

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	

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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

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

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

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

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

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

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

22 DR. BOTKIN: I'm Jeff Botkin, University

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

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

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

11 DR. GORMAN: I'm Richard Gorman, a
12 Pediatrician in a suburban private practice with one
13 of my mentors across the table, Dr. Silber for more
14 years ago than probably either of us want to mention.

15 I am the Chairperson of the Section of Clinical
16 Pharmacology and Therapeutics at the American Academy
17 of Pediatrics as well.

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

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

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1 within the Office of Pediatric Therapeutics.

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

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

9 CHAIRMAN FOST: Thank you. Jim?

10 DR. JOHANNESSEN: I'd like to read the
11 meeting statement for this morning. The following
12 announcement addresses the issue of conflict of
13 interest with regard to the discussion of a referral
14 by an institution review board of a proposed clinical
15 investigation that involves both an FDA regulated
16 product and research involving children as subjects
17 that may be supported by the Department of Health and
18 Human Services and is made part of the record to
19 preclude even the appearance of such at this meeting.

20 Based on the submitted agenda for the
21 meeting and all financial interest reported by the
22 committee participants, it has been determined that

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1 all interests and firms regulated by the Food and Drug
2 Administration present no potential for conflict of
3 interest at this meeting with the following
4 exceptions. In accordance with 18 USC 208B(3), a full
5 waiver has been granted to Dr. Paul Boepple for
6 consulting and speaking for a company with the product
7 at issue with an aggregate value of less than
8 \$10,000.00.

9 A copy of the waiver statements may be
10 obtained by submitting a written request to the
11 agency's Freedom of Information Office, Room 12A30 of
12 the Park Lawn Building. In the event that the
13 discussions involve any other products or firms not
14 already on the agenda for which an FDA participant has
15 a financial interest, the participants are aware of
16 the need to exclude themselves from such involvement
17 and their exclusion will be noted for the record. We
18 would like to note that Dr. Richard Gorman is
19 participating as a Pediatric Heath Organization
20 representative acting on behalf of the American
21 Academy of Pediatrics.

22 With respect to all other participants, we

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1 ask in the interest of fairness that they address any
2 current or previous financial involvement with any
3 firm whose product they may wish to comment on. Thank
4 you.

5 CHAIRMAN FOST: Mike Carome, you're here
6 on behalf of Dr. Schwetz to talk about the process?

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

9 CHAIRMAN FOST: Sara Goldkind?

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

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

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

5 So both HHS and FDA have federal -- have a
6 regulatory component called Subpart D which are
7 safeguards for children and pediatric research. And
8 they overlap in terms of these four categories that I'm
9 going to describe. An IRB looking at a protocol at an
10 institution has the authority to approve that protocol
11 under one of three categories; 404, 405 or 406 and
12 I've listed the corresponding FDA numbers as well, 51,
13 52 and 53.

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

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1 disorder or condition.

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

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

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

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

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1 doing so.

2 So that kind of summarizes how we've
3 gotten to today and what some of the work will be that
4 you all will be doing as the Pediatric Ethics
5 Subcommittee. Once you finish today and you provide
6 us with recommendations, then those recommendations
7 will be taken to the Pediatric Advisory Committee.
8 Now, just to recap a little bit further, I want to
9 explain what the three stipulations are if you decide
10 that you think that this should be approved under that
11 unique 407 or 50.54 category. You would have to
12 determine that the research presents a reasonable
13 opportunity to further the understanding, prevention
14 or alleviation of a serious problem affecting the
15 health or welfare of children; that the research will
16 be conducted in accordance with sound ethical
17 principals and that adequate provisions are made for
18 soliciting the assent of children and permission of
19 their parents or guardians as set forth in 408 and
20 50.55.

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

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

9 The Pediatric Advisory Committee
10 recommendations will be transmitted by our office with
11 comments to the FDA commissioner, along with a host of
12 supporting materials and appendices, one of which will
13 include the Chair's summary and the summary of the
14 public comments. And the FDA commissioner will then
15 make a determination about this protocol. The process
16 will not stop there, since this involves OHRP as well.

17 That entire packet will be bundled and sent to the
18 Office of Human Research Protection to the Agency and
19 that Agency will send a transmittal memo and their own
20 packet to the Assistant Secretary for Health, who's
21 been authorized to act upon -- act for the Secretary
22 in this regard.

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1 And the Secretary will then make a final
2 determination, the ASH will make a final determination
3 for the Secretary and included in the determination
4 will be an assessment of whether or not this protocol
5 ought to be funded since there's an NIH grant
6 associated with this protocol. So the possible
7 determinations that are open to the Secretary or the
8 Commissioner are to find that the research and facts
9 satisfies one of the earlier three categories. To
10 support the research under the unique category of 407
11 or 50.54 as submitted or to support the research under
12 407 or 50.54 with required or recommended
13 modifications or not to support the research at all.

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

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

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1 most important.

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

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

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

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

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

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

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

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

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

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

3 To drill down just a little bit into
4 those, can the use of normals be approved under
5 Section 4 only if the research is of not greater than
6 minimal risk? I'm sure we'll have some discussion
7 about some of the complexities and problems of minimal
8 risk. The definition of minimal risk, according to
9 the regulations, it's defined as the probability and
10 magnitude of harm or discomfort anticipated in
11 research and it meets the criteria if those risks are
12 not greater in and of themselves, than those
13 ordinarily encountered in daily life or during the
14 performance of routine physical or psychological
15 examinations or tests.

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

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

4 Just to put this in perspective, a recent
5 article on a survey of IRB Chairs and if that's hard
6 to read, it doesn't matter, it's supposed to look sort
7 of all over the place, that's what it is. This is a
8 questionnaire that was sent to a large number of IRB
9 chairs of IRBs that review research involving children
10 and in the left column are a list of procedures in
11 which they were asked whether they would classify
12 these as minimal risk, a minor increase over minimal
13 or more than minimal. And I'll just take one line to
14 show you the problem, if you can read down to the
15 fourth line down, "allergy skin testing", 23 percent
16 of the IRB chairs thought that that was minimal risk,
17 43 percent voted it was a minor increase over minimal
18 and 27 percent thought it was more than that.

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

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

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

22 So under 407, it could be approved if the

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

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

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

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

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

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

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1 three decades in understanding puberty and its
2 disorders.

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

13 Now puberty is a transitional period
14 between juvenile state and adulthood during which
15 secondary sex characteristics appear. The adolescent
16 growth spurt occurs, reproductive capacity is
17 achieved and profound psychologic changes take place.

18 It's a real landmark in development. Now, what have
19 we learned over the last 30 years, and I point out
20 some mileage markers. The onset of puberty really
21 occurs in the fetus. At puberty and infancy, it's
22 followed by what we call the juvenile pause, which is

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

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

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

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

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

22 Now, the definition of releasing hormone

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

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

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

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

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

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

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

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

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

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

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

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

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1 all of these play a role in controlling the onset of
2 puberty. The KAL-1 gene and FGRF leads to Kallmann
3 syndrome and all are involved with the passage of
4 these neuroexcitatory (phonetic) neurons from the nose
5 to the brain. Now, what about pre-puberty versus
6 puberty, well, there's a circadian change in LH pulse
7 amplitude during puberty, initially at night and then
8 during the day, a striking increase in pituitary
9 sensitivity to GnRH, readily releasable pool of
10 gonadotropins during during the pre-pubertal and
11 pubertal period and the gonadotropin response to GnRH.

12 And the pre-pubertal state, as I mentioned, is
13 characterized by functional GnRH deficiency.

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

22 In boys we have -- the initial is

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

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

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1 Now, the onset of menses is earlier in
2 Black girls than in White girls and the -- this is not
3 -- this has changed in a very minor way over the last
4 25 years. Now, one of the important concepts which
5 one of our former fellow, Carlos Martin Hennenberg in
6 Barcelona pointed out is that the younger the age of
7 the onset of puberty, the longer is its duration. So
8 we're dealing here with a marker of menarche let's say
9 but the onset of puberty may occur earlier than we
10 thought but menarche is not.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 DR. GRUMBACH: Yeah, Skip.

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

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

5 DR. GRUMBACH: We've seen true precocious
6 puberty really by three months of age, and we had a
7 child who is having menstrual cycles by five months of
8 age, and that's an example of true precocious puberty.

9 Now, the turn on, this mini-puberty is a very subtle
10 affair. The girls do not develop breasts, although it
11 may play a role in premature thelarche and it's a very
12 subtle thing. In boys they may have some acne, a
13 little bit of testicular enlargement. And we can
14 differentiate that from something that is progressive.

15 And in boys it shuts off at about six months and in
16 girls by -- it can kind of peter on as late as two
17 years. You can make this distinction by -- again, by
18 tempo. Is this -- I mean, do they move onto develop
19 breasts?

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

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

5 CHAIRMAN FOST: Dr. Gorman.

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

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

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

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

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

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1 CHAIRMAN FOST: Dr. Bodkin.

2 DR. BOTKIN: This is very helpful. I
3 guess I don't have a clear sense yet though of what
4 the contemporary gold standard is for making the
5 diagnosis of these conditions and why it is that the
6 field is in need of improvement of that gold standard.

7 Do you have a sense of what sensitivity specificity
8 is of the contemporary gold standard and again, what
9 are the deficiencies or limitations of the current
10 approach?

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

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

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

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

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

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1 steroids is really centrally mediated.

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

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

18 So the point is that there is a difficulty
19 in standardization and you really have to know the
20 that is giving you this data. All I can say is this
21 is a really exceedingly useful and very critical test.

22 Now, the issue, I think we have to hear from Bob, the

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

4 CHAIRMAN FOST: Other questions? Jeff?

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

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

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

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

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

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

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

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

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

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

3 CHAIRMAN FOST: Other questions?

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

9 CHAIRMAN FOST: If there are no other
10 questions, thanks very much. We really appreciate it.

11 Next, we're going to hear from Dr. Robert Rosenfeld,
12 who is the principal investigator of the study that's
13 been submitted.

14 DR. ROSENFELD: Well, good morning. In
15 a way I'm glad to be here, in a way I'm quite
16 apprehensive about this but being here is a matter of
17 principle, because I think we're talking about
18 something that has implications for pediatric
19 endocrine research and pediatric research in general.

20 It'd like to just make a few comments that address
21 your questions to Mel at the very end, just emphasize
22 a few points.

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1 Mel gave a wonderful background. The
2 major problems are that there has been an
3 unavailability on a regular basis of the commercial
4 product -- commercial GnRH. There are tremendous
5 differences in the radioimmunoassays, particularly for
6 measuring LH. Mel was talking a lot about the
7 difficulties in measuring sex steroids, but the
8 difficulties in measuring LH which is the key hormone
9 that initiates puberty, if you can call one versus
10 another key. There have major methodologic changes so
11 that one cannot translate from the old data to the new
12 with great certainty. And finally, although this
13 protocol is relatively arduous at this time, it -- the
14 long-term goal is to simplify the diagnosis of
15 precocious puberty because I'm quite certain that
16 we're testing the hypothesis but we have a lot of
17 preliminary data that a simple GnRH agonist test with
18 a baseline and a sample a few hours later, and maybe
19 24 hours later, depending on the case, can eventually
20 be the way that we proceed.

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

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

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

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

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

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

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

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

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

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

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

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

22 And these things contrast with

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1 gonadotropin deficiency. There's no sense telling a
2 14-year old boy in high school who hasn't started
3 puberty to wait, he'll grow out of it and then he
4 doesn't grow out of it and he's miserable and psycho-
5 socially for years until the diagnosis is finally
6 made. And at that point, it becomes a relief to have
7 a diagnosis.

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

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

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

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

22 And then there's the problem of early

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1 breast development and Mel talked about the PRO study.

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

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

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

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

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

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

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

5 So not that's all the endocrinology I'm
6 going to talk about and I'll give you some background
7 on our studies and how we got into it and where GnRH
8 agonist testing comes from. So GnRH was discovered in
9 1977. It's desensitizing -- the desensitizing effect
10 of GnRH agonist was exploited, if you will,
11 pharmaceutically in the best sense and led to the
12 development of the first effective treatment for
13 central precocious puberty which was chronic GnRH
14 agonist treatment and Mel went through the
15 desensitizing effects of chronic GnRH agonist
16 analogues and I want to point out today that we are
17 not -- the testing that we're doing is not the same as
18 this. We're not looking at the desensitizing effect.
19 We're look at the effect of a first injection.

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

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

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1 substitution in a small molecule.

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

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

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

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

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

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1 standard, our provisional gold standard test, was a
2 sleep test based on the principles that Mel talked
3 about. So this requires a GCRC to sample blood every
4 20 minutes overnight, just like in the protocol that
5 we're proposing today, so the open bars are awake and
6 the closed solid bars are asleep. So these are the
7 boys with constitutional delay. You can see that they
8 had larger and bigger responses than the gonadotropin
9 deficient boys.

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

22 So anyway it was 0.35 units on top of a

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1 baseline that was sometimes around one is a hard call.

2 So we compared it using a similar protocol, virtually
3 identical to what we're using today to the nafarelin
4 test and this shows the LH response is with the pre-
5 pubertal boys. So the boys of constitutional delay
6 are in solid bars. You have a handout of this, the
7 solid dots. The gonadotropic deficiency are open
8 circles. There were about 10 normal controls that we
9 got and you can see that we differentiated the great
10 majority and the best differentiation was out here at
11 four hours. And when we looked at the delta LH,
12 again, that same kid who we couldn't differentiate on
13 the sleep test, couldn't be differentiated by this
14 test. But again, here we can discriminate 19 out of
15 20 cases using a delta LH that was now mid-range in
16 the curve of about five units per liter.

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

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1 Price who was the vice president of Syntex but within
2 a year they were sold out. They passed the license on
3 to Searle. Searle wasn't interested in a diagnostic.

4 I wish that I would have gotten a use license but if
5 I had gotten a use license, you'd tell me I was here
6 for money today and I'm not here for money. I'm here
7 for passion.

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

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

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

7 And then the FDA decided, "Whoops, we
8 shouldn't have been letting you use Lupron under a
9 nafarelin IND", so we got a Lupron IND and this was
10 the last support we ever got from TAP. The support we
11 got was they let us look at their -- refer to their
12 NDA and on this IND we have an R01 funded study that
13 has to do with hyperandronism in children and adults.

14 And this is important to those studies but I'm not
15 going to go into that further. So the study under the
16 first FDA Orphan Drug Grant was a dose response study
17 of leuprolide in adults and compared it to GnRH and
18 then historical nafarelin data and the bottom line is
19 that the results showed the Lupron 10 micrograms per
20 kilogram the -- this is the highest that -- well,
21 actually we had a few studies with 20 micrograms per
22 kilo that aren't shown on the slide.

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1 This high dose of Lupron was similar to
2 nafarelin in LH and sex steroid stimulation but
3 interestingly, it was less potent in FHS stimulation.

4 All the doses of leuprolide, the area under the
5 curve, the peaks, were less than those to nafarelin.
6 And of course, this is factual here. It gives you a
7 short-lived early response.

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

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

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1 here with the polyclonal -- you know, here's this one
2 kid who's the partial case that we couldn't
3 distinguish with the test but here we are with the
4 Delfia assay using a specific beta sub-unit assay and
5 we get a lot of overlap with normal. So that was --
6 that's been a major challenge to this day. So why?
7 Well, there's microheterogeneity of LH. Your handout
8 says microheterogeneity of immunoreactive LH but it's
9 the LH standards as well as the LH anti-serum, so that
10 LH is a sialylated (phonetic) molecule and it has a
11 lot of epitopes and some assays pick up certain ones
12 and some assays pick up others. And the RIA that we
13 had been using had been a specially developed one that
14 had enhanced specificity for bioactive LH but the
15 specificity was incomplete whereas the Delfia was and
16 is a beta sub-unit specific assay.

17 Now, the Delfia assay, I want to point
18 out, is a commercially available assay that anybody
19 can buy, so it's commercially available. Back in the
20 early days, before the mid-1990s, excuse me, before
21 the mid-1995s, RIAs were mostly in house and were very
22 unique polyclonal, very unique to the laboratory but

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

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

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

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

22 And we have considerable promising

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

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

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

14 DR. ROSENFELD: Pardon me?

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

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

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

14 We've had one child who had a transient
15 local rash. We studied 245 adults. We had one IV
16 related problem. We had one local allergic reaction,
17 so now we've got what, in adults and children the
18 allergic reaction is two out of 500, so it's a half a
19 percent and we're not sure whether that's to the LHRH.

20 It's probably to the excipient. And then the adults
21 had a number of hormone related side effects that we
22 ascertained by a post-study letter.

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 gonadotropic deficiency versus constitutional delay is
2 pretty straightforward.

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

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

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

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

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

22 Although we project 20 in each group, as

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

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

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

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

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

12 And the normal range is to be set at the
13 fifth to ninety-fifth percentile of healthy volunteers
14 and the secondary variables are that will calculate
15 the fifth to ninety-fifth percentile for
16 constitutional delay in boys and for central
17 precocious puberty in girls I added the boys and girls
18 there because those we anticipate having big enough
19 numbers and those are the major targeted study groups.

20 The leuprolide test, we're looking at these hormone
21 response, primary variables, they are group specific.

22 All of this is sex specific and state specific, in

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1 other words, pre-pubertal versus early pubertal.

2 And for pituitary response, we're using LH
3 and free alpha sub-unit. And for the gonads, we're
4 using the sex specific sex steroid and inhibit-B
5 potentially anyway. And then we will set the sex and
6 state specific fifth to ninety-fifth percentile ranges
7 for normal healthy volunteers. And for constitutional
8 delay in boys and central precocious puberty in girls.

9 Further analysis of data, so boys, where the common
10 problem is delayed puberty, the primary comparison is
11 gonadotropin deficiency versus constitutional delay,
12 and compare the pre-pubertal groups to the early
13 pubertal groups.

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

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

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

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

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

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

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

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

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

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

11 CHAIRMAN FOST: Other questions? Yes.

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

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

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

11 MS. O'LONERGAN: Thank you.

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

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

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

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

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1 appropriately.

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

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

7 DR. ROSENFELD: I don't think so.

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

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

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

22 DR. ROSENFELD: Well, there are two main

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

11 CHAIRMAN FOST: Dr. Gorman?

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

18 DR. ROSENFELD: There's nothing in life
19 that's black or white.

20 DR. GORMAN: I could not agree more.

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

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

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

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

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1 waiting or six months of minimal testosterone
2 injections?

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

18 DR. GORMAN: Thank you.

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

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

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

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

21 CHAIRMAN FOST: Dr. Botkin?

22 DR. BOTKIN: I have question about the

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

10 So I guess my question is --

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

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

18 DR. ROSENFELD: Yeah.

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

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

4 DR. ROSENFELD: Yes.

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

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

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

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

21 CHAIRMAN FOST: Yes, Dr. Boepple?

22 DR. BOEPPLE: Yes, when Dr. Grumbach was

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

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

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

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

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

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

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

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

13 DR. ROSENFELD: I think so.

14 CHAIRMAN FOST: Is there any literature on
15 that?

16 DR. ROSENFELD: I don't know of any.

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

19 DR. ROSENFELD: People don't usually talk
20 about misdiagnosis.

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

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

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

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

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

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

17 CHAIRMAN FOST: It says it in the consent
18 form.

19 DR. ROSENFELD: Pardon me?

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

22 DR. ROSENFELD: Well, it probably says,

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

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

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

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

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

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

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

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1 more. We are not doing more than one injection.

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

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

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

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

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

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

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

15 DR. ROSENFELD: Well, I --

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

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

22 DR. GORMAN: I resemble that remark.

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

7 CHAIRMAN FOST: Dr. Botkin and Ms.
8 Knudson.

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

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

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

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

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

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

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

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1 think it is.

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

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

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

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

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

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

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

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

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

18 (A brief recess was taken.)

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

22 DR. GARFINKEL: Thank you. It's a

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

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

20 CHAIRMAN FOST: Thank you.

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

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

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

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

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

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

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1 to the federal funding.

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

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

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

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

22 And in addition, in an effort to enhance

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

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

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

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1 protocol was initially submitted on September 7th of
2 2004 and typically there is an administrative pre-
3 review before the protocol is brought to a convened
4 meeting and this pre-review generated administrator
5 comments to the PI. The submitted Form C indicated in
6 that person's opinion that the study involved -- no,
7 that the submitted Form C involved a greater than
8 minimal risk with direct benefit to children with
9 disorders of puberty but inquire whether -- what the
10 circumstance was in terms of healthy children,
11 recognizing the potential conflict in regulatory
12 situations.

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

22 The first convened meeting that reviewed

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

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

22 So from that meeting on November 23rd, a

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

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

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

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

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

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1 institutional review boards across the country in
2 determining what minimal risk means, what more than
3 minimal risk means. You've heard certainly the
4 expression of the PI that this is a minimal risk
5 protocol but clearly the variety of responses to this
6 type of survey, this is the same point that Dr. Fost
7 demonstrated, I think it's justifiable that there is
8 discussion, debate and consideration of what
9 constitutes minimal risk. The specifics in terms of
10 this protocol centered specifically around, yes, the
11 use of leuprolide specifically in a non-FDA approved
12 manner in healthy children, but also there was some
13 consideration of a overnight and in some cases two
14 overnight hospital or GCRC stay as well as the
15 presence of intermediate term catheters for as long as
16 48 hours or longer.

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

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

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

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

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1 oversite.

2 CHAIRMAN FOST: Thank you, Dr. Garfinkel.

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

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

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

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

4 CHAIRMAN FOST: Dr. Rogol, Dr. Nelson.

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

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

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1 DR. ROSENFELD: Thanks for the
2 opportunity.

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

5 DR. ROSENFELD: Thanks for the
6 opportunity to clarify that. Yes, that's exactly what
7 I said. And I want to reiterate that this is a Catch
8 22 situation about getting collaborators. If this
9 protocol, let's say hypothetically does not get
10 approved, then do you think I'm going to be able to
11 get a collaborator? If it does get approved, then
12 collaboration comes easily, once we know the level of
13 approval and such and can go forward.

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

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

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

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

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

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

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

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

9 CHAIRMAN FOST: Thank you. Dr. Nelson.

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

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

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

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1 minimize that risk, et cetera.

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

10 DR. ROSENFELD: Encouraged.

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

21 CHAIRMAN FOST: Further questions?

22 DR. BOEPPLE: Yes, I just wanted to

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

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

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

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1 to review was fairly typical. There was a submission
2 of a protocol in late September. The protocol was
3 reviewed and met at a convened meeting in November and
4 there was feedback given to the principal investigator
5 by mid-November and then by the creation of the -- by
6 the necessity of re-review by the CRC, and substantive
7 changes to the protocol that occurred based on that,
8 there was a resubmission in January and so that -- the
9 3rd of January. So, then you're correct. I mean, from
10 that point forward, so that's from January to November
11 and I would actually want to consult, if I may, with
12 my Director of Regulatory Compliance for a moment to
13 hear about the time line of submission.

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

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

21 (Pause)

22 CHAIRMAN FOST: If you want your associate

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1 to just talk directly, that's fine.

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

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

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

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

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

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

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1 appropriately.

2 CHAIRMAN FOST: Thank you. Dr. Gorman?

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

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

22 There is not, in this particular protocol,

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

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

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

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

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

14 CHAIRMAN FOST: Dr. Botkin?

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

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1 assessment?

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

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

8 DR. GARFINKEL: Certainly there's debate.

9 DR. BOTKIN: Within your IRB.

10 DR. GARFINKEL: With regard to this
11 particular protocol?

12 DR. BOTKIN: Right.

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

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

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

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

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

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

22 MS. KNUDSON: Yeah, I would like to follow

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

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

16 CHAIRMAN FOST: Dr. Rosenfield?

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

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

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

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

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

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

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

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

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

20 So full approval, conditional pending, or deferral.

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

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

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

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

20 DR. MALECKAR: I would say at least 75 to
21 80 percent make it back to another meeting.

22 DR. GORMAN: Thank you.

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

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

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

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

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

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

9 Said there were numerous Lupron adverse
10 event product liability lawsuits that TAP had settled
11 all via secrecy agreement. In '99 there were 6,000
12 adverse events related to Lupron reported to the FDA.

13 She said, quote, "The PI falsely claims that side
14 effects are due to chronic leuprolide use in adults. "
15 I have seen internet messages, children who underwent
16 leuprolide challenges tests and suffered ill effects
17 afterwards. The PI falsely claims only Lupron depot
18 has been responsible for adverse reactions.

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

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

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

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

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1 precocious puberty.

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

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

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

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

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

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

22 They support the participation of normal

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

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

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

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

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

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

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

22 Second, I can verify directly that the

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

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

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

5 With that we will adjourn and we will
6 reconvene at 10 minutes after 1:00. Lunch is in the
7 hotel restaurant somewhere near the front. See you at
8 10 minutes after 1:00;

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

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1 AFTERNOON SESSION

2 (1:18 p.m.)

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

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

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

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

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1 recommend approval under Section 404 a minimal risk,
2 407, meeting the criteria for 407, approve with
3 modifications or approve only if modifications and so
4 on. So we'll safe that till the end, but I think if a
5 more informal process can help us identify where
6 consensus is and where it isn't the voting will be
7 more efficient.

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

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

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1 DR. GOLDKIND: That's correct.

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

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

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

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

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

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1 And this is an ethical problem because if
2 it doesn't succeed in accrual, then the first five,
3 10, 15, 20 or 40 children who are enrolled would have
4 donated their services, their time, their
5 inconvenience, their discomfort for nothing if there's
6 not enough data to reach reasonable conclusions.

7 Ultimately -- so there's an issue number
8 four that I didn't put up there, which is the
9 compensation issue. I think we need to talk about
10 that, whether it's problematic, somebody raised that
11 during the break, the question of whether it's
12 problematic that the normal subjects are getting
13 compensation and the children with disorders are not.

14 Second, whether the compensation that's being given
15 or offered to the normal subjects is an undue
16 inducement. So we need to have a little conversation
17 about that.

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

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1 404 as minimal risk or under 407, meeting all the
2 criteria of 407, which I'll review when we get there.

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

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

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

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1 sort of component analysis of the protocol?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 CHAIRMAN FOST: Dr. Nelson.

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

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

16 DR. NELSON: Even if you remove the
17 leuprolide, which I realize is a hypothetical, 36 to
18 48-hour IVS, overnight admissions, et cetera, I don't
19 think fit minimal risk and I'm going to say why.
20 First of all is the question of definition. Even
21 though it's not in the regulations, one question is,
22 whether from a going forward perspective, it's

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

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

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

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

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

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

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1 CHAIRMAN FOST: Dr. Rogol.

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

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

18 DR. BOEPPLE: These were healthy --

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

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

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

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

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1 working with and that's just on the ground experience.

2 I'm not saying whether it's right or wrong but it can
3 be done in real live children who are otherwise
4 completely healthy. Actually, they were stringently
5 healthy. So that's just a different perspective,
6 Norm.

7 CHAIRMAN FOST: Yes.

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

14 CHAIRMAN FOST: The first two comments
15 expressed the view that all things considered, it
16 needed to be classified as greater than minimal risk.

17 Dr. Nelson said he thought it could still be done in
18 an acceptable way with the appropriate attention to
19 details. I'm still not quite there where Ms. Dokken
20 stands on that, but Dr. Rogol and Ms. O'Loneragan,
21 could you comment on whether you -- you both,
22 obviously believe the study is doable and ethically

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

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

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

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

11 DR. ROSENFELD: I had a comment.

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

15 (Laughter)

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

22 CHAIRMAN FOST: Or doctors.

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

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

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

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

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

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1 know, a spray that freezes the skin for instance.

2 CHAIRMAN FOST: Paula Knudson?

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

6 DR. ROGOL: Yes, we did.

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

10 MS. KNUDSON: All right.

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

17 DR. NELSON: More than minimal risk? Yes.

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

21 DR. ROGOL: Do I disagree or agree?

22 CHAIRMAN FOST: Does anyone disagree? You

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1 disagree.

2 DR. BOEPPLE: Before we go on, what will
3 become of this statement? In other words, I think
4 that we will make a statement with respect to Dr.
5 Rosenfield's protocol at the end of this and as you
6 point out, there are different component parts of it.

7 So is there any precedent setting that will go on
8 today with respect to a normal healthy child being
9 able to be admitted to a GCRC overnight and have
10 frequent blood sampling given all of the things we've
11 talked about and making sure the facility is
12 appropriate for children, setting things up in a way
13 that assent and permission, both the child and the
14 parent is maintained?

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

21 CHAIRMAN FOST: Dr. Nelson?

22 DR. NELSON: Maybe Mike or Sara might want

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

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

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1 MS. DOKKEN: Dr. Goldkind.

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

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

22 DR. BOEPPLE: I accept that. So if

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

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

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

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

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

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

14 CHAIRMAN FOST: Dr. Prohaska?

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

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1 the Secretary and it will be posted on the web.

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

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

13 If it's a very user friendly environment
14 with experienced people doing this, that's one issue.

15 If it's somebody who is not in -- you know, scatter
16 beds, it's not an environment that really is conducive
17 to the kind of care that we demand be given to our
18 children under these circumstances, that's another
19 matter and I find it difficult to really juggle all
20 this in the sense, Norm, of -- I really put -- I
21 really rate environment very high and I rate the
22 investigator very high.

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

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

12 The only question I have and this is
13 simply a concern, is there will be 500,000 407s if one
14 is all the time considering that this more than
15 minimal risk category, no direct benefit, healthy
16 children has to come to such a big elaborate meeting.

17 I see no way out of it and probably what we're
18 dealing is with something where there's some level in
19 between missing that does not yet exist and so one of
20 the things that might be interesting about this
21 meeting and our thoughts is to bring that to the
22 attention of all those that are working in this field

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

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

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

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

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

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

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

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

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1 Dr. Garfinkel.

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

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

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

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

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

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

16 CHAIRMAN FOST: Huh?

17 DR. GRUMBACH: It does say neighborhood.

18 CHAIRMAN FOST: Neighborhood?

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

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

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

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

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

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

8 CHAIRMAN FOST: Thank you. Dr. Botkin.

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

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

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

8 And so it seems to me burden, thinking of
9 it in those terms, is put the kid in the hospital for
10 36 hours with an IV and injection of a drug with what
11 I assume actually is sort of unknown long term
12 implications. Is that more burden than you would, in
13 good conscience subject the child to is not able to
14 consent to that involvement? It seems to me that
15 that's pretty straightforward, and the answer is, yes.

16 And you can't -- the regs don't allow us to
17 countermand that by saying, but look at the great
18 information we could get. You know, in the adults you
19 can compare the risks and the benefits and make a
20 choice. In kids, the regs don't allow us to do that
21 and I, at least personally think that's a pretty good
22 approach.

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

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

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

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

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

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

16 But then the question is, what's the lower
17 limit relative to the scientific adequacy of the
18 study, I understand things -- I mean, you could
19 probably take that curve and take it off maybe every
20 30 minutes or 45 or every hour maybe to get your curve
21 overnight sleep but I couldn't, when I was doing the
22 math in the protocol, get down to the 10 kilos or get

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

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

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

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

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1 what they were saying.

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

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

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

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

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

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

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

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

22 So those were the operations of it.

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1 That's what we did.

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

4 DR. ROSENFELD: A comment on the
5 calculations; I can say that our -- well, our RSA or
6 the GCRC has called around the country and this five-
7 percent guideline is pretty common in GCRCs around the
8 country but the calculation is based on this. As an
9 example, a 50-kilogram child, we assume that blood
10 volume is seven percent of body weight, and that's
11 3500 ccs. And we take five percent of that, that's
12 175 cc's.

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

17 CHAIRMAN FOST: Dr. Boepple.

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

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

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

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

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

10 DR. NELSON: Just to close the loop on the
11 math, based on the five percent in the 3500 and the
12 175, if you -- you know, basically that would be about
13 -- it would be three and a half per kilo. So it's
14 pretty close to the two to three per kilo that per
15 kilo people are used to thinking about as opposed to
16 five percent. So I think the math, whether you do
17 about five percent or whether you pick three is close
18 enough to where it's a difference that doesn't make a
19 difference.

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

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

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

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

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

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

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1 infectious diseases. We call this immunization.

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

13 CHAIRMAN FOST: Dr. Nelson.

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

21 DR. GORMAN: (Inaudible)

22 DR. NELSON: I understand that. I just

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

6 DR. GORMAN: Can I follow up?

7 CHAIRMAN FOST: Sure.

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

20 DR. NELSON: Fifteen second rebuttal?

21 CHAIRMAN FOST: Sure.

22 DR. NELSON: The question then would be

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

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

8 DR. NELSON: Thank you.

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

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

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

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

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

22 CHAIRMAN FOST: Ms. Knudson.

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

5 CHAIRMAN FOST: Dr. Nelson.

6 DR. NELSON: The earlier example I gave
7 about the adolescent getting a 24-hour IV, I was on
8 the side that thought that could be considered minimal
9 risk because I didn't think it made sense for a 15-
10 year old who was saying, "Fine, I'll be in overnight
11 to allow you to do that", that I thought it made sense
12 for that to keep coming back to a 407 panel if it
13 wasn't minimal risk.

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

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1 everything else is being done to minimize risk
2 appropriately.

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

10 DR. BOEPPLE: Are you asking me?

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

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

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

6 DR. BOEPPLE: Huh?

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

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

13 CHAIRMAN FOST: Dr. Gorman?

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

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

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

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

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

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

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

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

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

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1 minimal risk.

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

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

6 (Laughter)

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

11 DR. GRUMBACH: I would echo that.

12 CHAIRMAN FOST: Okay, Dr. Boepple?

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

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

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

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

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

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

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

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

11 CHAIRMAN FOST: Thank you.

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

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

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

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

2 CHAIRMAN FOST: I know.

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

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

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

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

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

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

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

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

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

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

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1 secretion and response to that analogue.

2 So, you know, if the answer is that
3 doesn't exist, then there's a need -- it strikes me
4 that there is a need for an improved diagnostic test.

5 So the first question is, did I get it right, but
6 then the second question is, and I think it goes back
7 to Jeff's question is, the role then of true normals,
8 not normals who present to a clinic with some question
9 of am I normal because they have some manifestation of
10 precocious puberty or delayed puberty but turn out to
11 turn up normal. That's really a different group than
12 true normals which they don't have anything. How
13 important is that for the interpretation of the
14 results of the diagnostic tests.

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

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

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

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

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

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

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

22 And I think we need true normals to get

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

9 CHAIRMAN FOST: Thank you. Dr. Botkin?

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

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1 ideologies and the normal ideologies.

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

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

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

3 CHAIRMAN FOST: Other comments? Yes.

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

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

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

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

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

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

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

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

22 CHAIRMAN FOST: Thank you. Dr. Nelson and

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1 then Dr. Diaz.

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

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

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

5 So being able to define those sort of
6 statistical parameters around a test, where if you
7 don't have normals, all you'd be able to say is you're
8 different than this group, which we know is abnormal.

9 You wouldn't be able to say, "Because of that we know
10 you're not abnormal in this way, but we can't be 100
11 percent confident you're truly normal in that way".
12 So there may be in a simplistic way, not being an
13 endocrinologist nor a statistician, being able to say
14 to a parent, "We're 99 percent confident", versus,
15 "You know, we're only 80 percent confident here and
16 you need to come back next year and let's do this
17 again".

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

21 CHAIRMAN FOST: Dr. Diaz.

22 DR. DIAZ: I think to have normative data

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

7 CHAIRMAN FOST: That's the next question.

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

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

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1 armamentarian. And right now, we don't have a
2 substitute for that in the sense that people have used
3 it, these GnRH agonists, off-label, obviously, and
4 there is one large series of normals that are, 140
5 that were reported from Barcelona and that's really
6 the only normative, really normative data where they
7 did various stages of puberty and again, as Bob
8 pointed out, the issue is what kind of assay are you
9 using, but that's the only normative data. These were
10 140 normal kids, 70 males and 71 females in which they
11 had normative data, but that's the only in the whole
12 literature.

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

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

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

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

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

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

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

13 Now --

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

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

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

22 DR. ROGOL: Well, in one respect if it

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

7 CHAIRMAN FOST: Dr. Boepple?

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

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

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1 get in that direction.

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

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

9 CHAIRMAN FOST: Dr. Botkin?

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

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

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

5 DR. ROSENFELD: It's both, that's the
6 short answer. And you have already determined that you
7 are going to give the sleep test, you already ruled
8 that you think that it's more than minimal risk so you
9 know, it's not a reasonable study to do on an everyday
10 basis, but what you said is true, it's potentially
11 easier and it will prevent -- and it is going to be
12 compared to a sleep test for the purposes of this study
13 and that's the provisional gold standard, the protocol.

14 These children will be followed for progression of
15 puberty. So that's really the ultimate outcome and we
16 did that in the previously published study that I
17 showed you at 95.

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

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

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

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

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

17 CHAIRMAN FOST: Dr. Rogol?

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

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1 reasons. That's the only place they can be done and
2 nobody other than a research group would pay for them.

3 They're phenomenally expensive. You have to pay for
4 the hospital bed. You pay for 48 LH tests at whatever
5 per and so that, irrespective of whether the overnight
6 test is the gold standard or not, it can't be done.
7 It's like painting yourself in a corner. So if Dr.
8 Rosenfield, in this particular one, can show that the
9 four-hour or 24-hour single point in the test that he
10 does, that has implications down the line for a
11 practical way of making this particular variety of
12 diagnosis, because we can say anything we want about
13 the sleep test, it won't be done.

14 CHAIRMAN FOST: Dr. Silber.

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

17 CHAIRMAN FOST: Yes.

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

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1 severity of the limitations.

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

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

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

22 CHAIRMAN FOST: I understood Dianne's

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

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

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

16 DR. ROGOL: I believe that.

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

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

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

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

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

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

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

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

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

17 CHAIRMAN FOST: Yes.

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

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

10 CHAIRMAN FOST: Dr. Rosenfield?

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

21 DR. GRUMBACH: Before you go on --

22 DR. ROSENFELD: Is that KCM 94?

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

4 DR. ROSENFELD: I didn't get the handout.

5 DR. GRUMBACH: Endocrinology, leuprolide
6 acetate, 500 micrograms subcutaneous you give them to
7 141 normal children and adolescent, 60 boys, 81 girls,
8 age range five to 17 years, serum epistage (phonetic),
9 LHT and a variety of other studies at 0, 3 and 24
10 hours, and they got an increase in LH in pubertal girls
11 and pubertal boys and so forth. So this is a follow-
12 up.

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

16 DR. ROSENFELD: What journal?

17 DR. GRUMBACH: European Journal of
18 Endocrinology.

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

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

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

11 DR. ROSENFELD: -- is very highly
12 specific with more sensitivity and a point that I made
13 that you may not -- may have gone over a lot of
14 people's heads was that the sensitivity of that assay
15 at .15 is well below what we use to consider normal.
16 It used to be that normal was under one. Now we know
17 that normal is under .15 with a gray zone being between
18 .15 and .6. And the -- as best I can tell, the
19 sensitivity of the assay she uses is around .5.

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

22 CHAIRMAN FOST: I think we need to move

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

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

12 CHAIRMAN FOST: Dr. Diaz?

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

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

21 DR. NELSON: Yes.

22 MS. DOKKEN: I don't feel qualified to

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1 comment, so I guess I abstain.

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

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

13 MS. KNUDSON: I totally agree with you.

14 DR. BOEPPLE: As do I.

15 CHAIRMAN FOST: Dr. Rogol?

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

18 CHAIRMAN FOST: Dr. Silber?

19 DR. SILBER: Yes.

20 CHAIRMAN FOST: Ms. O'Lonergan?

21 MS. O'LONERGAN: Yes.

22 CHAIRMAN FOST: Okay, so virtually

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

4 (A brief recess was taken.)

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

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

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

22 In the interest of time, I just want to

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

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

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

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

21 DR. ROGOL: Except for probably the
22 overnight test.

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

4 DR. GARFINKEL: It may or may not be
5 relevant, but just as a -- the consent form indicates
6 \$150.00 as the maximum.

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

13 DR. NELSON: Well, no, I think it's fairly
14 standard to not pay subjects who are patients if, in
15 fact, they are going to benefit from the results
16 particularly the closest that gets to standard of care.

17 So it would just raise a question to whatever
18 incremental burden there is to it, whether there should
19 be an appropriate compensation for that such as the
20 overnight. I mean, I think that would be a legitimate
21 question but --

22 CHAIRMAN FOST: And your view on that?

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

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

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

19 MALE PARTICIPANT: (Inaudible)

20 MS. KNUDSON: It's prorated.

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

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

10 The second reason for payment is as an
11 honorarium to express appreciation. I'll just -- in
12 the interest of time, I'll just state my view on that
13 and the panel can then react to it. If that's what
14 it's for, it should be given after participation and
15 should not be mentioned ahead of time because to
16 mention it ahead of time, turns it into an inducement.

17 If you're really thanking somebody, you thank them
18 after they did what they did. You don't say, "If you
19 do this, I will thank you".

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

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1 his or her participation.

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

9 DR. ROSENFELD: Neither. This is less
10 than babysitting money in Chicago, which is around, I
11 understand \$10.00 an hour.

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

14 DR. ROSENFELD: Yes, it's going to the
15 child.

16 CHAIRMAN FOST: The child doesn't do
17 babysitting.

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

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

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1 DR. ROSENFELD: No, I don't quite know
2 what you're getting at, I mean, but I remember hearing
3 Skip Nelson give a grand rounds at the University of
4 Chicago about how kids thought it was unfair to be paid
5 less than what an adult was paid for the same study or
6 paid for -- what an older child was paid, and so I
7 guess you could take this as a philosophical argument.

8 We do not think it is undo inducement. I guess you
9 could say it's inducement but it's not undue
10 inducement.

11 CHAIRMAN FOST: Other comments?

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

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1 and --

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

4 DR. ROGOL: Yes, this was for --

5 DR. GARFINKEL: Twelve hours?

6 DR. ROGOL: Pardon?

7 DR. GARFINKEL: Twelve hours?

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

15 What we did, as I remember, now this is --
16 unfortunately I'm old and I don't remember so well, was
17 that -- and I may have it mixed up with another
18 protocol, that kids from a distance away, there weren't
19 very many of them, could not come to us by themselves.

20 So if a parent had to take time off work, they were
21 compensated for gas in coming up.

22 Most of the time the kids did not want to

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

9 CHAIRMAN FOST: Other comments? Yes,
10 Paula.

11 MS. KNUDSON: This is not -- I'm sorry,
12 this is not a longitudinal study. It's a one-time
13 event for these kids. I think it's hard for me to
14 imagine -- and I may be very out of touch with young
15 people today, but it's hard for me to imagine that the
16 idea of \$150.00 isn't very appealing to adolescents and
17 certain to an eight or nine-year old. I think it is an
18 inducement, whether it's -- I would like to think that
19 the consent form would not speak to the issue of money.

20 It could say, "We will have a thank you gift for you
21 at the end of the study", or it could just say nothing.

22 I actually don't discount the idea of altruism on the

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

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

6 CHAIRMAN FOST: Ms. O'Lonergan?

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

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

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

16 MS. O'LONERGAN: Right.

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

22 DR. ROSENFELD: Yes, it's important to

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

7 CHAIRMAN FOST: Dr. Nelson.

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

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

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

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

14 CHAIRMAN FOST: Dr. Gorman?

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

22 CHAIRMAN FOST: Other comments? Is there

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

3 The last substantive issue is the accrual
4 issue, is some questions were raised by the GCRC about
5 the accrual possibility and we received a message from
6 a member of the Pediatric Advisory Committee, a
7 statistician, who read this in preparation for tomorrow
8 who noted that comment and wondered about the accrual.

9 Dr. Rosenfield has commented on it but he is now going
10 to clarify it.

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

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

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

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

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

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

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

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

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

22 CHAIRMAN FOST: That can come under

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1 modifications. So we'll get to that. So we need now a
2 formal vote on whether the committee recommends
3 approval of the study or recommend that the study not
4 be done and if there is a recommendation, whether that
5 is under 404, I think we've already answered that.
6 There was unanimity that this was more than minimal
7 risk and, therefore, cannot be approved under 404.
8 Does not fit 405 and 406 and therefore only under 407.

9 So I think all that is needed is an up or a down vote
10 on 407, a recommendation for 407, with or without
11 modifications.

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

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

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

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

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

2

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

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

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

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

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

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

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

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

12 DR. NELSON: I don't want to get too
13 prescriptive. I guess what I'm saying is --

14 DR. ROSENFELD: There are various side
15 effects that are reported with long-term Lupron --

16 DR. NELSON: No, I think it's reasonable
17 to say that something like -- you know, I don't want to
18 -- something like, there are these reported risks of
19 Lupron that you may see in the Internet or in the
20 packet insert if you get ahold of that, these risks --
21 you know and list maybe the top -- you know, these
22 risks are A, B, C, D, pick the -- you know, these are

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1 associated with long-term treatment and we don't
2 believe are related to a single dose. If you do, we
3 can talk about it. I mean, I'm just --

4 DR. ROSENFELD: No, that's --

5 DR. NELSON: Yeah, I mean, I just think
6 that there is likely a parent, there may well be
7 parents in this room that would feel somehow deceived
8 even if it's not relevant. They want to make that
9 judgment of relevance on their own. That's my point.

10 DR. ROSENFELD: Got it.

11 CHAIRMAN FOST: Ms. Dokken?

12 MS. DOKKEN: This is also about the
13 consent/assent process and specifically about the forms
14 for the healthy children and their parents. I
15 mentioned it once before; in the parent consent form,
16 the discussion of no benefit is on page 4 and I'm not
17 familiar with other consent/assent forms for healthy
18 children, but it seems to me that page 4 is a long ways
19 into the document to get to something that I think is,
20 you know, very relevant information. And then on the
21 children's assent form, again, for the healthy
22 children, the initial statement is something and then,

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1 "Help us find out if children like you are growing and
2 developing normally", which is identical language to
3 that which is used in the assent form for the children
4 with the condition and I think that's -- to say
5 "children like you", in the healthy children assent
6 form, I think, is misleading. So those are just some
7 comments about the form.

8 CHAIRMAN FOST: Thank you, other comments?
9 Dr. Botkin?

10 DR. BOTKIN: I guess I'd want to make a
11 broader comment about the 407 process in general and my
12 concern is the possibility of having a 407 process
13 undermine the existing regs. So the question is, you
14 know, what is it about a 407 panel that makes it
15 somehow more perceptive, more ethical, more appropriate
16 to approve a study that could not be approved under the
17 existing regs by the local IRB?

18 I don't know that I know the answer to
19 that question but I guess I interpret the existence of
20 the 407 to have an out for those projects that are
21 truly compelling in some way, truly extraordinary such
22 that for certain circumstances for well-articulated

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1 reasons, we're willing to override what are otherwise
2 justifiable and solid regulations by which all other
3 studies need to live by.

4 Now, that isn't in the regs, but I guess
5 I'm sort of tipping my hand here to say that my
6 personal criteria here would be to say is there
7 something truly compelling about this situation that
8 permits us to override the normal standards to which we
9 would hold child protections and research?

10 CHAIRMAN FOST: And do you think there is?

11 DR. BOTKIN: No, not for the healthy kids.

12 CHAIRMAN FOST: When we discussed it
13 whether it's addressing a serious problem that it's a
14 serious problem we have.

15 DR. BOTKIN: Well, how I would put this
16 together, you know, pending, of course, listening to
17 other folks about this is to say that I do think
18 there's a need for improved testing in this domain. I
19 haven't been convinced that that improved testing can't
20 be accomplished by including the two categories of
21 kids, basically those kids who are normal but present
22 with a clinical concern and those kids who truly have

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1 pathology. I haven't been convinced that including the
2 healthy kinds in there is essential to the primary goal
3 of determining or improved diagnostic test.

4 CHAIRMAN FOST: Excuse me, I just want to
5 clarify the last slide that we had before the break,
6 namely whether the proposal presents a serious problem.

7 One of those questions was, is the absence of this
8 normative data on healthy kids a serious problem? And
9 I thought that you had voted yes on that. You're now
10 saying, you don't think --

11 DR. BOTKIN: No, I think I was voting on
12 the fact that this is addressing a serious problem but
13 it's not clear to me that the inclusion of the healthy
14 kids is essential to address the problem. I think the
15 rest of the study does that as approved.

16 CHAIRMAN FOST: Dr. Nelson, Dr. Gorman.

17 DR. NELSON: I guess it would be important
18 to separate out that latter judgment, Jeff, from the
19 former question about the role of 407 panels within the
20 overall review process because it's -- it comes to the
21 question of what the standard is and one way of viewing
22 is, is that the National Commission couldn't think of

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1 everything. And when they came up with the three
2 categories, they realized we need a fourth just in case
3 they didn't think of everything. And what has
4 certainly evolved over time in a lot -- in the bulk of
5 the 407 reviews have been the role of control data and
6 the importance of that kind of data from a scientific
7 perspective which, you know, in the '70s you could say
8 was -- you know, maybe a different set of issues. So
9 it's -- so your latter question, I think is separate.
10 In other words, whether you think this protocol does
11 what you think it needs to do and there was some
12 differences around the table. That's a very different
13 question from the bigger policy issue of a 407 review
14 as a pop-off valve, if you will.

15 You know, since 407 still needs to be
16 conducted according to ethical standards, I don't --
17 you know, I don't see this as much different than the
18 other three except it's trying to fill in gaps that at
19 this point exist within the other three categories.

20 CHAIRMAN FOST: Go ahead.

21 DR. BOTKIN: Well, I guess to what extent
22 then what are the ethical standards to which 407 review

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1 panels are held? You know, it's not minimal risk for
2 healthy children any longer. Presumably, we could
3 pretty much approve anything we wanted to with respect
4 to the level of risk. Now, you might say, "Well, the
5 benefit has to be proportional to the risk in some
6 fashion and that would be the primary ethical
7 determinant, but we're not really given that guidance
8 either. It seems to me that that's pretty much opened
9 us to determine what our own ethical standards are in
10 that regard, which is potentially problematic.

11 DR. NELSON: I would agree, but let me
12 articulate, at least what I would see as one which is
13 if you make a determination that a protocol like this
14 is a minor increase over minimum risk in all of its
15 manifestations and some being minimal risk, the
16 question then comes down to the justification of
17 healthy children versus ill children in the exposure of
18 that level of risk. I mean there are arguments in the
19 literature which you're familiar with that have said
20 that that difference -- that it is appropriate, as much
21 as Susan Weiner's arguments that it is appropriate and
22 ethical for that level of risk to also be appropriate

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1 for healthy children under what conditions, under the
2 need for the scientific data which goes back to the
3 original concern. So, you know, one could make an
4 argument for that.

5 Getting outside of that risk category,
6 yeah, we might be on uncharted territory.

7 CHAIRMAN FOST: Dr. Gorman and then Ms.
8 O'Lonergan.

9 DR. GORMAN: I wanted to try to amplify a
10 little bit on what I thought I heard Dr. Botkin say
11 which I feel that my opinion is shaping up in much the
12 same way. While I understand the concern about using
13 these outliers of delayed puberty in boys and
14 occasionally accelerated puberty in girls, they're not
15 completely normal. They're not abnormal either when
16 you end up at the end of your observation period and
17 find out that they go through puberty, they're just
18 delayed. I am still in the prevailing clinical opinion
19 that those people are -- or those children are normal,
20 and, therefore, would let them participate in the study
21 and eliminate all normals, the truly normal normals,
22 whoever they might be and then I would be able to

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1 approve this study under 404 in the sense that
2 everybody who came to this study even those who turned
3 out not to have the disease, would have the prospect of
4 benefit, and therefore, I would think it was above
5 minimal -- slightly above minimal risk but with the
6 prospect of direct benefit even though the people with
7 delayed puberty, constitutionally delayed puberty,
8 turned out to be normal adults.

9 MALE PARTICIPANT: 405.

10 DR. GORMAN: I'm sorry, 405, thank you.

11 CHAIRMAN FOST: Ms. O'Lonergan?

12 MS. O'LONERGAN: Yes, part of -- I have
13 maybe a comment on the 407 process. So it's my
14 understanding that the IRB in this case, the IRB in
15 Chicago, that the IRB is the one who seeks the 407
16 review; is this correct?

17 CHAIRMAN FOST: I think so, yes.

18 MS. O'LONERGAN: Okay, in that case, the
19 IRB, the local IRB has made some determination that
20 they feel at least that it is possible that there is
21 something to be learned that's valuable here. I would
22 think that if the IRB said, "No way, this is really

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1 terrible research and we oughten to be doing it at
2 all", they wouldn't have sought a 407 panel. So I'm
3 coming at it in a different direction.

4 We have the opinion of the Chicago IRB
5 that, yes, we think this is worth looking at and that
6 there's some value in it. So it's more than just is
7 this exceptional and can we rule on anything we want.
8 I think the IRB is telling us that they feel that it's
9 an appropriate venue for looking at this because
10 they've made a determination that there is some value
11 here.

12 DR. BOTKIN: And I would add as did
13 evidently NIH reviewers.

14 CHAIRMAN FOST: Dr. Silber.

15 DR. SILBER: With some trepidation, since
16 this is my first time, but thinking about what Jeff was
17 saying, I don't think we here collectively, although
18 there are many brilliant people, are any better at
19 making these judgments than thoughtful people on the
20 IRB that already reviewed it. I think the only reason
21 we are seeing this is because it's mandated. There is
22 no way the IRB could have approved it even if they

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1 would come to the conclusions that we can. So what I
2 kind of sense with this meetings that we have is that
3 there is 407 and there is 407.

4 In other words, those things that for
5 reasons that they cannot be done in any other way have
6 to come to us, but that are very reasonable and
7 approvable would actually be the kind of things that
8 hopefully will be perhaps a bit more fast in coming
9 through, but that the real purpose of this is the 407s
10 where you say, "Oh, my God, this really is something
11 that perhaps shouldn't be done". And I think there is
12 no difference between us and them other than what the
13 regulation forces us to do because we have no other
14 choice.

15 CHAIRMAN FOST: Ms. Dokken.

16 MS. DOKKEN: Just commenting on what both
17 Dr. Botkin and Dr. Silber said, I think when I raised
18 the question before about who determines or who decides
19 what's a serious problem, that was my discomfort, too,
20 is serious relative to, you know, the host of problems
21 that are out there and do we somehow have to rank order
22 them like how would this relate to, you know, an avian

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1 flue pandemic and would you use, you know, healthy
2 children then, and it's like -- but, you know, if we
3 can go with Dr. Silber's two definitions of what comes
4 to 407, you know, one with a normal voice and one with
5 a big voice, but I think this all points out and I
6 don't know, you know, what the role of this group and
7 I'm not normally on it, but in gathering general
8 recommendations about the overall 407 process, and you
9 know, along the way proposing some ways of clarifying
10 pieces of it at least.

11 CHAIRMAN FOST: We don't have time to
12 discuss that here. Obviously, it's being heard by
13 people in the room and FDA officials and obviously, you
14 can send comments to them afterwards, but I think
15 discussion of the whole 407 process is just not within
16 our charge in the time left.

17 There have been several proposals here for
18 it sounded like approval with modifications and I need
19 to know whether these are mandatory or optional and I'm
20 going to list them and we need some discussion and
21 maybe a quick poll about whether these suggestions
22 should be required. The first was disclosure, of the

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1 results not being disclosed to the normal children.

2 DR. NELSON: Do you want to take them one
3 by one or all together?

4 CHAIRMAN FOST: I'm just listing them
5 first.

6 DR. NELSON: All right.

7 CHAIRMAN FOST: Second, there should be a
8 procedure for withdrawal of samples, that is when the
9 children reach an age of maturity, they should be
10 recontacted so they could get their samples destroyed
11 if they want to.

12 Third, there were changes to the consent
13 form proposed. There were a couple and I had one or
14 two of my own and I think those so far were the three
15 proposals. We could discuss the consent form changes
16 one by one, but let's take the first one, disclosure
17 results. I agree with Dr. Nelson's comment that it's
18 an opportunity for confusion and stigmatization and
19 unsureness about what it means and it doesn't seem to
20 me it would interfere with Dr. Rosenfield's study to
21 simply have part of the contract be that results to
22 normals will not be disclosed unless there is something

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1 clearly pathological.

2 DR. ROSENFELD: Maybe I could cut through
3 this. They all sound reasonable to me and we can do
4 them very easily.

5 CHAIRMAN FOST: Okay.

6 DR. BOEPPLE: But you don't want them to
7 be mandated, do you?

8 DR. ROSENFELD: If that slows the
9 process, I don't want them mandated, but I can have
10 them, you know, in your hands in a short period of
11 time.

12 CHAIRMAN FOST: Dr. Boepple, whose name I
13 have been mispronouncing all day and he's been
14 patiently allowing me to do it.

15 DR. BOEPPLE: Well, I think that the first
16 two are generally stipulated in all clinical research
17 or most clinical research, that results of research
18 studies are generally not provided and that's certainly
19 true of genetic studies and --

20 CHAIRMAN FOST: It's highly variable.

21 DR. BOEPPLE: All right, why is this
22 different? Why are we telling the University of

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1 Chicago what to do if it's highly variable?

2 DR. NELSON: Because they didn't put it in
3 the protocol.

4 CHAIRMAN FOST: I don't think it should be
5 highly variable.

6 DR. BOEPPLE: I think that if it's highly
7 variable, and there's an institutional perspective on
8 this that has made a judgment about how they proceed,
9 that we're not in a position to have to tell them, "No,
10 you were wrong when you decided that".

11 CHAIRMAN FOST: But we are in a position,
12 whether we should or not is a separate --

13 DR. BOEPPLE: Well, I don't think we
14 should.

15 CHAIRMAN FOST: Dr. Nelson.

16 DR. NELSON: Contrary to my other comments
17 about not being prescriptive, I think this is a slam
18 dunk in terms of what you don't do. Any diagnostic
19 test only is meaningful in clinical medicine unless you
20 have a sign or a symptom that causes you to do that
21 diagnosis. There's very few asymptomatic tests where
22 the specificity and sensitivity are such that you ought

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1 to even disclose it, so I think it's just fairly
2 straightforward. These kids coming in normal, you
3 don't disclose results.

4 Now, if at the end of this study you can
5 say, "Here's the normal curve", and you're truly
6 normal, I have no problem going back to that population
7 and saying, "You thought you were normal, you are".
8 That's fine, but one by one coming through getting
9 these numbers I think that's crazy. So I would be very
10 prescriptive on that and the other DNA sample stuff is
11 actually consistent with the National Bio-ethics
12 Advisory Committee report. I mean, that should be
13 standard across the board. Any IRB not doing that is
14 not doing what I consider standard of research ethics.

15 CHAIRMAN FOST: Let me just summarize the
16 consent form changes to see if Dr. Rosenfield keeps
17 shaking his head so at least the panel will know that
18 they wouldn't be upsetting him.

19 One, Ms. Dokken's comment that the non-
20 beneficial nature should be stated right up front with
21 the normals, not --

22 DR. ROSENFELD: Oh, that I'm not clear

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1 about. I don't know about whether there's some
2 mandated order to the consent form.

3 CHAIRMAN FOST: There's another section of
4 the consent form where the -- there's a separate
5 benefit section where it says to the normals "you may
6 benefit", and I think it's unlikely that they'll
7 benefit. I would just say we don't expect any benefit
8 to you. So Dr. Boepple has spoken against the notion
9 of a recommendation requiring these changes. Are there
10 -- is there anyone else who disagrees with him? That
11 is, I'm stating as the default position here that if
12 there's a recommendation it would be requiring these
13 changes. Is there anyone else who agrees with Dr.
14 Boepple that that should not be required, it should
15 just be recommended? Dr. Botkin?

16 DR. BOTKIN: Yeah, I guess I would defer
17 to that local IRB on these issues as well, and it's --
18 they don't seem to me to rise to the level of lack of
19 discretion on the local IRB. So I would vote more to
20 an intermediate, which is to say the committee raised
21 some concerns about these issues and the IRB -- local
22 IRB is recommended to revisit discussion of that or

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1 something to that effect.

2 CHAIRMAN FOST: Other comments on that
3 suggestion? Does that change anybody's view?

4 All right, I'm going to suggest we survey,
5 we go around the room and each person should address
6 the following question.

7 DR. GOLDKIND: Norm, excuse me.

8 CHAIRMAN FOST: Yes.

9 DR. GOLDKIND: Skip had raised the comment
10 earlier about including adverse event report
11 information in the consent form. Do you want to have
12 that on your list as well?

13 CHAIRMAN FOST: Oh, yes, okay, I'll add
14 that to the list.

15 DR. NELSON: And also Deborah's comment
16 about -- I mean, the normal consent ought to start off
17 by saying, "We want you to be part of this study
18 because you're normal not because we think you may or
19 may not be developing normally". I mean, the other
20 implies disease, so --

21 CHAIRMAN FOST: Okay, so we're going to go
22 around the room. Yes, Dr. Botkin?

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1 DR. BOTKIN: Well, I wonder whether -- we
2 could talk about some modifications, but I wonder
3 whether we might at this point think about
4 modifications that at least for me might save the
5 healthy child portion of the study and whether we might
6 get some feedback about that.

7 I mean, would it be conceivable to run
8 this study by not putting the healthy kids in for 36
9 hours but simply doing say this single leuprolide
10 injection and then blood draws at four hours and 24
11 hours, would that be -- and I'm not necessarily saying
12 I think that would be a acceptable way to go from my
13 standpoint but I'm wondering whether there are ways to
14 scale back the intervention for those healthy kids and
15 still get you some of the data that you might be
16 interested in obtaining.

17
18 DR. ROSENFELD: Well, my reply to this,
19 I'm going to address as a scientific level. I know
20 that when I first started this type of study with
21 neophron (phonetic) a long time ago, they asked me for
22 more frequent sampling. I also know that the zero,

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1 three and 24-hour misses information. I know that it
2 misses certain peaks. The peak steroid value often
3 occurs in 16 hours. I'd like to try to define, you
4 know, how often it occurs at 16, 20, 24.

5 I also know that if I reduce this, I
6 reduce the chance of having this published in a place
7 that people will see it and as my own experience
8 attest, there are certain journals that aren't widely
9 read and so they are out of people's radar. So I think
10 for now for this group of subjects, until we finish the
11 study, I feel strongly about obtaining samples at most
12 of these time points at least.

13 To do it the way it's designed would be an
14 optimal way to do it. The sleep test enhances the
15 ability to discriminate and it would be nice to know,
16 it would be important to know scientifically what the
17 normal is with the current standards because that
18 hasn't -- just hasn't been done. Sleep study standards
19 are ancient, you know, done with old assays. There
20 aren't the data. So I think since there are still
21 research centers that do that I think it's
22 scientifically justified to do that, scientifically

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1 important.

2 CHAIRMAN FOST: Any other comments? Okay,
3 here's the poll instructions. Each person should say,
4 first whether they recommend approval of the study and
5 if no, that would be -- you don't have to say anything
6 else unless you want to. If the recommendation --- I
7 guess the reasons would be helpful, what the key
8 reasons were. If yes, you need to also say whether you
9 think this approval should be conditional on number
10 one, non-disclosure of results, that is whether you
11 think that should be mandatory or simply recommended.

12 Number two, giving the children a chance
13 to withdraw their samples when they reach an
14 appropriate age mandatory or recommended; three,
15 consent form changes and in the interest of efficiency,
16 I'm going to suggest all three as a package but if you
17 want to comment on them individually and differentiate
18 fine, but the three main consent form changes are one,
19 to clarify up front that this is not -- you are not
20 sick, you are normal and this is not of any benefit to
21 you; second, get rid of the phrase "we're not trying to
22 find out if you are growing normally; and three, that

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1 something would be included about adverse events in
2 long-term use of Lupron. So the package of consent
3 form changes, you either think are essential or simply
4 recommended. Does everybody understand the
5 instructions. On your marks, get set, Ms. O'Lonergan.

6 MS. O'LONERGAN: I would recommend
7 approval of it. I think it does address a serious
8 problem and has a reasonable scientific design to
9 accomplish its goals. I would want the recommendations
10 or the mandating non-disclosure results, what is that
11 child being able to withdraw genetic material and then
12 the consent for changes.

13 CHAIRMAN FOST: Those are all mandatory,
14 did you say? All right.

15 DR. SILBER: Approval for this research
16 project and required contingencies for all three.

17 CHAIRMAN FOST: Required for all three,
18 thank you. Dr. Boepple?

19 DR. BOEPPLE: Approval, mandatory non-
20 disclosure of results, recommended dealing with genetic
21 samples and recommended consent form changes.

22 MS. KNUDSON: I would vote for approval

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1 with modifications, mandatory not to disclose results,
2 mandatory to add language about withdrawing samples and
3 mandatory the revisions to the consent form.

4 CHAIRMAN FOST: Thank you. I would vote
5 for approval also conditional on all the changes. I
6 just want to make a comment on why I concluded this. I
7 think assent, meaningful assent, protects the children
8 from the misuse that Jeff has spoken to so eloquently.

9 That is if assent is take seriously and children
10 really know they don't have to do this if they don't
11 want to, this has nothing to do with them really or
12 anything about their health, and they can stop any time
13 they want because I'm not worried about anything bad
14 happening to them.

15 In that regard, I think a recommendation
16 should be made to the IRB to consider assent monitoring
17 in the study. I think this is a study in which it
18 would be a good idea to take a sample and which the IRB
19 should oversee, some sampling of the children who are
20 in it, that is interview them afterwards and see if
21 they really understood what happened to them, if they
22 really understood that they couldn't have gotten out of

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1 it and if at any point, you see any red flags in that,
2 then the trial should be suspended and revisited.

3 DR. BOTKIN: I would disapprove the study
4 as written. I wouldn't approve it as the IRB had
5 approved it, which was excluding the healthy volunteers
6 in the protocol and I guess as I've stated before, my
7 feeling is that I think there is scientific rationale
8 for this but I don't think it rises to the level that I
9 think it should be approved out of compliance with the
10 existing regulations. I think that potentially opens
11 the door to lots of studies that have scientific
12 rationale but don't conform with the regs. So the
13 point is here, I just don't think this is a compelling
14 enough justification for inclusion of the healthy kids.

15
16 I think mandatory non-disclosure of
17 results in the healthy kids, if that's the study,
18 sounds fine. I would make the other changes
19 recommended for revisiting by the University of Chicago
20 IRB.

21 CHAIRMAN FOST: Thank you. Ms. Dokken?

22 MS. DOKKEN: I would recommend approval

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1 and mandatory on the three modifications.

2 CHAIRMAN FOST: Thank you. Dr. Nelson.

3 DR. NELSON: Norm, I'm a non-voting
4 member, so I guess I'll --

5 CHAIRMAN FOST: Oh, I'm sorry, thank you
6 for reminding me. Dr. Diaz?

7 DR. DIAZ: I would recommend approval with
8 all three being mandatory.

9 CHAIRMAN FOST: Thank you. Dr. Gorman?

10 DR. GORMAN: I would vote for disapproval
11 as written. I would defer to the IRB in Chicago as
12 understanding of this study and feel that it could go
13 forward with the exclusion of the healthy normal
14 controls. While I believe that precocious puberty and
15 delayed puberty are serious issues, I do not feel that
16 the development of this particular diagnostic test
17 rises to that particular status.

18 In terms of the recommended informed
19 consent and assent changes, I think the prohibition of
20 sharing the results until the research is completed
21 should be mandatory. A side bar conversation has
22 reassured me that there is a system in place at the

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1 University of Chicago in dealing with storage samples
2 for genetic and other research and I would like that to
3 be appended to the protocol as a mandatory requirement
4 and the others, I would consider as discretionary as to
5 the location of where the indication that this is not
6 for individual benefit appears in the informed consent
7 and assent.

8 CHAIRMAN FOST: Thank you. So I think we
9 have seven to two if I'm counting right in favor with
10 some variation and some of the modifications.

11 DR. ROSENFELD: Is Dr. Grumbach voting?

12 CHAIRMAN FOST: I don't think he's -- is
13 he a voting member? He did not vote. Dr. Rogol is not
14 a voting member. Are there any closing comments?

15 Thank you all for coming. I hope this is not like the
16 patient who received a telegram "Union Local 221 wishes
17 you a speedy recovery by a vote of 15 to 13".

18 (Laughter)

19 DR. GOLDKIND: Thank you very much to
20 everyone on the panel, to the folks from the University
21 of Chicago and to you, Norm, for conducting the meeting
22 so well.

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1 CHAIRMAN FOST: Thank you very much.

2 (Whereupon, at 4:03 p.m. the above-
3 entitled matter concluded.)

4

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