

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

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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

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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,

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1 Office of Pediatric Therapeutics.

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

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

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

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

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

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

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

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

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

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

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

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

22 CHAIRMAN NELSON: Robert Nelson. I'm at

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

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

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

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

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

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

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

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1 Pittsburgh.

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

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

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

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

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

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

22 DR. YANOVSKI: Jack Yanovski. I'm a

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

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

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

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

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1 and regulations.

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

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

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1 employment.

2 Today's agenda involves a discussion on
3 pediatric obesity and clinical trial designs for the
4 evaluation of devices intended to treat pediatric
5 obesity for future development of a guidance document.

6 In accordance 18 U.S.C. Section 208(b)(3), waivers
7 have been granted to Drs. Patricia Choban and Thomas
8 Inge. A copy of the written conflict of interest
9 waivers statements may be obtained by submitting a
10 written request to the agency's Freedom of Information
11 Office, Room 12A30 of the Parkline Building.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 EXEC. SEC. JOHANNESSEN: I was taking a

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

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

5 CHAIRMAN NELSON: Okay. Good morning.

6 MS. MUSCI: Good morning.

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

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

12 CHAIRMAN NELSON: Perfect.

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

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

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

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

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

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

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

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1 okay, here we live in this upscale town in New Jersey.

2 There's no cafeteria. No real cafeteria. This is
3 the cafeteria -- parents, volunteers, serving bagels
4 with butter and cream cheese. That's all you get, and
5 milk. All right. You bring your own drink. No
6 snack, nothing.

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

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

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1 cookies, chips, whatever. Okay.

2 Now she's in middle school. Now they have
3 French bread pizza, Domino's, Wendy's, subs. More
4 good stuff. Okay. And, you know, the truth is the
5 majority of the kids are not overweight, and they're
6 all eating this stuff. Okay? All right. There was,
7 you know, a few overweight kids, but they were all
8 eating -- my daughter is sitting there with her turkey
9 sandwich, celery sticks, fresh fruit, water, you know.

10 And they have an award that you can get, whoever
11 brings the healthy lunch to school. My daughter's a
12 shoe-in. She doesn't even go up anymore. What's the
13 point, you know? Most of the overweight kids do have
14 the healthy lunches, by the way. Parents send them
15 in.

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

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

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

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

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

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1 We're not Rice-a-Roni people. We never had
2 Spaghetti-O's. You know, I'm Italian. Wouldn't eat
3 that stuff, okay? Everyone in school, of course,
4 knows she's on a diet, so, you know, that really is
5 hard. And that could be hurtful. There are always --
6 there's always a mean girl at the table, you know, the
7 cute little blond who wears a size 12, you know, who's
8 perfect. Okay. And you know there's always, you
9 know, a little girl size 12, you know. There's always
10 one like that. Kids for the most part are very nice.

11 She's very popular, my daughter. She has a lot of
12 good friends, but, you know, there's always one.

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

21 They're worse than the kids. So you're on the team,
22 but you're on the bench. I asked the coach, "Why

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

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

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

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

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

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

12 Okay. So what do I want? Why am I here?

13 I would like my daughter to participate in a hospital
14 in New York in a program, and I would like her to have
15 lap band surgery, because she is 60 pounds overweight,
16 and from -- we were in Jenny Craig in March. She's
17 gained about 18 pounds since then. Okay? Since being
18 -- after being on a diet. Eighteen pounds. All right.

19 And a good number of my husband's family are
20 overweight, and -- not my husband. He's the only one,
21 actually, and look, I love my in-laws. They're good
22 people, and they're all professionals, you know.

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

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

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

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

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

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1 all for listening to me.

2 CHAIRMAN NELSON: Thank you.

3 MS. MUSCI: You're welcome.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9 And, more recently, the ADA sent out a
10 notification to its members that Type II diabetics who
11 are morbidly obese need to consider bariatric surgery.

12 You know, and I'm a surgeon, so I'm always impressed
13 when non-surgeons start talking about people should
14 have surgical therapy for something.

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

22 We can argue about micronutrient things, but how

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

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

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

18 DR. BROWNE: Got it.

19 CHAIRMAN NELSON: You've got two more
20 minutes.

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

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

9 The gastric band also is not an
10 intergastric balloon or a gastric pacer, technology
11 and devices that will come along and are being studied
12 now, although there current results are not very good.

13 It's removable, adjustable, the lowest morbidity and
14 mortality, and it works.

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

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1 adolescents is small numbers and short term, for sure.

2 There is evidence from Australia from Dr. Fielding
3 and Dr. Nixon, and then there's evidence from my group
4 at the University of Illinois at Chicago, and we have
5 evidence now from Atlanta, as well, with Dr. Wulkan
6 that you'll hear from later today.

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

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

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

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

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

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1 comorbidities.

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

11 They've got to reach the 60% excess weight loss mark.

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

14 CHAIRMAN NELSON: The next speaker is Mark
15 Holton.

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

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

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

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

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

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1 restricts how much the child can eat.

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

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

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

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

16 Pouch enlargement -- what does it look
17 like? Well, basically it's a dilated proximal pouch.

18 Three different patients there, a couple of these are
19 adult patients, actually, but it's an example of what
20 the pouch looks like when it gets dilated.

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

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

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

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

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

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

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

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

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

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

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1 in this country, that's 500 deaths versus 50 deaths.
2 There's a three to four-fold greater morbidity. The
3 complications are more severe with the gastric bypass.

4 The new data from around the world says that the
5 long-term efficacy is virtually the same.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9 I'm going to try this again.

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

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

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

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

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

22 So there are several surgical options for

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

8 There have been some lap band results. In
9 2004, the Italian data showed an 8.1% complications
10 with an average decrease in BMI from 34 to 28% and
11 certain 28% by 16 months. And in 2004, Renedal looked
12 at some adults with an N of 444, with a 15%
13 complication rate but a 44% excess body weight loss at
14 one year.

15 What are the advantages of the lap band?
16 It is technically easier, but for me, there's two
17 things about it, three things about it, that are
18 actually good to know. One is it's pretty reversible.

19 If you don't like it, or something happens that is a
20 problem because of it, it's a relatively easy thing to
21 dismantle and remove. There are no aspects of
22 malabsorption. You did not divert anything. You're

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

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

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

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

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

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

20 CHAIRMAN NELSON: You have another minute.

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

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

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

16 Thank you for your time.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 DR. NADLER: Okay. So the compliance
9 data. Here are the numbers. So, of our 58 patients,
10 at six months we have 29 of 38, so 76%, 18 of 23 a
11 year out, and the rest you can see. So yes, we lose a
12 few. I would argue that any time you go to a major
13 national meeting and you hear what the follow-up for
14 bypass or other surgical procedures are, they don't
15 approach these numbers. It's more like in the 30% to
16 40% range. It's probably not a problem with gastric
17 bypass, because you don't need the same follow-up, but
18 compliance rates of 80% can be achieved, and we have
19 achieved them, so it should not be a consideration in
20 limiting the availability of this device.

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

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

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

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

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1 comorbidities between the groups was the same.

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

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

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

12 CHAIRMAN NELSON: The next speaker is Mark
13 Wulkan.

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

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

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1 have done?

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

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

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

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

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

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

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

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

22 How long is appropriate follow-up? Well,

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

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

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

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

22 DR. YUSTEIN: Dr. Nelson, would you mind

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1 if I made two comments?

2 CHAIRMAN NELSON: Go ahead.

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

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

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

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

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

16 Well basically, as you can see from the
17 rest of our agenda, it's basically Question One,
18 Question Two, Question Three, Question Four, Summary.

19 Now I'm under no illusion that we can deal with these
20 questions in any linear fashion. But on the other
21 hand, each question as I go through them I'll show you
22 the overall, and we might as well just sort of get

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

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

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

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

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

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

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1 assessments.

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

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

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

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

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

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

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1 will be required.

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

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

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

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

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

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

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1 the table. It's a matter of discussion and guidance.

2 On the other hand, if I find that there seems to be,
3 sort of, two dominant points of view, say over
4 differences of opinion and the like, it won't be so
5 much as a vote, but I might, at least for my own
6 interest, get a sense of the weight of that. If it's a
7 50/50 split, I mean, are these two legitimate
8 positions, or is it just a vocal minority saying it
9 ought to be this, et cetera. Not really a vote, but
10 sort of a sense of how many might fall on one side or
11 the other, because that would at least provide a
12 little more nuance to the discussion. But we won't
13 have any votable issues in that sense.

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

16 DR. KRAL: I'd like to make a suggestion,
17 since devices can be very many different things, and
18 there is a parsing of how we should do these devices.

19 I really think the discussions of most of the
20 questions will be related to the specifics of the
21 generic type of device. For example, may I talk about
22 a band? A band as an --

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

3 DR. KRAL: I'm sorry?

4 CHAIRMAN NELSON: Go ahead.

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

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

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1 know but yet can be judged relative to those
2 characteristics.

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

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

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

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

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

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

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

3 DR. KLISH: I would like to respond.

4 CHAIRMAN NELSON: Go ahead, Dr. Klish.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 alter structure and function, if you will, until one
2 reaches that age of skeletal maturity, regardless of
3 how the endocrinologist would tell us to measure that?

4 Would you go that far --

5 DR. INGE: No.

6 CHAIRMAN NELSON: -- or would you say --

7 DR. INGE: No.

8 CHAIRMAN NELSON: How would you then?

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

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

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

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

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

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

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

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

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

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

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1 in obese girls.

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

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

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

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

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

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

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

8 I think we ought to broaden our scope.

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

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

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

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

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

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

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

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

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

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

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

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

13 CHAIRMAN NELSON: What was the third?

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

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

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

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

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

17 Deborah Dokken?

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

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

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

16 Judith?

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

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

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

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

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

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

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

22 But let me -- when you said no

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1 comorbidities -- Newman, yes, you're right. You're on
2 there, Tom. And then Dr. Roccini's on there and then
3 --

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

13 Jack, and then I'll come over here.

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

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

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

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

21 Dr. Pories?

22 DR. PORIES: My point, but more eloquently

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1 stated.

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

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

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

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

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

20 CHAIRMAN NELSON: Just don't say lap
21 dance.

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

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

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

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

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

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

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

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

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1 discussion.

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

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

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1 device in mind.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 A second point would be about the
14 psychological/psychiatric requirements that's listed
15 there, and I would want to make a recommendation that
16 we think about two aspects of that. One is the
17 psychological impacts of obesity itself, and I think
18 that ought to be part of the comorbidity requirement.

19 So the negative impacts of the condition itself I
20 think is distinguishable from the psychological
21 characteristics that one might want to have as an
22 inclusion criteria for consideration of a device. In

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

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

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

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

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

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

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1 these behavioral therapies.

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

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

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

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

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

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

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1 CHAIRMAN NELSON: Sure.

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

15 CHAIRMAN NELSON: Cincinnati. How's that?

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

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

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

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

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

14 DR. INGE: Those are two things.

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

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

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

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

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

19 DR. INGE: That's fair.

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

22 DR. ROCCINI: I'd like to echo your

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

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

20 CHAIRMAN NELSON: Dr. Gorman.

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

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

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

19 CHAIRMAN NELSON: Paula Knudsen.

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

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

11 CHAIRMAN NELSON: Dr. Rappley.

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

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

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

11 CHAIRMAN NELSON: Okay. Dr. Kral.

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

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

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

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

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

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

9 DR. KRAL: That's right.

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

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

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

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

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

3 DR. KRAL: I'm sorry?

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

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

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

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

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

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

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

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

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

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

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

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

12 CHAIRMAN NELSON: Dr. Champagne.

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

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

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

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

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

18 DR. CHOBAN: Thirty-five with comorbidities
19 and 40 without.

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

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

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

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

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

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

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

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1 DR. YANOVSKI: So, I mean, I think it's
2 very instructive to look at Dr. Dietz's page 4, which
3 has the BMI centiles at the 99th percentile, not the
4 95th, which is a much less stringent point. So for
5 males age 16, the 99th centile is a BMI of 33.9, and at
6 19, the 99th centile is only 36 BMI, right? So we
7 should just --

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

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

12 CHAIRMAN NELSON: The double.

13 DR. YANOVSKI: The two-slide version.

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

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

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

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

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1 criterion.

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

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

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

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

16 DR. ARSLANIAN: Yes.

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

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

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

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

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

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

22 DR. ARSLANIAN: But then we have to

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

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

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

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

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1 start a new list at that point.

2 Dr. Lustig.

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

22 They will get operated on eventually by

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 So with that as sort of a summary, what

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

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

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

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

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

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

14 After adults, your first pediatric trials
15 should focus on an adolescent age group, perhaps 12
16 and above, and only proceed to children younger than
17 12, say, between six and 12, after those trials have
18 also shown some efficacy and safety data that makes it
19 reasonable to proceed.

20 CHAIRMAN NELSON: Dr. Fost.

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

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

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

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

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

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1 something, but that's not the purpose of this meeting.

2 The purpose of this meeting is to try to advise the
3 FDA on how to design trials of safety and efficacy.

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

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

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

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

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

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

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1 make a lot of sense for this sort of thing.

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

18 CHAIRMAN NELSON: Dr. Newman.

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

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

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

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

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

13 MEMBER FANT: Yes, I have a --

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

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

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

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

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

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

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

19 CHAIRMAN NELSON: Dr. Yanovski.

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

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

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

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

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

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

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

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

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

21 (Laughter.)

22 So my question is the specific question is

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

6 DR. KRAL: Exclusion criteria, I think.

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

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

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

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

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

3 So GI devices, an exclusion criteria must
4 be any kind of GI disease, meaning from tooth to anus.

5 Let's not forget tooth because it has to be the
6 ability to masticate if there's going to be any
7 restriction of passage through the GI.

8 The other exclusion criteria which we must
9 have and we're going to get to that an awful lot, I
10 know, and that is that there have to be for the
11 patient in question material resources that are
12 sufficient -- material resources that are sufficient.

13 And there just has to be a means of guaranteeing the
14 ability to have costly monitoring. So material
15 resources. We're going to get into all those other
16 resources that we can, we're going to nail down, but
17 this one ought to be --

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

22 DR. KRAL: I want to be specific on the

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1 BMI.

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

5 DR. PORIES: In adult bariatric surgery,
6 we still know to some degree, the adoption of the BMI.

7 It's not a very good measure. First of all, it's not
8 uni-gender. We measured some 3,000 patients, then we
9 weighed under water in East Carolina and I came home
10 and my wife and I said you know, there are two
11 different curves for men and women. She says you'll
12 have to get all those people wet.

13 Well, the same thing is true in race. A
14 Caucasian woman, an African-American woman and an
15 Asian woman, if they have the same BMI have very
16 different levels of adiposity. So I think we have to
17 be a little careful about choosing that as a measure.

18 And I'm not sure about what happens in children. I
19 think comorbidities make a better measure. And we
20 probably will need to go back through data and develop
21 an obesity comorbidity score that we can actually
22 stratify these patients to answer this question.

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

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

5 CHAIRMAN NELSON: Speak up closely to the
6 microphone.

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

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

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1 exaggeration.

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

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

9 DR. PORIES: That's what I said.

10 DR. ARSLANIAN: I would not go --

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

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

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

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

4 CHAIRMAN NELSON: Dr. Klish.

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

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

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

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1 when you get above a BMI of 30.

2 And the third comment about BMI that I'd
3 like to make is that because it's -- one of the
4 imperfections of the BMI is that we only have charts
5 now that measure, that allow us to measure the
6 percentiles up to the 95th percentile. We're talking
7 about the 99th percentile now, but the present CDC
8 charts don't have a 99th percentile on them which
9 creates a problem and we were talking in the break
10 about the possibility of using Z scores, a concept,
11 God forbid, the pediatric community will go crazy
12 about. But a Z score of 3 is a percentile of 99, the
13 99th percentile is a Z score of 3.

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

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

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

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

10 Issues of long term, let me just go back.

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

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

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

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

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

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

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

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

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

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

10 CHAIRMAN NELSON: What kind of measures?

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

13 CHAIRMAN NELSON: Growth and development.

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

22 Safety endpoints, the number of device

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

8 CHAIRMAN NELSON: Dr. Inge.

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

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

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

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

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

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

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

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

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

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

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

22 DR. ARSLANIAN: This is Blue Ocean

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

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

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

13 DR. ARSLANIAN: I would love to do it.

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

16 DR. ARSLANIAN: I will.

17 CHAIRMAN NELSON: Dr. Kral?

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

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

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

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

14 DR. LUSTIG: In the pediatric group.

15 DR. ARSLANIAN: Yes, yes, we have.

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

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

22 DR. KRAL: In adolescents?

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1 DR. ARSLANIAN: Yes.

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

4 DR. ARSLANIAN: Absolutely.

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

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

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

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

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

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

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

13 CHAIRMAN NELSON: But it tracks, it tracks
14 there.

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

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

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

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

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

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1 also be a relevant thing to assess.

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

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

17 CHAIRMAN NELSON: Right.

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

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

3 Dr. Arslanian, respond to that.

4 DR. ARSLANIAN: It's Pittsburgh against --
5 no, I think, Jack, this is a weight reduction
6 operation, so I would go with the primary endpoint as
7 being a BMI change and the secondary endpoint would be
8 reduction in comorbidity because there you're going to
9 have really hard time defining the reduction in
10 comorbidity. For example, if you take a sleep apnea
11 kid is it going from apnea hypopnea index of 9 to 7 or
12 7 to 6, so it gets even muddier.

13 So I would like to keep it simple.

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

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

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

5 Dr, Klish?

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

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

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

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

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

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

11 Go ahead.

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

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

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

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

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

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

22 MEMBER DAUM: Yes, I want to hear her

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1 comments.

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

4 MEMBER DAUM: Right.

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

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

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1 Is that right?

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

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

7 Dr. Newman.

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

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

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

12 CHAIRMAN NELSON: I've got Dr. Gorman and
13 Dr. Pories, but let me just go back and ask a question
14 that was raised. Dr. Kral asked a question about
15 efficacy endpoints, primary efficacy endpoint versus
16 call it a primary maintenance endpoint. To some
17 extent, there's a burden, as you've mentioned on a
18 device manufacturer for going through a trial to the
19 point where it gets approved. It's very different
20 than saying okay, it works, but does it have a
21 sustained effect over X period of time, whatever X is,
22 2 years, 5 years, 10 years, whatever.

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

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

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

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

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

8 DR. ARSLANIAN: When I look at the data
9 provided in our handbook, with respect to at what
10 point in adults the BMI plateaus, it seems after 12
11 months it plateaus. And my hypothesis will be by
12 three years in adolescence, it's going to be pick up.

13 So I thought the two-year cut point was a reasonable
14 one.

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

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

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

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1 mentioning the time it takes to stabilize at a nadir.

2 I'm not discussing the time it takes to reach nadir.

3 I'm talking about the time beyond nadir that you have
4 a maintenance. That's where I came up with the one
5 year.

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

8 CHAIRMAN NELSON: We don't have to have
9 100 percent unanimity on one versus two, but I do get
10 a sense that more people fault two than one and one
11 was the original suggestion.

12 Dr. Choban.

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

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

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

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

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

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

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

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

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

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

3 The question you raise is if we demand an
4 efficacy endpoint that has a short horizon, whether at
5 12 months or 24 months, I guess could be a point of
6 debate with more people falling on 24 months than 12,
7 that it would then -- I assume the reason people are
8 going slowly is because they do it out of safety
9 concerns and we might actually end up with a safety
10 signal that would be inappropriate relative to what's
11 currently being practiced. Is that fair?

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

22 CHAIRMAN NELSON: So would there be

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1 agreement around the question of what percent excess
2 BMI loss would be the appropriate threshold to reach?

3 I assume sample size is statistical significance. I
4 mean what would be a clinically significant and
5 appropriate percent excess BMI loss at two years?

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

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

16 Jack?

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

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

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

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

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

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

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1 from pharmacotherapy, a 10 percent weight loss in
2 adults and in very few admittedly studies in kids,
3 suggested that we do see benefits in comorbid
4 conditions, so that's not an unreasonable standard.
5 If we're going to hold these devices to a similar
6 standard than we do to pharmacotherapy which I think
7 is not unreasonable, at least as a starting point, a
8 10 percent weight loss that's sustained two years
9 would be a major victory.

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

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

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

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

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

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

22 But you're asking about constancy of the

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

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

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

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

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

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

5 I think if you have a comorbidity, the
6 hard endpoint is the resolution or ablation of that
7 comorbidity, but in terms of not having a comorbidity,
8 the healthy obese child and I know that's an oxymoron,
9 but the healthy obese child wants to not be picked on.

10 They want their peer relationships to be normal.
11 They want to be chosen on the sports team before the
12 last pick. They want to not be excluded from the
13 dance competition as one of our public people said
14 today.

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

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

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

9 DR. GORMAN: I think it's harder to
10 measure and maybe more variable as an endpoint, but
11 I'm looking at the primary effectiveness endpoint. Do
12 we really want to get people down to the 50th
13 percentile going back to Dr. Newman's comment. I can
14 make the obesity epidemic disappear in the next six
15 minutes by just re-doing the charts. If I go and
16 remeasure everybody and set the 99th percentile at the
17 99th percentile for what it is in 2005, the obesity
18 epidemic disappears because there's only 1 percent
19 again above the 99th percentile. I don't think that's
20 a good thing to do. I think there are biological
21 conditions.

22 CHAIRMAN NELSON: Which is why it's eight

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1 percent above one percent.

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

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

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

18 DR. ARSLANIAN: In the individual's mind.

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

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

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1 obese, that she falls in love with a guy.

2 (Laughter.)

3 It does. I see it every day.

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

6 (Laughter.)

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

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

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

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

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

12 CHAIRMAN NELSON: Dr. Ward.

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

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

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

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

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

19 So Dr. Lustig?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 CHAIRMAN NELSON: Jack?

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

22 So indeed, there is an issue about how

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

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

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

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

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

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

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

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

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

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

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

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1 we have the long-term ones.

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

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

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

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

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

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

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

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

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

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

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1 in question.

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

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

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

22 I am always amazed when people put

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1 together rare facts. I think of vaginal cancer after
2 hormonal exposure during pregnancy or the -- and
3 perhaps germane to this discussion the occurrence of
4 gastric carcinoma 40 years after lye ingestions. How
5 did someone put that together? And I think when
6 adverse events occur that are -- could be
7 complications, side effects or actually effects of
8 this therapy, whatever the device is, come to light,
9 5, 10, 15 years later, having a registry that could
10 then be queried for that particular adverse offense to
11 see if it was isolated or a pattern would be very,
12 very useful.

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

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

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

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

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

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

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

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

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

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

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

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

11 (Laughter.)

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

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

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1 labeled safe and effective?

2 DR. KRAL: Two years provision.

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

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

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

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

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1 seems difficult to tease that apart.

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

3 MEMBER DAUM: Could I make one quick
4 comment?

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

7 (Laughter.)

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

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

13 Go ahead.

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

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

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

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

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

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1 follow up.

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

4 (Whereupon, at 12:19 p.m., the meeting was
5 recessed, to reconvene at 1:15 p.m.)
6
7
8
9
10
11
12

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

14 1:23 P.M.

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

22 So I think it's reasonable to push on and

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1 some of the things that were discussed this morning
2 that I think will come back, for example, would be
3 long-term issues. You know, we really didn't sort out
4 -- I heard two year at one point, I heard a five year,
5 but for short term at what point do you let it emerge.

6 We can get into that in talking about registries and
7 the like.

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

13
14 So I'm not going to read the background
15 material on the questions, but I think we've had a lot
16 of conversation about a complex range of issues as
17 we've talked about patient selection inevitably we
18 were tying that to design. And there's been comments
19 here and there about how that might happen, etcetera.

20 So would be nice now is to make explicit,
21 specifically the design issues.

22 And some of the questions that we need to

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

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

14
15 Also, get into the question of sham
16 procedures. Obviously, a device that you can turn off
17 and on, even when the device is implanted which the
18 band has that characteristic, another context where
19 devices have been improved, the beta Vagal Nerve
20 stimulator would be another example of that kind of
21 characteristic where you implant it and you don't turn
22 it on and you can turn it off, etcetera and then also

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1 issues of blinding and masking.

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

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

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

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

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

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

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

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

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

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

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

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

16 Dr. Kral and then Dr. --

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

21 CHAIRMAN NELSON: Why?

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

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1 is it scientific nor is it usually feasible.

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

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

6 (Laughter.)

7 CHAIRMAN NELSON: Well --

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

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

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

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

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

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

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

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

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

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

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

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

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1 why don't you say something.

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

10 And in that trial, it was patients were
11 randomized to on or off, but they both required
12 surgery to have the device implanted. It was a Vagal
13 Nerve stimulator. So all the patients got the
14 surgery, but half the patients actually did not have
15 it activated during that time of the evaluation. So
16 sometimes surgery can be performed and there can be
17 two groups, but the one group can be off and then that
18 group was later turned on.

19 DR. KRAL: The implementation is the same
20 in those two. I'm not discussing on/offers.

21 CHAIRMAN NELSON: I think that's where we
22 need to make sure we're talking about apples and

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1 apples and not different things. I mean there are --
2 in many ways, I think, if I could try to move us along
3 on it so we're not focusing on issues that we all
4 agree on. I don't think anybody would say you should
5 take someone who's meeting the patient characteristics
6 we had talked about before, even if we haven't quite
7 nailed them down perfectly, and have nothing happen to
8 them.

9 So any device in some sense would be an
10 add-on to what would be considered appropriate
11 management. Is that fair or not?

12 DR. YUSTEIN: Yes.

13 DR. KRAL: But people won't do it because
14 you can take an example that we were involved with
15 with the ASD occlusion devices. If you have a
16 randomized trial where patients have the right to
17 choose whether they want to stop or start, we found a
18 number of patients would come, get randomized, and if
19 they didn't get the arm that they wanted to, they left
20 your institution and they went to another institution
21 and they kept going through the process until they
22 randomized to the device that you wanted.

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1 And physically, it inhibited the ability
2 to do that kind of a trial. And we're talking about
3 people who have the same -- you listen to the speaker
4 in the public portion of the meeting who addressed
5 that very same thing. She would not be about going
6 in, getting assigned to standard treatment. She would
7 be off to the next location.

8 DR. INGE: The effect size is just too big
9 to equipoise either as a patient or -- I think what
10 we're talking about is the effect is just so large
11 here, that as a patient it's just not -- there's no
12 equipoise for those who are seeking treatment.

13 CHAIRMAN NELSON: Norm and then --

14 DR. FOST: Correct me if I'm wrong, my
15 understanding is that the number of children who have
16 to date received any kind of surgical or device
17 intervention is very -- is a very small percentage of
18 the whole. That is over 90 percent of children who
19 this group thinks is in need of some more effective
20 intervention is enormous. They presently don't have
21 access to it. What we're trying to do is facilitate
22 clinical trials that would lead to approval of

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1 devices, so that more children could get access to
2 them.

3 So number one, I don't understand the
4 ethical approach of inviting a group of children who
5 presently have no access to effective treatment and
6 inviting them to be in a trial in which they would at
7 least have a 50 percent chance of getting effective
8 treatment and possibly even subsidized. I don't know
9 to what degree that would happen.

10 DR. KRAL: That's coercive.

11 DR. FOST: No, it's not.

12 DR. KRAL: Yes, it is.

13 DR. FOST: You have children who presently
14 have access to no effective treatment and you're
15 offered -- coercion involves threats. Coercion --

16 DR. KRAL: It's an offer they can't
17 refuse.

18 DR. FOST: Coercion refers to situations
19 in which somebody is going to be worse off if they
20 don't accept your offer.

21 This is a situation in which somebody has
22 a 50 percent chance of being better off. And it's

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1 true of every single randomized trial there is in
2 which -- not everybody gets the intervention because
3 in part because you don't know ahead of time whether
4 the intervention is good or not good.

5 DR. KRAL: One thing that's not entirely
6 true though is that they do have access to gastric
7 bypass to probably bands --

8 DR. FOST: Then why are 90 percent --
9 correct me, but my premise was, I thought I understood
10 from all the presentations that the overwhelming
11 majority of these children are presently not getting
12 any surgical intervention, not lap bands or gastric
13 bypass.

14 DR. KRAL: Well, it depends on what
15 children you're talking about. The children who are
16 seeking surgical treatment are seeking and getting
17 surgical treatment. And so if we're talking about the
18 people that might be coming in for a trial like this,
19 it's people who in their own minds have made that big
20 jump and leap of faith that surgical treatment is for
21 me.

22 And that's what's different about surgical

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1 populations.

2 DR. FOST: Is there not a much larger
3 population who is not seeking it either because they
4 don't know it exists or they can't afford it or
5 because it's not reimbursed?

6 DR. KRAL: There is and what would be
7 immoral about inviting those people into a trial that
8 would expand their opportunity from -- of getting
9 something effective from zero to 50 percent?

10 DR. FOST: I certainly don't understand
11 why that's not a scientifically valid question and I
12 also don't understand why it's ethically problematic.
13 If it is, then all randomized trials are unethical,
14 all placebo-controlled trials.

15 CHAIRMAN NELSON: Well, to focus the
16 question, there was a claim made in the open session
17 that because of the established efficacy of a known
18 device that's being used even off label in the
19 adolescent population, that it would be unethical to
20 do randomized-controlled trial. In other words, if
21 someone came in, someone comes in to your program --

22 DR. FOST: Arguably with that device --

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1 first of all, I don't know --

2 CHAIRMAN NELSON: I know your view, Norm.

3 But I'm trying to get an idea of the --

4 DR. FOST: Your comment is addressed to a
5 lap band.

6 CHAIRMAN NELSON: Right.

7 DR. FOST: There's zero information on the
8 next device coming down the pike.

9 CHAIRMAN NELSON: I understand that.

10 DR. FOST: Zero.

11 CHAIRMAN NELSON: So what I'm asking is of
12 the surgeons, in their view, would it be unethical to
13 have a control group that's anything other than a lap
14 band? In other words, as a question --

15 DR. INGE: Comparison, sure. But I think
16 we're talking about the process of randomizing to
17 surgery or no surgery. But certainly --

18 CHAIRMAN NELSON: There are surgical
19 trials that have done that. I mean they've done it
20 with sham surgery and they've done it with either -- I
21 mean there's a current trial that's prenatal fetal
22 surgery versus postnatal surgery that's funded by

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1 NICHHD.

2 DR. INGE: And you know what, the
3 randomization, the trial just tell apart very recently
4 because the patients leaked out if they didn't have
5 what they wanted and they leaked out into other places
6 that weren't doing the trial.

7 CHAIRMAN NELSON: Are you talking about
8 the twin-twin transfusion trial?

9 DR. INGE: Right. Right.

10 CHAIRMAN NELSON: Yes, there were
11 procedures available and that's why I want to get --
12 it may be a feasibility issue but trying to clarify
13 feasibility from ethics I think is an important
14 distinction.

15 DR. INGE: And I'm making the feasibility
16 argument because I think that they will be leaked to
17 other modalities which are effective, like bypass
18 surgery.

19 CHAIRMAN NELSON: But that's a different
20 claim than an ethical claim to say --

21 DR. FOST: Then why are they not presently
22 getting bypass surgery. I understood there's tens of

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1 thousands of morbidly obese children out there who are
2 presently not getting any surgical or device
3 intervention. So your statement that they will go
4 seek it, why aren't they going seeking it now?

5 DR. INGE: Again, I'll come back to the
6 fact that the people who are seeking surgery, who have
7 made this --

8 DR. FOST: I'm not talking about that.
9 I'm talking about the 10,000 children who are
10 presently getting nothing or getting just conventional
11 --

12 CHAIRMAN NELSON: Go ahead, Jack.

13 DR. YANOVSKI: So to my view, ethically
14 what we have, a situation we have some large
15 uncontrolled -- sorry, small, uncontrolled trials
16 which are essentially the same basic information we
17 have in many studies where we then say oh, now we need
18 to do a real study. Right?

19 So even for the lap band in which we have
20 some efficacy data in various selected populations.
21 We don't really have enough data to say yes, go ahead.
22 That's why we're here to help them design trials

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1 which will be able to assess that device and future
2 devices.

3 And the deed of equitable assignment of
4 subjects to groups for comparison is basic to all of
5 our interpretive capacities. Now we made decide that
6 we need to be a little more expansive, so for
7 instance, allow patients to cross over early if
8 there's failures.

9 So for instance, if they don't have a
10 certain amount of weight control within two months.
11 They may then be able to cross over to the other
12 group. That would be one model. Now the group is
13 activation of the devices so that everyone will get a
14 chance to use the device so that's -- I mean, for
15 instance, even in the pharmacotherapy trials that are
16 recently published, * (1:42:45) study by Berkowitz,
17 used that exact assignment. The first six months is a
18 randomized trial and the second six months everybody
19 gets to use the medicine. We have the same trial
20 design for other pharmacotherapy trials.

21 So you don't have to be exclusive in
22 thinking that a randomized trial means now and

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1 forever, the control group never gets therapy.

2 DR. FOST: And we could also discuss a
3 trial of lap band versus bypass. I mean that's up for
4 discussion.

5 DR. INGE: And then the other argument
6 that's made and I guess in this venue is that we do,
7 before taking a child or anyone to surgery, have to
8 show that they failed some measure, other measures.
9 And so it's sort of a randomization to continue to
10 failure or to surgery, so that's where I think the
11 difficulty comes as well.

12 DR. FOST: That's the most ethical, the
13 strongest ethical justification for doing a trial,
14 namely the conventional treatment is failing. That's
15 true of all new -- the main reason we do clinical
16 trials is because the existing treatment is not as
17 effective or as safe as we wish it would be.

18 So when we do a new cancer chemotherapy
19 trials, the statement that we think the treatment that
20 you're presently getting is not good enough.

21 CHAIRMAN NELSON: Before going to Dr.
22 Arslanian, let me try and capture principles, if you

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1 will.

2 What I've heard is the feasibility issues
3 of the availability of weight loss management
4 programs, either surgical or nonsurgical, that people
5 will walk with their feet if the trial is designed in
6 a way that 50 percent of them don't get something,
7 that they perceive as effective.

8 So that a design of a trial that would
9 allow for a sufficient evaluation period of the new
10 treatment against a currently established standard
11 treatment, should be as limited as possible to balance
12 both the efficacy endpoint and allowing whether it's a
13 crossover or whether it's a crossover after a standard
14 period of time, crossover for failure or just
15 crossover for time, which were the two options that
16 you mentioned, Jack, would allow for the scientific
17 endpoint, but define it with the feasibility of people
18 feeling they're getting treatment in this context
19 which is sort of the real world of trying to balance
20 those two and that's the challenge of doing that.

21 Is that a fair -- I mean, independent of
22 what device it is or the like. The difficulty here is

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1 the debate over what is the established standard
2 against which you would do it. Is it just the fact
3 that nobody is getting any treatment because they
4 don't have access to appropriate programs that are
5 just underway versus the moral dilemma someone in
6 those programs gets into when they realize they have a
7 standard of care that they need to provide when
8 someone shows up at their door. And you can't design
9 a trial that's below the standard of care, the very
10 institution at which you're providing that care. So I
11 think it's a balance between those two.

12 We'll go to Dr. Arslanian and then --
13 okay, pass.

14 Dr. Kral and then Dr. Fost.

15 DR. KRAL: Two issues, Dr. Yanovski.
16 There's no jumping in and jumping out of when there's
17 surgery involved. There really isn't. That's a key
18 issue.

19 Let me try a scientific argument. There
20 is adequate evidence that people who agree to be
21 entered and randomized into a study have different
22 characteristics than those who don't agree to be

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1 entered into it.

2 DR. FOST: That's why they're randomized.

3 DR. KRAL: If you have equal -- if you can
4 fulfill equipoise and I strenuously continue to argue
5 that there is no equipoise in a situation --

6 DR. FOST: You're assuming that the
7 intervention is safe and effective. If you're sure of
8 that, then right, there's no point of doing the trial.

9 I thought we were talking about technologies that --
10 for which we don't have any good evidence as to
11 whether they're safe or effective.

12 CHAIRMAN NELSON: Let me ask a clarifying
13 question, although the FDA can't talk about devices,
14 I can certainly ask a concrete question. To make this
15 clear, is there beliefs among one or more of the
16 expert panel and those listening to us that existing
17 treatments such as the lap band or other treatments
18 you may know of are effective enough that any trial
19 done of any new therapy has to be effectively an
20 active control equivalence or a superiority trial
21 using the drug language and not.

22 DR. FOST: Respectfully, that's not --

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1 we're not here to approve the lap band today.

2 CHAIRMAN NELSON: No, I'm not asking that.

3 But you have someone arguing there's no equipoise --

4 DR. FOST: The FDA's question is if
5 there's a device or a surgical procedure for which
6 there is not yet convincing evidence of safety and
7 efficacy in children, FDA wants to know how to design
8 trials to do that. So let's forget lap band for a
9 minute. Let's talk about a widget. And somebody
10 thinks that a widget is good for this disease. The
11 FDA wants to know how to do such a trial.

12 My only point is I don't see any
13 scientific or ethical reason to be opposed to a
14 randomized trial in which children who have failed
15 other treatments would randomly half of them get the
16 widget and half not. Or perhaps, if you want to do an
17 equivalence trial, compare the widget against
18 something that you think is already effective.

19 CHAIRMAN NELSON: Norm, I'm not
20 disagreeing with that point, but I'm asking as part of
21 the apparent disagreement here is the different views
22 about whether there is, in fact, existing treatments

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1 that if you withheld them, it would be unethical,
2 whether it's a sham, whether it's a control, whether
3 it's whatever that you can't withhold those.

4 DR. FOST: Then it's unethical. We
5 shouldn't be sitting here. The surgeon should be out
6 putting these things into the tens of thousands of
7 kids for whom you have effective treatment and you're
8 offering that.

9 CHAIRMAN NELSON: I promised Tom I'd get
10 back to him and I want to make sure I don't skip him
11 to go with people that are just -- Tom?

12 MEMBER NEWMAN: I think what addresses
13 this point is that I don't know that the argument
14 about ethics is really necessary. I agree with
15 Norman, I don't have an ethical problem with doing
16 randomized trial, but I think it is not necessary.

17 DR. FOST: I agree with that too.

18 MEMBER NEWMAN: So maybe we don't need to
19 argue about it. The reason to do the -- to randomize
20 a randomize trial was to assemble comparable groups so
21 you've got strength of causal inference, so you can
22 say what happened to these children who got whatever

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1 the device is, would not have happened otherwise, and
2 the reason why it happened is because they got the lap
3 band or whatever it is. And I just don't think that's
4 a problem.

5 These are children who have been -- their
6 BMI has been at 40 or 45 for years and the possibility
7 that they would have spontaneously lost 100 pounds is
8 just not something I think we need to worry about. So
9 I don't think you need to do randomized trials for the
10 causality, if your endpoint is something as objective
11 as weight and if your effect size is dramatic as what
12 we all expect.

13 If your effect size is quality of life for
14 something like that, for which you might have a softer
15 thing or you might require blinding, then I think you
16 do need a randomized trial. So I think you do the
17 randomization for the causal inference. You do the
18 blinding so that you know what it is that -- your
19 intervention has -- affects the intervention and not
20 just knowing that you got something.

21 And I think that if the outcome is a soft
22 outcome, you probably would need to do some sort of

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1 sham something or some sort of way to have a
2 randomized blinded trial which is why I would vote for
3 the objective outcomes.

4 CHAIRMAN NELSON: It seems so reasonable.

5 (Laughter.)

6 Dr. Gorman? I'll get back to you. So
7 Gorman, and then Klish.

8 DR. GORMAN: I think the design of the
9 trial is, in fact, dictated by the outcome that you're
10 trying to measure at the end, and I would agree with
11 everything that Dr. Newman said. I would just try to
12 remove the jargon of participation of soft outcomes
13 for the outcome that I think is more important, but
14 that's perfectly within your prerogative to do.

15 And I think that randomized clinical
16 trials would be important with certain devices which
17 the outcome, be it body mass index or weight loss,
18 might not be so impressive as some of the results
19 we've already seen, meaning that they would be used in
20 less seriously affected individuals.

21 So as we move down the path to more -- to
22 people with less and less disability, comorbidity or

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1 body mass index, then I think the importance of
2 randomized clinical trials will be more important.

3 MEMBER NEWMAN: And as you're looking for
4 smaller effect sizes, right, as you're looking for a
5 10 or 15 or a smaller weight loss that might happen
6 anyway, that's when you need the randomized trial.

7 CHAIRMAN NELSON: Dr. Klish?

8 DR. KLISH: Just thinking about this from
9 a practical standpoint from running a program where
10 patients are coming in be it to get medical or
11 surgical therapy, I would see no problem during
12 randomly controlled trials for the new devices that
13 are coming down the pike. You do them very much like
14 drug trials which we do now. You would randomize them
15 to behavior control, behavior control plus whatever
16 you're going to test.

17 The only problem with that is the lap band
18 and I was thinking through as to how you would
19 actually approach the patients because they're already
20 knowledgeable about them. They come to us asking for
21 surgery and I could easily set up, design a study
22 comparing gastric bypass to lap band, but comparing

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1 lap band to behavioral therapy would be much more
2 difficult because I wouldn't get -- most patients that
3 come for surgery come for surgery. And they already
4 know about these devices and the lap band, etcetera.

5 So I don't think in the present world at
6 the moment it would be easy to control, you know, to
7 do a randomized controlled study with the lap band.

8 Now in saying that, you could probably do,
9 we are already trying to do case control studies,
10 where we are trying to match patients by case
11 characteristics for the Roux-en-Y gastric bypass and
12 that could easily be done for all these very invasive
13 surgical procedures.

14 CHAIRMAN NELSON: Let me go to Dr. Rappley
15 and then Dr. Inge.

16 MEMBER RAPPLEY: I would like to hear
17 advice on what kind of design would help us establish
18 whether or not this effect can be sustained or a
19 period of time that justifies the intervention and
20 that would address the safety concerns about
21 restriction and malabsorption over long periods of
22 time in a growing child.

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1 CHAIRMAN NELSON: Is there a comment on
2 that question? She agrees that we should try to
3 answer that question. The idea is -- if I could
4 summarize where we are, I mean it seems like RCT
5 doesn't have much support, both scientifically and
6 ethically unless you're in a situation where you're
7 doing less invasive treatments for less sick people or
8 head to head what in a drug side would be an active
9 control trial against one established treatment versus
10 another that you may have a question as to whether it
11 is effective and safer, lap band versus some other
12 device.

13 Within that framework though, the question
14 is how to -- sustainability. I mean it gets then to
15 the length of the trial. I mean at what point -- we
16 talked about a two-year endpoint, but the
17 sustainability issue again comes up.

18 Thoughts on --

19 MEMBER RAPPLEY: And the safety issue too.

20 CHAIRMAN NELSON: And the safety, but
21 separate from registering, again, the balance is and
22 this goes to -- I mean it's actually part of this too,

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1 is the duration of a pre-market study which is what's
2 the point at which you want to let it out into the
3 universe of users versus the duration of a registry or
4 some other post-marketing assessment, what's the
5 duration of a pre-market assessment of maintenance of
6 the endpoint and safety, separate from post-marketing?

7 I heard some people say two years was okay for that,
8 but I guess it's again just a question to see if
9 that's -- anybody have anything else to say that's
10 separate from a registry?

11 Tom?

12 MEMBER NEWMAN: I think it really depends
13 on the level of morbidity and risk of the people who
14 are getting it initially. If the people who are
15 getting it are people with bad comorbidities who
16 otherwise are going to need tracheostomies, if it
17 works for a year or two, even if two, three, five, ten
18 years later, there's bad things, it's probably already
19 going to be worth it for them.

20 So if you start with them, that's when you
21 can start to accumulate the follow up. What you want
22 to be careful of is if there are adverse effects,

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1 esophageal problems or who knows what that might
2 happen in 5 or 10 or 15 years, you want to be slow to
3 start using this device in people for whom, if that
4 happened, it would make them wish they hadn't had it.
5 That's not so likely if they start out with bad
6 comorbidities, so it's a reason to start with people
7 who even if the benefit is relatively short-term,
8 long-term effects would not have made it a bad
9 decision to use it.

10 CHAIRMAN NELSON: Dr. Inge.

11 DR. INGE: I think one other consideration
12 here is that many people hypothesize that the
13 adolescent reaches a degree of morbid obesity in just
14 a few years, may well have different biological
15 reasons why this has happened. In say, for instance,
16 the prevalence of monogenetic forms of obesity may be
17 higher in this population than the adult population.
18 So I think it's reasonable to think of these patients
19 as different. And it's reasonable to think of these
20 patients as likely going to have, it's likely that
21 they will have a higher recidivism rate than you see
22 in adults.

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1 Now if we have a device that has a six-
2 month nadir in weight and then we see the greatest
3 risk for weight regain, then you might design a trial
4 with an endpoint that is earlier. Whereas if you have
5 a device that has a predictable nadir at three to four
6 years, it might well mean that it's more reasonable to
7 look both effectiveness and safety and weight regain
8 at a later time frame.

9 CHAIRMAN NELSON: Given the discussion, to
10 nail down the issue of control group, we've been asked
11 to think about sham treatments or procedures.
12 Separating that from turn on/turn off types of devices
13 which I don't think don't present a whole lot of
14 problems from that standpoint.

15 Can you imagine circumstances under which
16 a sham treatment or procedure is done in order to
17 assure blinding and masking of allocation within a
18 control trial in this environment, where we are now,
19 knowing what we know?

20 DR. ARSLANIAN: No.

21 CHAIRMAN NELSON: Dr. Choban?

22 DR. CHOBAN: I think you're back to that

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1 does not change structure or function kind of device
2 that's often in the future someplace, so that it is
3 easy to turn it off and on, but I think you come back
4 again that if in the initial trials of whatever that
5 said device is, you've got this profound effect, that
6 you're back to -- that you know that you can get this
7 profound effect with this very low risk that I'm not
8 sure turning it off and on or sham treatment is a
9 great idea unless you're going to -- I guess if
10 there's some finite period of time that then they know
11 that if, in fact, in the current population you may be
12 studying, you again see that profound effect. They
13 get to cross over fairly rapidly to the okay, I get it
14 turned on then.

15 CHAIRMAN NELSON: I don't think the on/off
16 is really the issue here. The question is will you do
17 a surgical procedure where you insert a knife through
18 the skin of a child and not actually insert a device
19 in the course of that procedure.

20 DR. ARSLANIAN: 46407.

21 CHAIRMAN NELSON: I'm not saying you could
22 do it from a -- we'll get there, but I'm just saying

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1 could you imagine --

2 DR. FOST: Well, I think if we've agreed
3 on the adults first issue, so you'll be talking about
4 a device or procedure that's been shown to be highly
5 effective and safe in adults and now we're talking
6 about extending it and maybe you needed a sham
7 procedure in adults. I have less concern about that
8 because you have a fully consenting person, but given
9 that, you have a device or a procedure that's fully
10 established in adults and we're now just trying to see
11 if adolescents are any different. I can't imagine
12 there's a compelling argument to use a sham surgical
13 procedure.

14 CHAIRMAN NELSON: Dr. Arslanian and then
15 Dr. Klish.

16 DR. ARSLANIAN: Even without having adult
17 data, I think the sham operation in my definition is
18 more risk with no direct benefit to the patient.

19 CHAIRMAN NELSON: Can I just simplify, is
20 there anybody in here who thinks that a sham surgical
21 procedure is something that would be incorporated in
22 any kind of device trial.

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1 DR. FOST: In children.

2 CHAIRMAN NELSON: In children. We don't
3 need to then keep --

4 DR. FOST: I think we have to get to the
5 theoretical widget. If we're talking about something
6 as invasive as the lap band, then obviously none of us
7 are going to deal with that. But if it's something
8 much more trivial where, for instance, it might be a
9 subcutaneous reservoir of some sort, it's conceivable
10 that if there were really compelling reasons to
11 imagine that the pediatric population might be
12 different from the adult experience in terms of its --
13 the widget's efficacy.

14 I have difficulty blanketly rejecting an
15 approach which is going to be the best way of knowing
16 whether something worked or not when you don't -- when
17 I don't know what we're talking about.

18 CHAIRMAN NELSON: Let me reframe that and
19 then I'm going to ask Ron who had his hand up to make
20 a comment and then we'll see how much further we're
21 going to go.

22 There are procedures that penetrate a

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1 child's skin such as vena-puncture that are considered
2 either minimal risk or depending on the number of
3 times you do it, a minor increase over minimal risk
4 that don't offer the prospect of direct benefit, but
5 if it's important to understanding or ameliorating
6 that child's condition that we can do that under the
7 existing regulations and do it in a way that's
8 considered ethical by most observers.

9 So at least one could say if there was a
10 sham procedure that met that standard, then that might
11 be feasible, but at this point it's a matter of
12 speculating on what the nature of that procedure might
13 be.

14 DR. YANOVSKI: Correct me I'm wrong, if we
15 have an individual with a condition or disease in whom
16 there's the prospect of benefit from the treatment,
17 then a randomized trial is an appropriate thing in
18 which case the sham procedure might be really the
19 appropriate --

20 CHAIRMAN NELSON: It's --

21 DR. YANOVSKI: It's the prospect of
22 benefit, a 50-50 chance.

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1 CHAIRMAN NELSON: I realize it's a
2 prospect of benefit, but you know whether you're going
3 to put it in or not. And normally, that's --
4 normally, the conditions under which that's applied
5 aren't a surgeon deciding not to put the device in as
6 a prospect. So that would be a reach, I think most
7 people would feel, probably.

8 Is it fair to say that would be a reach?
9 Let me ask Ron, how much more we can say about shams?

10 DR. YUSTEIN: I think -- I was actually
11 going to agree with Dr. Yanovski and the point he was
12 making when I had my hand up originally. I was going
13 to say in a lot of adult trials we do endoscopic sham
14 procedures, but then you kind of answered that because
15 you said and I guess in the world of pediatricians and
16 I'm not familiar with these regulations as well as you
17 are, that even vena puncture is considered more than
18 --

19 CHAIRMAN NELSON: No, no, no, no. Let me
20 be concrete.

21 There's variability among IRBs, so take
22 what I say as just one IRB, one experience.

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1 Where I work we have approved endoscopies
2 for the purpose of esophageal biopsies with procedural
3 sedation under appropriate limits under the minor
4 increase over minimal risk, no prospect of direct
5 benefits. So if you're talking about endoscopy or
6 putting a balloon, then that could potentially fit
7 there, if you put the endoscope down and didn't put
8 the balloon in. But that's very different than doing
9 a laparoscopy or doing a laparotomy and then deciding
10 not to do something on the inside of the abdomen.

11 Those would be the issues that would have
12 to be sorted out.

13 DR. YUSTEIN: Just like Dr. Yanovski said,
14 there are probably devices coming down the pike that
15 can be simply inserted like that and some that may not
16 even need a procedure that a person could swallow
17 something that then expands in their stomach.

18 CHAIRMAN NELSON: Yes, but that's the
19 standard we have to meet.

20 Let me go to Norm and get his expertise in
21 this area as well and then let me see what hands
22 remain, I'll look around and get a list on.

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1 DR. FOST: First of all, you can't
2 anticipate before the trial begins which arm is the
3 minimal risk, arm. Ninety percent of new ideas in
4 medicine fail. I don't know about devices, but for
5 drugs, most -- only 10 percent or so are things that
6 interface with treatment ever turn out to be a really
7 good idea. So you don't know ahead of time.
8 Generally, it's better to be in the placebo group.

9 (Laughter.)

10 Dave DeMet says that. If I'm brought to
11 the emergency room unconscious and there's a trial
12 going on for my disease, please put me in the placebo
13 group for whatever that trial is.

14 So to prejudge the issue of which arm is
15 the riskier and which is the safer and which one
16 you're better off in is to say you know how the trial
17 is going to turn out and it's obviously not the case.

18 Second, so therefore, the question is
19 whether being in the trial as a whole has a reasonable
20 prospect of benefit. Obviously, both arms aren't
21 going to be beneficial. One of them will and one of
22 them won't be.

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1 So it will always be the case that half
2 the children in a trial will not have gotten any
3 benefit from it, other than the indirect benefits of
4 being in a trial.

5 So the question is not is the placebo arm
6 nonbeneficial, the issue is is being in this trial
7 offer a prospect of benefit and at trial with sham
8 procedures for children in this situation as a default
9 position. There might be -- it should be argued at
10 least if something comes around in which a compelling
11 case can be made, then we should hear it, or the FDA
12 should hear it.

13 But as a conceptual matter, I don't see
14 any problem with having, for adults, for example, a
15 sham controlled surgical trial and I wouldn't say that
16 the people who are getting the sham are getting
17 something of more than minimal risk. I don't know
18 ahead of time which -- they may be better off in the
19 sham procedure and it may be that the benefit of being
20 in the sham procedure outweighs the risk, that is,
21 there may be a prospect of benefit of being in the
22 sham arm of a control trial.

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1 CHAIRMAN NELSON: With all due respect,
2 let me provide a counter argument and then since --
3 merely to illustrate that there could be two ways of
4 looking at this and then we could go to Dr. Kral. The
5 notion of not knowing whether something is or is not
6 effective, I think, is appropriate, but what's
7 different here is you know the risks you're putting a
8 child to for the purpose of the sham procedure and
9 you're then choosing not to implement the particular
10 device at which you don't know the efficacy.

11 So my argument would be that you know,
12 unless you're going to make an argument that the sham
13 procedure potentially has some efficacy which might be
14 the case if you're doing something in the head, but I
15 haven't heard that kind of argument here. That in
16 fact, the risk to that group needs to be restricted
17 beyond what would be in the overall trial. So that's
18 -- the risk of the sham -- nothing to do with
19 efficacy. I agree, efficacy, you can't make that
20 claim, but --

21 DR. FOST: Being in a sham group may have
22 two potential benefits. First of all, there may be a

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1 placebo effect from it. It may affect outcome. But
2 secondly, it may be that it spares you from the
3 adverse effects of the --

4 CHAIRMAN NELSON: Right, but the sparing
5 from the adverse effects is generally not what people
6 think of the prospect of direct benefit. Individual
7 cases we'd have to get into discussing that, but I
8 just want to -- I don't think it's straight forward in
9 that regard. But let get back to Dr. Kral.

10 DR. KRAL: I'm pleased that Dr. Fost has
11 made it so easy to reconcile our differences. When
12 you stated that 90 percent of medical treatments are
13 bound to fail before they go --

14 DR. FOST: Drugs, new drugs.

15 DR. KRAL: Yes, drugs. It's just the
16 opposite in surgery. So that was very easy.

17 (Laughter.)

18 DR. FOST: How do you know that? There
19 have been so few trials of any surgical --

20 DR. KRAL: They don't fail.

21 (Laughter.)

22 DR. ARSLANIAN: He's wearing his child

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1 psychology --

2 (Laughter.)

3 DR. KRAL: Now then, I'd like to make a
4 constructive suggestion and that is that a case
5 control type of trial method could be appropriate in
6 which the -- and I'm not talking about randomized,
7 that's off the table now, I hope.

8 For example, available treatment would be
9 a case control or possibly best community standard.
10 There's going to be an awful lot of argument about
11 whether it's best medical or whether it's optimal
12 medical.

13 So case control strategy to me would be
14 the way --

15 CHAIRMAN NELSON: How would you find
16 control cases?

17 DR. KRAL: Easy. The pool of interested
18 candidates for treatment would appear in any pediatric
19 clinic or office and it does not require randomization
20 process to be able to find --

21 CHAIRMAN NELSON: I guess the reason I ask
22 the question is if --

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1 DR. KRAL: We're not talking about these
2 urgent cases and all these --

3 CHAIRMAN NELSON: These are not the people
4 who show up wanting surgery, but somehow you're
5 finding them and they've not made the choice to come
6 seek to have surgery. So if you found them
7 beforehand, I guess it undercuts in my mind that they
8 might not be interested in randomization. But --

9 DR. KRAL: I'm not asking randomization.

10 DR. ROCCINI: You could do it two ways.
11 You could do people at an institution where a
12 candidate for the study and then refuse to go into the
13 study because they didn't want to take the risk of say
14 a surgical study. And then you could use them as case
15 controls, except that they had a different motivation
16 whether they wanted to go into or not.

17 Or you could do a second approach where
18 you would have some centers who are in this study and
19 then other centers who would like to be part of this,
20 but are not in the study and then therefore don't have
21 the ability to do the particular procedure that you
22 want and so the standard of care on those centers

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1 would then could serve as your case controls.

2 DR. KLISH: I see large numbers of those
3 patients. They come in for medical therapy, know
4 about surgery, but don't want surgery and they are the
5 same age, same weight, the same gender, so they could
6 be case controlled.

7 DR. KRAL: This very discussion was in the
8 SOS study, the Swedish Obese Subject study where the
9 ethics committees of all the involved universities and
10 agencies said that we cannot randomize, we cannot
11 randomize in this SOS study. So there's a registry
12 study and then there's an allocation of reasonable
13 case controls to this surgery or the intervention
14 group. That was for adults.

15 CHAIRMAN NELSON: Let me go to Dr.
16 O'Fallon and then Dr. Newman and Dr. Rappley.

17 MEMBER O'FALLON: The thing that's
18 bothering me is that we haven't really talked about
19 the effect that these different designs will have in
20 terms of the patient populations they provide.

21 Now one of the problems -- we'll just
22 start at the beginning. Those early studies that have

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1 produced those dramatically wonderful results have
2 been on selected patients and it wasn't a "you all
3 come" thing at all. Those patients were chosen.

4 So we know how the treatment works in
5 those favorable and in some sense, perceived favorable
6 populations. And so it is a problem when we start to
7 move it out to beyond that group of people and
8 especially what I'd like to point out is that children
9 -- I've heard all of you talking about the fact that
10 children are different in subtle ways. And in
11 particular, they do grow and they do mature and what
12 effects on adults may not predict some of the
13 potential bad things that could happen, good things
14 too, but bad things that could happen to the kids.

15 So I think we have to be really careful
16 about choosing designs where we just pick people. I'm
17 really concerned about that.

18 Now case control sounds kind of good.
19 It's better than just picking, but the problem with
20 case control is you have to have some sort of idea of
21 whether the factors that are going to affect the
22 results and sometimes we know them going in and

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1 sometimes we don't. And that's where the
2 randomization comes in, that if you have
3 randomization, some of those things we don't know
4 about are being equalled out by just the flip of a
5 coin.

6 So that's one of the reasons for having
7 them. But -- and the problem here is that sometimes
8 treatments are harmful. We've been talking as if
9 treatment is always going to be good. There are times
10 when treatments are bad, when they hurt. And so we
11 have to be careful about those things too.

12 So anyway, I want to say be careful about
13 drawing conclusions based on pilot studies or early
14 studies because they may not predict what's happening
15 as we open up the patient group.

16 CHAIRMAN NELSON: Tom?

17 MEMBER NEWMAN: A very small point of
18 request, case control studies has a particular meaning
19 in epidemiology, what kind of study and the cases are
20 people who have had some bad outcome and the controls
21 didn't and what the study design being referred to
22 here I think is a matched study. So if you could

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1 refer to it as a matched cohort study, one of the
2 people who get the procedure are matched to people who
3 don't, because it isn't the case control study.

4 CHAIRMAN NELSON: Thank you for that
5 clarification to us non-epidemiologists.

6 I'll get you, but I want to go to Dr.
7 Rappley and Dr. Botkin and then I'll come over to Dr.
8 Choban.

9 MEMBER RAPPLEY: I still haven't heard how
10 -- which would be the preferable method to look at the
11 safety issue? It seems to me that only the randomized
12 method would allow you to look at the long-term safety
13 issue of restrictive and malabsorption, the outcomes
14 of those.

15 But maybe I don't see another way. So
16 enlighten me.

17 DR. KRAL: Malabsorption is not on the
18 table. You keep repeating malabsorption .
19 Malabsorption is not part of it.

20 MEMBER RAPPLEY: I thought we heard some
21 information at least that I read from yesterday was
22 that even with the restrictive methods, there was some

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1 degree of malabsorption.

2 CHAIRMAN NELSON: I think if we use that
3 structure function distinction and we think of the
4 variability that devices could do, some may well
5 affect function dramatically. You've got minor
6 structural to major functional changes and so -- I
7 think -- I'm going to go to Jeff and then to Dr.
8 Choban, but one lesson I learned in the antidepressant
9 experience was that absent the placebo group, you
10 couldn't see the safety signal.

11 So I think -- there may be -- that may be
12 a hard question to answer, but I think we should spend
13 a little time, at least thinking about it. But let me
14 see what Jeff wants to say, then Dr. Choban and Dr.
15 Klish.

16 DR. BOTKIN: I'm wondering if the primary
17 outcome measure is change in BMI by some measure,
18 whether that would adequately be addressed by having
19 the participants serve as their own controls with a
20 six-month standard therapy period of time or medical
21 therapy period of time followed by surgical
22 intervention and observing for BMI changes in that

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1 group.

2 And it does seem for secondary outcome
3 measures, changes in risk, blood pressure, lipid
4 levels, etcetera, that you do need some sort of
5 external control population and that the match design
6 may be necessary for evaluating those. So that was
7 just to float that idea.

8 CHAIRMAN NELSON: Dr. Choban.

9 DR. CHOBAN: I guess that it's trying to
10 take sort of this theoretic view of this study design
11 and then coming back to surgery is -- it tends to be
12 like when you admit people to the hospital and you
13 take them to the operating room, you start incurring
14 all these costs that are more than just usually
15 putting somebody in a drug study. And so who pays for
16 this?

17 And the need to have a pair source of some
18 sort for these long-term studies if we're going to say
19 we need this, it's a real problem in real life when
20 the patient shows up and they lost their job because
21 they used to work at the car manufacturer and they
22 don't exist any more, of how we get your labs drawn

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1 and those kind of issues.

2 So I think particularly in these -- in
3 kids, you know, how you're designing these trials and
4 you're saying that the manufacturers are going to pay
5 for the whole OR? And the whole length of stay and
6 all these -- so I think just as a caveat, as you
7 figure this in and you're trying to figure out where
8 you get your -- not -- whatever the right word is,
9 your matched controls --

10 CHAIRMAN NELSON: Your matched controls
11 are easy, because they're getting what they would have
12 gotten, the intervention group --

13 DR. CHOBAN: Where do they come from? In
14 adults study in almost every series of adult gastro-
15 bypass patients anyway, of people who show up and want
16 surgery, and the surgeon's feel they're appropriate
17 candidates for surgery, we can only get about two-
18 thirds of them through the system, usually because of
19 pair issues. So there's this third cohort that at
20 least when you look retrospectively, matches kind of
21 disturbingly well except on the issue of race.

22 They're as sick. They're as big. They're

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1 as diabetic. They're as hypertensive, as the people
2 you get to surgery than the others. There may be this
3 other cohort that you end up with the system you're
4 unable to treat. So --

5 DR. INGE: But that's off the table in a
6 device trial because the manufacturer does pay for it.

7 DR. CHOBAN: The whole thing?

8 DR. INGE: Sure. Absolutely. Even
9 complications are in the contract.

10 CHAIRMAN NELSON: I think there's a
11 difference when you get into that environment. Having
12 had some experience at least watching what happens in
13 other surgical trials, there is a tension between
14 those who can pay and those who can't pay and then
15 even with third party payors when they hear it's
16 research deciding how they're going to pay for what
17 would otherwise be considered standard care. And so
18 it's a complicated issue, but I'm not sure it's
19 something that we can solve beyond saying yeah, it
20 could be a problem.

21 I've got Dr. Inge.

22 DR. INGE: And this may just be

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1 repetitive, Ron, but it just seems as though you might
2 get more efficiency out of the time here if we did
3 common and specific devices because I think there's a
4 lot of talk about this nebulous device where John
5 feels like and I do too that it's not ethical, it may
6 not be appropriate or feasible to put someone to sleep
7 without any possibility of benefit, but if, in fact,
8 the decision is something that doesn't require going
9 to sleep or doesn't require major risk, then you might
10 well design something differently. So again, I would
11 just throw it out. It's so difficult to have this
12 discussion and have any real meaning to it, I would
13 think, unless we --

14 DR. YUSTEIN: I realize that and that's
15 why we're looking for general principles. We know
16 that there's going to be situations where it's going
17 to require flexibility on our part to kind of take
18 that into account and there's no way you can address
19 all of the different possibilities, but there are
20 devices that require less invasive placement
21 techniques and some that may, in the future, require
22 noninvasive. So we're looking for general principle

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1 guidelines and you certainly may not be able to give
2 us all those now.

3 CHAIRMAN NELSON: Dr. Pories.

4 DR. PORIES: We've actually published two
5 randomized studies in the morbidly obese patients.
6 The first one was a simple test on antibiotics, but
7 the second one was the two groups at two different
8 operations, signed consent for both. They were
9 blinded. The nurses were blinded. Sometimes our
10 surgeons are a little blind too --

11 (Laughter.)

12 You can do that ethically. We also have a
13 study in which those patients who were turned down by
14 insurance, but had been scheduled for surgery were
15 used as match controls. There was a little difference
16 in race, but not much. But frankly, that works pretty
17 well.

18 We've also tried prospectively to
19 randomize people to surgery versus nonsurgery and it
20 just couldn't be done because if we turn them down,
21 they simply just went somewhere else.

22 CHAIRMAN NELSON: The only trial that I'm

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1 aware of that's doing that, there's no back door to
2 where you can get surgery elsewhere. So otherwise, I
3 agree, that trial itself would fail too.

4 Dr. Newman and then Dr. Yanovski, and then
5 I'm going to try to summarize a little bit. And see
6 if we can get over to safety which is still on the
7 table and not been addressed.

8 MEMBER NEWMAN: I wanted to address Dr.
9 Rappley's question about how can you look at safety
10 issues without a randomized trial and it depends
11 entirely on what outcomes you're looking at.
12 Certainly, there are some outcomes, esophageal
13 problems, problems with the reservoir, problems with
14 the device that just are not going to happen in any
15 control group and you don't need a randomized trial to
16 say that here is the rate of infection or device
17 leakage, things that just -- so it's really other
18 outcomes that happen periodically anyway, you know,
19 acne or headaches or things that teenagers get, you're
20 just not going to be able to address those without a
21 randomized trial.

22 So it really is based on the biology of

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1 the device and thinking these are the outcomes that
2 this device is likely to cause and then being able to
3 infer without a randomized trial the device caused
4 this and you can get some estimate of how often it
5 happens and just if you want to look at other things
6 that happen that might not be related to device or we
7 don't understand the biology, then you're not going to
8 be able to do it without a randomized trial.

9 CHAIRMAN NELSON: Dr. Yanovski.

10 DR. YANOVSKI: I disagree.

11 CHAIRMAN NELSON: Let me just try and
12 summarize what I've heard at the risk of hopefully not
13 just producing more conversation.

14 Randomized control trials were discussed.

15 I didn't hear a lot of support for those kinds of
16 trials and maybe there might be limited circumstances
17 where you might consider that, but by and large there
18 wasn't a high degree of enthusiasm for that kind of
19 sort of straight up, classic trial.

20 The kinds of trials that garnered some
21 support, even if they were just mentioned briefly as
22 much to be passed over, first we had had a large

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1 discussion in the morning about the important of
2 running phases. We haven't talked about that now, but
3 I think it's worth keeping that there. And if you
4 imagine a run-in phase, whether it's for enrichment of
5 the population goes on to the second or whether it's
6 -- which would be for adherence or for lack of
7 response.

8 I mean there's various ways of viewing a
9 run-in phase. It could enrich those who don't
10 respond, so you have a higher efficacy signal or it
11 could weed out those who won't adhere and so you have
12 -- but for whatever reason, a run-in phase.

13 And then possible designs after that. One
14 would be the crossover design. Everybody who wants a
15 device would eventually get it, but they'd be willing
16 to wait whether it's two months or three months or
17 four months, it might depend or six on the nature of
18 the device and the nature of the population.

19 Then there's the -- what I would call a
20 single arm trial with the matched cohort which would
21 be everybody who wants the device gets the device.
22 Everybody who has followed, but doesn't want a device

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1 gets part of the matched cohorts for non-randomized
2 and then you've got to worry about comparability to
3 groups.

4 And then the patient is their own control
5 which is sort of the run in baseline and then change
6 from baseline would be another potential design and I
7 know that's used in a fair amount of psychological
8 interventions where you have change from baseline and
9 you have a delayed intervention which would naturally
10 occur just from the fact that you're enrolling these
11 people over time.

12 So those are sort of the -- I may have
13 skipped one that might be your favorite, but seem to
14 be the kinds of designs people are thinking are more
15 appropriate in this kind of venue in general with some
16 outliers, depending upon the trivial nature of an
17 intervention perhaps, if it doesn't require
18 penetration of the skin as opposed to orifices for
19 insertion, etcetera. I mean different ways we might
20 design it, depending on the risk. But that seem to be
21 what I heard. Is that fair?

22 And then -- but I guess the safety issue,

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1 is that -- is there more we can say about that or are
2 we just not saying a lot about it because it's hard to
3 say or is it because there's not much more to say? We
4 had a little bit of discussion of that with tautology
5 that Dr. Kral gave before, but it would be difficult,
6 I guess, in any of these designs, other than the mass
7 cohort design, to determine safety, I guess, would be
8 hard to say. Is that fair? No? Unfair?

9 Dr. Pories and then I'll go over here.

10 DR. PORIES: Well, there are two concerns.

11 One is the obvious one, putting in the device, how
12 does the device work and does it travel and so on?
13 But the other one is what are the long term effects of
14 these and that they may be quite substantial. So I
15 think you have allow more room in this kind of device
16 that deals with nutrition in growing children than you
17 would, let's say, with someone like a cardiac
18 pacemaker in an old man.

19 CHAIRMAN NELSON: So the length of time
20 would have to be different.

21 DR. PORIES: I like the idea that you
22 talked about of getting a two-year -- you didn't like

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1 my word provisional. I sort of liked that, but it's
2 not official. But the idea that you come back after
3 two years and look at it again, but the study will
4 continue.

5 CHAIRMAN NELSON: So one way of phrasing
6 that would be you'd have a five-year study, a two-year
7 assessment of safety and efficacy in that window.
8 Everyone is enrolled, stays in that. For those the
9 next three years, there's a fairly high intensity
10 safety and efficacy component follow-up, but that's
11 very different than if you had a long-term registry
12 which may not collect all of the same kind of data in
13 a registry fashion which would be much more limited.

14 AUDIENCE MEMBER: Well, you ought to have
15 -- let me emphasize since I run a registry, that you
16 must have a registry.

17 CHAIRMAN NELSON: Well, we'll get to that,
18 but I'm just making that distinction because registry
19 would be less data than you would have in another
20 three years of a study that everybody had already
21 consented to.

22 Dr. Garofalo, Newman and then --

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1 MEMBER DAUM: Could I say one thing
2 directly to this comment or would you rather I wait?

3 CHAIRMAN NELSON: Feel free, go ahead.

4 MEMBER DAUM: So I think that the only
5 downside of the two-year or five-year approach is that
6 there's no provisional part to it by FDA rules. So
7 what would happen then is it would be licensed, so
8 you'd have people continuing in a trial that went
9 three more years being observed, I guess, mostly if
10 there's not a control group, for example. And it
11 would be licensed which would allow theoretically
12 greatly increased use.

13 Now if something went wrong with a three
14 to five-year follow up, the downside is that people
15 would then be using this device freely and it would be
16 very difficult to intervene at that point. But
17 otherwise, I think it's a good approach.

18 CHAIRMAN NELSON: I'm sure if it was a
19 serious enough safety issue, the FDA would figure out
20 a way to intervene.

21 MEMBER DAUM: I like the approach. I mean
22 that's why I brought it up this morning. I think it's

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1 potentially a good sort of win-win.

2 CHAIRMAN NELSON: Dr. Garafalo?

3 DR. GARAFALO: So along those lines, I
4 just wondered if there should be some discussion about
5 a formal data safety monitoring board, so if the trial
6 is on-going some way to look, have an independent body
7 that looks at serious safety problem. It might not be
8 necessary, but sometimes it's reassuring. I just
9 wanted to open that up.

10 CHAIRMAN NELSON: That was a question
11 raised under 4. We can discuss it here as well for
12 the kinds of safety monitoring that you would want to
13 have to be on-going.

14 Dr. Ward or Dr. Newman, do you want to
15 dive in at this point?

16 MEMBER NEWMAN: I wanted to come back to
17 the safety issue and how long you have to follow
18 people and whether you need a trial. And I thought of
19 another example. I'm just trying to look up and see
20 if I have it right, but I guess I want to ask that
21 people who are experts in this device, whether they
22 think that we can -- we will be able to infer

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1 causality for all of the likely adverse effects that
2 might be seen. And the example that occurred me, I
3 was just trying to look up, was the silicon breast
4 implants, you know, where there everyone said these
5 things are inert, they can't possibly do anything.

6 And maybe they didn't do anything, but
7 that was where if there had been what would have had
8 to have a gigantic randomized trial, one would have
9 been able to say sooner more definitively whether
10 collagen vascular disease or whatever it was that was
11 associated with them or thought to be, whether that
12 was causal.

13 That's the sort of thing that would be if
14 devices might cause something that right now we're not
15 thinking about at all, then maybe we would want a
16 randomized trial with a long, long follow-up period.
17 I'm -- that's how confident we are that we understand
18 the biology.

19 DR. WARD: I would maintain that you could
20 obtain the same data from what's been described as
21 this current study design if you had an unoperated set
22 of patients and then you have another group, if we

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1 heard about steatosis this morning, that might be
2 increased by extremely rapid weight loss, so this
3 optimal therapy may have adverse effects that are not
4 adequately anticipated.

5 I think having a two-year trial is
6 essential, but then a longer term capture of data
7 would be very important. Those who are very
8 knowledgeable about nutrition and about potential
9 deficiencies may be induced.

10 CHAIRMAN NELSON: Let me ask a question of
11 those who deal with this population. If the argument
12 in favor of a mashed cohort design, single arm device
13 is based partly on the sort of choices that these
14 children and their parents would make over time,
15 what's the odds that those who selected not to have
16 surgery will continue to select not to have surgery so
17 that -- and that your matched cohort would eventually
18 become a surgical cohort?

19 Do they generally stick with their choice
20 not to have surgery regardless of how well the
21 nonsurgical interventions are working?

22 DR. KRAL: There's not enough evidence on

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1 that.

2 CHAIRMAN NELSON: Excuse me?

3 DR. KRAL: Not enough evidence.

4 CHAIRMAN NELSON: We don't know.

5 DR. KLISH: At the present time, there's
6 so few done in adolescence you don't know. It hasn't
7 gone through that community, but my feeling to date is
8 that they select what they want when they come in to
9 see us.

10 DR. PORIES: With adults, they stick to a
11 decision.

12 CHAIRMAN NELSON: Adults stick to it?
13 Okay.

14 DR. CHOBAN: And I think part of the
15 adults, when it's not been entirely their choice, but
16 a choice, if you will, hoisted upon them by the lack
17 of a payor, they switch jobs to try to get other
18 insurance. They've decided they want surgery.
19 There's a lot of people who --

20 CHAIRMAN NELSON: So their choice may
21 change, but their choice doesn't change because
22 they're just trying to make their choice more

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1 effective is what you're saying? They just find ways
2 of getting what they want.

3 DR. CHOBAN: They find ways. If they've
4 decided that that's what they want, they tend to find
5 a way, at least in adults.

6 CHAIRMAN NELSON: To make it happen.

7 DR. CHOBAN: With kids and parents, that
8 interaction and also is the kid then becomes more --
9 gets older and fights for the decision more. I don't
10 know.

11 CHAIRMAN NELSON: It may be difficult.
12 Dr. Kral?

13 DR. KRAL: With adults, they will change
14 their mind regardless of those kinds of constraints.
15 I've had patients 10 years, 15 years have surfaced and
16 they say you don't remember me, Dr. Kral, but I talked
17 to you about surgery once. I'm ready now.

18 CHAIRMAN NELSON: Dr. Rappley and then Dr.
19 Gorman had their hands up.

20 MEMBER RAPPLEY: I'd like to ask the
21 gastroenterologist and endocrinologist if you think
22 that two to five-year frame would allow appropriate

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1 assessment of the kinds of nutritional problems we
2 might anticipate with very restrictive diets in
3 growing children?

4 DR. YANOVSKI: Seems like a reasonable
5 period of time of follow up to me.

6 DR. INGE: I agree.

7 CHAIRMAN NELSON: Dr. Gorman?

8 DR. GORMAN: Realizing that the pace of
9 change in this particular area may be much more
10 dramatic than we might suspect at the moment, I could
11 imagine study designs either with a data safety
12 monitoring committee or timed interval analysis with
13 set endpoints that the agency and the manufacturer
14 could agree on that would allow a device to come to
15 market before the end of the study so that there's
16 demonstrated efficacy and no strong safety signal at
17 some fixed time before the end of the study. It could
18 come to market. The study would continue.

19 So I think that part of what we've talked
20 about is I think we have this desire to have all the
21 information before we let something go forward. I
22 think there needs to be some appreciation that we may

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1 not have all of the information that we want before we
2 let something to market, realizing that there may be
3 something right behind that that makes this whole
4 discussion of that particular device obsolete by the
5 time we get the five-year study finished.

6 So we're thinking here and I've been very
7 impressed with this lap band technology and tomorrow
8 there may be something come out that will make it
9 completely obsolete and this discussion will be -- so
10 I would like to consider or have the agency consider
11 some fixed time intervals where they'll do evaluations
12 of both safety and efficacy, allow something to come
13 to market while the study continues.

14 CHAIRMAN NELSON: Okay, Jeff?

15 DR. BOTKIN: From a safety perspective, it
16 seems that there are probably two types of issues.
17 One would be device related in which case, obviously,
18 whatever the specific device was, you'd have to assess
19 the anticipated safety issues, but there also seems to
20 be a standard set of nutritional concerns that would
21 cross all weight-loss devices.

22 And so I wondered whether nutritionists

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1 and others who are knowledgeable here would be able to
2 put together a sort of standard package of
3 longitudinal assessments of key nutritional parameters
4 that would be relevant across-the-board for these
5 types of devices.

6 And then a second point, I would want to
7 include individuals in either the registry or the
8 longitudinal study who have had the device removed and
9 make sure those folks don't drop out of the study
10 design, but you continue to follow them for any longer
11 term adverse effects from the device.

12 CHAIRMAN NELSON: Let me -- go ahead.

13 MEMBER O'FALLON: You know, we haven't
14 even mentioned things like sexual maturity or any of
15 those issues and they could be even further out than
16 that in which case I mean we'd have to device about
17 how to deal with it, but maybe that will go into that
18 registry thing.

19 CHAIRMAN NELSON: I've got a couple of
20 hands.

21 DR. INGE: It again dawns on me the
22 ridiculous of some of this in that I can tell you from

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1 experience in the bypass population which is granted a
2 more risky operation that we have no, not the same
3 degree of federal scrutiny of but that's a separate
4 comment, that the nutritional consequences really were
5 not adequately or were not completely divulged
6 yesterday. Really, are quite undisturbing.

7 In other words, for an operation that has
8 a very significant degree of restriction in some
9 malabsorptive components, that from the standpoint of
10 macronutrient adequacy, albumin levels in let's say
11 lean body mass is quite reassuringly preserved with
12 current management regimens, out to several years.

13 So I don't have those concerns and I think
14 that probably the fact that this is a restrictive
15 device that's -- well, if we're talking about the
16 band, a restrictive device that's adjustable, we would
17 have fewer concerns about micronutrient deficiencies
18 than we have with say the bypass as well. And the
19 micronutrient deficiencies with the bypass are
20 thankfully few.

21 So again, it's sort of informing the
22 designer, informing the endpoints, if you will or the

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1 safety endpoints for a device from a population that's
2 arguably been exposed to a more significant
3 intervention.

4 CHAIRMAN NELSON: Dr. Roccini and then Dr.
5 Kral.

6 DR. ROCCINI: This may sound a little
7 crazy. I think we would greatly benefit as part of
8 all these potential device trials for weight loss
9 management with the initiation of a national obesity
10 registry which we keep track of patients who are obese
11 or children who are obese over a long period of time
12 that could be used as case matches to look at long-
13 term side effects and the like and be potential
14 candidates for these new device trials and could use
15 these industry-sponsored device trials as a means to
16 support and subsidize such a long-term registry, a
17 little bit like what we've done in Sweden with their
18 obesity surgical trials.

19 CHAIRMAN NELSON: Dr. Kral and then Dr.
20 Pories.

21 DR. KRAL: Although I earlier today
22 pointed out that under nutrition or deficiencies can

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1 be relatively easily handled. I have to protest a
2 little bit against Dr. Inge here. There is evidence
3 indeed over the long term that even a restrictive
4 operation does have certain prevalence of deficiencies
5 that are discovered mainly because of patients who
6 have not come back to be monitored to know whether
7 they are going to be deficient or not on the one hand.

8 And unfortunately, there's evidence that
9 adolescents are particularly vulnerable to develop
10 deficiencies over the long term after obesity surgery.

11 CHAIRMAN NELSON: It sort of raises two
12 questions. I'll go to Dr. Pories with just looking at
13 the question and I don't know if we've really
14 adequately addressed one, I think can be, and that's -
15 - my impression is when we talk about concurrent diet,
16 exercise, behavior modification that a lot of our
17 assumptions is that device trials would be placed on a
18 foundation of appropriate interventions and it's not
19 as if we wouldn't provide concurrent diet, exercise
20 and behavior modification.

21 The question is is it standardized as
22 opposed to a confounder which could be variable over

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1 the course of the trial and provide a confusion to the
2 interpretation of the results.

3 The question you raise and we haven't
4 really talked about assent, transition to adulthood,
5 the adolescent decision making as part of this trial
6 process and haven't focused on that per se. I guess
7 it would be nice to do that even if it's a brief
8 conversation, but at least think about that for a
9 second.

10 Dr. Pories, you wanted to make a comment?

11 DR. PORIES: The American Society for
12 Bariatric Surgery has been concerned about registering
13 and so they have a program in the Surgical Review
14 Corporation which is a nonprofit of identifying
15 centers of excellence. We now have 106 centers, have
16 all combined into a consortium and as of about a week
17 ago we had 47,000 patients in that database that is
18 prospective and one of the important things is that
19 the care paths, anti-operations have standardized to
20 go prospectively.

21 So we do have at least a pretty good
22 beginning on the registry program.

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1 CHAIRMAN NELSON: Who is paying for it?

2 DR. PORIES: The hospitals and the
3 surgeons. There is no industry involvement. You may
4 have remembered that when I introduced myself
5 initially I said I happen to be the chairman of that.
6 I said there is a conflict that you ought to know
7 about --

8 CHAIRMAN NELSON: You're paying for it
9 with your own money, so I guess it's a little bit less
10 of a conflict.

11 DR. PORIES: We're sort of proud of it.

12 CHAIRMAN NELSON: Okay. I thought we
13 would just ask Jack, although he's intramural, whether
14 we could dig into NIG's extramural pocket, but that
15 pocket is getting thinner and thinner over the time.

16 DR. YANOVSKI: I don't have control over
17 anybody's money.

18 CHAIRMAN NELSON: Well, we've got a little
19 bit more time before the break or we could take a
20 break now, but I think we really haven't talked about
21 issues of assent, the role of the adolescent in this
22 per se. We've talked about trial designs. I mean

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1 thoughts specifically on those issues?

2 We'll go Norm, then Jack.

3 DR. FOST: Well, it seems to me all the
4 speakers and all the papers speak to the need for
5 really a strong commitment to carry through on these
6 sorts of enterprises. It's not just a procedure and
7 we don't talk to you again. And that commitment,
8 therefore, requires a willing family and a willing
9 patient.

10 So it seems to me the standards for assent
11 have to be very high. I mean it can't just be a
12 formal sign something. There has to be a real
13 evaluation that the youngster is really interested in
14 this and is committed to it and eager, wants to follow
15 up and so on. So it seems to me it has to be a very
16 high standard.

17 CHAIRMAN NELSON: So here the ethics and
18 the efficacy fit together I guess.

19 Jack?

20 DR. YANOVSKI: So there are two issues,
21 first one, I couldn't agree more than careful
22 attention to assent and I mean I suppose we could be

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1 more directive than that of discussing that assent
2 should be obtained perhaps away from the family. That
3 should be a consideration perhaps, so you can assure
4 that the adolescent really doesn't want to do this.
5 It would be very difficult in the family situation to
6 get a real view of what the adolescent wants to do.

7 And the second issue is that since these
8 trials would be two to five years, many adolescents
9 will be achieving their majority and so provision has
10 to be made for a re-consenting of the previously
11 assented individual and then the transition, in terms
12 of confidentiality and information. So both of those
13 have to be part of the trial design.

14 But at the risk of beating a dead horse,
15 although I heard someone say randomize designs are off
16 the table, I really feel strongly that we ought to not
17 necessarily take them off the table, particularly for
18 the widget design. Even for the current experiments
19 that might be imagined, the fact that the way trials
20 are constructed now, those patients have come to a
21 center because they decided they want to have surgery
22 does not mean that with appropriate advertising and

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1 outreach populations could not be constructed that
2 would be willing to participate in randomized designs.

3 And we know perfectly well that the
4 standard of evidence, the reason why the standard of
5 evidence is ranking for randomized trials highest is
6 because we really do get reads both on efficacy and
7 safety that are unmatched. And although you do need
8 large populations, large samples, I should say, to get
9 good reads on safety which is always a major concern,
10 so even in the drug trials setting 1500 or 2000 people
11 is nothing, compared to what's going to happen when
12 you have on the market and have hundreds of thousands,
13 if not millions of people using medications.

14 The same holds true for surgical
15 interventions. So appropriate sample size to pick up
16 the biggest problems are necessary, but we won't be
17 picking up the rare events in these trials. So we
18 have to -- we should probably also be talking about
19 what kind of samples we're going to be asking to be in
20 the studies because if the effect sizes are as large
21 as what we've seen for the adjustable band, it's not
22 going to require many subjects for efficacy, but we're

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1 going to have to specify safety levels of what rarity
2 of adverse event we want to be able to detect.

3 CHAIRMAN NELSON: How about if over the
4 break I ask Judith O'Fallon to give us a calculation
5 of -- after the break -- about the sample size for
6 these different trials? Is that --

7 (Laughter.)

8 I've got a computer you can borrow. Tom's
9 got his computer. Deborah and then Paula, and then
10 we'll take a break.

11 MEMBER DOKKEN: I think my comments
12 relates as much to consent as assent because what I've
13 been struck with certainly in the last two days is
14 we're talking about a vulnerable population, both the
15 teenagers and their families, who have been struggling
16 with this condition and what it means, both physically
17 and emotionally. And then I think a lot today we've
18 been talking about long term, five years beyond and
19 basically what I heard in a layman's message is that
20 it's not just the surgery, it's a lifestyle change
21 that requires a real shift for the patient and for the
22 family, as long as the patient is still within the

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1 family.

2 And because, yes, we're talking about
3 clinical trials in the design, the whole purpose is
4 then eventually it goes beyond trials. And just how
5 always that that importance of the real dramatic
6 lifestyle shift is always a part of the message of
7 this because I have this awful feeling some time down
8 the road we may see some of these devices on TV just
9 as we see pharmaceutical products.

10 You know, that a lot of information that
11 may be important like you're going to have to change
12 your whole life isn't always part of that. So we're
13 certainly not there, but I just don't want that left
14 out and it does relate to in the very beginning to
15 consent and assent and do people know that they're
16 taking the life style piece on as well as the
17 procedure.

18 CHAIRMAN NELSON: Paula?

19 MS. KNUDSEN: I'd like to say we're now
20 talking about a longer term trial than we had earlier.
21 And what I would like to be certain is that there
22 will be a sharing of data to advise families of the

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1 most up-to-date data, both positive and negative. And
2 I don't know how manufacturers will feel about sharing
3 proprietary information and it's very concerning that
4 they'll be acquiring data that will not be made known
5 to new families coming on board into this now longer-
6 term study.

7 CHAIRMAN NELSON: Let me just make a
8 comment on that and then we'll take a break and if I
9 could also ask, I know there's some people that may be
10 catching planes before the end of the next session,
11 two people have talked to me. If there's other people
12 besides the two that have talked to me, just let me
13 know, but there are surgical trials where the consent
14 form has been changed to each case it goes. So it
15 raises an interesting question as to whether a new
16 device trial there ought to be clear guidance about
17 the information that's provided which is very
18 different than a drug trial as to whether or not --
19 you put this in 47 people and this is what's happened.

20 It's an open question, but I know that
21 there are approaches to surgical trials in the
22 pediatric arena that have used that approach of saying

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1 we've done this in 47 people and each time it's 48,
2 it's 49, it's 50, it's 51 when it's an early trial.

3 And the IRB does have to approve it within
4 the period of time it takes to do that, as a minor
5 change.

6 DR. YUSTEIN: We do that fairly often and
7 change the informed consent as gain information and
8 then if you're talking about a post-approval study as
9 part of a PMA, those sponsors are required to submit
10 annual reports and those annual reports contain
11 additional updated information, as well as the reports
12 of the condition of approval study which can then feed
13 back into revising the informed consent for patients
14 still enrolled.

15 So there's mechanisms to incorporate new
16 information back to the patients.

17 CHAIRMAN NELSON: Okay, well, let's take a
18 break and then start again at 5 after 3. Is there
19 anybody who is going to be leaving during the break?

20 (Off the record.)

21 CHAIRMAN NELSON: What I'd like to do, I'd
22 like to do, I've asked one of them to open with some

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1 remarks and then to be followed by a second. And that
2 way they have an opportunity to sort of say their last
3 word before they split and then we can pick them apart
4 after they've left.

5 (Laughter.)

6 So I think we've covered a lot of
7 territory. I think there's two things that we need to
8 accomplish before the end of the day, depending on
9 when that end of the day is. One is to pick up
10 unanswered threats and the other is to tackle the
11 fourth question which really relates to long-term
12 safety and efficacy. We've talked on that off and on.

13 So in the interest of seeing what threads
14 there are to pick up, there's a few people that are
15 going to be leaving. I've sort of asked -- at a 3:15
16 shuttle to go to the airport -- two of them. I've
17 asked Dr. Inge to just make some remarks before he
18 goes where he sees some loose threads are that we can
19 then pick apart after he leaves.

20 And then Dr. Lustig will sort of build off
21 those remarks and then the people that have to catch a
22 shuttle will be excusing themselves and we'll go on

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1 with our conversation.

2 So Dr. Inge.

3 DR. INGE: First of all, I just want to
4 thank the FDA for taking on this issue and I certainly
5 think that I've learned more than I've offered during
6 this time, but the real -- we've talked about a lot of
7 important issues and the ones that still are
8 unresolved that I think will be figured critically
9 into this process will be the entry criteria, for
10 instance, and in particular, while I applaud Silva's
11 throwing up a potential to talk about with a BMI
12 percentile of 95 with comorbidities and a percentile
13 of 99 without, I really think as a surgeon we have to
14 write letters of medical justification for a high-risk
15 intervention and I just -- I think that's appropriate.

16 I think that we have to be medically
17 justified in offering this. And the data that I've
18 seen thus far would indicate that medical
19 justification can only be established when you're
20 treating the comorbidity.

21 And so I would strongly suggest having a
22 comorbidity as a basic intra-criteria and although it

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1 is somewhat arbitrary, having a BMI centile that's
2 singular and probably 99, which seems to correlate at
3 least in the unpublished data that Bill Dietz shared
4 with us, correlate with a level of adiposity that's
5 roughly commensurate with morbid obesity in older age
6 groups would be appropriate.

7 The other issue is that I'm entirely in
8 agreement with would be a staged approach where an
9 initial trial may be done in adolescents of say 12 to
10 17 year olds and then considering younger age groups,
11 I think is entirely reasonable.

12 The notion of a 6-month lead in within the
13 institution or within the program that the surgery is
14 going to be done, to me, is another area of question.

15 In fact, it might be more appropriate to consider a
16 six month period where an individual has not made
17 successful weight loss milestones in his past in
18 whatever organized attempts were available to him or
19 her might be more appropriate. And then certainly it
20 would require a month or two of program observed
21 follow-up to really get the sense that this patient is
22 going to be compliant would be my recommendation.

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1 The final thing is that during that month
2 or two of observation that we do look for no weight
3 gain and in fact, our program I think that we've
4 realized the benefit to seeing them lose weight during
5 that period as one other indicator of compliance with
6 a health care provider's recommendations.

7 The notion of a multi-disciplinary team
8 with pediatric expertise and also with either
9 pediatric surgical or adult surgical bariatric
10 expertise cannot be over-emphasized.

11 And then just to echo again the endpoint,
12 I think, of primary relevance to an operation whose
13 goal is weight loss would be BMI change in my mind.
14 So again, thank you for allowing me to participate in
15 what I think has been a fabulous meeting.

16 CHAIRMAN NELSON: Thank you. Dr. Lustig?

17 DR. LUSTIG: I want to thank the FDA also.

18 It's wonderful to see them being proactive rather
19 than reactive. This is a problem that's upon us now
20 and it's good to really get this out because this is a
21 big issue and I applaud you for putting this together.

22 I agree with almost everything Dr. Inge

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1 said so let me just comment on the things I disagree
2 with and then you can take it from there.

3 Number one, I think the six-month lead in
4 is absolutely essentially. We actually have a 12-
5 month lead in because you have to fail two
6 pharmacotherapies. I think six months is essential
7 for those patients in whom the surgery would be
8 considered elective. I actually think that there are
9 patients who are going to require bariatric surgery
10 that are not elective. I think because they're
11 emergent because of either airway issues, because of
12 pseudo tumor, etcetera and I think that those patients
13 should be in a tandem design in separate arm. I said
14 that earlier and I still think that's true.

15 Those patients really can't be randomized
16 and they can't wait. They're sick and they need help
17 and if they die they would have died anyway. No
18 amount of standard medical therapy was going to help
19 them. I think we have to be cognizant of that. I
20 think we're doctors first and researchers second.

21 We have to help patients who are going to
22 die before they die and I think that most patients can

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1 be followed appropriate, they're going to go somewhere
2 else and get it anyway or if they get their
3 tracheostomy, they're going to go somewhere else and
4 they're going to get the surgery. We might as well
5 capture that data. So I disagree on that point.

6 The other thing I think that's very
7 important is that obesity is not one disease. Obesity
8 is a phenotype of many different diseases, for
9 instance, we can't expect the melanocortin-4 receptor
10 patients to respond in the same way as what you would
11 call cryptogenic obesity where the same way is
12 hypothalamic obesity or the same way as pseudo
13 hypoparathyroidism. A whole slew of other causes.

14 There are about 18 different causes of
15 pediatric obesity. And I think they're all going to
16 ultimately be different in terms of their response to
17 any surgical or device intervention and I think that
18 it's incumbent upon us to know who they are in
19 advance, so for instance, if you're 99th percentile
20 and you've got a comorbidity, you ought to be having
21 MC-4 receptor genetic analysis and that should be on
22 the books as part of the pre-op workup prior to being

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1 randomized into a trial.

2 So you know who these people are. It
3 doesn't mean they should be excluded. It means that
4 they may need to be post-op evaluated or stratified
5 separately after the fact.

6 Those are the primary places where I would
7 disagree with Dr. Inge. Other than that, I
8 wholeheartedly support all of his comments.

9 CHAIRMAN NELSON: Thank you both for your
10 insightful comments during the meeting.

11 What I'd like to do is at least put
12 Question Four on the table so all the questions are
13 before us.

14 I bear no illusion that our comments will be
15 restricted to Question Four, but at least so that
16 everything is there and as we deal with the issues
17 people feel important to deal with, we get all that
18 covered.

19 Question Four relates to long-term
20 assessment. We've talked about that and these devices
21 are going to be there potentially for quite a while
22 and there would be a need for long-term safety and

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1 effectiveness issues whether it's long-term safety
2 issues or maintenance of weight loss, etcetera.

3 So basically some of the issues on future
4 growth and development, future comorbidities, the
5 importance of maintenance of weight loss, what that
6 might even be, for what period of time and then the
7 type of information that might be collected in a post-
8 approval study which could be either with or without a
9 registry, a registry could be considered different.
10 And then the role of data monitoring committees which
11 we've touched on and any other subject projections
12 that we need to sort of talk about.

13 So those are the full range of the issues
14 that by the end of the day and the end of the day will
15 be five o'clock absolutely and could be earlier if
16 we've exhausted I guess what we might say in the focus
17 group world, if we've achieved thematic saturation.

18 (Laughter.)

19 We'll stop at that point as well, whenever
20 that is achieved.

21 So let me at least start and say there's a
22 couple of things on the table and if we want to clean

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1 them up first or leave them messy based on Dr. Inge's
2 comments, I'm going back to some of the earlier
3 discussions about entry criteria. What I heard was
4 more of an emphasis on the importance of a comorbidity
5 and we're not talking endpoint analysis, we're just
6 talking entry criteria and comorbidities could still
7 be a secondary objective. We don't need to go there
8 again.

9 The other thing I heard which one can
10 interpret one of two ways was the importance of
11 understanding the different etiologies of obesity and
12 at least making sure that you know who they are when
13 they're in the trial.

14 Now you could go two ways with that. You
15 either leave them in, but then you've got a
16 potentially messy trial if, in fact, they respond
17 differently to your intervention than it would be if
18 you don't have enough to stratify them to do any kind
19 of meaningful subgroup analysis, that could get very
20 confusing.

21 So it wasn't clear to me if you'd want to
22 keep them in or exclude them, depending on what it is

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1 and since it's not my area, we may want to just talk
2 about some exclusions much more concretely. And then
3 make sure we wrap up some of the other issues.

4 So why don't we -- those two issues that
5 are sort of there, what -- the BMI and the comorbidity
6 issue that Dr. Inge put on the table and then whether
7 there's more concrete exclusions that we should
8 perhaps begin to identify.

9 We'll go with Dr. Klish.

10 DR. KLISH: I agree with Dr. Inge
11 regarding the comorbidities in adolescents making that
12 an entry criteria because I do think at least at this
13 stage of the game need to think of this as a disease
14 that we are approaching and approaching it as a
15 disease.

16 Eventually, I think, it will open to
17 patients that don't have comorbidities, but I have a
18 hard job in my mind justifying doing these procedures
19 without any information -- on an adolescent population
20 without having any information on risk without having
21 the potential benefit of eliminating a comorbidity.

22 The second issue was -- I forgot --

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1 CHAIRMAN NELSON: The exclusion issues --

2 DR. KLISH: I disagree a little bit with
3 Dr. Lustig. There is ultimately I think genotyping is
4 going to become very important and very interesting in
5 terms of response to therapy, but we're just starting
6 to explore that area in terms of response, based on
7 various genotypes. Now he was also referring to some
8 of the known genetic abnormalities that cause obesity.
9 You said hypothyroidism and I don't know if you said
10 Prader-Willi and things of that nature.

11 My feeling is at least in initial trials
12 and my experience of Prader-Willi, I have extensive
13 experience, we follow about 300 of them, that I would
14 not include them initially in the study because I
15 think they would become a confounding variable, just
16 based on the other characteristics. And I think
17 that's probably true of many of these other genetic
18 syndromes that have obesity associated with them like
19 hypothalamic obesity which is rare, but very
20 complicated.

21 CHAIRMAN NELSON: Before going on to Dr.
22 Yanovski and Dr. Kral, let me ask you a clarifying

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1 question.

2 The thought occurred to me we have been
3 talking a lot about the importance of a motivated
4 adolescent and an assenting adolescent. What about
5 children who are of the developmental physical age of
6 an adolescent, but yet cognitively delayed in
7 different ways? How much does that impact on the
8 efficacy of whether it's surgical or nonsurgical
9 interventions for obesity and would you exclude that
10 group as well or is that a separate group?

11 DR. KLISH: At the moment, we are
12 excluding that group within our program because we can
13 offer that group alternate forms of therapy. You
14 treat the retarded child very much like you would
15 treat the young child where you're basically treating
16 the parents and structuring the home environment. So
17 at the present time, we're not offering surgery or we
18 do gastric bypass, but offering that surgery to that
19 group of individuals.

20 That doesn't mean eventually we might, but
21 I still think we need more information about risk
22 before we start opening the doors to all those other

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1 what I consider vulnerable populations.

2 CHAIRMAN NELSON: Okay. Dr. Yanovski?

3

4 DR. YANOVSKI: So I guess it may be
5 reiterating a position, but I agree with Dr. Inge that
6 at least in the beginning folks with a centile over
7 the 99th are probably the more appropriate group to
8 begin such treatments with and again, those with
9 comorbid conditions, I agree with Dr. Klish, who said
10 that's the group that has the higher prospect of
11 potential benefit in therapy, especially in an unknown
12 widget therapy which we've been asked to consider.

13 But I think we should in the context of
14 trials allow latitude for investigations to include
15 other populations, perhaps, of lower BMI under very
16 careful conditions and after the initial efficacies
17 have been shown for perhaps more significantly ill
18 children. And similarly, when it comes to including
19 or excluding children in the beginning, the
20 individuals with the unknown obesity causes and the
21 healthiest mentally would be the ones to choose, I
22 agree.

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1 The point of the rare genetic disorders,
2 even in the melanocortin-4 receptor indication which
3 are mutations which are believed to be the most
4 prevalent, perhaps, it's only 3 to 5 percent of the
5 super obese and in most series, so okay, maybe 7
6 percent. So it's still not going to be the majority
7 of patients. It's going to be difficult to have a
8 valid analysis of that group. So it may behoove the
9 investigator to exclude them, but at least they should
10 be aware of who is who.

11 It might be appropriate to stratify or at
12 least to randomly allocate such individuals without an
13 intent to evaluate them separately, but at least to
14 assure quality between any groups that are randomized.

15 They might want to know that information.

16 I agree also that groups with Prader-Willi
17 should certainly be parts of, if every study, separate
18 studies where we expect the response to be
19 significantly different.

20 CHAIRMAN NELSON: Dr. Kral?

21 DR. KRAL: On the issue of comorbidities,
22 I think it's extremely important that there be a menu

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1 of comorbidities and a table of contents or a menu of
2 methods that are used to determine the comorbidities.

3 And why I'm making a point of this is I've studied
4 this for so many years. We heard several times
5 earlier that where you look -- if you look, you find.

6 If you don't look, you're not going to find.

7 Such phenomena, for example, a relaxed
8 lower esophageal sphincter is not necessarily going to
9 pop out of anybody. Even a ventricular hypertrophy is
10 not going to pop out at anybody. But when you start
11 looking for it, you're going to find it and you're
12 going to find rather often.

13 So to have comorbidity inclusion as an
14 inclusion criterion in that case it has to be very
15 stringent definition of these comorbidities, then it's
16 going to be one of the -- I don't know if we have to
17 go Oregon to get the public to vote on which ones they
18 think are more important than the others, but that is
19 not an easy task to get a rank order, though I think
20 we will all immediately agree that pseudo tumor
21 cerebri and sleep apnea are way up there, but we can
22 wonder about endotrico * (3:26:26) and I will, in

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1 distinction to what Dr. Lustig had said before, I
2 really once again want to emphasize that quality of
3 life impairment is a comorbidity of substantial
4 importance.

5 CHAIRMAN NELSON: I see no hands. I'm
6 actually looking up, I'm trying to find the website
7 that Dr. Pories had mentioned for the labs at NIH
8 because he showed me some of that -- Google is not
9 bringing up the exact site at this point, but -- is it
10 under NIDDK?

11 DR. KLISH: NIHNIDDKLABS. You have to be
12 an investigator to get into it.

13 CHAIRMAN NELSON: Ah. I don't have the
14 secret handshake.

15 DR. PORIES: You have Dr. Yanovski here
16 who's wife runs that.

17 CHAIRMAN NELSON: Right, so one question
18 has come up and this is obviously something we can't
19 do today as to whether some of the instruments that
20 are part of this might be adaptable to the pediatric
21 setting, but I mean that's obviously a level of detail
22 we can't drill down to in this conversation, but you

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1 know so here's the site for those that are curious.

2 So what about the long-term assessment?
3 We've talked about registries. Just to sort of
4 summarize where we've been, what I've heard is
5 efficacy two years; safety, two years with hesitation,
6 meaning two years might be okay to let it come out
7 into use, but you ought to look for five years at
8 least to make sure things aren't a problem within that
9 trial. The question which I'm assuming is
10 uncontroversial, the need for longer follow up in a
11 registry format, potentially, of the individuals who
12 have these devices.

13 And we've talked about what you might see
14 within that five-year trial within that three-year
15 period which would be a fairly intensive sort of
16 nutritional and safety follow up.

17 What about in the registry? I mean one of
18 the questions is two-fold, what is maintenance of
19 weight loss and what period of time? How long is long
20 enough? What type of information would you think is
21 important in that registry format post-approval?

22 Dr. Pories?

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1 DR. PORIES: Again, I think that's
2 reasonably worked out. Obviously, with diabetes, it's
3 quite easy. What is there, glycolylated hemoglobin.
4 We have look at the back term employment, how bad is
5 the arthritis. We have a scale for that. So I think
6 there are scales.

7 Much more difficult are the problems with
8 terms like neuropathies that go even into paralysis
9 and blindness and somehow you've got to be able to
10 pick those up.

11 CHAIRMAN NELSON: I could see registries
12 would have to be either passive or active. I mean
13 it's one thing -- the first question is would
14 everybody who gets a device from -- if this was
15 accepted, be registered period? I mean in other
16 words, it's in you, you're registered. Everybody or
17 -- the problem is if it's not everybody, then who do
18 you pick?

19 DR. PORIES: Everybody would.

20 CHAIRMAN NELSON: Everybody, all right.
21 So then you've got everybody. Then the question is do
22 you just rely on sort of a passive reporting system

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1 much like where something big pops up, they go see
2 their doctor for a problem and the doctor says ah,
3 you're in the registry, I'm going to send it in, or do
4 you have an active sort of case report form that gets
5 filled out every year, filled out every two years. I
6 mean where the individual in the registry, say like
7 the nurse study which my wife happens to in. We get
8 an envelope that she fills it out, sends it back. And
9 is it sort of like that, where you do that constantly
10 and you can even ask other questions, etcetera.

11 So what do people see that registry being?

12 Let's forget the money for the moment. Let's --

13 DR. ARSLANIAN: Active plus GPS.

14 (Laughter.)

15 CHAIRMAN NELSON: Active plus a chip in
16 the device, GPS.

17 DR. ARSLANIAN: I'm serious.

18 CHAIRMAN NELSON: I don't think even the
19 Patriot Act would allow that.

20 (Laughter.)

21 DR. ARSLANIAN: Especially the modified
22 one.

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1 DR. YUSTEIN: If I could just make one
2 comment on the registries. FDA doesn't do registries.

3 We can ask companies as a condition of approval to do
4 a registry, but you have to remember that's usually
5 the company doing it, unless professional societies
6 step forward and try to coordinate registries across
7 products. If that doesn't happen, then it's usually
8 the individual company doing their own registry, but
9 we don't do registries here. NIH does some. I think
10 CMS does some for some of their Medicaid patients, but
11 FDA doesn't do the registries here.

12 CHAIRMAN NELSON: Let me just ask a
13 question. Would it be useful for us to spend some --
14 I mean we could spend some time thinking about the
15 logistical problems of what at most you could require
16 which would be a sponsor-specific device registry,
17 device by device by device. I mean if we thought that
18 was important, at least then you'd want to be able to
19 have uniform data across devices --

20 DR. YUSTEIN: Sure. If there are certain
21 items that you believe that are important to collect
22 for all kinds of devices in a registry and for how

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1 long that registry should go on, yeah, that would be
2 very helpful.

3 CHAIRMAN NELSON: Well, then let's take
4 length of time first. That might be easier. Five
5 years, 10 years, 20 years, 30 years?

6 I hear age 30, I hear 10 which if he's
7 going into an adolescent gets close to 30. I've heard
8 5. So -- but 10 seems to emerge more than less.

9 DR. YUSTEIN: Can I nominate permanent?

10 CHAIRMAN NELSON: You can, but it might --
11 we always want more data than less, but the reality is
12 if -- let's imagine it's a device -- it's a condition
13 of approval where the sponsor is being asked to do it,
14 what's a reasonable period of follow up time, 10 years
15 or 20? This is an adolescent. Let's say it's in a
16 12-year-old.

17 DR. KLISH: It's difficult to go much
18 further than five years.

19 CHAIRMAN NELSON: Logistically.

20 DR. KLISH: Logistically.

21 CHAIRMAN NELSON: Logistically.

22 DR. CHOBAN: In the face of devices that

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1 are obsolete in six months.

2 CHAIRMAN NELSON: Dr. Kral?

3 DR. KRAL: Well, should we take the
4 example of the lap band? It's supposed to be in there
5 for life. Now if you buy an appliance, how many years
6 would you like that to be? If it's guaranteed for
7 life, that's a pretty good thing, isn't it?

8 Here's what I want to bring up. Same
9 point I made before about comorbidities and the
10 diagnoses. The same thing has to pertain to
11 complications or side effects of a device that are
12 specific to that device. Let me take the
13 example of the lap band. It would be incumbent to
14 very precisely determine how esophageal function is
15 going to be followed up and monitored. Unfortunately,
16 many of the proponents, if not advocates of the lap
17 band who have been speaking in the public forum here,
18 even though they came in on their own money they told
19 me, have said that oh, occasionally, there will be
20 some esophageal dilatation. Yes, swallow a little bit
21 of liquid and see if that's going to diagnose it or
22 not. That's not sufficient. That's not adequate.

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1 There has to be a precise definition of how to
2 determine whether there is, for example, a functional
3 problem with the esophagus that evolves over a number
4 of years.

5 And those functional problems can be of
6 different nature because we've just recently learned
7 the importance of it. Antacid gastroesophageal reflux
8 used to be acid was the biggie but increasingly one
9 has begun to understand that even if it's antacid
10 reflux --

11 CHAIRMAN NELSON: Alkali injury?

12 DR. KRAL: Yes, from --

13 CHAIRMAN NELSON: I'm familiar with Alkali
14 injuries as an ICU doc.

15 DR. KRAL: Of course. So the same thing
16 is going to pertain to even a nerve function in the
17 esophagus. What about micro aspirations? I've seen
18 cases after lap bands who have come with a persistent
19 cough who have interstitial fibrosis of the lung,
20 probably secondary to nocturnal aspiration with a
21 band. So there's going to have to be criteria and
22 looking for it, one imagines are device specific

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1 phenomena.

2 CHAIRMAN NELSON: Let me ask, just
3 sticking with that example which I think is great,
4 let's -- it's now post-approval in adolescents
5 hypothetically.

6 DR. KRAL: Ten years.

7 CHAIRMAN NELSON: So 10 years. And then
8 the question is okay, 10 years, you've given a couple
9 of complications. I mean are you going so far as to
10 say that yearly these individuals as part of a
11 registry requirement or is it a standard of care that
12 they should have that should be a part of say a
13 package, an insert package for the approval that says
14 they should have a swallow that demonstrates A, B and
15 C at certain frequency?

16 I mean I guess having said what you said,
17 what are then the -- is it in the package insert there
18 would be this information about what the doctor should
19 do or would you have the registry actively saying this
20 has to happen as part of the monitoring of the safety
21 of the device for both? How would you carry that out?

22 DR. KRAL: It would have to be active. It

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1 would have to be active and it would have to be
2 mandated. That there would be a compliance with it
3 and the methodology has to be guaranteed to be
4 followed.

5 CHAIRMAN NELSON: So you would advocate
6 then say a swallow?

7 DR. KRAL: I think it's beyond the scope
8 of this, but you're the Chairman, the scope of this to
9 come up with a menu of the specific methodology that
10 we're going to use to study what aspect of esophageal
11 function, for example.

12 CHAIRMAN NELSON: I guess that's not my
13 intent. I guess the intent was to explore the degree
14 to which the burden of that active surveillance would
15 -- what was the sort of level of burden that people
16 felt could be applied because then there's a balance
17 between that burden and the realistic and it may be
18 one thing to say that if someone has a device in, that
19 the physician caring for that individual ought to do
20 these studies as part of a reasonable standard of care
21 is one statement and then report as a registry
22 requirement finding.

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1 That's very separate than the device
2 manufacturers a part of initial approval saying to the
3 people with the device your doctor should do this or
4 you should ask for it and they can always say no,
5 that's their right. But that's very different than
6 the device manufacturer pushing that statement.

7 DR. KRAL: Well, I guess that's going to
8 have to follow the standard model of the numbers of
9 malpractice lawyers per capita that are going to
10 adjudicate what is a standard of care when problems
11 arise. In other words, can the practitioner who is
12 the licensed practitioner taking care of the patient
13 who is having a device put in, be given the entire
14 burden of making sure that a standard of care is being
15 followed or should it be incumbent upon the one who
16 produces this, like a cigarette, and says that it can
17 be used freely.

18 CHAIRMAN NELSON: Other than -- exploring
19 I see hands. Why don't we go to Dr. Hudson, Dr.
20 Rappley and then to Dr. Choban.

21 MEMBER HUDSON: This is very comparable to
22 what we face in oncology all the time, so for some

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1 reality testing our registries at the bottom line are
2 doing vital status and tumor status, especially as our
3 population ages, so it's unrealistic to think that
4 even within 10 years as you have a mobile adolescent
5 population that you may keep them on site, unless they
6 commit to the 10-year study as part of the study.

7 So it seems to me that you're going to
8 have maybe some minimal things that perhaps could be a
9 mail survey or through the physician's office, but
10 when you start mandating we want you to have
11 procedures, diagnostic procedures on a periodic basis,
12 that's a whole different level. And a lot of these
13 things there may be some complications that you did
14 not anticipate and then as that becomes, that
15 awareness evolves, other studies may be added.

16 So it seems like there's going to be some
17 things that we mandated as optimal clinical management
18 for individuals, monitoring nutrition, etcetera, but
19 there may be some very basis complications that you
20 would ask just like our registry letters come through
21 every individual hospital's cancer registry, we fill
22 out some specific information and it's like a one

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1 pager. That may be more reasonable on a global effort
2 from the company saying we're tracking these devices
3 and we want to know XYZ what's happening to your
4 patient, are they alive and do they have diabetes,
5 etcetera, whatever you can. But once you start
6 getting into what is the swallow study showing, I
7 don't know how you're going to be able to mandate
8 that. It seems like it's going to be recommended as
9 optimal care, best care from what you guys know.

10 CHAIRMAN NELSON: Dr. Rappley?

11 MEMBER RAPPLEY: I'm trying to sort out
12 from all of this conversations what we would think
13 should be required in the two-year interval and then
14 what would be required in the two to five-year
15 interval and then where does the registry fit in with
16 that two to five years? Is it an additional five? It
17 becomes a more a reporting in that way.

18 So I'm not clear about --

19 CHAIRMAN NELSON: All right, let me ask
20 for clarification. The 10 year seems to rise to the
21 surface. Was that 10 years -- I assume that's 10
22 years after the device implantation? Yes. So that's

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1 five years on top of the study, but if you're not in
2 the study, it will be 10 years from the time you got
3 it in. And I think the distinction between the
4 registry component or of sending out a letter,
5 etcetera and those things it can be, that would be
6 optimum standard of care I think is an important
7 distinction.

8 Probably what we should do at the very
9 least is to identify what we think ought to be on
10 that, if there's an active surveillance process,
11 what's in that data set going out to get whether it's
12 from the doctor or from the patient and then what
13 might be beyond that.

14 MEMBER RAPPLEY: And wouldn't your
15 findings from your two-year and five-year intervals
16 inform that?

17 CHAIRMAN NELSON: Well, the two year is
18 the efficacy and safety and then the five year is the
19 extended efficacy and safety within the single trial,
20 understanding that then people would be potentially
21 getting the device once it's out after those two
22 years, who would then not be in that trial and be

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1 getting just the registry.

2 Does that -- Jack?

3 DR. YANOVSKI: I tried to make a list of
4 things I thought would be general enough to apply to
5 many situations, so for the long-term follow up vital
6 status, height and weight would be very reasonable to
7 know, and then whether there have been removals or
8 revisions of the device that have been required,
9 infections and other serious adverse events and then
10 device-specific complications would be a relatively
11 short list based on what had been uncovered. And then
12 obesity-specific complications or comorbidities,
13 either new or resolved would be sort of a relatively
14 short list, might be doable in a couple of pages.

15 CHAIRMAN NELSON: Dr. Choban?

16 DR. CHOBAN: I agree. I was sort of
17 thinking of the same list, particularly if the device
18 is removed, that these people don't evaporate from the
19 data base at that point, that there's some -- what do
20 they evolve into?

21 If we're talking about devices that become
22 obsolete in six months, that then are transitioned to

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1 a different device, that to be able to track that some
2 way would seem to be useful but if you are now relying
3 on the manufacturer to do that, I don't see them much
4 interested in doing that.

5 So I guess as people transition from
6 device to device, if that's what happens, how do we
7 keep track of those? So that's one. But the other
8 thing I think I'd add to that, particularly in
9 speaking about adolescents and the females to track
10 pregnancies and reproduction in that as well and what
11 has been the fetal outcomes.

12 CHAIRMAN NELSON: Let me ask you a
13 question. Assuming that for the moment we have no
14 national registry funded either through the good
15 graces of the Centers and the doctors or through other
16 federal mechanisms, if one had a uniform data set
17 among these registries, the only way you could find
18 out if Person A disappeared from registry 1 and
19 appeared suddenly in registry 2, now with a device, I
20 mean you can ask was it removed, registry 1 and then
21 they disappear. You don't know unless they answer it
22 or something new put in. The only way to really begin

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1 to do that is to sort of do a meta analysis of all of
2 these individual data bases. Is there a mechanism by
3 which if there's registries across say a product --
4 this wouldn't be a product-specific -- across a
5 disease-specific set of devices for doing that?

6 DR. PORIES: Crossing the registries is
7 very difficult.

8 CHAIRMAN NELSON: Well, let's assume they
9 all have the same data in it.

10 DR. PORIES: The fact is that in order to
11 maintain peer review and HIPAA rules, you have to give
12 each these folks a code and you can't criss cross to
13 codes, there's no way to deal with that. That's one
14 of the benefits of our new laws.

15 (Laughter.)

16 CHAIRMAN NELSON: So unless we
17 specifically had on the forms have you had this device
18 removed and a new device put in, what was that device,
19 but then you wouldn't really know if that person who
20 said -- if there are two people who had that happen to
21 them, which person they are in the new data base is
22 what you're saying.

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1 DR. ARSLANIAN: Unless the device has a
2 number.

3 CHAIRMAN NELSON: I mean the devices
4 probably have numbers, but I guess this is a -- we
5 don't have to sort of -- it just shows some of the
6 problems with not having it coordinated.

7 DR. PORIES: The other thing is that you
8 want those entries to be reliable, so we're using a
9 kit that we send to the patient as well as to the
10 surgeon and then that kit has to be filled out by
11 another health provider so if somebody gets it done in
12 Greenville, North Carolina and then they move to
13 Columbia, South Carolina, that they can see any health
14 care provider to fill out that sheet, but we prefer
15 not to have the patient fill it out.

16 CHAIRMAN NELSON: What's your adherence to
17 that process?

18 DR. PORIES: We're just starting. Prayer.
19 We believe in prayer.

20 (Laughter.)

21 DR. CHAMPAGNE: I would just add that one
22 thing that would be helpful too in this registry would

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1 be some information that relates to the nutritional
2 status of the individual and also their self-perceived
3 quality of life.

4 CHAIRMAN NELSON: Are there easy ways you
5 can ask that on a two-page questionnaire?

6 DR. CHAMPAGNE: Well, I'll have to put
7 some thought into it, but I think that you'd want
8 something that sort of gave you a feeling or gave you
9 some data to suggest that their nutritional state was
10 adequate. We usually do something very cumbersome to
11 determine that, but the quality of life issue, I
12 think, is probably easier, an easier piece.

13 I'm just thinking free of nutritional-
14 related diseases perhaps. I'm just thinking in terms
15 of the long term.

16 CHAIRMAN NELSON: If a health professional
17 completes it, that's one thing, but if you sent me a
18 questionnaire and said to me are you free of
19 nutritional diseases, I'm not sure how I would answer
20 that.

21 DR. CHAMPAGNE: No, I'm not going to say
22 that for you. Actually, in terms of follow up, I

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1 think it would be really great to have a long-term
2 follow up -- well, even if it's 10 years that is
3 actually performed by the research team. That way
4 it's standardized and you follow a common protocol and
5 I think the data is very important. But maybe -- and
6 maybe you'll do that for five years, but somehow
7 giving us some clue as to nutrition and quality of
8 life.

9 CHAIRMAN NELSON: But I think in the real
10 world that since we're advising the FDA, not NIH,
11 saying that you've got to get your people back in 10
12 years and do a full assessment, it's very different
13 than saying to a program, submit a grant to basically
14 bring everybody back in 10 years and do a full
15 assessment. So it may be useful to do, it's kind of
16 hard to imagine putting it as a condition of approval.

17 DR. PORIES: Employment and marital status
18 can actually give you a fairly good indication of
19 quality of life.

20 It's not great, but --

21 (Laughter.)

22 CHAIRMAN NELSON: Dr. Rappley? I'm not

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1 going to go near that one, but Dr. Rappley.

2 MEMBER RAPPLEY: I already said what I
3 wanted.

4 CHAIRMAN NELSON: Dr. Hudson.

5 MEMBER HUDSON: One thing that you guys
6 were talking about centers of excellence or especially
7 centers that would do this and the way the cancer
8 registries work is your hospital or your center is
9 accredited by the American College of Surgeons and
10 there's guidelines. So it's not like everybody has to
11 do this. It may be the centers of excellence or some
12 of those centers will seek this accreditation where
13 they will monitor and track and in that case it may be
14 for life what happens to these devices and a variety
15 of things on these types of patients who have these
16 devices. That's one mechanism to make it more
17 reasonable that everyone won't do it, but these
18 specific centers of excellence will want that
19 accreditation that they're a service that they know
20 what happens long term.

21 MEMBER RAPPLEY: Is that the basis on
22 which the hospitals donate money to this because they

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1 can then say to the public that we participate in this
2 and this is our comprehensive obesity program and sort
3 of community outreach?

4 DR. PORIES: That's exactly right.

5 CHAIRMAN NELSON: So in a sense, if the
6 pediatric bariatric program is organized in a way that
7 it was good to be in that club, there might be a way
8 of trying to sort of set standards relative to that.

9 DR. PORIES: And they're starting to do
10 just that.

11 CHAIRMAN NELSON: Okay. Well, I think
12 it's reasonable to pause and ask are there questions
13 that remain that we haven't answered because we
14 haven't given an answer that can be given as opposed
15 we have an answer because it's not answerable.

16 And so let me just -- and I'm not going to
17 -- I assume Ron you don't need me to summarize
18 everything that's been said.

19 DR. YUSTEIN: We'll read the 500-page
20 transcript when that comes out.

21 CHAIRMAN NELSON: Well, why don't I turn
22 to you and say at this point, having listened to this,

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1 and sort of looking at -- I mean just explain this, by
2 the way. Each question here is the center solid
3 circle and around each one were the various issues
4 that the FDA said might be considered in addressing
5 the questions that are in those solid circles such as
6 growth and development, post-approval maintenance
7 registry and then the ethical issues are floating
8 around in yellow.

9 So why don't you --

10 DR. YUSTEIN: Do you want me to try to
11 summarize like what -- some of the take-home messages
12 I wrote down?

13 CHAIRMAN NELSON: Whatever you think would
14 be useful and then just, so at the end of the day you
15 feel you've had the questions answered to your
16 satisfaction and then we'll also even take an
17 opportunity to go around the room and just see if
18 anybody has any thing they think haven't been said
19 that need to be said and need to be on the table.

20 DR. YUSTEIN: Like I said nothing is
21 written in stone, but these are just some of the
22 general things that I heard today.

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1 As far as patient population, there was a
2 fair number of people that suggested that the 99th
3 percentile for BMI and the requirements for
4 comorbidities was a fair inclusion criteria, excluding
5 or at least not studying with the main group, patients
6 with Prader-Willi or other genetic causes of obesity.

7 Perhaps a staged introduction of studies
8 by age group, for example, as we get information on
9 the device in adults to allow it into the older
10 adolescent patient population trials first and then as
11 we get information from that, bring it down into the
12 lower adolescent age groups.

13 Overall, probably two-year pre-market
14 study and try to consent patients so that we have
15 follow up guaranteed in them as original study groups
16 through five years with concentrating between two and
17 five years on adverse events, nutritional status, plus
18 the maintenance of weight loss.

19 Possibility of registries for those
20 patients not enrolled in the original studies, but
21 also receiving the device, we can talk internally
22 about logistics of registries. Internally, we

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1 recognize that registries are difficult and the longer
2 you go out, the less likely you are to get useful
3 information, but certainly, you gave us some
4 components of registries that would be important to
5 look at.

6 From the endpoint standpoint, I heard that
7 although most of the ones we listed would be
8 appropriate for secondary endpoints that generally
9 people felt that change in BMI for age or percent
10 change in BMI for age was probably the more likely or
11 the best candidate for primary endpoint and that the
12 others, including quality of life measurements, if we
13 can find a good tool, comorbidities, etcetera, would
14 be good secondary endpoints.

15 One question I had for Dr. Yanovski and
16 earlier when we were talking a little bit about using
17 endpoints to justify sample sizes, we were talking
18 about what was a reasonable degree of effectiveness
19 that might appear in a hypothesis and we had said at
20 10 percent weight loss which is often what's quoted in
21 the literature. But we're also suggesting using a BMI
22 as the endpoint.

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1 Is there a way to -- a way when people
2 come into do their sample size calculations, is there
3 a way to estimate what a reasonable change in BMI
4 percent for age over that two years might be, rather
5 than in as a percentage of 10 percent change? We're
6 kind of using apples and oranges. It's something we
7 can think about, but it's often -- we often get asked
8 when sponsors come in with study designs, one of the
9 main issues that our statisticians deal with is the
10 sample size and that's often based on -- it's
11 hypothesis driven and they hypothesize what a
12 meaningful change is going to be.

13 Oftentimes our sponsors choose to quote
14 the literature and use the 5 to 10 percent change in
15 weight, although we often stress that those are
16 usually, have been results from -- are usually based
17 on studies that are less invasive. Some of our
18 products are more invasive, so we tend to try to go
19 for a little bit higher baseline expectation, that
20 it's going to give more than 10 percent, especially if
21 it's a surgically-implanted device.

22 So I mean we look at 10 percent as kind of

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1 a baseline. And then we use percent EWL so
2 transferring them over, you have to multiply by two or
3 three. So we often tell sponsors in adult trials that
4 we expect at least to be clinically meaningful 20 to
5 30 percent excess weight loss, to try to go back to
6 the 10 percent absolute weight loss. So that's kind
7 of an issue that we struggle with.

8 One thing perhaps that I was still a
9 little confused about, if we do -- I heard that
10 several options for control trials and control
11 matches, etcetera, but it also was mentioned that the
12 possibility of a single arm study would be possible,
13 especially if we knew a lot about the effectiveness of
14 the device from adults or older kids or other
15 information that we had.

16 How do we -- if we have a single-arm
17 study, how do we control for diet, exercise,
18 behavioral therapy? How can we tease apart whatever
19 results we get at the end of the day from what might
20 have been contributed from a rigorous behavior
21 modification program?

22 When sponsors come in and they have a

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1 device that has a borderline effectiveness, maybe in
2 adults or preliminary pilot studies, and if it's a
3 single-arm study, but yet the patients are on a very
4 aggressive 500 calorie a day deficit diet, plus
5 exercise, plus they're meeting in work groups and
6 undergoing the Jenny Craig kind of group sessions, how
7 do we tease apart the results that you may get if
8 you're only talking 5 or 10 percent weight loss? So
9 that's still an issue we still kind of struggle with
10 and I think that's going to show up more in the single
11 arm trial design.

12 And the notion of the six-month lead in, I
13 guess we didn't kind of come to conclusion about that.

14 I heard kind of -- and not that we need to come to
15 conclusion on everything, but I heard some differing
16 opinions, possibly on whether or not there needs to be
17 some kind of six-month lead in or not even six-month
18 lead in and what we would assess during that time, the
19 point of that lead in would be.

20 And then Diane has reminded me, I'm not
21 sure if we commented on data safety monitoring boards
22 that everybody thought that was a good idea during

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1 these trials.

2 CHAIRMAN NELSON: Okay, let me make a
3 couple of comments and then I'm actually just go
4 around the room and let people remark to those issues
5 or any other issues.

6 What I heard with the single-arm trial was
7 that it was very much linked to the matched control
8 and part of the challenge of that is the match would
9 also include that 500 calorie diet, so you've got a
10 nonsurgical matched control and that was part of also
11 the discussion of the advantages of a six-month lead
12 in, again with the exclusion of those that Dr. Lustig,
13 I believe, mentioned that would be emergent, people
14 who have comorbidities that would justify immediate
15 intervention is that you have all of them in a sense
16 on that.

17 It's sort of similar kinds of designs as
18 an add-on trial in a drug setting where you basically
19 have everybody on the same treatment and then those
20 who don't want surgery don't get it and those that do
21 want surgery get it, so you're basically doing a
22 matched controlled study, but it's a nonrandomized

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1 assignment and doing your best at matching those
2 groups, based on the discussion.

3 Now there may be a device you might be
4 willing to randomize. There may be a population that
5 might be willing to do that, depending on the nature
6 of the device, but that's where the devil would be in
7 the details when that device or that widget comes
8 forward, I think as Jack pointed out, that those may
9 well be limited circumstances. We just don't know
10 until we see it.

11 And then I think the Data Monitoring
12 Committee didn't have a lot of discussion because I
13 think a lot of people thought it was a good idea, that
14 you need to have such a committee involved. This is a
15 clinical trial. Even if it's unblinded, I mean I
16 think a data monitoring committee, it's independent of
17 the issue of they can see the data, even if this is an
18 unblinded surgical trial.

19 It's a question of independent assessment
20 and oversight, not so much as protecting the data and
21 reviewing that in a way that doesn't break blinding.
22 So I'm assuming that everybody thinks that's a good

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1 idea.

2 DR. YUSTEIN: Can I add one other question
3 before you go around to the folks?

4 CHAIRMAN NELSON: Sure.

5 DR. YUSTEIN: Something I brought up
6 yesterday during my talk, but I kind of -- it kind of
7 slipped into the back of my mind. If people can
8 comment on whether outside the U.S. data would be
9 acceptable, and if so, as a portion of the study or
10 would you be willing -- or do you think that the
11 practice of pediatric medicine and bariatric medicine
12 is similar enough between here and let's just say
13 Western Europe that would -- we would be willing to
14 accept studies done entirely outside the U.S. If
15 people can kind of comment on that because as you can
16 imagine --

17 CHAIRMAN NELSON: We can comment on that,
18 but I'm just wondering if anyone abroad would want to
19 eat the kinds of things that we would eat at baseline.
20 It's not just clear to me the data would be
21 comparable on that score alone.

22 DR. YUSTEIN: I don't disagree with you,

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1 but I think a lot of manufacturers -- like I said
2 earlier, it's cheaper for them to go overseas and do
3 their studies and that's often something that we face
4 at the FDA. That's often a contentious issue is
5 deciding how many patients and if all need to be done
6 in the U.S.

7 CHAIRMAN NELSON: Then why don't we do
8 this because it may take the bulk of our time and we
9 don't -- if people say something controversial, the
10 intent is not to have people then respond to that, but
11 just sort of go around the room one by one, people can
12 say whatever they feel is important, answer these
13 questions in their own way and we'll see what emerges.

14 Feel free to clean up any misunderstandings or any
15 important points that you think have to be made and
16 respond to Ron's questions.

17 So I'm going to start with Jack and we'll
18 just run around. If you don't have anything to add,
19 just say "nothing to add" and we'll just see where we
20 end up at the end of the day.

21 DR. YANOVSKI: So thanks. It's been a
22 great process today for all of us to think about what

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1 devices might offer and how we might best assess it.

2 In terms of a 10 percent change in weight,
3 these kind of devices, I imagine, are going to be
4 considered in people who weigh 250 to 400 pounds, so
5 with that in mind a 10 percent change is going to 25
6 to 40 pounds, so that's at least a couple BMI units,
7 so let's say two BMI units would be equivalent to
8 that. So that kind of gives you an idea of what would
9 be a minimum change in weight that would be
10 acceptable.

11 In terms of the excess weight loss, as a
12 person taking care of a lot of overweight adolescents,
13 we immediately recognize that the 50th percentile is not
14 even a number that we ever mentioned in patients and
15 the whole concept of excess weight relative to the
16 50th percentile is what is being calculated. So we
17 tend to think of how close could we get them to the
18 95th percentile point. But no one really brings that
19 up as a goal or a point at which you might assess the
20 excess weight relative to that point, but it's another
21 thought.

22 So I think if we could go back to about

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1 changes in BMI for adolescents it's not going to be a
2 problem since most of them have largely completed
3 their growth. They're all going to be over a meter
4 and a half or 1.6 meters, just to think about it as a
5 couple of BMI unit change. In younger children, it's
6 going to have to be individually calculated when the
7 time comes for that. So you have to recognize that as
8 a separate issue.

9 The other part, Skip's comment about data
10 monitoring committees, we all assume that's going to
11 be the case and other than that, I guess the only
12 other thing we didn't talk about is whether we should
13 -- how concerned we should be on future growth and
14 development. I think that has to be part of any
15 assessment in pediatric studies, more so in the
16 younger, even more so in the younger than in the
17 adolescents, but still is a major concern and as Dr.
18 Choban mentioned, things like pregnancy in girls and
19 life events will be important parts of that
20 assessment.

21 DR. KLISH: Just a couple of things that I
22 didn't say earlier and I wanted to just get it on the

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1 record and then a couple of responses to some of your
2 comments. Two things I wanted to say about
3 comorbidities as an indicator for selection for
4 surgery.

5 The one comorbidity I worried the most
6 about is depression because in many cases the
7 depression is not being caused by the obesity, but
8 it's being -- it precedes the obesity and the cure for
9 the obesity may not cure the depression and
10 adolescents are very vulnerable and they are very high
11 risk for suicide. So we take that comorbidity very
12 seriously and kind of deal with it, a little bit
13 separately than the rest. It may not make it an
14 indication for surgery.

15 The other indication that seems to be
16 played down in this that I want to play up a little
17 bit is NASH, nonalcoholic steatohepatitis. And the
18 reason I say that is because I come from primarily
19 Hispanic area and NASH in the Hispanics is very
20 significant comorbidity.

21 In the City of Houston this year, not in
22 my program, but in the University of Texas program, I

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1 have heard they have transplanted two adolescents for
2 nonalcoholic steatohepatitis. So that's obviously a
3 serious comorbidity that should be kept at the top
4 when we're usually looking at indications.

5 I want to defend Tom a little bit about
6 this six-month lead in or the way he discussed the
7 lead in where he said that he didn't think that he
8 needed a six-month lead in, but he needed one or two
9 months to get to know the patient. The reason he said
10 that is not all programs have the capability of
11 providing a full behavioral program to their patients
12 and he felt that if the six-month lead in could be
13 done elsewhere where they have that program and then
14 transfer into the surgical program, that it would be
15 an adequate way of leading into surgery. And I kind
16 of agree with that, I think, if he has a relationship
17 with somebody else who is doing that kind of
18 treatment.

19 And then the last thing I should comment
20 on is the European data, having many friends, I think,
21 now in Europe that are involved in clinical studies, I
22 find that the data that they get is just as valid as

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1 the data we get in this country, assuming that they
2 use the same protocols. So I think if you mandate the
3 protocol, and it's done in Europe, you're going to get
4 very good data.

5 I'm not particularly sure that's true all
6 over the world, but you did say Western Europe which
7 is where I have the most knowledge.

8 DR. CHOBAN: Again, it's been very
9 enlightening to be involved. And I think my biggest
10 concern would be about this six-month run in period
11 and at least being fairly overt about what it actually
12 is. I think what Tom had tossed out, that if you go
13 to -- back step for a minute. If you go to the adult
14 series, I mean most of these patients don't show up
15 asking for an operation as the first time they've ever
16 thought about treating their weight. They've done
17 four or five or six series of dietary attempts, often
18 with drugs, often with VLCDs, doctor monitors, spend
19 years and years of their life and money doing this.

20 So as a parent, I'm not a pediatrician, but
21 as a parent, I can't imagine the first thing I'm going
22 to haul my kid in for is an operation. I think often

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1 these kids have done multiple, serious dietary
2 attempts. So if they can come in with the data from
3 that, to document that they've done this, I think to
4 make them go through yet another system is somewhat
5 onerous.

6 And this couple months to get to know him,
7 you do get to know the family, what is the social
8 support, does the kid really want this? Probably a
9 couple of months is more than enough to accomplish
10 that goal.

11 If we're using it to try to find out
12 matched controls, then there's a different motivation
13 for why you're making them do that and I'm not
14 entirely sure it's fair.

15 So I think that's the only thing, as you
16 set up these trials, I think to have a well
17 documented, previous dietary attempt is reasonable.
18 If they have that historically to make them do it
19 again, just so I can watch it, is probably not
20 necessary.

21 I think one of the things, the only thing
22 I haven't heard when we were talking about that assent

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1 consent, I think the issue that got brought up of
2 being very explicit about the dissent issue and that a
3 kid really is allowed to dissent, is probably worth
4 including in consents.

5 DR. KRAL: This has been very impressive
6 and thought provoking on many different levels, very
7 well done. I commend the Chairman for doing a good
8 job.

9 A few issues that I just heard, I have
10 never in my whole career operated on an obese patient
11 with an anti-obesity procedure within less than three
12 months of my having seen the patient the first time,
13 number one. And you can draw your conclusions
14 afterwards.

15 And number two, I've never, ever
16 outsourced any of the evaluations that I felt
17 necessary to be done believing that some kindhearted
18 internist somewhere would be able to do the job for me
19 and give me a patient in the old traditional
20 authoritarian, custodian manner of the cognitive
21 specialists with a wig and a long gown who will come
22 to the -- the technician who is going to do something

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1 to the GI tract. I've not gone along with that model.

2 I've always insisted on myself having the hands on.

3 So I don't believe in that model. I do
4 believe that a lead in is extremely important and it
5 has to involve the surgical team and those who work
6 the closest with the patient and I don't think it's
7 going to be -- should be outsourced because I also
8 think there happens to be some parameters that are
9 usually not recognized very much and they've gone by
10 the wayside and that is the so-called doctor-patient
11 relationship. When it comes to surgeon-patient
12 relationship, it's something with very different
13 magnitude than that of a doctor-patient relationship,
14 generically.

15 I'd like to make a comment about foreign
16 and foreign data. Dr. Klish chose to look at the
17 validity of the data that is collected. I'd like to
18 give a very different perspective. I hope you don't
19 mind if I use the example of the lap band. The lap
20 band experience in Europe and in Australia, for
21 example, has been substantially different than that
22 we've had in the United States and it continues to be

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1 substantially different.

2 Now does that mean we cannot trust the
3 data that has been collected elsewhere or is there
4 something going on? And I would like to maintain from
5 my personal experience and from what I know about
6 this, that there are substantial differences in the
7 way people in the United States handle food,
8 culturally and behaviorally, compared those other
9 societies where the gastric-restricted model has been
10 working so much better for them.

11 There are also other aspects of the
12 delivery of care in fee-for-service systems in others.

13 So I don't think we can directly translate these
14 wonderful things we heard from Australia, some of
15 them, or from Switzerland or the Danish experience,
16 for example. And immediately think that they're going
17 to be translatable and we're going to get the same
18 results.

19 Now there's no data that I'm aware of on
20 adolescents and young people, whether this pertains,
21 but my guess is that it would because I think that
22 parents behave differently in different cultures than

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1 they do generically in the United States. And I think
2 the marketing of food products and other things is
3 very different, even though "Coca-Cola-onization" has
4 gone very far.

5 As far as -- so those are the two points
6 that I think I can comment on that haven't been fully
7 -- as far as depression is concerned, it's
8 extraordinarily difficult to disambiguate the chicken
9 and egg in this situation. It is extraordinarily
10 difficult. And I know this because we've done
11 studies, particularly on the effects of early life
12 trauma as a precursor of even neuronal integrity
13 changes in different parts of the brain known to be
14 associated with depression and depressive reactions,
15 it's very difficult to know where the process starts
16 and where the process particularly starts in an obese
17 adolescent.

18 Usually, the obesity has started well
19 before there's any indication of depressions that
20 could be secondary. On the other hand, we mustn't
21 discount the many genetic forms of depression that are
22 beginning to be recognized more and more.

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1 So it ain't easy, but of course, we have
2 to be very, very cognizant and on the lookout for
3 evaluating depression as a comorbidity or as a primary
4 factor. No question about that.

5 I think Dr. Yanovski has made it clear
6 that we seem to be working on the model of a work
7 downwards strategy, work downwards, in other words, we
8 have the adults clear, then go to adolescents and any
9 discussions then seem to be completely derived from
10 dealing on an adolescent and you heard the example
11 that Dr. Yanovski gave which was well, we're talking
12 about 250 to 400 pound patients and 10 percent, that's
13 25 -- well, we're going metric inch by inch, so 25 to
14 40 pounds.

15 Well, I don't think we've nailed that down
16 entirely, but it's probably reasonable to take that
17 approach as we approach using devices and studying
18 them in younger and younger age groups, but soon we
19 will probably be discussing people who are not 250 to
20 400 pounds and I don't mean only the dramatic examples
21 that Dr. Lustig brought up with pseudo tumor cerebri
22 or sleep apnea or somebody who comes in with DKA or

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1 that it has progressed to that state. So we just
2 need to keep that in mind.

3 But thank you very much, everybody.

4 DR. CHAMPAGNE: I'd like to just thank the
5 FDA for inviting me. I haven't learned a lot
6 participating in this panel because this is a totally
7 new area compared to what I normally do.

8 It strikes me that the learning period
9 could be a period where we can view the subject as
10 being their own control, collecting data, I know this
11 has been brought up and I think that point was
12 mentioned and I think it would be an ideal thing to
13 consider. I think if we can implement a standardized
14 protocol that focuses on nutrition, physical activity,
15 behavior change in the same manner for every
16 institution that's going to do this, hospital,
17 whatever, that it could be a way of getting around the
18 need for randomized clinical trial which we already
19 agreed was not probably going to work. But I think
20 that we could take advantage of this run-in period to
21 look at a period of time where the subject could be
22 their own control.

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1 CHAIRMAN NELSON: Thank you. Dr.
2 Arslanian?

3 DR. ARSLANIAN: Actually, I agreed to come
4 to this activity because I was curious about what is
5 all this about and I'm glad to say that I'm not
6 disappointed and I enjoyed the interaction
7 tremendously and I think the diversity of the
8 expertise made it so much fun.

9 I just want to add a few things which were
10 not added. I think we have to have a very clear
11 glossary of what the comorbidities are and how they
12 are being evaluated because the fact that somebody
13 does not complain of sleep-related abnormalities does
14 not necessarily he or she does not have sleep apnea,
15 especially if we're going to make the comorbidity and
16 eligibility or exclusion criteria.

17 Or I can argue against that Inge's
18 proposal that it should only be children with
19 comorbidity who are included, then I can tell him that
20 any kid who has a BMI above the 99th percentile would
21 have insulin resistance as a comorbidity. So I think
22 that's why we have to have very clear definition of

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1 what comorbidities we mean and what severity and what
2 extent.

3 The other issue I think is the run-in
4 period. I believe the run-in period is important. It
5 should be there. However, the duration of it can be
6 argued, three months, six months and that all depends
7 on what device one is talking about.

8 The third issue, the long-term outcome is
9 very important because unfortunately, adolescents
10 don't make me trust them what will happen and how they
11 will behavior and what the outcome of any intervention
12 would be long term. So probably those are the only
13 things that I would like to add. And then the issue
14 of the potential active control trial, but I'll not
15 dwell on that any further.

16 CHAIRMAN NELSON: Thank you, Dr. Pories.

17 DR. PORIES: I want to second what
18 everybody here has said about your direction of this.
19 I never thought you'd get through this. And I've
20 really learned a lot.

21 In terms of the primary endpoints, I would
22 add two or three serious comorbidities such as sleep

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1 apnea, diabetes to the BMI, rather than just sticking
2 to the BMI as the only primary endpoint.

3 We haven't talked about the Tanita scale
4 which only costs about \$1200 and provides a pretty
5 good verifiable level of body composition and lean
6 weight and I think that's a pretty good indicator that
7 we decided to use it at NIDDK.

8 We've used a six-month lead in at East
9 Carolina for probably 15 years, simply so we get to
10 know the patients. It gives a very good idea about
11 compliance. If the person doesn't comply in the first
12 six months, they're not going to comply afterwards.

13 In terms of safety monitoring board, I
14 think that's essential and I believe that that can be
15 attached to the registry. The registry should be
16 independent of the program and the monitoring board
17 should be independent of the registry and both should
18 be on tap at all times to monitor what's happened to
19 the patients.

20 Finally, I have a little story about
21 outside U.S. data. Dr. Scopinala has done the bilio-
22 pancreatic bypass for years. His experience in Italy

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1 and our experience in Italy are totally different just
2 based on diet. We have many more nutritional problems
3 than they do in Italy and I'm sure that the people do
4 it here and Dr. Scopinala are reliable and ethical
5 surgeons. So I have the same concerns about taking
6 outside data.

7 Thank you again.

8 CHAIRMAN NELSON: Olive oil or red wine?

9 DR. ARSLANIAN: Olives.

10 CHAIRMAN NELSON: That's would I would
11 think. Olives would be my hypothesis.

12 MEMBER DOKKEN: Just quickly, I think my
13 main take home message from this has been sort of the
14 complexity and what I referred to before about the
15 lifestyle change that impacts both the child and the
16 family.

17 And I guess that that leads me to a
18 certain troubling, nagging worry which relates to
19 something that Judith O'Fallon referred to before
20 which is because it is so complex and because it is
21 such a big process or program, how is that going to in
22 the sense of distributive justice, how is it going to

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1 relate to sort of the demographics of the problem and
2 since I'm on here as a family member, and the family
3 member who has had a number of significant health care
4 issues to deal with, one of the things that has been -
5 - the life saver is having the resources, whether it's
6 your insurance or your friends that you can network
7 with to get additional information to get you through
8 the morass or whatever it is.

9 And so I do worry about hearing about
10 something that feels a little bit, even when we --
11 someone referred to the lead in period and these will
12 be people who have had multiple attempts before, so
13 why would you need a long lead in period?

14 Well, the only people who are going to
15 have multiple attempts before will have had the
16 resources to do that. So I know it's not part of the
17 clinical trial per se, nor is it part of the FDA
18 responsibility, but I just feel like I need to say
19 that.

20 MEMBER MOORE: I think that -- I haven't
21 said too much today because I feel like I've been
22 learning mostly, but I think one of the things that

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1 the FDA may wish to consider as you're working with
2 sponsors to design trials is that these devices are
3 likely not going to be all sliced bread. And I think
4 we've been myopic a little bit here because we've got
5 this lap band and there's been a lot of discussion
6 about it.

7 And the lap band requires an invasive
8 surgical procedure, so it's more like doing surgery or
9 it is surgery, really, but surgery with a device
10 implant. It's possible that they'll be devices which
11 arise that are not nearly as invasive, that may be
12 even worn or strapped on that may be swallowed, that
13 may dissolve, who knows? It may be implanted
14 subcutaneously with local anesthesia, etcetera. And
15 so I think that you need to have some kind of way to
16 differentiate between what's required of an invasive
17 or surgical-type device versus what's required for a
18 device which is less invasive or completely non-
19 invasive.

20 And I think that the single arm study is
21 probably appropriate and all the things that have been
22 said almost entirely deal with that invasive-type

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1 device. And I would agree that a single arm matched
2 study would be the way to go with that or you might
3 even consider offering objective performance criteria
4 as you've offered with some of the cardiovascular
5 devices that I've worked with that basically rely on
6 data from other sources as the control for the
7 measure, such as adult data for a given device or even
8 the pediatric surgical data, the straight up surgery
9 without a device.

10 In the noninvasive type devices, I think
11 because these are likely to give you less benefit and
12 to be harder to distinguish from medical therapy or
13 behavioral therapy, you may want to require RTCs
14 because these may get very confused. They may be a
15 lot less benefit and then you have to go, you're in
16 that really muddy water that we talked about earlier.

17 And so that would be the one thing I would add.

18 I don't think we've emphasized this, but
19 you know, devices will be -- will run the spectrum of
20 your imagination and not just something that has to be
21 implanted by one of these surgeons that we've had talk
22 about a great deal to us.

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1 CHAIRMAN NELSON: Paula, with your
2 permission, Bob Daum needs to leave at 4:30. Do you
3 mind if I go a little bit out of order?

4 Bob?

5 MEMBER DAUM: Thank you. I apologize for
6 needing to do that, but I have to deal with Dulles
7 Airport and it took me two and a half hours to get
8 here from Dulles the other night, so I'm anticipating
9 trouble going back as well.

10 I'm just going to comment in a couple of
11 areas that I'd like to emphasize that haven't been
12 said, and try to do it as quickly as I can. First of
13 all, I think randomized control trials do have a place
14 in consideration of designing trials for devices. I
15 think there is comfort if we know things work or
16 almost certainly work in adults in avoiding the need
17 for randomized controlled trials, but without that
18 reassurance, my level of comfort and going forward
19 without a control trial really goes down.

20 The second issue, of course, just to
21 emphasize again something that I have said earlier and
22 so did others, is that the relative risk of the

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1 procedure itself to enter the trial and get the device
2 going, obviously, impacts at least in my view, about
3 whether we need a randomized control -- whether
4 randomized controlled trial is feasible or not. And
5 so that if the risk of putting the device on, such as
6 a skin patch or something is quite low, then I would
7 drift back in my thinking toward the more Cadillac
8 approach which would be to have a good, randomized
9 control trial.

10 The second point I wanted to just
11 emphasize is this business of comorbidities which I
12 think everyone at the table agrees are something that
13 are very important. And I think I'd like to emphasize
14 a systematic search. It's a point that others have
15 made, but just to emphasize them, of ones that the
16 endocrine people and the obesity doctors feel are
17 important in patients that are going to be enrolled
18 and to make sure that employed in the study design is
19 at least the comorbidities that are believed to be
20 important have sufficient sample size to make sure
21 that they're likely to be measurable in the outcome
22 parameters. I think that's really, really important,

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1 that there be a systematic search and that some key
2 ones, I think you used the word life threatening ones,
3 be chosen for powering the study so that we have good
4 data at the end.

5 Obviously, most of the discussion we had
6 here was really with drums of the lap belt behind us
7 and there's obviously a wide range of devices that
8 could be used. And I think we had a good discussion
9 so that if it weren't lap belt driven and abdominal
10 surgery necessitated to start it off, FDA can get our
11 sense of how to go.

12 I think that the initial study to see
13 whether it works or not should be done on -- I would
14 favor, actually stacking the odds a little bit so that
15 we have highly motivated patients entering that are
16 likely to comply with the protocol so that we can
17 really see if the thing works. And I think extending
18 it to other groups can be a secondary goal.

19 I strongly urge some kind of long-term
20 assessment. Dr. Pories has his registry and maybe
21 some kind of copy of that can be made. I personally
22 don't think the sponsor should be the one to really

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1 orchestrate it on their own. It's a little like the
2 fox starting the chicken cook in my view. But I think
3 there ought to be a mechanism and sitting around the
4 table, I don't think we came up with it, but there
5 ought to be a mechanism for tracking these patients
6 long term, even if it's not a formal study tracking
7 long term. But some mechanism should be sought.

8 I just want to echo the comments of I
9 don't think that since a lot of obesity clearly is
10 cultural that we can really use data, international
11 data to decide if an approach such as the lap belt or
12 another device really works in the United States. I
13 think we need home data for this one.

14 And lastly, I guess I just can't help but
15 make one quick comment about this. We used to treat
16 very high fever in the emergency room by dipping babies
17 in ice water. And it was kind of a crude technique
18 and really it didn't address the cause of the fever.
19 And somehow obviously we're charged to look at devices
20 and I think -- I agree that we've had a wonderful
21 discussion. I think it's a great forum established by
22 FDA and Skip, I think you've done a wonderful job

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1 leading us through this maze to be honest. But
2 somewhere there needs to be a similar quality
3 discussion about what the causes of this obesity
4 epidemic are and our belief that there could be a
5 treatment or surgical cure reminds me a little bit
6 about like dipping babies in ice water. And that's
7 all I have to say. Thanks.

8 CHAIRMAN NELSON: Thanks. Paula.

9 MS. KNUDSEN: I would just like to say
10 that regardless of the invasiveness or non-
11 invasiveness of the device, I think the most important
12 thing is the relationship between the physician,
13 actually between the team and the patient.

14 I think it makes for much greater
15 compliance. It makes for much greater follow up. I
16 would consider it of the greatest importance and also,
17 it would increase my comfort level that there would be
18 sensitivity to the dissent of the adolescent. I can
19 imagine parents being frantic and being pressuring
20 their adolescent to go ahead and have the surgery
21 because it takes so long to achieve anything else by
22 less dramatic means.

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1 So I would like to be certain that there
2 is a relationship so that it is very clear that this
3 is something the adolescent really does want.

4 CHAIRMAN NELSON: Judith.

5 MEMBER O'FALLON: He has been watching me
6 take notes and he's afraid I'm going to say it all.

7 CHAIRMAN NELSON: I was looking at Judith
8 and she's got two pages of notes and I said Judith,
9 are you going to say all that?

10 (Laughter.)

11 She assured me that she just has a few
12 remarks.

13 MEMBER O'FALLON: I do, just a few issues.

14 The first is that I do think randomized trials are
15 thinkable in devices, but not everywhere, obviously.
16 And I think that they become more possible as we go
17 out from adults that we can start thinking in terms of
18 randomized trials, and in particular, I was thinking
19 that as they get down to the eight and nine year olds,
20 as they will inevitably, that those types of things
21 could use -- there could be randomized clinical trials
22 of say the best behavior management therapy versus the

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1 device or other thing like that, the widget. And that
2 would really give us a chance to see whether -- how
3 these behave in a certain population of patients. And
4 obviously then follow up becomes extraordinarily
5 important.

6 We have different populations being
7 discussed. Remember, stratification can be a very
8 useful tool. I am not happy with the idea of any of
9 these matched studies. For the most part, these
10 matched studies are irrevocably biased and it becomes
11 very, very difficult to actually assure ourselves that
12 we're comparing apples to apples. It's probably
13 apples to pineapples. Because we don't know which
14 factors are the most important issues and we can't
15 match on them. That's where the randomization gets in
16 there.

17 I am very concerned about the
18 trustworthiness of adult data. It's wonderful for
19 adults, but these are growing kids and I do not -- I
20 am not confident that adults data is going to
21 accurately predict results in children. So again, the
22 follow up becomes very important.

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1 I suggest that follow up should go to age
2 30, the reason being that most people will -- as I
3 understand it, most people believe that the kids have
4 grown up by that point and so the effects of those
5 therapies they received in childhood should, most of
6 them, be pretty well visible. So I would recommend
7 following them until age 30.

8 CHAIRMAN NELSON: I'm starting to wonder
9 about some family issues, but we won't go there. Dr.
10 Gorman got that. Sorry, bad joke.

11 Dr. Newman?

12 MEMBER NEWMAN: Just address the questions
13 or the issues that Dr. Yustein mentioned. First, as
14 Dr. Moore said, if we're going to talk specifically
15 about inclusion criteria, we need to be talking about
16 a specific device and so sort of a prototype device is
17 the lap band, I would favor for inclusion criteria at
18 least the 99th percentile for 2005, not this 99th
19 percentile that eight percent of people can be in, but
20 a real 99th percentile, plus comorbidity and I think
21 having that as inclusion criteria that the logical
22 outcome would be a resolution of the comorbidity, that

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1 the change in BMI would be secondary.

2 If you were going to look at something
3 other than change in comorbidity and a change in BMI,
4 I think the BMI change that we're looking for would be
5 really a much bigger one than this sort of 10, 20
6 percent. It would be probably at least sort of 30
7 percent of the excess BMI and that as long as you're
8 looking for such a huge effect, you probably don't
9 need a randomized trial, but as soon as you start
10 saying that we're going to consider this device works
11 at a smaller effect size, then you probably do need a
12 randomized trial.

13 In terms of how do distinguish between the
14 effects of the device and the behavioral and dietary
15 interventions that go with it. I agree with several
16 people about the need for a run in and if the people
17 have not responded to diet or behavioral modifications
18 and the change has been zero or close to zero in their
19 BMI and then after the device the BMI suddenly starts
20 dropping and their symptoms get better, then I think
21 that's how you distinguish the effect of the device
22 from the behavioral and dietary recommendations.

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1 I'm not that familiar with this patient
2 population, so I'm not sure what the comorbidities
3 could be, should be. I'm thinking pseudo tumor
4 diabetes and sleep apnea. Maybe also some of the
5 orthopedic problems. If the children can't walk, that
6 seems to me an important outcome and the nonalcoholic
7 steatohepatitis, I would say it definitely shouldn't
8 just be biochemical things like insulin resistance or
9 hyperlipidemia or things that are -- or even high
10 blood pressure, things that are asymptomatic. It
11 should be things that are affecting the child's
12 everyday life.

13 CHAIRMAN NELSON: Michael?

14 MEMBER FANT: I really don't have anything
15 else to add with regard to the comments as they
16 pertain to the devices and the procedures that are
17 currently in use. I'd like to reiterate my point and
18 the point that Dr. Moore raised with respect to the
19 heterogeneity of the devices. And I can envision
20 devices that are going to come down the pike that
21 their intended use or their potential usefulness in
22 these kids may not have the same impact or be directed

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1 at the same targets as the currently available
2 modalities. And that they actually may be more useful
3 earlier in the course of the progression of obesity.

4 They may be more useful as adjuncts to
5 what we now call conservative, conventional medical
6 management and examining the usefulness in these kids
7 at a point that precedes them reaching the inclusion
8 criteria that we've been talking about today may be
9 more appropriate. So I think having the flexibility
10 to adapt the inclusion criteria to the device and the
11 potential usefulness should be kept in mind.

12 The other point that I'd like to make is
13 with regard to the inclusion of international data and
14 I really don't see -- I've never seen additional
15 information as an all or nothing phenomenon. I think
16 you really can't have too much information. The
17 problem comes in how we use it.

18 I agree that we should not use the data to
19 assume that we're going to get the same result in our
20 population as we see investigators getting in Asia,
21 Europe, Latin America, etcetera. But on the other
22 hand, if we don't get beneficial results, comparable

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1 to prior international studies, I think it would be a
2 mistake to disregard a potentially useful therapy in
3 this country.

4 I think the way I view that is a potential
5 opportunity, if those differences are real and both
6 studies were done appropriately. That's an
7 opportunity to perhaps understand what we could be
8 doing better with this population of patients so that
9 this therapy can work. And we can we do something to
10 improve our medical management or our behavioral
11 aspects of the patient's life, diet, etcetera, that
12 may actually diminish the need for the surgery or the
13 device or make the device more effective, once they
14 get it. So those are my only comments.

15 CHAIRMAN NELSON: Bob, with your
16 permission -- Norm has got a taxi to catch.

17 DR. FOST: Sorry to rush out. Just two
18 comments. I just want to add my voice to the
19 comorbidity as the major outcome rather than surrogate
20 measure of BMI which is different than what I heard
21 Dr. Yustein say.

22 Second, I would also add to that comments

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1 I made earlier about centers of excellence and large
2 numbers of patients in any one center as this should
3 not be like so many multi-center trials where
4 everybody gets five patients and gets their name on a
5 paper. There's lots of technical expertise here in
6 multiple areas, multi-disciplinary areas, so any
7 trials of whatever is being studied, should be
8 restricted to centers that really have a large, full-
9 blooded team and has a minimum number of subjects in
10 the trial. Thank you.

11 CHAIRMAN NELSON: Thanks. Bob?

12 DR. WARD: I am glad to see this shift
13 from BMI actually to comorbidities. I think they're
14 the most important aspect.

15 I want to lend my support to even though
16 it may be terribly difficult, to advocate for the RCT
17 because of the frequency of adverse events in this
18 population over time, knowing whether they are
19 increased or decreased, I think is going to be
20 terribly difficult if we simply use this matched
21 control trial.

22 I think the registry is important. I

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1 think the CDC could be the repository, potentially the
2 NIH, but I think with the magnitude of obesity in the
3 country, it's clearly a national problem and needs to
4 be a national focus and I think we need to raise it to
5 that level.

6 It's of concern that once this device or
7 any device is approved that is easy to use, I mean we
8 saw the technical difficulties of an endoscopic Roux-
9 en-Y. That was impressive, but if this could be put
10 in 30 minutes, as soon as it's approved, it will be
11 used by groups that are not members of multi-
12 disciplinary teams.

13 And we've discussed with the FDA in the
14 past, what kinds of restrictions can be applied to the
15 application of -- for example, a drug and they're very
16 limited. So I don't know what the solution for that
17 will be, other than having as good data as possible
18 about efficacy and adverse events before it's fully
19 approved.

20 CHAIRMAN NELSON: Marsha?

21 MEMBER RAPPLEY: I would like to speak to
22 looking at factors that contribute to the

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1 sustainability of the desired outcome. And that would
2 probably mean some assessment in the leave-in period
3 as well as post-procedure period, that if we could
4 understand how to sustain this beneficial effect, then
5 we may be able to accomplish the distributive justice
6 piece if we understand what it is that families and
7 children require to not only lose weight, but maintain
8 a lower weight, that when we look at a nutritional
9 assessment package that we anticipate the nutritional
10 problems of young adults and get a sense of whether
11 those are more severe among the children who become
12 young adults in these restrictive diets. And I also
13 support the data monitoring board.

14 I think that the urgency is very
15 compelling to act and to provide a measure that -- an
16 action that is very satisfying to families and to
17 ourselves as physicians. But I think the onus for
18 safety is only on us. It doesn't reside within anyone
19 else and when our patients, when our subjects are
20 children, and when the impact of what we do lasts a
21 lifetime, that bar has to be very, very high for the
22 safety consideration.

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1 So I would argue then that before we set
2 aside -- before we adopt the notion that we cannot do
3 this with a randomized control child which is the gold
4 standard, yet we need to be very certain because we'll
5 be lowering our standard in addressing the safety
6 issue when we set that aside.

7 MEMBER HUDSON: I'd like to emphasize,
8 especially from the context of learning from pediatric
9 oncology care that children, adolescents are uniquely
10 vulnerable and this is in ways that we understand and
11 may be in ways in regards to this specific procedure,
12 related to weight control that we don't completely
13 understand. So we have a responsibility to define the
14 efficacy of these interventions and the sequelae of
15 these interventions by longer follow-up.

16 So I think it's just critical that we
17 commit to longer -- to evaluating these outcomes long
18 term and I think that a panel of medical experts
19 should define the important comorbidities as have been
20 discussed here, but also that we should have select
21 centers or hopefully supported research that will look
22 at the survivors or these procedures.

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1 There are self-perceptions of health
2 status and functional status and also psychosocial
3 outcomes as it relates to marriage, employment,
4 intimacy, etcetera which are so critical in adjustment
5 and happiness and well-being later on. I think the
6 registries should be committed to as well, or
7 recommended at least in selected centers and one thing
8 that we really didn't address within this context is
9 how we will accomplish some of these -- evaluating
10 some of these outcomes as we have to transition
11 children, adolescents from pediatric centers to adult
12 health care centers and that may be a challenge as
13 well that we'll face.

14 DR. GORMAN: I'd like to basically agree
15 with the shift in trial design continuing emphasis on
16 randomized or close to randomized trials and the
17 emphasize on comorbidities as the primary outcome
18 under both biochemical disease, biochemical and
19 psychological comorbidities as potential primary
20 outcome measures.

21 I think the centers of excellence need to
22 be in general hospitals, not pediatric hospitals. I

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1 think that handles a lot of the issues of the bonding
2 of the team, that it will allow for the transition of
3 assent to consent and will facilitate the likelihood
4 of long-term follow up. That doesn't mean there
5 shouldn't be centers of excellence in pediatric
6 hospitals, as we move down to younger and younger age
7 ranges, but if we're going to start these studies in
8 adolescents, which I think I've heard as a general
9 consensus for the more invasive devices, then perhaps
10 general hospitals would be a better place with the
11 teams to start.

12 With the duration of follow up that Dr.
13 O'Fallon has mentioned, I think that we had better be
14 careful about looking at environmental shifts of the
15 baseline. Just like diseases, most diseases change in
16 both their incidence as well as their prevalence and
17 obesity may be one of those.

18 And as we go forward for 30 years, we may
19 find that obesity increases and therefore the
20 effectiveness of the device may be changed against the
21 changing pace of disease.

22 I would also like to echo Dr. Fant's

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1 statement that we should include international data
2 and if they do better than we do, we should find out
3 why so that we can institute best practices.

4 One last comment on the run in. One of
5 the nice things about being a general pediatrician is
6 I don't have much data, so when I come to these
7 meetings, a lot of data gets poured into my head in a
8 very short period of time. During Dr. Skelton's
9 presentation yesterday where he talked about the New
10 Kids Program in Wisconsin -- I know Wisconsin is not a
11 normal state, very few people have escaped from their
12 normal. Dr. Nelson may be the only example. Only 20
13 percent of the people -- of the children who enrolled
14 in his New Kids Program had ever tried to lose weight
15 before. So these are people with an average BMI of
16 40.

17 CHAIRMAN NELSON: Wisconsin.

18 DR. GORMAN: Well, it was Wisconsin, the
19 cheese heads, I think. But I think the reality is
20 that this is an area where I think kids are going to
21 be different than adults in a real way that they may
22 not have had the prolonged life struggle against their

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1 disease and they may be being brought by their parents
2 rather than their own concerns about their disease.
3 And I think that the run in period whether it be two
4 months, three months, four months, five months or six
5 months or a year, I think it needs to be real and it
6 needs to be structured in a way that makes you believe
7 that those interventions cannot help these
8 individuals.

9 DR. GARAFALO: Just to finish with a
10 couple of comments. So I'm going to dissent from the
11 evolution away from the BMI as the primary efficacy
12 endpoint. I think we start from there and as we learn
13 more about these other secondaries, we definitely need
14 to look at those in further potentially future trials
15 or certainly as just initially in a descriptive way
16 until we know more about them. I think we talked a
17 lot about duration of the trial. We talked about
18 sample size for efficacy, but I didn't really hear
19 much about sample size for safety. I mean in the drug
20 side that generally we don't power for safety. Here,
21 I wasn't sure how devices are looked at when you have
22 a small number of potentially small number of patients

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1 in the trial.

2 So perhaps it's related to the
3 invasiveness of the device, so as you get to more
4 devices that come down the pike that are less
5 invasive, you might not need the same number of
6 patients studied to understand if you're going to have
7 rare or relatively rare serious adverse events.

8 So that all the safety and even the data
9 safety monitoring board, the necessity for that would
10 evolve from how invasive the device was that was under
11 consideration.

12 I do agree that all of these therapies and
13 obesity, in general, you need long-term follow up to
14 really evaluate continued therapeutic, the efficacy of
15 the relative efficacy because it's uncontrolled and
16 potentially you lose a lot of patients to follow up,
17 harder to interpret, but the long-term data would be
18 useful and registries would be useful.

19 CHAIRMAN NELSON: Let me just make a
20 couple of quick comments on my own and then turn for
21 final comments to Ron, Diane and/or Sarah.

22 One thing that occurs to me, we talked

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1 about the adolescents. There's agreement on that.
2 The importance of a robust assent process, just to
3 emphasize that, actually fits pragmatically with what
4 I've heard about the importance of the adolescent
5 being invested in the program and then for that run
6 in. But it also fits in with the fact if we're
7 talking about a five year trial and enroll anyone over
8 the age of 13, that it would be a tragedy, if in fact,
9 every child who turned 18 when you actually ask them
10 what they wanted to do, changed their mind. That
11 would be a sort of disastrous outcome. So the
12 importance of a robust assent process from a number of
13 different perspectives, I think, is important.

14 I'm more sympathetic to the BMI than I am
15 to the comorbidity as much, but personally, I think
16 Tom has said it in the most reasonable way. The
17 extent to which one is certain of the degree to which
18 you can predict change, gives you a sense of the
19 robustness of that endpoint. and as that robustness
20 sort of disappears, and as the degree of intensity or
21 invasiveness of the device to where you go from the
22 range of gastric bypass, calling that a device through

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1 lap bands to speculating about ingested or transdermal
2 sort of devices, (a) the differences become
3 predictably less, at least in our hypothetical mind,
4 although I suspect that's just a bias, but the
5 opportunity for a randomized control trial becomes
6 much more palatable, partly because we're less certain
7 about the size of the effect that we may see and the
8 importance of that kind of process for determining
9 something.

10 So I mean there's a relationship between
11 all of these different factors that I think where you
12 put the emphasis is going to depend on the details of
13 the nature of the device and the degree -- and all of
14 the various things that people have said.

15 So I've heard a fair amount of
16 commonality, the differences, I thought were at times
17 differences of emphasis rather than differences of
18 disagreement and I certainly hope you all feel that
19 you got your questions answered in a way that was
20 helpful and productive in trying to put together a
21 draft guidance that could emerge anywhere from eight
22 months to two years from now, hopefully not longer.

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1 So if we have final comments, Ron, Sarah?

2 DR. YUSTEIN: I just wanted to thank the
3 entire panel again on behalf of the CDRH for what I
4 think was a great meeting. I think we came out with
5 some very good, concrete recommendations, but on the
6 other hand I think we left enough flexibility that we
7 can adapt as needed for certain products.

8 And so thank you very, very much for your
9 time and your input and Skip, thank you. I think you
10 did a tremendous job in leading a very difficult
11 process for a very large panel and we appreciate that.

12 (Applause.)

13 DR. MURPHY: I wanted to thank you all
14 too. It wasn't quite Blue Ocean, but the
15 effectiveness of the give and take between the
16 different disciplines was really important and it
17 really worked here over the last two days. And I
18 think that those reflect on your leadership and on the
19 participation, the engagement of everybody in this
20 room and you really have provided us with some very
21 useful advice.

22 Sarah?

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1 DR. GOLDKIND: I would like to just echo
2 what Ron and Diane have said. We've been framing this
3 meeting for a long time, worrying if we gave you a
4 daunting and overwhelming task and you really rose to
5 the occasion, all of you did, with Skip's leadership,
6 so thank you very much.

7 CHAIRMAN NELSON: Well, thank you and
8 thank you, everyone. Jack, do you have a final
9 question or comment?

10 DR. YANOVSKI: I realize that my back of
11 the paper calculation, I gave you an incorrect number.

12 The change in BMI. I just wanted to make sure -- it
13 should be more like 5 to 7 BMI units not more like 2.

14 I don't know why I said that, so my apologies.

15 CHAIRMAN NELSON: Okay, great. Thank you
16 very much and everyone who is staying, fine, everyone
17 who is traveling, safe travels.

18 Thank you.

19 (Whereupon, at 4:57 p.m., the meeting was
20 concluded.)

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