

UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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ONCOLOGIC DRUGS ADVISORY COMMITTEE

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PEDIATRIC SUBCOMMITTEE

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WEDNESDAY

NOVEMBER 28, 2001

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The Subcommittee met at 8:00 a.m., at the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Victor M. Santana, Chairman, presiding.

PRESENT:

VICTOR M. SANTANA, M.D., Chairman

PETER C. ADAMSON, M.D., Consultant (Voting)

FRANK BALIS, M.D., Guest (Non-Voting)

MARTINE BAYSASS, M.D., M.S.C., Industry Guest (Non-Voting)

MARK BERNSTEIN, M.D., Guest (Non-Voting)

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PRESENT: (CONT.)

JAMES M. BOYETT, Ph.D., Ad Hoc Member

SUSAN L. COHN, M.D., Ad Hoc Member

CHARLES A. COLTMAN, JR., M.D., Guest (Non-Voting)

ALICE ETTINGER, M.S.N., R.N., C.P.O.N., C.P.N.P, Ad
Hoc Member

JERRY Z. FINKLESTEIN, M.D., Ad Hoc Member

STEPHEN L. GEORGE, Ph.D., ODAC Member

STEVEN GOODMAN, M.D., M.H.S, Ph.D., Guest Speaker

JOSEPH GOOTENBERG, M.D.

NANCY KEENE, Patient Advocate

ERIC KODISH, M.D., Ph.D., Guest (Non-Voting)

EDWARD L. KORN, Ph.D., Guest (Non-Voting)

J. STEVEN LEEDER, Pharm.D., Ph.D., Guest Speaker

JODY PELUSI, F.N.P., Ph.D., ODAC Consumer
Representative

DAVID G. POPLACK, M.D., Guest (Non-Voting)

DONNA PRZEPIORKA, M.D., Ph.D., ODAC Member

WAYNE RACKOFF, M.D., Industry Guest (Non-Voting)

MARY V. RELLING, Guest Speaker

C. PATRICK REYNOLDS, M.D., Ph.D., Ad Hoc Member

ERIC KEITH ROWINSKY, M.D., Guest (Non-Voting)

PRESENT: (CONT.)

MALCOM SMITH, M.D., Ph.D., Guest (Non-Voting)

CLINTON F. STEWART, Pharm.D., Guest Speaker

SUSAN L. WEINER, Ph.D., Patient Advocate

KIMBERLY L. TOPPER, M.S., Acting Executive Secretary

Richard Pazdur, Division Director, Division of

Oncology Drug Products

Steven Hirschfeld, FDA Division of Oncology Drug

Products, CDER

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

8:08 a.m

CHAIRMAN SANTANA: Good morning. Let's go ahead and get started.

For those of you that don't yet know where we are, it's November the 28th, and this is an Advisory Subcommittee Meeting of Pediatric Oncology to the FDA. The purpose of this meeting is a continued discussion that this group has had advising the FDA for the last year or so on issues relating to the implementation of the Pediatric Rule.

My recollection is that there has been at least two prior meetings in which -- three, four, how many? This is No. 4. So there's been three prior meetings in which we discussed some specific issues about some diseases in pediatrics and how they may relate to issues in adult oncology and the implementation of the rule. Today the specific purpose of the meeting is to look at study designs in pediatric studies and how those can be used to support some of the indications in the Pediatric Rule.

So, with that, we have an extensive agenda

1 of various presentations, followed by some discussion,
2 and then at the end of the day we will have a few
3 questions that specifically the FDA wishes us to
4 comment on.

5 So, with that very brief introduction, I
6 want to go ahead and introduce the Committee to itself
7 and to the public.

8 Oh, I'm sorry, go ahead, yes. Kimberly,
9 go ahead.

10 MS. TOPPER: This is the conflict-of-
11 interest statement. The following statement addresses
12 the issue of conflict of interest with regard to this
13 meeting and is made part of the record to preclude
14 even the appearance of such at the meeting.

15 Based on the submitted agenda and
16 information provided by the participants, the Agency
17 has determined that all reported interests in firms
18 regulated by the Center for Drug Evaluation and
19 Research present no potential for a conflict of
20 interest at this meeting with the following
21 exceptions:

22 Since the issues to be discussed by the

1 Committee will not have a unique impact on any
2 particular forum or products but may affect the entire
3 class of products with all similarly-situated
4 manufacturers, in accordance with 18 USC Section
5 208(b), general matters waivers have been granted to
6 each of the special government employees participating
7 in today's meeting. A copy of these waiver statements
8 may be obtained by submitting a written request to the
9 Agency's Freedom of Information Office, Room 12A-30 of
10 the Parklawn Building.

11 We would like to disclose that Dr. Frank
12 Balis, an employee of the National Institutes of
13 Health, has received a waiver from his institution
14 allowing him to participate in today's meeting.

15 Further, Dr. Wayne Rackoff from Janssen
16 Research Foundation and Dr. Martine Bayssas from Debio
17 are participating in this meeting as industry
18 representative, acting on behalf of regulated
19 industry. As such, they have not been screened for
20 any conflicts of interest.

21 With respect to FDA's invited guests and
22 guest speakers, Dr. Eric Rowinsky, Dr. Charles

1 Coltman, Dr. J. Steve Leeder reported interests which
2 we believe should be made public to allow the
3 participants to objectively evaluate their comments.

4 Dr. Rowinsky would like to disclose that
5 he has grants from Pfizer, Abgenix, Diiachi, Enzon,
6 AstraZeneca, OSI Pharm, Genentech, Schering, Janssen,
7 Glaxo, Immunogen, Supergen, Aventis, Bristol Myers
8 Squibb, Eli Lilly, Allergan, MGI Pharm, and Shire; is
9 involved in research with the firms indicated and
10 receives consulting fees from the firms indicated as
11 well as from Pharmacia and BTG.

12 Dr. Coltman would like to disclose that he
13 owns founder's stock in ILEX Oncology, Incorporated,
14 and is on Bristol Myers Squibb's Advisory Board.

15 Dr. Leeder would like to disclose that
16 between 1997 and 2001 he has served as a consultant to
17 Abbott and Schering-Plough on issues concerning
18 pharmacogenetics, Hoffman LaRoche, Bristol Myers
19 Squibb, R. W. Johnson, PRI, and Abbott regarding
20 issues related to idiosyncratic drug toxicity, and Eli
21 Lilly on issues concerning pediatric clinical trial
22 design.

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

7 With respect to all other participants, we
8 ask, in the interest of fairness, that they address
9 any current or previous financial interests with any
10 firm they may wish to comment upon.

11 The next thing is, because we have a
12 person hooked in by telecon, it is critical that you
13 all speak directly into the microphones. Just because
14 they have this big holey pad does not mean it's
15 picking up your voice. Please speak directly in.
16 Thank you.

17 CHAIRMAN SANTANA: Thank you, Kimberly.

18 What I would like to do now is introduce
19 the Committee for the public record. So please
20 indicate your name and your affiliation, and if we
21 could start with Wayne over here in the corner and go
22 around, please.

1 DR. RACKOFF: Wayne Rackoff. I'm a full-
2 time employee at Johnson & Johnson, Janssen Research
3 Foundation, and currently working in oncology drug
4 development.

5 DR. BAYSSAS: Martine Bayssas, an employee
6 of Debiopharm in Switzerland, working in clinical
7 oncology development.

8 DR. COLTMAN: Charles Coltman, President
9 and CEO of the Cancer Therapy and Research Center and
10 Chair of the Southwest Oncology Group.

11 DR. BALIS: Frank Balis, Pediatric
12 Oncology Branch, National Cancer Institute.

13 DR. KODISH: Eric Kodish. I'm at Rainbow
14 Babies and Children's Hospital in Cleveland and
15 Director of the Rainbow Center for Pediatric Ethics,
16 and PI for our COG activities.

17 DR. SMITH: Malcom Smith, Head of the
18 Pediatrics Section of the Cancer Therapy Evaluation
19 Program at the NCI.

20 DR. BERNSTEIN: Mark Bernstein, Pediatric
21 Oncologist at the University of Montreal and a member
22 of the Children's Oncology Group.

1 DR. STEWART: Clinton Stewart, Department
2 of Pharmaceutical Sciences, St. Jude Children's
3 Research Hospital, Memphis, Tennessee.

4 DR. LEEDER: Steve Leeder, Clinical
5 Pharmacology at Children's Mercy Hospital in Kansas
6 City.

7 MS. RELING: Mary Relling, also
8 Pharmaceutical Sciences, St. Jude's Children's
9 Research Hospital in Memphis.

10 DR. ROWINSKY: I'm Eric Rowinsky. I'm the
11 Director of Clinical Research at the Institute for
12 Drug Development of the CTCRC in San Antonio, Texas.

13 DR. GOODMAN: I'm Steve Goodman. I'm in
14 the Division of Biostatistics in the Department of
15 Oncology at Johns Hopkins School of Medicine.

16 DR. KORN: Ed Korn, Biometric Research
17 Branch, National Cancer Institute.

18 DR. GEORGE: Stephen George, Duke
19 University Medical Center, also Group Statistician for
20 COGB, member of ODAC.

21 DR. BOYETT: James Boyett from St. Jude's
22 Children's Research Hospital, Chair, Biostatistics.

1 DR. PRZEPIORKA: Donna Przepiorka, Center
2 for Cell and Gene Therapy, Baylor College of Medicine,
3 and member of ODAC.

4 CHAIRMAN SANTANA: Victor Santana,
5 Pediatric Oncologist from St. Jude's Hospital. I need
6 to inform people that I did not select this Committee.
7 So the representation from St. Jude is purely by
8 chance.

9 DR. FINKLESTEIN: Jerry Finklestein,
10 Pediatric Oncologist, UCLA, and Long Beach Memorial
11 Medical Center in California.

12 MS. ETTINGER: Alice Ettinger, pediatric
13 nurse practitioner at St. Peter's University Hospital
14 in New Jersey.

15 DR. WEINER: I'm Susan Weiner. I'm a
16 patient advocate. I was a parent. I'm President of
17 the Children's Cause.

18 DR. PELUSI: Jody Pelusi. I'm an oncology
19 nurse practitioner at the Phoenix Indian Medical
20 Center, and I sit today as the consumer
21 representative.

22 DR. REYNOLDS: Pat Reynolds, Children's

1 Hospital, Los Angeles, Hematology/Oncology.

2 DR. COHN: Sue Cohn, Children's Memorial
3 Hospital in Chicago.

4 MS. KEENE: Nancy Keene, patient advocate.

5 DR. ADAMSON: Peter Adamson, Children's
6 Hospital, Philadelphia; Head of the Children's
7 Oncology Group, Developmental Therapeutics.

8 DR. HIRSCHFELD: Steven Hirschfeld, FDA
9 Division of Oncology Drug Products, CDER.

10 DR. PAZDUR: Richard Pazdur, Division
11 Director, Division of Oncology Drug Products.

12 DR. GOOTENBERG: I'm Joe Gootenberg. I'm
13 the Center for Biologics, Oncology, Pediatric
14 Oncology.

15 CHAIRMAN SANTANA: Okay, well, thank you
16 to everyone and welcome.

17 I will now pass on the microphone to Dr.
18 Pazdur for some very brief welcome comments, and then
19 on to Dr. Hirschfeld.

20 DR. PAZDUR: As Victor stated, this is the
21 fourth meeting of the Pediatric Oncology Subcommittee,
22 and I just want to reiterate that this emphasizes a

1 commitment of the Division to looking at development
2 of pediatric drugs in oncology.

3 Not only have we had four Subcommittee
4 meetings, but we have had an effort to promote
5 pediatric oncology by hiring additional pediatric
6 oncologists within the Division to, hopefully, review
7 pediatric applications and form an improved dialog
8 with the oncology community, both the pediatric
9 oncology community, academic pediatric oncology
10 community, as well as the industry representatives
11 that deal with pediatric drugs.

12 I think that this will hopefully be a
13 longstanding discussion and a longstanding
14 Subcommittee, and we have plans for this to be a
15 continuing effort to have this dialog with the
16 pediatric community in general.

17 Really those are the only brief words that
18 I have, and I will turn over the podium to Steve.
19 Steve?

20 DR. HIRSCHFELD: Good morning. I'm
21 Commander Steven Hirschfeld, U.S. Public Health
22 Service, Pediatric Oncologist.

S A G CORP.

202/797-2525

Washington, D.C.

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1 I also wanted to welcome everyone to this
2 meeting. What I wanted to briefly touch on is
3 rationale for why we are here at this particular
4 meeting, which has to do with the application of the
5 Pediatric Rule, but to understand the Pediatric Rule,
6 we have to put it in context.

7 Clinical research, at least that's been
8 recorded, has been occurring for the past
9 approximately 2,400 years. The first clinical
10 experiment that was recorded, at least in Western
11 history, was Hippocrates, who was examining a man with
12 a broken skull and poked around, in anticipation of
13 Sheldon Penfield, and wanted to see which parts of the
14 body were going to move. Hippocrates realized the
15 implications of what he was doing and made a statement
16 that: Research should only be carried out to the
17 benefit of the patient.

18 That was then codified in the term "primum
19 non nocere," "do no harm," but Hippocrates didn't
20 actually write his work. It was written by his
21 students, and that's probably why it came out in
22 Latin.

1 So children have been involved in clinical
2 research over the centuries. Children were the first
3 participants in vaccinations, in intravenous therapy
4 for cholera about 150 years ago, in x-rays, in the
5 development of prophylactic antibiotics, in
6 endotracheal intubation. In fact, almost every
7 procedure -- general anesthesia, isolation wards --
8 has been first done in children.

9 Children were also involved in the very
10 first randomized clinical trials in oncology at the
11 National Cancer Institute in the 1950's. Also, the
12 first studies which examined the use of adjuvant
13 chemotherapy were done on children. There are many
14 other firsts that were done using children.

15 Nevertheless, the therapies to address the
16 health needs of children did not follow directly, and
17 it was through the use of public events involving
18 children that the founding principles of modern food
19 and drug law were established. It was antitoxin
20 contamination, which led to the passage of the
21 Biological Protection Act in the United States, which
22 was the first one in recorded history, at the turn of

1 the 20th century. All these phenomena are 20th
2 century phenomena and not prior.

3 It was a scandal that was published in
4 Collier's Weekly of the poisoning of children through
5 opiates in an elixir which was meant to calm colic
6 which led to the establishment and the signing of the
7 Drug Protection Act by Theodore Roosevelt.

8 It was the poisoning of children and
9 adults by tainted sulfanilamide that led to the
10 passage of the Food and Drug Act, the initially act,
11 which established the principles of safety and
12 labeling.

13 Then in 1962, again, a scandal involving
14 children not in the United States, but globally, where
15 children of mothers who took thalidomide had birth
16 defects, led to the passage in 1962 of the Amended
17 Food, Drug, and Cosmetic Act, and that established the
18 principle of efficacy.

19 Although children played a critical role
20 in the process of establishing protections for
21 research, the children were not the direct
22 beneficiaries. Many therapies were not made available

1 for children.

2 May I have the next slide?

3 The paradigm for pediatric development was
4 as an afterthought to adult drug development. There
5 are typically pre-clinical studies which led to adult
6 studies and then would follow with pediatric studies.
7 What we would like to examine is a new paradigm to see
8 if there could be development which could be
9 concomitant pre-clinical studies which will lead to
10 concurrent development of adult and pediatric studies
11 or perhaps, if conditions warranted, pre-clinical
12 development, which would lead immediately to pediatric
13 development and then adult studies.

14 Next slide. It wasn't until the last
15 decade that there were federal initiatives put into
16 place to attempt to correct the inequities which were
17 termed "children as therapeutic orphans" during the
18 1970's and 1980's. In 1994, there was a rule enacted
19 which attempted to lower the threshold for achieving
20 pediatric labeling for drugs, and it was a voluntary
21 effort.

22 Unfortunately, it didn't have the

1 anticipated success. So two other approaches were
2 established. One was a section of the Food and Drug
3 Modernization Act of 1997, which established an
4 incentive program.

5 Next slide. And this incentive program,
6 which we will not discuss further today, but just to
7 place today's discussion in context, allows an
8 extension of six months to the exclusivity, whether it
9 is patent or some other licensing exclusivity, to a
10 company. It has been a wonderful success in terms of
11 stimulating pediatric research.

12 There is no linkage between the adult and
13 the pediatric indications. It is a voluntary program.
14 A sponsor may only proceed when receiving a written
15 request from the FDA, and in oncology, as we have
16 discussed publicly previously, it can be approached by
17 a Phase I, followed by portfolio Phase II studies.

18 In the Oncology Division we have issued
19 over 20 written requests of which approximately 17
20 have studies already underway. We consider this a
21 highly successful effort and commensurate with the
22 overall effort in the FDA, of which there are over 200

1 written requests, hundreds of studies underway, and
2 there are over 40 products that have been granted
3 exclusivity extensions.

4 In addition to this incentive program,
5 there's a mandate program -- advance, please -- which
6 is the 1998 Pediatric Rule that states that pediatric
7 studies must be done if the indication for an
8 application under review can be found in children and
9 a therapeutic advance or widespread use are
10 anticipated, and both these terms are explained in the
11 preamble to the regulation.

12 It applies to drugs and biologicals. If
13 the indication does not apply to children, a waiver
14 can be granted. The default position is that the rule
15 is applied and a waiver must be requested. However,
16 recognizing the biological differences in some classes
17 of disease, there are automatic waivers, and, in
18 particular, now in oncology the diseases which are
19 common in adults such as breast cancer, colon cancer,
20 lung cancer, prostate cancer, receive automatic
21 waivers.

22 What we examined in previous discussions

1 is the circumstances of when the rule may apply. What
2 we would like to examine today is, how should we apply
3 the rule? So the general question for the Committee
4 is: Given that circumstances that trigger the rule
5 have already been invoked, how should the 1998 rule be
6 applied? That is the particular charge which we would
7 like you to address during the course of the day.

8 I would like to conclude with some
9 acknowledgments. I would like to, first of all,
10 acknowledge our Division Director, Dr. Richard Pazdur,
11 who when he came to the FDA had an approach to
12 pediatric oncology akin to W.C. Fields' approach, but
13 since then has become exemplary and outstanding in his
14 commitment to the development of therapies for
15 children with cancer.

16 I would also like to acknowledge some
17 visitors who have come from Europe particularly for
18 this meeting as observers: Dr. Gilles Vassal from the
19 Institut Gustave Roussy; Dr. Francesco Pignatti from
20 the European Medicinal Evaluation Agency, the EMEA,
21 and Dr. Anne Mathieu Boue from the Agence Francaise de
22 Securite Sanitaire des Produits de Sante, which is the

1 French equivalent of the FDA. We'll see how that
2 comes out in the transcript.

3 (Laughter.)

4 And, lastly, but not least, I wanted to
5 acknowledge Kimberly Topper, who did the
6 administrative equivalent of leaping onto a galloping
7 horse and has been refreshingly pleasant and
8 professional, and because of her own personal
9 qualities, has brought to the preparations for this
10 Committee a depth of understanding and a particular
11 sensitivity that we all appreciate. So we thank you,
12 Kimberly.

13 CHAIRMAN SANTANA: Steven, I also do want
14 to echo some of the comments that you made that I
15 think I personally, from the other side of the table,
16 have noted a greater sensitivity and interest on the
17 part of the FDA in addressing issues in pediatric
18 development. So I also want to publicly recognize the
19 efforts that you and Richard and the other members of
20 the Agency have to this revival of interest in this
21 area that I think ultimately will benefit both our
22 patients and clinical investigation.

1 With that, I want to go ahead and dedicate
2 some time to an open public hearing. If there is
3 anybody in the audience that wishes to address the
4 Committee, I invite you now forward. There's a
5 microphone here in the middle of the room. Please
6 identify yourself by name or any affiliation or any
7 conflict of interest. So I now offer that opportunity
8 to the public.

9 (No response.)

10 CHAIRMAN SANTANA: If there's nobody in
11 the public who wishes to address the Committee, we
12 will move forward.

13 The first point of presentation and
14 discussion, Eric Kodish from the Ethics Center for
15 Children at Rainbow's, will address the Committee.
16 Eric?

17 By the way, there are some handouts that
18 you should all have in front of you.

19 DR. KODISH: Good morning. Thank you.
20 Thank you, Dr. Santana. Nice to see you again, and
21 thank you to the FDA and especially to Dr. Hirschfeld
22 for inviting me here.

1 I am really pleased to be able to start a
2 session with some discussion of ethics. I think it is
3 where we should start. My remarks are going to be
4 divided into four parts. I am going to talk at the
5 beginning about some basic principles of pediatric
6 ethics. I am going to share some data with you from
7 our own research on informed consent in pediatric
8 oncology. I am going to move then to some specific
9 discussion of research ethics in pediatrics, and
10 conclude with a few comments on the special ethical
11 issues that relate to developmental therapeutics.

12 There we go, slide show. And the next
13 slide.

14 The Academy of Pediatrics, in its vision
15 statement, suggests that children are both vulnerable
16 and symbolic of our legacy. This slide I think
17 captures a lot of what we need to think about when we
18 think about pediatric ethics. So I show it.

19 The next slide shows some of the
20 principles of ethics, and beneficence is listed in red
21 because, in my view, pediatric ethics really comes
22 down to beneficence. That is not to undermine the

1 importance of the other principles. Justice, for
2 example, is often overlooked when we think about
3 medical ethics and pediatric ethics. An example of
4 the importance of justice would be the reason that we
5 are here today, which is, in my view, to give voice to
6 children who are a politically avocal audience. We
7 need to speak for them.

8 So to advocate for justice for children,
9 we need to get access for new medications for
10 children. As Steve's original comments pointed out,
11 children have long been left behind in this process.

12 When we think about beneficence, we need
13 to think about both individual beneficence and
14 collective beneficence. When I say "collective
15 beneficence," I mean for the good of all children or
16 of all people.

17 The next slide shows a little bit of what
18 I think is the difference between medical ethics when
19 it comes to general ethics and pediatric ethics.
20 Over the past several decades, autonomy has become the
21 dominant principle in adult medical ethics that's
22 derived from this principle of respect for persons,

1 and it is translated into an emphasis on informed
2 consent as being really the key issue. So that
3 competent adults can make their own decisions.

4 Pediatrics ethics is different because
5 beneficence I think needs to be the dominant
6 principle, and this is individual beneficence. The
7 best interests of the child is really the first and
8 most important issue in pediatric ethics, and I would
9 argue in research ethics for children, too.

10 The next slide. So the geometry of
11 pediatric ethics looks a little bit different than the
12 geometry of other bioethics. What you see in this
13 slide is my view of that with the child at the top of
14 the triangle, quite intentionally, and often a
15 triangular set of relations between parents and
16 clinicians. For our purposes today, you might want to
17 substitute the word "investigator" on your right for
18 clinicians. I think many of those who are doing
19 individual drug trials in children are clinician
20 investigators, and parents are an important part of
21 this decisionmaking process. So we will refer back to
22 this slide as my talk goes on.

1 The next one. There are two common
2 questions that come up in pediatric ethics committee
3 meetings, I think in IRB deliberations, and in general
4 ethics discussions in pediatrics. The first is, what
5 should we do? Should a particular therapy be given?
6 Should a particular child be enrolled in a study?
7 That is a beneficence sort of decision. The other
8 sorts of questions that come up are, who should make
9 a consent decision? That is a sort of a procedural
10 one on the bottom versus a substantive question on the
11 top.

12 Again, having revealed my bias early, I
13 think beneficence is really the most important
14 question; that is, what should be done for a
15 particular child? Sometimes we need to recognize that
16 the answers are incompatible. That is, the question
17 of what should be done, what is best for a child in
18 the view of a physician, an ethics committee, a nurse,
19 may be different from who gets to decide. I think too
20 often we come down on the question in pediatrics of
21 who makes the decision. So I would like us to focus
22 more often on this question.

1 Next. This is an important point.
2 Informed consent in some ways is a meaningless concept
3 in pediatrics. It is really parental permission and
4 assent, which I will mention in a bit, that come down.
5 The autonomous authorization of adults on their own
6 behalf is more robust -- that is, morally more
7 relevant -- than permission for children by a proxy or
8 surrogate, and the Academy, again, says this very
9 nicely, I think. The pediatrician's responsibilities
10 exist independent of parental desires or proxy.

11 Next slide. So parental permission is not
12 the moral equivalent of informed consent. It is
13 important, but it is not the same thing as consent.
14 Surrogate decision is less authentic, and that is the
15 primary reason. People, in making proxy decisions,
16 whether it is a parent or a physician or an IRB, may
17 want to think about two different standards of
18 decisionmaking, best interest versus substituted
19 judgment.

20 Next slide. Substituted judgment, again,
21 is derivative from the respect of autonomy, and it is
22 when a subjective decision is made on behalf of a

1 child; the decisionmaker tries to put themselves in
2 the shoes of the child and make a decision based on
3 what that child would want, as opposed to a best
4 interest, which is more of a mathematical calculation
5 of risks and benefits for the general individual. It
6 is more based on this idea of beneficence.

7 This is just to say that there are two
8 different theoretical ways of making decisions on
9 behalf of children. I think in practice we use an
10 admixture of them all the time without even
11 recognizing it. Those of you in the audience who have
12 taken care of children with cancer can, I think,
13 probably remember kids that you have cared for where
14 you were trying to make a decision for them, and part
15 of what you were thinking had to do with how that
16 child seemed to be at the time, what they were
17 feeling, what it would be like to be them. That is
18 more of a substituted judgment sort of decision as
19 opposed to maybe the more detached clinical
20 decisionmaking, which is over here.

21 Next slide. So I alluded a minute ago to
22 the assent of the child, and informed consent

1 pediatrics is really a combination of permission of
2 the parent and assent to the child in cases where the
3 child is old enough to assent. It is important to
4 recognize that for many children with stage four
5 neuroblastoma, for example, they are too young to even
6 be involved in this, and then you are left without
7 this sometimes important part of the equation.

8 On the other hand, teenagers with Ewing's
9 sarcoma or rhabdomyosarcoma, this is a critically
10 important issue, and I will talk about that in the
11 next couple of slides.

12 There are two different -- next one,
13 Steve; thank you -- two different ways of thinking
14 about assent also: a clinical definition and a
15 research definition. The clinical definition I am
16 going to show you here is from the Academy's Bioethics
17 Committee, and the elements are very analogous to the
18 moral elements of informed consent for adults. An
19 awareness of the nature of a child's condition is
20 required. The child needs to know what to expect with
21 tests or treatments -- again, this is clinical --
22 under assessment that the child understands, including

1 an assessment of whether there is undue pressure to
2 accept or assent, and, finally, soliciting an
3 expression of the child's willingness to proceed.

4 Before you go to the next slide, I just
5 want to point out this asterisk, and the next slide
6 shows that in the clinical context we need to note
7 that no one should solicit a patient's views without
8 intending to weigh them seriously. This is a morally
9 very important issue.

10 When a child will have to receive medical
11 care, despite his or her objection, the patient should
12 be told that fact and should not be deceived. In
13 fact, many have argued that the child should have an
14 apology coming to them after this is done in the
15 clinical context. An immunization for a young child
16 might be an example of this sort of thing going on.

17 The next slide is the research definition
18 of assent from the federal regulations, and it is a
19 child's affirmative agreement to participate in
20 research. Mere failure should not, absent affirmative
21 agreement, be construed as assent. This is a
22 critically important slide because it shows the

1 difference between assent in the clinical context and
2 in the research context. That is, in the clinical
3 context it is reasonable to override a dissent of a
4 child sometimes. In the research context I'm not
5 quite sure it ever is.

6 Next slide. So research is
7 supererogatory; that is, it is an optional thing.
8 Assent/dissent should be determinative in the research
9 context, but not the clinical context. There probably
10 should be veto power for all three moral actors, as I
11 showed on the triangle, in the research setting. For
12 all studies, I think, the older the child, the more
13 ethically justifiable the study is if assent is
14 provided.

15 Now many of you are probably thinking,
16 well, what about a situation where there's overlap
17 between research and clinical care? Certainly those
18 situations exist. Those are very difficult cases. In
19 those situations I think the real question gets to be,
20 what are the alternatives for that child at that point
21 in time? We will get into that a little bit later in
22 the talk.

1 Next slide. This is part two of the talk,
2 where I am going to share with you some data that we
3 have been collecting with funding from the National
4 Cancer Institute to look at informed consent for
5 childhood leukemia randomized clinical trials for
6 newly-diagnosed patients. Obviously, this is our most
7 common disease in pediatric oncology, and we have been
8 really grateful to the NCI for the opportunity to look
9 at informed consent in a very rigorous way. I am just
10 going to share a little bit of what is a huge and
11 fascinating dataset this morning.

12 We have been observing an audiotape in the
13 consent process for children that are recruited to
14 RCTs in the legacy group, the children's cancer group,
15 and we have been interviewing parents and getting
16 reports from clinicians. Here's what we have found in
17 a nutshell:

18 The trial is well-explained to parents.
19 We have good evidence that, with rigorous coding rules
20 that I won't go into this morning, clinicians are
21 explaining the trials to parents in a great amount of
22 detail. Many parents do not understand their choice

1 about the clinical trial. That means they don't
2 understand that it is even a choice whether or not
3 they go on study or not. About 32 percent of parents
4 don't understand that, and this is an "n" of 108
5 parents that we have analyzed. It is a pretty big
6 sample. Fifty percent of parents don't understand
7 that their child will be randomly allocated to receive
8 treatment.

9 Minorities and those in lower social
10 position are at greatest risk for not understanding,
11 and they ask fewer questions during the consent
12 conference. I will show you some data about that.

13 It is important for this meeting to note
14 that the data may not be generalizable in the relapse
15 context, but I think this is a very serious potential
16 concern for the Phase II window studies, where we have
17 newly-diagnosed children. The reason it may not be
18 generalizable to the relapse context is that parents
19 and kids are experienced with the system by that
20 point.

21 Next slide. One of the interesting
22 measures we have used is a standardized validated

1 measure for decisionmaking preference that we have
2 adopted for pediatrics. This has been developed in
3 the adult context, and this shows a decision choice
4 that parents make in the interviews that we do with
5 them after the consent process, ranging from up here
6 to the doctor gets to make all the decisions, to down
7 here I get to make all the decisions; in the middle is
8 a completely shared responsibility, and then there are
9 No. 2 and No. 4 variations on that, with shared but
10 more emphasis to doctor up here, more emphasis to
11 parent down here. The reason I show this is that I
12 think decisionmaking is really the critical ethics
13 issue that we're here to talk about today.

14 The next slide shows data from our 108
15 parents, and I think it is quite interesting, the No.
16 1 choice, of course, is a complete equal sharing of
17 decisionmaking, but what I want to point out is to
18 your left on this slide this group of parents who in
19 general prefer doctors to have a little more power in
20 the decisionmaking, and only one parent out of our 108
21 said, "I get to make the decision." So I think this
22 is a context where parents really do want help from

1 physicians and nurses in making the decision, their
2 hard decisions.

3 Next slide. This is the number of
4 question data, and what we found in the numbers of
5 questions that parents asked during informed consent
6 is that there is a very wide standard deviation; that
7 is, we have some conferences where there's 150
8 questions and some conferences where there's 2.

9 This shows all cases by social class.
10 This is the Hollingshead Index of Social Position for
11 the social scientists in the audience. This is higher
12 social class; this is lower social class, and you can
13 see that there is a real dropoff in minority parents,
14 but also an overall dropoff by social class in the
15 numbers of questions that get asked.

16 Thank you. The next slide, my
17 statistician suggested that we handle this by looking
18 at the log of parent questions to help narrow that
19 standard deviation, and we have run a ANOVA on that
20 that shows a very significant decrease in the number
21 of questions for all cases as social class goes down.

22 Parents asking questions is a symbol, but

1 also an important way of getting information for the
2 parents. So I think question-asking is a key
3 variable, and we will be looking in the future at ways
4 to increase the number of questions that parents ask.

5 The next slide. That is all the data I
6 wanted to show this morning. I am going to get now to
7 some comments on research ethics specifically.

8 The pediatric research ethics has a
9 fundamental problem with the Nuremberg Code, if one
10 takes it literally. The first precept is that the
11 voluntary consent of the subject is absolutely
12 essential, meaning that the person involved should
13 have legal capacity to give consent.

14 The next slide shows rhetorically maybe
15 that we have a problem. If the answer is, no, we
16 can't adhere to Nuremberg, then children as a group
17 will suffer. I think the answer needs to be, yes, and
18 then the question is, how can children be adequately
19 protected in studies?

20 The next slide shows three ways that we
21 can do this. We can respect the principle of
22 Nuremberg and still do pediatric research. We can use

1 parents as surrogates, which I have said is parental
2 permission. We can involve children in the decision,
3 which is assent, and we can provide some societal
4 protection. The most common way of doing this at
5 least is IRB approval. I am not sure that the media
6 provides much societal protection, but some might
7 argue that those sorts of exposes would also provide
8 societal protection. Certainly the government
9 agencies like FDA can provide societal protection, and
10 that is important.

11 As a research ethics investigator, I would
12 have to say that this is a much more powerful,
13 effective way of protecting children than these two
14 things. That doesn't mean that these are unimportant.
15 I think we need to make these better, but right now is
16 the effective way that we protect children.

17 Next slide. So how do IRB's look at
18 pediatric research protocols? Well, as most of you
19 know, Subpart D of the federal regulations requires
20 that children have additional protections; that
21 children who are recruited to studies need to fall
22 into one of four categories in order for IRB's to have

1 even the ability to approve protocols.

2 The fact that a child falls into one of
3 these four categories, or a protocol does, I should
4 say, doesn't mean that an IRB has to approve the
5 protocol, but those of you who have submitted these
6 forms to IRB's know that you need generally to check
7 off one of these boxes.

8 I think for today's purposes it is 46.405
9 that is the key category, and this is research
10 involving greater than minimal risk, but has the
11 prospect of direct benefit to the individual subject.
12 IRB's can approve this kind of research if the risk is
13 justified by anticipated benefit to the subject, if
14 the risk/benefit ratio is less than or equal to the
15 alternatives -- again, alternatives is a key -- and if
16 parental permission and assent is obtained.

17 I just want to point out the benefit to
18 the subject here, because the next slide shows that
19 risk in research ethics always means risk to the
20 subject, but benefit may include several different
21 kinds of benefit. In adult studies all of these
22 benefits can be added together to justify the risk.

1 In pediatrics we are limited to benefit to
2 the subject, but other benefits may include those to
3 other patients, to society. For example, the number
4 of child life-years that are saved in pediatric cancer
5 is astounding when you add up the benefits of our
6 therapy economically. Benefits to investigators or
7 sponsors are important benefits that may accrue in
8 these studies. So in pediatrics we are limited to
9 thinking about these benefits if we are going to
10 follow the regs.

11 Next slide. This is probably the most
12 important slide in my talk, and it is maybe the
13 simplest slide, but I think what we are talking about
14 is balancing the best interest of the child-subject
15 against science which is there to benefit others. If
16 we find ourselves ever getting to the point where this
17 end of the teeter-totter is getting a little bit
18 heavier than this, and the best interests of the child
19 aren't represented as the most important feature, then
20 I think we are getting into trouble. So if I could
21 propose a line that we ought not cross, that is the
22 line.

1 The next slide. This is part four of the
2 talk, which gets to some of the specific issues in
3 developmental therapeutics. Phase I oncology studies
4 in general and in children, I think, for these studies
5 there exists a controversy over therapeutic intent.
6 I think that most of the developmental therapeutics
7 community truly has therapeutic intent. I think that
8 most practicing oncologists have therapeutic intent
9 when they deliver therapy in a conventional Phase I
10 study.

11 There are, however, IRB members, medical
12 ethicists out there who hotly dispute the idea that
13 there can be any therapeutic intent when the chance
14 for benefit is 5 percent, 10 percent, those sorts of
15 things. I think that we are best to stay away from
16 language of intent because in ethics I think intent is
17 always a difficult topic. It is hard to know how to
18 objectively evaluate intent. So I avoid this
19 controversy by moving away from it.

20 I think another one we want to move away
21 from is commensurate experience. There is a category
22 that some of you know, 406, where commensurate

1 experience is allowed to justify research with a minor
2 increase over minimal risk if there is no prospect of
3 benefit to the subject. Now I am talking like a
4 regulator, but you need to be conversant with this
5 language.

6 I think that this category doesn't really
7 fit Phase I research, and there is a tendency for this
8 sort of thinking to creep into what should be 405
9 research; that is, research with the prospect of
10 benefit to the child. It is not a valid justification
11 that children have already been through chemo, so that
12 it is okay to expose them to one more agent. If
13 anything, I think, quite the opposite, we need to
14 protect children from that sort of mentality.

15 So prospective direct benefit to the child
16 is the ethical and the regulatory key to Phase I
17 studies. I think there are problems defining benefit,
18 and I think it needs to be more than a tumor
19 measurement. I think strategically one of the reasons
20 that IRB members and ethicists are concerned that 5
21 percent or 10 percent isn't enough to be benefit is
22 that they don't always see the other sorts of benefits

1 that children may get from participating in these
2 studies.

3 I think the alternatives is a key feature,
4 and the next slide shows some of the alternatives that
5 relapsed patients with a poor prognosis and their
6 parents may face: a Phase I option, an option for
7 alternative or complementary medicine, and the option
8 of hospice care. This is not to say that these are
9 separate pathways. There is the potential for
10 combination therapy, if you will.

11 The next slide, again, just briefly shows
12 that I think for many individuals these are pathways
13 to hope; these are ways of looking for hope, and I
14 think hope is a clinically, ethically, fundamentally
15 important issue here.

16 Next slide. So subject selection is not
17 a controversy for Phase I in children, unlike studies
18 that some of the PPRU's may be doing, where you can
19 decide for a new antibiotic whether subject selection
20 should be in a sick group or a well group, and you can
21 talk about financial reimbursement. I think for Phase
22 I cancer studies we are not dealing with the subject

1 selection controversy. I think it qualifies as
2 research with the prospect of direct benefit, and I
3 think the potential for benefit mitigates, but it does
4 not eliminate, the need for protection from research
5 risk. I don't think we are going to be able to get
6 around this. We need to view these children as
7 needing some sort of protection from research risk.

8 The next slide has a few comments about
9 alternative medicine. I have great concerns about the
10 vulnerability of children to alternative medicine
11 practitioners, and I think that it is a very prevalent
12 phenomena, obviously under-recognized. It is harder
13 to find exactly what alternative medicine is.

14 I sit on a Task Force for the Academy on
15 Complementary Alternative Medicine, and we have spent
16 lots of time trying to figure out exactly how to
17 define CAM. It is a very difficult issue to define.
18 There are differences for kids, though, in that,
19 again, this is parents generally giving the substances
20 to their children that may not be innocuous
21 substances. We have an obligation, as Steven said, to
22 primum non nocere, to prevent harm first. We need to

1 study these, and I think we are doing a better job
2 with that now. Most importantly, we need to
3 communicate with families at the time of informed
4 consent for these studies about whether and what sorts
5 of alternative treatments these kids are taking.

6 Next slide has a few comments about
7 hospice. It is not incompatible with a Phase I study.
8 I think we need to be very proactive. Hospice care is
9 underdeveloped in children, and we need to advocate
10 for the benefits of hospice care for children with
11 cancer. I think most ethicists would expect that
12 Phase I investigators and hospice docs would be sort
13 of separate sorts of individuals, but I don't think
14 that necessarily has to be the case.

15 Hospice, when done right, I think, rejects
16 the idea of a right way to die. It allows for each
17 child and family to have the unique circumstances. I
18 think it needs to be part of the consent process for
19 Phase I studies. I think that is a responsibility
20 that we have to dying children.

21 Phase II window designs, as I told Dr.
22 Smith earlier, I look forward to the conversation on

1 this. I think the subject selection here is more
2 controversial. We need to define how poor is poor
3 prognosis, and context here is everything. That is to
4 say, a newly-diagnosed patient and their family is
5 going to view the opportunity to be in a trial very
6 differently than someone who has been through therapy
7 and relapses six months or a year later.

8 Phase II windows also qualify as research
9 with the prospect of direct benefit to the subject,
10 but it may not be as good as the alternatives, that
11 is, multi-agent therapy, in allowing IRB's to approve
12 this sort of research. IRB's should not be approving
13 this research if they don't think that it is as good
14 as the alternatives, that risk/benefit ratio I showed
15 earlier.

16 I think that the new therapeutic paradigms
17 may change the ethical acceptability of these studies.
18 The potential for synergy between some of the newer
19 approaches and the older approaches is something that,
20 as an oncologist, I think has a terrific amount of
21 potential. So I don't want to eliminate the
22 possibility of Phase II window designs as the science

1 changes, but I think that there are some serious
2 problems.

3 Next slide has my conclusions. The first
4 is that good ethics starts with good science. That is
5 to say, if the science is bad, if it's not an
6 important issue, if it doesn't have the potential to
7 help children in this context, it is unethical; it's
8 a waste of resources; it's putting children at risk.
9 There are a lot of reasons that make it unethical.

10 That does not mean necessarily that good
11 science is inherently ethical. I think that some
12 research with tantalizing potential may need to be
13 rejected on ethical grounds.

14 The accelerated drug development research
15 I think needs to proceed, but I think we need to be
16 very careful to build the system in such a way that we
17 get long-term follow-up data, that we need to use
18 stopping rules in a careful way, and DSMB's, and that
19 we have an obligation from justice, the principle of
20 justice, to proceed at a faster pace.

21 The next slide, and final one, makes the
22 paradoxical conclusion that children are both

1 vulnerable subjects in need of protection and a
2 neglected class that needs better access to the
3 benefits of research.

4 Thank you for your attention.

5 (Applause.)

6 CHAIRMAN SANTANA: Thanks, Eric.

7 We now have plenty of time for questions
8 for Eric and discussion.

9 DR. HIRSCHFELD: First, I want to thank
10 Rick for that thorough and thought-provoking summary
11 of the key issues.

12 I would like to note that the regulations
13 that Dr. Kodish cited apply only to Health and Human
14 Services-funded research, but I will also let you know
15 that an adaptation of those regulations has been
16 undertaken by the Food and Drug Administration; that
17 they have been available for public comment over the
18 last several months, are now in the process of being
19 finalized. So that all research that comes under FDA
20 regulation would have the benefit of having these
21 regulations apply to them.

22 I have a question for Rick, though.

1 Another triangle that is often stated in the research
2 paradigm is that there are three components to
3 participate in research. There's the risk, the
4 benefit, and the consent. Ideally, those are all
5 vested in the same person, but in pediatric research
6 the consent is often taken out in a formal context,
7 although there are assent procedures, and the benefit
8 may be taken out, too. So the child participating in
9 a study is left only with the risk.

10 I would like to ask you if you could
11 comment at any time during the course of the day's
12 discussion, the earlier in the development cycle that
13 we are looking at a particular potential therapeutic
14 product, the less we know about the risk and the less
15 we know about the benefit. If you could give us some
16 guidance as to how we might approach these difficult
17 issues in examining trial designs?

18 DR. KODISH: I think risk and benefit both
19 need to be in the equation. So I think with a novel
20 approach one needs to -- and when I say "one," I mean
21 both IRB members and parents and the older kids --
22 needs to take into account the numerator and the

1 denominator of that equation, if you will. So the
2 fact that the potential benefit to the child is also
3 an unknown quantity needs to be factored into the
4 decision.

5 I think an approach that looks only at the
6 risks without looking at the potential to benefit that
7 child is an impoverished way of looking at the
8 situation. I think also that benefits need -- and
9 this is where it gets tricky between the substantive
10 and the procedural issues, if you will -- benefits in
11 some sense can only be defined by that child and their
12 family, because they are unique in the situation. So
13 the meaning to that individual family unit of going on
14 an experimental protocol is something that I am
15 reluctant to say IRB's or investigators get to make
16 those decisions.

17 That is why you need informed consent
18 permission/assent as part of the process. It can't
19 just be that purely objective thing. So I think it is
20 a two-part process, and I think the sequence that we
21 currently use is right, and sequence is important
22 here. That is, IRB's have to approve this first

1 before it gets to parents and kids to make a decision
2 on.

3 Does that help?

4 MS. ETTINGER: I wanted to make a comment
5 and thank you for considering the ethics of children.
6 As a nurse and as a clinicians here, I think we know
7 that we have always tried to include the children in
8 age-appropriate language to explain whatever is
9 happening to them, including their treatment, their
10 side effects, what the disease is about. It's always
11 been a struggle for all of us who have ever been in
12 that position.

13 I have also noticed through the years that
14 there are many more handouts and resources available
15 for that. I think that is really important, many of
16 them having been developed either on a local level or
17 on a national level. I think that that has made it a
18 little bit easier.

19 I have also noted that culturally, as well
20 as socioeconomically, but culturally there are some
21 cultures that really put obstacles in the way of the
22 clinician in terms of discussing what is going on with

1 their children. I have found that through the years
2 that that has been an issue that we work with,
3 particularly I have to say nurses because that is my
4 discipline, but particularly to try to overcome that
5 barrier.

6 I also just want to comment about my
7 experience with hospices. I think that that is
8 something -- I don't know how to overcome that
9 barrier, but I have found that many hospice programs
10 will not allow children to be in the hospice program
11 if they are undergoing Phase I therapy. I think that
12 that's to the detriment of the family and the child.
13 If they are on any kind of medication or whatever,
14 they can't, not even hyperalimentation in some cases.

15 So I think that there are many obstacles
16 that we really do need to overcome.

17 DR. KODISH: Yes. I would like to follow
18 up on that with just a very practical point. My talk
19 suggested that hospice care needs to be part of the
20 discussion for informed consent, but if you are in a
21 context where hospice care is not possible, you need
22 to do your homework first, obviously, before informed

1 consent, and be sure that hospice care is a real
2 possibility for that child.

3 Again, I think we need to advocate as a
4 community of pediatric oncology care providers that
5 hospices need to change these rules. I think many of
6 those situations are adult hospices, and I think the
7 more developed pediatric hospices are pretty
8 comfortable with the idea of children getting anti-
9 neoplastic therapy or supportive care and still get
10 in-services from hospice.

11 DR. GOOTENBERG: Just in terms of
12 definition, from my point of view, in terms of the
13 term for hospice, in that case I don't think that if
14 hospice is failing or if someone is in a situation
15 where hospice is not yet really to where alternative
16 care covers a bigger --

17 DR. KODISH: Right, or hospice philosophy,
18 care, but, agreed; point well taken.

19 Mr. Chairman?

20 DR. GOODMAN: I thought it was a wonderful
21 presentation.

22 DR. KODISH: Thank you.

1 DR. GOODMAN: I am going to ask a sort of
2 provocative question, which won't necessarily reveal
3 what I actually think, but I just wanted to get your
4 thoughts. I will pose it sharply: How can you say
5 that it is ever -- no, I don't want to say "ever" --
6 ever more ethical to give an untested and unproven
7 therapy in a clinical setting as opposed to an
8 untested and unproven agent in a research setting?

9 I mean, the alternative, one alternative
10 you didn't actually explicitly write there -- you had
11 the Phase I and hospice and CAM -- was giving a
12 therapy that, in fact, had never been adequately
13 tested in a controlled way. Its track record had been
14 established in uncontrolled settings because it was
15 impossible to mount administration in a research
16 setting.

17 So I would like you to -- I mean, this has
18 often been commented on in adult situations where
19 doctors say, "It's permissible for me to give the
20 agent to all of my patients, but I have to get special
21 permission when I want to give it to half my
22 patients." So I would like you to comment on that

1 because you focus on the risks of research, but, of
2 course, there are risks of giving agents in a clinical
3 setting, in the absence of research as well.

4 DR. KODISH: Yes, I think the point that
5 you're getting at, I have two responses. One is that,
6 to sort of take your side and the way the question was
7 framed, maybe that ought to be --

8 DR. GOODMAN: I didn't tell you my side.

9 DR. KODISH: I know. But maybe that ought
10 to be considered alternative medicine. That is even
11 more provocative perhaps, but maybe that is the
12 category we ought to shift that into. That's the
13 clinical trial lists answer to the question.

14 I think the other answer is probably
15 better, and the concept actually was coined by my
16 colleague, John Lantos, about neonatology research,
17 and this is the inclusion benefit, the idea that
18 children are benefitted from inclusion in clinical
19 trials and the things that Dr. Murphy of Children's
20 Memorial, things like that, have written that say that
21 perhaps the fact that kids in studies do better needs
22 to be part of the consent process.

1 I personally don't advocate for that in
2 big Phase III randomized trials like the data I showed
3 you for leukemia, but I think in the Phase I setting,
4 as we get more and more experimental, in some ways it
5 becomes safer and safer to be in the research context
6 and less safe to be in the clinical context.

7 I think that the other key issue to talk
8 about here is hope. I think what is being
9 administered, whether it is in the research or
10 clinical context, in many cases is high doses of hope.

11 DR. PRZEPIORKA: Thank you. A very nice
12 talk. I just had one question I wanted to start with,
13 and that has to do with, when would you trigger
14 assent? I mean, according to current guidelines, it
15 is when it is appropriate. How does one determine
16 when it is appropriate?

17 DR. KODISH: Funny you should ask. In
18 about two weeks I have a research meeting on pediatric
19 research ethics where we are going to tackle that
20 specific issue and look at some of the geriatric
21 ethics literature, which has looked at people whose
22 competency level is declining, with the thought that

1 there is sort of some analogy there. That meeting is
2 taking place in two weeks. So I'll probably have a
3 better answer for you in a month.

4 At this point I would say that we don't
5 want to overregulate assent. We certainly don't want
6 to put a specific age on it. We need to rely on
7 clinician investigators to use good judgment, because
8 some children who have had cancer diagnosed at eight
9 and then relapse when they're ten, for example -- I am
10 talking about the hard age range -- will be on sort of
11 accelerated developmental trajectory where they have
12 the maturity of a 17-year-old and should be making
13 that decision primarily themselves. But others, when
14 their disease relapses, they will regress and become
15 infantile almost in some cases. Certainly putting any
16 specific age on it I think is going to be a problem.

17 So I think we need to continue to push the
18 idea of assent as a concept without putting regulatory
19 specifics on it. Many IRB's, I think, around the
20 country now are getting more proactive in requiring
21 assent forms, which is a very interesting move in
22 pediatric research ethics. My personal opinion about

1 that, as a PI, I hate the idea that we need to do more
2 paperwork, but symbolically I think it is important
3 because it requires a second signature; it requires
4 that the investigator at least pay some attention to
5 what is going on in the child.

6 We have data from the big study I showed
7 you that was just accepted in Pediatrics -- it will be
8 published sometime in the next year -- that looks at
9 these cases and looks at what happens when the child
10 is in the room for the discussion, the assent process.
11 What I can tell you about that data is that children
12 are not asking very many questions about the research.
13 They're asking, "Is my hair going to fall out?", "When
14 am I going to go back to school?" Those are the sorts
15 of things that kids themselves want to know.

16 CHAIRMAN SANTANA: I also want to echo
17 some of what Eric said; that I think one has to be
18 careful in this whole process of applying a regulation
19 regarding to assent too strictly because there's so
20 much variability in the patient population, et cetera,
21 their understanding and comprehension.

22 But I think one way to view it is that it

1 is more of an information-sharing process, and then
2 what level of information is shared is the critical
3 factor. But there should always be some sharing of
4 information between two or three parties. It is that
5 level of information and that degree that I think
6 defines when you trigger a written document or when
7 you trigger a fast, hard rule. So that is one way
8 that I have kind of tried to address this issue of
9 assent in my own interpretation.

10 One thing that you did not mention that I
11 would like for you to comment is this concept of
12 viewing assent as a respect for the child in terms of
13 his or her moral development by allowing them to
14 participate in that information-sharing. Then when
15 they become adults, you truly then have the respect
16 for the person in terms of their autonomy. So it is
17 an early process, I guess, of moral development, of
18 weighing in the judgment of that individual, so that
19 ultimately when he becomes an adult, he will have that
20 experience or that capacity to make those judgments.

21 And you didn't comment on that. If you
22 wish to comment, I would appreciate it.

1 DR. KODISH: I'm not sure I can say it any
2 better than you just said it, Victor. The idea is
3 that the 18th birthday is not a magical day when all
4 of a sudden someone wakes up as if an epiphany has
5 occurred and they're an adult. If we don't give
6 children the ability to develop their decisionmaking
7 capacity, we are not nurturing them. So I think you
8 said it right.

9 CHAIRMAN SANTANA: Do you have a comment,
10 Peter? Paul? Where's Paul?

11 DR. ADAMSON: If Mary's here, we'd have a
12 group.

13 (Laughter.)

14 DR. KODISH: She is right across the
15 table.

16 (Laughter.)

17 DR. ADAMSON: I have two unrelated
18 comments. The first has to do with consent and
19 assent, and I think an area that we as pediatric
20 oncologists have to do a better job. Trials are
21 becoming increasingly more complex with more biologic
22 end-points, pharmacologic end-points. I think we need

1 to do a better job in separating out for both parents
2 as well as children what is of direct benefit to the
3 child and what component of research is, in fact, of
4 no direct benefit to the child.

5 In Phase I, I think it is very clear-cut
6 that, when we administer an investigational drug, it
7 is with the prospect of direct benefit to the child.
8 However, when we obtain pharmacokinetic sampling,
9 there is no direct benefit to the child.

10 Oftentimes, although I think we make it
11 clear in Phase I, oftentimes we present studies as a
12 package deal to a family. I think we have to be much
13 clearer, saying, "These are the tests that are
14 important for your child's safety. This is a drug and
15 the risks that we think are going to be of direct
16 benefit, and these are areas that are going to help us
17 learn that in most circumstances are minimal risk or
18 a minor increase over minimal risk, but that are truly
19 a pure research component that's of no direct
20 benefit."

21 I think that is where assent becomes
22 highly critical for a child, because those components

1 should be made very clear to a child, that this is
2 optional; that you don't have to sit here for a day
3 and have your blood drawn.

4 Having said that, in my experience, and I
5 think the experience of others, most children want to
6 help other children, and they are going to agree to do
7 it. But they should absolutely have an affirmative
8 assent that they are willing to do that. I think they
9 derive benefit when they are given that component of
10 assent.

11 My other comment was again related to
12 assent, but one area that I would ask you to clarify.
13 That is, assent is virtually always required for
14 research, whereas it may not always be required for
15 clinical care.

16 I think in pediatric oncology it may be
17 that the two aren't always separable, and the upfront
18 Phase III randomized trials for children with leukemia
19 serve as a good point. Oftentimes what a child will
20 experience in a randomized trial may essentially be no
21 different. Independent of what arm they go on,
22 they're going to experience leukemia therapy.

1 Yes, I think it is important to gain
2 assent, but I don't think in that circumstance
3 necessarily that the assent should be binding. In
4 other words, if a child doesn't assent to go onto a
5 trial, when it is an upfront trial with a prospect of
6 cure, I think it is the parents' consent that will
7 carry the day. We have to be careful saying, well,
8 we're going to get your opinion on this; we're going
9 to weigh it. But, ultimately, for a Phase III
10 randomized trial, it's more, as Victor said, I think
11 more of an informational meeting and to answer
12 questions, and not to gather assent; whereas, in a
13 Phase I study I think assent, in fact, carries a lot
14 more weight and in many circumstances a child's assent
15 may overrule a parent's consent.

16 DR. KODISH: Thank you. Very interesting
17 comments.

18 I am going to get to the second part of
19 your comments first and say that I think it is in the
20 best interest of the child to get leukemia treatment,
21 going back to the Chad Green case that many of you
22 will remember from 20 or 30 years ago. I think that

1 we do have a clinical obligation to act in the best
2 interest of the child that overrides assent.

3 For standard therapy for ALL, I think we
4 need to be very careful with the distinction between
5 randomized clinical trial and standard-of-care ALL
6 treatment for kids. I am sympathetic to the point of
7 view that says research is the best treatment for
8 children with cancer.

9 Personally, I believe that, but, as a
10 matter of public policy, as a matter of the appearance
11 of impropriety or conflict of interest, I think my
12 vote would be to separate those out and say that, if
13 a child dissents to randomization -- let's say it is
14 a 17-year-old who understands randomization and says,
15 "You know, standard therapy is embedded in May of 1961
16 and that's what I want." I think we need to give them
17 that. I really do.

18 I don't think it is a huge loss to the
19 research enterprise, to the best interest of other
20 children, and I think it is a matter of respect for
21 that child. I don't think it happens real often.

22 To reinforce a couple of comments you made

1 in the first part of your remarks, this idea is
2 referred to as bundling of treatment and research
3 issues by IRB's sometimes. Some IRB's like it when
4 these things are bundled, and others like them to be
5 disentangled. I agree with you, it is best to try to
6 disentangle them.

7 I think the issue of risk for that non-
8 therapeutic component is key, and I think a PK study
9 is clearly minimal risk. But if you are talking about
10 an extra tumor biopsy, it is an order of magnitude
11 higher, and the risk needs to be a key part of that.

12 Then to maybe put into other terms what
13 you said about the kids themselves, I think what we
14 want to do is foster altruism for those children. I
15 think, as you said, many children are capable of it,
16 and we want to provide a context where they are able
17 to express that altruism in a way that also allows
18 them to say, "No thanks, I'd rather be on the
19 Internet."

20 DR. GEORGE: I had a question, I guess
21 following up more on this assent issue. You presented
22 data, but wasn't clear from that, did you ask any of

1 the children what they understood about this process?

2 DR. KODISH: Unfortunately, no. Our study
3 design was such that we interviewed parents, but we
4 don't have -- we have observation of children during
5 the time that they are in the room. We know the sorts
6 of questions that they are asking their doctors and
7 their parents, but we haven't interviewed kids.

8 DR. GEORGE: But it is a relevant point
9 for what we are discussing, I think, with respect to
10 assent. It would be very nice to know what kind of
11 things the children are understanding and at what
12 developmental stage.

13 DR. KODISH: Yes, and it is going to be in
14 my competitive renewal application.

15 (Laughter.)

16 CHAIRMAN SANTANA: Dr. Patrick Reynolds.

17 DR. REYNOLDS: You present the dilemma
18 that all of us face in Phase I trials, which is the
19 prospect of benefit, which in the initial dose
20 escalations is arguably extremely slim. At the same
21 time you present the concept of hope.

22 Now given the tight linkage between the

1 child and the parent, what I am not hearing, though,
2 is that this prospect of hope for the parents on a
3 Phase I trial is actually a component of benefit.
4 It's not a benefit to the child, but it is a benefit
5 to the parents. So can't that be part of the
6 equation?

7 DR. KODISH: I mean, you get to a really
8 interesting point in pediatric ethics, which is, do we
9 have a narrow definition of best interest or do we
10 have a more broad definition of best interest? Those
11 of us who would focus on a narrow best interest
12 definition would say that it is only the child, that
13 we can somehow surgically remove the child from the
14 family unit and view them as a separate entity, but,
15 in fact, I think you're absolutely right, children
16 feed off parents; parents feed off children. It would
17 be, I think, incorrect to try to have a narrow best
18 interest definition.

19 I think it is permissible to include the
20 hopes of parents, especially for younger children. I
21 think when it gets to older children, we need to have
22 them a play a more significant role.

1 I don't want that to happen at the expense
2 of suffering for that child, and that is why I say
3 that Phase I investigators need to do a conscientious
4 job in the consent process to talk about palliative or
5 hospice care as one of the alternatives.

6 Recognizing that many parents will come
7 into that conference not wanting to hear a word of it,
8 and that can get ugly, but I think it's important to
9 have that ritual of informed consent.

10 CHAIRMAN SANTANA: Nancy?

11 MS. KEENE: That was a great talk, Rick.
12 Thank you.

13 DR. KODISH: Thanks, Nancy.

14 MS. KEENE: It was a pleasure to listen
15 to, and I wanted to thank you for your last bulleted
16 point under "Conclusions" that included the necessity
17 for long-term follow-up data being collected and
18 analyzed.

19 As you know, because we have known each
20 other for several years, I don't usually use personal
21 anecdotes in settings such as this, but I am going to
22 use one to illustrate the point that I would like to

1 make.

2 I'm the parent of a 10-year survivor of
3 high-risk ALL who has multiple late effects, none of
4 which have generated a single data point. At the
5 institution that treated us, it only checked for
6 recurrence of disease, did not check for late effects
7 of treatment. So we went elsewhere at the end of
8 treatment.

9 However, I called the data manager at that
10 institution because, as you know, I am a big believer
11 in clinical trials, and said, "Tell me what
12 information you need from our subsequent health care
13 providers for the trial." And he said, "Just call me
14 back if she dies."

15 The reason I use -- social skills aside
16 (Laughter), it does illustrate a good point. It
17 illustrates that mortality has been the focal point
18 for quite a long time, and that we need to make a
19 cultural shift, at least for those diseases for which
20 there is a high cure rate currently, to include the
21 concept that late effects, indeed, are part of risk,
22 and that acute risk does not define risk.

1 You could argue that one cannot make an
2 informed consent if you're only notified about acute
3 risks, and if we only collect information on acute
4 risks, we are not collecting the information we need
5 to give people the data they need on which to base an
6 informed consent.

7 So I was the Chair of the first CCG
8 Patient Advocacy Committee and then the Chair of the
9 first COG Patient Advocacy Committee, and we have
10 worked very hard to incorporate mandatory data
11 collection on late effects, with not much success.

12 We scaled that back -- I've been sick for
13 two weeks, and my voice, I'm losing it -- we scaled
14 that back to a request for at least guidelines for
15 known expected late effects of treatment to be
16 incorporated in all new trials. There is a movement
17 toward doing that. That would at least give families
18 and subsequent health care providers information that
19 they need to get necessary follow-up surveillance in
20 the future.

21 So it is just sort of a plea on my part to
22 all of you who are involved in development of future

1 clinical trials that we make this a focus.

2 DR. KODISH: I want to take up one point
3 from that, which is that informed consent in the
4 context of Phase I or Phase II window studies, really
5 I think we have an opportunity to do a much better
6 job. I think parents, from my reading of our own
7 data, are generally in a state of shock, and it is
8 very difficult for parents to make an assessment of
9 the short-term and the long-term issues.

10 I think in the setting that we are here to
11 talk about today there is the opportunity to really do
12 a terrific job with informed consent and trying to
13 think of some of those short-term and potentially, if
14 things go well, long-term issues.

15 MS. KEENE: Can I follow up on that?
16 There are a couple of Phase I trials that I have
17 reviewed the information for and helped to rewrite for
18 CCG that are presented to parents of newly-diagnosed
19 kids. There was one for a radioenhancer for kids with
20 pontigliomas. Those families are at incredible risk
21 for presentation of the information and understanding.

22 As you know, I told you when you were

1 developing that study, I said, I can't wait to see
2 your data, but I'm going to predict that it's parallel
3 universes, that many of the physicians are going to be
4 giving good explanations and many of the families are
5 not hearing, and those that hear, some of them are not
6 going to understand.

7 So I think that in the few situations in
8 Phase I and the Phase II windows studies where
9 families are newly diagnosed it is going to be very,
10 very, very difficult to get a truly informed consent.

11 DR. KODISH: Yes, it's apples and oranges.

12 CHAIRMAN SANTANA: Dr. Cohn.

13 DR. COHN: I was just going to give a
14 followup a couple of speakers ago to Peter's comment
15 about how sometimes some of these studies are bundled
16 in terms of what is truly research and what is of
17 benefit to the child and what's not.

18 I just think that one of the things that
19 we have developed, which I think is a much better
20 informed consent form than what we have seen in the
21 past, is something that we have recently developed in
22 our Neuroblastoma Strategy Committee in the COG, which

1 is that we have a biology consent form now that very
2 much separates out what studies need to be done for
3 clinical purposes, such as NMEC, and which studies are
4 strictly research. Then we have checkboxes that
5 parents and children can actually say, "I agree to
6 this," "I don't agree to this," "I agree to the whole
7 thing," "I only want the NMEC done," or whatever.

8 I think that that is something that
9 probably should be done in more consent forms. I
10 don't think bundling together is necessarily the
11 appropriate way to go.

12 DR. KODISH: Thank you, Sue. I think
13 consent forms have gone up a notch, actually, in my
14 estimation, based on the data that I have collected.
15 I came into the study thinking the consent forms were
16 sort of a waste of time, but they can actually be very
17 helpful tools when done the right way.

18 DR. WEINER: I wanted to thank you, Rick,
19 for a wonderful talk and you, Steve, for leading this
20 discussion today with the consideration of ethics.

21 I think that, though we are discussing
22 matters of public policy, I think that it is very

1 important to understand how that translates into an
2 individual case. So the question of bundling touches
3 on it, and also the issue of conflict of interest.

4 When you presented the triangle in your
5 slide, you said that you listed it as clinician, but
6 you said it could be the investigator as well. I just
7 wanted to point out that there are many, many
8 instances in which these roles are conflicted, and
9 there are many things that can follow from that kind
10 of conflict of role, which may or may not be in the
11 best interest of the child.

12 The fact that we've led off this
13 discussion, the day today with discussion of ethics I
14 think is critical, but I think, to use a cliché, it
15 matters where the rubber meets the road. There may be
16 times when clinical considerations really have to be
17 assigned apart from an investigator's role. I would
18 like to know your comments about that?

19 DR. KODISH: I wish my colleague, Dr.
20 Shurin was here because she's really developed a
21 terrific expertise in these conflict-of-interest
22 issues. My response is that, to the extent that

1 procedural solutions would help, I am in favor of
2 that. I think having the Phase I investigator be a
3 separate individual from the treating physician makes
4 a lot of sense. I think we want to be careful not to
5 leave behind the value of conflict of interest.

6 I think it is especially critical for
7 children with cancer. Look, it is not a big market.
8 We're here at an FDA meeting, and at other FDA
9 meetings I have seen, you know, a very interesting
10 confluence of interests around big markets and
11 potential benefits for patients. We are talking about
12 still an orphan disease essentially, and we need to
13 take advantage of whatever sort of academic/industry
14 collaboration we can get, if it is going to benefit
15 children.

16 I am sympathetic to procedural ways of
17 trying to protect individual children, but I want us
18 to understand the overall context.

19 DR. WEINER: I'm sorry, it is not that
20 particular conflict necessarily that I meant to refer
21 to, because, of course, it can have to do with the
22 need to enroll more patients on the part of an

1 academic investigator or the need for professional
2 advancement or the need to make sure that a protocol
3 is followed to the letter.

4 So those are instances in which there may,
5 indeed, be a conflict between the clinical care of the
6 child and what is important for the research.

7 DR. KODISH: Yes, and I think IRB is
8 really the place where those sorts of things need to
9 be decided because they're so center-specific. So I
10 sort of trust the IRB risk/benefit assessment with
11 risks to the child versus potential benefits to the
12 investigator that you mentioned as being the place
13 where those sorts of decisions are made.

14 DR. COLTMAN: As a parent with an acutely-
15 ill child with cancer, I should be so lucky as to have
16 my child have late effects of treatment.

17 CHAIRMAN SANTANA: Wayne?

18 DR. RACKOFF: Thanks, and I agree this was
19 an excellent opportunity to have a discussion before
20 the facts essentially.

21 I want to follow up on Susan's question,
22 not because it was formulated as a followup, but it is

1 a linked question and it is taking the conflict-of-
2 interest question to the macro level.

3 What we are talking about here today is
4 the application of a rule, the rule of law, and the
5 question is, is it necessary, do you think it's
6 necessary to in some way inform families that a study
7 is being done as part of a mandated rule?

8 It comes back to what I thought was an
9 excellent comment on your summary slide of, we start
10 with good science. It's necessary but not sufficient
11 to make it ethical. We always -- in our informed
12 consents, if it is a corporate-sponsored study, there
13 is a notice of sponsorship and indemnity, and the
14 like.

15 I do not want to add anything, believe me,
16 to informed consent documents, but as we think about
17 application of the rule, do we need to think about
18 information about the rule and how to disseminate it?

19 DR. KODISH: Yes, the reason I hesitate is
20 that it is a very interesting question that I hadn't
21 considered before. My first-blush answer is, no, that
22 that ought not be a necessary requirement of the

1 consent document because it is broad societal policy,
2 I think. The understanding that our society is
3 evolving toward doing better for our children sort of
4 goes without saying. Parents I don't think are going
5 to be, truthfully, all that interested in FDAMA and
6 the six-month exclusivity and the Pediatric Rule and
7 the sorts of trigger language that we have been
8 talking about. I think they are going to be
9 interested in what is best for their children and
10 maybe helping other children, but I don't think there
11 is any need to disclose something that's that
12 ubiquitous.

13 DR. ROWINSKY: How would you distinguish
14 that disclosure between industry studies or studies
15 done because of other reasons -- for example, a large
16 market where you might do a study first or just
17 investigate or initiate a study when the risk/benefits
18 are basically very similar to the child him or
19 herself? So I don't really think that that needs to
20 be mandated -- I mean, or disclosed.

21 CHAIRMAN SANTANA: Steve, do you want to
22 shed some light?

1 DR. HIRSCHFELD: Yes. I think Dr. Rackoff
2 raised a very important point, and it is never the
3 intent on the part of the FDA to mandate a particular
4 study or to mandate a particular family or child to be
5 enrolled in a study, but, rather, to mandate if the
6 conditions are met, that a particular drug be studied.
7 I don't think it should play a role, because if it is
8 a good scientific study and it is appropriate context,
9 in that setting those are the critical factors. I
10 think it would, in fact, confuse people and give a
11 level of imperative that is not there and not
12 intended.

13 While addressing that -- and I might ask
14 Dr. Pazdur to make a comment, too -- it may sound
15 semantic, but, from our point of view, there's no
16 difference between what is called alternative medicine
17 and any other type of medicine. From our perspective,
18 there are either products that have data that supports
19 a claim or they don't have data that supports a claim.
20 We view all potential therapies as an equivalent
21 universe or an equivalent cohort.

22 Dr. Pazdur, would you like to comment?

1 DR. PAZDUR: I pretty much agree with you,
2 Steve. I would be worried that, if this was put in
3 informed consent, that it could be interpreted as some
4 false approval or urgency or need or some priority
5 above other studies, and that really is not the intent
6 of this. I would not want to get that confusion
7 basically into the informed consent that, well, the
8 FDA mandated this study, so, therefore, this is better
9 than any other study. That is not the intent
10 necessarily to create a priority here of trials for
11 children to go on.

12 So I pretty much agree with the statements
13 that have been made previously.

14 DR. FINKLESTEIN: Thank you. I have two
15 comments regarding your excellent talk and then a
16 question.

17 For the audience, I would like to comment
18 a little further on Nancy Keene's statement. Late
19 effects is part and parcel of what we do in pediatric
20 oncology. We spend a lot of effort on late effects.
21 So I would not like the audience to get the feeling
22 here that we ignore it in pediatric oncology. But, in

1 actual fact, it is highly emphasized.

2 I compliment you on not giving or
3 assigning a percentage to risk/benefit. I have the
4 advantage, as I look around the audience here, to
5 state that I am probably the senior pediatric
6 oncologist in this room. So I remember in the sixties
7 when we were highly criticized for treating children
8 with acute leukemia because the percentage was such
9 that none of them were going to survive. As we well
10 know, survival in acute lymphocytic leukemia over the
11 past few decades has increased tremendously. So I
12 compliment you for not using a percentage.

13 My question has to do with your informed
14 consent data. You do assign numbers in terms of
15 parents understanding their choice of a clinical trial
16 and not understanding randomization. If we take away
17 the term "parents" and become more global, what is the
18 data for adults in general in terms of their own
19 clinical trials? What is their understanding? Are
20 parents any different when they're parents? Namely,
21 are the adults different when they are parents versus
22 when they are confronting the question themselves?

1 DR. KODISH: Thank you, Dr. Finklestein.
2 The question of how parents do in terms of
3 understanding the key issues compared to adults has
4 not been studied. We are actually in the process of
5 a very small pilot comparison of our data to a
6 colleague of mine who is doing similar direct
7 observation research in adults who are offered
8 participation in colon and breast cancer trials. We
9 haven't done the data analyses yet.

10 My suspicion is that there won't be a lot
11 of difference. That is, there are significant
12 barriers, I think, to understanding for adults who are
13 thinking about participation in clinical trials.

14 The best dataset that I know of on this
15 comes from the Advisory Committee on Human Radiation
16 Experiments done in the nineties under the Clinton
17 Administration, where they did a subject interview
18 study, and there were in that dataset, which is a much
19 larger dataset, significant barriers to sort of type
20 2 and type 1 errors, if you will; that is, people who
21 are in studies who don't know that they're in studies
22 and people who aren't in studies who think that they

1 are. It is the former sorts of problems that I think
2 are the most significant when they happen.

3 It wasn't all that common, but when it
4 happens, when someone is in a study and they don't
5 know they are in a study, I think that is a concern.

6 CHAIRMAN SANTANA: Dr. Boyett.

7 DR. BOYETT: I would like to follow up on
8 a comment from Dr. Reynolds and ask you about the
9 Phase I trial and the issue that the individual
10 patient should have the prospect for direct benefit.
11 I would interpret that as being the same direct
12 benefit for each trial that is enrolled on a Phase I
13 study.

14 I wonder if that is the correct
15 interpretation in the setting where a Phase I trial
16 has been completed in the adult population,
17 establishing either the MTD, maximum tolerated dose,
18 or establishing an optimal biologic dose for a
19 particular disease. Then when we begin to start a
20 Phase I trial in pediatrics, the tradition has been
21 that we start at 80 percent of that dose from the
22 adult trial. Does that mitigate the potential for

1 direct benefit for the early cohorts of patients
2 enrolled in a pediatric Phase I trial, and is that a
3 problem?

4 DR. KODISH: I think that the question of
5 dosing in the traditional Phase I paradigm is a
6 problem in terms of direct benefit to the subject. I
7 think that as we tinker with potentially new study
8 designs that are going to start at 100 percent or 120
9 percent, or whatever the right level is to begin with,
10 we need to be aware that we are increasing the
11 potential for direct benefit at the same time that
12 we're increasing the risk.

13 So it gets back to the comments of Dr.
14 Hirschfeld at the beginning of this discussion that
15 there is a numerator and a denominator that we need to
16 try to consider. It is going to be, I think,
17 especially with the wave of new approaches and new
18 mechanisms of drugs that we're looking at, very, very
19 important to do that. I think there is good reason to
20 hope that some of the denominator issues, that the
21 risks will be lower as we get away from conventional
22 dose toxicity relationship issues.

1 Some of the studies that have suggested
2 sort of choice to the subject, or in this case choice
3 to the subject parent at picking their own dose level,
4 I think are very intriguing in my mind, the idea that
5 lower dosing may be lower in terms of potential
6 benefit for the child. So it is a discussion I look
7 forward to having as the rest of the day goes on.

8 CHAIRMAN SANTANA: I want to keep the
9 meeting on time, so we will take one last question,
10 and the person on my list was Dr. Bernstein. So you
11 have the last question, Dr. Bernstein.

12 DR. BERNSTEIN: Well, mine was really more
13 just a comment to say that, coming from a city where
14 there are lots of immigrant populations, the questions
15 become much more vexed at times in immigrant
16 populations whose cultural traditions are very
17 different and whose whole concept of who gives consent
18 and whether the child should even be allowed to
19 participate in the assent process are very different.

20 DR. KODISH: Right, and I conclude by
21 saying we need to respect that, and that's why this
22 issue of risk/benefit as an objective measure, in my

1 mind, sort of trumps in pediatric ethics. We need to
2 be respectful of those considerations and always do
3 what's best for the individual child.

4 CHAIRMAN SANTANA: For the record, there's
5 a point of clarification. Donna?

6 DR. PRZEPIORKA: If the FDA could comment
7 as we globalize drug development, does the ICH have a
8 statement on inclusion of pediatric participants in
9 clinical research?

10 DR. HIRSCHFELD: There's an ICH document
11 called ICH E-11 which addresses this specifically and
12 has some, what we hope is an appropriate international
13 advice on the ethics and on the consent/assent issues.
14 It is available on the Internet and probably at your
15 local convenience store, too.

16 (Laughter.)

17 But it is a widely circulated document
18 that does address this.

19 CHAIRMAN SANTANA: Okay, moving right
20 along, the next topic of discussion, I invite Dr.
21 Steven Leeder for the review of developmental
22 pharmacology and as it may relate to the ethics.

1 DR. LEEDER: Well, I can start off by
2 saying that it is an honor for me to be here.
3 Probably of all of the people in the room, I am the
4 one that is least involved with cancer chemotherapy on
5 a day-to-day basis, which is not to apologize for me
6 to being here, but more to let you know that some of
7 the issues that are arising with respect to dosing are
8 ones that have to be dealt with in pediatric
9 pharmacotherapy in general. The issues I am going to
10 be raising are coming from the broader context of
11 pediatric pharmacotherapy.

12 To start off, I have tried to make this
13 presentation as concise as possible and yet deal with
14 the major issues. The one that was presented to me is
15 at the bottom of this slide. But what I am going to
16 do is, first of all, just using some selected
17 examples, review some general principles that are
18 related to drug metabolism specifically in children
19 throughout the developmental spectrum and try to raise
20 some issues rather than provide concrete answers,
21 because there may not be any just yet, related to the
22 issue of choosing a dose for the right child at the

1 right developmental stage based on available adult
2 data.

3 I think it is useful just to refresh our
4 memories as to how dynamic a process the first 15, 16,
5 18 years of life really is. In particular, we know
6 that in the first year of life there is a lot going
7 on. Weight doubles by five months of age and triples
8 by one year of age. Body surface area doubles by 12
9 months of age. You need to understand, if there is
10 that much growth going on, of course, there is a
11 rather dramatic caloric expenditure to fuel that. It
12 is estimated that caloric expenditures will increase
13 three- to fourfold over that same time period.

14 Now the green arrow in the center of the
15 slide and the question mark means that there is a lot
16 that we don't know what's going on, because for
17 healthy children the process of growth and development
18 is largely marked by placing a dot on a growth chart.
19 Then, of course, we head into that period of
20 adolescence where those of us who are parents facing
21 this really don't understand what's going on. The
22 only thing that can be said with any certainty is that

1 our children are far more intelligent than we are at
2 this stage of life.

3 (Laughter.)

4 Whether it is cancer chemotherapy or
5 pharmacotherapy in general, of course, the goal is to
6 find the right dose/response relationship. In the era
7 of therapeutic drug monitoring, the focus was on the
8 right dose to get to the right target concentration.
9 As we moved into the pharmacogenetic era, it was more
10 the right dose for the right patient. As we enter the
11 genomic era, it is really the right dose with the
12 right medication for the right patient to give us the
13 optimum response. Of caws, we often don't get it
14 right the first time, and there's a feedback mechanism
15 that allows us to alter the dose in response to lack
16 of efficacy or excessive toxicity.

17 So then what are the key determinants that
18 will help us establish what is the right dose
19 effect/response? I am largely going to focus, almost
20 exclusively going to focus, on the issue of drug
21 clearance as it changes through a development because
22 of the impact that this has on choosing an appropriate

1 dose. I am not going to deal so much with the
2 response end of things, although clearly the ontogeny
3 of drug targets and the ontogeny of resistance
4 mechanisms, for example, drug transporters, is
5 something that certainly needs to be studied and is
6 relevant to this discussion.

7 But I am going to focus on three main
8 elements, and that is the acquisition of functional
9 drug metabolizing enzyme activity. I am not going to
10 discuss transporter activity today. I am going to
11 address the dogma that drug metabolism activity is
12 increased in childhood relative to adults, and going
13 to raise the issue of metabolite shunting, and I will
14 explain this a little bit as we move along.

15 Just to review the acquisition, the first
16 element of the talk, the acquisition of functional
17 drug biotransformation or drug metabolism activity,
18 the fetus is largely devoid of activities that we
19 would consider to be protecting the host from small
20 molecular weight compounds, whether they be
21 medications or environmental contaminants. There are
22 some members of the cytochrome P450 family that are

1 expressed almost exclusively in the fetus, one example
2 being P450 3A7, where it likely plays a role in DHEA
3 metabolism and maintaining pregnancy. Also, there are
4 some sulfatransferases agents that play a similar
5 role.

6 After birth, most of our drug metabolism
7 activities are acquired in isoform and probably
8 tissue-specific patterns of expression. There are
9 some cytochrome P450's, for example, where the onset
10 of expression is measured in days; for example, P450
11 2C9 and P450 2D6. There are others where there is a
12 little bit of delay, and the onset of expression is
13 timed more in weeks. Then there are some, such as
14 P450 1A2, where activity really doesn't level off
15 until four to six months of age. I will show you some
16 in vivo data that support these claims.

17 We generally consider activities to peak
18 sometime in childhood and decline to adult levels at
19 some later point. Much of these data have been
20 gleaned from therapeutic drug monitoring studies. We
21 will discuss this issue in a little bit more detail as
22 well.

1 These are some in vitro data from France.
2 The purpose of this slide is to show that at the fetal
3 neonatal interface there is a transition of cytochrome
4 P450 3A activity, so it's not unlike the switch in
5 hemoglobin that occurs at this same time.

6 In the turquoise bars is the activity of
7 P450 3A7, measured by a relatively selective
8 substrate, the 16 alpha hydroxylation of DHEA. We can
9 see that levels in the fetus are relatively high
10 compared to after birth. The peak in activity, at
11 least from these in vitro data, appears to be in the
12 first week of life, with a decline thereafter.

13 On the other hand, the more mature form or
14 the adult form, if you will, of the cytochrome P450 3A
15 subfamily, 3A4, as measured by testosterone 6-beta
16 hydroxylation, which has fallen off the slide, it
17 seems, is relatively low in the fetus. In fact, some
18 of this activity that is observed may actually be 3A7
19 activity, but after birth there is an increase.

20 The point I would like to draw your
21 attention to on this slide is the fact that, even at
22 three to twelve months of age, the activity observed

1 in vitro is less than that observed at later ages.

2 Much of what we know or what we can infer
3 concerning P450 2C9 activity can be drawn from the
4 metabolism of phenytoin or Dilantin, which is a P450
5 2C9 substrate.

6 In this particular study, the
7 investigators were looking at the appearance of
8 saturable metabolism; that is, where the clearance of
9 the drug is dependent upon the initial concentration,
10 with lower clearance, slower clearance, being observed
11 at higher concentrations.

12 In essence, these investigators found no
13 relationship between initial drug concentration and a
14 measure of half-life that incorporated the saturation
15 metabolism that occurs with phenytoin in the first
16 week of life. Between two and three weeks of life, or
17 one and three weeks of life, they did see a linear
18 relationship of saturation between initial phenytoin
19 concentration and this apparent half-life measurement.
20 In fact, at later ages the slope of the line is not as
21 steep, implying that at a given concentration the
22 half-life is lower in older infants. The point being

1 here is that the appearance of satural metabolism,
2 which is thought to be a cytochrome P450 2C9 activity,
3 is acquired over the first two to three or four weeks
4 of life.

5 Along with that is the fact that on the
6 milligram-per-kilogram-per-day basis, children require
7 higher doses of phenytoin than do adults to achieve
8 the same target serum concentrations.

9 My last example here is theophylline
10 metabolism as a measure of P450 1A2 activity. Early
11 on in birth, after birth, here on the axis we have
12 post-conceptual age, and to make the math easy, you
13 may want to subtract 40 to get post-natal age. But,
14 early on, the newborn is highly dependent upon renal
15 clearance to remove theophylline from the system. As
16 post-natal age increases, there is a decrease in the
17 amount of unchanged theophylline which finds its way
18 into the urine.

19 Corresponding to that decrease is an
20 increase in the amount of the 8-hydroxylation product,
21 which is a function of P450 1A2 activity, implying
22 that it is only after four months of age or so that

1 1A2 activity has been acquired.

2 Now we are very much interested at our
3 institution in mapping the ontogeny and some of the
4 other pathways, and the one of the ones, one of the
5 pathways we were interested in was cytochrome P450
6 2D6. I have to say that the data that I am going to
7 show have not been subjected to peer review. They
8 have been presented in preliminary form, this
9 preliminary form, at a number of meetings, but they
10 have not been subjected to peer review.

11 But in this case what we are doing in a
12 population of healthy newborns is to map the develop
13 of the P450 2D6 pathway, and it turns out we think we
14 are also seeing some developmental changes in a
15 cytochrome P450 3A pathway as well. Later on, I can
16 go through the ethical considerations of doing such a
17 study in healthy infants, but for the next few slides
18 we are going to focus on this yellow metabolite, which
19 is an OD-methylated product of dextromethorphan, the
20 DM component of cough and cold remedies, as a measure
21 of P450 2D6 activity, and this turquoise metabolite,
22 which is missing the methyl group at this position and

1 the methyl group at this position, which is thought to
2 be a product of both an initial 3A dependence step,
3 followed by a P450 2D6 dependence step.

4 In a nutshell, when we look at the yellow
5 product, which is the 2D6 product, and we look at the
6 percentage of what we can recover in the infant's
7 urine, at two week's of age we see that 80 percent of
8 what we ultimately recover is the 2D6-dependent
9 metabolite. And if one looks at the known 2D6
10 polymorphism, where 7 to 10 percent of the Caucasian
11 population is actually deficient in this activity, we
12 see that at two weeks of age, if a child's genotype
13 says that they will be a 2D6 extensive metabolizer,
14 that is, have functional activity, they do appear to
15 have this activity at two weeks of age.

16 On the other hand, when we look at the
17 proportion of metabolites that appear in the urine as
18 this 3A, P450 3A-dependent metabolite, the mean is
19 somewhere around 14 percent, but this increases to
20 approximately 50 percent of what we recover by four
21 months of age.

22 To put this into context, in adults

1 roughly 30 percent of what we recover in the urine in
2 a typical phenotyping study will be this turquoise
3 metabolite. So around one month of age children have
4 the relative contributions of 2D6 and 3A4 that adults
5 have, but this clearly changes as they get older. At
6 one year of age here, while the differences are not
7 statistical significant, we are seeing a tendency for
8 more of the dextromethorphan metabolite, more of the
9 3A-dependent metabolite showing up in the urine, and
10 this exceeds what we see in adults.

11 Now this raises some interesting issues,
12 particularly if one has a drug that requires
13 bioactivation. So where I have "pro-drug" on this
14 slide, for illustrative purposes you may want to
15 convert that to codeine, and for "active metabolite,"
16 you may want to put in the word "morphine," and for
17 "alternative metabolite," you may want to put in anti-
18 methylated or non-pharmacologically active metabolites
19 of codeine.

20 So, under normal circumstances, and this
21 appears to be the case for codeine and also tramadol
22 and other analgesics, the pro-drug itself is not

1 pharmacologically active, but there is a metabolite
2 that is generated, in this case by cytochrome P450
3 2D6, that is thought to have the bulk of the
4 pharmacologic activity.

5 In a situation where competing pathways
6 may actually be increased over the normal situation,
7 so in adults the studies have actually been done with
8 codeine with induction of the 3A pathway by rifampin,
9 it can be seen that some of the active metabolite, or
10 at least some of the pro-drug, the parent compound, is
11 diverted away from the pharmacologic bioactivation
12 pathway, so that you see less of the active compound
13 being formed and you can also observe that the
14 pharmacologic effects have been reduced as well.

15 In a pediatric context, I don't know that
16 this phenomenon has been described, but I think as we
17 learn more about how there may be pathway shifting, we
18 need to bear in mind that a particularly unique
19 pediatric consequence of these developmental changes
20 in drug metabolism may be the fact that we divert drug
21 away, that there may be a diversion of drug away from
22 a potentially useful pathway.