UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE

MEETING

Wednesday, November 16, 2005

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

PRESENT:

ROBERT M. NELSON, M.D., Ph.D. CHAIR
ROBERT DAUM, M.D. MEMBER
ANGELA DIAZ, M.D., M.P.H. MEMBER
DEBORAH L. DOKKEN, MPA MEMBER
MICHAEL E. FANT, M.D., Ph.D. MEMBER
ELIZABETH A. GAROFALO, M.D. INDUSTRY REPRESENTATIVE
RICHARD L. GORMAN, M.D. PEDIATRIC HEALTH ORGANIZATION REPRESENTATIVE (NON-VOTING)
MELISSA M. HUDSON, Ph.D. MEMBER
JOHN W. M. MOORE, M.D., M.P.H. MEMBER
THOMAS B. NEWMAN, M.D., M.P.H. MEMBER
JUDITH R. O'FALLON, Ph.D. MEMBER

CONSULTANTS PRESENT:

SILVA A. ARSLANIAN, M.D. CONSULTANT
JEFFREY BOTKIN, M.D., M.P.H. CONSULTANT
PATRICIA S. CHOBAN, M.D. CONSULTANT
DOUGLAS S. DIEKEMA, M.D., M.P.H. CONSULTANT
NORMAN FOST, M.D., M.P.H. CONSULTANT
THOMAS INGE, M.D., M.P.H. CONSULTANT
WILLIAM KLISH, M.D. CONSULTANT
PAUL KNUDSEN CONSULTANT
JOHN KRAL, M.D., Ph.D. CONSULTANT
ROBERT LUSTIG, M.D. CONSULTANT
WALTER PORIES, M.D.,F.A.C.S. CONSULTANT
ALBERT ROCCINI, M.D. CONSULTANT

ROBERT WARD, M.D.	CONSULTANT
JACK YANOVSKI, M.D., Ph.D.	CONSULTANT
CATHARINE CHAMPAGNE, Ph.D.	CONSULTANT
JACK YANOVSKI, M.D., Ph.D.	CONSULTANT
JAN N. JOHANNESSEN, Ph.D.	EXECUTIVE SECRETARY
SARA GOLDKIND, M.D., M.A.	OFFICE OF PEDIATRIC THERAPEUTICS, FDA
DIANNE MURPHY, M.D.	OFFICE OF PEDIATRIC THERAPEUTICS, DFA
RON YUSTEIN, M.D.	OFFICE OF DEVICE EVALUATION, FDA

Pediatric Obesity Agenda
Pediatric Advisory Committee Meeting
November 16, 2005

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4:15	Surgical Intervention Including Devices	Victor Garcia, M.D. Professor of Surgery, U of Cincinnati	

5:15	Committee Questions of Clarification for Speaker		
6:00	Adjourn		

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

(8:07 a.m.)

CHAIRMAN NELSON: I guess we'll have to get really close to these microphones.

So if we could begin to get our coffee at tables and start to drink them, so in 15 minutes we're ready to have some great conversation. But to remind the members of the Committee, before we actually get started, this first session, an hour and a half, is to consider a Subcommittee Review of a 5054 45 CFR 46.407 Panel that occurred yesterday. And the rest of the consultants and other individuals for the portion of the meeting that's going to be dealing with obesity will join us after the break, which is why the table looks quite empty.

So, welcome. And I guess I'll turn the initial starting of the meeting to Jan who will deal with the Conflict of Interest Statement.

EXEC. SEC. JOHANNESSEN: Good morning. The Food and Drug Administration is convening today's meeting of the Pediatric Advisory Committee. The following announcement addresses the issue of Conflict

of Interest with regard to the discussion of a referral by an institutional review board for proposed clinical investigation that involves both an FDA-regulated product and research involving children as subjects that may be supported by their Department of Health and Human Services and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Food and Drug Administration present no potential threat and appearance of conflict of interest at this meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusions will be noted for the record.

We note that Dr. Norman Fost, Dr. Jeffrey Botkin and Dr. Robert Ward are participating in the meeting as voting consultants and that Paula Knudsen

is participating as the acting voting consumer representative. We would also like to note that Dr. Elizabeth Garofalo has been invited to participate as an industry representative, acting on behalf of regulated industry. Dr. Garofalo is employed by Pfizer. Dr. Richard Gorman is participating as a pediatric health organization representative, acting on behalf of the American Academy of Pediatrics.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment on.

Thank you.

CHAIRMAN NELSON: Now, before we start with the opening comments and overview, since there's a number of fresh faces on the committee and it's a new day, why don't we go around the table and introduce ourselves as a start. Dianne, if you want to begin.

DR. MURPHY: I'm Dianne Murphy and I'm the Director of the Office of Pediatric Therapeutics at the FDA.

DR. GOLDKIND: I'm Sara Goldkind. I'm the Bioethicist in the Office of Pediatric Therapeutics.

DR. GAROFALO: I'm Elizabeth Garofalo and I'm the industry representative. I work for Pfizer.

DR. GORMAN: I'm Richard Gorman, a Pediatrician in a suburban private practice and the Chairperson of the section on Clinical Pharmacology and Therapeutics for the American Academy of Pediatrics.

MEMBER HUDSON: I'm Melissa Hudson. I'm a Pediatric Hematologist/Oncologist at St. Jude and a new member of the Pediatric Advisory Committee.

DR. BOTKIN: I'm Jeff Botkin, Department of Pediatrics and Medical Ethics at the University of Utah.

MEMBER DAUM: I'm Robert Daum. I'm in Pediatric Infectious Diseases at the University of Chicago and a new member of the Advisory Committee.

DR. FOST: Norm Fost, Departments of Pediatrics and Bioethics, and Director of the Bioethics Program and Chair of the IRB at the University of Wisconsin.

MEMBER DIAZ: Angela Diaz at the Department of Pediatrics and Community Medicine at Mt. Sinai School of Medicine and Director of Adolescent Medicine.

DR. WARD: I'm Bob Ward, a Pediatrician and Pharmacologist at the University of Utah. I'm directing the pharmacology program there.

MEMBER FANT: I'm Michael Fant. I'm at the University of Texas Health Science Center in Houston. I'm a Biochemist and a Neonatologist on the faculty there. I'm a member of the Pediatric Advisory Commission.

MEMBER NEWMAN: Tom Newman. I'm a General Pediatrician and Professor of Epidemiology and Biostatistics and Pediatrics at UCSF and Head of the Clinical Epidemiology Program there.

MEMBER O'FALLON: Judith O'Fallon. Mayo Clinic Emeritus Professor of Biostatistics, a member of the Committee.

CHAIRMAN NELSON: I'm Robert Nelson, also known as "Skip." If you hear that name around, I'm the new Chair of the Committee and previous member,

and I'm in Pediatric Critical Care Medicine and Bioethics at Children's Hospital in Philadelphia and the University of Pennsylvania.

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

DR. KNUDSEN: I'm Paula Knudsen from the University of Texas Health Science Center in Houston and I am an IRB Administrator.

MEMBER MOORE: John Moore from UCLA, Pediatric Cardiologist.

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

CHAIRMAN NELSON: Thank you. And Dianne or Sara, Opening Comments?

DR. MURPHY: Well, comments are welcome, particularly to our new members. I heard you had an excellent training session last night. We're going to start on a slightly different foot and actually, Skip, if you would just say a few things to them about this process this morning, for the new members, I think

that would be appreciated.

CHAIRMAN NELSON: Well, before then I turn to Norm about the actual protocol we discussed yesterday, a brief comment. The Subpart D, which is in both the Federal Regulations in two places pertinent to this meeting, both the HHS that oversees NIH-funded research and with the FDA in 21 CFR 50 and 56. There's three sections under which a local IRB can approve protocol. One is minimal risk, the other is minor increase over minimal risk with some other conditions set to it, one of which is that the child had a condition. The third is prospect of direct benefit with a balancing of the reasonableness of the risks against the benefits and being rated a minimal risk. And then there's a fourth category that if the local IRB thinks that the research presents a reasonable opportunity to understand a serious problem affecting the health or welfare of children, that they can refer that protocol, but they can't approve it under the other three categories, that they can then refer that protocol for review at the federal level.

Up until about, I guess a year and a half

ago now, there was no public process by which that review could take place. And when the Pediatric Advisory Committee was chartered as a part of the Pediatric Research Equity Act, its charter was written to be able to provide such advice and the mechanism through which it was set up to do that is through a Pediatric Ethics Subcommittee, of which the previous two reviews I chaired and now Norm Fost is the Chair of that Ethics Subcommittee.

It turns out that, according to the Federal Advisory Committee Act, the only committees that can actually advise the FDA Commissioner and Secretary of HHS is a fully constituted advisory committee. So we need to then discuss, consider, and vote on the recommendations of the Subcommittee in order for it to be passed on to the FDA Commissioner as part of that process. After the FDA Commissioner puts together an assessment of that review and then makes a determination, that then goes to OHRP within HHS, which puts it together for the Assistant Secretary of Health to make a determination on behalf of the Secretary of HHS.

So that's why we're here. Because yesterday, there was a meeting that went for all day to consider a protocol submitted by the University of Chicago that I believe is -- everyone should have received all of the briefing materials for that. There's a few minor changes to the slides and I think one new set of slides from yesterday, which you should have, I think, before you, to be able to refer that. And that's our task, which we will, hopefully, complete by 9:45 a.m.

Is that sufficient?

DR. MURPHY: Yes. What -- the overview that I was going to provide later, Skip, is for the next topic. So that's why I was asking you to make sure --

CHAIRMAN NELSON: Oh.

DR. MURPHY: -- the new members --

CHAIRMAN NELSON: Okay.

DR. MURPHY: It's in the wrong place on the agenda because we didn't realize we were not going to have everybody here.

CHAIRMAN NELSON: No problem.

DR. MURPHY: So we wanted to surprise you and change the agenda without telling you.

CHAIRMAN NELSON: Okay.

DR. MURPHY: Thank you.

CHAIRMAN NELSON: So Norm is going to give a summary of the deliberations from the Pediatric Ethics Subcommittee Meeting of yesterday. Norm?

DR. FOST: Thank you, Skip.

So the protocol that we reviewed yesterday is from the University of Chicago Medical School. Dr. Robert Rosenfield is the principal investigator and this is a study to assess gonadotropin-releasing hormones for their use in disorders of puberty. Next slide, please.

The purpose of the study is to establish the diagnostic effectiveness of a stimulation with this agent leuprolide and the norms for it. That is, to get normal data. This will improve the differential diagnosis of the most common disorders of puberty so that we may provide more accurate and earlier treatment for these disorders. Next slide.

The basic problem is that there are many

children with disorders in pubertal development, mainly precocious puberty or delayed onset of puberty. The Gold Standard Test has been a sleep study, which requires admitting a child overnight usually to a clinical research unit. This is expensive and not generally covered by insurance and, therefore, really not available to large numbers of children and endocrinologists.

An alternative way of assessing these children includes stimulation, inadodropins with injection, inadodropins releasing hormones, but there have been frequent changes of the available product in doing this. That is, there have been several products, some of which are no longer available in the U.S. Some are no longer available at all. And the current product, Leuprolide, which in its long-term form is called Leupron, is what is being used but there is a lack of normal values that is valued for normal children in the age ranges of patients that present. So Dr. Rosenfield is proposing to study patients with various pubertal disorders in a control group with normal, healthy children and the central

problem that the University of Chicago IRB had with this involved the use of the normal children. Next slide.

The illness in this study is that everything I'm saying is true of both groups, but the major issue here involved a healthy control, so I'll just be referring to them.

The children in the healthy control group would be between seven and I think the upper age is 17 or 18 years old. They would be admitted for 36 hours, so for part of two days and one overnight admission to a clinical research center. They would receive one self-contained injection of Leuprolides and micro (*8:19:53 inaudible). This drug is improved for treatment of pubertal disorders in children, but it is not approved as a diagnostic agent.

There would be a $150 payment to the normal children and no payment to the patients or the children who had a disorder. Next slide.

So the procedures include a 36-hour admission, one injection of Leuprolide, a physical exam, an in-dwelling venous catheter from which blood

would be obtained -- I'll come back to the amount in a few minutes -- x-rays to determine the bone age, DNA banking for future as yet unspecified genetic tests, if and when they become available, and children would be discharged on iron to help them reconstitute whatever blood they lost. Next slide.

There were no public comments at the meeting, that is, no spoken public comments. We received letters, eight letters, and this is a brief summary of those letters. Four of them were from patients, that is from adults, who had received Lupron and these individuals were concerned about serious adverse affects, both long-term and short-term use, in themselves and others. They expressed concern that the chemical itself is hazardous and that double gloving is needed and that this was not identified in the protocol in the Consent Form. There were charges in these letters of misconduct against TAP, a company that had been involved in the distribution of Leuprolide. There was concern about alleged numerous lawsuits against TAP that had been settled under secrecy agreements so that information was not

publicly available. There was concern about the disappearance of a popular web site of Lupron victims, which reportedly had over a million hits a year and then allegedly disappeared, and concerns about inadequate information on the Consent Form about serious adverse affects of Lupron and Leuprolide.

Another letter came from a parent whose child had both Cancer and a delayed onset of puberty. That is, so this child had been in clinical trials for Cancer and also in a clinical trial involving Leuprolide for its use as a gonadotropin releasing hormone and this parent commented favorably on the effectiveness of the drug, its safety, the low risk of the trail that her child was in, and on the importance of getting better information so that there could be better tests for precocious puberty. Next slide.

There were three letters from professional societies, the Endocrine Society, the Lawson-Wilkins Pediatric Endocrine Society, and the American Society for Reproductive Medicine. These letters had a certain sense of deja vue about them. They all stressed the importance of normal controls in

pediatric research. They expressed concern about the 46.407 process, about the cumbersome nature of trying to get studies and normal controls done, concerns about the variation among IRBs and the definition of minimal risk that made it challenging for investigators to do this kind of research, but made no specific comments on the protocol. So they expressed mainly general concerns about the 46.407 process and about the importance of normal control data. Next slide.

So as Skip Nelson said, this is a summary of the sections, development sections, of the common rule under which research involving children, particularly normal, healthy controls, were done. Section 46.404, just to refresh your memories, involves research not involving greater than minimal risk. The University of Chicago IRB felt that this study could not be approved for the normal controls. They felt that the risks of the study were greater than minimal and, therefore, could not be approved under Section 46.404.

Section 46.405 has to do with research

involving greater than minimal risk, but presenting the cost break of direct benefit to the subjects, the IRB concluded that there was no direct benefit to these normal controls and, therefore, could not be approved under Section 46.405.

Section 46.406 involves research that's greater than minimal risk and the prospect -- and no prospect of direct benefit for individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition, and since the normal children do not have a disorder or a condition, it could not be approved under Section 46.406.

So the Chicago IRB thought the subjects could be approved, but this would require approval by the Secretary, namely research not otherwise approvable, but which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children. They felt it did meet those criteria, but the approval of the Secretary was needed, hence, the process that we're here today to conduct. Next slide.

So, the protocol was submitted to the

University of Chicago IRB in November of 2004 and I should add that there was considerable concern expressed by individuals yesterday about the long time for this process. It's now a year later. Much of that time was at the University of Chicago, the study apparently was submitted to FDA sometime around June of 2005.

So the Chicago IRB approved the study for patients, that is for children who had disorders in which they considered it a minor increment over minimal risk with the prospect of direct benefit. What would happen to the children with pubertal disorders is not very different from what would have happened to them if there was any study at all. Almost everything that is being proposed in the study would be part of what would be, in the investigator's opinion, the correct work-up for these children. So there was no added risk for them and there was the prospect of direct benefit. So the issue was normal controls, which required the approval for which required the 46.407 process. Next slide.

So the options for our Committee

yesterday, for the Pediatrics Ethics Subcommittee, were first, to revisit the issue of 46.404, that is, it is permissible for the Advisory Committee and for this Committee today to decide that the Chicago IRB was mistaken, was unduly conservative, and that if the study is at minimal risk and could be approved under Section 46.404, this Committee today could make that recommendation. So we first considered that possibility, that is, to revisit the question of whether the use of normals could be approved under Section 46.404, namely research not involving greater than minimal risk. Next slide.

Minimal risk, to refresh your memories, is defined in the Common Rule as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or test.

One of the recurring problems in applying this definition is, to understate the case, enormous disagreement about what the phrase "routine physical

or psychological examination or test" means. Next slide.

Some individuals, some IRBs believe that that phrase refers to the kinds of tests that would be conducted on a routine health supervision visit, a child who comes in for a health supervision visit. But others have interpreted it to refer or to include risks that would occur on a routine visit to a specialist. So, for example, form IRBs have approved non-therapeutic kidney biopsies, small bowel biopsies, based on a statement by the investigator that a -- an nephrologist, that in my clinic, a kidney biopsy is routine. Everybody I see gets a kidney biopsy or a lot of them do, and I haven't had any problems with it, so to do it on a research basis doesn't involve anything more than happens on a routine basis.

There was published in JAMA last year a survey of IRB Chairs -- and the next slide, please -- I don't know if you can see this. I can't. But the fourth line down, on the left, I believe, is the -- on the left column is a list of various studies that have been where -- this was a questionnaire sent to IRB

Chairs, IRBs that review research involving children, and the left is a list of various interventions, and they were asked whether they thought this was minimal risk, minor incremental over minimal, or more than a minor incriment over minimal, and the main point of the slide is there is just enormous scatter in these results. One of the more striking ones is skin testing for allergy -- I think it's about fourth down on the left -- and roughly 40 percent and 25 percent of the respondents selected either minimal risk, more than minimal or minor increment over minimal. That is, it was almost random distribution. If you look at the first line, which I think is a venapuncture, a single draw of a small amount of blood, and look at the far right column, two or so IRB Chairs thought that was more than a minor increment over minimal.

So there's inconsistency among IRBs around the country and great frustration by investigators who see some of these studies being approved in some centers and not others. In fact, their institutions with multiple IRBs in which one IRB will approve a certain procedure in children and the other one will

not. So there is some high -- there is a high noise to signal ratio in the interpretation of that phrase. And the bottom line is there is no right answer to it or no universally agreed upon answer, so the Committee yesterday and the Committee today will simply have to deal with it as best you can and see what you think. Next slide.

So, we discussed four issues to see where consensus might lie and then had a formal vote, which I'll mention at the end. That is, we divided the questions before us into four issues.

The first issue was whether the proposal to study the responsive normal children involved more than minimal risk and we divided those into medical risks and psychological risks. The medical risks seemed to be mainly three: risks of Leuprolide and the asterisk there means that a majority of the committee -- I think, these asterisks were actually unanimous, but unanimous minus one perhaps. So nearly everybody on the Committee thought that the administration of Leuprolide, although a very low risk, and the panel members did not agree with the

public comments that there were serious adverse affects from this. The consensus was that that was more than minimal risk, that the procedures involved the in-dwelling catheter, it was more than minimal risk. There was agreement that the amount of blood volume -- and I would say we spent most of the day yesterday discussing how much the blood volume actually was -- and finally determined that the amount was about three cc's per kilogram and that this was not -- this was at minimal risk, this was not more than minimal risk. And finally that the psychological risks of being hospitalized for 36 hours with the various procedures also constituted more than minimal risk. So, in summary there was unanimity among the Ethics Subcommittee that this study -- the Chicago IRB had this right. We agreed with them that the study could not be approved under the eges of minimal risk. Next slide.

So, the remaining question was whether it could be approved under Section 407 or whether we could recommend such an approval. To do so, several criteria had to be met. The first was whether the

need for improved diagnostic tests for a diagnosis of problems of puberty was a "serious problem" affecting the health of children, one of the criteria for the Secretary to approve such a study.

Whether this is a serious problem, we divided into two questions: one, is the diagnosis and problems of puberty -- are problems of puberty a serious problem? Yes. These are medically serious. They are psychologically serious, and it's epidemiologically serious. There are large numbers of children who have precocious puberty or delayed onset of puberty and this is a serious problem. There was no need to discuss that.

But the second question was whether the need for improved diagnostic tests, particularly the need for normal data following a Leuprolide stimulation test, whether that was a serious problem, that is whether the existing armamentaria available to endocrinologists was really sufficient to evaluate these children or whether it was a serious problem, that the lack of normative data for a stimulation test was a serious problem. Everybody thought that it was

a serious problem. That is, that was unanimous, but two panel members thought that it wasn't necessary to use normal controls to answer this problem. That is, two of the panel members thought that in the workup, in the study of children with disorders, there would inevitably be some children who turned out not to have a serious -- not to have major medical problems and whose data could, therefore, be used as normative data. And that it wasn't necessary to regroup so-called normal controls to get this data.

So, in summary, seven of the nine panel members thought that normal controls were important to establish the normative data that were needed to -- and those two are here today, who can comment and say this in more detail during the discussion.

So, there was unanimity that improved tests were needed, but two out of nine panel members thought that you didn't need normal controls to do that. Next slide.

The next issue was whether the research was designed in a way that "presents a reasonable opportunity to further the understanding, prevention,

or alleviation of a serious problem affecting the health or welfare of children." So, the Committee here was operating on the principle that design is a serious ethical issue. That is, if -- even if the study is addressing an important problem, if the study can't be carried out or if the study is not likely to answer that question, then it's wrong to exposure children to even minimal risks, if nothing is likely to be learned from it. And here, the central issue was whether Dr. Rosenfield was likely to achieve his accrual goals and this discussion was stimulated, in part, by a letter sent to the Chicago IRB from the Clinical Research Center in their independent review of the study. They noted that two prior studies that Dr. Rosenfield had been doing involving similar issues, similar children, one of which had been approved in 1994 and the other in 1998, had only accrued 29 out of a target of 240 children over the ten or eleven-year period. And so they, the statistician on the GCRC Review Committee had expressed concern about whether the present study was really likely to succeed. Dr. Rosenfield replied that

the accrual of the patients, that is, the children in the Children With Disorders Arm of the study, was already quite satisfactory. That is, he was confident that he was going to be able to meet his accrual goals in that category. Whether or not he will be able to achieve normal controls, of course, is unknown because he can't proceed on that part of the study until he gets approval from the Secretary.

So, the Committee was -- a majority of the Committee was persuaded by this response that there was sufficient evidence of successful accrual that the study -- that the design of the study and the accrual goals could be met.

Next is the -- the next slide is the last issue -- involved payment. The proposal involved payment of $150 to the children in the control group, but no money to the children with disorders, to the patients. This $150 payment would be in the form of a check, written out directly to the children, not to their parents. So, we had a brief discussion, trying to figure out whether this payment was compensation for costs. It seemed that the children did not

themselves have cost, so it didn't seem to be compensation, or -- but a suggestion was made that this was an appropriate -- it was comparable to wages that the children might obtain for babysitting, as the amount of money that was being offered to them was less than they might have made from babysitting. There was discussion about whether it was an honorarium and, if so, it should not be disclosed ahead of time, so that it -- lest it be seen as an inducement; that is, if it was an honorarium, the suggestion was made it should be given after the involvement of the children is completed so they wouldn't be induced to join the study just for the money. And the third possible explanation for it was that it might be necessary as an inducement. That is, that enrollment might be difficult and that this payment was an important part of being able to complete the study.

As best we could figure out, I think it appeared that the payment was something, some combination of an honorarium and an inducement, so we then discussed briefly whether, if it was an

inducement, is it an undue inducement and nobody on the panel thought so. So, the consensus was that whether it's an honorarium or an inducement, the amount was not undue and the Committee did not have a problem with it. Next slide.

There was then some discussion of -- so the conversation, as you can sense, was drifting towards approval, recommendation for approval of the study, and various members of the Committee thought that if it were to be approved, that some modifications would be needed, or at least recommended. And the -- those are listed on this slide.

First, there was concern about the disclosure of results to the normals and there was unanimity that results should not be disclosed, that the significance of the results were unknown by definition because previous normative data were not available, that there was great potential for stabilization, possibly even insurability problems, and that while it would be appropriate to give the results of the study as a whole to parents and

children after it was concluded, while it was in process with the results being of uncertain significance, that results should not be disclosed. And so, there was -- I'll come to the vote on this issue in a minute.

Second, there was concern that since DNA samples were being collected for unspecified future genetic testing, that children should have the chance to withdraw from the study at any point, and that that right to withdraw should include a right to have the samples destroyed when they reached an age of majority, or before, if they wanted them. So, a second modification that was suggested that to ensure, to take steps to ensure the children could have their samples withdrawn.

Third, there were Consent Form changes, which the -- the three central concerns were a concern that the Consent Form had overstated the possibility of benefit to the children -- that's the second line there. The first line that the non-beneficial nature of the study for the control of children was not prominently featured and should be prominently

featured at the beginning of the Consent Forms.

And third, there was agreement that the Consent Form should say something about the possible adverse effects of long-term Lupron use, even though there were not thought to be any serious adverse effects of Leuprolide in the way it was being given, that subjects and parents should -- were entitled to know that there were possibly concerns about adverse affects from long-term use.

So, the next slide, I think, summarizes the vote -- well, this is just to review the conditions of 407 once more. So, Section 407 says that the Secretary can approve -- such research can be approved, as research of more than minimal risk without a prospect of direct benefit. If approved by the Secretary, following a recommendation that concludes that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. The research will be conducted in accordance with sound ethical principles, adequate provisions are made for soliciting the assent

of children and the permission of their parents or guardians as set forth in Section 408.

One member of yesterday's panel thought that there should be SN monitoring in this study. That is, that the acceptability of the protocol hinge on the ability of the children to say no, and to stop at any point, and that there was sufficient concern about this study, that the IRB should consider doing some assent monitoring. That is, a sample of the children in this study, after they participated, to see if they understood what had gone on, if they understood the non-beneficial nature of it and understood that they could withdraw at any time.

The next slide is the last, which is the actual votes. So, Question Number 1 was whether the Committee recommended that the Secretary approve this study under Section 404. That is, as minimal risk, and that was a unanimous "No." It was unanimity that this study involved more than minimal risk. Could it be approved as written under 407, and the answer to that was "No."

But the question, could it be approved with

modifications, and the answer to that was seven to two. A final option, of course, was they could recommend that it not be approved at all, but the previous bullet shows that the Committee, by a vote of seven to two, recommended approval.

Thank you.

CHAIRMAN NELSON: Thank you, Norm. Just two brief comments on the slides. I think the lower age limit for the study is eight for girls and nine for boys, if I recall for the controls. It's important to note we're only discussing the controls. And then, I might just add, in the interest of equal time, 21 CFR 50.51, 50.52, 50.53 and 50.54 are the same FDA regulations that you saw as 404, 405, 406, 407. So, they are comparable language.

So, with that, why don't we just open up the presentation for discussion. Tom, and then Bob.

MEMBER NEWMAN: Maybe the two who dissented would like to comment, but I guess I'm inclined to agree, or at least, not to understand the need for the normal controls. It seems to me if all of the children that are in the precocious or possible

precocious puberty are getting the current Gold Standard, which is a sleep study, then the results of the new test could be compared with the Gold Standard and we would be able to calibrate the new tests according to the sleep study, and so I guess I don't see why we need to have the normal controls if they're all getting the votes.

CHAIRMAN NELSON: Bob, should we open that question up, or do you want to --

MEMBER DAUM: I think we ought to address that question first.

CHAIRMAN NELSON: Okay.

MEMBER DAUM: Is Dr. Rosenfield going to

CHAIRMAN NELSON: He will at the point that I invite him to --

(LAUGHTER.)

CHAIRMAN NELSON: If you -- and you were there, so why don't you see where we can go up to that point.

MEMBER DAUM: Well, I mean, he can comment better than I do, or else the three Endocrinologists

on the Committee who all thought it was important to have normal controls -- I think their central argument was that the children in the -- with disorders are not normal children. There is something different about them. And that the issue that a Pediatric Endocrinologist faces when evaluating such children is, is this child normal or not, or is he not. And there are urgent treatment decisions that hinge on it and just watchful waiting is often not acceptable.

So, they just thought, from a scientific standpoint, that comparing children with treatable disorders with those who did not require treatment was not the question. The question was, was the child before you a normal child? Now, obviously, there are right-line boundaries between these categories, but that was the argument.

MEMBER NEWMAN: But -- I mean, I thought that was the purpose of the sleep study, was to distinguish between -- I mean --

CHAIRMAN NELSON: But not everybody will have a sleep study going forward, and so the sleep study is only done as a research-only test.

MEMBER NEWMAN: Right, but I -- but the sleep study, it seems to me, could be used to calibrate the new test because the children who are going to get this test are already going to know that there is some concern about their pubertal development. We will already know that they are not normal. We won't need the test to tell us that they don't have something maybe wrong with them about puberty, so that the group of children in whom this test would be applied in practice are all going to be children to whom there is some concern about pubertal development.

So, we already know that. So we don't need a test to tell us that. We know that. What we need to know is are they children with whom there's a concern about pubertal development who have something that we need to treat or not, and it seems to me that that's why we're doing the sleep study, to be able to -- if that's the current Gold Standard to be able to tell.

CHAIRMAN NELSON: I think, Tom, you're giving the presentation of the two people that

objected, and they can certainly say that, but the other seven felt that that was, in fact, incorrect. That you want to be able to tell people who present with, say, the late puberty who might appear normal if they were nine, but abnormal if they're 14, that, in fact, they were normal, not that they were untreatably abnormal. So it's -- in the absence of that data, it's a guess. And in terms of being able to say what the individual test might show once you do it, what the sensitivity and specificity is in saying, "Hi, you came to see us, but you were, in fact, normal on this test, which we've now developed." It is difficult to say in the absence of normative data. And having only normative data on people who present with the problem, in fact, doesn't allow you to draw that conclusion. So, that was --

MEMBER DAUM: If I could state it another way, I think this is paraphrasing Dr. Rosenfield. If you submitted an article to a rigorous journal that did what you suggested, that a critical reviewer would say, "Where are the controls?" You showed me what the difference is between children who had serious

disorders requiring treatment and those who are, but you haven't showed me what the value -- what the Leuprolide values are for children who are completely healthy. And that that's the standard that practitioners would want to know.

DR. FOST: Jeff, and then --

DR BOTKIN: I think, Dr. Newman, as one of the minority two -- I think Dr. Newman said nicely, expressed my concerns with the study, and I would just add to that, not that I don't think that there's some scientific validity to collecting data on so-called healthy children. We've had some language difficulties because, just as you had stated, many of the children who present with atypical pubertal development are, in fact, normal children, healthy children. It's just that you don't know that until they've undergone some sort of evaluation. So, I think, it seems to me the primary and most important clinical outcomes of this study can be answered with those children alone, without the so-called healthy controls. It seems to me that there's a secondary set of hypothesis that Norm sort of referred to, which is,

well, are those kids really normal and can we identify some differences between children with atypical puberty who turn out to be fine and kids who show no evidence of atypical puberty. Now, that may be an interesting question from a scientific standpoint, understanding normal pubertal physiology, et cetera, but for me, it was not a compelling enough reason to override the normal standards by which we hold pediatric research to, and therefore, for me, it was not approvable for that reason.

CHAIRMAN NELSON: Bob?

MEMBER DAUM: From the input either of the Endocrinologists or from the written input from Loss and Wilkins Society, was there agreement that as proposed, that this would set standards for this kind of testing that could be applied all over the country?

CHAIRMAN NELSON: Yes.

MEMBER DAUM: Could I -- there is another component of the response to the issues that Tom and Jeff and others are raising. Part of the answer has to include a perspective of what the study actually involves. That is, is this a big deal? So, you know,

if we were doing brain biopsies to figure this out, it would be a non-starter. But there was a lot of discussion to the point that there was an overreaction on the part of the Review Committees and this whole process for something that really is really -- well, technically more than minimal risk under the definition, really not very risky. And as the Endocrinologists on the Committee described cumulatively many decades of experience in doing this kind of GCRC admission to children, it's not a big deal. It's fun for most of them. It's an adventure. For the occasional child to whom this is really unwelcome, he or she is easily screened out and there's no desire to include them. So that this is, when all is said and done, it's not much more than it being a puncture or -- and certainly the medical risk was to be quite trivial. So that had something to do with it. That is, it's not a silly question that Dr. Rosenfield's answered. There's a coherent reason for wanting these numbers. If the study involved really much more invasive or risky procedures, then your argument might have carried more weight.

CHAIRMAN NELSON: Rich?

MEMBER GORMAN: Before I make my comments, yesterday and in this part of the presentation, I'm speaking as a voting member of the Ethics Subcommittee and not representing the American Academy of Pediatrics, which when we move to the regular Advisory Committee, I'm a non-voting member and speak for the Academy. So, --

CHAIRMAN NELSON: So, you're going to give two different opinions, depending on --

(LAUGHTER.)

MEMBER GORMAN: I hadn't thought about that, but it would suit some other people's needs perhaps.

Dr. Newman and Dr. Botkin have summarized, I think, some of the scientific issues that made me or led me to believe that yesterday as a dissenting vote, that constitutional delay of puberty is within the range of normal and those children or young adults can be considered as normal controls for the study, and therefore, was one of the dissenting votes.

One of the things that I heard

repetitively from the Endocrinologists yesterday was in considering pubertal issues, one of the issues was tempo. They kept repeating that as to how children develop and how rapidly that progresses. And this may be an unfair analogy, but it is one that I drew in my own mind yesterday, was that this test, in effect, becomes a rapid diagnostic test, as well as a standard norm. And then you have to decide how important that is to the tempo of making the diagnosis. Rapid strep tests do not radically change my practice of pediatric medicine. Lymph node biopsies for people with -- or breast biopsies with people with suspected Cancer would really be a serious issue that would alleviate concern. And I felt that this particular test fell much closer to the rapid strep test in the sense that Endocrinologists would most often take this test and then continue to observe as opposed to individuals who have a breast biopsy would rapidly, if it was Cancerous, would end up being taken to surgery or Chemotherapy or Radiation, depending upon what was appropriate, or if it was not abnormal, would be alleviated of their present concern. I felt in most

cases, this particular test would end up with watchful waiting as the outcome and, therefore, didn't think it met the criteria of a serious health issue that would alleviate an issue of childhood disease.

CHAIRMAN NELSON: Rich, let me comment on that later point to amplify Norm's comment, which goes away a little bit from the scientific necessity of the normal controls. And that's to speak, at least to my perspective, on what the serious problem under 407 or 5054 really means in the context of this process.

If you look at 5052 and 40 -- no, sorry. I'm going to stop saying numbers after a while -- but 5053 and 45 Subpart 46.406, has language of vital importance. Okay? So, what -- and the question before us is there's really two levels, and I think this came out in the discussion yesterday of a review at the federal level. There are existing gaps in the Regulations that some would perceive needing to be filled, which precisely, in my mind, would be the use of normal, average, healthy children as controls for minor increase over minimal risk research that results in information that's important, diagnostically, or

therapeutically for a condition. All right, and that's what this question is.

If you look at most of the reviews that have forward, except, I think, for two, all of them have been around that issue. The past two were around this issue, and all of them have been around the issue and there's literature that argues that, in fact, it's unethical not to allow us to enroll average, healthy, normal children in minor increase over minimal risk research. All right, but the Regulations, currently as they're written, and I don't anticipate that they'll change anytime soon, don't allow that. That's very different than saying we do federal review for really big problems, whatever those problems might be, pandemics, whatever. And, if, in fact, we hear from the scientific community and from the therapeutic community that they believe the use of normal, healthy average controls is important to the interpretation of a diagnostic test for a serious problem that affects even a small group of people, my fear is if we don't allow that to go forward under the minor increase over minimal risk, but they just don't have the condition.

They say, we'll orphan that same population who's been orphaned by the lack of availability of testing, diagnostic testing or otherwise that precisely put them in the position they're in in the first place, so I think there's a serious problem if we hold it to too high a standard, other than the scientific necessity within the protocol of some sort of social worth or social purpose if that we, in fact, will do a disservice to the population where this diagnostic test would be important. So, that's -- to try and set a context, this is not pandemics, but it's important. Norm?

MEMBER DAUM: Right, but Skip, one piece of that is what do you have to do to the normal controls to get to the data. If it's a venapuncture --

CHAIRMAN NELSON: Well, that's why I said it's a minor increase over minimal risk and it just -- one final -- if you look at the National Commission's report, the answer to those people, in fact, that category, minor increase over minimal risk, had two dissenters. And if you look at the answer of the

Chair to that, they said, (a) it's a really, really, really low risk, and (b) it's scientifically necessary. So the question is applying that.

So, that's the broader picture and I guess I -- the scientific necessity is one question. It's important to get some resolution, but to say it might be scientifically important, but it's not really that big a problem, that's a whole separate set of issues. And I'm hearing both, but I think that we just need to keep them separate.

Rich and then Jeff.

MEMBER GORMAN: For about 20 years, I've been trying to extend or make available to more children more research on their issues, especially concerning pharmaceuticals. In this particular case, I didn't think the science justified the inclusion of normal controls because I felt children with constitutional delay of puberty could serve that purpose and then the research could be approved under one of the numbers, which I think, is 405.

DR. BOTKIN: You know, I think we may have a difference in how we would prefer to look at 407

reviews, but absent clearly articulated standards by which 407 Panels make their decisions, I think it is a matter of individual interpretation by panel members. I personally would prefer to say that the existing Pediatric Regulations have pretty solid ethical justification and, therefore, we ought to have quite compelling reasons not to, what I would perceive, undermining those by using the 407 approach that uses a different articulated ethical standard. Now, you've articulated one, but those are not within the Regulations themselves. In other words, the 407 Panel could decide to use healthy, normal children with a substantially greater than a minor increase over minimal risk if it chose to do so. Now, I don't think that would happen, but those standards aren't within the Regulations. So, I think -- it seems to me that there probably needs to be some ongoing national debate about what level of risk constitutes an appropriate approvable standard within 407, and the Regulations do say, in accordance with ethical principles. And I think somebody needs to think more carefully and articulate what ethical principles we're

talking about in that context, if we're not talking about the ones that underlie the established principles behind the other categories.

CHAIRMAN NELSON: Before going to Norm, I agree with that, Jeff. The protocol before us, though, does fit minor increase over minimal risk, so, you know, we need to -- we're doing a casuistic case-by-case basis. It's not a greater risk than that. So, that's the protocol before us.

DR. BOTKIN: I think you're right, although I would say that the Ethics Subcommittee never said that this was a minor increase over minimal risk, it said it was more than minimal risk. It might have been an action to perhaps agree on that explicitly.

CHAIRMAN NELSON: Norm?

DR. FOST: Well, two things. First, I don't think the present Subpart D has a firm ethical basis. I don't agree with Jeff about that. That is, the whole idea of doing any non-therapeutic research on children, I don't think, has ever been adequately justified. The argument is, well, it's good for

children as a whole and children as a whole will suffer if we don't allow non-therapeutic research without consent. But that's true of adults, too. That is, we could advance knowledge of all sorts of adults disorders much more quickly if it weren't for this pesky incent issue, if we just said it's the interest of the class that matters. And that's not considered an adequate reason to do research on adults without consent, and it shouldn't be on children.

So, the whole infrastructure from the beginning was a compromise without any real moral justification, in my view. I don't think it's a horrendous compromise, but I don't think it has a firm ethical basis, point one. Point two, that compromise that was made, "Well, let's just keep it to stuff that's really minimal risk," is not being followed. I was at those discussions and I know what was intended was things that happen on a routine visit to a General Pediatrician and there are now non -- there's one IRB in the U.S. that has approved non-therapeutic Bronchoscopies for years on children on the ground that it's minimal risk because the investigator says,

"I've been doing them for 20 years and I've never had a serious complication. And also kidney biopsies, small valve biopsies and everything else you see on that list. So I think there's been enormous slippage. It needs to be revisited and I think making it a big deal through the 407 process, even for an admission, the 36-hour admission to the GCRC, is a good idea. I think that sends a signal to IRBs, we take the non-therapeutic intrusions very seriously. So, I'm not sympathetic to the concern that this system needs to be greased or oiled. I think it's already too greasy.

CHAIRMAN NELSON: Now, let me, for the moment, put in abeyance this conversation and then ask Bob, is there an issue you wanted to get on the table that when you originally said, "I'd like to talk?" Other issues? Go ahead, Melissa -- right?

MEMBER HUDSON: Well, for those who attended the meeting, could they provide some insight about recruitment and how the recruitment cannot be coerced by the parent? Because I don't think it would be on a child's radar to look at postings to volunteer. And if they were young, the money would

have to go to the parent. So can they provide some information about how the child is protected? I assume that if they were difficult venapuncture or they appeared frightened, they would not be recruited? Just how is that process evaluated when the patient is -- the volunteer appears and it's the parent with the child.

CHAIRMAN NELSON: A couple of comments on that. There was a fair amount of discussion about it. I think the Subcommittee was reassured that the process was reasonable. Personally, I disagree with your observation if they're nine years old, it goes to the parent. I mean the parent has an obligation to be the steward, if you will, of the child's use of that money, but most RBs often try to direct it in different ways to the child or make it clear that that's the intent of the -- of the compensation or honorarium or inducement. Based on the amount, people didn't feel that that was inappropriate and if, in fact, most children who are eight or nine, if they don't want to do it, $150 is not going to make them do it. So that was part of the discussion, I think, that

Norm alluded to about the assent monitoring and the capability to say, "Stop." And there was -- and there's been some children that have said, "Stop." And we had a discussion of that and people were reassured that that could be handled appropriately within sort of Pediatric Standards by people who've been doing this for a number of years within their GCRC.

Norm, do you want to elaborate?

DR. FOST: Well, one other issue just along these lines was whether -- there was considerable discussion about whether this is a single location GCRC or scatter bits. The Committee thought it was relevant that it was a single location with experienced Pediatric nurses. There are scatter beds in which ordinary floor nurses might not be as tuned in to these things. So, we thought there was a physical setting in place that was accustomed to treating children well in this regard.

CHAIRMAN NELSON: The analogy was to a "sleep-over." You know, you could set it up in a way that that would be the nature of the experience for a

child, a sleepover.

Judith?

MEMBER O'FALLON: So this now brings up the issue of the sample size. There was a lot of evidence throughout the whole packet that there were concerns about whether they could get enough patients to do this study and I understand that Dr. Rosenfield addressed that. But the other part is then how many controls do we need here. And if they have to go outside, as there were suggestions in the packet that we got, they were going to make it a multi-institutional study, well then, do these -- these other places have this nice, friendly sleep-over environment for the kids to have this test? So, I mean, it does -- this is all kind of interrelated.

DR. FOST: Yeah, I mean, as Dr. Rosenfield said, it's a catch-22. He can't assess his ability to get control until he has approval. And he's optimistic. There are other, certainly other studies of this sort in which parents have -- and their children have volunteered. So he's optimistic about it, but he can't test the hypothesis until an IRB lets

him try.

MEMBER O'FALLON: But seriously, how many controls are they looking for? I don't remember seeing it. I may have missed it.

DR. FOST: I don't have the numbers at my fingertips.

CHAIRMAN NELSON: I think it's 20, 20, 20. I think it's the same number, the same groups that they had within the patient population.

MEMBER O'FALLON: Okay.

CHAIRMAN NELSON: And, as I recall, a large portion, not quite the majority, of the diseased children have already been recruited in the year that this has, in fact, been open. And I think it's fair to say that it's hard to call up another investigator and say, "You know, I'm going before a Federal panel. Do you want to join me?"

(LAUGHTER.)

CHAIRMAN NELSON: Which, as opposed to, "I'm already through the Federal panel and these are the issues." And it would be certainly appropriate to -- I mean, there will be ongoing oversight. I think

one of the themes from the past two reviews is that this has ongoing oversight, both at the local and Federal level and, in fact, I can't imagine, with this discussion, hopefully, that someone would have it done in a scatter bed GCRC that has no pediatric experience. And I don't think, knowing the Endocrinology world, that that's what would happen. It would be within Pediatric GCRCs that could accomplish the same sort of approach and appropriateness to do that. So that was, I think, the discussion. The Committee was reassured by that.

DR. MURPHY: Skip, this is Dianne.

CHAIRMAN NELSON: Dianne?

DR. MURPHY: I think yesterday that Dr. Rosenfield did mention he had already identified a number of units that he thought would be applicable and have --

CHAIRMAN NELSON: Yes, there are collaborators, right.

DR. MURPHY: -- and have accommodations in the -- to the degree which you were describing. It would be, you know, child-friendly, et cetera. So I'm

just trying to -- for those who weren't there yesterday to weigh the information, that they have thought about this. They have identified units. They know the type of areas that they would like to proceed to utilize.

CHAIRMAN NELSON: Right. Norm?

DR. FOST: I should have mentioned in my presentation also that Dr. Rosenfield was very pleased with the suggestions for modifications of the protocol on the Consent Form. He didn't see those as intrusive. So, he was -- reflected a willingness to try to make sure it gets done in the right way.

CHAIRMAN NELSON: Are there other issues that the Committee feels are important to discuss?

DR. DIEKEMA: So as the new person, new kid on the block, I should probably follow the rules that rookies should keep their mouths shut for a while, but I'm just inquiring a little bit about the process here, I guess. This protocol was submitted first to the U of C IRB in November of 2004 and it's now November of 2005. Let's assume for a moment that this is a compelling research question, which I presume

someone feels it is, to have gone to all this trouble to get it considered. And let's assume that -- I can tell you that this is fairly prompt for the U of C IRB, to get a review done in two months. Here we are, a year later, still considering this. Let's just cut to supposing that this research was about the need for controls to assess a cure for Leukemia with one dose of one drug or something like that. Is this really an acceptable timeframe and process for this kind of review, and what about the investigator's willingness to put up with this kind of length of process to get this done? Are we concerned about the need for research to go forward in the face of a year to get it to this point?

CHAIRMAN NELSON: I can just comment on that. I'm sure Norm can then elaborate further. In this particular protocol, it did not arrive for even consideration at the Federal level until June. For those previous members -- I wouldn't say "old" members, but previous members of the Committee, June was our last meeting. So, it arrived around the time of that last meeting. Now there's a certain time it

takes to put a meeting like this together, so you can imagine that. But most of the process of the past year, at least half of it, was within the University of Chicago.

Now, should there be -- you know, are there ways to speed it up and other options? Yes. This is a year and a half into a process that didn't exist, even though the National Commission recommended the process exist in 1977. So -- and could there be ways of trying to optimize it? Perhaps. I mean, we can have that kind of broader discussion, but within the timeframe, this is actually fairly spry. I mean, we're responding reasonably quickly, compared to what's happened in the past, which has been a long time.

DR. DIEKEMA: In no way should my comment have been to impugn this Committee or the FDA's part of the process. I'm just looking at the whole process, from soup to nuts, and so if the fault is at the U of C IRB, I can assure you that wouldn't be the first time. It's still a long, long process, and I'm looking at it as the need to do the research versus

the length of time it takes to get to this point.

CHAIRMAN NELSON: Right. My suggestion would be -- I mean if we have time, we can spend time talking about that process and suggestions and things and we can do that with our time. It is what it is for this particular protocol. I mean, I guess my preference is we could decide to take action on at least this protocol and then whatever time we have before the break, and talk further about the process and ideas people may have for trying to improve it, which I'm sure would be worthwhile.

Norm?

DR. FOST: I had three comments. First, seven of those twelve months were at the U of C. And with regard to that, notwithstanding what I've said before about this system being too slippery, I also think the system is wildly over regulated and dis-regulated. That is, I think doing the really simple things that should take five minutes does take three months and that's beyond the purview of this Committee, but I think both things are true. That it's just way too difficult to do the simplest things. We

published a study showing a dramatic reduction in medical records research at our institution following the Institution of HIPPA. There have been three similar studies published now elsewhere, one in Europe that database medical records research is in a nosedive because of what, I think, are just wildly difficult regulations. They're just stopping good people from doing important studies.

DR. DIEKEMA: That's my point really.

DR. FOST: So, I'm in agreement with you on that. The last point I wanted to make about the scientific merit of this and the questions of the normal control that I forgot to mention, because Dr. Rosenfield mentioned it several times. This has been approved -- some rigorous -- this has been invented by NIH Study Section, that is, some people with a lot of scientific credibility in this field, have approved this. And in light of what I just said, how difficult it is to do research, how difficult it is to get NIH funded, to survive that filter, I think, is a pretty good, at least, procedural screening test for the importance of doing it in this way.

CHAIRMAN NELSON: Thanks, Norm. Let me ask a question of the Committee. We've heard Dr. Rosenfield's name mentioned a number of times. Is there any desire on the part of members of the Committee to hear him respond to some of these issues or ask him, at least, if he feels we've adequately represented those issues? Norm?

DR. FOST: Yes. I mean, I think -- I don't know how -- I have no sense yet of where the Committee is leaning on this, and some objections have been raised by a series of people, so I think Dr. Rosenfield should have a chance to respond to them.

CHAIRMAN NELSON: Tom?

MEMBER NEWMAN: Can I respond to what Norman just said?

CHAIRMAN NELSON: Feel free, Tom, while Dr. Rosenfield formulates his thinking.

MEMBER NEWMAN: I mean, I guess, yes, I guess the Study Section approved this and thought -- and liked the design and I will definitely acknowledge that there will be some journals who would prefer to have normal controls. I just -- I agree with the

other two Committee members that scientifically that is not necessary. And I think what it really comes down to is your other argument that this isn't a big deal because if you're studying the accuracy of the CT Scan, for example, to diagnose Appendicitis, you don't need to do it on children who don't have abdominal pain. The group of children with whom we want to study that test are children who have abdominal pain and might have Appendicitis and then you compare the CT Scan with the Gold Standard of Surgeons and find out how accurate it is. I just -- I think --

CHAIRMAN NELSON: Tom, the --

MEMBER NEWMAN: -- in this case, you're saying that the test is not a big deal and may be even less of a big deal with a CT Scan.

CHAIRMAN NELSON: Let me just -- with all due respect, I don't think that I suspect -- if I thought anyone was going to be convinced differently by your argument or that you'll be convinced differently by their arguments, I would continue to have us discuss it. It's not clear to me that we'll do other than -- is just get back into the same

discussion and do it twice. So --

MEMBER NEWMAN: So if someone thinks that they have something new to say on that point that might change people's minds, I'm happy to hear it, but I suspect it's going to be just back again for the next twenty minutes to what we just discussed for the last twenty. So, Norm?

DR. FOST: I don't know if it's new or not, but I think your example is a good one, Tom. That is, children with abdominal pain may have abnormal CTs for reasons that I don't -- maybe their Appendix lights up a little bit, too, from Gastroenteritis or something. Who knows? The assay sensitivity of a CT Scan, it seems to me, requires knowing the children who had nothing going on in their abdomens. So it seems to me a metaphor or an example that, at least, supports the other point of view also.

CHAIRMAN NELSON: So, let me -- speak closer. No, I'm planning to ask him now if I get a chance. Dr. Rosenfield's, whose topic it was, the adequacy of the controls with people who have constitutional delay, is that an adequate control

group?

So, you've heard the discussions and the key issue to address is the importance of average, normal, healthy children who don't present with some phenomenological condition for the establishment of the controls.

DR. ROSENFIELD: Well, in a short time, I don't think I can review the whole subject and outline the rationale as well as it's outlined in the written research protocol. And I think that Dr. Fost and Dr. Nelson represented the overview of the Committee, and I would like to just point out that the Committee as a whole was convinced by a vote of seven to two. And at that time, there was an Endocrinologist present who vouched for the importance of this. It -- it's just that I can't answer everything in moments, but I'd say I know that Pediatricians have been brought up with the concept that constitutional delay of puberty, for example, is a variation of normal. Most of these children go on to have normal puberty. But to use -- but you have to realize these are outliers of the population. In other words, this group of children

are -- the 2.5 percent at the extreme end of normal, and to use those children, our priorities is as normals, gets into circular reasoning. And I agree very much with Dr. Fost that you don't know what "normal" is until you test it. I didn't make a big point about it in my slides yesterday, but the few normals that we accumulated in a precursor protocol with a different agent had a very -- had a narrower range of normal that, in response to the precursor of (*9:21:20 inaudible) than it was the late puberty. It's not clear whether these are really normal and there's reason to believe that there's some population within the constitutionally delayed children that has some sort of abnormality now. And a similar argument holds true for children in early puberty. There's quite an argument about whether puberty that occurs at seven years of age and is, therefore, early, there is some concern about whether those children are just a normal thing happening early or whether this is an abnormality of some sort, or a pre-stages of predisposition to that normality.

So, it's just that those children tend to

go through puberty at a slower tempo than normal. So it's not clear that they're really normal. So to use them as normal gets into circular reasoning and will obscure science for a long period of time. Your question about why not just use the sleep test, you know, you're comparing each person to himself. And the -- one of the issues that wasn't mentioned in Dr. Fost's summary is that all of the historical data on normals -- the great majority of it was with National GRH, which has a very different profile and does not give quite the same results as Leuprolide does. Leuprolide gives a more prolonged and somewhat different stimulants to the Pituitary Gland and to the gonads as well.

And furthermore, the historical data is based on an over generation of assays that are no longer necessarily available and of an equal quality. And although they are -- there are a variety of Gonaditropin (*9:23:36 phonetic) assays around the country. CAP approves them as long as there are other people doing them and there are, you know, as many companies as many kids have their own assay with

different results. Some of those assays aren't as good as others or as specific. It's very important for proper Pediatric research to have very sensitive assays to make these distinctions about very early puberty. When does early puberty begin? What are the first markers? What's normal? And we now have sensitive assays that are very specific that are commercially available. And this wasn't true of any historical data. There's no historical data that actually is available at this moment to allow us to discern when early puberty begins and whether it's beginning normally.

So, if there were other -- if the Endocrinologists on the panel were here, they would say the same thing. So, I think that briefly summarizes maybe some additional points. If you'd like, I'll answer some -- any questions you have, but I'm not sure I can -- I think it's fairly well summarized.

CHAIRMAN NELSON: Thank you.

DR. MURPHY: Skip, can we ask Dr. Rosenfield questions?

CHAIRMAN NELSON: Excuse me, Dianne?

DR. MURPHY: I want to ask him a question.

CHAIRMAN NELSON: Go ahead.

DR. MURPHY: One of the things that came up yesterday was the timing also, and if you had this group of referred patients versus normals, is there any knowledge that we could try as to potentially not being able to differentiate the timing of the response? That was one of the things that, I think, was discussed yesterday.

DR. ROSENFIELD: Are you talking about the timing of the response to tests or --

DR. MURPHY: Yes.

DR. ROSENFIELD: -- the timing of puberty? Well, the four-hour time period is something that the previous tests with natural Gonaditropins (*9:25:25 phonetic) and hormonal factorial (*9:25:30 phonetic) does not test at all, nor does factorial allow you to look at the overall gonadal response.

Another issue that was mentioned is that the -- Dr. Gorman mentioned the -- why do you need a test when the tempo of puberty will tell you what you

need to know? But the tempo of puberty can take years and for a boy in high school, starting high school, who is delayed or -- this delay can be terribly distressing psychologically, not for all boys, but for many of them. And so it's important to make a prompt diagnosis to optimally manage these children.

And as I pointed out yesterday to the panel, there is constitutional delay and then there's constitutional delay. Constitutionally delayed children are late bloomers in a common parlance, so it's sort of an ordinary common variation. But the ordinary ones are screened out. Our protocol doesn't study constitutional delay until they're 14 years old and in high school. By that time, they are clear outliers and in our experience of the patients that we study, about a third of them are Gonaditropic (*927:02 inaudible) deficient rather than simply being delayed. And it's not a determination that can be made by in clinic. If it's made in clinic, we don't even study it.

CHAIRMAN NELSON: Do you want to ask him again?

MEMBER NEWMAN: Skip, could I --

CHAIRMAN NELSON: Go ahead.

MEMBER NEWMAN: With this variation in the assays around the country, if someone chooses to apply the same testing protocol at a distant site, will they be able to interpret their results based on your testing?

DR. ROSENFIELD: As I say, the assay that we're using is now commercially available and I think the design of -- once we have approval, hopefully, and then the decision has to be made whether to do it on the central site or just use the same assay at each of the sites, would probably be really the best way to know what the noise in the system is and to have a more generally valid set of results.

CHAIRMAN NELSON: Judith?

MEMBER O'FALLON: I'm a Statistician, so I want to ask that question again, about the numbers. How many of the -- how many normals do you plan to accrue under the, you know, modified protocol?

DR. ROSENFIELD: 20, 40 60, 80. Twenty pre-pubertal boys, 20 pre-pubertal girls, 20 early

pubertal boys, 20 early pubertal girls. And the issues about accrual, for your information, as I mentioned yesterday in your absence, was that that was a pre-review by the GCRC and the final protocol address. For the principal outcome variables, we have sufficient power. That has to do with constitutional delay of puberty and idiopathic central proposal (*9:28:52 phonetic) puberty. We have sufficient power to carry out that study.

MEMBER O'FALLON: But that's the normals you're planning on getting?

DR. ROSENFIELD: Well they -- yes.

MEMBER O'FALLON: I thought the normals were -- you're going to take them between eight and something --

DR. ROSENFIELD: Eight and fifteen.

MEMBER O'FALLON: And they're just supposed to be normal and they're supposed to -- and you're going to get 80, right?

DR. ROSENFIELD: Yes.

MEMBER O'FALLON: Okay. Forty boys and forth girls?

DR. ROSENFIELD: Yes.

CHAIRMAN NELSON: At this point, to give a feel for the tempo of the meeting, ideally we will have, in the next 15 minutes, completed our discussion. To give you an idea of how I want to carry the tempo, there are 13 voting members around the table, and if we started voting one-by-one, it would give you a full minute to sort of expound on the reasons for your vote and the like. So, before doing that, I'd like to ask if there's any informational or further discussion or issues people want to raise that you think might change your mind, as opposed to just express your mind --

MEMBER MOORE: I'd like to make one more --

CHAIRMAN NELSON: -- because you'll have an opportunity to do that. John?

MEMBER MOORE: Part of how I spend my time involves starting an IV on patients who are about to be catharized. And I have to say that on an eight- or a nine-year-old, sometimes these patients prefer to be sedated before they have an IV started. And just the

thought of that procedure is sometimes a fairly traumatic experience for a child. And I just find it difficult to imagine that an eight- or a nine-year-old would actually freely assent to having that done, and once they understand what's being done, when they're a perfectly normal child, they really have been given no reason why they have to undergo this procedure. So, I mean, I'm -- to me, this is the main issue here, is submitting them to this. I think it's a combination of financial incentive really that's to the parent and, you know, the parents have more or less persuaded the child to participate in this kind of a protocol. So I have a hard time with that whole issue of this is just more than minimal risk because there are a number of risks, and, too, the medical risk is probably not more than minimal, but the emotional and psychological risks, just based upon my own practice, I think, is probably, you know, fairly substantial, at least for some children. And that obviates the whole issue of is the IV easy or hard to start, which I think most Pediatricians in the group here understand the issues there.

The other question, in my mind, that I'm sort of weighing this against as I sit here, is the adequacy of control data that could be obtained from patients who are -- children who have constitutional delay. And I can see how that may not be very adequate and may leave this whole issue very blurry, but I'm just concerned about the risk of this protocol to the normal children and the fact that there are 80 of them makes me uncomfortable.

CHAIRMAN NELSON: Well, let me ask you, would you be reassured to hear evidence or experience to the contrary? I mean, I think your concerns were discussed and raised, but I in both GCRCs and actually in my own work interviewing normal, healthy, average children about being in research, there are children who, if you approach them with emracream (*9:32:52) and appropriate -- in an appropriate context and without giving the money to the parent and, in fact, soliciting the child's assent independent of the parent, are capable of doing this and doing it without great psychological harm. So --

MEMBER MOORE: No, I certainly believe

that, that there are children who could undergo this protocol, these controls, who would not be troubled by it, but I also think that -- I mean, the process of sorting them out from those who would be troubled by it is the critical issue. And I know from my own practice that there are many children who would be troubled by this. And I'm not exactly sure, you know, by just asking them, especially when you're giving money to them and it's all getting very confusing, what the incentives are here.

CHAIRMAN NELSON: Well, I guess all I can say is that the Committee talked -- the Subcommittee talked about that yesterday and felt reassured that the investigators, under the guidance of their local IRB, were capable of doing that. Beyond that, you know -- that, in fact, was the discussion.

So, I guess -- let me ask again. Does anybody think they are going to change their mind based on further discussion? I'm happy for people saying why they vote the way they vote, but, you know, we can go on -- you know. Norm?

DR. FOST: Well, I hope to change Dr.

Moore's mind. The -- I agree with you that the heart of it is the assent of the child, whether he or she really wants to do this, understanding he doesn't have to. Point one, I agree with Skip there. There's empiric evidence from Skip's studies that there are children who do want to do this for altruistic reasons even. Number two, if the assent is taken seriously, it'll weed out those who really don't want to. And I agree with you, probably most do not want to, and it's going to be a struggle to do it. That's why I said that the asset monitoring, to me, is at the heart of this. If we ensure that the only kids that are doing it are kids who really want to do it, and understand they don't have to -- and by the way, they might be siblings, so they may have some desire to help their brother or their sister and so on. So I agree with you that the real willingness of the kids to do it is at the heart of it and that's why I voted to approve it, only on the condition that there was assent monitoring and there was not disagreement with that from the -- we had a Vice Chair of the IRB here yesterday and they -- he seemed user-friendly to that

suggestion. So that could be a condition of the approval.

CHAIRMAN NELSON: Now, I might just point out, procedurally, we can make further modifications if, in fact, you want to strengthen what Norm just said, from this Committee, is a condition of your vote one way or the other. This Committee can add further modifications to the Subcommittee. So, it's really, in terms of what we're -- there are really three ways you can go. One is the Subcommittee's decision is fine. Approval is -- it's approval, but you want to add further modifications, strengthening something, et cetera, as you see it, which is -- certainly, that's happened actually on one other decision of the previous two. The third is to say that this just shouldn't go forward. So there is that opportunity to do that. If you have further concerns that you'd want to make a stipulation based on this discussion.

MEMBER MOORE: I'm a little confused as to how you monitor the assent process. I mean, I agree -- I mean I'm generally in favor of giving control data, don't get me wrong. But I think that if I was

really comfortable with the fact that children who would likely be distressed by this could truly just opt out, or would truly just opt out, I would be more comfortable.

One of the things that actually makes me uncomfortable about this is the money. And I'm afraid that there are some parents, you know, who would see this as a little incentive and pressure their child. And I don't know if there's a way to do this without that incentive to the parent. Maybe there is, maybe there isn't. Maybe some kind of financial inducement is needed to get anybody to show up for this. But I think that it is important to have some type of independent, independent of the protocol apparatus assent monitoring for this, so that somebody, social worker or psychologist, somebody in the hospital is actually reviewing these candidates that has nothing to do -- no interest in the protocol.

CHAIRMAN NELSON: And this, I just point out, will be done in a GCRC, which by NIH support, has a research subject advocate as part of that process. So we certainly could make a stronger statement about

the need for that.

Judith?

MEMBER O'FALLON: Okay, here's my concern. There are going to be -- we're looking for 40, let's say, girls between the ages of eight and 15 or 14. That's roughly six per year. I'm wondering -- you know, I'm not a medical doctor. I'm wondering about a Pediatrician who's seeing normal kids, taking care of regular, old kids, not -- you know, not -- what do you call it? -- not an expert in some area here. How much variability are we going to be able to get at with only 40? I'm concerned about -- I hate to say this, but I'm really worried about whether 40 kids between the ages of eight and 14 will give us a very good idea about how the normal process is evolving in that very volatile age range. You know, in terms of measuring the -- well, whatever -- whatever it is that you're going to be measuring. I know there are hormone levels, but --

MEMBER MOORE: Ruth, until you start doing that, you can establish a confidence interval around the variability of that, there's no way you can answer

that question. So, I mean, you can't say it's a question that can't be answered without starting to try and answer it.

MEMBER O'FALLON: No, I'm -- I'm in favor of getting the -- actually, I'm in favor of looking at the normals, but I am concerned about how much you're going to get in that volatile period, how much information, and whether it's going to be so much all over the map that it's -- on any one of the hormone measurements that you take, that it's going to not really help a lot and you're going to find out you need to have a lot more kids, in which case, they'd be coming back for more normals.

MEMBER MOORE: The devil's in the details, and that's why there's continued oversight of the research. But it really comes down to preliminary data that could give you a confidence interval and you have no preliminary data on which to do that.

MEMBER O'FALLON: It's not a confidence interval, people, exactly because we're looking at a process. We're going --

MEMBER MOORE: It's about distribution

over time, but you don't know how that's going to be --

MEMBER O'FALLON: Yeah, I mean, it's going to be like over a regression line, is what we'd be dealing with.

CHAIRMAN NELSON: So what I'd like to do, and I'm going to say this slowing to give Melissa a chance to gather her thoughts because I'd like to start at that end of the table and, Rich, and Elizabeth are non-voting members, so you would be first up. So, what I'd like each person to do is basically -- you know, we have a Subcommittee Report, we have a recommendation from the Subcommittee, seven to two to approve -- I should say, to recommend that this Committee send forward to the Commissioner a recommendation for approval under 407 and 5054 with the stipulations that Norm mentioned in terms of the protocol. I don't know if those stipulations can be put back up on the slide just so people see those, if you want to look at them. Now, if -- if you would approve, but you think you would do that only with an additional stipulation, what I would suggest is just

add that and then at the end of the voting, I'll take those stipulations and basically see if there is, among the people that voted in favor and those, in fact, that vote against, if there's a consensus or not around those stipulations, rather than go one-by-one to each one of those. So if, for example, on the assent strengthening that's something that you want to strengthen, if you haven't heard it before, say it, and then after the process is done, we'll go through and clean up those additional modifications just to sort of move us along. So, it's really either "approve" or "disapprove" or "approve with modifications." If you say you'd approve it with modifications, just what is the nature of that modification and then we'll go around and then clean up those modifications at the end, assuming that the vote is for approval or approval with modifications at that point. Does that make sense?

Okay. So I'd like to start with Melissa.

MEMBER HUDSON: Well, I think the objectives outlined in the study are important and will help us gain important knowledge in diagnostics

for these children, and I believe that it's important to have control of the situation because of the variability in children with constitutional delay. I would approve, with the understanding that there be very strict assent monitoring. And I've been reassured, at least what I've heard so far, that this is an institution that would have that as a priority and that they're used to implementing these studies in children who had a fear or clearly were not -- were being coerced by their parents, and the situation would be eliminated.

CHAIRMAN NELSON: Okay. Jeff?

DR. BOTKIN: Do I get --

CHAIRMAN NELSON: You are a voting consultant to the Committee, I was informed. If you need time to think, I'd be happy to pass you, but usually you're pretty quick on your feet.

DR. BOTKIN: Well, a nice surprise to get to say something additional. I would maintain my assessment from yesterday, which would be not to approve the inclusion of healthy children in the protocol. I think it's otherwise approvable and would

provide valuable scientific evidence for the evaluation of kids with either delayed or precocious puberty, in the absence of healthy children in the protocol. I also would strongly support the assent monitoring if the protocol goes forward.

CHAIRMAN NELSON: Okay. Bob?

MEMBER DAUM: I have a bit of a problem and request some help from the Chairman. I didn't realize until this discussion started that Dr. Rosenfield is, of course, at my institution, and not only that, is in my department. So, I feel like -- I think I would consider that a conflict. I do consider it a conflict, and I would prefer not to vote, or to abstain.

CHAIRMAN NELSON: Well, then, we'll consider that a non-vote. You wouldn't be allowed to review a grant on NIH, nor would you be on the IRB protocol, so I think we should hold that same decision.

MEMBER DAUM: No, I was actually going to jump up and ask you if you wanted me to leave the room.

CHAIRMAN NELSON: No, that's all right.

MEMBER DAUM: I just didn't know this was going to happen.

CHAIRMAN NELSON: That's fine. I think it would be appropriate for you not to vote.

MEMBER DAUM: Okay. Having said that, you can determine whether you'd like to have my opinion or not.

CHAIRMAN NELSON: No.

(LAUGHTER.)

CHAIRMAN NELSON: Norm?

DR. FOST: I would vote to approve, with all the -- with conditions that are on the screen, plus the additional requirement for consent or assent monitoring by someone not connected with the study.

CHAIRMAN NELSON: Okay. Angela?

MEMBER DIAZ: I also vote to approve, with the three modifications and closely monitoring of the assent.

CHAIRMAN NELSON: Okay. Bob?

DR. WARD: I would vote to approve, and I actually think it's essential to have the normal

controls because of our lack of understanding of variability with this test in children who wouldn't be presenting to an Endocrinologist. I think Norm's concern about having assent monitoring is essential because of the magnitude of the monetary rewards, in particular. And I think Judith's point about power analysis is important and I would wonder if there shouldn't be a mid-way analysis of variability to decide whether we properly powered this so that at the end of the day, we have a definitive test.

CHAIRMAN NELSON: I would hope that that's routine on IRB oversight, but we an make that much more --

DR. WARD: I didn't see it specified.

CHAIRMAN NELSON: No, it's not specified, right. Michael?

MEMBER FANT: Yeah, I vote to approve, with the previously stated modifications. Just one comment with the discussion that centered around the inclusion of controls. Based on the discussions that I've heard, I really think those discussions sway me more toward the necessity to include normal controls.

I don't think we can assume that kids that end up having constitutional delay and are otherwise considered "normal" can be considered as normal for the purposes of this study. And I think the kids who you are trying to get a better understanding of, a diagnostic tool, they may be short-changed if we're not allowed to include normal controls in this process. So, only with those comments, I vote to approve with the previously stated modifications.

CHAIRMAN NELSON: Okay. Tom?

MEMBER NEWMAN: Well, my concerns about the scientific value including the normal controls, I think, were addressed, to some extent, by Dr. Rosenfield when he said that actually the sleep study is not a very good Gold Standard and hasn't been well standardized, so having some children about whom there is no concern might actually be helpful in making this test more interpretable. So, I'm reassured about that. I share the concern about the incentive, and actually got a little bit more worried when somebody mentioned maybe siblings of patients who have this might, you know, want to do it because then, you know

-- whatever we say about your participation is voluntary, you don't have to do it, this child is going to go home with a parent who may have wanted them to do it. So, I do have a little bit of concern there about this incentive. I'm going to give a weak "yes" and defer to the Ethics colleagues who have actually researched this, and certainly compared to a Bronchosopy, this is not too bad.

(LAUGHTER.)

CHAIRMAN NELSON: We can come back to the sibling issue. Judith?

MEMBER O'FALLON: Yes, I would like to -- I vote yes. I do have the concerns about whether we've got enough normals, but I think they're needed. And I do agree with all of the above-mentioned modifications.

CHAIRMAN NELSON: Okay. I'll just skip me. I'd like to go last. And I'll go to Paula.

(LAUGHTER.)

CHAIRMAN NELSON: That's not why, but -- Paula?

DR. KNUDSEN: I vote yes, with the

modifications and the added stricture that for certain, the Pediatric assent monitor must be distinct from the research team.

CHAIRMAN NELSON: John?

MEMBER MOORE: Yeah, I vote to approve, with the same caveat. I think that it's important, at least for the control group patients -- for the study patients, it's probably not as critical -- that there be an independent monitor that is not related to the protocol or the research team.

CHAIRMAN NELSON: Deborah?

MEMBER DOKKEN: I vote to -- is this on? I vote to approve, but also to underscore the independent assent monitoring.

CHAIRMAN NELSON: Thank you, and what I'll do is give you my vote, but then as I go through the modifications, I'll do those in the context of re-stating what I've heard and then seeing if there is consensus around requiring those modifications as additional stipulations. So, I would vote to approve as well, and what I've heard on the concerns are three. The first is a consensus around the importance

of assent monitoring. Now how that's done, I think, is open to debate. I mean, there's not been a lot of experience with assent monitoring, but at least, in the GCRC environment, there is an independent research subject advocate and there is a mechanism by which they can monitor assent. How that's done, how you pull a child separate from the parent, I mean, it is a complicated question, John, and in many ways, they'll be breaking new ground. But I think that is an important stipulation, to say there should be a process in place. I've also heard, not from everyone, but from enough -- and I'll see if this is a consensus or not -- is the importance of whether to mid-point review or review at some point about the variability of the data coming from normals and what does that mean in terms of sample size, and if it's going to turn out to be a thousand kids, I mean that's an extreme because there's such variability in the data to reassess, but not to just run through the 80 without some assessment of that issue. So a mid-point analysis of the variability -- and this is not a clinical trail, so this is not as if you take a look

at the data, you have to then do another 50. It's just an assessment of the actual data itself. So, I think that can be an important -- even though I think they should do that as part of the continuing review, we'll make it an explicit request. Is that fair?

(NODDING OF HEADS AFFIRMATIVELY.)

CHAIRMAN NELSON: And then the third thing I heard, I think, the comment of siblings. I don't recall if that was discussed in the protocol. It may just be an aside. I agree with Tom's issue. It's unclear, the balance between a sibling who wants to act altruistically and the risk of undue influence within the family environment. And it's also unclear if you need siblings and that's a controversial issue. So, it's not clear to me if (a) it's necessary. It's also not clear to me if we need to make it a stipulation. But we could certainly add it as part of the mix of concern. I don't know, Norm, if you have further thoughts on that?

DR. FOST: Yeah, I mean, Will Gaylon wrote a great article about 20 years ago saying that parents had a right to raise their kids not to be selfish

little bastards.

(LAUGHTER.)

DR. FOST: That is, some parents want to teach their kids community service, and sometimes it means some sort of mild and modest physical sacrifice. And again, we're not talking about brain biopsies and we have assent monitoring. I think that's within the realm of what parents can legitimately ask their kids to do. I think it's sufficiently undeveloped an area that we shouldn't make it a condition here. I think we can add it as a comment. But I would be concerned if we excluded siblings.

CHAIRMAN NELSON: Hopefully, if there's a robust assent monitoring that you'd pick up those siblings who are being coerced by those who are in the tradition of Will Gaylon's approach on that. I guess -- you know, I think that would be fine with me and if that's fine with the rest of the people, we can assume that that could be an issue within the assent monitoring.

Rich?

MEMBER GORMAN: In the search for normal

controls, I would suggest that siblings of people with constitutional growth delay may not be the ideal group to select.

CHAIRMAN NELSON: Important point. Important point. Okay. So, we can add that as a comment without any particular direction in terms of stipulations.

So, let me summarize, then, what I've heard and then see if there's anything else. The vote is, by my count, eleven to one, in favor of approval of recommendation to the Commissioner, which will then go through the process to approve under 45 CFR 46.407 and 21 CFR 5054, with the stipulations by the Subcommittee, but then in addition to that, two further stipulations with commentary around siblings, but the further stipulations is a robust assent monitoring process within the framework of the GCRC and the research subject aggregate system, and then the second is the importance of a mid-point assessment of the variability of the normal data and a re-affirmation of the appropriateness of the sample size and re-assessment of the utility of that data against

the abnormal data that has already been collected and with appropriate decision-making by the IRB under those circumstances.

Are there any other comments?

DR. BOTKIN: This might be a little late in the process to raise this question, but perhaps others have a better recollection of the protocol than I do. I think there's a certain element of confusion in my mind about whether the sleep study was going to be the Gold Standard or whether the clinical outcome of the kids was going to be the Gold Standard. In some circumstances, you seem to be saying that he was going to compare the Leuprolide assessment with the sleep study in order to demonstrate equivalence. In another section of the protocol, he said these kids would be followed longitudinally so that the sensitivity and specificity of both the sleep test and Leuprolide test could be independently assessed. I think part of the question Rich just addressed is you're using the healthy controls -- in fact, some of those kids may well turn out to have delayed puberty and unless you follow that whole set of kids

longitudinally, I guess the question is how are you going to independently assess the sensitivity and specificity of both tests independently as well as the clinical status of the healthy controls? So, maybe you adequately addressed this in the protocol, but I'm not certain.

CHAIRMAN NELSON: As I recall, the discussion of that was the primary objective is the comparison with the sleep study. The secondary objective is the longitudinal analysis and sensitivity and specificity. I mean, it's -- so, you're right. It's both in the protocol, but one's the primary and one's the secondary objective.

DR. BOTKIN: And so did he adequately describe the fact that they will be clinically following all of these children over a period of time to assess their pubertal development?

CHAIRMAN NELSON: He certainly said it in the comments that I heard him say yesterday. Now, whether we can find chapter and verse in the protocol, I don't recall. But that is both -- those are both objectives of the study, one being primary and one

being secondary. I'm confident that that's how it's going to happen. But you're right, you're a little late.

(LAUGHTER.)

DR. MURPHY: So, Skip, pursuant to this conversation, is Dr. Botkin suggesting that that is one of his recommendations, that we make it clearer?

CHAIRMAN NELSON: I mean, I think it is clear. I mean, I guess we could certainly go back and look at the protocol and decide is it clearly enough described. But in Dr. Rosenfield's comments from yesterday, it was pretty clear what, in his mind, was the primary objective as opposed to the secondary objective; one being, obviously, a more short-term analysis based on the testing, and the other, obviously, more long-term because you've got to wait and see what an eight- and nine-year-old does when they get to 16. So I'm comfortable with deferring to your office and to OHRP to make sure that that's adequately described in the protocol. But I think Dr. Rosenfeld described it in verbal comments yesterday.

DR. MURPHY: Thank you.

CHAIRMAN NELSON: Angela?

MEMBER DIAZ: In the protocol, healthy controls are being compensated and were not patients and yesterday I learned that that's the norm of, I guess, the industry. And it's something that I -- I usually either compensate everyone or not. Even if it's not part of this protocol, I'm just interested in hearing if that's really the norm.

CHAIRMAN NELSON: I think the difference is, here, the individuals are coming in that this protocol is direct benefit and offers diagnostic testing. And it is the norm if, in fact, you're going to benefit with respect to your own health care to not provide whether you call it compensation or inducement, money for that exchange, as opposed to -- so, if this was a basic science protocol where this testing, even for the diseased group, did not offer benefit, then it would have been to compensate as well. So that's the important difference, not that they happen to be patients.

MEMBER DIAZ: No, no, I know.

CHAIRMAN NELSON: That is -- that is the

standard. That is the standard.

What I'd like to do, if I hear no objection, is to basically close this portion of the meeting, have our break, and then we're on to a different subject.

(NO RESPONSE.)

CHAIRMAN NELSON: Hearing no objections -- we're running a few minutes late. Maybe if we try to start at ten after ten, which gives us about 12 minutes by my watch.

(Whereupon, the above-entitled matter went off the record at 9:58 a.m. and resumed at 10:16 a.m.)

CHAIRMAN NELSON: Good morning and welcome. We'll eventually go around the table for introductions, but from the start, I guess, -- do you want to start with that?

We're going to start with comments that Jan has to make and we'll proceed from there.

EXEC. SEC. JOHANNESSEN: I'd just like to note the mistake that is entirely mine on the roster. I omitted to include on the roster Dr. Catharine Champagne, who is the Chief of Dietary Assessment and

Counseling at Louisiana State University at the Pennington Biomedical Research Center. So I apologize for that omission. We will have an updated Agenda for you tomorrow.

I think, at this time, I can also read the meeting statement. "The Food and Drug Administration is convening today's meeting of the Pediatric Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. The Advisory Panel Meeting provides transparency to the agencies deliberative process. With the exception of the industry representative and the Pediatric Health Organization representative, all members and consultants of the Committee are special government employees or regular Federal employees from other agencies subject to Federal Conflict of Interest Laws and Regulations. FDA has determined that members and consultants of this Committee are in compliance with Federal Conflict of Interest laws, including but not limited to 18 USC 208 and 21 USC 355(N)(4). Under 18 USC Section 208, applicable to all Government agencies and 21 USC 255(N)(4), applicable to FDA, Congress has authorized

FDA to grant waivers to special government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential conflict of interest. Members and consultants who are special government employees at today's meeting have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their employer, spouse or minor child related to the discussion of today's meeting. These interests may include investments, consulting, expert witness testimony, contracts, grants, gratis, teaching, speaking, writing, patents, royalties and primary employment."

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

In accordance with U.S. -- 18 USC Section 208(B)(3), waivers have been granted to Doctors Patricia Joban (*10:18:17 phonetic) and Thomas Inge. A copy of the written Conflict of Interest with waiver

statements may be obtained by submitting a written request to the Freedom of -- Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

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

Finally, in the interest of public transparency, with respect to all other participants, we ask that they publicly disclose, prior to making any remarks, any current or previous financial involvement with any firm whose products they may wish to comment on.

This statement will be available for review at the registration table during this meeting, and will be included as part of the official meeting transcript. Thank you.

CHAIRMAN NELSON: Thank you, Jan. In

looking at the Agenda, I note both Dianne and Ron are listed as having opening comments. Is there a particular direction, or who would like to go first or second?

DR. MURPHY: Mine are shorter.

CHAIRMAN NELSON: Okay. Should we do introductions --

DR. MURPHY: Yes. I'm --

CHAIRMAN NELSON: Dianna, should we do introductions before or after your introduction, of the people around the table?

DR. MURPHY: Why don't you do introductions before?

CHAIRMAN NELSON: Okay. So, let's go around the table and introduce. We have new people and new people who don't know the old people. So, if we could start down on my left, at the end, and just go around the table introducing ourselves?

DR. INGE: Hi, I'm Tom Inge, Pediatric Surgeon from the University of Cincinnati at Cincinnati Children's Hospital.

DR. YANOVSKI: Jack Yanovski, National

Institute of Child Health and Human Development. I'm an intramural investigator. I work on pediatric obesity in clinical trials.

DR. KLISH: Bill Klish. I'm a Professor of Pediatrics, Pediatric Gastroenterologist from Bailor Collect of Medicine.

DR. CHOAN: Pat Choban. I'm a General Surgeon in private practice in Columbus and an adjunct Professor of Human Nutrition at Ohio State.

DR. KRAL: I'm John Kral, a Professor of Surgery and Medicine and my interests are obesity, appetite regulation, and developmental aspects.

DR. CHAMPAGNE: Catharine Champagne. I'm a Nutritionist, a Ph.D. at Pennington Biomedical Research Center. My focus is dietary assessment and counseling and we focus on obesity and nutrition at our center.

DR. LUSTIG: I'm Robert Lustig. I'm a Pediatric Neuroendocrinologist at UCSF and the Director of our Weight Assessment for Teen and Child Health Clinic.

DR. ROCCHINI: Al Rocchini. I'm a

Pediatric Cardiologist at the University of Michigan and I have done -- I have interest in pediatric obesity and hypertension.

DR. ARSLANIAN: Silva Arslanian. Pediatric Endocrinologist, Children's Hospital of Pittsburgh. I'm the Director of Pediatric CCRC and for the last year, the new Director of the Weight Management and Wellness Center. And my area of research is insulin resistance during childhood growing levels.

DR. PORIES: I'm Walter Pories. I'm a Professor of Surgery of Biochemistry at East Carolina University and Chief of the Metabolic Institute. I'm also a Chairman of the Surgical Review Corporation, which is a non-profit organization for the quality improvement of pediatric surgery.

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

MEMBER MOORE: I'm John Moore, Pediatric Cardiologist at UCLA. I'm a member of the Pediatric Advisory Committee.

DR. KNUDSEN: I'm Paula Knudsen and I'm an IRB Administrator at the University of Texas Health Science Center in Houston and the Consumer Representative to this Panel.

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

CHAIRMAN NELSON: Robert Nelson, also know as "Skip" on the Pediatric Critical Care Physician and Biologist at the Children's Hospital of Philadelphia and University of Pennsylvania.

MEMBER O'FALLON: Judith O'Fallon. Biostatistics, Emeritus Professor of Statistics for Mayo Clinic.

MEMBER NEWMAN: Thomas Newman, Professor of Epidemiology and Biostatistics and General Pediatrician at the University of California in San Francisco.

MEMBER FANT: Michael Fant. I'm a Neonatologist and Biochemist at the University of Texas Health Science Center in Houston. And I'm a member of the Pediatric Advisory Committee.

DR. WARD: I'm Bob Ward, a Neonatologist and Pediatric Pharmacologist at the University of Utah. I'm a consultant to the Advisory Committee.

MEMBER DIAZ: Angela Diaz, Professor of Pediatrics and Community Medicine at Mount Sinai School of Medicine. I'm a member of the Pediatric Advisory Committee.

DR. FOST: Norm Fost. Professor of Pediatrics and Bioethics. Director of the Bioethics Program and shared IRB at the University of Wisconsin.

DR. DIEKEMA: Doug Diekema, Associate Professor of Pediatrics at the University of Washington and Interim Director of the Center for Pediatric Bioethics at Children's Hospital in Seattle.

MEMBER DAUM: I'm Robert Daum. I'm a Professor of Pediatrics at the University of Chicago and Head of the Section of Pediatric Infectious Diseases.

DR. BOTKIN: I'm Jeff Botkin, Professor of Pediatrics and Medical Ethics at the University of Utah and Associate Vice President for Research at the University.

MEMBER Hudson: I'm Melissa Hudson. I'm a Pediatric Hematologist/Oncologist at St. Jude Children's Research Hospital and a new member of the Pediatric Advisory Committee.

MEMBER GORMAN: I'm Richard Gorman, a Pediatrician in a suburban private practice. I'm the Chair of the Section of Clinical Pharmacology and Therapeutics for the America Academy of Pediatrics and am a non-voting member of the Pediatric Advisory Committee, representing the American Academy of Pediatrics.

MEMBER GAROFALO: I'm Elizabeth Garofalo. I'm a Pediatric Neurologist by training, and I am the Industry Representative, non-voting member, for the Pediatric Advisory Committee. I work for Pfizer.

DR. GOLDKIND: I'm Sara Goldkind. I'm the Bioethicist in the Office of Pediatric Therapeutics within the Commissioner's Office of the FDA.

DR. MURPHY: I'm Dianne Murphy. I'm a Pediatrician and the Director of the Office of Pediatric Therapeutics at the FDA.

DR. YUSTEIN: Ron Yustein. I'm a Deputy

Director for the Office of Device Evaluation in the Center for Devices and Radiological Health

CHAIRMAN NELSON: Thank you. Dianne?

DR. MURPHY: First of all, I want to welcome members of the Committee and guests and consultants. We do recognize your commitment of time and expertise and we deeply appreciate it because we know from trying to obtain people who have a level of expertise that we need who can participate in some of these often difficult because of busy schedules and with the many commitments you have. We want to make sure that you realize how grateful we are. We really do need your input into this important issue and we're glad to see you here today.

I want to make a few comments about today's meeting because it is actually a very positive activity. This is a meeting we are having because the Center for Devices anticipated an issue. They wanted to develop -- they could see that there was going to be a need to develop options for the pediatric population in the area of intervention for therapeutic intervention for the treatment of obesity.

They wanted to develop the trials with good science and sound ethical principles. They approached Dr. Goldkind in our office because they realized that the pediatrics scientific trial issues are frequently compounded by the ethical issues. And you will see that in the four pages of questions that we have provided you. This is not an easy subject. This requires even in the planning a cross-center, cross-FDA multi center approach. And the planning, we hope, is reflected in the selection of your expertise in that we had individual representatives from the Center for Foods, the Center for Drugs, the Center for Devices was the lead on all this and it was their initiative to brig this forward.

So, you will be advising all of us, is what I'm trying to tell you, in your discussion today. You have before you, as I noted, an extensive series of questions. I can tell you in the decade that I've worked for FDA, I've never seen such an extensive series of questions. A lot of thought and time has gone into them and we really know that you have quite a task before you.

Today we are going to attempt to provide you additional background information to set the stage for your discussion. And I'm just going to walk through the Agenda very quickly with you. You are going to have next, Dr. Houston, who is going to present to you background information on the development of devices in this area for this indication, an outline for you of the issues that have been identified that we are going to be dealing with today.

We then are going to have Dr. Dietz from CBC provide for us the context of the epidemic in which we are addressing, which is that of obesity in this country.

And then the science -- a different talk -- we call it the scientific overview, not that Epidemiology isn't scientific, Dr. Newman, but that -- trying to get at the clinical medical issues, if you will, the comorbidities that are associated with this epidemic.

And then we will have Dr. Wendler address some of the assent issues, which per earlier

discussions that some of the individuals weren't here for, you will see are very important in developing these trials.

Then Dr. Hoelscher -- and I'm probably mispronouncing that name, I apologize -- will provide us some insight and background information on conservative interventions that are frequently utilized in the population that would be considered for enrollment or potential enrollment in these trials.

Then the presentation by Dr. Garcia will include some of the surgical interventions and device application interventions that are presently utilized.

Then we are going to be at the end of the day and you'll have an opportunity to cogitate upon all this information and think about it and apply it to your discussion for tomorrow. If we get through this earlier -- I guess we could begin the discussion earlier today, Skip. I leave that up to you, but our plan right now is that it's going to take us pretty much to the end of the day.

And with that, I will turn this over to

Ron.

CHAIRMAN NELSON: Thank you, Dianne.

DR. YUSTEIN: Good morning again. My name is Ron Yustein and I'm coming before you today wearing actually two hats. I am the Clinical Deputy Director for the Office of Device Evaluation, CDRH, but also for the past five years, since I've been at the FDA, I've also been the Lead Clinical Reviewer for all devices for the treatment of obesity. I am an adult Gastroenterologist and I don't claim to be a Pediatrician, but I have been the Lead Reviewer for all obesity devices for the past five years.

I did want to second Dianne's points and thank the Panel for attending and participating today. These are issues that we are struggling with in CDRH and certainly appreciate all your input and help. I'd also like to thank the Office of Pediatric Therapeutics, Dr. Murphy and Dr. Goldkind, Jan and also our own Nancy Pluhowski for setting up this meeting. It's quite challenging for the logistics. I think this is definitely one of the larger panels I've seen in my five years at the FDA and I'll bet you it's

up there.

I would also like to thank the public for participating. I think we have several people scheduled on the public agenda.

Before I go into my presentation, I wanted to address one issue that arose last night at our training session. Dr. Tillman and myself were asked a question regarding MedSun and Children's Hospitals. I can't remember who asked that question. But I did talk to our Office of Post-Market Surveillance today and out of the 300 MedSun Hospitals that are in the active surveillance, post-market surveillance program, 22 are children's hospitals and that includes hospitals in Los Angeles, San Diego, Phoenix, Miami, Minneapolis-St. Paul, all across the U.S. I do have that list with me if anybody is interested at the end.

Okay. So, my outline for the 25 or 30 minutes I have to talk to you, I'm just going to go over some of the goals for this meeting as we see it in the Center for Devices, what we hope to get out of this panel; number two, just briefly touch on the epidemic, why we're here; number three, just give you

a little bit of brief background on CDRH and ODE, what we do -- "ODE" is the Office of Device Evaluation; fourth, give you a little background on the devices we have approved for obesity, and then talk about some of the typical features of adult trials for adult trials for obesity, and I won't be mentioning any specific products -- I'm not allowed to due to confidentiality rules -- talk about any specific applications, but I'll give you general ideas of some of the issues we face. And then I'll kind of sum up and end by giving you a preview of the questions in a summarized form so that you can kind of keep those in the back of your mind while you hear all the rest of the presentations today.

Okay, so what are our meeting goals? First and foremost is to provide an open forum for discussion between the Agency, academia, the clinical community, the public and even industry on what we consider a vital public health issue, to discuss the epidemiology of obesity in the U.S. pediatric population as well as the current treatment options, and that's what you'll be hearing about during the

course of today. And then finally, what we'll be focusing on tomorrow is to discuss issues related specifically to designing and performing clinical trials for devices to treat obesity in the pediatric population with, hopefully, obtaining good recommendations from the panel for possible use in a guidance document.

A couple of points I'd just like to remind you of. The first one is a key point. Although prevention of obesity is certainly an important topic and a key issue when discussing this epidemic, that's probably for a different forum and a different time, and what we would like to focus on is the present situation, the treatment of obesity for patients who already have the disease or disorder. So, we'd like you to kind of try to avoid the temptation to go into prevention of obesity. We recognize that that's very important, but here in the Center for Devices, we are usually dealing with people that already have the condition.

And number two, as emphasized last night by Dr. Tillman in our training, we'd like you to keep

in mind the differences between drugs and devices, not only in the entities themselves, but the differences in how we regulate the devices, and just remember that devices are their own unique entity.

A picture is worth a thousand words, and I'm sure Dr. Dietz will go into this in much more detail, so I'm not going to spend any time, but essentially the pink bars are why we're here today. This is from 2002 and this is in the pediatric population, but in the adult population, we're seeing a very similar trend as well.

Current treatment options. This is basically from the adult world. Currently you have -- what I have here is a graph where on the left-hand side are the things that I consider less invasive, but probably less effective as well, and on the right side are the more invasive and more effective. I think what you'll probably find today, as we talk, is that diet and exercise and medications, although effective in some patients, are probably not as effective as our current surgical and bariatric techniques.

Yet, there is probably a void here in the

middle where there is the opportunity for other products or therapies that are more effective than these, but also safer for less morbidity than this. Certainly, these two items may go back and forth and maybe over the next several years, they'll even creep up into this part of the spectrum as more drug companies get involved in obesity, but the way we see things at the Center for Devices is that at the current time, this gap will probably be filled by devices, endoscopically or surgically implanted devices to treat obesity.

I just wanted to mention -- you've heard a lot about CDRH last night and the way we regulate devices. I just wanted to kind of go over some things again. Our mission at the Center for Devices and Radiological Health is to promote and protect the public health by ensuring the safety and effectiveness of medical devices. And these are the ways we do that. We assess pre-clinical and clinical data. We have regulation and oversight over investigative trials for significant risk devices. We approve devices or clear devices for marketing, which are

reasonably safe and effective. We keep or remove unsafe or ineffective devices from the market and we monitor devices after marketing.

Just as Dr. Tommin (*10:37:24 phonetic) mentioned yesterday, another point that I want you to remember is that we do not regulate medical procedures or surgeries. We do not regulate Tonsillectomies, we do not regulate Appendectomies, and likewise, we do not regulate bariatric procedures such as Rulenwhy gastric bypass (*10:37:36 phonetic).

Again, Dr. Tillman showed a similar slide last night. I wanted to just remind you as we go through the day that we do have different regulatory requirements for valid scientific evidence. The randomized -- multiple randomized control of studies are not necessarily required. Valid scientific -- sorry -- valid scientific evidence, according to our regulations, can include other entities besides well controlled studies, including partially controlled studies, case histories and even significant human experience.

I wanted to give you some background on

devices and obesity and where we have been to this point, but before I get into some specifics, I wanted to give a couple of definitions. I'm sure most of you know these, but for those who aren't familiar. The first one is that we -- in CDRH, we tend to use "BMI," "body mass index" as a parameter to assess obesity. That is, the ratio of somebody's height -- sorry, it's weight in kilograms over height squared, meters squared. We tend to use the middle column, which defines various stages of being obese, but for children, perhaps this is different. In the literature, it's been reported that percentile use instead of absolute numbers such as BMIs.

The second definition, I wanted to just bring to your attention, for those that aren't familiar with the surgical literature because this is something we tend to use in the Center for Devices, is an end point assessment called the "Percent Excess Weight Loss" or "percent EWL." And that basically is the amount of weight loss as a fraction or a percent of the amount by which the person was over their ideal weight at baseline. So, for example, if you have a

patient that's 300 pounds at baseline and their ideal body weight by life tables for frame, for height and frame, is supposed to be 180, that person's excess weight is 120 pounds. If they lose over the course of 12 months by some method, 40 pounds, they've lost 33 -- their excess weight loss, percent excess weight loss is 33 percent. And that's just a concept. You're going to see some of these numbers coming up in a couple of slides and I just wanted to explain that.

In our history of devices -- we've been around since 1976, CDRH. We have only approved two devices for the treatment -- specifically for the treatment of obesity. Both of these are for the treatment of obesity in adults. One is the Garren-Edwards Bubble and the second is the Inamed LAP-BAND, which I'll discuss here in a second.

But I just wanted also for you to keep in mind that, certainly, this may just represent the tip of the iceberg. That these two types of devices I'm going to show you may not be the only types of devices people may be thinking of developing.

The Garren-Edwards Bubble was approved by PMA back in 1985. This was brought in front of an Advisory Panel which did recommend approval. It is a cylindrical polyurethane balloon, which is inserted into the stomach and then inflated. The indications for us were a temporary aid to diet and behavior modification in people who were at least 20 percent over their ideal body weight.

I wanted to give you a little bit of background on what data was presented to FDA and the Advisory Panel in support of this submission. The data was from a 78-patient, adult patient study conducted at three sites on the East Coast. And to sum up the data that was presented, the effectiveness data, the medium plant time for the balloons was 7.5 months. And you can see the numbers here. I'm not going to read each one, but you can see that as time went on, people lost a little bit more weight, but you can also notice that the number of patients followed-up each time was lower. But this was the data presented to the Advisory Panel, which recommended approval.

The safety adverse events which were seen during the clinical trial was one spontaneous deflation of the balloon, with subsequent pyloric obstruction, one spontaneous deflation of the balloon with a subsequent small bowel obstruction, and one gastric ulcer.

So what happened after marketing? Well, in the next two years after the device was allowed on the market, there were 100 MDRs and "MDRs" are our Medical Device Reports, that's our post-market surveillance with companies to let us know about the adverse events that occurred for significant -- serious patient injuries, malfunction or death. There were over 100 that were presented to the FDA over the next two years, including 79 that required surgery to remove a deflated balloon from the small bowel, that had caused small bowel obstruction. The company voluntarily discontinued marketing in 1988, and then voluntarily withdrew their PMA in 1992. So this device is no longer available in the United States.

The second device approved by the FDA for the treatment of obesity is Inamed LAP-BAND. It's an

adjustable gastric band and many of our surgeons on the panel can probably give you more details about this, and I believe the sponsor will be making an open public session presentation today as well. Basically, this is an inflatable band that is surgically placed -- oops, sorry -- surgically placed around the stomach. It has a port -- a tubing that connects to a port underneath the skin and fluid can be inserted into it, and depending on how much fluid you put in, the band gets tighter, or if you remove fluid, the band becomes looser and it changes the diameter of this narrowing. The indications for use are for weight reduction for severely obese patients 18 years and older, with a BMI of greater than or equal to 40, or a BMI greater than equal to 35 with one severe comorbidity. One of those were about 100 pounds overweight. This clinical study, I believe, had a couple of patients that were 17 or 16 years old, but not many.

This is front our summary of safety and effectiveness that is on the public web site, basically showing you the level of evidence that was used to support approval. The sponsor did

approximately a 300-patient study, which -- the data submitted was three years pre-market. Patients were used as their own control, baseline versus follow-up weights. And the chart on the left-hand side, the table on the left-hand side, basically shows you some of the results that were obtained, and you see about a 35 percent excess weight loss over three years. You see the mean change in weight was about 50 to 60 pounds over those three years. And the BMI dropped from 8 to 10 points during those three years.

The right-hand side of the slide shows some of the safety issues which were reported during the clinical trial. The most common ones being nausea and vomiting, which occurred in 51 percent. Reflux symptoms, which occurred in 34 percent. And so forth.

Post-marketing experience. Since that time -- like I said, that was approved in June of 2001 -- there was an issue with some leaking from the port and the tubing that this sponsor became aware of and reported to the FDA. They worked to redesign the port and submitted a PMA Supplement. Dr. Tillman mentioned to you PMA Supplements last night. That's the way the

sponsor made a correction to the original device. They did bench testing to show that the new device would work better than the other one as far as leaking. And they also put out an advisory, you know, that stressed the new device as well as the new technique in 2002.

As far as U.S. clinical experience since that time, from what I could tell, it appears -- and maybe our surgeon can comment later -- that it may be replacing vertical banded gastroplacy as the restricted procedures choice, which is the second procedure choice behind a gastric bypass. Also, the results, if you look in the literature over the past couple of years, the results as far as excess weight loss are approaching what our European colleagues, who have been using this device much longer, have been obtaining and that is, that the excess weight loss is approaching 50 to 60 percent in the one- to two-year range, which is significantly better than we've seen in the clinical trial, as might be supported by the fact that our surgeons are getting better at implanting them and uses and experience is increasing.

If you look in the literature, there are some other products that are out there, including newer balloons that are being studied in Europe. There is also some literature on gastric stimulators where leads are placed on the gastric wall and electrical impulses are imparted to the stomach wall. I'm not at liberty to discuss any of those applications here, but those are things that you can look in the literature for and read about. Just to show you that there are other possible potential things coming down the pike.

So what are some of the issues? When we study obesity in adults, which is where most of our experience is in CDRH, what are some of the issues that we struggle with? Number one is patient eligibility, and these are -- I'm just going to point out some of the things that we tend to see in our submissions and our protocol applications. Of course, our sponsors tend to limit their studies to the age of 18 and over. We tend to use a BMI as an eligibility criteria. And for a reason, I'm not necessarily sure why, but we've tended to stick with the original

surgical recommendations for obesity, which is the BMI greater than 40, or the BMI of 35 or greater with at least one comorbidity.

There are occasions where a device may be less risky, where a surgical implantation may not be required, and therefore, we have also entertained the idea that those requirements may not be needed and, perhaps a BMI as low as 30 may be acceptable if the device is low risk.

We tend to require that the patients have a duration of disease for three to five years prior to undergoing a procedure for a device implantation, and that's been documented, and that they also have failed to respond to more conservative therapy.

Some of the other issues that we've seen, and this isn't necessarily across-the-board, but sometimes sponsors choose to exclude patients with poorly controlled diabetes, either because they don't heal as well, or there may be some other issues related to diabetic gastropothy in eating and diet. Some sponsors choose to exclude patients with bulimia or other eating disorders because after these

procedures, patients often need to follow specific dietary recommendations. Certain sponsors may, from experience abroad, or in other places, may come up with other characteristics of patients that they see as predictors of who may be more successful with their device, and so they may limit the exclusion -- the eligibility criteria to those patient populations. And then a lot of our devices are anatomical devices that alter or affect the structure or anatomy, and so making sure that somebody has normal swallowing and GI motility is often part of our eligibility.

Before I talk about pivotal study designs, I just wanted to mention a point that probably -- that didn't come up last night in our training session, but I wanted to emphasize, and that is that you all are probably used to CDER or drug trials where there's Phase 1, 2, 3, and 4 trials. In CDRH and the Office of Device Evaluation, we have basically two trial types. We have pivotal -- pilot studies, also called "feasibility studies," and then we have our pivotal study. And then, of course, there's the post-marketing study. But our pre-market studies are

usually pilot studies and pivotal. Our pilots are usually very small, usually 10, 15, 20 patients. Some are in that range. It may be one, two or three sites. Often times, if a company has studied their device in Europe and has some preliminary data from that, we may accept that as their pilot study. We usually use pilot studies to make sure that the device can be implanted safely, used safely, and that there are no major safety concerns to move forward to the pivotal study.

For obesity studies, our pivotal study designs, we have been encouraging, when possible, for sponsors to conduct randomized, controlled studies and possibly, when available, SHAM controlled studies. Of course, SHAM controlled studies are easier when the surgically implanted device has an active or an inactive mode where the patient may not know that the device is in active or inactive mode -- is in active or an inactive mode, or for perhaps endoscopically placed devices that a Gastroenterologist or Surgeon might put in with an upper Endoscope where you can SHAM procedure where the patient undergoes an upper

Endoscopy, but just doesn't have the device put in, maybe has 50 cc's of water or saline put into the Endoscope and a SHAM procedure is done.

So, in summary, we try to have an active group where the device is active and then any concurrent diet, behavior and exercise that the sponsor believes is necessary and the control group has either the sham procedure or an inactive device placed, plus the same diet, behavior and exercise regime. Usually, if this takes place, we then offer -- if it's an implantable device that was inactive, we offer the patient, after "X" amount of time, to be switched over to the active mode. If it was a sham procedure, often times the patient will be offered the opportunity after that primary assessment time to be given the active device.

The problem with that situation is the following. On the right-hand side, we have the fact that a device may not be effective or may not reach its maximum effectiveness for several months or even a year after implantation. And you have to balance that with the ethical fact and consideration of the fact

that you're withdrawing -- you're withholding potentially -- potential therapeutic options from a patient in the sham or control group. And that's been an issue we've often struggled with, not only internally, but with manufacturers.

There are other possible designs that, certainly, we would entertain. Like I mentioned before, our level of evidence allows sponsors to propose all different kinds of study designs. Some of the other possible ones might be a control using the approved products. At this point, the only one is the LAP-BAND. And, of course, that might be a superiority trial or non-superior trial with a pre-specified delta. Sponsors may wish to do a randomized control study with the control being a surgery. I think most manufacturers would stay away from this because of the high bar set with the RYGB and the good results obtained with that. They may elect to do a control group using optimal medical care, diet, behavior, exercise, pharmacological agents, et cetera. Or, like the LAP-BAND study, they may elect to do a study where the patient is used as their own control and a single

arm study.

Another issue we deal with is when is the right time to assess the primary end point. Drug studies tend to be shorter. They tend to be four weeks or six weeks or three months or four months. Well, for an implantable device that's a permanent implant, you want to know that the device is safe and effective for a longer period of time.

We've -- right now, you know, we expect at least one year of pre-market data, if it's a permanent implant. There may be some devices coming down the pike where the intended use isn't to be a permanent implant, where its intended to be used for three to six months for somebody who needs cardiac surgery to lose a few -- 30 or 40 pounds so they can get on the operating room table, et cetera. So that has to be taken into account as well.

However, for the permanent implants, we do anticipate that we would be asking for, as a center, long-term studies follow-up in the post-market realm to assure safety and effectiveness. And by that, I mean, at least follow-up for another two to five years

post-marketing to assess that long-term safety and effectiveness.

End points. Another issue that we deal with and we'll be asking you to deal with. In our adult studies, we tend to use the ones that the surgeons tend to use, which is the percent excess weight loss, which I explained in the earlier slide. However, there are other end points that people can come forward with. Absolute changes in weight. Changes in BMI on an absolute or percentage scale. Also you can look at people that obtain normal BMI. Quality of life assessments. Change in medical comorbidity, such as Hypertension, Dislipodemia, Sleep Apnea, et cetera. And although not used anymore, change in HIPPA waist circumference.

We also tend to look at safety and STAR's procedure or surgery-related adverse events because many of these devices is not just taking a pill. It either requires, most of the time, a procedure to be placed, or a surgical procedure to be placed. It is often adverse events that are just from the procedure itself. And then you have the separate category of

adverse events that might be related to the device itself.

Concurrent treatments. You know, one of the issues with obesity is that there are other ways for people to lose weight besides whatever we do to them. Diet is often an important part of the protocol. Some sponsors may wish to have patients on an ad-lib diet after the procedure or device is placed. Some may elect to use the device as a adjunct to diet and have a specific calorie restriction, such as a daily 500-calorie-a-day deficit diet. Some groups elect to have patients also enrolled in behavioral or group therapy, behavioral modification groups. Some may have built into the protocol specific exercise or physical activity plans that are supervised during the trail. But either way, we try to avoid allowing subjects to use weight loss medications or even herbal medications that may affect weight loss.

So, what are we going to ask you tomorrow? And I'd like you to keep this in mind as you go through the rest of today when you're going to be

hearing presentations from other national experts, to keep these questions in the back of your mind because, hopefully, they may help you answer or spark some discussion about these issues.

But before I get to the four questions, I wanted to just have this slide up here because I think it's important and this goes back to differentiating devices from drugs. And I want you to keep in mind that devices come in lots of different shapes and forms. They can be permanent, unremovable -- if that's a word -- implants that are in for life, such as Coronary Stents, which once you place them, you cannot take them out unless you take out that artery with surgery. They can be what we call "permanent," but they're removable. In other words, they're permanent in the sense that they're long-term. They're meant to stay in for a long time, but they can be taken out. An example of that is the LAP-BAND. It's meant to stay in for a long time, but it can be surgically removed. The device can be a temporary, removable implant. The Garren Bubble I showed you is actually -- was meant to be a temporary implant and

can be punctured and removed endoscopically. They can be external devices. Not all devices have to be implanted or placed into the stomach or abdomen. Perhaps there can be devices that are external compression devices that reduce the size of your stomach. I don't know.

Devices can be anatomy-altering devices. They can actually change the anatomy in a way that wasn't originally there. They can alter what parts of the Intestine are hooked to other parts of the Intestine or they can be anatomy preserving where they don't necessary -- when the device is removed or taken out, the anatomy reverts back to its normal original anatomy. And they can be any combination of the above. So I just want you to kind of keep those points in mind because you may have different answers to some of these questions based on those types of devices. Unfortunately, since we're trying to be proactive here at this meeting, I can't come to you and tell you every type of device that's going to be coming down the pike. So we're going to be asking for general recommendations.

So let me summarize the four questions that we're going to ask you tomorrow. These are, as you know, the questions are several pages on your sheet, but I just wanted to summarize them here.

Our first question deals with the patient population. Who do you think are the right people to study in these trials and to allow these kinds of devices to be implanted to be studied? Are there criteria based on age, weight, BMI status? Should they have reached certain developmental milestones? Should there be a requirement for certain medical comorbidities? If so, how many? Should there be a requirement for a failure of prior conservative medical and/or pharmacological therapy? And if so, how many? What kind of psychological assessments should be done for these patients prior to considering enrollment? Are there other specific exclusion criteria or diseases which you think might be important to exclude from these trials? The assent and consent issues. How do we address that? And then something I didn't have on here that I thought about based on a question that got asked last night is, what

is the role of outside U.S. data? Do you, you know -- sponsors will probably tell you that it's cheaper to go abroad to do clinical studies than here in the United States. Is that acceptable? Is the pediatric and obesity practice of medicine abroad, in Europe or Asia, et cetera, equivalent to the United States, such that you would allow that or you would recommend that, or that you would say, "No, we think that the majority or all of the patients should be U.S. patients."

Question Number Two. What do you believe are the appropriate end points for studying the devices to treat obesity in the pediatric population? I told you that we tend to use excess weight, percent excess weight loss as the primary end point in our adult studies. Is that appropriate for kids? What at the appropriate primary and secondary effective end points? I told you what we tend to look at for safety. Do you think those are appropriate? Are they adequate? Are they enough? What is the appropriate duration for assessment of the primary end point? Is one year pre-clinical data sufficient? You know, or is six months sufficient? That is another thing we'd

like you to address.

Question Number Three, and this is probably going to be the big one tomorrow. What are the appropriate study designs for these trials? I told you that we try to recommend, we try to encourage that sponsors do randomized controlled studies. We don't design the studies, the sponsor does. We have feedback on those studies, but like I said, there's many different routes to approval or clearance and they don't all have to come through a randomized controlled study. And if the sponsor believes there is another least burdensome way to do that, it's their option to. But we try to encourage the best study that we think is going to give us the data that's appropriate. Are randomized control trials appropriate in this population? If so, is a sham control appropriate for this population? If not, what are the appropriate controls if a controlled study is appropriate? How would you go about minimizing some of the other confounding factors? I mentioned diet, exercise, behavioral therapy, medication use, et cetera. Do you agree with what we've been doing for

adults? The appropriate duration of the pre-market study. Dr. Tillman stressed to you yesterday that we're trying to learn the appropriate balance between pre-market and post-market. How much do we need to know pre-market versus how much can we leverage post-market? What's the appropriate duration for that pre-market study? What are the roles of the Data Monitoring Commission, Committee or Data Safety Monitoring Board during those studies?

Question Number Four. What are the long-term safety and effectiveness issues that can be addressed, and how should we address them? As I mentioned, several of these devices are meant -- maybe meant to be in place for years, and how does that affect how you would evaluate it? Is it important to look at the effect on future growth and development parameters, effect on future comorbidities? Is maintenance of weight loss -- if the weight loss is assessed out at one year, do you want to see what it's out at three years, five years? And what is the role of a post-approval study to collect that information? Can some of that information be collected post-market

instead of pre-market? And can we use possibly registries? Can any of the organizations or academies help us out with registries that might be able to lower the burden on some of our smaller manufacturers that might be looking for that?

So with that, I'm going to go ahead and end my talk. Hopefully, I stayed on time, or about on time, and I will be at the table to answer any questions as the day goes on.

Thank you for your attention and, again, thank you for participating.

CHAIRMAN NELSON: Thank you, Ron. I would ask any members of the Panel, if you have questions to write them down. We're not going to take them at the moment, since we're running a bit late and I'm sure there'll be time this afternoon and tomorrow for further discussion.

So I'd like to turn now to the presentation by Dr. Dietz on the Epidemiology of Obesity.

DR. DIETZ: Thank you, Dr. Nelson. It's a great pleasure to be here with you today to talk to

the Pediatric Advisory Committee on such a critical topic. My task is to present you with the Epidemiology by way of background for this problem.

I should begin by saying that my opinions, as we're now asked to declare, are my opinions and not those necessarily of the CDC or of HHS.

I think that you're probably familiar with these maps showing the obesity trends in the United States in young adults. I would remind you that obesity in adults is defined as a body mass index greater than or equal to 30, and that approximately 30 percent of all adults in the United States have a BMI greater than or equal to 30. These are self-reported data so they underestimate the problems of obesity. But NHANES, the current NHANES suggests that about 30 percent of adults are obese and there are no significant disparities among men, although very significant disparities among women. Thirty 30 of Caucasian women, 40 percent of Mexican American women, 50 percent of African American women meet these criteria.

The prevalence of severe obesity, defined

as a BMI greater than or equal to 40, or morbid obesity, has increased even more rapidly than obesity per se. About five percent of all U.S. adults are now in this category, more women than men, and about 15 percent of African American women. And a BMI of 40 is one of the cut points for Bariatric surgery in the adult population.

Now when we talk about pediatric obesity, we use percentiles to reflect the growth of youth. And one of the questions that has arisen is how valid is the BMI as an index of fatness in the pediatric population. These are data that Data Freedman published this year which were derived from Dexis studies of about a thousand kids in York, a convenience sample. And I'm showing you here the correlation coefficients adjusted for race and age between BMI and fat mass index. Fat mass index is fat divided by height and meter squared. And obviously, fat mass index and fat-free mass index equal body mass index. And I'm showing you here just two groups. The same results hold for younger children and older adolescents. But notice that at the lower percentiles

of BMI, there really is not -- there is a very, a reasonable correlation, but a fairly low level, whereas, above the 85th percentile, there's a very high correlation of BMI with fat mass index. And that becomes even greater at a BMI greater than the 95th percentile, suggesting that at this high level, above the 95th percentile, the BMI is a reasonable index of increased body fat.

I should also point out that in adolescence, a BMI at the 95th percentile corresponds to the BMI of 30. And although you'll hear different terminology, and historically we've used the term "overweight" to describe children greater than the 95th percentile. I think that the fact that there's no ICD-9 code for overweight means that we're going to have to start in the pediatric population using the term "obesity" to describe children greater than the 95th percentile, which is concordant with the adult definition.

Interestingly enough, the 85th percentile corresponds roughly to a BMI of 25, so that the overweight group in the pediatric population is

probably reasonably referred to between the 85th and 95th percentiles.

It's clear that there have been rapid increases, as Ron has shown you, between 1980 and the time that NHANES became continuous. There was a twofold increase in the prevalence of overweight 6 to 11-year-olds and a threefold increase in the prevalence of overweight adolescents. And most recently, we have begun to see the occurrence of disparities not just similar to adults in the female population, as I'll show you in a minute, but increasing disparities among adolescent males. These are 12 to 19-year-olds. You can see that there was a relatively modest increase among the Caucasian population between NHANES 3 and the concurrent NHANES. But more dramatic increases in African American and Mexican American boys. The highest prevalence is in Mexican American boys, about 25 percent, suggesting that the absence of the disparities which currently exists in the adult population, are soon going to change as these adolescents go on to adulthood.

And our next slide, please. This doesn't

seem to be working again. Among adolescent girls, you see the same pattern of prevalence that you do in the adult population. The highest prevalence is in African American girls, followed by Mexican American girls, followed by Caucasian girls. Again, the rates of increase in the Caucasian population seem to be lower than those in the other groups.

We've also been interested recently in what constitutes "morbid" obesity for adolescents and have done some preliminary runs. These are from a manuscript that's in preparation -- next slide, please -- in which it appears to us that a reasonable definition of "morbid obesity" is a BMI at the 99th percentile. This shows the BMI at the 99th percentile for males roughly at a BMI of 35. Among girls, it's -- and these are adolescents, obviously -- it's about a BMI of 40. Notice that about two percent of the adolescent population has a BMI greater than or equal to 40, and this cut point at the 99th percentile identifies a reasonable number of adolescents. Next slide, please.

In addition, using the Bogalusa data,

which is one of the few data sets that track children into adulthood and also has existing, by chemical, comorbidities. It does seem to be a reasonable pathologic diagnosis in terms of the frequency of risk factors, and in this case, these are elevated insulin or glucose levels, elevated lipid levels, or elevated blood pressure. These actually seem to increase at the 98th percentile for two or more risk factors and about the 99th for three or more risk factors, suggesting that this diagnosis of the 99th percentile for the diagnosis of "morbid obesity" meets several important criteria. One, it identifies a reasonable number of adolescents. Secondly, it has some pathologic corollaries. Thirdly, it has some face validity based on the BMI identified by that percentile. Next slide, please.

You're very familiar, I'm sure, with the consequences of a childhood and adolescent obesity. I won't dwell on all of these, but clearly, the psychosocial are among the most frequent, and although they're not great published data to this effect, I think the experience, my experience in treating

overweight children and adolescents, as well as those of others in the field, would suggest that the more severe obesity is, the more likely you are to have very severe family dysfunction and psychosocial complications, particularly at a BMI greater than or equal to 40.

There is this apputative metabolic syndrome consisting of cardiovascular disease risk factors. These are also increased -- next slide -- among the obese children and adolescents. There are data from NHANES 3 and although the metabolic syndrome, this cluster of findings, high triglycerides, low HDL, high fasting glucose, high blood pressure, adapted from the adult criteria for the pediatric population occur in four percent of all children. They're rare in the normal population, but among overweight children, this cluster exists in 25 percent of all individuals. And you can see, there is a graded response to these among overweight children and adolescents. There's a higher prevalence in the at-risk group, but the highest prevalence exists among overweight children. Next slide, please.

The next problem, I think, is this question of persistence into adulthood. And -- well, actually, before I do that, I just want to point out that hepatic steatosis is one of the more recently recognized complications of obesity. The estimates are high variable, but probably about 20 percent of pediatric patients have hepatic steatosis. It does seem to increase with severity, although the dose response of some of these -- the obesity to some of these complications is quite variable across groups. And in -- there is an anecdotal experience that hepatic steatosis does occasionally progress to psoriasis and, in even more limited experience that suggests that certainly weight loss resolves elevated liver enzymes and may improve the psoriatic changes that are found in the livers of these severely affected individuals.

The concern about persistence into adulthood, I think, is emphasized by the next slide, which are also data from Bogalusa, Louisiana. These data suggests that onset of overweight prior to eight years of age is associated with a much more sever

course if that obesity persists into adulthood. Only 25 percent of obese adults were overweight children, but among that severely overweight group, with a BMI greater than 40, the -- about 50 percent of all, of that group, of people with a BMI in adulthood over 40, had onset of their overweight prior to eight years of age. And the mean BMI in this group is 41.7. So even though childhood onset obesity contributes a minority of adult obesity, it may have a disproportionate effect on the morbidity and costs of adult obesity. Next slide, please.

I know that you're familiar with the increase in prevalence of Type II Diabetes in populations and some urban centers, this accounts for almost half of all new cases of Type II Diabetes -- next slide -- and the course of Type II, I think, is poorly described. There's just one study that I'm aware of which has looked at the natural history of Type II Diabetes in adolescents. These are data from Pima Indians and what we've done here is to superimpose the curves of the cumulative incidents in nephropathy for individuals with onset at 15 to 24

years of age, 25 to 34 years of age, and 35 to 44 years of age. And I think you can see that these curves are super imposable.

It appears, in this same article, that the frequency of retinopathy associated with Type II Diabetes, with onset in adolescents is slower, the progression to retinopathy is slower in adolescents than it is in later onset disease. But these data, are, of course, a concern because they suggest that in early adulthood, individuals who are obese and have been diagnosed as having Type II Diabetes in adolescents are going to progress rapidly or are going to require Dialysis and treatment for the other complications of Type II Diabetes, such as retinopathy and micro vascular complications.

Next slide. There has also been a lot of recent controversy that I'm sure you are aware of with respect to mortality, and I'm not going to address that now, although we can talk about that, if you like, in the discussion. But I wanted to point out to you that this study, which was a very large Norwegian study in which adolescents were screened for

Tuberculosis and their weights and heights were obtained at the time of that screening and then followed up. This study, like other studies of its type, show about a twofold increase in mortality associated with a BMI above the 95th percentile and that relative risk is about the same for both genders. But the implications, in terms of U.S. epidemic, are on the following slide. In this study, in Norway, only about one percent of the population in 1963 to 1975 had a BMI greater than or equal to 30. In the United States, that -- the prevalence of a BMI greater than or equal to 30 is about 14 percent, suggesting that although the mortality rates may -- are double, the total risk group, the group at risk for this early mortality is substantially greater than it was in Norway from 1963 to 1975. And the recent JAMA, articles which were the controversial articles, did not dispute the fact that there was an increased mortality above -- of BMI at the 95th percentile -- sorry, a BMI of 30 in the adult population.

Next slide. I'm just going to deal briefly with costs because the cost in the pediatric

population really paled beside the costs in the adult population. But there's a very substantial emerging literature that is focusing on the costs of obesity in the adult population. Most of this literature is focused on the cost of illness, which are substantially greater for the obese individuals than non-obese individuals, and I'll show you some clear data in a minute about that.

But these other costs are probably at least equal to the cost of illness and those include the costs of absence from work, the costs of reduced productivity, the costs of injuries and the costs of disabilities. Next slide. These costs seem to increase in proportion to the severity of obesity. This slide shows some data that Roland Sturm has subsequently published, showing the distribution of costs among people at different BMI levels. And you can see that these costs are relatively equally distributed across these three BMI groups, but the proportion of people in each of these groups declines. That is, there are fewer people in -- at a BMI of 40 than there are in a BMI of 35 to 40, than there are in

a BMI of 30 to 35, suggesting that the per capita costs are going to be greatest among the very severely obese individuals, and those groups are likely to be disproportionately represented among children who had onset of their weight at less than eight years of age. Next slide.

This is another perspective. These are data from General Motors that have looked at the cost of weight plus additional risk factors in adulthood and stratified this by BMI category and by the frequency of complications. And I think you can see that the highest costs here are among those with a BMI greater than or equal to 35 and multiple complications.

In some respects, this type of analysis can be used to examine the potential cost effectiveness of interventions, that the cost of the intervention can be balanced against the cost savings achieved by either reducing someone's weight or reducing the frequency of complications.

Now, on the issue of costs, it is not clear to what extent the pediatric onset overweight is

contributing to these costs. That has not been established, but clearly, the contribution of pediatric obesity to severe adult obesity and multiple complications of severe obesity would suggest that there is, likewise, a disproportionate increase in those costs. Next slide and then the next slide.

I know that you're going to send time on a lot of these other therapeutic approaches, most importantly the surgical approaches or device approaches. But I do think, and I think it's appropriate that as you begin to think about this, that you begin to think in a stratified fashion. Certainly, I think we need more evidence with respect to the cost effectiveness of interventions in the pediatric age group because early behavioral interventions -- and I noticed, by the way, in your background work, that behavior modification is somehow separated from diet and physical activity when, in fact, behavior modification is the strategy to implement diet and physical activity. But these are certainly conservative approaches that should be applied to all patients before moving on to the more

invasive therapies like aggressive dietary therapy and pharmacological and surgical therapy.

But in the interest of time, I think I'll stop there and take your questions. I hope this information has been helpful.

CHAIRMAN NELSON: That's great. Thank you, Dr. Dietz. A brief comment before we go to some questions, given the addition of a new slide and my assumption that we may be referring back to the some of the same data in our discussions later today and tomorrow, I've asked that we get a copy made of the new slides and -- two per page instead of three per page so we can actually look at the data more closely.

DR. DIETZ: That's fine. I assumed that this was a young group with good eyes.

(LAUGHTER.)

CHAIRMAN NELSON: Whatever. So we do have time for a few questions of clarification about the data. I don't know how long you can be with us during the course of the day.

DR. DIETZ: I have to leave in about ten minutes.

CHAIRMAN NELSON: Okay, so we have a few minutes for clarifying questions. Dr. Gorman?

MEMBER GORMAN: Thank you, Dr. Dietz.

One of the statements you made was that when we look retrospectively at adults, that only 25 percent, or a quarter roughly, of overweight adults were overweight children. When you turn the telescope around the other way, do we have any data of how many obese children become obese adults and stay obese as they track forward?

DR. DIETZ: Those data are harder to come by because of the lack of longitudinal studies and the estimates vary. In adolescents, it looks like 70 to 80 percent of those obese adolescents stay obese as adults.

And although there haven't been contra studies, my view is that the later obesity studies in childhood and adolescents, the more likely it is to track in adults. And severity at any age seems to increase the likelihood to track to adulthood. But those are poorly supported statements.

DR. LUSTIG: Dr. Dietz?

CHAIRMAN NELSON: Dr. Lustig?

DR. LUSTIG: Sir, Rob Lustig.

Two questions, actually. The first question, you made a very convincing case for a BMI at the 99th percentile as being morbid obesity for children. I was wondering how that stacked up against the BMIZ score and where that was the --

DR. DIETZ: That's three standard deviation.

DR. LUSTIG: And does that make any more sense than --

DR. DIETZ: Well, we debated that. You know, I think pediatricians have enough trouble measuring BMIs and putting them in percentile fashion. And to ask them to go to these sources beyond the --

DR. LUSTIG: We don't want to sacrifice them either.

DR. DIETZ: Well, the 99th percentile could easily be added to the growth charts. And when we publish this, we're going to publish those cut points. So, you know --

DR. LUSTIG: The second question was,

since Whitaker's data demonstrated that, in fact, there is a fair amount of tracking, even at age four months, going up to overweight at seven years -- and you have shown us convincingly that overweight at eight years is a risk factor -- should we be targeting kids even lower in terms of what's on the -- because the target population is actually the one that's showing the increased incidence of obesity.

DR. DIETZ: It's an important question. And I would refer you to the paper we published in Pediatrics which looked at the frequency with which young children shifted percentiles, both upward and downward. And there's still a fair amount of shifting going on at age four.

If you look categorically, you can see a relationship, but I'm not sure that that is going to help us very much with an individual patient. The other thing I think we have is that how much shifting for whom constitutes a risk. I don't think we know the answer to that question, although I think this early childhood, the data on early childhood, do suggest the risk in that group increased.

CHAIRMAN NELSON: Okay. I've got four people on the list. First is Dr. Kral.

DR. KRAL: Dr. Yustein in his introduction mentioned that the Office of Devices here usually only deals with manifest disease and is not interested in preventive disease. Do you have an opinion on that in this context of what we're dealing with today?

DR. YUSTEIN: I didn't say we weren't interested. For the purpose of the meeting today, we would like to focus on how devices tend to be devices that treat the disease and don't prevent diseases. So we're kind of being selfish in asking for your assistance on our devices.

I didn't want to give the impression that we weren't interested in the prevention of the disease, but for our devices, I don't think there are any devices coming down the pike that are meant to prevent obesity.

DR. KRAL: But we're discussing pediatric obesity.

DR. DIETZ: Well, I'm hesitant to make a comment on FDA policy.

(Laughter.)

DR. DIETZ: But I think that the criteria developed by the expert committee for the recommendations of pediatric surgery is still with a therapeutic intent. And you will recall that that is BMI supporting with a major comorbidity, like pseudo tumor or like type II diabetes or like sleep apnea, and BMI greater than or equal to 50, with additional or with more modest complications.

Now, I agree with you that we can get into a discussion of whether surgery in that group is preventing more severe developed disease or treating an existing disease in the pediatric population.

My own view is that obesity by itself is a disease. I am hesitant to say, well, we should just open the doors across the border for this, but I think that it's clear given the complications that we have that it is.

CHAIRMAN NELSON: Dr. Botkin?

DR. BOTKIN: Two quick questions. You had mentioned the psychosocial consequences of obesity. I'm wondering to what extent children who are obese

have comorbid psychiatric or psychological conditions or dysfunctional families. Is there any data on those sorts of issues?

Then, secondly, what do we know about socioeconomic status of children with obesity?

DR. DIETZ: Well, with respect to the first, it appears that depression predisposes to obesity, not the reverse, although, again, that's not been a well-studied problem.

The data that I cited with respect to dysfunctional families and disparity of obesity come out of my own clinical experience. That has not been well-described, although there is a pretty robust literature on the adult side of the psychosocial complications of severe obesity in adulthood in both the cause and consequential fashion.

The socioeconomic effects have changed. We kind of have analyzed the more recent data. But yours show there was a direct relationship between obesity and socioeconomic class in children.

The data in adults have recently become very muddled. And the only group in the 1999 to 2003

are MHANES, from which there is an inverse relationship of obesity and socioeconomic class is in Caucasian women. Although there used to be a relationship in African American and Mexican American women, that no longer holds. There doesn't seem to be any relationship between SES and obesity in men.

CHAIRMAN NELSON: Let me go to Dr. Daum, then Diaz, and then Klish. And then we'll go to the next presentation. So Dr. Daum?

MEMBER DAUM: Thanks.

You showed a slide with a list of the costs of obesity that I presume mostly was generated from thinking about this in grown-ups. I guess are there any comparable data or ideas about the cost of obesity in children, school performance, for example, socialization that supports?

DR. DIETZ: No, unfortunately not. Those are important questions. The only data on costs are from a paper that we published from the National Hospital Discharge Survey, which showed a threefold increase in costs of obesity and obesity-associated diseases in pediatric population over about a 20-year

period.

But those are still pretty modest, I think about -- I can't remember. I think the last year we looked at was 1999 or 2000. I think it's about $175 million, as opposed to the billions of these costs in the adult population.

So I think it's fair to think about costs in terms of the projected impact of obesity on medical costs, rather than the direct cost of obesity per se.

MEMBER DAUM: And, again, I guess my question goes beyond dollar costs.

DR. DIETZ: Yes. No, there have been no -- there are some quality of life analyses, but it's hard to put a cost figure on those other costly activities. I think it's a very important question, but those are not analyses.

CHAIRMAN NELSON: Dr. Diaz?

MEMBER DIAZ: In addition to looking at Mexican Americans, did you look at other groups of Hispanics, like Cubans, Puerto Ricans, South Americans? And if so, do you see any differences?

DR. DIETZ: Unfortunately, the MHANES only

classifies as Mexican Americans. And the other Hispanics have not been analyzed separately.

CHAIRMAN NELSON: Dr. Klish?

DR. KLISH: Did I hear you say that you now think that the word "obesity" should be used to describe children? I think nomenclature is going to become an issue as we discuss these devices in children. And, you know, as you know, that's been kind of a difficult problem nationally trying to use the nomenclature of adults and apply it to children or vice versa.

I might also point out that Dr. Yustein's graph or little table is wrong, too, because the children need to be ratcheted down one space in that table.

DR. DIETZ: What I said was that I think what is going to change the medical use of the nomenclature is the need to align the diagnostic criteria with billable diagnoses. I think in terms of conversations with patients the term "overweight" still --

DR. KLISH: That's an individual

doctor-patient relationship. I mean, the scientific world is where the confusion lies. And it would be nice to take a stand on nomenclature at some point.

DR. DIETZ: The IOM did so. The IOM report on prevention of childhood obesity said we're going to call this "obesity" and referred to kids above the 95th percentile.

I am less compelled to rush into this because I am not sure what the public understands by the term "obesity." We can agree. I am sure we can agree in this room. But that agreement to me is what is critical to what patients' and the public's understanding is of this problem.

CHAIRMAN NELSON: Actually, we do not have a lot of time because you may not know this, but the public session needs to stay at 1:30. If you guys can eat lunch in less than an hour, we've only got an hour for 107 slides in the next presentation, which we won't have any ability to have a conversation about the next presentation the more we take here. So if it's burning or not?

DR. INGE: One quick question follow-up on

Dr. Kral's is -- and I understand the reason for not wanting to focus in this session on prevention of obesity, the disease obesity, but I think it is critical to get an opinion, your opinion, that is, on the notion of preventing comorbidities of a child that meets whatever definition of obesity with a device. Is there any role for considering prevention of comorbidity?

DR. DIETZ: Yes. You know, we're only beginning to understand the role of physical activity in reduction of comorbidities in the pediatric population, let alone devices. I really believe that, like the adult population, what we're going to see is that physical activity reduces many of the biochemical comorbidities and possibly disease comorbidities as it does.

So I would be personally very reluctant to think about the use of devices as reducing comorbidities without a more robust literature on whether there are other lessened basis rates to accomplish that.

CHAIRMAN NELSON: Thank you.

I would like to move to the next presentation. I already tipped my hand on tempo. We're scheduled for lunch at 12:30. It's now 11:30. There are 107 slides in the next one as I counted them, which violates my rule of one minute per slide, but maybe you'll be very quick.

So I'm assuming if you get through, we'll have time for questions before lunch. If not, we may have to defer those until this afternoon since the public session scheduled at 1:30 means we really do need to break at 12:30 because I can't imagine all of you would eat lunch in less than an hour. In fact, you're not supposed to given the topic of the meeting.

DR. HASSINK: Well, thank you, Dr. Nelson.

"OBESITY: A NATIONAL HEALTH ISSUE" --

SCIENTIFIC OVERVIEW

DR. HASSINK: It is always a challenge to talk about the pathology of obesity and limit it to what should I leave out. So we will try to move quickly, but my attempt here to give you an overview of some of the pathophysiology and pathology of obesity and drill this down into what the individuals

present with, the children that come to clinic come with.

We have been running our weight management clinic at A. I. DuPont for the past 17 years. We watched the obesity epidemic explode and the morbidity increase. And we see patients, just so you know, from infancy to age 21 in a multidisciplinary hospital-based setting.

Just to make a point that the adipose tissue has its own growth trajectory, this is a graph of a patient at the 50th percentile for weight. And you see that adipose tissue and body composition change during childhood.

This is just to remind you that this is a very dynamic process in childhood with a lean body mass index in mid-adolescence for boys, ramping-up of adipose tissue in girls. And this is in normal children. Clearly obesity alters this trajectory very much.

You can also see by having a tight growth trajectory that this tissue system is under a lot of metabolic and control, which we'll talk about in a

minute.

Obesity is excess adiposity. You see the research methodologies that have been used to measure adiposity, densitometry, underwater weighing very difficult in children, DEXA CT/MRI.

Clinical measurements revolve around anthropometry. People have used bioelectrical impedance. Right now, as you heard Dr. Dietz talk, BMI is the clinical methodology for measuring obesity.

This is just one of the CDC obesity growth charts. If you're measuring under age two, you need to use weight per length charts, which are also available from the CDC.

The adipose tissue we're talking about here is white adipose tissue. There is brown adipose tissue present in the newborn and in situations of cold, stress, and starvation. But white adipose tissue, just to make the point, is a multicellular tissue composed of adipocytes.

There are stem cells in this tissue capable of differentiating into muscle, cartilage, adipose tissue, and bone. There are also endothelial

and vascular elements in the tissue.

Interestingly enough, there are also macrophages that infiltrate the adipose tissue and are correlated with the degree of adiposity. And this may be one of the pathophysiologic links between obesity and inflammation when you're talking about cardiovascular disease and diabetes.

This is just a high-powered micrograph of what that tissue looks like. You see that the cell is taken up with fat storage. The nuclei are in the periphery. There are vascular and stroma elements as well. And this is just a higher-power view.

Adipose tissue is a very metabolically active tissue and organ system. In contrast to the older view of the cells were there basically just to store fat for fuel, we now know, thanks to the discovery of leptin in 1994 by Friedman's group, kicked off the age of viewing adipose tissue as a cytokine-producing, hormonal regulating tissue important in growth and glucose homeostasis. It is also involved with energy regulation at the level of the CNS and the periphery.

This is a sampling of the cytokine production from the adipose tissue. You are all familiar with many of these. Leptin has probably received the most notoriety, adiponectin, inflammatory cytokines as well.

Leptin is produced by the ob gene. It's produced in white adipose tissue. It was thought originally just to be made in fat, but it has been discovered to be made in stomach, the placenta, and mammary gland. That raises some interesting questions about fetal growth and programming, ovarian follicles, and multiple fetal organs.

Leptin receptors are found in most tissues of the body, but the hypothalamic nuclei that are involved in energy regulation are a major target of leptin.

You can see here a cartoon showing the adipocyte with impact on the hypothalamus via neuropeptide Y. This would downregulate hunger in animals, increases activity and increases thermogenesis. And when this was discovered in the ob-ob mouse and they were given leptin, they lost

their obesity. However, most humans are leptin-resistant. And so leptin administration is not very effective in the human setting for reducing obesity.

This is another drawing just to illustrate a very important point about the complexity of obesity. These are the four hypothalamic nuclei. You can see that the ARC 08 nucleus gets input from peripheral energy stores and also is involved in autonomic regulation of leptin secretion form fat.

The paraventricular nuclei also get input about energy stores and help regulate feeding behavior. The dorsal medial nuclei get input from the lateral hypothalamus about hunger. And the ventral medial nuclei are involved in sympathetic regulation and vagal regulation of insulin secretion.

All these nuclei communicate with each other, with the cerebral cortex, which communicates with the outside world and with the periphery. This is a highly complex system due to the fact that when you talk about obesity, you are talking about energy regulation, which is linked to our survival.

Other cytokines of note that the adipose tissue produces: TNF alpha alters insulin signaling and increases insulin resistance. IL6 is involved with acute phase reactants, such as CRP. Adiponectin in adults has been linked to a risk of cardiovascular disease. It actually goes down as obesity increases and modulates endothelial adhesion and inhibits inflammatory responses.

Worthwhile just thinking about for a moment is the connection between obesity and inflammation. As I said, macrophages migrate into the adipose tissue. And this is because the adipocyte-secreted TNF alpha stimulates the preadipocytes in endothelial cells to produce monocyte temotrac in protein.

Also, increased leptin and decreased adiponectin stimulate transport of macrophages in adipose tissue. So you have the scenario here of a huge inflammatory mass with the onset of obesity.

The interaction between the environment and the gene is complex in obesity. We know that there is a higher risk of a child being obese with

parental obesity. There is probably a genetic modification of the risks for comorbidity.

There are also environmental interactions, which point to possibly critical times in growth, such as the intrauterine environment, that predispose children to obesity and diabetes. And maternal diabetes is one of these. There may also be periods of critical growth that impact later obesity. Early infancy or puberty may be some of those.

The field of nutritional genomics attempts to study the impact of what we eat on our genetic regulation. So this is a highly complex system.

Obviously you heard from Dr. Dietz, and we will be talking a lot about this. It is a multi-system disease with effects on all major organ systems. It can result in earlier onset of adult disease, as we're seeing in the type II diabetes in our adolescents; end stage disease in the children that progress to fibrosis and cirrhosis from their nonalcoholic hepatitis; and provides some new insights into old diseases, such as the link between insulin resistance and the sleep apnea syndrome.

I think most important to this discussion is to recognize that obesity is a very individual process. Obese children and adolescents have their unique weight gain trajectories, genetic predispositions, and comorbidities. They also have unique family situations, psychological needs, and community settings. So although we talk about population data, this really boils down to patient by patient.

You can see these are three weight trajectories of three charts I had in my office last week. I didn't put them on the BMI charts because the BMI charts don't go up as high as we needed, but this little girl had a morbidly obese parent who died in his 50s of diabetes. She had early disregulation of feeding and eating. She had sneaking behavior and lack of appreciation of satiety, has developed upper airway obstruction, requiring BiPAP, and ankle pathology and bone marrow edema and destruction of her ankles.

Patient C is a little girl with two parents with type II diabetes and at age 12 developed

type II diabetes and nonalcoholic statahepatitis.

Patient B here was a little girl crossing percentiles early in childhood, developed some peer difficulties in school, had mild hypercholesterolemia, so very different trajectories, all in the obese population.

I want to spend some time now on the pathology of obesity. This is the ground-level view of what pediatricians are seeing or are going to see. The first is to talk about some obesity-related emergencies, a slide I didn't have in the talk several years ago, but we're seeing it now. Just to point out, we have seen every single one of these complications in our patient population.

The first I'll talk about is a paper that was written by Morales in 2004 entitled "Death Caused by Hyperglycemic Hyperosmolar State at the Onset of Type II Diabetes." He described seven obese African American youth who are considered to have died from DKA, despite meeting the criteria for hyperosmolar state.

Morales said -- and this is Morales'

statement from the paper -- "All had previously unrecognized type II diabetes. And death may have been prevented with earlier diagnosis of treatment."

This is kind of the nightmare for the pediatricians. Patients presented to medical care with symptoms which were not at that time linked to presentation of type II prior to their death of vomiting, abdominal pain, dizziness, weakness, polyuria, polydipsia, weight loss, and diarrhea.

They were found comatose at home or died in the emergency room. The diagnostic criteria for this state is a markedly elevated plasma glucose of over 600, serum CO2 over 15, small ketonuria ketonemia, high osmolality, and stupor or coma. And this is rare, but it certainly has appeared on the radar screen of emergencies related to the obese adolescent.

DKA is not uncommon in type II. In some studies, up to 25 percent of children have diabetic ketoacidosis. If vasal insulin sensitivity is low, there is an increase in susceptibility to relative insulin deficiency. And this may be more common in

the African American and Hispanic patients in type II who present with a higher baseline insulin resistance.

This is just to illustrate the point that obesity is linked with insulin resistance. Hyperglycemia can cause some beta cell toxicity, decreasing insulin secretion, and creating a state of relative insulin deficiency, lipolysis, and DKA.

Pulmonary embolism has been seen in children. The symptoms are as they are in adults: dyspnea, chest pain, hypoxia, hepoptysis. It has been seen with surgery and trauma. We have seen it in our population are pinning a femoral fracture. We have seen it present in the ER with a child with a family history of a coag disorder. The risk factors are obesity here, maybe some enhanced risk from the obesity hyperventilation syndrome and children who have coagulation problems.

We have also seen, surprisingly, cardiomyopathy of obesity. We had a 17-year-old boy come into clinic morbidly obese. He weighed 600 pounds, walk-in, dyspneic, on evaluation had biventricular cardiac failure and cardiomyopathy.

This results from high metabolic activity of excess fat, which increases the total blood volume in cardiac output, resulting in left ventricular dysfunction, dilatation, and can be enhanced by right ventricular dysfunction due to pulmonary hypertension secondary to upper airway obstruction. This is his X-ray just showing an enlarged heart and heart failure.

These complications, although rare, are severe and life-threatening and I think have to be placed in the armamentarium of the pediatrician about what to look for.

There is another level of comorbidities which require immediate attention. I say to the pediatricians these are the ones you don't want to leave your office without making these diagnoses. And I will start in with pseudo tumor cerebri.

This is a state of raised intracranial pressure with papilledema and normal cerebrospinal fluid in the absence of ventricular enlargement. This would be what you would see on fundoscopic exam. You can't see the dismargin. It's swollen. And the vessels are sort of bulging out over that.

The diagnosis, these kids can present with headaches, vomiting, blurred vision, or diplopia. Sometimes neck, shoulder, and back pain have also been reported. Papilloedema is part of the pathology, but the headaches may occur prior to you being able to visualize that.

The morbidity here is the loss of the peripheral visual fields and reduction of visual acuity. You might see this at diagnosis, and we certainly have. We have seen it, incidentally, at diagnosis with children coming in for other complaints, obese children. They have papilloedema. And then when you look at them, they have visual field cuts, but they haven't reported them. If this is untreated, it leads to visual impairment or blindness.

It is hard to get incidence and prevalence data on some of these conditions, but obesity occurs in about 30 to 80 percent of affected children with this. And in a series of case-controlled studies in adolescents and adults, obesity and recent weight gain were the only factors found more often in the pseudo tumor patients. We still don't know why exactly this

happens, and we don't know how to predict in whom it will happen.

There are drugs associated with pseudo tumor, just for a quick review, growth hormone therapy, nalidixic acid, ciprofloxacin, tetracycline, with no dose-response relationship, vitamin A. One wonders certainly. If they have had pseudo tumor, you wouldn't want to give them these drugs. And you don't know what to say prophylactically since we don't know how to predict who is going to get it.

The treatment is with acetazolamide. In a severe case, a lumboperitoneal shunt may have to be placed to reduce the pressure while you are attempting weight loss. Clearly, fundoscopic exam should be part of the child care. Visual field cuts need to be looked for. And pseudo tumor is a diagnosis exclusion. You have to rule out other causes of increased intercranial pressure.

This next one is a particularly pediatric complication because the growth plates are open in pediatrics: slip capital femoral epiphysis. You have to suspect this and immediately evaluate an obese

child coming in with a limp. Most of them with SCFE are obese. And you can also see this present with complaints of groin, thigh, or knee pain because of the sensory cutaneous innervation around the hip capsule.

It really is medial and posterior displacement of the femoral epiphysis through the growth plate relative to the femoral neck. And you diagnose it on clinical exam with reduced abduction and internal rotation. And you diagnose it on X-ray. You'll see in a minute the X-rays of one of our patients. It can be bilateral in 20 percent.

You see here this is a normal hip with the femoral head seated on the femoral neck. This is the slip. This is painful, requires immediate pinning.

The preferential site of the slip is within the epiphysis. It's the zone of hypertrophic cartilage cells. It's under the influence of gonadal and growth hormone.

And some associated causes, again, you usually can't predict who is going to get this. We don't know exactly why this happens, but these are

some associated causes, continued weight gain, renal failure, history of radiation therapy, hypothyroidism, and then the hormonal effects.

So hips and knees need to be checked in every obese child. You can't ignore a complaint of a limp and you can't write off a gait as just due to excess weight. You really need to look for the pathology here.

In Japan, the annual incidence is estimated to be 2.22 per 100,000 boys and .76 per 100,000 girls 10 to 14. The point here is it's five times higher than the previous estimate. It was hard to find estimates in this country, but this is probably being driven by the obesity epidemic.

Blount's disease is another pediatric orthopedic morbidity. It's bowing of the tibia and femur, unilaterally or bilaterally. It results from the overgrowth of the medial aspect of the metathesis.

Two-thirds of the patients with Blount's may be obese. And this also requires surgery. We have seen this severe enough to compromise ambulation and cause peripheral neuropathy when you don't treat

it.

Obstructive sleep apnea is not a usual complication in obese children. And this is defined as prolonged partial upper airway obstruction or immediate intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns.

The histories you usually get include what you would expect: nighttime awakening, difficulty awakening, restless sleep, daytime somnolence, napping, enuresis, poor concentration, and poor school performance.

The etiology is thought to be some combination of increased fat mass, increased muscle relaxation during sleep, exacerbated in kids with enlarged tonsils and adenoids. And there is a link in adults and one study in kids that shows people with elevated insulin seem to have more problem with this.

The gold standard of diagnosis is nighttime polysomnography and because the severity of obstruction may not correlate with either the degree of obesity or severity of sleep symptoms.

Abnormal sleep patterns are surprisingly common in the obese children. And obstructive sleep apnea has been noted in obese infants as young as five months of age.

The real functional morbidity here is the significant decreases in learning and memory, attention. This can look a lot like ADD in an obese child. The long-term sequelae are pulmonary hypertension, systemic hypertension, and right heart failure. So in school children who are not doing well, this should be one of the things you should look for if they're obese.

Weight loss can reduce apneic episodes, hypoxemia, and daytime sleepiness. Tonsilladenoidectomy can buy you some time if you need it. The treatment modality here is a CPAP or BiPAP. It's extremely effective but very hard to get adolescents to use. It's kind of an invasive thing at night. They don't like it very much.

So families need to be asked specifically about these symptoms because it may be normative in the family. It should be considered in kids with poor

school performance and concentration difficulties. And it can occur during intercurrent illnesses with tonsil enlargement and with further weight gain.

Dr. Dietz highlighted the liver disease due to obesity. This has become a real issue. There's a nonalcoholic fatty liver disease that describes a continuum of conditions that range from simple steatosis through nonalcoholic steatohepatitis to cirrhosis and end-stage liver disease. And you diagnose this when you get increased liver enzymes on blood draw and a fatty liver on ultrasound, but the gold standard of diagnosis remains liver biopsy because you need to see the inflammatory cells and the fibrosis.

Twenty to 25 percent of obese children in some series have had evidence of steatohepatitis. Nobody, again, knows why certain children get this, but it's felt to be obesity, fatty infiltration of the liver with a second hit possibly with a genetic predisposition and a second environmental hit causing inflammation fibrosis, which may progress to cirrhosis.

The natural history of this disease is not well-known in children. Here you have a liver biopsy from a ten-year-old. You can see the fat infiltrating the hepatocytes. You can see portal bridging fibrosis already at age ten.

In Japan, the prevalence was 2.6 percent has been reported in the population and which rose in their obese children to over 50 percent. So fatty liver is quite common. Obesity and type II diabetes are the strongest predictors of the progression of fibrosis. And the progression of fibrosis is really the pathological event.

Age may also be a risk for cirrhosis because it may reflect the increased time you have for that second hit thought to initiate the fibrosis. And a liver with fat in it may be at increased risk of damage from viruses or endotoxins or alcohol or industrial components.

Predictors of elevated liver enzymes in some studies have been shown to be male gender, Hispanic ethnicity, and elevated BMI, but these are just in one study. Predictors of fibrosis, BMIZ

score, insulin resistance may be leptin, but still the natural history is not well-known.

You can reverse the elevations of the amniotransferases and fatty liver with ten percent weight loss. Because it's hard to get approval for a second biopsy, it's hard to know what is happening to fibrosis that exists.

Metformin has been used to treat these children. It can normalize liver enzymes in about half with biopsy-proven NASH and reduced hepatosteatosis by about a third as it improves insulin sensitivity.

The caveat here is when liver biopsies were performed in adults after weight loss, all had reduced steatosis, but you can't always reduce the fibrosis if it's preexisting. And in this study, rapid weight loss in some studies has been linked to increase fibrosis. So you have to use caution when dropping the weight rapidly.

So nonalcoholic fatty liver disease in childhood now is diagnosed as an exclusion. You want to make sure you're not dealing with any of the

hereditary hepatitis syndromes.

Gallstones are just like in adults. They're diagnosed with abdominal pain and tenderness. The obesity accounts for a higher percentage of gallstones in children. Fifty percent of cholecystitis in some series in adolescents were associated with obesity. And it requires surgical intervention.

When we move to the chronic obesity-related comorbid conditions, we are really talking about conditions, by and large, linked by insulin resistance, such as type II diabetes, polycystic ovarian syndrome, hypertension, and hyperlipidemia. I also put the psychological conditions. And we're going to talk about those at the end because they're extremely important in the childhood population. Here you see just an illustration of that.

Important to think about is insulin-mediated glucose disposal by muscle varies almost tenfold in healthy individuals. So we're coming to the table with different predispositions for

insulin resistance. The more insulin-sensitive the muscle, the less insulin needs to be secreted to maintain normal glucose homeostasis because that is as important. The more insulin-resistant an individual and the greater degree of compensatory hyperinsulinemia, the more likely they are to develop these associated diseases.

Energy regulation and control of insulin also occur at the level of the CNS. The CNS integrates afferent signals regarding energy intake. And normally the CNS exerts an inhibitory effect on insulin secretion. And obesity can occur in settings of neuroendocrine pathology, CNS pathology, trauma, or cancer.

At the level of the adipocyte, adipose tissue in obesity becomes refractory to insulin suppression of fat mobilization. So there is an increased release of free fatty acids. These fatty acids are linked with the onset of peripheral and muscle hepatic insulin resistance.

So postprandially there is an excess of circulating lipid metabolites and leads to fat

deposition in other tissues. And it's sort of intuitive that fat in muscle, fat in liver doesn't belong there and can be pathologic.

Hyperinsulinemia stimulates fatty acid synthesis in the liver. Elevated insulin may increase degradation of APOV 100, compromising triglyceride transport out of the liver. And so there you have net accumulation of fat in liver. In muscle, elevated free fatty acid and accumulated triaceglycerol appear to inhibit insulin signaling.

The resulting suppression of muscle glucose transport leads to reduced muscle glycogen synthesis. And we have done treadmill studies on our kids with BMIs over 40. Despite normal hearts, by and large, and lungs, their exercise performance is at the level of cardiomyopathy patients. And we think that the muscle impairment in energetics here plays a rule.

Metabolic syndrome, just to review, the American Diabetes Association came out with a statement they're not sure if we should be using this term or just talking about individual risk factors. But the cluster that you look at here is abnormal

blood lipids, low HDL, high triglycerides, high LDL, and impaired glucose tolerance, along with obesity and elevated blood pressure.

There is an increased incidence of impaired glucose tolerance in an obesity clinic population. And this was in a 2002 article, which reported 25 percent of obese children age 4 to 10 had impaired glucose tolerance. Twenty-one percent of obese adolescents in this population had impaired glucose tolerance.

This is a physical finding often associated with insulin resistance, although it doesn't have to be all the time, called acanthosis nigricans. And it is a pigmentary excess in the skin. It can appear in the neck axilla and other skin folks. Obese patients have been reported to have higher fasting insulin and lower insulin sensitivity when they have acanthosis. This fades when weight reduction occurs.

Diabetes clearly is one of the emerging, rapidly emerging complications of obesity. And this is just how you diagnose diabetes in any child, high

random plasma glucose with symptoms of diabetes, an elevated fasting plasma glucose, or a glucose over 200 on an oral glucose tolerance test.

In the setting of type II, elevated fasting insulin and hyperglycemia, that's the occurrence. And only 20 percent in a lot of series present with the classic polyuria, polydipsia, and weight loss. It's an emerging problem in the pediatric endocrinology clinic, accounting for a lot of the new diabetic diagnosis. This is just the same kind of track here with insulin resistance, beta cell dysfunction giving rise to diabetes.

The defects are excessive hepatic glucose production and defective beta cell secretion and function. And the duration and severity of hyperglycemia dictate the microvascular complications.

In an article in 2003, it was noted that the lifetime risk of diabetes for individuals born in 2000 is one in three for males and two in five for females.

The risk factors for type II diabetes are clearly obesity and having a first or second degree

relative with type II diabetes. Ethnicity also plays a role here, with African American patients, Hispanic, Asian, and Native American descent predisposed to a greater degree.

Also, it's not unusual to see diabetes present in puberty when you naturally are more insulin-resistant. Inactivity may contribute to some of the increased insulin resistance, which is predisposing to diabetes as well as visceral facta position and children with polycystic ovarian syndrome. And there is a slight female to male preponderance.

As I said before, maternal diabetes or impaired glucose tolerance during gestation may infer an increased risk of obesity and diabetes in that child.

Our Native American population is getting hard hit with diabetes, with rates up to 50 per 100 thousand in Pima Indians. In a study from Cincinnati in 1994, their estimated rate of type II was 7.2 per 100,000 incidence of diabetes. This was a tenfold increase for them over the previous ten years. And in

an article in 2004, it was noted that the worldwide incidence of diabetes type II has tripled since 1985.

Associated findings are polycystic ovarian syndrome, acanthosis nigricans, dyslipidemia, and hypertension. Just a point about PCOS, which we used to just think of as an adult disorder, these girls present with dysmenorrhea, oligomenorrhea, regular menses, hirsutism, and acne. You find hyperandrogenemia. They may have cysts on their ovaries. They will develop eventual problems with fertility. And girls with premature adrenariky need to be followed because they seem to be at increased risk for this.

In a study of an adult female population study in Atlanta, unselected, the prevalence of this was 6.6 percent, making it one of the more common endocrinopathies in females.

Hypertension is common in children with obesity. Twenty to 30 percent of obese children in clinic settings have elevated blood pressure. Obese adolescents had a higher risk of obesity as adults.

Obesity is linked to the end organ

morbidity of cardiac hypertrophy. We find LVH on ultrasound not infrequently and long-term renal disease, cardiovascular disease, and stroke. It does respond to weight loss, dietary change, and pharmacotherapy.

Hyperlipidemia, the pattern you see in children is hypertriglycedemia, elevated LDL, and low HDL. Increased central facta position and hyperinsulinemia are thought to be drivers of this. Overweight adolescents have increased predisposition to lipid abnormalities in adults.

I want to spend a little bit of time on the psychological morbidity in obesity, obesity-associated psychological conditions: depression, anxiety, low self-esteem, teasing, bullying, binge eating disorder.

There are also additional psychological conditions that may impact treatment. Clearly if you have a patient with undiagnosed ADD or ADHD or bipolar illness, adjustment disorder, or oppositional defiance disorder, treatment and compliance are going to be more difficult. So these are crucial issues to take

into consideration when you evaluate your patients.

The study Dr. Dietz alluded to was in depression in obese adolescents from grades 7 to 12. A depressed mood predicted follow-up obesity, but baseline obesity did not predict follow-up depression.

This was a study from Appalachia. It talked about obesity trajectories. And I think a lot more thought needs to be given to the trajectory of obesity during childhood.

They had four groups. One was a normal weight group. One was a group that was obese in childhood that resolved in adolescence. The third group was obesity in adolescence but not in childhood. And the fourth group was chronic obesity, pretty much since infancy.

When they studied these groups as to their psychological morbidity, there was no difference among groups in gender, family structure, parenting style, family history of mental illness, drug abuse, crime, or traumatic events.

The chronic and childhood obesity were associated with having undereducated parents and low

family income. The obese children, chronic obesity was significantly associated with higher rates of oppositional defiance disorder and for boys depression.

I don't think this is the definitive study, but I think this teases out some of the things we need to be thinking about when we look at the context in which our obese children sit, the context of their families' environment and their own psychological states.

When you look at health-related quality of life, obese children and adolescents have likelihood of having impaired health-related quality of life greater than healthy children or adolescents. And this number is comparable to children with cancer undergoing chemotherapy, which gives you an indication of some of the severity of this. They reported lower pediatric quality of life scores in all domains, which were physical, psychosocial, emotional, social, school functioning. Interestingly enough, in this group of children, the parents rated them even lower than they did themselves.

Obese children and adolescents with obstructive sleep apnea reported lower quality of life scores than other obese children. And these scores did not vary by age, sex, socioeconomic status, or race. And BMI scores among obese children and adolescents was inversely correlated with physical functioning.

I would echo Dr. Dietz's comments that when you see these children, you realize how complex their situation is and how crucial the understanding is that you need to understand their psychological state, the family dynamics and functioning, the family psychological state, and something about parenting if you hope to have them comply with therapy of any sort. So I think this point can't be overstated.

I think I will end there. And I have this obesity being unique, complex, pathologic, and multifactorial. And you see my Freudian slip there to echo complexity because I think it can't be overstated that this is a complex pathologic disorder that requires extremely careful evaluation of these children to know what the right thing to do in their

situation is.

Thank you.

CHAIRMAN NELSON: Thank you. I wouldn't have thought it possible, but you almost put us back on time.

(Laughter.)

DR. HASSINK: I take the Chair's comments seriously.

CHAIRMAN NELSON: So we actually have over 20 minutes that we could spend discussing the large volume of information that you presented to us before going to lunch. So I'll open it up for questions and clarification from anyone on the panel. Tom?

COMMITTEE QUESTIONS OF CLARIFICATION

FOR SPEAKER

MEMBER NEWMAN: Thank you for that real whirlwind tour. Just the one thing that went by really fast that really did catch my eye is it seemed like there was one thing where rapid weight loss would be bad. And that was the alcoholic liver. Can you just back up? It was like 50 percent. I mean the fatty liver.

DR. HASSINK: That comes from one adult study. And it's hard to know what to make of this in pediatrics, but they did notice that there is a metabolic change in rapid weight loss that increases free fatty acids and may exacerbate the nonalcoholic hepatosteatosis.

Since rapid rapid weight loss is not that common in childhood so far --

MEMBER NEWMAN: No. But with these devices, it might be.

DR. HASSINK: Yes. And I think you just have to take that as a point of interest. It hasn't been reproduced in childhood. And it comes from a study. So I don't really know how to set that in context for you other than it's been noted in adults.

MEMBER NEWMAN: Would this be something you could diagnose with ultrasound or would it require a liver biopsy?

DR. HASSINK: The diagnosis of fibrosis and inflammation, that component requires a liver biopsy. And that's been the holdup in really understanding what the trajectory of this disorder is

in childhood.

So you can see the fat come and go. And that's actually pretty easy to see. Weight loss you can see the fat just disappear out of the liver. And you can see the liver enzymes come down. They can come down pretty fast as soon as you get weight loss.

What you really don't know is, is there any residual inflammation in fibrosis. And I will tell you that kids walk into clinic with elevated liver enzymes that are not all that high and have fibrosis already if you biopsy them.

So this is kind of a little bit of a black box yet in understanding what the natural history of this is and who goes on to the fibrotic and cirrhotic endpoint. And I don't have a good answer for how you want to --

CHAIRMAN NELSON: Dr. Botkin?

DR. BOTKIN: This might be covered later in the day, but I wonder if you could tell us what is known about how obese children differ from non-obese children with respect to dietary habits and exercise patterns.

DR. HASSINK: We know there are a lot of epidemiologic links with TV watching, which is the most well-substantiated. So that links with sedentary behavior plus eating behavior. So we know that the more TV watched, the more likely kids are to be obese. So we know that epidemiologically. We know it anecdotally from what we have seen clinically.

We know that some eating patterns, such as bingeing or rapid eating, tend to be a little more common and linked to obesity. We know snacking and grazing behaviors are more common and linked to obesity and consumption of highly sweetened sodas and juices are more common or at least take the predisposed individual and can create the obesity.

So we do know some things about activity and inactivity. And those are the things that we try to reverse with behavioral modification and lifestyle change.

CHAIRMAN NELSON: Bob?

DR. WARD: Do we have any clear data showing reversal of these morbidities with rapid weight loss, such as the cardiomyopathy, the sleep

apnea?

DR. HASSINK: I think that you have to look at each morbidity. For example, the orthopedic problem is a simple one. When it's there, it's there. If you've slipped, you've slipped. Maybe you can prevent the slip in the other hip if you don't end up pinning it.

The liver disease, we know we can get the fat out and the enzymes down. So there is data there. The obstructive sleep apnea, with weight loss, clearly there is data that that can be reversed.

The metabolic complications, in adults we know a lot about type II diabetes and that being reversed. So the metabolic complications tend to be amenable to reversal or the severity, dropping the severity of those.

The sort of anatomic complications, like the orthopedic complications, once they're there, they're there. Whether you can take it all the way every time, I don't think we know that.

CHAIRMAN NELSON: Dr. O'Fallon and then Dr. Lustig.

MEMBER O'FALLON: I was struck by the fact that Dr. Dietz on all of his lists, he had asthma, which, of course, we're aware of as being another exploding incidence.

And, yet, you never mentioned it. And he never actually did either. He just had it on his list. And so I'm wondering, is that a mistake or is that something? Do we have any evidence that --

DR. HASSINK: No. I had it on my list and still consider it strongly. The prevalence of asthma, the incidence has gone up with the obesity epidemic. So if you look at them, they kind of parallel each other.

And a lot of the epidemiologic, sociologic factors that predispose to obesity are also common with asthma. And also the inflammatory kind of situation you're in with asthma may be linked with obesity. And inflammation may also be another link.

Is it directly? The reason I took it off is is it directly caused by obesity? Certainly you see obesity-related. There's fatty infiltration of the lung. And you get diffusion problems. And in

some animal studies, there's decreased surfactant production. But that is sort of the bench work.

Is it directly linked? I think you can fairly say that asthma is made worse by obesity and obesity is made worse by asthma. And there are a lot of epidemiologic links. And there may be some pathologic links.

So it shouldn't have been left off. But if I put one more thing on, Dr. Nelson would have probably burned my slide.

MEMBER O'FALLON: But let me ask, is there any kind of evidence yet about whether a weight loss will improve asthma?

DR. HASSINK: I think there probably is. I don't know it. I know clinically there is. I know there is a paper out there somewhere.

CHAIRMAN NELSON: I'm going to jump the queue. I gather Dr. Kral had his hand up first, and I think he wants to comment on the asthma point and maybe a couple of the other hands.

DR. KRAL: Yes. There are several papers showing reduction of asthma after obesity surgery.

CHAIRMAN NELSON: Okay. I'll take comments out of order on asthma for the moment. Any other points? Then we'll go back to Dr. Lustig?

DR. LUSTIG: Dr. Hassink, with the 107 slides, I guess I'm not too surprised that you didn't address all the issues, but one of the things since we're talking about scientific overview here is about classification and causation. All obesity is not alike.

DR. HASSINK: Right.

DR. LUSTIG: For instance, Prader-Willi is very different from brain tumors is very different from metabolic syndrome patients, et cetera. How do the comorbidities stack up in various forms of obesity?

DR. HASSINK: Good point. I could have spent the hour talking about causes of obesity. There are clearly -- and just to bring the point about genetic obesity, there are clearly monogenetic causes of obesity that are well-known to just Prader-Willi or X-link. We've learned a lot about them. Most obesity is considered to be polygenic, but there are

polymorphisms also related to etiology of obesity.

It's a difficult question. One question would be, are there any obese people that are spared certain comorbidities? I think you see that clinically, but I don't know the evidence about what their predisposing factors would be which would allow them, for example, to be spared diabetes until they get to be 400 pounds.

DR. LUSTIG: Well, in the adult literature, for instance, the lowest quintile, the waist-hip ratio, has a cardiovascular morbidity/mortality rate.

DR. HASSINK: Right.

DR. LUSTIG: That is the same as the general population --

DR. HASSINK: Right, right.

DR. LUSTIG: -- and an increased subcu component with a normal visceral component.

DR. HASSINK: there is also some discussion about physical activity and the protective effect and if our fit obese people are at the same risk as unfit obese people.

So I think there is a lot more we need to understand about the heterogeneity of the obese population, which kind of gets back to my point about this has to be taken kind of individually and set in the context of at least the individual and possibly knowing more about that individual's predisposition to obesity and what that bodes for the individual later on. And I think that's a point very well-taken.

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

MEMBER GORMAN: You know, in our preparator material, there was some concern in some of the surgical interventions about postoperative malnutrition in terms of inability to get effective micronutrients as well as calories and protein. And in that vein, not particularly that particular issue, is there a risk that we should be aware of in losing weight to fast?

DR. HASSINK: I think that in adults who have a malabsorptive component to their gastric surgery and don't take their dietary supplements, you see problems with vitamin deficiencies and

malnutrition.

I think slower weight loss at least -- I don't have surgical experience, but slower weight loss, you know, the clinical sine qua non, we use a pound a week or so on a normal diet. Usually you don't see any kind of problems. Even faster than that, you don't see any problems.

I think at this point I would be looking at the adult surgical literature and looking at patient compliance with what they have been asked to do in terms of the nutritional supplementation. And I think that has to be a key factor.

MEMBER GORMAN: As a follow-up question, is there any evidence in that the rate of initial change of weight predicts the maintenance of that weight loss?

DR. KRAL: No, there's no evidence.

DR. HASSINK: I'm blanking on that.

DR. KRAL: No, there's no evidence.

DR. HASSINK: Can anybody help me from the expert panel?

DR. KRAL: Yes. There's no evidence.

I've really looked for it.

DR. HASSINK: Okay.

CHAIRMAN NELSON: I've got Dr. Diaz and then Dr. Inge, Dr. Moore, and Dr. Pories. And that will probably take us to lunch, but we'll see.

MEMBER DIAZ: Is the inflammatory picture in child, in obese children, similar to adults?

DR. HASSINK: This is sort of emerging work. And it's thought that obesity in terms of what the adipose tissue is doing in children is similar to adults. I mean, it's a very good question.

Is the adipose tissue system acting in children metabolically like it acts in adults? But you can say that the inflammatory issues are at least now thought to be similar in children and adults? But I think that is a very interesting question about the whole metabolic function of the adipose tissue system.

CHAIRMAN NELSON: Dr. Inge?

DR. INGE: Yes. This is just more a comment. I can appreciate the panel's interest in understanding the consequences of rapid weight loss in inappropriate population adolescents.

And, actually, to that point, Dr. Garcia, who will speak later this afternoon, probably will present a great deal of evidence in that regard from our program, which is really using as a model the gastric bypass for rapid weight loss in adolescents and some of the cardiac consequences, some of the obstructive sleep apnea consequences, and some of the consequences in terms of other metabolic responses that will be very informative. For things that he doesn't present I think we can actually come up with some evidence in that regard.

CHAIRMAN NELSON: Dr. Moore?

MEMBER MOORE: Thank you for that discussion, Sandra. A question. In a family with a child who is obese, what is the data showing that the parents are likely to be obese also?

And, as a follow-on to that, what is the likelihood of therapy just targeting the child? You know, behavioral therapy basically can be effective in that environment.

DR. HASSINK: Thank you.

I think that population over the clinic

data -- and I have looked at this. I can just tell you in my population about a half to two-thirds -- about two-thirds of the patients have at least one parent obese. I do have about a third who bring in a kid with no parental obesity at the time, although there may have been parental obesity in the past.

So I think we can say that it's not unusual to have multigenerational obesity in these kids, although you can see an obese kid without parental obesity. That's for sure. And I don't know the wider data.

Treating children alone, I think I know better the data treating parents alone. And there is some data in the behavioral literature on lipid treatment and obesity treatment that if you just take the parents, especially the younger children, and intervene with them in terms of how to make behavioral and lifestyle changes, you get a weight loss in the kids.

Adolescents, if the group is tailored, if you're talking about lifestyle intervention, if it's tailored to the adolescent, there's some success with

adolescent groups, but they also do well. And the parents also have an ongoing component of the treatment as well or at least a discussion about lifestyle change.

So mostly this is done in the context of the family. It's hard to tease out the child when the nutritional activity or environment is so impacted by what the family does. And it really nowadays is needing the family to almost protect the child against the sort of adverse nutritional activity environments that exist everywhere.

DR. ARSLANIAN: May I add to that?

CHAIRMAN NELSON: Go ahead. On this point, sure.

DR. ARSLANIAN: Related to this point. The data which is in a research setup has shown that targeting families together with the child, the 10-year outcome was better, statistically significantly better, where 30 percent of those children were normal overweight, versus if they just targeted the child or random target. So I think there are very robust data in that area.

DR. HASSINK: Pretty much you can't do this without the family. And I would venture to say you can't do any obesity-related therapy without having involvement of the family.

CHAIRMAN NELSON: Dr. Pories?

DR. PORIES: This is just a quick follow-up to the comment about malnutrition. It's an extremely important point. If you follow the adult patients long enough, as we have, you can see the polyagra, the beri-beri, the Korsakow Fornicky syndromes. And I think in terms of children, the question of malnutrition is extremely important.

CHAIRMAN NELSON: I see no other questions or comments. Let me ask the panel one question and also first thank you for your presentation. I don't know. You're welcome to stay and listen.

The first question for the Committee is Dr. Dietz had mentioned Institute of Medicine prevention of obesity report. To the extent that people may refer to that, you may know that by memory. I don't. Would it be worth having a copy of that available for our discussions or not?

DR. ARSLANIAN: Yes.

CHAIRMAN NELSON: Okay. So we will talk with the FDA about getting that. I can download it for $30.50 if you'll reimburse me right now.

(Laughter.)

CHAIRMAN NELSON: But that is the question. So we'll work on that.

Jan has an announcement before we break for lunch.

EXEC. SEC. JOHANNESSEN: If people are here who are going to be participating in the open public hearing at 1:30, I think it would be useful if we would just get together right now at the beginning of the lunch break. And we can just decide who is going to speak first and get the times, make sure everything runs smoothly.

CHAIRMAN NELSON: Then with respect to lunch, there is a dining room out to the left and to the left. There is a buffet. Timeliness in terms of ordering off the menu if we all did it would be suspect, although some people were having to do that yesterday. So I would encourage you to look at the

buffet.

There is a private room that may or may not fit all the panel members. But at least yesterday the place was relatively empty. So we had that to ourselves. So that may not be an important issue.

I would encourage people. We're scheduled to start the public session at 1:30. So it would be nice if we're back here at 1:25 since it takes some time to get settled and get organized, which would give us by my clock a good hour for lunch.

So see you in an hour.

(Whereupon, a luncheon recess was taken at 12:24 p.m.)

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

(1:32 p.m.)

CHAIRMAN NELSON: I'm told by Jan, who is generally correct, not always, that I have something I need to read before we have the open public session.

"Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

"For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

"For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

"Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships.

"If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking."

So our first speaker if we're ready is Linda McAfee.

MS. McAFEE: You will give me the high sign when my time is low?

CHAIRMAN NELSON: No problem.

OPEN PUBLIC HEARING

MS. McAFEE: I am Director of Medical Advocacy for the Council on Size and Weight Discrimination. The council is a group that does not take any funding from the weight loss industry at all.

I have been a patient advocate for a number of years. And this is probably my ninth advisory committee meeting I have gone to, I think at most of them. I've decided to tell you, instead of actually making a presentation, because pediatrics is not an area of expertise for me. Obesity is. And I'm

hoping to learn from this and perhaps put some written comments into the FDA afterward.

But I wanted to bring up a few things today that I had heard that I thought needed a little more addressing. And hopefully we'll be able to do the same tomorrow.

One of the big problems with anything having to do with obesity, whether it's drugs or devices, is that there is a real problem establishing risks and benefits. And, of course, this is just a risk and benefit analysis.

Partly the risk is inherent in the problem of clinical trials. You just can't get everybody. You're already going to find things out after the market. The problem here is benefits because benefit is extremely controversial in the obesity field now.

There was a lot of talk this morning about overweight and obese. That's a really important distinction to make just epidemiologically because when the study came out this spring from Catherine Fleagle in JAMA, the year before that, they had come out with a figure of 400,000 people who died from

obesity. Then they were forced to revise that downward to like 360,000.

Well, what Catherine found was that overweight itself is actually protective so that they have a long -- it saved 82,000 lives. That's not the same as obesity. Obesity has quite a nasty little punch mortality-wise. So it's really important to remember that, particularly when you are going to do things on children.

And we're not talking about pseudo tumor cerebri here. I'm talking about people who have children have a risk factor for a risk factor as adults. And it's really important to understand that.

That is a real problem in the workplace, just like when I went to the Redux hearings and fen-phen hearings. There was a concern there, and it turned out to be right. Everybody got those drugs. They found a way.

I mean, people are going to Tijuana routinely now for LAP-BAND surgeries. So this is something that because of the social prejudice we suffer it's particularly difficult for us to make that

kind of risk-benefit analysis for ourselves because we have to factor in the social prejudice.

That's not something that you should factor in. This should not be a medical solution to social prejudice. And it's really important for you when you deal with this to confront your own prejudices and then think about that a little bit.

One of the problems with this field is also that we are not all the same. Again, someone alluded to it today from the panel. There is a very Nineteenth Century view of obesity. And it's based on this is how you look. So you all look the same way to us. So your bodies all work the same way. You all got there the same way. You all get back to thinness the same way. That's extremely untrue.

It's clearer and clearer that many of the things that kill us are really related to insulin resistance and not to just adipose tissue. Now, granted, I mean, so much is coming up now about the different sites of the hormone pump. You know, it's very confusing now to know exactly how direct that is, but I can tell you that everything I look at when time

after time you see a headline that says obesity causes this cancer and then a year later, let's say, oh, it's insulin resistance that causes this.

So that's a really important distinction to make when you're talking about who to treat. In fact, there's only been one prospective study on weight loss. And this is one of the major problems.

People cannot keep weight off long enough for it to be studied, which is astounding when I think about it. So we really don't know half of what we think we know.

The one prospective study that was done is not a randomized clinical trial, but it was prospective. And it was large with the American Cancer Society data.

What they showed with adults was that if you started out the study without the comorbidities, you did not gain any mortality, no mortality change, by losing weight. But if you had comorbidities, it did change it.

So these are just some things to think about. This is an emerging technology. It's really

very difficult to address these at the best of times. But when you have studies with 11 people in them, 33 people in them, that's not good enough. We are going to have to have bigger studies.

And they are going to have to include the profile similar to the profile that we see. They're going to have to include a lot of diabetic kids because those are the kids who will get the most benefit out of it.

I am really looking to see because this is an emerging technology, because risk and benefit are uncertain, I think that you really have to look at allowing these things for only the ones who would get absolutely the most benefit out of it.

And later on -- I mean, I know the company is anxious to sell a lot of whatever they have. And I understand that, and I support that. Later on broaden the indication. But in the beginning, I think it has to be a really narrow indication.

And it is such an individual thing that I really -- I was talking to someone earlier. One of the problems is you really do need like a board of

people that you present a case to who decide what is the situation here. This is a family of 3 or 4 generations of people who weighed 200 pounds. You know, why are you trying to get them to 125? It doesn't make sense. It's very complicated.

I know I am almost out of time. I want to talk about the value of the term "epidemic." That's thrown around all the time here. I hope that you understand that has an emotional value that you really have to factor out when something is an epidemic.

We're used to infectious disease epidemics and killer epidemics. This is not the same thing. It's a huge number of people who got fat, but putting the "epidemic" label on it is really a sales pitch more than anything else.

It's not to say, again, that there isn't a problem that people are getting much fatter. It's just that label that you have to be careful about, I think.

One thing also, there is talk about blood pressure today. The one study on weight loss surgery that is really long-term, the Swedish obesity study,

looked at when people did maintain their weight loss. Blood pressure initially went down, but by three years, it went back up to the baseline. Right?

So there is something else going on here with hypertension. It's not just that simple as losing weight. Maybe something has been damaged by years of obesity. I don't know. But something is going on. So we can't just say we'll resolve hypertension and associated risk factors by weight loss. It is not that clear.

I guess that's all I really had to say. I hope I'll talk to you tomorrow. And I would like to open it for any questions anybody has. I was a fat child. I can tell you about being a fat child. Anybody?

CHAIRMAN NELSON: How about if we wait to see if we have time at the end of the open public session if there are questions.

MS. McAFEE: Absolutely.

CHAIRMAN NELSON: We can address those.

MS. McAFEE: I will be here tomorrow, too. Thank you.

CHAIRMAN NELSON: Thank you for your comments.

The next presentation is by Vernon Vincent of Inamed. Did I pronounce that right?

MR. VINCENT: Yes. Thank you very much for the opportunity to speak.

My name is Vernon Vincent. I am the Director of Clinical and Technical Programs, Inamed Health Corporation. I have held this position for quite some time.

I do have a financial interest in this. My company did pay my way here. And I have been intimately involved with the field of obesity surgery, specifically the LAP-BAND, for about 15 years.

Many of you here, this team and maybe the surgeons to my right, know the LAP-BAND very well. The purpose of this presentation is to provide and introduction to the rest of the panel first to the LAP-BAND, but in the following presentations about the procedure and the data for the surgeons, perhaps an overview of just how it works and what it is and what it isn't could be beneficial.

I want to really consider that we're talking about severe obesity. This is not a cosmetic issue. We're talking about existing illness, adolescents and adults that have severe obesity or have a concurrent form of diseases that are causing disabilities and increasing their risk of mortality.

An option does exist for this. And the surgical treatment that I would like to tell you about is the LAP-BAND adjustable gastric banding system.

This is preaching to the choir, I apologize, just to set the stage. And I'll use the term "academic pediatric obesity" is continuing to increase. And we're seeing thousands and thousands of very sick young people today. Prevention would be wonderful. We should definitely work on that. We were talking today about kids that are coming now that are overweight.

So on many of your minds has to be the question of why a surgical device or a surgical procedure for adolescents for obesity. Well, I think the point I would like to make and that many of the other panel members will make is that there is an

urgent need now.

The obesity epidemic has affected children and adolescents today, 200, 300, and 400 pounds or more overweight. Serious illness and physical and psychological disabilities exist as a result of their weight. Severely obese adolescents do not lose this condition with very rare exception. And with that, they carry an increased risk of adult morbidity and mortality.

So in surgical treatment for obesity, there is a number of discussions about ideal procedure. I'm not sure that that exists. Goals include it should provide for a safe, significant, and sustained weight loss. It shouldn't kill you to have it done, but it should last a long time. It should be generated, improving a resolution and obesity-related cohort conditions, should improve psychosocial development, should not compromise nutrition or growth, should be reversible and allow for adoption of future advances in obesity therapy, should be acceptable to the patients, and it should be acceptable to the health care providers and health

care community.

In the media, obesity surgery, bariatric surgery, has become a catch phrase that is commonly misquoted. Patients that have one procedure are commonly described as having had another. And it's all lumped together.

So I would like to point out that there is more than one procedure in this bucket of obesity surgery category. Most common is the gastric bypass and widely practiced around the world and definitely most common in the United States.

Stomach stapling from many of your residencies you probably think of the VBG, vertical banded gastroplasty, that is still practiced and still done around the world; and then banding in various iterations and designs. The procedures vary according to surgical invasiveness and alteration and the morbidity and mortality risks, such as to the procedure.

The LAP-BAND adjustable gastric banding system we believe provides an alternative that satisfies many of the goals I describe previously.

It's effective. It's safe, no major change to the anatomy for its placement. It's reversible in the worst case. You can cut out, remove, leaving anatomy essentially intact.

When appropriately managed, there's no significant effect on nutrition. Normal food can be eaten, much reduced amount. And it is adjustable. This is very appealing for young women of child-bearing age or if you have acute illness that you need to have increased nutrition.

This isn't a new device. The original open adjustable silicon gastric band was first implanted experimentally in 1986. These devices are still in people, functioning today.

Laparoscopic development began in 1991 and concluded in 1993 with the first placement of a LAP-BAND laparoscopically in Belgium. Worldwide adoption has followed through systematic training and support throughout the world.

The clinical trial was conducted here in '95 to '98, with the FDA panel approval coming in June of 2001. And the label currently is very specific

you've got to be 18 years old. Approximately 180,000 procedures have been done to date worldwide.

Continuous improvement in the technique and patient management nuances, as Dr. Yustein mentioned this morning, continue to enhance outcomes that are constantly moving forward.

It's easiest to understand this device if you see one.

CHAIRMAN NELSON: I assume these procedures are not used?

MR. VINCENT: Correct. So now we watch this short animation. This video clip gives a very simplistic presentation of laparoscopic surgery. Laparoscopic surgery includes access through trocars with a scope and instruments.

Ideally this procedure is designed for and intended to be done laparoscopically. Dissection is completed around the top of the stomach in an unlocked position. Every sample you have is locked closed. In the illustration on the screen, you can see the unlocked band being threaded around the stomach and locked in its place.

The access for it is typically planted in a rectus muscle several inches, under the skin additionally in some people. And percutaneous adjustments are available at any time after placement. Typically a month or six weeks after the initial surgery would be the first opportunity for an adjustment. So it's placed in a very loose position, gradually tightened so that you have a controllable outlet.

Some people amazingly need very little restriction, and some will need considerably more. And that opportunity for variation is there. As I mentioned, pregnancy, you can completely deflate and get out of the way essentially and let the pregnancy continue briefly after losing weight.

Simple picture of the uninflated band and inflated band. All we're doing with this device is creating a neostoma, a new outlet high on the stomach, with a very small pouch so that the intake is greatly reduced and then its transition to the rest of the stomach is delayed. There is no change to the intestinal tract, no anatomical alteration, just a

delay in passage, significant reduction. So by definition, it's a pure restrictive procedure.

There are over 1,100 LAP-BAND publications and abstracts to date. I brought a few folders. I apologize. I didn't realize the size of the Committee. I brought a few folders with the recent adolescent publications. They're on the table here.

Summarizing all of the publications, international and U.S., -- there are 17 U.S. papers now -- we can expect approximately a 40 percent excess weight loss at one year, 50 percent at 2 years, and 60 percent at 3 years and beyond. Five international papers and one U.S. paper on adolescents with the LAP-BAND occur in the press.

How do the procedures compare? One very important detail with regards to adolescents or anyone having surgery is the mortality rate of the procedure.

What is the risk of the procedure? Surgery March of '04 with systematic review conducted by Australia, citing the literature available at the time, citing a tenfold difference, a one in 200 risk of death with the gastric bypass versus a one in 2,000

risk with the LAP-BAND, interesting difference if it were my child who had the surgery.

There are a few small observational studies in print. There are a couple on the JI-bypass, a procedure that is essentially gone, several on the gastric bypass, one on the VBG, as I mentioned, six on the LAP-BAND.

All of these studies report positive benefit. Weight loss is sustained. And health is improved for children. All of these procedures work.

This is a fairly challenging slide. This is the data from the six publications with varying endpoints, some reporting a percent of weight loss in terms of BMI lost. We have a couple of the authors present today for these people. You'll be hearing personally about them.

Informational point. there are other studies ongoing around the world. There is a randomized controlled clinical trial in Melbourne, Australia, LAP-BAND versus the medical therapy in Monash University, Professor Paul O'Brien, Professor John Dixon enrolling adolescents, the LAP-BAND versus

a very intense medical program.

There is also a health economics, a cost-effectiveness study funded by the government in Melbourne, and it's being run by the Melbourne University looking at ten modalities, different programs, and one surgery on it is the LAP-BAND. So these are details that a year or two it should be interesting to follow.

A small note on Inamed. Inamed Health has maintained the commitment, not only to the letter of the approval letter or FDA in an approval, that we would continue training and providing support, but it is very much our philosophy.

The LAP-BAND is provided only to surgeons qualified to give -- they are invited to a certain training program with advanced laparoscopic experience documenting animals in this program.

We spend a lot of time helping build those programs so that they, in fact, do provide follow-up and patient support. This is probably more important, definitely more important, for the adolescent opportunity than others.

Again, the surgeons that are here that are in studies with adolescents, the LAP-BAND will explain the components of those teams. We absolutely support that, and we absolutely support current indications and are not supporting or encouraging off-label use. We are supporting investigation in the clinical trial.

To summarize, the LAP-BAND system is an effective tool in the treatment of severe obesity. And these principles are applicable to the adolescent population. Lower risk of death and more serious complications than any other surgical option are embodied in the LAP-BAND procedure. Anatomy is not altered or rearranged. It's adjustable and reversible, worst case can be removed or it can be left intact.

Thank you very much for your attention. I appreciate this opportunity. Thank you.

CHAIRMAN NELSON: Thank you.

The next speaker is Joseph Skelton from the Medical College of Wisconsin.

DR. SKELTON: I have no financial interest. I am the Director of a multidisciplinary

weight management program at the Children's Hospital of Wisconsin. I am going to give you my two cents as someone who has hung up a shingle about two and a half years ago and has since seen 500 overweight children an families.

I'll make two important points in speaking, but I'll be brief. One is something that you have already heard. This problem of obesity is affecting the health of children now. I have some small data to show you from our program.

And then also children are little adults is the second big important point I want to make and echo the recommendations from the American Surgical Association that any trial or evaluation of a control group should be a large experience in dealing with children.

This is just a short abstract that we had recently presented looking at our first 284 patients that we had seen. I want to focus on -- can I go back, please?

Our children are very overweight. We are seeing children with the medical comorbidity of being

overweight. You see that the mean BMI is 35. And this is in children 2 to 18 years of age. For children with a BMI of 40, over a quarter of our children had a BMI of greater than 40, which, as you have heard before, is criteria for bariatric surgery in adults. It's actually now over 80.

And you can see just by looking at the laboratory studies this is affecting their health now, with over half of the children having elevated total cholesterol level and nearly two-thirds of the children having evidence of insulin resistance.

Even though there are a lot of people even in this room that can report more studies than this, we were very concerned with the children that we're evaluating. I can tie this to NASH. Twenty percent of our children had an elevated ALT. We ended up biopsying eight of those children. All eight had NASH with seven of those eight having fibrosis and cirrhosis. And, like I said, many people across the nation can tell you even worse stories of this problem.

The most important point I think I want to

make, in addition to these children being very ill, is these children have significant psychosocial stressors that need to be evaluated by people experienced with this problem. We looked at 58 children that had been in our program for nearly a year. And even though we did some success with the majority of our kids, we found some very interesting things.

I'm looking here at the different colored bars. It's kind of hard to pick up. But as far as report of psychological history of having a behavioral issue or a mental health issue, you were necessitating the evaluation by a mental health professional. Even though only about a quarter of our children actually had a history of it, nearly half of the parents reported having some form of psychological history. So this is very important, the concept of children when you are actually having to treat them with the family. There are significant family stressors, including mental illness, that can be a big confounder.

As far as previous weight management attempts, this was actually surprising that hardly any

of the children had been in either a formula or even an informal program, including buying over-the-counter books, diet aids, and only a tenth had made a change in weight. About a third of them had done something with the family as far as changing what they were eating.

And then their eating activity behavior, this can also be significant when you are looking at something as invasive as bariatric surgery. Children are very picky eaters. And then you even add in a very strict diet that you will put the children on after bariatric surgery that can be even more difficult.

Over half the children sneak food, eat large amounts of food, and then have high-level sedentary activity, so my second point being, hopefully you are considering issues like this and need to be with people very experienced in dealing with the overweight children and their families. And the particular mental health, behavioral health providers, not only pediatric psychologists and psychiatrists but those with a history or experience

in health psychology and hopefully in weight management.

Thank you.

CHAIRMAN NELSON: Thank you.

The next speaker is Dr. George Fielding from New York University.

DR. FIELDING: Thanks very much. And I would like to thank you for the opportunity to speak. I've got no financial relationship with industry. I've paid my own way here to give this presentation.

What I would like to do is just give a brief overview of results that I have for LAP-BAND analysis over the last six years, some of it in Australia, some of it here.

I've chosen to use the LAP-BAND in these children because of its gentle nature and its adjustability. The other aspect of this is that I was actually obese myself as a child and adult. I had the surgery seven years ago, which has given me a little bit of advantage to the take on it.

There are three phases in the results I would like to present here briefly. I did 41 bands in

adolescents in Australia since between '98 and 2004. Since coming to New York, I have done another 58 in a shorter time frame.

If you look at the data from Brisbane with a mean age of 17, it might cut off. At the time it was close to 19. The mean age in that group is 17. And you can see on the left the number of patients per year and their descending weight.

And you can see that their BMI actually does fall from a mean of 43 to a mean of 29 by 2 years. And then it pretty much stays static. And the excess weight was in the 60 percent. This is being maintained with normal follow-up.

In terms of whether this surgery actually offers a successful outcome, one of the measures of the success is how many patients lose half of their excess body weight. And in these children, 80 percent lost at least 50 percent of their excess weight for 3 years; likewise, getting the body mass index below 30, which is really a good determiner of success.

One of the issues that is always raised about surgical treatment of adolescents is that of

compliance. And I'd just like to report that children, both in Australia and here, their compliance is clearly better than adults. There are a lot of different reasons for that.

If you look at it, one way of measuring that is how often that actually turned up before. And we found that they came on average 12 times in the 2 years, which is exactly what we asked them to do. Some of them came very frequently. It really hasn't been an aspect of their management that has proved difficult.

I then came to New York about two years ago now. We had the largest surgery experience in the world, done over 4,000 LAP-BANDs between the 2 of us doing the surgery there. The key issue with the program, which I will espouse, since I started doing this quite a while ago is the dedication to long-term follow-up. It's the integral component of success with any bariatric surgery.

The second integral component is that there are multiple disciplines involved in the provision of the care. And the basic requirements are

obviously in-house nutrition and psychological back-up.

When you're dealing with adolescents, it's very important. It's great we now incorporate a pediatric surgeon into the team. We have specialized teenage psychological care at the NYU Child Study Center. So we've got the components in place for a successful team management of this problem from the tour.

We look at the -- these were done in New York, done 58, 46. This is an absolutely classic breakdown of sex difference in bariatric surgery in adults as well, 5 13-year-olds, 40 between 14 and 17, which I'm going to concentrate a little bit more on, and 13 older people, who really in many ways I think function more as adults. They are mainly Caucasian, 5 Hispanics, and 3 African Americans.

They do have comorbidities. And if you look at the breakdown, probably a fifth of the children have dyslipidemia, depression, and diabetes. Low back pain is very common and then the whole host of comorbidities that do appear in adults, including

sleep apnea, requiring CPAP. They have the whole gamut of comorbidities exactly as one would see in the adult population.

The average weight of the children who have come to New York has been nearly 300 pounds, the average BMI 47. It takes about half an hour to do this procedure. And the average length of stay is one day, but we're increasingly sending the children home on the same day as surgery. So it's not a major venture physically for the patient. And I would really stress how gentle this really is because there is no intestinal surgery at all.

Interlooping perioperative complications, all patients were discharged within 24 hours. As I said, there's an increasing use of the same day. There's no death, no pulmonary embolus, no acute reoperations. One boy came in with a perforated appendicitis a week after his band. He weighed 450 pounds. But he is in acute remission and seems to be doing this at NYU.

This is pretty hard to read from here, but basically it shows very similar data to what I found

in Brisbane, which is as time goes on, the weight loss is generated and maintained. And it will deliver somewhere between 50 and 60 percent excess weight loss, which can be maintained.

One of the things we have looked at in the children who have got longer than a year follow-up -- and this is only a small number so far, but you can see that their nutritional panel is on for vitamin B-12, which we maintain during our series.

Just for a minute, to look at the 14 to 17-year-olds, which I think are the main emphasis of this whole panel, the overall data is the same as I've shown. It's a quick operation, a short length of stay. It's mainly being done in Caucasians, but there is an increasing number of Hispanics and African Americans. This is the breakdown of age, 19 17-year-olds, 11 16, 7 15, and so on.

We have now performed the surgery in this age group in 15 children in our FDA study and 25 prior to initiation of the FDA study. The weight loss has been great. There have been a couple of complications. The well-known complication of

LAP-BAND is a slipped band and where the stomach comes up through the band, gets stuck, and it generates reflux. And so they require reoperation. We have had two of those. I mentioned the boy who had the perforated appendix.

I would just like to spend a short time about reflux because this has been a discussion that has been very prevalent in the adult population. For the 58 children complaining of reflux after the surgery, typically in the evening after an evening meal, they had diagnostic esophagrams, which showed two of them had slips and two of them basically had hiatal hernias.

The hiatal hernias were repaired, the band hadn't slipped, and the other two bands had slipped. These were all done as day cases. All four resolved all their symptoms and had ongoing weight loss after resolution of that complication.

We have had an FDA-approved study now for about the last five months. It's an ongoing study for five years. Initially it was 50 children. And it's involved psychological assessment repeatedly, yearly

bone scans, and then ongoing observation of weight loss and symptomatology for a five-year period.

We're thrilled to have gotten this experience, and we're recruiting patients quite rapidly. As I said, we've recruited 23 already in about the last 5 months.

This is just a breakdown of that data, now 23. And 18 have had surgery. It's very similar to the previous data I have showed you.

This just shows the pre-op weight is about the same. It's about 300 pounds, BMI 47. The operation is half an hour. And they're all home within 24 hours.

You can see here 37 percent of them had diabetes or an off glucose tolerance test, likewise with back pain and cholesterol and depression. These children are not well, and they have all the diseases that their parents and grandparents have related to their weight.

The lipid panel has been maintained in a short follow-up so far. Likewise, the nutritional panel has been maintained, the early follow-up on the

FDA children. And the weight loss has been nice and steady with 17 percent weight loss at 3 months.

So, in conclusion, I would like to just offer a feeling that this surgery is safe in adolescents. And it does produce an effective weight loss. And it's best performed, as many have said, by obtaining a lot of experience in the surgery and in the multidisciplinary studies.

Thank you.

CHAIRMAN NELSON: Thank you.

The next speaker is Jeffrey Zitman, Columbia University.

DR. ZITMAN: Thank you.

I have no financial connection or relationship with the Committee or the maker as well. I actually had not prepared any slide show, which I guess is both good and bad, but I do have just a couple of comments.

I won't repeat everything that Dr. Fielding said about the Band, but what I would like to do is just take a couple of minutes to give you our perspective as to how we put our program together.

Our program is really in the birthing stage as we speak.

We decided a little more than a year ago, "we" being a meeting of the pediatricians, pediatric endocrinologists, pediatric gastroenterologists, nurse-practitioners, and psychiatrists, as well as bringing in the adult bariatric surgeons, that there really was a role for adolescent bariatric surgery at our institution.

We looked at what was available in terms of surgery. We decided that a Lab-Band was the better choice, as opposed to bypass, simply because of the reasons that Dr. Fielding just went through.

And so in putting together our team, we researched the literature that was there in both the adult and population, researched the problem. And we developed a protocol, which we applied for and received permission from the FDA to perform, which in many ways mirrors what George just showed you.

Our study involved patients who are teenagers, 14 to 17. We were approved for 15 patients as a pilot study, after which we were invited to apply

for an additional 50 patients.

Because of his study, in addition, we are also going to be looking at excess weight loss and changes in BMI. We are also going to be looking at a variety of basic metabolic scientific issues as to what goes on with these patients. So perhaps I can give you some additional insight as to what the actual metabolic changes are. And that's where we are at this point.

We have not actually opened our program in terms of advertising. It was just through word of mouth. In the first 2 weeks being in the same city as Dr. Fielding, we had 27 phone calls inquiring about the program from as far away as Tennessee and Indiana.

So I stand here simply to say I think there is a clear need for surgical intervention in some of these patients and our job as pediatric surgeons and pediatric practitioners involved in teams who are working with this is to make sure that these patients are screened appropriately and get the best care.

I would emphasize that in our program, we

work very closely with the adult bariatric surgeons. We are a children's hospital, and we're part of a large complex. Our bariatric surgeons are part of our team so that when they turn 19, 20, and 21, that care will be continued.

Thank you.

CHAIRMAN NELSON: Thank you.

Let me ask if there is anyone else who would like to speak during the open public session. Could you introduce yourself, say where you're from, and declare any conflicts before getting into what you have to say?

MR. DOWNEY: Yes, I will. Thank you.

My name is Morgan Downey. And I am the Executive Director of the American Obesity Association. I have a number of conflicts of interest. Our association gets support from the weight loss industry in general, including commercial weight loss programs, like Weight Watchers and Jenny Craig; pharmaceutical industry; biotechs; and a few companies in the surgical area, including Inamed, for one.

I just wanted to touch on a couple of observations from the morning's presentations. I would like to do this in context, though. We opened our office here about eight years ago. I would say it's pretty steady that we get maybe four or five calls or letters or e-mails a day from parents who are frantic to find some kind of service, good, appropriate service, for their children who are suffering with obesity.

Most times they have exhausted diet and exercise programs. They are very frustrated that the pediatricians and internists that they deal with oftentimes just won't see an obese adolescent child and if they do don't really have any tools or counseling to give them in terms of weight loss.

I think it was Dr. Yustein this morning who presented a very good slide on the spectrum of interventions from device and from diet and exercise pharmacology than this gap in surgery, but that's not really a gap. That gap is being filled, but it's being filled outside of the medical model. That is being filled by drugs and devices, products and

services that are largely unregulated, frequently dangerous, and often fraudulently sold and represented.

And the FDA in terms of their enforcement on dietary supplements and the FTC in terms of enforcement of deceptive advertising practices have documented this very highly. So that is not really a gap. That is where people are going in a really desperate effort to find some consistency.

I would also like to say that we released last week a survey that we did in connection with Inamed where we interviewed, the company interviewed, adults with morbid obesity. And we looked at kind of two scales. One was the degree of intimacy with their sexual partner. And the other one was their experience with job discrimination.

In both categories, as you might expect, there was a very, very high level of poor relations with their intimate partners and a very high level of experience with what they felt to be employment discrimination. That, unfortunately, I think gets conveyed very quickly to children and adolescents who

are overweight of what they have to look forward to.

And while we might be very concerned about glucose levels and blood pressure and the other important health indicators, I don't think those psychosocial problems that come with morbid obesity should at all be underrated here in terms of the importance.

I will just summarize by saying we have worked for several years on the drug side of the FDA to improve the guidances they have for approval of weight loss drugs. And it's been a frustrating problem because it has gone on for so long without resolution.

And I would just encourage the Committee here that we need strong, well-controlled, rigorous studies of interventions for children and adolescents. And time is of the essence. This is a real crisis. And we need to move quickly to develop those and get those out to the research community.

Thank you.

CHAIRMAN NELSON: Thank you.

Let me ask if there is anyone else who

would like to have an opportunity to speak during the open public session. And if you could introduce yourself, where you're from, and any conflicts before launching?

DR. BROOKS: My name is Dr. Jeffrey Brooks. I'm an adult gastroenterologist and Chairman of Stats Medical. I do have an interest in one of the companies involved in the program. We are currently testing a second generation balloon. So I do have a monetary interest in this.

I just wanted to point out to the Committee because it seems like everyone is talking about LAP-BAND and for good reason -- it's a terrific thing. But I would like you to also think about what Dr. Yustein said today, that there are non-permanent, nonsurgical means that are coming around the pike. And I would like you to keep that in mind when you make your decisions on the four questions tomorrow.

CHAIRMAN NELSON: Thank you.

Anyone else who is interested in speaking during the open public session?

(No response.)

CHAIRMAN NELSON: Seeing none and hearing none, this brings a close to our open public session. And, barring any objections, we can move to our next presentation a little bit early. Jeff?

DR. BOTKIN: Are you going to entertain questions for any of the public presenters?

CHAIRMAN NELSON: I wasn't planning to unless you had a question you think you would like to ask.

DR. BOTKIN: I do.

(Laughter.)

CHAIRMAN NELSON: Okay. Go ahead.

DR. BOTKIN: It's a question for Dr. Fielding. And I wonder whether you could just briefly describe what other components you had to your program in the way of dietary management, exercise, psychological counseling, et cetera, and whether you can ascribe any of the presented benefits to those other components, as opposed to --

DR. FIELDING: Sure. The first thing is just to spend a minute on why one thinks the LAP-BAND works. My own feeling is it works by stopping people

being hungry. Above all else, that's what it does. And that's more important than the punitive, restrictive component.

You can actually render someone who has been starving their entire life actually not interested in food. It then gives them a chance to set them up to be able to then eat small amounts of food without strength. That's the endpoint.

To get from there to the adolescents, I believe it needs to be the kids' idea. The number one thing that I have found that has led to success is that the child has gone to the parent and said, "Mom, I want to do this. I've read about it. I've seen it on TV. I've seen it on the internet," when the child goes to the parent and the parent then goes looking.

So in my sense from the people we've seen so far is that the kids are very committed to doing this. So then they come along. And in our population, they've all done everything. They've all been to Weight Watchers. They've all had dietary resources. A lot of them wore the fat hat for every holiday they've ever had. So these are very

experienced people in the world of obesity. And they might be only 14, but they spent most of their life doing that.

So when they come to see us, then that's the first thing we find out, how have you really tried to deal with this, yourself, as a family unit, whatever? So they get a sort of evaluation.

And, two, with only one exception since I've been in New York, the people at the Child Study Center have said, "This kid is ready to do this" with one exception.

We then have a nutritionist that we have on board as part of our team. She sees every patient. And she assesses them preoperatively. And then I see them, and we talk about it all.

The key second ingredient of the work, actually, we're doing is seeing them afterwards. The one thing I know, there are people who are very up in odds about how they feel about this. Are these kids going to be difficult to look after?

But honestly this is a very different population than, say, someone who is in a transplant

program or somebody who has got cystic fibrosis or chronic disease. These kids if you can make them fit, they become well. They evolve into a well person. So they want that so badly. They have been trying all of their life to do it.

And, finally, here is a tool they can use. And they can smell the change. They know what is going to happen. And so they really comply. They come to visits. They come to get their adjustments.

They whine to me occasionally. They talk about their food and all that. I chat with them about what it's like being fat, and I chat with them about peer pressure. But it's not usually a formal "You must do this and you must do that."

It's just a kind feeling of being looked after, being made not hungry. I don't know if any of you have ever been fat, but the hardest thing about being fat, the reason they're fat is they're hungry. And so this tool gets rid of that. And it's as gentle as anything.

But it's one of the reasons, one of the mechanisms of "You have to do it this way. You must

attend 35,000 sessions. And you must walk 50,000 steps." All of that continues because most kids want to be part of the peer group. Most kids want to play ball. Most kids want to go to dances. It's just when you're a human being, you can't.

And so the natural evolution is to say, well, they consume more life than they do. And that's why they're so compliant, which is different than any other form of chronic illness that you have to manage. That's my take on it.

CHAIRMAN NELSON: There seem to be a lot of questions. And I'll point out we have eight minutes for all of them. So I'll go to Dr. Yanovski and then come over this way.

DR. YANOVSKI: Really, the crux for many of us is subject selection, which is can you tell us about the characteristics of your patients? Are they paying for this procedure themselves? How much are they paying? Are you rejecting anyone? And on what basis?

DR. FIELDING: The main reason for us, the hardest, is it's awful to have to reject someone who

really wants this. But if they just don't get it, I won't give them the surgery.

I can tell within five minutes whether they get what this is about. They get that it's going to involve a change in the way they live and change in what they eat, that they can't eat the same way as all their buddies so, and that it's an evolution for them or if I think they are being coerced at all by their parents against their will, then that's the time to say, "Look, no one in this room is ready to do this yet. Go back to the Child Study Center and spend time with them. Think about it some more." That's what I tell them.

DR. YANOVSKI: So it sounds like you only take the most willing of the willing.

DR. FIELDING: Right.

DR. YANOVSKI: And then there was one other question. So the socioeconomic status --

DR. FIELDING: Well, the socioeconomic status that I have dealt with so far has been the upper half, rather than the lower half, because they're the ones who have insurance, number one. And

that's who come initially.

Surprisingly, quite a few insurance companies have covered this in adolescents. Particularly the ones that cover it in adults cover it, of course. We have a very good relationship in Manhattan with the insurance companies for the LAP-BAND.

Once we have set up where is the aid of the FDA, that's out the window simply with insurance companies. And so we have been blessed in a patient of mine who is very wealthy who has helped to fund children who can't pay for it.

And so the last five or ten, the last five or ten of these children, are poor African American and Hispanic kids. And so we're starting to get a mix of what is going on in the community. And we have now reached out to the big Harlem children's zone in New York. We're going to be getting children to sit down with us.

And so what I hope to go over in time is does it work in really rich kids, does it work in really poor kids, and how does it all work. So to

date, it has been what you would expect. Ours are really intelligent kids. These kids really are suffering. They're bright, and they're the ones going to their moms and dads, saying, "I want to do this."

CHAIRMAN NELSON: All right. There were some hands to my right. Are they still up? Bob?

MEMBER NEWMAN: Your follow-up looked like it stepped off fairly quickly by 12 months. Is that because some of the kids are just not 12 months out from the surgery?

DR. FIELDING: No. That's what we've been doing so far in Manhattan. What we do is we see them monthly to two-monthly depending on where they live. The adjustment schedule, typically we make three or four adjustments in the first year. Then we keep them coming for the first two years. And then afterwards, we drop it back to three-month intervals.

MEMBER NEWMAN: Have either children in New York or in Brisbane undergone pregnancies after this? What has been your experience with that?

DR. FIELDING: One girl at Brisbane got pregnant at the age of 15, had the baby, and kept

doing follow-up. One of the really great things about this band is that you can manage your pregnant with the band inflated so they don't gain weight or you can deflate it or whatever.

And I've actually published on this one about 50 women who have had babies with Bands who had previously had babies showing a statistical improvement in theory and the same body weight and attributes of the children.

The biggest difference is you just don't get the follow-up deficiency that you get with the bypass. So the incidence of some of that sort of stuff is much less.

CHAIRMAN NELSON: Thank you.

So we'll now transition to our regular presentations and call the question period after the open public comment period to a close. And the presentation is from Dr. David Wendler on subject selection and assent in pediatric research.

DR. WENDLER: Thank you.

ASSENT IN PEDIATRIC RESEARCH

DR. WENDLER: I was asked to speak about a

couple of things in a short time. So, rather than try to give much in-depth analysis about any of this, what I thought I would do instead -- hopefully this will be helpful to the group -- was to try to present a framework for thinking about both of these issues. I'm going to focus on subject selection and assent in particular, just give a framework for thinking about both of them. And I won't try and answer too many questions. Then if people want to go into more depth, we can do that during the questions if we have time.

Okay. So, just to let you know, I work for the NIH, but I make up everything that I say. And the people who give me money don't approve of what I say, and they typically don't agree with what I say.

Okay. So, first of all, quickly on subject selection, the way that I think about this is to think about framework. I'm trained as a philosopher. So in the trying to think about framework, we first ask ourselves, well, what are the goals of the project? What is it that you are trying to accomplish? Try to think about and get clear in your head what the goals are and think about what

happened and ways to achieve those goals.

So at least when I sit down and scratch my head and try to think about the goals of subject selection, this is basically what I come up with, that you want to distribute benefits and burdens fairly and assure the value of the research, validity of the research, minimize risks, risks to both individual subjects and also aggregate subject support as well, maximize the benefits and protect.

So I think that's basically the framework. And for this part, I'll just give a quick point on each one of these goals and then go on to assent.

So one way to think about this, as people in this room know, there has been a big shift in the psychology of research and research ethics. Twenty years ago, everybody talked about protection, minimizing risks, protecting people from risks. While those things are still obviously important, there's a lot more emphasis these days on ensuring access, making sure people have fair access to participation in clinical research.

So a quote from about ten years ago from

Levine, "People are clamoring for access to clinical trials. And Fannie Mae and others like them are owed such as a matter of justice."

So if you think about it from this perspective, the way I think about this is to start out very simply assuming that everybody in the world is eligible for your study and then exclude populations or individuals from that set only when you have a good reason to exclude them. That's one way to ensure that you're resulting inclusions and exclusions are fair.

So a couple of obvious reasons why you might exclude people, the first one is you're doing research and trying to do science and you're trying to learn something. So the first thing you should do is you should exclude people who can't help you answer the question that you're trying to answer. So this puts forth the value in the study, obviously simple things.

If they don't have the disease that you're studying, you can't enroll them and also things about validity. And these are questions that get tough for

researchers. So somebody who doesn't come back to the clinic every time, they're supposed to come back once a week, and they miss a day, they miss two visits.

When does a helpful subject become one who is endangering the validity of the study and becomes in practice one of the harder questions with respect to subject selection.

At least initially you should make sure that these are people are in position, whether or not they're going to achieve that, but at least the physicians that carry out the demands of the study.

A simple example in terms of the value, at least typically studies about different kinds of cancer trials exclude people with brain tumors who get drugs are not able always to determine whether the symptoms are a result of the tumors or a result of the drug. So sometimes you have to exclude people or that reason.

This is an example I was just talking about. You also have a set number of clinic visits. We'll have to come back to it. You're not going to be able to do good science if you can't make your clinic

visits.

Physical risks. There might be physical risks. Obvious cases. One of the things I'll just mention briefly we can talk about more if people are interested, I think typically when people talk about minimizing risks with respect to subject selection, they think about it with respect to the risks to individual subjects. They think about minimizing risks to this person, minimizing the risks to that person.

I think that's obviously important. I think that leaves out an important consideration, namely minimizing the aggregate risks of a research study. You do that by choosing some subjects over other subjects. And I think that becomes a valid reason for exclusion, although some people worry about that as discriminatory.

So maximizing benefits, I sat on an IRB when they were first starting to roll out protease inhibitors. And we had a big debate about who we were going to allow in these initial studies. Should we allow people with high CD4 counts who tended to be

relatively healthy or should we enroll people with lower CD4 counts who needed the access to the drugs and were sicker and had less time to get them, which brings up one of my key points and I think is the hardest to get these goals? But the problem is that what we find out when we start thinking about individual cases is that these goals aren't always consistent. You can minimize risks by choosing one population. You can maximize value by choosing another population.

Protecting the vulnerable. You guys are talking about kids. In one sense, all of them are vulnerable. But there are different levels of vulnerability depending upon the status of the kids, kids who are very young, kids who are particularly sick.

As some people know, there's been a big debate lately about research on wards of the state. Some of that was going on in the last 15 to 20 years. And depending upon who the guardians are for the wards of the state, I think I would consider them in most cases to be more vulnerable than kids who have

attached families.

So this is a point that I was making, that in a lot of cases these different goals come into conflict. So you might want to say let's enroll older kids because they understand more and more and are able to make their own decisions, but at least in some cases they face greater risks than little kids do. And so you're faced with balancing off minimizing the risks versus maximizing their understanding.

Another example of this is, as people know, that there are some regulations that vary the level of risk to which you can expose a kid depending upon whether or not the kid has the disease that you're studying. And one of the justifications that some people who agree with this have offered is that, well, even if there is no prospective direct benefit in the study in front of you, for sick kids, there is more likely a benefit from the result of the studies in the future. You might think that's important, but then, on the other hand, if they are sick, they may be more vulnerable than healthy kids, so another kind of concept you have.

Unfortunately, although I am a philosopher, I like to come up with tricky sorts of concepts. In this case I have never been able to figure one out. So you fall back on relatively unhealthy metaphors, like balancing competing goals. I think you just have to look at the individual cases and see what's more important.

So that is sort of the framework for thinking about subject selection. And I will try to give a simple sort of framework for thinking about assets in pediatric research.

So as people here know there are a few exceptions, but in most cases kids are enrolled in research, it doesn't offer any compensating potential benefit. They have to have the permission of their legal guardians. It could be their parent.

Also, most guidelines -- this is true of the U.S. It's also true of most guidelines that I have been able to find around the world, also require what is called the assent of what is called the U.S. vote, the affirmative agreement of children. And you can here italicized "who are capable of providing."

That is one of the big things to date that I'll come back to in just a minute.

So there is a lot that we need to know. I'm going to focus on capacity to give consent, but I think there are a lot of important issues that we know very little about in this area. And we need a lot more research.

One of them is just the appropriate process. If you've decided you're going to get assent to a particular study, what is the right way to do it? One of the obvious questions is whether or not you salute the assent of the kids in conjunction with the parents.

There are some people who think that is the right way to do it, the families or units. It's a part of families, and that proper respect applies given how these decisions are made as a group.

Other people worry that kids who are in that context are not going to feel free to say they do and they don't want to be in research. And that's a reason to get their essence separately.

I'll just give you one quick little bit of

data. Sorry this doesn't show up very well here. This is just a study that was published very recently from a group out of Penn, American Journal of Bioethics. They took a bunch of kids who had come into emergency rooms and they were asking them to be part of research. You can't see the bottom. It gives you a response rate. Seventy-five percent of the kids were 11 to 19. The mean age was just about 14.

Most of them are African American males because this was a study of violence. Kids were brought into the ER who had been injured as a result of violence in New York City.

One of the things they did was they asked kids at the end whether or not they felt that it was their decision to enroll in the research or not. And there were two groups. There were kids who had a family member in the room with them at the time they were asked to give assent, and there were kids who were alone in the room. And you see pretty clear differences here.

So when there is a family member in the room, 17 of the kids said it's your choice, but 10 of

them said maybe it was or that it wasn't. When they were alone, almost every single one of them said that it was their choice.

Here's at least some suggestion for the not surprising fact that maybe when kids are in the room with the family members, they don't feel necessarily comfortable to make their own decisions.

Now, one of the things that I think is just a slight caveat on that, I think a reasonable question about the extent to which why we're asking kids to make their own decisions, one of the interesting pieces of data I think in this study was that there are 16 participants who said that it was not or may have not been their choice to participate.

They then asked those kids whether or not they were glad they were participating. Almost every single one said that they were. Fourteen of the 16 said that it wasn't their choice, but they were glad they had been in the study as well. Two of them said they may have been glad.

So you get some sense, one, about the pressure kids are exerting, having exerted on them,

but maybe sometimes just the pressure that's being exerted is steering the kids in the right direction.

Another thing with respect to the process, I think that in research ethics, we've gotten so focused on consent forms and, by implication, assent forms that I think one of the mistakes that investigators more often in IRBs make is that they conflate giving kids information with obtaining their assents. And one implication is that what often happens is in studies where they're not getting assent, the kid doesn't get information, assent to be provided as part of a consent form or part of an assent form.

And I think almost unconsciously sometimes it ends up when you're waiving the requirement for us and kids aren't getting the information, there's no form. People don't have any other way of getting information to them.

I think that's a big mistake. I think the reason why you give information and the reason why you ask them to make their own decisions are very different and shouldn't be run together.

Another thing that is not in the federal regulations surprisingly but it is in some other regulations is the notion of dissent. That's distinct from assent. So there are some regulations that happen. I just gave an example here from -- we were in Tanzania last year discussing some people with this.

So Tanzanian regulations say the researchers must recognize when a child is very upset by a procedure and accept that as genuine dissent from their being involved.

Now, I suspect, though, somebody else knows better than I do why this isn't a U.S. regulation. One suspicion is that what was going on. People thought, "Well, if you have an assent requirement, then you don't need a dissent requirement." Assent is required. Then dissent is an objection. So it's not assent.

The problem is that it doesn't seem to provide sufficient protection when the asset requirement is waived. At least some people, including myself, think there are good reasons to

respect dissent, even when you don't require assent. To do that, you need a separate requirement, which is in the U.S. federal regulations.

But from what I know, I think respecting dissent is important, but I think it is important also to assess it. I don't think that requiring dissent means that you knock a kid out of a study the first time they get a little upset, they get nervous, or they cry.

I think the first move is to assess, try to address and remove the source of distress. Sometimes just stopping for a minute, letting a kid take a break, letting a kid decide when they're going to have a procedure can make a big difference. I think that ongoing more than minimal stress is a reason to take kids out of research, even when they're not capable of providing assent.

A topic I would suggest at the beginning, I think there is a moderate debate, an interesting debate, going on about this now, which is the question of which kids are capable of assent. As I mentioned in the beginning, the U.S. regulations, like most

others, say you've got to get the assent of kids if they're capable of giving assent. Then there's very little guidelines for either investigators for IRBs in terms of what constitutes capacity to give assent.

So here are the U.S. regulations. They say in making this determination, you should look at the age, maturity, and psychological state of the children, obviously not very helpful. What about the age? What about the maturity? What about the psychological state our investigators supposed to be looking at?

So there is more debate going on in this recently. Surprisingly, there hasn't been that much, but in the last couple of years, there has been a fair amount. This is my attempt to try to cull out the various arguments that people have been making.

So I think in order to figure out what the right age is for assent to figure out the point at which children are capable of giving assent, you've got to ask fundamental, conceptual, theoretical, moral questions about why is it that we're asking for the assent of some kids but not other kids. We need to

ask that fundamental question before you can figure out which kids are capable and which kids aren't capable of giving assent.

I think there are a couple of arguments, bases for assents. So here are a couple of them. I'll just go through these very quickly. I'll tell you my preferred one without arguing for it. And then we can discuss it if people want to.

So a lot of people that I talk to on this just say it's respectful. In order to put a kid in research, it's respectful to ask their decision. Other people talk about respect for families. There's this rule of sevens, which goes back at least 1,000 years, which I will talk to briefly.

The National Commission talked about two things: respect for what they called developing autonomy, respect for ability to understand. I don't think any of those have been arguments for basis of assent, ability to make their own decisions, which, although I think it seems like the obvious right, I think it's probably the right one.

So, first, respect for children, I think

this is a powerful ones for IRBs, for investigators, for parents. And the argument is basically that getting people and allowing people to make their own decisions is central to respecting that.

Then the problem with this argument is just that respect as a general ethical requirement doesn't have a lot of content. I think what respect tells you is that you should treat people in the way they deserve to be treated. And that just begs the question about the age at which proper treatment of kids involves asking them for their assent. I don't think it gets you very far.

Another one is respect for the family unit. People who focus on this I think draw different conclusions. One conclusion you could draw is kids as long as they are a part of families have parents, parents made decisions for them. It's not up to the kids. It should be up to the parents. I think that's one way to look at it.

Another way to look at it is to say, well, families have different processes. Maybe what we should do is we should figure out what the average

does, what a typical family does or maybe what we should do, we should let parents do it in whatever way they do.

So, one, I think it's not clear to me what the implications of this are. Secondly, the fact that families do it one way or another way isn't clear to me as a compelling argument that that is the way we should do it in the research projects.

Rule of sevens I mentioned briefly goes back a long time. I think I've seen some people cite this. And I think people who cite it actually cite it inaccurately.

If you look back through history, what the rule of sevens says, it comes with a legal doctrine which says up until about the age of seven, kids can't be held legally responsible. So that if they commit a crime, you can't put somebody who is under seven in jail. They're not responsible for what they do. From 7 to 14, the assumption is they are not rational, they are not responsible, not able to make their own decisions. It's not until 14 that the presumption gets to their being rational.

For some reason, people seem to conclude from this that the age of seven is ripe, but the way I understand, if you went with the rule of sevens, I don't know that there is a reason to do it, but if you did it, it seems like 14 is the right one.

I was giving this talk a year ago in Cairo. Somebody at the end told me that a lot of the sayings of Mohammed about the way you treat kids actually tracks this breakdown of 7 and 14. So if anybody is an historian and wants to track back, you can find out about it.

The National Commission made two arguments when they started giving suggestions and recommendations that ended up being a basis for the U.S. federal regulations. The first one was when they called respect for developing autonomy.

So the idea here is that as kids get older, they start being able to make certain decisions for themselves. They get better at this. And the assumption according to the National Commission was that around seven is a time at which you should start respecting this developing autonomy by giving kids

their own decisions.

I don't see why seven is the right age, but, again, all of these are going to be caricatures of these views. So anybody who holds these views, I apologize I'm not doing justice to any of them. I'm just going to get through them right now.

Another one that the National Commission gave was in terms of ability to understand. They commissioned a couple of child psychologists to do some studies on when kids understand what. And what they found out is that by about the age of seven, kids can understand certain aspects of the research participation. Not surprisingly, for some reason, the National Commission concluded from that that that was the age at which you get kids' assent.

The problem is I don't see any special reason why the information that kids learn at seven -- if you look at the data, there are lots of things kids can understand before seven. Three-year-olds know that needles hurt. They know what it is to stay overnight someplace. And most of the data suggest that seven to nine-year-olds have a very poor

understanding of long-term risks. So it's again unclear why the break hits at age seven.

This is just a brief summary of my own literature, not anybody else's. I think that the only compelling arguments I can think for having kids make decisions, one is what is standardly called the biomedics literature. The other is nonmedical.

You don't want to hurt kids. I think the way that you incorporate that requirement isn't by asset. I think it's by the assent requirement that I mentioned earlier. If the research is causing kids serious distress, they should plan on taking them out.

But I don't think that's a reason to get the prospective assent to the research. The only good reason I can come up with for doing that is that the simple standards are bread and butter respect for autonomy, which suggests that that is the basis that you don't start getting assent from kids until they are able to make these decisions.

So based on that conceptual analysis, I went through the literature and tried to figure out what that age might be. There is very little data.

There's a little bit that has been done. The literature that exists right now in my reading suggests that at some time between about 12-15, obviously with a great exception, -- some kids don't get it by 15, there are really smart kids who get it before 12 -- sometime in that age is when kids are able to make these decisions for themselves.

That's it.

CHAIRMAN NELSON: Thank you.

So let's open up for questions and discussion. Over to Dr. Kral.

COMMITTEE QUESTIONS OF CLARIFICATION FOR SPEAKER

DR. KRAL: The way you pose the problems here, it begs the question whether there should be some kind of testing of the kid to decide whether they on the Vineland scale, for example, have a social intelligence or I didn't want to use the word "intelligence" testing.

DR. WENDLER: Right. Yes. I think that is a great question. So one of the responses that's a perfectly right response to this talk, you might say,

"Okay. Your argument is that you require assent to the point at which the kids are able to make decisions for themselves. Kids get to that point at varying ages. So isn't the implication of your view what we should do is we should do individual testing for every single kid? You're at the point at which they are able to make these decisions, require the consent of those kids but not of the other ones."

I don't think that's a crazy way to go. It's not the very that I nurse for a couple of reasons. One, as far as I know, no one has yet come up with such an instrument that's really going to work, research-specific. This is the problem as people are saying now. The buzz word is that consent and assent are task-specific. So the fact that you can understand one study doesn't mean you are going to be able to understand another study.

The implication of that is that although general kinds of tests may be helpful for knocking out the extremes, they are not going to be very good gauges of which kids really can understand this study versus that study.

So these are individualized tests people are trying to work on. None of them are very good right now. They take a lot of time. My view basically is that you have a dilemma here. You could put your resources in towards testing every kid or not.

My view would be if you didn't have a dissent requirement, so if you were going to say that kids who can't pass this test, we're not going to pay attention to what they say at all, then I think you have a really strong reason to assess every individual kid.

But I think if you have a dissent requirement in place, then the analysis looks very different. With a dissent requirement in place, I think what you basically then do is what I think you should do is pick an age toward the upward end of the range, so 14 or 15. I think 14 is probably the right age. You are going to miss a couple of kids. There are going to be some kids who can really understand and they're not respecting it. I think that would be a big deal if you're not paying attention to what they

say at all. But as long as you have assent requirements in place, all they have to then do is start objecting or asking questions. And you stop at that point. And, in effect, by default, they end up getting respected.

So I think that sticking with the upper as a general default and then having a dissent requirement in place is the way to go. Something could come up. I have actually argued this in adult research that we're really serious about informed consent, we should try to develop instruments for assessing every single person. In adult literature, we have estimated that probably between 30 to 35 percent of people don't understand key elements of the research and they participate. That would worry all of us.

I think one way to do it is to try to develop really simple tests. I don't think they're there yet, but I think there is a possibility of doing that. And I think if you came up with those instructions, we should use them.

CHAIRMAN NELSON: Dr. Champagne?

DR. CHAMPAGNE: The study that you had of the Cohn study of the kids in the ER, these are randomized for whether htye were asked with a parent in the room or without a family member in the room versus whether they had a family member to be in the room with them?

DR. WENDLER: My understanding is it wasn't randomized. It's just as a default as the kids came in. Some of them did, and some of them didn't.

In fact, I don't know if you could use -- I probably went too fast for you to see the numbers. But the numbers don't even fully add up. They had an n of 70, but my --

DR. CHAMPAGNE: Twenty-seven in each group.

DR. WENDLER: Yes. It looks as though they didn't come around to thinking about this question until they had done the first bunch of kids. That's only 54 that they made this assessment in.

So one thing to say about that is that it's, at most, very, very preliminary data. I think it is interesting data for these purposes, but it's

not definitive at all.

DR. CHAMPAGNE: I guess it just concerns me. I think kids who don't have other family around them to make decisions, if you force them to make decisions, they will make decisions. They may not make the best decisions.

So I think when we're talking about things where you have family involved, I mean, you're looking at very different things there, I think. So I think whether they have a parent in the room with them versus whether they have an arret available to help them make those dieticians is different cohorts.

DR. WENDLER: And you say whether randomized, you've got to believe that kids who show up to the ER with the parent versus kids who don't are very different kids who have very different sorts of lives. So the fact that they have answered differently isn't surprising at all. I think it's absolutely --

CHAIRMAN NELSON: Dr. Fost?

DR. FOST: Your last slide suggested that children in general over 12 to 15 are capable of

understanding things well enough. So with regard to our task, let's say we have a 13/14-year-old child of normal developmental maturity who has got severe obesity who is at high risk for a comorbidity soon or later, diabetes and so on, and there is a trial going on which his parents want him to be in, he doesn't want to be in.

Now, normally when we have children with life-threatening diseases, Hodgkin's disease, leukemia, and so on, and they don't want to receive arduous treatments, you say, "Shut up," and they get pity. And courts will generally order treatment over a child's objections.

And that is, what is your view of what the guidance should be with regard to obesity and clinical trials?

DR. WENDLER: That's a great question. I like the pediatricians shut out there. I think on this point -- and I disagree with the regulations in a lot of cases, but I think on this point they have got it pretty much right.

I mean, I think the crucial question you

first have to ask yourself is, one, is being in this trial offering some very important potential medical benefit to the kids, yes or no? If the answer is no, that's important. Secondly, if it is, is that potential medical benefit available outside of the research context? And if it is, then I think that's obviously more reason why you should respect your assent and not try to force kids into this study.

The hard cases are cases where -- we'll take some of these studies. Let's imagine that they look really good. So do some clinical trials on it. We think there is very important professional medical benefit.

Can you imagine cases where you wouldn't be available outside of the research context?

DR. FOST: Suppose it is. The child just doesn't want any kind of surgery.

DR. WENDLER: Suppose it is available? Well, I mean, for the research efforts, I think it's easy. I really think that the research adds an important additional ethical concern. I think that we should try very, very hard not to force kids to be in

research studies. I think there are good reasons for that, not only for the kids but for the people who are doing the research, the general public.

So my first response would be what you should do is you should put that kid into a research trial. Then you should take them to the clinic, and you should have some very good, astute pediatrician try to work with them and try to get them to do it. Maybe if not, you force them into it. But I think you can.

Once the kid is that age and they understand, I think my suggestion is not of the researchers, the study, not in a research context, do it purely on clinical grounds. At least then everybody can feel confident that if you're forcing this kid, you're doing it for what everybody believes is their interest.

CHAIRMAN NELSON: Before going to Jack, practically speaking, in some settings, you need a willing adolescent, even if it's a treatment that the parent says ought to be done. So you end up, for pragmatic reasons and ethical reasons, in sort of the

same position as to whether you would honor assent or not.

And one question, which you don't have to answer now, would be given the previous presentation about the willing participant and it's got to be the kids' idea whether efficacy is going to track assent. This is a question that we may discuss at length tomorrow, which would be a pragmatic resolution to how you would deal with this particular conflict.

I believe it is a question. It sort of goes to Dr. Yanovski.

DR. YANOVSKI: So as someone who obtains consent and seeks assent a lot in adolescents, in younger children, it seems to me that we have to be very careful when we talk about obesity therapies that we differentiate them from therapy for cancers that are going to kill people in the next three to six months because they're not in general going to cause mortality in the short term; rather, in the long term.

Because of that, most, almost all, of the adolescents or even younger children who are suffering even quite severe complications of weight will get to

be at the age of consent before they would reach a point where any of the surgeons in this room would choose not to treat them.

And I think it's very important to realize that we must respect the autonomy and potential autonomy of those subjects in a way that may not be certainly appropriate for conditions that are lethal in the short term.

DR. WENDLER: Yes. I think that is a really important point. So, one, you could postpone in a way you can't with other conditions. And I think, to go back to Norm's question, I think it makes the question of whether this is an important medical benefit to proffer the decision was make because wasn't that applicant A versus next month, next year?

CHAIRMAN NELSON: Dr. Gorman?

MEMBER GORMAN: It seems in some way that you've turned our paradigm of us seeking assent into thinking that perhaps dissent is a more potent way of determining a subject's willingness to participate in this study. Do you have any thoughts on actively seeking out dissent or do we have to wait until

they're squealing?

DR. WENDLER: Here is a great question. I don't know if I have a good answer. Here is my general philosophy when people ask about how you implement this in practice. I think what you should do is let's say you have a kid that -- at least in my view, I don't think we should be asking consent from an eight-year-old.

What you should do, both in terms of respect and also to the point that Skip is making, just in terms of getting their cooperation, kid understanding, kid not being afraid, I think you sit them down. You try to explain as clearly as you can in a way that that kid can understand what you're proposing to do, what you are planning to do. And then you say to them, "Okay. Here we go. And if at any point you're confused, if at any point you have any questions, if at any point you get scared, you want us to stop, if there's anything you need, you just let us know." And then you just start them off basically keeping an eye on the kid.

And if the kid starts to complain, if the

kid starts to have problems, as I mentioned, you stop and you try to assess it. If not, you just keep on going.

So it's sort of the here we go with an eye on the kid and a good clinician who works well with kids by their side to make sure things are going okay. And maybe at least for younger kids, if you could do it, have a parent around, the parent is a good barometer of how well the kid is doing.

CHAIRMAN NELSON: I guess I would just like to point out -- and I see some other hands -- that to the extent that one argues in favor of an active solicitation of dissent versus a developmentally adjusted process of assent, where you're not looking for all the elements of informed consent, it may end up that those two positions are practically the same, you know, whether you view it as asking them to say yes in a simple way, the way that you stick them with a needle, versus all of the other risk-benefit, et cetera, versus actively asking them if they want to say no to you doing that.

So it may be it doesn't make a difference

depending on how you implement either approach.

DR. WENDLER: I think asking sort of prospectively for protestations is the equivalent of asking for assent. I wouldn't do it that way. And I think although in some cases it becomes pretty similar practice, I think it's helpful to keep the sort of conceptual grounding for the two practices. I think that they have fundamentally different justification.

I think that the reason why you are respecting dissent isn't something about autonomy. When philosophers talk about autonomy, basically what they mean is they mean allowing people to control the course of their lives, allowing them to control what they do and what they don't do.

I don't think that is what Myer is saying. That's I don't think how you ground this. I think what dissent is grounded in, dissent is grounded in the context of non-prospective drug benefit research. You shouldn't be causing harm to the kid. And you shouldn't be causing more than minimal distress.

So the reason why I think you should respect assent is because it's an indication that

you're starting to cause harm to a kid, that they're starting to suffer in one way or another.

And the idea is that how are the kids going to know? Typically -- I mean, this isn't always the case, but typically in a research setting, kids are undergoing things that they are not that familiar with in a setting.

If they are not familiar, I think the appropriate thing isn't to ask them up front prospectively, "How do you think this is going to affect you?" It's "Here we go. And let us know how it's affecting you as you go along."

MEMBER GORMAN: So your process would really be in slightly different terminology, assent with a very low threshold for voluntary withdrawal, not to throw in any more terminology?

CHAIRMAN NELSON: Yes. I mean, Dave is alluding to a debate that is going on. In many ways, the debate is between him and I on precisely the point you are raising. So we could go on if you'd like. Is that fair?

Was there a hand over here? Dr. Lustig,

go ahead.

DR. LUSTIG: I have two related questions. The first question, obviously the obesity therapies that are currently available and effective that we know about from adults are clearly high-risk in terms of implantable surgery, are you suggesting that we should not be considering patients under 14 for those procedures because of the issue of assent?

DR. WENDLER: Oh, sorry. No. For me, right here all I am saying is picking a cutoff for when you should acquire assets, I think the question of who is appropriate for human study is a different question. That for me is the question of the subject selection that I talked about a little bit earlier.

I think if you end up concluding for one of these studies, that the appropriate population to do it in is five to eight-year-olds, then in my view, you shouldn't be asking for the assent to those. But you should be respecting their dissent.

DR. LUSTIG: Also part of that question is, do you believe there is an age gradation based on risk? In other words, let's say there was an obesity

therapy that was minor risk. Could you potentially offer that to kids at a lower age and still expect appropriate assent?

DR. WENDLER: Yes. I think that's a great question. As people know, there are sort of minimal risk standards comparing risks to the risks of the others' daily life.

We posted a paper recently on the actual risks in daily life. And one of the things that you find out for kids is that there is a big increase in the risks that kids face once they become early teenagers for two reasons mostly: because of playing sports and because now they and their friends are driving cars and kids are dangerous behind the wheel.

I think what that data raises, it raises an interesting question of whether or not you should have age-relative interpretations of minimal risk. If it's true that the risks in the daily lives of older kids is higher than the risk in the daily life of younger kids, does that imply that you should allow riskier non-beneficial research in older kids?

In the end, I think maybe the answer is

yes. I mean, I think that the fact that they just have higher risks in their daily life, I don't think that's a good reason to expose them to greater risk.

But what is interesting is that increase in the risks the kids get in daily life, when they get into their early teens, that correlates with the point at which most kids get to the point where they can understand and make their own decisions.

I think that the fact that the kid can understand and make those decisions, I think that is a moral reason for considering allowing slightly higher risk in older kids.

So, for instance, if you had a hypothetical study where it's going to be risky, you don't know if you could benefit the kids and you could do it in anybody from 5 to 18, I would say I think there is a good reason assuming risks are equivalent and the value is equivalent across the populations. I think the fact that the older kids can understand better is a reason to do what the older kids and exclude the younger kids, at least first.

CHAIRMAN NELSON: I've got Dr. Diekema,

Dr. Newman, and Dr. Inge. And we do have a break depending upon when you guys want it. Dr. Diekema?

DR. DIEKEMA: Hi, Dave. I wanted to reiterate that I think it's important to distinguish between dissent and assent. I actually chair an IRB where we will oftentimes have a different age for those two. We'll require assent in, say, kids above 10 or 12 but then tell the investigators, particularly in a study that doesn't offer the prospect for direct benefit, that dissent needs to be respected, with the difference being in assent we see, in part, a vehicle for communicating what is going to happen to a child.

My other comment is that I think it is important to recognize that assent is different from consent in a number of ways, but one important way I think is that assent, really, we should be properly focusing on what children care about, as opposed to a comprehensive view of what the research project is about.

Most eight-year-olds don't care if you're going to bank their data, for example. I think it's silly to ask them if that's okay. But they do care if

you're going to put a needle in their arm. They do care if you're going to do a surgical procedure.

So I think assent is sometimes interpreted more broadly than it should be, that somehow the child has to be told about the entire research study and everything that's going to happen in that study; whereas, in reality, I think the proper question is, what does a ten-year-old care about? And that's what you talk to them about.

CHAIRMAN NELSON: I see that as a comment. So in the interest of time, unless David wants to expand on it, we'll go to Dr. Newman and then we'll go over to Dr. Kral.

DR. WENDLER: Go ahead.

MEMBER NEWMAN: I am trying to visualize very, very concrete situations where the dissent process would happen with the obesity devices. I'm just thinking, you know, so here is a child. He's scheduled for surgery. He's on the OR schedule. And someone doesn't get the ID the first try.

I'm just trying to think, in what way could you actually practically do that because, I

mean, I've seen kids where it doesn't go well and then they don't cooperate. And then they say, "No. I only want her to do it, not him," I mean, that kind of manipulation.

And then if this is a research thing and as soon as the kid says, "Stop," you have to stop, how does that play out or if they say, "No. I don't want to do the follow-up visit. I'm sick of this. I don't want to go there," but they're in research?

DR. WENDLER: Yes. That's a good question. The first thing I think with surgery trials, it's sometimes is hard to figure out how you're going to -- as long as the anesthetist is doing his job, it's hard to figure out maybe how you can get dissent.

I think that is something that maybe you're not going to get, but for me that is okay because I said before the reason why I think you should justify and the reason why you're getting dissent and respecting dissent is the extent to which it's an indication of the kid suffering. If the kid is out and really isn't feeling anything, then the kid

can't get dissent, but we also assume that the kid is not suffering. So that I am not too worried about.

I just wanted to emphasize one point is I think this is really important. I think respecting dissent is very important, but I think it's also very important not to confuse it with the first time the kid objects, the first time you get any fighting, you completely take the kid out of the study. I think that's a mistake.

What you're trying to do is you're trying to protect the kid from distress and harm. Sometimes it turns out that the only way to do that is to take the kid out of the study. In those cases, I think you should take the kid out of the study.

A lot of cases, the kinds of cases that you describe, there's other ways of doing it. You know, if the kid really does want person A, rather than person B, to sort of push the GERD or put their central line in and you can do it, why not? And if that's a way to address their distress, then I think that's the appropriate response to take. And then you just go ahead with them.

CHAIRMAN NELSON: I think I had forgotten to write down Dr. Kral's name when he raised his hand earlier. So Drs. Kral, Inge, and then O'Fallon.

DR. KRAL: Every now and then, in despair or otherwise, people have questioned there should be some kind of competence testing before allowing anybody to become a parent or procreate.

I would like to get back to the first question, the same question I asked from the beginning, but this time I'm going to ask about parents. Should there be a testing of the parents' ability to take upon them the responsibility in the assent process of their offspring?

DR. WENDLER: I think that the way that we do it with adults, whether they're making decisions for themselves or they're making decisions for other people, right now is we have a default that they're competent and they are able to understand and make decisions.

Now, I think that's the default we still go with, but if we look at the literature, as I mentioned, -- I had written on this a couple of times

a couple of years back -- if we start looking at the literature, there has now been a fair amount of empirical data on understanding. They take people into the study and they ask about the risks or they ask about could they have said no.

You find out that understanding is a lot -- it's not what you hope it is. It's a lot less. I mean, I estimated at the time that 30 or 40 percent of people don't understand at least one key element of the research participation, like the risks in it, like the fact that they could say no, things that I think we all think are important.

I take it that what that suggests is that this default is under pressure. I think we should. I mean, I would advocate what we should try to -- we don't have them right now. But what we should do is we should try to develop very simple tests to assess whether or not people understand. And if they do, then we go ahead. And if they don't, then we stop.

What it shows is that the first time around, people are impoverished. About two-thirds of people will get it, but at least a third of people

won't.

But if that third, if you just do a remedial educational step with them, you find out you identify what they didn't get. They didn't get that they could say no. They didn't get the risk. They didn't get this is a randomized study. If you then focus on that aspect of the study, the vast majority of them will get it just the second time around.

Just to give you one really quick example, I sit on the IRB for the National Institute on Drug Abuse in Baltimore. For every single one of the studies, we require the investigators -- we sent out a list of questions that they have to ask the subjects and the subjects have to get right after the consent process to go in the study. If they don't get any of those right, they have to go back. They can't get an anonymous study.

So I think we need to develop the method. They're not there yet. But I think if we get the right methods, it's not going to be that onerous of a process. And I think it will make a difference.

CHAIRMAN NELSON: Dr. Inge?

DR. INGE: Yes. I think, you know, that it is important to point out and to see if we have agreement that this is a treatment trial we're talking about, but for an elective surgical procedure, that there probably are chances for direct benefit for each subject and that because we need the long-term participation in agreement of the subject for what we might consider optimal outcomes, that I just would ask the question, is there a reason to or is there a disadvantage to requiring assent at even the lowest age at which you will be enrolling patients, so even younger? If indeed the decision is made to have younger patients participate in such a study, is there a valid reason not to require or disadvantages to requiring their assent?

I would advocate that that would be what we should do.

DR. WENDLER: Right. Well, I would think the obvious disadvantage is you might get a no. And you might get a no based on somebody who doesn't understand a study, doesn't understand what they're saying no to.

I guess maybe here is the fundamental question. A couple of people have said before you need the cooperation of these kids, but I don't think that soliciting their assent and getting their cooperation are the same thing.

I mean, I think you can solicit their cooperation. You can give them information. You can answer their questions. You can tell them what you can do. I think you can do all of that for ethical reasons. And when you have to get their compliance, there's an added pragmatic scientific reason to do all of that.

I think that is all very important. But the question of assent is an additional question. Then the question of whether or not you stop and you say, "Okay. We explained it all to you. We're about to go forward. You give us a thumbs up and a thumbs down. And if you put your thumb down, we're not going to go ahead."

Now, I think if you've got this sort of a puzzle, you've got a medically beneficial study, there's more reason to think the kid is going to say

okay if they understand the benefit to them, but if they say no, then there are more worries, particularly if, as I had said earlier, I think one of the crucial questions is whether or not the potential benefit they can get is one they can get next month, as Jack was saying, or whether or not this is an operation that is also available outside of the research context.

I think that makes a big difference, as the regulation states, so that you can only waive the assent when it's both for important medical benefit and that potential for medical benefit is not available outside of the research products.

I know we're running out of time. Let me give you one really quick example of a case that I saw at the clinical center. This is a kid who had an inborn immune deficiency, immune apheresis of the kidney. They had to get some cells.

I think it's similar to surgery in the sense that the kid had to cooperate. They had to roll him down to the pheresis unit. He had to sit in the chair. He had to let them put the blinds in. He had to stay relatively stationary, couldn't pull the

things out. He had to be there for about a half an hour.

We had a couple of kids we did this with. One of the kids, the assent was required. He was an eight-year-old kid and explained the whole procedure, explained the whole procedure to the kid. He said, "Okay. All right.

"Have you got it? Do you understand? Do you have any questions?

"No."

I was actually the consultant at the time. And I said to the kid, I said, "Okay. Now it's up to you. Do you want to do this?"

The kid said, "Absolutely not. I want to play basketball with my friends in the hallway."

In that case, we didn't do that procedure. But I don't think that -- I think it's clear, and I should talk to his mother about this afterwards.

And we did it with his brother. His brother was younger. So we didn't have to get the assent of his brother afterwards. And his brother went along fine.

I think in these cases, again, the difference between asking them to make an affirmative agreement is very different than asking them to cooperate. And I think it was clear in this eight-year-old, who ended up saying no.

If we hadn't said, "It's up to you," if we had just said, "This is what we're doing. We're going along," everybody I talked to who knew this kid, had been taking care of this kid for six years, his mom, his older sister, were convinced he would have gone along, he would have been fine, he would have cooperated, he was a good kid. But we had to sap him, "Is it okay with you?" Once he's given that choice, he said no.

So I think there's a difference between the two. I think if you do it right, you can solicit cooperation. You can give kids the information you want. You can reassure them in the way you need to without asking them to make this prospective decision about yes or no.

We sort of do this all the time, right? Your significant other makes a decision about what

you're going to do on Friday night or where you're going to go to dinner. If you had a choice, you would say no, right, but you will go along.

(Laughter.)

CHAIRMAN NELSON: We're going to have the opportunity to dig into these issues when we tackle the various questions tomorrow since they're all wrapped up with each other. So I want to thank David for his presentation and for stimulating conversation. And we now have the opportunity to take what I hope is only a ten-minute break.

(Whereupon, the foregoing matter went off the record at 3:20 p.m. and went back on the record at 3:34 p.m.)

CHAIRMAN NELSON: We have two more presentations to go before the end of the day. And I might say I'm buying time as people get into their seats.

About the two presentations, the panel and those in the audience will note that we do not have physical handouts of the slides. We will have those available for tomorrow I am told. Part of the reason

you don't have them now is we just got them. And they're only in display format at the moment. But we'll make sure we have copies of those for distribution for reference if you so choose during our discussions tomorrow.

So we have two presentations this afternoon, one on conservative intervention and one on surgical intervention, which one might think are two ends of the poles, although I know many surgeons who think often surgery might be the most conservative approach. But we'll see how this dichotomy plays out, at least in the presentations.

Our first presentation on conservative intervention is Deanna Hoelscher from the University of Texas in?

DR. HOELSCHER: Houston.

CHAIRMAN NELSON: Houston. There are many Universities of Texas, but in Houston.

DR. HOELSCHER: Thank you. I would like to thank you all for inviting me here.

CONSERVATIVE INTERVENTION

DR. HOELSCHER: I see a few friendly faces

in the audience, most particularly Dr. Klish, whom I spoke to when I was putting this presentation together. We didn't realize we both were going to be here at the same time. Thank you very much.

What I would like to do today in my talk is just give you a brief definition of child overweight. I know you have seen this before, but I just want to kind of establish the parameters I am using, give you some rationale on why we use conservative approaches and then talk about different methods.

I'm loosely basing that on least invasive to most invasive, although I've got protein-sparing modified fasts there, which is a little bit more invasive than perhaps use of pharmacologic agents, and then some conclusions and recommendations.

Just an overview of child overweight and interventions. During my talk, I'm going to be using the same nomenclature that I'm sure you've heard this morning already to define overweight and at risk of overweight with kids, the 95th percentile or greater based on the CDC growth charts, and then between the

85th and 95th percentile.

Just a few points for you to keep in mind. The prevalence of overweight among children varies by gender and race, ethnicity, and there are disparities in the rates among different groups.

Another thing, another important feature of this, is the prevalence of overweight is not a normal distribution, but there is a skew towards heavier weights.

We just collected data on over 23,000 kids in Texas in schools. If you look at their heights, you get this great normal distribution, just like in textbooks. But you look at weight, that's not what you see. And you see the tails skewing to the heavier weights.

The primary aim of these overweight interventions is energy balance. So you want to balance energy in versus energy out. What there is is very little data on preschool children. And because I have such a short time for my presentation, what I'm going to try and do is group these different types of interventions together and kind of give you a broad

overview and point out a couple of studies so you can kind of see the literature that we're working with here. In general, I'm not going to be talking about preschool children because they're not highlighted in most of this work.

And then, finally, practice is not evidence-based in the strictest sense. And that reason is because there is not enough data. As you can see, we really are lacking in a lot of data about conservative interventions.

We just did a review that looked back 20 years about interventions for treatment of childhood obesity. And we came up with 44 studies that had done that. So that's really kind of a small literature.

So how do children differ from adults? You heard a little bit about that with some of the other presentations, but I would like to point these out again as they have implications for interventions.

One is there is reliance on parents as gatekeepers for both food and physical activity. So when you talk to the kids, you have to talk to the parents as well in most cases.

There's also consideration of growth and development from a biological standpoint. And I'll give you an example of that in just a moment. With adults, you don't have to worry about them getting taller, unfortunately.

There's cognitive and emotional development that plays into this. One of the things that we have just heard about since is at about the age of 14. Well, about the age of 12 is when children start to distinguish concrete abstract concepts from concrete concepts. So that is a very important age there. You've got to take that into account.

Another thing that is important with kid sis their peer relationships, very important, more so than in adults. The degree of overweight is different in kids the way it is classified currently. And you have heard a lot about that already.

Another thing about children is they have a big social environment going on, which is the schools, that we have the workplace, but the workplace varies a lot more in adults than the school environment does. And the kids interact within that.

Also, when you're looking at interventions for kids, you have to consider eating disorders, development of eating disorders, disordered eating patterns. And then there are critical periods of adiposity increases, adiposity rebound in puberty or two.

So if you look at the rationale for conservative approaches to child overweight, the traditional view has been that overweight in children is benign or cosmetic and that kids will grow out of it. So the treatment paradigm has been to keep the weight stable so that the kids could grow into the weight and that weight loss, if any, should be modest and you should use diet together with physical activity and behavioral counseling.

And if you look, what I have here -- let me go back just a second. This is one of the CDC growth charts. This is the height, and this is the weight. So if you look along those percentiles, I will be talking about that next.

What I have mapped here is I took the CDC weight chart along the 75th percentile from age 6 and

a half to 18 and a half. And I looked at the difference in weight. This is in pounds each year.

So you can see from age 6 to 7, kids depending on whether it's boys or girls gain from 6 to 7 pounds if they follow along that 85th percentile. That's a one-year gain.

The reason why this is useful is for a couple of reasons. One is you can see how growth might assist you. Because these kids are gaining this much weight and you can kind of equate five pounds to one BMI unit, then you can see that if you can hold the weight constant, that you can change BMI because they're growing along with that. So that's one concept you can look at.

Another thing, if you look at this, the periods where you can have the most effect on a treatment or prevention are when they're gaining the most weight. So this tends to be right around puberty here. The girls go through it first, and then the boys go through it second, as you well know.

Then when you look at this, you say, well, is there empirical evidence to back this up? Nancy

Butte from the Children's Research Center and Ken Ellis have a study ongoing. They looked at 337 Hispanic kids, and they followed them for a year.

They followed them, and they looked at kids who were normal weight who remained normal weight at the end of the year. They were normal weight. They became overweight at the end of the year. And then there were kids who were overweight and remained overweight at the end of the year. And they looked at how much weight they gained.

If you look at the red line here, these are the kids that were normal weight at the beginning of the year and at the end of the year. You can see that that is within these growth parameters here.

The kids who were normal weight who became overweight, they gained 15 pounds. This is a mean of 15 pounds. So you can see that's well above kind of the growth trajectory there.

And the kids who were overweight and remained overweight gained a mean of 16 pounds. So you can see that that is outside of the normal growth curve, at least this one, which is the 75th

percentile.

Now, the current view on conservative approaches for child overweight say that overweight in children is associated with both morbidity and mortality and that it leads to increased risk for severe obesity in adulthood. And BMI tracks over time. We've got data that show that pretty clearly.

With children extreme weights, growing into weight is not an option. And I'll show you an example of that in a second. So treatment paradigms need to change to reflect that.

This is using some of that data from that chart I showed you before. And if you look at it, you have a boy. This is just looking at boys because the boys and the girls are different. But if you have a boy who is 6 and a half and if he weighs at the time he's 6 and a half 115 pounds more than where the 75th percentile is on the chart, chances are he will not grow into it because chances are he will gain more weight than that throughout time. You would want to keep that 115 pounds constant if you wanted him to end up at the 75th percentile when he was 18 years old.

As you can see, you get to about 10.5. If a child weighs 83 pounds over what the percentile is on the growth chart, then chances are they will not grow into this.

So this kind of gives you an idea of the type of weights that we're talking about and what can be achieved and what can't when you look at some of the results obtained from these conservative interventions.

One more thing. The determination of energy intake in children, to lose weight, you have to determine how much change you need in energy intake. And with kids, you have to figure growth into the equation, which can be difficult because they go through different growth periods.

Estimates from Butte and Ellis, again, from this same technical paper that they did show that there is probably a deficit of about 300 calories a day that you need to have to prevent further weight gain in overweight children.

So 300 calories a day, just to let you know, is about 2 12-ounce sweetened beverages. And

it's equivalent to walking about about 60 to 120 minutes a day depending ont he intensity.

Just an overview of behavior modification, diet and physical activity programs is most diet and physical activity programs, which I will talk about now, generally have behavior modification components in them. Most programs have all three. And when I speak about physical activity, I am also talking about sedentary activity, too, because a lot of times they're seen as two different constructs, the time kids spend in media use, computer time, TV time, and then the time they spend actually being active. But you kind of go about some of those interventions the same way.

The other thing about a lot of these programs is there is intensive parental involvement in this. The studies to date have mostly been conducted in clinic settings. There's a few that have been conducted in schools. And I'll show you those.

For diet, when you look at diet as a conservative intervention, as a definition, basically what you're talking about is you're restricting food

intake, either through a change in macronutrient composition, if you change the fat or the carbohydrate composition, or you're reducing energy intake.

The duration if you look at trials with adolescents and children, it ranges from several weeks to about three years. The maintenance of effects, there's limited data. There have been very few studies that have followed up over time.

The compliance varies among studies. Side effects with a regular diet, like if you're put on a stoplight diet, a traffic light diet, or following the dietary guidelines, there's relatively few side effects. With a protein-sparing modified fast, the side effects can be more dangerous, can include protein losses, hypokalemia, hypoglycemia, inadequate calcium intake, and orthostatic hypotension.

The weight loss achieved with the protein-sparing modified fast, you can get weight losses of one to two kilograms, which is 2.2 to 4.2 pounds per week. And with diet alone, you can obtain up to one kilogram per week. A lot of times that's not consistent. You go through plateaus throughout

that.

The pros of a diet approach, dietary approach, is it's safe for most of the more moderate diets. The cons are you need to get the parents involved. That can also be a pro that you get the parents involved in that as well.

They're costly. They're long-term. There's limited data on effectiveness of diet by itself. Usually diets paired with physical activity is part of a behavioral program. And there are side effects for a protein-sparing modified fast.

There are also some diets with altered macronutrient content that people are looking at now, but they have mainly been evaluated only in small trials for limited periods of time. And I'll show you an example of those.

One of the diets that is used most often -- and you will see this come up with Lynn Epstein's work -- is the stoplight or the traffic light diet. And it uses a traffic light concept to characterize foods. So gold foods or green foods are low-calorie, high-fiber, no restriction foods. The yellow foods or

amber foods, as they're known, they are essential foods, but they have a higher nutrient density. And so you eat those in moderation.

And then the red foods are foods to limit. Generally in Epstein diets, they have been limited to less than four servings. In other diets, they have been more restrictive.

The energy goals tend to be about 900 to 1,300 calories per day. A lot of times self-monitoring is involved, where they write everything they eat and drink. That's a very effective behavioral technique.

This guide has been adapted in various forms. How it is written, it's pretty complicated, but it has actually been used in many different settings, a little bit more simplified. It also follows the U.S. dietary guidelines, where appropriate. So it's consistent with that.

One of the new promising directions looks to be reduced carbohydrate or glycemic load diets. There aren't a lot of studies that have looked at this to date. A lot of these come from the work of David

Ludwig.

They're smaller studies. The first one, Kara Ebbeling study, was a randomized controlled trial that involved 16 obese adolescents. Fourteen of them finished the trial. And they got a difference of two BMI units between the control group and the intervention from. Now, again, this is a very small group that we're looking at.

The Spieth, et al., study was a retrospective cohort, which was looking at 107 obese kids. They did a load glycemic index diet. Basically what these are, they're diets that are limited in sugared beverages and sweets. And they found a difference of 1.12 BMI units, which is about 2.6 kilograms.

In summary, it looks like what these studies are, they're relatively small. All the evidence isn't in. They're very preliminary. But one of the reasons they might work is they restrict calories because you're eliminated sugared beverages, sweets, things that kids eat a lot of an that they tend to like to eat a lot of.

The protein-sparing modified fast involves about 1.2 to 2.2 grams of protein per ideal body weight. For children, this usually involves a hospital stay. And they need to be given vitamins and minerals, potassium, and calcium along with this. They need to have consistent monitoring of ketones as well.

There's a gradual reintroduction of carbohydrates. And this should be done as part of the behavioral program. So they should be learning how to eat in the real world as well as doing the protein-sparing modified fast.

This is for a limited period of time. In one study with 8 adolescents, they found a mean weight loss of 13.5 kilograms over 5 weeks. But, as you can see, it's a very small sample size. There was no control. Five of those kids continued on for an additional period of time and gradually lost up to I think it was 30 kilograms over time. Two of those maintained that over a year. Three of those gained weight back. With the published trials, with children, as you have seen, there are few subjects.

There are no randomized control trials. There's relatively little data on this.

With physical activity, sedentary activity, interventions in children, what these are is programs designed to promote adolescent weight loss by increasing activity or decreasing sedentary behavior. And the duration of treatment in trials has been 3 months to 54 weeks. A lot of them have bene around eight months. They generally tend to increase physical activity from 30 to 60 minutes a day for 3 to 7 days a week.

The maintenance of effects, there's really not a lot of data on this. The compliance, again, it varies. The weight loss achieved, from these studies, it's kind of difficult to quantify. And the reason why is most of these are done with exercise physiologists. And they tend to look at change in percent body fat. And there are significant changes in percent body fat. It's kind of hard to equate those to BMI or weight, as I have done with some of the others.

The pros are that exercise is generally

easier to maintain than diet over time, at least in adults. And it builds on usual child activities. The cons for these include safety issues, which can be a concern; time and money if the parent is involved.

A lot of determinant studies show that the parent needs to be involved. Some of our own work has shown that girls who are involved in sports teams tend to get more physical activity, but that involves a parent getting involved again.

Sedentary activities are very self-reinforcing. If any of you all have done video games, you know that you never win the first time you sit down, that you are always encouraged to go on to a new level. So it's really hard to break away once you get in to that.

Here are a few examples of physical activity. Actually, these are both physical activity interventions. A lot of these are out of Gutin's lab. And both of these were looking at obese children.

The Owens study looked at 74 obese children that were 7 to 11, so elementary school age. They did four months of training. And the training

consisted of 5 days, 40 minutes per day. And they found significant decreases in visceral adipose tissue and then total body fat mass over that time.

A more recent study, in 2002, looked at 80 obese adolescents. The obesity was classified by tricep skin folds. These kids were 13 to 16 years old. This was an 8-month, or school-long, intervention, 5 days per week, 30 minutes per day. And there were significant decreases in visceral adipose tissue and percent body fat. They found no differences between moderate and high-intensity exercises.

A more recent publication by this group shows that these effects are dose-dependent. So the kids who participate more in the physical activity program had better results as far as decreases in body fat.

The third type of intervention, conservative intervention, is the use of behavioral modification. And here we're talking about behavioral modification strategies and counseling techniques. And so these involve goal setting, stimulus control.

Motivational interviewing is used a lot now. Self-monitoring is used. And modifying dietary habits, physical activity patterns.

It is also used to address underlying psychological issues related to food and physical activity. The duration of treatment ranges all the way from one session to three years. Most tend to be about six months in length.

Maintenance of effects, this is the one area where there has been relatively good follow-up. And there has been some maintenance of effects, particularly in some of Lynn Epstein's work. The compliance, again, varies. And I'll talk a little bit more about that later.

Side effects are few. The weight loss achieved tends to be about 4 to 15 pounds overall if you look at the whole range of studies done. It tends to be safe. Again, another pro could be that the parents get involved with this. You have to have the parents involved.

The cons are that it's costly, personnel-intensive. Results aren't consistent. And

it's long-term. And it involves considerable family involvement. So you're getting everybody involved with this.

The most successful work in this field has been done by Lynn Epstein. And as one example, if you look across 4 RCTs that he did, there were 154 overweight kids ages 6 to 12.

In general, when you look at the behavioral modification, just in the side on this, it tends to be most of the data are for kids in elementary school. So they tend to be 6 to 12 years old. There's less data available on adolescents 13 and above and kind of the effects of behavioral interventions on them.

In these, there was involvement of parents. There was family counseling. And there were different levels of family counseling. So in some cases, both the parent and a child received an intervention. In some cases, it was a non-specific target.

With long-term effects, 30 percent of the kids from these studies were no longer overweight

after 10 years. And then 34 percent of them had a decrease in percent overweight of at least 20 percent.

Another thing is when you looked at them at five and ten years out, what was kind of interesting is in some of the studies, both the parents and the kids were targeted and the parents lost weight.

The parents regained weight at five years. The kids maintained their weight. So it looked like these interventions were more effective for the kids than they were for the parents and that maybe parental monitoring wasn't the only way that they were -- they were an important component but not the most important component.

One of the criticisms of Epstein's work or several of the criticisms have been that he focused on a specialized population. So it's mostly a white middle class population. He omitted anybody who had psychological problems. A lot of his interventions aren't very well described in the literature. And the kids all had two parents at home. So it was kind of a specialized population.

One of the things when we were conducting this review a while back was we looked at school-based tertiary prevention studies, interventions, and you can translate this to be treatment studies.

What we found, there were five that met our criteria for this review. And when we looked at them, we were kind of amazed because all of them showed effects on percent overweight, percent Rohrer's index, percent obesity index.

And one of the things that we found -- now, again, this is not an adequate body of literature to make, to base a lot of evidence on, but it is pretty promising when you look at it. Only one of these was an RCT, though. So there really needs to be more work in this area.

But if you look at it, if you think about why they might have been successful, there are a couple of reasons. One is most of these were done in the school level. So there was peer support. So the only way kids might have been pulled out, but the whole school was getting some sort of intervention. So it was framed within a broader social context

there.

Another thing is there is a consistent intervention effect because they were there at school every day. So it was a place that you could reach them.

Another type of intervention that maybe shows a promising direction is weight loss camps. Kirschenbaum and Craig are conducting three of these camps. They're in North Carolina, California, and New York. And they range from ages 10 to 23 depending on which camp you're looking at. The camps include diet, physical activity, behavioral therapy four times a week, a family program. And then there is an after-care program.

Now, one reason this is specific for kids is most of us adults can't pack up and go to a camp for an extended period of time, but they actually have courses at some of these camps that the kids could take courses along with that. And then there is peer support because the other kids are overweight there as well.

They have presented some preliminary

results at NAASO. The preliminary results look very promising. Now, it remains to see what happens when these get into the published literature.

The final conservative intervention that I will be talking about is the use of pharmacotherapy. And that is the different kinds of drugs that are used. It's actually a real short part of the presentation because there aren't a lot of drugs that are approved.

The duration of treatment in trials has been from 3 months to 54 weeks. There's little data on the maintenance of effects. Actually, this should be attrition for Orilstat. In the Orilstat trial, the attrition was 35 percent. Sixty-five percent remained in the study. The side effects range from hypertension to loose stools to risk of fat-soluble vitamin-deficiency depending on which pharmacologic agent you're using.

The weight losses, if you look at the Orilstat study, there was a mean difference of 2.6 kilograms weight change between placebo and control. And I'll talk a little bit more about that later. You

can expect to see about a one to two-pound-per-week loss in clinical practice.

The pros are there is consistent weight loss, little parental involvement, and little behavioral change necessary, although in most cases these drugs have bene tested in trials where behavioral treatment was a necessary adjunct to the pharmacologic treatment.

The long-term safety in children has not necessarily been evaluated. And there are side effects. There are other drugs currently proposed. Some are being used in practice. One of them includes metformin. There are others. Leptin is being looked at.

Most pharmacologic regimes, as I said before, work best in combination with behavioral, diet, and physical activity changes. And that is true in the adult literature as well.

These are the drugs currently approved for treatment of obesity in adults and children in the U.S. Actually, the only one that is approved for kids is Orilstat, which is the last one. The two most

important ones used are Sibutramine and Orilstat, which are the last two. Sibutramine is an appetite suppressant. And it works through the not adrenergic and sertranergic pathways in the brain. Orilstat is a gastrointestinal lipase inhibitor.

Orilstat, there was a randomized control trial published in JAMA just this year. It was a multi-center 54-week RCT. And, actually, the results of this were released in 2003, which is why Orilstat went on the market at that point in time.

It was a double-blind study. They looked at kids with BMIs that were greater than 2 units above the 95th percentile, 12 to 16 years old. They got a 120-milligram dose of Orilstat 3 times a day plus a mildly hypocaloric diet, exercise, and behavioral therapy. The parents also had to agree to participate in this with the kids.

So the results at the end of the time were a difference in placebo and control of 2.61 kilograms after a year, which is about .66 BMI units. There was 35 percent attrition, as I said before. And the compliance was actually pretty good. It was about 70

percent of the kids taking the drugs.

With Sibutramine, there was a randomized control trial published in JAMA a couple of years ago. There have been a couple of other trials since then. Again, the other trials have been relatively smaller trials. This was with 82 kids between 13 and 17 years of age for 6 months. And then they got an open label for an additional six months. This was done within the context of a family-based behavioral treatment program.

So you had the control with the behavioral treatment plus placebo versus the behavioral treatment versus Sibutramine. And there was a difference of 4.6 kilograms between the groups. And that was after six months. That difference was not as large after 12 months, after the open label part.

So, in conclusion, there are limited data right now on obesity treatment and our prevention studies conducted with preschool kids. Pharmacologic treatment has been evaluated on adolescents only, age 12 and older. So we have no data on elementary school kids.

Behavioral modification programs that target diet and physical activity have been evaluated and are effective in children younger than 12. The evidence there is pretty good, but you need intensive family involvement along with that.

Increases in physical activity and decreases in sedentary activity are promising intervention strategies. One of the problems with that is if you have kids who are too large, it's difficult for them to move in the first place. So they have to be at a point where they can move. And preferably you would want them with a group of peers when they're engaged in physical activity intervention.

Children with extreme BMI weight or that have associated morbidity may need to engage in more aggressive interventions than those presented here. You have seen the data on how much weight kids gain from year to year. You have seen what the conservative interventions do.

So, for example, the other day we're out measuring kids in Texas. And there was a girl who was

10 years old who was 115 kilograms, or 250 pounds. At that point you're not going to grow into the weight, and it's hard to begin some of these other interventions.

Currently conservative interventions are not complemented by a supported environment for food availability and physical activity in most schools and communities.

So you might have a great program. The parents might be very supportive. But then the kid has to go out and live in the real world and real world that's not often supportive of the changes that they need to make and the decisions they have to make as well.

I would like to acknowledge some of my colleagues who helped with this presentation and offered some consultation, which include Dr. Klish and some colleagues from the Children's Nutrition Research Center at Baylor College of Medicine.

Thank you very much.

CHAIRMAN NELSON: Thank you.

We do have some time for clarifying

questions. Dr. Yanovski?

DR. YANOVSKI: Just a couple of questions. So my read of Epstein's work, including the ten-year follow-on data, are that, indeed, he reports that maybe 30 percent are no longer overweight.

DR. HOELSCHER: Right.

DR. YANOVSKI: But he also reports that 50 percent of those children have not really lost at all in their relative BMI percentile or however he expresses it.

DR. HOELSCHER: Right.

DR. YANOVSKI: Would you say that is correct?

DR. HOELSCHER: Yes, yes.

DR. YANOVSKI: So it's sort of a half empty and half full glass that those studies can be looked at as either partially successful or really at least in half the time not even successful for those 8 to 12-year-olds that he studies with intact families, high SES, the most advantageous race, and so forth.

DR. HOELSCHER: No. You are absolutely right. I think my take on it is from what we have

seen to date, that is the most effective. But even that is not maybe what we would like to see in terms of effectiveness. You are absolutely right.

DR. YANOVSKI: The second question is, at least if I recall correctly, Figueroa published a randomized control trial of low-fat diet versus a very low-calorie diet and found that, although in the short term weight losses were greater by -- it's either a year or maybe it's a year and a half. The weights were exactly the same. And, if anything, the low-fat group had done slightly better. Am I remembering correctly?

DR. HOELSCHER: Yes, yes. I didn't include that in this.

DR. YANOVSKI: So I think there is an RCT in the LCTs.

DR. HOELSCHER: Yes, you're right. Sorry.

DR. YANOVSKI: And the last thing is I believe that Berkowitz, et al., at the last NAASO meeting released data from a multi-center Sibutramine study. Did you have a chance to find out about that?

DR. HOELSCHER: I didn't see that at

NAASO.

DR. YANOVSKI: Yes. He presented the data a couple of places over the last year; again, a large multi-center study, finding essentially the same results as in the single-arm study, single-site study; in fact, large differences. But also there still continued concerns about pulse rates not really coming down and blood pressure not really coming down in proportion to the weight loss.

But I think it's important that none of these therapies are without potential harm.

DR. HOELSCHER: Right. And I didn't mention but in the Sibutramine trial, there were a lot of kids that were discontinued or they had to decrease the meds because they had side effects.

DR. YANOVSKI: And I guess one last thing, Gutin stated, if I recall also correctly, that since he stopped the exercise intervention, which is really very intense, pretty much all of the advantages go away from the exercise.

DR. HOELSCHER: The cardiovascular, yes.

CHAIRMAN NELSON: Drs. Klish, Lustig, and

then Inge.

DR. KLISH: Deanna, when we talked -- and I didn't bring this up. Perhaps you can answer it now. I'm not aware of any studies that show that significant weight loss in children that are overweight actually interferes with linear growth as they're losing weight. Did you run into any studies that would imply that? I think it may come up in discussion sometime tomorrow about rapid weight loss and linear growth.

DR. HOELSCHER: No. Even the protein-sparing modified fast, the linear growth was not affected in those studies. In the pharmacologic agents, it didn't show it. In Epstein's work, it didn't show that that was affected. In some of the prevention studies, it wasn't shown. Yes, you're right.

DR. KLISH: Thanks.

CHAIRMAN NELSON: Dr. Lustig?

DR. LUSTIG: Yes, a comment and a question. One, the comment is that there was a paper that was released earlier this year from Sao Paolo,

Brazil on Sibutramine, where they used a lower dose, got equal efficacy to Berkowitz without the hypertension tachycardia problem. And there were no --

DR. HOELSCHER: That was the 60 --

DR. LUSTIG: Sixty adolescents, correct.

DR. HOELSCHER: -- kids in that study, yes.

DR. LUSTIG: So there may be a dose effect that may be important there.

My other question was, do you have any data on predictors of response? In other words, is there any information out there as to who benefits from what?

DR. HOELSCHER: There are some studies that have assessed readiness to change. And I didn't mention that in here. I haven't seen a lot. In the behavioral literature, a lot of times we do stages of change, where we look at how ready are they to change.

I know that is being used a lot in clinical practice. There may be a study out that's done with weight loss. I'm not familiar with it. I

know it's been done in adults. I don't know so much about the application in kids. But I know in behavior literature, we look at readiness to change, the stages of change, pre-contemplation, contemplation, preparation, and so on.

Do you know of some? Are there some?

DR. LUSTIG: I was thinking more about biochemical variables.

DR. HOELSCHER: Oh, yes. You know, when you look at the studies, it seems that the kids that are at the lower -- they do stratify them. I can't tell you right off the top of my head who and which strata respond better. Someone else probably knows that better than I do here.

DR. LUSTIG: I assume the readiness to change translates roughly to the kids' idea in the presentation we heard in the public session. It's got to be the kids' idea. Is that a fair statement of readiness to change in preparation for change?

DR. HOELSCHER: Yes. The way we assess it in a behavioral manner is, you know, are you ready to make a change within a certain time period, within the

next six months, within the next three months. So the child would say yes.

CHAIRMAN NELSON: Dr. Inge?

DR. INGE: I think anecdotally many of the investigators and researchers in pediatric weight loss would admit that the extremely obese population of, say, children or adolescents represented a somewhat different population in terms of their treatment outcomes.

Do you have any evidence, really, or any data which you have run across that specifically looks at that group either in a primary study population or as a subgroup analyzed separately to look for treatment effects for behavioral therapy?

DR. HOELSCHER: Actually, that's a good question because a lot of times they limit the people who are in these studies. For example, the drug studies, I mean, based on the data we saw earlier, they stop at an upper BMI of 44, which, as we have seen, it kind of goes on past that. And that's very large. But even in some of these behavioral studies that went back, they kind of truncated the top as far

as the super obese that you might be referring to.

CHAIRMAN NELSON: Dr. Yanovski?

MEMBER YANOVSKI: I think that there might be two groups that would be relevant for Tom's point. I was actually going to ask pretty much the same question with a twist. VLCDs have been used with kids who have been quite heavy. And so that might be more relevant in terms of their outcome. Unfortunately, it's not all that good after a year. And then, you know, we published an open label study with Orilstat with kids whose average BMI was 45 kilograms per meter2.

But more to the point is are there any of these studies who have combined not only severe overweight but with complications of weight, which is the group that I think maybe that would be proposed to be offered, these kinds of medical devices and surgery?

Our Orilstat study did that, but it's an open label study and shouldn't really be mentioned. But do you know of any others?

DR. HOELSCHER: Most of these, I don't

recall that they had, you know, that that wasn't an endpoint or they weren't really looking at -- I think what's important to remember here is this child overweight is relatively recent.

And we didn't even classify it, really, until 2000. So when you look back, you have to kind of interpret how they classified it. I mean, we had it classified, but it wasn't as standardized as it is now.

And so I think people weren't necessarily looking for complications so much in some of what has been published to date. So I am sure there are trials ongoing.

I know there are several type II. I'm more familiar with the prevention trials, actually, than the treatment trials, but I know that those look at cardiovascular risk factors. But I'm not aware of any of these because Epstein's really didn't look at that. That wasn't the primary focus.

Southern's work, Gutin's work, I think they really didn't know.

CHAIRMAN NELSON: Dr. Fant and then Dr.

Botkin.

MEMBER FANT: Yes. This is a spinoff from Dr. Lustig's question. As we think about surgical interventions over the next couple of days and the requirement, the general requirement that the kids failed more conventional, conservative approaches to managing the weight, is the data robust enough or do you have any feeling about how that should be defined in a way that is meaningful?

All of the approaches that you talk about, one is as good as the other or should there be a more standardized process that they go through as they march toward surgical intervention or do we just not know enough to say, "Well, as long as they make a good faith attempt to do one or two that are available, then that is good enough"?

DR. HOELSCHER: When you said that, what I thought of was Bray's algorithm for treatment. And I know that the Texas Pediatric Association has an algorithm for treatment that has you go through behavioral therapy for so long, assess their readiness. If they're ready, you wait. At a certain

point, you add pharmacologic treatment. At a certain point, then you consider surgery.

So it's an algorithm that kind of looks at how well they do at a certain point. And it's a certain flowchart. So there is a certain pathway that you go down.

And I don't know. Dr. Klish, you might want to talk more about that. That might be useful for you to look at because I think it's incorporated, both evidence-based medicine as well as perhaps clinical experience, which at this point is the state of the art, I think.

MEMBER FANT: Are we learning anything about which kids are likely to benefit or which kids are likely to fail based on certain characteristics or are things at the state where we just need to see how they do as they go through this process?

DR. HOELSCHER: I don't know a lot of literature that is doing that. I mean, this last study I was talking about is even -- well, one of the studies I was talking about, it was a Yan study with Gutin where he was looking at the kids who

participated, had different levels of participation in the physical activity and there was a dose-dependent effect.

You know, even those were just kind of -- a lot of people do the before and after outcomes and don't necessarily tease it out to see what are the determinants, kind of the post hoc analyses that you need to do to follow that up.

So I'm not aware of a lot of that work being done right now and who is the best candidate. How can you assess them? Some of the best work actually might be done in hospitals right now, but it's not published. So I don't know unless anybody else has.

CHAIRMAN NELSON: Well, we may if we explore that question in any depth start answering the questions we're going to discuss in detail tomorrow. So I'm not sure how much we need to go further on this unless, Dr. Klish, you have a quick question.

DR. KLISH: Well, I was just going to comment. I think within those of us who treat obesity medically, there is a submerging feeling that obesity

does have phenotypes and does have markers that allow us to perhaps distinguish ahead of time which kids might be more successful and which aren't two psychological markers.

I know right off the top of my head, in our experience, angry kids tend to do better in medical management, behavioral management, than those that have an internal locus of control, you know, the ones that feel responsible for themselves. And those are markers of success.

CHAIRMAN NELSON: Let me go to Dr. Botkin and hopefully to our next and last presentation.

DR. BOTKIN: Two questions. I wonder if there is a period of time that you would say conservative measures have to sort of run their course. In other words, how long would you enroll a child in a conservative measure or approach before you would determine that it was ineffective for that child? Is there such a time period that you think is reasonable?

And then, secondly, have folks used any quality of life measures in this domain with

conservative measures that have been reported?

DR. HOELSCHER: I know there are some studies that have done that. I'm not real familiar with that aspect of it. As far as the time period, I would say based on most of the studies, it looks like six months is a good time period at which you should see an effect. And if you don't see an effect after six months, you probably need to change course.

A lot of these studies have been done six to eight months when you look across the gamut of them. So that should be enough time to see an effect. In some of them, you will see an effect in three to four months, but six months is probably a better time frame, I would think.

CHAIRMAN NELSON: Thank you.

DR. HOELSCHER: Thank you.

CHAIRMAN NELSON: And thank you for the presentation and the answers.

So we have one more presentation and discussion and questions before the end of the day, which has been a long day. And that's Dr. Victor Garcia from the University of Cincinnati, who is going

to be speaking to us on surgical intervention including devices, and who is using his own laptop. And we just need to switch over to the technology.

Go ahead.

DR. GARCIA: Thank you for the opportunity and for the invitation to discuss surgical intervention as well as devices in addressing adolescent obesity.

SURGICAL INTERVENTION INCLUDING DEVICES

DR. GARCIA: My charge as I was directed was to review the various procedures and relevant anatomy, the assumption being that there were many members in the audience who were not familiar with the surgical procedures. I understand, though, that you have already had a discussion or a display of the LAP-BAND. So in the course of my presentation, I won't dwell on that.

I will take the time that is allotted to me to go over briefly the outcomes and allow opportunities for questions and specifically focus on the safety of bariatric procedures as well as the effectiveness. And in discussing these procedures, I

am going to be somewhat all-encompassing in talking not only about the most common ones but also the devices that are available and in use not here necessarily but throughout Europe and Australia and Latin America.

I'm also going to pursue the advantages as I view it as far as doing bariatric surgery in adolescents and then, finally, give you somewhat of a personal note but also somewhat justified by the literature out there as far as what my concerns and issues are about doing bariatric surgery in this population.

For purposes of discussion as far as the surgical procedures that are available, there is a plethora of them, not all of them as effective as the other, but I think that in most instances, the surgical procedures will restrict caloric intake and/or increase malabsorption.

If we go, then, with the first or the most severe as far as the malabsorptive procedures, the two that are in existence and are used some more so than other are the biliary pancreatic diversion, with or

without duodenal switch. And then there is the distal roux-en-y gastric bypass.

We then I think logically would look at truly restrictive procedures. And the first one that was developed was the vertical band or gastroplasty. There was then the introduction of the gastric band and then with the use of laparoscopy and adjustable gastric band.

And then recently because of interest in trying to decrease their attendant risk in operating on super obese patients, there has been, then, an interest in sleeve gastrectomy, recognizing that it really only offers at least just temporary weight loss.

And then there are the more common procedures. Certainly the one that is most commonly done here in the United States, it's a combination of the restrictive and malabsorptive. And that's the roux-en-y gastric bypass.

There are two other procedures that are performed throughout Europe, Italy, for example. One is the intragastric balloon. And the other one is the

gastric stimulator, the implantable gastric stimulator. In both these instances, the morbidity and mortality is considerably lower than with the more invasive procedures, but as you will see in the course of this presentation, with the lower morbidity, lower risk, the excess weight loss and the durability of that weight loss are somewhat limited.

Let's talk in a little bit more detail about the vertical band, the gastroplasty. There are those proponents of it who feel that this is actually quite effective. It certainly does not have the micronutrient deficiencies that one sees with the biliary pancreatic diversion or with the roux-en-y gastric bypass.

But, as one recognized quite readily, while the weight loss was quite admirable for the first year or so, there was regain. And one found also that, particularly for patients who tended to eat high caloric foods, one could easily bypass the effect of the rather small gastric pouch as well as the outlay. The other finding with time is that this outlet would dilate again, allowing the individual to

eat quite a bit.

The sleeve gastrectomy we touched on. It's resection of a good portion of the stomach. It does result in weight loss, again weight loss with a lower morbidity and mortality. As a matter of fact, in those who had the most experience with it, the mortality is zero. The complication rate was also relatively low.

And then we have the adjustable gastric band. The way this mechanism works, then, as I think you have already been told, is it creates a small pouch through which there is a limited amount of food intake and is tight. The mechanism of this, we are still open for discussion. It's of interest that, despite I think significant weight loss, that there is increase in relin levels, as opposed to with the gastric bypass.

The malabsorptive procedures are really the distal gastric bypass as well as the biliary pancreatic or duodenal switch. This procedure as well as the distal gastric bypass are associated with such significant nutritional deficiencies that I don't

think that they are appropriate for discussion for the adolescent patient population.

However, the biliary pancreatic or duodenal switch is clearly the gold standard in the sense that it has the best weight loss in the sense of 70 to 80 percent depending on the series that you read. Again, the complication rate makes it not suitable for the adolescent.

Let's very briefly talk so that we're I think complete in our discussion about these devices about the intragastric balloon as well as the implantable gastric stimulator.

There have been two consecutive studies done here in the United States looking at this device. Again, as one would imagine, just with simply putting a device or wires on the stomach, the complication rate is actually very, very low. But, as one would imagine, the excess weight loss is mild to moderate in the sense of 23. With a sort of enhanced screening, that excess weight loss in this study was increased to 40 percent.

Well, then there is this phenomenon of

putting in a balloon endoscopically. One inflates this with about 500 to 700 cc of saline. It dwells in the stomach. And, again, one can enjoy some decrease both in BMI as far as weight, but, again, the weight loss is moderate.

There are some studies, case reports, that suggest that with the retrieval of this device, that the weight loss is sustained, but the vast majority of patients who have this taken out regain their weight.

The most common procedures, then, that are available to us in the armamentarium are really the two. The biliary pancreatic or duodenal switch, as I mentioned, is not really suitable for adolescents, though it is considered a procedure for the super super obese. Individuals who with this procedure in its standard form may not achieve the weight loss that they would desire.

So we have, then, the roux-en-y gastric bypass. There are a number of approaches. We'll discuss, then, both the open approach and the laparoscopic approach. And you'll see that the weight loss as well as the complication rates are comparable,

despite using the laparoscopic approach. And we'll also discuss, then, the adjustable gastric band.

I will not, then, since you have already had a discussion as far as the gastric band dwell on the video, but I did think it would be worthwhile for this audience, particularly those who are non-surgeons, to appreciate, then, the complexity of this procedure.

Although it is quite effective as far as achieving weight loss, it is one that in the scale of zero to 10 with 10 being the highest degree of difficulty to perform the operation laparoscopically, experts in this field feel that this is something on the order of about 9.5 in difficulty.

I emphasize this because it will touch on some of my concerns about bariatric surgical procedures, who should be doing them and in what context.

But in performing this operation, one would vary the roux-en-y. The longer this limb, then the greater the risk of nutrient deficiencies. That having been stated, as long as this limb is in the

order of 75 to 150 centimeters, at least in the studies that are published to date, one does not see the significant protein/calorie malnutrition.

However, because one bypasses, then, a segment of the jejunum as well as the duodenum, there is still fairly common iron deficiency anemia as well as impaired calcium and a number of other micronutrients.

As this procedure is being performed more and more frequently, one sees increasing reports of the consequences of these micro deficiencies via-a-vis beri-beri, encephalopathy, increased bone turnover, osteoporosis. I suspect the list will go on and on.

As a result of this approach, one then makes the stomach the size of a football into about a 20 to 30 cc pouch. An additional component of this procedure is to narrow the connection between the neo stomach and the small intestine so that the stomach or the food can empty at a much slower rate. Because of the smaller stomach, the patient then gets full much more quickly.

Of interest is that, even though we were

all excited with the fact that grunion levels had decreased, perhaps this was contributed to the mechanism subsequent to these, there are some conflicting reports that the sense of satiety does not have any relationship to grunion levels, either pre or post.

Here's the completed operation with these, now stomach as well as the intestine. We won't dwell on the LAP-BAND, but I did want to then direct your attention to the next question is what is the outcome? What is the comparative effect of these procedures?

This is the study from the Swedish obese subjects study published in the New England Journal of Medicine. It compares for you, then, a controlled population that received considerable therapy as far as the management of obesity as well as a group of patients who underwent an adjustable band as well as vertical banded gastroplasty and the gastric bypass.

And what I'll draw your attention to is the fact that while this study is one of the longest studies, it has the advantage of having the control group, be it a randomized control group, it does then

demonstrate to us the findings that are I think duplicated in a number of other studies published throughout the world as well as here in the United States. And that is that the gastric bypass procedure offers us a much more dramatic, much more rapid, and much more sustained weight loss compared to the purely restrictive procedures.

Nonetheless, with that weight loss in this study, one found that there was not only resolution of comorbidities, which we in our own experience at Cincinnati Children's comprehensive weight management program have also seen, but of interest is that when compared to the control group, there was a lower incidence of certain comorbidities, specifically diabetes, hypertriglyceridemia, and hyperuricemia. There were not significant differences noted as far as hypercholesteremia and hypertension.

The conclusion of these authors is that long-term weight loss was a consequence as far as bariatric surgery. It also helped as far as improving their lifestyle and the amelioration with some of the risk factors known to be associated with excessive

weight.

There was a subsequent study, more so a meta analysis, looking at the surgical treatment of obesity. And given that the viewing of this slide is not perhaps the best in this room, let me just simply summarize that what it demonstrates is, again, what was demonstrated in the Swedish obesity subject study. And that is that roux-en-y gastric bypass had a much greater weight loss. Biliary pancreatic diversion had the best. And then following that was the vertical banded as well as the adjustable gastric band.

What is the cost of these procedures? That is to say, what are the consequences from a standpoint of morbidity and mortality? As I alluded to in the beginning of my remarks, with the procedures that offer you or more weight loss or rapid weight loss, more sustained weight loss, one sees, not surprisingly, a higher complication rate, specifically mortality rate, as well as morbidity rate.

However, the authors of this study in their analysis felt that there was not a statistically significant difference in mortality between these

procedures, even though the data here, the numbers, the absolute numbers, here would suggest otherwise.

So we could summarize, then, on this more easily seen cartoon the bariatric surgical outcomes for adjustable gastric band, roux-en-y gastric bypass, the sleeve balloon, and the inflatable gastric stimulator that the morbidity, the mortality is lowest with the adjustable gastric band.

The excess weight loss is on the order of about 47 to 50 percent, again depending on who the author of the series is. The roux-en-y gastric bypass has a higher excess weight loss, but, again, the complication rate and mortality rate, .5 percent, is somewhat higher. Even higher yet but, yet, with much greater excess weight loss is the biliary pancreatic duodenal switch. None of these are available in the United States except for the inflammable gastric stimulator, which is part of a trial.

The additional I think important finding or demonstration as far as bariatric surgery is a number of studies. And I know of three to date. There is only one here that I have decided to display

again in the interest of time.

There are three studies that would suggest that as a result of the weight loss associated with surgical weight loss, there is improvement in survivorship; that is, that long-term mortality is decreased. And this is the work of Christou in Canada where he found that there was a significant reduction in mean percent excess weight loss, that bariatric surgery resulted in that, that these individuals then also had significant risk reductions as far as developing cardiovascular disease and the other comorbidities we recognize associated with obesity.

But I think of particular import to this audience as it pertains to the adolescent, who is less likely, then, to lose weight when they're in the morbid obesity stage of super obesity is that their relative reduction in the risk of death.

I think this is of particular interest for those subgroups who perhaps are at greatest risk who are a shortened life span as a result of obesities, particularly minorities, black males, Hispanics, who are not perhaps available or have access to some of

the sort of robust and conservative management programs we just heard about.

In 2001, when presented actually with a number of patients with severe obstructive sleep apnea, so severe that they were going to be trach-dependent, we were approached then to contemplate doing a bariatric surgical procedure.

We are a result of that initial experience, then, developed with then one of your members of your panel the first children's hospital-based bariatric surgical program in the country.

And we have at the time of this slide presentation preparation 63 adolescents with a mean age of 17.5, and I want you to note a BMI of 58.1, a range of 44 to 85. Ladies and gentlemen, these are not adolescents who are just simply 10 or 15 pounds overweight.

Now, fortunately, our experience was comparable to that with adults. We had no procedure-related deaths, though we did have one death of a child who nine months afterwards while

convalescing in a nursing home for his osteoarthropathy developed infectious colitis, which was unrecognized, and he then went into hypoglycemic shock and multi-organ failure and died as a consequence of that.

We did have two children who had severe complications, beri-beri with sequelae over two months. And I think that that was related to severe vomiting. It was not really appreciated. And we had a number of minor complications.

Of particular interest to those of us when we developed this program were some of the findings that I am going to share with you now in this sequence of slides. When performing a roux-en-y gastric bypass, these children were obviously concerned of how detrimental or deleterious this may be as far as a child's body composition.

We looked at 13 patients, though all of our patients, then, we asked them to have DEXA scans as long as they can fit within the DEXA machine. We looked at 13 patients at 3, 6, and 12 months and looked at their weight, fat, and lean mass, again,

asking the question, does this rapid weight loss have a detrimental effect and adverse effect on their body composition?

We were intrigued to note that at 3 months, the fat loss was about 19 percent and lean mass loss was about 17 percent, but at 3 to 12 months, we still continued with significant fat loss but with very little nonsignificant lean body mass loss, suggesting to us that despite, then, this rapid weight loss and probably as a result of our regimen as a result of high protein intake, that lean body mass was preserved in adolescents.

We looked at then also how obstructive sleep apnea was or was not affected by the weight loss. We have 34 patients to share with you, 19 of whom had undergone both pre and post-op sleep studies.

Now, of note, what we found in this cohort of patients is that there was a fairly high prevalence of obstructive sleep apnea in these patients, 55 percent. But what we also were pleased to see is that as a result of the weight loss, that there was in all patients either resolution or improvement of their

obstructive sleep apnea and that when compared to adults, that the apnea hypoxia index improved nearly 20-fold compared to at least the literature would suggest 3 to 5-fold in adults, suggesting that perhaps earlier intervention would result in a better outcome.

I don't need to sort of educate this distinguished group about the consequences of obstructive sleep apnea as it pertains to the changes as far as the cardiac hypertrophy and that that in and of itself is an independent risk factor for sudden death. So this is clearly a very, very critical finding.

We also looked at left ventricular hypertrophy in this group, five patients who had pre and post-operative echocardiograms. There are more details to this. What we did find is that as a result of the weight loss, there was decrease as far as left ventricular wall thickness as well as a decrease in ventricular mass, a decrease.

Compare this, then, this figure, with the only adult study that we were able to find that only demonstrated about a 14.5 percent decrease in left

ventricular mass after surgical weight loss, again suggesting that perhaps intervening earlier will result in the better outcome.

Dr. Inge has been quite instrumental in looking at the metabolic profile. And as a result of his stewardship, we have some I think rather interesting findings suggesting that insulin resistance, which was elevated in a significant percentage of these patients, decreased by 70 percent overall in completely normalizing all but one. In addition, there was a twofold improvement in beta cell function.

Now, related to the metabolic syndrome in diabetes, I think it's important to look at what our adult colleagues have demonstrated and specifically that the duration and the severity of diabetes directly determines whether weight loss will help improve or resolve.

This is Bill Schaueser's work, which looked at, then, a cohort of patients. What he demonstrated and what I just want to point out to you is that the duration of diabetes was a highly

significant factor determining whether a patient had either resolution or experience improvement as well as the amount of weight loss, the excess weight loss, suggesting, then, or prompting, then, a number of distinguished individuals, to include Dr. Pories, to publish this sort of editorial or article in Diabetes Care just recently, giving us the sort of provocative question, surgery as an effective early intervention for diabesity, combining, then, diabetes and obesity, why the reluctance.

And, again, he simply corroborates, then, the findings of Schaueser and Paul O'Brien and others that early intervention in the management of these is really a subject for type II diabetes, will help achieve and maintain significant weight loss and that remission was predicted by greater weight loss in a shorter history of diabetes. Improvement in insulin sensitivity following surgery was best predicted by the extent of weight loss as well as improvement in beta cell function.

Recently Bill Schaueser and his group published on again, another aspect of the metabolic

syndrome and the effect of weight loss. And that is the fatty liver.

In our own patient population, where we perform liver biopsies on all the patients who undergo roux-en-y gastric bypass, over 90 percent of them have some form of nonalcoholic fatty liver disease and a fairly significant percentage have already fibrosis.

So this is of a particular concern to us, recognizing that some gastroenterologists, pediatric gastroenterologists, feel that nonalcoholic fatty liver disease and NASH may be the next indicator for liver transplantation.

What Bill Schaueser and Mattar did is that they biopsied not only at the time of surgery but had a cohort of patients that actually undwent biopsy afterwards.

Again, these findings are perhaps not surprising but certainly very reassuring. And that is that with weight loss, there was reduction of the prevalence of metabolic syndrome but that there was also marked improvement in the liver steatosis. Again, this was a biopsy after weight loss. That was

about 15 months afterwards. And in some 37 to 20 percent, inflammation or fibrosis resolved.

Now, the question, then, given the fact that bariatric surgery or surgical weight loss is in many respects salutary, what would be the appropriate timing of it? Well, first off, it's our contention that the child should have attained physiologic as well as skeletal maturation, that they will have reached the stage of cognitive development that will have them acquire formal operations. That is to say that they are capable of thinking about the possibilities and consequences of what happens if I do or do not take my nutritional supplements. And then, finally, they are of acceptable psychological health as well as looking at the weight-related quality of life.

The advantages, then, are that there are procedure-related benefits as a result of bariatric surgery, which suggest that it is safe and effective long-term, that there is as far as the comorbidities resolution and amelioration of most, if not all, but that this is the function of the duration of the

disease and that there is also the reducing of the incidence of these comorbidities as well as an improvement in the quality of life. There is also some suggestive evidence again in adult studies that there is increased survival compared to a medical management.

But there are some concerns. And I will just dwell on just a few of them. Of particular concern is that of metabolic bone disease. A recent study, then, published in 2004 would suggest that there is an increase in bone turnover and decrease in bone mass.

The authors looked at urinary telepeptides as well as osteocalcine. But the question that still remains and why this is certainly an area further for research is, is this simply a phenomenon as a result of the super obese and morbidly obese child patient losing that excess weight?

There are concerns as far as the nutritional deficiencies. They are more common with bypass procedures. And there are those of us who might think that they don't exist with the clearly

restrictive operation. That's not the case. There are some future deficiencies associated with fairly restrictive operations. But clearly they are more common with the bypass procedures.

Even with the roux-en-y gastric bypass, there is a fairly high incidence of iron deficiency anemia as well as choline deficiency, vitamin B-12 deficiency, and thiamine deficiency, again, requiring nutrient supplementation, not just in the short term but lifelong. And that sort of begs the question about compliance.

Now, I mentioned about the fact that this operation is an operation of some degree of difficulty. One has to then take this into consideration when one looks at what would be the threshold for operating on an adolescent.

There are two schools of thought. One would be a conservative higher BMI threshold. Another school of thought would accept the NIH guidelines.

Let me suggest to you, then, that one should look at a conservative guideline as one offering an operation, particularly one where we're

not clear as far as the outcome, when in the course of the life course that the complication rate or the risk of complication is lowest, when medical therapy clearly is ineffective, when the outcomes are likely to be the best and when the likelihood of recidivism is the lowest.

If I make the assumption that you then agree with that as a definition, we look at, then, a higher BMI threshold and what the outcomes are related to operating on a patient who is heavier.

And one sees that as early as 1987, noted experts in this field noted that the super obese individual was less likely to lose their excess weight, but they were more likely to gain and that also they were more likely to experience procedure-related complications.

BMI, preoperative weight, is an independent risk factor for procedure-related complications and death. We need to conclude that by having a higher BMI threshold to operate, whether it's the laparoscopic adjustable band or roux-en-y, might, in fact, have an opposite-than-intended effect in

terms of the outcomes we want for this adolescent patient population.

Experience does matter. One of the consequences of, then, the burgeoning of bariatric surgery as a discipline is that many individuals who were not qualified entered into the field. And as a consequence of that, the complication rate belied what was seen in the published literature.

This is an article from the Harvard Business Review that for coronary artery bypass, for coronary angioplasty, for esophageal cancer surgery, complex procedures, that who does it and in the context and in what setting have a direct impact on mortality risk. I would propose or submit to you that adolescent bariatric surgery would also fall in that category.

This is work done by Dave Flum that simply supports that contention. Even though the mortality rate for roux-en-y gastric bypass is on the order of about .5 percent, when we looked at the state registry, he found then, again, that the mortality rate was considerably higher, on the order of about

1.9 percent, and that for the surgeon who in his first 30 to 40 cases had a 40-fold higher mortality rate than if he had done 200 or 150 cases.

There is an argument for reasonablization of complex procedures. And in my estimation here, the literature is nearly incontrovertible, that for certain complex operations -- and I would submit that for very active surgery, that outcomes are directly related to surgeon as well as hospital volume.

This is something that is not just shared by those of us here. This is a conclusion or recommendation of Lars Sjostrom of the Swedish obesity subject study, who felt that, really, an obesity center for every 500,000-person population would be in order and that this center would perform 500 to 1,000 operations per year and that the center would be mandated to perform life-long follow-up.

What are the attributes of the bariatric surgical program for adolescents? I think that, despite the fact that there is no evidence out there, we can still borrow from our colleagues who have done remarkable work in diabetes, cystic fibrosis, and base

our bariatric surgical program for adolescents on those best practices.

But it also should be a multidisciplinary team providing comprehensive evaluation standard, standardized care as far as surgical intervention, as well as postoperative medical, psychological, as well as surgical surveillance. And I submit that there needs to be a support group, not just for peers but also for the parents.

One needs to recognize that incomplete data is worse than no data. It is essential in embarking on the clinical trial of the one that perhaps we're postulating that one look at maximal retention as far as study participants because our ability, then, to draw definitive conclusions about the absolute and relative efficacy and safety of whatever procedure you're entertaining is limited.

So to have a 50 percent follow-up is in my estimation unacceptable. We would have to have complete evaluation of all enrolled patients as a critically, if not absolutely essential, aspect of any clinical trial for barriers of surgery in adolescents.

I'll read this for this, but this is a response from Paul O'Brien, a respected bariatric surgeon, a major proponent of the adjustable gastric band. In preparation for this presentation to this distinguished group, I queried him, given the fact that he is in the midst of a randomized study looking at LAP-BAND and optimum nonsurgical therapy.

His response is as follows, "On compliance of adolescent, awful, much worse than adults, maybe just because they're adolescents or it may be that they just don't sense the severity of the problem as do adults. It may be that they are always dependent on mum, m-u-m, or dad bringing them along. And so the logistic catches it.

"For whatever reason, I would guess they would score about three to four out of ten on compliance test scores; whereas, our adult patients would probably average around seven to eight.

"On effectiveness, this is a good operation. It's good if they attend, better rate of weight loss than the adults. Bad habits. They're probably more susceptible to peer pressure than the

adults and so have episodes of social eating and drinking, which destroy the good results so quickly.

"And with a lack of attention to the eating rules, eating too much too fast, the incidence he feels is going to be much higher as far as prolapse. Clearly there is a need for a carefully randomized control trial." And then, of course, there is always the salutation, "Good luck."

I would conclude that the success for adolescent bariatric surgery is an imperative. These children are desperate. They suffer more than one could imagine as far as their so-called medical comorbidities. Their quality of life is abysmal.

But what I would suggest is that to those surgical hospital volume is a critical component and the choice of operation may be a component as what we do here is really going to guarantee the success of whatever operation we propose. The basis for that is going to be blue ocean strategy.

I will conclude my comments and take any questions anyone might want.

CHAIRMAN NELSON: Thank you.

One quick comment before we start the questions. I think a number of your slides probably would be worth the panel being able to refer back to in our deliberations tomorrow.

So I hope we can get a copy to make printed copies for the panel, be able to distribute for tomorrow's discussion, if we can solve that as a technical issue, even if it's a .pdf file or something, because I gather you're using something other than PowerPoint. If we could figure that out?

DR. GARCIA: That's not a problem.

CHAIRMAN NELSON: Good.

DR. GARCIA: We have the technology.

CHAIRMAN NELSON: Perfect. So just to give you timing, and then I'll to our first question. We're scheduled to go until 6:00. What we'll do is we'll either go until 6:00 or until exhaustion, whichever occurs first. Okay? So start over with Dr. Kral.

DR. KRAL: Two comments and a comment/question. Comment number one, you did a very good job of presenting this wide array of information.

Second comment for everybody to note, Dr. O'Brien's from Australia, from Melbourne, ideas about adolescents' performance after LAP-BANDing contrasts that to Dr. Fielding's presentation before. Are we talking about the same population and the same people? And I will let you draw your conclusions.

The comment/question is I was rather surprised that you juxtaposed the outcomes of the super obese adult with projected outcomes of the super obese adolescent. Do you not believe that these are very, very different phenomena?

The super obese adult comes in end-stage disease with prolonged chronic disease and certainly does not have any of the resilience of the younger individual, any pediatric surgical patient, compared to the adult, and particularly when it comes to this type of surgery.

In other words, I think it's unfair, and I wonder what your opinion is. Do you think they're the same?

DR. GARCIA: Well, certainly the super obese, one would have to stratify that population.

The super obese has had tumor or has coronary artery disease. Yes, that's a different individual.

But the super super obese adolescent who by virtue of his mass, if that's what you're alluding to, still represents a technical challenge that I think is not addressed when we look at our guidelines.

Is that the question you were asking?

DR. KRAL: Yes. I mean, there's no contest that the earlier you intervene so that you don't even allow a progression to that extent is better. That wasn't the basis of the question.

DR. GARCIA: Okay.

DR. KRAL: The basis of the question is that the adolescent has not had as severe a eating disorder, has not had as long a period of time to evolve any of the occult or other comorbidities that are involved as the adult does.

Certainly we should have highly technically proficient surgeons doing this and it should be centralized, but --

DR. GARCIA: I don't know the question to that. I don't know the answer to that question. What

I do know and I think raises a number of concerns is that within a much shorter period of time, that adolescent has achieved super obesity.

So one has to wonder what consequences that has, both metabolically as well as physiologically. And they're not even addressing the psychosocial.

But the other thing that we are noticing is that the incidence of metabolic syndrome and diabetes is certainly much, much greater, much higher, in our pediatric population. As a matter of fact, Cincinnati was one of the first institutions to publish a tenfold increase in diabetes. And, again, most of those individuals were obese.

So to suggest that because they're adolescent they don't have the comorbidities that an adult has I don't think is accurate.

DR. KRAL: No, but it's not accurate to compare the obvious resilience of the younger individual. And let's not even discuss pediatric. Even in adults, the younger the patient, even at ISO B's; in other words, at the same level of obesity, the

outcomes are better.

DR. GARCIA: The outcomes in what respect, Dr. Kral?

DR. KRAL: Any one, any kind you want.

DR. GARCIA: So weight loss?

DR. KRAL: The significant one is the safety and the operative safety, the safety of doing the surgery. That's what we're discussing, right?

DR. GARCIA: Right. Well, certainly that adolescent who does not have coronary artery disease and lung disease, if he were to have a complication --

DR. KRAL: Can take the joke better.

DR. GARCIA: Yes, yes.

DR. KRAL: Yes. Okay.

DR. GARCIA: But why suggest them to that risk?

DR. KRAL: Oh, I agree. Prevention is even better.

CHAIRMAN NELSON: If you want to pursue this line of discussion, we could continue, but we want to go to Deborah. And then I'll come back.

MEMBER DOKKEN: I also was struck by what

seemed to me as a lay person a pretty dramatic difference between hearing that compliance was no problem and that compliance was awful. And it brought me back to our discussions about assent that we have had earlier in the day.

So I guess, again, as a lay person and not a clinician, where is the true picture about compliance on two ends of the spectrum that said it was no problem and that it was awful?

DR. GARCIA: I don't believe that compliance is no problem. That's all I'll say.

CHAIRMAN NELSON: Anyone else want to answer the question?

MEMBER DIAZ: When it comes to adolescent behavior, just look at normal adolescents and draw your conclusions.

DR. GARCIA: But that is not to say that it is insurmountable. That is not to say that it is insurmountable.

MEMBER DOKKEN: That it is important to address.

DR. GARCIA: And, if anything, it requires

more attention than perhaps many of us are giving it.

DR. PORIES: We run a children's camp and try very hard between the camps during the year to follow these kids. Our success rate is about 35 percent. This is with the buddy system and all sorts of ways. So I fully agree. Follow-up is a problem.

CHAIRMAN NELSON: Before going over here, there were three hands that came up. Were we continuing the compliance theme basically? Okay. So Dr. Gorman and then Dr. Garofalo.

MEMBER GORMAN: I think this might emphasize for us tomorrow in our discussion to focus on multidisciplinary approaches to this, even inside the surgical arena. Dealing with children with chronic diseases and adolescents with chronic diseases, be they diabetes or other, has given pediatricians a large body of information of how to deal with adolescent noncompliance, sometimes successfully.

CHAIRMAN NELSON: Dr. Garofalo?

MEMBER GAROFALO: Yes. So my question is you showed some data about morbidity and mortality

comparing the different surgical operations. So some of the data might be more limited. Some there is longer experience.

So can we generalize from what we know about the banding, you know, if it has been very carefully done? And do we think that data is going to hold us and it's more generalized and it's more available?

DR. GARCIA: I think that, as with any surgical procedure -- and I think that it would be oversimplification to say that this is something that you can see one and then just do it.

So I would anticipate that with generalization, even though the learning curve is not as steep as with roux-en-y gastric bypass, that you will see a higher complication rate than what one sees published with a Paul O'Brien or a George Fielding.

And that's why I'm a strong proponent of regionalization in centers of excellence. If we're doing that now as an afterthought for adults, it should not be an afterthought for the adolescents. It must be a priority.

CHAIRMAN NELSON: So we're going to go back to Dr. Choban and Dr. Klish.

DR. CHOBAN: I had two things. I may have missed something. What is blue ocean strategy?

DR. GARCIA: I was hoping somebody was going to ask.

DR. CHOBAN: Oh, okay.

(Laughter.)

DR. CHOBAN: Was I not paying attention earlier?

DR. GARCIA: No. You know, when dealing with this issue of adolescent compliance, have you ever just wondered why the makers of sneakers are doing so well or the makers of jeans? What is it that allows a business to market so successfully to an adolescent?

It's peer, but there's also a science behind this. On another venture, we're working with a collective marketing firm that markets for -- what is it? Abercrombie. What is it called?

MEMBER GAROFALO: Abercrombie and Fitch, Limited.

DR. GARCIA: Abercrombie and Fitch. They know how to push the button, and they know how to get that teenager to come back. They know how to establish brand loyalty.

And as physicians and health care and medical personnel, I think we need to look at blue ocean strategy. Blue ocean strategy is really looking at the development of iPod and Sonys, not looking at what the evidence demonstrated but also looking at how Cirque de Soleil, for example, in looking at the circus, how it was done. And Cirque de Soleil used blue ocean strategies. And now we're willing to pay $150 to go to the circus.

That's blue ocean strategy and what needs to be applied as part of this comprehensive program.

DR. CHOBAN: That sort of actually brings me to my second issue, the Abercrombie and Fitch reference anyway. If you've seen the ads, you know, it's kind of like I find a few of them a little askew.

In my adult population, we have seen a fair degree of they can get a little promiscuous. I've done some younger people, 16, 17, 18. And they

have been primarily the children of my other patients. Two of them I can think of when you ask mom, you know, when you see mom, you also, "Oh, how is" so and so?

"She's pregnant." And mom is not very happy and sort of looking at me like I'm responsible. You know, sorry.

How do you address that? I mean, I think it is a real issue for people who have been somewhat socially isolated because of how they appear and suddenly it's like "I'm like everybody else, and we can kind of swing a little too far the other way."

DR. GARCIA: Tom, how many pregnancies have we had? Four? Something like that? Yes.

DR. CHOBAN: Sixty-three?

DR. GARCIA: Yes.

DR. CHOBAN: That's a lot. I mean, in a pediatric adolescent population is that?

DR. GARCIA: So what you touched on is that you now have this metamorphosis. I mean, they have now lost weight. But I think we have ignored the fact that they have been ostracized, stigmatized,

marginalized. And now that they are this new being, they don't have the life skills, they don't have the sort of concrete formal operations to really think about what the consequences are that when "Sam decides to ask me out and says, 'I love you,'" that it's not true love.

I really think that this compliance issue is not just compliance with eating a five, three, one ratio or getting your protein first, but it's looking at, really, life skills globally.

In addition, in addition, a good proportion of our patients, their parents are super obese, if not morbidly obese. But, in their defense, when they come in, they'll tell us, "I don't know how to cook. I didn't know about eating a bagel and why I'm so hungry shortly thereafter."

When you take this on, you take on more than just doing an operation. You take on really a true education of both the child as well as the family. And it's not insurmountable.

CHAIRMAN NELSON: Dr. Klish?

DR. KLISH: I don't want to talk about

blue oceans or sex, but I have a totally different question. You described several studies where they are comparing medical management to surgical management. And the conclusion was that there was more mortality and morbidity in the medically managed group than the surgical managed group.

You may have said it. I may have missed it. But how were the medically managed patients selected in these studies? In other words, were they the medical patients that were successful in early weight loss or did they just take all comers to a medical therapy which has, at best, maybe anywhere from 15 to 20 percent success rate?

The reason I'm saying that is I think if you had a fair comparison, you would only compare to the successful medical managed patients if you're truly trying to go head to head looking at how well bariatric surgery works.

DR. GARCIA: Well, but if you took it -- none of these studies were randomized controlled trials. If you then look at them as intent-to-treat analysis, then whether they were successful or not,

then you would still I think have a valid comparison.

For the Swedish obesity, it was individuals who were then part of an obesity treatment. Now, it wasn't an Epstein aggressive, but it was still an obesity management.

DR. KLISH: I agree. When you look at it from the terms of intent to treat. That may be fair at this state of the art, but if we become better medically to handpick our patients that we think are going to be more successful, then those kinds of studies aren't going to be relevant, I think.

I'm trying to grasp this in my own mind as well because theoretically if we get more successful, you have to somehow know how to compare these things head to head.

DR. GARCIA: I truly hope, Dr. Klish, that you do become much more successful soon.

DR. KLISH: Well, I think it is happening. Success is increasing. Every year our success gets a little bit better.

CHAIRMAN NELSON: I'm not surprised that our statistician wants to comment on intent-to-treat

analysis.

(Laughter.)

MEMBER O'FALLON: Well, not necessarily comment on that, but, rather, I have been sitting here listening to you and trying -- I mean, you're saying, in essence, that they are -- O'Brien or whatever his name was from Australia was saying that they are terrible at compliance but the way they don't even get to the surgery until they have already "failed" the medical management or behavioral management. Is that not correct?

Okay. So already the people that get the surgery have already shown that they can't follow the medical management. And, yet, you're turning -- I mean, it seems that we're kind of in a loop here.

And then I wonder, are you saying -- in essence, we really do have in these centers for adolescent overweight or obesity, don't you have to have more effective programs for delivering behavioral? I mean, it's important, both before and after they get the surgery.

DR. GARCIA: Yes. And, yes, you are there

because you have not done well with the behavior. But one recognizes that once you reach a certain level of adiposity, that there are physiologic drive, stimuli that just make that behavior just not possible.

So, even though if I weigh 300 pounds or 400 pounds, even though I may know and want to or have a desire to not eat that extra, there are drives that I'm not going to be able to control. And that's where surgery comes in to play, where it will limit not only the amount. Depending on the procedure, it will limit what kind of foods that I can eat. Otherwise I'll get sick or have dumping syndrome.

MEMBER O'FALLON: One of our earlier speakers made the point that there are different kinds of hunger, that a great deal of the time it isn't really physical. It's in some senses up here that they are hungry. And that part maybe hasn't been fixed by the surgery.

CHAIRMAN NELSON: I didn't realize you were Cartegian.

DR. KLISH: Can I make one other comment?

CHAIRMAN NELSON: Continuing this line of

--

DR. KLISH: In the same line because you also implied with your last comment that it is impossible for a super obese individual to get back to normal weight using medical management.

DR. GARCIA: It's unlikely.

DR. KLISH: That's not true because we all have experienced that.

DR. GARCIA: It's unlikely. It's very difficult.

DR. KLISH: But it does happen?

DR. GARCIA: It does happen, yes, but it's very difficult vis-a-vis the --

CHAIRMAN NELSON: On my list, Dr. Daum, Dr. Kral, and now Dr. Botkin.

DR. BOTKIN: First of all, I want to say thank you for that talk because you've certainly enlightened me about a lot of technical aspects and outcome aspects of surgical management of these patients.

I had two questions that sort of will help me at least prepare for tomorrow's discussion. The

first one is, do you have any experience with this operation in younger people?

You talk about adolescents a fair extent. What about preadolescents or even younger children than that? Is there an experience with it? And have people attempted it and as good as what you showed?

DR. GARCIA: I do not have any personal experience. Our age limit is 13. There have been some reports or at least if not reports, I've been told by bariatric surgeons much wiser or at least older than I am that they have done even bypasses on a number of younger patients, but I have not seen reports in the literature or preadolescents. Sorry.

DR. BOTKIN: Thank you.

My second question goes to the children, the adolescents, you reported to us. It sounded like you selected extremely obese people for this operation. I wonder if you would comment on your thoughts about choosing less obese individuals for this kind of surgery.

DR. GARCIA: I personally think we should. I think that as a result of that higher BMI

threshold, besides the concerns that I outline in my presentation, that you will have some adolescents who will strive to gain weight in order to meet that threshold.

I think that when you look at the comorbidities and we say, "Oh, we have to have comorbidities," I am always struck by the logic there. There was a point in time that you waited until an individual had a heart attack before you perhaps intervened.

So now we know we don't wait. We look for other risk factors for the markers. We developed those markers by looking very critically at what were the precursors for these sentinel events.

Do you wait for the adolescent, then, to do knee replacement therapy before you consider osteoarthropathy when there is an indication or do you wait until you have a reversible cardiac chamber before you must intervene?

If we know that, again, the assumption or the observation is that this individual has failed efforts to lose weight and you know the natural

history, as the previous speaker alluded to, that once you are a certain BMI at a certain age, you are not going to suddenly grow into it. Then why wait, then, until that individual is super obese to perform a procedure that has risks that are directly associated with or directly related to the size of the patient?

So in many respects, it's kind of intuitive to wait until --

DR. BOTKIN: As just a final follow-up on the same issue, could you comment on how far down you turn the knob if you are charged with patient selection for this?

DR. GARCIA: How low?

DR. BOTKIN: Yes.

DR. GARCIA: Well, I could very comfortably and safely say I would go no longer than the NIH criteria. But I would also suggest that given the chronicity of this disease, knowing that there are ethnic and racial differences, there are some Italians who are obese who don't have diabetes, that there are many Hispanics and African Americans who as a result of their obesity are going to lose 20 years of their

life, it suggests to me that we need as a discipline to look more critically, then, at predictors and markers of adverse outcomes and use that as a criteria, not absolute BMI but the reactive protein. Let's look at that and see if that is something that we should look at as a marker for that individual who has failed, despite multiple attempts has failed, not wait until they are insulin-dependent or hypoglycemia or have nonalcoholic steatolipitoids.

CHAIRMAN NELSON: Dr. Kral?

DR. KRAL: A comment to the discussion between Dr. Klish and Dr. O'Fallon about selection and patients selected for failure and do we really have criteria for selecting patients. I have looked at that throughout my career. It isn't getting much better, and we are not very good at it.

Ben Italy and I wrote in JAMA around 1980 about the dilemma of what we then called morbid obesity, severe obesity. The dilemma was that the patients who probably most needed the surgery are those with the least resources to be able to follow through and do everything that is necessary. We had a

mini discussion about the adolescents here before, whether they have the means to pull it off well.

You mentioned among the devices -- and this is the point I wanted to make -- the electrostimulator. The failure with the electrostimulation was absolutely abominable in the beginning until they came up with what they called a selection algorithm which selects around 30 percent -- correct me if I am wrong on this. It's around 30 percent. Only about 30 percent of their candidates are eligible and fulfill the selection criteria. Only then will they improve and get some kind of effectiveness out of the electrostimulator.

So the devil is really in trying to find selection criteria. And they're not that difficult. They're the same, actually. And I don't use the word "conservative" but conventional or nonsurgical treatment. The selection criteria are the same. It's the stable family. It's the stable economy. It's all of that stuff. That works best for your outcomes, the same with surgery, too.

So there is an extraordinary need, as

you've just pointed out, for stratification and for many different parameters. And certainly race is one of them.

CHAIRMAN NELSON: I see hands going up, and I am going to write them down. But I just want people to think. We have been at this now nine and a half hours today. And the last thing I want you to do is start talking about tomorrow's question. All right? So to the extent that we want the wisdom of the current speaker, I think that is important. But we don't need to start talking about the questions that we're going to deal with tomorrow, which we started this slide into a little bit.

I'm going to go to Dr. Botkin. Then I'm going to look around the room and get the names of the people that have their hands up and hopefully everyone will consider the risk and benefit continued.

(Laughter.)

CHAIRMAN NELSON: So, Jeff, it's to you. And then we'll --

DR. BOTKIN: If you have a 15 or 16-year-old who had failed conventional approaches and

you were wanting to discuss a surgical procedure with an adolescent in the family, would you consider each of these to be on the table for discussion or do you have a clear preference or sequence?

And, sort of in parallel with that, if one were to do a LAP-BAND, is there a contraindication later or any experience with later going to one of the more invasive procedures?

DR. GARCIA: You know, I'll answer that question with some trepidation because I stand here in the company of adult bariatric surgeons who taught me and certainly have done orders of magnitude more procedures than I have.

Having said that, I do present the three procedures that I alluded to as the more common ones to the patients that I have. I tell them in very concrete terms, both the patient and the parent, about the risk-benefit ratio of a LAP-BAND as well as the roux-en-y gastric bypass. I also tell them that there is another procedure.

And, again, most of our patients are super obese. And in that patient population, the biliary

pancreatic duodenal switch, they would be considered candidates for that because they were enjoying I think a better success.

So I mention that that is yet another operation. And the advantage of that operation is that they won't have the limitations in how much they need. They will have some, but they won't have it to the same extent as they will with the restrictive procedure. I really asked them to think about that.

With that as my practice, I will tell you that I have had not one patient recommend or at least agree to have the LAP-BAND, even though I try to push them to have the LAP.

I think it's not that they don't appreciate the safety and the efficacy of it. They want that weight off. They come so desperate. At that BMI, they are so desperate they want the weight off yesterday.

So I draw up for them what the profile is as far as the weight loss, that yes, it will be slower with the LAP-BAND, but eventually you'll get up comparable to a little bit closer to where you are

with the roux-en-y gastric bypass. They want it. They want it off yesterday. And that is fascinating.

CHAIRMAN NELSON: The list I am working with right now is Hudson, Choban, Ward. And, Richard, was that your hand up there?

DR. BOTKIN: Skip, let me finish up with that same question. I think a quick answer, if you had a LAP-BAND first, would there be any contraindication later if you weren't satisfied with going ahead with the other bariatric procedures?

DR. GARCIA: I mean, I can comment on what more experienced surgeons have told me. I have not been that experienced. Dr. Pories can share with you what his thoughts are on that.

I will tell you that the individuals who have taught me who have done literally three to four thousand procedures, some LAP-BANDs, there is technical difficulty that those who would say that, oh, if you have a LAP-BAND, you could just pull it out and just simply go ahead and do a roux-en-y gastric bypass and it's no selecting a walk in the park. That's not what the experienced bariatric surgeons

will tell you. Those who have been in the fray, in the battle, in the trenches, they will say that it is technically more difficult.

Dr. Pories?

CHAIRMAN NELSON: Do you agree with that characterization?

DR. PORIES: You can convert them. It's difficult. There are a fair number of adhesions. It will probably increase the mortality of the operation, maybe twofold or threefold. It's probably something like two or three percent.

So yes, it can be done. It is difficult. I would imagine in the near future, as we get more experience doing it, we'll find more mortality as well.

CHAIRMAN NELSON: Dr. Hudson?

MEMBER HUDSON: You alluded to the experience of other chronic disease and long-term follow-up and that from that experience, we know that it's important to get to follow children into adulthood to assess some late treatment complications of these procedures.

Well, in fact, I'm monitoring a very vulnerable population. And it's increasingly challenging because they're mobile, they don't want to come back, and the institution in various places that not support that type of medical follow-up. How do you accomplish this or how have other surgeons accomplished this?

For us, long-term follow-up in oncology is beyond five years. So will the centers of excellence have this mechanism? Are there registries that are developed to monitor morbidity and all of these problems long term? How are you guys doing it now?

DR. GARCIA: Tom? We're not doing as good a job as I think we should. And we're still trying to get our hands on that because, unfortunately, there is not funding, then, to sort of do that robust analysis and follow-up. We're not doing as good a job as we should.

I come back, then, to my contention. It's my own contention that I think we in looking at these adolescents can learn lessons from our business colleagues of how they can come back again and again.

And we've got to think outside of the medical model and look at the life skills, look at how you can enjoy life. I mean, one of my consultants whom I sort of banty back and forth with, you can build this room and we would have computers that would be operated by people dancing on the floor.

And, again, there is this expertise where you can actually design areas so that, instead of that analyst going to the club, he wants to come to your hospital. Maybe it's not in the hospital setting but come to your facility because we have made it attractive, we have made it fun.

And I think to me the strategy is thinking outside. When he comes in or she comes in, everyone talks about protein and design. You know, we're doing our exercise. They could be doing protein and exercise and may not even realize it.

MEMBER HUDSON: But, see, you're still talking short-term follow-up because the long-term follow-up that tells us what the impact is on morbidity or even some of these shorter-term parameters, they're adults at that point. So you have

to change from engaging your adolescents to keeping the adults engaged. So is it a registry?

DR. GARCIA: Yes, yes. And, actually, Tom has such a registry to do that follow-up. One of the questions that we don't have that no one is asking yet is, we are a children's hospital. How do you follow these as adults? What are you doing as far as transitioning into health care?

DR. INGE: I also think that this brief comment, that it's important to consider the differences between cohort management in the study and cohort management, which is incredibly difficult, no matter what disease process or treatment program you look at in an adolescent population, an adolescent population distinguishes itself in multiple studies, but including the transplant literature, where the grafts are viable, is demonstrably worse for the adolescent than the younger school-aged children or in the adult population as directly compared head to head.

So I think that we do have an extremely significant challenge ahead of us for the clinical

treatment, but I do think that in regard to what the panel will be looking at; that is, you know, trial design, that there will be ways to ensure a valid scientific interpretation of data via standard trial cohort management techniques.

DR. GARCIA: But on that point, as far as the transplant literature and the graft laws, I think that there are some differences there because if you have a child who is taking steroids and wants to get off his steroids or has steroids because she wants an improved basis for the -- I think it's very different for a child who has lost weight and has a new figure and, yet, is still not able to compel them to --

CHAIRMAN NELSON: Dr. Choban?

DR. CHOBAN: Yes, but one of the things we were charged or that was described yesterday as part of our panel and what industry gets held to and what kind of studies is we talk about things being the least burdensome. Yet, we have talked about things like multiple failures of diets and multiple failures of drugs and things like that before.

These adolescents we have also talked

about have difficulty running the gauntlet can get access to roux-en-y gastric bypass is sort of what we have talked about. We are trying to think of a more generic scope.

So I guess as you look at LAP-BANDs versus the stimulators, there are some of the things that have less risk and do -- I guess do we trade selecting for success by taking only those adolescents who can run the gauntlet versus okay, we're going to give them a try with it since we don't have good selection criteria, if it's a fairly low-risk procedure, is that a reasonable balance? If you think it's lower-risk, it's almost like we're willing to accept a little higher failure rate in terms of weight loss if we're not buying more problems with it.

So is that a reasonable thing in this adolescent population who is having trouble running the gauntlet versus is that not a reasonable assumption if we're thinking of them as sort of vulnerable?

DR. GARCIA: Let me sort of address that from two perspectives. Number one is that I don't

think that we're anywhere close. At least in our experience, there are individuals who come from a very sort of nuclear family who have done well. And there are those who have come from a very nuclear family and they have not done well. There are those who have really -- they have a single parent and they are a lower socioeconomic group and they are a minority. Some have done well, and some have not done well. And we sit in our meetings and say, "Well, who would have thought?" So to say run the gauntlet, I don't know that we have that particular skill. I don't think we have that in our material.

My concern as far as going with a lesser procedure that has a lower risk is that if we take, then, the experience of a Paul O'Brien, who would suggest that they are eating faster and they are eating more, that that may then result in a higher incidence of prolapse, that that so-called low risk may not really stand a test of time unless we do something as far as getting them to be better compliant.

DR. CHOBAN: GPS trackers in the band?

CHAIRMAN NELSON: Dr. Arslanian, do you want to talk on this point or --

DR. ARSLANIAN: Yes. Just to give an example about adolescent being different from adults, the diabetes control and complications trial, which was an intervention with 21 centers in the U.S., North America, where the group of type I diabetics were divided into receiving intensive diabetes management versus conventional and every center included adolescents as well as adults.

So it was the same team providing the care to these people, these patients. And at the end of the trial, whether the adolescents were in the intensive or in the conventional, the HBA1C level was by one percent higher in the adolescents. So there is no question that with the same team. And, plus, there was a very intense selection process that went on at the beginning.

So here this is a landmark study with very intense selection process that was applicable to adolescents and adults, the same team providing the care to these people. And, yet, adolescents had one

percent higher HBA1C level pointing again that no matter what approach you have, there is a difference in how they receive and perceive your intervention.

So I think we have to keep that in mind as we approach any intervention with adolescent age group.

DR. GARCIA: This is very soft, but I stand before you as I think having a unique experience in dealing with adolescents, first during my time at West Point as a battalion commander in charge of adolescents, then as a military officer in the Army for 20 years, again charged with adolescents.

What I come away with is that the way you motivate adolescents to do things as even run up the hill and face a fire is not what seems to be obvious to the casual observer. That's the blue ocean strategy that I really challenge you to sort of explore to think outside the box, outside of the usual medical approach in dealing with an ill patient, to get them to comply.

The consequences are almost unbearable to think of with the sort of prodigious epidemic that we

have as far as obesity, the public health crisis that this represents, that for that small but, yet, significant segment of the population that weight management or conventional therapy is not going to work, that the only hope that they have is surgical weight loss.

CHAIRMAN NELSON: Just two more names on the list. It's Ward and Gorman. We're getting to the point where we'll end up stopping at 6:00 unless we get exhausted sooner. So Dr. Ward?

DR. WARD: I have a very simple question. You describe the endoscopic partial gastrectomy as having a complication figure of 9.5. How would you rate the LAP-BAND placement endoscopically?

DR. GARCIA: I'm sorry? You meant laparoscopically?

DR. WARD: Yes. Laparoscopically how would you rate the difficulty of placement of the LAP-BAND?

DR. GARCIA: I have never put in a LAP-BAND. So I would have to defer that to someone who has done a LAP-BAND.

CHAIRMAN NELSON: The degree of difficulty of the LAP-BAND is?

DR. GARCIA: The degree of difficulty is what the experts would suggest to be on the order of about five or six.

CHAIRMAN NELSON: Five or six. Five or six? Does five or six sound right?

MR. VINCENT: Three or four.

DR. CHOBAN: Four or five.

CHAIRMAN NELSON: Three or four. Okay.

DR. CHOBAN: I think I would say four or five. There's a learning curve on the LAP-BANDs, too. But it's not as tight.

CHAIRMAN NELSON: Four to five. It sounds as though that's a consensus.

DR. GARCIA: It's simpler than being a roux-en-y gastric bypass.

DR. CHOBAN: Yes.

CHAIRMAN NELSON: Dr. Gorman?

MEMBER GORMAN: You were very eloquent in your presentation about the need for earlier intervention, not of the super obese but down to the

NIH guidelines of 35, I think was their BMI, at which they felt you could do surgical intervention.

Is there any data past that point that would guide our discussion tomorrow for even earlier intervention, which I think you implied you might be interested in doing but stay within the safety of the guidelines?

DR. GARCIA: Is there any data.

MEMBER GORMAN: On surgical intervention.

DR. GARCIA: On surgical intervention at a much lower BMI.

MEMBER GORMAN: Correct.

DR. GARCIA: As far as having done them successfully? Not that I am aware of.

MEMBER GORMAN: Thank you.

DR. INGE: Actually, in the packet in the rec book, George Fielding's article, where he was a senior author, Dolin was the first author, there was a small handful of adolescents in that cohort that came in with BMIs that caught my eye of less than 35.

DR. GARCIA: Oh, I'm sorry. I thought you meant by age.

DR. INGE: I meant by BMI.

DR. GARCIA: Oh, I'm sorry. I thought you meant by age.

DR. INGE: But it's very sparse.

CHAIRMAN NELSON: Dr. Kral, do you want to add to that information?

DR. KRAL: No. There are published studies. Partly the SOS study itself had an inclusion criterion which wasn't quite as strict. And they reviewed that back in '97, their experience then.

But there are several series, one from Italy on designing coworkers in a multi-center study. And then there is the about-to-be-published study from Melbourne from O'Brien, who actually has done in adults BMI 30 to 35 against.

And he was prevailed upon to not use the word "best" medical but optimum or state-of-the-art medical treatment in the prospective randomized trial. So there's data out there on 30 to 35 BMI.

DR. GARCIA: I misunderstood the question. I thought you were talking about lower age.

CHAIRMAN NELSON: Since we seem to have

transitioned away from questions to the speaker to discussion among the panel, I think it's a good time to say that we're going to have nine hours to do that tomorrow, eight if you exclude lunch.

So I would like to thank Dr. Garcia for an excellent presentation, remind people that we start at 8:00 a.m. tomorrow. And I don't think you could count on this room being secured. So anything that you think is eyeable, you should take with you. And I think you could probably even just carry the papers you've got because they may get cleaned up inadvertently overnight.

So we'll see you at 8:00 o'clock tomorrow morning.

(Whereupon, the foregoing matter was recessed at 5:53 p.m., to be reconvened on Thursday, November 17, 2005 at 8:00 a.m.)