UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE

PEDIATRIC ETHICS SUBCOMMITTEE

Tuesday, November 15, 2005

The subcommittee came to order at 8:30 in Salons A and B of the Ballroom, Gaithersburg Hilton, Gaithersburg, MD. Norman Fost, M.D., Chairman, presiding.

PRESENT:

NORMAN FOST, M.D., M.P.H.	CHAIR
ANGELA DIAZ, M.D., M.P.H.	MEMBER
DEBORAH L. DOKKEN, MPA	MEMBER
RICHARD L. GORMAN, M.D.	MEMBER
ROBERT M. NELSON, M.D., Ph.D.	NON-VOTING MEMBER
JAN N. JOHANNESSEN, Ph.D.	EXECUTIVE SECRETARY
PAUL BOEPPLE, M.D.	CONSULTANT
JEFFERY R. BOTKIN, M.D., M.P.H.	CONSULTANT
MELVIN GRUMBACH, M.D.	CONSULTANT
THERESA O'LONERGAN, M.A.	CONSULTANT
ALAN ROGOL, M.D., Ph.D.	NON-VOTING CONSULTANT
TOMAS SILBER, M.D., M.A.A.S.	CONSULTANT
PAULA KNUDSON	ACTING CONSUMER REPRESENTATIVE
MICHAEL CAROME, M.D.	ASSOCIATE DIRECTOR OHRP
KEVIN A. PROHASKA, D.O.	OHRP
SARA GOLDKIND, M.D., M.A.	FDA
DIANNE MURPHY, M.D.	DIRECTOR OFFICE OF PEDIATRIC THERAPEUTICS, FDA

C-O-N-T-E-N-T-S

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

(8:37 a.m.)

CHAIRMAN FOST: Good morning. Thank you all for coming. We have a hopefully not too long but a very interesting day and we'll reach some conclusions. We should start with introductions of members of the committee, so if we can start at that end, just a word about who you are.

MS. O'LONERGAN: I'm Terry O'Lonergan. I'm a research subject advocate in a pediatric GCRC. I'm from Denver, Colorado.

DR. SILBER: I'm Tomas Silber. I'm Director of an adolescent fellowship at Children's Hospital and the Office of Ethics at the same place.

DR. ROGOL: My name is Al Rogol. I'm at the University of Virginia and I was asked to sit on the panel. You will note that I am a non-voting member today because in your packet comes something from the Lawson-Wilkins Pediatric Endocrine Society. It has my signature on it, and it is not me. I am the conduit from Lawson-Wilkins because I am the secretary of the Lawson-Wilkins. So, please understand this

does not represent Al Rogol's ideas 100 percent, it represents 900 pediatric endocrinologists. It was vetted both through our Drug and Therapeutics Committee as well as the Executive Committee upon which I sit. I signed it as the Secretary.

DR. GRUMBACH: I'm Mel Grumbach from the University of California at San Francisco, Department of Pediatrics.

DR. BOEPPLE: I'm Paul Boepple from the Massachusetts General Hospital Pediatric and Reproductive Endocrine Units and from the MDH Institute of Health Professionals.

MS. KNUDSON: I'm Paula Knudson. I'm the IRB Administrator at the University of Texas Health Science Center in Houston.

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

CHAIRMAN FOST: Norm Fost, University of Wisconsin, Professor of Pediatrics, Director of the Bio-ethics Program, and Chair of the IRB.

DR. BOTKIN: I'm Jeff Botkin, University

of Utah. I'm a Pediatrician, Bio-ethics, Associate Vice President for Research at the University.

MS. DOKKEN: I'm Deborah Dokken. I'm the family representative on the Pediatric Advisory Committee.

DR. NELSON: Robert Nelson, also known as Skip, in case you hear that name occasionally. I'm at the University of Pennsylvania, Children's Hospital, Philadelphia Pediatric Critical Care Medicine and the Bio-ethics.

DR. GORMAN: I'm Richard Gorman, a Pediatrician in a suburban private practice with one of my mentors across the table, Dr. Silber for more years ago than probably either of us want to mention. I am the Chairperson of the Section of Clinical Pharmacology and Therapeutics at the American Academy of Pediatrics as well.

DR. MURPHY: I'm Diane Murphy. And I am the Director of the Office of Pediatric Therapeutics at the Food and Drug Administration.

DR. GOLDKIND: I'm Sara Goldkind. I'm the Bio-ethicist at the Food and Drug Administration

within the Office of Pediatric Therapeutics.

DR. PROHASKA: Good morning, my name is Kevin Prohaska. I work in the Office for Human Research protections in the Policy Division and I'm the Children's Research Coordinator.

DR. CAROME: And I'm Mike Carome. I'm the Associate Director for Regulatory Affairs in the Office of Human Research Protections.

CHAIRMAN FOST: Thank you. Jim?

DR. JOHANNESSEN: I'd like to read the meeting statement for this morning. The following announcement addresses the issue of conflict of interest with regard to the discussion of a referral by an institution review board of a proposed clinical investigation that involves both an FDA regulated product and research involving children as subjects that may be supported by the 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 interest reported by the committee participants, it has been determined that

all interests and firms regulated by the Food and Drug Administration present no potential for conflict of interest at this meeting with the following exceptions. In accordance with 18 USC 208B(3), a full waiver has been granted to Dr. Paul Boepple for consulting and speaking for a company with the product at issue with an aggregate value of less than $10,000.00.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Park Lawn Building. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record. We would like to note that Dr. Richard Gorman is participating as a Pediatric Heath 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 FOST: Mike Carome, you're here on behalf of Dr. Schwetz to talk about the process?

DR. CAROME: I think Sara's going to give the instruction on behalf of HHS.

CHAIRMAN FOST: Sara Goldkind?

DR. GOLDKIND: I'm going to present on behalf of both federal agencies. And on behalf of OHRP and FDA I want to thank all the panel members for coming to participate. I want to thank the principal investigator and all the IRB representatives from the University of Chicago. We clearly think this is an extremely important endeavor in advancing understanding of pediatric research, both scientifically and ethically. And we want to thank your efforts today.

So without further ado, what I would like to quickly talk about is where -- how it is that we've come to be here today, what the panel needs to

accomplish today and where this panel's work fits into the process itself, because once today is complete there's still additional steps that will occur afterwards.

So both HHS and FDA have federal -- have a regulatory component called Subpart D which are safeguards for children and pediatric research. And they overlap in terms of these four categories that Im going to describe. An IRB looking at a protocol at an institution has the authority to approve that protocol under one of three categories; 404, 405 or 406 and I've listed the corresponding FDA numbers as well, 51, 52 and 53.

And those categories relate first of all to level of risk, not involving greater than minimal risk if the protocol is deemed as such, it can be categorized in the first listed there. If it involves more than minimal risk, then the IRB has to decide whether or not that protocol offers the opportunity for direct benefit to the individual subjects involved in the research or offers the opportunity for generalizable knowledge to subjects with a similar

disorder or condition.

And if those stipulations are met, then the protocol can be categorized in one of these first three listings by the IRB at the institution and it does not come to a federal panel. However, if the IRB feels that the research is not otherwise approvable under one of those first three categories but does present an opportunity to understand, prevent or alleviate a serious problem effecting the health or welfare of children, then the protocol can be submitted to OHRP and FDA for federal review and so we have comprised, as you'll see, an expert -- panel of experts in pertinent disciplines to review this protocol.

And some of the considerations that you as the Pediatrics Ethics Subcommittee can entertain today are the determination of risk the determination of benefit, whether or not you feel that the protocol can go forward with -- as it is or whether there are suggested modifications or necessary modifications to the protocol, whether, when you review the parental permission and assent documents you feel that there

are suggested modifications or necessary modifications to those documents and then we are also going to provide for you four questions for consideration and we would ask that at the end of the day that you determine specific answers to those questions as well as the approval category that this protocol would be under and that would be the approval category within Subpart D, as I've just described. And certainly, you can consider any other pertinent issues that you think need to be vetted today.

So possible recommendations that are open to the Pediatric Ethics Subcommittee are to allow the protocol to proceed because it satisfies one of the first three categories that I mentioned earlier or to allow the protocol to proceed with modifications because those modifications would then allow the protocol to be categorized in one of the first three Subpart D categories or to allow the protocol to proceed with or without modifications because it, indeed, would satisfy the 407 unique category that I just described or to recommend that the protocol not be allowed to proceed providing specific reasons for

doing so.

So that kind of summarizes how we've gotten to today and what some of the work will be that you all will be doing as the Pediatric Ethics Subcommittee. Once you finish today and you provide us with recommendations, then those recommendations will be taken to the Pediatric Advisory Committee. Now, just to recap a little bit further, I want to explain what the three stipulations are if you decide that you think that this should be approved under that unique 407 or 50.54 category. You would have to determine 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; that the research will be conducted in accordance with sound ethical principals and that adequate provisions are made for soliciting the assent of children and permission of their parents or guardians as set forth in 408 and 50.55.

Now, we also want you all to understand that although HHS and FDA have a different numerical

system and these are actually under a different set of regulations, the Subpart D categories that we are discussing are completely comparable. So after today's meeting, the Chair is going to summarize the Pediatric Ethics Subcommittee review and tomorrow, Dr. Fost will present the Pediatric Ethics Subcommittee recommendations to the full Pediatric Advisory Committee, the parent committee to this one.

The Pediatric Advisory Committee recommendations will be transmitted by our office with comments to the FDA commissioner, along with a host of supporting materials and appendices, one of which will include the Chair's summary and the summary of the public comments. And the FDA commissioner will then make a determination about this protocol. The process will not stop there, since this involves OHRP as well. That entire packet will be bundled and sent to the Office of Human Research Protection to the Agency and that Agency will send a transmittal memo and their own packet to the Assistant Secretary for Health, who's been authorized to act upon -- act for the Secretary in this regard.

And the Secretary will then make a final determination, the ASH will make a final determination for the Secretary and included in the determination will be an assessment of whether or not this protocol ought to be funded since there's an NIH grant associated with this protocol. So the possible determinations that are open to the Secretary or the Commissioner are to find that the research and facts satisfies one of the earlier three categories. To support the research under the unique category of 407 or 50.54 as submitted or to support the research under 407 or 50.54 with required or recommended modifications or not to support the research at all.

And so that gives you a very quick overview of a complex deliberative process associated with this protocol.

CHAIRMAN FOST: Thank you, Sara. I just wanted to make a few other comments of introduction and then just one other perspective of what our work is today. First, I want to encourage all our speakers to try to keep your comments down. The time is limited and it is the discussion part that will be the

most important.

Second, committee members, it's important to remember that we will have to vote on specific questions at the end of the day and I will in a minute, suggest what some of those questions might be and then add to them as we go.

Third, I think it's important to remember, we are not an IRB. There's always a temptation to revisit every aspect of the protocol or the work of an IRB. We're not here to review the IRB at the University of Chicago or anywhere else. If there are aspects of the protocol or the IRB process that effect risk, benefit and recommendations to the Pediatric Advisory Committee or ultimately to the Secretary, then they should be made. But our role here is not to review the work done elsewhere.

With that as an introduction, let me just make a few other comments. This is an attempt to just -- to try to identify early on in the day the issues that we may be voting on at the end of the day that help the panel members, the committee members put in perspective the comments of the speakers. So the

purpose of the study, as stated by Dr. Rosenfield, is to establish the diagnostic effectiveness of a test using leuprolide and the norms for it. This will improve the differential diagnosis of the most common disorders of puberty so that we may provide more accurate and earlier treatment of these disorders.

As Sara Goldkind said, there are four possible ways that this protocol might be approved and I'm going to suggest that we're really going to only focus on two of them. Under Section 404 the protocol could be approved if the risk is not greater than minimal. The IRB at the University of Chicago determined that the risk was greater than minimal and they concluded that they could not approve this protocol under that section, but this committee could reach a different conclusion. They might decide that the risk is minimal and that it's approvable under that.

Under 405 the protocol could be approved if there were a prospect of direct benefit but the central issue here is the use of normal healthy controls. We're not here really to discuss, I don't

think, the children with pubertal disorders, who I think there was agreement that they could benefit from being in this study but for the normal controls there was not a prospect of direct benefit and to the IRB concluded that it was not approvable under 405.

Similarly, Section 406, which involves research of a minor increment over minimal risk, requires that it be a study that will advance knowledge of the subject's disorder or condition. And since normal controls don't have a condition or the condition that we're concerned about, the IRB concluded that they could not approve it under that section.

And then finally a Section 407, which is why the Chicago IRB asked for this review today, that is to ask if the Secretary could approve it because it doesn't meet any of the other criterion. So the two major options that I think under discussion will be whether this can be approved under 404 because the committee concludes that it's not -- the risk is not any more than minimal risk or 407 and Sara outlined the criteria for that. I'll come back to it in a

minute. So these are the two options, I think, that will be the focus of our discussion.

To drill down just a little bit into those, can the use of normals be approved under Section 4 only if the research is of not greater than minimal risk? I'm sure we'll have some discussion about some of the complexities and problems of minimal risk. The definition of minimal risk, according to the regulations, it's defined as the probability and magnitude of harm or discomfort anticipated in research and it meets the criteria if those risks 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 tests.

The problem is the phrase "routine physical or psychological examination or test" is interpreted in different ways. That is, there is disagreement among IRBs and critics as to whether this refers to risks that a child encounters on a routine visit or a health supervision visit to a general pediatrician or whether it might include risks that

occur on a routine visit to a specialist. So we'll have views on that expressed, I'm sure, by the speakers and by the panel members.

Just to put this in perspective, a recent article on a survey of IRB Chairs and if that's hard to read, it doesn't matter, it's supposed to look sort of all over the place, that's what it is. This is a questionnaire that was sent to a large number of IRB chairs of IRBs that review research involving children and in the left column are a list of procedures in which they were asked whether they would classify these as minimal risk, a minor increase over minimal or more than minimal. And I'll just take one line to show you the problem, if you can read down to the fourth line down, "allergy skin testing", 23 percent of the IRB chairs thought that that was minimal risk, 43 percent voted it was a minor increase over minimal and 27 percent thought it was more than that.

So almost random distribution of these risks in IRBs, that's not only what IRBs' Chairs think, IRBs react differently to these. So there's a lot of variability and I suspect there will be

difference of opinion among the committee. If you'll notice on the top line, even a single blood draw of 10 milliliters of blood was determined as more than a minor increase over minimal by two IRB chairs.

I just want to focus on one or two other issues other than the ones that Dr. Goldkind mentioned, if the Committee is going to recommend that this be approved under Section 407. One of the criteria is that the protocol presents a reasonable opportunity to further the understanding of a serious problem effecting the health or welfare of children. And I suspect there will not be much disagreement that problems of puberty are serious problems effecting the welfare of children. I think the question that we're going to need focus on is whether the use of this test effects a serious problem. That is, whether the existing methodology for diagnosing and managing these problems is adequate or whether the present armamentarium presents a serious problem and whether this test, this diagnostic procedure, is needed to alleviate that problem.

So under 407, it could be approved if the

IRB and ultimately if this committee recommends that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem effecting the health or welfare of children. And I suggest that there probably will be not much debate that abnormal pubertal development is or can be a serous problem but the question is whether the availability of a reliable diagnostic test is presently a serious problem.

We will be -- I will be presenting at the end of the day votable issues and I'm just putting three up here that I can anticipate. We may add to this list as the day goes on. So you might just think about these as you listen to the speakers and the discussion. Issue Number 1 is whether the proposal to study the response of normal children to leuprolide involves minimal risks and these might include medical risks, including the medical adverse effects of the drug. It might include the procedures that will be used to study the children. It might include the amount of blood that's taken. That may not be a comprehensive list. And second, the IRB was concerned

about the psychological risks of hospitalization and the procedures, even if there were no medical reasons.

Issue Number 2, I think we will have to determine whether the need for improved diagnostic tests for diagnosis of problems of puberty is a serious problem effecting the health of children and Number 3, is the research designed in a way that presents a reasonable opportunity to further the understanding of this problem effecting children. We'll hear later in the day, I'm sure, discussions about design, sample size and so on. Thank you.

With those comments, we now are pleased to have with us Dr. Melvin Grumbach, who is going to give us an Overview on Precocious Puberty.

DR. GRUMBACH: Dr. Fost, Members of the Committee, I'd like to tell you I'm very pleased to be here. I was asked to do something rather formidable and that is to describe puberty disorders on the head of a pin. And what I've done is give you a handout which covers a good deal of material about puberty and I will attempt to, in this presentation to highlight some of the advances that's occurred over the past

three decades in understanding puberty and its disorders.

I'd like to start by a quote from John Wooten, who is an iconic basketball coach at UCLA who said, "It's what you learn after you know it all that counts", and I think in this presentation, you'll understand what I'm driving at. This is an outline of what we're going to talk about; the definition of puberty, 30 years of progress, physical signs, gonadtropis and sex hormones, something about the neuro-endocrinology, hormone studies, sexual precocity and if we have time, delayed adolescence anorapa.

Now puberty is a transitional period between juvenile state and adulthood during which secondary sex characteristics appear. The adolescent growth spurt occurs, reproductive capacity is achieved and profound psychologic changes take place. It's a real landmark in development. Now, what have we learned over the last 30 years, and I point out some mileage markers. The onset of puberty really occurs in the fetus. At puberty and infancy, it's followed by what we call the juvenile pause, which is

a period in which essentially the hypothalamic, pituitary, gonadal axis is shut down.

There's augmented LH response to IV GnRH administration as a mark of puberty onset and this has been available for over three decades and would still be available if pharmaceutical companies had agreed to continue making this native peptide. We have what's known as the Knobil paradigm after Ernie Knobil and that is, it's a very important concept and I'll illustrate this with a slide and that is if you administer GnRH or LHRH, in a pulsatile manner, you stimulate the gonadatrops to secrete pituitary gonadtropis in a pulsatile manner and stimulate the gonads. Should you give it in a continuous manner intravenously, you actually desensitize the LHRH receptor in the pituitary and in essence down-regulate gonadotropin secretion and hence put the gonads at rest.

Now, at the onset of puberty, there's a striking increase in the amplitude of pulsatile LH secretion as a marker of puberty onset, just as by giving an intravenous injection of LHRH you can also

provide a marker of puberty onset. Now, there have been enormous advances in imaging techniques, especially MRI, ultrasonography of the uterus and ovaries that help us in the differential diagnosis. I'd like to point out the really important conceptual difference between so-called adrenarche and gonad arche. Adrenarche is the increase in the secretion of androgen precursors from the reticular zone of the adrenal gland which occurs at about -- beginning about six years of age versus gonad arche which is the awakening, reawakening of the gonads which occurs at the onset of true puberty.

Now, another important landmark is the sensitis of potent long-acting GnRH agonists and these have been available since the mid-1980s. Now, a point here is that by administration either subcutaneously or intra-nasally of these GnRH agonists, you can suppress gonad -- LHRH dependent precocious puberty with a striking decrease in gonadotropin and sex steroid secretion and essentially arrest the rapid growth and skeleton maturation.

Now, the definition of releasing hormone

dependent sexual precocity or central hypothalamic versus gonadotropin releasing hormone independent sexual precocity which leads to all sources of sex steroids that occur either independent of pituitary gonadotropin or LHRH secretion. Now, more recently we've gotten into the genetics and the genome advances, you know, the discovery of new genetic forms of GnRH, independent sexual precocity and a very important landmark has been the role of estrodiol, the extra gonadal and testicular origin in the pubertal growth spurt, skeletal maturation, an accretion of bone mineral of the male. We all thought it was testosterone, it turns out that it is estrodiol, although testosterone is a precursor.

Now, we're going to talk a little bit about these GnRH neurons and they're really very unique. When you think that all of civilization has rested on the presence of roughly 1200 to 1600 neuro-secretary neurons that are hypothalamus, which even -- which didn't start there. They started in the nose and migrated to the hypothalamus, it's a wonder that we're all here. This is a -- this on the left is a

cell line that's been developed and in the isolated cells, will show pulsatile secretion of LHRH or GnRH and in the monkey from the posode (phonetic) in the nose, these neurons were obtained and as you see, they also show spontaneous pulsation.

Now, what is necessary for this intrinsic pulsatile activity which is what this is all about, and that is there is spontaneous activity, the neurons keep time and they show synchronized secretion. Many neurons are synchronized to develop a pulse and we need to know a lot more about this, but we're -- advances have been very spectacular in this regard.

Now, this is a Knobil paradigm which shows LH in the sold line and FSH in the open circles. What happens in the monkey, whether that has been over-ectomized and has an ablation of the medial basal hypothermic LHRH pulse generator and you see that pulsatile administration on your left, leads to pulsatile secretion of these gonadotropins whereas continuous infusion of LHRH or GnRH suppresses secretion and again, it's restored with pulsatile administration.

Now, this is just to illustrate very quickly adrenarche versus gonad arche. Adrenarche occurs first, it's a physiologic process but there are situations in which adrenarche is present but not gonad arche and visa versa. So that these are independent processes and but both contribute to pubertal development. Now, what are the hormonal components of puberty? Well, we have gonadotropic releasing hormone, neurosecretory neurons. We have gonadotropins in the pituitary gland which secrete LH and FSH in a pulsatile manner under the influence of the pulsatile GnRH and then we have gonadal sex steroids, principally estrodiol and testosterone.

Now, one of the landmarks was the discovery of pulsatile secretion of gonadotropins in the human and this is a Tanner G2 boy and as you see, he's pulsating his LH at night but very small amplitude pulses during the day. The pulsatile secretion at night leads to an increase in serum testosterone in the circulation which drops down in the morning after the LH falls off. And here you see a study that was sort of the basis of this pivotal

test, using native or natural GnRH, stuff that we did in our lab in 1972. It's sort of deja voix but the point is this is an injection of LHRH, 100 micrograms and as you see there's a very brisk response in the adult, in the child in puberty and a very small response in the pre-pubertal individual. And here is an illustration of both pulsatile FSH in the female and the male and LH early in infancy during shutdown in what we call the juvenile pause between infancy and the onset of puberty and this is what happens at puberty with augmented pulsatile secretion of LH.

Now, I don't want to spend a lot of time on this but this is pointed out that if you look to the bottom here, that this juvenile pause, and this is what we're talking about and this is where the LHRH test and LH agonist tests are so valuable because it's during this period that you get a very blunted LH and FSH response to the administration of either subcutaneously or intravenously or GnRH or GnRH agonist. And it's here that we feel that this is -- the central nervous system restraint is very prominent whereas later, during puberty and later life, the

gonadal steroid suppression mediation, feedback is dominant. So that's a big change.

I'd like to call your attention to the pre-pubertal child and late pubertal male and female and here we have this dual restraint mechanism, CNS inhibition and sex steroid which lead to suppression of GnRH secretion and put the gonadatrops to sleep as well as the gonads and then with the onset of puberty, we've got augmentation of these GnRH pulses from the medial basal hypothalamus pulse generator and it leads to gonadotropin secretion and the secretion of sex steroids.

And here we have, in terms of what really influences LHRH neuron, we have excitatory amino acids, for example and kiss peptin (phonetic) 1 a recently discovered stimulatory agent and we have GABA which is inhibitory. Now, very important as I mentioned to you, detecting monogenic disorders effecting the onset of puberty and these are all genes that have been described. This should be DAX1, not PAX1, I'm sorry. And the point about it is that through molecular genetics and genomics, we now can --

all of these play a role in controlling the onset of puberty. The KAL-1 gene and FGRF leads to Kallmann syndrome and all are involved with the passage of these neuroexcitatory (phonetic) neurons from the nose to the brain. Now, what about pre-puberty versus puberty, well, there's a circadian change in LH pulse amplitude during puberty, initially at night and then during the day, a striking increase in pituitary sensitivity to GnRH, readily releasable pool of gonadotropins during during the pre-pubertal and pubertal period and the gonadotropin response to GnRH. And the pre-pubertal state, as I mentioned, is characterized by functional GnRH deficiency.

Now, these are the stages which you're all familiar with but just to illustrate what we talk about when we talk about stages. Now, the sequence of clinical puberty in girls differs from that in boys. We have the pubertal growth spurt which occurs in girls and it's really there before the onset of any secondary sex changes, either breast development or public hair, and we have menses.

In boys we have -- the initial is

testicular enlargement, sexual hair, phallic enlargement and in mid-puberty, the growth spurt. And this is illustrated here which shows the growth curves in both females and males and the -- you see the estrodiol, obviously has played a role in this pubertal growth spurt in the girls. We now know that estrodiol plays an important role and is a key hormone in both the pubertal growth spurt and apifstrial (phonetic) affusion in the male as well as the female.

Now, let me just get down to this. Lot of the area of concern has been a study that was published in 1997 which suggested that breast development was occurring earlier than previously thought in both -- especially in African American girls and this is illustrated here. On the top is selarche (phonetic), pubarche and menarche, but I'd just like to point out, this is the 50 percent line for the appearance of breast development and as you see, here at 5, 6 and 7, there is an increase in the appearance of breasts in Black girls and a very minor increase in White girls.

Now, the onset of menses is earlier in Black girls than in White girls and the -- this is not -- this has changed in a very minor way over the last 25 years. Now, one of the important concepts which one of our former fellow, Carlos Martin Hennenberg in Barcelona pointed out is that the younger the age of the onset of puberty, the longer is its duration. So we're dealing here with a marker of menarche let's say but the onset of puberty may occur earlier than we thought but menarche is not.

Now a general working diagnosis of the definition of puberty onset in girls is that it's a little less than six or seven years, it's slowly progressive. It's a little less than six or seven years and early puberty is seven to eight. Now, evaluation of children with early puberty remains an important clinical issue and that's why this test is so important. There's no change in prevalence of late puberty. Boys are later than girls, as you appreciate. Now the earliest events of puberty appear to be occurring earlier, apparent association with increased weight in girls versus boys and over

nutrition is the major toxic environmental factor and overweight in children tripled in the last 25 years and we are seeing earlier onset of puberty associated with obesity.

Now, the tempo of puberty has not accelerated despite the earlier onset in some cases but the mean age of menarche and thelarche by stages does not occur much earlier.

Now, the age of reproductive capacity has not changed. The age of menarche is similar over recent decades. The attainment of breast development Stage 5 and genital Stage 5 in boys is not earlier, the tempo of puberty is not accelerated. Increasing prevalence of obesity correlates with earlier onset of puberty in girls and concerns that in five to eight year old girls, definite recommendation of normalcy could lead to compromised medical care.

Now, I just want you to look at the top. Tempo is terribly important. Early changes with little or no progression, we don't worry much about but progressive sometimes quite rapid changes are an important sign of pathology, textural pathology and

just barely early but rapid change in tempo is a source of concern.

Now, if called normal, what are we missing? If called abnormal, must one initiate treatment, height, early menses, behavior? Not solely the responsibility of the general pediatrician based on statistics of pubertal onset, so tempo, tempo, tempo is important. Now a general definition of techoprocosity (phonetic) is the appearance of secondary sex characteristics before six or seven years in girls or nine years on boys. Now, the sources of sex steroids may be exogenous which is becoming a source of great concern with the availability of gel preparations of sex steroids both testosterone and estrodiol. And then we have endogenous from the gonads or the adrenal.

Now, the -- what we're talking about here is a pubertal spectrum. We have precocious puberty on one hand, normal puberty and delayed puberty. Now, the source of puberty may be the first clinical feature of intra cranial pathology, chromosomal disorders, metabolic or enzymatic defects and they

have these consequences which are associated with a primary disorder, short stature because of premature fusion, psychological adaptation and fertility. Now, we have premature thelarche, which is a normal variant which can be distinguished from slowly progressive puberty and rapidly progressive puberty in girls.

Now, I'd like just to point out the most common idiopathic true precocious puberty in girls and we must distinguish this sexual form of precocious puberty which is GnRH dependent from other forms of sexual precocious puberty which are associated with CNS lesions. Now, on this slide, I illustrate that idiopathic true precocious puberty is greatly predominant in girls. They organic form is in relation to idiopathic true precocious puberty is dominant in boys. So we're very concerned in a boy with signs of sexual precocity that he may be harboring a central nervous system lesion.

Now, this is what we're concerned about. Six to seven and seven to eight years, this is a study we did a number of years ago, the age of onset of idiopathic true precocious puberty females, males,

number 106, and this is the area that we're concerned about, is this earlier onset of normal puberty or is this really true precocious puberty?

The laboratory studies that we all do and I'd like point out how important the -- initially the LHRH test which is not available any more and the LRH agonist test is, and the analysis of pulsatile gonadotropin secretion. Now the imaging studies are bone age, pelvic ultrasonography and head MRI and these have been tremendously important in unraveling the source of true precocious puberty. Now, what are the objectives for the management and treatment of true precocious puberty? Detection and treatment of an expanding intra cranial lesion is at the top of the list, the arrest of premature sexual maturation until the normal age of onset of puberty, regression of secondary sexual characteristics already present, attainment of normal mature height, suppression of the rapid rate of skeletal maturation.

Now, we're concerned about the prevention of emotional disorders and handicaps and alleviation of parental anxiety, promotion of understanding by

counseling, early sex education and acceleration of social age. The reduction of risk of sexual abuse and early sexual debut, that's really important. Prevention of pregnancy in girls and preservation of future fertility and diminish the increased risk of breast cancer associated with early menarche.

Now, we're talking about the action of LHRH hormone agonist and this is a selected highly specific pharmacologic clamp on secretion of gonadotropins and you're going to hear more from Bob Rosenfield about this.

Now, in summary and finally, I'd like to leave you with life can only be lived forward but we must -- must be understood backward. Thank you.

CHAIRMAN FOST: Thank you very much. We have time for questions for Dr. Grumbach. Dr. Nelson?

DR. GRUMBACH: Yeah, Skip.

DR. NELSON: I'm struck, I guess, by two things. The timing of the turnoff of the infantile pulsatile secretion and the question is, is there any diagnostic confusion that might be generated by combining a population those who may have failed to

turn off if you see it say at one year of age or two years of age, versus those who turn off but then turn on early. Is there any issues there in separating out those two groups?

DR. GRUMBACH: We've seen true precocious puberty really by three months of age, and we had a child who is having menstrual cycles by five months of age, and that's an example of true precocious puberty. Now, the turn on, this mini-puberty is a very subtle affair. The girls do not develop breasts, although it may play a role in premature thelarche and it's a very subtle thing. In boys they may have some acne, a little bit of testicular enlargement. And we can differentiate that from something that is progressive. And in boys it shuts off at about six months and in girls by -- it can kind of peter on as late as two years. You can make this distinction by -- again, by tempo. Is this -- I mean, do they move onto develop breasts?

I mean, a child of four months that develop breasts is a source of concern even though premature thelarche at this age, I mean, thelarche at

this age is not uncommon. What you need to find out is the bone age advance. Are they moving ahead in terms of rapid growth. So it's all put together, to answer your question, Skip.

CHAIRMAN FOST: Dr. Gorman.

DR. GORMAN: Could you give us some sense of the number of people who are referred to your service, undergo the diagnostic work up of whatever one it is you choose to do at your particular institution who end up having true disorders? And I'd like you to differentiate between girls with primary thelarche and boys with constitutional -- what pediatricians in the office see as constitutional delay of puberty? We send them to the endocrinologist, you do your fine work up. What fraction of that end up having conditions that require intervention by the endocrinologist?

CHAIRMAN FOST: Back to the microphone. Oh, you have a microphone.

DR. GRUMBACH: That's a tough question to answer. We see, for example, an infant or a one and a half or two-year old child sent to us with premature -

- with breast development, no signs of pubic hair. We get a bone age. The bone age is not advanced. We go back and say, "Let's see what happens, whether this is progressing or not". We don't even do a blood test in measuring estrodiol but if the child begins to grow rapidly or develops increasing breast development, then we go into the full scale work up.

In boys with constitutional delayed adolescence, that is a very difficult differential diagnosis from a central hypothelapic (phonetic), hypo-gonadotropic, hypo-gonadism, or a pituitary tumor. So if a 15-year old boy is sent to us without any signs of puberty, we do a complete work-up and I would say in at last 15 to 20 percent of those that are sent to us, we do find something. And these include very serious lesions, including hypothelapic (phonetic) tumors. We just had a child with an astrocytoma and we've had kids with a cranial sarcoma that we were able to pick up so that by dental films five years earlier it was there. But it's -- what we're concerned here about particularly is the CNS lesion.

CHAIRMAN FOST: Dr. Bodkin.

DR. BOTKIN: This is very helpful. I guess I don't have a clear sense yet though of what the contemporary gold standard is for making the diagnosis of these conditions and why it is that the field is in need of improvement of that gold standard. Do you have a sense of what sensitivity specificity is of the contemporary gold standard and again, what are the deficiencies or limitations of the current approach?

DR. GRUMBACH: Dr. Botkin, I think really that's the key, that's the key question for us all to decide. I would not be here if LHRH or GnRH, the native, were still available, because we've had a long history of that. We have normals, we have the whole bit. It's not available and it's a very important test, and let me tell you why. Yes, we could do pulsatile secretion overnight but that means admitting the child to the hospital and doing a whole series of tests. We use this test in a very important way and that is to differentiate, number one, central nervous system direction of changes in secondary sex

characteristics versus issues in which the gonads or the adrenals or another source of sex steroids is present.

In other words, all of the LHRH dependent forms of sexual precocity will show an augmented response to the injection once -- single injection of GnRH or antagonist, and that in line with getting sex hormone studies, estrogen, estrodiol in girls and testosterone in boys, bone age, and an MRI if the work-up indicates that.

Let me just mention a terrible problem we have in pediatric endocrinology and that is the unreliability in many hospital and commercial labs, not all, of serum testosterone and especially estrodiol levels. Some of them are absolutely worthless. In our own hospital, okay, we don't trust the testosterone in kids because we get figures that are 100, 150 when they turn out by really doing it in a very specific manner to be 20.

And this is a really very important problem and again the GnRH test help us to distinguish situations in which this is -- the accretion sex

steroids is really centrally mediated.

CHAIRMAN FOST: Could I just ask that in a different way, Mel? To what degree are you presently thwarted in your ability to work up these kids and manage them effectively because of the absence of normative data on the leuprolide challenge?

DR. GRUMBACH: Well, that's -- Norm, that's a really tough question. There is some normative data in the literature. One of the problems that we have is the fact that there's no standard gonadotropins. In other words, there are about -- there are whole variety of gonadotropins and they all may be fine if you stick to one, but it's not necessarily generally applicable. For example, there's a third generation, highly specific test which has relatively low values whereas the routine that are available have much higher value.

So the point is that there is a difficulty in standardization and you really have to know the that is giving you this data. All I can say is this is a really exceedingly useful and very critical test. Now, the issue, I think we have to hear from Bob, the

issue of is there enough normative data that's really meaningful, I'd like to leave to Norm, I'd like to leave to Bob's discussion.

CHAIRMAN FOST: Other questions? Jeff?

DR. BOTKIN: Yeah, I'm sorry, I want to follow up a little bit on that. I'm still uncertain about whether the desired transition to a new and better test. Is the intent behind that primarily to reduce the burden on kids in order to maintain the same level of accuracy or do you think this transition may actually improve the accuracy with which kids are diagnosed?

DR. GRUMBACH: The -- I think there is a possibility -- nobody's done head-on-head native versus Lupron acetate as a provocative test. So we really can't answer the question is one better than the other, but I don't think that's the important question. I think the important question is, since the native is not available, is the Lupron acetate test a substitute for this and I'd have to say from our experience that yes, it is, that it can serve as a substitute for it.

Now, it's given not intravenously but subcutaneously and it -- but it does clarify all the things that the old GnRH test did.

CHAIRMAN FOST: Mel, in your answer to my question, you said that one of the problems is inter-laboratory variability. So even if you had superb normative data from one study, that wouldn't help that problem. That is, it sounds to me like you -- there's a persistent problem that labs aren't consistent.

DR. GRUMBACH: Well, it might, in the sense, norm, that it might really lead to some general -- there are laboratories that -- commercial laboratories that are available and some hospital laboratories, which really do come up with sterling data that will agree. I'd like to point out sex steroids are relatively easy to measure. There is just a recent paper out in which measuring testosterone by gas mas spectroscopy which is the gold standard, and then they did 10 different platforms and they got very diverse results. I'm talking about immunol assays. Now in the old days we did extraction. We did chromatography, to measure

testosterone and estrodiol. Now it's all done in serum. So the problem is really very vast in terms of getting good data for kids.

Now, this test does help in the sense the it cuts through a lot of the chaff. Now whether -- you know, if you have your standard laboratory, you know what the -- roughly the baseline is. You know whether you get a response or not. It's really the qualitative change that's important. The quantitative things are really not -- you know, are much more subtle and not as essential as a real qualitative increase.

DR. ROGOL: Doctor, how do your colleagues, let's say in Europe, Australia, Canada, et cetera, deal with this issue?

DR. GRUMBACH: The -- in some of these countries, the GnRH is still available, the basic test, but very widely in Europe and I think Bob will be discussing this, I mean, going back to the `90s, a GnRH agonist has been used as the test. Some people feel that it's at least as good as the native test and may even be better. So this has been going on. This

is not a new page. This has been going on for -- you know, for over a decade.

CHAIRMAN FOST: Other questions?

DR. GRUMBACH: And as a matter of fact, in your handout you'll see some of the -- I did collect some of the abstracts and some of the citations which the use of GnRH agonists and particularly many of these are from Europe.

CHAIRMAN FOST: If there are no other questions, thanks very much. We really appreciate it. Next, we're going to hear from Dr. Robert Rosenfeld, who is the principal investigator of the study that's been submitted.

DR. ROSENFIELD: Well, good morning. In a way I'm glad to be here, in a way I'm quite apprehensive about this but being here is a matter of principle, because I think we're talking about something that has implications for pediatric endocrine research and pediatric research in general. It'd like to just make a few comments that address your questions to Mel at the very end, just emphasize a few points.

Mel gave a wonderful background. The major problems are that there has been an unavailability on a regular basis of the commercial product -- commercial GnRH. There are tremendous differences in the radioimmunoassays, particularly for measuring LH. Mel was talking a lot about the difficulties in measuring sex steroids, but the difficulties in measuring LH which is the key hormone that initiates puberty, if you can call one versus another key. There have major methodologic changes so that one cannot translate from the old date to the new with great certainty. And finally, although this protocol is relatively arduous at this time, it -- the long-term goal is to simplify the diagnosis of precocious puberty because I'm quite certain that we're testing the hypothesis but we have a lot of preliminary data that a simple GnRH agonist test with a baseline and a sample a few hours later, and maybe 24 hours later, depending on the case, can eventually be the way that we proceed.

I should mention that I've made -- you'll notice -- I'll try to point them out as we go along,

made a few changes from the latest handout when I looked through things last night. I wanted to be as sure as possible of being accurate and clear.

So what I'm going to discuss today is give you an overview, talk about the nature of the problem, give you some background and/or chronology and at Dr. Goldkind's request, talk about antecedent studies in some detail and adverse events of leuprolide in some detail. Then discuss the protocol and really I'm going to discuss it fairly briefly because I don't' think this is rocket science. This is a very straightforward kind of protocol for a single center grant.

We can talk about whether multiple centers ought to get involved and then I'll give you a summary. So as an overview, GnRH agonists are promising diagnostics and this protocol focuses on delayed puberty which is, for some reason, especially a diagnostic problem in boys. Boys, when they start high school, if they haven't started puberty, they have problems and girls it's less common of a problem for some reason. And the issue here is that the most

common cause of delayed puberty is constitutional delay of puberty which we'll abbreviate as CDP which is generally considered to be an extreme variation of normal, but I'll show you a caveat or so later. But to differentiate that from gonadotropin deficiency early is a real challenge. And then the second major issue is distinguishing premature precocious puberty from other disorders and this is especially a problem in girls. And the issue here is to distinguish idiopathic, true, sometimes called central precocious puberty, which well abbreviate as central precocious puberty which, again, is usually an extreme variant at normal, at least considered to be, again, with some caveats, and to distinguish that from normal early pubertal, normal pre-pubertal and premature pseudo-puberty and diverse types.

So those are the common issues and those are the major issues which this protocol addresses and which this protocol is powered to address. And there is a need for normative data on healthy pre-pubertal and early pubertal children and that's why you're here today. So conceptually, I want to give you a

definition of premature and delayed puberty. There's a normal distribution of when children go into puberty and the two and a half percent that present early are premature and the two and a half percent that present late are delayed. And yet, data on constitutional delay of puberty and central precocious puberty of the idiopathic source, are the source of most of the so-called normal data in the literature even though they are outliers on a normal curve.

So here's the first problem, differentiating constitutional delay of puberty from gonadotropin deficiency. So this is a classic slide from Wilkins textbook. This boy -- this boy, let's see the --

CHAIRMAN FOST: There's a separate pointer up there. It's easier. Turn the pen away from you. There you go, that's it. There you go.

DR. ROSENFIELD: Still alive. So here's boy who at 17 is pre-pubertal. And he's constitutional delay and Wilkins was able to photograph this young man as he progressed through puberty. So puberty can be delayed as much as to 18

years of age. If puberty hasn't begun by 18, it is generally considered to be gonadotropin deficiency. So this problem occurs mostly in boys and constitutionally delayed boys, remember they present to you in high school when they start high school and they develop increasingly poor self-image after 14 years of age. They tend to be picked on. They tend to be teased. They aren't as bulky. If they have athletic interests they are at a physical disadvantage. Some boys can handle it and some can't.

These boys grow out of it. These are late bloomers. It is a common problem for the most part. But nevertheless, psychologically, a disturbing one and the cause is usually a normal variant. The work-up is ordinarily minimal and they require reassurance. Some of them because of self-image problems do quite well with a six-month course of very low dose testosterone to boost their growth a bit, boost their puberty to a visible amount and get them going. That's usually -- if we do anything, that's about all we do, common standard pediatric endocrine practice.

And these things contrast with

gonadotropin deficiency. There's no sense telling a 14-year old boy in high school who hasn't started puberty to wait, he'll grow out of it and then he doesn't grow out of it and he's miserable and psycho-socially for years until the diagnosis is finally made. And at that point, it becomes a relief to have a diagnosis.

The problem too, is differentiating idiopathic central precocious puberty from normal variance and other pseudo-puberties. So here's a little four-year old girl who has gone into puberty. So precocity is predominantly a problem in girls and this is a scary problem for the child and their parents. They're moody. Their parents are scare to death they'll start having periods, they're scared of the child being victimized and in the rapidly progressive form of sexual -- of central precocious puberty, they get the growth over with early and experience early growth arrest and adult short stature.

Over 90 percent of them are idiopathic and as just a normal stage happening early. The work-up

is often minimal but if the child is rapidly progressive and their height potential is deteriorating and/or there are other signs of central nervous system or other involvement, a brain MRI is probably the only thing that is necessary in those cases. Quite often we can reassure them, particularly in the six to seven-year old group that Mel was talking about, early puberty where we're not quite sure how serious it is but often that's slowly progressive and they don't need anything but reassurance. But those who are rapidly progressive are generally treated with GnRH agonists and this is an FDA approved indication for this drug.

On the other hand pseudo-precocity may be a normal variant. I'm talking about the kind of puberty that goes on at six to seven-years of age, that kind of early breast development Mel was focusing on. We're not quite sure how normal that is or whether it will be something more serious like a tumor or some -- or syndromes or rare genetics disorders masquerading as true puberty.

And then there's the problem of early

breast development and Mel talked about the PRO study. When this came out saying that puberty was happening earlier in girls, the New York Times in `99 had a front page article "Yesterday's Precocious Puberty is Norm Today", but then we spearheaded a drive against that through the Wilkins Pediatric Endocrine Society and it took a couple of years before the New York Times said that -- called us doubters to fault that theory of early puberty, but then eventually the two major endocrine groups raised doubts about the earlier onset of puberty. So this is a very contentious issue and while there is some evidence that breast development may be occurring one to two years earlier, namely at the six to seven-year range, especially in obese and in Black girls, as Mel pointed out the age of puberty is unchanged, so the tempo is unusually slow and the question is, is this really the same as true puberty.

So that gives you the major issues in a nutshell, just reviewing them and then I'll go through the background of -- background endocrinology of puberty in a couple of slides, not in great detail

that Mel did but this shows the -- so this shows the puberty that's going on in the fetus. The system is in place. It gets turned off by the -- all the estrogen the fetal placenta unit is making during late pregnancy and then when the baby is delivered and those estrogens of pregnancy go away, you can see sub-clinically the mini-puberty and this is a sub-clinical mini-puberty that's related to the maturation of the central nervous system inhibitory systems, but then in mid-childhood this inhibition by higher CNS centers of hypothalamic releases, gonadotropin releasing hormone wains and puberty is allowed to progress. And so here's the sub-clinical mini-puberty of the newborn, here's adrenarche which is a pseudo kind of puberty that Mel talked about but then true puberty beings with pulsatile GnRH secretion during sleep.

The more the pituitary sees the pulsatile GnRH the more sensitive the pituitary becomes to it. The more the pituitary secretes it's gonadotropins, the more sensitive the gonads become to it and this whole process has a circular auto-amplification that culminates in -- culminates in further progression of

puberty. So these are the key events for the kind of -- to understand that kind of study we're doing today. Pulsatile GnRH occurs during sleep leading to a sleep related rise in LH. It's the earliest even of puberty and followed by increasing gonadotropin and gonadal function. So at the hypo-thelamic level, you have GnRH secretion. You have gonadotropin releasing hormone that drips into the pituitary portal system and stimulates LH and FSH to secrete the gonadotropins LH and FSH. These stimulate the gonad to do its two things. LH is particularly important in the secretion of sex steroids and FSH is particularly important in stimulating egg and sperm production and these all amplify one another.

As I said, the rationale for GnRH agonist study really depends upon the fact that the response to the agonist reflects the previous exposure to GnRH so that the more GnRH is secreted, the more pituitary response, the more then gonad response, and when you give an injection of GnRH or GnRH analogue to a pre-pubertile child the system is sleepy, hasn't been awakened, so has a sluggish response but when you give

this injection of GnRH or GnRH agonist to really a mature child, the system is revved up and responds better. So that's the rationale for GnRH or GnRH agonist testing.

So not that's all the endocrinology I'm going to talk about and I'll give you some background on our studies and how we got into it and where GnRH agonist testing comes from. So GnRH was discovered in 1977. It's desensitizing -- the desensitizing effect of GnRH agonist was exploited, if you will, pharmaceutically in the best sense and led to the development of the first effective treatment for central precocious puberty which was chronic GnRH agonist treatment and Mel went through the desensitizing effects of chronic GnRH agonist analogues and I want to point out today that we are not -- the testing that we're doing is not the same as this. We're not looking at the desensitizing effect. We're look at the effect of a first injection.

So, in 1985, I initiated some GCRC studies under an expanded Syntex IND for the nafarelin treatment of precocious puberty. Nafarelin was one of

the first commercially available GnRH potent analogues to treat central precocious puberty. And I was interested in the potential of an acute response to this potent analogue as being a potentially useful diagnostic test. So we -- when we had patients with central precocious puberty who met criteria to be treated, we examined very closely their hormonal responses to the first dose of their treatment medication nafarelin. Now we're talking about three different ages here today and I thought it would be useful to show you on the top that natural GnRH is a decapeptide. It's a very small molecule. Nafarelin, which we started out with and did all our pilot studies, is substituted here right in the middle at this one spot and this substitution protects this from degradation by the end of peptidasis of the pituitary and so it doesn't -- it's not inactivated in the pituitary instantly like natural GnRH. And leuprolide acetate, which was originally marketed as Lupron and still is, but now there's a generic form that we're using, is substituted again, in the middle, a simpler substitution. But again, this is a very simple

substitution in a small molecule.

So our first study was with central precocious pubic girls, starting nafarelin which is shown here as GnRHA and we compared this to a three-hour infusion of natural GnRH, which is shown in the gray bars. The gray bars show pre-pubertal normal controls, historically and there's an infusion of natural GnRH compared to a single injection of the GnRH agonist.

And the results showed that the LH and FSH responses to the GnRH agonists were greater and more prolonged than to GnRH and in particular I want to point out that the estrodiol response at 24 hours was markedly different and that, in fact, that relates to the earlier slight -- seemingly slight but very significant increase in gonadotropin output that occurs over the long period of time after the GnRH agonist, as compared to an infusion of the natural product.

So, at that point this looked like a promising diagnostic in support of the concept and we embarked on precursors of the current protocol that

were pilot studies to explore the diagnostic potential of nafarelin in children with known or suspected disorders of puberty, mostly constitutional delay or central precocious puberty and here's results of a typical study. We performed nafarelin tests in girls at various pubertal stages and these, again, were really girls with delayed puberty or precocious puberty and you can see that these are typical kind of responses. The -- oops -- the left is pre-pubertal, the middle is early pubertal, the right is late pubertal. LH, FSH and estrodiol, we sampled intensively over the first four hours and then the time scale changes. We sample less frequently over the remainder of the day. And FSH doesn't change a lot over this period of time, but LH rises gradually in the beginning and then a lot after menarche and you can see that accompanying this is an increasing estrodiol responses.

So then we turned to differentiate gonadotropin deficiency versus constitutional delay and we studied -- and I'm going to show you the published data on pre-pubertal boys. So our gold

standard, our provisional gold standard test, was a sleep test based on the principles that Mel talked about. So this requires a GCRC to sample blood every 20 minutes overnight, just like in the protocol that we're proposing today, so the open bars are awake and the closed solid bars are asleep. So these are the boys with constitutional delay. You can see that they had larger and bigger responses than the gonadotropin deficient boys.

And this shows the delta, the different between sleep and awake. And you can see here, let's see is there another -- there's only one child with gonadotropin deficiency that overlapped between gonadotropin deficiency and constitutional delay, so we were able to distinguish these disorders by the sleep test by a delta LH of 0.35 units per liter in 18 of 19 boys. Now, 0.35 units per liter ain't a hell of a lot. The sensitivity in the assay in those days and it was really a special gold standard kind of assay was one unit per liter and I'll come back to that later on.

So anyway it was 0.35 units on top of a

baseline that was sometimes around one is a hard call. So we compared it using a similar protocol, virtually identical to what we're using today to the nafarelin test and this shows the LH response is with the pre-pubertal boys. So the boys of constitutional delay are in solid bars. You have a handout of this, the solid dots. The gonadotropic deficiency are open circles. There were about 10 normal controls that we got and you can see that we differentiated the great majority and the best differentiation was out here at four hours. And when we looked at the delta LH, again, that same kid who we couldn't differentiate on the sleep test, couldn't be differentiated by this test. But again, here we can discriminate 19 out of 20 cases using a delta LH that was now mid-range in the curve of about five units per liter.

So at that point, we ran into our first snag. In 1992, Syntex sold out. Naperson went off patent. All the executives bailed out. I'd been to the FDA with Syntex and gotten and had discussions about using a nafarelin test as a diagnostic for polycystic ovary syndrome. I visited there with Bob

Price who was the vice president of Syntex but within a year they were sold out. They passed the license on to Searle. Searle wasn't interested in a diagnostic. I wish that I would have gotten a use license but if I had gotten a use license, you'd tell me I was here for money today and I'm not here for money. I'm here for passion.

So I obtained an IND and for a year we -- Syntex gave us their last lots of nafarelin. We started switching to leuprolide and we initiated several GCRC protocols with co-investigators, particularly in hyperandrogenism in adult women and children, studies of disorders of puberty like we're talking about here. We were able to get one year of bridge funding from TAP to use Lupron during this time but we've gotten no further support from TAP.

In 1994, under the FDA Orphan Drug Program, we got a grant to look at -- to formally do dose response studies with Lupron and compare it to nafarelin and GnRH and to carry out studies in gonadotropin deficiency and constitutional delay of the sort that we propose here. And then we got

another FDA grant again through the Orphan Drug Program, to look at adult gonadotropin deficiency to try whether we could intermittently -- find a regiment of intermittent low dose spacing of Lupron that would be stimulatory to development. But that's a side issue.

And then the FDA decided, "Whoops, we shouldn't have been letting you use Lupron under a nafarelin IND", so we got a Lupron IND and this was the last support we ever got from TAP. The support we got was they let us look at their -- refer to their NDA and on this IND we have an R01 funded study that has to do with hyperandronism in children and adults. And this is important to those studies but I'm not going to go into that further. So the study under the first FDA Orphan Drug Grant was a dose response study of leuprolide in adults and compared it to GnRH and then historical nafarelin data and the bottom line is that the results showed the Lupron 10 micrograms per kilogram the -- this is the highest that -- well, actually we had a few studies with 20 micrograms per kilo that aren't shown on the slide.

This high dose of Lupron was similar to nafarelin in LH and sex steroid stimulation but interestingly, it was less potent in FHS stimulation. All the doses of leuprolide, the area under the curve, the peaks, were less than those to nafarelin. And of course, this is factual here. It gives you a short-lived early response.

And -- but with Lupron, the 10 microgram per kilo dose gave comparable LH and sex steroid responses to nafarelin, and so that's the dose that we've been going with. But then we ran into sex. So the first of these is that radioimmunoassay results are unlike monoclonal assay results or LH results -- for LH assays. So we had a limited number of samples left over that we could run, both by our RIA which is a poly-standard for those days, the `90s, radioassay and compared that to the Delfia assay which is specific for the beta sub-unit of LH.

So again, this is the kind of data I showed you previously that with the radioimmunoassay at four hours, we could distinguish gonadotropin deficiency from constitutional delay and normal, but

here with the policlonal -- you know, here's this one kid who's the partial case that we couldn't distinguish with the test but here we are with the Delfia assay using a specific beta sub-unit assay and we get a lot of overlap with normal. So that was -- that's been a major challenge to this day. So why? Well, there's microheterogenaity of LH. Your handout says microheterogenaity of immunoreactive LH but it's the LH standards as well as the LH anti-serum, so that LH is a sialilated (phonetic) molecule and it has a lot of epitomes and some assays pick up certain ones and some assays pick up others. And the RIA that we had been using had been a specially developed one that had enhanced specificity for bioactive LH but the specificity was incomplete whereas the Delfia was and is a beta sub-unit specific assay.

Now, the Delfia assay, I want to point out, is a commercially available assay that anybody can buy, so it's commercially available. Back in the early days, before the mid-1900s, excuse me, before the mid-1995s, RIAs were mostly in house and were very unique policlonal, very unique to the laboratory but

now there are a number of immunometric (phonetic) assays and the Delfia is really the best characterize of them. And we realize that free alpha sub-unit could be cross-reacting in our radioimmunoassay for so-called bioactive LH and we have some preliminary data that I'm not going to show you today but we have some preliminary data on even fewer samples than this that support this concept. The free Alpha sub-unit may be a better marker for the distinction of constitutional delay and gonadotropin deficiency than LH itself. And free Alpha sub-unit is hardly commercially available.

And then we ran into another snag and that is we had the failure of our freezer over the weekend and we lost all of our samples for 201 so we can't go home again. Meanwhile, we had -- and there's a little more detail here than on your handout. Meanwhile we have obtained some other sex specific potentially interesting end points. These were studies in 11 boys and seven girls with variance of puberty whose bone ages were 7.8 years of age done in collaboration with Carol Foster, that came out last year. And again

wrong button. I guess I'm used to using the mouse, you know, where you just move your finger a little bit and you get a different click, but here's inhibit B is interestingly enough higher in boys than girls and activin in baseline is higher in girls than in boys. And this may be -- these two things, each of them, would serve to make for a higher FHS level in girls and this is Carol Foster's interest and we're hoping to help her pursue it. And she's in the process of revising a grant that we are going to collaborate in.

So summary to date, leuprolide is not quite the same as nafarelin, particularly with regards to RHS stimulation. Whether that's important or not, we don't know. We can't go back to the discriminatory RIA that we had. I pointed out to you that although it was probably the best there was out there, and laborious I should mention, it lacked specificity at the low end like other RIAs. It was sensitive only to one unit per liter and I didn't show you -- the Delfia is sensitive to .15 unit and when you get to one unit in the Delfia assay, you're in puberty.

And we have considerable promising

preliminary data in children from multiple peer review studies of -- at many levels, our own GRC -- GCRC has reviewed our protocols. These protocols have been the subject of at least two site visits that I can remember and we've had FDA panels review them and R01 panels review them. And now since we lost our old samples, we have to start over.

And so what I'm talking about is not exciting science but I think this is trench work that has to be done to improve diagnostics and I'm probably running late but --

CHAIRMAN FOST: You're fine. We actually have made up some time, so --

DR. ROSENFIELD: Pardon me?

CHAIRMAN FOST: We've made up some time, so it's okay.

DR. ROSENFIELD: Okay. Well, you'll have a chance to ask questions, so I'm sure you will. So at this point I'm going to show you the adverse events of giving one -- of this leuprolide test, which is giving one injection which is a short acting leuprolide and this is different from leuprolide

Depot. So we're tested now with leuprolide. We've gone through our records as of the end of October, 500 and -- what is it, 500, my eyes aren't too good, 577 adults and children at our institution. No serious adverse events. We had a few anticipated side effects. Breaking them down to children versus adults, children under 18, we've done 332 studies. We've had IV related problems in three, like soreness or hematoma and one of those, the child didn't want to be restuck and withdrew from the study. That's the only withdrawal from this protocol that we've had and that's really from the protocol I'm talking about, a child with delayed puberty.

We've had one child who had a transient local rash. We studied 245 adults. We had one IV related problem. We had one local allergic reaction, so now we've got what, in adults and children the allergic reaction is two out of 500, so it's a half a percent and we're not sure whether that's to the LHRH. It's probably to the excipient. And then the adults had a number of hormone related side effects that we ascertained by a post-study letter.

Everybody who gets this protocol gets a self-addressed stamped envelope to send us back and tell is if they had problems. And none of the kids responded but 14 adults responded. Three said they had menstrual pattern changes but one of those had pre-existing polycystic ovary syndrome so you would expect the menstrual pattern to be irregular.

And 11 of them had what you can generally -- I generally call post -- pre-menstrual type symptoms with mood changes, cramps, headaches, vague complaints. Three of these were in males and one of the males actually said that he thought that his sex life was improved for a day after the test, so it's not all bad. So I just thought it would be worth showing you this slide, again, to emphasize the rarity of significant side effects from this drug especially in children.

Now, there are a number of adverse events reported from leuprolide treatment. So there is wide use of leuprolide in the form of Lupron as a long-term treatment. It's FDA approved for the treatment of children with central precocious puberty and it's

commonly used off-label for the management of some children with short stature. It's FDA approved for the treatment of adult men with prostate cancer which is a far cry from kids, and it's used widely off-label in adult women with endometriosis, fibroids and it's used in fertility treatment interestingly enough. So there are a number of side effects of long-term treatment that have been reported. The Depot injection leads to sterile abscesses at the injection sites in maybe five to 10 percent of cases, although I'm heard rumors that this is not going to be a problem, as great a problem recently.

And then there are a number of hormone related side effects; menstrual irregularity, pre-menstrual syndrome type of symptoms. Memory effects have been claimed but the memory effects were mostly in the mid-`90s which was the heyday where it was thought that estrogen deficiency played a role in Alzheimers and in 2003 there was an editorial in three papers, editorial by Jaffe in three papers in JAMA pointing out the data were very contradictory. And then osteopenia is the consequence of long-term

reduction of estrogen levels and so that's not a surprising side effect.

Now, interestingly, the latest paper to review for birth defects after accidentally giving leuprolide after conception shows no increase in birth defects, but the number is small and I'm sure not definitive. So then I'd like to address the response to adverse public comments that were four letters that raised some issues about leuprolide acetate.

And I would say that they are misinformed and/or they are related to long-term therapy, not to -- not one of them that I could track down in about three-quarters of the day that I had time to spend on it fell into any -- were related to one injection. In spite of these letters, the package insert are those of two years of treatment of old men for prostate cancer. They are not for young children. There is no black box warning. The human evidence or adverse effects on auto-immunity are insufficient for the FDA to warrant a warning in their labeling about auto-immunity consequences and it's not a hazardous drug requiring chemotherapy precautions.

Other public comments, the Lawson Wilkins Pediatric Endocrine Society, the Endocrine Society, the American Society for reproductive medicine are unconcerned about leuprolide acetate test toxicity. The Lawson Wilkins Society notes that leuprolide is used in the routine diagnostic testing of children to determine the initiation of puberty, that it's highly useful and that normative data are sparse. Now this goes along with what Dr. -- supports what Dr. Grumbach mentioned to you and it raises an interesting intellectual question.

Since I've told you that there aren't -- and they say there's a sparsity of normative data, how does the pediatric endocrine community find this test so useful? Well, I can tell you right now, to anticipate some of your questions, they rely on historical data and I've told you the assays have changed. They're comparing factorial to agonist and different agonists have been used. Different timings have been used at times. The field is a mess. And the Endocrine Society adds -- supports the use of Lupron but adds that while determining sleep-related

LH secretion is the gold standard, it is and I add, potentially less evasive than the leuprolide test and our goal is to go from these kinds of studies are done to a quick outpatient study, like a lot of people are already doing in their offices.

So turning now to the protocol, just a few slides, the hypothesis is that the hormone responses to a GnRH agonist test will distinguish among the disorders of puberty as well as the sleep test. The specific aims are to distinguish among the causes of premature puberty, number one, and distinguish among the causes of delayed puberty, number two. Last night I changed the wording of this to more closely -- to be more accurate and clear and more closely reflect the wording of the research protocol as it is written.

So we're distinguishing idiopathic central precocious puberty from healthy volunteers and expecting these what we call premature thelarche and what Mel calls early puberty, the six to seven-year olds to lie somewhere in between and to distinguish gonadotropic independent precocity, for example, tumors from idiopathic central precocity. And the

gonadotropic deficiency versus constitutional delay is pretty straightforward.

So just a bit -- one more bit of background about constitutional delay and idiopathic precocious puberty as extreme variations of normal; common practice assumes that these are normal variants, even though I showed you that these are outliers on the standard distribution and they assume this because the pubertal tempo, menstrual cyclicity and fertility in adult life are typically within the broad range of normal. And in addition, it's familial in about half the cases.

Boys with delayed puberty, late bloomers, typically half the time have a father or a mother who were late in their pubertal development. Like father like son so to speak. On the other hand, there's evidence that a small percent of these normal variants may not be normal and the evidence for that is the slow tempo of those staring puberty at six to seven years of age, which Mel had mentioned. There's also a family history of delayed puberty in about 10 to 15 percent of gonadotropin deficiency patients raising

the question whether delayed puberty is a heterozygous manifestation of gonadotropin deficiency.

And then there is a recent paper that gonadotropin releasing hormone receptor CNPs, cyclical orphisms are nominally associated with variations in the timing of puberty and there's evidence from mouse studies that chromosome 6 may harbor genes that regulate pubertal timing.

So one of the points from this is that normal population data are needed to avoid misclassification. So here's the study design. Simply, there are 20 per group of each test. Normal volunteers are what's at issue here. We are defining pre-puberty and puberty conservatively because everybody will agree what if you're -- that this is a normal range to be pre-pubertal in and everybody will agree that is this a normal range to be early pubertal in. The patient groups are constitutional delay versus gonadotropin deficiency and central precocious puberty versus gonadotropin independent precocity and premature thelarche.

Although we project 20 in each group, as

you'll see, some sub-groups get small. What I want to emphasize -- well, before we get to that, I'll just show you -- talking about study design, show you the results of the typical study, illustrate the design and the kind of kid we studied. So a 16-year old boy walks into your office. He started high school. Maybe he's teased in gym. Maybe he's short. He's pre-pubertal. His testes are not clearly pubertal yet. His testosterone level in clinic is pre-pubertal and his LH using a third generation assay, the Delfia assay is really at the limited sensitivity assay. So what does this kid have? He could be gonadotropin deficient.

And so we do a sleep study followed by a Lupron test, a leuprolide test, I should say, because we're using generic. So you can see that in the early evening, while he's awake, his gonadotropin levels are very low. When he goes to sleep, he gets a sleep-related rise in LH. We're taking the average of these. The average of these and looking at the difference and to figure out the norms and what we see in each of these groups. And at the end of the

evening, you can see the LH falls off but we give him a shot of leuprolide. He gets a tremendous long burst of LH output and in response to that, here's what his testosterone does. So his testosterone starts at zilch in the early evening, rises to top zilch by the end of the evening in response to this sleep-related LH secretion indicating that the pulse generator that's begun to start up during sleep hasn't been around long enough to wake the testes up very much and when we give this child leuprolide to stimulate a large LH increase, his testosterone doubles which doesn't look like much on this scale but it comes up into the pubertal range, doubles. And so we interpret this provisionally as a boy with constitutional delay who is in very early puberty and probably won't show pubertal -- outward signs of pubertal progression judging from those testosterone levels for probably a year.

And some families will want to have -- families of children will wish to have a booster course of testosterone for psychological reasons but some won't. But in any case we can reassure a family

like this and actually this boy has been followed on out and has gone through puberty which is really the gold standard. So a bit about data analysis for -- that addresses a statistical question which was raised by an FDA analyst. Sleep test, we provisionally set a significant increase in LH according to our previous studies to define pubertal onset but that's just for interpreting data for the moment, till we can gather full norms. This is an example of how we pediatric endocrinologists have to operate on historical data, not having accurate, up to date data.

And the normal range is to be set at the fifth to ninety-fifth percentile of healthy volunteers and the secondary variables are that will calculate the fifth to ninety-fifth percentile for constitutional delay in boys and for central precocious puberty in girls I added the boys and girls there because those we anticipate having big enough numbers and those are the major targeted study groups. The leuprolide test, we're looking at these hormone response, primary variables, they are group specific. All of this is sex specific and state specific, in

other words, pre-pubertal versus early pubertal.

And for pituitary response, we're using LH and free alpha sub-unit. And for the gonads, we're using the sex specific sex steroid and inhibit-B potentially anyway. And then we will set the sex and state specific fifth to ninety-fifth percentile ranges for normal healthy volunteers. And for constitutional delay in boys and central precocious puberty in girls. Further analysis of data, so boys, where the common problem is delayed puberty, the primary comparison is gonadotropin deficiency versus constitutional delay, and compare the pre-pubertal groups to the early pubertal groups.

Some boys with constitutional -- one of the difficult problems, diagnostic problems that we have but it's sort of unusual is the child who starts puberty but seems to get stuck there and has partial gonadotropin deficiency. But the main group is really going to be pre-pubertal gonadotropin deficiency versus pre-pubertal constitutional delay. Secondarily, we're going to look at gonadotropin deficiency in healthy volunteers and constitutional

delay versus healthy volunteers. Girls are tertiary in this study with regards to delayed puberty.

In girls where the common problem is premature puberty our primary goal is to develop good norms to distinguish constitution -- excuse me, to distinguish central precocious puberty from what are really pre-pubertal healthy volunteers and define clear cutoffs. And secondary end points are to distinguish central precocious puberty from pseudo-pubertal groups like gonadotropin independent precocity or premature thelarche which, again, premature thelarche is what Mel has been calling early puberty.

And boys are tertiary in this because we don't anticipate very many numbers, because it's not a big clinical problem. And I've asterisked a few places where power is limited for subgroups but we will -- I get enough of these patients to get informative information. So in summary, at last, GnRH agonist testing is a minimal risk as far as I'm concerned. I've shown you our studies. There are other studies using leuprolide in the literature.

There is absolutely no literature showing an adverse effect beyond these hematomas and local transient allergic reactions to a single injection of the GnRH agonists, none whatsoever. The study designed is straightforward. It's really a study of normal versus abnormal. We have adequate statistical power for the primary comparisons but not for all the subgroup comparisons admittedly and the protocol, as it's written discusses that as it was written and finally approved, discusses all that.

And the significance for clinical care is great. This protocol will develop badly needed data on the hormonal responses to leuprolide in normal pre-pubertal and pubertal children using commercially available state of the art assays that are available to everybody. It will also provide data on the diagnostic value of the test for the most common pubertal problems.

CHAIRMAN FOST: Thank you, Dr. Rosenfield. Questions for Dr. Rosenfield? Yes, Dr. Diaz.

DR. DIAZ: Hi. You mentioned sexual abuse as a risk for children that develop early sexually.

Is there literature showing that kids that develop sexually early are more likely to be sexually abused than those that are not?

DR. ROSENFIELD: I didn't say that there was literature on it. There's a poor literature on it. The parents are scared to death of this. Just imagine -- well, you know, the predator, there's all this newspaper stuff about predators and parents that see their kid like this are really just scared to death.

CHAIRMAN FOST: Other questions? Yes.

MS. O'LONERGAN: Yes, can you give me an idea of the difference in the dose from the 10 micrograms per kilogram for the test, what is the typical dose and duration of therapy for treatment?

DR. ROSENFIELD: The leuprolide acetate when -- this form that we're using, when it was developed for treatment, and it's still approved -- the approved dose in prostate cancer is -- in adult men is one milligram a day. And that's the standard when you're using leuprolide acetate. Now, one milligram a day comes out to about 10 micrograms per

kilo. Now, there's a paradox here because when you get to the Depot leuprolide, the dose for treatment of precocious puberty is only at a maximum 15 milligrams per month and can be as low as seven and a half. And in adults some of the studies in adults are only using three and a half milligrams a month. So apparently, once you expose the pituitary to a low dose long enough, it has this down regulating effect, but the dose that we use to stimulate is really the dose that's recommended to use this agent for treatment.

MS. O'LONERGAN: Thank you.

CHAIRMAN FOST: Dr. Rosenfield, I have a few questions. In the GCRC review, and the materials you sent us, they pointed out that the two prior studies you were doing, one from 1994 and one in 1998, only -- according to them only 29 of the 240 children that you had targeted were evaluated. And so I'm wondering, if that's true, what's the likelihood that you're going to come anywhere close to --

DR. ROSENFIELD: Well, you can see that we've studied a lot of kids. I showed you in my slides that we've studied 300 some kids. So we

continue to accrue kids. We -- they recommended that we partner with other collaborators and we have initiated feelers but this is sort of a Catch 22 kind of situation. Not many investigators are looking forward to the kind of experience that I'm having today and have had for the last year and a half. Their IRBs can give them trouble. So I'm -- I think my strategy is to test the water. I'd like to -- I'm trying to show you what we've accomplished and what the need is and I would like to see this protocol go forward.

Once we get it going forward, then we can go to Sally Radowick (phonetic) at Hopkins, or Carol Foster at -- who has now moved to Iowa or whoever and say, "We have a approved protocol. This is the way it is. Your IRB, you know, it's been vetted. Your IRB ought to be able to do it". So, as I say, it's a Catch 22 situation and it has to be now put into -- I mean, you can imagine that a drug company doesn't want to get involved in this process right now. I would like to find another manufacturer and use a different agent if somebody would get it product labeled

appropriately.

But in the absence of that, we're plugging along.

CHAIRMAN FOST: So, is that number correct, that you've only recruited 29 out of a 240 target?

DR. ROSENFIELD: I don't think so.

CHAIRMAN FOST: How many of the 240 have you recruited?

DR. ROSENFIELD: Well, remember I lost a whole bunch. I lost all my old samples in 2001. So I can't tell you exactly since 2001 how many I've recruited but I would say we recruit about, oh, I would estimate that we recruit about a dozen children a year with delayed puberty or constitutional delay but we're not getting any normals. So we've gone nowhere with normals because we lost our normal samples in that freezer thaw and now we have a hold on normal samples.

CHAIRMAN FOST: So ever a dozen a year, it would take 20 years to --

DR. ROSENFIELD: Well, there are two main

groups, though. There are really two main groups. The main groups are constitutional delay in boys and central precocious puberty in girls. The others are interesting cases in point. So I want to -- I think that's a good point that you make and that I want to make the point that the primary goal here is -- that's reasonable to do in the near term is to look at the most common problems for which there's the most pressing clinical need and that's delayed puberty in boys and premature puberty in girls.

CHAIRMAN FOST: Dr. Gorman?

DR. GORMAN: If you can answer this question with a yes or no, do you think that most constitutionally delayed puberty in boys are they normal or do you believe that they are outliers from normal with the list of potential conditions that you listed?

DR. ROSENFIELD: There's nothing in life that's black or white.

DR. GORMAN: I could not agree more.

DR. ROSENFIELD: I showed you the data. These are outliers to begin with. I think there's no

doubt that in the community most of the boys with constitutional -- the great majority are normal variance, but in a place like mine or a place like any of these active admissions come from, we see selected cases and we have in our institutions, you know, the most difficult challenging cases. And it gets down to the -- this is a real issue in medicine in general about quote "cost effectiveness". And what's serious, how many people do you need to be concerned about their problem and getting a proper diagnosis.

I'd like to be able to offer it to everybody. Now, the nation as a whole may not be able to economically afford to offer the best care to everybody and you can ask what's the best care, but we're getting off into another --

DR. GORMAN: Let me try to ask that same question a slightly different way. After you complete your work-up, how many of the people who enter your system, realizing that you have a highly selective system of the most difficult cases, end up leaving the University of Chicago with a diagnosis of constitutional delay and being offered either watchful

waiting or six months of minimal testosterone injections?

DR. ROSENFIELD: I would say that -- if you're talking about our clinics, I would say that probably 90 to 95 percent of the boys that come into our clinics with constitutional -- you know, with delayed puberty, we'd give a diagnosis of constitutional delay, we can tell by examination that they're further along than their parents think they are and send them home, but the ones, like I showed you there, the example of the 16-year old boy, the ones that we can't tell of those, I'd say that our numbers are about two to one that they're constitutional delay versus gonadotropin deficiencies, so that if to an endocrinologist at 14 they're delayed then the odds become greater, substantial that they're going to have gonadotropin deficiency.

DR. GORMAN: Thank you.

CHAIRMAN FOST: Dr. Nelson, then Dr. Botkin.

DR. NELSON: Two hopefully brief questions. One, you gave some data on your leuprolide

test. I'm wondering if you have at least an estimate of the same information based on your sleep study, number of children that have had a sleep study and adverse events there, since that's also part of the protocol and then just answer concretely whether the pediatric GCRC at the University of Chicago is a scatter bed GCRC or a dedicated unit.

DR. ROSENFIELD: The sleep test, we had -- I didn't count them up, Sara didn't ask me for those details and it was a lot of work, but I do -- I did survey briefly. We have had more withdrawals from a sleep test than we've had from the leuprolide test. There's only -- out of those 300 some kids, with leuprolide we only had one who withdrew because he didn't want to be stuck again. With the sleep test, it was more of a problem. I think we lost three kids at that point in the sleep test procedure because they were poor needle stick problems and if they don't want to be stuck again, hey, that's life. The CRC is an in-patient unit. It's a discrete unit.

CHAIRMAN FOST: Dr. Botkin?

DR. BOTKIN: I have question about the

healthy kids which is the primary focus, I think of the controversy that we're dealing with and I think that, I guess my question is dealing with a number of different types of healthy kids in this context. One is kids who present either with delay or precocious puberty or signs thereof, who prove to be normal and then you have the other population of kids who don't have any signs or symptoms of either delay or precocious puberty that are proposed to be enrolled.

So I guess my question is --

DR. ROSENFIELD: I just -- what group are you talking about? We're talking about the healthy controls or about patients?

DR. BOTKIN: Well, you have patients who come in with signs or symptoms of either a delay or precocious puberty and many of those kids will prove to be healthy, normal variance, right?

DR. ROSENFIELD: Yeah.

DR. BOTKIN: So I guess my question is, from a clinical context what you're really interested in doing is discriminating between kids who are basically healthy but who have clinical symptoms of

either precocious puberty or delay and those kids who have organic problems that need some sort of medical intervention.

DR. ROSENFIELD: Yes.

DR. BOTKIN: So I guess my question is, why do you need data on kids who are essentially healthy and don't have clinical signs of either precocious puberty or delay since in the clinical context you'll never actually be performing a leuprolide test on those kids? You really need to discriminate between the healthy group with delay or precocious puberty from the kids with pathologic aspects of those conditions.

DR. ROSENFIELD: Well, I think when it comes to the early puberty kids, it's very difficult to know about that six to seven-year old group. I have no idea whether that group is really normal or not. I could -- I really -- I don't know whether they're the same as central precocious puberty and I think part of it goes beyond clinical practice. Part of it goes beyond trying to push the envelope and understand puberty better. I'd like to know what the

difference is between those kids and normal and those kids and the kids with idiopathic precocious puberty because I think in the long term, the prognosis may be different and I'm sensitized to that by my great interest in polycystic ovary syndrome and the emergence of this is a fairly -- is an increasingly recognized syndrome along with the increasing so-called epidemic of obesity in the country and wondering whether -- how obesity effects this. And I must say that outcomes in these disorders are poorly defined and poorly known. I know of no -- I mean, the normal outcome of central precocious puberty and the normal outcome of constitutional delay is really antidotal. There are a lot of testimonials, fathers who have been delayed or mothers who have been early, they've grown up, fostered these kids but there's not a lot of data on that.

And I think it's important to know what normal is. And I think the risk of the test is minimal.

CHAIRMAN FOST: Yes, Dr. Boepple?

DR. BOEPPLE: Yes, when Dr. Grumbach was

describing his overview, one of his statements was that if the natural sequence GnRH was still available easily commercially, that perhaps the use of GnRH agonist wouldn't be something we would be talking about. And I'd just like to have you underscore your thoughts with respect to this because it strikes me that having a super potent agonist as a diagnostic challenge actually does provide some additional benefit over the natural sequence even if it hadn't been previously available particularly if you're trying to distinguish an adolescent who lacks signs of puberty and I just wanted to have you have a chance to underscore that point.

DR. ROSENFIELD: Well, thank you. Well, I'm a great believer that the -- that this is a better test than an ordinary GnRH test. The ordinary GnRH test measures the readily releasable pool of LH. I showed you in one graph that you have in your handout that there's a transient peak of LH that's really preformed LH and there is abundant literature that it is imperfect in discriminating gonadotropin deficiency from delayed puberty with considerable overlap. I

also -- and what the GnRH agonist does is that after the readily releasable pool of LH is secreted from -- LH is released from the pituitary gland, the releasing hormone additionally promotes synthesis of new hormone and this is the so-called storage or newly synthesized pool and you'll notice the discrimination between constitutional delay and gonadotropin deficiency in our data is at the four-hour time point which is the point at which we're seeing the ability to synthesize new gonadotropin. So I think that's one benefit of it right there.

And then, although it's not the subject of this particular protocol, this test has provided us with an invaluable new tool to understand ovarian function and in particular. It can also serve as a one-shot test to test in boys the pituitary gonadal axis because you can test not only the pituitary response but then gonadal response to it. So it has dimensions beyond natural GnRH and again, I think it is as safe.

CHAIRMAN FOST: Dr. Rosenfield, a few more questions; with regard to the pressing need, is it

your view that the existing methodologies are resulting in misdiagnosis and mismanagement of children and is there anything published on that or you have -- is there antidotal evidence? Is that a common problem or --

DR. ROSENFIELD: Well, I think that nobody -- I think the pediatricians are operating off the seat of their pants with pediatric influence are using historical data and I don't know --

CHAIRMAN FOST: Do you think they're making mistakes and the children are being misdiagnosed?

DR. ROSENFIELD: I think so.

CHAIRMAN FOST: Is there any literature on that?

DR. ROSENFIELD: I don't know of any.

CHAIRMAN FOST: All right, a couple of small questions.

DR. ROSENFIELD: People don't usually talk about misdiagnosis.

CHAIRMAN FOST: The blood volume, you're going to draw about 240 ccs.

DR. ROSENFIELD: We're going to draw less than five percent in 24 hours and less than 10 percent of --

CHAIRMAN FOST: I wanted to get at the actual volume. You said you needed --

DR. ROSENFIELD: There's a caveat in the research protocol that that volume holds for children with sufficient body weight and the blood -- the amount of blood withdrawn is suggested for children under that.

CHAIRMAN FOST: The protocol said that you need eight ounces, which is 240 cc's. So you would not draw that --

DR. ROSENFIELD: No, we don't. I don't know -- I don't know exactly where you're seeing that in the protocol but --

CHAIRMAN FOST: It says it in the consent form.

DR. ROSENFIELD: Pardon me?

CHAIRMAN FOST: It's in the consent form also.

DR. ROSENFIELD: Well, it probably says,

and if it doesn't it should, that it's adjusted accordingly for -- it's adjusted in proportion to body weight.

CHAIRMAN FOST: And one last question, with regard to the psychological consequences of the admission to the GCRC, there's a prior study showing that some young children, seven, eight, nine-year olds, can have severe psychological reactions for this kind of admission especially when it's a research admission. One study, they interviewed these children afterwards and they had nightmares, they had fantasies of research meant. They thought it was like an autopsy and so on. Can you report on your experience with any of that? Do you think there are any serious adverse effects for young children particularly admitted to a unit like this?

DR. ROSENFIELD: I can -- we have no evidence of that. As I say, I don't -- as I say, if the child protests, they can withdraw. There's no major effort made to -- you can't hold a child against their will. And as I mentioned, we send out a post-envelope afterward you know for -- a self-addressed

envelope to return. We've gotten on follow-up with concerns in that regard.

CHAIRMAN FOST: Okay. We think we're making up a little bit of time from the public session, so we'll take one or two more questions and then take a brief break. Dr. Silber?

DR. SILBER: I want to apologize, I'm local so I just got paged out in one part and so you may have covered this. But when you talked about the risks, I remember you're mentioning patients with rashes et cetera, a couple of patients with rashes. The question is, in any of these follow-up of administration has there been any description of an anaphylactic or an anaphylactic reaction since a one-time test could have that complication?

DR. ROSENFIELD: Well, a one-time -- number one, there aren't any. Every -- every GnRH product carries a warning that there was once upon a time an anaphylactic reaction to natural GnRH and that occurred in a patient who was congenitally GnRH deficient. It had to be -- require more than one exposure. You have to have a sensitizing dose or

more. We are not doing more than one injection.

CHAIRMAN FOST: Thank you. Dr. Gorman, Dr. Botkin and then I think we'd better -- I'm sorry and Ms. Knudson. Go ahead, Rich.

DR. GORMAN: I'd like to stray from the area of hormones and tests for just a second and talk about the -- what appears to be an optional sub-study on blood drawing and preservation for molecular analysis and perhaps perpetual cell lines. Is that -- is there any provision which I did not see in either the informed consent or the protocol for patients subsequently withdrawing their consent for that part of the study?

DR. ROSENFIELD: Well, maybe the IRB people can comment, give us a little time. I think there's language written into there. I know that we've discussed this issue with the IRB. I have tried to comply with all the regulations.

DR. GORMAN: Working with an institution on an IRB, I also understand that institutional assumptions are made about protocol and how you store samples. It just wasn't clear to those of us who are

external to your institution how that would be handled and some clarification might be useful.

DR. ROSENFIELD: Well, you know, it's stored confidentially and I have access to it, if you're talking about that kind of thing but at this moment, the great majority of it is just storage. We haven't -- there aren't -- although Mel talked about genetic defects causing some of these disorders. They cause only a small number and we haven't been involved -- we haven't identified a collaborator to look at any particular one.

DR. GORMAN: You were just so eloquent about how you would allow children to withdraw their assent and consent during the procedure of the study.

DR. ROSENFIELD: Well, I --

DR. GORMAN: I was wondering if you were equally eloquent in how they could withdraw their consent about the use of their blood samples.

DR. ROSENFIELD: I can tell you that part of my lack of eloquence, not that -- I appreciate your calling me eloquent but I deny it.

DR. GORMAN: I resemble that remark.

DR. ROSENFIELD: Yeah, and you're a gentleman but I have some -- I have about three other -- three or four other active CRC protocols and I know that language is written into them and if it's not written into this one, it's an oversight, you know, but they are eligible --

CHAIRMAN FOST: Dr. Botkin and Ms. Knudson.

DR. BOTKIN: A somewhat minor point, the IRB had looked at the kids who are participating who have clinical symptoms of either delay or precocious puberty and the question was whether they would benefit from enrollment in this protocol. So I wanted to ask a bit about that. My assumption in reading the protocol was that these were kids who would be enrolled prior to a definitive diagnosis as they initially presented as opposed to recruiting kids who already had pre-existing diagnosis; is that correct?

DR. ROSENFIELD: That's right. The kid that I showed an example of is very typical.

DR. BOTKIN: Okay, and if that's the case would any clinical decisions be made based on the

experimental portion of the testing protocol or would all the clinical decisions be made on the sleep test results, the so-called gold standard?

DR. ROSENFIELD: It's based on a combination, just like everybody else in practice does it. We go on historical data and with tongue in cheek and with qualifiers that we're highly confident but come back again, so to speak, in brief. The test -- the assays are run in a CAP certified laboratory so the results are certifiable.

DR. BOTKIN: So basically the fact that they're enrolled in the protocol and having the additional experimental interventions may improve the accuracy of the diagnosis and therefore alter the clinical care they might get?

DR. ROSENFIELD: Yes, and you realize that when the Lawson Wilkins Society in their letter talks about this being a clinically useful test, they aren't doing it in the CRCs. They are doing it outpatient uncontrolled without precautions that we take in our clinical research center and they're operating on incomplete data that isn't as good as most of them

think it is.

MS. KNUDSON: Dr. Rosenfield, I'm not a clinician and I just have something that I would like to get clear in my head. You said that normal data was very important in order to avoid misclassification. I understand that treatment is different for the different classifications but is early treatment very important for those or is watchful waiting or other diag --

DR. ROSENFIELD: Oh, early treatment is really terribly important for central -- girls with rapidly progressive central precocious puberty. You want make that diagnosis quickly because it will effect their adult height potential. That's a permanent consequence, not to mention psychological things that some people can -- some families can handle better than others.

Also it has implication. You know, that diagnosis has implications for brain tumors and various other malformations. Delayed puberty it's -- every boy would like to be like every other boy. When he starts high school and he's not in puberty, he

would like to instantly be -- if he's short and delayed, he'd like to be instantly taller and you know -- so, it's important psychologically to make a diagnosis early. It's a real shame to let a child with gonadotropin deficiency to have them be told that they're going to outgrow it and they go to their sophomore year and their junior year and boy, are they different, and probably different for the rest of their lives. Stamped, you know, they've missed out on a social opportunity, appropriate social opportunities in early high school.

CHAIRMAN FOST: Last question and then we'll take a break. Dr. Rosenfield, with regard to the normal controls, if you found a normal control who had results that were somewhere around minus two standard deviations, would -- well, my general question is, are you planning to disclose results to the families or the children of the normal controls either all of them or if they have slightly abnormal values are you planning to tell them about that?

DR. ROSENFIELD: I think I'd have to ask an ethicist what the right answer of the question --

it strikes me as having some kind of PC overtones and I'm not quite sure what the right answer is. For one thing, it's a very hypothetical question because we don't have 20 normal controls and you know, to construct fifth or ninety-five percentiles requires throwing out the top and the bottom.

I know with normal adults with these tests we inform them of clearly abnormal results, not in this particular study were we don't have them defined. I think they would be interesting follow-ups but whether I'll be allowed to by ethicist is another matter.

CHAIRMAN FOST: Okay. We're quite a lot behind but we think we'll make some of it up in the public session, so if we could take a 10-minute break and reconvene at 11:15, that would be desirable. Thank you.

(A brief recess was taken.)

CHAIRMAN FOST: We are now pleased to have Dr. Marc Garfinkel, who is Vice Chair of the IRB at the University of Chicago. Dr. Garfinkel.

DR. GARFINKEL: Thank you. It's a

pleasure to be here today and to help represent the University of Chicago and support Dr. Rosenfield in his application before this Committee. So I come as one of the three Vice Chairs of the University of Chicago IRB. I am trained clinically as a transplant surgeon. I am not a pediatric endocrinologist. I also bring with me today from the University of Chicago our Millie Maleckar and Pasha Osofo (phonetic) who are Director and Assistant Director respectively of the Administrative Regulatory Compliance for Human Subjects. I'll also again apologize to the Committee and to the public audience who may have received a version of the slides. These are slightly different than what's in your hand-out and that's in large part related to some unavoidable last minute changes in terms of who would be making these comments.

And finally, I recognize that we're a bit late and that I'm allocated a full 30 minutes on the agenda. I will take significantly less time.

CHAIRMAN FOST: Thank you.

DR. GARFINKEL: I'd also like to respond to Dr. -- I'll start by also responding to Dr.

Gorman's question since there was an inquiry that -- in terms of the language regarding withdrawal. There is standard template boiler plate language with regards to withdrawal from the study in general. In this particular -- and that is on every protocol approved by the IRB. It indicates that a human subject is able to, at any time, withdraw from the study without effecting their care. And that that notification must occur in writing. To answer his question specifically, there is not necessarily the distinction of the withdrawal of the sample or the destruction of the cell line emanating from that sample on the protocol.

So my objective this morning is to provide an overview, a REPO review of Our Biological Sciences Division and University of Chicago Hospital's Institutional Review Board and then after that to provide an overview of the review process specifically associated with this protocol and how it came to this convened meeting today.

There are essentially three areas of institutional review boards at the University of

Chicago. The one which is germane today is the one which we represent is the biomedical or clinical research portion of the IRB and that represents the Biological Science Division which is the over-arching entity which oversees the medical school as well as all biological departments.

In addition, there are -- there is a Social Services IRB which oversees protocols related to the School of Social Services Administration and a Social and Behavioral Sciences IRB which serves the Departments in the Humanities, the Redmond (phonetic) School of Business and the Law School. As is the case with IRBs at most academic institutions and elsewhere, our IRB -- and this is directly off our website, is charged with the responsibility for review, approval and surveillance of all research involving human subjects carried out in the Biological Sciences Division and the University of Chicago Medical Center and this review and surveillance is conducted to insure the protection of the rights and the welfare of all research subjects including volunteers patients and this occurs regardless of the status with regards

to the federal funding.

Currently, in our institution, there are over 2,000 active protocols involving human subjects that fall under our purview and surveillance. And that's active protocols. That doesn't mean that they're all enrolling subjects. Some of these are still open only for the purposes of continuing data analysis. In addition, this is out of a total of almost 15,000 total protocols historically, so new protocols as they come in are being assigned numbers in and around the range of 15,000 and of these protocols, our best estimate is that about 200 involve children.

Now, there are three committees that meet monthly and there are three vice chairs that assist the chair, Jonathon Moss. These committees are composed largely of faculty scientists, non-scientists from the faculty and elsewhere in the university as well as community members whose opinions are important as well. The committee membership is drawn from a variety of backgrounds from within the institution including ethics, pediatrics, cardiology, cancer

surgery, nursing, pharmacy, teaching and law to name a few. And these committees are supported in large measure and very well by a growing an excellent administrative staff, most of whom hold the title of administrators or regulatory compliance.

Now, in the past half decade there has been a significant period of growth for clinical protocols at the University of Chicago as well as commensurately the IRB in order to support that. There has been an approximate doubling of active protocols since the year 2000. And commensurate with that, the BSD/IRB staff has doubled in size from six to 12 full time members. In addition, in 2001, there was only one committee that would meet monthly and sometimes more frequently as necessary. And that has now tripled to three full time committees, each of which meets separately on a monthly basis. Committees A and B are generally charged with reviewing new protocols and Committee C is generally charged with the responsibility of continuing renews either annually and more frequently if necessary.

And in addition, in an effort to enhance

the efficiency of this system, we are currently implementing an electronic submission system. All of our firms are currently electronically available on line but we'd like to make the entire submission process paperless.

With regards to protocols involving children, all protocols involving children as subjects require the submission of an additional supplemental form in addition to the regular protocol submission form. We all this a Form C and this form -- for Children, and this form asks investigators to identify a few things; number one, a justification which specifically details the potential benefits to pediatric subjects, if any exist. It also asks the investigator to identify a risk benefit assessment with a specific opportunity to characterize the research into one of the three approvable categories of which Dr. Fost spoke earlier according to the Subpart D as well as a confirmation of the method and strategy for consent and assent of minors.

So now to get to the specifics of this protocol and the IRB's interaction with it. This

protocol was initially submitted on September 7th of 2004 and typically there is an administrative pre-review before the protocol is brought to a convened meeting and this pre-review generated administrator comments to the PI. The submitted Form C indicated in that person's opinion that the study involved -- no, that the submitted Form C involved a greater than minimal risk with direct benefit to children with disorders of puberty but inquire whether -- what the circumstance was in terms of healthy children, recognizing the potential conflict in regulatory situations.

And then throughout the month of October, there was further communication between the PI and the administrative staff that very clearly, and as you heard eloquently stated today, the PI's believe that the study represented minimal risk to healthy subjects, but that based on discussions with the IRB, previous committees and the administrative staff, that there was some compulsion to fill out the forms indicating greater than minimal risk.

The first convened meeting that reviewed

this protocol then occurred on November 9th of 2004 and that received a pending conditional review. There were several administrative components that had to be revised and were but for the purposes of this conference, the key finding of that committee was that the research involving children with a pre-pubertal disorder could indeed be involved under Section 405 because it inferred come possibility of direct benefit. But that committee classified the research as a minor increase over minimal risk with no prospect of a direct benefit for healthy children or their disorder as these healthy children have no disorder, at least related to pre-puberty, premature puberty, thus requiring a 407 review.

There was minimum debate, I think it was taken very much at face value that this research was, indeed, conducted according to ethical standards and that there was, indeed, an opportunity of this study to -- it was well designed and that there was indeed an opportunity of the study to contribute to the understanding of a condition effecting children.

So from that meeting on November 23rd, a

letter was issued to the PI. Subsequently a response letter was received. As this is a GCRC protocol, it underwent GCRC review as well and the GCRC requested certain changes into the protocol that were substantive with regards to the protocol and the handling of DNA samples et cetera, but not necessarily substantive with regards to the issue at hand in terms of the risks related to pediatric subjects. Because of the substantive changes to the protocol, however, this had to be reviewed on a subsequent IRB meeting and that occurred on January 11th and at that time, again, full approval was granted of the protocol as written with the caveat that healthy subjects were not to be enrolled in anticipation of this review today.

Also in recognition that this was coming this protocol was forwarded then to Dr. Mary Ellen Sheridan, our Associate Vice President for Research as a important courtesy notification that this review was forthcoming. The -- in the interim before this meeting could be scheduled a continuing review was completed and at that time, it was reiterated that there was full and complete approval of the protocol

as written with the exception of the enrollment of healthy subjects and then here we are today on November 15th.

So just to briefly summarize and I think Dr. Fost summarized this very succinctly in his additional comments, the IRB's deliberations regarding Subpart D for children with a pre-pubertal disorder the study has greater than minimal risks and not approval under 404 but offered the direct prospect of benefit to these children so it was approved under 405. For those without the pre-pubertal disorder under normal controls the study was deemed greater than minimal risks and not approvable under 404, not offering the prospect of direct benefit and not offering the prospect of information about these particular children's disorders, since they have none, so it was determined by this committee that it could only be approved after review such as this today.

I would like to echo, and I was pleased to see Dr. Fost had introduced the article that appeared in the Journal of the American Medical Association last year, the challenges facing not only our own but

institutional review boards across the country in determining what minimal risk means, what more than minimal risk means. You've heard certainly the expression of the PI that this is a minimal risk protocol but clearly the variety of responses to this type of survey, this is the same point that Dr. Fost demonstrated, I think it's justifiable that there is discussion, debate and consideration of what constitutes minimal risk. The specifics in terms of this protocol centered specifically around, yes, the use of leuprolide specifically in a non-FDA approved manner in healthy children, but also there was some consideration of a overnight and in some cases two overnight hospital or GCRC stay as well as the presence of intermediate term catheters for as long as 48 hours or longer.

And again, I think Dr. Fost called to attention the disparity in something as simple and truly routine among children as allergy skin testing with 23 percent of IRB chairs demonstrating or considering this to be minimal risk, 43 percent considering it to be a minor increase over minimal

risk and 27 percent considering this to be a significant more than minor increase over minimal risk. Perhaps underscore some of the challenges that our board faced in determining exactly the level of risk associated with this protocol for healthy children.

I should also point out that this -- and it was represented in this study that -- or acknowledged as one of the limitations, is that whereas the opinion of the chair which was surveyed here, constitutes one component of those deliberations, the overall consensus of the committee had the opportunity to override that of any particular chair and it was recognized that this survey was limited and that it did not necessarily recognize all opinions by all potential IRB members.

So based on this and based on our own deliberations, we struggled with the interpretation and the application of the regulations specifically in terms of the interpretation of minimal risk. And I'm pleased that we can be here to support Dr. Rosenfield and his application and we appreciate the guidance and

oversite.

CHAIRMAN FOST: Thank you, Dr. Garfinkel. Questions for Dr. Garfinkel? I'll start. The question I raised earlier to Dr. Rosenfield about sample size or the feasibility of the study with regard to comments by the GCRC. And as I understood Dr. Rosenfield's response, he didn't disagree, that is he's previously only been able to recruit 10 percent over a 10-year, 11-year period.

Even if the study were at minimal risk it's generally considered to be an ethical problem a the study is not able to evan achieve the goals that it seeks, that is to even bother these children, even the children with disorders. So did the IRB consider that, take it into account? Did you discount it? How can you -- how did you handle that issue?

DR. GARFINKEL: That's probably a fair observation. I think the deliberations of the IRB centered largely around the language in the consent, the mechanics of sample collection, as well as the classification of the risk to the children. I think it's an important consideration but the minutes do not

reflect any individual debate or discussion in terms of the achievability of the desired results based on power of the study or sample size.

CHAIRMAN FOST: Dr. Rogol, Dr. Nelson.

DR. ROGOL: Norm, I'd like to follow up on that. I didn't hear quite exactly what you heard. What I heard was that the two main groups were relatively simpler to recruit. The issue, he could not recruit any of the normals because that wasn't permitted and I would think that the primary analysis and Bob can correct me if I'm wrong, I think the primary analysis can be done on three separate groups; boys with delayed puberty versus gonadotropin deficiency and girls with CPP and the control group that is appropriate to those two age groups.

The others, as I understood him to say was those were much less common and those were secondary or tertiary analyses. That's what I heard and if that's the case, I don't think it's quite fair to say it's 10 percent of the total number. What the real issue is, is what percent of the primary analysis number leaving out the normals. Did I misinterpret?

DR. ROSENFIELD: Thanks for the opportunity.

CHAIRMAN FOST: Can you go to a mike? We need to pick up --

DR. ROSENFIELD: Thanks for the opportunity to clarify that. Yes, that's exactly what I said. And I want to reiterate that this is a Catch 22 situation about getting collaborators. If this protocol, let's say hypothetically does not get approved, then do you think I'm going to be able to get a collaborator? If it does get approved, then collaboration comes easily, once we know the level of approval and such and can go forward.

CHAIRMAN FOST: So are you saying now that you do not think you could achieve the sample size are your institution? You would need other centers?

DR. ROSENFIELD: I can get the major at my own center. I can get the primary. I have probably over half of the primary constitutional delay and central precocity already.

CHAIRMAN FOST: I'm sure you have the patients, but just let me ask one more time, I guess

I'm still confused. The two prior studies had a target of 240 children. I'm not sure what categories they were in. And according to the GCRC only 29 were recruited. Is that correct?

DR. ROSENFIELD: You've got to remember that that's pre-review. We used to break down in pre-cursor categories. You see, we had pre-cursor categories, pre-cursor studies and we're talking now about this protocol which is focused considerably and only talks about pre-pubertal and early pubertal. We're not talking about late pubertal, which was a category in this before in which we recruited under another protocol. So that's misleading.

And the categories of constitutional delay and central precocious puberty are easily accruable in the time like that we're talking about. And we await -- and 60 of those, you know -- previously we were supposed to recruit 60 normal controls, boys and girls. That's 120; 20 pre-pubertal, 20 pubertal -- excuse me, 20 pre-pubertal, 20 early pubertal, 20 later pubertal girls, 20 pre-pubertal, 20 pubertal, 20 post-pubertal boys. That's 120 of all of this is

controls. We haven't had funding. Now, we're stopped from proceeding with the healthy controls.

We have, for this protocol, dropped the post-menarchial girls because they really aren't relevant to this and in the current protocol which was redesigned partly for GCRC review and to focus and to make it more feasible, we've cut down the number of groups that are necessary.

CHAIRMAN FOST: Thank you. Dr. Nelson.

DR. NELSON: This is a question for Dr. Garfinkel. And that's the IRB's experience with other in-patient GCRC protocols and the discussions surrounding staying overnight or two nights as you mentioned and you know, what the IRB's view is of the GCRC and what's done to minimize risk, et cetera, just focus on that aspect separate from the other components of the research.

DR. GARFINKEL: So if I may just reiterate the question, the question is, does the IRB, in general, consider an overnight stay in the CRC to constitute additional risk to children?

DR. NELSON: Yes, and what's done to

minimize that risk, et cetera.

DR. GARFINKEL: So there was -- so that is considered with other protocols. With this particular protocol, Dr. Rosenfield has indicated a few things. First of all, in terms of the indwelling catheters, the children can withdraw from the stud at any time. Second of all, parents are allowed to remain with the children in the GCRC which significantly lessens the anxiety and distress or at least designed to do that.

DR. ROSENFIELD: Encouraged.

DR. GARFINKEL: Encouraged. So -- and but I think that that standard is taken consistently across the board. I'm not saying that the IRB would necessarily use that alone as a criteria for raising the bar over minimal risk and I think that the central thing in the IRB's deliberations that assigned this as greater than minimal risk here was the administration of the leuprolide in a non-FDA approved manner. But that was thrown in as an extra component to the entire constellation of risk associated with the protocol.

CHAIRMAN FOST: Further questions?

DR. BOEPPLE: Yes, I just wanted to

clarify the time line because one of the things that Dr. Rosenfield eluded to was the -- in a sense the chilling effect on clinical research that some of these regulatory requirements may have and that's -- you know, that's a corollary to the basis of the regulations in the first place, but the protocol was submitted to your IRB mor than a year ago and here we are, you know, 14 months later. But -- so I just wanted to clarify the time line a bit because it seems as if at the University of Chicago a determination had been made in January by the IRB. It was sent to one of your university's research leaders but then the submission to the folks here at the federal level didn't occur until June; is that right?

Because I think one of the things that may emerge in our discussion is, "Holy mackerel, if it takes 14 months to get something even discussed, that's a problem". And yet if more than half of that resided at the home institution, that's perhaps a different story.

DR. GARFINKEL: So I would say that the time frame for the -- from time to initial submission

to review was fairly typical. There was a submission of a protocol in late September. The protocol was reviewed and met at a convened meeting in November and there was feedback given to the principal investigator by mid-November and then by the creation of the -- by the necessity of re-review by the CRC, and substantive changes to the protocol that occurred based on that, there was a resubmission in January and so that -- the 3rd of January. So, then you're correct. I mean, from that point forward, so that's from January to November and I would actually want to consult, if I may, with my Director of Regulatory Compliance for a moment to hear about the time line of submission.

DR. BOEPPLE: But I guess what I was questioning was it true that -- I mean, it sounded like there was a decision to get to this point at the University of Chicago in January but that the initial communication didn't occur until late June.

DR. GARFINKEL: Just a moment, if I may, in the name of giving you accurate information.

(Pause)

CHAIRMAN FOST: If you want your associate

to just talk directly, that's fine.

DR. GARFINKEL: So Millie Maleckar is our Director of Regulatory Compliance for Human Subjects.

DR. MALECKAR: So there's just a number of communication that went back and forth between the IRB office and Mary Ellen Sheridan who is our Associate Vice President for Research. She's also our institutional official for our FWA. So there's just a number of communications that went back and forth between our office, the University Research Administration and Dr. Rosenfield that led to the delay of the submission of this protocol to the 407 panel.

CHAIRMAN FOST: When was it first submitted for 407 review, in June?

DR. MALECKAR: I don't recall the exact date. I would say it was early --

CHAIRMAN FOST: So January to June it was internal to the --

DR. MALECKAR: Internal communications because this was, again, our first 407 review, so we wanted to make sure that everything was addressed

appropriately.

CHAIRMAN FOST: Thank you. Dr. Gorman?

DR. GORMAN: I started to ask this question earlier and I'll try again. In terms of standard operating procedures for sampled or banked blood at the University of Chicago, it appears that it will be identifiable by the principal investigator, stored indefinitely and potentially be used to create an immortal cell line. Do the children in this study or their parents have the right and the ability to withdraw their consent for that use?

DR. GARFINKEL: Yes, I'm sorry, I addressed that at the beginning of my comments, I think, but first of all, there is standard boilerplate template language in all of the consent forms for all of the protocols that's an essential component and has to be there that indicates the ability of the subjects to withdraw from the study and in particular at any moment. That, of course, requires written notification and has the stipulation that data heretofore garnered can still be used by the PI.

There is not, in this particular protocol,

the stipulation or the side comment about the blood and the ability to remain within the protocol and have that blood destroyed. That's a good concept and I think it's something that's important to our review process but in this particular protocol, having reviewed the consent form during the break in response to your question, there's no particular separate stipulation that says -- that specifically notifies the subjects that that can be destroyed.

Having said that, there's no stipulation that says they can't and the ability to withdraw, provides to withdraw either partially or completely.

DR. GORMAN: The secondary concern that follows onto that question is, is that these samples continue and this is the two-edged sword, we always get with samples. If you can identify -- you need to identify them to be able to withdraw them and destroy them. But if they're de-identified, you have a different set of issues where you can't offer the subject the ability to withdraw their blood from the sample but it then cannot be identified back to the subject.

So I think either of those two routes are fine. Pick one.

DR. GARFINKEL: That's a good comment, and we typically ask the investigator submitting new protocols in a similar vein to kind of approach that, do we identify what will become of knowledge, particularly done from tests done on human normal subjects, that find abnormalities. And again, it doesn't really -- it doesn't necessarily matter in terms of the approval of the protocol as to whether that information will be shared with the subject or with their physician as long as that strategy is prospectively identified.

CHAIRMAN FOST: Dr. Botkin?

DR. BOTKIN: I think both you and Dr. Fost sort of highlighted variability with different IRBs and folks who serve on IRBs about how risk determinations are made. As I look at your IRB notes, I don't see much debate over the question and I see unanimous votes on the determination that experimental intervention is a minor increase over minimal risk. Is that a fair characterization of your IRB's

assessment?

DR. GARFINKEL: That accurately reflects, per the minutes, the discussion held about this protocol during that meeting, yes.

DR. BOTKIN: So as far as you're concerned, there's not debate about this particular protocol on that question?

DR. GARFINKEL: Certainly there's debate.

DR. BOTKIN: Within your IRB.

DR. GARFINKEL: With regard to this particular protocol?

DR. BOTKIN: Right.

DR. GARFINKEL: So I think there was discussion and some debate about it, but I think the minutes summarize the consensus opinion. Perhaps, it's an indication, however, and you bring this up appropriately, that the minutes need to reflect appropriately all discussion leading to that consensus.

DR. ROSENFIELD: Could I make one comment in this regard? I'd like to say that I think IRBs are under tremendous pressure in this kind of decision

right now and it is better to play on the side of safety, so to speak and defer to a panel like this than to make a choice that will later be second-guessed as being an incorrect one and run the risk of citation. And I think IRB -- as an outsider, that's my perception of the burden on an IRB. They carry an institutional burden.

DR. BOTKIN: Dr. Rosenfield, did you have an opportunity -- I know you've said that you think this is a minimal risk intervention. Did you have an opportunity to make that argument to your IRB in person?

DR. ROSENFIELD: I made the argument to Jonathon Moss in person and to one of the -- to the ethicist on the committee in person, but their interpretation of national rules, they felt that to -- my understanding is that they felt that to rule otherwise could potentially jeopardize the institution and I wouldn't want to do that.

CHAIRMAN FOST: Other questions for Dr. -- Ms. Knudson.

MS. KNUDSON: Yeah, I would like to follow

up on Skip's question, Dr. Garfinkel. Did the IRB find out from the CRC what their experience is with other healthy normal children that have been admitted under other protocols, had it been a satisfactory experience or are they having a difficult time?

DR. GARFINKEL: So, we have a number of protocols that utilizes the CRC. It's been a longstanding and well funded part of the institution for a long time. With regards to making a specific inquiry with regards to that component of the stay as it related to this protocol, no, that was not done. But I think there was significant institutional experience and recall from our many protocols that do rely on both out-patient and in-patient interaction with --

CHAIRMAN FOST: Dr. Rosenfield?

DR. ROSENFIELD: Again, this is a single institution. All adverse events in the CRC are reported at the CRC and they're reported to the IRB. So the IRB has the whole experience.

MS. KNUDSON: I really wasn't speaking about adverse events. I just wanted to know what the

experience had been both from the children, the parents and the staff of the CRC when they have children involved, children as young as some of these.

DR. ROSENFIELD: Well, you're asking whether the IRB heard that and I can't speak to that.

CHAIRMAN FOST: Other questions for Dr. Garfinkel? Dr. Gorman?

DR. GORMAN: Dr. Garfinkel, would you be willing to share the percentages in rough numbers of protocols. You said in your presentation or pre-sent presentation, you said you have 2,000 active protocols under the IRB review. What fraction of those got through on the first pass, what fraction of those were disapproved and what fraction of those were -- I see you have some sort of grouping of conditional, which I'm not sure I know what that means but I suspect it means we want more information and we'll look at it again.

DR. GARFINKEL: So the generally applied options for review and outcome after review of a protocol are the following, full approval, approval with conditions, what we call pending conditional.

And that has the opportunity to go to a number of places. Having a conditional review, often, as you say asks for additional information from the PI and that additional information can be something as simple as the correction, typographical errors on protocol submission forms, the protocol itself, the consent forms, rewording changes, things that are generally held as administrative changes, and so that can be then signed off after an administrative review. That can go back to the original reviewer if the reviewer feels that it takes an actual committee member or it can go back to the IRB chair.

So that's the second of three subparts. And then the third option is deferral in which case either it's felt that there are significant enough problems with the safety and contents of the protocol such that it shouldn't rest on one person to review and either approve or not approve that protocol, but that it should come back to a fully convened meeting. So full approval, conditional pending, or deferral.

Of the new protocols that are submitted on a monthly basis to the IRB. Probably five to eight

percent or so are deferred. The vast majority are conditional pending, most with administrative review but some with substantive committee member or IRB chair review. So I would say 80 percent, and then full approval usually is achieved without any revisions by about 10 percent.

DR. MALECKAR: As Dr. Garfinkel chairs the continuing review committee, I think those numbers are different for new protocols and -- yeah, for new protocols. Generally, I would say 15 to 20 percent of new protocols end up being deferred. I would say the majority of the rest, again, are given pending conditional status.

DR. GORMAN: Do you have any idea of how many of the deferred ones die and how many of the deferred ones come back for approval? And the reason I persist on this particular point is to try to get a flavor for exactly how rigorous in one sense -- one terminology the IRB is.

DR. MALECKAR: I would say at least 75 to 80 percent make it back to another meeting.

DR. GORMAN: Thank you.

CHAIRMAN FOST: Other questions for Dr. Garfinkel, if not -- oh, Dr. Rosenfield.

DR. ROSENFIELD: I just thought of a better answer for your question. The majority -- I'm Associate Program Director in the Clinical Research Center. I have been for 20 years. I don't think I would have lasted if we were -- you know, had a bad reputation with the nurses. The -- we really carry out the majority of the tests in the Clinical Research Center. And I gave you figures earlier on 300 and some children with one withdrawal. I think that speaks -- which was due to a blood problem. I think that speaks to the general tenor of the child research at our CRC.

CHAIRMAN FOST: Thank you. If there are no further questions for Dr. Garfinkel, are there any members present in the audience who would like to make any comments, public comments? Absent that, I'm just going to read a summary of the written public comments that were submitted and then we can break for lunch and we'll be able to get right into discussion right after lunch.

So what I have done is summarized the -- what I think were the key points made by those who submitted letters. There were about six, I believe. Melissa Harry wrote and said she was a patient who was treated for nine months with leuprolide, I misspelled it there, she said she had serious side effects but didn't say what they were. Said she thought enough research has been published to warrant discretion in the use of gonadotropin releasing hormones on vulnerable populations such as children and provided references. It was a short letter.

Lynn Millican wrote a quite long and detailed letter commenting on the proposed research to use a challenge dose of leuprolide. She said that subjects should be informed that it is listed as a quote "hazardous drug", end quote, according to NIH, OHSA and MSDS, I'm not sure what MSDS is, requiring two pair gloves and a chemotherapy gown, describes serious side effects such as memory loss, seizures, brain lesions, cardiac and gastrointestinal abnormalities, bone and joint abnormalities, immune dysfunction and death to name a few.

She referred to a Lupron Victims network with a website that included thousands of victims and over a million hits a year which she said was silenced, had mysteriously disappeared. Referred to fabrication and falsification from the company, alleged in four studies. Said there was information in the Federal Register about this. Referred to her own congressional testimony on the subject.

Said there were numerous Lupron adverse event product liability lawsuits that TAP had settled all via secrecy agreement. In `99 there were 6,000 adverse events related to Lupron reported to the FDA. She said, quote, "The PI falsely claims that side effects are due to chronic leuprolide use in adults. " I have seen internet messages, children who underwent leuprolide challenges tests and suffered ill effects afterwards. The PI falsely claims only Lupron depot has been responsible for adverse reactions.

She urges that meaningful consention involve statements that is it a hazardous drug, clarify whether NIH and OSHA standards will be used. A handout of all adverse effects, reported adverse

effects, informing subjects that there are Lupron victims and agree to pay all costs associated with leuprolide adverse effects.

Susan Hayward, also a consumer of Lupron, said there was a high incidence of precocious puberty and endometriosis in the general population. She didn't attribute these to Lupron. Her point was that more research is needed on prevention of these disorders. She believes part of the problem is in the food supply. Referred also to the National Lupron Victims Network whose website, she said, was taken down mysteriously after a million hits. Quote, "I believe Taketa and Abbott Labs formed TAP as a hedge for future lawsuits, thereby protecting the parent companies". She had criticisms of TAP.

She expressed concern about patients with anti-thyroid antibodies receiving leuprolide who she said had developed thyroid abnormalities due to Lupron. Described mood swings, suicidal ideation and suicidal attempt following Lupron depot and attached nine exhibits, including references, copies or articles, package inserts and a parents guide to

precocious puberty.

Andrea Dunaif, if I'm pronouncing that correctly, Dr. Andrea Dunaif is President of the Endocrine Society, which quote, "Supports the participation of normal children as control subjects in clinical research under clearly defined circumstances", end quote, but in her letter she did not define the circumstances. The regulation stipulating 407 review may substantially constrain the enrollment of normal children as control subjects increase in clinical research and she expressed on behalf of the Society that the increasingly narrow interpretation of acceptable risk is of particular concern. "The Society does not support the concept that any pharmaceutical, even if approved for children and routinely used in diagnostic testing, should be considered, typo, my typo, should be considered a minor increase over minimal risk and hence, by its use in healthy children, mandates review by a 407 panel", end quote. She called for the rational use of the 407 process and greater guidance to IRBs for determining minor increases over minimal risk.

Drs. Joe Sanfillippo and Robert Rebar, writing on behalf of the American Society for Reproductive Medicine, said they were not familiar with the specific protocol, but the quote, "Feel", speaking for the Society, "they feel strongly that it can be important to obtain data from healthy children in order to improve our evaluation and treatment of young patients with hormonal problems. Without data from a normal population, it may be difficult, if not impossible, to ascertain the safety and efficacy of some medications and treatments".

Dr. Rogal, writing on behalf of the Lawson Wilkins Pediatric Endocrine Society, noted that the IRB had classified the study as a minor increase over minimal risk due to the length of hospitalization and the use of leuprolide which represent more medical attention than a healthy child would quote, "ordinarily encounter in daily life or during the performance of routine physical or psychological tests".

The Lawson Wilkins Pediatric Endocrine Society does not review clinical research protocols

and thus, does not and cannot issue statements regarding the risk benefit ratio of a specific project. However, leuprolide used in routine testing of children is a highly useful test for which normative data are sparse and a necessary pre-requisite for the precise diagnosis of pubertal disorders in children, and added that the 407 process may suffer from uninformed or bias lay statements.

Dr. Rogal went on to write, "There is tremendous variation in the interpretation of minimal risk by different IRBs. Therefore, the Lawson Wilkins Society strongly supports two panel members who are pediatric endocrinologists to represent the scientific and clinical viewpoints of their colleagues in the Society. The Society does not support the concept that any pharmaceutical, even if approved for children and routinely used in diagnostic testing, should be considered -- this is my typos, I'm sorry -- should be considered a minor increase over minimal risk and hence, by its use in healthy children mandates a review by a 407 panel".

They support the participation of normal

children as control subjects in clinical research under clearly defined circumstances but those circumstances were not defined.

DR. JOHANNESSEN: Did you want to mention the one --

CHAIRMAN FOST: Oh, thank you. One came in today. All right, relatively brief. "My name is Susan Weiner and I am the President and founder of the Children's Cause for Cancer Advocacy, a consumer based national education and advocacy organization that works on discovery and development of better cancer therapies for our children and insuring quality care for childhood cancer patients and survivors.

I was also the mother of a child with cancer who, by coincidence, was enrolled in a clinical trial of GnRH, the agent under review by the 407 panel. I've worked on the ethic of research involving children as liaison at the Institute of Medicine and as a member of the Secretary's Advisory Committee on Human Research Protections. Because of this coincidence of personal and professional experience, I feel obligated to submit comments to the Pediatric

Ethics Committee concerning the risks and benefits of testing GnRH as a diagnostic test for precocious puberty.

Three brief points. First, the standards which I, as a parent, used in deciding whether to enroll my son in a trial of GnRH were the very same standards I would have used if I considered enrolling my normal unaffected child. This point underscores the ethical notion recommended by the IOM and other bodies that children with a disorder or a condition, just because of their status, should not be exposed to greater risks than normal children.

In considering clinical trial enrollment, I assessed the risk to my child of exposure to the drug itself, the IV placement, the administration procedures including the time necessary for evaluation, special protections available for him and the environmental and psychological conditions he would be exposed to during the testing. From a parent's perspective, the assessment of risk and benefits is the same for any child.

Second, I can verify directly that the

agent itself is safe and effective and further, that the research procedure involved minimal risk. My son was on GnRH for about three years and amazingly experienced no side effects. In addition, the testing and evaluation procedures in the study were virtually the same as the current protocol under consideration except for duration, six hours versus 36 hours. During his life, my son was a hospital traumatized child particularly sensitized to IVS. But because the physician, nurses and I took special precautions to insure his comfort and well-being, there was minimal psychological and physical risk.

Finally, GnRH successfully suppressed my son's precocious puberty and despite his illness and disabilities, this treatment gave him a chance for a more normal, better adjusted life with his peers. Being sexually mature as an infant, young or pre-adolescent child obviously poses unacceptable developmental, physical and psychological consequences. If diagnosed early, an agent known to be safe and effective could prevent these abnormal conditions. I believe that research that tests the

possibility of early diagnosis of precocious puberty will enable children a cure for a disorder that should never be their developmental burden. Thank you for the opportunity".

With that we will adjourn and we will reconvene at 10 minutes after 1:00. Lunch is in the hotel restaurant somewhere near the front. See you at 10 minutes after 1:00;

(Whereupon at 12:08 p.m. a luncheon recess was taken.)

AFTERNOON SESSION

(1:18 p.m.)

CHAIRMAN FOST: Thank you all, I hope most of you got lunch. Dr. Gorman, did you get food?

DR. GORMAN: Thank you, Norm, I did.

CHAIRMAN FOST: What I've done -- what I'd like to do is put up on the screen a list of slides that in the morning I prematurely called votable questions, changing it to points for consideration or issues to discuss, what seem to me some of the major questions that came out this morning and the process here will be to see if we can get in an informal way, some consensus on the group. And we'd like everybody to participate and everybody to comment on each one of these questions. We will go around the table several times to do that, but this can be done informally also.

So for the next hour or so the goal will be to have an informal discussion, see what the questions are and to see where consensus is or where it may not be. Ultimately, the only votes we will have will be on strictly legal questions of whether we

recommend approval under Section 404 a minimal risk, 407, meeting the criteria for 407, approve with modifications or approve only if modifications and so on. So we'll safe that till the end, but I think if a more informal process can help us identify where consensus is and where it isn't the voting will be more efficient.

So I'm just going to run through what seem to me some of the central issues and there's one I know I didn't get up there involving inducements. We haven't talked about the financial incentives or payments, so that's not on my slides, so if there are others, people, I'm sure will say what they are and we'll develop a full list.

So issue number one is, does this proposal to study the response of normal children involve minimal risk? Remember the University of Chicago IRB concluded that it did involve more than minimal risk but this group doesn't have to agree with that. This group could make a recommendation -- correct me if I'm wrong Sara, but we could make a recommendation that it's approvable under 404.

DR. GOLDKIND: That's correct.

CHAIRMAN FOST: Okay, to do that we would have to conclude that all the risks are minimal, whatever the risks of leuprolide are; the risk of the procedures, and including the blood volume et cetera and the psychological risk of hospitalization and the procedure. So that's one issue and we'll come back to that and discuss it.

Issue number two is if this is going to be approved under 407, the committee will have to be -- agree that it's addressing a serious problem effecting the health of children. There are two possible ways of effecting and interpreting that. One, as I mentioned this morning, is whether precocious disorders of puberty are a serious problem and I suggested that we don't need a lot of time to discuss that. I think the speakers made the case that these are serious problems, medically and psychologically.

The second issue that might warrant some discussion is whether the lack of availability of good diagnostic tests or the lack of availability of normal standards, normal values with regard to leuprolide

stimulation, whether that's a serious problem because my sense of it is, that's the problem that Dr. Rosenfield is trying to address, that is namely better standards for diagnostic testing. So the committee to approve under 407 might want to take a position on whether they perceive that as a serious problem.

Issue three is a design question; is the research designed in a way that quote "presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem effecting the health and welfare of children", end quote. And here I don't think the issue is a traditional designed one in the sense of is Dr. Rosenfield getting the right tests and using the right dose, or even if the sample size is adequate, but there were questions of accrual raised of the likelihood of achieving accrual raised by the GCRC, not discussed apparently by the IRB so this group, it seems to me, should at least discuss that, whether they think the accrual problems raised by the GCRC are sufficient as to make it unlikely or at least problematic as to whether the study will succeed.

And this is an ethical problem because if it doesn't succeed in accrual, then the first five, 10, 15, 20 or 40 children who are enrolled would have donated their services, their time, their inconvenience, their discomfort for nothing if there's not enough data to reach reasonable conclusions.

Ultimately -- so there's an issue number four that I didn't put up there, which is the compensation issue. I think we need to talk about that, whether it's problematic, somebody raised that during the break, the question of whether it's problematic that the normal subjects are getting compensation and the children with disorders are not. Second, whether the compensation that's being given or offered to the normal subjects is an undue inducement. So we need to have a little conversation about that.

Ultimately, we will need to vote, I think, on only these issues but someone feel free to correct me. One, the committee will need to vote that the Secretary approve the study as written, period, and then decide whether they think it's approvable under

404 as minimal risk or under 407, meeting all the criteria of 407, which I'll review when we get there.

Second, the committee could recommend that it be approved under 404 or 407 with modifications, that is approved only if certain changes are made, or third, the committee could recommend non-approval. Remember Dr. Goldkind's comment this morning, that our recommendations are only to the Pediatric Advisory Committee which meets tomorrow. It's their responsibility to make the final recommendations to the Secretary. So they could undo anything that we do. We're only advising them.

Is this a complete enough list to get us going? Are there any issues that anyone wants to add to the agenda? Dr. Botkin?

DR. BOTKIN: Yeah, just a question; the Chicago IRB approved the enrollment of kids with pubertal disorders but not the healthy children as controls. So is our primary obligation here to focus -- well, is it our exclusive obligation to focus on that component that was not approved by the Chicago IRB or do we open up the larger set of issues about

sort of component analysis of the protocol?

CHAIRMAN FOST: Good question. Why don't you go on and say -- I had assumed that the part of the study involving children with disorders was not controversial other than accrual, but if you think that we should revisit that, this would be a good time to say it. Do you think more discussion is needed on that arm of the protocol?

DR. BOTKIN: No, actually. I mean, I might have -- I think there are some issues that could be discussed but I wouldn't say that from my perspective it's controversial enough to require discussion from my perspective.

CHAIRMAN FOST: All right, well, if there's time at the end, maybe -- I mean in our final comments. That is, in making recommendations to the Secretary, I think there are two kinds of recommendations; one absolute recommendations, that is the Committee could conclude that it should only be approved if certain changes are made and other it could be gratuitous recommendations which would be meaning that it go back to the IRB and to Dr.

Rosenfield is suggested. So maybe at the end we'll consider that.

All right, why don't we get going then on issue number one? Does the proposal to study the response of normal children involve minimal risk? The floor is open for comments and we're going to go around the room so everybody will talk. Yes, Ms. Dokken.

MS. DOKKEN: I guess one of the things -- and I'll put this out here at the risk of I am a family member and a consumer, so I don't want to come across as sounding uninformed or biased. But I've been troubled in some of the presentations and the materials that we received that the risks are most often talked about in terms of the Lupron and from my point of view, there are pretty enormous risks involved with a 36-hour hospitalization, a 36-hour IV, whether or not parents are, you know, allowed to be in the room, particularly looking at the age group, where the children could be as young as nine.

And I don't want us to just focus on talking about the -- you know, the very few adverse

events related to the use of Lupron in children, but I want to keep those other risks front and center and I think that was also in a couple of the public comments was that really almost questioned the whole 407 process. Again, the emphasis was on the pharmaceutical product and just because you were using pharmaceuticals, it shouldn't have to mean a 407 review, but I don't think that we're just talking about the Lupron here.

We're talking about something else but at least from the family member point of view to me is extremely important to know about and to put on equal footing.

CHAIRMAN FOST: Could you just say a little bit more about -- we do have psychological risks on the slide so it's quite appropriate, but say a little bit more about what your concerns are about what may be worst case scenarios this experience might be like with the children is one question and second, do you think this is -- these are deadly or do you think it's a matter of consent, that they just need to be more carefully described in the consent form?

MS. DOKKEN: Well, first of all, when you're talking about, you know, a benchmark of the experience of healthy children. I mean, in this day and age with our health care system, a 36-hour hospital stay is pretty serious. So I think you're talking about, you know, if you think about children who have not had the experience of being in a hospital or even, you know, frequently visiting a hospital, I think that could be a very troubling experience.

I think, you know, an IV and -- I'm sorry, I lost track of your last question.

CHAIRMAN FOST: Do you think these concerns are sufficiently severe as to be fatal to the study? That is, it shouldn't be done or are you raising a point that they should be more explicitly described in the --

MS. DOKKEN: Maybe both. I mean, one part of me wonders also looking at the flyer. I mean, I'm trying to imagine what parent and healthy child would, you know, possibly say, you know, "Let me sign up". So maybe the market will almost take care of the problem but then that brings us back to the accrual

issue. I do think that the consent and the assent form, the mention for the health in the versions for the healthy children, the fact that it, you know, is not a direct benefit is on page 4 or, you know, somewhere pretty buried, so yes, I think that kind of thing ought to be way up front, not at the end of the form.

CHAIRMAN FOST: Dr. Nelson.

DR. NELSON: I think maybe to elaborate a little bit and agree with Deborah, I think even if you took out the leuprolide, all of the other procedures are problematic with respect to minimal risk. Even though there is not in the regulations certainly --

CHAIRMAN FOST: Say that again, Skip. I missed what you said.

DR. NELSON: Even if you remove the leuprolide, which I realize is a hypothetical, 36 to 48-hour IVS, overnight admissions, et cetera, I don't think fit minimal risk and I'm going to say why. First of all is the question of definition. Even though it's not in the regulations, one question is, whether from a going forward perspective, it's

reasonable to start from the recommendation for example, of the Institute of Medicine Committee from last year, that minimal risk has to be indexed to the daily life or the routine psychological or physical examination of average healthy normal children, not children with precocious puberty.

So even though I would agree from what I've heard, the risks are indeed minimal, that still doesn't mean it's minimal risk. Now, so that's why I was asking about is the GCRC a dedicated facility, is it not scattered beds, which means they're spread out in the general population, which I think would be problematic. You know, a lot of it is -- you know, this is in effect, a two-day sleep-over. You know, what's the environment like for that nine-year old.

I mean, a teenager is probably given a video game and they're fine for two days, but what's it like, I mean, what else is done. There are ways that would assure me that that's a reasonable experience from the perspective of a nine-year old but that's a lot of sort of on the ground issues that perhaps local knowledge is important, too.

Can it be done? Yes, I think it could be done in structuring it that way but it would take some effort to make sure that a nine-year old's experience was as if they were going next door and spending two days sleeping over with their neighbor, which is sort of a daily life.

Now, this pump that's hooked up, which I guess pulls off a little itsy bitsy amount of blood every 20 minutes, how much does that restrict movement, I mean, those -- which as best I could tell from the sleep -- from the sleep test, but you know, they're sleeping, but are they -- can they move their arm. I mean, there's a lot of -- those kinds of details, how often you stick the IV in. My experience is we would usually say if you have to try three times it's no longer minimal risk, or, you know, and you would stop even if the child said keep going.

So those are a lot of the details that I think we don't have to necessarily flesh out here but in my mind take it outside of the minimal risk category into a risks can be minimized but it's not minimal risk.

CHAIRMAN FOST: Dr. Rogol.

DR. ROGOL: Let me give a somewhat different opinion or at least perspective. I have done two seven-year longitudinal studies in kids. Longitudinal means same kid over seven years. And we had them in the GCRC which is partially dedicated to kids, that is they are kid friendly. The nurses are there. Two out of 23 in the first study dropped out for reasons because they moved out of town and I think four, maybe five out of 55 of the second dropped out. They kept coming back.

The second one, only a few went through seven years because once they finished puberty, the study was over. And there are ways -- these kids did come back. They were away from their parents. And that was actually the biggest deal of all for both the kids and the parents.

DR. BOEPPLE: These were healthy --

DR. ROGOL: These are healthy normal kids. They had to be normal height, normal weight, normal weight for height, not taking any medication. And the parents and the kids actually looked forward -- the

kids were usually with another kid at the same time. They knew how long they were going to be in the hospital and yes, when a catheter came out, one or two of the nights were lost because the kids didn't want to get stuck but they came back.

So I think for those of us who have done some of these studies, although all of these issues are real issues, there are people, I for one of them, who have gone through this a number of times with the same children coming back. So, yes, we explain things to them, we tell them to bring video games. It is a sleep-over, that's exactly the right word, because they usually enjoy being away from mom and dad and mom and dad usually enjoy them being away for a night.

I'm serious about that. It may seem like a joke. I am not kidding. And in fairness, if they thought or their parents thought that this was more than minimal risk, they wouldn't have kept coming back. We did not give them anything, so that does take the leuprolide out of it. We took blood samples every five, 10 or 20 minutes, depending upon what the protocol -- what version of the protocol we were

working with and that's just on the ground experience. I'm not saying whether it's right or wrong but it can be done in real live children who are otherwise completely heathy. Actually, they were stringently healthy. So that's just a different perspective, Norm.

CHAIRMAN FOST: Yes.

MS. O'LONERGAN: I supervise all the research at our Pediatric General Clinical Research Center and we have a 10-patient in-patient unit and it is packed and half of them are with normals, so it can be done beautifully. And I echo the sentiments that it's a sleep-over. You can have string cheese even.

CHAIRMAN FOST: The first two comments expressed the view that all things considered, it needed to be classified as greater than minimal risk. Dr. Nelson said he thought it could still be done in an acceptable way with the appropriate attention to details. I'm still not quite there where Ms. Dokken stands on that, but Dr. Rogol and Ms. O'Lonergan, could you comment on whether you -- you both, obviously believe the study is doable and ethically

acceptable. Do you think it should be classified as minimal risk or more than minimal risk?

MS. O'LONERGAN: Probably more than minimal risk.

DR. ROGOL: Well, I unfortunately am waffling, so I will come down on the side of more than minimal risk.

CHAIRMAN FOST: So we're getting close to unanimity on that. Is there anyone who disagrees with that?

DR. ROSENFIELD: I had a comment.

CHAIRMAN FOST: I don't know, it doesn't violate any federal rule. We have uniformed officers here, so --

(Laughter)

DR. ROSENFIELD: I just want to say that it was a misconception that the IV was ever in more than 36 hours. That was the protocol, so it's never more than that, and the option, of course, is to take out the IV after a short period of time and reinsert it and children don't want that by and large.

CHAIRMAN FOST: Or doctors.

DR. ROSENFIELD: And we -- in young children, again, we actively encourage parents staying. We have videos for them, that kind of thing and with older children, we actively encourage recruitment of a friend for a sleep-over.

DR. BOEPPLE: Could I just chime in? There are preparations that, when applied to the skin induce anesthesia not only at the superficial skin level but deeper, such that placement of an IV catheter is essentially painless. That doesn't change the fact that kids don't necessarily enjoy sharp things coming at them, but even that as a procedure, can be dealt with in much the same way that we've talked about having child friendly, you know, facilities be available.

CHAIRMAN FOST: Dr. Rogol? Any other comments? Dr. Nelson?

DR. NELSON: By deeper, you're referring anterpheresis (phonetic) as opposed to emlicream (phonetic) or --

DR. BOEPPLE: Emlicream goes deeper than the skin level. I mean, it's more effective than, you

know, a spray that freezes the skin for instance.

CHAIRMAN FOST: Paula Knudson?

MS. KNUDSON: I just -- I'm sorry, I would just like to ask Dr. Rogol, did you pay your healthy volunteer children on those studies?

DR. ROGOL: Yes, we did.

CHAIRMAN FOST: Can we come back to that, Paula, because we're going to have to discuss the finances as a separate issue.

MS. KNUDSON: All right.

CHAIRMAN FOST: Could we just drill down a little bit more on this risk? The people that have commented believe the risk -- they've commented mainly on the psychological risks. Does anyone think that the leuprolide itself administration constitutes more than minimal risk?

DR. NELSON: More than minimal risk? Yes.

CHAIRMAN FOST: Okay, anyone disagree with that? I'm just trying to get as much precision on this position.

DR. ROGOL: Do I disagree or agree?

CHAIRMAN FOST: Does anyone disagree? You

disagree.

DR. BOEPPLE: Before we go on, what will become of this statement? In other words, I think that we will make a statement with respect to Dr. Rosenfield's protocol at the end of this and as you point out, there are different component parts of it. So is there any precedent setting that will go on today with respect to a normal healthy child being able to be admitted to a GCRC overnight and have frequent blood sampling given all of the things we've talked about and making sure the facility is appropriate for children, setting things up in a way that assent and permission, both the child and the parent is maintained?

Are we going to -- I don't know if we had any clear resolution of that because I think it would be valuable for us to address that front and center, whether that is something that we would consider more than minimal risk as a -- you know, as a separate line item here.

CHAIRMAN FOST: Dr. Nelson?

DR. NELSON: Maybe Mike or Sara might want

to comment on that, but having bee involved in some of these things prior to there being a federal advisory public process, the whole issue of precedent establishment in cases and how that impacts on IRB decision making, I think is a complex process. As one example, there was a -- and this is a public document so I'm not saying -- where the question was a 24-hour IV in a consenting adolescent with an overnight stay with the administration of heavy water through that IV, where the individuals were consulted but not as a panel since there was no vote and not a public process were split not evenly but almost evenly over whether that would be minimal risk or more than minimal risk with the final determination letter saying that it was not minimal risk it was more than minimal risk.

So whether that sets any precedent that this group has to agree with or disagree with, you know, I was on that and I won't say which side I was on but it's unclear -- it's a case specific decision and how it then becomes part of this oral or written tradition that impacts on IRB decision making is a much more complex question.

MS. DOKKEN: Dr. Goldkind.

DR. GOLDKIND: I'd like to address your question. I think it's a good one and you can actually access the 17 or so 407 panel records on OHRP's website and you can do the same for the much more limited number of 50-54 referrals that the FDA has had on public dockets and if you will, these records, the summary of today's meeting and eventually the summary -- the letter from the Pediatric Advisory Committee Chair all become public and they're referable just as any case precedent would be in a legal sort of venue. While they're certainly not binding, they do contribute to the general understanding of pediatric research as we, you know, continue to try and further our scientific and ethical orientation to is.

As we heard earlier today, IRBs are very confused about how to interpret minimal risk and minor increase over minimal risk and some of the other parameters of Subpart D and this contributes to the general advancement of understanding.

DR. BOEPPLE: I accept that. So if

someone were to look at this, the public record of this meeting down the line, and let's say we were to approve it under the 407 provisions, and then an IRB had to consider a study in normal healthy children that involved only blood drawing but not the administration of a therapeutic, is the public record going to be sufficiently detailed for them to get any insight into this discussion or not?

CHAIRMAN FOST: No, I mean, the reports -- Dr. Nelson was the prior Chair of this committee and his reports were five to 10 single spaced pages and this one will have sufficient detail also. I should say also our transcript is available Jan tells us, but you should be aware that as we're meeting here, there are IRBs around the country, probably approving studies with exactly the same war risk, labeling it minimal or not requiring a 407 process. There is as yet no clear --

DR. BOEPPLE: Well, I understand it, that's why I'm asking the question.

CHAIRMAN FOST: Precedent would be way too strong a word. That is the system is still

sufficiently informal and amorphous that IRBs sort of can go the way they want. Whether there would be consequences if somebody brought a lawsuit against them and somebody said, "Hey, you know, your friends in Chicago got 407 approval". I mean, you can't avoid that things are in the public domain that people will refer to them, but there's no binding law being written.

DR. GOLDKIND: But Dr. Boepple, your point is well-taken. As much as this group can flesh out some of the thinking behind why it feels that this ought to be classified as a minor increase over minimal risk, that would be advantageous.

CHAIRMAN FOST: Dr. Prohaska?

DR. PROHASKA: Yes, I just want to say that fundamentally we agree with what Dr. Goldkind had to say. Just one point of clarification, the first five or six 407 panels that were convened are not available on the OHRP website. And then also, relative to the nature of your deliberations regarding the risk categorization, we make all attempts to try to include that in our final memo that we forward to

the Secretary and it will be posted on the web.

CHAIRMAN FOST: Thank you, yes, Dr. --

DR. GRUMBACH: One of the problems that we all face, I think, is that the same shoe doesn't fit every foot and the issue is really -- in my mind one of the important issues is the environment. Now, you heard from Alan Rogol and you've heard from Bob and I think Paul would also agree that this is an exceedingly important point and I find it very difficult to make broad generalizations and that's why I think institutional review boards are very important.

If it's a very user friendly environment with experienced people doing this, that's one issue. If it's somebody who is not in -- you know, scatter beds, it's not an environment that really is conducive to the kind of care that we demand be given to our children under these circumstances, that's another matter and I find it difficult to really juggle all this in the sense, Norm, of -- I really put -- I really rate environment very high and I rate the investigator very high.

CHAIRMAN FOST: Thank you. So yes, Dr. Silber.

DR. SILBER: I'm thinking out loud. We're stuck. The reason we are stuck is there's a very clear definition of what is more than minimal risk. And this study clearly is not an everyday experience for kids. So there's really no possibility to not have this reviewed by 407. On the other hand, there are things that are really risky and shouldn't be done and there are other things that, as has been mentioned, one works very well on risk reduction.

The only question I have and this is simply a concern, is there will be 500,000 407s if one is all the time considering that this more than minimal risk category, no direct benefit, healthy children has to come to such a big elaborate meeting. I see no way out of it and probably what we're dealing is with something where there's some level in between missing that does not yet exist and so one of the things that might be interesting about this meeting and our thoughts is to bring that to the attention of all those that are working in this field

of IRBs because at this point, it's either very capricious which has been pointed out by several speakers, or if really taken to the spirit of -- to the letter of it rather than the spirit, it will mean an avalanche. For instance, the study that you mentioned, the longitudinal study, would not -- would have had to have come to a 407. So just leave that not so much for this particular decision because it's clear that this is more than minimal risk but for something to be taken by somebody at a certain point in time.

CHAIRMAN FOST: I think our purpose today is not to develop a better policy, although everybody in the room probably has a clear idea of what the policy ought to be, but --

DR. BOEPPLE: I'd just like to point out, if you think there would be an avalanche of these submissions and yet we've heard that over the course of how many years now since it's been in effect, there have been maybe a couple of dozen, I think the effect of this on clinical research is that people aren't as diligent and thorough as Dr. Rosenfield has been to

follow through. They say, "Hey, if this is going to take a year of my life and you know, kill a couple of Sequoias to do the paperwork, we'll do something else". And I think that is something we should recognize.

CHAIRMAN FOST: Could we get back -- since I'm the one who has to write the report, I want to -- as Sara Goldkind said, the more precise we can be about how we reached our conclusions, the more helpful it will be in the future. So there's been -- everyone has said that the psychological risks, they think are more than minimal but --

DR. BOEPPLE: I don't know that everybody said that.

CHAIRMAN FOST: Everybody who spoke has said that. Well, I asked if there's anyone -- well, that's what I'm trying to find out now, is where the agreement and disagreement lie. Let's start then at the bottom. Is there anyone in the group who thinks the psychological risks are within minimal risk or not more than minimal? One person, okay.

Okay, let's go back to the others. Yes,

Dr. Garfinkel.

DR. GARFINKEL: I speak with not necessarily a clear answer as to yes or no, do I consider this more than minimal risk, but just to amplify this point and another consideration; one of the paragraphs in the conclusion of the JAMA paper that both you and I discussed, Dr. Fost, talked about in terms of the risks to pediatric subjects and whether that was -- whether the actual experience was outside the realm of their day to day experience is one thing, but there was one line that talked about a drug that had a one in 100,000 risk of death associated with that administration.

Now, certainly, the experience of that drug is not within the normal experience of a healthy child. Having said that, driving across town at rush hour traffic probably carries with it the risk of 100 -- that one in 100,000 risk of death and so there's the consideration of whether the experience has to be the same or carry the equivalent risk.

CHAIRMAN FOST: Right. I mean, the problems of that -- the phrase about "risks of

ordinary life", is also much debated and criticized. First, it doesn't address ordinary life where, ordinary life in Scarsdale or in Cabo, Afghanistan.

Second, it doesn't address -- even if the risks of ordinary life were very high, it wouldn't follow from that that in research you should be able to add onto those risks by doing something that essentially doubled your -- you know, if you had a one in 100,000 risk of dying by a car, okay, well, we can give you another one in 100,000 risk. So that whole -- these are policy issues that need to be discussed elsewhere but all we need to do today is decide on whatever basis, how --

DR. GRUMBACH: But, Norm, it does say "neighborhood", doesn't it?

CHAIRMAN FOST: Huh?

DR. GRUMBACH: It does say neighborhood.

CHAIRMAN FOST: Neighborhood?

DR. GRUMBACH: Yes, neighboring -- part of that was in the environment of the child.

CHAIRMAN FOST: The word "neighborhood" doesn't exist in there. We had some hands, Dr.

Boepple, Dr. Rogol, Dr. Botkin, Dr. Boeppel, Dr. Botkin, Dr. Nelson.

DR. BOEPPLE: I'd just like to comment on the basis for my having indicated my opinion here. I -- as a pediatric endocrinologist at Mass General over the last 22 years, I've been involved in clinical research in children with disorders of puberty, specifically young children who have had precocious puberty in one of the largest clinical studies that was done starting in the early `80s and going on for more than a decade. We treated more than 100 children with central precocious puberty, with a close cousin of leuprolide, one of the other GnRH analogues in the same family.

Families and their child came back every three to six months, at times for a decade and admittedly these were children that had a medical condition and there was benefit that they were deriving from their participation. But these were families that nevertheless and children that came back and grown up people now 20 years down the road that write and tell us about the fact that they've applied

to medical school. I think that with the appropriate attention to environment, facilities, personnel, process that the psychological burden of entering the doors of a hospital and spending overnight there need not be considered as -- necessarily as risky psychologically as we've said, and so that's my perspective and the rationale for my statement.

CHAIRMAN FOST: Thank you. Dr. Botkin.

DR. BOTKIN: Part of the difficulty I always have in this context is the word "risk" itself, which is a probabilistic term. It tends to suggest that, you know, what we're worried about is the probabilistic events in the future that might be adverse for that particular child. Obviously, another circumstance is it's not so much probability. You get stuck with a needle, it is going to hurt. It's not a matter of a risk of hurting. It will hurt and the question is, does it hurt enough to constitute an inappropriate burden.

So I actually like to think in terms of the word "burden" even though it doesn't appear in the regs. And I think the justification for the minimal

risk was simply that kids who can't consent on their own to participate in research to include them in research without their ability to consent is sort of a morally perilous thing to do. And if you're going to do it, you probably need to keep the risks or burdens to that participation quite low, and quite low meaning about what average normal kids experience.

And so it seems to me burden, thinking of it in those terms, is put the kid in the hospital for 36 hours with an IV and injection of a drug with what I assume actually is sort of unknown long term implications. Is that more burden than you would, in good conscience subject the child to is not able to consent to that involvement? It seems to me that that's pretty straightforward, and the answer is, yes. And you can't -- the regs don't allow us to countermand that by saying, but look at the great information we could get. You know, in the adults you can compare the risks and the benefits and make a choice. In kids, the regs don't allow us to do that and I, at least personally think that's a pretty good approach.

So from my perspective, I think this is a pretty big deal for kids, even though I would very much agree or am convinced that the actual risk of ay serious adverse psychological effects or serious adverse physical effects is low. It's the burden itself and it's the burden the kids would have over that period of time that's clearly more than minimal.

CHAIRMAN FOST: Dr. Nelson, then Dr. Diaz.

DR. NELSON: Well, with your permission, Norm, I guess I would like to move to blood volume and to be concrete because I think we could all say what we've just said and say it differently and say it more, I'm not sure we would say anything further about minimal risk.

Five percent blood volume over 24 hours, I guess the question is, where did that come from? I've seen -- you know, what I've been comfortable with in any single draw is two, maybe three milliliters per kilo single draw. I mean, part of that, you remember when I transfuse someone I give them 10 per kilo, and if you look at some standards, I think people have thought two per kilo on a signal draw. Five percent

blood volume, basically, if you assume blood volume is anywhere from 65 to 80 but let's make it 70 for the ease of the math, 70 per kilo, and norm, I think it was up to 240 so the question is how low, but let's take 2100, 210 to make the math easy.

You know, basically if you're 70, 70 -- I'm doing it in my head, 70 milliliters per kilogram, five percent of that is going to be three and a half per kilo. So you have to -- to get up to 240, you're going to have to be a 70 or 80 kilo kid. So I guess -- you know, I guess it's sort of -- to worry the question, you know, it's not clear to me where five percent came from. I mean, I guess if that's three and half per kilo, it's close but I would have probably have just said two or three per kilo.

But then the question is, what's the lower limit relative to the scientific adequacy of the study, I understand things -- I mean, you could probably take that curve and take it off maybe every 30 minutes or 45 or every hour maybe to get your curve overnight sleep but I couldn't, when I was doing the math in the protocol, get down to the 10 kilos or get

down to the number they seem to be excluding. I couldn't find where they got down to that low number.

CHAIRMAN FOST: So what you're suggesting is that the upper limit be defined in a more quantitative way?

DR. NELSON: Well, I'm used to thinking two to three cc's per kilo and it's not clear to me if you're any better off if you do that in a day versus a single draw, but you know, over time you might equilibrate to it. A pint for an adult is what you'd give when you give blood to the Red Cross and that's -- I would think is minimal risk but -- and these are eight-year olds which are probably on the order of 40 kilos, maybe 35 kilos. I'm not an endocrinologist but is that about right? So you're talking two or three per kilo would be, you know, even three and a half per kilo is going to be 140 to 160 cc's.

So I just didn't see that level of detail worked out. I did see where it was not -- where is was less than 240. I agree that it was less than 240 but I didn't find that kind of detail and the lower weight limit, I just couldn't make it connect with

what they were saying.

CHAIRMAN FOST: Dr. -- I had the same problem. Dr. Diaz?

DR. DIAZ: Actually, the point that I was going to make was already made.

CHAIRMAN FOST: Okay, thank you. Yes, Ms. O'Lonergan.

MS. O'LONERGAN: Typically, what I do in our center is I require a diagram that tells how many cc's per kilo weight and have that operationalized like in the data safety monitoring plan, so that the nurses have a chart and my worry is the operationalizing of it, that it needs to be very clear for those people drawing blood or when it's automatically set to extract blood, that it has to be a certain amount and certainly the detail is required.

CHAIRMAN FOST: Dr. Rogol and then Dr. Boepple.

DR. ROGOL: About 25 years ago, we ran into this problem in general at the University of Virginia and unfortunately, I was picked to try to solve this problem and we started out with something

that's really easy. The math isn't so easy, but I guess if you call a pint 490 cc's for a 70-kilo person, the math does become relatively easy. So the upper limit, barring anything else was 500 over 70 or seven percent of body weight over six weeks.

And then if you weren't going to draw any more, we move that down to somewhere around three and a half or four per kilo, which takes body size out of it completely. That is, you give your recommendation in terms of milliliters per kilo. The operations are absolutely critical because if you're drawing blood through a catheter that has heparin in it or saline, as an anticoagulant, you've got to count all of those cc's. So it's not that you just have -- operationally, it's a little bit more difficult and the other -- otherwise, all of the kids who came in, they came in once every four months. They took iron for one month and we checked their hematocrit. It had to be above X, I can't remember what that was right now. It had to be above X before we could start again three or four months down the road.

So those were the operations of it.

That's what we did.

CHAIRMAN FOST: This protocol includes putting the children on iron. Dr. Rosenfield?

DR. ROSENFIELD: A comment on the calculations; I can say that our -- well, our RSA or the GCRC has called around the country and this five-percent guideline is pretty common in GCRCs around the country but the calculation is based on this. As an example, a 50-kilogram child, we assume that blood volume is seven percent of body weight, and that's 3500 ccs. And we take five percent of that, that's 175 cc's.

So we draw -- we can draw up to 175 cc's in a 24-hour period in a 50-kilogram child. For a 20-kilogram child, the amount is 40 percent of that or 70 cc's.

CHAIRMAN FOST: Dr. Boepple.

DR. BOEPPLE: Well, I think that the discussion we've had just now from Dr. Rosenfield and Dr. Rogol makes excellent logical sense but both of them and others at this table, then had the experience of having put those guidelines into practice over the

course of 15, 20 years and they work. I think that's the important thing, and in the clinical studies that I was describing again, not in normal volunteers but in young children and adolescents with disorders of puberty with similar kinds of guidelines that began with similar lines of principles. We then developed experience, prepared reports to the IRB in terms of the incidents of times when symptomatic events occurred in terms of lightheadedness and the like, which were very rare, what the hemoglobin was before and after the blood drawing episode, what it was when the child came back three months later where their blood count has been restored.

So while these may have been logical but seemingly perhaps kind of arbitrary decisions at the outset. Now we have 20 years or more of experience, having done this very same thing. I submitted a paper to, I think, Journal of Pediatrics, 15 years ago and one of the reviewers said, you know, this was reported in 1862 by some surgeon in the Civil War where if you estimate how much blood you lose, you're going to be able to calculate what your hemoglobin drops. So it

wasn't accepted for publication but there is experience here. It isn't just seat of the pants calculations.

CHAIRMAN FOST: Does anyone think that the blood volume is more than -- that's proposed -- two questions. Does anyone think the blood volume guidelines that Dr. Rosenfield is using need to be revised? Does anyone think that they involve more than minimal risk as written? Dr. Nelson.

DR. NELSON: Just to close the loop on the math, based on the five percent in the 3500 and the 175, if you -- you know, basically that would be about -- it would be three and a half per kilo. So it's pretty close to the two to three per kilo that per kilo people are used to thinking about as opposed to five percent. So I think the math, whether you do about five percent or whether you pick three is close enough to where it's a difference that doesn't make a difference.

Do I think that if you were doing that alone it would be minimal risk, you know a lot of that depends upon how you get the blood and that's kind of

hard to separate. If you lost that blood volume from a single stick, would it be a problem? No. Is it minimal risk? Yes.

DR. BOEPPLE: I would just carry on. If that doesn't bother you in terms of a single stick, it's even less problematic when it's spread out over an extended period of time in which fluid is replaced to the intra-vascular space.

DR. NELSON: From the blood alone, I agree, yes.

CHAIRMAN FOST: I have the impression of a consensus that the psychological risks are thought to be more than minimal risk with one dissent. That the blood volume is thought to be within minimal risk. What about the leuprolide? Dr. Nelson has expressed in here that he thinks it is more than minimal risk. Are there other comments on that? The medical risks of leuprolide as administered. Dr. Gorman.

DR. GORMAN: At the risk of being accused of confusing clinical practice with research, I inject unknown biological substances into patients on a daily basis for the minimal prospect of protecting them from

infectious diseases. We call this immunization.

I have a fair number of febrile and other types of responses to these particular injections. And while I have a great appreciation for the fact that when you manipulate anyone's hormones, in almost any way, the outcomes can be troublesome. I don't think that this is any different in terms of the risk than what occurs when a subject or a patient comes into the office and is immunized and I would consider this under my understanding of minimal risk, if dissected out of all the other risks of this study, of this particular procedure meeting minimal risks.

CHAIRMAN FOST: Dr. Nelson.

DR. NELSON: It would take us off in a different direction, but I don't consider vaccine administration minimal risk. So you know, and so from that standpoint, I think analogy doesn't hold. It's not so much the needle itself, it's what's in it. And I think if we -- that's just -- it doesn't fit what I consider the average normal healthy child definition.

DR. GORMAN: (Inaudible)

DR. NELSON: I understand that. I just

don't consider that minimal risk. I mean, it's a long debate. I consider that prospect a direct benefit greater than minimal risk. I mean, we could -- vaccines are not the topic here, so it would be a much longer conversation.

DR. GORMAN: Can I follow up?

CHAIRMAN FOST: Sure.

DR. GORMAN: Thank you. I think that the original definition of minimal risk and I know there have been subsequent definitions had to deal with the risks that were associated with a routine visit to the pediatrician. And during that routine visit, vaccinations were administered. Whether you consider vaccines to be minimal risk or not, I think is a different discussion which can go on for a long time, but if the definition of minimal risk revolves around what occurs at a routine office visit, a routine office visit most often has a part that includes vaccinations.

DR. NELSON: Fifteen second rebuttal?

CHAIRMAN FOST: Sure.

DR. NELSON: The question then would be

what's the vaccination schedule in 1977, when the minimal risk definition was written.

DR. GORMAN: You'll be happy to know that I know that. Diphtheria, tetanus and pertussis and oral polio were given at two, four, six and 18 months. Measles, mumps and rubella were given somewhere between one year and 18 months.

DR. NELSON: Thank you.

DR. BOEPPLE: I think it would make sense to me at least to step back from your question one or two steps and decide upon what we're basing out response. Leuprolide, you recall, is an analogue of GnRH. If these were GnRH per se, in a preservative fluid, would that by minimal risk? That's a natural hormone. It's mixed up in benzol alcohol, so that's not so natural. It's given at a dose that's super-physiologic, so is that natural or not, but now you're dealing with a compound that's a manmade entity, a modification of a hormone and yet, with safety data behind it, which I think is pretty compelling.

So I don't mean to voice my -- even my vote at this point, but I'd like people to address

what component of this they're responding to. Is it anything you inject into somebody or are there some other nuances here that we should be attending to.

CHAIRMAN FOST: Other comments as to whether leuprolide is more than minimal risk? We're going to go around and poll people. This will not be a formal vote from the committee but just to make sure I have people's views. I'm going to do that in a few minutes, but I want to get to the last thing. Does anyone think that procedures themselves, the catheters, the needle stick, are themselves, more than minimal risk? Yes, yes, yes, anybody disagree with that?

DR. BOEPPLE: Again, I mean, we have to qualify this. If you're doing it in a certain environment, if you can do it with anesthetic to the site of catheter placement, if you can do it with an experienced operator, meaning a phlebotomist/nurse/physician who deals with kids every day of their life in a clinical/research setting, then I think that needs to be taken into account.

CHAIRMAN FOST: Ms. Knudson.

MS. KNUDSON: I would just like to say that all of those maneuvers are simply minimizing the risk but the risk has to be acknowledged, then you minimize it.

CHAIRMAN FOST: Dr. Nelson.

DR. NELSON: The earlier example I gave about the adolescent getting a 24-hour IV, I was no the side that thought that could be considered minimal risk because I didn't think it made sense for a 15-year old who was saying, "Fine, I'll be in overnight to allow you to do that", that I thought it made sense for that to keep coming back to a 407 panel if it wasn't minimal risk.

So I'm less worried about the teenager. I get a little worried about the nine-year olds and the eight-year olds and particularly when they're sitting around for more than 24 hours and the like and so it's not so much all of that stuff, I get a little concerned about the length of time and we could arbitrarily pick a number. It's hard to know what that number might be but I think this is on the higher end in my view in terms of the duration even though

everything else is being done to minimize risk appropriately.

CHAIRMAN FOST: If I may, Dr. Boepple, one of the concerns about that mode of analysis that if it's done really carefully by a really skilled person, nothing bad is likely to happen, that is what has been used by IRBs to justify non-therapeutic bronchoscopies, kidney biopsies and liver biopsies as minimal risk.

DR. BOEPPLE: Are you asking me?

CHAIRMAN FOST: No, I'm telling you, that is there are IRBs in the country that approve non-therapeutic bronchoscopies because the investigator says, "I've been doing this for 20 years and I've never had a problem", and I'm quite sure that that's not what the National Commission had in mind when they said things that happen on a routine visit to a doctor. So the notion of objective likelihood of risk I think, as Jeff put it, as burden is really part of what's going on there and not whether anything bad happens, it's just is this something that happens to you on a routine visit to a doctor".

DR. BOEPPLE: Well, let's drill down. Is it the pain of the placement of an IV catheter? Is that the concern, and if so, that's addressed by the appropriate anesthesia in most instances.

CHAIRMAN FOST: I didn't mean to be --

DR. BOEPPLE: Huh?

CHAIRMAN FOST: I didn't mean to be commenting on this particular issue, but again --

DR. BOEPPLE: Yeah, but see, I'm trying to get at the component parts of where the concerns are and where not the process does not address those concerns.

CHAIRMAN FOST: Dr. Gorman?

DR. GORMAN: I think that we're -- I think Skip said this very well, in the sense that it's not -- when you start to parse out each little piece, it seems okay, but the total burden somehow comes out to be more than the sum of its individual parts. So I can't tell you -- I think everything that you do to reduce burden makes a lot of sense and makes us more reassured that you're going to minimize pain and suffering while you don't really change what's

actually going on. A person will be in a unit and we're not talking about this protocol, per se, right this second. They'll be in a unit, they'll have an indwelling catheter. They'll have an IM injection. They'll have the blood drawn repetitively. They'll be restrained -- excuse me, not restrained, immobilized in their seat for various periods of time over the course of that 24 hours while procedures are being done to them. They won't have straps on, I hope.

So I think there's going to be, when you add up all those pieces, the pie looks bigger than every little piece. When you parse out every piece and you try to do it as well as you can, you are minimizing the burden and the risks but you haven't quite eliminated them.

CHAIRMAN FOST: Okay, I just would like to pole the -- this is not a formal vote of any regulatory question, we'll come to those, but I would just like to make sure that everyone has a chance to comment on whether they think this protocol, as designed, is more than minimal risk and if you could just quickly go down through the four things and say,

yes, yes, no, no, to them so that when I write it up I will know whether there was unanimity or a majority or what. So a typical response would be I think this is more than minimal risk, which I think everyone, with the possibility of Dr. Boepple, I'm not sure, we'll find out in a minute. And I take it it is minimal risk because I think the leuprolide and the psychological procedures are more than minimal but not the other two.

So if we could start with Ms. O'Lonergan and go around and Jan will record those.

MS. O'LONERGAN: Do you want -- okay, the protocol I think, yes, is more than minimal risk. The leuprolide, I think, is more procedures, perhaps more in blood, probably not if it's carefully done and psychological risk, probably more than minimal risk.

CHAIRMAN FOST: Thank you. Dr. Silber? Microphone please?

DR. SILBER: Oh, leuprolide more than minimal risk, procedures I don't know, I put that together with psychological risks so that would be more than minimal risk. Blood volume, not more than

minimal risk.

CHAIRMAN FOST: Dr. Rogol? I realize you're not a voting member but you can comment.

DR. ROGOL: I was hoping I wouldn't have to.

(Laughter)

DR. ROGOL: I think that overall it's more than minimal risk. Leuprolide is more, probably the procedures are more, blood volume is not and psychological, I think is not.

DR. GRUMBACH: I would echo that.

CHAIRMAN FOST: Okay, Dr. Boepple?

DR. BOEPPLE: I think that's pretty much the way I saw it as well. More than minimal risk overall, leuprolide more than minimal risk. Blood volume and psychological, not and procedures, I -- and procedures placement of an IV, I'd say not because of the issues -- the way that you can deal with it.

MS. KNUDSON: I will disagree. The only item that I think is not minimal risk is the blood volume. All the others, I agree are more than minimal risk. Did I say that right?

CHAIRMAN FOST: I agree with that. I would say the leuprolide and the psychological risk, definitely and the procedures probably, and the blood volume not.

DR. BOTKIN: I would agree with that as well. I think the key question for me is sort of the package of everything together but I would agree with that component analysis. The only thing that is not more than minimal risk is the blood volume.

MS. DOKKEN: I would definitely say more than minimal risk and that each of the components is with the exception, I can't even comment on blood volume because, Skip, I couldn't keep up with your math.

DR. NELSON: I did that right, just trust me. Well, of all the various procedures, let me just say those which I think could be considered minimal risk and that would be the blood volume, but I also think the psychological risks of the hospitalization itself and the environment could become minimal risk depending upon all the various environmental factors that were mentioned. Absent that, you might not even

want to do, but present that, I think it's possible that that could be brought into that minimal risk category, but you know, the devil is in the details.

DR. DIAZ: I think it's more than minimal risk except for the blood volume but I think it can be minimized by preparing the child and the family and also taking into account like when the kid is there are they going to be schooled in how to deal with those kind of things, more like the daily life of the child.

CHAIRMAN FOST: Thank you.

DR. GORMAN: The protocol in its entirety is more than minimal risk. I think leuprolide can be minimal risk. I think the blood volume can be minimal risk. I don't think that you can take the hospitalization and procedures and make them less than more -- let's try that one more time.

I think the combination of the procedures, the hospitalization, would continue to be more that minimal risk.

CHAIRMAN FOST: Dr. Nelson. Do you want to vote twice?

DR. NELSON: This isn't vote, Norm.

CHAIRMAN FOST: I know.

DR. NELSON: I just want some clarity. So if someone has a dedicated unit that does just nutritional studies where it involves staying overnight and it's just attached to a health care facility, you're saying that that's not minimal risk if all they're doing is collecting urine and poop and feeding them X and they're staying overnight watching TV and videos?

DR. GORMAN: Sure, but up until the point where they put the needle in my muscle and take the blood out of my veins, I'm right with that as minimal risk.

CHAIRMAN FOST: Okay, so this cannot be approved under 404, we'll come to that in a minute, a few minutes, in awhile. So if it's to be recommended at all, it would be under 407, but before we get there, there are some components of 407 that we need to discuss and the next one is this, is, is this a serious problem effecting the health of children? And as I suggested, I don't think we need discussion as to

whether the problems of puberty are a serious problem but if somebody wants to discuss it, they can. So I would like to suggest that we have some discussion on whether the need for normative data from normal children is as serious problem effecting the health of children, including children with pubertal abnormalities.

MS. DOKKEN: I have more a question of clarification that to me like everything else, the phrase "serious problem", you know, is wide open to definition. It's, you know, to whose estimation and then does that mean that no matter how many serious problems there are, you know, it would continue to be possible to just enroll more and more normal healthy children for everything that was deemed a serious problem. And I'm not asking that in a challenging way. I really --

CHAIRMAN FOST: No, there are many projects that might be submitted for 407 approval and which a committee would recommend no, I don't think it should be approved. So just the fact that it comes to this committee doesn't mean -- that's the purpose of

the committee is to -- and the other committee is to decide whether it can move forward. We haven't reached that point.

MS. DOKKEN: So it's expert agreement on whether or not it's serious.

CHAIRMAN FOST: Not experts. Everybody on this panel being an expert on something, so all we're asking now is whether it's a serious problem. Just because it's a serious problem doesn't mean we have to approve it. We're trying to first decide if it's a serious problem. Dr. Nelson.

DR. NELSON: Let me try and summarize what I heard from the discussion this morning and see if it's accurate. It sounded like other than clinical evaluation and then ancillary testing looking for possible diagnosis that may have led to this phenomena logic presentation of either early or late puberty, that right now there's no test where one could administer an agonist and get a simple blood draw whether in an hour or at four hours or the next day or something that would allow one to tease apart whether that individual child does or does not have normal

secretion and response to that analogue.

So, you know, if the answer is that doesn't exist, then there's a need -- it strikes me that there is a need for an improved diagnostic test. So the first question is, did I get it right, but then the second question is, and I think it goes back to Jeff's question is, the role then of true normals, not normals who present to a clinic with some question of am I normal because they have some manifestation of precocious puberty or delayed puberty but turn out to turn up normal. That's really a different group than true normals which they don't have anything. How important is that for the interpretation of the results of the diagnostic tests.

I'm sympathetic to the need for that because I've seen that to be true in other circumstances but it's not clear to me I've heard a sort of slam dunk statement that sort of answered the question that I think you had asked earlier, Jeff on that point, unless you think you were satisfied by the answer. So I think it's -- so I guess that's what I heard and my approach on that and it would be nice to

hear a little bit more about the normals in that interpretation of the diagnostic studies on the phenomena logical abnormals who turn out to be chemically normal and chemically abnormal.

CHAIRMAN FOST: Could the endocrinologists comment some on that. That is Dr. Botkin's suggestion that kids who come as patients would turn out to be normal, aren't they sufficient test controls?

DR. ROGOL: I made a comment to my colleagues before. I think that's absolutely the group you don't want to have as your normals because they came to you for something and there was a motivation and it's the kids and the parents, the younger the kids, it's the parents that think the kid has a problem or not, and I think you need to have at least in the very beginning true normals. That is they don't come for any other reason, but they're normal.

The issue here, and I think -- and I wanted to hear what my colleagues have to say is, how do we know until we have these data what the range of normal -- remember, there's no such thing as normal.

Normal is within a range. I don't care whether you call it the third to the ninety-seventh or fifth to the ninety-fifth, there's a range of normal and for us in puberty it's different at every pubertal stage. That's what makes things confusing. But I think at least from the very beginning you need one full set of truly normal kids at the ages that we're talking about and then you can see.

These diseases, if that's what you want to call them, are not dichotomous diseases. This is not -- you have breast development as a girl at age seven years and 364 days you are abnormal, and you wait two days to have breast tissue and you are now normal because you are eight years and one day. And so I think until we have those data, we cannot make a learned, if that's the right word, or at least a well-reasoned answer to that. It may turn out that once we get the normals it's easy. We don't need to go back and do any more normals. But until that time, I don't think we are able to make a determination. That's why we need them, at least that's my outlook on it.

And I think we need true normals to get

back to the original question, rather than people who were sent for something and didn't have it, because the diagnosis of precocious puberty is not made on a single test, on a single exam. Growth rate, bone age, all the things that you heard about this morning, tempo of development are all part of the calculus and you come up with a diagnosis in that manner. So that's how I would answer the question.

CHAIRMAN FOST: Thank you. Dr. Botkin?

DR. BOTKIN: Yeah, I guess I'm still not convinced from a clinical perspective. Now, I understand why from a scientific perspective you may want to see what healthy kids who don't have precocious puberty look like compared to kids who seem to have precocious puberty who turn out to be normal versus those kids who have a pathologic ideology. I mean, that's interesting from understanding normal physiology, normal development et cetera, but from the perspective of kids who come into the clinic who have already got something that's precocious say, for the end of the spectrum. What you care about in that context is discriminating between the pathologic

ideologies and the normal ideologies.

And it would be interesting if you look at the two populations, say normal kids who have early development and normal kids who don't have early development. Now, let's imagine that you find some endocrinologic differences between those populations but yet as you follow the kids who have early development, they turn out to have normal height, they turn out to have normal fertility, et cetera, then you've found something that would be interesting from a physiologic standpoint, but it's essentially irrelevant to your clinical management of those patients. So that's where I think the question of, you know, is this a serious -- well, perhaps that's not the right question. I think number 3 actually gets to this issue a little bit more.

So I guess I'm not yet convinced that having the data on sort of normal, normal kids is of compelling interest because it's really secondary to your clinical management of the problem since in the clinic you're never going to be drawing -- you're not going to be doing leuprolide tests on kids who don't

have some clinical variance that you're trying to explain.

CHAIRMAN FOST: Other comments? Yes.

DR. BOEPPLE: Maybe a concrete example would be helpful because I think as Dr. Grumbach pointed out, this period of time during childhood and adolescence when everything is kind of a still pond here in terms of the hormones of puberty. They're low in everyone. So I think one of the ways I could express this challenge is could you identify somebody who's never going to go into puberty by destroying a blood test when they're five years old?

Well, it's hard to tell that kid at five years old from a normal five year old because the levels are low in both of them. Now, just take that a little bit further. What if it's a 12-year old, what if it's a 14-year old who doesn't show signs of puberty yet, how do you distinguish whether or not that's an individual who if they show no clinical signs of puberty, no physical characteristics that Dr. Grumbach reviewed for us, how do you then know if that individual, and it's usually a boy, is going to go

into puberty or not? And the only way to know that is by studying normals who have gone through some of these -- or at these very early stages of the transition between childhood and puberty, and when you then see that particular pattern in someone who really doesn't manifest it outwardly yet, you say, ah-ha, that's a kid whose got some early signs of the neuro-endocrine changes of puberty and that can provide some reassurance.

And I think that one of the things we haven't mentioned here is the value of being a little bit more confident in these analyses without time becoming the issue. You were just saying how wouldn't it be nice to follow kids longitudinally and I think Bob showed the Lawson Wilkins slide where the guy at 17 you know, by 21, ah, we know what's going on there, but do you want to tell the 17-year old, you know, "We'll know what's going on in another three or four years".

It would be nice to know what's going on now, and I think one of the ways you can understand whether someone at a very early stage or even at a

pre-clinical stage in terms of puberty has a suggestion that they're going to make the jump into hyper-space and go through puberty on their own is to get some data from kids who are at that clinical stage themselves, who are normal, healthy children.

And if I may, just one other point I wanted to make here is, a number of the questions this morning related to questions about how many kids really have a problem. You know, if they present with delayed puberty, precocious puberty, how many of them are just benign variants and how many really have a disease? And to my hearing, the crux of that question or those questions was, it doesn't happen very often, therefore, maybe this is not quite as big a deal as these guys are telling you.

Well, I'm here to say that being able to tell the 90 percent of families whose kids don't have a problem with more definitiveness that they don't, is you know every bit as valuable as it is identifying the five or 10 percent who do have a problem and that's where I see the need for better diagnostics.

CHAIRMAN FOST: Thank you. Dr. Nelson and

then Dr. Diaz.

DR. NELSON: I guess you have to think about the problem and to see if it makes sense. I think I heard earlier that this might be more important for children who have delayed puberty where one could, in fact, be reassuring if you saw a normal response that, in fact, phenomenologically things will happen eventually and that patience is appropriate but it's not in retrospect four years later you realize that well, they in fact, didn't, that you could demonstrate that and even in the abnormal.

So it really comes down to, you know, it's not so much discriminating the normal/abnormal as it is if you see someone with a normal response who's come into the clinic with a problem, that's why they presented, of being able to determine what the sensitivity and specificity of a test that you've done in reassuring that parent that, in fact, everything is normal. Because of the biological variability, I can't imagine it's going to divide out like those earlier slides we saw at .35 where there was just one kid that overlapped, I suspect that what you'd find is

an 80/20 split or something that would lead you to in some patients say, "We have no concern here and others to say, "We'll need to follow this up with another test because this one is indeterminate.

So being able to define those sort of statistical parameters around a test, where if you don't have normals, all you'd be able to say is you're different than this group, which we know is abnormal. You wouldn't be able to say, "Because of that we know you're not abnormal in this way, but we can't be 100 percent confident you're truly normal in that way". So there may be in a simplistic way, not being an endocrinologist nor a statistician, being able to say to a parent, "We're 99 percent confident", versus, "You know, we're only 80 percent confident here and you need to come back next year and let's do this again".

I could imagine where that might be helpful rather than waiting the five years to see what might happen.

CHAIRMAN FOST: Dr. Diaz.

DR. DIAZ: I think to have normative data

is important and you have to have the full range of normal, those that present healthy and those that present with symptoms and turn out to be normal, that you have a full range. And my question is, what sort of numbers would you need to really establish this normal data, the normaltive data?

CHAIRMAN FOST: That's the next question. We'll come to it in a minute. Thank you. So if I could just rephrase my question that I asked Dr. Grumbach and Dr. Rosenfield this morning and maybe our other endocrinologist and others could comment, is the present diagnostic array available to pediatric endocrinologists a serious problem? That is, are endocrinologists who evaluate these children really constrained in giving parents the sorts, and children the sort of information that they need?

DR. GRUMBACH: The gold standard in the past, one of the most helpful test, and remember, this is a constellation of tests and a good deal of it is statistically directed, is the -- is a replacement for the old LRF test or GnRH test, which was a native hormone. And that has proved useful in our diagnostic

armamentarian. And right now, we don't have a substitute for that in the sense that people have used it, these GnRH agonists, off-label, obviously, and there is one large series of normals that are, 140 that were reported from Barcelona and that's really the only normative, really normative data where they did various stages of puberty and again, as Bob pointed out, the issue is what kind of assay are you using, but that's the only normative data. These were 140 normal kids, 70 males and 71 females in which they had normative data, but that's the only in the whole literature.

CHAIRMAN FOST: And because of that, when a child with one of these conditions comes into your clinic and you work them up with the present data that you have, are you left in a situation where you say, "Mr. and Mrs. Jones and Little Boy Jones, I really can't tell you for sure what's going on. If only I had this other data, I would be able to be more helpful to you"?

DR. GRUMBACH: I think that's a hard question to answer because we do have guidelines from

before. I mean, this is not, you know, a magic new agent that's opening things up. It's more potent than the natural hormone but we've had a lot of data from that. So we have an idea of which way things are going. It may be more discriminatory in narrowing the diagnostic window in certain clinical conditions, and Bob pointed out how the differential diagnosis of delayed adolescent in boys it may be helpful, but I would like to point out, we don't wait for kids to finish their -- go through high school and waiting to see what's going to happen.

Incidentally, that wasn't a Lawson Wilkins slide. That was a -- that came from a group in Columbia that did this many, many years ago, but the point about it is, we don't want kids to lose, particularly these children lose their adolescence. We don't want them to wait to be 17 to find out whether they have isolated gonadotropin deficiency or delayed puberty, so we do treat these patients at fourteen and a half.

CHAIRMAN FOST: And if you had Dr. Rosenfield's data 10 years from now, if he completes

the study as planned, you would be able to avoid treating some of those?

DR. GRUMBACH: Well, this is the choice of the child and the parents, the boy and the parents and we -- you know, so often, as Bob has pointed out, you do a physical examination. You find some pubic hair, you find a little bit of testicular enlargement, you know that kid's going to go. And then it's up to you, do you want to give a boost or not. In other instances, you don't know and that's where in a high proportion of patients using this test, you can make that distinction.

Now --

CHAIRMAN FOST: You mean, we can make it now or if we had more data?

DR. GRUMBACH: If you had more -- I mean, we make it now speculating, speculating on what the normative data is.

CHAIRMAN FOST: Dr. Rogol and Dr. Boepple, could you comment on whether the present diagnostic armamentarium is a serious problem?

DR. ROGOL: Well, in one respect if it

were, we wouldn't do anything. We don't throw up our hands as Dr. Grumbach just said. On the other hand, it leads us in an appropriate direction. Would I like to have it, would it help me in putting all these things together? Yes. If I don't have it, do I have to give up my medical license, no.

CHAIRMAN FOST: Dr. Boepple?

DR. BOEPPLE: Yeah, I think it's always more helpful to have more information upon which to base decisions. If I heard correctly, Dr. Rosenfield has funding to do these studies from the NIH, which means that a scientific review of this question has been done and answered in the affirmative. And I would say -- I don't want to leave you with the notion that pediatric endocrinologists, when dealing with families, are as non-committal as we might be appearing here. I think we try to provide reassurance but if that reassurance were backed up by something a little more meaty, I think that would be an improvement over what we're doing now.

So, yes, I think there are improvements to be made and I think this is a very reasonable way to

get in that direction.

CHAIRMAN FOST: Dr. Grumbach and then Dr. Botkin.

DR. GRUMBACH: If we didn't have this test, we would not fall on our swords. Okay, but on the other hand, there is a real need to help us in improving out diagnostic batting average and this test could do that.

CHAIRMAN FOST: Dr. Botkin?

DR. BOTKIN: I guess I want to still figure out whether the improvement in the test that would emerge from this study would be gaining a test that would be equivalent to the sleep test but easier to perform because you wouldn't have to put the kids in the hospital or, in fact, would it be a better test in which case, it seems to me you're going to have to be comparing the results of this test, a leuprolide test, with the ultimate clinical outcomes of the kids as opposed to comparing it with the results of the sleep test.

And I thought the hypothesis for the study really was just to compare, to say that this was going

to be equivalent, in which case, it seems to me the argument is what we need is a better test because it's easier but not because it's going to enable us to reduce false positives and false negatives.

DR. ROSENFIELD: It's both, that's the short answer. And you have already determined that you are going to give the sleep test, you already ruled that you think that it's more than minimal risk so you know, it's not a reasonable study to do on an everyday basis, but what you said is true, it's potentially easier and it will prevent -- and it is going to be compared to a sleep test for the purposes of this study and that's the provisional gold standard, the protocol. These children will be followed for progression of puberty. So that's really the ultimate outcome and we did that in the previously published study that I showed you at 95.

And with the new immunoassays for LH, when combined with the new current generally available assays, which are now available, it promises to be improved over anything that we have at the current time and provide improved information.

DR. BOTKIN: Okay, so then, six, eight, 10 years from now, the study goes forward, you'd be able to make a determination about --

DR. ROSENFIELD: I hope it doesn't take six or eight years to get this study to go forward.

DR. BOTKIN: So over some period of time, as you follow these kids out, you'll be able to make a determination at some point in the future to day the leuprolide test has this sensitivity and specificity compared to the sleep test. It has this sensitivity and specificity, therefore, the standard of care is now one or the other.

DR. ROSENFIELD: Yeah, I mean, right now we'll be able to make short term comparison of the sleep test. Long term, we'll get some validation data over progression of puberty and outcome.

CHAIRMAN FOST: Dr. Rogol?

DR. ROGOL: There is actually another thing that will come out of this, especially if all you need is either the four-hour or the 24-hour sample. That's doable eventually outside of a research unit. Sleep tests can only be done in a research unit for two

reasons. That's the only place they can be done and nobody other than a research group would pay for them. They're phenomenally expensive. You have to pay for the hospital bed. You pay for 48 LH tests at whatever per and so that, irrespective of whether the overnight test is the gold standard or not, it can't be done. It's like painting yourself in a corner. So if Dr. Rosenfield, in this particular one, can show that the four-hour or 24-hour single point in the test that he does, that has implications down the line for a practical way of making this particular variety of diagnosis, because we can say anything we want about the sleep test, it won't be done.

CHAIRMAN FOST: Dr. Silber.

DR. MURPHY: Norm, could I ask a question, in response to that?

CHAIRMAN FOST: Yes.

DR. MURPHY: Are you saying essentially that the sleep test is of such difficulty that in essence, if that became all that was available that there might be children who would be denied that diagnostic test? I'm just trying to get an idea of the

severity of the limitations.

DR. ROGOL: Absolutely that is correct because it can be done relatively simply. We've done them. We've done hundreds of them and it can be done in a research unit but in the research unit, it has to pass scientific muster on down the line, in addition to all of these factors, so outside the few units -- let's say there are 25 units in the country, it could not be done and children would be denied that diagnostic test.

DR. MURPHY: And so let's assuming that things get worse in our health care system instead of better and that that test is not available, then how would you proceed if this process doesn't move forward? I'm just trying to get the full picture here.

DR. ROGOL: Perhaps I'm missing a point in logic but as I see it, if one can define this as equivalent to the gold standard, it becomes a new gold standard. They are equal and then you compare this test to the leuprolide test that perhaps four or 24 hours and you can say they're within the range of normal for a child of that age or they are not.

CHAIRMAN FOST: I understood Dianne's

question this way, Alan, what -- since you can't do a sleep test on everybody across the country how do you -- if Dr. Rosenfield's data aren't available and you can't do a sleep test on everybody, how do you make the diagnosis?

DR. ROGOL: Using in the main the rest of our armamentarian, bone age, growth rate, physical exam but the most important issue is a single doctor seeing them over several months because it's the issue Dr. Grumbach brought up so well of tempo. You've got to put all of those things together and I think if you ask each one of us what we do, we couldn't tell you exactly what we do.

CHAIRMAN FOST: So you could get to more definitive answers sooner if you had --

DR. ROGOL: I believe that.

DR. GRUMBACH: Norm, I just want to point out to the committee that nobody is paying for a safe test. I mean, you can't get insurance companies to pay for it and number one, it's done in a pediatric clinical research unit or a scattered bed, but it's done with very special nursing care. And this is used

very selectively in certain really special clinical situations where you feel that this is really necessary but you're not going to get reimbursed by insurance. Not many hospital centers really can do it in terms of nursing care and in terms of sample collection and so forth. This really takes a very special motivated team to do.

CHAIRMAN FOST: Okay, Dr. Boepple, and then we need to move along.

DR. BOEPPLE: Right, I'd just say that while it may be characterized by some here as gold standard, I think it's what we were just saying, it's certainly not standard of care. So I mean, the fact that it's not done does not mean that people aren't getting, you know, appropriate care. And I had something else I was going to say.

DR. GRUMBACH: Do you want to (inaudible) general experience with that test?

DR. BOEPPLE: Oh, and I guess what I would say is that another thing is one of the ways that people are proceeding in their clinical offices as pediatric endocrinologists is they're doing exactly

what Dr. Rosenfield has proposed to do except that then we get the results and we're trying to interpret them without a body of data that allows us to make as best judgments as we can. So there are people that are using leuprolide acetate as a single subcutaneous injection and drawing bloods at different time points and measuring hormone levels and when those results come back, we're left with having to make a judgment and we probably do okay but we could certainly do better with some data that's been collected carefully in both normals and in patient groups.

CHAIRMAN FOST: Okay, what I'd like to do is survey group so, Tom, you can make your comment as we go around, just but starting with Doctor --

DR. SILBER: Can I make a question, though, first?

CHAIRMAN FOST: Yes.

DR. SILBER: And my question is, I just learned about the Barcelona group that did apparently a very detailed study. Are endocrinologists using that data. If yes, where and with what results and if no, why not?

DR. GRUMBACH: We use that data because that's the only normal data that has a large population in different stages of puberty, but it is -- one of the problems I might mention is, it's a three-hour test and I think they had three and eight hours, something like that, so the -- this is where things have come up with Bob, taking samples you get a better idea of the curve, but that's all we have to guide us in the use of those tests.

CHAIRMAN FOST: Dr. Rosenfield?

DR. ROSENFIELD: I searched the literature again last night and either Mel knows something that I don't, which is quite possible and it happens from time to time, or he's mistaken. The paper that I know of in 1994, that's cited in my review, has, well, around 50 control subjects. Only about 15 of them were normal and the rest of them were, again, this hodgepodge of kids with variance of normal, considered to have variance of normal, early puberty, there was rapidly progressive or slowly progressive or delayed, and --

DR. GRUMBACH: Before you go on --

DR. ROSENFIELD: Is that KCM 94?

DR. GRUMBACH: Yeah, you're a little bit of base. Yeah, in 1999 the European journal -- you got this in a handout.

DR. ROSENFIELD: I didn't get the handout.

DR. GRUMBACH: Endocrinology, leuprolide acetate, 500 micrograms subcutaneous you give them to 141 normal children and adolescent, 60 boys, 81 girls, age range five to 17 years, serum epistage (phonetic), LHT and a variety of other studies at 0, 3 and 24 hours, and they got an increase in LH in pubertal girls and pubertal boys and so forth. So this is a follow-up.

You're absolutely right, Bob, on the earliest study they had a mixture but this is a study that they did in 1999.

DR. ROSENFIELD: What journal?

DR. GRUMBACH: European Journal of Endocrinology.

DR. ROSENFIELD: I would have to research this. I think the important thing, one of the important things, the dose is different. It's not an optimal dose. They gave a single dose to all -- 500

micrograms to children of all sizes, whether they were this big or that big. And that's what they've done all along. They didn't do intermediate sampling. You know, she does 0, 3 and 24. I think 4 is -- well, 1 and 4 give you somewhat different information. And I don't know for sure, but in all of her other studies the characteristics of the immunoassay for LH are not defined and the delphia assay --

DR. GRUMBACH: They didn't use the delphia assay.

DR. ROSENFIELD: -- is very highly specific with more sensitivity and a point that I made that you may not -- may have gone over a lot of people's heads was that the sensitivity of that assay at .15 is well below what we use to consider normal. It used to be that normal was under one. Now we know that normal is under .15 with a gray zone being between .15 and .6. And the -- as best I can tell, the sensitivity of the assay she uses is around .5.

DR. ROGOL: I'm trying -- I've got a full text thing coming up, so I'll let you know.

CHAIRMAN FOST: I think we need to move

along. What I'd like to do is a quick survey again of the group on this question of whether you think this is a -- the proposed study is addressing a serious problem effecting the health of children. We'll start on the other end, Dr. Gorman?

DR. GORMAN: I think the health problem of precocious and delayed puberty, I think of as serious, especially from the aspect of the individuals who suffer from it and their families. I have not been nearly as convinced that improved diagnostic tests reach that level of seriousness.

CHAIRMAN FOST: Dr. Diaz?

DR. DIAZ: I think on the issues of puberty, adolescents with pubertal issues is a problem, in particular with their social life and how then fit. Even if they are within normal range, if they develop early or late, you know, they have to deal with certain issues in their social network.

CHAIRMAN FOST: And so your answer was yes or no? Yes. Dr. Nelson?

DR. NELSON: Yes.

MS. DOKKEN: I don't feel qualified to

comment, so I guess I abstain.

DR. BOTKIN: Well, I think my answer is going to be yes in that again, not on the question of whether precocious puberty abnormalities are a serious problem but whether the lack of a good diagnostic test is a serious problem for these kids. I guess I've been convinced that there is a significant need for improvement in the quality of testing.

DR. DIAZ: I agree. I think this last discussion was very helpful in that regard, so I'd say yes, because of the need for a more efficient affordable diagnostic system.

MS. KNUDSON: I totally agree with you.

DR. BOEPPLE: As do I.

CHAIRMAN FOST: Dr. Rogol?

DR. ROGOL: Yes on both accounts, both as a serious problem and that we need better diagnostics.

CHAIRMAN FOST: Dr. Silber?

DR. SILBER: Yes.

CHAIRMAN FOST: Ms. O'Lonergan?

MS. O'LONERGAN: Yes.

CHAIRMAN FOST: Okay, so virtually

unanimous. Why don't we take -- we have two more substantive issues and then a formal vote to take. So if we could come back at 3:10.

(A brief recess was taken.)

CHAIRMAN FOST: It's time to reconvene. Ready to roll. Dr. Rosenfield just wanted inserted in the record -- I don't want to take a lot of time with it -- that the study that Dr. Grumbach was referring to is not sufficient to the task. I think the committee was already persuaded that that was the case.

DR. ROGOL: I've looked at it and for reasons that I don't need to go into, the area that we're looking at, that is the young kids, it isn't helpful.

CHAIRMAN FOST: Okay. We have two more issues to discuss and then we need to vote on the key questions. So the next issue which I'm taking out of order so that Dr. Rogol can participate has to do with financial inducements. There is a payment of -- it's up to $300.00, as I recall, for the controls but no payment to the patients.

In the interest of time, I just want to

suggest a common justification. So two questions; one, is it problematic if there's a difference, that is if the patients are not getting paid and the controls are, and second, is the payment to the controls problematic, is it going to undo inducement?

It is common in studies of this sort not, non-therapeutic studies, not to pay patients and the reason is, endocrinologists can correct me, is that they are getting a work-up that has benefit to them, that this is part of their medical care. They would be getting this work-up or something very similar to it anyway. That is, they're not being asked to do anything extra above what they would be doing as patients, therefore, no --

DR. ROGOL: More importantly, they stand to benefit.

CHAIRMAN FOST: Right, there is a potential benefit. So even if there were not study, though, they would be undergoing pretty much everything that is in this study that is, if it were available.

DR. ROGOL: Except for probably the overnight test.

CHAIRMAN FOST: Except for the overnight test. All right, then I wasn't completely accurate. So let's -- yes, Dr. Garfinkel.

DR. GARFINKEL: It may or may not be relevant, but just as a -- the consent form indicates $150.00 as the maximum.

CHAIRMAN FOST: Okay, I'm sorry, thank you. So we'll come to undo inducement in a minute, but on the first question, the floor is open for discussion on whether it's problematic that the children with disorders or possible disorders are not being paid. Dr. Nelson and Dr. Rogol.

DR. NELSON: Well, no, I think it's fairly standard to not pay subjects who are patients if, in fact, they are going to benefit from the results particularly the closest that gets to standard of care. So it would just raise a question to whatever incremental burden there is to it, whether there should be an appropriate compensation for that such as the overnight. I mean, I think that would be a legitimate question but --

CHAIRMAN FOST: And your view on that?

DR. NELSON: Well, I think the answer is yes, but frankly, I see this in my mind as falling into the super-irrogatory (phonetic) you know, in other words, the suggestion advice gratuitous as opposed to required.

DR. ROGOL: I agree actually on both accounts. I'll stand back from the business about the overnight. If the overnight is available at a place like ours, it would get done. At other places, it might not get done but I think that that is the operating procedure we've used. Patients do not get compensated, normal controls do.

CHAIRMAN FOST: Other comments on that issue? So take that as a sign nobody thinks it's a serious problem. Dr. Nelson is recommended that they get some, at least modest honorarium. Is there anyone else who wants to comment on that? It will come as a suggestion, not as a requirement. Okay.

MALE PARTICIPANT: (Inaudible)

MS. KNUDSON: It's prorated.

CHAIRMAN FOST: Now, on the second issue, is this an undo inducement? Just for organization

sake, let me clarify that there are three kinds of payments that go to research subjects. One is for expenses, the children don't have expenses for the most part. The parents might, but this money, as I understand it was going as a check made out to the child, so there's no payment to the parents. Am I right about that? So there's no compensation for whatever expenses or lost work time that they might have.

The second reason for payment is as an honorarium to express appreciation. I'll just -- in the interest of time, I'll just state my view on that and the panel can then react to it. If that's what it's for, it should be given after participation and should not be mentioned ahead of time because to mention it ahead of time, turns it into an inducement. If you're really thanking somebody, you thank them after they did what they did. You don't say, "If you do this, I will thank you".

So and my view is, if that's the purpose of it, the amount is fine, but it should be not discussed and should be simply given to the child after

his or her participation.

The third reason is as an inducement and by definition, an inducement is given because you feel enrollment would be jeopardized without it, that you couldn't successfully complete the study. And so I guess for openers, I'd like to hear from Dr. Rosenfield, because I couldn't tell from the materials whether this is an honorarium or an inducement.

DR. ROSENFIELD: Neither. This is less than babysitting money in Chicago, which is around, I understand $10.00 an hour.

CHAIRMAN FOST: This is going to the child not to the parent.

DR. ROSENFIELD: Yes, it's going to the child.

CHAIRMAN FOST: The child doesn't do babysitting.

DR. ROSENFIELD: I mean, it's what they would make babysitting if they were to spend their time babysitting.

CHAIRMAN FOST: So you're saying this is compensation for lost wages?

DR. ROSENFIELD: No, I don't quite know what you're getting at, I mean, but I remember hearing Skip Nelson give a grand rounds at the University of Chicago about how kids thought it was unfair to be paid less than what an adult was paid for the same study or paid for -- what an older child was paid, and so I guess you could take this as a philosophical argument. We do not think it is undo inducement. I guess you could say it's inducement but it's not undue inducement.

CHAIRMAN FOST: Other comments?

DR. ROGOL: Ms. Knudson asked me a question before and the way we started out on this and of course, remember we did longitudinal studies, so you can't start and stop at the same level. You've got to keep them coming back and they understand that very well. We started with a gift card to -- not McDonalds that was for sure off limits -- but to either a clothing store or movies or something like that and things escalated, as I remember, this is now several years ago, to in the sixth and seventh year 150 bucks each time they came in. And they knew this beforehand

and --

DR. GARFINKEL: This was for a sleep study, Alan?

DR. ROGOL: Yes, this was for --

DR. GARFINKEL: Twelve hours?

DR. ROGOL: Pardon?

DR. GARFINKEL: Twelve hours?

DR. ROGOL: Oh, no, 24 plus, maybe 26, something on that order. And the kids actually got a lot more mileage out of that because about 12 of them out of the 23 got a heck of a good science project for school out of their participation in this. Some of the kids really got into it, but that's the direct answer to your question.

What we did, as I remember, now this is -- unfortunately I'm old and I don't remember so well, was that -- and I may have it mixed up with another protocol, that kids from a distance away, there weren't very many of them, could not come to us by themselves. So if a parent had to take time off work, they were compensated for gas in coming up.

Most of the time the kids did not want to

miss school, believe it or not and so most of our stuff was done on the weekends. And so it was a Friday night to a Saturday and sometimes the kids would go directly from Sunday night to Monday and then go to school directly from the GCRC. So that is part of the mix of how we dealt with parents and helping them along. But the direct answer to your question is, it started out with a gift certificate and moved on.

CHAIRMAN FOST: Other comments? Yes, Paula.

MS. KNUDSON: This is not -- I'm sorry, this is not a longitudinal study. It's a one-time event for these kids. I think it's hard for me to imagine -- and I may be very out of touch with young people today, but it's hard for me to imagine that the idea of $150.00 isn't very appealing to adolescents and certain to an eight or nine-year old. I think it is an inducement, whether it's -- I would like to think that the consent form would not speak to the issue of money. It could say, "We will have a thank you gift for you at the end of the study", or it could just say nothing. I actually don't discount the idea of altruism on the

part of kids if they can understand that this is a serious problem and they might, indeed be able to help other kids.

So the idea of not putting money in the flier, in the consent form appeals to me a lot.

CHAIRMAN FOST: Ms. O'Lonergan?

MS. O'LONERGAN: The amount is fairly common for a one-time study in the center I use, and IRBs generally require that you put that in there. It's part of the informed consent.

MS. KNUDSON: I understand very well but that's --

CHAIRMAN FOST: That's, I think, because if it's an inducement, then people need to know about it.

MS. O'LONERGAN: Right.

CHAIRMAN FOST: Dr. Rosenfield, maybe I can put my question in a more operational way. If you had not inducement, do you think you would have trouble recruiting? Is this important to achieving your recruitment goals?

DR. ROSENFIELD: Yes, it's important to

achieve it. I'd say that it's one thing to do it for babysitting money, and another thing to do it just purely out of altruism. I think we would get a few out of pure altruism, but I think -- because as I say, it's less than babysitting wages, and I think it takes some combination of both.

CHAIRMAN FOST: Dr. Nelson.

DR. NELSON: I think most people -- well, the issue of payment is controversial and there's a fair range of opinion and I think it would be difficult from my point of view for us to be terribly prescriptive about a recommendation around that given that variability. Now, if I thought we could be prescriptive, I would be, so I'm not shying away just based on variability.

You know, for teenagers, the amount is not excessive if you look at it as a wage-based model, which is generally what people think and for an eight or nine-year old which is the youngest, it might be, but the eight or nine-year old doesn't really have an understanding of money potentially. Some do, some don't. I would be more concerned that they had an

opportunity to sort of get out of the study as it's going on and more issues of protection during it. If the money doesn't mean that much to them, they're going to decide they don't want to do it, not because they're getting $150.00.

So I don't think they're going to be unduly influenced by knowing that amount or even if they were in sort of a wow, what could I get for that, the first time that IV hits the arm, if that's an issue, they're out of there. So as long as there's a mechanism for them to do that. So I guess in this point, I think the approach of the IRB is reasonable and I don't think we should be prescriptive.

CHAIRMAN FOST: Dr. Gorman?

DR. GORMAN: I'd like to agree with Skip in the sense that I think that this is an area where the local IRB would have a much better feel for the likely subject population. And I don't think from the IRB experience that I've had that it falls to be so egregiously out of the limits of what we would consider normal as to raise any red flags.

CHAIRMAN FOST: Other comments? Is there

anyone on the panel who objects? Then we'll take that to be unanimous for the moment.

The last substantive issue is the accrual issue, is some questions were raised by the GCRC about the accrual possibility and we received a message from a member of the Pediatric Advisory Committee, a statistician, who read this in preparation for tomorrow who noted that comment and wondered about the accrual. Dr. Rosenfield has commented on it but he is now going to clarify it.

DR. ROSENFIELD: Well, I just want to comment that she refers to remarks made by the GCRC biostatistician. In October and November of `04, you will remember that you were told that in response to certain GCRC recommendations the protocol was revised and came back to the IRB and the GCRC and that's what you have before you. And that process was addressed with the biostatistician in the final -- in the documents that you have.

And that states -- that document states in the statistical analysis section what I presented here today and what we reviewed and I clarified when Dr.

Rogol reasked the question, what the principal end points are and what the -- which have to do with -- well, it has to do with the principal end points, and there's no doubt, as I pointed out in my slide, that some of the sub-groups are small but they will be informative and in many respects -- because the sub-groups will be small because they're unusual but they will be informative, in many instances, give statistically significant responses, even if not clinically useful responses.

Nevertheless, the principal outcomes with constitutional delay in boys versus gonadotropin deficiency are doable. The accrual is proceeding along and the studies of central precocious puberty are proceeding along. We need -- we lack healthy volunteers to complete that aspect of the study properly. So, as I mentioned to you, we are approximately halfway in our recruitment of the abnormal groups, particularly constitutional delay and simple precocious puberty.

CHAIRMAN FOST: Thank you. Comments? Does anyone on the panel think that accrual is a

sufficient problem as to jeopardize a recommendation for the study? Dr. Nelson?

DR. NELSON: I guess, no, and I think the investigator is in a Catch 22, that to the extent that other sites might want to come on board, I suspect they'll be more willing to do that after this process rather than before. And the question then would be the adequacy of continuing oversight to make sure accrual is appropriate and that is the responsibility of the local IRB. And if we wanted to recommend that OHRP keep a special eye on it, I suspect they might but beyond that it's not clear we need to do more.

CHAIRMAN FOST: Thank you. Other comments? If not, I will take that to be a sign that people are not troubled with it and move now onto the formal voting issues.

DR. NELSON: Norm, could I ask a quick -- there may be a few other minor -- I mean, we can do it now or do you want to do it in modifications? I guess there may be a few other issues for modifications. It's up to you where you want to put that.

CHAIRMAN FOST: That can come under

modifications. So we'll get to that. So we need now a formal vote on whether the committee recommends approval of the study or recommend that the study not be done and if there is a recommendation, whether that is under 404, I think we've already answered that. There was unanimity that this was more than minimal risk and, therefore, cannot be approved under 404. Does not fit 405 and 406 and therefore only under 407. So I think all that is needed is an up or a down vote on 407, a recommendation for 407, with or without modifications.

So why don't we have some discussion about that and then we'll eventually poll everybody. Dr. Nelson.

DR. NELSON: By discussion do you want modification as part of that discussion?

CHAIRMAN FOST: Anything that you want to say, this is an appropriate time to say it.

DR. NELSON: Anything, okay, as long as it's on topic. Well, let me just -- I mean, I'd give a few other issues that I think I'd like to see addressed if it was approved with modifications. And there's

three an it mainly relates, I guess, to consent issues.

First is, it's fairly standard practice not to disclose results to people where you don't know the results of those -- the meaning of those results and I think since, at this point in time, you don't know what normal means, it would make me a little nervous if you're simply disclosing results on a prospective time-based fashion to the kids that are getting it done where they don't present with a condition because the issue of false positives I think has to be dealt with.

I'm fine with after the research is done with the approach of going back to them and saying, "This is what it all means", but I would specifically say, "You shouldn't disclose results to the normal controls", as one recommendation for people to consider.

The second is, I would agree with Rich. I think there does need to be a separation of withdrawal of DNA samples and sampling from the more general withdrawal. People are going to forget they've got

some immortal cell lines sitting around at the University of Chicago. I think that needs to be pulled out, made explicit and dealt with separately and the finally the more complicated issue and this I'm a little uncertain but I'll make a suggestion, is the decision to exclude from the consent process any of the information, which I agree is not immediately relevant to the risk of a single dose of the Lupron, but you know that parents are going to be looked around the Internet, so they're going to see all the stuff that's out there and there may well be a parent who feels that even if in general, parents would still agree to expose -- have their child exposed to the risk that there may well be a parent who would say, "If I had known, I wouldn't have done that".

So I'm not saying I think the risks need to be in there because it's part of the process, but I don't think it's wise, personally, not to have mention of that issue, even if it's framed in the context as you framed it in the protocol, but to completely withhold that information from the parents so a parent who thinks they would want to assess the risk in the

context, you know, "I wouldn't have given my child a single dose if I had known that", framing that in the consent document in some way, I think should be considered.

So those are my three sort of consent issues to just put on the table and get as part of the mix.

DR. ROSENFIELD: Skip, could you clarify that last point because I didn't understand your point? Are you suggesting that rather than listing these various things that have been reported --

DR. NELSON: I don't want to get too prescriptive. I guess what I'm saying is --

DR. ROSENFIELD: There are various side effects that are reported with long-term Lupron --

DR. NELSON: No, I think it's reasonable to say that something like -- you know, I don't want to -- something like, there are these reported risks of Lupron that you may see in the Internet or in the packet insert if you get ahold of that, these risks -- you know and list maybe the top -- you know, these risks are A, B, C, D, pick the -- you know, these are

associated with long-term treatment and we don't believe are related to a single dose. If you do, we can talk about it. I mean, I'm just --

DR. ROSENFIELD: No, that's --

DR. NELSON: Yeah, I mean, I just think that there is likely a parent, there may well be parents in this room that would feel somehow deceived even if it's not relevant. They want to make that judgment of relevance on their own. That's my point.

DR. ROSENFIELD: Got it.

CHAIRMAN FOST: Ms. Dokken?

MS. DOKKEN: This is also about the consent/assent process and specifically about the forms for the healthy children and their parents. I mentioned it once before; in the parent consent form, the discussion of no benefit is on page 4 and I'm not familiar with other consent/assent forms for healthy children, but it seems to me that page 4 is a long ways into the document to get to something that I think is, you know, very relevant information. And then on the children's assent form, again, for the healthy children, the initial statement is something and then,

"Help us find out if children like you are growing and developing normally", which is identical language to that which is used in the assent form for the children with the condition and I think that's -- to say "children like you", in the healthy children assent form, I think, is misleading. So those are just some comments about the form.

CHAIRMAN FOST: Thank you, other comments? Dr. Botkin?

DR. BOTKIN: I guess I'd want to make a broader comment about the 407 process in general and my concern is the possibility of having a 407 process undermine the existing regs. So the question is, you know, what is it about a 407 panel that makes it somehow more perceptive, more ethical, more appropriate to approve a study that could not be approved under the existing regs by the local IRB?

I don't know that I know the answer to that question but I guess I interpret the existence of the 407 to have an out for those projects that are truly compelling in some way, truly extraordinary such that for certain circumstances for well-articulated

reasons, we're willing to override what are otherwise justifiable and solid regulations by which all other studies need to live by.

Now, that isn't in the regs, but I guess I'm sort of tipping my hand here to say that my personal criteria here would be to say is there something truly compelling about this situation that permits us to override the normal standards to which we would hold child protections and research?

CHAIRMAN FOST: And do you think there is?

DR. BOTKIN: No, not for the healthy kids.

CHAIRMAN FOST: When we discussed it whether it's addressing a serious problem that it's a serious problem we have.

DR. BOTKIN: Well, how I would put this together, you know, pending, of course, listening to other folks about this is to say that I do think there's a need for improved testing in this domain. I haven't been convinced that that improved testing can't be accomplished by including the two categories of kids, basically those kids who are normal but present with a clinical concern and those kids who truly have

pathology. I haven't been convinced that including the healthy kinds in there is essential to the primary goal of determining or improved diagnostic test.

CHAIRMAN FOST: Excuse me, I just want to clarify the last slide that we had before the break, namely whether the proposal presents a serious problem. One of those questions was, is the absence of this normative data on healthy kids a serious problem? And I thought that you had voted yes on that. You're now saying, you don't think --

DR. BOTKIN: No, I think I was voting on the fact that this is addressing a serious problem but it's not clear to me that the inclusion of the healthy kids is essential to address the problem. I think the rest of the study does that as approved.

CHAIRMAN FOST: Dr. Nelson, Dr. Gorman.

DR. NELSON: I guess it would be important to separate out that latter judgment, Jeff, from the former question about the role of 407 panels within the overall review process because it's -- it comes to the question of what the standard is and one way of viewing is, is that the National Commission couldn't think of

everything. And when they came up with the three categories, they realized we need a fourth just in case they didn't think of everything. And what has certainly evolved over time in a lot -- in the bulk of the 407 reviews have been the role of control data and the importance of that kind of data from a scientific perspective which, you know, in the `70s you could say was -- you know, maybe a different set of issues. So it's -- so your latter question, I think is separate. In other words, whether you think this protocol does what you think it needs to do and there was some differences around the table. That's a very different question from the bigger policy issue of a 407 review as a pop-off valve, if you will.

You know, since 407 still needs to be conducted according to ethical standards, I don't -- you know, I don't see this as much different than the other three except it's trying to fill in gaps that at this point exist within the other three categories.

CHAIRMAN FOST: Go ahead.

DR. BOTKIN: Well, I guess to what extent then what are the ethical standards to which 407 review

panels are held? You know, it's not minimal risk for healthy children any longer. Presumably, we could pretty much approve anything we wanted to with respect to the level of risk. Now, you might say, "Well, the benefit has to be proportional to the risk in some fashion and that would be the primary ethical determinant, but we're not really given that guidance either. It seems to me that that's pretty much opened us to determine what our own ethical standards are in that regard, which is potentially problematic.

DR. NELSON: I would agree, but let me articulate, at least what I would see as one which is if you make a determination that a protocol like this is a minor increase over minimum risk in all of its manifestations and some being minimal risk, the question then comes down to the justification of healthy children versus ill children in the exposure of that level of risk. I mean there are arguments in the literature which you're familiar with that have said that that difference -- that it is appropriate, as much as Susan Weiner's arguments that it is appropriate and ethical for that level of risk to also be appropriate

for healthy children under what conditions, under the need for the scientific data which goes back to the original concern. So, you know, one could make an argument for that.

Getting outside of that risk category, yeah, we might be on uncharted territory.

CHAIRMAN FOST: Dr. Gorman and then Ms. O'Lonergan.

DR. GORMAN: I wanted to try to amplify a little bit on what I thought I heard Dr. Botkin say which I feel that my opinion is shaping up in much the same way. While I understand the concern about using these outliers of delayed puberty in boys and occasionally accelerated puberty in girls, they're not completely normal. They're not abnormal either when you end up at the end of your observation period and find out that they go through puberty, they're just delayed. I am still in the prevailing clinical opinion that those people are -- or those children are normal, and, therefore, would let them participate in the study and eliminate all normals, the truly normal normals, whoever they might be and then I would be able to

approve this study under 404 in the sense that everybody who came to this study even those who turned out not to have the disease, would have the prospect of benefit, and therefore, I would think it was above minimal -- slightly above minimal risk but with the prospect of direct benefit even though the people with delayed puberty, constitutionally delayed puberty, turned out to be normal adults.

MALE PARTICIPANT: 405.

DR. GORMAN: I'm sorry, 405, thank you.

CHAIRMAN FOST: Ms. O'Lonergan?

MS. O'LONERGAN: Yes, part of -- I have maybe a comment on the 407 process. So it's my understanding that the IRB in this case, the IRB in Chicago, that the IRB is the one who seeks the 407 review; is this correct?

CHAIRMAN FOST: I think so, yes.

MS. O'LONERGAN: Okay, in that case, the IRB, the local IRB has made some determination that they feel at least that it is possible that there is something to be learned that's valuable here. I would think that if the IRB said, "No way, this is really

terrible research and we oughten to be doing it at all", they wouldn't have sought a 407 panel. So I'm coming at it in a different direction.

We have the opinion of the Chicago IRB that, yes, we think this is worth looking at and that there's some value in it. So it's more than just is this exceptional and can we rule on anything we want. I think the IRB is telling us that they feel that it's an appropriate venue for looking at this because they've made a determination that there is some value here.

DR. BOTKIN: And I would add as did evidently NIH reviewers.

CHAIRMAN FOST: Dr. Silber.

DR. SILBER: With some trepidation, since this is my first time, but thinking about what Jeff was saying, I don't think we here collectively, although there are many brilliant people, are any better at making these judgments than thoughtful people on the IRB that already reviewed it. I think the only reason we are seeing this is because it's mandated. There is no way the IRB could have approved it even if they

would come to the conclusions that we can. So what I kind of sense with this meetings that we have is that there is 407 and there is 407.

In other words, those things that for reasons that they cannot be done in any other way have to come to us, but that are very reasonable and approvable would actually be the kind of things that hopefully will be perhaps a bit more fast in coming through, but that the real purpose of this is the 407s where you say, "Oh, my God, this really is something that perhaps shouldn't be done". And I think there is no difference between us and them other than what the regulation forces us to do because we have no other choice.

CHAIRMAN FOST: Ms. Dokken.

MS. DOKKEN: Just commenting on what both Dr. Botkin and Dr. Silber said, I think when I raised the question before about who determines or who decides what's a serious problem, that was my discomfort, too, is serious relative to, you know, the host of problems that are out there and do we somehow have to rank order them like how would this relate to, you know, an avian

flue pandemic and would you use, you know, healthy children then, and it's like -- but, you know, if we can go with Dr. Silber's two definitions of what comes to 407, you know, one with a normal voice and one with a big voice, but I think this all points out and I don't know, you know, what the role of this group and I'm not normally on it, but in gathering general recommendations about the overall 407 process, and you know, along the way proposing some ways of clarifying pieces of it at least.

CHAIRMAN FOST: We don't have time to discuss that here. Obviously, it's being heard by people in the room and FDA officials and obviously, you can send comments to them afterwards, but I think discussion of the whole 407 process is just not within our charge in the time left.

There have been several proposals here for it sounded like approval with modifications and I need to know whether these are mandatory or optional and I'm going to list them and we need some discussion and maybe a quick poll about whether these suggestions should be required. The first was disclosure, of the

results not being disclosed to the normal children.

DR. NELSON: Do you want to take them one by one or all together?

CHAIRMAN FOST: I'm just listing them first.

DR. NELSON: All right.

CHAIRMAN FOST: Second, there should be a procedure for withdrawal of samples, that is when the children reach an age of maturity, they should be recontacted so they could get their samples destroyed if they want to.

Third, there were changes to the consent form proposed. There were a couple and I had one or two of my own and I think those so far were the three proposals. We could discuss the consent form changes one by one, but let's take the first one, disclosure results. I agree with Dr. Nelson's comment that it's an opportunity for confusion and stigmatization and unsureness about what it means and it doesn't seem to me it would interfere with Dr. Rosenfield's study to simply have part of the contract be that results to normals will not be disclosed unless there is something

clearly pathological.

DR. ROSENFIELD: Maybe I could cut through this. They all sound reasonable to me and we can do them very easily.

CHAIRMAN FOST: Okay.

DR. BOEPPLE: But you don't want them to be mandated, do you?

DR. ROSENFIELD: If that slows the process, I don't want them mandated, but I can have them, you know, in your hands in a short period of time.

CHAIRMAN FOST: Dr. Boepple, whose name I have been mispronouncing all day and he's been patiently allowing me to do it.

DR. BOEPPLE: Well, I think that the first two are generally stipulated in all clinical research or most clinical research, that results of research studies are generally not provided and that's certainly true of genetic studies and --

CHAIRMAN FOST: It's highly variable.

DR. BOEPPLE: All right, why is this different? Why are we telling the University of

Chicago what to do if it's highly variable?

DR. NELSON: Because they didn't put it in the protocol.

CHAIRMAN FOST: I don't think it should be highly variable.

DR. BOEPPLE: I think that if it's highly variable, and there's an institutional perspective on this that has made a judgment about how they proceed, that we're not in a position to have to tell them, "No, you were wrong when you decided that".

CHAIRMAN FOST: But we are in a position, whether we should or not is a separate --

DR. BOEPPLE: Well, I don't think we should.

CHAIRMAN FOST: Dr. Nelson.

DR. NELSON: Contrary to my other comments about not being prescriptive, I think this is a slam dunk in terms of what you don't do. Any diagnostic test only is meaningful in clinical medicine unless you have a sign or a symptom that causes you to do that diagnosis. There's very few asymptomatic tests where the specificity and sensitivity are such that you ought

to even disclose it, so I think it's just fairly straightforward. These kids coming in normal, you don't disclose results.

Now, if at the end of this study you can say, "Here's the normal curve", and you're truly normal, I have no problem going back to that population and saying, "You thought you were normal, you are". That's fine, but one by one coming through getting these numbers I think that's crazy. So I would be very prescriptive on that and the other DNA sample stuff is actually consistent with the National Bio-ethics Advisory Committee report. I mean, that should be standard across the board. Any IRB not doing that is not doing what I consider standard of research ethics.

CHAIRMAN FOST: Let me just summarize the consent form changes to see if Dr. Rosenfield keeps shaking his head so at least the panel will know that they wouldn't be upsetting him.

One, Ms. Dokken's comment that the non-beneficial nature should be stated right up front with the normals, not --

DR. ROSENFIELD: Oh, that I'm not clear

about. I don't know about whether there's some mandated order to the consent form.

CHAIRMAN FOST: There's another section of the consent form where the -- there's a separate benefit section where it says to the normals "you may benefit", and I think it's unlikely that they'll benefit. I would just say we don't expect any benefit to you. So Dr. Boepple has spoken against the notion of a recommendation requiring these changes. Are there -- is there anyone else who disagrees with him? That is, I'm stating as the default position here that if there's a recommendation it would be requiring these changes. Is there anyone else who agrees with Dr. Boepple that that should not be required, it should just be recommended? Dr. Botkin?

DR. BOTKIN: Yeah, I guess I would defer to that local IRB on these issues as well, and it's -- they don't seem to me to rise to the level of lack of discretion on the local IRB. So I would vote more to an intermediate, which is to say the committee raised some concerns about these issues and the IRB -- local IRB is recommended to revisit discussion of that or

something to that effect.

CHAIRMAN FOST: Other comments on that suggestion? Does that change anybody's view?

All right, I'm going to suggest we survey, we go around the room and each person should address the following question.

DR. GOLDKIND: Norm, excuse me.

CHAIRMAN FOST: Yes.

DR. GOLDKIND: Skip had raised the comment earlier about including adverse event report information in the consent form. Do you want to have that on your list as well?

CHAIRMAN FOST: Oh, yes, okay, I'll add that to the list.

DR. NELSON: And also Deborah's comment about -- I mean, the normal consent ought to start off by saying, "We want you to be part of this study because you're normal not because we think you may or may not be developing normally". I mean, the other implies disease, so --

CHAIRMAN FOST: Okay, so we're going to go around the room. Yes, Dr. Botkin?

DR. BOTKIN: Well, I wonder whether -- we could talk about some modifications, but I wonder whether we might at this point think about modifications that at least for me might save the healthy child portion of the study and whether we might get some feedback about that.

I mean, would it be conceivable to run this study by not putting the healthy kids in for 36 hours but simply doing say this single leuprolide injection and then blood draws at four hours and 24 hours, would that be -- and I'm not necessarily saying I think that would be a acceptable way to go from my standpoint but I'm wondering whether there are ways to scale back the intervention for those healthy kids and still get you some of the data that you might be interested in obtaining.

DR. ROSENFIELD: Well, my reply to this, I'm going to address as a scientific level. I know that when I first started this type of study with neophron (phonetic) a long time ago, they asked me for more frequent sampling. I also know that the zero,

three and 24-hour misses information. I know that it misses certain peaks. The peak steroid value often occurs in 16 hours. I'd like to try to define, you know, how often it occurs at 16, 20, 24.

I also know that if I reduce this, I reduce the chance of having this published in a place that people will see it and as my own experience attest, there are certain journals that aren't widely read and so they are out of people's radar. So I think for now for this group of subjects, until we finish the study, I feel strongly about obtaining samples at most of these time points at least.

To do it the way it's designed would be an optimal way to do it. The sleep test enhances the ability to discriminate and it would be nice to know, it would be important to know scientifically what the normal is with the current standards because that hasn't -- just hasn't been done. Sleep study standards are ancient, you know, done with old assays. There aren't the data. So I think since there are still research centers that do that I think it's scientifically justified to do that, scientifically

important.

CHAIRMAN FOST: Any other comments? Okay, here's the poll instructions. Each person should say, first whether they recommend approval of the study and if no, that would be -- you don't have to say anything else unless you want to. If the recommendation --- I guess the reasons would be helpful, what the key reasons were. If yes, you need to also say whether you think this approval should be conditional on number one, non-disclosure of results, that is whether you think that should be mandatory or simply recommended.

Number two, giving the children a chance to withdraw their samples when they reach an appropriate age mandatory or recommended; three, consent form changes and in the interest of efficiency, I'm going to suggest all three as a package but if you want to comment on them individually and differentiate fine, but the three main consent form changes are one, to clarify up front that this is not -- you are not sick, you are normal and this is not of any benefit to you; second, get rid of the phrase "we're not trying to find out if you are growing normally; and three, that

something would be included about adverse events in long-term use of Lupron. So the package of consent form changes, you either think are essential or simply recommended. Does everybody understand the instructions. On your marks, get set, Ms. O'Lonergan.

MS. O'LONERGAN: I would recommend approval of it. I think it does address a serious problem and has a reasonable scientific design to accomplish its goals. I would want the recommendations or the mandating non-disclosure results, what is that child being able to withdraw genetic material and then the consent for changes.

CHAIRMAN FOST: Those are all mandatory, did you say? All right.

DR. SILBER: Approval for this research project and required contingencies for all three.

CHAIRMAN FOST: Required for all three, thank you. Dr. Boepple?

DR. BOEPPLE: Approval, mandatory non-disclosure of results, recommended dealing with genetic samples and recommended consent form changes.

MS. KNUDSON: I would vote for approval

with modifications, mandatory not to disclose results, mandatory to add language about withdrawing samples and mandatory the revisions to the consent form.

CHAIRMAN FOST: Thank you. I would vote for approval also conditional on all the changes. I just want to make a comment on why I concluded this. I think assent, meaningful assent, protects the children from the misuse that Jeff has spoken to so eloquently. That is if assent is take seriously and children really know they don't have to do this if they don't want to, this has nothing to do with them really or anything about their health, and they can stop any time they want because I'm not worried about anything bad happening to them.

In that regard, I think a recommendation should be made to the IRB to consider assent monitoring in the study. I think this is a study in which it would be a good idea to take a sample and which the IRB should oversee, some sampling of the children who are in it, that is interview them afterwards and see if they really understood what happened to them, if they really understood that they couldn't have gotten out of

it and if at any point, you see any red flags in that, then the trial should be suspended and revisited.

DR. BOTKIN: I would disapprove the study as written. I wouldn't approve it as the IRB had approved it, which was excluding the healthy volunteers in the protocol and I guess as I've stated before, my feeling is that I think there is scientific rationale for this but I don't think it rises to the level that I think it should be approved out of compliance with the existing regulations. I think that potentially opens the door to lots of studies that have scientific rationale but don't conform with the regs. So the point is here, I just don't think this is a compelling enough justification for inclusion of the healthy kids.

I think mandatory non-disclosure of results in the healthy kids, if that's the study, sounds fine. I would make the other changes recommended for revisiting by the University of Chicago IRB.

CHAIRMAN FOST: Thank you. Ms. Dokken?

MS. DOKKEN: I would recommend approval

and mandatory on the three modifications.

CHAIRMAN FOST: Thank you. Dr. Nelson.

DR. NELSON: Norm, I'm a non-voting member, so I guess I'll --

CHAIRMAN FOST: Oh, I'm sorry, thank you for reminding me. Dr. Diaz?

DR. DIAZ: I would recommend approval with all three being mandatory.

CHAIRMAN FOST: Thank you. Dr. Gorman?

DR. GORMAN: I would vote for disapproval as written. I would defer to the IRB in Chicago as understanding of this study and feel that it could go forward with the exclusion of the healthy normal controls. While I believe that precocious puberty and delayed puberty are serious issues, I do not feel that the development of this particular diagnostic test rises to that particular status.

In terms of the recommended informed consent and assent changes, I think the prohibition of sharing the results until the research is completed should be mandatory. A side bar conversation has reassured me that there is a system in place at the

University of Chicago in dealing with storage samples for genetic and other research and I would like that to be appended to the protocol as a mandatory requirement and the others, I would consider as discretionary as to the location of where the indication that this is not for individual benefit appears in the informed consent and assent.

CHAIRMAN FOST: Thank you. So I think we have seven to two if I'm counting right in favor with some variation and some of the modifications.

DR. ROSENFIELD: Is Dr. Grumbach voting?

CHAIRMAN FOST: I don't think he's -- is he a voting member? He did not vote. Dr. Rogol is not a voting member. Are there any closing comments? Thank you all for coming. I hope this is not like the patient who received a telegram "Union Local 221 wishes you a speedy recovery by a vote of 15 to 13".

(Laughter)

DR. GOLDKIND: Thank you very much to everyone on the panel, to the folks from the University of Chicago and to you, Norm, for conducting the meeting so well.

CHAIRMAN FOST: Thank you very much.

(Whereupon, at 4:03 p.m. the above-entitled matter concluded.)