UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE

MEETING

Thursday, November 17, 2005

The meeting came to order in the ball room of the Hilton Washington North, 620 Perry Parkway, Gaithersburg, MD, at 8:00 a.m. Dr. Robert Nelson, Chair, presiding.

PRESENT:

ROBERT W. NELSON, M.D., Ph.D.	Chair
ANGELA DIAZ, M.D, M.P.H.	Member
MICHAEL E. FANT, M.D., Ph.D.	Member
MELISSA M. HUDSON, M.D.	Member
THOMAS B. NEWMAN, M.D., M.P.H.	Member
JUDITH R. O'FALLON, Ph.D.	Member
MARSHA D. RAPPLEY, M.D.	Member
DEBORAH L. DOKKEN, MPA	Patient-Family Representative
ELIZABETH GAROFALO	Industry Representative
PAULA KNUDSEN	Consumer Representative
JAN N. JOHANNESSEN, Ph.D.	Executive Secretary

PRESENT: (continued)

JANET ENGLUND, M.D.	Consultant
DAVID K. SHAY, M.D., M.P.H.	Consultant
ROBERT WARD, M.D.	Consultant

ALSO PRESENT:

SUZIE McCUNE, M.D.,	Division of Pediatric Drug Development
LARRY GRYLACK, M.D.	Division of Pediatric Drug Development
SOLOMON IYASU, M.D.	Office of Pediatric Therapeutics
DIANNE MURPHY, M.D.	Office of Pediatric Therapeutics
MELISSA TRUFFA, R.Ph.	Division of Drug Risk Evaluation
DEBRA BIRNKRANT, M.D.	Division of Antiviral Products
LINDA LEWIS, M.D.	Division of Antiviral Products
ANNE TRONTELL, M.D.,MPH	U.S. Public Health Service
DAVID SHAY, M.D.,MPH	Centers for Disease Control and Prevention

P-R-O-C-E-E-D-I-N-G-S

8:06 a.m.

CHAIRMAN NELSON: Good morning. We've got a long day before us. The first thing we should do is just go around and reintroduce ourselves, both for the benefit of, perhaps, the people in the audience, and there's some new people around the table. And then after that, we have an open public hearing, in which we have five or six speakers depending upon whether one person shows up during that time, and perhaps more if anyone else in the audience wants to cross and hasn't identified themselves, and then we'll get into the questions.

So how about -- if I recall we started at that end yesterday, didn't we? No, we started at that end, so we'll start over here.

DR. YUSTEIN: Ron Yustein, Deputy Director, Office of Device Evaluation, CDRH.

DR. MURPHY: Diane Murphy, Director, Office of Pediatric Therapeutics, Office of the Commissioner, FDA.

DR. GOLDKIND: Sara Goldkind, bioethicist,

Office of Pediatric Therapeutics.

MEMBER GAROFALO: Elizabeth Garofalo, Pediatric Neurologist. I'm the industry representative. I work for Pfizer.

MEMBER GORMAN: Richard Gorman, pediatrician in suburban private practice, representing the American Academy of Pediatrics, the non-voting member.

MEMBER HUDSON: Melissa Hudson. I'm a hematologist oncologist from St. Jude Children's Research Hospital. I am the new member of the Pediatric Advisory Committee.

MEMBER RAPPLEY: Marsha Rappley, developmental behavioral pediatrics from Michigan State University, and I'm a member of the PAC.

DR. BOTKIN: Jeff Botkin, general pediatrician, biomedical ethics, from the University of Utah.

MEMBER DAUM: I think I have this memorized now. I'm Robert Daum from the University of Chicago, pediatric infectious disease guy, and a new member of the Committee.

DR. DIEKEMA: Doug Diekema, pediatrics and bioethics, University of Washington and Children's Hospital of Seattle.

DR. FOST: Norm Fost, general pediatrician, Director of the Bioethics Program and Chair of the IRP at the University of Wisconsin.

DR. WARD: Bob Ward, DNA and field pharmacologist, University of Utah and Director of the Pharmacology Program.

MEMBER FANT: Michael Fant, neonatologist and biochemist at the University of Texas Health Science Center and a member of the Pediatric Advisory Committee.

MEMBER NEWMAN: Tom Newman, Departments of Epidemiology and Biostatistics and Pediatrics and a general pediatrician and member of the Pediatric Advisory Committee.

MEMBER O'FALLON: Judith O'Fallon, Emeritus Professor of Biostatistics from the May Clinic after 30 years in cancer research. I'm a member of the Committee.

CHAIRMAN NELSON: Robert Nelson. I'm at

Children's Hospital, Philadelphia, and the University of Pennsylvania. I do pediatric critical care medicine and bioethics.

EXEC. SEC. JOHANNESSEN: Jan Johannessen. I'm the Executive Secretary of the Pediatric Advisory Committee.

MS. KNUDSEN: I'm Paula Knudsen, Consumer Representative to the Advisory Committee. I am an IRB administrator at the University of Texas Health Science Center in Houston.

MEMBER MOORE: John Moore. I'm a pediatric cardiologist at UCLA, member of the Committee.

MS. DOKKEN: Deborah Dokken. I'm the Patient Family Representative on the Pediatric Advisory Committee.

DR. PORIES: I'm Walter Pories, Professor of Surgery and Biochemistry at East Carolina University. I'm Chief of the Metabolic Institute there.

DR. ARSLANIAN: Sue Arslanian, pediatric endocrinology, Children's Hospital, University of

Pittsburgh.

DR. ROCCINI: Al Roccini, pediatric cardiology, University of Michigan.

DR. LUSTIG: Robert Lustig. I'm a pediatric neuroendocrinologist at the University of California San Francisco.

DR. CHAMPAGNE: Catharine Champagne from the Pennington Biomedical Research Center in Baton Rouge, Louisiana. I am a nutritionist, and my area is dietary assessment, counseling and lifestyle change.

DR. KRAL: I'm John Kral. I'm Professor of Surgery and Medicine, licensed child psychologist, founding member of the American Society for Bariatric Surgery, Charter Member of NASO, and my interest is developmental aspects of obesity.

DR. CHOBAN: Pat Choban. I'm an adult bariatric surgeon in private practice in Columbus and Adjunct Professor of Human Nutrition at Ohio State.

DR. KLISH: Bill Klish. I'm a pediatric gastroenterologist, Baylor College of Medicine, Houston.

DR. YANOVSKI: Jack Yanovski. I'm a

pediatric endocrinologist, head of the Unit on Growth and Obesity in the NICHD intraneural research program, and I study pediatric obesity.

DR. INGE: Tom Inge, Assistant Professor of Surgery and Pediatrics, University of Cincinnati, and pediatric surgeon at Cincinnati Children's Hospital with a special interest in bariatric surgery and bariatric research.

CHAIRMAN NELSON: Thank you. I think the first order of business is reading the conflict of interest of statement. Am I right, Jan?

EXEC. SEC. JOHANNESSEN: The Food and Drug Administration is convening today's meeting of the Pediatric Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. The Advisory Panel meeting provides transparency into the Agency's deliberative processes. With the exception of the Industry Representative and the Pediatric Health Organization Representative, all Members and Consultants of the Committee are special government employees or regular federal employees from other agencies subject to federal conflict of interest laws

and regulations.

FDA has determined that Members and Consultants of this Committee are in compliance with the federal conflict of interest laws, including but not limited to, 18 U.S.C. 208, 21 U.S.C 355 and 4. Under 18 U.S.C. Section 208, applicable to all government employees, and 21 U.S.C. 355 and 4, applicable to FDA, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Members and Consultants who are special government employees at today's meetings have been screened for potential conflicts of interest of their own, as well as those imputed to them, including those of their employer, spouse, or minor child related to the discussion of today's meeting. These interests may include investments, consulting, expert witness testimony, contracts, grants, credos, teaching, speaking, writing, patents and royalties, and primary

employment.

Today's agenda involves a discussion on pediatric obesity and clinical trial designs for the evaluation of devices intended to treat pediatric obesity for future development of a guidance document. In accordance 18 U.S.C. Section 208(b)(3), waivers have been granted to Drs. Patricia Choban and Thomas Inge. A copy of the written conflict of interest waivers statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parkline Building.

In addition, Dr. Elizabeth Garofalo is participating as the Industry Representative, acting on behalf of all regulated industries and is employed by Pfizer Global Research and Development. And Dr. Richard Gorman is participating as the Pediatric Health Organization Representative and is representing the American Academy of Pediatrics.

Finally, in the interest of public transparency with respect to all other participants, we ask that they publicly disclose, prior to making any remarks, any current or previous financial

involvement with any firm whose products they may wish to comment on. This statement will be available for review at the registration table during this meeting and will be included as part of the official meeting transcript. Thank you.

CHAIRMAN NELSON: Thank you. So the first order of business is going to be the open public hearing. Jan will bring up the order and list of speakers. Let me read the opening statement and also read part of the letter that we have so I don't forget before the end of the open public session.

Both the Food and Drug Administration and the public believe in the transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or any group that

is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So before we launch into the live speakers, let me just make note of the letter that was submitted as part of the public commentary from the American Academy of Pediatrics. I think everyone has a copy of this, and I assume there was copies at the table for -- it may be gone, but it was available.

It's basically four paragraphs. I'm only going to read two. The first one just mentions what the academy is about. The second one highlights the importance of obesity as a health problem, which we heard much about yesterday.

The third paragraph starts off, "The Academy has developed extensive policy guidelines regarding the prevention and treatment of pediatric obesity and recognizes that there is a role for surgical procedures for weight management in highly selected adolescents. However, as suggested by published guidelines, trials for devices used in severely obese pediatric patients should be conducted with appropriate oversight and by a multidisciplinary team of caregivers with pediatric expertise.

The Academy is not supportive of fast-track approvals of any banned devices. The Academy recommends strong support for and solicitation of research to determine the long-term safety and efficacy of devices used to treat pediatric obesity and the effects of these on co-morbidities of childhood obesity.

There are a significant number of barriers to successfully treating obese children, particularly those with the greatest severity, such as lack of or inadequate insurance coverage and reimbursement, a shortage of multidisciplinary teams of providers

including those with expertise in nutrition, mental health, and exercise and physical activity, and inadequate capacity and availability of treatment programs and services.

Pediatric patients and their families need to be consulted about the program lifestyle changes that are required after surgery, and they need to receive continuous and comprehensive evaluation and psychological support.

Furthermore, the patients need ongoing surveillance for potential post-operative complications. Collaboration and coalitions among pediatricians, nutrition, behavioral health, physical therapy, and exercise physiology professionals will be essential for long-term successful outcomes. Working with the communities and schools to develop needed counseling services, physical activity opportunities, and strategies to reinforce the gains made in clinical management is also important."

So let's move into our speakers, and the first person is Lisa Musci. Did I get that right?

EXEC. SEC. JOHANNESSEN: I was taking a

guess at the spelling of your name. I apologize if I got it wrong.

MS. MUSCI: M-U-S-C-I is the correct spelling.

CHAIRMAN NELSON: Okay. Good morning.

MS. MUSCI: Good morning.

CHAIRMAN NELSON: And we have five or six speakers, so if you divide that into an hour you get basically nine to ten minutes.

MS. MUSCI: I don't even think I'll be that long.

CHAIRMAN NELSON: Perfect.

MS. MUSCI: Okay. I'm not a medical professional. I'm a mother of a 12-year-old who's obese. She's about 60 pounds overweight. Okay. I have this little thing prepared. I hope I get this message across.

Okay. So, you know, I don't know what was said yesterday. I wasn't here. I was back home in New Jersey. We all know it's been well publicized that overweight children and obese children have a higher risk of suffering from Type II diabetes, high

cholesterol, and later on in life, stroke, heart disease, certain types of cancer.

We know the longer a person is overweight, the chances of developing these health risks are greater, and no parent wants this for their child. I certainly don't. Okay.

We've sought out many solutions. We didn't just come here today. Since about the third grade -- my daughter was eight years old -- we have tried to lose weight. We've gone to a nutritionist, Weight Watchers, Jenny Craig, hired a personal trainer. She has a membership to a fancy gym. We do cheerleading, basketball, soccer, dance. I can't even think of them all. Gymnastics. I hired a person to work with her, because she really couldn't keep up with the class.

We're not rich people, but we've done everything that we can. Okay. But this is the real world. I don't know how many people have kids, 12-year-olds, but this is the real world.

I volunteered as a lunch aid in the school. When my daughter was in elementary school,

okay, here we live in this upscale town in New Jersey. There's no cafeteria. No real cafeteria. This is the cafeteria -- parents, volunteers, serving bagels with butter and cream cheese. That's all you get, and milk. All right. You bring your own drink. No snack, nothing.

Another day there's a big pot of water. Throw hot dogs in it, and you sell the hot dogs a dollar each. First graders coming up eating three hot dogs. I would say to them, "Are you sure you want to buy three?" You know, there so small. "Yeah, I want three." They're not overweight. Okay? So that's another thing.

All right. Now my daughter is -- oh, if you want to bring lunch, this is what kinds bring: Lunchables, you know, which I don't know if people know what that is. It's a luncheon meat. It's filled with all kinds of sugar, fat. It comes with some unhealthy snack and fruit juice. Fast foods. All the parents bring their kids McDonald's, all that stuff, because there's no cafeteria. So that's what they have. The kids themselves, they bring all kinds of

cookies, chips, whatever. Okay.

Now she's in middle school. Now they have French bread pizza, Domino's, Wendy's, subs. More good stuff. Okay. And, you know, the truth is the majority of the kids are not overweight, and they're all eating this stuff. Okay? All right. There was, you know, a few overweight kids, but they were all eating -- my daughter is sitting there with her turkey sandwich, celery sticks, fresh fruit, water, you know. And they have an award that you can get, whoever brings the healthy lunch to school. My daughter's a shoe-in. She doesn't even go up anymore. What's the point, you know? Most of the overweight kids do have the healthy lunches, by the way. Parents send them in.

Okay, so now this is the reality. After school, play date, someone invites you over to their home. They're not serving celery sticks. They're offering you chips, cookies, doughnuts, whatever, juice, ice cream. Nobody's giving you something healthy. Girl Scouts. My daughter's a Girl Scout. By the way, she's a very well-adjusted child. She has

great self-esteem, she sings, she has a beautiful singing voice. She's not shy, she gets up, she does what she has to do. Girl Scout meetings. Cookies, chips, juice. So here we are, you know, trying to serve the community, be a Girl Scout, and there's all this goodies here.

And then, you know, you say, "Oh, well maybe you could bring something." You know, you just don't want to be like someone standing there eating your little healthy snack, because you want to fit in when you're 12 years old. You want to be. I mean, as adults, we all want to fit in. Imagine being 12. Okay.

After school tutoring. It's wonderful. They have popcorn and iced tea there. My daughter said one day she couldn't believe how sweet the iced tea was, because we're not used to having that. Sleepovers, birthday parties, pizza, soda, chips, burgers, hot dogs, fries, sweets. All right?

So how do we follow the nutritionist's plan? Okay, you could take the healthy lunch to school. That's what we do. We cook healthy at home.

We're not Rice-a-Roni people. We never had Spaghetti-O's. You know, I'm Italian. Wouldn't eat that stuff, okay? Everyone in school, of course, knows she's on a diet, so, you know, that really is hard. And that could be hurtful. There are always -- there's always a mean girl at the table, you know, the cute little blond who wears a size 12, you know, who's perfect. Okay. And you know there's always, you know, a little girl size 12, you know. There's always one like that. Kids for the most part are very nice. She's very popular, my daughter. She has a lot of good friends, but, you know, there's always one.

Okay, so then they say exercise, so, you now, I told you all the things. We live in a great town, they have a great Parks and Recreation Department, okay. So when you're 12, and you join sports, and you're overweight, nobody really wants you on the team when you can't run as fast, and you're not as agile as everyone else, including the parent coach, who sometimes they want to win more than the kids to. They're worse than the kids. So you're on the team, but you're on the bench. I asked the coach, "Why

don't you play Ashley? Let her play a little, you know, let her play some more." "Well," he says, "you know I have to now" at the time "because she's in fourth grade." But he was so happy to tell me that "Next year I don't have to put her in at all." Well, isn't that nice?

But that's the real world, you know? It's real nice to say that we have to do all these things, but these things really don't happen. Gymnastics. I told you in earlier, we hired someone. We're not rich people, but we hired someone to work with her so that she could do all these things.

CHAIRMAN NELSON: To make sure you get in your key points, you have another two minutes.

MS. MUSCI: Okay. All right. So here we go. She couldn't do that back flip. She can't do balance beams. Dance. Hard to keep up with the dance class. The instructors lose patience. We had a dance instructor that eliminated several overweight girls from certain dance competitions. She didn't want them in, okay? Well, you know, and my daughter is a good dancer. All right. And then, you know, of course

it's hard to put on the tights and all that other stuff when you're overweight.

It's very important for my daughter to look nice. She's a real girl's girl. She wants to wear the pretty clothes, not baggy sweatshirts. She's conscious of her body, and she's been asked by the mean girl, "Why do you wear sweatshirts?" And she told her, "I'm overweight." She's not ashamed, and sometimes I'm self-conscious of my body. So there was nowhere else for the girl to go, and I'm glad that my kid had the moxie to say that.

Okay. So what do I want? Why am I here? I would like my daughter to participate in a hospital in New York in a program, and I would like her to have lap band surgery, because she is 60 pounds overweight, and from -- we were in Jenny Craig in March. She's gained about 18 pounds since then. Okay? Since being -- after being on a diet. Eighteen pounds. All right. And a good number of my husband's family are overweight, and -- not my husband. He's the only one, actually, and look, I love my in-laws. They're good people, and they're all professionals, you know.

We're not uneducated people that we don't know. They know more about nutrition and diets than most people, but they do have a weight problem, and it's a big struggle for them all the time. They're always on diets. They're always battling with weight, and I see her going in that direction. Okay?

And we just went to my niece's wedding. She's 4'11". She's almost 300 pounds. Okay? She could barely walk down the aisle. It was so sad. All right? I don't want that for my daughter. She has so much to give, so much to offer. I don't want her life to be cut short. I don't want her to be an unhappy, overweight person. We've tried everything, and I would like this panel to really consider lap band surgery for children.

And you talk about development. I'm not a doctor, but how well could somebody be developing if they're 60 pounds overweight?

CHAIRMAN NELSON: We've reached past ten minutes now.

MS. MUSCI: Okay, well, all right, I'm sorry. I didn't expect to go on and on. Thank you

all for listening to me.

CHAIRMAN NELSON: Thank you.

MS. MUSCI: You're welcome.

CHAIRMAN NELSON: So the next speaker is Allen Browne. Morning.

DR. BROWNE: Good morning. And sorry -- my voice is going to make it, I think. I appreciate this chance to speak with you all. I'm a pediatric surgeon, and I'm also a lap band surgeon, which makes me a little unique in this country, although we've got most of the pediatric lap band surgeons in the country in this room today to help the Committee out, and what I'd like to do is talk about this adolescent obesity from a pediatric surgeon's perspective, admitting that two years ago I didn't have any perspective, because one of the good things about pediatric surgery was I thought all my patients were not fat.

The adolescent adjustable gastric band interest group or AGBIG, is not any formal sort of thing, but as my partner Dr. Mark Holterman and I have presented some of our thoughts and experience, our colleagues in pediatric surgery have come out of the

woodwork, out of their nurseries and off their pediatric floor, and said, "What's going on here?" They're very interested, and we have a group.

Dr. Holterman and I have managed to work with the FDA and do have an IDE, and we are studying the efficacy and safety of the adjustable gastric band in adolescents, and there are two other units in this country who are rapidly on our heels, NYU and Babies' Hospital at Columbia. And there's another eight centers throughout the country that have just kind of come up who want to know how are we doing this? They're very interested in what's the safe, ethical, effective way to help out adolescents who are morbidly obese.

And I guess -- let me emphasize that a second. As pediatric surgeons, we work with sick people by and large, so as much as we're very supportive of all the preventive things that are going on in this country, there are a bunch of kids who are sick right now, and they need help right now.

And as I looked at this starting a couple of years ago, after I figured out that I could not

ignore the dismal quality of life that morbidly obese adolescents had, I kind of came across some thoughts that I hadn't had before. The morbidly obese children are sick. They're just kids, but they are sick, and they have lots and lots of problems. And if you approach them that way, then you can listen to the lady who just spoke to us and start to hear these families, and I think you change your approach to this problem.

I think all of us, as health care providers, know that -- and read in the paper now and see on the TV now -- that these people have an illness that if untreated and uncured has a very dismal prognosis. One of the things that got me involved in it is there's a dismal prognosis medically, and there's a dismal prognosis psychologically, there's a dismal prognosis economically for our country, because these people don't make any money and cost us a lot of money.

And it's reasonably easy to go on from that to say, "Well, we need to do something now." And people have argued about now and should we do it now,

should we wait until they get older, but those of us who treat diseases would like to treat it earlier than later. It's like taking out an acute appendix rather than a ruptured appendix. So I think that I came to these givens as I began to figure out what I, a very accomplished laparoscopic pediatric surgeon -- I'm one of the crazy pediatric surgeons that does laparoscopy on two and three kilogramers -- could do to help out the morbidly obese adolescents.

And so I looked at bariatric treatment, and this is an interesting thing for a surgeon, you now. We all have AD/HD, and our results hit us in the face or don't hit us in the face, so as you look at bariatric treatment, you can look at this one of two ways. If you look at the individual treatments of nutrition, behavior management, activity, and pharmacology, this was nicely gone over yesterday, and it demonstrated that the results are dismal, and it's not a field that's been able to make many strides.

If you look at surgery, and I know Dr. Flores and some of the other people here, and as you can tell I've been around awhile, so I've watched

surgery go through a lot of different attempts on this, and actually, as a matter of fact, however, surgery, along with the other modalities, has a certain track record. And the other modalities comment has to do with I think very strongly, and I can feel comfortable with this because the ASBS feels this way, too, a multidisciplinary approach is the way this works. Surgery works not as a soproet, not as something that you walk into Walgreen's, get, and then walk back out, but it works as a part of a program, as a part of helping these sick people with a problem that they have with their lives.

Now, results, because what's good results in bariatric therapy? Let's forget how these results are obtained. Well, there are bariatric therapy reports that have an 80% response rate. That's 80% of people, eight out of ten. They lose 60% of their excess weight. Well, how much excess weight you got to lose to get healthier is a big argument. You can lose 10%, and your diabetes and hypertension will get better, but does 10% make the other things better? Well, we really don't know.

Maintain the response for five years. Unfortunately, most of the pharmacology -- and that sort of stuff goes on for two months, six months, eight months -- this is a lifelong disease. We want to resolve the comorbidities. We're trying to help these kids get healthier. There's the bottom line, and that's what we tell all the kids in the New Hope Program at the University of Illinois at Chicago. And we do want to prevent comorbidities.

Now that's a real interesting study, because now you're got to have a couple of cohorts, historical or not, matched. You've got to watch in the long run. You've got to count who gets diabetes, who get hypertension, who gets a job, who goes to college, who gets married.

Well, what works and what doesn't work? And this goes back to my AD/HD again. Well, interestingly enough, the FDA, not a surgical organization whatsoever, said in 1993 that what works is actually bariatric surgery, and this is a little astounding if one looks at the status of bariatric surgery in 1993, because that was before the

adjustable gastric band, before laparoscopy, and before the high quality of bariatric surgery that we have becoming much, much more common throughout the United States with ASBS and things like that. The way people are doing it now is really much, much, much, better, and that is evidenced by the morbidity and mortality results that are obtained in the good series.

And, more recently, the ADA sent out a notification to its members that Type II diabetics who are morbidly obese need to consider bariatric surgery. You know, and I'm a surgeon, so I'm always impressed when non-surgeons start talking about people should have surgical therapy for something.

There are questions. When should the morbidly obese children be treated? Well, I touched on this a little bit, but I think probably when they're morbidly obese, how risky is the treatment? Well, we can argue about that, and we can argue about wound infections and prolapse, and we can argue about suture line leaks and abscesses and things like that. We can argue about micronutrient things, but how

risky is non-treatment? And this is a hard job, and this is something that we have to do with good data collection as we look at both sides of the story to see how you balance this off.

Now the comorbidities, and I think the important part about the comorbidities isn't the medical, psychological, social, or economic, but it's the other question, because that's where we're working, and when do they start? When do they get harder to treat, and can they be prevented? Now when do they start effects me, because I'm pediatric, and boy, the more you look, the more you find. If you start looking for left ventricular ipotrefocal and ovulary sclerosis non-alcoholic steatohepatitis, you find it.

CHAIRMAN NELSON: Make sure you have time for your recommendations.

DR. BROWNE: Got it.

CHAIRMAN NELSON: You've got two more minutes.

DR. BROWNE: Now, the adjustable gastric band, the important thing about that is it's not a

real wide gastric bypass. It's not a bilio-pancreatic diversion. It's not sleeve resection. It's not in many senses, most importantly being the morbidity and the mortality. And it's also not in the sense of -- the FDA has a unique influence over the gastric band that it does not have over the other procedures. The FDA can really squelch the gastric band availability and use in this country, or it can facilitate it.

The gastric band also is not an intergastric balloon or a gastric pacer, technology and devices that will come along and are being studied now, although there current results are not very good. It's removable, adjustable, the lowest morbidity and mortality, and it works.

Now nobody argues about the first three. They argue about the last one, and you got some data yesterday from non-lap band surgeons, which was really not accurate of modern results. The Australian government has analyzed this. There are recent papers, and we've learned lessons that you need to have people talking about this who use it and know how to manage it. It does work. The evidence in

adolescents is small numbers and short term, for sure. There is evidence from Australia from Dr. Fielding and Dr. Nixon, and then there's evidence from my group at the University of Illinois at Chicago, and we have evidence now from Atlanta, as well, with Dr. Wulkan that you'll hear from later today.

Okay, I got to the recommendations. Now, so what do I want to help you with? Because that's what I want to do. You're and advisory committee; I'm a pediatrician; you're a pediatrician. Well, we have to figure out a way to get a real national demonstration going. The adjustable gastric band plus a comprehensive weight management program, that's the gold standard. That's what can work, and anything else that wants to challenge it is going to have to have a pilot study that gets close to those results that we can do there.

And one of the ways to do this is to facilitate IDEs. Well, Dr. Holterman and I have already facilitated three of them, but we need a common evaluation and management protocol, and that way we can share our data, and we can efficiently

demonstrate that this works for people who want to know it works. We can efficiently tweak it so it gets better and better, very similar in this to projects I've worked in oncology and trauma.

And what do we do specifically about your questions today? Well, I personally feel that adolescence is not an age group, it's a headset. We all lived through it. I'm not sure quite how, for some of us, but we did, and really it's about 13 to 17. But it's a clinical judgment who's an adolescent and who can work with the adjustable gastric band. That's what the team is for. That's why the team evaluates them to figure out who should get this put on.

I think the NIH guidelines are very conservative, because they're based on gastric bypass data, a much more dangerous operation, and they're based on adults who, for a given BMI, a child is much more overweight than an adult. We need to follow the patients, and it's the end points we need to use, excess weight loss, but also the resolution of the comorbidities and the prevention of development of

comorbidities.

There is no place for a randomized study, because there's no treatment that approaches the adjustable gastric band. You can't talk a family into something that's four or five times more dangerous for dying and three more times more dangerous for complications, and there's no place for a randomized study for surgical procedures and non-surgical procedures, because the other procedures don't have the results yet. They've got to reach that 80% mark. They've got to reach the 60% excess weight loss mark.

Thank you. I'd be happy to work with you in the future.

CHAIRMAN NELSON: The next speaker is Mark Holton.

DR. HOLTON: Good morning. In the interest of disclosure, we are working with the lap band in FDA IDE trial, and the bands are being provided by the Inamed Corporation for the children at no cost.

For the last two years or so, we've been involved with laparoscopic adjustable gastric band as

a treatment of adolescent morbid obesity. We have started our center called the New Hope Project at the University of Illinois in Chicago.

We've been through how the band looks. We were fortunate enough to work with an adult surgeon, adult bariatric surgeon who has very extensive experience in putting on gastric bands, and we started doing it on children. So he was -- Dr. Corrigan was involved in the FDA AB trial and was very influential in getting the band approved by the FDA for adult usage, and now he's the leader of our group as far as teaching us, the pediatric surgeons, how to put it on adolescents.

We've seen the band as an improvement in the band. We like the lap band guard, the BG. It gives us more adaptability for sever obesity down to normal obesity, less obese people. This is how the radiograph looks on the band. On the A-panel there is the lap band's position. We often do the barium swallows that show the pouch. You see a small amount of contrast coming through the stoma there, the neostoma, and the small proximal gastric pouch is what

restricts how much the child can eat.

Before the pediatric surgeons got involved with Dr. Corrigan, he had done ten patients off-label, and the adolescents were 16 to 20 years old, compared to 506 adults, and looking at the 18-month weight loss -- about two-thirds of the way down the column -- basically there's no difference in excess weight loss. There's basically no significant difference in operative time, and the pre-operative BMI were very, almost identical in the two groups.

There was a slightly increased incidence of pouch enlargement with the adolescents and a higher rate of having to re-operate on those children before we got involved. So just to stress to you that I think as we go forward with bariatric surgery in adolescents, we need to have people used to taking care of adolescents involved, because it's a different beast. It's a different species.

The weight loss, like I said, is actually slightly better, although not a significant difference at this point for the adolescents. These kids seem to lose weight faster than the adults do.

Now there's a little bit of a conflicted adolescent here. Basically, these kids -- I think they lose weight faster because they want -- for the first time in life they have control over their weight, so they exercise, they go crazy, they really watch their weight, and they want to get down to a weight the same size as their peers as soon as possible. But on the other hand, they're still adolescents, so they want to eat like their buddies, so they still have the three pieces of pizza or try to slam it down, and the milkshake, so it takes a lot more work with the dietitian and nurse practitioners, everybody, to sort of get them, to get them through this changing their lifestyle and their eating behaviors.

Pouch enlargement -- what does it look like? Well, basically it's a dilated proximal pouch. Three different patients there, a couple of these are adult patients, actually, but it's an example of what the pouch looks like when it gets dilated.

So how do we treat that? Well it looks kind of scary, but actually it's not very scary. The

way we treat it is we take the fluid out of the band, let the patient -- put the patient on a liquid diet for a while. The stomach shrinks down, and then we just kind of slowly re-inflate the band. Now the key thing is to catch that before it gets to the point where it can't be treated without surgery, so sometimes if you re-operate on these kids for pouch enlargement, basically it's a simple thing of repositioning the band, and mortality is low, and basically non-existent, and they're home the same day with a slight adjustment.

So we've modified our protocol. Not too much. The only thing we've done -- we follow these kids more closely. Down in the lower right part of the slide there it says a follow-up. We bring them back after a week, then six weeks, then monthly, but we check on them every week. It's like an email -- email is great for this. We check on them, we communicate with them, they send us updates, they keep a diary, and we follow these kids very closely.

As far as the team concept, we have just about everybody in the hospital excited about this

project, and the pediatricians and all the pediatric specialists are sending us their kids with asthma, with sleep apnea, with kidney problems, and it's really quite -- for the first time a lot of the pediatricians can see a way to get this patient cured from their comorbidity.

These are some of the people involved. Now, as far as the eight patients we have on trial right now, they range in age from 15 to 17 years. The comorbidity is on the upper right. Fifty percent of them have sleep apnea so far. Fifty percent have hypertension. A quarter have hyperlipidemia, 45% insulin resistance, 70% by either a blood test or ultrasound test have fatty liver disease. There's dysmenorrhea, and only a quarter of these kids have clinical depression.

The results of surgery -- the average length of surgery is less than an hour. We've been keeping these kids overnight just because we're kind of cautious about the trial, and we told the FDA we'd keep them overnight, but they're basically staying overnight and having a slumber party with the nurses

because they're walking out of the recovery room. They basically, you know, they're fine. They don't have pain. They're just really comfortable, but we're just sort of extra cautious with them.

The weight loss so far at six months -- we'll go to the lower right corner there -- our eight patients range in weight loss from 56 to 120 pounds. Complications are zero. We've had one kid come back to the ER once because she was having a little bit of trouble swallowing. By the time she drove for two hours to come and see us, the swallowing got better. We did a barium swallow in the ER, and it was fine. She went home, so that's the only thing we've seen so far in our patients. So basically we think this is a good thing to expand, and we'd really like to be seeing this used across the country.

Now, this final question -- what my main point is, as pediatricians, we always get asked, "If this was your child, what would you do?" Well, I look at the data, and basically, there's a one in 200 risk of mortality with a gastric bypass, a one in 2,000 with the lap band. If you operate on 100,000 children

in this country, that's 500 deaths versus 50 deaths. There's a three to four-fold greater morbidity. The complications are more severe with the gastric bypass. The new data from around the world says that the long-term efficacy is virtually the same.

As far as compliance problems in adolescents, you're going to have compliance problems with adolescents no matter what you do, and if you have these kids coming back every month to see you, it's a much better way to kind of keep a handle on what's going on with them.

Yesterday somebody asked the question, "Well, if they have an unsuccessful gastric bypass procedure -- in other words, they don't lose a significant amount of weight -- can you go ahead and do a gastric bypass?" And Dr. Corrigan's mention was but a three percent mortality he would estimate with that, so the calculation I did, and I'm not a statistician, so correct me if I'm wrong, but if you have 20% of your patients, maybe, who don't respond to gastric bypass, and they have a three percent mortality, the aggregate risk of mortality in the

group is .006. If you add to an existing lap band mortality, basically you still have a procedure that's nine-fold safer than a gastric bypass.

If I was a parent, I would insist on starting with the band. I'd be happy to answer any questions.

CHAIRMAN NELSON: Thank you. The next speaker is Marjorie Arca.

DR. ARCA: Good morning. My name is Marjorie Arca. I'm a pediatric surgeon at Children's Hospital of Wisconsin, and I do not have any financial associations to disclose today.

I just wanted to bring to this forum's attention a couple of consensus papers regarding surgical candidates for morbid obesity. I'm sure yesterday you spoke about the NIH consensus for surgical intervention for morbid obesity. This came out in 1991. At that time it was decided that reasonable candidates for surgical intervention for morbid obesity included adults with BMI greater than or equal to 40 or a lower BMI, that is to say 35, with high risk morbid conditions, and as I was Googling

this last night at 2:00 a.m., this listed severe sleep apnea, Pickwickian Syndrome, obesity and related cardiomyopathy, diabetes. These may induce physical problems that are interfering with lifestyle.

In 2004, a position paper came out -- the general pediatrics, Dr. Inge, Dr. Skelton, and Dr. Garcia were part of that committee -- where, as pediatricians and pediatric surgeons we came together because we saw this problem becoming, and we tried to figure out what is the most reasonable thing to do. And the consensus panel recognized there are several key differences between adults and children, and I think it's good to focus on this a little bit, just because that is question number one which you have to discuss today.

These key differences equaled the following: The severity of complications in children and adolescents with BMI greater than 30 may not warrant surgical therapy. Yes, they will be sicker -- yes, they are sicker than their cohorts, but they're not as sick as their adult counterparts. Children, as everyone else, cannot give legal consent, and there is

data to say that behavioral therapies were effective in adolescents compared to adults, and 20% to 30% of obese adolescents will not become obese adults.

So given these premises, the committee came together and tried to proposed criteria on what are the -- what to impose in terms of surgical therapy in adolescents.

I'm not getting this. The other one? Sorry for the small print.

So, this is Table 2 in that particular paper. Adolescents being considered for bariatric surgery should have failed six months of organized attempts at weight management as determined by their primary care provider; have attained or nearly attained physiologic maturity, and by that I think we said 15, age 15 in boys and about age of 13 in girls; be very severely obese with a BMI of greater than 40, with serious obesity related comorbidities or have a BMI greater than 50 with less severe comorbidities. These are a lot more stringent than the adult NIH consensus guidelines. Demonstrate a commitment to comprehensive medical and psychological evaluations

both before and after surgery; agree to avoid pregnancy for at least one year post-operatively, just because of the nutrient problems that can occur with the severe weight loss during that time; be capable of and willing to adhere to nutritional guidelines post-operatively; provide informed consent to surgical treatment; demonstrate positional capacity and have a supportive family environment.

I'm going to try this again.

Okay, and the serious comorbidities are outlined in Table 1: diabetes, obstructive sleep apnea, pseudotumor cerebri, where you have such an increasing intrapenial pressure secondary to comorbidities that you actually go blind, and there are less serious comorbidities that can be seen, as well: hypertension, non-alcoholic steatohepatitis. Those are things that you're heard about over and over again this course of two days.

They focused also on importance of a multidisciplinary program. You can't just go to your friendly neighborhood bariatric surgeon and say, "I want this done." There's several people, key people,

that need to be involved, including the child's primary caregiver, and the surgeon, as you can see, is hopefully the very last in that array of people that these children have to see.

Surgical eligibility, again, should have a multidisciplinary team with expertise in adolescent weight management and bariatric surgery, and this team should meet and carefully consider the indications, contraindications, risks and benefits of bariatric surgery for these individual children and adolescents.

This team has agreed that after failure of conservative management, that surgical approach is the best alternative for the patient, and adolescent bariatric surgery should be performed only at facilities capable of treating adolescents with complications of severe obesity where detailed clinical data collection can occur. And I would also say that these children, if they have complications, should be treated in a pediatric center so that you have people who are experts in critical care medicine helping you out if these complications can occur.

So there are several surgical options for

severely obese patients, and I'll just briefly talk about the lap band and the laparoscopic gastric bypass. You've seen how the lap band works, where an adjustable band is placed around the proximal part of the stomach, and the band is progressively tightened to create a small pouch, and there is a need for adjustment of the balloon serially.

There have been some lap band results. In 2004, the Italian data showed an 8.1% complications with an average decrease in BMI from 34 to 28% and certain 28% by 16 months. And in 2004, Renedal looked at some adults with an N of 444, with a 15% complication rate but a 44% excess body weight loss at one year.

What are the advantages of the lap band? It is technically easier, but for me, there's two things about it, three things about it, that are actually good to know. One is it's pretty reversible. If you don't like it, or something happens that is a problem because of it, it's a relatively easy thing to dismantle and remove. There are no aspects of malabsorption. You did not divert anything. You're

just decreasing the intake of the patient, and so when you're looking at a potentially childbearing woman, or adolescent who's going to undergo childbearing years, that's probably something to think about.

There are complications of the lap band, including erosion, infections, leakage, port migration, gastric obstruction, esophageal dilation. The success of the lap band needs serial close follow-up and will inevitably fail if the patient likes sweets like high carb powdered liquids.

Unlike gastric bypass, where the rerouting of the anatomy causes the patient very bad feelings of tachycardia and palpitations when you eat high sweets, and it becomes almost like a Pavlovian response that you cannot eat this thing, because you just feel bad, that doesn't happen with the lap band.

If you look at the gastric bypass, which is currently the gold standard, there is considerable anatomic rerouting. It causes -- you do staple the proximal part of the stomach and create a bypass for NY gastroenterostomy, which I'm sure was discussed yesterday. It has its own set of complications and

problems including anastomotic leak valve obstruction, internal and external herniation.

But my thought with the gastric bypass is as follows: Especially in young children, it's difficult to reverse. In adults it's difficult to reverse, as well. It is more permanent and has permanent rerouting of the child's anatomy, and my thought is, for the child's lifetime, you have very limited access to that distal stomach and the proximal duodenum because you've stapled it off. And, in fact, in the most recent obesity journal, there was a report of a woman who initially had a lap band and then had undergone subsequent gastric bypass because of failure of the lap band who presented with a gastric cancer in the pouch and did not really present the classic symptoms. And my thought is no one really knows what's going on with that distal stomach and the duodenum, and it's very difficult to be accessed to that without operations later on.

CHAIRMAN NELSON: You have another minute.

DR. ARCA: So I probably should have put recommendations instead of conclusions. I urge the

panel to consider that there is a role of the lap band in the surgical treatment of morbidly obese children and adolescents, but the patient should meet strict criteria as outlined, and when you're deliberating the first of the four questions, I would refer you to that consensus statement in pediatrics. I'm sure there's a lot of hours put in and a lot of very critical thinking put into that, those recommendations.

And I do think that because of the problem that we've got in this country with obesity, there is a need for multi-institutional trials to get valuable data for this epidemic and that we need a center, a central data depository so we can present the American public with the appropriate data as we are trying to tackle this obesity epidemic.

Thank you for your time.

CHAIRMAN NELSON: Thank you. The next speaker is Evan Nadler.

DR. NADLER: I have no financial relationships to disclose. I'm a pediatric surgeon from NYU. I work with Dr. Fielding. Been there for about 15 months. I've been involved with all of the

study patients, and as a laparoscopic pediatric surgeon who's done both adjustable gastric banding and open and laparoscopic bypasses, I wanted to speak to you a little bit to try to clarify some of the issues yesterday that I feel like the panel may still have some questions upon.

First of all, the lap band is borders of magnitude easier to place than doing a laparoscopic gastric bypass. The three to four, four to five is splitting hairs, but it's definitely much easier to do than the laparoscopic gastric bypass.

These are results from yesterday. I'm just going over that again. One thing I should have mentioned is that for most pediatric surgeons who have done many laparoscopic nascent fundal implantations, the anatomy behind the esophagus where the lap band goes is very familiar territory, and that's what makes the procedure so much easier for us is that it's an area that we're comfortable with.

The other secret of pediatric surgery or pediatric bariatric surgery is that the other technical advantage is that if you do lap band in an

overweight adult, especially the males, sometimes there's a fat pad over the stomach that makes it difficult for the band to be placed. For whatever reason, it seems that in children that fat bad doesn't exist, and so again, it's technically easier to place a lap band in a child than it is in an adult. That's been my experience, it's been Dr. Fielding's experience, and I think Dr. Wulkan's experience, as well.

So just a quick review of our results from yesterday. I'm not going to go into it again. You've sort of heard lots of people talk about it. So what I want to just speak a little bit about is some of the aftercare, because it hasn't been touched up. I'm also going to present our compliance data, since there was some disagreement data about what the real compliance in our program is, and I'll just give you the data, and you can conclude whatever you want.

But the keys to our success are patient selection, a strict follow-up program, and again, the compliance. And all patients before even meeting with George or I has to go to an information session that's

a group session. It's with adults currently, but as our numbers increase in children, we're going to have teenage-specific information session. They have to go to a psych eval, and they have to get their nutritional evaluation. And that's before they even meet the surgeon.

So what I would say about the compliance issue is we're self-selecting compliant patients, because we run them through hoops before they even get to us, before they get to the surgeons. And getting to the surgeon doesn't buy you an operation either. Then you need to go get your EKG, your chest x-ray, bone densitometry, ultrasound of your gall bladder, your nutritional labs, you have a follow-up nutritional evaluation, and then you get PFTs or a sleep study if indicated. So again, before you get to the operating room table, you have gone through multiple -- or, gotten over, multiple hurdles to get to the operation.

So the reason our compliance is so good is that if you can't make it to all these tests, and you know, if we get called from the bone densitometry

people that somebody's missed a couple of appointments, they just don't get surgery.

Post-op. Patients are seen basically two weeks post-op for a wound check. At six weeks is when they get their first adjustment, which I don't think anybody's really talked about the adjustments, but it's a very important part of the follow-up program. And then, although on our FDA IDE trial, we see the patients at three-month intervals for the first year and then six months after that, we actually encourage our patients to come back monthly, especially in the early post-operative period, because it takes some special tweaking of the band in the first three months to really get it to work for these patients to lose weight.

Basically, they lose some weight pre-op because we put them on a two-week liquid diet prior to the operation to get their liver fat stores to decrease to make the operation technically easier. And they lose some weight then. They may lose a little bit more weight in the immediate post-op period, and then they plateau until about three months

or so, and what happens during that period of time is that children get a bit discouraged, and you have to really give them positive reinforcement to get them to keep coming back and keep up with the program.

One of the other questions yesterday, I think, was about how do we monitor these people long-term. They do see the nutritionist every time they come to see us, and then they have a psych visit every six months, so it is critically important that these children get sustained supportive care from the other folks, not just the surgeons, to make sure that the lifestyle changes that they're undergoing are continued.

So one of the questions yesterday was -- or one of the concerns yesterday was about the rapid weight loss associated with the band. Well, actually, the weight loss associated with the band is very gradual. The weight loss associated with the bypass is what's rapid. So we aim for a goal weight loss of about one to two pounds per week in all of our patients, and if you remember, one of the talks yesterday on the dietary management, the protein-

sparing low-calorie diet has -- they're goal is one to two kilograms a week, so our diet actually -- our weight loss strategy is actually lower or more gradual than some of the diets that are being proposed. So there shouldn't be any concern about the band in terms of rapid weight loss.

And basically what we tell the patients is if they lose weight too quickly or develop any symptoms, they come in, and we might remove some fluid from the band, especially if they're having difficulty swallowing. If they lose weight too slowly, or they overeat, or they're hungry, then they may get some additional fluid to the band.

So there's a lot of self-reporting here, and it's very important that you keep contact with your patients closely, and I'd like to stress that any center that's thinking about doing this really needs to involve their adult colleagues, because these guys have much more experience in how to manage the band post-op.

The technical aspects of the band are easier, and most pediatric surgeons can do the

procedure without too much difficulty, but it's the adjustments post-op that are really the art form that go with this procedure, and I think that pediatric centers have to keep their adult colleagues in the loop.

CHAIRMAN NELSON: If you could start wrapping up, please.

DR. NADLER: Okay. So the compliance data. Here are the numbers. So, of our 58 patients, at six months we have 29 of 38, so 76%, 18 of 23 a year out, and the rest you can see. So yes, we lose a few. I would argue that any time you go to a major national meeting and you hear what the follow-up for bypass or other surgical procedures are, they don't approach these numbers. It's more like in the 30% to 40% range. It's probably not a problem with gastric bypass, because you don't need the same follow-up, but compliance rates of 80% can be achieved, and we have achieved them, so it should not be a consideration in limiting the availability of this device.

Other data, just to answer some of the other questions yesterday. The super-obese were

brought up. Data from Chris Wren and our institution has shown that the band works for super-obese. Some people advocate it as a bridge to bypass. Others advocate just the band alone. Either way, patients who are super-obese who get a lap band lose weight.

The low BMI study out of Australia is being duplicated at our institution, and our data is basically the same. They're not in publication yet, but basically, there was a question yesterday about BMI of 30, I think, and we've shown in the adults anyway that it's equally as effective.

And then, I searched the internet last night like mad, but I couldn't find this paper in print. It was presented at Sages last year in April, and it was, I thought, a very illuminating paper which was, I believe, from the folks at Columbia in their adult program. They compared their bands to their lap bypasses in terms of excess weight loss and reduction of comorbidities, and yes, the band has a lower percent excess weight loss than the gastric bypass. However, what they found, which I think is really the most important thing, is that reduction in

comorbidities between the groups was the same.

So does the extra 10% of a bilipancreatic diversion or laparoscopic gastric bypass -- is it worth the extra mortality if the results in terms of reducing comorbidities are the same? And my answer would be no.

CHAIRMAN NELSON: You're out of time, which is -- Thanks.

DR. NADLER: I'd just like to thank you, and if anybody has any questions, I'd be happy to speak to them.

CHAIRMAN NELSON: The next speaker is Mark Wulkan.

DR. WULKAN: I'm not sure if speak without slides. I haven't done that in a while, but I'm going to try.

I have no financial relationships to disclose. I want to tell you how I became a pediatric laparoscopic band surgeon. A patient came to me who was about 411 pounds and trached because his sleep apnea was so bad, and I'm sort of the local laparoscopic surgeon, and he wanted to know what can I

have done?

I was aware of the band. I was aware of the fine work that Drs. Garcia and Inge have done, and I researched it and talked to the parents, and they actually came to me requesting a band. Well, there are several issues. One is the patient was a Medicaid patient. They certainly didn't have the means to pay for it even if it was approved. And they didn't have adequate insurance to cover it.

I talked to the Medicaid director in Georgia and talked to him about this patient. We went over the literature together, and actually what has happened now is Medicaid is approving the lap band in children on a case-by-case basis, and due to that we've actually done six or seven patients already. We're doing them off-label. The patients have all done well. I'm not going to go into our results. They're similar to everybody else's.

I want to talk to the Committee about what their recommendations are going to be for the lap band and try to address those directly. One is patient selection. Who's going to get this? Well right now,

the kids that I'm doing are similar to the first patient I described to you who, by the way, now no longer has his tracheostomy and swam for the first time in three years.

I think in the beginning, a BMI if 30 is obviously too low. Maintaining a BMI of 40 with the comorbidity as has been set out by the folks who perform gastric bypass, with the risk benefit ratio of gastric bypass in mind when they developed those criteria, I think it's probably too high. I think the NIH criteria to start with is appropriate. The only question I have in my mind is whether it is appropriate to require a comorbidity in a child. I would venture to say, though, that if you look hard enough in all these kids and all the children with a BMI over 35 even, you can find a comorbidity.

The other thing that I want to emphasize as it relates to the lap band is the responsibility of this Committee to recognize what happens if we make it too hard to get the lap band. Several of the patients that have come to me have already been through -- I'll call it a mill that we have locally in Atlanta -- that

basically, along with adult patients they go through a program for Rule I gastric bypass. It's not a pediatric program. There are no pediatricians involved. There's no specific pediatric follow-up involved, and they come to me for a second opinion before they sign on the dotted line. And that is happening in our community. I don't know how many of those patients don't come to me or don't go to Dr. Inge or Dr. Garcia, where there are well established, mature pediatric programs with pediatric practitioners.

And I think that if we don't make the options available to kids, they're going to find a way. The people that are coming to us now are highly motivated, which is probably why our compliance rates are so high. But I think that we have to be careful if we sit there and say that well, gosh, we need five years' worth of data before we can even consider approving this, how many kids are going to get hurt by waiting five years? And I think that's a question that the Committee members have to ask themselves.

How long is appropriate follow-up? Well,

there's great follow-up in adults now out 11 years in the United States that there is no reason to think it wouldn't be similar in children, as the short-term follow-up has been similar.

The other thing I want to emphasize again is that I don't think we want to open this up so that everybody on a street corner that has a bariatric surgery sign out front can start doing lap bands in kids. I think that you need to have a pediatric multidisciplinary team as has been described to you before.

And in the interest of time, I'm not going to go on, because I already know that we have gone over, but I would implore the Committee to come up with criteria that allows us to evaluate the lap band in an efficient way so that we all feel comfortable approving this for children so that we can begin to treat the problem instead of simply talking about the problem. Thank you.

CHAIRMAN NELSON: Thank you. So this ends the open public hearing session of the meeting.

DR. YUSTEIN: Dr. Nelson, would you mind

if I made two comments?

CHAIRMAN NELSON: Go ahead.

DR. YUSTEIN: First comment on -- Dr. Allen had mentioned in his talk about an FDA statement in 1993 regarding what people should do regarding obesity. I'm not familiar with that, and that doesn't sound like a comment that would come from the FDA. It sounds more like an NIH recommendation. The FDA centers that deal with products, devices, drugs, biologic centers, don't make recommendations like that. Sometimes our Center for Food and Nutrition makes recommendations on dietary guidelines, but making specific recommendations on how patients should be treated by physicians is usually not a statement that the FDA makes, so I'm not really sure where that came from.

The second statement comment I wanted to make is that, just to remind the Committee that we're not here today to talk specifically about the lap band. You've heard a lot of public comment on the lap band. We're here to talk about how to study devices like that and others that may be coming, but the

Committee is not going to be deciding who gets the lap band, when the lap band should be used. We're talking -- we're going to be talking about how to best study these devices so that we can come to those conclusions eventually.

I hope that -- I think that some of these public comments, although very useful, may have led people a little off track, and especially since there's only one device approved, most of the comments were related to that one device, but I don't want you to focus on the fact that, you know, who gets the lap band. You're not deciding who gets the lap band and who doesn't get the lap band.

CHAIRMAN NELSON: I appreciate that clarification, but have no fear.

Well basically, as you can see from the rest of our agenda, it's basically Question One, Question Two, Question Three, Question Four, Summary. Now I'm under no illusion that we can deal with these questions in any linear fashion. But on the other hand, each question as I go through them I'll show you the overall, and we might as well just sort of get

into that, and let's -- so in effect, we'll go through them.

Now, as we go through the discussion, I think there's always a challenge in a group this size to have a conversation that centers around a particular theme that might have been brought up in the questioning. So as I see hands I'll write them down, but if I hear something that sort of crystallizes as a particular line of discussion that ought to be pursued, what I might then ask is that people focus on that question, and we deviate from the list, then we get back from the list.

So if you see me kind of go back and forth, that's fine, but that's only with the interest of, instead of having four balls in the air, we can maybe keep one in the air at any one moment. So bear with me as I go back and forth on that. We'll always get back to the other question, so if I deviate, you know, write down your thought so you don't lose it, and what I'll try to do intermittently is summarize what I'm hearing as much to sort of crystallize, and if it crystallizes then we don't have to keep

repeating that theme. We can then try to develop our thoughts further, and we'll see how it goes.

So here are, briefly, the oversight and the questions. You have the questions in written from before you. There is a fair amount of introductory information, and I'll read some of that, but effectively we're being asked for, and the FDA admits that these are complex questions, involving a mix of both science and ethical components. Each of the questions involves a summary of the issues and focusing on areas for which we, meaning the FDA specifically, need our guidance. And broadly they're seeking the advice in four different areas, four different questions.

The first question is the appropriate pediatric population, balancing scientific and ethical issues. The second is appropriate pediatric endpoints for measuring the success of those and also the timing of those endpoints. The fourth is appropriate trial design. You've heard some suggestions, including issues of assent and the like, and then the recommendations on long-term safety and effectiveness

assessments.

Now with apologies to Dr. Garcia, and you know I think it is appropriate for us to try and engage in some blue ocean thinking, but we should recognize that there are some dangers in doing that. So, for those who are interested, that was taken with a Cannon Elf on full zoom, so you can do it with a little camera.

So the first question, the appropriate pediatric population, and this is -- I'm not going to read through all four questions, as I know is often the ritual done at FDA meetings, and then you go one, two, three, four. If we read all four questions, it'd take us the first hour, so, given the length of the questions. So we're just going to go Question One, talk, Question Two, talk, Question Three, talk.

Appropriate pediatric population. Inherent differences in adult and pediatric populations make the selection of the appropriate patients for device treatment more problematic for the younger age group. Whereas most adults have reached physical, emotional, and sexual maturity by the time

they seek aggressive weight loss management, the pediatric population may not have. In addition, since many adults have been overweight or obese for years, medical comorbidity such as hypertension, diabetes and dyslipidemia have had more opportunity to develop and manifest when compared to the pediatric population. Furthermore, adult patients have usually failed multiple attempts at conservative and/or supervised treatment regimens, whereas children may not have had adequate supervised attempts at weight loss.

This makes the selection of appropriate patients for studies of devices which may require invasive surgery or which may permanently alter certain functions or anatomy more challenging. Although the selection of patients certainly would be influenced by the relative risk benefit ratio in the particular device, this will not always be known prior to initiating a study.

As such, FDA would like recommendations from the Committee for selecting an appropriate candidate population for device study in general, recognizing that in certain situations flexibility

will be required.

Now in formulating recommendations around patient population, the question identifies a number of patient characteristics that could be seen as either absolute or preferred but not mandatory, and these would include age requirements, weight requirements with different ways of describing those weight requirements based on BMI or percent or absolute weight, et cetera, developmental milestone requirements, medical comorbidity requirements, and these list five of those: failure to respond to conservative or less invasive therapy -- we've heard failure to actually comply with the lead-up to surgery during one of the presentations -- psychiatric, psychological requirements, or any diagnoses or existing conditions which should be excluded from that patient population. So these are -- and they're asking us not only to consider it, but also, ideally, to be able to prioritize in the order of importance these different characteristics.

In addition, issues of assent and parental permission play into this, and I'm assuming that we'll

go back and forth from some of the science, and I've also heard the theme of equipoise be raised as well in the presentation, which may not allow us to entirely avoid the conversation about prior results, but that's an issue that we'll have to deal with.

Now just to give you any idea, as I tried to figure out the way the relationship of these various questions, you know, I'm not going to keep this up, but here it is all on one slide if you're interested. But we'll see how it goes.

So really, the first question before us appropriate pediatric populations. In other words, what's the population that we're going to study. Now we're going to get into study design and endpoints and long-term assessments, follow-up maintenance and those kinds of issues as we move along. The first question is population. As we, and if we can focus on that question, we'll keep themes in the air and balls in the air, and we'll see how it goes. So that's the first task.

I might also say, as people formulate their thoughts, there is really no votable issues on

the table. It's a matter of discussion and guidance. On the other hand, if I find that there seems to be, sort of, two dominant points of view, say over differences of opinion and the like, it won't be so much as a vote, but I might, at least for my own interest, get a sense of the weight of that. If it's a 50/50 split, I mean, are these two legitimate positions, or is it just a vocal minority saying it ought to be this, et cetera. Not really a vote, but sort of a sense of how many might fall on one side or the other, because that would at least provide a little more nuance to the discussion. But we won't have any votable issues in that sense.

So with that, why don't we dive in? Dr. Kral?

DR. KRAL: I'd like to make a suggestion, since devices can be very many different things, and there is a parsing of how we should do these devices. I really think the discussions of most of the questions will be related to the specifics of the generic type of device. For example, may I talk about a band? A band as an --

CHAIRMAN NELSON: You're allowed to talk about anything.

DR. KRAL: I'm sorry?

CHAIRMAN NELSON: Go ahead.

DR. KRAL: A band would be generically rather different, for example, than an electrostimulator with some small leads. As far as permanence and as also related to the structural changes that occur. So I think if would not be a good idea to use device -- for all devices, I think populations are going to vary depending upon the type of device.

CHAIRMAN NELSON: Right. I think that's fair. The challenge would be to then say, okay, what is it about the nature of different approaches? So, for example, if it's degree of invasivity, if it's degree of reversibility, if it's degree of ease of management. In other words, identify not so much device by device or types of device, but what are the characteristics? Because I would, you know, it may be possible that ten years from now someone else might come up with an idea for a device that we just don't

know but yet can be judged relative to those characteristics.

DR. KRAL: Well, we're surgeons here, and surgery seems to be part of the stealth theme in all of this. Surgery will alter both structure and function. When we're talking about devices, we're talking about a device that will alter structure and function. Some of them alter structure more than others. Some are virtually reversible. For example, leads from an electrostimulator to gastric muscle are rather reversible, almost totally reversible. Pulling out the lead has not left any significant structural change, while having had an implantable balloon around the cardia region of the stomach for a prolonged period of time will have caused irreversible structural changes. Whether they're minimal or not, whether they're transient or not we can leave to another kind of debate. However, there's a substantial difference between these two generic concepts.

CHAIRMAN NELSON: So let me just pursue that, since we want to talk about patient -- having

said that, how would you carry that sort of, the distinctions of reversibility and degree of alteration of structure and function into consideration around patient characteristics for trials?

DR. KRAL: Well, I think when we're discussing factors such as age groups and various population characteristics, it's substantially important, particularly for age and developmental stage of putting in something that creates rather irreversible structural changes versus those that are rapidly reversible through development.

I think it's rather obvious that the greater the perturbation caused by the device, the higher the level of the burden on us to decide what stage of development we can impose this. I think there could be a very different age category that would have a lap band, for example, than one that might have an electrostimulator, if there could be any agreement that that might be a viable therapeutic strategy.

CHAIRMAN NELSON: Okay, based on your comments, I do note a couple of hands. Do we want to

go with people's response to that, or should I go to the list, or --

DR. KLISH: I would like to respond.

CHAIRMAN NELSON: Go ahead, Dr. Klish.

DR. KLISH: I agree with your comments in terms of structure of function and the variability of these various devices in regards to that. But there are also some commonalities in these devices. For instance, they probably are all going to take away control to a certain extent, you know, which is different than other forms of dieting. They all are going to be used in a somewhat more vulnerable age group that has to be taken into some account. So even though there are differences, there are also you know, common things that we have to associate with all of these devices.

CHAIRMAN NELSON: Let me go to Dr. Inge, and then I'll come back to that.

DR. INGE: All right, thanks. I want to make one general comment and then one back, sort of on point with the H question. The general comment is that a lot of people have referred to the

recommendations that were published in pediatrics, primarily authored by me but with a large, broad input.

Those recommendations -- I'll just want to bring your attention to the fact were actually drawing up several years ago now, and really were based on some sort of a guidance for clinical management. So, in other words, I'd just like to say that in the absence of any clinical management guidance in the literature, they served a purpose. I think that for the purpose of this Committee in designing or giving recommendations about potential trial design for devices, which may well have a different risk, that we should take into consideration that the guidelines were quite restrictive.

Now, relevant to some of the other thinking that went in to the guidelines, and relevant to age, I'd like to make a more specific comment for discussion, and that is that I think not, regardless of the device or technique, but a general comment that can be made regarding age is that adolescence -- childhood and adolescence are periods of rapid change

in a variety of health spheres and a variety of social spheres. There are several of these spheres that I think bear relevance to a discussion about age of appropriateness or a device for weight loss including one's linear grown or sematic growth.

The height is the most outwardly measurable indicator of sematic growth, although more specific indicators of grown and growth cessation, that is, obtaining adult stature, are certainly available and include a rather simple x-ray of the hand and wrist that can tell you when an individual reaches their completion of linear growth, completion, you might say, of sematic growth, but not completion of social grown or psychological maturity, which is also the second variable, I think, that bears significant relevance to a discussion of placement of a device that would require the cooperation and input and good behavior, if you will, of a teenager.

So just some baseline facts and metric facts about height. If you look at growth curves that are widely available from the CDC, females tend to plateau in their height, that is, attain adult

stature, somewhere between the ages of 12 and 14 for normal teenagers. That is, for average. This data is accrued from a large population base survey. Obese, and particularly being severely obese, actually will have a height -- attain their adult stature in height perhaps one or two years before that. And so if we're concerned about stunting one's growth, I don't think that that is a major consideration for the majority of individuals that we're going to be considering today or at least for teenagers.

Now the -- so that's one fact. The real uncertainty, I think, that we all must have, though, is the, sort of, the maturity level, that ability to concretely think about problems and concretely think about their involvement in process that is truly lifelong, regardless of the device we're considering.

So I guess the summary from this would be that there are some things that we can easily measure, and that is completion of growth or near completion of growth. Even if one has not completed growth, there is, I think, good reason to believe that nutritionally depriving someone who's morbidly obese probably won't

have a serious sustained effect on their growth, and I think that there are other experts here that can more specifically talk to you about it from an endocrine standpoint. But the maturity level speaks to not selecting an age on a, you know, number age. Rather, a multi-disciplinary team that can evaluate the ability of a patient to really aid in the own treatment.

CHAIRMAN NELSON: Let me just ask you a clarifying question, but just to tell people what I've got for the list is Pories, Dokken, O'Fallon, Daum, Botkin, Lustig, and Jack Yanovski. But let me ask a question and then see if people want to continue this line of questions.

There was one, if I recall, one slide from yesterday suggested that at the cessation of linear growth, when you reach skeletal maturity, that that would be a point at which the risk, if you will, of an intervention would be significantly less, and you sort of implied that, at least as I listened to your comments, would you go so far as to say that one shouldn't consider a device, something that would

alter structure and function, if you will, until one reaches that age of skeletal maturity, regardless of how the endocrinologist would tell us to measure that? Would you go that far --

DR. INGE: No.

CHAIRMAN NELSON: -- or would you say --

DR. INGE: No.

CHAIRMAN NELSON: How would you then?

DR. INGE: No, I wouldn't, because I think there are mitigating factors. There are mitigating diseases encompassed in this disease of obesity that would certainly mitigate the risk -- that effective treatment of a disease, let's say diabetes or obstructive sleep apnea that's life-threatening, would mitigate a risk to taking someone who has achieved, let's say, 90% of their adult stature and the risk that they might not achieve adult stature. I think that that risk that they might not achieve adult stature, if you significantly calorically restrict them, is low in the first place, so I think that we can't really measure that, but I think that it's low, because there are other paradigms in pediatrics where

you may actually do something to stunt growth, and when that intervention is taken away, then catch-up growth will occur.

There's also -- so I don't think that that's -- so in answer to your question, I don't think that you should draw a line at have they completed linear growth to consider treatment if, in fact, the indication for treatment is, you know, significant enough.

CHAIRMAN NELSON: With that indication being, at least from you list, a reduction or prevention of a comorbidity that you think that individual is at risk for, as a balance against the risk of the intervention itself. So the risk and benefit of the intervention would be balanced against the comorbidity and not simply the fact of obesity at a certain level. Is that fair?

DR. INGE: Right. And not the risk of the comorbidity. The presence of the comorbidity.

CHAIRMAN NELSON: Right. The presence of a comorbidity could offset, then, a desire to do that in the same way we use steroids in asthma even though

we know that it's going to stunt growth to some extent.

DR. INGE: Absolutely, and I think that what we're seeing in secular trends has to make us aware in a panel meeting like this that, if not today, tomorrow, or, you know, a year or two from now, these trends may continue, and the weight of the comorbidity or the health burden of obesity will actually worsen over time.

CHAIRMAN NELSON: Let me see if there's comments on this conversation before I get back to the list. Dr. Lustig?

DR. LUSTIG: I want to expound on that point specifically. There are several things that we know about the endocrinology of obesity that, you know, pertain directly to Dr. Inge's comments. For instance, obstructive sleep apnea is actually known to cause delayed puberty. Also, obesity causes increased estrogen, which actually suppresses hypothalamic function, which ultimately also delays puberty in boys, although it tends to advance it in girls, one of the reasons why we're seeing an advancement of puberty

in obese girls.

In addition, we know that obesity, because of the excess insulin which drives the IGF form receptor at the level of the bone actually advances bone age so that you actually get increased growth at an earlier time. So, in fact, the majority of statural growth will have been achieved in an obese patient at an earlier age, so I actually think that Dr. Inge is quite correct, and I think that he brings up a very good point that statural growth and even puberty should not be the overriding issues but, in fact, the psychological maturity of the patient with respect to the specific device that's being evaluated is actually probably the most important thing.

So, for instance, in the lap band, where you would actually have to have cooperation, you have to have a different level of psychological maturity in terms of cooperation, in terms of self-reliance, whereas, say, with a gastric stimulator you could actually have something lower. That's the reason I asked the question of Dr. Wendler yesterday about assent based on risk.

CHAIRMAN NELSON: Dr. Yanovski, do you want to continue this, or do you want to stay in line?

DR. YANOVSKI: Sure, I'll just quickly say I agree with Dr. Lustig entirely that the majority of linear growth has been completed in most overweight girls, particularly less so in boys, but enough that the chances of it impacting significantly on adult height is little. Second, because they've achieved so much of their adult height, even if they were to lose a small amount of final adult height, it's unlikely to affect their lives significantly. And third, as far as I'm aware, even with rather significant weight losses induced by very low calorie diets, there's no evidence to my knowledge that there's a permanent stunting or loss of height centile in adulthood from such procedures.

CHAIRMAN NELSON: Okay. Let me go back. I've got Dr. Pories, Dokken, O'Fallon, Daum, Botkin. Dr. Pories?

DR. PORIES: This is partly in line with that. I'm concerned about this focus on late adolescence. The adolescents that I operated on,

frankly, looked like adult women, even though they were 16. Right now at East Carolina, we've got a ten-year-old who weighs 300 pounds. We have a number of kids who are much younger who have severe obesity and are very sick. And I hope that we, as we talk, we don't forget that group, because until now no one under 16 has even been mentioned.

I think we ought to broaden our scope.

DR. INGE: A brief point of clarification then for the endocrinologist in particular with respect to the growth chart plateau for normal populations between 12 and 14, for ladies -- for women, that is. Would we have a number or a range that would indicate for the severely obese that they would likely have achieved adult stature, or would we make a recommendation to have as, on a case-by-case basis, an individual test of having achieved that as a starting point to answer the height or linear growth question?

DR. YANOVSKI: I guess, perhaps we're answering a different question because, for most of us, we don't -- at least, I don't believe that

skeletal maturation or pubital development, per se, are going to be important limiting factors on who should be considered for obesity therapy. It's not going to be how much they have left, because at least, to the best of our knowledge, there isn't going to be a significant impact on adult height, even if they lose weight, that losing weight from an obese point of view is not the same as losing weight in a child who is at the fifth percentile.

So I think the question shouldn't even be on the table. It's more the neurocognitive maturity that may be more relevant for these devices and other procedures than the height maturity, at least in my opinion.

CHAIRMAN NELSON: Is there a general agreement on that? Okay, so well then how would you tackle, then, the ten-year-old and the psychological maturity question that Dr. Pories puts before us?

DR. YANOVSKI: Actually, if I can -- I have sort of a general -- so we're talking really about what should be the way we structure research to answer the questions when these devices should be used

in clinical practices, how I've taken our job here. And if we do that, if we think about it in that regard, there is two general pediatric principles that we've applied in the past to think about this.

The first is that we work our way down in terms of age, showing efficacy first in an older age group and then in a younger, unless it's a condition which uniquely affects younger children and regardless, even once we've established it as functioning well in older children, there needs to be additional studies in younger children because of the differences in physiology and developmental status.

And I think those -- if you think about research design, we have to consider those ideas, that showing that it works for adolescents does not mean that we should just blanketly allow it for all children, and so there has to be a staged approach for most of these things. So, for any of these devices they need to be demonstrated to work in older adolescents and then applied younger, and the number of age categories is something we might want to talk about.

And then second, because we know that different devices might function better for different levels of obesity, it may also be appropriate to consider different studies in different degrees of obesity or dysfunction related to obesity. So while obviously for the most invasive -- well, I shouldn't say obviously -- in my opinion for the most invasive devices, we should be starting and perhaps only with great trepidation use them, even study them, in individuals without any complications of their weight for things that would be a far less invasiveness, and you can imagine a device that did not require surgery that might still be considered by the FDA. It might be appropriate for that to be studied not only, or perhaps not at all in the super-obese as was talked about before, but only in much more mild obesity. But those are individual questions I think that at the IRB level are going to wind up being answered, whether the risks and benefits would be appropriate.

So to my mind, we need to require that different age groups be studied separately for each device, that for the most invasive devices, the most

severely affected be studied first and perhaps only in the -- first or only is really going to be the discussion, and that Tanner stage and bone age I don't believe are really the most relevant issues here. And then the second question would be what will constitute severity of obesity for complications of obesity. And Dr. Inge's, I think, very nice paper from a couple years ago specifies the most severe complications in a very cogent fashion as really the life-threatening ones, so Type II diabetes, obstructive sleep apnea, and pseudotumor cerebri, I think, those are the three that are most -- I believe those are --

CHAIRMAN NELSON: What was the third?

DR. YANOVSKI: Pseudotumor cerebri are all very reasonable items to be considered the most severe conditions related to overweight in adolescents. And so those, to my mind, anyway, represent uniquely severe complications that might be appropriate as criteria for the first studies of devices that are significant.

CHAIRMAN NELSON: What I'd like to do in fairness is just go though the list that I've got here

just to sort of let people get a chance to get other issues on the table, but what I'd like to remember to get back to you about or others on the same question is I heard yesterday, I think it was in Dr. Garcia's challenge -- presentation -- raised the question of why would you pick the sickest if, in fact, that's the highest morbidity and mortality for the most invasive procedures?

I mean, in other words, you're increasing the risk that you attempt to prevent by picking those who are at greater risk, which would sound as an argument against the -- only do the big things in the people that are really sick.

So if you want to just ponder that, and then we can -- let me run the list and get the other issues on the table, and then we can get back to it.

Deborah Dokken?

MS. DOKKEN: My comment feels a little out of timeframe, because I really wanted to lay out something that was more our process as we went through the questions and related specifically to Question One, although I know the list of possible

considerations for selection that we have from the FDA is only a guideline, I did want to make sure we added to that list based on a lot we've heard yesterday and this morning some consideration of family, family constellation, family support, et cetera, because that seems to be intertwined. So I didn't want to lose track of that and wanted it to be H or whatever on that list.

CHAIRMAN NELSON: Just out of curiosity, when the people in this field talk about psychological requirements, are you assuming family support under that, or is that a separate category? I'm asking the field people. I mean, I don't do that normally, but this is -- both? All right, so we'll make sure that the family thing is in there.

Judith?

MEMBER O'FALLON: Actually, I had asked to be on, but my comments are very much along the line of his. Now as a statistician, I think kind of in the big -- as a big research program, so I'm thinking in the terms of having a whole great, big program going on all the time, of there'd be different studies going

on all the time of different things, and the FDA was asking us what kind of principles should we be looking at in terms of the choice of populations. And a lot of what he had to say is what I had come up with, too.

I would say that to study the ones with the most severe disease defined in terms of, say, body mass index for age first. And, but if you don't want to do that, you could stratify by BMI by age. Okay? I think they've got to do -- well, I was suggesting that they start with the most fully developed, mature, patients first, and I don't know how you would stratify, or maybe you'd stratify by Tanner stage or bone age, I don't know. You guys in the field would have to say what was the best way to do that. But you would want to go after their maturity level. That would be a very important thing.

Psychological stability, especially in the first studies. They'd have to start with the ones who are psychologically stable. If possible, it seems to me that you'd want to start with the ones without any comorbidities. If you really want to evaluate the effect of a therapy, it seems to me that you have to

start in that sense, in a better group of people. And if you don't see any worrisome adverse events in those guys, then you start opening it up to, say ones with a severe, one severe comorbidity, and then maybe more, you know, that type of thing. I don't know how it would work exactly, but I do think that to give the therapy a chance to show what it's doing, you have to give it a good set of patients.

And then, Deborah, I already had that strong family support would be very important for those initial studies. After that you could start to relax that, but if the idea is to characterize the therapy, it seems to me you have to give it a good shot, and do it exactly as you say, by stages. So you start giving it the best group and then moving it out to see how it acts in some of the tougher populations.

CHAIRMAN NELSON: Let me just pause for a moment. I'll get back to the list which, to reassure people, has Daum, Botkin, Hudson -- I can't read my writing. Well, we'll figure that out, and now Gorman's on.

But let me -- when you said no

comorbidities -- Newman, yes, you're right. You're on there, Tom. And then Dr. Roccini's on there and then --

When you said no comorbidities, there was a lot of muttering from this side of the room. I think from a trial design in the drug world, often getting rid of comorbidities is, in fact, what happens, but it may be that in this world, that's, in fact, the opposite of what ought to happen. So if people want to comment on that issue more explicitly other than just all shaking your head, no, that was a bad idea?

Jack, and then I'll come over here.

DR. YANOVSKI: I think it's, because we're studying pediatrics, we're uniquely benefited by the fact that there are adult data, and the adult data show us pretty clearly that these procedures (a) can be done, and (b) are done in folks with comorbidities with rather good success, at least for bariatric surgery and perhaps even the more recent devices. And because we have that experience, we generally don't require us to study the best case scenario. We can go

to the people who really should receive treatment and who will ultimately be treated, perhaps most readily, in the real world.

So it's our desire to study those people who will be most likely to use the therapies, and I've written this before that, you know, we should really find out whether the therapies we apply work and the folks who are most likely to get it. So that's why we're lucky that we already know that it works in the best case scenario in adults, and so it's very likely to work in the best case scenario in pediatrics. So we better find out who will actually benefit the most from it.

CHAIRMAN NELSON: We're not talking about endpoints, but if resolution of the comorbidity might be an endpoint, then obviously you need to have the comorbidity to have it, and in the drug world, comorbidities are thought to obscure efficacy and are not an endpoint necessarily, so it's a different type of approach.

Dr. Pories?

DR. PORIES: My point, but more eloquently

stated.

CHAIRMAN NELSON: Okay. Now let me go back to Dr. Daum.

MEMBER DAUM: So a procedural question first, I guess, is that how do we make it known to you when we -- our comment is germane to what's being on the table?

CHAIRMAN NELSON: At this point I'm just running the rest of the list, and feel free to sort of wander if you want.

MEMBER DAUM: Well, I wanted to wander about something that was said at the very beginning of the discussion, and I think that we ought to have some consensus or clarification on the issue of what kind of device we're talking about, because it seems to me that we could get pretty unfocused if we just have a general discussion about devices.

The laptop -- the laptop. [laughter] The lap band --

CHAIRMAN NELSON: Just don't say lap dance.

MEMBER DAUM: No, it's the 90's. You

can't go to the lap dance, but the lap band is clearly the device that was emphasized mightily in the open discussions and some of the presentations, but I wanted to at least consider what would happen if a device became available for testing that was totally not invasive. Something that you just placed on the skin, for example. How would we feel about these criteria that we're struggling with and trying to focus on if it was literally no morbidity to placing the device?

And so I think we need to consider in the discussion devices with high morbidity and high invasiveness and devices with no morbidity and no invasiveness, and perhaps that would even drive the selection of the population. My feeling is that it would, and I think we need to discuss what kind of device we're talking about or at least have two or three parallel discussions.

CHAIRMAN NELSON: Well, I mean, I would encourage that. I think you're right, and it's important to then frame in some sense the characteristics of the device as they impact on the

appropriate pediatric population. We need to, not so much be device-specific as characteristic-specific in terms of degree of invasiveness, et cetera, et cetera.

MEMBER DAUM: The risk of placement and morbidity of maintenance and ease of removal, I mean, all these things are important characteristics to consider. If those answers are all close to zero, then I think we could get much more creative and expansive about populations that we'd like to study.

If the device has got a high morbidity and/or it's impossible to get out once it's been in for a while, then we have a different consensus about who might be candidates for this. Very different discussions here.

MEMBER RAPPLEY: And other essential features I think we need to consider is the systemic impact of the device, particularly when we're talking about a growing child or a young person, and weighing that then against either the presence or the risk of other severe diseases associated with the condition. But if we had that set of general principles, then it might be easier to have that conversation, that

discussion.

CHAIRMAN NELSON: I'll go to Tom, because I think he probably wants to respond to this.

MEMBER NEWMAN: This was exactly the point I wanted to make, and actually I have a suggestion about maybe one way to move forward. If what the FDA would like from us is something specific in terms of BMI of 35 or 40 or 45 or more and/or comorbidities, or something more specific than general comments about the more invasive the device, the worse the disease has to be, one way to approach that discussion would be to say since we've heard so much about the lap band, if we come up with something specific, it could be about a device with that level of reversibility and invasiveness and so on, and then just then have some general principles that devices which are less reversible or more difficult or cause more complications might require a higher level of comorbidity or BMI, and the, you know, something which is less invasive it would go down from there. But if we are going to come up with anything that is at all specific, we probably ought to have some prototype

device in mind.

MEMBER DAUM: I think that's a great idea, but I think we should also give some weight to advising the FDA about a device of a much lower morbidity and much higher ease of application.

MEMBER NEWMAN: Although it'd be very hard to do that specifically because as you said the range of invasiveness could go all the way down to, you know, something that would really be suitable for everybody and available over the counter.

CHAIRMAN NELSON: Let me just make one comment, then I'll go to Dr. Kral, who sort of started this theme and see if he wants to expand on it.

People keep using the word "invasive." I'm an ICU doc. I don't do anything invasive, you know, which is sort of a pediatrician who really wanted to be a surgeon but didn't -- so, you know we heard this alteration in structure and alteration in function. I mean, I guess, you know, if in fact, I mean, anesthesia these days has such a low morbidity and mortality at this point. I mean if, in fact, simply because you invade the body doesn't mean it's

invasive, I guess is what I'm getting at.

So I think if we use the word invasive I'd ask you to be a little bit more concrete about what you really mean, and I liked the distinction between alteration of structure and alteration in function, because you can have an alteration in structure, which is the lap band, without an alteration in function. In listening to the presentations as far as malabsorption and the other kinds of complications that take place, which then have -- the degree of invasiveness gets bigger and bigger. Obviously, if you're not even penetrating the skin, then that's not really even a structural alteration in any meaningful way.

And then this reversibility. So I really only heard reversibility and then degree of alteration in structure and function as the two characteristics of a range of devices that seem to happen, and I'm --

MEMBER NEWMAN: And the risks of morbidity and mortality of putting it in.

CHAIRMAN NELSON: Yes, but, I mean, in many ways unless you're, you know, I guess the

surgeons would have to comment on that specifically, but, you know, in the pediatric population the risks of surgery, even fairly invasive surgery, is at this point so low it's not clear to me that there's much for discrimination.

Well, I mean we could hear more about that, but let me -- I think Ron may want to say some comments about devices, and then I'll go.

DR. YUSTEIN: Let me -- I'm just worried because of the time limit, so I just wanted -- on the first question, so I just wanted to see if we can refocus. I think what you're struggling with is something that we struggle with at the Center for Devices. I think you see how complex devices can be and that when Dr. Tillman gave you the presentation the other night, when she said a drug is a drug is a drug versus a device, your experience and what we experience.

But for the sake of time, perhaps it might be easier to think are there specific conditions or ages or weights or comorbidities that you would say we shouldn't be studying? I mean, is there a way you can

narrow us down so that, yet, if a sponsor or manufacturer came in and said, "We want to study down to ten-year-olds or, you know, we want to go down to a BMI of 25 or 30, are there certain things that you feel that we shouldn't be studying in kids for the treatment of obesity in general?

And I realize, you know, one of the ways we phrased the question was to try to keep in mind, be flexible because the devices are so different. Some of them can be surgically implanted, some of them can be endoscopically implanted, which is less risk. We can probably can probably work with that, but if you can kind of give us some minimal guidelines as to, you know, no-go, go. You know, if there are certain patient population issues that you say no, there's no way at this point that we could see studying patients with certain BMIs or certain ages or who haven't reached a certain maturity level of a certain kind.

Does that help a little? I was worried about the time on this one.

CHAIRMAN NELSON: Well, we'll get there. No, it is, but I could imagine if gastric stimulation

was thought to work, it's in my mind theoretically possible someone might figure out how to do that transdermally, in which case you might be willing to enroll a seven-year-old in just a transdermal gastric like you would just a trans -- you know a tens or something, I mean, you might. If that's doable.

Let me, again in the interest of fairness, go back to the list which I have Botkin, Hudson. Tom, I can take you off? So, Jeff?

DR. BOTKIN: Thanks. A little bit of a change of gear. I wanted to just raise a couple of issues, and as somebody who's sort of new to this obesity arena, one of the things that's been a little frustrating with the discussion is the language and definition issues, and I think what we've heard is overweight, obese, super-obese morbidly obese, severely obese, and I don't know to the extent that there's been any attempt by others or any common understanding of what these terms mean. Obviously, there seems like BMI is the key criterion with or without perhaps comorbidities along with that. I don't know that it's the job of this group, but it

might be very helpful to try to define as we move into more of a research domain to put some numbers behind these definitions or at least some common language so folks know what we're talking about. Or try to stick with the numbers themselves.

BMI over 40. That's a group we want to say is somehow different than kids who have a BMI between 30 and 40 and such, and I don't know what those, of course, would be, but some movement away from terms like severely obese, super-obese, etcetera, would be helpful if there's specific criteria that are supposed to underlie those terms.

A second point would be about the psychological/psychiatric requirements that's listed there, and I would want to make a recommendation that we think about two aspects of that. One is the psychological impacts of obesity itself, and I think that ought to be part or the comorbidity requirement. So the negative impacts of the condition itself I think is distinguishable from the psychological characteristics that one might want to have as an inclusion criteria for consideration of a device. In

other words, we've heard that you have to have certain positive psychological characteristics, a willingness to change, for example, as an inclusion criteria to be considered, so I think we ought to separate out those two aspects and ought to seriously consider having negative psychological impacts of obesity to be on the list of comorbidities, as opposed to making a distinction between so-called medical comorbidities and non-medical or psychological comorbidities. I'm not sure there's really a distinction there.

And then one final point. I'm always a little leery about issues of assessing predicted compliance as an inclusion criteria for entry into research, and I think the potential concern is that those can end up possibly being more -- there's a possibility for bias there.

I think there's a potential perception that socioeconomic criteria are related to one's ability to comply, and so you may end up systematically biasing your research assessments against folks with lower socioeconomic status, single parent families, et cetera, on the assumption that

they're going to have difficulties with compliance, perhaps without any data to confirm that, and therefore systematically have this research oriented towards kids of higher socioeconomic status, et cetera. So if we have a compliance criterion that we're going to promote, we ought to make sure that there's something substantive behind that criteria and that we try not to allow that to be biased against big segments of the population that are suffering with this problem, as well.

CHAIRMAN NELSON: Thanks, Jim. I'm going to just go through, and let me tell you the list at this point. Hudson, Roccini, Gorman, Knudsen, Rappley, Kral, Choban, and Champagne. So, Dr. Hudson?

MEMBER HUDSON: I'd like to make a comment and get more discussion about the rigor of the assessment of the failure of conventional therapy as a selection criteria. So what I've learned is it appears there's two groups, so either their super or morbidly obese, or they're obese with this comorbid conditions, and from the information that we've received thus far, they're unlikely to respond to

these behavioral therapies.

Then, if we talk about lowering the BMI guidelines for a population that perhaps does not have those comorbidities but trying to approach them at an earlier trajectory of their illness, then we may be going down as low as 30 to 35 on the BMI, and if you are in a center where many of us have heard they have this wonderful multidisciplinary team that looks at all these aspects of the patient and then works with them over a period of months or perhaps they're even working in trials to compare conventional therapy versus these surgical approaches, that's great, but most centers don't have that.

So what are you going to say? Is it going to be the parents or the child's self-report, "I tried everything. I don't know," which is typically, you know, we have the feeling that they really have not done a good faith effort at complying with the behavioral therapies.

So I think that we need to have very consistent or firm guidelines considering that there won't -- there potentially won't be all these

multidisciplines around to assess in a team nature. You know, will there be certain nutritional standards or monitoring over a period of months included in the assessments and assessments with the physical activity, et cetera?

And the reason I think this is important is that we don't really have long-term follow-up on these procedures beyond five years, and it seems that we're trying to get them to a state where they can participate or comply with the behavioral changes, which we're told in these morbidly obese patients they cannot, or if they can comply, they need to incorporate and change their lifestyle and make this their new lifestyle to continue to have success after these procedures. Or we may see that five years beyond this, they're back right where they started because we've not made these behavioral changes. So I think we need some specific recommendations regarding some of those other parameters other than just the comorbidities or a BMI.

DR. INGE: Mr. Chairman, just one response to that specifically?

CHAIRMAN NELSON: Sure.

DR. INGE: You know, we actually grappled with this considerably in formulating that pediatrics paper. The difficulty, really, is there are no -- there is no one way to do it. There is no one proven method for weight loss using behavioral therapy and dietary therapy. There, really, if you look at the nation, you know, you can count on very few hands the number of pediatric weight management programs in every state, some states having none. So it's very difficult to draw a line of what you have to fail in order to get to an effective therapy for a patient that may live in -- and I don't want to pick any particular city -- but some small town --

CHAIRMAN NELSON: Cincinnati. How's that?

DR. INGE: How about that. We actually have one, but some small town that is, perhaps, hundreds of miles from a pediatric behavioral weight management program, which we would, you know, I think consider a gold standard for that therapy.

CHAIRMAN NELSON: I think we're straying from the research focus, because it's one thing to say

they may not have availability in their community. It's another thing to say if there's a research program, what is it that has to happen as part of that program?

DR. INGE: It's an important inclusion criterion, though.

CHAIRMAN NELSON: Yes, but I've heard -- I'm still going to go back to the list, but I've heard two potentially conflicting views. One is -- you know there's a difference between failure to respond to non-device interventions versus failure to comply with a program leading up to the use of the device because you've complied but not responded. You know, so

DR. INGE: Those are two things.

CHAIRMAN NELSON: So what I've heard in some of the presentations was the use of an adherence to lead-up as a screening for success to surgery, which is different than, in my mind, a sort of potentially prejudicial assessment of the inability to adhere based on socioeconomic or other characteristics, but yet -- versus a practical demonstration of the ability to adhere as a lead-in to

a device -- adhere and not respond to a device.

So that raises the question as to whether or not you'd always have a lead-in period, if you will, of non-device interventions in a research format, whether it's six months, which I gather from this would probably not be unreasonable, that you could comply and you fail to respond as opposed to you don't comply. Does that make sense?

DR. INGE: It does, but whether research or not, that -- surgery can't be the first option. It's just how you describe what has to happen before in that six months which gets very tricky depending on availability of resources.

CHAIRMAN NELSON: Well, but I'm assuming that if this was done in, again, a research mode, not a health care delivery mode, as that would be defined in all the deemed centers that are capable of providing that. Is that fair?

DR. INGE: That's fair.

CHAIRMAN NELSON: Okay. I'm going to -- Dr. Roccini, you've been patient.

DR. ROCCINI: I'd like to echo your

comments. The other thing I'd like to reemphasize is that we are dealing with a vulnerable patient population, and because of that, I think it's important that one considers the attempt to treat or study those that are the sickest and most capable of participating in such a project.

There are other approaches within research clinical trials such as compassionate use activities that would enable the younger patient who has very severe, life-threatening comorbidities to get access to the trial but wouldn't have to clutter up the trial as far as a design standpoint. And I think that, you know, one of the very first speakers really echoed this, is that in most pediatric trials, we do start in an older age group and in a group of patients who have the greatest potential for benefit where one is looking at risk benefit, since all of these things have risk, and since we are dealing with such a vulnerable patient population.

CHAIRMAN NELSON: Dr. Gorman.

MEMBER GORMAN: I think the discussion has moved over to the position that I wanted to state,

which is that the major difference between pediatric patients and adult patients in this particular arena may not be their age or BMI percentages, but their failure to have previously attempted weight management in some way. When adults come we've been assured that multiple attempts have been made for weight management. In this population, I think it would be mandatory that the research design, and probably the clinical therapy design later on, included a diet, exercise, and behavioral modification program.

I think the only one that I've seen that has long-term efficacy data is Weight Watchers, and I think that goes down to age 12, and I don't think that's a particular hard criteria to put out there for people. You know, they may not get a University of Cincinnati in every city, but I think there's probably a chapter of Weight Watchers in every small town in America.

CHAIRMAN NELSON: Paula Knudsen.

MS. KNUDSEN: Well, most of what I wanted to say has, indeed, been said. I really want to stress that I think that these patients and their families

are doubly vulnerable. They're children are vulnerable because they are children, and they are all psychologically vulnerable because they have probably failed repeatedly many times prior to arriving at your doorstep. I would like to suggest that the FDA insist that sponsors who wish to market these devices only place these trials in institutions where there are multidisciplinary teams in place with systematic assessment pre-surgery and systematic assessment following surgery.

CHAIRMAN NELSON: Dr. Rappley.

MEMBER RAPPLEY: I think that we should have some justification for setting a lower age limit, as perhaps was requested by the device people and the comment about a ten-year-old who was so morbidly obese. And some of the things we might think about have already been raised that ability to have abstract thought to understand what one is turning into in the -- for the child -- to a center.

And the second is also to look at the dynamic in a younger child. It really is not the child who controls the food intake or the environment

in which they have access to exercise or other activities, and so if we were to set -- it seems obvious that the question we do not want to do such a procedure on a child who is five, but I think we need to speak to why that is, to have some justification for that, and that may be because at a certain age, we could say seven, we could say ten, those children really don't have control over either their intake or their expenditure in the way that a pre-adolescent and an adolescent person does.

CHAIRMAN NELSON: Okay. Dr. Kral.

MS. DOKKEN: I don't want to complicate things, but my concerns about the exaggeration of undernutrition of obese was aptly taken care of by previous speakers, but I have a concern here that might be rather daunting. We've heard time and again the importance of psychological and cognitive maturation. I'd like to -- I'm going to put on my behavioral neuroscience cap in this particular instance. You've probably heard of the rather recent data on the maturation process when it comes to such factors as judgment and what we often consider to be

higher cognitive functions related to volition and the late time for that maturation. We can all smile over the fact that it turns out it's more closer to age 25 than it is to age 18, and recent data strongly emphasize that.

Our own research has been looking at the neuronal maturity or neuronal integrity in the prefrontal region, which is one known for its importance for, among other things, volitional breakdown and motivational factors, and we actually have evidence not only from experiments in non-human primates, but also from observations in clinical populations that there are changes in the neuronal integrity in the prefrontal white matter and in -- generally, in the integrity and function that can be imprinted early on and that actually seem to be permanently imprinted. It's rather scary.

I'm not now considering the nutritional aspects. I think that has been taken care of appropriately. But early psycho trauma is not to be discounted on the one hand, and on the other hand when we're requiring and requesting and demanding that

there be a level of psychological maturity or a motivational or cognitive maturity, when we can't expect that to happen before age 25. I don't know how to get around this.

CHAIRMAN NELSON: Pragmatically, though, I mean it's -- I agree that we talk about psychological maturity, but then the question is how do you measure it?

DR. KRAL: That's right.

CHAIRMAN NELSON: But pragmatically, if you design a trial where you've got a six-month lead-in period, which we discussed, and where you've got, basically, the device as an add-on to the continued behavioral and nutritional support, would that six-month lead-in period where you make a distinction between failure to respond versus failure to adhere, would those who lack the psychologic maturity or lack the family support or lack all of the other things that may be difficult to measure per se, will they be the ones that fall away due to the inability to adhere? And you'd maintain, then, through the ability to adhere but not respond those regardless of age, but

those who have the family context and the developmental maturity to, in fact, be appropriate for the device, from a pragmatic point of view. Would that work or not work?

DR. KRAL: Well, I'm a surgeon, and pragmatism is something very close to my vocation. One thing that we mustn't forget -- I mean six months is an awful long time at age six, and it's not as awful a long time at age 14 or 16. So to come up with these rules of thumb, reasonable as it might seem, I think it's the moving target that's so difficult for us to deal with in these questions, because not only are we trying to take this -- and I understand the frustration in asking for definitions of obesity, and we want to look at a BMI number. Of course we want to look at a BMI number.

Much more important is actually the trajectory of weight development. That is much more important than a magic BMI number. And what is a trajectory? It is a time course. Six months? And how are we going to define failure? Inability to get back on the trajectory.

DR. INGE: The child that's crossing centiles is the concept?

DR. KRAL: I'm sorry?

DR. INGE: The child that's crossing centiles rapidly, is that what you mean?

DR. KRAL: Yes. The trajectory -- there's a normative trajectory for -- and probably has to be race specific. It has to be gender specific. But we know what a development curve is. There's nothing so familiar to pediatricians as that.

CHAIRMAN NELSON: So I've got Dr. Choban, Champagne, Diekema, Fost, and Arslanian.

DR. CHOBAN: I'm going to try to address two things, and I think in our 152-slide presentation yesterday that I'm sure we all completely remember, one of the things I really liked about that is the way she put the data together was an emergency, you know, somewhat less urgent, but it really began to tie together our sense of urgency. And I think this is where we're coming back to the ten-year-old who's 300 pounds and already has sleep apnea. Our sense of urgency in needing to treat that child is greater

than, you know, the 50-pound overweight child who doesn't have any comorbidities right now.

And that's where trying to combine BMI with comorbidity allows us to take sort of population numbers and truly now individualize it for that patient. I mean, you know, every so often you do see the 82-year-old who is 200 pounds overweight and seems "healthy," but that's not the norm, and as -- the BMI of 35 who already has diabetes is saying, "I'm not tolerating this. My physiology -- you're tipping me off the scale."

So I think, you know, from looking at Dr. Dietz's data, with his BMI distribution of morbid obesity in the 99th percentile, and I mean, I'm sort of looking at this, going, I think actually the NIH data are fairly conservative numbers when they go to kids, because at that same BMI these kids are fatter is what it's looking to me, and I'm a surgeon. Am I missing something?

So that's my first comment. I would say I think those are pretty reasonable. I think as devices which have a, you know, what tends to happen now, and

whether you consider surgery a device, the different devices -- as risk goes up, effectiveness also tends to go up. And so, yeah, you know, if we get something the effectiveness is way up, and the risk goes down, everybody's going to want it. So I think as -- you will -- has to be a flexibility to incorporate those devices. So that's one.

My second comment is in this failure of therapy approach. Just as sort of an FYI, Harvey Sugarman and the group from MCV presented date because one of the things we as adult surgeons are encountering is now more and more insurance companies are requiring six months of dietary therapy within 12 months of considering surgery. And so Sugarman's group went back and looked at that, and they looked at the cohort of patients of whose insurance companies required that versus a cohort from a different insurance company and looked at the outcomes, and they were looking at gastric bypass. And what they found is that whether or not -- the six-month requirement did not select for a better group. It did not select for a better outcome. In fact, in the non-six-month

group, they had slightly better weight loss at a year and a half.

The concerning thing is 30% of that six-month group dropped out, so I think it's a fine line between a compliance test and a barrier to care. And earlier you used the statement of, "They fall away." These people still have the disease. I mean, when they fall away, just because we don't have to look at them anymore doesn't mean they magically got healthy. So I think we have to be careful of testing compliance versus placing barriers to care.

CHAIRMAN NELSON: Dr. Champagne.

DR. CHAMPAGNE: Yes, I'd like to address -- before my burning issue had to do with the failure to respond to conventional therapies, but of course Dr. Hudson brought that up, which has been discussed several other times. I just want to know how we are going to, or how the FDA is going to put an evaluation on the adequacy of previous attempts at nutritional management or behavior -- weight management through behavior, you know conservative therapies.

We -- at our center we do a lot of -- we

do work with kids. We work with adults. We actually go through a very detailed screening of our participants in our studies, and there's -- a lot of our behavioral screening has to do with, you know, issues that have to do with potential compliance, as well as previous attempts at weight management.

CHAIRMAN NELSON: Let me make a suggestion that we table that particular question until we get to trial design, because if we have this six-month period, whether we call it a lead-in in the trial or we call it -- I mean, it becomes somewhat irrelevant, so because it'd be nice soon to get clarity around the weight and comorbidities.

Let me just ask concretely. People think the NIH guidelines ought to be used -- I guess, which is the BMI of 40 for surgery or 35 for interventions, or should it be lower?

DR. CHOBAN: Thirty-five with comorbids and 40 without.

CHAIRMAN NELSON: I was going to add comorbidity, so it's 35 with the comorbidity and 40 without?

DR. INGE: I think the only risk for --

DR. ARSLANIAN: But that should be adjusted for pediatrics.

DR. INGE: The only risk for that is if we start considering earlier ages at some point in time where they may not have made linear height, because obviously height is included in the BMI equation. So, you know, that would argue for using centiles or z-scores if we're going to be talking about populations that may not have achieved linear eight. If we're not, then there's really no reason to argue about it.

CHAIRMAN NELSON: So as a non-endocrinologist, at what age/developmental stage do you reach a point where the BMI becomes a static as opposed to a moving target? Is that the adolescent age?

DR. INGE: Certainly 18, but certainly before that it changes very little over the years between, you know, again, arguably 12 to 14, starts to change very little.

CHAIRMAN NELSON: But at least in terms of the adolescent population, it's useful?

DR. YANOVSKI: So, I mean, I think it's very instructive to look at Dr. Dietz's page 4, which has the BMI centiles at the 99th percentile, not the 95th, which is a much less stringent point. So for males age 16, the 99th centile is a BMI of 33.9, and at 19, the 99th centile is only 36 BMI, right? So we should just --

CHAIRMAN NELSON: So that's in the double version or the single version?

DR. YANOVSKI: I'm sorry, I guess it's the one we got --

CHAIRMAN NELSON: The double.

DR. YANOVSKI: The two-slide version.

CHAIRMAN NELSON: I mean, it's -- okay.

DR. YANOVSKI: Okay, I only have the -- the one that was given us this morning was two slides per page. All right. The BMI of the 99th centile at age 16 for males is 34 or thereabouts. Now it's, understandably since females have largely completed their growth by age 16, the BMI of the 99th centile is about 40 or even, in some cases by 19 it's actually higher in females. It goes up to 45 for 19-year-old

females. So you have to consider both age and sex when deciding on these criteria, and I think it would be -- it would certainly be difficult for me as a pediatrician to recommend that we have a less stringent BMI criteria as a cut point than we do for adults. So, and maybe this is a statistical anomaly, but I think it's really the question that, remember, BMI is, you know, weight per height squared, so the shorter a child is the more penalty, if you will, in BMI they have. And the same is true, really, for adults that the factor that should be used is really not, you know, height squared but sort of height to the two-point-something power that has been studied.

But that aside, I think we need to then consider maybe a dual kind of cut, which is greater than 99th centile, but also greater than, but at least not less than, some arbitrary number of kilos to be lost or some arbitrary BMI in addition. So I think, you know, either we're going to make age-specific, sex-specific cut points, so it'll be the 99 point something percentile to get up to a more appropriate BMI, or we're going to need to have a second

criterion.

Also, to answer to second question about when does the BMI become static, if you look at the CDC charts, it actually doesn't become static until age 20.

CHAIRMAN NELSON: Imagine yourselves are sitting down, and you've got to write the protocol now, so is it -- it's 40 -- let's take adolescent and pick that as 12 and up. Forty or 35 with a comorbidity, I mean, is that --

DR. ARSLANIAN: Ninety-ninth percentile with or without comorbidity, 95th percentile with comorbidity and above.

CHAIRMAN NELSON: So use the percentile instead of the BMI?

DR. ARSLANIAN: Yes.

CHAIRMAN NELSON: Okay, and then, now let's tackle -- I've heard two suggestions for the ten-year-old or the eight-year-old. One is to just let them, if individual decisions are made on a compassionate use basis to sort of get the benefit of the trial without designing it for them, or the other

is to construct it as a crossing percentiles type of picture.

DR. ARSLANIAN: I have hard time in the absence of robust systematic data in the older adolescent age group going with younger children, ten in one, no knowing what the safety profile will be, not knowing what the effectiveness will be.

DR. INGE: One quick point of clarification for the group, if you look at the curves, a 12-year-old with a -- at the 97th percentile has a BMI of 27, and so I think we really need to infuse some, you know, facts about the, you know, some facts into the decision-making. And so we're talking about at the 97th percentile, a 12-year-old female has a BMI of 27. Would we want to offer surgery with the understanding of that factor?

CHAIRMAN NELSON: What's the odds of a significant comorbidity, given what you just said at that level?

DR. INGE: It happens. There are cases of a significant comorbidity --

DR. ARSLANIAN: But then we have to

discuss, are we talking -- what is a comorbidity, and HDL of 30, or severe sleep apnea necessitating a C-pack?

DR. INGE: Well, the other thing is when do those comorbidities develop, as ranked by BMI? And what Bill Dietz told us --

DR. ARSLANIAN: But we don't have that data, so right now we are looking at a cross-section, so if we are to not reinvent the wheel, and not to be here until Thanksgiving, I think we have to come with some reasonable approaches, and in my mind it would be that consistently they are not age and applicable to the pediatric population, 99th percentile and above, with or without comorbidity, and 95th percentile and above, or above 95th percentile with a significant life-threatening comorbidity. Not a low HDL, not a borderline blood pressure, not a touch of diabetes.

CHAIRMAN NELSON: I'm going to ask Dr. Lustig to give a comment, then I'm going to take a break, but so people that had their hands up are reassured while you're having you're coffee, then I'll go with Diekema, Fost, and Newman, and then we'll

start a new list at that point.

Dr. Lustig.

DR. LUSTIG: There are two issues that are sort of skirting around all at the same time. Let's sort of make it one. What we've done in our program is to actually ask for two failures of various pharmacotherapies, rather than one, in an attempt to try to ensure compliance. The fact of the matter is, though, that you're going to have a lot of kids that are going to end up with emergent issues like Silva just talked about, like the kids with pseudotumor, like the kids with obstructive sleep apnea that actually end up in the OR with a tracheostomy. Thos patients are going to end up somehow being treated open-label by someone, whether it be at a major medical center with a bariatric surgery program or not. Those patients are going to ultimately get this somewhere, and it's probably going to be ultimately by some fly-by-night surgeon. We have a lot of them in California who go from one hospital to another and never follow up with the patient.

They will get operated on eventually by

someone, and the fact of the matter is we want that data. We don't want that data not to be available to us. We ultimately want to be able to say, yes, these patients do well or don't do well, because they've been followed, and we have the ability to capture that data, whereas we won't have them if they're done elsewhere.

So I don't see any reason why we can't stratify these various different issues, as I think Jack had talked about. We can have patients that are on the elective track. We can have patients on the emergency track. They can both be ultimately operated on within FDA guidelines, and they can be set up separately so that, number one, the patients where we're worried about elective can have the appropriate compliance, the patients who are emergencies can be within a stratification system whereby those patients are at least operated on and captured, because if we don't do it, someone else will, and then we won't get the data, and we still won't know what's going on.

CHAIRMAN NELSON: Showing the illustration between patient population and trial design.

It's important, I think, to get coffee. Why don't we do that, and we'll reconvene, hopefully, in ten minutes, 12 minutes, and keep going. Thanks.

(Whereupon, the above-titled matter went off the record at 10:35 a.m. and resumed at 10:49 a.m.)

CHAIRMAN NELSON: We can begin to take our seats, the various wisdom being shared in individual conversations, hopefully, unrelated to the topics.

Now, as people are taking their seats, let me just tell you who's on the list. I'm not going to ask for more names at the moment, and I'll give them the chance of speaking first in fairness. Diekema, Fost, Newman, Fant, and Yanovski.

What I'd like to do is just make a couple comments. At the risk of having people disagree with what I say, I'll try to at least summarize a little bit of what I've heard and then identify, I think, a couple of issues that could require further clarification. But I think the first point is for people to remember that there's a lot of issues that we're going to be getting to, such as study design, so

we've heard comments related to how you design a study in terms of allowing enough flexibility for individuals that come in through different tracks, et cetera. I mean, we'll get to that.

We're going to be talking about long-term safety and efficacy registries, et cetera. We're going to be talking about endpoints, and the first question here was focused on population and the like, so what I'd like to do is summarize a couple of points that I've heard and then try to bring closure and move to the second question. And when I say closure, not necessarily a hundred percent, because I'm sure we're going to circle back on some of these issues as we begin to talk about trial design, et cetera.

But basically what I heard was the patient population would depend to some extent on device characteristics. To the extent it has less alteration of structure and function, higher degree of reversibility, and less risks associated with the implementation or implantation of that device, then the stringency with which you would set the characteristics of the patient population in terms of

eligibility for those would end up being relaxed. Now we didn't get into detail about what that actually would mean, but that seemed to be the shift.

Now, we seemed to begin to develop some agreement around the theme, and when I say agreement, this means more or less, around the importance of a lead-in phase, or this notion of you should have tried some other things before you go right to a device. When we get to study design, we can try to frame that maybe more concretely about what that means. But I began to hear that emerging. You know, the importance of implementation in teens, et cetera, the context, I think we all agree on that, and I don't think we need to beat that drum. I mean, if people don't hear that, they're not listening. That's pretty clear.

And so as we then get down to actual patient population to try and focus around this, there seemed to be agreement around if there's a threshold, that that threshold, if it's obesity alone, would be higher than if it was obesity with a comorbidity, which would be lower. There have been suggestions for thresholds which I haven't yet heard consensus, and

maybe there wouldn't be, around things like -- what I did hear was absolute weight and absolute BMI would be inappropriate. That much I heard, but I didn't hear agreement around BMI-for-age percentiles or weight-for-age percentiles or how you might actually structure that. There was one recommendation of 99th percentile, et cetera.

But certainly, and then the comorbidities, the importance of life-threatening comorbidities, as opposed to chemical comorbidities with, say, adult complications, but certainly diabetes. You might add hypertension, depending upon the degree of hypertension if it's placing you at risk for left ventricular hypertity, et cetera. Sleep apnea, Type II diabetes, melodus, and pseudotumor cerebri are sort of on the table as life-threatening comorbidities.

And then we didn't address exclusions, and what I heard during the break in individual conversations about questions that people think need to be addressed, there were two. One is, at least if we can't achieve agreement, getting some sense of the degree of disagreement around what that threshold

might be in terms of percentiles versus BMIs and what that is.

The second is should there be any exclusions? Prader-Willy, I mean, in other words, obesity we heard is a diverse -- it's not a single disease. As we approach this, should we -- should all comers be included, or should there be exclusions, assuming that you wouldn't have enough, potentially, of certain subgroups to make any meaningful analysis of the impact on that particular subgroup. I think there should be some discussion of that issue.

And then I would just remind people here we're not talking about clinical management. We're talking about research design, so I think it's important not to design research to where nobody wants to do it. And I think it was maybe Dr. Lustig who raised the question of having enough variability, or Dr. Pories, who basically said there needs to be different ways to go into that research. I think that's one question, but again, we can get into that in study design.

So with that as sort of a summary, what

I'd like to do is go to the list of the comments, and what I'm -- since we need to get through the questions, and since I'm assuming answers to other questions will also be things that are related to these issues, too, we'll see if we can push on a little bit.

That's right. So what I've got is Diekema, Fost, Newman, Fant, Yanovski, and then we'll sort of pause, take a deep breath, and see what we want to do at that point. Doug?

DR. DIEKEMA: Yes, I just wanted to offer something concrete in terms of age, because I think there are a number of things that can be said. First of all, it seems reasonable, as it often is with drug trials, that we not proceed with pediatric trials until at least there's some adult data on efficacy and safety.

Secondly, I haven't heard any compelling reason to include -- and so this might be a potential elusion criterion -- to include children who are six or seven and below in these sorts of trials for a number of reasons. Compliance becomes more of an

issue, behavioral therapy and nutritional therapies may not have had adequate time to be tried. Meaningful assent is very difficult. And again, I haven't heard a compelling reason to enroll them in these sorts of trials. So there's a potential exclusion criterion.

And number three, I think, again related to age, one potential consideration is to take a tiered approach. I've already talked about adults preceding pediatric patients, but then you could use some variation on the rule of sixes or the rules of sevens with six and below, seven and below being excluded.

After adults, your first pediatric trials should focus on an adolescent age group, perhaps 12 and above, and only proceed to children younger than 12, say, between six and 12, after those trials have also shown some efficacy and safety data that makes it reasonable to proceed.

CHAIRMAN NELSON: Dr. Fost.

DR. FOST: Amazingly, the first two comments I was going to make also, so I'll just second

the motion to hammer it home. It seems to me first there should be a proof of concept of whatever device we're talking about. And therefore, adults -- for some data from adults. And as a corollary to that, older children should be studied before younger children, particularly because almost every speaker has talked about the importance of compliance, commitment, adherence to dietary stuff that is the idea of a magic bullet device is not a good concept. So that would suggest that young children should be precluded, at least in the first phases.

Second, the discussion earlier seemed to assume that the more invasive the device, the more risky it was, and I don't think that's necessarily true. That is, there are some simple medical treatments like oxygen that can make you blind and ruin your lungs, and bicarbonate, which killed lots of preemies decades ago, and there's lots of very invasive surgery that's quite safe, and from which there is very low in mortality. So that is it begs the question to assume that we know what the risk of these devices are before we study them. So, as was

suggested earlier, there might be some cutaneous device that emits a medicine or a signal, so I think we should assume that all these things are potentially risky and of uncertain efficacy until there's at least been adult data showing that.

Third, the discussion -- I'm just nailing home something I think Skip just said, but the discussion about what about the poor ten-year-old or the poor eight-year-old and so on who also is morbidly obese and has comorbidities, the purpose of clinical trials is not to make sure everybody in American who needs treatment gets treatment. You're doing a trial because you don't know whether it's safe or effective or not. No matter how big your trial, you're going to be excluding tens of thousands of children. So the purpose of a trial is to get scientific information about safety and efficacy, and the fact that somebody's not in it because they're ten or eight or even 15, there'll be thousand's of 15-year-olds excluded from any trial that's done, anyway. So I think we need to stop concerning ourselves here today about unfortunate children who desperately need

something, but that's not the purpose of this meeting. The purpose of this meeting is to try to advise the FDA on how to design trials of safety and efficacy.

And the last point, it seems to me that very high standards for entry criteria are appropriate, because this is such an amorphous field, and there's so much complexity to it, that is, the first question is does any proposed device work at all in the best of circumstances? If it doesn't work in the best of circumstances, there's not much hope for it out there in the non-research community.

So what do I mean by strict criteria? Number one, a homogenous population. So these questions about things like Prader-Willy and so on seems to me should be excluded. I mean, we're looking for idiopathic obesity, if that's the correct term. To introduce into that mix children with metabolic disorders, syndromes, genetic syndromes, chromosomal disorders, and so on is to make it more difficult to interpret the results. They may fail for whatever reason.

So number one, it seems to me, it ought to

be as homogeneous a population as possible with regard to etiology and pathogenesis. Second, whatever the standards for entry, they should be very high. That is, they should be very sick kids or kids who are at very great risk for morbidities, because the potential for benefit is greater for those. The smaller the child or the fewer the comorbidities, if there's any risk, you're stacking that against the lower possibility of benefit.

Third, it seems to me an element of any of the trials ought to be only in specialized centers with multidisciplinary approaches. Every speaker has said that, and that gets back to the magic bullet theory.

Fourth, if it's going to involve surgery, and not all devices will, the balloons presumably could be studied by a gastroenterologist, but if it's going to involve surgery, there ought to be a requirement that studies have a minimum number of patients or subjects in one center. That is, skill matters we've heard, so that there -- large multi-center trials at 20 places don't sound to me like they

make a lot of sense for this sort of thing.

Last, what we've heard from everybody is that some evidence of commitment, since compliance and adherence to diet and other things after the device are going to be important, some preliminary evidence of commitment, whether it's multidisciplinary -- that is, a medical-behavioral approach having failed or whatever it is, is appropriate. And if that discriminates on socioeconomic grounds, again, the purpose of a clinical trial is you don't want to exclude people by racial categories or by gender, but it seems to me it is appropriate to exclude people who can't comply or adhere, just as you wouldn't do a transplant on somebody who can't possibly give immunosuppressive drugs after the transplant. So it seems to me some evidence of commitment is a minimum criterion for the success of the program.

CHAIRMAN NELSON: Dr. Newman.

MEMBER NEWMAN: I agree with almost everything that Dr. Fost said. I think those are reasonable. I have just -- I think the point about oxygen is well taken, but I still think it would be

helpful for us, if we were going to come up with any kind of specific criteria, to be clear on what kind of device we're talking about, since I do think that our criteria for studies might be different from one device to another, so I sort of -- I have the feeling that people kind of have the lap band in mind, but I think it would be helpful to clarify what kind of device we're talking about if we're going to get at all specific.

And the other thing I think would be very helpful to clarify is when people use percentiles to say exactly what they mean, because that's not a real statistician, but someone in a biostatistics department, epidemiologist, when I hear 99th percentile, what I think is, oh, that's one percent of children are above the 99th percentile. Which I thought, gee, that sounds like too many, if that's -- that is not stringent enough if that's the only criterion and no comorbidities required. But then when I look at the slides, I see that 8.1% of 16-year-old boys are above the 99th percentile, which is kind of a strange way to define a 99th percentile that

includes 8% of the population. And what's, I think, become customary in the obesity field is to use percentiles from 1975 or 1970 or 1980 and just, without any further qualifications, just say without batting an eye, you know, 15% of children are above the 95th percentile. And I always, still, have a problem with that, but I think we need to be -- if we're going to say 99th percentile, we need to be very clear on what percent of children will actually be at that level.

CHAIRMAN NELSON: We're going to get there, Tom. Dr. Fant.

MEMBER FANT: Yes, I have a --

CHAIRMAN NELSON: I might say, if people agree with things that have been said, no need to say you agree. Let's just identify disagreements. We'll assume if there's no disagreement that people agree with what's said, in the interest of time.

MEMBER FANT: One additional thought that builds on some points, I think, that were made by Dr. Kral initially, with the diversity of the devices that are going to be coming down the pike, because I think

we've all been, you know, speaking subconsciously with the lap band in mind, and that type of device, but I think there's, you know, it's been noted that the diversity, the diverse group of devices that are going to come down, and I think how that impacts on study design and particularly point to the appropriate endpoints and timing of assessments is going to come into play, because --

CHAIRMAN NELSON: We're not answering those questions yet, Mike.

MEMBER FANT: I know, but it kind of relates to both. You know, I think it's just a natural evolution of things that there are going to be some devices that are going to come down the pike that don't get much the same pause and the same concern in terms of morbidities and risks, reversibility, that we've noted with the devices that are available currently. And the natural evolution of this is that if we are addressing extremes in obesity and the associated comorbidities, with those interventions that are currently available, pretty soon we're going to be talking about, well, if we're dealing with the

concept of trajectory, you know, we can identify patients before we get to that point, where based on the current evidence and the currently available therapies, we know that they're going to get to that point. Is there anything that we can do, and somebody's going to come along with a device saying that, you know, based on these data, we think that if we intervene with this device, we can prevent this population of kids from reaching that point.

You know, I think that there needs to be some sense that some of these devices, some of our selection criteria, may need to be flexible to accommodate a prevention strategy, as well as a therapeutic portion. Both of them therapeutic, but I think they get the sense of where I'm going with this. I don't have any specific numbers in mind, but I think that that's something that's going to need to be taken in to consideration.

CHAIRMAN NELSON: Dr. Yanovski.

DR. YANOVSKI: So, again, specifically addressing the idea of trial design, subjects should be, in general, in the first studies those without

known causes of obesity, what I prefer to call cryptogenic, as opposed to idiopathic, because we just don't know the cause yet. But there should be encouraged -- people should be encouraged to conduct subgroups, studies in subgroups where a valid analysis can be performed such as individuals with Prader-Willy or melanicort inform receptor mutations. I mean, if they're common enough, they should be identified and studied if possible, because the generalizability of the procedures will be improved.

I think, since even in pharmacotherapy trials we require at least a past medical history of failure to be successful with diet and exercise studies, that should certainly be a requirement for subject entry. In terms of establishing adherence, at least in the pharmacotherapy world, there's no requirement for a six-month adherence study. Even one month is considered adequate with, you know, something like weekly visits, so, you know, to establish adherence to a regimen, a month is generally enough.

Again, 12- to 17-year-olds would be appropriate to be studied first, before any studies

are conducted in younger children, and so the first studies, again, should be conducted in the adolescent age group. In my opinion, certainly for the first studies, only children over the 99th percentile for age should be even considered for study. And then we, at a minimum we should be requiring enough subjects and enough subjects to be stratified to assess those with very severe comorbidities such as Type II diabetes, obstructive sleep apnea, and pseudotumor cerebri versus other, more mild, and more manageable medically comorbidities. And then only later should we consider children who are below the 99th percentile for such approaches. And I guess these are all really relevant for the more invasive, more risky. I believe the more appropriate word is more risky procedures.

And then lastly, the question of psychiatric or psychological assessments is a real interesting one from our perspective, but I don't know that we have adequate tools to require it, and for that matter, whether it's really been shown to be necessary in adult studies of invasive procedures for obesity. It may be that individuals have been

sufficiently cherry-picked by the studies that have been published that we don't really know whether we need those kinds of tools, but at least I'm not sure that we could pre-specify which tools should be used, and if others have a better opinion of this, I'd really like to hear it.

CHAIRMAN NELSON: Now, before I go on with Dr. Arslanian and Dr. Pories, let me just make a comment and focus a question.

You remember this -- we study design and population related, we need to get to study design, we'll get to study design. My question is to the extent that we start talking about study design we may be further defining population. And so in the interest of getting to the question of end points now, do we want to further work on defining population apart from the one question I have? Because we're going to come back to it under study design, I'm fairly confident of that. So we need to keep moving. A ship that's not moving can't be steered.

(Laughter.)

So my question is the specific question is

I've heard agreement that we shouldn't be talking about absolutes and percentages, but there's some disagreement maybe on thresholds. So do we want to nail that question down now before we go on to endpoints, sticking to that specific question?

DR. KRAL: Exclusion criteria, I think.

CHAIRMAN NELSON: Well, I've heard homogeneity is important and if you can do an adequate subgroup analysis, then you do that separately and you would exclude individuals that have known cause of obesity for those subgroups as opposed to cryptogenic for the more broader trial. Is that --

DR. KRAL: I'd like to add something.

CHAIRMAN NELSON: Go ahead. And then we'll go to the --

DR. KRAL: To just very briefly revisit the idea that we can have generically different types of devices, there are those that are active on the GI tract, directly or indirectly, GI devices. And then we can consider, and here again, I'm drawing from my research, neuroprospecies(?) * (11:12:26) which could be central or peripheral and don't necessarily

directly act on the GI tract, so you can think of those as two generic components.

So GI devices, an exclusion criteria must be any kind of GI disease, meaning from tooth to anus. Let's not forget tooth because it has to be the ability to masticate if there's going to be any restriction of passage through the GI.

The other exclusion criteria which we must have and we're going to get to that an awful lot, I know, and that is that there have to be for the patient in question material resources that are sufficient -- material resources that are sufficient. And there just has to be a means of guaranteeing the ability to have costly monitoring. So material resources. We're going to get into all those other resources that we can, we're going to nail down, but this one ought to be --

CHAIRMAN NELSON: Let me just ask specifically on the question of the percentage, BMI, those kinds of things, or do you want to hold what you want to talk about until the trial design question.

DR. KRAL: I want to be specific on the

BMI.

CHAIRMAN NELSON: Dr. Pories and then Dr. Arslanian and then Dr. Klish and then we're going to move on to the next question.

DR. PORIES: In adult bariatric surgery, we still know to some degree, the adoption of the BMI. It's not a very good measure. First of all, it's not uni-gender. We measured some 3,000 patients, then we weighed under water in East Carolina and I came home and my wife and I said you know, there are two different curves for men and women. She says you'll have to get all those people wet.

Well, the same thing is true in race. A Caucasian woman, an African-American woman and an Asian woman, if they have the same BMI have very different levels of adiposity. So I think we have to be a little careful about choosing that as a measure. And I'm not sure about what happens in children. I think comorbidities make a better measure. And we probably will need to go back through data and develop an obesity comorbidity score that we can actually stratify these patients to answer this question.

CHAIRMAN NELSON: Dr. Arslanian and then Dr, Klish.

DR. ARSLANIAN: Just one comment to your question about what --

CHAIRMAN NELSON: Speak up closely to the microphone.

DR. ARSLANIAN: Sorry. Just one comment to Dr. Pories' question about what happens in pediatrics. We have shown data that despite similar BMIs, African-American children have different adiposity pattern from their Caucasian peers and their risk factors are different for diabetes versus atherogenesis. That's just an observation.

But I wanted to make three comments regarding some issues that were raised. Number one, if I understood correctly Jack's proposal that we include Prader-Willi even though it seems like the majority of the time we agree, Jack, here I will disagree vehemently because Prader-Willi patients are notorious for their self-mutilating ability to the point of picking their skins, pulling their teeth, bleeding themselves to death -- not to death, an

exaggeration.

I would be very concerned about having something that has a port somewhere that they dig their skin to get to the port or even any external device. So that's a cautionary note.

CHAIRMAN NELSON: I didn't hear him say that. I said if you wanted to do it, it would have to be a separate trial.

DR. PORIES: That's what I said.

DR. ARSLANIAN: I would not go --

CHAIRMAN NELSON: Maybe you wouldn't do it at all.

DR. ARSLANIAN: Yes, yes. The other issue about a trajectory, weight trajectory, I think it's going to be very hard to come up with a criteria for what is a trajectory, especially in a continuously growing childhood population and a population that is accelerating. Maybe one way around it would be to come up with a cutoff for a duration of obesity.

And the third is regarding the issue of commitment to the project or the trial. I think the best way around that issue would be as Dr. Nelson

suggested, a running period because there you weed out the ones who are not going to be committing in the long run. Those are just some suggestions.

CHAIRMAN NELSON: Dr. Klish.

DR. KLISH: Just a couple of comments about BMI and comorbidities. I personally feel that probably comorbidities should be the driving factor for selection, at least at the beginning, until we get enough information about risk versus benefit.

It also seems, in my experience with an adolescent bariatric surgery program that it's usually, it's frequently the reason my kids are referred in the first place, so I don't think it's going to be a major issue, at least initially.

With regards the BMI, yes, I agree that it's not a very -- it's not the best measure of body composition that has ever been invented, but it's all we have that's easy to do. And as Bill Dietz said, there are variations, wide variations in BMI versus body fat and lean body mass. However, as one goes up into the obesity area, this variation begins to narrow and it becomes a better definition of body fatness,

when you get above a BMI of 30.

And the third comment about BMI that I'd like to make is that because it's -- one of the imperfections of the BMI is that we only have charts now that measure, that allow us to measure the percentiles up to the 95th percentile. We're talking about the 99th percentile now, but the present CDC charts don't have a 99th percentile on them which creates a problem and we were talking in the break about the possibility of using Z scores, a concept, God forbid, the pediatric community will go crazy about. But a Z score of 3 is a percentile of 99, the 99th percentile is a Z score of 3.

It would be a much easier way of defining the population if you use Z scores. You wouldn't have to depend on a non-existent graph.

CHAIRMAN NELSON: I think we need to move on to Question 2. We're going to get back to study design and I suspect this issue will re-emerge when we get to the actual study design because then I suspect it will. I'm afraid if we keep going at this, we might be only on this issue for the rest of the day.

So I'm sure an opportunity will come up for it to be re-approached.

So what I'd like to do is move to the question of endpoints and I assume people can read. Do you feel, Ron, I need to read everything that's on that? All right, we'll move to a question of -- it's basically what you get and when you get it. So there's really two issues. What do you want to measure and when do you want to measure it?

Issues of long term, let me just go back. Long-term safety and efficacy, in other words, 10 years out, 5 years out; maintenance registries. That's the fourth question. So let's not get there. We just want to say okay, what's going to be your endpoint for the study of both safety and efficacy and when do you want to get it, 1 month, 6 months, 12 months, what's the point at which you want to do it?

And separate that in terms of primary endpoint, secondary endpoint, quality of life endpoints or other endpoints and then the role of comorbidities, improvement of resolution. I think that's been part of the discussion, a resolution of a

comorbidity may well be an endpoint. And then other safety endpoints, if people may want to consider.

And then talk about this in terms of ethical issues as well. So why don't I leave -- I think this is the best slide to focus the question and why don't we start talking about endpoints and timing.

And to the extent that you're thinking about trial design and not endpoints, we're going to come to that after lunch. So write down the ideas and let's try to stay focused, if you will, on endpoints, timing and assessment.

So with that, I see Dr. O'Fallon's hand up and then Dr. Inge. Go ahead.

MEMBER O'FALLON: Just let me lay out a few for shooting at. I think the primary -- on the basis of all that we have read and heard, I would advocate change in the body mass index for age. You know, age adjusted or whatever you've got, at 24 months, post-surgery as the primary efficacy endpoint because of what we saw about how they changed.

I think that definitive measurement times ought to be something like 3, 6 -- months after

surgery -- 3, 6, 12 and then every 6 months for the next five years, as measurement times.

Secondary efficacy, and because we're working with kids and we have to worry about growth and development issues, long term, which is different from the adult population, the secondary efficacy endpoints should be things like change in body mass index, well age adjusted BMI at other measured times that we've got. Anatomical measures.

CHAIRMAN NELSON: What kind of measures?

MEMBER O'FALLON: Anatomical. At waist, that type of stuff.

CHAIRMAN NELSON: Growth and development.

MEMBER O'FALLON: Yes, they called them anatomical, I thought. Change in medical morbidities, especially resolution of all those good things. Change in quality of life if we can figure out how to measure it. Change in diet. And change in exercise levels. Those are going to be measured and those should be secondary endpoints to be looked at as efficacy.

Safety endpoints, the number of device

procedures, serious adverse events, including hospitalizations for any device or procedure-related condition. Number of health-related SAEs, the immune system issues. Growth-related SAEs, the physical and intellectual problems. And the number of development and maturity adverse events. So those would be mine to shoot at.

CHAIRMAN NELSON: Dr. Inge.

DR. INGE: Yes, I think in the interest of time, I will applaud that list. The thing I wanted to add though is the concept or the pervasive concept of excess weight loss in the bariatric, adult bariatric literature which, I think, does have a useful value, but as applied to children, certainly, has different definitions that don't rely, shouldn't rely on adult insurance table average American weights with body frames that will be different in adolescents.

So I think there are ways of -- simple ways of defining excess weight for adolescents at various ages and BMIs and it typically is taking the weight at the BMI at the 50th percentile, the weight of the BMI at the 50th percentile and getting a delta.

So excess weight loss, if we use that as an endpoint and I'm not saying that it's a better endpoint or worse endpoint than delta BMI Z score, should be age appropriate.

CHAIRMAN NELSON: For the sake of simplification, how I would start off focusing on primary endpoint discussion and then we can go to secondly endpoint discussion and then call it life adverse, etcetera.

So in primary endpoint we've heard and my question is going to be are they the same suggestion change in BMI adjusted for age or percent estimated weight loss perhaps adjusted against 50th percentile for age. It sounds like those are closely, almost the same thing, but that may just be my lay perspective on these measurements. Is that -- Dr. Lustig?

DR. LUSTIG: They're not exactly the same. I actually have a problem with percent estimated weight loss, excess weight loss anyway, because we do know about the different fat compartments. Really, ultimately visceral fat is what you care about, subcu fat is a cosmetic issue. Visceral fat is where the

comorbidities come from. Percent excess weight loss really can't measure that in any meaningful way.

So I would just vote for, particularly in the pediatric population where we don't have stability, things are moving, I think that change in BMI for age is more than adequate for being able to determine this.

CHAIRMAN NELSON: Before we go to Dr. Arslanian, a change in BMI for age would reflect a change in visceral fat or do you have to get fancy with MRI scans and measuring and all that sort of thing?

DR. LUSTIG: Well, we know that once we get above that BMI greater than 2 SDs, you're accumulating visceral fat and that's ultimately why they've got the comorbidities and we've already said that comorbidities is going to be one of the things that's going to be influencing patient selection. So I think that those ultimately go hand in hand.

CHAIRMAN NELSON: Dr. Arslanian and then Dr. Kral.

DR. ARSLANIAN: This is Blue Ocean

approach. Maybe we can use excess BMI loss for the pediatric population, very similar to the excess weight loss except instead of putting the delta with, if you put delta BMI and the BMI actual minus the BMI for the 50th percentile for age. I think that would be a nice approach.

And I don't think measuring abdominal circumference or MRI is reasonable in all centers. Not everybody --

CHAIRMAN NELSON: We're talking about research. I asked only because I know that some people do MRIs to measure visceral fat.

DR. ARSLANIAN: I would love to do it.

CHAIRMAN NELSON: You could ask for the big, expensive study, if you wanted, I suppose.

DR. ARSLANIAN: I will.

CHAIRMAN NELSON: Dr. Kral?

DR. KRAL: I wonder whether there is any evidence, Dr. Lustig or Dr. Klish, that in the pediatric group there is any differential between what you'd like to call visceral and subcutaneous adipose tissue. Is there truly evidence for this? I'm not

talking about studies that I've done, for example, in various species including homo sapiens on the importance of regional differences. Is there truly evidence?

DR. LUSTIG: Actually, I think the answer to that question is at the end of the table, Dr. Yanovski was the first person to actually demonstrate that back in 1996.

DR. YANOVSKI: Lots of people have shown it. The difference between visceral and subcu fat and its effects on complications, I think Mike Gorhan has the best published data and Silva, you have data regarding that too, right?

DR. LUSTIG: In the pediatric group.

DR. ARSLANIAN: Yes, yes, we have.

DR. KRAL: Even though I might comment, it's not as tight as the adult data is.

DR. ARSLANIAN: No. We have shown when you adjust for the BMI and then divide it according to visceral fat, those with higher visceral fat have almost 50 percent lower in vivo insulin sensitivity.

DR. KRAL: In adolescents?

DR. ARSLANIAN: Yes.

DR. KRAL: In adolescents, this pertains only to adolescents.

DR. ARSLANIAN: Absolutely.

DR. KRAL: Which is extremely important in this study.

The suggestion I wanted to make, there's an elephant that's in the room and that is weight maintenance, it's not the issue here. Just as little in kids as it is in adults, and I keep hearing people say oh well, we know it works or it doesn't work. Sure, it works to get weight down, but the really key issue that we're here to discuss and that has to do with all obesity treatment is maintenance and I think that is particularly important to build that in to our endpoint here by having sequential measurements, that the trajectory has been normalized.

CHAIRMAN NELSON: True. I will only point out again the circularity of our questions. Maintenance was identified under Question 4 or something, long-term safety and efficacy.

DR. KRAL: But this has to be an endpoint,

that it is a maintained weight loss, not just achieving weight loss on a moment in time.

CHAIRMAN NELSON: You raised the question of timing and let me go back to that, but is there relatively -- I'm not asking for vote or -- this notion of change in BMI adjusted for age, does that seem reasonable for most people, with BMI sounds like being a surrogate measure for visceral fat within this population at these extreme numbers?

DR. ARSLANIAN: I wouldn't say a surrogate measure for visceral fat, but for adiposity, overall adiposity.

CHAIRMAN NELSON: But it tracks, it tracks there.

DR. YANOVSKI: So I guess a real question here is what happens to fat mass and we're using BMI as a surrogate for fat mass. And the question for me would be if these are going to be research studies, why can't we require a fat mass definition.

Now, it is true that it is difficult, for instance, to use DEXA scans in the very overweight adolescent, because most of them aren't well defined

when you get over 300 or so pounds. And so those individuals have to be studied by other means, but there are other perfectly effective ways of assessing body composition that don't require amazing resources, for instance, the use of deuterium dilution can be done by simply, by drinking some deuterium solution. We can get a measure of lean mass and -- or I should say fat-free mass and fat mass from that which is independent of what center you're in, because the samples are analyzed by central core facility.

Other less invasive things can also be used, but I think we should consider asking for a fat mass definition. But I also believe that if not the primary endpoint, one of the primary endpoints or very close to primary endpoint needs to be resolution of the comorbidity conditions that -- I mean again, since I proposed that the initial study should only with focus with comorbid conditions, that's going to have to be an important endpoint.

And seconding Dr. Kral's suggestion that we need multiple frequent visits in order to assess what's happening, the time course of the change will

also be a relevant thing to assess.

CHAIRMAN NELSON: Let me ask you, you've now submitted your protocol and you've suggested now two primary endpoints, which I know some protocols could -- good statisticians can handle that, but you've got resolution of comorbidity and whatever that is, let's say it's life threatening --

DR. YANOVSKI: So that's why in the initial studies, if they are so proposed only to study individuals with complications, particular comorbidities or maybe a range of comorbidities, that it's going to have to -- the primary endpoint is going to have to be the resolution of those comorbidities with fat mass as a secondary endpoint. But on the other hand when we move to -- remember, we're trying to make a general document.

CHAIRMAN NELSON: Right.

DR. YANOVSKI: For subsequent studies or maybe it will be a stratified analysis for those who are studied who do not yet have severe complications. It may be a more appropriate endpoint to have fat mass as the change we want to study.

CHAIRMAN NELSON: There seems to be a little yin and yang going on at two ends of the table.

Dr. Arslanian, respond to that.

DR. ARSLANIAN: It's Pittsburgh against -- no, I think, Jack, this is a weight reduction operation, so I would go with the primary endpoint as being a BMI change and the secondary endpoint would be reduction in comorbidity because there you're going to have really hard time defining the reduction in comorbidity. For example, if you take a sleep apnea kid is it going from apnea hypopnea index of 9 to 7 or 7 to 6, so it gets even muddier.

So I would like to keep it simple.

CHAIRMAN NELSON: And I know good statisticians can handle two primary endpoints if they want to and you can fail and succeed on both, but I don't think we have to drill down hopefully to that level of detail.

Let me ask a question before going over to Dr. Daum. Back to the question of measurement of fat, we've decided fat could be the primary endpoint in some way with a measure by BMI, change in BMI or

measured by deuterium. Comments on how that ought to be measured by something that's simple to do, height and weight, or something that's more complex to do, heavy water or other measurements?

Dr, Klish?

DR. KLISH: I'd love that to be a determiner because that would limit the number of places that these studies could be done, including ours, where we have every measurement known to mankind for measuring fat mass.

We elected not to measure it in our present bariatric surgery program which is all being done under protocol, only because I'm not sure how much it would have added to our data. There are no published norms for fat mass in children, so we didn't -- we don't have anything to compare it to. You know that the child that's going to go through bariatric surgery is going to lose fat. I mean that's just a given. It's intuitive.

And I guess the only reason you'd want to measure body composition or the various -- compositional spaces, body spaces, is because you

would be concerned about excess lean body mass loss rather than excess body fat loss.

I'm not sure the adult data implies that that is a major issue to have to measure it in these children, but I guess I'll throw that question out to see if there's somebody else with more expertise than I.

CHAIRMAN NELSON: In the interest of fairness, I'm going to go to Dr. Daum and then I'll come back to this side.

Go ahead.

MEMBER DAUM: Glad to be gone to in the interest of fairness.

My question is really one for the experts to help me with. The comorbidity issue keeps coming up and is obviously a very important one. And I'm also mindful of Dr. Fost's comments that what we're trying to do here is not think about these devices for every obese patient, but rather to design a trial to see if they work.

And so if the primary endpoint, at least for the sake of my comment were something based on

weight loss or BMI loss or whatever the experts tell me is the most appropriate way to assess that, it seems to me that comorbidities aren't all the same. And so if we've enrolled patients or have some kind of enrollment criterion where we've said we want to find people with comorbidities and obesity to enroll, some of the comorbidities are more life threatening than others and some are more minor than others. Is it possible to have them as a secondary endpoint or for that matter as a primary endpoint and power the study so that it's addressing a specific comorbidity. Surely, we're not going to lump comorbidities into one basket and say they were reduced by 22 percent.

So I'm looking for some sense of which ones are more important and could you possibly construct enrollment so that you had certain common or more serious comorbidities in the enrollment package and then you could look at the endpoints which is what we're talking about in a statistically relevant way.

CHAIRMAN NELSON: I'm sure Dr. Arslanian has some advice for you.

MEMBER DAUM: Yes, I want to hear her

comments.

DR. ARSLANIAN: I think the problem we face there is having proper sample size.

MEMBER DAUM: Right.

DR. ARSLANIAN: Because even though we're hearing the epidemic and this and that, the comorbidities are not that prevalent and right now we're facing a major problem with a multi-center and I did a funded study -- I have two, diabetes in children, and unfortunately, we're having a very hard time finding subjects. So I think we have to be very careful there.

MEMBER DAUM: That's why I'm asking the question because I think the worse thing to get into would be to throw comorbidities into the entry criteria and then be unable to answer the result and I presume goes with your comment that these comorbidities are different, one might anticipate that there would be good weight loss with great effect on comorbidity A, but not comorbidity B. And if the study weren't powered correctly to look at them separately, you have a mess.

Is that right?

DR. ARSLANIAN: I would agree with you. There are limits to the statisticians.

CHAIRMAN NELSON: Sounds like there's -- not consensus, but agreement. Muttering around the room, there seems to be agreement.

Dr. Newman.

MEMBER NEWMAN: Actually, for the obesity measure, I think the percent excess BMI is a great idea, understandable. I'm not in favor of the more basic methods of trying to estimate fat because it seems to me there should be some symmetry between the inclusion criteria and the outcomes, that is, if you're going to say it's some fat measure, then you should have to do that at baseline to decide who has it bad enough in order to be eligible for the trial.

I also am concerned about the sample size and think that you kind of would like to have sufficient sample size to address change in each different comorbidity and the more expensive you make the study and the more you have a bunch of very fancy outcomes, the more that compromises sample size. And

I don't think it's fair to the device manufacturers to make them pay for the more basic measures of fat, the inclusion criteria should say it's a certain BMI or certain BMI plus the comorbidity and we have to measure that comorbidity and decide who is eligible for the trial and we can see after the trial whether they don't have it any more, if we can measure it. I think for the people who get in, based on a comorbidity, the outcome has to be that that comorbidity that qualified them for the trial has gone away.

CHAIRMAN NELSON: I've got Dr. Gorman and Dr. Pories, but let me just go back and ask a question that was raised. Dr. Kral asked a question about efficacy endpoints, primary efficacy endpoint versus call it a primary maintenance endpoint. To some extent, there's a burden, as you've mentioned on a device manufacturer for going through a trial to the point where it gets approved. It's very different than saying okay, it works, but does it have a sustained effect over X period of time, whatever X is, 2 years, 5 years, 10 years, whatever.

I guess from the standpoint of saying to a manufacturer this is not approved for general use until you establish a primary efficacy endpoint, what's the time of that? What would be the horizon for that number? Is it one year, two years, three years, four years, five years, separate from how far out you'd want to have follow up subsequent to approval post-marketing, etcetera which is a separate question. So what number would we pick?

DR. KRAL: Well, I was the one who has been insisting in the bariatric surgical community that will not discuss data before five years in adults. However, I'm not going to make a very different argument when it comes to this setting. And that is that it need not be 5 or 10-year data. We know -- let's put it this way, weight can be reduced by almost anything. It can be a grapefruit diet. It can be acupuncture in the earlobe, anything will reduce weight. And so will devices, you name them. But very few things will be able to maintain weight.

You're asking the specific question what is the time frame? Certainly, it is enough to

demonstrate proof of concept of maintaining weight within a one-year framework actually in a growing child.

CHAIRMAN NELSON: We've heard 12 months is on the table. Do I hear another number, higher or lower? The time at which you'd allow for approval of primary -- Dr. Arslanian?

DR. ARSLANIAN: When I look at the data provided in our handbook, with respect to at what point in adults the BMI plateaus, it seems after 12 months it plateaus. And my hypothesis will be by three years in adolescence, it's going to be pick up. So I thought the two-year cut point was a reasonable one.

But I do agree that deep in my heart, I would love to see the longer one. But what's reasonable in a clinical trial is --

CHAIRMAN NELSON: We'll come back to the longer. I see heads nodding to two years. I see two years.

DR. KRAL: But there's confusion here. I'm not talking about -- Dr. Arslanian, you're

mentioning the time it takes to stabilize at a nadir. I'm not discussing the time it takes to reach nadir. I'm talking about the time beyond nadir that you have a maintenance. That's where I came up with the one year.

DR. ARSLANIAN: To me, just plateauing it's meaning that some are going up.

CHAIRMAN NELSON: We don't have to have 100 percent unanimity on one versus two, but I do get a sense that more people fault two than one and one was the original suggestion.

Dr. Choban.

DR. CHOBAN: Going again back to the adult setting and where the three-year trial for the lap band and the adults came from, was sort of the history of stomach stapling and GI bypasses and to some degree the notorious history that we've lived with and we kind of hurt ourselves with in bariatric surgery.

Pretty much at the end of a year, the stomach stapling where you just fired the stapler across and before that you pulled a couple of teeth out, a couple of those staples out of the middle of

the staple line, by three years in the vast majority, probably 90 percent of the patients, it had unzipped.

So I think when you're talking about a different standard, when we're coming from studies where we know the procedure is efficacious added about three years, it's holding up in adults at least, that the technical aspects of the device or the procedure or whatever, has already been confirmed in another population, then I think to be able to use a shorter standard in the pediatric population is probably reasonable, that from the point they've hit that low point it's now maintained at a year, it is probably you're okay because you know technically the device is intact at 3 to 5 years in adults.

I think it's going to be a different standard. I think you're going to have to revert to that longer standard of three to five years will the device continue to function or it doesn't unzip, you don't have some other problem. If we begin to use devices that are designed specifically for children and have not had an application in the adult population.

So I think you have to -- you're okay with those shorter time frames, provided in another population you sort of proved the technical competency of the device or procedure.

DR. INGE: I think one other important issue on this is when you look at these curves sometimes surgeons very carefully managing their lap band patients, let's just say, because we're trying to talk generic, but they will consciously use smaller inflation volumes over a longer period of time and see that nadir at three or four years.

And so if we artificially impose a time line that they might want to get to to achieve efficacy in a shorter time period, we might have a bearing on what actually happens there and so that has to be considered, if, in fact, the most careful and conscientious people are doing this so as to achieve a nadir longer than our time point.

CHAIRMAN NELSON: I will get to Dr. Gorman and Dr. Pories on the list, but let me ask you a question. So the concern there, some of the issues that you brought up were safety issues. Does the

device stay intact, does the repair stay intact, etcetera and we should talk about that explicitly.

The question you raise is if we demand an efficacy endpoint that has a short horizon, whether at 12 months or 24 months, I guess could be a point of debate with more people falling on 24 months than 12, that it would then -- I assume the reason people are going slowly is because they do it out of safety concerns and we might actually end up with a safety signal that would be inappropriate relative to what's currently being practiced. Is that fair?

DR. INGE: That's fair. I think you can construct your -- you can say that you only expect to see 10 percent of excess BMI loss effect to your time point and you might not be pushing someone to get their patient there at two years faster, but I think it really does matter where you draw the line for weight loss or BMI loss, if you're going to draw a short endpoint. And I'm not saying a short endpoint is inappropriate, as long as we realize what we're doing.

CHAIRMAN NELSON: So would there be

agreement around the question of what percent excess BMI loss would be the appropriate threshold to reach? I assume sample size is statistical significance. I mean what would be a clinically significant and appropriate percent excess BMI loss at two years?

DR. INGE: It's going to require very few patients I'm sure, but that would be -- the honest answer is it's whatever BMI loss it takes to treat the comorbidity and whether we can come up with a surrogate of that which is what I think we want to do, rather than to look for the comorbidity as a primary endpoint. Would it be arbitrarily what? I don't know.

CHAIRMAN NELSON: Ten percent, 15 percent, 20 percent, 50 percent?

Jack?

DR. YANOVSKI: So to address two issues, the first is the length of follow-up. So again, if we fall back on what is available, which is pharmacotherapy, in general, nadirs reached around six to eight months and gradual loss of whatever benefit at the present, so that by two years the vast majority

of people who have lost weight, done exercise for sure, and even with pharmacotherapy, have a large amount of benefit has been lost.

So by two years, you at least have an idea, a pretty good idea of whether there's going to be anything that is likely to be sustainable, that will be sustained or not is the second question. So I think two years is a reasonable period from the time of the operation to look for whether you've got good efficacy from the original procedure, relative to what's -- because we're thinking about this as something, devices as being in between diet and exercise or pharmacotherapy and the more invasive bariatric surgical procedure. So that's why I think two years is a reasonable place to look.

The second issue you raised which -- I forgot --

CHAIRMAN NELSON: Well, can we say anything about what the appropriate change is to decide that it's efficacious.

DR. YANOVSKI: Right, again based on data from both traditional diet and exercise programs and

from pharmacotherapy, a 10 percent weight loss in adults and in very few admittedly studies in kids, suggested that we do see benefits in comorbid conditions, so that's not an unreasonable standard. If we're going to hold these devices to a similar standard than we do to pharmacotherapy which I think is not unreasonable, at least as a starting point, a 10 percent weight loss that's sustained two years would be a major victory.

CHAIRMAN NELSON: I'm going to go to Dr. Gorman and Dr. Pories and then I'll take Dr. Kral at that point.

I just want to point out that there is a relationship between that endpoint and then how you design the trial because if you did a randomized control trial, you just power for a difference that you would see which could potentially be less, but if you set an absolute endpoint, you may be able to have a single arm trial that would either reach it or not reach it. So it gets into trial design.

Is this a comment -- you seem stressed? Do you want to comment, Dr. Kral?

DR. KRAL: Yes, I'm stressed by the fact, and this was asked yesterday, I think maybe Dr. Gorman asked it and that is is there any track record on the rapidity of weight loss with known modalities? And there are two very different aspects of this that have to be mentioned right now.

There's very good evidence from the 1970s on rapidity of weight loss after surgery where there are optimal amounts and there's optimal characteristics of too rapid a weight loss, will not be compensated nutritionally, will add to more complications. So I caution for that on the one hand.

But on the other hand, we can't really extrapolate from what Dr. Yanovski was mentioning and that is when it comes to behavioral methods or lifestyle methods with diet and exercise, for example, when cautions against too rapid a weight loss because one requires behavioral adaptation and it is believed that a less drastic and more rapid behavioral adaptation to what is necessary is beneficial. So we have the friction there.

But you're asking about constancy of the

efficacy that is being met. There's really polarity in this.

CHAIRMAN NELSON: I'm going to go to Dr. Gorman and Dr. Pories, but one thing to think about maybe too is to talk about safety endpoints and whether or not you could actually design exceeding a certain percent weight loss over time as an adverse event definition within a trial design, to actually make sure people don't go too fast.

So think about that and let me go to Dr. Gorman.

DR. GORMAN: I'm actually trying to answer the second question that you just asked which is what are the appropriate endpoints in terms of primary. And I think focusing on percent reduction of BMI is probably not the most important to the human subject in the trial. If I can go back and misquote my psychiatric friends, most psychiatric patients don't want to be cured, they just want the pain to go away.

And the reality when we're dealing with people who have obesity is that for the ones who enter this trial they're going to probably want their

quality of life to improve and I think that those will become the primary endpoints that will be important for the adoption of whatever device comes down the pike, down the long haul.

I think if you have a comorbidity, the hard endpoint is the resolution or ablation of that comorbidity, but in terms of not having a comorbidity, the healthy obese child and I know that's an oxymoron, but the healthy obese child wants to not be picked on. They want their peer relationships to be normal. They want to be chosen on the sports team before the last pick. They want to not be excluded from the dance competition as one of our public people said today.

And I think that the quality of life outcomes are going to be more important for the subject of a continued usefulness of any device that we talk about or the FDA goes to study as they go forward. And maybe a more important outcome than percent body loss, they have to get to the point where they're no longer stigmatized as being different. I think that's the out point that's to be the most

important for the subject in the trial. Maybe not from the science, but for the subject.

CHAIRMAN NELSON: May be, and then the question comes back is would you still make, given problems of measurement, you may still decide that that's a secondary endpoint instead of primary, even from the standpoint of subject perception and recruitment and retention, it's primary.

DR. GORMAN: I think it's harder to measure and maybe more variable as an endpoint, but I'm looking at the primary effectiveness endpoint. Do we really want to get people down to the 50th percentile going back to Dr. Newman's comment. I can make the obesity epidemic disappear in the next six minutes by just re-doing the charts. If I go and remeasure everybody and set the 99th percentile at the 99th percentile for what it is in 2005, the obesity epidemic disappears because there's only 1 percent again above the 99th percentile. I don't think that's a good thing to do. I think there are biological conditions.

CHAIRMAN NELSON: Which is why it's eight

percent above one percent.

DR. GORMAN: That's right, eight percent of the one percent. But I think even though it's squishier on some things, it will be wide subjects continue to participate in trials or choose therapies. They'll choose therapies.

CHAIRMAN NELSON: I suspect you are right, but that's very different than saying that that should be the primary endpoint from the study design perspective.

DR. GORMAN: I would continue to respectfully disagree. I think that is the primary endpoint because that's the endpoint that if we say that the primary besides the biological, that there's a social stigma to obesity, if we can make that go away in the individual's mind, that's the primary endpoint.

DR. ARSLANIAN: In the individual's mind.

DR. GORMAN: Correct, in the individual's mind. Or the society's mind.

DR. ARSLANIAN: Not a hard outcome. I can improve the quality, apply it of a teenager who is

obese, that she falls in love with a guy.

(Laughter.)

It does. I see it every day.

CHAIRMAN NELSON: I'd love to be on your IRB when you present that protocol.

(Laughter.)

Let me go to Dr. Pories and then Dr. Ward and then Dr. Lustig.

DR. PORIES: You know, some of these problems have been addressed in a program called LABS, the Longitudinal Assessment of Bariatric Surgery. It's a study being run by Dr. Yanovski's wife, Sue Yanovski at the NIH and at six participating centers. And we've dealt with this same -- these same questions for about the last 14 months before reaching some kind of solution.

But frankly, we use all of them. We have a Bruce Wolf comorbidity score that could be adopted here for children very well. It measures level of diabetes and arthritis and a variety of things and sleep apnea with clearly defined elements. And I think these could be adopted.

We also look at the BMI even though we realize it's not the greatest of measures. But I think it's very important to go beyond two years. Many of the real problems in bariatric surgery appear after two years with severe nutritional, unpredictable problems and they can also occur after just restrictive operations.

So I'd caution, I'd say let's adopt some measures from another well-funded NIH study and let's look beyond two years or two years being at least a sharp minimum.

CHAIRMAN NELSON: Dr. Ward.

DR. WARD: Skip, I would argue that the primary endpoint has to do with the patient's well being, measured by the comorbidities, measured by quality of life and that the BMI is actually a surrogate marker for those, that they correlate, but what matters to the patient is less the BMI percentage than it is the effects on their health.

And I would agree with what was just said that I think two years may be a reasonable endpoint for practicality, but what really matters is whether

this is a sustained effect or not. And the complications of the device are likely to tend to accumulate over a period of time and I think our study needs to take into account both detection of adverse effects from the intervention as well as the efficacy and both need to be considered in the duration of our observations that are carefully tracked.

CHAIRMAN NELSON: I'm going to get to Dr. Lustig and then Dr. Arslanian, but just to focus our discussion over the next 20 minutes until we then break for lunch, is can you measure some of these other endpoints besides BMI, quality of life, comorbidities, etcetera. It sounds like there may be some experience. Can that be measured?

And the second is we do need to talk about safety endpoints and an issue was raised about the length of the trial may depend more on safety endpoints than it might on an efficacy endpoint.

So Dr. Lustig?

DR. LUSTIG: I couldn't disagree with Dr. Gorman or Dr. Ward more about the point that quality of life being a primary endpoint here. All you have

to do is look at the adult data in terms of depression and look at the racial distribution and dichotomy. The fact is that African-Americans and not bothered by their obesity in the slightest, yet they have an enormous burden of morbidity in terms of Type 2 diabetes, focal segmental glomerulosclerosis, dialysis, etcetera.

The fact is that has a lot to do with societal and cultural issues in terms of how they feel about how they look and whether or not their lives are decent or not.

The fact is children are in the same situation, plus there are a lot of kids who have reactive depression and they will say it is about their obesity, but in fact, once you actually treat their obesity in various manners and with success, those don't necessarily disappear. And that's an overlay.

Now can it be measured? Yes, it can. The PETEs Quality of Life Questionnaire actually has been relatively useful in this regard. We've actually shown that our PETEs QL data correlates with our

attrition rate. So the higher they score on the PETEs QL, the more likely they are to come back, probably because they do feel better and they are looking for something, rather than that magic bullet that they couldn't find.

So I think there is value and I certainly think it can be a secondary endpoint, an important one. And it does matter how they feel about it. But it to call it a primary endpoint I think is a major mistake.

DR. WARD: Could I respond to that? I think it comes down to the definition of an FDA endpoint and you need to look at the guidance. It doesn't have to do with this necessarily scientific measure. It's going to have instead to do with what the patient requests.

DR. LUSTIG: The reason we're doing these is to try to alleviate disease. Let's look at the disease, not the quality of life.

CHAIRMAN NELSON: I guess it's a question of measurement, but if in fact, the quality of life is scored high on a subgroup where there's a high disease

burden, then there would be no discriminatory value on the part of the quality of life score for that subpopulation. That's what I hear from a scientific point of view, not -- quality of life is important. It's got to be in there, but to make it the primary, single primary efficacy endpoint, it sounds like there is some disagreement about whether that would be do-able or useful.

DR. INGE: There's also the notion that right now we don't have great validated instruments. And we have one PETEs QL that's a very blunt instrument that's not related to weight. There is one instrument that has been developed and has been validated, we're awaiting the publication of it, which is weight related.

So I think that we have to take on this responsibility of not adding too burdensome a design to the process as one of our charges as well, especially if the instruments are not quite where we want them.

CHAIRMAN NELSON: This is a good moment for our fellow to pitch in for the industry, I gather.

DR. GARAFALO: Thank you. I just wanted to comment that I think it' realistic to start where we were with adults, where we're looking at weight loss and saying now we're moving down into the pediatric population, adolescents and move your way down and that you could look at secondary endpoints really as proof of concept for other studies that you might design, but in the beginning of the program it made sense to start where we have the information, where we know we were adults. I think these are important questions, but I think we don't know nearly enough to design the trials that would answer those questions now.

CHAIRMAN NELSON: Jack?

DR. YANOVSKI: So relative to the quality of life issue, although it's true there's a difference between African-Americans and Caucasians in their scores, we did a paper just a couple months ago in JP and find indeed that BMI or BMI centile SD score are related to quality of life in both blacks and whites, although the scores were much lower in blacks.

So indeed, there is an issue about how

those scores would be interpreted. If they're not very how, how will they be suppressed. But I think the whole discussion here, quality of life versus medical comorbidities really rests on what we're defining the purpose of these procedures are. So if we're looking at a cosmetic procedure, so does it improve wrinkles, we might really want to know how people feel about that and does it make them feel better about it and does it do what they wanted that thing to do.

If we're talking about a medical procedure, or medical device, then we want to know whether it deals with the disease of question, not whether -- although it's important, whether it's accepted and patients think it's a good idea. It's usually not the case that that's the primary driver.

Obviously, a procedure that is not accepted will not be used. So that will fall out of favor very rapidly and there are examples of medications that are not used, even though they are effective when used properly, because patients can't tolerate them. And it's the same with devices.

So I think we have to decide what are we trying to deal with? A medical device whose purpose is to deal with a problem or a cosmetic device?

DR. WARD: If comorbidities were in that list as well, and again, because BMI relates to the comorbidities and I think that comorbidities will affect their long-term well being and their health.

CHAIRMAN NELSON: And Bob, I don't see any disagreement on that point. I thin it's just a question of measurement and where you start. My impression is I don't think we're going to gain any more light on this issue by talking about it more in terms of primary versus secondary. And I'd like to try to move us to safety before we get to lunch and the horizon of measurement for safety, because we've only got about 13 minutes before I'd like to take a lunch break.

I'd like to transition this to that discussion of safety per say and the question that was put out was maybe we need more than a two-year horizon for safety issues and you wouldn't want to just say it works fine and stop the trial and then lose everybody.

So focussing on that as the question. So let me go to Dr. Hudson and then to Dr. Kral.

MEMBER HUDSON: You're not going to like this. I'm going to make one comment and it's quick. The quality of life measures that we use in our long-term cancer survivors that address not only health perceptions, but also functional status. So whatever measures you use that may be a surrogate and your way to improving comorbidity. So I think the scale needs to encompass that as well.

CHAIRMAN NELSON: Dr. Kral and then Dr. Gorman.

DR. KRAL: As far as safety is concerned, this is a big issue when it comes to surgical techniques. One has to make a very clear distinction between the short term and the long term safety effects. There's the performance of an operation and what we often talk about is a 30-day mortality/morbidity rate, in other words, the performance of the surgery and what it entails. And if it's a device that's being implanted, it's the implantation, the fact of the implantation. And then

we have the long-term ones.

We have to make distinctions between side effects, between effects and between complications. There are effects that, for example, when it comes to vomiting that could be seen, it's in the eye of the beholder. If it's an effect of gastric restriction, is it against a full educational program to prevent vomiting from happening? Is it from a mechanical problem causing the vomiting or is it a behavioral problem that maybe is beneficial in a sense for obtaining an endpoint.

So these distinctions, I'm sounding more Talmudic or lawyerly here, but we really have to -- for example, we are creating on purpose undernutrition. Now the question is it going to be symptomatic or medically important undernutrition? Well, there's nothing easier in theory than supplementing to avoid under nutrition. Take your favorite nutrient?

You can mandate that it's going to be supplemented and it's going to be monitored by blood testing or whatever method you want to test.

That's easy to take care of, but then there's the unexpected and unwanted and not easily remediable or preventable side effects that are related to undernutrition.

There's a long track record on this in adults. There's some track record on this in kids too, actually. Intestinal bypasses were done back in the 1970s in children and in rather young adolescents, actually, there were small series, but we have to make the distinction between short term and long term when it comes to safety.

CHAIRMAN NELSON: Let me see if I can ask you to concrete name some endpoints. I mean I think the distinction between anticipated and unanticipated and if you put in something where you anticipate certain things are going to happen that can be mitigated or prevented or maybe, in fact, part of the therapeutic effect of the intervention themselves that you've mentioned as far as effects.

But what kinds of things would you say would need to be monitored specifically that would be potentially unanticipated or if anticipated would

reach a level of severity to where you'd want that captured, reported and considered as part of the assessment of whether a device should go forward or not go forward and then over what horizon?

DR. KRAL: I've looked at that and created a bit of a taxonomy as far as that's concerned. Interestingly enough, related to adjustable banding. It is actually in the population where we're looking at MC4R polymorphisms and how they would affect various outcomes.

They are device-related when it comes -- I'm sorry it's the band again, not my favorite topic, but it is the band. Typical device related are infections surrounding or in relation to either the band itself or its port. That's a very typical one. Wound infections are less of an issue, but they obviously have to be counted. And then you have generically surgically related complications and that is undergoing an anesthesia and a recovery in which there could be pneumonia and there could be thromboembolism and there can be hemorrhages and things like that. They're not specific to the device

in question.

As far as the band is concerned, we also try to discriminate between a device-related complication that might not specifically be related to the device itself, such as an eating behavior which would give rise to erosion or malfunction of the band, slippage or tipping or something like that. That has two components. So we have different classes there of safety issues. There are the generic ones related to any surgery. There are those that are specific to whatever the device is and then there are the use related safety issues.

CHAIRMAN NELSON: Let me go to Dr. Gorman and then I'll go to Dr. Inge.

DR. GORMAN: At the risk of being accused of laying undue burdens on industry violating HIPAA and any other sins I'm about to commit, I think that a registry of these devices, the subjects that are enrolled in these device studies should be established. And the number in that registry I will leave to my statistical friends to decide on.

I am always amazed when people put

together rare facts. I think of vaginal cancer after hormonal exposure during pregnancy or the -- and perhaps germane to this discussion the occurrence of gastric carcinoma 40 years after lye ingestions. How did someone put that together? And I think when adverse events occur that are -- could be complications, side effects or actually effects of this therapy, whatever the device is, come to light, 5, 10, 15 years later, having a registry that could then be queried for that particular adverse offense to see if it was isolated or a pattern would be very, very useful.

That would then take us out of the realm of having to predict the unknown by allowing us to go and look at those people in an on-going way, recognizing the difficulties of maintaining the registry and the mobility of American society.

Just realizing that 15 years from now, if there are four reports of early MIs in these patients, we could query the 400 people or the 1,000 people that are identifiable in the registry for that. I realize that also might be more study design than it is --

CHAIRMAN NELSON: Actually, it's under Question Four. But we will come back to a registry. I guess the question would be and I'll give Dr. Inge the last work on this, if you'd like before we break for lunch is since the point at which you would like to have any device marketed is when you determine it to be safe and effective, apart from the registry which you could recommend as we discussed that this afternoon which could be forever or for all devices, etcetera.

At what point would you say in terms of the horizon? We've talked two years for efficacy, but what's the horizon for safety regardless of what safety measures you have. Is two years enough or do you need to follow it out for five? I mean what's the safety horizon to where you get both the efficacy and the safety determination.

Dr. Inge, we can come back to this in further discussion, but why don't you have the last word before lunch.

DR. INGE: Sure. Two generic points which may be obvious, but certainly looking back at the

prior FDA trials for the band in adults and looking over the constellation of complications would certainly inform this trial as well, if we're talking about the band.

The second thing is just to echo again what Dr. Pories said in terms of what we're trying to do in basically a day's time what has taken very, very smart minds at NIH and around the country over a year now to try to put together and to leverage that in their advantage or to the advantage of the FDA would seem appropriate.

The third thing is more specific and that is I think that all of us that deal with pediatric patients do worry about the long-term risk and the long term risk of procedures of a prosthetic device that restricts essentially restricts the esophagus and having esophageal motility and dilatation and so forth looked at on a regular basis, perhaps more regularly than in adults would be appropriate. This is something that's going to be there presumably for life for perhaps twice the duration of time as a similar device in an adult and we really have to, I think,

focus on how it might affect the individual, individual organs that it's applied to and upstream of it.

CHAIRMAN NELSON: So do you have a time in mind that would -- I mean long term, assuming registry, let's assume that for the sake of discussion. Where would you allow it to emerge, having been labeled safe? Pick a number.

DR. INGE: It's very tough. Five to 10 years.

(Laughter.)

DR. INGE: This is post-marketing, I'm assuming.

CHAIRMAN NELSON: Well, no, you have a trial. The trial goes for X period of time and then the device emerges labeled safe and effective. The post-marketing we'll get into that long-term issue under another question, registries, etcetera. So at what point would you say the trial could end up we now think it's safe enough to be used for the population, assume good training, you've done all the appropriate etcetera, etcetera, etcetera. When can that be

labeled safe and effective?

DR. KRAL: Two years provision.

CHAIRMAN NELSON: Two years provisional? I'm not sure if the FDA has a provisional category.

DR. INGE: I think two years. If you look at end points that are organ specific, you know, on a regular basis, be it annually for two years, that that would be a point at which you could feel some comfort, but again, we're talking about decades and decades and it's not reasonable to require a safety endpoint decades later, but that would have to, it seems to me, be part of the recommendations for user or labeling of it to have studies done that look at this.

We also worry about the number of times a surgeon has to go back in to replace a defective device, again, in an individual that may live 60 years with the device rather than 30 which is a rough, maybe unfair, characterization, but adults versus adolescents are different.

CHAIRMAN NELSON: I suspect, given the comments that we'll come back to this when we talk about registry and long-term assessment because it

seems difficult to tease that apart.

It's 12:15. Why don't we --

MEMBER DAUM: Could I make one quick comment?

CHAIRMAN NELSON: Does it have to be done before lunch, can we do it after?

(Laughter.)

MEMBER DAUM: It might sort of get people thinking. It will take me less than one --

CHAIRMAN NELSON: We're not supposed to think about those questions during lunch. You can think about them, but you can't talk about them.

Go ahead.

MEMBER DAUM: One thing that there's actually precedent at FDA, actually in another branch, is to have an interim evaluation say at two years and then have as the requirement for going forward with the licensure at that point, insistence that the trial be continued so that's just one option to think about, rather than wait 5, 10 or 20 years. You can look at the data in two years and if the short-term safety data were there and the efficacy was there, with the

parameters you set up, you could insist that the trial go on, but go ahead and issue a license at that time.

CHAIRMAN NELSON: Let me ask Ron if that is a device even available for devices?

DR. YUSTEIN: What we're looking at now in the Center is the possibility of consenting patients, asking sponsors and manufacturers to consent patients for longer periods of time at the initial time that they come in to discuss the protocols with us. So therefore, if you select two years as the initial baseline for coming to panel, discussing a device and the panel says yes, this is safe and effective, we may have already consented a patient for five years and so they won't be lost to follow up and you'll still have that cohort to follow out to five years.

So we don't call that like a provisional thing. Once it's approved, it's approved. It's available for marketing. The manufacturer can go ahead and sell and promote the device. But we are looking now toward keeping patients enrolled longer and starting that earlier and trying to keep those original IDE cohorts available for that longer term

follow up.

CHAIRMAN NELSON: Okay, with that, let's break for lunch and reconvene at 1:15.

(Whereupon, at 12:19 p.m., the meeting was recessed, to reconvene at 1:15 p.m.)

A F T E R N O O N S E S S I O N

1:23 P.M.

CHAIRMAN NELSON: Well, we're now going to move to questions of trial design and I'm not going to attempt to summarize the morning conversation because I think there's two risks on that; (a) it would go too long, if I summarized it adequately; and (b) if I didn't summarize it adequately, we would then end up with a discussion of the points that I missed.

So I think it's reasonable to push on and

some of the things that were discussed this morning that I think will come back, for example, would be long-term issues. You know, we really didn't sort out -- I heard two year at one point, I heard a five year, but for short term at what point do you let it emerge. We can get into that in talking about registries and the like.

What I'd like to do is spend our time between now and the break and if we needed to spend time after the break really talking about study design per se and to specifically make sure that we touch on issues that are raised within that context.

So I'm not going to read the background material on the questions, but I think we've had a lot of conversation about a complex range of issues as we've talked about patient selection inevitably we were tying that to design. And there's been comments here and there about how that might happen, etcetera. So would be nice now is to make explicit, specifically the design issues.

And some of the questions that we need to

consider in the kinds of trials that would be recommended as part of an eventual guidance would be, for example, is a randomized control trial, the preferred trial design. You heard one public comment that that would, in fact, not be the case, but whether we agree or disagree with that is an open question.

Of course, if you have a control trial, you need to then decide what the control group is. We would need to then also decide is that true of all devices, some devices which would get us potentially into discussion of equipoise which was raised by one of the -- if you think that's an important issue within the design of a trial.

Also, get into the question of sham procedures. Obviously, a device that you can turn off and on, even when the device is implanted which the band has that characteristic, another context where devices have been improved, the beta Vagal Nerve stimulator would be another example of that kind of characteristic where you implant it and you don't turn it on and you can turn it off, etcetera and then also

issues of blinding and masking.

And so these are the issues that we really need to get into. So as part of that and as a reminder, we also want to touch on issues of assent as well. I heard by and large the group feeling that any research should be phased in with the adolescent population initially involved. Short-term trial two years. I mean that may not raise issues, but if you started with a 16-year-old, what happens when they turn 18 or a 15-year-old when they turn 18. And if we start going younger with lower-risk devices, how does that assent get handled, particularly if you're talking about sham control groups or other control groups. We need to have that be part of the discussion.

And then confounders that we would need to consider and then again, here we have under trial design one issue we tried to get at in duration which I think we answered for efficacy, what would be the duration of a pre-market study which again is very separate from the fact that we might need post-market monitoring as part of registry, etcetera. But what's

the point at which you decide something can emerge having been determined to be safe and effective, etcetera.

So those are the issues under trial design which are, depending on the designs, we begin to focus on, could be quite informative. So with that, Dr. Botkin?

DR. BOTKIN: I wanted to pick up quickly on Doug's comments from a little earlier that do relate to trial design and the relative breadth of the inclusion criteria that would be appropriate. And I guess it seems to me, first of all, I say I entirely agree with the general concept that doing adults first, doing older kids second, younger kids third is the right way to go, and being relatively stringent as to try to initially define safety and efficacy.

It seems to me the reality in this kind of situation though is frequently that you've got some significant level of experience from off-label use and if you have a device for which you have some data in the pediatric population from off-label use, we need to make a determination about the quality of those

studies, but then ultimately, I think you want to design a study that is going to inform you best about the use, the anticipated use of that device in the larger pediatric population.

So I think what that speaks to is you've got pretty good data about safety and efficacy, if you develop too stringent an inclusion criteria for this kind of study, then you've either got a restricted set of indications on that and a lot of off-label use which I think is inappropriate. I think what you want to do is try to be as broad as is reasonable in order to best describe the safety and efficacy with the whole population that's likely to get this thing once it's actually out there.

CHAIRMAN NELSON: Let me reframe that. I think that mirrors a comment that was made earlier about in a sense different approaches within the same trial. So there's a tension between designing a trial, as you mentioned, that could answer scientific question. We make fairly narrow entry criteria to do that which is, I think, where norm was having other people versus designing a trial that may have one

component or say the population, but allow for other ways in the trial that may have sort of a multi-faceted trial that might reflect clinical use where that data would be captured, as opposed to in the off-label environment.

So that's the tension between the two. So I guess trying to make that concrete, how would one reflect that tension in an actual trial design? How would you make that look? An open-label component for people that meet a certain level of severity? A randomized component for those who don't? I mean how would we actually make that happen when we think trial design per se?

Do people think that randomized control trials is the way to go for these devices or not?

Dr. Kral and then Dr. --

DR. KRAL: This is related once again to what kind of device we're speaking about. If it's anything that involves surgery, there's no way it can be a randomized control trial. No way.

CHAIRMAN NELSON: Why?

DR. KRAL: Well, it's neither ethical nor

is it scientific nor is it usually feasible.

CHAIRMAN NELSON: There are randomized control trials that have been done in surgery.

DR. KRAL: It doesn't mean that they fulfill those criteria.

(Laughter.)

CHAIRMAN NELSON: Well --

DR. FOST: Are you just referring to sham surgery? Why can't you randomize people to treatment and no treatment?

DR. KRAL: That's not a -- you're not --

DR. FOST: You have children that are presently getting no treatment, standard treatment, whatever they're getting, behavioral, nutritional, dietary. And the intervention group gets surgery.

DR. KRAL: So somebody is going to agree to the flip of a coin in which one will get allocated?

DR. FOST: I am not suggesting -- I was going to go on to say I don't think it's necessary in this case, but it's done every day. I mean there are many --

DR. KRAL: We're talking about this case.

DR. FOST: Okay. Why is that not a scientifically-valid question?

DR. KRAL: To expect somebody to agree to a flip of a coin between no treatment and having surgery --

DR. FOST: Standard treatment. Everybody would get standard treatment.

DR. KRAL: Because the efficacy has already been demonstrated to be so dramatically different and it's this drug mentality kills me. A drug can be stopped within one day and it's off, it's off or it's on. Surgery cannot be. It makes a structural and a functional difference that remains until it has been through sometimes Draconian measures reversed. That is not an equitable choice. That should be a flip of a coin and you're not going to be able to recruit and the selection criteria are going to be different? It's not going to be scientific. It's neither ethical nor is it scientific.

To randomize between two so different modalities and that's very clear in the instructions.

CHAIRMAN NELSON: Let me see if we -- Ron,

why don't you say something.

DR. YUSTEIN: I just want to make a quick comment. There are some devices that can be surgically placed and not activated and can be later activated. For an example, outside the obesity one, just because I can't talk about things that are on-going now, but a device that we approved recently in the Center was a neurostimulator for the treatment of major depression, drug refractory depression.

And in that trial, it was patients were randomized to on or off, but they both required surgery to have the device implanted. It was a Vagal Nerve stimulator. So all the patients got the surgery, but half the patients actually did not have it activated during that time of the evaluation. So sometimes surgery can be performed and there can be two groups, but the one group can be off and then that group was later turned on.

DR. KRAL: The implementation is the same in those two. I'm not discussing on/offs.

CHAIRMAN NELSON: I think that's where we need to make sure we're talking about apples and

apples and not different things. I mean there are -- in many ways, I think, if I could try to move us along on it so we're not focusing on issues that we all agree on. I don't think anybody would say you should take someone who's meeting the patient characteristics we had talked about before, even if we haven't quite nailed them down perfectly, and have nothing happen to them.

So any device in some sense would be an add-on to what would be considered appropriate management. Is that fair or not?

DR. YUSTEIN: Yes.

DR. KRAL: But people won't do it because you can take an example that we were involved with with the ASD occlusion devices. If you have a randomized trial where patients have the right to choose whether they want to stop or start, we found a number of patients would come, get randomized, and if they didn't get the arm that they wanted to, they left your institution and they went to another institution and they kept going through the process until they randomized to the device that you wanted.

And physically, it inhibited the ability to do that kind of a trial. And we're talking about people who have the same -- you listen to the speaker in the public portion of the meeting who addressed that very same thing. She would not be about going in, getting assigned to standard treatment. She would be off to the next location.

DR. INGE: The effect size is just to big to equipoise either as a patient or -- I think what we're talking about is the effect is just so large here, that as a patient it's just not -- there's no equipoise for those who are seeking treatment.

CHAIRMAN NELSON: Norm and then --

DR. FOST: Correct me if I'm wrong, my understanding is that the number of children who have to date received any kind of surgical or device intervention is very -- is a very small percentage of the whole. That is over 90 percent of children who this group thinks is in need of some more effective intervention is enormous. They presently don't have access to it. What we're trying to do is facilitate clinical trials that would lead to approval of

devices, so that more children could get access to them.

So number one, I don't understand the ethical approach of inviting a group of children who presently have no access to effective treatment and inviting them to be in a trial in which they would at least have a 50 percent chance of getting effective treatment and possibly even subsidized. I don't know to what degree that would happen.

DR. KRAL: That's coercive.

DR. FOST: No, it's not.

DR. KRAL: Yes, it is.

DR. FOST: You have children who presently have access to no effective treatment and you're offered -- coercion involves threats. Coercion --

DR. KRAL: It's an offer they can't refuse.

DR. FOST: Coercion refers to situations in which somebody is going to be worse off if they don't accept your offer.

This is a situation in which somebody has a 50 percent chance of being better off. And it's

true of every single randomized trial there is in which -- not everybody gets the intervention because in part because you don't know ahead of time whether the intervention is good or not good.

DR. KRAL: One thing that's not entirely true though is that they do have access to gastric bypass to probably bands --

DR. FOST: Then why are 90 percent -- correct me, but my premise was, I thought I understood from all the presentations that the overwhelming majority of these children are presently not getting any surgical intervention, not lap bands or gastric bypass.

DR. KRAL: Well, it depends on what children you're talking about. The children who are seeking surgical treatment are seeking and getting surgical treatment. And so if we're talking about the people that might be coming in for a trial like this, it's people who in their own minds have made that big jump and leap of faith that surgical treatment is for me.

And that's what's different about surgical

populations.

DR. FOST: Is there not a much larger population who is not seeking it either because they don't know it exists or they can't afford it or because it's not reimbursed?

DR. KRAL: There is and what would be immoral about inviting those people into a trial that would expand their opportunity from -- of getting something effective from zero to 50 percent?

DR. FOST: I certainly don't understand why that's not a scientifically valid question and I also don't understand why it's ethically problematic. If it is, then all randomized trials are unethical, all placebo-controlled trials.

CHAIRMAN NELSON: Well, to focus the question, there was a claim made in the open session that because of the established efficacy of a known device that's being used even off label in the adolescent population, that it would be unethical to do randomized-controlled trial. In other words, if someone came in, someone comes in to your program --

DR. FOST: Arguably with that device --

first of all, I don't know --

CHAIRMAN NELSON: I know your view, Norm. But I'm trying to get an idea of the --

DR. FOST: Your comment is addressed to a lap band.

CHAIRMAN NELSON: Right.

DR. FOST: There's zero information on the next device coming down the pike.

CHAIRMAN NELSON: I understand that.

DR. FOST: Zero.

CHAIRMAN NELSON: So what I'm asking is of the surgeons, in their view, would it be unethical to have a control group that's anything other than a lap band? In other words, as a question --

DR. INGE: Comparison, sure. But I think we're talking about the process of randomizing to surgery or no surgery. But certainly --

CHAIRMAN NELSON: There are surgical trials that have done that. I mean they've done it with sham surgery and they've done it with either -- I mean there's a current trial that's prenatal fetal surgery versus postnatal surgery that's funded by

NICHD.

DR. INGE: And you know what, the randomization, the trial just tell apart very recently because the patients leaked out if they didn't have what they wanted and they leaked out into other places that weren't doing the trial.

CHAIRMAN NELSON: Are you talking about the twin-twin transfusion trial?

DR. INGE: Right. Right.

CHAIRMAN NELSON: Yes, there were procedures available and that's why I want to get -- it may be a feasibility issue but trying to clarify feasibility from ethics I think is an important distinction.

DR. INGE: And I'm making the feasibility argument because I think that they will be leaked to other modalities which are effective, like bypass surgery.

CHAIRMAN NELSON: But that's a different claim than an ethical claim to say --

DR. FOST: Then why are they not presently getting bypass surgery. I understood there's tens of

thousands of morbidly obese children out there who are presently not getting any surgical or device intervention. So your statement that they will go seek it, why aren't they going seeking it now?

DR. INGE: Again, I'll come back to the fact that the people who are seeking surgery, who have made this --

DR. FOST: I'm not talking about that. I'm talking about the 10,000 children who are presently getting nothing or getting just conventional --

CHAIRMAN NELSON: Go ahead, Jack.

DR. YANOVSKI: So to my view, ethically what we have, a situation we have some large uncontrolled -- sorry, small, uncontrolled trials which are essentially the same basic information we have in many studies where we then say oh, now we need to do a real study. Right?

So even for the lap band in which we have some efficacy data in various selected populations. We don't really have enough data to say yes, go ahead. That's why we're here to help them design trials

which will be able to assess that device and future devices.

And the deed of equitable assignment of subjects to groups for comparison is basic to all of our interpretive capacities. Now we made decide that we need to be a little more expansive, so for instance, allow patients to cross over early if there's failures.

So for instance, if they don't have a certain amount of weight control within two months. They may then be able to cross over to the other group. That would be one model. Now the group is activation of the devices so that everyone will get a chance to use the device so that's -- I mean, for instance, even in the pharmacotherapy trials that are recently published, * (1:42:45) study by Berkowitz, used that exact assignment. The first six months is a randomized trial and the second six months everybody gets to use the medicine. We have the same trial design for other pharmacotherapy trials.

So you don't have to be exclusive in thinking that a randomized trial means now and

forever, the control group never gets therapy.

DR. FOST: And we could also discuss a trial of lap band versus bypass. I mean that's up for discussion.

DR. INGE: And then the other argument that's made and I guess in this venue is that we do, before taking a child or anyone to surgery, have to show that they failed some measure, other measures. And so it's sort of a randomization to continue to failure or to surgery, so that's where I think the difficulty comes as well.

DR. FOST: That's the most ethical, the strongest ethical justification for doing a trial, namely the conventional treatment is failing. That's true of all new -- the main reason we do clinical trials is because the existing treatment is not as effective or as safe as we wish it would be.

So when we do a new cancer chemotherapy trials, the statement that we think the treatment that you're presently getting is not good enough.

CHAIRMAN NELSON: Before going to Dr. Arslanian, let me try and capture principles, if you

will.

What I've heard is the feasibility issues of the availability of weight loss management programs, either surgical or nonsurgical, that people will walk with their feet if the trial is designed in a way that 50 percent of them don't get something, that they perceive as effective.

So that a design of a trial that would allow for a sufficient evaluation period of the new treatment against a currently established standard treatment, should be as limited as possible to balance both the efficacy endpoint and allowing whether it's a crossover or whether it's a crossover after a standard period of time, crossover for failure or just crossover for time, which were the two options that you mentioned, Jack, would allow for the scientific endpoint, but define it with the feasibility of people feeling they're getting treatment in this context which is sort of the real world of trying to balance those two and that's the challenge of doing that.

Is that a fair -- I mean, independent of what device it is or the like. The difficulty here is

the debate over what is the established standard against which you would do it. Is it just the fact that nobody is getting any treatment because they don't have access to appropriate programs that are just underway versus the moral dilemma someone in those programs gets into when they realize they have a standard of care that they need to provide when someone shows up at their door. And you can't design a trial that's below the standard of care, the very institution at which you're providing that care. So I think it's a balance between those two.

We'll go to Dr. Arslanian and then -- okay, pass.

Dr. Kral and then Dr. Fost.

DR. KRAL: Two issues, Dr. Yanovski. There's no jumping in and jumping out of when there's surgery involved. There really isn't. That's a key issue.

Let me try a scientific argument. There is adequate evidence that people who agree to be entered and randomized into a study have different characteristics than those who don't agree to be

entered into it.

DR. FOST: That's why they're randomized.

DR. KRAL: If you have equal -- if you can fulfill equipoise and I strenuously continue to argue that there is no equipoise in a situation --

DR. FOST: You're assuming that the intervention is safe and effective. If you're sure of that, then right, there's no point of doing the trial. I thought we were talking about technologies that -- for which we don't have any good evidence as to whether they're safe or effective.

CHAIRMAN NELSON: Let me ask a clarifying question, although the FDA can't talk about devices, I can certainly ask a concrete question. To make this clear, is there beliefs among one or more of the expert panel and those listening to us that existing treatments such as the lap band or other treatments you may know of are effective enough that any trial done of any new therapy has to be effectively an active control equivalence or a superiority trial using the drug language and not.

DR. FOST: Respectfully, that's not --

we're not here to approve the lap band today.

CHAIRMAN NELSON: No, I'm not asking that. But you have someone arguing there's no equipoise --

DR. FOST: The FDA's question is if there's a device or a surgical procedure for which there is not yet convincing evidence of safety and efficacy in children, FDA wants to know how to design trials to do that. So let's forget lap band for a minute. Let's talk about a widget. And somebody thinks that a widget is good for this disease. The FDA wants to know how to do such a trial.

My only point is I don't see any scientific or ethical reason to be opposed to a randomized trial in which children who have failed other treatments would randomly half of them get the widget and half not. Or perhaps, if you want to do an equivalence trial, compare the widget against something that you think is already effective.

CHAIRMAN NELSON: Norm, I'm not disagreeing with that point, but I'm asking as part of the apparent disagreement here is the different views about whether there is, in fact, existing treatments

that if you withheld them, it would be unethical, whether it's a sham, whether it's a control, whether it's whatever that you can't withhold those.

DR. FOST: Then it's unethical. We shouldn't be sitting here. The surgeon should be out putting these things into the tens of thousands of kids for whom you have effective treatment and you're offering that.

CHAIRMAN NELSON: I promised Tom I'd get back to him and I want to make sure I don't skip him to go with people that are just -- Tom?

MEMBER NEWMAN: I think what addresses this point is that I don't know that the argument about ethics is really necessary. I agree with Norman, I don't have an ethical problem with doing randomized trial, but I think it is not necessary.

DR. FOST: I agree with that too.

MEMBER NEWMAN: So maybe we don't need to argue about it. The reason to do the -- to randomize a randomize trial was to assemble comparable groups so you've got strength of causal inference, so you can say what happened to these children who got whatever

the device is, would not have happened otherwise, and the reason why it happened is because they got the lap band or whatever it is. And I just don't think that's a problem.

These are children who have been -- their BMI has been at 40 or 45 for years and the possibility that they would have spontaneously lost 100 pounds is just not something I think we need to worry about. So I don't think you need to do randomized trials for the causality, if your endpoint is something as objective as weight and if your effect size is dramatic as what we all expect.

If your effect size is quality of life for something like that, for which you might have a softer thing or you might require blinding, then I think you do need a randomized trial. So I think you do the randomization for the causal inference. You do the blinding so that you know what it is that -- your intervention has -- affects the intervention and not just knowing that you got something.

And I think that if the outcome is a soft outcome, you probably would need to do some sort of

sham something or some sort of way to have a randomized blinded trial which is why I would vote for the objective outcomes.

CHAIRMAN NELSON: It seems so reasonable.

(Laughter.)

Dr. Gorman? I'll get back to you. So Gorman, and then Klish.

DR. GORMAN: I think the design of the trial is, in fact, dictated by the outcome that you're trying to measure at the end, and I would agree with everything that Dr. Newman said. I would just try to remove the jargon of participation of soft outcomes for the outcome that I think is more important, but that's perfectly within your prerogative to do.

And I think that randomized clinical trials would be important with certain devices which the outcome, be it body mass index or weight loss, might not be so impressive as some of the results we've already seen, meaning that they would be used in less seriously affected individuals.

So as we move down the path to more -- to people with less and less disability, comorbidity or

body mass index, then I think the importance of randomized clinical trials will be more important.

MEMBER NEWMAN: And as you're looking for smaller effect sizes, right, as you're looking for a 10 or 15 or a smaller weight loss that might happen anyway, that's when you need the randomized trial.

CHAIRMAN NELSON: Dr. Klish?

DR. KLISH: Just thinking about this from a practical standpoint from running a program where patients are coming in be it to get medical or surgical therapy, I would see no problem during randomly controlled trials for the new devices that are coming down the pike. You do them very much like drug trials which we do now. You would randomize them to behavior control, behavior control plus whatever you're going to test.

The only problem with that is the lap band and I was thinking through as to how you would actually approach the patients because they're already knowledgeable about them. They come to us asking for surgery and I could easily set up, design a study comparing gastric bypass to lap band, but comparing

lap band to behavioral therapy would be much more difficult because I wouldn't get -- most patients that come for surgery come for surgery. And they already know about these devices and the lap band, etcetera.

So I don't think in the present world at the moment it would be easy to control, you know, to do a randomized controlled study with the lap band.

Now in saying that, you could probably do, we are already trying to do case control studies, where we are trying to match patients by case characteristics for the Roux-en-Y gastric bypass and that could easily be done for all these very invasive surgical procedures.

CHAIRMAN NELSON: Let me go to Dr. Rappley and then Dr. Inge.

MEMBER RAPPLEY: I would like to hear advice on what kind of design would help us establish whether or not this effect can be sustained or a period of time that justifies the intervention and that would address the safety concerns about restriction and malabsorption over long periods of time in a growing child.

CHAIRMAN NELSON: Is there a comment on that question? She agrees that we should try to answer that question. The idea is -- if I could summarize where we are, I mean it seems like RCT doesn't have much support, both scientifically and ethically unless you're in a situation where you're doing less invasive treatments for less sick people or head to head what in a drug side would be an active control trial against one established treatment versus another that you may have a question as to whether it is effective and safer, lap band versus some other device.

Within that framework though, the question is how to -- sustainability. I mean it gets then to the length of the trial. I mean at what point -- we talked about a two-year endpoint, but the sustainability issue again comes up.

Thoughts on --

MEMBER RAPPLEY: And the safety issue too.

CHAIRMAN NELSON: And the safety, but separate from registering, again, the balance is and this goes to -- I mean it's actually part of this too,

is the duration of a pre-market study which is what's the point at which you want to let it out into the universe of users versus the duration of a registry or some other post-marketing assessment, what's the duration of a pre-market assessment of maintenance of the endpoint and safety, separate from post-marketing? I heard some people say two years was okay for that, but I guess it's again just a question to see if that's -- anybody have anything else to say that's separate from a registry?

Tom?

MEMBER NEWMAN: I think it really depends on the level of morbidity and risk of the people who are getting it initially. If the people who are getting it are people with bad comorbidities who otherwise are going to need tracheostomies, if it works for a year or two, even if two, three, five, ten years later, there's bad things, it's probably already going to be worth it for them.

So if you start with them, that's when you can start to accumulate the follow up. What you want to be careful of is if there are adverse effects,

esophageal problems or who knows what that might happen in 5 or 10 or 15 years, you want to be slow to start using this device in people for whom, if that happened, it would make them wish they hadn't had it. That's not so likely if they start out with bad comorbidities, so it's a reason to start with people who even if the benefit is relatively short-term, long-term effects would not have made it a bad decision to use it.

CHAIRMAN NELSON: Dr. Inge.

DR. INGE: I think one other consideration here is that many people hypothesize that the adolescent reaches a degree of morbid obesity in just a few years, may well have different biological reasons why this has happened. In say, for instance, the prevalence of monogenetic forms of obesity may be higher in this population than the adult population. So I think it's reasonable to think of these patients as different. And it's reasonable to think of these patients as likely going to have, it's likely that they will have a higher recidivism rate than you see in adults.

Now if we have a device that has a six-month nadir in weight and then we see the greatest risk for weight regain, then you might design a trial with an endpoint that is earlier. Whereas if you have a device that has a predictable nadir at three to four years, it might well mean that it's more reasonable to look both effectiveness and safety and weight regain at a later time frame.

CHAIRMAN NELSON: Given the discussion, to nail down the issue of control group, we've been asked to think about sham treatments or procedures. Separating that from turn on/turn off types of devices which I don't think don't present a whole lot of problems from that standpoint.

Can you imagine circumstances under which a sham treatment or procedure is done in order to assure blinding and masking of allocation within a control trial in this environment, where we are now, knowing what we know?

DR. ARSLANIAN: No.

CHAIRMAN NELSON: Dr. Choban?

DR. CHOBAN: I think you're back to that

does not change structure or function kind of device that's often in the future someplace, so that it is easy to turn it off and on, but I think you come back again that if in the initial trials of whatever that said device is, you've got this profound effect, that you're back to -- that you know that you can get this profound effect with this very low risk that I'm not sure turning it off and on or sham treatment is a great idea unless you're going to -- I guess if there's some finite period of time that then they know that if, in fact, in the current population you may be studying, you again see that profound effect. They get to cross over fairly rapidly to the okay, I get it turned on then.

CHAIRMAN NELSON: I don't think the on/off is really the issue here. The question is will you do a surgical procedure where you insert a knife through the skin of a child and not actually insert a device in the course of that procedure.

DR. ARSLANIAN: 46407.

CHAIRMAN NELSON: I'm not saying you could do it from a -- we'll get there, but I'm just saying

could you imagine --

DR. FOST: Well, I think if we've agreed on the adults first issue, so you'll be talking about a device or procedure that's been shown to be highly effective and safe in adults and now we're talking about extending it and maybe you needed a sham procedure in adults. I have less concern about that because you have a fully consenting person, but given that, you have a device or a procedure that's fully established in adults and we're now just trying to see if adolescents are any different. I can't imagine there's a compelling argument to use a sham surgical procedure.

CHAIRMAN NELSON: Dr. Arslanian and then Dr. Klish.

DR. ARSLANIAN: Even without having adult data, I think the sham operation in my definition is more risk with no direct benefit to the patient.

CHAIRMAN NELSON: Can I just simplify, is there anybody in here who thinks that a sham surgical procedure is something that would be incorporated in any kind of device trial.

DR. FOST: In children.

CHAIRMAN NELSON: In children. We don't need to then keep --

DR. FOST: I think we have to get to the theoretical widget. If we're talking about something as invasive as the lap band, then obviously none of us are going to deal with that. But if it's something much more trivial where, for instance, it might be a subcutaneous reservoir of some sort, it's conceivable that if there were really compelling reasons to imagine that the pediatric population might be different from the adult experience in terms of its -- the widget's efficacy.

I have difficulty blanketly rejecting an approach which is going to be the best way of knowing whether something worked or not when you don't -- when I don't know what we're talking about.

CHAIRMAN NELSON: Let me reframe that and then I'm going to ask Ron who had his hand up to make a comment and then we'll see how much further we're going to go.

There are procedures that penetrate a

child's skin such as vena-puncture that are considered either minimal risk or depending on the number of times you do it, a minor increase over minimal risk that don't offer the prospect of direct benefit, but if it's important to understanding or ameliorating that child's condition that we can do that under the existing regulations and do it in a way that's considered ethical by most observers.

So at least one could say if there was a sham procedure that met that standard, then that might be feasible, but at this point it's a matter of speculating on what the nature of that procedure might be.

DR. YANOVSKI: Correct me I'm wrong, if we have an individual with a condition or disease in whom there's the prospect of benefit from the treatment, then a randomized trial is an appropriate thing in which case the sham procedure might be really the appropriate --

CHAIRMAN NELSON: It's --

DR. YANOVSKI: It's the prospect of benefit, a 50-50 chance.

CHAIRMAN NELSON: I realize it's a prospect of benefit, but you know whether you're going to put it in or not. And normally, that's -- normally, the conditions under which that's applied aren't a surgeon deciding not to put the device in as a prospect. So that would be a reach, I think most people would feel, probably.

Is it fair to say that would be a reach? Let me ask Ron, how much more we can say about shams?

DR. YUSTEIN: I think -- I was actually going to agree with Dr. Yanovski and the point he was making when I had my hand up originally. I was going to say in a lot of adult trials we do endoscopic sham procedures, but then you kind of answered that because you said and I guess in the world of pediatricians and I'm not familiar with these regulations as well as you are, that even vena puncture is considered more than --

CHAIRMAN NELSON: No, no, no, no. Let me be concrete.

There's variability among IRBs, so take what I say as just one IRB, one experience.

Where I work we have approved endoscopies for the purpose of esophageal biopsies with procedural sedation under appropriate limits under the minor increase over minimal risk, no prospect of direct benefits. So if you're talking about endoscopy or putting a balloon, then that could potentially fit there, if you put the endoscope down and didn't put the balloon in. But that's very different than doing a laparoscopy or doing a laparotomy and then deciding not to do something on the inside of the abdomen.

Those would be the issues that would have to be sorted out.

DR. YUSTEIN: Just like Dr. Yanovski said, there are probably devices coming down the pike that can be simply inserted like that and some that may not even need a procedure that a person could swallow something that then expands in their stomach.

CHAIRMAN NELSON: Yes, but that's the standard we have to meet.

Let me go to Norm and get his expertise in this area as well and then let me see what hands remain, I'll look around and get a list on.

DR. FOST: First of all, you can't anticipate before the trial begins which arm is the minimal risk, arm. Ninety percent of new ideas in medicine fail. I don't know about devices, but for drugs, most -- only 10 percent or so are things that interface with treatment ever turn out to be a really good idea. So you don't know ahead of time. Generally, it's better to be in the placebo group.

(Laughter.)

Dave DeMet says that. If I'm brought to the emergency room unconscious and there's a trial going on for my disease, please put me in the placebo group for whatever that trial is.

So to prejudge the issue of which arm is the riskier and which is the safer and which one you're better off in is to say you know how the trial is going to turn out and it's obviously not the case.

Second, so therefore, the question is whether being in the trial as a whole has a reasonable prospect of benefit. Obviously, both arms aren't going to be beneficial. One of them will and one of them won't be.

So it will always be the case that half the children in a trial will not have gotten any benefit from it, other than the indirect benefits of being in a trial.

So the question is not is the placebo arm nonbeneficial, the issue is is being in this trial offer a prospect of benefit and at trial with sham procedures for children in this situation as a default position. There might be -- it should be argued at least if something comes around in which a compelling case can be made, then we should hear it, or the FDA should hear it.

But as a conceptual matter, I don't see any problem with having, for adults, for example, a sham controlled surgical trial and I wouldn't say that the people who are getting the sham are getting something of more than minimal risk. I don't know ahead of time which -- they may be better off in the sham procedure and it may be that the benefit of being in the sham procedure outweighs the risk, that is, there may be a prospect of benefit of being in the sham arm of a control trial.

CHAIRMAN NELSON: With all due respect, let me provide a counter argument and then since -- merely to illustrate that there could be two ways of looking at this and then we could go to Dr. Kral. The notion of not knowing whether something is or is not effective, I think, is appropriate, but what's different here is you know the risks you're putting a child to for the purpose of the sham procedure and you're then choosing not to implement the particular device at which you don't know the efficacy.

So my argument would be that you know, unless you're going to make an argument that the sham procedure potentially has some efficacy which might be the case if you're doing something in the head, but I haven't heard that kind of argument here. That in fact, the risk to that group needs to be restricted beyond what would be in the overall trial. So that's -- the risk of the sham -- nothing to do with efficacy. I agree, efficacy, you can't make that claim, but --

DR. FOST: Being in a sham group may have two potential benefits. First of all, there may be a

placebo effect from it. It may affect outcome. But secondly, it may be that it spares you from the adverse effects of the --

CHAIRMAN NELSON: Right, but the sparing from the adverse effects is generally not what people think of the prospect of direct benefit. Individual cases we'd have to get into discussing that, but I just want to -- I don't think it's straight forward in that regard. But let get back to Dr. Kral.

DR. KRAL: I'm pleased that Dr. Fost has made it so easy to reconcile our differences. When you stated that 90 percent of medical treatments are bound to fail before they go --

DR. FOST: Drugs, new drugs.

DR. KRAL: Yes, drugs. It's just the opposite in surgery. So that was very easy.

(Laughter.)

DR. FOST: How do you know that? There have been so few trials of any surgical --

DR. KRAL: They don't fail.

(Laughter.)

DR. ARSLANIAN: He's wearing his child

psychology --

(Laughter.)

DR. KRAL: Now then, I'd like to make a constructive suggestion and that is that a case control type of trial method could be appropriate in which the -- and I'm not talking about randomized, that's off the table now, I hope.

For example, available treatment would be a case control or possibly best community standard. There's going to be an awful lot of argument about whether it's best medical or whether it's optimal medical.

So case control strategy to me would be the way --

CHAIRMAN NELSON: How would you find control cases?

DR. KRAL: Easy. The pool of interested candidates for treatment would appear in any pediatric clinic or office and it does not require randomization process to be able to find --

CHAIRMAN NELSON: I guess the reason I ask the question is if --

DR. KRAL: We're not talking about these urgent cases and all these --

CHAIRMAN NELSON: These are not the people who show up wanting surgery, but somehow you're finding them and they've not made the choice to come seek to have surgery. So if you found them beforehand, I guess it undercuts in my mind that they might not be interested in randomization. But --

DR. KRAL: I'm not asking randomization.

DR. ROCCINI: You could do it two ways. You could do people at an institution where a candidate for the study and then refuse to go into the study because they didn't want to take the risk of say a surgical study. And then you could use them as case controls, except that they had a different motivation whether they wanted to go into or not.

Or you could do a second approach where you would have some centers who are in this study and then other centers who would like to be part of this, but are not in the study and then therefore don't have the ability to do the particular procedure that you want and so the standard of care on those centers

would then could serve as your case controls.

DR. KLISH: I see large numbers of those patients. They come in for medical therapy, know about surgery, but don't want surgery and they are the same age, same weight, the same gender, so they could be case controlled.

DR. KRAL: This very discussion was in the SOS study, the Swedish Obese Subject study where the ethics committees of all the involved universities and agencies said that we cannot randomize, we cannot randomize in this SOS study. So there's a registry study and then there's an allocation of reasonable case controls to this surgery or the intervention group. That was for adults.

CHAIRMAN NELSON: Let me go to Dr. O'FAllon and then Dr. Newman and Dr. Rappley.

MEMBER O'FALLON: The thing that's bothering me is that we haven't really talked about the effect that these different designs will have in terms of the patient populations they provide.

Now one of the problems -- we'll just start at the beginning. Those early studies that have

produced those dramatically wonderful results have been on selected patients and it wasn't a "you all come" thing at all. Those patients were chosen.

So we know how the treatment works in those favorable and in some sense, perceived favorable populations. And so it is a problem when we start to move it out to beyond that group of people and especially what I'd like to point out is that children -- I've heard all of you talking about the fact that children are different in subtle ways. And in particular, they do grow and they do mature and what effects on adults may not predict some of the potential bad things that could happen, good things too, but bad things that could happen to the kids.

So I think we have to be really careful about choosing designs where we just pick people. I'm really concerned about that.

Now case control sounds kind of good. It's better than just picking, but the problem with case control is you have to have some sort of idea of whether the factors that are going to affect the results and sometimes we know them going in and

sometimes we don't. And that's where the randomization comes in, that if you have randomization, some of those things we don't know about are being equalled out by just the flip of a coin.

So that's one of the reasons for having them. But -- and the problem here is that sometimes treatments are harmful. We've been talking as if treatment is always going to be good. There are times when treatments are bad, when they hurt. And so we have to be careful about those things too.

So anyway, I want to say be careful about drawing conclusions based on pilot studies or early studies because they may not predict what's happening as we open up the patient group.

CHAIRMAN NELSON: Tom?

MEMBER NEWMAN: A very small point of request, case control studies has a particular meaning in epidemiology, what kind of study and the cases are people who have had some bad outcome and the controls didn't and what the study design being referred to here I think is a matched study. So if you could

refer to it as a matched cohort study, one of the people who get the procedure are matched to people who don't, because it isn't the case control study.

CHAIRMAN NELSON: Thank you for that clarification to us non-epidemiologists.

I'll get you, but I want to go to Dr. Rappley and Dr. Botkin and then I'll come over to Dr. Choban.

MEMBER RAPPLEY: I still haven't heard how -- which would be the preferable method to look at the safety issue? It seems to me that only the randomized method would allow you to look at the long-term safety issue of restrictive and malabsorption, the outcomes of those.

But maybe I don't see another way. So enlighten me.

DR. KRAL: Malabsorption is not on the table. You keep repeating malabsorption . Malabsorption is not part of it.

MEMBER RAPPLEY: I thought we heard some information at least that I read from yesterday was that even with the restrictive methods, there was some

degree of malabsorption.

CHAIRMAN NELSON: I think if we use that structure function distinction and we think of the variability that devices could do, some may well affect function dramatically. You've got minor structural to major functional changes and so -- I think -- I'm going to go to Jeff and then to Dr. Choban, but one lesson I learned in the antidepressant experience was that absent the placebo group, you couldn't see the safety signal.

So I think -- there may be -- that may be a hard question to answer, but I think we should spend a little time, at least thinking about it. But let me see what Jeff wants to say, then Dr. Choban and Dr. Klish.

DR. BOTKIN: I'm wondering if the primary outcome measure is change in BMI by some measure, whether that would adequately be addressed by having the participants serve as their own controls with a six-month standard therapy period of time or medical therapy period of time followed by surgical intervention and observing for BMI changes in that

group.

And it does seem for secondary outcome measures, changes in risk, blood pressure, lipid levels, etcetera, that you do need some sort of external control population and that the match design may be necessary for evaluating those. So that was just to float that idea.

CHAIRMAN NELSON: Dr. Choban.

DR. CHOBAN: I guess that it's trying to take sort of this theoretic view of this study design and then coming back to surgery is -- it tends to be like when you admit people to the hospital and you take them to the operating room, you start incurring all these costs that are more than just usually putting somebody in a drug study. And so who pays for this?

And the need to have a pair source of some sort for these long-term studies if we're going to say we need this, it's a real problem in real life when the patient shows up and they lost their job because they used to work at the car manufacturer and they don't exist any more, of how we get your labs drawn

and those kind of issues.

So I think particularly in these -- in kids, you know, how you're designing these trials and you're saying that the manufacturers are going to pay for the whole OR? And the whole length of stay and all these -- so I think just as a caveat, as you figure this in and you're trying to figure out where you get your -- not -- whatever the right word is, your matched controls --

CHAIRMAN NELSON: Your matched controls are easy, because they're getting what they would have gotten, the intervention group --

DR. CHOBAN: Where do they come from? In adults study in almost every series of adult gastro-bypass patients anyway, of people who show up and want surgery, and the surgeon's feel they're appropriate candidates for surgery, we can only get about two-thirds of them through the system, usually because of pair issues. So there's this third cohort that at least when you look retrospectively, matches kind of disturbingly well except on the issue of race.

They're as sick. They're as big. They're

as diabetic. They're as hypertensive, as the people you get to surgery than the others. There may be this other cohort that you end up with the system you're unable to treat. So --

DR. INGE: But that's off the table in a device trial because the manufacturer does pay for it.

DR. CHOBAN: The whole thing?

DR. INGE: Sure. Absolutely. Even complications are in the contract.

CHAIRMAN NELSON: I think there's a difference when you get into that environment. Having had some experience at least watching what happens in other surgical trials, there is a tension between those who can pay and those who can't pay and then even with third party payors when they hear it's research deciding how they're going to pay for what would otherwise be considered standard care. And so it's a complicated issue, but I'm not sure it's something that we can solve beyond saying yeah, it could be a problem.

I've got Dr. Inge.

DR. INGE: And this may just be

repetitive, Ron, but it just seems as though you might get more efficiency out of the time here if we did common and specific devices because I think there's a lot of talk about this nebulous device where John feels like and I do too that it's not ethical, it may not be appropriate or feasible to put someone to sleep without any possibility of benefit, but if, in fact, the decision is something that doesn't require going to sleep or doesn't require major risk, then you might well design something differently. So again, I would just throw it out. It's so difficult to have this discussion and have any real meaning to it, I would think, unless we --

DR. YUSTEIN: I realize that and that's why we're looking for general principles. We know that there's going to be situations where it's going to require flexibility on our part to kind of take that into account and there's no way you can address all of the different possibilities, but there are devices that require less invasive placement techniques and some that may, in the future, require noninvasive. So we're looking for general principle

guidelines and you certainly may not be able to give us all those now.

CHAIRMAN NELSON: Dr. Pories.

DR. PORIES: We've actually published two randomized studies in the morbidly obese patients. The first one was a simple test on antibiotics, but the second one was the two groups at two different operations, signed consent for both. They were blinded. The nurses were blinded. Sometimes our surgeons are a little blind too --

(Laughter.)

You can do that ethically. We also have a study in which those patients who were turned down by insurance, but had been scheduled for surgery were used as match controls. There was a little difference in race, but not much. But frankly, that works pretty well.

We've also tried prospectively to randomize people to surgery versus nonsurgery and it just couldn't be done because if we turn them down, they simply just went somewhere else.

CHAIRMAN NELSON: The only trial that I'm

aware of that's doing that, there's no back door to where you can get surgery elsewhere. So otherwise, I agree, that trial itself would fail too.

Dr. Newman and then Dr. Yanovski, and then I'm going to try to summarize a little bit. And see if we can get over to safety which is still on the table and not been addressed.

MEMBER NEWMAN: I wanted to address Dr. Rappley's question about how can you look at safety issues without a randomized trial and it depends entirely on what outcomes you're looking at. Certainly, there are some outcomes, esophageal problems, problems with the reservoir, problems with the device that just are not going to happen in any control group and you don't need a randomized trial to say that here is the rate of infection or device leakage, things that just -- so it's really other outcomes that happen periodically anyway, you know, acne or headaches or things that teenagers get, you're just not going to be able to address those without a randomized trial.

So it really is based on the biology of

the device and thinking these are the outcomes that this device is likely to cause and then being able to infer without a randomized trial the device caused this and you can get some estimate of how often it happens and just if you want to look at other things that happen that might not be related to device or we don't understand the biology, then you're not going to be able to do it without a randomized trial.

CHAIRMAN NELSON: Dr. Yanovski.

DR. YANOVSKI: I disagree.

CHAIRMAN NELSON: Let me just try and summarize what I've heard at the risk of hopefully not just producing more conversation.

Randomized control trials were discussed. I didn't hear a lot of support for those kinds of trials and maybe there might be limited circumstances where you might consider that, but by and large there wasn't a high degree of enthusiasm for that kind of sort of straight up, classic trial.

The kinds of trials that garnered some support, even if they were just mentioned briefly as much to be passed over, first we had had a large

discussion in the morning about the important of running phases. We haven't talked about that now, but I think it's worth keeping that there. And if you imagine a run-in phase, whether it's for enrichment of the population goes on to the second or whether it's -- which would be for adherence or for lack of response.

I mean there's various ways of viewing a run-in phase. It could enrich those who don't respond, so you have a higher efficacy signal or it could weed out those who won't adhere and so you have -- but for whatever reason, a run-in phase.

And then possible designs after that. One would be the crossover design. Everybody who wants a device would eventually get it, but they'd be willing to wait whether it's two months or three months or four months, it might depend or six on the nature of the device and the nature of the population.

Then there's the -- what I would call a single arm trial with the matched cohort which would be everybody who wants the device gets the device. Everybody who has followed, but doesn't want a device

gets part of the matched cohorts for non-randomized and then you've got to worry about comparability to groups.

And then the patient is their own control which is sort of the run in baseline and then change from baseline would be another potential design and I know that's used in a fair amount of psychological interventions where you have change from baseline and you have a delayed intervention which would naturally occur just from the fact that you're enrolling these people over time.

So those are sort of the -- I may have skipped one that might be your favorite, but seem to be the kinds of designs people are thinking are more appropriate in this kind of venue in general with some outliers, depending upon the trivial nature of an intervention perhaps, if it doesn't require penetration of the skin as opposed to orifices for insertion, etcetera. I mean different ways we might design it, depending on the risk. But that seem to be what I heard. Is that fair?

And then -- but I guess the safety issue,

is that -- is there more we can say about that or are we just not saying a lot about it because it's hard to say or is it because there's not much more to say? We had a little bit of discussion of that with tautology that Dr. Kral gave before, but it would be difficult, I guess, in any of these designs, other than the mass cohort design, to determine safety, I guess, would be hard to say. Is that fair? No? Unfair?

Dr. Pories and then I'll go over here.

DR. PORIES: Well, there are two concerns. One is the obvious one, putting in the device, how does the device work and does it travel and so on? But the other one is what are the long term effects of these and that they may be quite substantial. So I think you have allow more room in this kind of device that deals with nutrition in growing children than you would, let's say, with someone like a cardiac pacemaker in an old man.

CHAIRMAN NELSON: So the length of time would have to be different.

DR. PORIES: I like the idea that you talked about of getting a two-year -- you didn't like

my word provisional. I sort of liked that, but it's not official. But the idea that you come back after two years and look at it again, but the study will continue.

CHAIRMAN NELSON: So one way of phrasing that would be you'd have a five-year study, a two-year assessment of safety and efficacy in that window. Everyone is enrolled, stays in that. For those the next three years, there's a fairly high intensity safety and efficacy component follow-up, but that's very different than if you had a long-term registry which may not collect all of the same kind of data in a registry fashion which would be much more limited.

AUDIENCE MEMBER: Well, you ought to have -- let me emphasize since I run a registry, that you must have a registry.

CHAIRMAN NELSON: Well, we'll get to that, but I'm just making that distinction because registry would be less data than you would have in another three years of a study that everybody had already consented to.

Dr. Garofalo, Newman and then --

MEMBER DAUM: Could I say one thing directly to this comment or would you rather I wait?

CHAIRMAN NELSON: Feel free, go ahead.

MEMBER DAUM: So I think that the only downside of the two-year or five-year approach is that there's no provisional part to it by FDA rules. So what would happen then is it would be licensed, so you'd have people continuing in a trial that went three more years being observed, I guess, mostly if there's not a control group, for example. And it would be licensed which would allow theoretically greatly increased use.

Now if something went wrong with a three to five-year follow up, the downside is that people would then be using this device freely and it would be very difficult to intervene at that point. But otherwise, I think it's a good approach.

CHAIRMAN NELSON: I'm sure if it was a serious enough safety issue, the FDA would figure out a way to intervene.

MEMBER DAUM: I like the approach. I mean that's why I brought it up this morning. I think it's

potentially a good sort of win-win.

CHAIRMAN NELSON: Dr. Garafalo?

DR. GARAFALO: So along those lines, I just wondered if there should be some discussion about a formal data safety monitoring board, so if the trial is on-going some way to look, have an independent body that looks at serious safety problem. It might not be necessary, but sometimes it's reassuring. I just wanted to open that up.

CHAIRMAN NELSON: That was a question raised under 4. We can discuss it here as well for the kinds of safety monitoring that you would want to have to be on-going.

Dr. Ward or Dr. Newman, do you want to dive in at this point?

MEMBER NEWMAN: I wanted to come back to the safety issue and how long you have to follow people and whether you need a trial. And I thought of another example. I'm just trying to look up and see if I have it right, but I guess I want to ask that people who are experts in this device, whether they think that we can -- we will be able to infer

causality for all of the likely adverse effects that might be seen. And the example that occurred me, I was just trying to look up, was the silicon breast implants, you know, where there everyone said these things are inert, they can't possibly do anything.

And maybe they didn't do anything, but that was where if there had been what would have had to have a gigantic randomized trial, one would have been able to say sooner more definitively whether collagen vascular disease or whatever it was that was associated with them or thought to be, whether that was causal.

That's the sort of thing that would be if devices might cause something that right now we're not thinking about at all, then maybe we would want a randomized trial with a long, long follow-up period. I'm -- that's how confident we are that we understand the biology.

DR. WARD: I would maintain that you could obtain the same data from what's been described as this current study design if you had an unoperated set of patients and then you have another group, if we

heard about steatosis this morning, that might be increased by extremely rapid weight loss, so this optimal therapy may have adverse effects that are not adequately anticipated.

I think having a two-year trial is essential, but then a longer term capture of data would be very important. Those who are very knowledgeable about nutrition and about potential deficiencies may be induced.

CHAIRMAN NELSON: Let me ask a question of those who deal with this population. If the argument in favor of a mashed cohort design, single arm device is based partly on the sort of choices that these children and their parents would make over time, what's the odds that those who selected not to have surgery will continue to select not to have surgery so that -- and that your matched cohort would eventually become a surgical cohort?

Do they generally stick with their choice not to have surgery regardless of how well the nonsurgical interventions are working?

DR. KRAL: There's not enough evidence on

that.

CHAIRMAN NELSON: Excuse me?

DR. KRAL: Not enough evidence.

CHAIRMAN NELSON: We don't know.

DR. KLISH: At the present time, there's so few done in adolescence you don't know. It hasn't gone through that community, but my feeling to date is that they select what they want when they come in to see us.

DR. PORIES: With adults, they stick to a decision.

CHAIRMAN NELSON: Adults stick to it? Okay.

DR. CHOBAN: And I think part of the adults, when it's not been entirely their choice, but a choice, if you will, hoisted upon them by the lack of a payor, they switch jobs to try to get other insurance. They've decided they want surgery. There's a lot of people who --

CHAIRMAN NELSON: So their choice may change, but their choice doesn't change because they're just trying to make their choice more

effective is what you're saying? They just find ways of getting what they want.

DR. CHOBAN: They find ways. If they've decided that that's what they want, they tend to find a way, at least in adults.

CHAIRMAN NELSON: To make it happen.

DR. CHOBAN: With kids and parents, that interaction and also is the kid then becomes more -- gets older and fights for the decision more. I don't know.

CHAIRMAN NELSON: It may be difficult. Dr. Kral?

DR. KRAL: With adults, they will change their mind regardless of those kinds of constraints. I've had patients 10 years, 15 years have surfaced and they say you don't remember me, Dr. Kral, but I talked to you about surgery once. I'm ready now.

CHAIRMAN NELSON: Dr. Rappley and then Dr. Gorman had their hands up.

MEMBER RAPPLEY: I'd like to ask the gastroenterologist and endocrinologist if you think that two to five-year frame would allow appropriate

assessment of the kinds of nutritional problems we might anticipate with very restrictive diets in growing children?

DR. YANOVSKI: Seems like a reasonable period of time of follow up to me.

DR. INGE: I agree.

CHAIRMAN NELSON: Dr. Gorman?

DR. GORMAN: Realizing that the pace of change in this particular area may be much more dramatic than we might suspect at the moment, I could imagine study designs either with a data safety monitoring committee or timed interval analysis with set endpoints that the agency and the manufacturer could agree on that would allow a device to come to market before the end of the study so that there's demonstrated efficacy and no strong safety signal at some fixed time before the end of the study. It could come to market. The study would continue.

So I think that part of what we've talked about is I think we have this desire to have all the information before we let something go forward. I think there needs to be some appreciation that we may

not have all of the information that we want before we let something to market, realizing that there may be something right behind that that makes this whole discussion of that particular device obsolete by the time we get the five-year study finished.

So we're thinking here and I've been very impressed with this lap band technology and tomorrow there may be something come out that will make it completely obsolete and this discussion will be -- so I would like to consider or have the agency consider some fixed time intervals where they'll do evaluations of both safety and efficacy, allow something to come to market while the study continues.

CHAIRMAN NELSON: Okay, Jeff?

DR. BOTKIN: From a safety perspective, it seems that there are probably two types of issues. One would be device related in which case, obviously, whatever the specific device was, you'd have to assess the anticipated safety issues, but there also seems to be a standard set of nutritional concerns that would cross all weight-loss devices.

And so I wondered whether nutritionists

and others who are knowledgeable here would be able to put together a sort of standard package of longitudinal assessments of key nutritional parameters that would be relevant across-the-board for these types of devices.

And then a second point, I would want to include individuals in either the registry or the longitudinal study who have had the device removed and make sure those folks don't drop out of the study design, but you continue to follow them for any longer term adverse effects from the device.

CHAIRMAN NELSON: Let me -- go ahead.

MEMBER O'FALLON: You know, we haven't even mentioned things like sexual maturity or any of those issues and they could be even further out than that in which case I mean we'd have to device about how to deal with it, but maybe that will go into that registry thing.

CHAIRMAN NELSON: I've got a couple of hands.

DR. INGE: It again dawns on me the ridiculous of some of this in that I can tell you from

experience in the bypass population which is granted a more risky operation that we have no, not the same degree of federal scrutiny of but that's a separate comment, that the nutritional consequences really were not adequately or were not completely divulged yesterday. Really, are quite undisturbing.

In other words, for an operation that has a very significant degree of restriction in some malabsorptive components, that from the standpoint of macronutrient adequacy, albumin levels in let's say lean body mass is quite reassuringly preserved with current management regimens, out to several years.

So I don't have those concerns and I think that probably the fact that this is a restrictive device that's -- well, if we're talking about the band, a restrictive device that's adjustable, we would have fewer concerns about micronutrient deficiencies than we have with say the bypass as well. And the micronutrient deficiencies with the bypass are thankfully few.

So again, it's sort of informing the designer, informing the endpoints, if you will or the

safety endpoints for a device from a population that's arguably been exposed to a more significant intervention.

CHAIRMAN NELSON: Dr. Roccini and then Dr. Kral.

DR. ROCCINI: This may sound a little crazy. I think we would greatly benefit as part of all these potential device trials for weight loss management with the initiation of a national obesity registry which we keep track of patients who are obese or children who are obese over a long period of time that could be used as case matches to look at long-term side effects and the like and be potential candidates for these new device trials and could use these industry-sponsored device trials as a means to support and subsidize such a long-term registry, a little bit like what we've done in Sweden with their obesity surgical trials.

CHAIRMAN NELSON: Dr. Kral and then Dr. Pories.

DR. KRAL: Although I earlier today pointed out that under nutrition or deficiencies can

be relatively easily handled. I have to protest a little bit against Dr. Inge here. There is evidence indeed over the long term that even a restrictive operation does have certain prevalence of deficiencies that are discovered mainly because of patients who have not come back to be monitored to know whether they are going to be deficient or not on the one hand.

And unfortunately, there's evidence that adolescents are particularly vulnerable to develop deficiencies over the long term after obesity surgery.

CHAIRMAN NELSON: It sort of raises two questions. I'll go to Dr. Pories with just looking at the question and I don't know if we've really adequately addressed one, I think can be, and that's -- my impression is when we talk about concurrent diet, exercise, behavior modification that a lot of our assumptions is that device trials would be placed on a foundation of appropriate interventions and it's not as if we wouldn't provide concurrent diet, exercise and behavior modification.

The question is is it standardized as opposed to a confounder which could be variable over

the course of the trial and provide a confusion to the interpretation of the results.

The question you raise and we haven't really talked about assent, transition to adulthood, the adolescent decision making as part of this trial process and haven't focused on that per se. I guess it would be nice to do that even if it's a brief conversation, but at least think about that for a second.

Dr. Pories, you wanted to make a comment?

DR. PORIES: The American Society for Bariatric Surgery has been concerned about registering and so they have a program in the Surgical Review Corporation which is a nonprofit of identifying centers of excellence. We now have 106 centers, have all combined into a consortium and as of about a week ago we had 47,000 patients in that database that is prospective and one of the important things is that the care paths, anti-operations have standardized to go prospectively.

So we do have at least a pretty good beginning on the registry program.

CHAIRMAN NELSON: Who is paying for it?

DR. PORIES: The hospitals and the surgeons. There is no industry involvement. You may have remembered that when I introduced myself initially I said I happen to be the chairman of that. I said there is a conflict that you ought to know about --

CHAIRMAN NELSON: You're paying for it with your own money, so I guess it's a little bit less of a conflict.

DR. PORIES: We're sort of proud of it.

CHAIRMAN NELSON: Okay. I thought we would just ask Jack, although he's intramural, whether we could dig into NIG's extramural pocket, but that pocket is getting thinner and thinner over the time.

DR. YANOVSKI: I don't have control over anybody's money.

CHAIRMAN NELSON: Well, we've got a little bit more time before the break or we could take a break now, but I think we really haven't talked about issues of assent, the role of the adolescent in this per se. We've talked about trial designs. I mean

thoughts specifically on those issues?

We'll go Norm, then Jack.

DR. FOST: Well, it seems to me all the speakers and all the papers speak to the need for really a strong commitment to carry through on these sorts of enterprises. It's not just a procedure and we don't talk to you again. And that commitment, therefore, requires a willing family and a willing patient.

So it seems to me the standards for assent have to be very high. I mean it can't just be a formal sign something. There has to be a real evaluation that the youngster is really interested in this and is committed to it and eager, wants to follow up and so on. So it seems to me it has to be a very high standard.

CHAIRMAN NELSON: So here the ethics and the efficacy fit together I guess.

Jack?

DR. YANOVSKI: So there are two issues, first one, I couldn't agree more than careful attention to assent and I mean I suppose we could be

more directive than that of discussing that assent should be obtained perhaps away from the family. That should be a consideration perhaps, so you can assure that the adolescent really doesn't want to do this. It would be very difficult in the family situation to get a real view of what the adolescent wants to do.

And the second issue is that since these trials would be two to five years, many adolescents will be achieving their majority and so provision has to be made for a re-consenting of the previously assented individual and then the transition, in terms of confidentiality and information. So both of those have to be part of the trial design.

But at the risk of beating a dead horse, although I heard someone say randomize designs are off the table, I really feel strongly that we ought to not necessarily take them off the table, particularly for the widget design. Even for the current experiments that might be imagined, the fact that the way trials are constructed now, those patients have come to a center because they decided they want to have surgery does not mean that with appropriate advertising and

outreach populations could not be constructed that would be willing to participate in randomized designs.

And we know perfectly well that the standard of evidence, the reason why the standard of evidence is ranking for randomized trials highest is because we really do get reads both on efficacy and safety that are unmatched. And although you do need large populations, large samples, I should say, to get good reads on safety which is always a major concern, so even in the drug trials setting 1500 or 2000 people is nothing, compared to what's going to happen when you have on the market and have hundreds of thousands, if not millions of people using medications.

The same holds true for surgical interventions. So appropriate sample size to pick up the biggest problems are necessary, but we won't be picking up the rare events in these trials. So we have to -- we should probably also be talking about what kind of samples we're going to be asking to be in the studies because if the effect sizes are as large as what we've seen for the adjustable band, it's not going to require many subjects for efficacy, but we're

going to have to specify safety levels of what rarity of adverse event we want to be able to detect.

CHAIRMAN NELSON: How about if over the break I ask Judith O'Fallon to give us a calculation of -- after the break -- about the sample size for these different trials? Is that --

(Laughter.)

I've got a computer you can borrow. Tom's got his computer. Deborah and then Paula, and then we'll take a break.

MEMBER DOKKEN: I think my comments relates as much to consent as assent because what I've been struck with certainly in the last two days is we're talking about a vulnerable population, both the teenagers and their families, who have been struggling with this condition and what it means, both physically and emotionally. And then I think a lot today we've been talking about long term, five years beyond and basically what I heard in a layman's message is that it's not just the surgery, it's a lifestyle change that requires a real shift for the patient and for the family, as long as the patient is still within the

family.

And because, yes, we're talking about clinical trials in the design, the whole purpose is then eventually it goes beyond trials. And just how always that that importance of the real dramatic lifestyle shift is always a part of the message of this because I have this awful feeling some time down the road we may see some of these devices on TV just as we see pharmaceutical products.

You know, that a lot of information that may be important like you're going to have to change your whole life isn't always part of that. So we're certainly not there, but I just don't want that left out and it does relate to in the very beginning to consent and assent and do people know that they're taking the life style piece on as well as the procedure.

CHAIRMAN NELSON: Paula?

MS. KNUDSEN: I'd like to say we're now talking about a longer term trial than we had earlier. And what I would like to be certain is that there will be a sharing of data to advise families of the

most up-to-date data, both positive and negative. And I don't know how manufacturers will feel about sharing proprietary information and it's very concerning that they'll be acquiring data that will not be made known to new families coming on board into this now longer-term study.

CHAIRMAN NELSON: Let me just make a comment on that and then we'll take a break and if I could also ask, I know there's some people that may be catching planes before the end of the next session, two people have talked to me. If there's other people besides the two that have talked to me, just let me know, but there are surgical trials where the consent form has been changed to each case it goes. So it raises an interesting question as to whether a new device trial there ought to be clear guidance about the information that's provided which is very different than a drug trial as to whether or not -- you put this in 47 people and this is what's happened.

It's an open question, but I know that there are approaches to surgical trials in the pediatric arena that have used that approach of saying

we've done this in 47 people and each time it's 48, it's 49, it's 50, it's 51 when it's an early trial.

And the IRB does have to approve it within the period of time it takes to do that, as a minor change.

DR. YUSTEIN: We do that fairly often and change the informed consent as gain information and then if you're talking about a post-approval study as part of a PMA, those sponsors are required to submit annual reports and those annual reports contain additional updated information, as well as the reports of the condition of approval study which can then feed back into revising the informed consent for patients still enrolled.

So there's mechanisms to incorporate new information back to the patients.

CHAIRMAN NELSON: Okay, well, let's take a break and then start again at 5 after 3. Is there anybody who is going to be leaving during the break?

(Off the record.)

CHAIRMAN NELSON: What I'd like to do, I'd like to do, I've asked one of them to open with some

remarks and then to be followed by a second. And that way they have an opportunity to sort of say their last word before they split and then we can pick them apart after they've left.

(Laughter.)

So I think we've covered a lot of territory. I think there's two things that we need to accomplish before the end of the day, depending on when that end of the day is. One is to pick up unanswered threats and the other is to tackle the fourth question which really relates to long-term safety and efficacy. We've talked on that off and on.

So in the interest of seeing what threads there are to pick up, there's a few people that are going to be leaving. I've sort of asked -- at a 3:15 shuttle to go to the airport -- two of them. I've asked Dr. Inge to just make some remarks before he goes where he sees some loose threads are that we can then pick apart after he leaves.

And then Dr. Lustig will sort of build off those remarks and then the people that have to catch a shuttle will be excusing themselves and we'll go on

with our conversation.

So Dr. Inge.

DR. INGE: First of all, I just want to thank the FDA for taking on this issue and I certainly think that I've learned more than I've offered during this time, but the real -- we've talked about a lot of important issues and the ones that still are unresolved that I think will be figured critically into this process will be the entry criteria, for instance, and in particular, while I applaud Silva's throwing up a potential to talk about with a BMI percentile of 95 with comorbidities and a percentile of 99 without, I really think as a surgeon we have to write letters of medical justification for a high-risk intervention and I just -- I think that's appropriate.

I think that we have to be medically justified in offering this. And the data that I've seen thus far would indicate that medical justification can only be established when you're treating the comorbidity.

And so I would strongly suggest having a comorbidity as a basic intra-criteria and although it

is somewhat arbitrary, having a BMI centile that's singular and probably 99, which seems to correlate at least in the unpublished data that Bill Dietz shared with us, correlate with a level of adiposity that's roughly commensurate with morbid obesity in older age groups would be appropriate.

The other issue is that I'm entirely in agreement with would be a staged approach where an initial trial may be done in adolescents of say 12 to 17 year olds and then considering younger age groups, I think is entirely reasonable.

The notion of a 6-month lead in within the institution or within the program that the surgery is going to be done, to me, is another area of question. In fact, it might be more appropriate to consider a six month period where an individual has not made successful weight loss milestones in his past in whatever organized attempts were available to him or her might be more appropriate. And then certainly it would require a month or two of program observed follow-up to really get the sense that this patient is going to be compliant would be my recommendation.

The final thing is that during that month or two of observation that we do look for no weight gain and in fact, our program I think that we've realized the benefit to seeing them lose weight during that period as one other indicator of compliance with a health care provider's recommendations.

The notion of a multi-disciplinary team with pediatric expertise and also with either pediatric surgical or adult surgical bariatric expertise cannot be over-emphasized.

And then just to echo again the endpoint, I think, of primary relevance to an operation whose goal is weight loss would be BMI change in my mind. So again, thank you for allowing me to participate in what I think has been a fabulous meeting.

CHAIRMAN NELSON: Thank you. Dr. Lustig?

DR. LUSTIG: I want to thank the FDA also. It's wonderful to see them being proactive rather than reactive. This is a problem that's upon us now and it's good to really get this out because this is a big issue and I applaud you for putting this together.

I agree with almost everything Dr. Inge

said so let me just comment on the things I disagree with and then you can take it from there.

Number one, I think the six-month lead in is absolutely essentially. We actually have a 12-month lead in because you have to fail two pharmacotherapies. I think six months is essential for those patients in whom the surgery would be considered elective. I actually think that there are patients who are going to require bariatric surgery that are not elective. I think because they're emergent because of either airway issues, because of pseudo tumor, etcetera and I think that those patients should be in a tandem design in separate arm. I said that earlier and I still think that's true.

Those patients really can't be randomized and they can't wait. They're sick and they need help and if they die they would have died anyway. No amount of standard medical therapy was going to help them. I think we have to be cognizant of that. I think we're doctors first and researchers second.

We have to help patients who are going to die before they die and I think that most patients can

be followed appropriate, they're going to go somewhere else and get it anyway or if they get their tracheostomy, they're going to go somewhere else and they're going to get the surgery. We might as well capture that data. So I disagree on that point.

The other thing I think that's very important is that obesity is not one disease. Obesity is a phenotype of many different diseases, for instance, we can't expect the melanocortin-4 receptor patients to respond in the same way as what you would call cryptogenic obesity where the same way is hypothalamic obesity or the same way as pseudo hypoparathyroidism. A whole slew of other causes.

There are about 18 different causes of pediatric obesity. And I think they're all going to ultimately be different in terms of their response to any surgical or device intervention and I think that it's incumbent upon us to know who they are in advance, so for instance, if you're 99th percentile and you've got a comorbidity, you ought to be having MC-4 receptor genetic analysis and that should be on the books as part of the pre-op workup prior to being

randomized into a trial.

So you know who these people are. It doesn't mean they should be excluded. It means that they may need to be post-op evaluated or stratified separately after the fact.

Those are the primary places where I would disagree with Dr. Inge. Other than that, I wholeheartedly support all of his comments.

CHAIRMAN NELSON: Thank you both for your insightful comments during the meeting.

What I'd like to do is at least put Question Four on the table so all the questions are before us.

I bear no illusion that our comments will be restricted to Question Four, but at least so that everything is there and as we deal with the issues people feel important to deal with, we get all that covered.

Question Four relates to long-term assessment. We've talked about that and these devices are going to be there potentially for quite a while and there would be a need for long-term safety and

effectiveness issues whether it's long-term safety issues or maintenance of weight loss, etcetera.

So basically some of the issues on future growth and development, future comorbidities, the importance of maintenance of weight loss, what that might even be, for what period of time and then the type of information that might be collected in a post-approval study which could be either with or without a registry, a registry could be considered different. And then the role of data monitoring committees which we've touched on and any other subject projections that we need to sort of talk about.

So those are the full range of the issues that by the end of the day and the end of the day will be five o'clock absolutely and could be earlier if we've exhausted I guess what we might say in the focus group world, if we've achieved thematic saturation.

(Laughter.)

We'll stop at that point as well, whenever that is achieved.

So let me at least start and say there's a couple of things on the table and if we want to clean

them up first or leave them messy based on Dr. Inge's comments, I'm going back to some of the earlier discussions about entry criteria. What I heard was more of an emphasis on the importance of a comorbidity and we're not talking endpoint analysis, we're just talking entry criteria and comorbidities could still be a secondary objective. We don't need to go there again.

The other thing I heard which one can interpret one of two ways was the importance of understanding the different etiologies of obesity and at least making sure that you know who they are when they're in the trial.

Now you could go two ways with that. You either leave them in, but then you've got a potentially messy trial if, in fact, they respond differently to your intervention than it would be if you don't have enough to stratify them to do any kind of meaningful subgroup analysis, that could get very confusing.

So it wasn't clear to me if you'd want to keep them in or exclude them, depending on what it is

and since it's not my area, we may want to just talk about some exclusions much more concretely. And then make sure we wrap up some of the other issues.

So why don't we -- those two issues that are sort of there, what -- the BMI and the comorbidity issue that Dr. Inge put on the table and then whether there's more concrete exclusions that we should perhaps begin to identify.

We'll go with Dr. Klish.

DR. KLISH: I agree with Dr. Inge regarding the comorbidities in adolescents making that an entry criteria because I do think at least at this stage of the game need to think of this as a disease that we are approaching and approaching it as a disease.

Eventually, I think, it will open to patients that don't have comorbidities, but I have a hard job in my mind justifying doing these procedures without any information -- on an adolescent population without having any information on risk without having the potential benefit of eliminating a comorbidity.

The second issue was -- I forgot --

CHAIRMAN NELSON: The exclusion issues --

DR. KLISH: I disagree a little bit with Dr. Lustig. There is ultimately I think genotyping is going to become very important and very interesting in terms of response to therapy, but we're just starting to explore that area in terms of response, based on various genotypes. Now he was also referring to some of the known genetic abnormalities that cause obesity. You said hypothyroidism and I don't know if you said Prader-Willi and things of that nature.

My feeling is at least in initial trials and my experience of Prader-Willi, I have extensive experience, we follow about 300 of them, that I would not include them initially in the study because I think they would become a confounding variable, just based on the other characteristics. And I think that's probably true of many of these other genetic syndromes that have obesity associated with them like hypothalamic obesity which is rare, but very complicated.

CHAIRMAN NELSON: Before going on to Dr. Yanovski and Dr. Kral, let me ask you a clarifying

question.

The thought occurred to me we have been talking a lot about the importance of a motivated adolescent and an assenting adolescent. What about children who are of the developmental physical age of an adolescent, but yet cognitively delayed in different ways? How much does that impact on the efficacy of whether it's surgical or nonsurgical interventions for obesity and would you exclude that group as well or is that a separate group?

DR. KLISH: At the moment, we are excluding that group within our program because we can offer that group alternate forms of therapy. You treat the retarded child very much like you would treat the young child where you're basically treating the parents and structuring the home environment. So at the present time, we're not offering surgery or we do gastric bypass, but offering that surgery to that group of individuals.

That doesn't mean eventually we might, but I still think we need more information about risk before we start opening the doors to all those other

what I consider vulnerable populations.

CHAIRMAN NELSON: Okay. Dr. Yanovski?

DR. YANOVSKI: So I guess it may be reiterating a position, but I agree with Dr. Inge that at least in the beginning folks with a centile over the 99th are probably the more appropriate group to begin such treatments with and again, those with comorbid conditions, I agree with Dr. Klish, who said that's the group that has the higher prospect of potential benefit in therapy, especially in an unknown widget therapy which we've been asked to consider.

But I think we should in the context of trials allow latitude for investigations to include other populations, perhaps, of lower BMI under very careful conditions and after the initial efficacies have been shown for perhaps more significantly ill children. And similarly, when it comes to including or excluding children in the beginning, the individuals with the unknown obesity causes and the healthiest mentally would be the ones to choose, I agree.

The point of the rare genetic disorders, even in the melanocortin-4 receptor indication which are mutations which are believed to be the most prevalent, perhaps, it's only 3 to 5 percent of the super obese and in most series, so okay, maybe 7 percent. So it's still not going to be the majority of patients. It's going to be difficult to have a valid analysis of that group. So it may behoove the investigator to exclude them, but at least they should be aware of who is who.

It might be appropriate to stratify or at least to randomly allocate such individuals without an intent to evaluate them separately, but at least to assure quality between any groups that are randomized. They might want to know that information.

I agree also that groups with Prader-Willi should certainly be parts of, if every study, separate studies where we expect the response to be significantly different.

CHAIRMAN NELSON: Dr. Kral?

DR. KRAL: On the issue of comorbidities, I think it's extremely important that there be a menu

of comorbidities and a table of contents or a menu of methods that are used to determine the comorbidities. And why I'm making a point of this is I've studied this for so many years. We heard several times earlier that where you look -- if you look, you find. If you don't look, you're not going to find.

Such phenomena, for example, a relaxed lower esophageal sphincter is not necessarily going to pop out of anybody. Even a ventricular hypertrophy is not going to pop out at anybody. But when you start looking for it, you're going to find it and you're going to find rather often.

So to have comorbidity inclusion as an inclusion criterion in that case it has to be very stringent definition of these comorbidities, then it's going to be one of the -- I don't know if we have to go Oregon to get the public to vote on which ones they think are more important than the others, but that is not an easy task to get a rank order, though I think we will all immediately agree that pseudo tumor cerebri and sleep apnea are way up there, but we can wonder about endotrico * (3:26:26) and I will, in

distinction to what Dr. Lustig had said before, I really once again want to emphasize that quality of life impairment is a comorbidity of substantial importance.

CHAIRMAN NELSON: I see no hands. I'm actually looking up, I'm trying to find the website that Dr. Pories had mentioned for the labs at NIH because he showed me some of that -- Google is not bringing up the exact site at this point, but -- is it under NIDDK?

DR. KLISH: NIHNIDDKLABS. You have to be an investigator to get into it.

CHAIRMAN NELSON: Ah. I don't have the secret handshake.

DR. PORIES: You have Dr. Yanovski here who's wife runs that.

CHAIRMAN NELSON: Right, so one question has come up and this is obviously something we can't do today as to whether some of the instruments that are part of this might be adaptable to the pediatric setting, but I mean that's obviously a level of detail we can't drill down to in this conversation, but you

know so here's the site for those that are curious.

So what about the long-term assessment? We've talked about registries. Just to sort of summarize where we've been, what I've heard is efficacy two years; safety, two years with hesitation, meaning two years might be okay to let it come out into use, but you ought to look for five years at least to make sure things aren't a problem within that trial. The question which I'm assuming is uncontroversial, the need for longer follow up in a registry format, potentially, of the individuals who have these devices.

And we've talked about what you might see within that five-year trial within that three-year period which would be a fairly intensive sort of nutritional and safety follow up.

What about in the registry? I mean one of the questions is two-fold, what is maintenance of weight loss and what period of time? How long is long enough? What type of information would you think is important in that registry format post-approval?

Dr. Pories?

DR. PORIES: Again, I think that's reasonably worked out. Obviously, with diabetes, it's quite easy. What is there, glycolylated hemoglobin. We have look at the back term employment, how bad is the arthritis. We have a scale for that. So I think there are scales.

Much more difficult are the problems with terms like neuropathies that go even into paralysis and blindness and somehow you've got to be able to pick those up.

CHAIRMAN NELSON: I could see registries would have to be either passive or active. I mean it's one thing -- the first question is would everybody who gets a device from -- if this was accepted, be registered period? I mean in other words, it's in you, you're registered. Everybody or -- the problem is if it's not everybody, then who do you pick?

DR. PORIES: Everybody would.

CHAIRMAN NELSON: Everybody, all right. So then you've got everybody. Then the question is do you just rely on sort of a passive reporting system

much like where something big pops up, they go see their doctor for a problem and the doctor says ah, you're in the registry, I'm going to send it in, or do you have an active sort of case report form that gets filled out every year, filled out every two years. I mean where the individual in the registry, say like the nurse study which my wife happens to in. We get an envelope that she fills it out, sends it back. And is it sort of like that, where you do that constantly and you can even ask other questions, etcetera.

So what do people see that registry being? Let's forget the money for the moment. Let's --

DR. ARSLANIAN: Active plus GPS.

(Laughter.)

CHAIRMAN NELSON: Active plus a chip in the device, GPS.

DR. ARSLANIAN: I'm serious.

CHAIRMAN NELSON: I don't think even the Patriot Act would allow that.

(Laughter.)

DR. ARSLANIAN: Especially the modified one.

DR. YUSTEIN: If I could just make one comment on the registries. FDA doesn't do registries. We can ask companies as a condition of approval to do a registry, but you have to remember that's usually the company doing it, unless professional societies step forward and try to coordinate registries across products. If that doesn't happen, then it's usually the individual company doing their own registry, but we don't do registries here. NIH does some. I think CMS does some for some of their Medicaid patients, but FDA doesn't do the registries here.

CHAIRMAN NELSON: Let me just ask a question. Would it be useful for us to spend some -- I mean we could spend some time thinking about the logistical problems of what at most you could require which would be a sponsor-specific device registry, device by device by device. I mean if we thought that was important, at least then you'd want to be able to have uniform data across devices --

DR. YUSTEIN: Sure. If there are certain items that you believe that are important to collect for all kinds of devices in a registry and for how

long that registry should go on, yeah, that would be very helpful.

CHAIRMAN NELSON: Well, then let's take length of time first. That might be easier. Five years, 10 years, 20 years, 30 years?

I hear age 30, I hear 10 which if he's going into an adolescent gets close to 30. I've heard 5. So -- but 10 seems to emerge more than less.

DR. YUSTEIN: Can I nominate permanent?

CHAIRMAN NELSON: You can, but it might -- we always want more data than less, but the reality is if -- let's imagine it's a device -- it's a condition of approval where the sponsor is being asked to do it, what's a reasonable period of follow up time, 10 years or 20? This is an adolescent. Let's say it's in a 12-year-old.

DR. KLISH: It's difficult to go much further than five years.

CHAIRMAN NELSON: Logistically.

DR. KLISH: Logistically.

CHAIRMAN NELSON: Logistically.

DR. CHOBAN: In the face of devices that

are obsolete in six months.

CHAIRMAN NELSON: Dr. Kral?

DR. KRAL: Well, should we take the example of the lap band? It's supposed to be in there for life. Now if you buy an appliance, how many years would you like that to be? If it's guaranteed for life, that's a pretty good thing, isn't it?

Here's what I want to bring up. Same point I made before about comorbidities and the diagnoses. The same thing has to pertain to complications or side effects of a device that are specific to that device. Let me take the example of the lap band. It would be incumbent to very precisely determine how esophageal function is going to be followed up and monitored. Unfortunately, many of the proponents, if not advocates of the lap band who have been speaking in the public forum here, even though they came in on their own money they told me, have said that oh, occasionally, there will be some esophageal dilatation. Yes, swallow a little bit of liquid and see if that's going to diagnose it or not. That's not sufficient. That's not adequate.

There has to be a precise definition of how to determine whether there is, for example, a functional problem with the esophagus that evolves over a number of years.

And those functional problems can be of different nature because we've just recently learned the importance of it. Antacid gastroesophageal reflux used to be acid was the biggie but increasingly one has begun to understand that even if it's antacid reflux --

CHAIRMAN NELSON: Alkali injury?

DR. KRAL: Yes, from --

CHAIRMAN NELSON: I'm familiar with Alkali injuries as an ICU doc.

DR. KRAL: Of course. So the same thing is going to pertain to even a nerve function in the esophagus. What about micro aspirations? I've seen cases after lap bands who have come with a persistent cough who have interstitial fibrosis of the lung, probably secondary to nocturnal aspiration with a band. So there's going to have to be criteria and looking for it, one imagines are device specific

phenomena.

CHAIRMAN NELSON: Let me ask, just sticking with that example which I think is great, let's -- it's now post-approval in adolescents hypothetically.

DR. KRAL: Ten years.

CHAIRMAN NELSON: So 10 years. And then the question is okay, 10 years, you've given a couple of complications. I mean are you going so far as to say that yearly these individuals as part of a registry requirement or is it a standard of care that they should have that should be a part of say a package, an insert package for the approval that says they should have a swallow that demonstrates A, B and C at certain frequency?

I mean I guess having said what you said, what are then the -- is it in the package insert there would be this information about what the doctor should do or would you have the registry actively saying this has to happen as part of the monitoring of the safety of the device for both? How would you carry that out?

DR. KRAL: It would have to be active. It

would have to be active and it would have to be mandated. That there would be a compliance with it and the methodology has to be guaranteed to be followed.

CHAIRMAN NELSON: So you would advocate then say a swallow?

DR. KRAL: I think it's beyond the scope of this, but you're the Chairman, the scope of this to come up with a menu of the specific methodology that we're going to use to study what aspect of esophageal function, for example.

CHAIRMAN NELSON: I guess that's not my intent. I guess the intent was to explore the degree to which the burden of that active surveillance would -- what was the sort of level of burden that people felt could be applied because then there's a balance between that burden and the realistic and it may be one thing to say that if someone has a device in, that the physician caring for that individual ought to do these studies as part of a reasonable standard of care is one statement and then report as a registry requirement finding.

That's very separate than the device manufacturers a part of initial approval saying to the people with the device your doctor should do this or you should ask for it and they can always say no, that's their right. But that's very different than the device manufacturer pushing that statement.

DR. KRAL: Well, I guess that's going to have to follow the standard model of the numbers of malpractice lawyers per capita that are going to adjudicate what is a standard of care when problems arise. In other words, can the practitioner who is the licensed practitioner taking care of the patient who is having a device put in, be given the entire burden of making sure that a standard of care is being followed or should it be incumbent upon the one who produces this, like a cigarette, and says that it can be used freely.

CHAIRMAN NELSON: Other than -- exploring I see hands. Why don't we go to Dr. Hudson, Dr. Rappley and then to Dr. Choban.

MEMBER HUDSON: This is very comparable to what we face in oncology all the time, so for some

reality testing our registries at the bottom line are doing vital status and tumor status, especially as our population ages, so it's unrealistic to think that even within 10 years as you have a mobile adolescent population that you may keep them on site, unless they commit to the 10-year study as part of the study.

So it seems to me that you're going to have maybe some minimal things that perhaps could be a mail survey or through the physician's office, but when you start mandating we want you to have procedures, diagnostic procedures on a periodic basis, that's a whole different level. And a lot of these things there may be some complications that you did not anticipate and then as that becomes, that awareness evolves, other studies may be added.

So it seems like there's going to be some things that we mandated as optimal clinical management for individuals, monitoring nutrition, etcetera, but there may be some very basis complications that you would ask just like our registry letters come through every individual hospital's cancer registry, we fill out some specific information and it's like a one

pager. That may be more reasonable on a global effort from the company saying we're tracking these devices and we want to know XYZ what's happening to your patient, are they alive and do they have diabetes, etcetera, whatever you can. But once you start getting into what is the swallow study showing, I don't know how you're going to be able to mandate that. It seems like it's going to be recommended as optimal care, best care from what you guys know.

CHAIRMAN NELSON: Dr. Rappley?

MEMBER RAPPLEY: I'm trying to sort out from all of this conversations what we would think should be required in the two-year interval and then what would be required in the two to five-year interval and then where does the registry fit in with that two to five years? Is it an additional five? It becomes a more a reporting in that way.

So I'm not clear about --

CHAIRMAN NELSON: All right, let me ask for clarification. The 10 year seems to rise to the surface. Was that 10 years -- I assume that's 10 years after the device implantation? Yes. So that's

five years on top of the study, but if you're not in the study, it will be 10 years from the time you got it in. And I think the distinction between the registry component or of sending out a letter, etcetera and those things it can be, that would be optimum standard of care I think is an important distinction.

Probably what we should do at the very least is to identify what we think ought to be on that, if there's an active surveillance process, what's in that data set going out to get whether it's from the doctor or from the patient and then what might be beyond that.

MEMBER RAPPLEY: And wouldn't your findings from your two-year and five-year intervals inform that?

CHAIRMAN NELSON: Well, the two year is the efficacy and safety and then the five year is the extended efficacy and safety within the single trial, understanding that then people would be potentially getting the device once it's out after those two years, who would then not be in that trial and be

getting just the registry.

Does that -- Jack?

DR. YANOVSKI: I tried to make a list of things I thought would be general enough to apply to many situations, so for the long-term follow up vital status, height and weight would be very reasonable to know, and then whether there have been removals or revisions of the device that have been required, infections and other serious adverse events and then device-specific complications would be a relatively short list based on what had been uncovered. And then obesity-specific complications or comorbidities, either new or resolved would be sort of a relatively short list, might be doable in a couple of pages.

CHAIRMAN NELSON: Dr. Choban?

DR. CHOBAN: I agree. I was sort of thinking of the same list, particularly if the device is removed, that these people don't evaporate from the data base at that point, that there's some -- what do they evolve into?

If we're talking about devices that become obsolete in six months, that then are transitioned to

a different device, that to be able to track that some way would seem to be useful but if you are now relying on the manufacturer to do that, I don't see them much interested in doing that.

So I guess as people transition from device to device, if that's what happens, how do we keep track of those? So that's one. But the other thing I think I'd add to that, particularly in speaking about adolescents and the females to track pregnancies and reproduction in that as well and what has been the fetal outcomes.

CHAIRMAN NELSON: Let me ask you a question. Assuming that for the moment we have no national registry funded either through the good graces of the Centers and the doctors or through other federal mechanisms, if one had a uniform data set among these registries, the only way you could find out if Person A disappeared from registry 1 and appeared suddenly in registry 2, now with a device, I mean you can ask was it removed, registry 1 and then they disappear. You don't know unless they answer it or something new put in. The only way to really begin

to do that is to sort of do a meta analysis of all of these individual data bases. Is there a mechanism by which if there's registries across say a product -- this wouldn't be a product-specific -- across a disease-specific set of devices for doing that?

DR. PORIES: Crossing the registries is very difficult.

CHAIRMAN NELSON: Well, let's assume they all have the same data in it.

DR. PORIES: The fact is that in order to maintain peer review and HIPAA rules, you have to give each these folks a code and you can't criss cross to codes, there's no way to deal with that. That's one of the benefits of our new laws.

(Laughter.)

CHAIRMAN NELSON: So unless we specifically had on the forms have you had this device removed and a new device put in, what was that device, but then you wouldn't really know if that person who said -- if there are two people who had that happen to them, which person they are in the new data base is what you're saying.

DR. ARSLANIAN: Unless the device has a number.

CHAIRMAN NELSON: I mean the devices probably have numbers, but I guess this is a -- we don't have to sort of -- it just shows some of the problems with not having it coordinated.

DR. PORIES: The other thing is that you want those entries to be reliable, so we're using a kit that we send to the patient as well as to the surgeon and then that kit has to be filled out by another health provider so if somebody gets it done in Greenville, North Carolina and then they move to Columbia, South Carolina, that they can see any health care provider to fill out that sheet, but we prefer not to have the patient fill it out.

CHAIRMAN NELSON: What's your adherence to that process?

DR. PORIES: We're just starting. Prayer. We believe in prayer.

(Laughter.)

DR. CHAMPAGNE: I would just add that one thing that would be helpful too in this registry would

be some information that relates to the nutritional status of the individual and also their self-perceived quality of life.

CHAIRMAN NELSON: Are there easy ways you can ask that on a two-page questionnaire?

DR. CHAMPAGNE: Well, I'll have to put some thought into it, but I think that you'd want something that sort of gave you a feeling or gave you some data to suggest that their nutritional state was adequate. We usually do something very cumbersome to determine that, but the quality of life issue, I think, is probably easier, an easier piece.

I'm just thinking free of nutritional-related diseases perhaps. I'm just thinking in terms of the long term.

CHAIRMAN NELSON: If a health professional completes it, that's one thing, but if you sent me a questionnaire and said to me are you free of nutritional diseases, I'm not sure how I would answer that.

DR. CHAMPAGNE: No, I'm not going to say that for you. Actually, in terms of follow up, I

think it would be really great to have a long-term follow up -- well, even if it's 10 years that is actually performed by the research team. That way it's standardized and you follow a common protocol and I think the data is very important. But maybe -- and maybe you'll do that for five years, but somehow giving us some clue as to nutrition and quality of life.

CHAIRMAN NELSON: But I think in the real world that since we're advising the FDA, not NIH, saying that you've got to get your people back in 10 years and do a full assessment, it's very different than saying to a program, submit a grant to basically bring everybody back in 10 years and do a full assessment. So it may be useful to do, it's kind of hard to imagine putting it as a condition of approval.

DR. PORIES: Employment and marital status can actually give you a fairly good indication of quality of life.

It's not great, but --

(Laughter.)

CHAIRMAN NELSON: Dr. Rappley? I'm not

going to go near that one, but Dr. Rappley.

MEMBER RAPPLEY: I already said what I wanted.

CHAIRMAN NELSON: Dr. Hudson.

MEMBER HUDSON: One thing that you guys were talking about centers of excellence or especially centers that would do this and the way the cancer registries work is your hospital or your center is accredited by the American College of Surgeons and there's guidelines. So it's not like everybody has to do this. It may be the centers of excellence or some of those centers will seek this accreditation where they will monitor and track and in that case it may be for life what happens to these devices and a variety of things on these types of patients who have these devices. That's one mechanism to make it more reasonable that everyone won't do it, but these specific centers of excellence will want that accreditation that they're a service that they know what happens long term.

MEMBER RAPPLEY: Is that the basis on which the hospitals donate money to this because they

can then say to the public that we participate in this and this is our comprehensive obesity program and sort of community outreach?

DR. PORIES: That's exactly right.

CHAIRMAN NELSON: So in a sense, if the pediatric bariatric program is organized in a way that it was good to be in that club, there might be a way of trying to sort of set standards relative to that.

DR. PORIES: And they're starting to do just that.

CHAIRMAN NELSON: Okay. Well, I think it's reasonable to pause and ask are there questions that remain that we haven't answered because we haven't given an answer that can be given as opposed we have an answer because it's not answerable.

And so let me just -- and I'm not going to -- I assume Ron you don't need me to summarize everything that's been said.

DR. YUSTEIN: We'll read the 500-page transcript when that comes out.

CHAIRMAN NELSON: Well, why don't I turn to you and say at this point, having listened to this,

and sort of looking at -- I mean just explain this, by the way. Each question here is the center solid circle and around each one were the various issues that the FDA said might be considered in addressing the questions that are in those solid circles such as growth and development, post-approval maintenance registry and then the ethical issues are floating around in yellow.

So why don't you --

DR. YUSTEIN: Do you want me to try to summarize like what -- some of the take-home messages I wrote down?

CHAIRMAN NELSON: Whatever you think would be useful and then just, so at the end of the day you feel you've had the questions answered to your satisfaction and then we'll also even take an opportunity to go around the room and just see if anybody has any thing they think haven't been said that need to be said and need to be on the table.

DR. YUSTEIN: Like I said nothing is written in stone, but these are just some of the general things that I heard today.

As far as patient population, there was a fair number of people that suggested that the 99th percentile for BMI and the requirements for comorbidities was a fair inclusion criteria, excluding or at least not studying with the main group, patients with Prader-Willi or other genetic causes of obesity.

Perhaps a staged introduction of studies by age group, for example, as we get information on the device in adults to allow it into the older adolescent patient population trials first and then as we get information from that, bring it down into the lower adolescent age groups.

Overall, probably two-year pre-market study and try to consent patients so that we have follow up guaranteed in them as original study groups through five years with concentrating between two and five years on adverse events, nutritional status, plus the maintenance of weight loss.

Possibility of registries for those patients not enrolled in the original studies, but also receiving the device, we can talk internally about logistics of registries. Internally, we

recognize that registries are difficult and the longer you go out, the less likely you are to get useful information, but certainly, you gave us some components of registries that would be important to look at.

From the endpoint standpoint, I heard that although most of the ones we listed would be appropriate for secondary endpoints that generally people felt that change in BMI for age or percent change in BMI for age was probably the more likely or the best candidate for primary endpoint and that the others, including quality of life measurements, if we can find a good tool, comorbidities, etcetera, would be good secondary endpoints.

One question I had for Dr. Yanovski and earlier when we were talking a little bit about using endpoints to justify sample sizes, we were talking about what was a reasonable degree of effectiveness that might appear in a hypothesis and we had said at 10 percent weight loss which is often what's quoted in the literature. But we're also suggesting using a BMI as the endpoint.

Is there a way to -- a way when people come into do their sample size calculations, is there a way to estimate what a reasonable change in BMI percent for age over that two years might be, rather than in as a percentage of 10 percent change? We're kind of using apples and oranges. It's something we can think about, but it's often -- we often get asked when sponsors come in with study designs, one of the main issues that our statisticians deal with is the sample size and that's often based on -- it's hypothesis driven and they hypothesize what a meaningful change is going to be.

Oftentimes our sponsors choose to quote the literature and use the 5 to 10 percent change in weight, although we often stress that those are usually, have been results from -- are usually based on studies that are less invasive. Some of our products are more invasive, so we tend to try to go for a little bit higher baseline expectation, that it's going to give more than 10 percent, especially if it's a surgically-implanted device.

So I mean we look at 10 percent as kind of

a baseline. And then we use percent EWL so transferring them over, you have to multiply by two or three. So we often tell sponsors in adult trials that we expect at least to be clinically meaningful 20 to 30 percent excess weight loss, to try to go back to the 10 percent absolute weight loss. So that's kind of an issue that we struggle with.

One thing perhaps that I was still a little confused about, if we do -- I heard that several options for control trials and control matches, etcetera, but it also was mentioned that the possibility of a single arm study would be possible, especially if we knew a lot about the effectiveness of the device from adults or older kids or other information that we had.

How do we -- if we have a single-arm study, how do we control for diet, exercise, behavioral therapy? How can we tease apart whatever results we get at the end of the day from what might have been contributed from a rigorous behavior modification program?

When sponsors come in and they have a

device that has a borderline effectiveness, maybe in adults or preliminary pilot studies, and if it's a single-arm study, but yet the patients are on a very aggressive 500 calorie a day deficit diet, plus exercise, plus they're meeting in work groups and undergoing the Jenny Craig kind of group sessions, how do we tease apart the results that you may get if you're only talking 5 or 10 percent weight loss? So that's still an issue we still kind of struggle with and I think that's going to show up more in the single arm trial design.

And the notion of the six-month lead in, I guess we didn't kind of come to conclusion about that. I heard kind of -- and not that we need to come to conclusion on everything, but I heard some differing opinions, possibly on whether or not there needs to be some kind of six-month lead in or not even six-month lead in and what we would assess during that time, the point of that lead in would be.

And then Diane has reminded me, I'm ont sure if we commented on data safety monitoring boards that everybody thought that was a good idea during

these trials.

CHAIRMAN NELSON: Okay, let me make a couple of comments and then I'm actually just go around the room and let people remark to those issues or any other issues.

What I heard with the single-arm trial was that it was very much linked to the matched control and part of the challenge of that is the match would also include that 500 calorie diet, so you've got a nonsurgical matched control and that was part of also the discussion of the advantages of a six-month lead in, again with the exclusion of those that Dr. Lustig, I believe, mentioned that would be emergent, people who have comorbidities that would justify immediate intervention is that you have all of them in a sense on that.

It's sort of similar kinds of designs as an add-on trial in a drug setting where you basically have everybody on the same treatment and then those who don't want surgery don't get it and those that do want surgery get it, so you're basically doing a matched controlled study, but it's a nonrandomized

assignment and doing your best at matching those groups, based on the discussion.

Now there may be a device you might be willing to randomize. There may be a population that might be willing to do that, depending on the nature of the device, but that's where the devil would be in the details when that device or that widget comes forward, I think as Jack pointed out, that those may well be limited circumstances. We just don't know until we see it.

And then I think the Data Monitoring Committee didn't have a lot of discussion because I think a lot of people thought it was a good idea,that you need to have such a committee involved. This is a clinical trial. Even if it's unblinded, I mean I think a data monitoring committee, it's independent of the issue of they can see the data, even if this is an unblinded surgical trial.

It's a question of independent assessment and oversight, not so much as protecting the data and reviewing that in a way that doesn't break blinding. So I'm assuming that everybody thinks that's a good

idea.

DR. YUSTEIN: Can I add one other question before you go around to the folks?

CHAIRMAN NELSON: Sure.

DR. YUSTEIN: Something I brought up yesterday during my talk, but I kind of -- it kind of slipped into the back of my mind. If people can comment on whether outside the U.S. data would be acceptable, and if so, as a portion of the study or would you be willing -- or do you think that the practice of pediatric medicine and bariatric medicine is similar enough between here and let's just say Western Europe that would -- we would be willing to accept studies done entirely outside the U.S. If people can kind of comment on that because as you can imagine --

CHAIRMAN NELSON: We can comment on that, but I'm just wondering if anyone aborad would want to eat the kinds of things that we would eat at baseline. It's not just clear to me the data would be comparable on that score alone.

DR. YUSTEIN: I don't disagree with you,

but I think a lot of manufacturers -- like I said earlier, it's cheaper for them to go overseas and do their studies and that's often something that we face at the FDA. That's often a contentious issue is deciding how many patients and if all need to be done in the U.S.

CHAIRMAN NELSON: Then why don't we do this because it may take the bulk of our time and we don't -- if people say something controversial, the intent is not to have people then respond to that, but just sort of go around the room one by one, people can say whatever they feel is important, answer these questions in their own way and we'll see what emerges. Feel free to clean up any misunderstandings or any important points that you think have to be made and respond to Ron's questions.

So I'm going to start with Jack and we'll just run around. If you don't have anything to add, just say "nothing to add" and we'll just see where we end up at the end of the day.

DR. YANOVSKI: So thanks. It's been a great process today for all of us to think about what

devices might offer and how we might best assess it.

In terms of a 10 percent change in weight, these kind of devices, I imagine, are going to be considered in people who weigh 250 to 400 pounds, so with that in mind a 10 percent change is going to 25 to 40 pounds, so that's at least a couple BMI units, so let's say two BMI units would be equivalent to that. So that kind of gives you an idea of what would be a minimum change in weight that would be acceptable.

In terms of the excess weight loss, as a person taking care of a lot of overweight adolescents, we immediate recognize that the 50th percentile is not even a number that we ever mentioned in patients and the whole concept of excess weight relative to the 50th percentile is what is being calculated. So we tend to think of how close could we get them to the 95th percentile point. But no one really brings that up as a goal or a point at which you might assess the excess weight relative to that point, but it's another thought.

So I think if we could go back to about

changes in BMI for adolescents it's not going to be a problem since most of them have largely completed their growth. They're all going to be over a meter and a half or 1.6 meters, just to think about it as a couple of BMI unit change. In younger children, it's going to have to be individually calculated when the time comes for that. So you have to recognize that as a separate issue.

The other part, Skip's comment about data monitoring committees, we all assume that's going to be the case and other than that, I guess the only other thing we didn't talk about is whether we should -- how concerned we should be on future growth and development. I think that has to be part of any assessment in pediatric studies, more so in the younger, even more so in the younger than in the adolescents, but still is a major concern and as Dr. Choban mentioned, things like pregnancy in girls and life events will be important parts of that assessment.

DR. KLISH: Just a couple of things that I didn't say earlier and I wanted to just get it on the

record and then a couple of responses to some of your comments. Two things I wanted to say about comorbidities as an indicator for selection for surgery.

The one comorbidity I worried the most about is depression because in many cases the depression is not being caused by the obesity, but it's being -- it precedes the obesity and the cure for the obesity may not cure the depression and adolescents are very vulnerable and they are very high risk for suicide. So we take that comorbidity very seriously and kind of deal with it, a little bit separately than the rest. It may not make it an indication for surgery.

The other indication that seems to be played down in this that I want to play up a little bit is NASH, nonalcoholic steatohepatitis. And the reason I say that is because I come from primarily Hispanic area and NASH in the Hispanics is very significant comorbidity.

In the City of Houston this year, not in my program, but in the University of Texas program, I

have heard they have transplanted two adolescents for nonalcoholic steatohepatitis. So that's obviously a serious comorbidity that should be kept at the top when we're usually looking at indications.

I want to defend Tom a little bit about this six-month lead in or the way he discussed the lead in where he said that he didn't think that he needed a six-month lead in, but he needed one or two months to get to know the patient. The reason he said that is not all programs have the capability of providing a full behavioral program to their patients and he felt that if the six-month lead in could be done elsewhere where they have that program and then transfer into the surgical program, that it would be an adequate way of leading into surgery. And I kind of agree with that, I think, if he has a relationship with somebody else who is doing that kind of treatment.

And then the last thing I should comment on is the European data, having many friends, I think, now in Europe that are involved in clinical studies, I find that the data that they get is just as valid as

the data we get in this country, assuming that they use the same protocols. So I think if you mandate the protocol, and it's done in Europe, you're going to get very good data.

I'm not particularly sure that's true all over the world, but you did say Western Europe which is where I have the most knowledge.

DR. CHOBAN: Again, it's been very enlightening to be involved. And I think my biggest concern would be about this six-month run in period and at least being fairly overt about what it actually is. I think what Tom had tossed out, that if you go to -- back step for a minute. If you go to the adult series, I mean most of these patients don't show up asking for an operation as the first time they've ever thought about treating their weight. They've done four or five or six series of dietary attempts, often with drugs, often with VLCDs, doctor monitors, spend years and years of their life and money doing this.

So as a parent, I'm nota pediatrician, but as a parent, I can't imagine the first thing I'm going to haul my kid in for is an operation. I think often

these kids have done multiple, serious dietary attempts. So if they can come in with the data from that, to document that they've done this, I think to make them go through yet another system is somewhat onerous.

And this couple months to get to know him, you do get to know the family, what is the social support, does the kid really want this? Probably a couple of months is more than enough to accomplish that goal.

If we're using it to try to find out matched controls, then there's a different motivation for why you're making them do that and I'm not entirely sure it's fair.

So I think that's the only thing, as you set up these trials, I think to have a well documented, previous dietary attempt is reasonable. If they have that historically to make them do it again, just so I can watch it, is probably not necessary.

I think one of the things, the only thing I haven't heard when we were talking about that assent

consent, I think the issue that got brought up of being very explicit about the dissent issue and that a kid really is allowed to dissent, is probably worth including in consents.

DR. KRAL: This has been very impressive and thought provoking on many different levels, very well done. I commend the Chairman for doing a good job.

A few issues that I just heard, I have never in my whole career operated on an obese patient with an anti-obesity procedure within less than three months of my having seen the patient the first time, number one. And you can draw your conclusions afterwards.

And number two, I've never, ever outsourced any of the evaluations that I felt necessary to be done believing that some kindhearted internist somewhere would be able to do the job for me and give me a patient in the old traditional authoritarian,c custodian manner of the cognitive specialists with a wig and a long gown who will come to the -- the technician who is going to do something

to the GI tract. I've not gone along with that model. I've always insisted on myself having the hands on.

So I don't believe in that model. I do believe that a lead in is extremely important and it has to involve the surgical team and those who work the closest with the patient and I don't think it's going to be -- should be outsourced because I also think there happens to be some parameters that are usually not recognized very much and they've gone by the wayside and that is the so-called doctor-patient relationship. When it comes to surgeon-patient relationship, it's something with very different magnitude than that of a doctor-patient relationship, generically.

I'd like to make a comment about foreign and foreign data. Dr. Klish chose to look at the validity of the data that is collected. I'd like to give a very different perspective. I hope you don't mind if I use the example of the lap band. The lap band experience in Europe and in Australia, for example, has been substantially different than that we've had in the United States and it continues to be

substantially different.

Now does that mean we cannot trust the data that has been collected elsewhere or is there something going on? And I would like to maintain from my personal experience and from what I know about this, that there are substantial differences in the way people in the United States handle food, culturally and behaviorally, compared those other societies where the gastric-restricted model has been working so much better for them.

There are also other aspects of the delivery of care in fee-for-service systems in others. So I don't think we can directly translate these wonderful things we heard from Australia, some of them, or from Switzerland or the Danish experience, for example. And immediately think that they're going to be translatable and we're going to get the same results.

Now there's no data that I'm aware of on adolescents and young people, whether this pertains, but my guess is that it would because I think that parents behave differently in different cultures than

they do generically in the United States. And I think the marketing of food products and other things is very different, even though "Coca-Cola-onization" has gone very far.

As far as -- so those are the two points that I think I can comment on that haven't been fully -- as far as depression is concerned, it's extraordinarily difficult to disambiguate the chicken and egg in this situation. It is extraordinarily difficult. And I know this because we've done studies, particularly on the effects of early life trauma as a precursor of even neuronal integrity changes in different parts of the brain known to be associated with depression and depressive reactions, it's very difficult to know where the process starts and where the process particularly starts in an obese adolescent.

Usually, the obesity has started well before there's any indication of depressions that could be secondary. On the other hand, we mustn't discount the many genetic forms of depression that are beginning to be recognized more and more.

So it ain't easy, but of course, we have to be very, very cognizant and on the lookout for evaluating depression as a comorbidity or as a primary factor. No question about that.

I think Dr. Yanovski has made it clear that we seem to be working on the model of a work downwards strategy, work downwards, in other words, we have the adults clear, then go to adolescents and any discussions then seem to be completely derived from dealing on an adolescent and you heard the example that Dr. Yanovski gave which was well, we're talking about 250 to 400 pound patients and 10 percent, that's 25 -- well, we're going metric inch by inch, so 25 to 40 pounds.

Well, I don't think we've nailed that down entirely, but it's probably reasonable to take that approach as we approach using devices and studying them in younger and younger age groups, but soon we will probably be discussing people who are not 250 to 400 pounds and I don't mean only the dramatic examples that Dr. Lustig brought up with pseudo tumor cerebri or sleep apnea or somebody who comes in with DKA or

that it has progressed to that state. So we just need to keep that in mind.

But thank you very much, everybody.

DR. CHAMPAGNE: I'd like to just thank the FDA for inviting me. I haven't learned a lot participating in this panel because this is a totally new area compared to what I normally do.

It strikes me that the learning period could be a period where we can view the subject as being their own control, collecting data, I know this has been brought up and I think that point was mentioned and I think it would be an ideal thing to consider. I think if we can implement a standardized protocol that focuses on nutrition, physical activity, behavior change in the same manner for every institution that's going to do this, hospital, whatever, that it could be a way of getting around the need for randomized clinical trial which we already agreed was not probably going to work. But I think that we could take advantage of this run-in period to look at a period of time where the subject could be their own control.

CHAIRMAN NELSON: Thank you. Dr. Arslanian?

DR. ARSLANIAN: Actually, I agreed to come to this activity because I was curious about what is all this about and I'm glad to say that I'm not disappointed and I enjoyed the interaction tremendously and I think the diversity of the expertise made it so much fun.

I just want to add a few things which were not added. I think we have to have a very clear glossary of what the comorbidities are and how they are being evaluated because the fact that somebody does not complain of sleep-related abnormalities does not necessarily he or she does not have sleep apnea, especially if we're going to make the comorbidity and eligibility or exclusion criteria.

Or I can argue against that Inge's proposal that it should only be children with comorbidity who are included, then I can tell him that any kid who has a BMI above the 99th percentile would have insulin resistance as a comorbidity. So I think that's why we have to have very clear definition of

what comorbidities we mean and what severity and what extent.

The other issue I think is the run-in period. I believe the run-in period is important. It should be there. However, the duration of it can be argued, three months, six months and that all depends on what device one is talking about.

The third issue, the long-term outcome is very important because unfortunately, adolescents don't make me trust them what will happen and how they will behavior and what the outcome of any intervention would be long term. So probably those are the only things that I would like to add. And then the issue of the potential active control trial, but I'll not dwell on that any further.

CHAIRMAN NELSON: Thank you, Dr. Pories.

DR. PORIES: I want to second what everybody here has said about your direction of this. I never thought you'd get through this. And I've really learned a lot.

In terms of the primary endpoints, I would add two or three serious comorbidities such as sleep

apnea, diabetes to the BMI, rather than just sticking to the BMI as the only primary endpoint.

We haven't talked about the Tanita scale which only costs about $1200 and provides a pretty good verifiable level of body composition and lean weight and I think that's a pretty good indicator that we decided to use it at NIDDK.

We've used a six-month lead in at East Carolina for probably 15 years, simply so we get to know the patients. It gives a very good idea about compliance. If the person doesn't comply in the first six months, they're not going to comply afterwards.

In terms of safety monitoring board, I think that's essential and I believe that that can be attached to the registry. The registry should be independent of the program and the monitoring board should be independent of the registry and both should be on tap at all times to monitor what's happened to the patients.

Finally, I have a little story about outside U.S. data. Dr. Scopinala has done the bilio-pancreatic bypass for years. His experience in Italy

and our experience in Italy are totally different just based on diet. We have many more nutritional problems than they do in Italy and I'm sure that the people do it here and Dr. Scopinala are reliable and ethical surgeons. So I have the same concerns about taking outside data.

Thank you again.

CHAIRMAN NELSON: Olive oil or red wine?

DR. ARSLANIAN: Olives.

CHAIRMAN NELSON: That's would I would think. Olives would be my hypothesis.

MEMBER DOKKEN: Just quickly, I think my main take home message from this has been sort of the complexity and what I referred to before about the lifestyle change that impacts both the child and the family.

And I guess that that leads me to a certain troubling, nagging worry which relates to something that Judith O'Fallon referred to before which is because it is so complex and because it is such a big process or program, how is that going to in the sense of distributive justice, how is it going to

relate to sort of the demographics of the problem and since I'm on here as a family member, and the family member who has had a number of significant health care issues to deal with, one of the things that has been -- - the life saver is having the resources, whether it's your insurance or your friends that you can network with to get additional information to get you through the morass or whatever it is.

And so I do worry about hearing about something that feels a little bit, even when we -- someone referred to the lead in period and these will be people who have had multiple attempts before, so why would you need a long lead in period?

Well, the only people who are going to have multiple attempts before will have had the resources to do that. So I know it's not part of the clinical trial per se, nor is it part of the FDA responsibility, but I just feel like I need to say that.

MEMBER MOORE: I think that -- I haven't said too much today because I feel like I've been learning mostly, but I think one of the things that

the FDA may wish to consider as you're working with sponsors to design trials is that these devices are likely not going to be all sliced bread. And I think we've been myopic a little bit here because we've got this lap band and there's been a lot of discussion about it.

And the lap band requires an invasive surgical procedure, so it's more like doing surgery or it is surgery, really, but surgery with a device implant. It's possible that they'll be devices which arise that are not nearly as invasive, that may be even worn or strapped on that may be swallowed, that may dissolve, who knows? It may be implanted subcutaneously with local anesthesia, etcetera. And so I think that you need to have some kind of way to differentiate between what's required of an invasive or surgical-type device versus what's required for a device which is less invasive or completely non-invasive.

And I think that the single arm study is probably appropriate and all the things that have been said almost entirely deal with that invasive-type

device. And I would agree that a single arm matched study would be the way to go with that or you might even consider offering objective performance criteria as you've offered with some of the cardiovascular devices that I've worked with that basically rely on data from other sources as the control for the measure, such as adult data for a given device or even the pediatric surgical data, the straight up surgery without a device.

In the noninvasive type devices, I think because these are likely to give you less benefit and to be harder to distinguish from medical therapy or behavioral therapy, you may want to require RTCs because these may get very confused. They may be a lot less benefit and then you have to go, you're in that really muddy water that we talked about earlier. And so that would be the one thing I would add.

I don't think we've emphasized this, but you know, devices will be -- will run the spectrum of your imagination and not just something that has to be implanted by one of these surgeons that we've had talk about a great deal to us.

CHAIRMAN NELSON: Paula, with your permission, Bob Daum needs to leave at 4:30. Do you mind if I go a little bit out of order?

Bob?

MEMBER DAUM: Thank you. I apologize for needing to do that, but I have to deal with Dulles Airport and it took me two and a half hours to get here from Dulles the other night, so I'm anticipating trouble going back as well.

I'm just going to comment in a couple of areas that I'd like to emphasize that haven't been said, and try to do it as quickly as I can. First of all, I think randomized control trials do have a place in consideration of designing trials for devices. I think there is comfort if we know things work or almost certainly work in adults in avoiding the need for randomized controlled trials, but without that reassurance, my level of comfort and going forward without a control trial really goes down.

The second issue, of course, just to emphasize again something that I have said earlier and so did others, is that the relative risk of the

procedure itself to enter the trial and get the device going, obviously, impacts at least in my view, about whether we need a randomized control -- whether randomized controlled trial is feasible or not. And so that if the risk of putting the device on, such as a skin patch or something is quite low, then I would drift back in my thinking toward the more Cadillac approach which would be to have a good, randomized control trial.

The second point I wanted to just emphasize is this business of comorbidities which I think everyone at the table agrees are something that are very important. And I think I'd like to emphasize a systematic search. It's a point that others have made, but just to emphasize them, of ones that the endocrine people and the obesity doctors feel are important in patients that are going to be enrolled and to make sure that employed in the study design is at least the comorbidities that are believed to be important have sufficient sample size to make sure that they're likely to be measurable in the outcome parameters. I think that's really, really important,

that there be a systematic search and that some key ones, I think you used the word life threatening ones, be chosen for powering the study so that we have good data at the end.

Obviously, most of the discussion we had here was really with drums of the lap belt behind us and there's obviously a wide range of devices that could be used. And I think we had a good discussion so that if it weren't lap belt driven and abdominal surgery necessitated to start it off, FDA can get our sense of how to go.

I think that the initial study to see whether it works or not should be done on -- I would favor, actually stacking the odds a little bit so that we have highly motivated patients entering that are likely to comply with the protocol so that we can really see if the thing works. And I think extending it to other groups can be a secondary goal.

I strongly urge some kind of long-term assessment. Dr. Pories has his registry and maybe some kind of copy of that can be made. I personally don't think the sponsor should be the one to really

orchestrate it on their own. It's a little like the fox starting the chicken cook in my view. But I think there ought to be a mechanism and sitting around the table, I don't think we came up with it, but there ought to be a mechanism for tracking these patients long term, even if it's not a formal study tracking long term. But some mechanism should be sought.

I just want to echo the comments of I don't think that since a lot of obesity clearly is cultural that we can really use data, international data to decide if an approach such as the lap belt or another device really works in the United States. I think we need home data for this one.

And lastly, I guess I just can't help but make one quick comment about this. We used to treat very high fever in the emergency room by dippy babies in ice water. And it was kind of a crude technique and really it didn't address the cause of the fever. And somehow obviously we're charged to look at devices and I think -- I agree that we've had a wonderful discussion. I think it's a great forum established by FDA and Skip, I think you've done a wonderful job

leading us through this maze to be honest. But somewhere there needs to be a similar quality discussion about what the causes of this obesity epidemic are and our belief that there could be a treatment or surgical cure reminds me a little bit about like dipping babies in ice water. And that's all I have to say. Thanks.

CHAIRMAN NELSON: Thanks. Paula.

MS. KNUDSEN: I would just like to say that regardless of the invasiveness or non-invasiveness of the device, I think the most important thing is the relationship between the physician, actually between the team and the patient.

I think it makes for much greater compliance. It makes for much greater follow up. I would consider it of the greatest importance and also, it would increase my comfort level that there would be sensitivity to the dissent of the adolescent. I can imagine parents being frantic and being pressuring their adolescent to go ahead and have the surgery because it takes so long to achieve anything else by less dramatic means.

So I would like to be certain that there is a relationship so that it is very clear that this is something the adolescent really does want.

CHAIRMAN NELSON: Judith.

MEMBER O'FALLON: He has been watching me take notes and he's afraid I'm going to say it all.

CHAIRMAN NELSON: I was looking at Judith and she's got two pages of notes and I said Judith, are you going to say all that?

(Laughter.)

She assured me that she just has a few remarks.

MEMBER O'FALLON: I do, just a few issues. The first is that I do think randomized trials are thinkable in devices, but not everywhere, obviously. And I think that they become more possible as we go out from adults that we can start thinking in terms of randomized trials, and in particular, I was thinking that as they get down to the eight and nine year olds, as they will inevitably, that those types of things could use -- there could be randomized clinical trials of say the best behavior management therapy versus the

device or other thing like that, the widget. And that would really give us a chance to see whether -- how these behave in a certain population of patients. And obviously then follow up becomes extraordinarily important.

We have different populations being discussed. Remember, stratification can be a very useful tool. I am not happy with the idea of any of these matched studies. For the most part, these matched studies are irrevocably biased and it becomes very, very difficult to actually assure ourselves that we're comparing apples to apples. It's probably apples to pineapples. Because we don't know which factors are the most important issues and we can't match on them. That's where the randomization gets in there.

I am very concerned about the trustworthiness of adult data. It's wonderful for adults, but these are growing kids and I do not -- I am not confident that adults data is going to accurately predict results in children. So again, the follow up becomes very important.

I suggest that follow up should go to age 30, the reason being that most people will -- as I understand it, most people believe that the kids have grown up by that point and so the effects of those therapies they received in childhood should, most of them, be pretty well visible. So I would recommend following them until age 30.

CHAIRMAN NELSON: I'm starting to wonder about some family issues, but we won't go there. Dr. Gorman got that. Sorry, bad joke.

Dr. Newman?

MEMBER NEWMAN: Just address the questions or the issues that Dr. Yustein mentioned. First, as Dr. Moore said, if we're going to talk specifically about inclusion criteria, we need to be talking about a specific device and so sort of a prototype device is the lap band, I would favor for inclusion criteria at least the 99th percentile for 2005, not this 99th percentile that eight percent of people can be in, but a real 99th percentile, plus comorbidity and I think having that as inclusion criteria that the logical outcome would be a resolution of the comorbidity, that

the change in BMI would be secondary.

If you were going to look at something other than change in comorbidity and a change in BMI, I think the BMI change that we're looking for would be really a much bigger one than this sort of 10, 20 percent. It would be probably at least sort of 30 percent of the excess BMI and that as long as you're looking for such a huge effect, you probably don't need a randomized trial, but as soon as you start saying that we're going to consider this device works at a smaller effect size, then you probably do need a randomized trial.

In terms of how do distinguish between the effects of the device and the behavioral and dietary interventions that go with it. I agree with several people about the need for a run in and if the people have not responded to diet or behavioral modifications and the change has been zero or close to zero in their BMI and then after the device the BMI suddenly starts dropping and their symptoms get better, then I think that's how you distinguish the effect of the device from the behavioral and dietary recommendations.

I'm not that familiar with this patient population, so I'm not sure what the comorbidities could be, should be. I'm thinking pseudo tumor diabetes and sleep apnea. Maybe also some of the orthopedic problems. If the children can't walk, that seems to me an important outcome and the nonalcoholic steatohepatitis, I would say it definitely shouldn't just be biochemical things like insulin resistance or hyperlipidemia or things that are -- or even high blood pressure, things that are asymptomatic. It should be things that are affecting the child's everyday life.

CHAIRMAN NELSON: Michael?

MEMBER FANT: I really don't have anything else to add with regard to the comments as they pertain to the devices and the procedures that are currently in use. I'd like to reiterate my point and the point that Dr. Moore raised with respect to the heterogeneity of the devices. And I can envision devices that are going to come down the pike that their intended use or their potential usefulness in these kids may not have the same impact or be directed

at the same targets as the currently available modalities. And that they actually may be more useful earlier in the course of the progression of obesity.

They may be more useful as adjuncts to what we now call conservative, conventional medical management and examining the usefulness in these kids at a point that precedes them reaching the inclusion criteria that we've been talking about today may be more appropriate. So I think having the flexibility to adapt the inclusion criteria to the device and the potential usefulness should be kept in mind.

The other point that I'd like to make is with regard to the inclusion of international data and I really don't see -- I've never seen additional information as an all or nothing phenomenon. I think you really can't have too much information. The problem comes in how we use it.

I agree that we should not use the data to assume that we're going to get the same result in our population as we see investigators getting in Asia, Europe, Latin America, etcetera. But on the other hand, if we don't get beneficial results, comparable

to prior international studies, I think it would be a mistake to disregard a potentially useful therapy in this country.

I think the way I view that is a potential opportunity, if those differences are real and both studies were done appropriately. That's an opportunity to perhaps understand what we could be doing better with this population of patients so that this therapy can work. And we can we do something to improve our medical management or our behavioral aspects of the patient's life, diet, etcetera, that may actually diminish the need for the surgery or the device or make the device more effective, once they get it. So those are my only comments.

CHAIRMAN NELSON: Bob, with your permission -- Norm has got a taxi to catch.

DR. FOST: Sorry to rush out. Just two comments. I just want to add my voice to the comorbidity as the major outcome rather than surrogate measure of BMI which is different than what I heard Dr. Yustein say.

Second, I would also add to that comments

I made earlier about centers of excellence and large numbers of patients in any one center as this should not be like so many multi-center trials where everybody gets five patients and gets their name on a paper. There's lots of technical expertise here in multiple areas, multi-disciplinary areas, so any trials of whatever is being studied, should be restricted to centers that really have a large, full-blooded team and has a minimum number of subjects in the trial. Thank you.

CHAIRMAN NELSON: Thanks. Bob?

DR. WARD: I am glad to see this shift from BMI actually to comorbidities. I think they're the most important aspect.

I want to lend my support to even though it may be terribly difficult, to advocate for the RCT because of the frequency of adverse events in this population over time, knowing whether they are increased or decreased, I think is going to be terribly difficult if we simply use this matched control trial.

I think the registry is important. I

think the CDC could be the repository, potentially the NIH, but I think with the magnitude of obesity in the country, it's clearly a national problem and needs to be a national focus and I think we need to raise it to that level.

It's of concern that once this device or any device is approved that is easy to use, I mean we saw the technical difficulties of an endoscopic Roux-en-Y. That was impressive, but if this could be put in 30 minutes, as soon as it's approved, it will be used by groups that are not members of multi-disciplinary teams.

And we've discussed with the FDA in the past, what kinds of restrictions can be applied to the application of -- for example, a drug and they're very limited. So I don't know what the solution for that will be, other than having as good data as possible about efficacy and adverse events before it's fully approved.

CHAIRMAN NELSON: Marsha?

MEMBER RAPPLEY: I would like to speak to looking at factors that contribute to the

sustainability of the desired outcome. And that would probably mean some assessment in the leave-in period as well as post-procedure period, that if we could understand how to sustain this beneficial effect, then we may be able to accomplish the distributive justice piece if we understand what it is that families and children require to not only lose weight, but maintain a lower weight, that when we look at a nutritional assessment package that we anticipate the nutritional problems of young adults and get a sense of whether those are more severe among the children who become young adults in these restrictive diets. And I also support the data monitoring board.

I think that the urgency is very compelling to act and to provide a measure that -- an action that is very satisfying to families and to ourselves as physicians. But I think the onus for safety is only on us. It doesn't reside within anyone else and when our patients, when our subjects are children, and when the impact of what we do lasts a lifetime, that bar has to be very, very high for the safety consideration.

So I would argue then that before we set aside -- before we adopt the notion that we cannot do this with a randomized control child which is the gold standard, yet we need to be very certain because we'll be lowering our standard in addressing the safety issue when we set that aside.

MEMBER HUDSON: I'd like to emphasize, especially from the context of learning from pediatric oncology care that children, adolescents are uniquely vulnerable and this is in ways that we understand and may be in ways in regards to this specific procedure, related to weight control that we don't completely understand. So we have a responsibility to define the efficacy of these interventions and the sequelae of these interventions by longer follow-up.

So I think it's just critical that we commit to longer -- to evaluating these outcomes long term and I think that a panel of medical experts should define the important comorbidities as have been discussed here, but also that we should have select centers or hopefully supported research that will look at the survivors or these procedures.

There are self-perceptions of health status and functional status and also psychosocial outcomes as it relates to marriage, employment, intimacy, etcetera which are so critical in adjustment and happiness and well-being later on. I think the registries should be committed to as well, or recommended at least in selected centers and one thing that we really didn't address within this context is how we will accomplish some of these -- evaluating some of these outcomes as we have to transition children, adolescents from pediatric centers to adult health care centers and that may be a challenge as well that we'll face.

DR. GORMAN: I'd like to basically agree with the shift in trial design continuing emphasis on randomized or close to randomized trials and the emphasize on comorbidities as the primary outcome under both biochemical disease, biochemical and psychological comorbidities as potential primary outcome measures.

I think the centers of excellence need to be in general hospitals, not pediatric hospitals. I

think that handles a lot of the issues of the bonding of the team, that it will allow for the transition of assent to consent and will facilitate the likelihood of long-term follow up. That doesn't mean there shouldn't be centers of excellence in pediatric hospitals, as we move down to younger and younger age ranges, but if we're going to start these studies in adolescents, which I think I've heard as a general consensus for the more invasive devices, then perhaps general hospitals would be a better place with the teams to start.

With the duration of follow up that Dr. O'Fallon has mentioned, I think that we had better be careful about looking at environmental shifts of the baseline. Just like diseases, most diseases change in both their incidence as well as their prevalence and obesity may be one of those.

And as we go forward for 30 years, we may find that obesity increases and therefore the effectiveness of the device may be changed against the changing pace of disease.

I would also like to echo Dr. Fant's

statement that we should include international data and if they do better than we do, we should find out why so that we can institute best practices.

One last comment on the run in. One of the nice things about being a general pediatrician is I don't have much data, so when I come to these meetings, a lot of data gets poured into my head in a very short period of time. During Dr. Skelton's presentation yesterday where he talked about the New Kids Program in Wisconsin -- I know Wisconsin is not a normal state, very few people have escaped from their normal. Dr. Nelson may be the only example. Only 20 percent of the people -- of the children who enrolled in his New Kids Program had ever tried to lose weight before. So these are people with an average BMI of 40.

CHAIRMAN NELSON: Wisconsin.

DR. GORMAN: Well, it was Wisconsin, the cheese heads, I think. But I think the reality is that this is an area where I think kids are going to be different than adults in a real way that they may not have had the prolonged life struggle against their

disease and they may be being brought by their parents rather than their own concerns about their disease. And I think that the run in period whether it be two months, three months, four months, five months or six months or a year, I think it needs to be real and it needs to be structured in a way that makes you believe that those interventions cannot help these individuals.

DR. GARAFALO: Just to finish with a couple of comments. So I'm going to dissent from the evolution away from the BMI as the primary efficacy endpoint. I think we start from there and as we learn more about these other secondaries, we definitely need to look at those in further potentially future trials or certainly as just initially in a descriptive way until we know more about them. I think we talked a lot about duration of the trial. We talked about sample size for efficacy, but I didn't really hear much about sample size for safety. I mean in the drug side that generally we don't power for safety. Here, I wasn't sure how devices are looked at when you have a small number of potentially small number of patients

in the trial.

So perhaps it's related to the invasiveness of the device, so as you get to more devices that come down the pike that are less invasive, you might not need the same number of patients studied to understand if you're going to have rare or relatively rare serious adverse events.

So that all the safety and even the data safety monitoring board, the necessity for that would evolve from how invasive the device was that was under consideration.

I do agree that all of these therapies and obesity, in general, you need long-term follow up to really evaluate continued therapeutic, the efficacy of the relative efficacy because it's uncontrolled and potentially you lose a lot of patients to follow up, harder to interpret, but the long-term data would be useful and registries would be useful.

CHAIRMAN NELSON: Let me just make a couple of quick comments on my own and then turn for final comments to Ron, Diane and/or Sarah.

One thing that occurs to me, we talked

about the adolescents. There's agreement on that. The importance of a robust assent process, just to emphasize that, actually fits pragmatically with what I've heard about the importance of the adolescent being invested in the program and then for that run in. But it also fits in with the fact if we're talking about a five year trial and enroll anyone over the age of 13, that it would be a tragedy, if in fact, every child who turned 18 when you actually ask them what they wanted to do, changed their mind. That would be a sort of disastrous outcome. So the importance of a robust assent process from a number of different perspectives, I think, is important.

I'm more sympathetic to the BMI than I am to the comorbidity as much, but personally, I think Tom has said it in the most reasonable way. The extent to which one is certain of the degree to which you can predict change, gives you a sense of the robustness of that endpoint. and as that robustness sort of disappears, and as the degree of intensity or invasiveness of the device to where you go from the range of gastric bypass, calling that a device through

lap bands to speculating about ingested or transdermal sort of devices, (a) the differences become predictably less, at least in our hypothetical mind, although I suspect that's just a bias, but the opportunity for a randomized control trial becomes much more palatable, partly because we're less certain about the size of the effect that we may see and the importance of that kind of process for determining something.

So I mean there's a relationship between all of these different factors that I think where you put the emphasis is going to depend on the details of the nature of the device and the degree -- and all of the various things that people have said.

So I've heard a fair amount of commonality, the differences, I thought were at times differences of emphasis rather than differences of disagreement and I certainly hope you all feel that you got your questions answered in a way that was helpful and productive in trying to put together a draft guidance that could emerge anywhere from eight months to two years from now, hopefully not longer.

So if we have final comments, Ron, Sarah?

DR. YUSTEIN: I just wanted to thank the entire panel again on behalf of the CDRH for what I think was a great meeting. I think we came out with some very good, concrete recommendations, but on the other hand I think we left enough flexibility that we can adapt as needed for certain products.

And so thank you very, very much for your time and your input and Skip, thank you. I think you did a tremendous job in leading a very difficult process for a very large panel and we appreciate that.

(Applause.)

DR. MURPHY: I wanted to thank you all too. It wasn't quite Blue Ocean, but the effectiveness of the give and take between the different disciplines was really important and it really worked here over the last two days. And I think that those reflect on your leadership and on the participation, the engagement of everybody in this room and you really have provided us with some very useful advice.

Sarah?

DR. GOLDKIND: I would like to just echo what Ron and Diane have said. We've been framing this meeting for a long time, worrying if we gave you a daunting and overwhelming task and you really rose to the occasion, all of you did, with Skip's leadership, so thank you very much.

CHAIRMAN NELSON: Well, thank you and thank you, everyone. Jack, do you have a final question or comment?

DR. YANOVSKI: I realize that my back of the paper calculation, I gave you an incorrect number. The change in BMI. I just wanted to make sure -- it should be more like 5 to 7 BMI units not more like 2. I don't know why I said that, so my apologies.

CHAIRMAN NELSON: Okay, great. Thank you very much and everyone who is staying, fine, everyone who is traveling, safe travels.

Thank you.

(Whereupon, at 4:57 p.m., the meeting was concluded.)

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