the gadolinium MRI that it is age related and you can extrapolate a little bit to the adolescent and adult with congenital heart disease perhaps. But when it comes to young children with small body size the answer is no.

DR. CHESNEY: Dr. Loewke, does that help with your question about whether we can extrapolate adult to pediatric data?

DR. LOEWKE: Yes, it does. Thank you.

DR. CHESNEY: Yes, Dr. Fogel?

DR. FOGEL: Listening to all my colleagues talk, you know, I do agree that for children who are in the adolescent age group that are getting close to adulthood you could potentially extrapolate from adults to children. But I guess, again using the terminology of surrogate, when you are talking about this you are really talking about using adult studies as surrogates for looking at childhood efficacy in these patients. You know,

using surrogates has all sorts of issues and problems. I mean, the Fleming and Demetz article basically states that a whole lot, and I would still be very, very wary about doing that.

But using gadolinium-enhanced MRI or CT as a gold standard, if you do it already why do more clinical trials? I think what we are missing in the literature is rigorous, large-scale trials that look at this. We have numerous reports with small numbers of patients that add up to a certain number--maybe add up to a mildly large number of patients but we don't have large-scale, rigorous clinical trials that look at it. Then, there is anecdotal evidence but I think if we are going to serve our patients properly we need to have the data to then show them.

DR. CHESNEY: Dr. D'Agostino, did you have a comment?

DR. D'AGOSTINO: I wanted to comment on the trial design. I am not sure, given what I have heard and what I know about these procedures, that clinical outcomes are necessarily a useful way, just to endorse what Mark was saying, because there are so many other things that go along with the actual decisions in terms of what medical practice

is going to do beyond the imaging.

The other comment is that I would have thought, again from what I know and what I have read, that a simple trial that you can do here is basically to have the individual go through this procedure with and without the imaging agent, or different levels of the imaging agent, and then ask the question does the higher level of the imaging agent somehow or other add more information to improve the clinical decision on that individual. It is a simple trial and the point is how do you decide on the clinical information. You know, the sort of subjective way of having a panel do it, and so forth, blinded or unblinded, is a matter for discussion but I don't think we want to run to the notion of clinical outcomes, and I do think that the trial design doesn't have to be very complicated and we should try to avoid that. But the outcome being clinically meaningful is a real trick, be it a gold standard or something else.

DR. CHESNEY: Dr. Sable, and then I think we will go on to question number two.

DR. SABLE: I want to add one more comment about extrapolation. I think that it is important--and I am kind of biased--to

differentiate what I do from what all of my colleagues do. All of my colleagues are already using contrast in some percentage of the studies and that is probably the rule throughout the country. Conversely, there are almost no pediatric echocardiographers using contrast and the idea of us using contrast, although I am obviously an advocate for it, is a much bigger leap. For us to even think about using it in our clinical practice needs an incredible amount of push and support. So, even if you could extrapolate, if I have a 17-year old who comes into my lab who has the exact same criteria as an adult and I want to do a contrast study, it is going to be a much bigger issue for me to do it. But we do have patients that we would like to do in our lab. So, the practicality of the issue is that even if you could extrapolate, the pediatric cardiac community needs additional enhancement to undertake contrast.

I will just kind of end by using the example from Dr. Gardiner's talk yesterday. A company that makes Definity and a nuclear medicine agent was very adamant that we think about using his agent for a population of maybe 4,000 studies a year but didn't even mention using one of his other

agent for a population that has a million studies a year. So, I think that just kind of brings home the point that there is just a huge gap between using contrast echo in the practical setting and using the other agents.

DR. CHESNEY: Dr. Siegel and then Dr. Santana.

DR. SIEGEL: Just one comment about the research possibilities, I think designing these trials in children is going to be difficult because you can't really use different concentration doses of drugs. It would be very difficult to get it through an IRB and you certainly can't do it in the same patients. You would have a very mixed patient population.

One of the issues we haven't addressed is, you know, do we need to get down to the level of doing animal research and really getting back to basics? It is the only way I think we will be able to look at different doses versus enhancement and different flow rates, if that is important to you, versus enhancement, and I don't think we will be able to do that on a pediatric population. Adults, yes, probably but not in children.

DR. CHESNEY: Thank you. Dr. Santana and

then we will see if we can start--

DR. D'AGOSTINO: Can I make a comment?

DR. CHESNEY: Yes.

DR. D'AGOSTINO: When I was talking about the trial I was saying a simple trial but I didn't say it would be simple to do.

[Laughter]

It is a different matter altogether in terms of can you operate it. But the design of running to a clinical outcome and so forth I think is a much harder to thing to do and probably has tremendously difficult interpretation problems.

DR. SIEGEL: I think we are proving this whole thing is going to be difficult to do.

DR. CHESNEY: Dr. Santana first and then Dr. Loewke.

DR. SANTANA: Having experienced sitting through pediatric oncology committee meetings at two separate meetings where we discussed the issue of extrapolation of adult oncology data to pediatrics, I have learned two lessons that I think may be relevant to this discussion. The first is that although I think in general we agree that it is not wise to extrapolate adult data directly into pediatrics because there may be different disease

processes; there may be different issues of tolerance; and ultimately there are differences in functionality, PK, organ maturity, when forced to think about this issue, the pediatric oncology committee did come up with a few examples in which we were able to fulfill the criteria that the disease process was similar enough that it was not ethical to do efficacy trials in children, and we should put our resources in doing the type of PK safety studies that are more relevant.

So, the challenge I think for my colleagues--although we all like to say that in general terms we should not extrapolate, the challenge is to come up with examples in which you can extrapolate and that will save us time, effort and safety for our patients so that then we can do those studies more wisely and capture that data quickly and get more information out to consumers and practitioners.

So, that was just a word of wisdom by extrapolation. We all like to say, no, let's not extrapolate; they are different. But force yourself to think that there may be scenarios in which you will be able to extrapolate and those are the ones that I think we need to bring forward to

resolve some of these issues.

DR. CHESNEY: Dr. Loewke?

DR. LOEWKE: I just wanted to make a comment that seeing more doesn't necessarily mean a benefit. These drugs are not without risk. So, obviously, the utility of the information you are getting is very important and that is, again, a risk-benefit assessment.

DR. CHESNEY: Dr. Glode and Dr. Fink, and then I think we need to push on to begin question two.

DR. GLODE: I just wanted to clarify a question and I think reemphasize the comment that Dr. Siegel just made. It seemed to me, or at least I wanted to confirm that for some of these agents not only dose but infusion rate are issues to be potentially studied.

The comment I wanted to make is just a comment very similar to what Dr. Siegel just commented on in terms of if your goal was to find the lowest effective dose--again, a presumption that a lower dose translates to a safer dose--I don't know how you are going to do that in children. In animals, yes, and hope that that translates or something. But it does seem very

problematic to say here is our standard dose X and we are randomizing people to half X, and the endpoint is that we couldn't read your study and it gave us no valuable information. So, now we need to sedate your child again and do another study. So, the study design is pretty problematic in trying to get to the lowest dose that gives you an interpretable image.

DR. CHESNEY: Dr. Fink?

DR. FINK: It strikes me that we are spending all this time talking about these agents. It is wonderful. It would also be interesting to see if equal time was spent looking at the equipment. How much of the equipment we are talking about is actually licensed for use in neonates? There are huge improvements in resolution at least with MR and CT that could be done with better design of the equipment or attachments that optimize it for the infant where you get the collectors and the collimators much closer to the patient.

My guess is that there would potentially be more to gain by equipment redesign and algorithm specifically designed for the neonate than by the dyes, and you might be able to cut dosages far more

dramatically by getting manufacturers of the equipment interested in looking at the problem.

Just out of curiosity, are any of these devices actually licensed for use in premature infants or neonates? Because it seems like they come on the market for adults and they get used in kids because that is what is available.

DR. LOEWKE: I don't think that CDRH is here--they were here yesterday--to answer that question.

DR. CHESNEY: Dr. Maldonado?

DR. MALDONADO: Just about that, actually I approached Dr. Feigel, who is the Center Director of Devices, recently because I was curious about how we will go to approve a device for children. He told me that the Center for Devices doesn't approve those devices for particular populations. You are right, Dr. Fink, they are approved for a participant image in this case but there is no reference to where these devices could be used.

DR. CHESNEY: Approved for human use and neonates are human. So. I keep putting off question two but let's have two more, Dr. Fogel and Dr. Danford.

DR. FOGEL: Yes, I just wanted to respond

to the question about dosing. At least for MRI for example, as I mentioned yesterday, gadolinium is an adjunct to the rest of the study and not a study in and of itself for the vast majority of the studies, not all but for the vast majority of the studies. So, if you have an MRI scan that has half a dose of gadolinium versus a full dose of gadolinium versus a dose and a half of gadolinium, you wouldn't necessarily get uninterpretable information from the entire study because you would have done the non-contrast part as well and maybe gotten the information but you certainly would be able to make a diagnosis. Now, would it change the clinical outcome? Would the surgeon not like it as much as if we had done the 3D and had them take a look at the 3D? Probably not but you certainly would get that information.

If you address it along the same lines as you would in a blood pressure clinical trial, it is the same thing versus getting a placebo. I mean, you know, you have to accept that when you enter into a clinical trial there are some people who will benefit and some people who won't benefit.

DR. CHESNEY: Dr. Danford?

DR. DANFORD: I am going to quibble for

just a minute with Dr. Loewke's remark that we really need to prove that better imaging translates into better outcomes. In an ideal world, of course, we would prove that but, as a practitioner in pediatric cardiology, I think that the better you see this stuff the better job your surgeon and your interventional cardiologist is going to be able to do for the patient. We haven't yet reached the plateau where we have such high quality imaging that we absolutely know stuff. It is still shades of grey and degrees of confidence and we are still surprised sometimes by what our surgeons find that we were not expecting.

And, I think the proliferation of all of these imaging modalities that we have heard about speaks to that. You wonder why are we developing all of these things. Don't we already have either an accurate diagnosis or not? I think it is more a shades of grade phenomenon and the better imaging we get, I think the better outcomes we are going to have. I have no data to support that but I think that is true.

DR. CHESNEY: Thank you, Dr. Danford. I know Dr. Siegel has to leave a little bit early this morning--oh, that is different than my

question two. My question two says please discuss each of the following questions for cardiac CT. I must have the wrong set of questions. Sorry.

DR. SANTANA: Dr. Chesney, may I make a comment?

DR. CHESNEY: Dr. Santana?

DR. SANTANA: As I have heard all the discussions yesterday and today, I am still a little bit like Skip was yesterday, disoriented, because we are talking in certain scenarios about anatomy, in certain scenarios about perfusion, in other scenarios about the tools, the machines, the operators, in other scenarios about the agents. So, one thing that would be very helpful to me, as we go through each of the modalities, is if the panel of experts, one or many, could specifically tell us what is the question that is most clinically relevant to them. If they were given one choice to do a study with this modality and this patient population, what is the burning question that they want answered. Rather than, you know, trying to design fifty trials, it may be better if they would help us or the FDA by saying this is the question that is most relevant right now. Let's put our money into it; let's put our

effort into it; let's move forward.

DR. CHESNEY: Thank you. That was maybe your idea yesterday. Somebody raised that as a potential way of addressing this.

DR. D'AGOSTINO: That is what I raised yesterday but was 24 hours too early I guess.

DR. CHESNEY: Well, you phrased it differently in the van. It came out very clearly, what is the burning issue for each one of our experts. The FDA has put a lot of thought into these questions so we want to be sure to address them as well, but maybe each of you could start by saying in the best of all possible worlds, this is the question that I would like addressed and then I will address (a) through (f). Dr. Siegel, you are starting.

DR. SIEGEL: Okay, we will start with cardiac CT. I think there were sort of three basic elements discussed yesterday and it is really safety, dose and efficacy. If I look at that for CT, the safety has been proven. My issue is dosing and actually other elements of technique.

I don't know the dose that will work best for CT. We use doses that are based on information dating back to the '60s and '70s and that is the

standard dose we use now. My feeling is that for CT we can get away with a lower dose. I have used it but we have no large series on that. So, my question is what is the minimum dose that we can use that will provide an effective or diagnostic image?

The other issue for CT is what is the flow rate that will also provide an effective and diagnostic image? So, those are the issues I need, the more technical factors to optimize a study for children.

DR. CHESNEY: That is very valuable. Maybe we could go (a) through (f) now and you can just give us one-word answers and then we will move on.

DR. SIEGEL: Okay, imaging agents further study? No, I think it is a mature population and the safety of these agents has been proven.

What population should be studied? I think we addressed that before. We could divide it into four populations, the vascular lesions, valvular lesions, septal lesions and complex heart disease.

I will step back for a second and say if we look at the vascular lesions such as the aortic

lesions, the arch lesions and some of the pulmonary slings we may be able to extrapolate on that. There are series both in the MR literature, primarily in the MR literature and some in the CT literature and certainly in the adult literature that CT is efficacious for the diagnosis. Those are large structures; it is going to be valuable.

But I think the other three categories, valvular lesions, septal lesions and complex heart disease are patient populations that need to be studied. You can further say patient population by age, and I think the age we really need to look at is the younger patients. For CT, those are patients who are six years of age and younger, the ones who are more likely not to cooperate or hold their breath and are smaller in size.

Moving on, what disease states should be studied? To me, that is the same as sort of the patient population unless you have another definition.

What endpoints? Again, endpoints, to me, are going to be different from gold standard, and that would be clinical outcome either leading to further studies to validate the finding on CT or termination of imaging studies. We could, of

course, talk about research but I think that will come a little bit later.

How should a trial be designed? If I think the burning concern is dose and flow rates, as I mentioned, it is going to have to be animal studies. We cannot do that on children. It just will not be approved. I can't imagine any IRB approving that. So, that would have to be an animal study with varying doses. I have the numbers but I don't think we have to say the exact numbers. Varying flow rates and then looking at enhancement, standardizing the study by automated means and looking at various structures in the heart and even outside the heart. That I think is the type of trial that I would be designing.

By designing that type of trial you would also be able to look at whether there is diagnostic information, whether we can see these structures. Hopefully, at that point we would be able to translate some of this use in children. Perhaps these studies could also be done in adults; they are being done and we might want to look at that information when those trials are completed to see if we can extrapolate that information and where our starting point would be.

How should the standard for comparison be defined? Is there a gold standard? I think if we were to do those studies the gold standard would be cardiac cath. I think that has been the gold standard for a while. That is probably what I would suggest for the animal studies.

I think if we do a pediatric population it is going to be more different because of the radiation issue and we would not really be able to say let's do a cardiac catheterization on everybody; the risk is going to be too great. You would have to redefine your gold standard and then I might say let's go for echocardiography, hopefully with some contrast agent by that time, to minimize radiation risk. That is always going to be the concern when we design any study for CT.

DR. CHESNEY: Thank you. Comments? Dr. Nelson and Dr. D'Agostino and then maybe Dr. Loewke could tell us if we have answered everything for question number two or three.

DR. NELSON: I agree with your observations about the risk and how it would be hard to design a trial like this, but let me see if I can ask you a question that might give a little bit of an opening. Would there be a population

that might be going to surgery anyway where the surgeon would say if you don't see this as well as you would because you have done half a dose of contrast I can check it operatively and it won't put the patient in any different risk relative to having been exposed to the risk of a lower quality study because you have done a lower dose of the CT? If it is possible that the gold standard would still be done, in whatever instance this might be, and the person doing it would not have lost information that they wouldn't be able to verify at that time that you might be able to make an argument for putting the child at that risk. You might, but it is a reach.

DR. SIEGEL: Right now you couldn't vary the dosage. I think if I go and start saying instead of using 2 mL let's do our studies with 1 mL I am experimenting without approval.

DR. NELSON: I am assuming you would design a protocol that way. I am just thinking that the point at which, from a risk perspective, an IRB might say it is justified is if the gold standard would still be done, and at the time that that gold standard would be done, such as surgery, the operator would not have lost information that

they couldn't otherwise verify, and there might be a chance that they would let you take the risk of a lower quality study.

DR. SIEGEL: In some places it might, but you are absolutely right, you might say that I want to do, you know, 1 mL/kg based on the adult work--it has to be based on something, and that would be a possibility. Then the patient--to be part of the study the clinician would either have to agree to do a cardiac cath because he is going to do it anyhow or the patient is going to surgery. I mean, I have that type of study now, a rather limited study, so I think that is doable. But, again, it is going to be a little more difficult to get through a number of IRBs.

Just as a quick comment, a few years ago I tried to get a similar study through by saying I would like to do patients with reduced milliamperage or current. We were using 200 and I said let me drop it to 150, 100 and then 50, and I couldn't get it approved because they were concerned it wouldn't be a diagnostic study and I would be repeating it. So, by dropping the contrast, I think there may be the same concern about that. I think we can design a study. It is

going to be a little bit more difficult to do given the radiation. That is why I suggested the animal model. But I agree with you, there would be some possibility to do that.

DR. CHESNEY: Dr. D'Agostino?

DR. D'AGOSTINO: I have three comments. The answer to part (a) where you said nothing needs further study, I thought that was the whole purpose of the question, to sort of identify which agents do need further study.

The second and third questions I have is that if we had the design that I was calling simple before and one was the echo and the other was the imaging agent, that gives you the two measurements on the individual to make those comparisons and try to get the clinical benefit, and so forth, so it fits in very much I think with what I was suggesting earlier.

The third question in terms of the dose, couldn't one do some animal studies, maybe some sort of Phase II type of studies getting some idea of the dose, and then move on to the Phase III study where you have the dose fixed and also the injection rate, and so forth? I mean, a little mixture of the animal studies to get some

information and move to something like a dose-ranging study with a small number of subjects to give you an idea. The study for the efficacy is the fixed dose, fixed infusion echo versus the CT.

DR. SIEGEL: Going backwards, I think I agree with you on the last point. I think I mentioned that we start with an animal study with the varying doses and then translate it to pediatric patients using echo as the comparison of the standard.

The contrast agents that are being used for this have been studied in detail. There is a lot of information out there. They are approved. Their safety is known. I don't think we are going to see new contrast agents. It is not the contrast agents; it is really the dose and flow rate that we are dealing with. These are safe. They work. We don't need to develop new ones. What was your second question?

DR. D'AGOSTINO: What I was calling a simple design before, that you need two measurements and you could do an echo on an individual and then the imaging agent at a fixed dose.

DR. SIEGEL: I agree. You start with the

CT and then we do the echo to confirm it.

DR. CHESNEY: Dr. Stylianou, you had a comment?

DR. STYLIANOU: I have a comment also. As far as the animal studies are concerned, even if you do the animal studies you still have to test in humans eventually. And, my guess is that a clinical trial is probably unrealistic because of the toxicity involved. One possibility would be a case-control type of study. You could have two groups and match them by some characteristic like age, body mass index or some kind of characteristic, and you can have a study doing it that way.

DR. CHESNEY: A prospective study?

DR. STYLIANOU: A prospective study.

DR. D'AGOSTINO: What are you matching?

DR. STYLIANOU: At this time I am not sure how to match but at least it would be a way--

DR. D'AGOSTINO: But what is it? People with two different procedures?

DR. O'FALLON: Stratifying.

DR. STYLIANOU: Right.

DR. SIEGEL: But I don't see how this gets us to dose or flow rate issues.

DR. STYLIANOU: You test it. You said the doses are already safe but is it tested?

DR. SIEGEL: The current dose is tested but we don't know how low we can go on the dose--

DR. STYLIANOU: Right.

DR. SIEGEL: --and get a diagnostic image.

DR. STYLIANOU: So, basically you have to test a lower dose to see if it is effective.

DR. SIEGEL: Correct, and again it can be different in a pediatric population because if you get a non-diagnostic study you have irradiated a patient for no reason and then you have to either repeat that study or do another study. That is the dilemma we are in with CT because of the ionizing radiation.

DR. CHESNEY: Dr. Sable?

DR. SABLE: I think we need to be a little bit careful when we are designing studies. If we are going to use echo as a gold standard, which is safe, simple, low cost and portable, then why do we need to do another study that may be more risky? I think CT has a lot of wonderful potential for many things that are much better than echo--

DR. D'AGOSTINO: Couldn't you ask do you get more information out of the CT than the echo?

DR. SABLE: Well, if we are asking that, then we shouldn't be using echo as a gold standard.

DR. D'AGOSTINO: It is not a gold standard, it is a comparison.

DR. SABLE: I think when we design our studies we just need to be careful--

DR. D'AGOSTINO: But you can use a gold standard if you have a gold standard or you can use a comparison. The question is do you get some information from the CT.

DR. SIEGEL: Right. I mean, we are not saying that CT becomes the first imaging study. Echo is still the first imaging study. But let's say the echo is equivocal, then we are going on to CT, and I am basing this on our adult population, as I said, with congenital heart disease which is 1,200 patients and we have done a number--at least 300. We are doing them because of equivocal study or sometimes there is a murmur and it is the first diagnostic study we are doing. So, the question is, you know, is it efficacious and can we use it if there is an indication for it because of an equivocal echo or because it is an incidental pickup. If it is an incidental pickup, do we need to go further? But I don't think this is a

first-line imaging study.

DR. SABLE: Sure, and I certainly agree with all that. This is not a question that CT doesn't add a lot to equivocal echoes; the question is when we are designing studies, if we are putting echo as part of your study design to validate CT, then I think an IRB could look at that and say, well, why are you even doing the study? I think that is a different question than whether or not CT adds to equivocal echoes. I think we need to be careful about using circular logic.

DR. SIEGEL: Yes, I am agreeing with you. I think if we do the echo and it is diagnostic we don't go further. But we would have to identify the population that would have an equivocal echo, or perhaps postoperative if it is Mustard or Senning procedure and there is a question of a leak and you need a better definition. That is a large population and perhaps the postoperative patients might be another population. But we are not here to really design the study in detail right now.

DR. CHESNEY: If I could ask FDA about a procedural issue here, if we are going to have to discuss (e), trial design, on each one of these we are going to be here for several days. I am

wondering if we can't just omit (e) and--

DR. NELSON: And the ethics disappear--

DR. CHESNEY: And I am not making the ethics disappear; just to get through each one of the questions for everything but (e), and then we address issues of trial design. Can I get a show of hands from the pediatric committee? Does that sound like a reasonable approach?

DR. O'FALLON: I think we could talk about design in about three minutes and get that off the board. All right? May I do that?

DR. CHESNEY: Wait just a minute, I have to absorb that.

[Laughter]

DR. SANTANA: Joan, I agree with that. I think if we frame the question that Dr. D'Agostino and I have been trying to push, which is tell us what is the question that is more relevant in your disease and what you want to do, then we could have a brief discussion about how that trial should be designed rather than discussing every single permutation of every possible trial to be done. I think if we look at it that way we should be able to help the discussion.

DR. CHESNEY: All right. So, before we

address any of these questions we will just address the most important thing for you and how you would like to set up the study, and then we will come back to these questions. Is that what I am hearing? That is not what Dr. O'Fallon is suggesting, Dr. Santana. You are suggesting that we ask each person to tell us the most burning question and how they would design the trial.

DR. SANTANA: Right, like Dr. Siegel did. She did that I think very appropriately. She told us what her issues were if she wanted to answer this question. She wanted to look at dose. She wanted to look at infusion rate. She wanted to look at animal models and then she was thinking how she would take that into a clinical trial, comparing it to another modality. If we have that kind of discussion, we may be able to get some comments like Skip was making about whether it was ethical or whether there would be issues that would have to be approached in a different way.

DR. CHESNEY: I just have a feeling that we are going to be going on and on if we get into that. All right, Dr. O'Fallon, if you can solve it in three minutes we are wide open.

DR. O'FALLON: I have been sitting here

quietly, letting you guys have your say, but I think that we can cut through on the issue of design. I think that there is a basic strategy that applies to all of them. Not all of them will use every piece but there is a basic procedure that has to be used to go through this and we don't need to deal with it for every single modality.

I think that basically you have to define your study goals. Are you looking at movement? Are you looking at anatomy or are you looking at what? Disease identification, whatever? But you decide the goal. Then you have to rank in your particular disease the contrast agents that are of most importance to you. Then you have to define what initial dose levels you want to study based on adult levels and/or animal models, but, you know, you have to decide what you want to do. Then you do your pharmacokinetics and dose levels and flow--in this case flow levels, but that would have to be well defined before you went into the children. But then when you had realistic levels you would go ahead and perform the PK and dose level which could include flow level studies.

Now you have to define your age groups. Are you going to do it in adolescents? Are you

interested in neonates? What are we dealing with? But you have to define that and you would have to do them I think in each age group in order to characterize the adverse events. You know, everybody is making the assumption that they know what they are, but they have to be defined to at least get some preliminary data on adverse events in each of these age groups that you choose to use it for.

Of course, you have to define your success endpoint which would be in terms of image quality or diagnostic utility. That you would have to design for each one of your things. That is what you would be talking about up here.

I mean, there is a basic strategy for doing the design in these studies and, like Dr. D'Agostino was saying, it is pretty much a simple deal because they really do have PK and dose level information in order to provide the kind of information that will be needed for labeling.

DR. CHESNEY: Dr. Beitz?

DR. BEITZ: I would say that what Dr. Siegel responded with was really excellent and is the kind of thing we are trying to get from the panel. So, if we could go through the different

modalities in turn and just get some brief answers and then let the panelists and other members have a discussion for maybe five, ten minutes afterwards and then go on to the next, that would be I think plenty.

DR. CHESNEY: Thank you. So, we will proceed to cardiac MRI. Dr. Maldonado?

DR. MALDONADO: I just have a quick question for Dr. Siegel. I think that you seem to be comfortable with the safety of these contrasts, as I heard, but I still don't understand why you want to go down in the doses if you feel that the safety is not a problem. The reason I ask this is because when we are trying to go to small molecules in my field, go down in the doses, we are trying to optimize safety without losing much in efficacy. Since you seem to be comfortable with the safety, are you trying to optimize the efficacy with going down with the doses?

DR. SIEGEL: Well, i think as we discussed yesterday, we think that less is better so it would be nice to be able to use less. The safety is proven. The other thing in CT is if we can lower the dose and give less volume we may be able to inject it faster and get better enhancement because

if we can increase the flow rate, then we can increase our enhancement so we will get better images. They will be better diagnostically; I am not sure, you know, that they will be better images from our quality standpoint. So, lowering the volume makes it easier to get the total amount of contrast in somebody who is small.

DR. CHESNEY: Thank you. Dr. Fogel, if you would first tell us what is the most burning issue for you if you had a wish-list, and then address (a) through (f) and very briefly (e)?

DR. FOGEL: Sure. Well, in my mind, I have to say there are two most burning issues. One is anatomy and being able to get efficacy data and safety data on anatomy with relation to dose. The second burning issue, real quickly, would be perfusion and viability, which I think is very under-utilized in congenital heart disease in our patient populations and I think gadolinium-enhanced MRI could add greatly to that. So, those are in general the two burning categories which I would like to see addressed.

What imaging agents need further study? Well, in MRI it is fairly easy. The vast, vast, vast majority is gadolinium and nobody is using the

manganese or the superoxide iron particles, although there are some studies being done but I don't know if they are being done in cardiac very much. So, for me gadolinium would be the only agent.

What patient population should be studied? Again addressing the anatomy and perfusion, for anatomy I think you could probably lump all the extracardiac vasculature into one patient population. The key would be the size of the patient whether they be neonates, infants, toddlers, children, and then adolescents. There was a good case made that you could probably extrapolate adolescents from adult data so I am not as strongly married to that as I am to neonates, infants, toddlers and children. So, I think those would be the patient populations.

In terms of the types of disease processes and the patient population, it would be those patients who have extracardiac anomalies like coarctation, postoperative tetralogy, postoperative transposition. Those would be the patient populations--the postoperative Fontan patients. Those would be the patient populations that I would target.

In terms of perfusion and viability, again I would say that we would have to address both the size issue--neonates, infants, toddlers, children, and I would put in as a patient population the people who are at most risk for myocardial perfusion defects and scarring of the myocardium. Those, for example, are patients after a Ross procedure where they get coronary manipulation; patients after transposition of the great arteries; after arterial switch procedures who also get coronary manipulation; and those patients, although rare, who have native coronary artery anomalies, like anomalous left coronary, and come to medical attention. All those patients would have the opportunity to benefit from myocardial perfusion.

What endpoints should be used? As Skip was alluding to, I think the gold standard would probably be surgery, and for perfusion I think nuclear medicine would probably be the gold standard that I would use for the perfusion defects because that is the most widely accepted, although it still has issues with radiation and things of that nature. But this is a wish-list; this isn't how we would actually do it in practice.

In terms of dosing, presently for

extracardiac anomalies, for example, we usually use a double dose of gadolinium so I would advocate maybe just four categories; double dose, one and a half, one and then half a dose of gadolinium, just thinking off the top of my head how one would do that and randomize people to those four dosing levels.

I would just like to point out that with MRI gadolinium is an adjunct and we will get other information from the study which will help the surgeon. I would also have a gold standard which would be surgical observation. You know, in any trial in the high risk procedures that we do, unfortunately, sometimes we will have pathologic observations but in either case we will have direct human observation which would be the gold standard.

I also want to point out that when we are looking at these dosages we know what the upper dose is and we have gotten a lot of safety data from anecdotal evidence from various studies, numerous studies in the literature on upper dose of gadolinium. It is the lower dose and the risk of not getting a diagnostic gadolinium study rather than giving too much and causing toxicity. So, I think that is an important point for us to

remember.

Then, how should the standard for comparison be defined? Is there a gold standard? In answering the other questions, you have to necessarily answer that. So.

DR. CHESNEY: Thank you very much. I am hoping that when we get through we can come back to issues of study design. Dr. Nelson?

DR. NELSON: Mark, for perfusion issues now what tests are being done? I mean, would you do a nuclear scan? DR. FOGEL: Normally what we will be doing will be nuclear scans and/or cardiac catheterization to see if there was any coronary artery stenosis or some microcirculation perfusion abnormality. So, these would have been done clinically anyway and the question would be whether or not MRI--because of its greater tissue characterization, no ionizing radiation, being non-invasive--would have a benefit so that in the future you would be able to obviate the need for cath and/or nuclear studies to a great degree and just be able to use MRI instead.

DR. CHESNEY: Go ahead.

DR. NELSON: Just as a follow-up, I think there can be some general principles outlined in

terms of trial design that if, in fact, the gold standard would be performed anyway--I mean, I think that is an important one, then you want to avoid a repeat procedure. So if, in fact, the gold standard would be done anyway and the risk of a repeat procedure is not there because you would then proceed to that gold standard without repeating your MRI, I mean, I think that is the general principle. So, I think you can outline some general principles of a trial design that would allow you to generalize across all of these possible scenarios.

DR. CHESNEY: Dr. Ebert had his hand up, then Dr. Fost and Dr. Santana.

DR. EBERT: Just a follow-up question, Dr. Fogel, I think earlier in your comments you mentioned that you could also design this is a way where you would not use contrast in an MRI. That could also serve as a control in some of these studies.

DR. FOGEL: Yes, well, what we basically do is we basically do the non-contrast studies first, if nothing else, as a localizer to how we are going to do the contrast studies. So, the contrast is more of an adjunct to it rather than

standing on its own merit, although there are some times when it does stand on its own merit but as a general rule we do the non-contrast enhanced first, get some information that way and add more information by doing the gadolinium.

DR. CHESNEY: Dr. Geva, you have some expertise in this area. I wondered if you wanted to comment. Then I have Dr. Fost, Dr. Santana and Dr. D'Agostino.

DR. GEVA: I just wanted to comment about the endpoint and reference standard for a potential study design. I would have some concern about relying on surgical observations alone. Number one, it does have its own limitations. Although it appears on the face of it as if the surgeon opens the chest and sees everything, that is far from being the case. I would propose for consideration as a blanket reference standard for studies on diagnostic accuracy you might want to look at something like summation of all available diagnostic information on a patient. Some of these patients will have clinically indicated cardiac catheterization with extra angiography. Actually, some will also have CT. Some will have surgical observation. Some will have autopsy findings.

That information can be combined together.

DR. FOGEL: I just want to say that I understand that surgery is not a be-all and end-all in and of itself, but any gold standard has a false-positive, false-negative and sensitivity and specificity rate. And, I think that for most gross anatomical manipulations that the surgeon is going to do for a diagnosis or for an extracardiac structure that they are going to be sewing together, they are going to be deeply involved in manipulating the tissue itself, and the success or failure of the surgery depends upon how well they manipulate the tissue we are trying to image non-invasively and that is the best gold standard that we have. I don't pretend to say that that is the be-all and end-all by any means, but at the moment I think it is the best we have. Comparing it to echo and angiography, I don't think that they are gold standards in the sense that for the things we are talking about, that patients have to go surgery for, it is ultimately going to be up to the surgeon to be able to manipulate the tissue in such a way to have a good clinical outcome for the patient, and that seems like to would be the gold standard we want to shoot for. Again, surgeons can

be wrong, heaven forbid, and it certainly is not 100 percent of a gold standard.

DR. CHESNEY: Thank you. Dr. Fost?

DR. FOST: A couple of questions, Dr. Fogel. So, you are proposing doing children who are already scheduled for a cath to look for perfusion problems, and you are suggesting doing an MRI before you go to cath?

DR. FOGEL: Well, this would be patients who you would be considering who might have some coronary artery issues and some coronary artery problems. I mean, there would be clinical justification in all patients who have coronary artery manipulation that you would want to see whether or not coronary artery manipulations that were preformed by the surgeon, for example after a Ross procedure or after an arterial switch procedure, whether or not that put any of the myocardium at risk. We do have some individuals after those surgeries who then get coronary ischemia. We see this on the EKG and other things. Or, decreased myocardial performance that might suggest that there may be some coronary perfusion issues that we would need to address. Now, the knee-jerk reaction and the first thing you would go

for would be a nuclear medicine study, and other individuals would go for cardiac cath. Therefore, as people are saying, you would have done those things anyway. These would be patients who are at risk who you would have done those things anyway for, and now you would add on the MRI as an additional test.

DR. FOST: So, this would be a non-therapeutic MRI for this child.

DR. FOGEL: Correct.

DR. FOST: And that meets minimal risk criteria.

DR. FOGEL: I would believe so, yes.

DR. FOST: Would they need separate sedation for that?

DR. FOGEL: Well, depending on the age group, they could potentially need extra sedation. That is correct.

DR. FOST: And are there data on that question in adults? That is, does MRI predict or correlate with cath data for perfusion problems?

DR. FOGEL: There is a number of papers that have been done in adults, looking at ischemic heart disease and comparing it against PET, that have shown that MRI was very good in that sense, in

actually advocating the use of MRI for that patient population. Can you then say that the coronary artery disease that we see in kids--can you then extrapolate that from ischemic heart disease to congenital heart disease coronary artery issues is another question. I don't think you can but if you have information in adults saying that it could potentially be useful, then I think that would be a good basis for you to then go ahead and move along into kids.

DR. FOST: Might it be different in infants than adults?

DR. FOGEL: Well, most of the time the microcirculation and the actual obstruction that you might find in the major coronary arteries are atherosclerotic in nature, as opposed to patients who have undergone cardiac-pulmonary bypass and actually taking the coronary arteries and moving them, and flipping them, and putting them in all sorts of other geometric ways you might not necessarily think that it may be as efficacious in kids as it might be in adults. Plus, with kids you have smaller children and you need a greater resolution to tell differences in myocardial perfusion. In children you might need a 1 mL or

sub milliliter pixel size to be able to tell issues of hypoperfusion whereas in an adult it may be 1.5 mL, 2 mL limit of resolution with which you might be able to tell perfusion defects. So, you may not necessarily think that you could do it in adults and not doing it in kids.

DR. FOST: Thank you.

DR. CHESNEY: Dr. Santana, D'Agostino and Nelson, and we will let you go first and then we will go on to the next question.

DR. LOEWKE: What I am hearing is you are looking at probably two types of clinical trials, one to get an anatomic delineation type of a claim, and one for a functional perfusion type of claim. I know you said this was a wish-list but I have to go back to your perfusion gold standard, just to throw it out there. Nuclear medicine is not approved. The radiopharmaceuticals are not approved for perfusion in kids. So, do you have any other suggestions?

DR. FOGEL: Yes, but it is actually, in fact, in clinical practice used all the time in children. I don't know the numbers specifically but the numbers were shown yesterday. It was a considerable number of patients in the childhood

population in whom it is used. I guess outside the regulatory arena it is considered the gold standard. Cardiac catheterization doesn't necessarily address the microcirculatory issues that would be addressed with perfusion defects that are shown by MRI as well as by nuclear studies.

So, I think if you were just going to use cardiac cath alone it would be a suboptimal trial and less accepted by the general community of physicians than if you use the radiopharmaceuticals. I know that that might present a regulatory issue from your standpoint but I think you might have--and I don't know if that is a total brick wall that can't be broken down or if it is something that can be finessed and side-stepped, but I think it would be better for general acceptance among the entire medical community if something like radionuclide pharmaceuticals were used. And, I am not a big fan of radiopharmaceuticals but it is a gold standard. So, that is what I would use.

DR. CHESNEY: That is why we are meeting. Dr. Santana, Dr. D'Agostino, Dr. Nelson, and then we are going on to the next question. We have just had another question added so we need to get

moving.

DR. SANTANA: Can you clarify for me--I should have asked this yesterday but it didn't come up until today when I realized what you were talking about in terms of your potential trial designs--how many times within a given MRI can you administer gadolinium or, because it has such a half-life time, is it that you can only do it once and you are over with it?

DR. FOGEL: Well, we can give it a couple of times as long as the dose during that entire session does not exceed the maximum dose which is 40 cc or a double dose up to 40 cc, depending on the kilo body weight. We do that a number of times for the perfusion abnormalities so, for example, we will inject half a dose of gadolinium, get three or four slices, and then wait a few minutes, inject another half dose, get three or four at different orientations and then do that a couple of times; then wait five minutes and then do the viability portion. So, you get basically two for the price of one.

DR. SANTANA: So, you could do a study in which there was an intra-patient escalation of dosing once you defined what the target lesion was

that you were after. So, to address some of your issues of dosing of gadolinium the patient could have an escalation--I was thinking about anatomy actually, not perfusion. Once you identified what the target lesion was that you were looking at with X dose, you could administer that patient a different dose and see if you improved your efficacy of defining that target lesion within the same patient. So, the incremental risk would be the risk of giving another dose certainly, and the incremental risk of more time under the machine.

DR. FOGEL: Right, you could do that with half a dose and one and a half doses, which would actually add up to two doses. You can't do it with the double dose because that is the maximum you can give. And, you couldn't do it with one dose because you couldn't give one dose and then do another dose because they are the same dose. But you could potentially do that with half a dose and one and a half dose so you could simplify the trial to a certain extent that way. That is a very good point.

DR. CHESNEY: Dr. D'Agostino?

DR. D'AGOSTINO: Fortunately, Victor just asked half of my question. The other half is to

the FDA. If you did a design that had no contrast versus contrast at some fixed level, would that be an acceptable design if you could show clinical benefit, gold standard and so forth with none versus some and get more information standard some?

DR. LOEWKE: You would have to be able to identify that the added information had clinical value.

DR. D'AGOSTINO: Exactly, you would have to show that you do get clinical benefit but, you know, could you do the MRI without any gad in it and then do it at a particular level and show that that particular level does, in fact, add information? Because you automatically do it at no level, right?

DR. LOEWKE: I mean, we have approached things before in that fashion. That was before we have moved forward with clinical utility. So, it would be very important that the added information really had value that you could clearly identify.

DR. D'AGOSTINO: Right, but it is not an unacceptable design?

DR. LOEWKE: It is something that would need further discussion.

DR. D'AGOSTINO: Yes, thank you.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: I have just two comments to follow-up on some of Norm's questions. There is precedent both for local protocols as well as for NIH-funded studies for limited procedural sedation to be considered a minor increase for non-therapeutic procedures. There is also precedent for trying to minimize the risk of sedation by combining the MRI being performed when there is an anesthetic being provided for other reasons, either operatively or that real fancy picture you showed us yesterday, Phil, of the UCSF slide in and out between MRI and catheterization which, sounds to me like the perfect venue for this kind of MRI/catheterization because you are just sliding the patient back and forth a few feet, it would seem.

DR. CHESNEY: We have been asked to include Dr. Moore in all of these modalities. So, that is going to be an additional question and I would like, unless there is some strong feeling, to move on to the cardiac ultrasound, hoping to take a break at the end of that and then we can address the nuclear imaging and angiography. But Dr. Siegel looks insistent.

DR. SIEGEL: One quick comment as we go through the rest of it, I just thought about one other way to do research and to maybe complicate it more, we forgot about simulation models. With all the computer designs out there now, we would be able to look at certain facets at least in CT and maybe in MR using computer models. That is just a thought. It just dawned at me that if I am looking at dose and I am measuring density I could probably do this with a computer phantom, setting up the appropriate computer example. So, it is just another thing to put on the table if anybody thinks that is appropriate as we discuss other modalities.

DR. CHESNEY: Thank you. I am glad you were insistent. Dr. Sable, are you ready?

DR. SABLE: Sure.

DR. CHESNEY: Please tell us what is your most burning issue in the best of all possible worlds, and then if you could address (a) through (f), please.

DR. SABLE: Well, I think to me the most burning issue is to try to incorporate contrast echo into evaluating left ventricular function and wall motion in complex patients in whom we can't get good pictures with routine echo. I think that

is probably the most important thing and would be a starting point as a basis to do other things with contrast echo.

I think in terms of what agents need to be studied in pediatrics, there is the most experience in adults with Optison and Definity so I would clearly focus on those two drugs, both looking at the necessary dosing and safety in anything that we do.

In terms of which populations should be studied, I think there are a couple of groups that I would divide them into. If you think about patients with poor windows, they can be patients like after cancer where you just need functional studies, or patients with complex heart disease that have unusually shaped ventricles or single ventricles, right ventricles acting as systemic ventricles such as in Mustard or stenting repairs. I think another group of patients would be those who would need stress echo evaluation, including patients with Kawasaki disease, heart transplant and patients who have undergone operations that involve the left coronary artery or the arterial switch procedure. I think later on we could move towards doing perfusion studies, but I think the

first step would be to look at left ventricular opacification both at rest and exercise.

In terms of using endpoints, I think that the ideal is using a gold standard and in this case probably MRI or nuclear medicine could be a gold standard, but I think the more practical approach to using an endpoint, and it is probably easier with echo than other modalities because we can vary without increasing risk sedation or time, we can get pre- and post-injection images to see if there is an improvement using the standard American Society of Echo wall motion score. We have 22 segments for every patient so the power of the study could be achieved relatively easily with not a huge number of patients.

In terms of trial design, I would start with a group of patients such as those with poor windows that I had mentioned, and pick a drug like Definity or Optison and use incremental dosing based on weight to get a sense of do we get improved images; how long does that image last for; and comparing it to the pre- and postop and pre- and post-injection state.

A second, probably softer endpoint would be does adding contrast obviate the need to do more

invasive studies? We could do a randomized, controlled study, although the ethics of that may be challenged based on adult literature and we may need to consider using historical controls.

That probably gets to trial design. I think I would start with using an older population and then gradually work my way down to smaller patients. I think I will stop there and answer questions.

DR. CHESNEY: Dr. Loewke?

DR. LOEWKE: I was wondering, you had mentioned stress testing, are you talking about exercise only? Pharm stress only? If you do exercise, how low can you go age-wise and actually get patients to cooperate? I will throw a monkey wrench in here as well. I believe--and there is somebody here I believe from Cardiorenal--that the pharm stress agents aren't approved in kids.

DR. SABLE: Certainly, that is true and there is maybe one more paper on stress echo in children that is on contrast echo in children. That being said, a large number of us do dobutamine stress echo. It is a little bit cumbersome, as one can imagine, to have somebody run and then throw them onto the bed to image them. You can do a

little better with some of the odometers where you are lying flat. Tal can probably speak to this. They probably do more than we do in their lab. But it is much easier to do dobutamine stress echoes and that would probably be the way we go. If you look at Dr. Kimball's study, I think they did 19 dobutamines and 2 ergometer stress echoes in their study. Clearly, we could be having the same panel meeting about dobutamine stress echo and come up with all the same issues that I just mentioned for contrast echoes. We are a little bit further along in that realm.

In terms of age, we have done them down to a year, a year and a half. Then you get into the whole issue of sedation and that clearly needs to be a part of any equation with echo if you are doing very small children. With older children, probably beyond four or five, it is not as much of an issue.

DR. CHESNEY: I have Dr. Ebert, Dr. Gorman, Dr. Moore and Dr. Geva.

DR. EBERT: I have a question for Dr. Loewke. As we go through some of these specifically, does the agency feel pretty comfortable about measures of safety, either short

term or long term, that you are going to incorporate into these, with MRI or with any of the other modalities?

DR. LOEWKE: Obviously, we would welcome any information that you can provide on how you feel safety should be incorporated into trial design.

DR. SABLE: I think with any type of stress echo or contrast echo we would need to monitor vital signs and pulse oximetry very frequently, probably similar to some of the conscious sedation protocols, for a set period of time after the study is done, probably at least an hour. Obviously, we would be watching for more severe adverse events and reporting those.

DR. CHESNEY: Drs. Gorman, Moore, Geva and Nelson.

DR. GORMAN: I was hoping not to have to ask this question because I was hoping it would come out, but what has been the barrier that has prevented these contrast agents from being used in echocardiography? Clearly, it is not fear of using things off-label because pediatricians do that all the time. Clearly, it is not that it hasn't been used in adults. So, what has been the barrier that

has prevented this modality from leaping, as all the other technologies have leapt, to pediatrics?

DR. SABLE: There are two answers to that. The first one is that every patient that comes to one of my colleague's labs is probably the only patient they are dealing with for at least a few minutes, and they are all going to have an IV and they are all going to be prepared to get contrast. So, it is kind of the mind set.

Whereas, in a busy echocardiography laboratory--we do about 50 studies a day in our laboratory and we usually have three or four rooms going at once--we have very limited nursing. We have maybe one nurse that is there to cover a sedated echo which we still use oral sedation for. So, putting an IV in, in the midst of a very busy echo lab is much different than for some of the other modalities.

The economics of echocardiography is that in many cases we are supporting other programs. We have a huge volume, a huge money-maker and it is hard for me to convince my administrators who are looking at the practicality of doing this that instead of doing seven echoes using one sonographer I want to do one echo using one sonographer, one

doctor and at least one or two nurses. So, I think that is a huge barrier. It is inappropriate but it is the reality.

The second barrier is what I alluded to earlier, that is, the drug companies which are making these agents--I have talked to them at several meetings--don't seem to have much interest and they seem to be scared of getting into pediatrics. Clearly, the talk we heard yesterday from Bristol-Myers was much more focused on the nuclear agent even though the discussion included both.

DR. GORMAN: I can understand the economic argument inside a hospital, but not much echocardiography actually goes on in hospitals. So, why isn't some entrepreneurial private practice group that does echoes doing this? I mean, if there is really a need out there for this--if there is really a diagnostic utility to this that clinicians will use, then generally what happens is people use it and either show it works or doesn't work and reimbursement follows after that.

DR. SABLE: Yes, I think that even though a large proportion of pediatric echo is done in community hospitals or in smaller clinics, contrast

echo is going to start in tertiary care large echo labs. So, I think it would primarily be hospital based early on. It has been something that I have been trying to push in my institution and I think it is somewhat resources and just a different way of thinking. A lot of the people who refer patients--a lot of my colleagues who refer patients for echoes are used to getting an answer in five or seven minutes so it is kind of changing the mind set. Hopefully, Dr. Kimball's paper will circulate through the pediatric cardiology community and the American Society of Echo that you heard yesterday will change the mind set. I think in general, for lack of a better term, it may be ignorance. Very few of us even think about it.

DR. GORMAN: One more, is there something uniquely different about these agents? Are these really something that has traveled the border of drugs and devices? Are these bubbles really bubbles or are they particles that don't break down?

DR. SABLE: I think they break down. I think another issue is that the way they interact with the echo machine--before I prepared for this talk I read a couple of contrast echo books and the

principles behind them, and the way you use them is complex and intimidating and it is really a whole new science to learn. So, I think it is more that than actually concern about safety or particles breaking down. I mean, the potential, as I presented yesterday, is so great and if it could be done in a routine echo setting--I have talked to a number of adult echocardiographers who do this on a daily basis and there is a huge learning curve to get started and a lot of us aren't willing to take this learning curve. Clearly, I am here as a representative of an academic echo lab that feels the learning curve is certainly worth it.

DR. CHESNEY: Drs. Moore, Geva, Nelson and then I think we will take a ten-minute break.

DR. MOORE: Well, I will just follow-up on that. Dr. Gorman played devil's advocate for me so I appreciate that. But our experience, interacting quite a bit with our own echo lab which has had an interest in contrast echo for years and interacts very closely with the adult echo lab because we are not a free-standing children's hospital, has really found a relatively limited utility in the smaller patients with regards to the current echo contrast agents. I wouldn't say that is to say there aren't

applications and there may not be huge future applications for it.

I would say in our own experience the limitation has primarily been added value in terms of the younger patients. We even started using some of the Optison type contrast in the cath lab looking at different shunts in very specific indications and found over time that it really wasn't giving us a lot of added value. Because of that, we limited its use.

The second comment that I would like to make would be with regard to Dr. Loewke's comment on the stress imaging issues. I polled our nuclear medicine people, our echo people and our CT and MR people before I came here just to get a sense of what their concerns were about some of these imaging agents. It was very interesting in that all of them mentioned the medical or drug stress imaging issue in children. They had all run into concerns and complications in that there really is very little data in any of the areas with regards to that, particularly as it pertains to congenital heart disease and some of the pathologies we deal with in children which are quite distinct from the pathologies we deal with in adults. There is

extensive literature in adults. And, as much as I am an advocate for translating information across agents and across diseases when it is applicable, I think in this particular area it is not applicable in that there is extremely limited information. It sort of crosses most of these imaging modalities. I know MR, at least in certain institutions, is starting to get active in stress MR imaging. Certainly, echo and nuclear medicine have been quite active, and I would say that that is an area that probably should be encompassed in this discussion from the FDA standpoint.

DR. CHESNEY: Thank you, very interesting; very helpful. Dr. Geva?

DR. GEVA: I just want to add to a previous comment that was made on a gold standard for perfusion studies both with regard to MRI and contrast echo. That is, in most adult ischemic heart disease studies the gold standard was coronary angiography and most comparisons were done to that.

DR. CHESNEY: Dr. Nelson, and then we will take a ten-minute break.

DR. NELSON: A change of pace for me, I want to ask a question about a different patient

population because I think one of the advantages of echo is that you can come to my patient and I don't have to drag my patient to the CT scanner or MRI scanner out of the ICU. The times where I ask for echoes are often the point of most frustration for the cardiologist because they are the ones they can tell me the least about, which is extracardiac anatomy, clots, looking at the superior vena cava, etc., and what can you tell me about that? And function when I have a patient who is going down the tubes and is on six different drugs and I am trying to figure out what combination works best.

So, I am not sure what the gold standard ought to be and whether or not using contrast echo to see if you can see extracardiac vessels, say, prior to an MRI scan or something where you could begin perhaps to develop the capability of doing those kinds of studies when patients can't go to get the other modalities--that is my question, whether there would be some benefit in going in that direction.

DR. SABLE: I think, clearly, contrast echo could improve the cardiac border visualization and help get more accurate assessment of left ventricular function, and probably even regional

wall motion abnormalities. It could also help with intracardiac thrombus. In terms of seeing extracardiac vessels, I am not sure how accurate it would be but I think clearly there is the potential to design studies, and I would certainly include patients with poor acoustic windows in the intensive care unit. In terms of the gold standard, especially in patients that are already intubated, a very simple design that may be very doable would be to compare to transesophageal echocardiography because, clearly, that can be done also at the bedside, and the main risk of that is sedation. If the patients are already sick enough that they are on ventilators, then that becomes a non-issue.

DR. CHESNEY: Thank you, a very good point. Let's take a ten-minute break and be back by 10:35 to tackle nuclear imaging and angiography. Thank you.

[Brief recess]

DR. CHESNEY: We want to move on to questions regarding cardiac nuclear imaging and Dr. Dilsizian is back so please start with your most pressing, most urgent wish and need.

DR. DILSIZIAN: Let me emphasize that in

nuclear cardiac imaging we should be looking at physiology, not anatomy and, therefore, the key applications would be in detecting myocardial perfusion. When I say perfusion, there are two categories. One, we are looking at ischemia which is an area of the myocardium that is hypoperfused that, if you revascularize, will improve. And, there are many causes of that. The other one would be viability. That is, the function of the heart is abnormal and now you want to say can I predict whether that area of the heart that doesn't move is scarred or viable. You would predict that by doing something that intervenes and then the function improves. So, again, physiologic studies both in perfusion and viability.

Now, you heard that nuclear perfusion imaging is actually used commonly in clinical practice in the pediatric population. It has more or less become standard clinical use. Then we heard that it is not really an FDA approved procedure. This is a very nice example of how we have taken the adult data on coronary artery disease, ischemia and viability and we have extrapolated to the pediatric population. As I said before in my talk, I know it is not scientific

but it has, in essence, stood the test of time of clinical application. In essence, none of us here and none of the pediatricians out there would be ordering a test for ten or twenty years that actually doesn't work. The fact that it has worked is a testament that the test is accepted in clinical practice. Now, should we now go back retrospectively and start testing these in kids to prove that it works clinically? That is one question.

I want to bring up an issue that has come up in adults, and this is the area of viability, which I am quite interested in, with FDG PET. FDG PET, as you know, has been used in adults to assess viability and one of the questions was does it impact morbidity and mortality. There are three studies in the literature, all retrospective, that have shown that if you show viability or hibernation with FDG PET and you send them to medical therapy versus those who went to surgery, the mortality and morbidity was significantly higher. They are all retrospective studies.

NIH decided to do a prospective trial where they were now going to use as part of the trial an imaging modality, as in FDG PET, to show

whether, indeed, prospectively you can differentiate those who do well or not, and the ethicists stood up and said you can't do that. There is literature to say--retrospective--that if you have hibernation or viability and you don't revascularize those patients don't do well. They don't seven-fold as much. So, that was an issue.

So, we have to come back and say it is true what we have said here, that there are some indications where we have used it clinically over ten years, and it has even been used as a gold standard. Do we really need to test and retest those?

Now, with that introduction, let me say that the agents that are currently used for perfusion imaging in nuclear would be thallium-201, technetium perfusion tracers and then upcoming PET radiotracers, which are rubidium and ammonia. The way I see this in the pediatric population is that clinically, even though it can be tested again and can be easily tested in, let's say, anomalous coronary artery patients who are already planned to go to surgery you can do a before and after perfusion study and determine that, yes, there was ischemia; that it improved after appropriate

surgery. You don't have to do many patients. You can just do a certain number of patients and test the concept that you have done it in adults and it actually works in kids.

I agree that in the adult population the disease is atherosclerosis and in the pediatrics it is different, it is anomalous or microcirculation. Therefore, the physiologic aspect of this, that is, ischemia and viability, become different from anatomy. Anatomy--and we have shown this in adults--is not the gold standard for viability. It is the metabolic component or ischemic component that determines whether an area, even if it is an occluded vessel, improves or not.

With thallium, because it redistributes quite rapidly, if the kid is injected with thallium and starts moving around under the camera you are already changing the information. So, it is a very unforgiving agent. Even though it is an elegant biologic agent, it is an unforgiving agent.

Technetium perfusion tracers, because they don't redistribute much, have the advantage of not only that if the kid moves you can restart it and you don't lose information because it doesn't change with time as much. It also has a better

radiation dosimetry.

So, the next stage, however, would be what about PET imaging? Now, PET imaging provides you absolute blood flow rather than relative. In essence, if you have an anomalous coronary artery you are saying is it hypoperfused or not relative to the other regions. We can tell with PET in absolute terms whether it is so or not.

The other advantage or technology change, and one of you brought up that question, is are we really going to be only concerned with tissue perfusion tracers or how about the technology? I can tell you that the technology has moved from 20 mm resolution to 12 mm, to 10 mm resolution with SPECT. You know what PET is these days? It is 4 mm resolution.

I want to go one step further to the so-called micro-PET which is currently used in animals. The resolution is very high. And some of you who were talking about neonates and preemies, perhaps--perhaps we shouldn't be using adult PET machines; maybe we should be using micro-PET in those patients to get the appropriate resolution. Again, there are a technological advances as well as perfusion tracers and, again, the PET flow

tracers have short half-lives and also will provide you with absolute blood flow and high resolution.

So, I think that what we are saying here is that we have currently used perfusion tracers, these thallium and technetium perfusion tracers. We may need further studies in a subset of patients who are undergoing surgery for, let's say, coronary anomalies where you show that, yes, there is a defect that improves. We may need to test that and get approval through the FDA.

But I think the next phase will be that we are probably going to be going to higher resolution, small kids, small hearts, absolute quantitation and better resolution techniques.

So, I think I have addressed most of these. The endpoints, as I said, is a tough one because we are looking at physiology, not anatomy but we can use anatomy as an initial marker for gross perfusion defects that change. But I think physiological endpoints that don't have anatomical or structural correlates would have to be used. The endpoints would have to be used as clinical outcomes--just do the patients feel better? Do they have less syncope? Less episodes of chest pain? Some sort of surrogate marker that is

clinical that says that, indeed, what you showed physiologically does translate to improvement in some of those endpoints.

So, gold standard, unfortunately, is going to be, again, physiological, metabolic markers. The gold standards have to be non-anatomic but more patient-related, symptoms-related.

DR. CHESNEY: Thank you. Questions for Dr. Dilsizian? Dr. Nelson, do you have a question?

DR. NELSON: Could you just remind me of the conversion between millisieverts and millirems?

DR. DILSIZIAN: It is the same.

DR. NELSON: Exactly the same?

DR. DILSIZIAN: Exactly the same. One thing I want to bring up since you brought up the dosimetry, as far as planning trials, I think that again we have to make sure that even though we would like to study kids, we also don't want to put the kids in a special patient population and say, gee, we can't study them because they are going to get high radiation exposure. In essence, it is almost a discrimination to the kids if we are not going to do appropriate testing. So, we have to start thinking of this and, as a panel, I would like to challenge you to maybe think first about

what is an additional acceptable risk in children? Is it 0.03, 0.01? Then perhaps we can start from there and decide on dosimetry. There is going to be additional risk but, at the same time, we don't want to eliminate studying certain very important metabolic tracers even beyond cardiology, in cancer treatment in kids, that have high radiation exposure. We need to come up with some sort of decision about what is the minimal acceptable risk for trial design and then subsequently do those designs.

DR. CHESNEY: Could I bring up something that may seem far out but it wasn't my suggestion and, whoever made it, please raise your hand because I thought it was an intriguing one. When you work in the laboratory you have to wear a little badge that picks up radiation exposure every day. Yet, I have children for whom I have ordered X-rays and I can barely hold the folder, it is so heavy, and they are not wearing any kind of meter or whatever--detector. They are very young. They are presumably going to have lots more tests for the rest of their lives. Is this an issue? Is this something you have thought about? We talk about dose for an individual study but there is

nobody summing all the studies over a period of time.

DR. DILSIZIAN: It is a tough one because I think none of the studies that are ordered in pediatrics--again, it is a risk/benefit ratio. Every test that you order, you think about it, whether there is more benefit than risk. The other thing is that there is always this background radiation exposure, whether you are flying frequently, and what does that number mean in general? I think it is tough to do that.

DR. CHESNEY: Dr. Geva, Dr. Fogel and Dr. Siegel.

DR. GEVA: I thought this was a brilliant comment and it is actually a question whether this should be an FDA mandated practice, that is, to form a patient-specific log of cumulative radiation exposure because it is true that we make those decisions as far as risk/benefit on an event-specific basis but there is no way to tell us whether a ten-year old with tetralogy of flow with pulmonary atresia who had six cardiac catheterizations, five of which were interventional and then a couple of hundred of chest X-rays, and so on and so forth, where that patient's cumulative

radiation dose stands relative to potential risk.

DR. CHESNEY: Who made that suggestion this morning? Dr. Fink? It was his idea.

DR. FINK: Dosimeters.

DR. CHESNEY: Dosimeters for children. Dr. Fogel, Dr. Siegel, Dr. Dilsizian and Dr. Nelson.

DR. FOGEL: I just wanted to ask--and it is my ignorance on the nuclear imaging part, but I imagine in children you would also have to sedate them to hold them still for the cameras to pick it up?

DR. DILSIZIAN: No, what we do is that every kid who is being imaged has to have a parent be there in the room with them, and they usually read a book or tell a story, and that is all. We don't really sedate them.

DR. FOGEL: So, even like a two-year old or a three-year old? What do you do for that?

DR. DILSIZIAN: Again, if you need to, yes, but most commonly it is not. If you need to, we do get an anesthesiologist to sedate them.

DR. FOGEL: So, most commonly these are done in your institution in patients who are older--

DR. DILSIZIAN: Yes.

DR. FOGEL: --who don't require sedation?

DR. DILSIZIAN: yes.

DR. FOGEL: Okay.

DR. CHESNEY: Dr. Siegel, Dr. Dilsizian and Dr. Nelson.

DR. SIEGEL: Just back to the radiation dose, I think the comment that we have heard is that it is a risk/benefit and we would hope that they wouldn't be ordered unless they are absolutely necessary. On the other hand, it is also our job to screen these. So, if a request comes down and I think there is a study that can be done, a substitute that has a lower radiation dose, I will suggest that. I think it goes both ways. The patients that we are examining that have all these radiographs--we have to assume that they are necessary when they are ordered and we can't substitute radiographs but for some of these other modalities that have radiation we may be able to adjust that factor by substituting another examination.

As far as radiation badges, that would be very difficult to do because we wouldn't know whether we are monitoring external surface or

internal dose. So, although it would be nice and, in fact, if you wanted to calculate the dose you could. It is quite doable. The question is what do we do with that information? I don't think you can predict cancer risk for any one patient, no matter what the radiation dose is. I think all we can do is minimize the dose that any one patient receives.

DR. CHESNEY: Dr. Dilsizian?

DR. DILSIZIAN: That is exactly what I was going to say. You know, before you collect this data you need to know what to do with that data. I would probably suggest that let's go back and look at all the nuclear medicine technologists that have collected the data and, you know, what have we done with that data? It seems like it is pretty safe but, again, you have to use the safety of clinical need versus what am I going to do with this data that I am accumulating? I think before we go ahead and recommend that we should think about that.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: I have advocated that there needs to be better guidance at the federal level, not so much from the FDA but from OHRP, about radiation risk with respect to what IRBs can do for

that. There is precedent for some level of radiation to be considered minimal risk, and there is precedent for another level of radiation to be considered a minor increase and, therefore, justified under non-therapeutic, non-beneficial conditions. But there is no guidance about what that number ought to be.

The other complex thing that I think Phil mentioned yesterday is cumulative dosing exposure. It is easy enough to say at a single level whether it is 100 mg or mSv. I gather that tissue dosing and what you are talking about is often less than that, and that would fit within acceptable boundaries I think as a single dose under either of those two conditions. But then, when you add in all the other ones the key idea that needs to be considered is incremental risk. I mean, if the child is having, say, 3 rem exposure over 6 months for clinical indications, what is the additional risk from another 100 mg from a nuclear study potentially? I mean, that is unanswerable but, strictly speaking, from a research perspective what should be evaluated is that incremental risk, not the total risk of the 3.1.

DR. CHESNEY: Dr. Fogel, Dr. Gorman and

Dr. Fink.

DR. FOGEL: In terms of the radiation, I guess I understand that for each individual we can't really predict who will have that risk and who won't. But, you know, in terms of science we need to collect the data and we need to be able to actually come up with a risk stratification in the general population and probabilities of what is going to happen given a certain cumulative dose. We have to start somewhere, and I think that the first step might be looking at the literature and, if it is possible, to calculate the dosage from some of the existing data that is out there, and then maybe see if we can track those patients down and follow-up and look at their cancer rate. That might be one way of doing it.

The other way of doing it is to be prospective about it and to start collecting data. We just have to start somewhere. There were a couple of papers that were shown yesterday by Dr. Geva about the notion that increased exposure to radiation could potentially cause an increased cancer rate in kids in the future. I mean, I think it behooves us to at least start somewhere.

DR. CHESNEY: Just an editorial comment,

for those of us who think you all are magic and can figure something out examining the patient, we are quick to send them down because you do such incredible things now. But we forget--we forget because we don't see the radiation; we are not in your position; we are not physicists and we forget--at least I do, I can't speak for everybody but I think in general we do and, therefore, the parents and patients are not always thinking. They understand the risk/benefit and we do too and I think we try to send them only for the right things, but it just occurs to me that, you know, we have got so far from World War II and nuclear energy that we just don't retain that concept, if that makes sense. Dr. Gorman and Dr. Fink.

DR. GORMAN: To get off the radiation issue for just a moment, yesterday you were talking about your favorite research subject of myocardiopathy, you were saying you could actually predict to some degree the number of deaths over a decade. When you have predicted, you elegantly showed us that you look at function on cellular levels. Looking at gold standards, is there some macrophysiology that we can look at for this micropathology? So, can we look at LV function to

show that your perfusion studies as they change actually do predict what they say they predict? Or, since you are able to predict death, can you predict things that are a little bit less invasive?

DR. DILSIZIAN: Good question. Unfortunately, perfusion and function can't be dissociated and that is where hibernation comes in. In essence, you can have a relatively narrowed vessel and what the heart does is try to compensate by reduced blood flow by reducing function, in essence, until someone decides to revascularize you. That state of narrowed vessel and not moving can also be scarred tissue. So, function and anatomy can't tell me whether that area is scarred or not and the only way we have been able to do this recently is to look at flow independent measures, i.e., FDG metabolism or, in the case of thallium, the redistribution phase which tells you about cellular viability that is flow independent.

So, it is not easy. So, now you are saying to me how do I test FDG viability or thallium redistribution? The way we have done that is we have said if you see the signal of high FDG uptake or thallium redistribution and send those patients to surgery you will see recovery of

function in that area. Therefore, it is a good signal. On the other hand, if the FDG metabolism is absent or thallium is absent and you revascularize, that area will not improve in function. You, therefore, use this dichotomous functional recovery as a way of looking at the gold standard, not anatomy.

DR. CHESNEY: Dr. Fink, and then we will move on to Dr. Moore and his set of questions.

DR. FINK: My comments are very similar to yours. The concern about radiation risk, thinking about the institution I work with, every preemie who doesn't feed well now gets hearing and speech orders or modified barium swallow, which is 2-4 minutes of fluoroscopy and probably worth several hundred chest X-rays in terms of radiation exposure. What I wonder about, when I order an antibiotic, you know, the computer pops up with what the price is. What would happen if radiologists just started routinely putting the radiation exposure either in the report or in the order sheet and make physicians more cognizant of it? Residents today look at all the advantages of radiography; they don't look at the risks. And, it would seem like a fairly simple thing to maybe make

physicians more sensitive by just giving routine feedback on the radiation even for just individual procedures, not going into the issue of accumulation and everything else.

DR. CHESNEY: Dr. Siegel?

DR. SIEGEL: It is a good comment, but if you are doing that, then you have to also include the risk of the alternatives because if barium swallow is performed for a reason to look at function, then perhaps the alternative might be a direct endoscopy with the sedation and the risk of the endoscopy. So, I think if you are offering that, it has to be really what the alternative is as well and its risk or the alternatives and their risk.

DR. LOEWKE: Dr. Chesney?

DR. CHESNEY: Dr. Loewke?

DR. LOEWKE: I have one question for Dr. Dilsizian. With regards to stress testing, can you tell me are you using exercise versus pharm stress, and if you are using exercise how young can you actually exercise a patient on a treadmill and still get good quality image results?

DR. DILSIZIAN: A great question. I always prefer to do stress testing, adults or kids,

because in essence what you do on the treadmill reflects much more what happens to that patient on a daily basis physiologically, whether it is climbing up the stairs or playing basketball. So, you are looking not only to reproduce the symptoms but also to look at arrhythmia of the cardiogram and also how far they go as a prognostic marker. So, treadmill is always preferred. In young kids, as you know, especially in teenagers, we have no problem. Perhaps the youngest one for exercise is about six years old. You know, he is actually excited to be on the treadmill and to run. But younger than that, obviously, is a problem. Fortunately, we don't do a lot of very young kids looking at ischemia on a treadmill. In those cases, again, a simple flow agent with a pharmacologic stress property would be the way to go.

DR. SANTANA: Joan, may I make one final comment?

DR. CHESNEY: Yes, Dr. Santana.

DR. SANTANA: I heard a little bit of discussion about setting up systems for tracking patients, tracking radiation exposure. That is always easier said than done in practicality. We

have been having a pilot project at our institution where we now have an electronic system and some of us were able to convince the ITS group to give us a tool so that when a test was ordered we would have to differentiate the protocol the patient was on to at least give us a tool that we could begin to track under what research studies tests were being done. And that is all I am going to say. It is very difficult--it is very difficult. The data is fraught with a lot of problems. So, you may think idealistically that these ideas are good but unless you really have adequate tools to do it right you wind up with really bad data that doesn't help anybody; it just confuses the problem more.

DR. CHESNEY: Thank you. Dr. Moore, could you tell us what your wish list highest priority would be and then go through (a) through (f) for angiography?

DR. MOORE: Well, this can be relatively short I think. One, the iodinated contrast agents are already approved for application in pediatric angiography so I don't know that that applies terribly.

In terms of research studies in that area, I would concur with the rest of the panel in terms

that limited dose or smallest dose that is effective has not really been defined. But, as has been mentioned in some of the other modalities, that is as much related to technique, flow rates and other issues as agent-specific issues. So, I am not so sure that the agent itself is the major factor in that setting.

In terms of populations and disease states, again, the ones that have been looked at the least have been in infants and in premature infants. Although in angiography there has been a reasonable amount of retrospective studies done looking at infants down to even 1.5 kg or less in terms of complications in angiography. So, I am not so sure that that is critical.

I guess my comment would be more to the future of angiography and certainly the future of catheterization, which I think is going to be away from radiation and away from some of the current agents and some of the newer imaging modalities which you heard about today or the last two days and some of the newer agents that are both being developed and will be developed in the future.

I guess my plea for the committee and for the FDA in particular is that it would be extremely

helpful as new agents are developed for these modalities, including angiography, that pediatrics, particularly the application safety and efficacy data in young children is included with the initial drug application because, as you noted today, the history of this is that they get studied and approved in adults and then they get used in children for many, many years before there is much impetus to look at them critically in children and it sort of sorts itself out. The problem is that, you know, while it sorts itself out an awful lot of patients have the potential for harm and a lot of patients get studies that they shouldn't get and don't get any benefit from. So, my strong plea would be for those agents that have been used off-label but have relatively extensive information, it is not clear to me, the additional benefit. But certainly for the newer agents and for future agents the focus on pediatrics as part of the initial application and study procedure I would think would be a huge benefit both to current and future kids with congenital heart disease.

DR. CHESNEY: Dr. Cummins?

DR. CUMMINS: That is what PREA actually allows for, for including kids in studies for new

drugs.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: I assume it is worded as it was in the original pediatric rule that it is restricted to the indication that the sponsor is looking for. If that is the case, then I would encourage you to take a page out of the oncology book and define indication by image and not by condition. If you define it by condition you are not going to be able to argue that if they are looking for approval that you can apply an adult indication based on coronary anatomy to a pediatric indication based on congenital heart disease. So, if the indication is defined at the image level you are able to apply the rule because then you have an indication that is the same.

So, my understanding is that PREA still restricts the FDA to requiring studies if it is within the confines of the indication that the sponsor is going after as opposed to exclusivity. That is where this discussion of extrapolation has some implications for that. If you are liberal, then you can require them to do that if you define it at image level as opposed to anatomy level.

DR. CHESNEY: Other comments or questions

for Dr. Moore?

[No response]

Last question, please discuss the relevance of new developments in the field of adult cardiac imaging that may have potential application to the pediatric population. Can we anticipate the need for future drug development for pediatric cardiac imaging?

I think almost everybody addressed those issues in their responses. Do we need more definition, or do we want to go around and ask each one of them for one area, or do we have enough information on that?

DR. LOEWKE: I think if anybody has any final comments, we would be glad to hear them.

DR. CHESNEY: Dr. Fink?

DR. FINK: An area we are seeing at our institution, and I don't think it is unique to Ohio, is the whole issue of cardiac function in the markedly obese adolescent. I don't quite know what the utility is of looking for cardiac lesions or cardiac artery disease but it clearly is a major clinical problem.

DR. SABLE: In terms of contrast echo, that would be a relatively good population to study

because it would probably be one of the easiest to extrapolate adult data or at least study design from because they are patients with theoretically normal structural hearts. As everyone knows, the percentage of adolescents with obesity is growing and I think the best way to do this, as was alluded to earlier by Dr. Moore, is that we probably could do some collaboration with some of our adult cardiology colleagues to get more powerful numbers.

DR. CHESNEY: That is an excellent point. Just last week when I was on service we had an 85 kg 10-year old come in, who ended up on the ventilator and we ended up doing a cath and looking for pulmonary hypertension, which he had along with his congenital heart disease. So, I think this is a growing area. Dr. O'Fallon?

DR. O'FALLON: But after the considerations on Monday, I would think that one of the things that you shouldn't do is just assume they are going to be like the adults because their immature metabolisms may be very different and you could still come up with some surprises in terms of the adverse event patterns.

DR. SABLE: Sure. I would agree we should study them as a separate group but they are closer

to adults. I think when we talk about extrapolation I wouldn't propose we just use adult data but I would think that it would be reasonable. The studies could be more similar than maybe doing one- and two-year olds with complex heart disease.

DR. CHESNEY: Dr. Fink?

DR. FINK: The other area that I think is not probably solved in adulthood but is becoming of significant pediatric importance, at least to pulmonologists, is the issue of sequential measurement of pulmonary hypertension in childhood lung disease.

DR. CHESNEY: Dr. Siegel?

DR. SIEGEL: Measurement of pulmonary hypertension, are we talking about functional or quantitative? Both? Pulmonary vascular--

DR. FINK: Pulmonary vascular--non-invasive or less invasive measurements of pulmonary vascular resistance.

DR. SIEGEL: At least from the CT view point, as I mentioned yesterday, I think what we are going to be able to look at now is with functional and qualitative data. The vessels we can already do with CT angiography and give you something about the size, but carrying it a step

further, I think we could certainly look at the perfusion at smaller levels with the use of this subtraction image and then the color mapping and the histogram mapping so that we could look at perfusion at different areas, which might give you some information, but I am not sure how to relate that actually to resistance per se, except to look at the vessels. We can take it to looking at perfusion in different areas of the lung, if that is helpful from a CT standpoint. They are doing some of that in adults. But looking at vessels per se, the only thing I could think of with CT would be CT angiography. So, I am interested to know what you are looking for particularly when you say resistance.

DR. FINK: Well, it is clear with pediatric lung disease that pulmonary hypertension has its onset years before it becomes clinically evident and for treatment of a variety of disorders, potentially the most common being severe asthma, it would be nice to track that because we are learning a lot about airway remodeling in asthma. There is clearly vascular remodeling that occurs and is probably more important, and we know nothing about it.

DR. SIEGEL: Right, so we are starting to do studies for that for CT angiography, looking at the larger and the smaller vessels and at the same time we are looking at the effects on the airway and lung function.

DR. CHESNEY: Interesting. Drs. Fogel, Sable and Moore.

DR. FOGEL: I wanted to address the two patient populations you bring up in terms of the obese pediatric patient. At least what MRI can offer in that realm is a combination of both contrast and non-contrast enhanced studies. In terms of the non-contrast enhanced studies, we can measure left ventricular mass and volume. From a contrast standpoint, if you had any inkling that those patients may have decreased myocardial perfusion we could potentially do that with a contrast enhanced methodology.

In terms of your pulmonary hypertension patients, what you are asking for is the "holy grail" of non-invasive imaging. That is what we have all wanted to do, to be able to non-invasively measure pressures and flow. We could in theory do that with using velocity mapping to get tricuspid regurgitation jets and then make an estimate for

pulmonary pressures then, since we know flows too by MRI, we could essentially calculate out what the resistance would be. But in practice, anybody who has a pulmonary hypertension estimate by either echo or MR or any one of the other studies, they always go to cardiac cath for a diagnostic determination as a good, definitive gold standard to directly measure the pressure in the pulmonary artery and then measure flows and get pulmonary vascular resistance. When that happens people also do drug studies to be able to see if there are any drugs that might be able to decrease pulmonary vascular resistance whether that be oxygen, nitric oxide, etc., etc., or some other drugs. But the pulmonary hypertension one would be pretty difficult in non-invasive. I am not saying we shouldn't start trying. I am just saying that it would be difficult to do.

DR. CHESNEY: "The holy grail" of imaging! Drs. Sable, Moore and Gorman.

DR. SABLE: I would certainly agree that pulmonary hypertension is a very complex issue. Ideally, you would study it in a state that is similar to what the patient is doing normally. That is where echo has significant advantages. I

think with some of the newer techniques, including contrast echo, myocardial performance indices and tissue Doppler we can get incremental increase and in a number of patients we can assess pulmonary blood pressure. As Dr. Fogel alluded to, the difference between pulmonary blood pressure, which is important, and pulmonary resistance, which is a much more complex number which uses pressure and flow and is really what we want to know about, it is much harder to get resistance than the actual pressure. In our patients that we treat with prostacyclin for primary pulmonary hypertension, we can get dramatically better in terms of exercise tolerance, quality of life and, yet, their PA pressure and RV function won't change at all. So, it is a very complex issue. I think we can help a little bit with contrast echo but it is going to be a while before anything but cath gives us the gold standard.

DR. CHESNEY: Dr. Moore and then Dr. Gorman.

DR. MOORE: I would just support what Dr. Fogel said and be relatively optimistic about what the potential is for MRI and some of the imaging agents in the future. We have been doing some work

in San Francisco with this combined lab looking at flow measurements and pressure measurements in the MRI scanner. And, there is a fair amount of work in a variety of centers or at least a few centers around the world looking at ways to combine some mildly--to coin a new term--invasive measurements with MR imaging to really get a much better handle on function and on resistance calculations. So, there may be the opportunity in the future with some of these newer agent modalities to get that information in a much more complete, easier, less invasive data set. I think certainly right now MRI and its imaging drugs will be the method for achieving that.

DR. CHESNEY: Dr. Gorman?

DR. GORMAN: We have spent the last 36 hours thinking about agents and the heart. At the risk of finding out far more than I want to know, are there agents that are being used in the other part of the body by your radiology colleagues or ultrasonography or nuclear medicine colleagues that we may anticipate coming back in the near future? Are there rapid developments in other areas of imaging in terms of agents that someone here would like to comment on?

DR. DILSIZIAN: Well, I could do that. One of the areas that I am actually currently working on is a new agent called BMIPP. It is a fatty acid analog. When we tested it in adult patients, the uniqueness of this agent is that it reflects ischemic memory. What do I mean by that? You see a patient in your office and the patient says, you know, last night as I was sleeping I was just having this discomfort in the epigastric region. I am not sure what it was. I woke up; I couldn't sleep. I took a couple of Maalox and it went away. I am concerned; is this cardiac in origin? So, what do we do? We get an EKG and say, well, there is no infarct but it doesn't say it is not angina. You say, you know, just to be sure let's schedule you for a treadmill test study of some sort.

Now, with the BMIPP agent we have shown in a Phase II trial that if you inject a person at rest in your office, it reflects whether the chest pain or the discomfort that the patient had up to 30 hours before is ischemic or not. The way we tested that, we put a patient on a treadmill and created ischemia with thallium, and up to 30 hours after the treadmill thallium study we injected the

fatty acid agent at rest and reflected ischemia exactly the same as on the treadmill thallium. So, it is potentially a useful thing for kids for example.

Again, coming back to an example, a patient comes in who survived after cardiac arrest or syncope. Is this ischemia in origin or is it arrhythmia? What do we know? Just inject this tracer and if it is ischemic in origin, it will show you.

So, you know, there are agents like this. Here we are talking about metabolic agents, fatty acid, FDG. In adults it has been approved already but, you know, it could play a very important role in metabolic disorders. We talked about cardiomyopathy in kids. Well, we know that they don't have any coronary disease; their function is abnormal. Well, what is the cause of the cardiomyopathy? It may be viral; it may be something else. Can we look at disturbances in metabolism and determine what is causing those things?

You know, if we think in broader terms than just congenital abnormalities, there may be some interesting metabolic disorders that we can

look at in kids to determine what their disorders are. Again, it is very premature obviously. We are going to test these in adults and then say, well, can we translate these to children.

DR. CHESNEY: Dr. Fogel?

DR. FOGEL: Yesterday I think all the speakers mentioned the future of the imaging agents. Just in terms of MR, we mentioned molecular imaging and newer relaxivity agents. But the specific question was more about adults in other areas. Specific to MR, there are two other kinds of imaging agents. There is the manganese ionic agent. I think it is called mangatopere, a trisodium. Then, there are also the superparmagnetic ion oxide agents. They are both used in liver imaging and they are presently being studied for liver imaging. I think they are approved for imaging in MRI in the liver. The reason why those might be applicable in pediatric cardiac imaging is because they are blood pool agents. They stay in the blood pool a whole lot longer so that you would be able to use those for coronary imaging as opposed to the gadolinium agents, which are first-pass agents which would just diffuse out into the extravascular space; they

won't stay in the blood pool.

So, those potentially hold promise in the future. My understanding, not having followed that particular literature too much, is that they do have an increased incidence of adverse events over and above the gadolinium agents. Whether or not that is an acceptable risk relative to the benefit one would get is another story. But those are at least two things for MRI, at least in the future, that might hold some promise.

DR. CHESNEY: Dr. Fogel, you mentioned yesterday that gadolinium is a heavy metal. Do we have any concerns about whether it is retained in the body over a period of time? Are there studies looking at people who have died who had had studies with gadolinium and we know it is not there anymore?

DR. FOGEL: I mean, we know that there is a number of studies in children looking at non-cardiac patients. The ones I mentioned yesterday, the five studies combined with over 1,300 patients were just a number of small studies. Those were purely safety studies. There are a number of other efficacy studies, especially in neuroimaging, where we have data and there is no

mention of any adverse events. Now, that doesn't necessary mean that there weren't any but at least in the papers themselves that were published there were no adverse events that were noted. So, it appears to be a relatively safe drug. The adverse events are very, very low; anaphylactoid reactions are very low.

I guess there is a theoretical consideration of transmetallation, as I mentioned yesterday, where copper and zinc can in theory displace gadolinium from its chelator and have the heavy metal stay in the body. You would think that if gadolinium stays in the body it is more toxic and, therefore, since it is excreted by the kidneys in renal patients it might be difficult. There has been a number of small studies, not a large clinical database but a number of small studies that showed that it was safe even to triple the dose that it is approved for. So, it seems to be relatively safe in theory. It has the potential but in practice it doesn't seem like it turns out to be the case in terms of it being difficult and toxic.

DR. CHESNEY: Let me turn to our FDA colleagues and see if there are any additional

questions or issues you wanted to raise with this erudite group of cardiac imaging folk.

DR. LOEWKE: No, I think it has been a very productive meeting. I wanted to thank all the panel members for coming and participating in the discussion. The presentations were fantastic and did a great job I think in priming for today's discussion.

I think some issues that you brought up are cross-center and cross-division level within the agency and I would just like to say that we will take these issues to our colleagues and discuss them further.

DR. CHESNEY: Dr. Beitz?

DR. BEITZ: I also wanted to say how excellent and insightful the presentations and comments were from the committee and our guest consultants.

I wanted to take this opportunity to make an announcement that Dr. George Mills has accepted a position as permanent director for the Division of Medical Imaging and Radiopharmaceutical Drug Products, and he will be starting in this position on March 7. George came to FDA in 1993 and is currently the acting deputy division director for

the Division of Therapeutic Biological Oncology Products. He is Board-certified in nuclear medicine and anatomic and clinical pathology, and he also holds an MBA from Pepperdine University. We look forward to working closely with him on the development of new imaging agents and searching for the "holy grail"--

[Laughter]

Before I finish, I would like to also recognize the fantastic efforts of Dr. Sally Loewke who has done an outstanding job as our acting division director for so many months. Thanks.

[Applause]

DR. CHESNEY: Dr. Cummins?

DR. CUMMINS: I just wanted to take a moment to thank everyone for their participation. For the panelists who came for the last two days, your talks were wonderful and the help many of you gave us in planning this meeting was just invaluable. I want to especially thank our peds advisory committee who I don't think could have had a broader set of issues to tackle in three days than suicide risk among depressed pediatric patients who were treated with the SSRIs to drug testing for pediatric cardiac imaging. It has been

quite a set of issues at this meeting and I want to really commend you all for taking your task seriously, doing your homework and sharing with us all of your wisdom and insights. We really value all that you shared with us. Thank you.

DR. CHESNEY: Let me thank the FDA on all of our behalf. We were just commenting in the van this morning--a lot of things happen in the van--

[Laughter]

--everybody commented on what a superb job you all are doing in preparing the materials for us for the meeting. It makes our job really very easy, and we thank you for having the opportunity to look at a whole variety of issues in three days. So, thank you.

DR. CUMMINS: If I could just make one more comment to that, any feedback, positive or negative, about the background materials is always appreciated because, you know, Rosemary, Eddy and I kind of overlook that and we try to balance not too long but comprehensive and giving you the background stuff you need, and if there is something that is missing that you would like to have, let us know.

DR. CHESNEY: Thank you, and be sure to

let Tom know if, for some reason, you are having trouble getting to the airport.

[Whereupon, at 11:30 a.m., the proceedings were adjourned.]

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